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Psychological and cognitive determinants of vision function in age-related macular degeneration.

Barry W. Rovner
Thomas Jefferson University, barry.rovner@jefferson.edu

Robin J Casten
Thomas Jefferson University, robin.casten@jefferson.edu

Robert W Massof
Johns Hopkins University School of Medicine, rmassof@lions.med.jhu.edu

Benjamin E Leiby
Thomas Jefferson University, bleiby@mail.jci.tju.edu

William S Tasman
Jefferson Medical College, wst1@ureach.com

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Barry W. Rovner, MD[a]

Robin J. Casten, PhD[b]

Robert W. Massof, PhD[c]

Benjamin E. Leiby, PhD[d]

William S. Tasman, MD[e]

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[a] Departments of Psychiatry and Neurology, Jefferson Medical College

Jefferson Hospital for Neuroscience

900 Walnut Street

Philadelphia, Pa 19107

barry.rovner@jefferson.edu

[b] Department of Psychiatry and Human Behavior, Jefferson Medical College

Jefferson Hospital for Neuroscience

900 Walnut Street

Philadelphia, Pa 19107

robin.casten@jefferson.edu

[c] Lions Vision Research and Rehabilitation Center

Wilmer Eye Institute

Johns Hopkins University School of Medicine

6th Fl, 550 N Broadway, Baltimore, MD 21205

rmassof@lions.med.jhu.edu

[d] Division of Biostatistics

Department of Pharmacology and Experimental Therapeutics, Jefferson Medical College

1015 Chestnut St., Suite M100, Philadelphia, PA 19107

bleiby@mail.jci.tju.edu

[e] Wills Eye Institute

Department of Ophthalmology; Jefferson Medical College

Wills Eye Institute

840 Walnut Street

wst1@ureach.com

Address for correspondence and reprints:

Barry W. Rovner, MD

Jefferson Hospital for Neuroscience

900 Walnut Street

Philadelphia, PA 19107

barry.rovner@jefferson.edu

TP: 215-503-1254

FAX: 215-503-1992

Abstract

Objective: Age-Related Macular Degeneration (AMD) is the leading cause of severe vision loss in older adults and may lead to substantial functional impairment. We investigated the relative contributions of ophthalmological, psychological, medical, and cognitive factors as predictors of vision function to broaden our knowledge of its varied determinants.

Methods: Baseline evaluation of 241 older outpatients with advanced AMD who were enrolled in a clinical trial testing the efficacy of a behavioral intervention to improve vision function. Vision function was characterized as an interval-scaled, latent variable of visual ability based on the near vision subscale of the National Eye Institute Vision Function Questionnaire-25 plus Supplement.

Results: Visual ability was highly correlated with visual acuity. However, a multivariate model revealed that patients' coping strategies and cognitive function contributed to their ability to perform near vision activities independent of visual acuity.

Conclusions: Patients with AMD vary in their coping strategies and cognitive function as well as their visual acuity, and that variability in these factors determines patients' self-report of vision function. Understanding patients' coping mechanisms and cognition may help to increase the precision of vision rating scales and suggest new interventions to improve vision function and quality of life of patients with AMD.

ClinicalTrials.gov Identifier: NCT00572039

Introduction

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in older adults, with almost 2 million having advanced disease (i.e., neovascular AMD or geographic atrophy) and over 7 million having early signs.[1] Their number will double by 2020, dramatically increasing the number of visually impaired adults who cannot read, drive, or live independently.[2] Fortunately, the anti-vascular endothelial growth factor (VEGF) antibodies ranibizumab and bevacizumab have greatly improved neovascular AMD's prognosis.[3] The MARINA and ANCHOR trials found that ranibizumab prevented vision loss in 95.5% of subjects.[3-5] About 30% gained 15 or more letters and 50% had improved mental health.[6] Although these are unprecedented outcomes, the converse is informative: the vision function of 70%, and the mental health of 50%, did not improve to this extent. Patients with visual acuity worse than 20/70 in the better eye after treatment, for example, would still have disabling impairment and rehabilitative needs. Thus, despite the success of anti-VEGF treatment, AMD-related disability remains a major public health problem.[7]

To measure AMD-related disability many investigators have used the National Eye Institute Visual Function Questionnaire (NEI VFQ).[8,9] Massof and Fletcher (2001) demonstrated that the NEI-VFQ items that assess difficulty with everyday tasks yield a latent visual ability variable that strongly relates to visual acuity.[10] The correlation of 0.523, however, indicates that visual acuity accounts for only about 27% of the variance, and suggests that other factors influence NEI VFQ scores. Depression and general health are two such factors.[11,12] Other clinical variables may also contribute and, unless accounted for, may introduce unmeasured sources of variability or "noise" into disability measurements in patients with AMD.

In this study, we investigated the influence of coping strategies, depression, physical health, and cognition on NEI VFQ scores that we obtained at baseline in a sample of older patients with AMD who were enrolled in the "Improving Function in AMD Trial" (IF-AMD). IF-AMD is a randomized, controlled clinical trial that compares the efficacy of Problem-Solving Therapy with Supportive Therapy to improve vision function in patients with AMD.

Methods

This study reports baseline data obtained prior to randomization into the IF-AMD clinical trial. We recruited 241 patients with AMD from the retina clinics associated with the Wills Eye Institute (WEI) in Philadelphia, PA from 2006 to 2010, and randomized subjects to Problem-Solving Therapy (PST) or Supportive Therapy in a 1:1 allocation ratio.[13,14] The primary aims of the IF-AMD trial are to test the immediate (3-months) and longer term (6-months) efficacy of PST to improve the primary outcome of vision function.

The inclusion criteria were: 1) age 65 years or older; 2) bilateral AMD (neovascular and/or dry); 3) visual acuity between 20/70 and 20/400 [inclusive; (best corrected)] in the better-seeing eye, and no worse than 20/400 in the fellow eye, and 4) moderate difficulty in at least one valued vision function goal. The exclusion criteria were: 1) presence of uncontrolled glaucoma, diabetic retinopathy, or planned cataract surgery within 6 months; 2) dementia, using a version of the Mini-Mental Status Examination (MMblind) that omits vision-dependent items;[15] 3) presence of life-threatening illness; and 4) residence in a skilled nursing facility. All subjects signed an informed consent form approved by Thomas Jefferson University's Institutional Review Board.

At baseline, a research nurse conducted clinical assessments in subjects' homes and gathered demographic information and assessed the following clinical variables:

Vision: Best-corrected vision was assessed with the Lighthouse Ferris-Bailey ETDRS Chart to measure distance visual acuity and the Pelli-Robson Contrast Sensitivity chart to measure contrast sensitivity. Near and distance acuities were assessed at 16 inches and 5 feet, respectively. A gooseneck lamp was used to standardize luminance levels. For statistical analyses, log transformations were used (i.e., logMAR and log contrast) for visual acuity and contrast sensitivity, respectively.

Physical Health: We used the Chronic Disease Score, which provides an index of medical comorbidity based on a weighted sum of medications taken for chronic illness, and the Multilevel Assessment Inventory Health Conditions Check List, which lists specific acute and chronic conditions.[16,17]

Depression: We used the Patient Health Questionnaire-9 (PHQ-9) to assess depression. The PHQ-9 includes the 9 criteria that comprise DSM-IV diagnoses of major or minor depressive disorders.[18] It is a dual-function instrument in that it generates both categorical diagnoses of depression and grades depressive symptom severity as a continuous measure. Symptoms are scored on an ordinal scale from 0 (not at all) to 3 (every day). The raw score for each patient is the sum of symptom scores across the 9 items. The raw scores range from 0 to 27 with higher scores indicating worse depression. Symptoms are scored from 0 (not at all) to 3 (every day).

Cognition: We administered the Animal Fluency Test (AFT) to obtain a brief assessment of cognitive function that is relevant to the completion of daily activities.[19] This verbal fluency test requires subjects to name as many different animals as possible in 60 seconds and is scored as the number of animals named. The test requires semantic knowledge of categories, vocabulary storage, speeded mental processing, and intact executive function. A reduction in the number of retrieved items, repetition of the same word, and listing of disqualified words indicate difficulty with sustained output, concentration, and retrieval. The average (standard deviation) score for white females aged 70 -89 with 12 years of education is 17.2 (4.2).

Vision Function: We used the NEI VFQ-25 plus Supplement, which consists of 25 items and a supplement of 14 additional items, derived from the original 52-item NEI VFQ.[8,9] It is used to assess self-reported vision function and generates 11 subscale scores and an overall score. In this investigation, we focused on items that are included in part 2 of the NEI-VFQ because they all require difficulty ratings of vision-dependent activities that many patients highly value. In particular, the near vision subscale consists of 6 items rating difficulties with: reading newsprint; doing housework or hobbies (e.g., sewing, using tools); finding something on a crowded shelf; reading small print on a medication bottle or legal form; determining if bills are accurate; and performing personal hygiene tasks (e.g., shaving, putting on makeup). Subjects rate these items on a 1 to 5 ordinal scale, with higher numbers indicating increasing levels of difficulty (i.e., no difficulty, a little difficulty, moderate difficulty, extreme difficulty, or stopped doing this because of your eyesight), or they can respond that they stopped doing the activity described by the item for other reasons/not interested(scored as missing data). Previous studies have demonstrated that the items of the near vision subscale are responsive to low vision rehabilitation and anti-VEGF treatment and can be used to estimate an interval scale suitable for the analyses we conducted.[6, 10, 20-23]

Coping Strategies: We used the Optimization in Primary and Secondary Control Scale (OPS) to assess the characteristic approaches, or control strategies, that subjects enact to achieve valued goals.[24] This instrument draws from the life span theory of control which posits that people use different health-related control strategies to greater and lesser extents when faced with adverse health conditions. We selected the OPS because of its applicability to patients with chronic disabling diseases like AMD who must find ways to adjust to vision loss. The OPS's reliability and validity and psychometric properties have been demonstrated in studies of older persons and patients with AMD.[25] Brennan et al (2004) adapted items specifically for patients with vision loss.[26] The OPS scale is divided into 4 control strategies, each comprised of 8 items rated from 0, "never true" to 4, "almost always true", yielding a raw score range of 0 to 32 for each control strategy; higher scores indicate greater use of the particular strategy.

Selective primary control refers to the investment of behavioral resources (i.e., time, effort, skills) into pursuing a goal. Representative items are, "I do whatever I can to continue my everyday activities despite my vision problem" and "If I invest enough time, I can continue my everyday activities despite my vision problem." *Selective secondary control* serves to enhance and maintain motivation and commitment to a goal, particularly when obstacles (i.e., vision loss) make achieving the goal difficult. Items include, "I think how important it is to me to keep up my daily activities in spite of my vision problem" and "I tell myself that it's up to me to make sure my vision problem does not interfere with what I want to do". C*ompensatory primary control* refers to the recruitment of help from others or the use of assistive devices (e.g., magnifiers) when an individual has difficulty attaining a goal. Items include, "If there is something that I can no longer do because of my vision problem, I actively seek out help from others" and "If I'm having trouble doing something because of my vision problem, I look for a device or aid that will help get it done." *Compensatory secondary control* refers to goal disengagement when the goal becomes unattainable, thereby freeing up the person to pursue other goals that are attainable. It also

includes self-protective strategies such as focusing on successes in other domains. Typical items include, “I can accept that there are things I can no longer do since I started having problems with my vision” and “I spend my time doing what I can do, rather than struggling with the things that have become difficult because of my vision problem.”

Statistical Methods:

Descriptive statistics for baseline demographic and clinical variables are presented as means and standard deviations (SD) for continuous data and frequencies and percents for categorical data. We used a latent variable model to investigate the relationship between the 6 items of the NEI-VFQ near activities subscale and various clinical and psychological characteristics.[27, 28] Because we expect subject responses to depend on multiple variables, we employed a structural equation model that assumes each subject has an ability to perform near activities (i.e., the composite latent variable) manifested by the 6 NEI VFQ items. The ability to perform a specific near vision NEI VFQ activity item is obtained by multiplying the factor loading for that item by the underlying latent ability. A subject should perform at a given level for a specific item when the product of the item factor loading and the underlying ability crosses a given threshold for that item. We assumed that the ability to perform near activities is a linear function of one or more clinical and/or psychological characteristics (e.g., age, visual acuity, cognition, coping strategies). That is, we modeled the ability to perform near activities using a linear regression model that assumes the component variables have independent effects on the estimated functional ability variable. We considered each of the potential predictors individually and selected all with $p<0.20$ for inclusion in a multivariable model. We used the latter liberal statistical criterion to maximize our ability to detect any significant associations. Latent variable models were fit using Mplus Version 6.[29]

Results

Subject clinical and psychological characteristics are summarized in Table 1. The mean [standard deviation (SD)] age of subjects was 82.8 (6.9) years and 63.1% were women. One hundred two (42.3%) had received anti-VEGF injections. Depressive symptoms, as reflected by mean PHQ-9 scores, were low in the sample as a whole; however, 31 subjects (12.9%) met criteria for a depressive disorder. This rate is consistent with a recent study of depression prevalence rates in patients with AMD.[30]

The value of the latent visual ability variable was estimated for each subject from the multivariable model. Estimated values ranged from -4.3 to 2.85 with a mean of 0 and a standard deviation of 1.2. Figure 1 depicts the relationship of the latent visual ability with visual acuity and shows the strong relationship between the two variables but also the considerable variability that remains. Table 2 shows the results of the univariable models wherein we evaluated the relationship between the predictor variables and the latent visual ability variable. The values represent the increase in visual ability associated with a one unit increase in that predictor. For example, a one-unit increase in contrast sensitivity was associated with a 0.32

increase in visual ability. Of the 12 possible predictors, visual acuity, contrast sensitivity, selective primary control, compensatory primary control, selective secondary control, the cognitive verbal fluency score (Animal Fluency Test), and age were statistically significantly associated with the latent visual ability variable (at the $p<0.20$ level) and were included in the multivariate model. Table 3 shows the results of the multivariable model wherein we considered the unique effect of each of the significant variables of the univariable model after controlling for the effects of the other variables. This model reveals that visual acuity, compensatory primary control, selective secondary control, and verbal fluency were independently associated with self-reported difficulty with near activities.

Discussion

We found that patients with AMD vary in their coping strategies and cognitive function as well as their visual acuity, and that variability in these factors determines patients' self-report of vision function independent of the effect of visual acuity. The subjects we studied were drawn from outpatients of an academic retinavitreous practice, had specific vision characteristics, and had enrolled in a clinical trial to improve vision function. These unique characteristics limit the generalizability of our findings. Nevertheless, the sample represents a large group of patients commonly seen in ophthalmologic practices whose severity of vision loss and disability present a challenge both to the patients and their ophthalmologists.

The strengths of the study include the large sample size, systematic ascertainment and assessment of subjects whose visual, affective, medical, and functional characteristics were evaluated with instruments of known reliability and validity, and the use of latent variable modeling to estimate an interval scale of visual ability based on the NEI VFQ near vision subscale. Although previous studies have demonstrated the NEI VFQ's validity in a conventional sense, they have used ordinal rather than interval-scaled item responses (i.e.,

categorical responses where the difference between responses may not be the same, versus numerical values where the difference between values is the same). Because ordinal responses have uncertain quantitative relationships with each another, there is an increased risk of measurement error.[31-33] Our use of an interval-scaled, latent visual variable yields a more precise measure that has enabled us to identify new clinical variables that illuminate patients' perceptions of disability. This study's limitations, however, include lack of measures of central scotomas, glare sensitivity, binocular vision, reading, and other performance-based tests that might better discriminate patients in terms of the direct effects of AMD on ability.

All vision-dependent tasks require a specific level of vision to perform them successfully and independently. A patient's rating of "difficulty" reflects the difference between the level of required vision and the patient's visual ability which depends, our data show, on his or her visual acuity as well as coping strategies and cognitive function.[34] We found that higher use of the coping strategy of compensatory primary control, such as relying on others for help and using optical devices, was associated with greater difficulty with near vision activities. This intuitively correct association indicates that this coping strategy, which aims to increase a patient's control over his or her life circumstances, represents a healthy psychological adaptation to vision loss and contributes to what drives their perceptions of disability. This finding provides support for ophthalmologists' recommendations to patients with AMD to pursue low vision rehabilitative interventions.

A second control strategy that was associated with visual ability was selective secondary control. A higher use of this strategy, which represents the willingness to persevere in the face of potential failure, predicted lower ratings of vision disability. Patients with AMD who utilize this strategy tend to look forward to the positive consequences of achieving a goal even as they work hard to achieve it. Understandably, they would tend to perceive less difficulty than others who lack the same level of motivation but who are otherwise similar in their vision

characteristics. The treatment implication of this finding is that interventions that strengthen the ability to tolerate frustration and keep on trying, like cognitive behavioral therapies, might reduce disability levels in vulnerable people. Interestingly, although depression is often related to vision function in patients with vision loss, in this sample it was not.[35-37] The unique characteristics of the sample (i.e., patients who enrolled in a clinical trial who had, on average, low levels of depressive symptoms), constrained the scores and limited the ability to detect any significant associations.

Better scores on a cognitive task that assesses verbal fluency were associated with lower perceived vision function difficulties. Greater ability in this cognitive domain indicates better sustained output, concentration, and executive function.[38] The latter refers to a group of complex cognitive abilities that include organizing, understanding, and appreciating information, and planning, initiating, and monitoring behavior which, in turn, enables rational problem-solving.[39] Thus, we might expect that patients with AMD who possess these cognitive skills would find ways to compensate for their vision disabilities and devise strategies to reduce task difficulty. This interpretation agrees with other studies which find that coexisting visual and cognitive impairments are highly disabling, and that patients with AMD who relinquish valued activities are at risk for incident dementia.[40-43] These studies emphasize the importance of assessing cognition in AMD studies, even in subjects without dementia, and encouraging patients to remain active despite vision loss to promote optimal cognitive and physical health.

The introduction of anti-VEGF treatments for AMD has spared many patients from progressive vision loss and severe disability. Although these treatments have expanded rapidly in the community in recent years, we know little of their impact outside of clinical trials.[44] Our data suggest that recognizing the role of patients' coping strategies and cognition may inform outcome studies of anti-VEGF treatment and may have direct implications for the clinical care of

patients. For researchers who use the NEI VFQ in clinical trials, characterizing subjects' coping strategies and cognitive function may improve the precision of vision rating scales, reduce measurement error, and suggest new interventions to improve vision function and quality of life. For ophthalmologists in clinical practice, encountering patients whose vision function is worse than expected given their visual acuity should prompt brief assessments of how patients are coping or of their cognition. These assessments might then lead to referrals for neurological or psychiatric evaluation to identify modifiable factors that may optimize functional vision. For highly motivated patients who use active control strategies, positive reinforcement and referral to low vision rehabilitation may help them achieve their goals. For patients who more passively accept their disability, sympathetic understanding of their functional limitations and expressions of support may be valuable interpersonal interventions. From the clinical standpoint, these findings highlight the need for evidence-based models to improve care at the interface of ophthalmology and psychiatry and to develop a comprehensive national health care policy to assist older persons with their visual needs.

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* deceased

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Figure 1. Scatterplot of Visual Ability vs. Visual Acuity

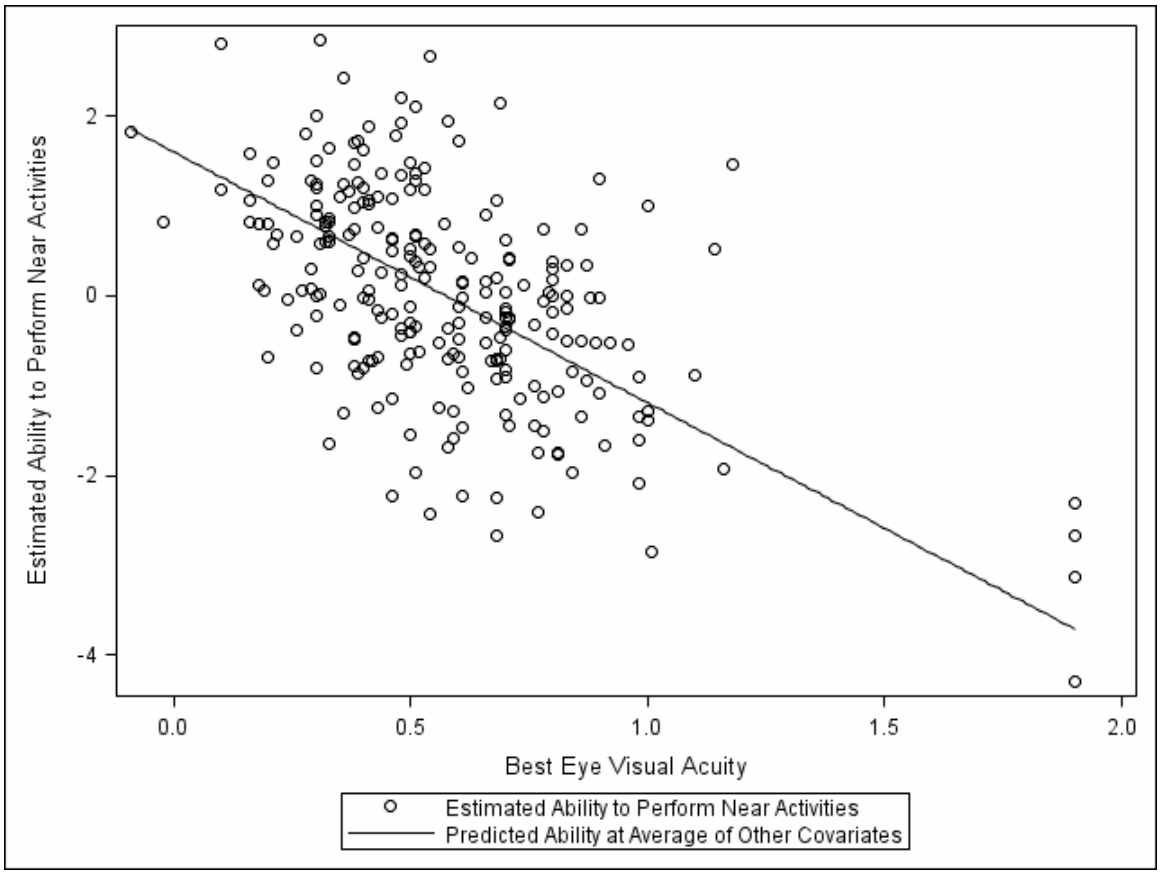

Table 1. Clinical and Vision Sample Characteristics of the Sample (N = 241)

Demographic and Medical Characteristics	
Age[1]	82.8 (6.9)
Female[2]	153 (63.1)
Education, yrs[1]	13.2 (3.1)
Chronic Disease Score[1,3]	5.6 (2.9)
Vision Characteristics	
Best eye logMAR[1, 4]	.57 (.29)
Best eye log contrast[1, 5]	.69 (.41)
Anti-VEGF treatment in past 3 months[2]	102 (42.3)
NEI-VFQ near activities[1,6]	53.3 (20.7)
Coping Strategies	
Selective Primary Control (range: 6 to 24)[1,7]	22.3 (2.4)
Compensatory Primary Control (range: 9 to 36)[1,7]	26.7 (6.0)
Selective Secondary Control (range: 9 to 36)[1,7]	30.1 (4.9)
Compensatory Secondary Control (range: 7 to 28)[1,7]	21.8 (4.0)
Depression	
PHQ-9 Scores[1,8] (range 0 to 27)	1.3 (2.5)
Cognition	
Animal Fluency Test[1,9]	14.8 (4.7)

[1] mean, SD

[2] n, %

[3] High score is worse medical morbidity

[4] High score is worse vision.

[5] High score is better contrast.

[6] Scored from 0 to 100 with higher scores indicating better function.

[7] A higher score is more frequent use of the control strategy.

[8] A higher score is worse depression.

[9] A higher score is better cognitive function.

Table 2. Bivariate Relationships of Predictor Variables to Vision Function

Variable	Estimate[a]	95% Confidence Interval		p-value
Visual Acuity	-2.02	-2.63	-1.41	<.001
Compensatory Primary Control	-0.046	-0.071	-0.020	<.001
Animal Fluency Test	0.056	0.024	0.088	0.001
Age	-0.030	-0.052	-0.008	0.006
Selective Primary Control	0.08	0.018	0.14	0.010
PHQ Severity	-0.055	-0.12	0.005	0.073
Selective Secondary Control	0.027	-0.004	0.057	0.080
Contrast Sensitivity	0.32	-0.05	0.68	0.090
Chronic Disease Score	-0.025	-0.075	0.025	0.330
Education	0.020	-0.028	0.068	0.410
Gender (male vs. female)	0.068	-0.24	1.31	0.660
Compensatory Secondary Control	0.005	-0.032	0.041	0.810

[a] Estimates are increase in visual ability associated with one unit-increase in each predictor variable.

Table 3. Multivariable Relationships of Predictor Variables to Vision Function: Regression Parameters

Variable	**Estimate**	**95% CI**		**p-value**
Visual Acuity	-1.93	-2.59	-1.27	<0.001
Compensatory Primary Control	-0.076	-0.11	-0.044	<0.001
Animal Fluency Test	0.054	0.019	0.090	0.003
Selective Primary Control	0.08	0.01	0.018	0.14
Selective Secondary Control	0.047	0.003	0.090	0.036
Contrast Sensitivity	0.20	-0.21	0.61	0.330
PHQ Severity	-0.032	-0.10	0.035	0.350
Age	-0.008	-0.033	0.016	0.510