

Visual Function in Older Eyes in Normal Macular Health: Association with Incident Early Age-Related Macular Degeneration 3 Years Later

Cynthia Owsley,¹ Mark E. Clark,¹ Carrie E. Huisingsh,¹ Christine A. Curcio,¹ and Gerald McGwin Jr^{1,2}

¹Department of Ophthalmology, School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, United States

²Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama, United States

Correspondence: Cynthia Owsley, Department of Ophthalmology, University of Alabama at Birmingham, 700 S. 18th Street, Suite 609, Birmingham, AL 35294-0009, USA; owsley@uab.edu.

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PURPOSE. In older eyes in normal macular health, we examined associations between impaired photopic acuity, mesopic acuity, spatial contrast sensitivity, light sensitivity, and the presence of low luminance deficit (difference between photopic and mesopic acuity) at baseline and incident AMD 3 years later. Associations were compared with an association between delayed rod-mediated dark adaptation and incident AMD, previously reported for this cohort.

METHODS. Enrollees were 60 years or older. Eyes at step 1 in the AREDS nine-step classification system based on masked grading of color fundus photographs were included. Photopic and mesopic acuity, contrast sensitivity, and light sensitivity, and the presence of low luminance deficit, were measured at baseline. Demographic, lifestyle, general health, and blood markers were assessed at baseline as potential confounders. Three years later fundus grading was repeated to determine AMD presence.

RESULTS. For the analysis, 827 eyes of 467 persons were eligible. Impaired mesopic acuity at baseline was associated with incident AMD, age-adjusted rate ratio (RR) 1.57 (95% confidence interval [CI] 1.04–2.35), whereas impaired photopic acuity, contrast sensitivity and macular light sensitivity, and the presence of a low luminance deficit were not. The mesopic acuity association was slightly weaker than the association between abnormal dark adaptation and incident AMD (RR 1.85, 95% CI 1.07–3.20).

CONCLUSIONS. Impaired mesopic acuity in eyes in normal macular health is a risk factor for incident early AMD 3 years later, however, photopic acuity, contrast sensitivity, and light sensitivity, and the presence of a low luminance deficit are not risk factors.

Keywords: AMD, risk factors, visual function

As strategies for preventing AMD and arresting its early progression are developed, there is a need for functional outcome measures suitable for use in clinical trials evaluating these treatments. Although visual acuity under photopic conditions has been a useful outcome in clinical trials on choroidal neovascularization, an end stage complication of AMD, visual acuity does not decrease substantially or at all in early disease,¹ rendering it inadequate as an outcome in early AMD trials. Recently, we showed that rod-mediated dark adaptation shows promise in this capacity, in that it is a functional biomarker of incident early AMD.² Older adults in normal macular health at baseline who had abnormally slow dark adaptation were approximately two times more likely to have early AMD 3 years later compared with those with normal dark adaptation at baseline. Furthermore, the slowing in dark adaptation over 3 years was accentuated in those who had AMD at follow-up as compared with those who did not.

It is important to consider other candidate functional outcomes for studies on early AMD, particularly cone-mediated tests shown to be useful in studying AMD at later stages. Sunness et al.^{3,4} noted that the magnitude of the drop in foveal visual acuity under mesopic conditions (where both cones and rods are active) as referenced against photopic acuity (referred to as low

luminance deficit) is associated with an increased risk for visual acuity loss in geographic atrophy (GA). More recent work has shown that eyes with noncentral GA have a more severe low luminance deficit than those in normal macular health,⁵ and that low luminance deficit is associated with an increased risk for GA progression.⁶ In a similar vein, visual acuity under mesopic conditions and at low contrast as scored by the SKILL card⁷ was more impaired in intermediate AMD eyes with reticular pseudodrusen, thought to be a more aggressive phenotype of AMD, as compared with eyes without reticular pseudodrusen.⁸

With respect to other aspects of cone-mediated visual function in early AMD, cross-sectional studies indicate that, compared with older adults in normal macular health, those with early AMD have deficits in low contrast visual acuity,⁹ mesopic visual acuity,¹⁰ photopic spatial contrast sensitivity,^{9,11} and photopic light sensitivity in the macula.^{11,12} Reticular pseudodrusen have also been linked to greater impairments in contrast sensitivity and macular microperimetry, as compared with those in normal macular health.^{13–15}

The purpose of this study was to examine the associations between tests of cone-mediated visual function and incident AMD. We specifically looked at relationships between impaired photopic visual acuity, mesopic contrast sensitivity, macular

light sensitivity, as well as the presence of a low luminance deficit, in eyes in normal macular health at baseline and incident AMD 3 years later, in a cohort for which slowed rod-mediated dark adaptation has already been established as an early AMD risk factor.

METHODS

This study is part of the Alabama Study on Early Age-Related Macular Degeneration (ALSTAR).^{2,16} ALSTAR was approved by the institutional review board of the University of Alabama at Birmingham (UAB; Birmingham, AL, USA) and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from participants after the nature and purpose of the study was described. Participants were recruited from two primary care ophthalmology practices in the Callahan Eye Hospital at UAB. At baseline participants were required to be 60 years and older and have an AREDS step of 1 (normal) in at least one eye based on the grading of three-field digital color stereo-fundus photographs (450 Plus camera; Carl Zeiss Meditec, Dublin, CA, USA).¹⁷ Step 1 of the AREDS nine-step classification system is defined as eyes with drusen area less than 125 μm , no increased pigment, and no depigmentation/geographic atrophy. Photographs were assessed by a grader, who was experienced with the nine-step AREDS classification system¹⁷ and masked to other study variables. Persons were excluded if either eye had previous diagnoses of glaucoma, other retinal conditions, optic nerve conditions, corneal disease, and if they had diagnoses of diabetes, Alzheimer's disease, Parkinson's disease, brain injury, or other neurological or psychiatric conditions as revealed by the medical record or self-report.

Demographic characteristics (age, sex, race/ethnicity, education completed) were collected through interview. Visual function was assessed for each eye separately. Best-corrected visual acuity was assessed via the Electronic Visual Acuity tester (EVA; JAEB Center, Tampa FL, USA)¹⁸ under photopic conditions (100 cd/m^2) and expressed as logMAR. Visual acuity under mesopic conditions was also assessed using the EVA with participants viewing the display through a 1.5-log unit neutral density filter that reduced background luminance to 3.16 cd/m^2 (a mesopic level). In addition, we computed the extent to which acuity worsened under mesopic conditions when referenced against photopic conditions, which has been previously referred to as the "low luminance deficit."⁴ Contrast sensitivity was estimated by the Pelli-Robson chart (Precision Vision, La Salle, IL, USA)¹⁹ with mean luminance of 100 cd/m^2 , the letter-by-letter scoring method,²⁰ and expressed as logarithm of sensitivity.

Light sensitivity in the macula was assessed using the Humphrey Field Analyzer (Carl Zeiss Meditec). The 24-2 SITA standard protocol was used following the manufacturer's recommended procedure for testing a white stimulus on a white background. Background luminance was at a low photopic level (10 cd/m^2). Light sensitivity in the macula was defined as the average sensitivity at the 16 targets falling within the macular region -9° to 9° on the horizontal and vertical meridians.²¹ Average sensitivity was expressed as decibels of attenuation (dB).

Other variables were assessed in order to evaluate their potential confounding role in the association between visual function tests at baseline and incident AMD. Smoking status²² and alcohol use²³ were collected through interview. General health was assessed by asking the participant about presence versus absence of 15 chronic medical conditions.¹⁶ General cognitive status was estimated by the Mini-Mental State Examination (MMSE).²⁴ Height and weight were measured to

generate body mass index (BMI). Blood (4–8 mL) was collected by phlebotomy and the resultant heparinized plasma collected for analysis. Plasma concentrations of apolipoprotein (apo) B and apo A-I, the major protein constituents of low (LDL) and high (HDL) density lipoprotein, respectively, were measured at Northwest Lipid Laboratory (Seattle, WA, USA).^{25,26} The concentration of C-reactive protein (CRP) was measured by ELISA as described.²⁷

At the 3-year follow-up color fundus photography and image grading with the AREDS nine-step classification system were repeated. The grader was masked to all baseline and follow-up participant characteristics. Measurement of photopic and mesopic visual acuity and contrast sensitivity and low luminance deficit was also repeated at follow-up. Macular light sensitivity testing was not repeated due to time constraints.

We wanted to compare the associations of impaired photopic acuity, mesopic acuity, contrast sensitivity, and light sensitivity, and the presence of low luminance deficit at baseline with incident AMD to the previously reported association between delayed rod-mediated dark adaptation and incident AMD.² In that previous report,² both the tested eye and the fellow eye were required to be AREDS step 1. In the present analysis tested eyes were also required to be step 1, but the fellow eye could be greater than or equal to 1; thus, to appropriately compare dark adaptation with the other vision tests as a risk factor for incident AMD, we recomputed the association between abnormal dark adaptation using the same criteria for including eyes as used in the present study. Thus, the association between abnormal dark adaptation and incident early AMD will be slightly different from that reported previously.²

Statistical analysis: categories of impairment for the visual function measures were defined as follows: photopic visual acuity, worse than 20/20 (>0 logMAR); mesopic acuity, worse than 20/40 (>0.3 logMAR); low luminance visual acuity deficit, a drop in visual by greater than or equal to 3 lines on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (≥ 0.3 logMAR) under mesopic test conditions when referenced against photopic visual acuity⁴; contrast sensitivity, less than 1.65 log sensitivity^{28,29}; and macular light sensitivity, less than 30 dB.²¹ Abnormal rod-mediated dark adaptation was defined as a rod-intercept of greater than or equal to 12.3 minutes.² The unit of analysis was the eye. Impairment groups were compared with respect to demographic, lifestyle, chronic medical conditions, and blood chemistry variables with logistic regression using generalized estimating equations to account for the correlated nature of the data. Poisson regression with robust standard errors was used to estimate unadjusted and adjusted risk ratios and 95% CIs for the association between the binary measures of visual impairment and incident AMD. General linear models were used to examine the change in visual function measures between baseline and follow-up among those who did and did not develop incident AMD. *P* values of less than 0.05 (two-sided) were considered statistically significant.

RESULTS

There were 651 persons enrolled at baseline in the ALSTAR study. A total of 827 eyes from 467 enrollees qualified for this analysis because these eyes had an AREDS grade of 1 at baseline. Participants were 304 women (65.1%) and 163 (34.9%) men. Mean age was 68.7 years old (SD 5.8 years), ranging from 60 to 88 years. The vast majority of the sample was white of European descent (95.9%).

Table 1 shows the relationship of demographic, lifestyle, chronic medical conditions, and blood chemistry variables

TABLE 1. Demographic, Lifestyle, Chronic Medical Conditions, and Blood Chemistry Variables of Sample Stratified by Visual Acuity (VA), Mesopic VA, and Low Luminance Deficit

	Photopic VA			Mesopic VA			Low Luminance		
	Impaired* (n = 439)	Normal (n = 386)	P Value	Impaired† (n = 485)	Normal (n = 340)	P Value	Deficit Present‡ (n = 379)	Deficit Absent (n = 446)	P Value
	n (%) Unless Otherwise Noted	n (%) Unless Otherwise Noted		n (%) Unless Otherwise Noted	n (%) Unless Otherwise Noted		n (%) Unless Otherwise Noted	n (%) Unless Otherwise Noted	
Demographics									
Age, mean (SD)	69.2 (5.8)	67.7 (5.3)	0.0002	69.2 (5.8)	67.6 (5.3)	0.0005	68.2 (5.4)	68.7 (5.8)	0.2725
Sex									
Male	152 (34.6)	131 (33.9)	0.8481	165 (34.0)	118 (34.7)	0.8610	140 (36.9)	143 (32.1)	0.1836
Female	287 (65.4)	255 (66.1)		320 (66.0)	222 (65.3)		239 (63.1)	303 (67.9)	
Race									
White	413 (94.1)	370 (95.9)	0.2165	458 (94.4)	325 (95.6)	0.5463	358 (94.5)	425 (95.3)	0.5759
Nonwhite	26 (5.9)	16 (4.2)		27 (5.6)	15 (4.4)		21 (5.5)	21 (4.7)	
Education									
Less than high school	8 (1.8)	7 (1.8)	0.2512	8 (1.7)	7 (2.1)	0.1048	7 (1.9)	8 (1.8)	0.7224
High school graduate or equivalent	78 (17.8)	59 (15.3)		95 (19.6)	42 (12.4)		66 (17.4)	71 (15.9)	
Some college or more	353 (80.4)	320 (82.9)		382 (78.8)	291 (85.6)		306 (80.7)	367 (82.3)	
Lifestyle									
Smoking status									
Current	16 (3.7)	15 (3.9)	0.9596	19 (3.9)	12 (3.5)	0.7484	15 (4.0)	16 (3.6)	0.4138
Former	177 (40.5)	153 (39.6)		199 (41.2)	131 (38.5)		141 (37.4)	189 (42.4)	
Never	244 (55.8)	218 (56.5)		265 (54.9)	197 (57.9)		221 (58.6)	241 (54.0)	
Drinking consumption per week§									
Abstainers	146 (33.3)	123 (31.9)	0.3305	153 (31.6)	116 (34.1)	0.5391	115 (30.3)	154 (34.5)	0.0744
Light	127 (28.9)	93 (24.1)		138 (28.5)	82 (24.1)		97 (25.6)	123 (27.6)	
Moderate	127 (28.9)	133 (34.5)		154 (31.8)	106 (31.2)		138 (36.4)	122 (27.4)	
Heavy	39 (8.9)	37 (9.6)		40 (8.3)	36 (10.6)		29 (7.7)	47 (10.5)	
BMI kg/m ² , mean (SD)	27.9 (5.0)	27.8 (5.5)	0.7449	27.8 (5.2)	27.9 (5.3)	0.7529	27.8 (5.3)	27.9 (5.2)	0.7373
Chronic medical conditions									
Number of medical conditions, mean (SD)	3.1 (1.9)	2.7 (1.8)	0.0160	3.0 (1.8)	2.8 (1.9)	0.2513	2.9 (1.8)	2.9 (1.9)	0.9437
Heart problems	129 (29.6)	116 (30.3)	0.8374	141 (29.3)	104 (30.9)	0.6721	114 (30.2)	131 (29.6)	0.8649
High blood pressure	223 (51.2)	177 (46.2)	0.1993	251 (52.1)	149 (44.2)	0.0575	194 (51.5)	206 (46.6)	0.2092
Hearing problems	113 (25.9)	92 (24.0)	0.5672	125 (25.9)	80 (23.7)	0.5479	98 (26.0)	107 (24.2)	0.5837
MMSE, mean (SD)	28.4 (1.8)	28.5 (2.7)	0.8627	28.4 (1.8)	28.4 (2.8)	0.9711	28.5 (1.7)	28.4 (2.6)	0.6345
Blood chemistry variables									
CRP µg/mL, mean (SD)	4.5 (6.4)	4.2 (5.2)	0.4797	4.5 (6.1)	4.2 (5.6)	0.6443	4.3 (5.6)	4.4 (6.2)	0.6928
ApoA-I mg/dL, mean (SD)	162.2 (30.7)	163.8 (29.8)	0.5085	163.6 (31.0)	162.1 (29.2)	0.5632	162.5 (30.9)	163.4 (29.8)	0.7019
ApoB mg/dL, mean (SD)	92.8 (30.1)	92.3 (23.2)	0.8431	93.5 (27.3)	91.3 (26.7)	0.2771	92.6 (24.0)	92.6 (29.4)	0.9980

* Impaired photopic VA was defined as worse than 20/20 VA (>0.0 logMAR). N = 2 missing data.

† Impaired mesopic VA was defined as worse than 20/40 VA (>0.3 logMAR). N = 2 missing data.

‡ Low luminance deficit was defined as a drop in VA by ≥ 3 lines on the ETDRS chart under mesopic conditions. N = 2 missing data.

§ Abstainers were defined as those who reported drinking no alcohol in the past year. Among those who reported drinking alcohol in the past year, light drinking was defined as less than 1 drink per week, moderate drinking was defined as 1 to 7 drinks per week for women and 1 to 14 drinks per week for men, and heavy drinking was defined as 8 or more drinks per week for women and 15 or more drinks per week for men.

TABLE 2. Demographic, Lifestyle, Chronic Medical Conditions, and Blood Chemistry Variables of Sample Stratified by Contrast Sensitivity and Macular Light Sensitivity

	Contrast Sensitivity			Light Sensitivity		
	Impaired* (<i>n</i> = 429)	Normal (<i>n</i> = 398)	<i>P</i> Value	Impaired† (<i>n</i> = 236)	Normal (<i>n</i> = 591)	<i>P</i> Value
	<i>n</i> (%) Unless	Otherwise Noted		<i>n</i> (%) Unless	Otherwise Noted	
Demographics						
Age, mean (SD)	69.7 (5.8)	67.3 (5.1)	<0.0001	70.3 (5.9)	67.8 (5.3)	<0.0001
Sex						
Male	142 (33.1)	143 (35.9)	0.4434	90 (38.1)	195 (33.0)	0.2571
Female	287 (66.9)	255 (64.1)		146 (61.9)	396 (67.0)	
Race						
White	406 (94.6)	379 (95.2)	0.6537	219 (92.8)	566 (95.8)	0.1832
Nonwhite	23 (5.4)	19 (4.8)		17 (7.2)	25 (4.2)	
Education						
Less than high school	7 (1.6)	8 (2.0)	0.7774	3 (1.3)	12 (2.0)	0.2045
High school graduate or equivalent	76 (17.7)	61 (15.3)		53 (22.5)	84 (14.2)	
Some college or more	346 (80.7)	329 (82.7)		180 (76.3)	495 (83.8)	
Lifestyle						
Smoking status						
Current	13 (3.0)	18 (4.5)	0.1962	13 (5.6)	18 (3.1)	0.0386
Former	161 (37.7)	171 (43.0)		76 (32.5)	256 (43.3)	
Never	253 (59.3)	209 (52.5)		145 (62.0)	317 (53.6)	
Drinking consumption per week‡						
Abstainers	157 (36.6)	112 (28.1)	0.0107	86 (36.4)	183 (31.0)	0.5221
Light	123 (28.7)	97 (24.4)		64 (27.1)	156 (26.4)	
Moderate	115 (26.8)	147 (36.9)		68 (28.8)	194 (32.8)	
Heavy	34 (7.9)	42 (10.6)		18 (7.6)	58 (9.8)	
BMI kg/m ² , mean (SD)	27.8 (5.4)	27.9 (5.0)	0.7725	28.0 (5.2)	27.8 (5.2)	0.5893
Chronic medical conditions						
Number of medical conditions, mean (SD)	3.0 (1.8)	2.8 (1.8)	0.0886	2.9 (1.9)	2.9 (1.8)	0.8037
Heart problems	131 (30.8)	114 (28.9)	0.5979	64 (27.4)	181 (30.8)	0.4075
High blood pressure	210 (49.3)	190 (48.1)	0.7617	119 (50.9)	281 (47.9)	0.5226
Hearing problems	102 (23.9)	103 (26.1)	0.5364	70 (29.9)	135 (23.0)	0.0929
MMSE, mean (SD)	28.4 (1.8)	28.5 (2.7)	0.7849	28.2 (1.9)	28.5 (2.4)	0.1105
Blood chemistry variables						
CRP µg/mL, mean (SD)	4.3 (5.8)	4.4 (5.9)	0.8971	4.3 (5.7)	4.4 (6.0)	0.8976
ApoA-I mg/dL, mean (SD)	162.2 (31.4)	163.8 (28.9)	0.5014	156.9 (31.7)	165.4 (29.3)	0.0058
ApoB mg/dL, mean (SD)	92.4 (26.0)	92.8 (28.1)	0.8343	91.5 (24.3)	93.0 (28.1)	0.5560

* Impaired contrast sensitivity was defined as <1.65 log sensitivity.

† Impaired light sensitivity in the macula was defined as <30 dB.

‡ Abstainers were defined as those who reported drinking no alcohol in the past year. Among those who reported drinking in the past year, light drinking was defined as less than 1 drink per week, moderate drinking was defined as 1 to 7 drinks per week for women and 1 to 14 drinks per week for men, and heavy drinking was defined as 8 or more drinks per week for women and 15 or more drinks per week for men.

with impaired photopic visual acuity, mesopic acuity, and low luminance deficit. Table 2 is the analogous table for impaired contrast sensitivity and impaired macular light sensitivity. For all visual functions tested, except low luminance deficit, age was strongly associated with vision impairment. Those eyes that exhibited impaired photopic acuity, mesopic acuity, contrast sensitivity, and macular sensitivity were on average approximately 2-years older than those with normal function. There were few other characteristics associated with impaired versus normal visual function. Impaired visual acuity was associated with a larger number of chronic medical conditions. Moderate users of alcohol were more likely to have normal contrast sensitivity and abstainers were more likely to have impaired contrast sensitivity. Smoking was associated with lower light sensitivity.

Table 3 shows the unadjusted and age-adjusted RR and 95% CI for the association between each visual function and incident AMD 3 years later. Impairments in visual acuity, contrast sensitivity and macular light sensitivity and the presence of a low luminance deficit were not associated with incident AMD. However, impaired mesopic visual acuity was associated with incident AMD, unadjusted RR of 1.61 (95% CI [1.07–2.43]), age-adjusted RR of 1.57 (95% CI 1.04–2.35). The severity of AMD found in the 99 eyes evaluated for mesopic acuity impairment at baseline that converted to AMD at follow-up is shown in Table 4. Those eyes with impaired mesopic acuity at baseline were not any more likely to have worse levels of AMD 3 years later as compared with those without a low luminance deficit at baseline ($P = 0.7023$).

TABLE 3. Associations Between Photopic Acuity, Mesopic Acuity, Low Luminance Deficit, Contrast Sensitivity, and Macular Light Sensitivity at Baseline and Incident AMD 3 Years Later

Visual Function Assessed at Baseline	Incident AMD at 3-y Follow-Up		Unadjusted RR (95% CI)	Unadjusted P Value	Age-Adjusted RR (95% CI)	Age-Adjusted P Value
	No AMD n (%)	AMD n (%)				
Photopic acuity						
Normal	348 (90.2)	38 (9.8)	Reference		Reference	
Impaired	378 (86.1)	61 (13.9)	1.41 (0.96–2.06)	0.0758	1.37 (0.93–2.02)	0.1107
Mesopic acuity						
Normal	310 (91.2)	30 (8.8)	Reference		Reference	
Impaired	416 (85.8)	69 (14.2)	1.61 (1.07–2.43)	0.0225	1.57 (1.04–2.35)	0.0308
Low luminance deficit						
No deficit	389 (87.2)	57 (12.8)	Reference		Reference	
Deficit	337 (88.9)	42 (11.1)	0.87 (0.60–1.25)	0.4453	0.88 (0.61–1.27)	0.4850
Contrast sensitivity						
Normal	350 (87.9)	48 (12.1)	Reference		Reference	
Impaired	378 (88.1)	51 (11.9)	0.99 (0.67–1.45)	0.9413	0.93 (0.63–1.36)	0.7060
Light sensitivity						
Normal	527 (89.2)	64 (10.8)	Reference		Reference	
Impaired	201 (85.2)	35 (14.8)	1.37 (0.91–2.06)	0.1294	1.31 (0.86–1.98)	0.2038

Table 5 shows to what extent photopic acuity, mesopic acuity, and contrast sensitivity and the extent of the low luminance deficit changed from baseline to 3-year follow-up for participants; eyes are stratified by no AMD at follow-up versus those with AMD at follow-up. None of the visual functions changed from baseline to follow-up, regardless of AMD status at follow-up, except for contrast sensitivity. The 3-year change in contrast sensitivity regardless of AMD status is so small that it is not viewed as practically significant.

The Figure compares the strength of association between incident early AMD and baseline photopic visual acuity, mesopic acuity, contrast sensitivity, light sensitivity, and the presence of a low luminance deficit, as well as for rod-mediated dark adaptation, previously reported for this cohort.² The age-adjusted RR for rod-mediated dark adaptation (based on 363 eyes) is slightly higher (RR 1.85, 95% CI 1.07–3.20) than for mesopic acuity (RR 1.57, CI 1.04–2.35).

DISCUSSION

The term low luminance deficit³ refers to the loss of visual acuity under mesopic conditions as compared with acuity under photopic conditions. Previously studied within the context of advanced AMD, low luminance deficit has been associated with an increased risk for visual acuity loss in GA⁵

and also greater risk for GA progression.⁶ Here, we report for eyes in presumably normal macular health (AREDS step 1¹⁷) at baseline, low luminance deficit is not associated with early AMD 3 years later. However, we have found that the absolute level of mesopic acuity is a functional risk factor for early AMD. The point estimate of the mesopic acuity risk factor is slightly weaker than delayed rod-mediated dark adaptation, although the dark adaptation risk factor had a wider confidence interval (Fig.). That impaired mesopic acuity is associated with incident early AMD suggests that some older eyes in seemingly normal macular health have disturbed cone-mediated spatial resolution under low luminance conditions, which increases their risk for early AMD. The mechanisms underlying impaired mesopic acuity in AMD have not yet been identified. Cone density, including that in the fovea, remains remarkably stable during the aging process,³⁰ and the foveal cone photoreceptor matrix is well preserved in nonneovascular AMD.³¹ While foveal acuity under mesopic conditions relies on cones, rod photoreceptors also have a role in mesopic acuity through rod-cone coupling. If rods around the cone-only foveola are abnormal because early AMD has already begun, then coupling to rods under mesopic lighting could result in poorly functioning cone-driven circuits, and in turn, a mesopic acuity deficit. In addition to changes in rod-cone coupling, disturbances in the operation of surround mechanisms maintained at

TABLE 4. AMD Severity for Those Participants With AMD at the 3-Year Follow-Up Stratified by Normal Versus Impaired Mesopic Acuity Baseline

AREDS 9-Step Classification System Grade at 3-y Follow-Up	All Eyes at Baseline n (%)	Eyes With Impaired Mesopic Acuity at Baseline (N = 69)	Eyes With Normal Mesopic Acuity at Baseline (N = 30)	P Value*
		n (%)	n (%)	
2	74 (74.7)	50 (72.5)	24 (80.0)	0.7023
3	13 (13.1)	10 (14.5)	3 (10.0)	
4	7 (7.1)	4 (5.8)	3 (10.0)	
5	2 (2.0)	2 (2.9)	0 (0.0)	
6	3 (3.0)	3 (4.4)	0 (0.0)	

* Fisher's exact test.

TABLE 5. Change in Each Visual Function Between Baseline and Follow-Up for Eyes That had Normal Macular Health Versus AMD at Follow-Up

	Baseline Mean (SD)	3-y Follow-Up Mean (SD)	Difference Mean (SD)	P Value
Photopic acuity, logMAR				
No AMD at FUP	0.04 (0.12)	0.05 (0.14)	0.01 (0.16)	0.0686
AMD at FUP	0.06 (0.13)	0.03 (0.13)	-0.03 (0.14)	0.0848
Mesopic acuity				
No AMD at FUP	0.34 (0.13)	0.35 (0.16)	0.01 (0.17)	0.2120
AMD at FUP	0.37 (0.13)	0.35 (0.15)	-0.02 (0.17)	0.3150
Low luminance deficit				
No AMD at FUP	0.31 (0.09)	0.31 (0.11)	-0.002 (0.14)	0.7364
AMD at FUP	0.31 (0.11)	0.31 (0.12)	0.008 (0.15)	0.6035
Contrast sensitivity, log sensitivity				
No AMD at FUP	1.61 (0.10)	1.60 (0.14)	-0.02 (0.14)	0.0047
AMD at FUP	1.62 (0.09)	1.61 (0.11)	-0.009 (0.12)	0.4874

Macular light sensitivity was not measured at follow-up so change from baseline to follow-up could not be computed for this variable. FUP, Follow-up.

the level of the two plexiform layers by horizontal and amacrine cells could contribute to decreased spatial resolution under mesopic conditions. There is previous evidence for reorganization of synaptic connectivity and degradation of inner retinal signal processing after photoreceptor degeneration in inherited retinopathies³² and in AMD.³³ Thus, mesopic acuity loss in older adults in normal macular health who are at increased risk for early AMD might be attributable to changes in rod-cone coupling or foveal surround mechanisms under mesopic conditions, issues worthy of further investigation.

Although low luminance deficit has been found to be a functional risk factor for late stage AM (GA), our results suggest that it is not a risk factor for early AMD. The difference between a mesopic acuity measure and a low luminance deficit measure is that the former is not “anchored” against a photopic measure, whereas the latter is. Low luminance deficit is the difference between photopic and mesopic acuity, whereas mesopic acuity is simply the measurement of mesopic acuity. An obvious difference between GA and early AMD is that in GA significant photoreceptor degeneration has taken place, which could potentially lead to differential patterns of photopic and mesopic acuity impairment.

In evaluating whether mesopic acuity is a good candidate as a functional outcome measure in trials for treatments or prevention of early AMD, it is important to look at the natural history of the measure over time. We found that the mesopic acuity was remarkably stable over 3 years, in eyes that converted to early AMD 3 years later as well as those eyes that did not. Thus, while results suggest that mesopic acuity is a risk factor for early AMD, they do not suggest promise for mesopic acuity as an outcome measure for early AMD trials because it is relatively insensitive to AMD onset and early progression. Thus, mesopic acuity can be contrasted with rod-mediated dark adaptation, which has previously been shown in this same cohort to worsen over 3 years.²

Not surprisingly, photopic visual acuity was not associated with incident early AMD. However, neither were photopic contrast sensitivity and macular light sensitivity. Yet cross-sectional studies have reported that those eyes with early AMD have worse contrast sensitivity and light sensitivity in the macula than eyes in normal macular health⁹⁻¹¹ (although not all agree²¹). Cross-sectional studies suffer from ambiguities between the timing of disease onset and risk factor measurement. They also have selection biases, including survival bias, particularly if the risk factor and disease are also associated with mortality (which has been reported for both vision impairment^{34,35} and AMD^{36,37}).

In the current study, light sensitivity testing was performed at a low photopic level (10 cd/m²). However, scotopic conditions may be better at revealing light sensitivity impairments in older adults that enhance their risk for developing early AMD. Histopathologic studies have demonstrated a selective vulnerability of rods over cones in maculas of aged and AMD eyes.^{30,31,38} Psychophysical studies have shown that scotopic sensitivity in aging and early AMD is

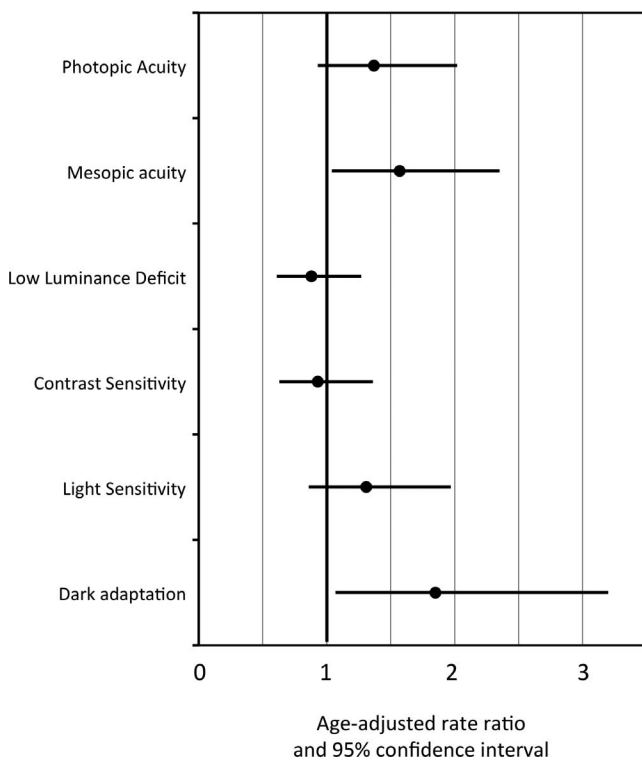


FIGURE. Age-adjusted rate ratios and 95% CIs for associations between baseline vision impairment (photopic acuity, mesopic acuity, contrast sensitivity, low luminance deficit, light sensitivity, rod-mediated dark adaptation), and incident AMD 3 years later. The analysis is at the eye level.

typically more impaired than photopic sensitivity,^{12,14,39,40} and that slowing of rod-mediated dark adaptation is a functional marker for incident early AMD.^{16,41-43} Thus, future prospective studies should address whether scotopic sensitivity impairment in eyes in normal macular health increases the risk for incident early AMD.

Strengths of this study include a very large sample of eyes in normal macular health at baseline ($N = 827$). The study was prospective in design, and thus we could establish that the psychophysically measured deficit was present prior to the onset of early AMD. The study focus was on the transition from normal aging to early AMD, an understudied epoch in AMD pathogenesis. We selected psychophysical tests that prior research suggested might be good candidate risk factors for AMD. Many potential confounders were assessed before examining the relationship between visual dysfunction and incident early AMD. Participants were recruited from primary care ophthalmology practices where the general population seeks care. Limitations must also be acknowledged. Some visual function tests that have potential as functional outcomes based on previous research on AMD (e.g., flicker sensitivity, short wavelength light sensitivity, scotopic sensitivity, photopic multifocal electroretinogram)^{12,40,44-47} were not included in the study protocol, but deserve further investigation. With respect to measuring the low luminance deficit, we used a 1.5-log unit filter as reported in the original paper describing the low luminance deficit in GA,⁴ and not the 2.0-log unit neutral density filter, which was used in the more recent publications on GA.^{3,6} Photopic light sensitivity in the macula was not assessed at follow-up so we could not compute how it may have changed over time. The study was not population-based with respect to the geographic region. Most participants were white of European descent, and thus the generalizability of our results to other subpopulations remains to be determined.

In conclusion, impaired mesopic visual acuity in older eyes in normal macular health is a risk factor for incident early AMD 3 years later. However, mesopic visual acuity does not grow worse over the subsequent 3 years, suggesting that it may not be a suitable outcome measure for evaluating interventions to prevent early AMD. Our study suggests that impaired photopic visual acuity, photopic contrast sensitivity, and light sensitivity under low photopic conditions, and the presence of the low luminance deficit, are not functional risk factors for early AMD.

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