Comparison of Visual Function in Older Eyes in the Earliest Stages of Age-Related Macular Degeneration to Those in Normal Macular Health

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Abstract

Purpose—To compare the ability of several visual functional tests in terms of the strength of their associations with the earliest phases of age-related macular degeneration (AMD), which bears on their potential to serve as functional endpoints in evaluating treatments for early AMD and prevention strategies.

Materials and Methods—Eyes from adults ≥ 60 years old were identified as being in normal macular health or in the earliest stages of AMD (steps 2, 3 or 4) through grading of color stereo-fundus photos by an experienced grader masked to all other study variables who used the 9-step Age-Related Eye Disease Study (AREDS) classification system for AMD severity. Visual function was assessed using the following tests: best-corrected visual acuity, low luminance visual acuity, spatial contrast sensitivity, macular cone-mediated light sensitivity, and rod-mediated dark adaptation.

Results—A total of 1,260 eyes were tested from 640 participants; 1,007 eyes were in normal macular health (defined as step 1 in AREDS system) and 253 eyes had early AMD (defined as step 2, 3, or 4). Adjusting for age and gender, early AMD eyes had 2 times the odds of having delayed rod-mediated dark adaptation than eyes in normal macular health (p = 0.0019). Visual acuity, low luminance acuity, spatial contrast sensitivity, and macular light sensitivity did not differ between normal eyes and early AMD eyes.

Conclusions—Eyes in the earliest phases of AMD were two times more likely to have delayed rod-mediated dark adaptation, as assessed by the rod-intercept, as compared to older eyes in

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normal macular health, whereas there was no difference in early AMD versus normal eyes in tests of visual acuity, low luminance acuity, macular light sensitivity, and spatial contrast sensitivity.

Keywords

age-related macular degeneration; aging; dark adaptation; functional endpoints; visual function

Visual acuity is the established and accepted functional endpoint for evaluating interventions in the treatment of exudative age-related macular degeneration (AMD).[1–3] However visual acuity is inadequate as an endpoint for evaluating treatments for early and intermediate AMD since visual acuity is largely undisturbed during these disease stages. Furthermore, for the same reason, acuity is not suitable as an endpoint in assessing AMD disease prevention strategies in those with normal macular health. Thus a challenge for the field is to identify visual functional measures that are impacted very early in the AMD disease course so that they can be evaluated in terms of their suitability as functional endpoints in trials targeted at early AMD or its prevention.

Previous research has suggested several aspects of macular visual function can be impaired in early AMD, both cone-mediated and rod-mediated functions. These include spatial contrast sensitivity, visual acuity under low luminance and/or low contrast, photopic and scotopic light sensitivity, flicker sensitivity, and dark adaptation.[4–20] The purpose of this study was to assess several visual functional measures in eyes in normal macular health and eyes in the very earliest stages of AMD. Our goal is to understand which aspects of visual function are significantly impacted in the initial stages of the disease. The major advantages of the current approach is that these measures are evaluated in the same eyes and are based on a very large sample of older adults whose macular health has been evaluated by a standard and accepted AMD classification system.

METHOD

This study was approved by the Institutional Review Board of the University of Alabama at Birmingham (UAB). The research adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants. The sample was part of the baseline cohort assembled for the Alabama Study on Early Age-Related Macular Degeneration (ALSTAR),[21] a prospective study of older adults in normal macular health at baseline whose purpose is to understand what medical, behavioral and functional characteristics are associated with the incident development of AMD three years later. Participants were recruited from two primary care ophthalmology practices in the Callahan Eye Hospital at UAB. Eligibility criteria for eyes in normal macular health were as follows: (1) Age 60 years old; (2) Normal macular health in both eyes as determined by 3-field digital stereo-fundus photos (Carl Zeiss Meditec 450 Plus camera, Dublin CA) evaluated by an experienced grader masked to other study variables. The eye's grade had to be 1 in the AREDS 9-step classification system,[22] indicating normal macular health. (3) No previous diagnoses of glaucoma, other retinal conditions, optic nerve conditions, corneal disease, diabetes, Alzheimer's disease, Parkinson's disease, brain injury, other neurological or psychiatric conditions as revealed by the medical record or by self-report. (4) Did not reside

in a nursing home or was not bed-bound. (5) Was willing to participate in a study that included a baseline visit to the Clinical Research Unit in the UAB Department of Ophthalmology and a follow-up visit three years later. Eligibility criteria for those with early AMD were identical to the criteria listed above except that eyes were required to have an AREDS grade in the 9-step system[22] of 2, 3, or 4. These grades correspond to the earliest phases of AMD, as outlined in Table 1.

Demographic characteristics (age, sex, race/ethnicity) were confirmed with participants through interview. Best-corrected visual acuity for each eye was assessed via the Electronic Visual Acuity tester[23] (EVA; JAEB Center, Tampa FL) under photopic conditions (100 cd/m^2) and expressed as the logarithm of the minimum angle resolvable (logMAR). Low luminance visual acuity was also assessed using the EVA for each eye with participants viewing letters through a 1.5 log unit neutral density filter, a method described by Sunness et al.,[24] which reduced background luminance to 3.16 cd/m^2. To determine how much logMAR decreased under conditions of the lower light level as compared to the photopic (100 cd/m^2) assessment, we defined a decrease in visual acuity under low luminance by the increase in logMAR; an increase in logMAR by 0.1 is equivalent to a decrease in visual acuity by one line (5 letters) on the ETDRS chart.[25] Contrast sensitivity for each eye was estimated by the Pelli-Robson chart[26] (Precision Vision, La Salle IL) with mean luminance of 100 cd/m^2, the letter-by-letter scoring method,[27] and expressed as logarithm of sensitivity.

Macular light sensitivity for each eye was assessed using the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA). The 24-2 SITA standard protocol was used following the instrument's recommended white stimulus on white background testing procedure. To obtain an estimate of light sensitivity in the macula, sensitivity for those test targets in the macular region were averaged; these test targets consisted of 16 targets falling within the region −9° to 9° on the horizontal and vertical meridia. Average sensitivity was expressed as decibels (dB).

Rod-mediated dark adaptation was measured in only one eye in each participant because of time constraints in the protocol. The eye with better visual acuity was selected for testing. Dark adaptation was measured psychophysically using the AdaptDx (MacuLogix, Hummelstown, PA), a computer-automated dark adaptometer described previously.[13, 28, 29] Before testing, the eye was dilated with 1% tropicamide and 2.5% phenylephrine hydrochloride so that a pupil diameter of 6 mm was achieved. Trial lenses were added for the 30 cm viewing distance if needed to correct for optical blur. The fellow eye was occluded with an opaque patch. The participant placed his/her head in the forehead-chinrest of the adaptometer. An infrared camera positioned behind the fixation light displayed the eye on a monitor viewed by the examiner, who facilitated the positioning of the participant's test eye to the red fixation light using a reticule displayed on the eye's image. The procedure began with a photo-bleach exposure to a flash (0.25 ms duration, 58,000 scotopic cd/m^2 s intensity; equivalent ~ 83% bleach) while the participant was focused on the fixation light. This bleach has been shown to be sufficiently intense to generate impaired dark adaptation parameters in early AMD patients using a 20-minute duration test protocol.[28] The photo-bleach flash, subtending 4°, was centered at 5° on the inferior vertical meridian (i.e.,

superior to the fovea on the retina) which was also the test target's position for measuring light sensitivity. Threshold measurement for a 2° diameter, 500 nm circular target began 15 seconds after bleach offset. During threshold measurement, the participant was instructed to always maintain fixation on the red fixation light and to press a response button when a flashing target first became visible within the bleached area. Threshold was estimated using a three-down/one-up modified staircase estimate procedure described previously,[28] and continued at 30 seconds intervals for 20 minutes. Log thresholds were expressed as sensitivity in decibel (dB) units as a function of time from bleach offset. The speed of dark adaptation was characterized by the rod intercept value. The rod intercept is defined as the duration required for sensitivity to recover to a criterion sensitivity value of 5.0×10^{-3} scotopic cd/m^2 (3.0 log units of attenuation of the stimulus).[28] The criterion sensitivity level is located in the latter half of the second component of rod recovery.[30] An increase in the rod intercept is caused by a slowing of the second component of rod-mediated dark adaptation and thus a rightward shift of the dark adaptation function.

Statistical Analysis

In defining normal versus impairment for each visual function, we selected cutpoints already established in the literature.[21, 24, 28, 31] Demographic and functional data were shown as means and standard deviations or percentages. Logistic regression using generalized estimating equations (GEE) were used to evaluate the relationship between impairment status and each functional measure; the GEE allows the model to account for the clustering within study participants that occurs when two eyes from the same individual are used. Age and gender were identified in the univariate analysis as potential confounders and were included in the adjusted model as covariates. Crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) were presented. A p-value <0.05 (two-tailed) was considered statistically significant.

To examine the relative strength of the association between each of the visual function measures and early AMD, standardized beta coefficients were computed. The standardized beta coefficients control for scale differences among various tests of visual function and were calculated from the adjusted model as the parameter estimate multiplied by the sample standard deviation. Visual functional measures having larger standardized beta coefficients (in absolute value) indicate stronger relationships with the outcome (early AMD).

RESULTS

There were 1,260 eyes from 640 participants in the analysis sample. In terms of eyes, 1,007 eyes were in normal macular health and 253 eyes had early AMD (Table 2). Early AMD eyes were more likely to be from older individuals (p < 0.0001) and from men (p = 0.062), as compared to eyes in normal macular health. Means and standard deviations for the visual functional tests are also presented in Table 2. Visual acuity under photopic conditions on the ETDRS chart[25] was on average only 2 letters worse in eyes with early AMD, and on average 1 letter worse under low luminance conditions, although both findings were statistically significant. There were no differences between the two groups in spatial contrast sensitivity, light sensitivity in the macula, or the magnitude of decrease in acuity under low

luminance. Rod-mediated dark adaptation as measured by the rod-intercept was significantly slowed in eyes with AMD as compared to those in normal macular health. Figure 1 shows the distribution of rod-intercept for both groups.

Table 3 shows the crude and the age- and gender-adjusted odds ratio (OR) for the association between impaired vision on that particular visual function measure and early AMD. Eyes with early AMD were 35% more likely to have worse than 20/20 visual acuity (0.0 logMAR) when adjusted for age and gender, although this was of borderline significance. After adjustment a similar proportion of early AMD eyes and normal eyes were worse than 0.30 logMAR (20/40). When the decrease in visual acuity under low luminance conditions was expressed in terms of the number of lines "lost" compared to photopic conditions, the proportion of eyes dropping more than 3 lines (15 letters) on the ETDRS chart was similar in the two groups. Similarly there was no significant difference with respect to impaired contrast sensitivity or reduced macular light sensitivity. Early AMD eyes had two times the odds of having delayed rod-mediated dark adaptation compared to eyes in normal macular health (p = 0.0019).

Standardized beta coefficients for each visual function test were computed in order to assess the strength of association for each measure independent of the units of measurement (Table 4). The coefficient for rod-mediated dark adaptation demonstrated the strongest association, nearly three times that of the next strongest measure (i.e., visual acuity).

DISCUSSION

Several visual functional tests have been suggested in the literature as potentially useful endpoint measures for evaluating treatments for the earliest phases of AMD or evaluating AMD prevention strategies. In this study we evaluated the association between the earliest phases of AMD and visual acuity, low luminance visual acuity, the magnitude of drop in acuity under low luminance conditons, spatial contrast sensitivity, light sensitivity in the macula, and rod-mediated dark adaptation. Our results indicate that among the tests evaluated, the only functional measure that was significantly associated with the earliest phases of AMD when adjusted for age is rod-mediated dark adaptation. The standardized beta coefficients, which remove differences in units of measurement across the various tests of visual function, also verified these findings. While the current findings suggest that dark adaptation is a promising candidate as a functional endpoint in evaluating treatments for the earliest phases of AMD or its prevention, future research will need to examine the natural history of dark adaptation in eyes transitioning from normal macular health to early AMD. Previous research has already demonstrated significant worsening of dark adaptation in eyes with early or intermediate AMD over a 12-month period, despite stable visual acuity and fundus appearance.[29]

There is growing evidence supporting the biological plausibility of rod-mediated dark adaptation as a sensitive marker for early AMD,[32–34] and our psychophysical findings here are consistent with this framework. Metabolic exchange between the choroid and photoreceptors in early AMD eyes may be hampered by depositions rich in hydrophobic esterified cholesterol in Bruch's membrane and in the sub-retina pigment epithelium (RPE)

space,[35, 36] which can create a diffusion barrier that impairs transport of essential nutrients such as vitamin A. These depositions impede translocation of multimolecular complexes, such as plasma lipoproteins, that deliver lipophilic essentials for rapid outer retinal uptake and distribution.[37, 38] These events can have negative ramifications for rod-mediated vision. Vitamin A deficiency preferentially causes rod dysfunction and eventual photoreceptor death.[39–43] In addition, slowing in the regeneration rate of the visual pigment rhodopsin and the recovery of light sensitivity after photopigment bleaching can result from diminished amounts of 11-cis-retinal (a derivative of vitamin A) available to combine with the protein opsin to form rhodopsin.[30] Cones and cone-mediated sensitivity may be less impacted by this nutritional barrier since; unlike rods that derive vitamin A preferentially from the RPE, cones have alternative sources of vitamin A through the retinal vasculature (i.e., Müller cells) and cone-selective retinoid targeting mechanisms.[44, 45] In addition, persons with early AMD tend to exhibit deficits in rod-mediated vision that are more severe than cone-mediated definitions measured in the same retinal areas.[6, 16, 46, 47] Our previous work has provided evidence in support of the nutritional barrier/retinoid deficiency hypothesis in that the rate of rod-mediated dark adaptation in older adults with normal retinal health or AMD became more rapid after a 30-day course of high-dose retinol, where as cone-mediated dark adaptation parameters were unaffected.[48]

This study has strengths and limitations. Strengths include the assessment of several different candidate psychophysical tests in the same eyes in order to evaluate their ability to differentiate normal and early AMD. In addition, the sample of eyes studied was very large compared to samples from previous psychophysical studies. Normal macular health and early AMD disease presence were determined by an accepted and a commonly used disease classification system[22] based on the grading of stereo fundus photos by graders with established reliability who were masked to all other participant characteristics. This study focused exclusively on AMD eyes in the earliest phases, as opposed to combining data from both early and intermediate disease. Limitations also must be acknowledged. Some visual function tests previously shown as having potential as functional endpoints in evaluating treatments for early AMD were not included in our study (e.g., flicker sensitivity, short wavelength light sensitivity, multi-focal electroretinogram, scotopic perimetry).[5, 14, 46, 49] Further investigation of this issue is merited, especially in light of a recent study suggesting that 14 Hz flicker and blue color thresholds have good diagnostic sensitivity and ease of test administration.[20] Rod-mediated dark adaptation was assessed in one eye only, unlike the other visual function tests measured in both eyes; however, even with the reduced sample size, there was adequate statistical power to demonstrate significant differences in rod-intercept between the two groups. In addition, the pattern of results was unchanged when analyses were restricted to eyes for which dark adaptation was measured.

In summary, rod-mediated dark adaptation, as assessed by the rod-intercept, was associated with the earliest phases of AMD, whereas tests of visual acuity, low luminance visual acuity, macular light sensitivity, and spatial contrast sensitivity were not. The analyses presented here are cross-sectional in nature, however the prospective nature of the ALSTAR study will ultimately be able to address to what extent these visual functions change over three years as eyes undergo aging with some transitioning from normal macular health to early AMD.

Acknowledgments

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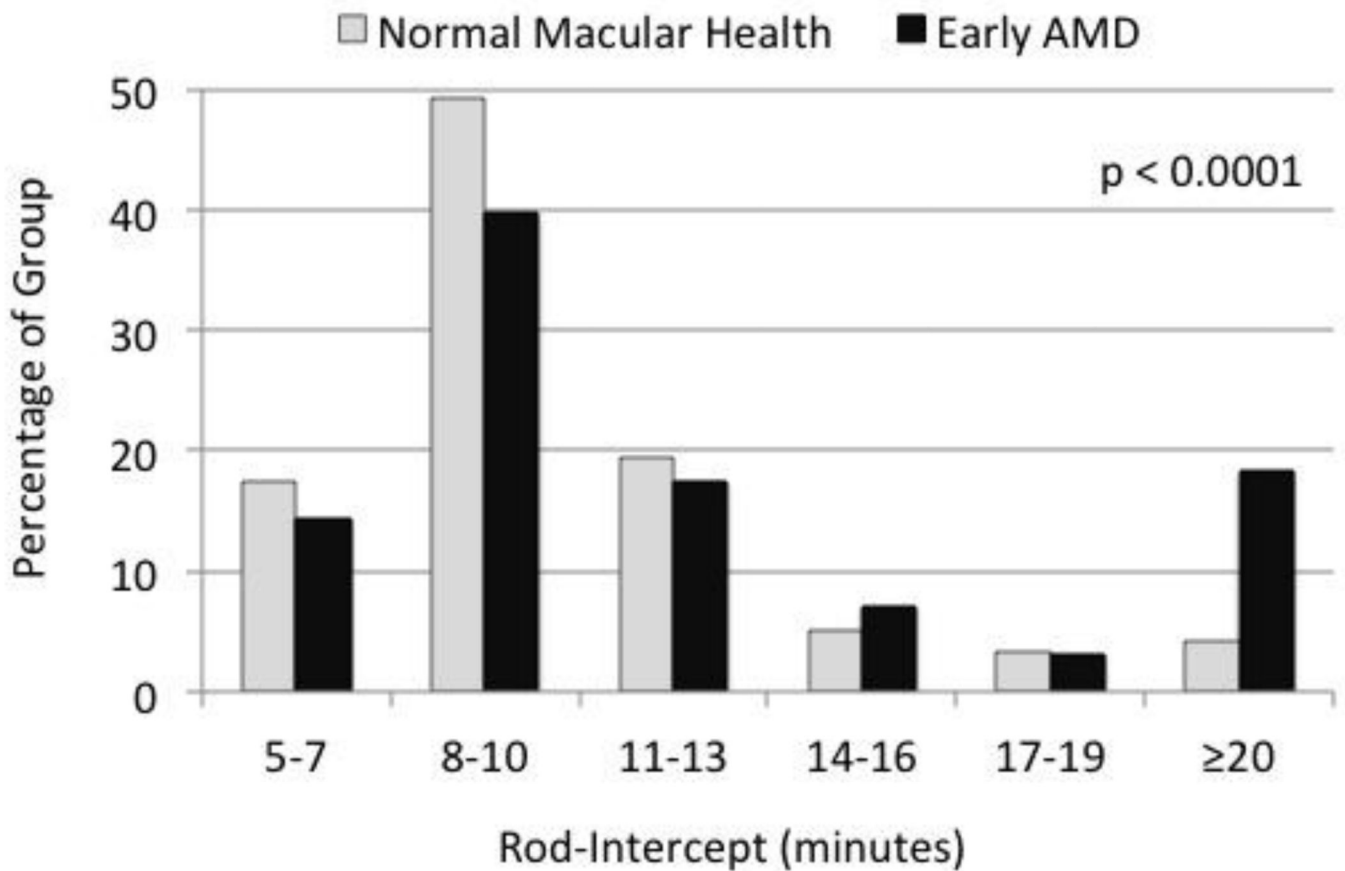
Figure 1.
Frequency histogram of the rod-intercept as measured by dark adaptation testing for the participants in normal macular health and those with early AMD. Frequency in each group is expressed as a percentage of the group with rod-intercept values in each of the indicated ranges. The p-value comparing the distributions of the two groups is $p < 0.0001$.

Table 1

Steps 1 through 4 in the AREDS 9-Step severity scale[22] which pertain to normal macular health and early AMD

Step	Description
1	Drusen area is < 125 μm; no increased pigment and no depigmentation/geographic atrophy. Step 1 defines normal macular health.
	Steps 2 – 4 define early AMD.
2	Drusen area is 125 μm but < 250 μm; no increased pigment and no depigmentation/geographic atrophy; Or Drusen area is < 125 μm and Questionable increased pigment and/or Questionable but < 350 μm depigmentation/geographic atrophy.
3	Drusen area 250 μm but < 350 μm and no increased pigment and no depigmentation/geographic atrophy.
4	Drusen area 350 μm but < 650 μm and no increased pigment and no depigmentation/geographic atrophy.\; Or Drusen area 125 μm but < 350 μm and Questionable increased pigment and/or Questionable but < 350 μm depigmentation/ geographic atrophy; Or Drusen area < 250 μm and 0 increased pigment and 350 μm but < 750 μm depigmentation/geographic atrophy

Table 2

Demographic and visual function characteristics of eyes in analysis sample stratified by normal macular health and early AMD

Characteristic	Normal eyes	Early AMD Eyes	p-value
	n = 1,007	n = 253	
Age, years, n (%)			
60 – 69	636 (63.2%)	116 (46.0%)	
70 –79	333 (33.1%)	105 (41.7%)	<0.0001
80 – 89	38 (3.8%)	31 (12.3%)	
Mean (SD)	68.8 (5.7)	71.1 (7.0)	<0.0001
Sex, n (%)			
Female	670 (66.5%)	150 (59.3%)	0.062
Male	337 (33.5%)	103 (40.7%)	
Race/Ethnicity, n (%)			
White	950 (94.3%)	243 (96.1%)	
Black	46 (4.6%)	7 (2.8%)	0.41
Other	11 (1.1%)	3 (1.2%)	
Visual acuity, logMAR, mean (SD)	0.043 (0.13)	0.069 (0.13)	0.0090
Low luminance visual acuity, logMAR, mean (SD)	0.35 (0.13)	0.37 (0.14)	0.034
Number of acuity lines lost under low luminance, mean (SD)	0.31 (0.10)	0.30 (0.11)	0.45
Contrast sensitivity, log sensitivity, mean (SD)	1.61 (0.10)	1.60 (0.11)	0.21
Light sensitivity, dB, mean (SD)	30.40 (2.03)	30.40 (1.65)	0.96
Rod-mediated dark adaptation, rod-intercept, minutes, mean (SD) [1]	11.2 (5.9)	15.3 (10.9)	<0.0001

[1] Dark adaptation based on 430 normal eyes and 126 early AMD eyes since dark adaptation was tested on one eye only.

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Table 3

Visual function for eyes in normal macular health versus early AMD eyes

	Normal Eyes (n=1007)	Early AMD Eyes (n=253)	Crude			Adjusted[1]		
			OR	p-value	OR	OR	95% CI	p-value
Visual acuity, logMAR, n (%)								
0.0	460 (45.8)	91 (36.0)	Ref	---	Ref	Ref	---	---
>0.0	545 (54.2)	162 (64.0)	1.50	0.0097	1.35	1.35	1.00–1.84	0.053
Low luminance visual acuity, logMAR, n (%)								
0.30	399 (39.7)	83 (32.8)	Ref	---	Ref	Ref	---	---
>0.30	606 (60.3)	170 (67.2)	1.35	0.058	1.19	1.19	0.87–1.62	0.28
Number of acuity lines lost under low luminance, n (%)								
3	500 (49.8)	127 (50.2)	Ref	---	Ref	Ref	---	---
> 3	505 (50.3)	126 (49.8)	0.98	0.90	0.94	0.94	0.71–1.25	0.69
Contrast sensitivity, log sensitivity, n (%)								
1.5	918 (91.3)	223 (88.1)	Ref	---	Ref	Ref	---	---
<1.5	87 (8.7)	30 (11.9)	1.42	0.11	1.17	1.17	0.76–1.79	0.48
Light sensitivity, dB, n (%)								
30	690 (68.8)	163 (65.5)	Ref	---	Ref	Ref	---	---
< 30	313 (31.2)	86 (34.5)	1.16	0.36	0.94	0.94	0.68–1.32	0.74
Rod-mediated dark adaptation, rod-intercept, minutes, n (%)[2]								
< 12.3	334 (77.7)	75 (59.5)	Ref	---	Ref	Ref	---	---
12.3	96 (22.3)	51 (40.5)	2.37	<0.0001	2.06	2.06	1.30–3.24	0.0019

[1] Adjusted for age and sex.

[2] Dark adaptation based on 430 normal eyes and 126 early AMD eyes since dark adaptation was tested on one eye only.

Table 4

Standardized beta coefficients

	Standardized Beta Coefficient
Visual acuity	0.139
Low luminance visual acuity	0.079
Number of acuity lines lost under low luminance	−0.074
Contrast sensitivity	0.016
Light sensitivity	0.093
Rod-mediated dark adaptation	0.386

Adjusted for age and sex.