A Relationship Between Unexplained Dizziness and Beta-amyloid Plaques Among Older Adults – Mayo Clinic Longitudinal Study of Aging

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Method Article

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Abstract

Background and Objective

Beta-amyloid (Aβ) plaque deposition, which can be detected by amyloid C-11 labeled Pittsburgh Compound B (^{11}C-PiB) Positron Emission Tomography (PET) imaging, is a key feature of Alzheimer's disease (AD) and occurs years before the onset of symptoms. It is well-documented that the onset of AD initially involves degeneration of cholinergic systems in the posterior parietal-temporal, medial-temporal, and posterior-cingulate regions, which have a strong relationship with the vestibular labyrinth. In the context of an aging population, the symptoms-related vestibular system ranks among the most frequent complaints in primary care but remains unexplained in 40–80% of cases over the age of 65. The objective of this study was to evaluate the cross-sectional and longitudinal association between the symptoms-related vestibular system and Aβ-PET imaging among older adults.

Methods

A retrospective study design. The study included 5707 participants without dementia, enrolled in the Mayo Clinic Study of Aging (mean age (SD) 74.4 (9.7) years) with cognitive evaluation and information about symptoms-related vestibular system, mainly dizziness or lightheadedness, at baseline and for every 15 months.

Results

Of the 5707, 924 (16%) participants were complaining of 'unexplained' dizziness or lightheadedness. The estimated risk of developing symptoms of dizziness or lightheadedness at 10 years was 49%. Data suggested that AD-related risk factors including, age, male gender, lower education, high comorbidity index, high-density lipoprotein, balance problems, presence of neurocognitive and neurobehavioral outcomes, and brain-related changes can contribute to the risk of developing 'unexplained' dizziness or lightheadedness among older adults. Adjusting for the risk factors, a statistically significant association between 'unexplained' dizziness or lightheadedness and Aβ-PET imaging was evident [HR = 1.8, P = 0.009]. This association seems to be significantly modulated by psychological outcomes including, depressive symptomatology and anxiety [HR = 1.0, P = 0.001].

Conclusions

'Unexplained' dizziness or lightheadedness was associated with Aβ plaque deposition among older adults. This association seems to be modulated by psychological outcomes. Although these symptoms can be linked by a common cause, it may suggest functional dizziness, also known as psychogenic dizziness or persistent postural-perceptual dizziness. Further studies are needed to support the findings.

Introduction

Ageing is one of the most well-established risk factors for many organic or systemic diseases. In the context of aging population, it can be complicated enough to care for elderly patient with a single disease; however, this is not the case if we are aiming to prevent or delay the onset of with Alzheimer's disease (AD) or a related dementia (Alkadhi & Eriksen, 2011; Masters & Beyreuther, 1998). AD has emerged as the predominant form of dementia in the elderly, affecting one person in ten over the age of 65, and 50 percent of individuals over the age of 85 (Evans et al., 1989; Qiu, Kivipelto, & von Strauss, 2009).

It is well-established that multiple chronic conditions, physical inactivity, and mental illness such as depression and anxiety can increase the risk of Beta-amyloid (Aβ) plaques build-up (also known as neuritic plaques or senile plaques) in the areas of the brain concerned with memory in cognitively normal adults (Livingston et al., 2020; Rodrigues et al., 2012; Santos et al., 2017). If left unrecognized, Aβ plaques deposition found to be associated with increased risk of decline on cognitive measures of visuospatial function, episodic and semantic memory, mental status, and increased risk of progression to AD (Livingston et al., 2020; Mormino & Papp, 2018; Murphy & LeVine, 2010). Hence, AD pathogenesis is widely believed to be driven by the presence of Aβ plaques in the aggregated brain regions (Murphy & LeVine, 2010). These regions involve degeneration of cholinergic systems in the posterior parietal-temporal, medial-temporal, and posterior-cingulate regions, which have a strong relationship with the vestibular labyrinth (Previc, 2013).

Neuroimaging studies have found that patients with preclinical AD have widespread white matter abnormalities at a stage like those reported in Alzheimer's disease, whereas gray matter structures were relatively intact. In addition, widespread white matter abnormalities o is reported to occur prior to the presence of amyloid-β plaques (Sachdev, Zhuang, Braidy, & Wen, 2013). Remarkably, C-11 labeled Pittsburgh Compound B (^{11}C-PiB) was the first successful Positron Emission Tomography (PET) is the leading neuroimaging tool to detect and provide quantitative measures of Aβ plaques *in vivo* at the early stages and follow its course longitudinally (Villemagne, Doré, Burnham, & Rowe, 2021; Vlassenko, Benzinger, & Morris, 2012; Wiley et al., 2009).

Dizziness is frequently described as a symptom of peripheral vestibular loss or a consequence or side effect of defined entities such as cardiovascular, infectious, and neurological disease or as a discrete syndrome associated with co-morbidities (Neuhauser et al., 2008). Dizziness is a subjective perception of disorientation or involuntary motion that occurs during head or body movement or when the head or body is still. Dizziness can be further characterized as lightheadedness, which is the sensation of impending loss of consciousness associated with transient diffuse cerebral hypoperfusion. The severity of dizziness or lightheadedness is a potentially disabling condition that has a distinct impact on physical activity, mental health, and cognitive status since it is provoked by postural change and head and neck movement (Sloane, Hartman, & Mitchell, 1994; Tinetti, Williams, & Gill, 2000).

Dizziness ranks among the most frequent complaints in primary care but remains unexplained in 40–80% of cases over the age of 65 and typically lacks uniform criteria for its classification and definition,

especially when not better accounted for by vestibular diagnosis (Bösner et al., 2018; Iwasaki & Yamasoba, 2014). A study found that cerebral atrophy was found in 86% of dizzy subjects and 85% controls and at least one white matter lesion was found in 69% of dizzy subjects and 78% controls; however, white matter lesions in the midbrain were significantly common in dizzy than in non-dizzy subjects (Colledge et al., 2002). This raises a concern of a potential link between 'unexplained' dizziness or lightheadedness and presence of Aβ plaques. The objective of this study was to evaluate the cross-sectional and longitudinal association between symptoms-related vestibular system and Aβ-PET imaging among older adults.

Methods

Study design

A retrospective study design was performed at the Mayo Clinic Florida. The Mayo Clinic Longitudinal Study of Aging Data Set (MCSA; (Roberts et al., 2008) was used to evaluate the cross-sectional and longitudinal association between dizziness or lightheadedness and Aβ-PET imaging. The MCSA was approved by the Institutional Review Boards and the Olmsted Medical Center. The study design and methodology of the MCSA have previously been published in detail. Briefly, eligible participants of the MCSA were non-demented and ≥ 50 years of age, with a concurrent, valid neurocognitive testing, neurobehavioral evaluation, and 11C-PiB PET imaging. The objective of the MCSA study was to establish a prospective population-based cohort to investigate (1) the prevalence of mild cognitive impairment; (2) the incidence of mild cognitive impairment; (3) conversion rates from mild cognitive impairment to dementia or AD; (4) risk factors for mild cognitive impairment; and (5) risk factors for the progression from mild cognitive impairment to dementia or AD.

Participants

Among 5707 participants in the MCSA, 924 participants who reported a mild to severe degree of dizziness or lightheadedness were selected. There were 483 (52.3%) male and 441 (47.7%) female participants with a mean age of 74.4 (9.7). The medical records for dizzy patients showed a non-organic origin of dizziness or lightheadedness. Demographics were compared between those with/without dizziness or lightheadedness using Wilcoxon signed-rank test or $\chi 2$ test as appropriate. Full details are presented in Table 1.

Out of those 5707, the total follow-up time 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). Wilcoxon signed-rank test was used to determine if there was a significant difference in score between baseline and the follow-up measurements. The $\chi 2$ test was used to compare categorical variables. Table 2 showed the mean difference between the baseline scores of neurocognitive evaluations and each event. P-value of < 0.05 is considered significant.

Table 1
Participants' characteristics by significant dizziness or 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%)	0.00 1
Gait speed ≤ 0.6m/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
Aβ-PET imaging	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
Neurocognitive evaluation 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

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
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
Aβ-PET imaging	(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

Statistical analysis

For the analytical assessment of neurocognitive testing and ^{11}C-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

The risk of dizziness or 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 or lightheadedness at 10 years was 49%. Figure 1 represents the survival curve. Potential risk factors to severity of dizziness or lightheadedness over time are presented in Table 3. Adjusting for age, sex, education, comorbidity (Charlson comorbidity index), and other risk factors, a statistically significant association between dizziness or lightheadedness and Aβ-PET imaging was evident [HR = 1.8, P = 0.009].

This association seems to be significantly modulated by neurobehavioral outcomes including depressive symptomatology and anxiety [HR = 1.0, P = 0.001]. Results are presented in Table 4.

Table 3
Factors contributing to dizziness or lightheadedness in older adults.

Variables	# of patients	HR	95% CI	*P-value*
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 ≤ 0.6m/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
Aβ-PET imaging	744	2.23	1.45–3.44	0.002
AD signature thickness, mm	1548	0.38	0.19–0.74	0.004

Table 4
Association between dizziness or lightheadedness and Aβ-PET imaging

Outcomes	# of patients	HR	95% CI	*P-value*
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
Aβ-PET imaging	743	1.87	1.16–3.02	0.009
AD signature thickness, mm	1547	1.20	0.54–2.68	0.650

Discussion

To the best of our knowledge, this is the first study to evaluate the relationship between dizziness or lightheadedness, that not better accounted for by peripheral vestibular diagnosis and Aβ-PET imaging among older adults. The data highlighted the risk of developing dizziness or lightheadedness overtime. Also, data suggested that AD-related risk factors including, age, male gender, lower education, high comorbidity index, high-density lipoprotein, balance problems, presence of neurocognitive and neurobehavioral outcomes, and brain-related changes can contribute to the prevalence of dizziness or lightheadedness among older adults. In addition, after controlling for the risk factors including neurocognitive and neurobehavioral outcomes, our model revealed a significant relationship between dizziness or lightheadedness and Aβ-PET imaging among older adults, in which neurobehavioral outcomes (depressive symptomatology and anxiety) appear to be intimately related to this relationship. This relationship may emphasize the complex interactions of different pathways underlying both depression, dizziness or lightheadedness, and Aβ-PET imaging. Besides what was being highlighted in the introduction section, there are several reasons that intuitively support our findings.

First, anxiety and depression, on one hand, and dizziness or lightheadedness, on the other, are common complaints among elderly people. Several studies underlined that depressive symptomatology and anxiety can be symptoms of underlying health problems, such as dizziness or lightheadedness, and vice versa (Best, Eckhardt-Henn, Tschan, & Dieterich, 2009; Carmeli, 2015; Kotova & Zamergrad, 2016).

Second, a previous study using the Baltimore Longitudinal Study of Aging examined a relationship between peripheral vestibular loss, in which dizziness is a common symptom, and the Aβ deposition

(Kamil, Bilgel, Wong, Resnick, & Agrawal, 2018). However, the study did not observe a significant relationship between measures of vestibular function and Aβ-PET imaging in cognitively intact older adults. Similarly, a study investigated whether current depressive symptoms are related to cortical Aβ deposition (Chung et al., 2016). They found that current depressive symptoms were not related to cortical Aβ, after controlling for potential confounds, including the history of major depression. They also observed that there was no difference in cortical Aβ between matched participants with high and low depressive symptoms, as well as no difference between matched participants with the presence and absence of depressive symptoms.

Third, the vestibular system was considered as a sixth sense as it contributes to a wide range of functions from the level of reflexes to the level of cognition and coordination. Connections between the vestibular system and cognitive functions have attracted much recent interest over the last century, motivated by emerging evidence that impaired vestibular function is a risk factor for cognitive decline. However, dementia and reduced cognitive function present immense challenges, and their intersection remain poorly understood and difficult to assess, even in the presence of Aβ plagues (Kamil et al., 2018). Typically, elderly individuals complain of persistent dizziness or lightheadedness even before the reduced vestibular function can be detected. Persistent dizziness or lightheadedness or chronic dizziness has an important cortical representation in the frontal and parietal regions (Nigro et al., 2019). Noteworthy, research has found that Aβ deposition and psychiatric outcomes can appear as early as 20 years before the first sign of AD, such as cognitive decline and memory loss (Dubois et al., 2016; Selkoe & Hardy, 2016). Future, a study provided preliminary evidence that region-specific, mainly frontal and parietal regions, Aβ deposition was present in some (but not all) depressive patients, especially in those with moderate-to-severe treatment resistance, and their depressive symptoms may represent prodromal manifestations of AD (Li et al., 2017).

Limitations of this study include the appropriate, valid outcome that detaches and measures the impact of dizziness or lightheadedness on health. It also includes a lack of uniform criteria for classification and definition of dizziness or lightheadedness in the medical records. However, we believe that ‘unexplained’ dizziness or lightheadedness may indicate functional dizziness, also known as psychogenic dizziness or persistent postural-perceptual dizziness (Kaski, 2020). Although the exact pathophysiology of functional dizziness is not yet clear, benign paroxysmal positional vertigo, vestibular migraine, and cerebral small vessel disease, anxiety disorders were the most contributing factors (Kaski, 2020). An acute ‘dizzy episode’ preceding these symptoms will be volunteered in many cases, and the disorder will usually emerge as this triggering event resolves. However, the processes are known to involve normal physiological and behavioral responses to an acute postural threat, which become inappropriately sustained after its remission. The usual response to dizziness or lightheadedness is to adopt protective balance strategies. Normal individuals demonstrate stiffening of posture and a shift in sensory information processing to increase reliance on visual and somatosensory cues in such situations. Those who develop a degree of functional dizziness or lightheadedness after an acute event show persistent high visual dependence, high anxiety, and hypervigilance to balance sensations compared with those

who recover well. Prior anxiety and neurotic personality (state and trait anxiety) appear to pre-dispose to this maladaptation.

Remarkably, neuroimaging studies demonstrated that activity and connectivity in brain regions that process visual, vestibular, and spatial information are different between individuals with and without functional dizziness. The results suggest that a failure of cortical network (top-down) suppression of ascending postural information may result in persistence of the acute, high-risk postural behavior as well as high risk of anxiety and depressive symptomatology. Functional dizziness is, therefore, typically characterized by persistent dizziness and perceived instability or balance difficulty, worse in the upright position and in busy visual environments (Popkirov, Staab, & Stone, 2018).

Complexity and health of dizzy older adults who are at risk of AD

The overall result of our study is, therefore, can be a valuable addition to current knowledge and may have clinical relevance, in that treatment response in dizzy patients with depression and/or anxiety could predict AD-related pathophysiology and aid clinicians in identifying patients in need of vigilant follow-up to assess cognitive functions. The suggested model for complexity and health of dizzy older adults who are at risk of AD is presented in Fig. 2.

Conclusions

‘Unexplained’ dizziness or lightheadedness was associated with Aβ plaque deposition among older adults. This association seems to be modulated by psychological outcomes. Although these symptoms can be linked by a common cause, it may suggest functional dizziness, also known as psychogenic dizziness or persistent postural-perceptual dizziness. Further studies are needed to support the findings.

Declarations

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

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Figures

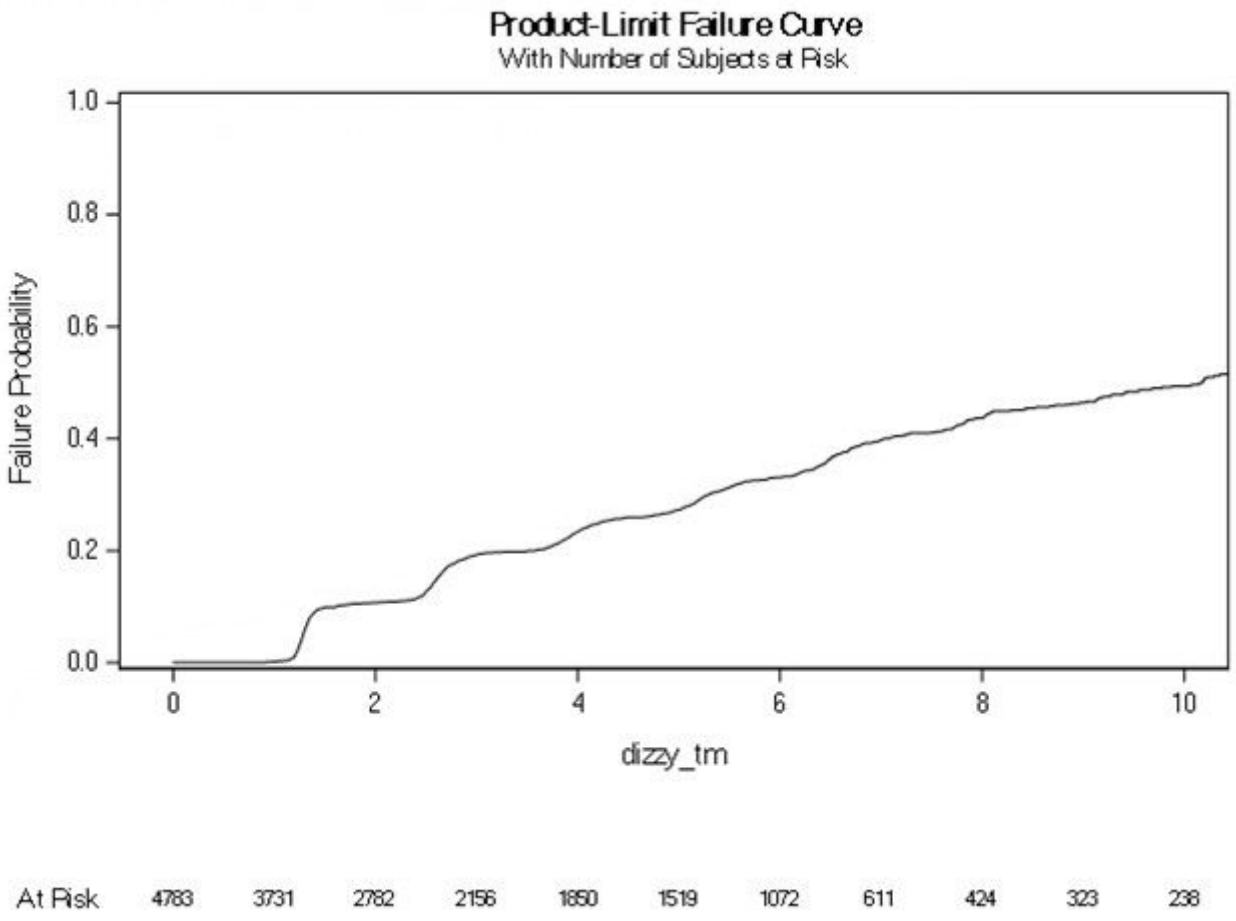

Figure 1

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

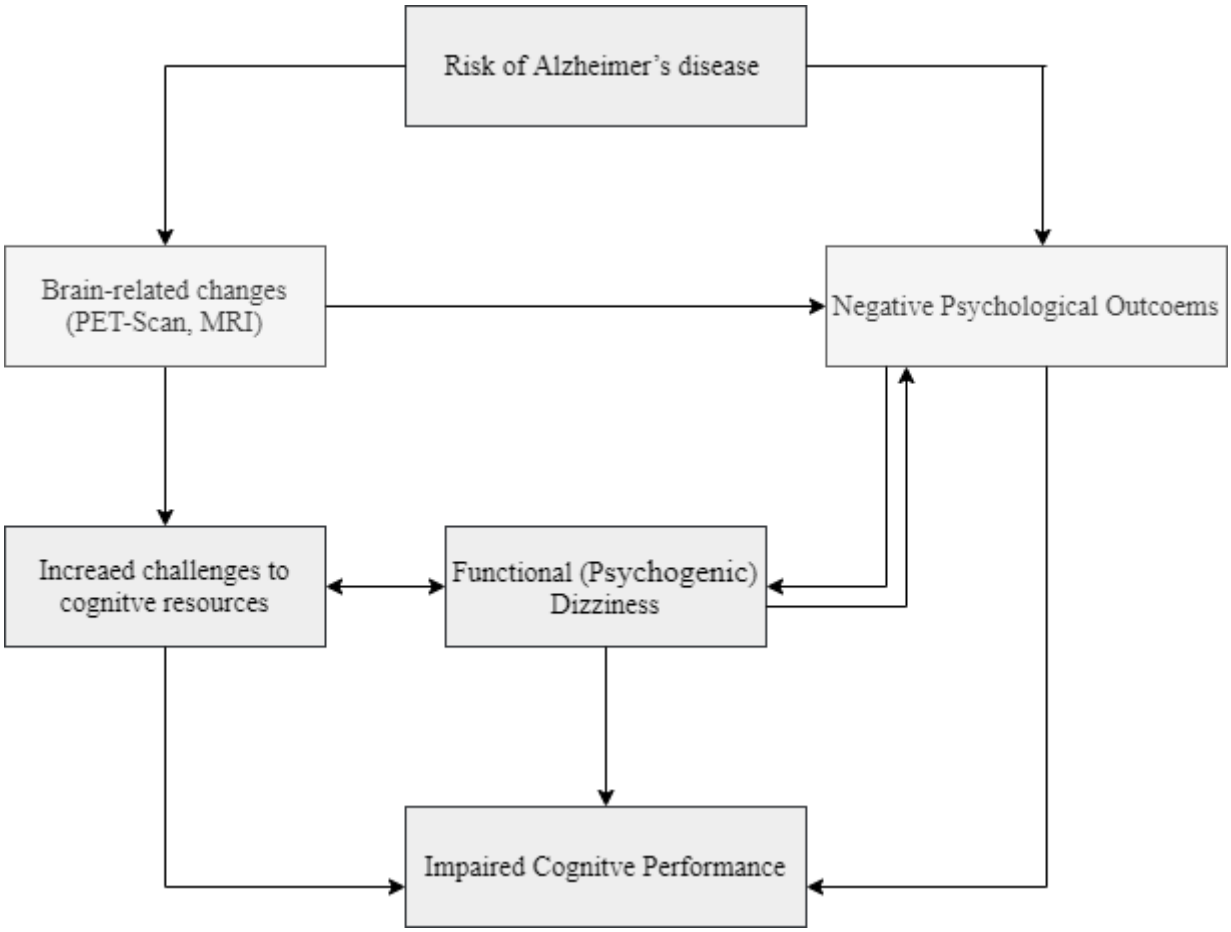

Figure 2

The author's suggested model Complexity and health of dizzy older adults who are at risk of AD