Cognitive dysfunction and the 25-item National Eye Institute Visual Function Questionnaire

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Abstract
Introduction: Visual function and cognitive impairment are interrelated; however, little is known about the impact of modifying treatable vision impairment on the development of cognitive dysfunction. This study examines the relationship between cognition and self-reported visual function using the National Eye Institute’s Visual Function Questionnaire (NEI VFQ).

Methods: Participants completed the NEI VFQ 25-Item questionnaire as well as the Mini-Mental State Examination (MMSE). Additionally, all participants were assigned a consensus clinical diagnosis based on established criteria. We used a general linear model and analysis of variance approach to compare means between multiple groups.

Results: A significant association between overall composite score on the NEI VFQ and total MMSE score was revealed (P = 0.04). On average, for every 1-point increase in MMSE score, the overall composite score increased by 0.40 units (95% confidence interval: 0.03–0.77).

Discussion: Reduced visual function should raise concerns about cognitive decline and prompt additional assessment.

Keywords
Alzheimer’s disease, cognitive dysfunction, Mini-Mental State Examination, National Eye Institute Visual Function Questionnaire, visual function

1 | INTRODUCTION

By 2030, one in five Americans are expected to be of retirement age; this historical demographic shift is accompanied with a surge in chronic, age-related diseases, as well as rapidly increasing healthcare costs. Visual impairment (VI) and Alzheimer’s disease (AD) are among the mounting health conditions that have become a significant public health and economic burden. Patients with AD often have ocular co-morbidities, but the impact of visual impairment on cognitive changes is not clear. Visual impairment has been associated with both an increased risk and increased severity of AD. VI and AD are interrelated: VI is a substantial predictor of cognitive dysfunction in AD, and visual deficits in AD may have a significant functional impact within certain cognitive domains. Vision tests, such as visual acuity, are not a comprehensive representation of visual impairment experienced by individuals, and do not account for the influence of visual disability on health-related quality of life (HRQOL) such as emotional well-being or social function. Recent studies have demonstrated a correlation between age-related eye diseases—macular degeneration, diabetic retinopathy, and glaucoma—and risk of developing AD. Further, it

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has been noted that subjective cognitive decline–related functional limitations were 3.5 times higher among adults with VI than those without. There is a dire need to identify modifiable risk factors in cognitive impairment to improve HRQOL for individuals with dementia. The interconnected relationship between visual impairment and cognitive dysfunction suggests that VI is a potential risk factor that could improve AD prognosis and HRQOL if identified and treated early. With 80% of VI able to be treated or cured, the development of effective vision screening tools in the elderly population is essential in identifying treatable vision problems. To date, no studies have evaluated the relationship between self-reported visual function and AD. The primary goals of this study are to examine the relationship between cognition and self-reported visual function using the National Eye Institute’s Visual Function Questionnaire (NEI VFQ; developed by RAND and funded by the NEI), and to evaluate the relationship between clinical consensus diagnosis and self-reported visual function.

2 | METHODS

This study was ancillary to the Alzheimer’s Disease in Primary Care study (ADPC; R01AG058537), which was funded as the first-ever examination of blood-based biomarkers for AD among primary care patients. To be enrolled in ADPC, participants must be age 60 or older with the presence of a memory complaint (self, other/informant, primary care provider) and are referred directly by their primary care provider. As part of ADPC, each participant undergoes a medical examination, interview, neuropsychological testing, 3T magnetic resonance imaging (MRI) of the brain, and amyloid positron emission tomography (PET) scans. This study recruited 131 participants from the ADPC cohort to complete the National Eye Institute Visual Function 25-Item Questionnaire (NEI VFQ-25) in English or Spanish, based on their preference. The 25-item questionnaire consists of 12 subscales that measure the impact of ocular disease on several domains of health, including: general health; general vision; near activities; distance activities; driving; peripheral vision; color vision; ocular pain; and vision-related role difficulty; dependency, social function, and mental health. Each subscale is scored from 0 to 100, with 100 being the best possible score. The driving subscale was excluded from the overall score for participants who do not drive. An overall composite score was calculated as an unweighted average of the answers to all list items, excluding the general health rating question. Additionally, each participant self-reported diagnosis of eye disease(s) or ocular condition(s). To assess global cognitive functioning, we used the Mini-Mental State Examination (MMSE), which is a widely used measure of global cognitive function. The MMSE is scored from 0 to 30, with 30 representing the best level of cognitive function. Clinical cognitive diagnoses were assigned algorithmically (decision tree) based on all neuropsychological tests in the protocol and results from the informant interview for completion of the Clinical Dementia Rating scale (CDR), and verified at consensus review as follows: normal control (NC) = no cognitive complaints, CDR Sum of Boxes (CDR-SB) score of 0 and cognitive tests scores broadly within normal limits (i.e., performance greater than that defined as meeting diagnostic criteria for mild cognitive impairment [MCI; i.e., ≤ 1.5 standard deviations below the normative range]); MCI: cognitive complaint (self or other), CDR-SB score between 0.5 and 2.0 and at least one cognitive test score falling ≤ 1.5 standard deviation below normative ranges; AD dementia: CDR-SB score ≥ 2.5 and at least two cognitive test scores 2 standard deviations below normative ranges. The final clinical diagnosis of AD was assigned according to National Institute on Aging–Alzheimer’s Association (NIA-AA) criteria, and MCI, the symptomatic predementia phase of AD, according to the appropriate NIA-AA criteria as well. Biomarker-based assignment using PET amyloid results are ongoing. This research was conducted under an institutional review board–approved protocol with each participant providing written informed consent; this research followed the tenets of the Declaration of Helsinki.

2.1 | Statistical analysis

We obtained mean and standard deviation for continuous variables and frequency distributions for categorical variables. Graphical approaches, including histograms and boxplots, were used to evaluate the normal distribution assumption. Our primary outcome variable was overall composite score calculated as mean of 12 subscales of NEI VFQ-25 and was analyzed as a continuous variable outcome. Our primary predictor variable was consensus diagnosis defined as normal, MCI, or AD and was included in our analysis as a categorical
grouping variable. Because of the link between age-related ocular diseases and cognitive impairment, we also used disease classification defined as no glaucoma, cataract, or age-related macular degeneration (AMD), cataract only, AMD only, and two or more conditions as a predictor in our analysis, which was included as a categorical grouping variable. Similarly, outcome variable MMSE scores were analyzed as continuous outcome variable using a linear regression model. Diabetic retinopathy and diabetic macular edema were not included as predictors as none of the participants reported having these conditions. We used a general linear model and analysis of variance approach to compare means by clinical classification and disease classification for normally distributed outcomes. A Kruskal–Wallis test was used for non-normal distributions. For analysis involving binary outcome variables, we used a logistic regression model. Additional covariates in the model included age, sex, race, education, and self-reported ocular disease. Age was reported as number of years and education level was reported as number of years attending school; both were treated as continuous variables in our analysis. Sex was categorized as female and male and was included in our analysis as a binary categorical variable. Similarly, race (four categories), disease classification (five categories), and clinical classification (three categories) were included in the model as categorical covariates. The type I error rate was set a priori at $\alpha = 0.05$.

3 RESULTS

One hundred thirty-one ADPC participants completed the NEI VFQ-25 as part of the interview. All individuals were ≥60, with the mean participant age being 71.63 years (standard deviation = 5.51). The sample consisted of 84 (64.1%) females and 47 (35.9%) males. Eighty (61.1%) of the participants were classified as NC, 35 (26.7%) as having MCI, and 16 (12.2%) as having clinical AD. Descriptive statistics for the participants can be found in Table 1.

A significant association between overall composite score on the NEI VFQ and total MMSE score was found ($P = 0.04$). On average, for every 1-point increase in MMSE score, the overall composite score increased by 0.40 units (95% confidence interval [CI]: 0.0266–0.7718). The association remained significant in an adjusted model ($P = 0.01$), which included sex, age, race, and education as covariates. On average, after adjusting for sex, age, race, and education, for every 1-point increase in MMSE score, the overall composite score increased by 0.60 units (95% CI: 0.1333–1.0796).

Figure 1 demonstrates the linear regression plot of the total MMSE score and the NEI VFQ-25 overall composite score. Comparison of overall composite score between pre-clinical and NC, MCI, and dementia due to AD diagnosis did not reveal any statistically significant difference among the three groups (mean pre-clinical and NC group = 89.8, mean MCI group = 87.69, and mean dementia due to AD group = 86.42, $P = 0.1869$). Individual NEI-VFQ subscales were compared to participant consensus diagnoses (normal, MCI, dementia due to AD) using a Kruskal–Wallis test, which demonstrated a statistically significant difference among the three diagnoses groups in vision-specific role difficulties (mean pre-clinical and NC group = 95, mean MCI group = 90.35, and mean dementia due to AD group = 82.03, $P = 0.04$). Furthermore, the comparison of overall composite score by ophthalmic conditions ($P = 0.8157$) was not statistically significant. This finding demonstrates that as MMSE decreased, or global cognition worsened, participants reported an increase in limitations and lack of accomplishment due to eyesight. No significant relationship was observed between the remaining subscales or overall composite score and consensus diagnosis.

4 DISCUSSION

The purpose of this study was to test the utility of the NEI VFQ-25 as a supplemental tool to address vision-related issues associated with AD in a primary care setting. This study administered the NEI VFQ-25 as a measure of visual function and the MMSE as a measure of global cognition. Our results demonstrated a significant relationship between visual function and MMSE score as a measure of cognitive function: As the NEI VFQ-25 overall composite score increased, the MMSE score also increased. These findings suggest that as self-reported visual function increases, the overall global cognition score also increases.

### TABLE 1 Descriptive statistics for overall sample

| Variable                | n (%)           |
|-------------------------|-----------------|
| Sex                     |                 |
| Female                  | 84 (64.12%)     |
| Male                    | 47 (35.88%)     |
| Race                    |                 |
| Non-Hispanic White      | 97 (74.05%)     |
| Hispanic                | 12 (9.16%)      |
| Asian                   | 3 (2.29%)       |
| Black/African American  | 19 (14.50%)     |
| Disease classification   |                 |
| No glaucoma, cataract,  | 79 (60.31%)     |
| AMD                     |                 |
| Glaucoma                | 4 (3.05%)       |
| Cataract                | 37 (28.24%)     |
| Age-related macular     | 5 (3.82%)       |
| degeneration            |                 |
| 2 or more               | 6 (4.58%)       |
| Clinical classification  |                 |
| Pre-clinical or normal  | 80 (61.07%)     |
| Mild cognitive impairment| 35 (26.72%)    |
| Dementia                | 16 (12.21%)     |
| Age                     |                 |
| Mean (SD)               | 71.63 (5.51)    |

Abbreviation: AMD, age-related macular degeneration.
Visual impairment and cognitive dysfunction often coexist in elderly patients. Our current results demonstrate a correlation between visual function and cognitive status. Implementing effective screening tools, such as the NEI VFQ-25, could identify reduced visual function secondary to correctable vision problems. Interventions, such as refractive correction, cataract surgery, or low vision devices, could, in turn, improve functioning and quality of life, which may lead to improved cognitive outcomes for these patients. One study evaluating the effect of cataract surgery on cognitive function and depressive mental status of elderly patients identified that vision-related quality of life, cognitive impairment, and depressive mental status are all strongly interrelated, and cataract surgery led to a significant improvement in vision-related quality of life, which, in turn, also improved cognitive impairment and depressive mental status in those individuals.16,17

There are several limitations to consider in this study. First, this is an epidemiological study, and the number of individuals in the cognitive dysfunction groups was relatively small and the sample was predominately female. A larger sample size and more equal sex distribution would strengthen the study. We plan on evaluating the NEI VFQ-25 and expanding this work into the Health and Aging Brain among Latino Elders (HABLE) study, which is a more comprehensive, community-based study enrolling Mexican Americans and non-Hispanic Whites. Moreover, the current analyses are cross-sectional in nature. Future studies will capture longitudinal data for additional analyses to evaluate change over time.

Despite these limitations, this study had the unique opportunity to collect robust data, through leveraging the ADPC infrastructure, that can contribute to the eye-care field by further understanding the connection between visual function and cognitive dysfunction. This is the first-ever study to report NEI VFQ and MMSE for AD screening. The current findings highlight the need to fully understand the factors contributing to development of cognitive dysfunction in VI patients and develop ways to intervene to improve health-related quality of life for these patients and potentially impact cognitive outcomes. Future longitudinal studies will focus on the relationship between domain-specific neuropsychological testing and visual function, as well as examine the impact of biomarker status on visual function.

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CONFLICTS OF INTEREST
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FIGURE 1 The overall composite score on the NEI VFQ 25 and total MMSE score (unadjusted analysis). NEI VFQ-25, National Eye Institute 25-Item Visual Function Questionnaire; MMSE, Mini-Mental State Examination
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