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

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Method Article

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Title:

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

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Conflict of Interest/Disclosure Statement

The author declares that there is no potential conflicts of interest or lack thereof.

ABSTRACT

Persistent dizziness or lightheadedness ranks among the most frequent complaints in primary care. Persistent dizziness is frequently described as a consequence or side effect of defined entities such as cardiovascular, infectious, neurological, and otological disease. Persistent dizziness is potentially disabling and has a distinct impact on participation, psychosocial interaction, and quality of life. We examined the relationship between persistent dizziness or 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 (overall and across multiple domains), magnetic resonance imaging for AD-signature "regional thickness," and ^{11}C -Pittsburgh compound B positron emission tomography (^{11}C -PiB PET) for Amyloid deposition are all investigated. Significant contributing factors to persistent dizziness in older adults were found and include [age, sex (male), lower education, high comorbidity index, high-density lipoprotein, balance problems, neuropsychiatric symptoms, cognitive impairments, and AD-signature" regional thickness]. 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.

KEYWORDS: Aging, Persistent Dizziness, Persistent lightheadedness, Alzheimer's disease

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 primary care as it can be easily provoked by physical activities (i.e., postural change and head and neck movement, Active or passive motion of self) or environmental or social stimuli (i.e., crowds) or behavioral factors (i.e., high level of anxiety, introverted temperaments, or pre-existing anxiety or depressive disorder) (Sloane, Hartman, & Mitchell, 1994; Tinetti, Williams, & Gill, 2000). In clinical practice, persistent dizziness/lightheadedness lacks uniform criteria for its classification and definition, especially when not better accounted for by vestibular diagnosis (Bösner et al., 2018; Iwasaki & Yamasoba, 2014). 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 functions including, memory impairment using various cognitive tasks and structural and functional neuroimaging. Alzheimer's disease (AD) is a neurodegenerative pathology that leads to behavioral and changes in memory loss and is ultimately fatal (Alzheimer's Association, 2016). 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 (Jack et al., 2018). Amyloid- β accumulation, which can be detected by ^{11}C Carbon-Pittsburgh

compound B positron emission tomography (^{11}C -PiB PET) imaging, causes synaptic dysfunction due to either a breakdown of Amyloid- β clearance or Amyloid- β overproduction (Hatsuta et al., 2015). The increased use of ^{11}C -PiB PET imaging has led to the observation that Amyloid- β is also present in approximately one-third of cognitively normal older adults (Mintun et al., 2006; Resnick et al., 2010). A high level of Amyloid- β deposition was found to be associated with deficits in spatial cognition, such as spatial memory and navigation, depression and anxiety, and increased risk of progression to AD (Baker et al., 2017; Mintun et al., 2006; Resnick et al., 2010).

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 (d'Oleire Uquillas et al., 2017; Dickerson et al., 2009; Jack et al., 2008; Jack et al., 2009). 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 (Harun, Oh, Bigelow, Studenski, & Agrawal, 2016; Nakamagoe et al., 2015; Previc, 2013; Smith, 2013). 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 Clinic Study of Aging (MCSA) in Olmsted County, MN (Roberts et al., 2008). 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 persons who reported dizziness or lightheadedness.

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 CU (based on normative data developed on a separate sample in this community) or having MCI 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 21 items that measure symptoms of depression (such as loss of interest) 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 $\approx 2,300$ ms, echo time (TE) ≈ 3 ms, and inversion time (TI) = 900 ms. 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 were classified as having an abnormal PiB-PET retention (elevated β-amyloid burden; A+) as we have previously validated by autopsy (Murray et al., 2015). The reader is referred elsewhere for details on PiB-PET imaging in the MCSA (Lowe et al., 2009).

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. For simplification, the 14 years were divided into five events (1 year +/- 6months; 3 years; 5 years; 7 years; and 10 +/- 2 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 χ^2 test as appropriate are presented in **Table 1**. The potential risk factors for persistent dizziness/lightheadedness over time are presented in **Table 2**. These include age, sex (male), lower education, high comorbidity index, high-density lipoprotein, balance problems, neuropsychiatric symptoms, cognitive decline, and AD-cortical thickness signature.)

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

Association between persistent dizziness and AD markers including neuropsychiatric symptoms and cognitive impairments

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, 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 A β 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 and AD markers. A study highlighted that the elderly men with lower education, high comorbidity index, high-density lipoprotein, balance problems, neuropsychiatric symptoms, cognitive impairments, and AD markers have a higher risk of persistent dizziness or lightheadedness. After adjusting for age, sex, education, and other variables, our study showed that there is a significant albeit weak association between neuropsychiatric symptoms and risk of persistent dizziness/lightheadedness, but 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 (Cantón-Habas, Rich-Ruiz, Romero-Saldaña, & Carrera-González, 2020; Livingston et al., 2020). 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 (Aizenstein et al., 2008; Bensamoun et al., 2016; Krell-Roesch et al., 2018; Yasuno et al., 2016). 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 (Krell-Roesch et al., 2018). However, when

1 compared to mild cognitive impairment without brain Amyloid- deposition, the elderly with mild
2 cognitive impairment and brain Amyloid- deposition were found to have an increased risk of
3 having neuropsychiatric symptoms. This implies that the underlying AD biology (i.e., brain
4 Amyloid- β deposition) may drive both cognitive and psychiatric symptoms (Krell-Roesch et al.,
5 2019). Similarly, a study investigated whether current depressive symptoms are related to brain
6 Amyloid- β deposition (Chung et al., 2016). After controlling for potential confounds, including
7 the history of major depression, they found that current depressive symptoms were not related to
8 brain Amyloid- β deposition. Fourth, a previous study using the Baltimore Longitudinal Study of
9 Aging examined a relationship between measures of vestibular function and brain Amyloid- β
10 deposition in cognitively intact older adults who have peripheral dizziness/vertigo (Kamil, Bilgel,
11 Wong, Resnick, & Agrawal, 2018). While that study did not observe a significant relationship
12 between the two, a study found that the proportion of central dizziness/vertigo tends to increase
13 with dementia (Lee, 2020). In our study, the tendency of the peripheral cause of dizziness was not
14 observed in their medical records.

15 Noteworthy, persistent dizziness/lightheadedness has an important cortical representation
16 in the frontal and parietal regions (Nigro et al., 2019). Research has found that brain Amyloid- β
17 deposition and psychiatric outcomes can appear as early as 20 years before the first sign of the AD
18 pathology, such as cognitive decline and memory loss (Dubois et al., 2016; Selkoe & Hardy,
19 2016). Along with our study findings, this can imply that persistent dizziness/lightheadedness
20 among the elderly can be an early sign of AD. Given that persistent dizziness/lightheadedness can
21 be associated with poor physical and mental health, the overall result of our study can be a
22 valuable addition to current knowledge and may have clinically relevant results to potentially
23 screen for and manage persistent dizziness/lightheadedness among older adults.

CONCLUSION

Significant contributing factors to persistent dizziness in older adults were found and include [age, sex (male), lower education, high comorbidity index, high-density lipoprotein, balance problems, neuropsychiatric symptoms, cognitive impairments, and AD-signature regional thickness]. 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 Legends

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

Table 1. Participants' characteristics by significant persistent dizziness/lightheadedness at baseline

	No (N=4758) ^a Mean (SD); Median	Yes (N=924) Mean (SD); Median	Total (N=5707) Mean (SD); Median	P-value ^b
Age, at baseline	72.9 (10.1); 73.9	74.4 (9.7); 75.7	73.2 (10.0); 74.2	0.001
Sex, male	2406 (50.6%)	483 (52.3%)	2895 (50%)	0.343
Education, years	14.4 (2.8); 12.0	14.0 (2.8); 14.0	14.3 (2.8); 14.0	0.001
Race, white	4635 (98.2%)	896 (97.7%)	5096 (89%)	0.366
Ethnicity, Not Hispanic	4686 (99.7%)	903 (99.3%)	5156 (90%)	0.094
Charlson comorbidity index	3.0 (3.0); 2.0	3.7 (3.3); 3.0	3.1 (3.1); 2.0	0.001
APOE ε4 positive	1181 (27.1%)	256 (29.5%)	1441 (25%)	0.146
Lipid test (HDL)	45.7 (13.9)	45.1 (14.9)	39 (22)	0.233
Balance difficulties	721 (15.5%)	249 (27.4%)	764 (13%)	0.001
Hearing Loss at baseline	1494 (31%)	367 (39%)	1868 (32%)	0.001
Gait speed $\leq 0.6\text{m/sec}$ ^b	144 (30%)	42 (4.5)	187 (3.2)	0.012
Beck Depression Inventory	4.4 (4.5); 3.0	8.1 (6.4); 7.0	4.9 (5.0); 4.0	0.001
Beck Anxiety Inventory	2.0 (2.9); 1.0	8.0 (6.5); 6.0	2.9 (4.3); 1.0	0.001
Global cognitive z-score ^c	-0.2 (1.2); -0.2	-0.6 (1.2); -0.6	-0.4 (1.2); -0.3	0.001
Memory z-score ^c	-0.4 (1.2); -0.3	-0.6 (1.2); -0.6	-0.4 (1.2); -0.4	0.001
Language z-score ^c	-0.3 (1.2); -0.2	-0.5 (1.3); -0.4	-0.3 (1.2); -0.2	0.001
Attention/executive z-score ^c	-0.3 (1.2); -0.1	-0.7 (1.4); -0.5	-0.3 (1.1); -0.2	0.001
Visuospatial skills z-score ^c	-0.2 (1.1); -0.1	-0.4 (1.1); -0.3	-0.2 (1.1); -0.3	0.001
Amyloid-β deposition	1.5 (0.3); 1.4	1.5 (0.3); 1.4	1.4 (0.2); 1.4	0.159
AD-signature thickness, mm	2.7 (0.2); 2.7	2.7 (0.2); 2.7	2.6 (0.1); 2.7	0.077

Note: data presented as N (%) for categorical and mean (SD); median for continuous characteristics. ^a 25 missing. ^b 465 missing data.

^d Global cognitive z-score was computed after scaling raw cognitive test scores (mean 0 ± 1) using data for cognitively unimpaired participants at baseline. Domain-specific z-scores were summed and scaled to obtain global z-scores.

Table 2. Factors contributing to persistent dizziness/lightheadedness in older adults.

Variables	# Of patients	HR	95% CI	<i>P-value</i>
Age at visit	4783	1.02	1.01-1.03	0.001
Sex, male	4783	1.13	1.01-1.28	0.032
Education, years	4778	0.95	0.93-0.97	0.001
Race, white	4745	0.89	0.57-1.41	0.640
Ethnicity, Not Hispanic	4723	1.11	0.35-3.45	0.852
Charlson comorbidity index	4782	1.07	1.05-1.09	0.001
APOE ε4 positive	4381	1.095	0.95-1.25	0.640
Lipid test (HDL)	1543	0.99	0.98-0.99	0.008
Balance difficulties	4654	1.07	1.06-1.08	0.001
Gait speed $\leq 0.6\text{m/sec}^d$	4410	1.30	0.93-1.83	0.130
Beck Depression Scale (BDS)	4684	1.07	1.06-1.08	0.001
Beck Anxiety Inventory (BAI)	4758	1.08	1.07-.10	0.001
Global cognitive z-score ^e	4426	0.83	0.79-0.88	0.001
Memory z-score ^e	4702	0.85	0.80-0.89	0.001
Language z-score ^e	4600	0.86	0.82-0.91	0.001
Attention/executive z-score ^e	4553	0.84	0.79-0.88	0.001
Visuospatial skills z-score ^e	4552	0.89	0.85-0.95	0.003
Amyloid-β deposition	744	2.23	1.45-3.44	0.002
AD-signature thickness, mm	1548	0.38	0.19-0.74	0.004

Table 3. Neuropsychiatric symptoms, Cognitive evaluation, and AD-biomarkers by follow-up events as compared to baseline.

Variables at baseline	Baseline Mean (SD); Median	1 year Mean (SD); Median	3 years Mean (SD); Median	5 years Mean (SD); Median	7 years Mean (SD); Median	10 years Mean (SD); Median
Beck Depression Inventory	(N=5590) 5.0 (5.1) 4.0	(N=3919) 4.7 (4.9) ** 3.0	(N=3569) 4.6 (4.7) 3.0	(N=2702) 4.8 (4.7) ** 4.0	(N=1731) 5.0 (4.9) ** 4.0	(N=783) 5.6 (5.2) ** 4.0
Beck Anxiety Inventory	(N=5682) 2.9 (4.4) 1.0	(N=3938) 2.7 (4.0) ** 1.0	(N=3583) 2.7 (4.1) ** 1.0	(N=2715) 2.7 (4.2) 1.0	(N=1753) 2.8 (4.3) 1.0	(N=796) 3.0 (4.7) ** 1.0
Global cognitive z-score ^e	(N=5280) -0.4 (1.2) -0.3	(N=3650) -0.2 (1.3) ** -0.03	(N=3274) -0.2 (1.3) ** 0	(N=2439) -0.1 (1.3) ** 0.1	(N=1559) -0.2 (1.2) ** 0	(N=64) -0.6 (1.2) ** -0.4
Memory z-score ^e	(N=5609) -0.4 (1.2) -0.4	(N=3884) -0.1 (1.2) ** -0.01	(N=3530) -0.1 (1.3) ** 0.1	(N=2651) 0.0 (1.3) ** 0.2	(N=1709) 0.0 (1.3) ** 0.2	(N=768) -0.3 (1.3) -0.2
Language z-score ^e	(N=5488) -0.4 (1.3) -0.2	(N=3801) -0.2 (1.2) -0.1	(N=3432) -0.2 (1.3) ** -0.01	(N=2586) -0.2 (1.3) ** -0.1	(N=1674) -0.3 (1.2) ** -0.1	(N=752) -0.7 (1.3) ** -0.4
Attention/executive z-score ^e	(N=5437) -0.4 (1.3) -0.2	(N=3745) -0.3 (1.3) ** -0.01	(N=3379) -0.3 (1.3) ** -0.1	(N=2522) -0.3 (1.3) ** -0.1	(N=1620) -0.4 (1.3) ** -0.3	(N=706)0.9 (1.2) ** -0.6
Visuospatial skills z-score ^e	(N=5426) -0.3 (1.1) -0.2	(N=3752) -0.1 (1.1) ** 0	(N=3362) -0.1 (1.1) ** -0.1	(N=2511) 0.0 (1.1) 0.1	(N=1604) -0.0 (1.1) 0.1	(N=706) -0.3 (1.0) ** -0.2
Amyloid- β deposition	(N=866) 1.5 (0.3) 1.4	(N=459) 1.5 (0.3) ** 1.4	(N=538) 1.6 (0.4) ** 1.4	(N=359) 1.7 (0.4) ** 1.5	(N=140) 1.8 (0.5) ** 1.7	(N=78) 1.9 (0.5) ^a 1.7
AD-signature thickness, mm	(N=1831) 2.7 (0.2) 2.7	(N=1152) 2.6 (0.2) ** 2.6	(N=1216) 2.6 (0.2) ** 2.6	(N=511) 2.6 (0.2) ** 2.6	(N=511) 2.6 (0.2) ** 2.6	(N=78) 2.5 (0.2) ** 2.6

Table 4. Hazard risk (HR) of association between persistent dizziness/lightheadedness and AD-biomarkers

Outcomes	#Of patients	HR	95% CI	<i>P-value</i>
Beck Depression Scale	4680	1.07	1.05-1.08	0.001
Beck Anxiety Inventory	4753	1.08	1.06-.10	0.001
Global cognitive z-score ^e	4425	0.94	0.88-1.01	0.108
Memory z-score ^e	4701	0.94	0.88-1.01	0.106
Language z-score ^e	4599	0.95	0.91-1.01	0.170
Attention/executive z-score ^e	4552	0.95	0.89-1.01	0.147
Visuospatial skills z-score ^e	4551	1.00	0.93-1.06	0.991
Amyloid- β deposition	743	1.87	1.16-3.02	0.009
AD-signature thickness, mm	1547	1.20	0.54-2.68	0.650