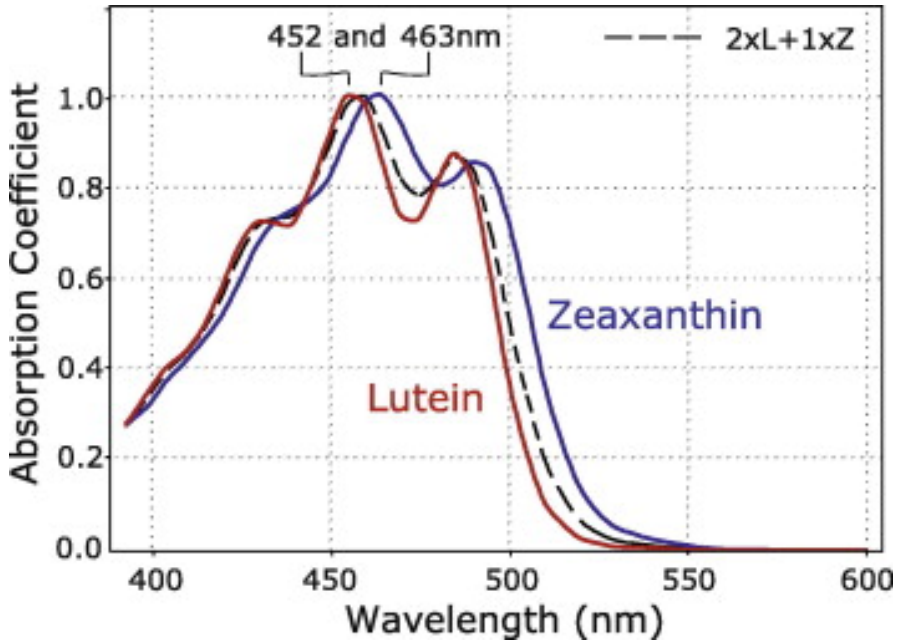
Recent Studies on the Relationship of Macular Pigment and Visual Function

Christopher Putnam, OD, PhD, FAAO

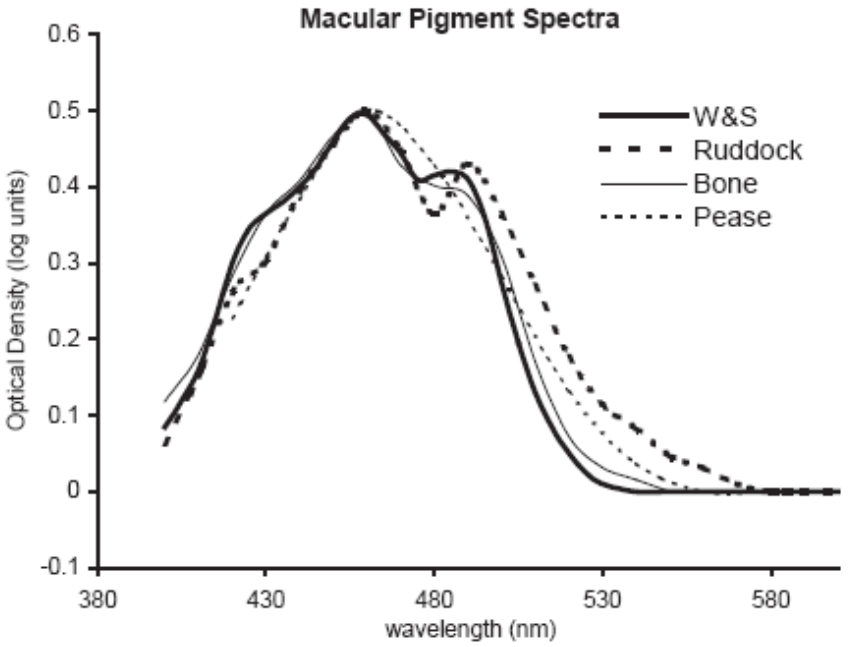
Carl Bassi, PhD

Macular Pigment Absorbance Spectrum

(Bernstein et al., 2010)



(Davies et al., 2004)



Carotenoids: The L and Z Family Tree

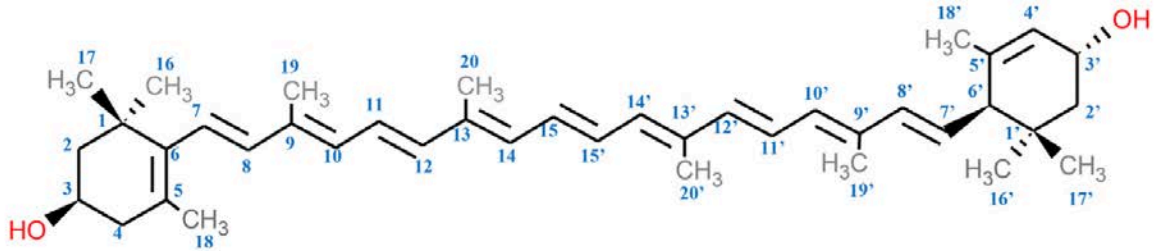
~600 total recognized in nature

~50 in typical Western diet

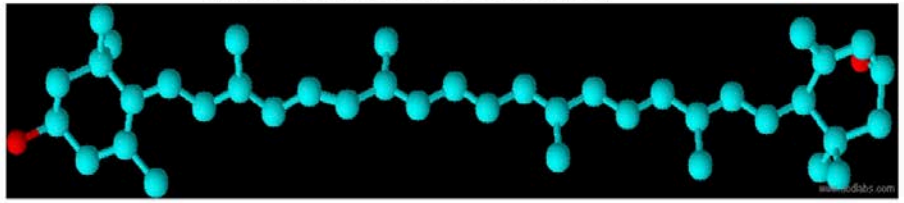
14 identified within human serum

Only 2 can be identified within human sensory retina

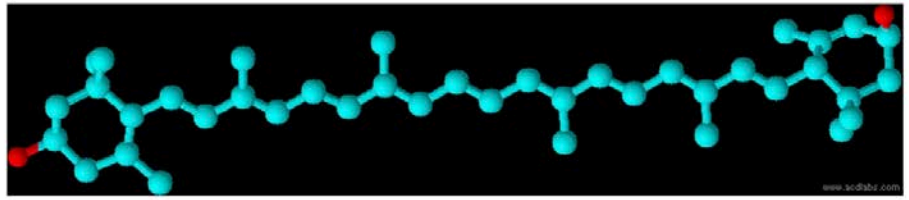
- Lutein and Zeaxanthin



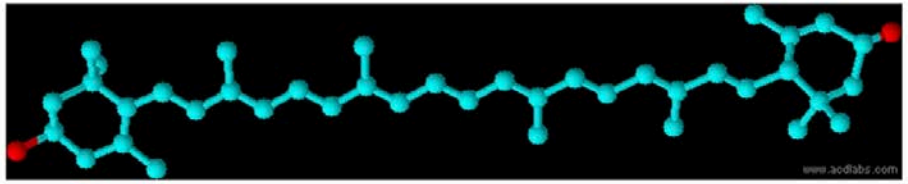
(a) Chemical structure of Lutein (2D)



(b) (3R, 3'R, 6'R)-Lutein



(c) (3R, 3'R)-Zeaxanthin



(d) (3R, 3'S)-meso-Zeaxanthin

Fig. 4. Chemical structure of macular pigment carotenoids. (a), (b) Lutein; (c) zeaxanthin; (d) *meso*-zeaxanthin.

Bernstein, P. S., Li, B., Vachali, P. P., Gorusupudi, A., Shyam, R., Henriksen, B. S., & Nolan, J. M. (2016). Lutein, zeaxanthin, and meso-zeaxanthin: the basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease. *Progress in retinal and eye research*, *50*, 34-66.

Carotenoids: The L and Z Family Tree

Factors potentially affecting the serum levels of lutein and zeaxanthin

1) Body fat
   - Increased body fat associated with decreased L/Z
2) Oxidative stress
   - Decreased L/Z levels associated with smoking
3) Gender
   - Nearly 30% greater L/Z levels in males vs. females despite similar dietary intake
4) Dietary fat
   - L/Z transported on circulating lipoproteins* with slightly higher affinity for HDL
   - Lutein binding protein = StARD3
   - Zeaxanthin binding protein = GSTP1

Macular Pigment

1) Protection Hypothesis

2) Neural Efficiency Hypothesis

3) Optical Hypothesis

Protection Hypothesis

L/Z are potent antioxidants

L/Z selectively filter high energy, short wavelength light

Protection Hypothesis

Identified an inverse association between AMD findings and amount of L/Z found in retina-Bone (2001)

Identified a markedly reduced risk of AMD associated with high plasma levels of L/Z, particularly Z. Delcourt et al. (2006)

Performed a meta-analysis using 5 databases to evaluate the potential protective effects of L

- Found reductions in risk of early AMD by 4% and late AMD by 26% -Ma et al. (2012)

Neural Efficiency Hypothesis

L/Z are the predominant carotenoids in frontal, occipital, cerebellar, and pons regions

(Craft et al., 2004)

L/Z levels show association with verbal fluency, memory, and processing speed

(Johnson, 2012)

Improve neural membrane integrity

(Sujak, 2012)

Enhance neural conduction speed

(Sies et al. 1997)

Neural Efficiency Hypothesis

MPOD was broadly related to cognitive ability including mini-mental state exam, visual-spatial abilities, language ability, attention and neuropsychological status battery

-Renzi et al. (2014)

MPOD related to cognitive function in older adults

- Vishwanathan et al. (2014)

MPOD associated with lower cognitive function in large, population-based sample of older adults

- Feeny et al. (2013)

L and Z supplementation showed increased cognitive function in elderly

- Johnson et al. (2012)

Optical Hypothesis

1) Reduction in chromatic aberrations

2) Reduction of photophobia

3) Enhancement of edges through luminance contrast differences

4) Extension of cone function through rod sensitivity suppression at mesopic levels

*Leads to improved resolution and color detection

Recent studies of Macular Pigment and:

1. Spatial properties in the retina
2. Visual function- Contrast Sensitivity and Glare
3. Intraocular scattering and MPOD
4. Eye disease (macular degeneration, albinism, central serous)
5. Development of myopia
6. Diabetes
7. Brain function
8. Cognitive function
9. Traumatic Brain Injury
10. Military applications

1. Spatial Properties of Macular Pigment

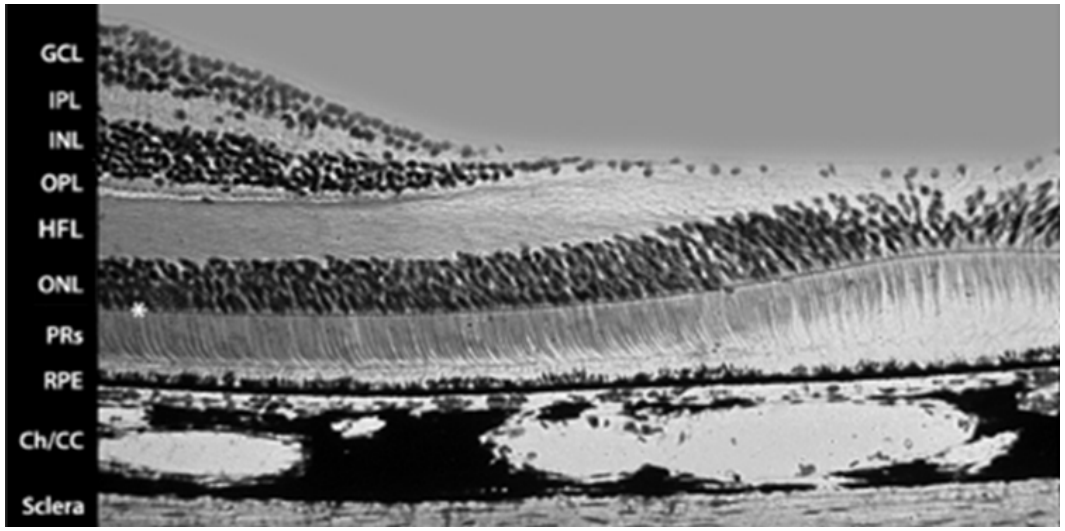
a) Putnam CM, Bassi, CJ. "Macular pigment spatial distribution effects on glare disability." *Journal of optometry* 8.4 (2015): 258-265.

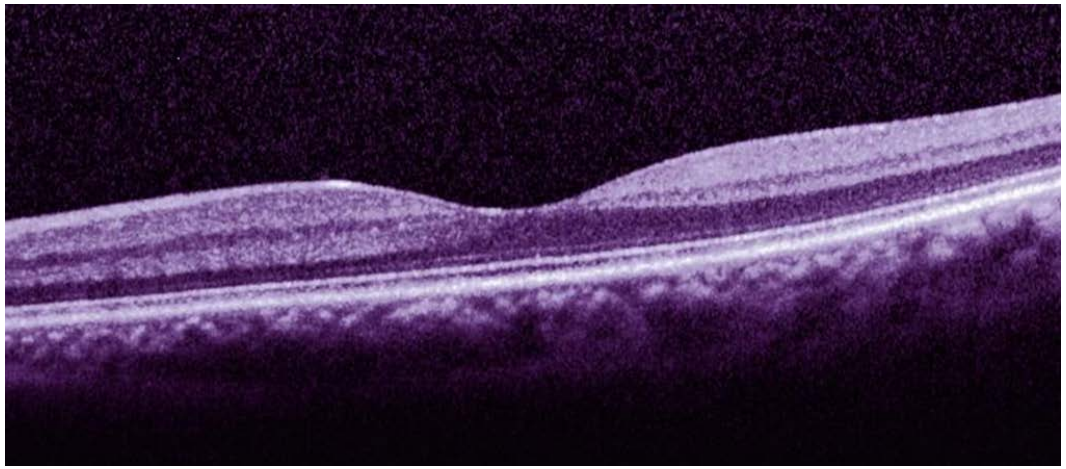
b) Putnam CM. “Novel description of macular pigment optical density spatial distribution using cHFP” *New Front Ophthal*. 2016.DOI: 10.15761/NFO.1000121

c) Nolan, J. M., Power, R., Stringham, J., Dennison, J., Stack, J., Kelly, D., ... & Beatty, S. (2016). Enrichment of Macular Pigment Enhances Contrast Sensitivity in Subjects Free of Retinal Disease: Central Retinal Enrichment Supplementation Trials–Report 1Central Retinal Enrichment Supplementation Trials. *Investigative Ophthalmology & Visual Science*, *57*(7), 3429-3439.

d) Alassane, S., Binquet, C., Arnould, L., Fleck, O., Acar, N., Delcourt, C., ... & Creuzot-Garcher, C. (2016). Spatial Distribution of Macular Pigment in an Elderly French Population: The Montrachet StudySpatial Distribution of Macular Pigment in Elderly. *Investigative Ophthalmology & Visual Science*, *57*(10), 4469-4475.

Macular Pigment Anatomic Location





Vertical distribution pattern of MP is identified primarily within the parafoveal plexiform layers and foveal Henle fiber layer

(Snodderly et al., 1984)

(Trieschmann et al., 2008)

(Subczynski et al., 2010)

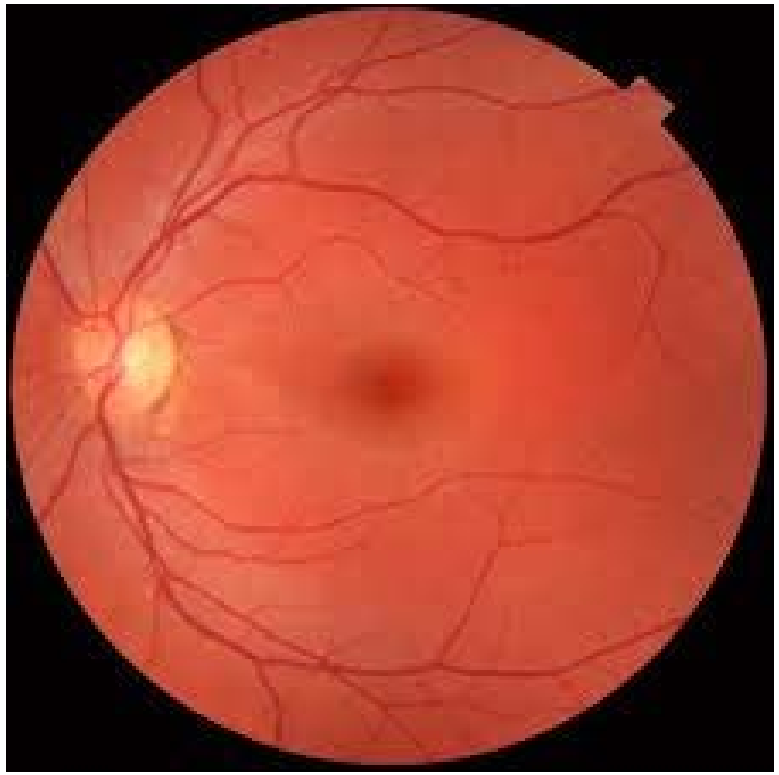
Optical density peaks at central fovea and follows an exponential decay pattern to undetectable levels @ ~7^0 eccentricity

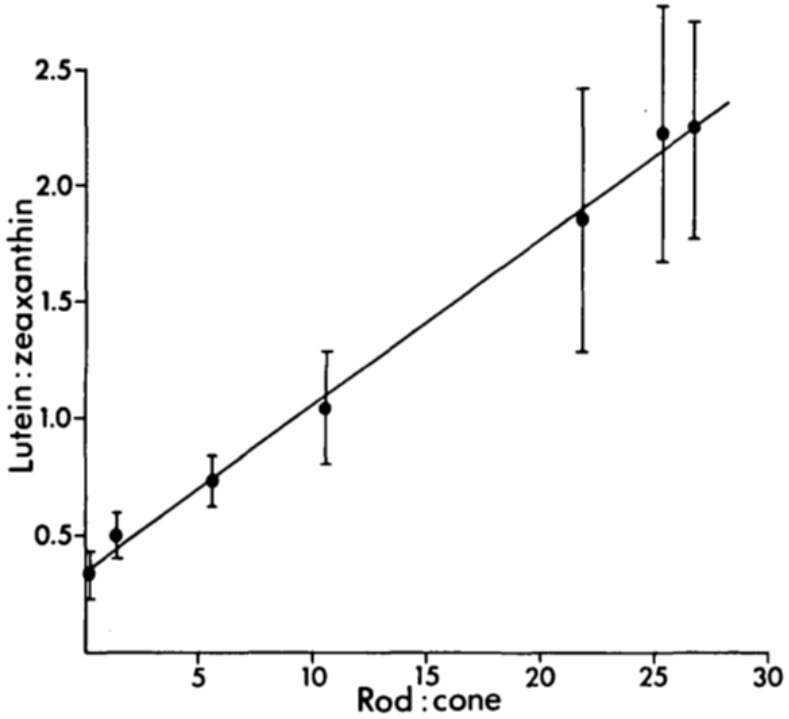
(Bone et al., 1992)

Müller glial cells influence MP deposition and transport within the central retina

(Reichenbach et al., 2013)

Lutein and Zeaxanthin: Macular Pigment



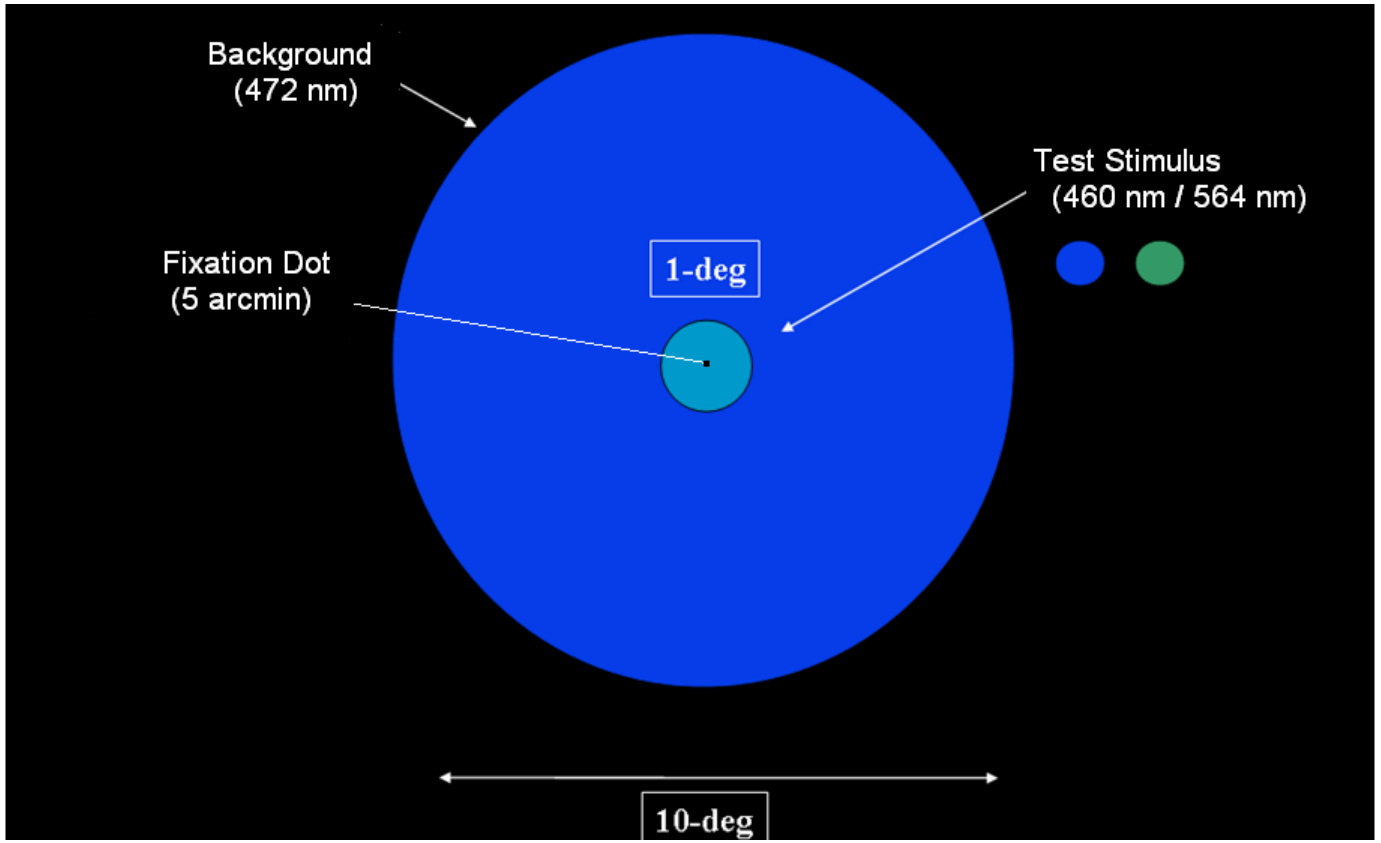


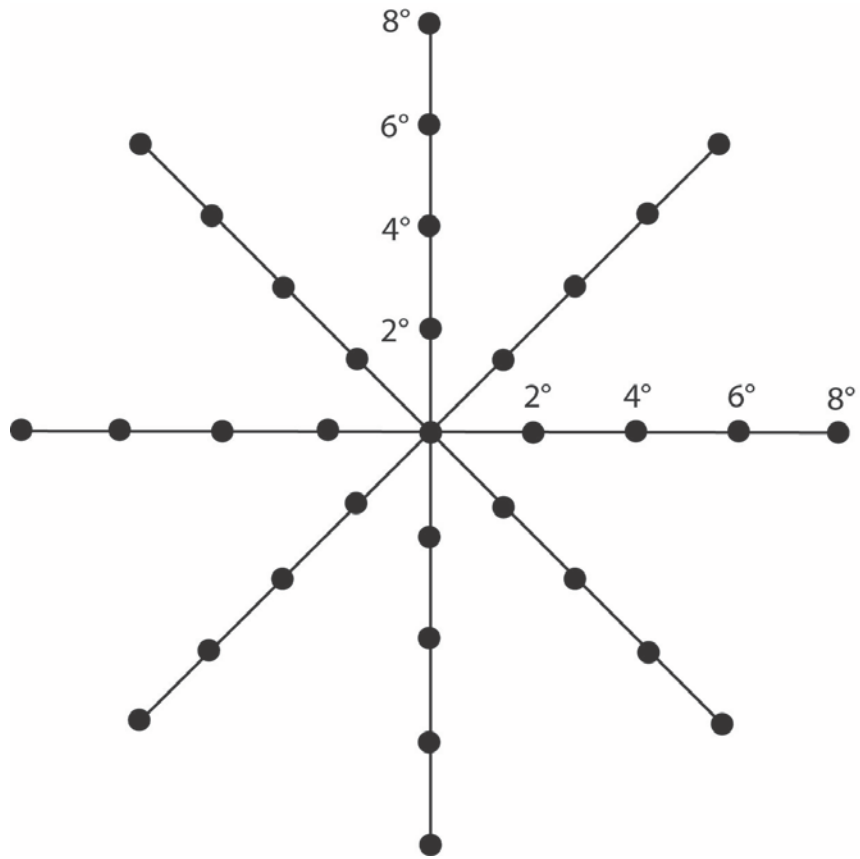
L/Z demonstrate a primarily pre-receptoral location although have been identified throughout retina

- Foveal L:Z 1 : 2.4 (*central 1.5mm)
- Perifoveal L:Z 1.8 : 1 (*1.5 - 4mm annular ring)
- Peripheral L:Z 2.7 : 1 (*outside 4mm)

Methods

Optical density setting




8°
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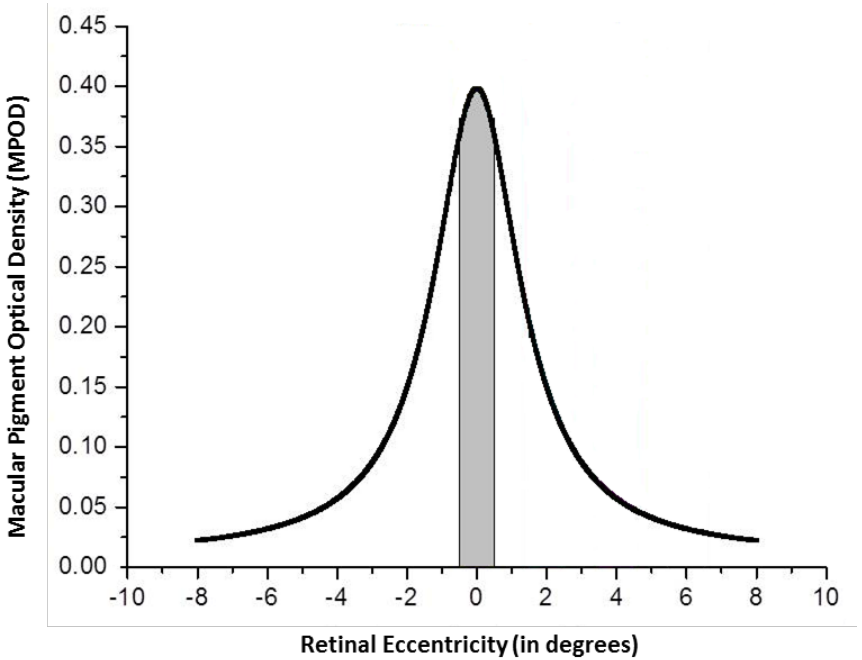
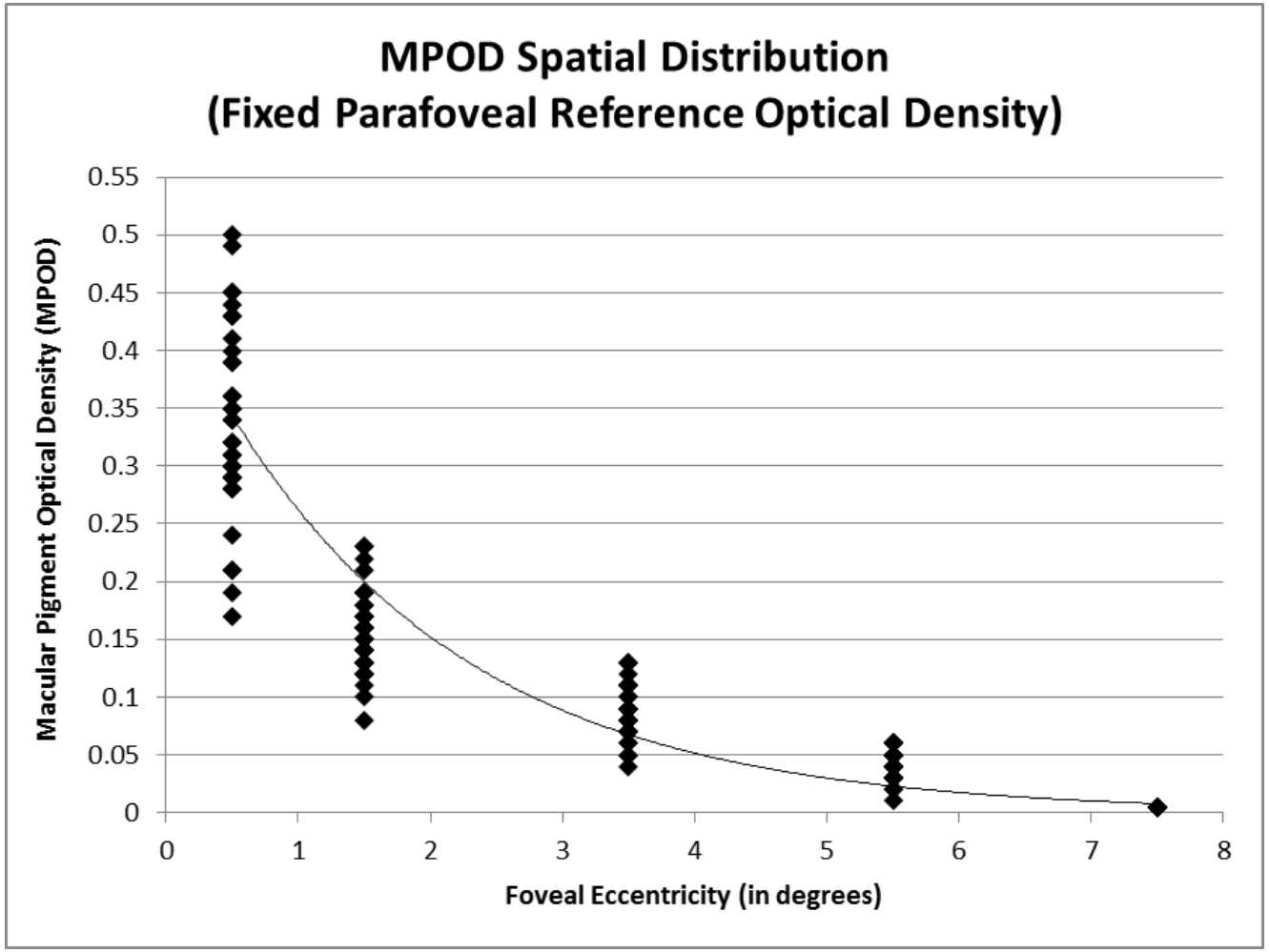


An example of the integration calculation performed across the 1^0 stimulus diameter for each subject. The 3.3^o, 10^o and 16^o integrated values were calculated in the same way, centered at 0^0 with an increasing width, respectively. The ordinate represents measured MPOD and the abscissa represents retinal eccentricity relative to the foveal center at 0^o. The negative values along the abscissa were used in the OriginPro9 program to allow integration under a continuous curve extending 16^o across the macula. The figure depicts MPOD spatial distribution extending form 8^o nasal eccentricity (abscissa = -8) to 8^o temporal eccentricity (abscissa = 8).



Best fitting 1st-order exponential decay function demonstrated by MPOD spatial distribution assuming a fixed, negligible parfoveal reference MPOD. The resulting exponential fit equation was $y = 0.451e^{-0.543x}$ with a covariance value of $r_2 = 0.912$.

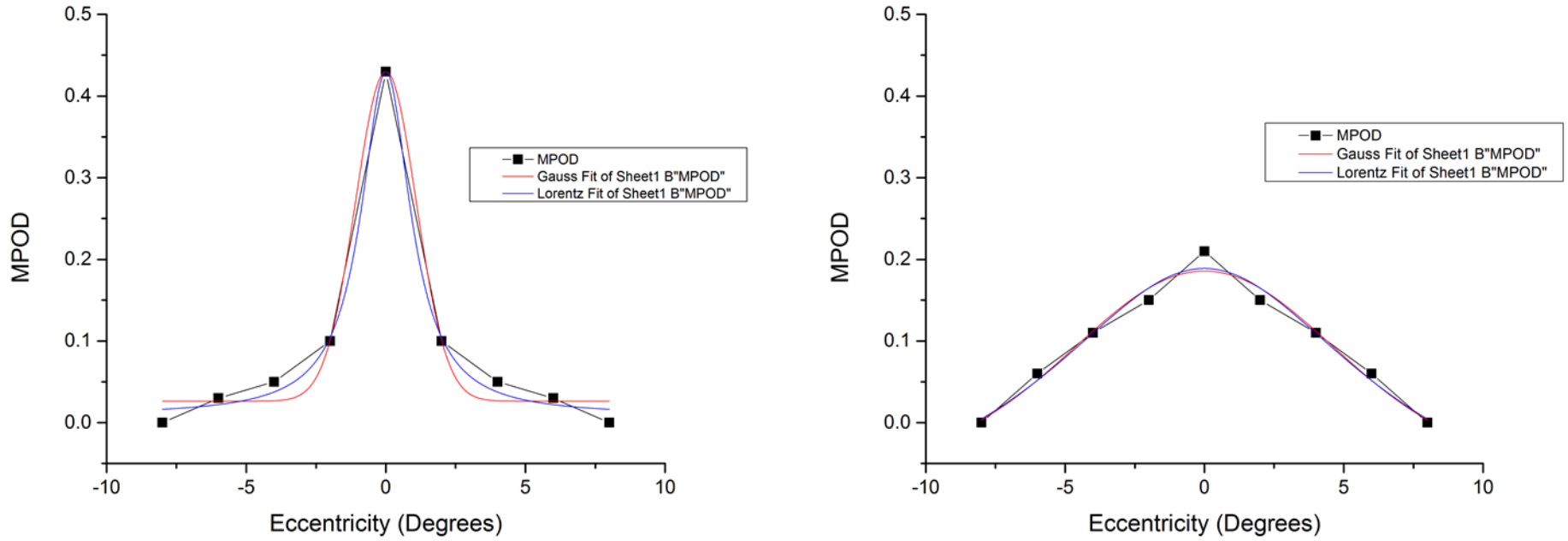


Figure 2

MPOD spatial distributions were fit to both Gaussian and Lorentzian distributions assuming stimulus point of highest retinal sensitivity for each subject. Substantial variability within the sample was seen from highly leptokurtic distributions demonstrated by subject #20 (left) to highly platykurtic distributions demonstrated by subject #21 (right).

	Kurtosis Value	Integrated AUC Stimuli
Subject 1	5.166	1.762
Subject 2	2.554	1.879
Subject 3	4.577	2.133
Subject 4	4.308	1.765
Subject 5	3.042	2.098
Subject 6	2.175	1.912
Subject 7	3.363	2.448
Subject 8	1.704	1.954
Subject 9	1.837	1.988
Subject 10	2.271	1.781
Subject 11	5.313	1.551
Subject 12	5.215	1.881
Subject 13	0.399	1.831
Subject 14	4.312	1.498
Subject 15	2.731	2.571
Subject 16	5.395	1.633
Subject 17	0.806	2.018
Subject 18	3.302	1.505
Subject 19	2.392	1.638
Subject 20	7.154	1.513
Subject 21	-0.763	1.705
Subject 22	1.627	2.371
Subject 23	4.603	1.666
Subject 24	1.937	1.579
Subject 25	2.112	2.135
Subject 26	2.246	0.851
Subject 27	0.825	1.245
Subject 28	1.222	1.087
Subject 29	3.719	1.346
Subject 30	2.591	2.587
Subject 31	1.049	1.693
Subject 32	3.102	1.566
Subject 33	-0.503	1.487
Mean	**2.781**	**1.778**
Std Dev	**1.809**	**0.393**

Table 1
Calculated values for kurtosis, integrated AUC assuming stimulus center and integrated AUC for the 33 subject sample using MPOD values measured at 0^o, 2^o, 4^o, 6^o and 8^o eccentricity. The kurtosis values showed a non-significant relationship with AUC calculations (r = -0.004, p=0.984) across the 33 subject sample.

Putnam, DOI: 10.15761/NFO.1000121

Comparison of Methods to Describe MPOD Spatial Distribution

Results:

Spatial mapping of MPOD was highly variable across all 33 subjects.

Mean r^2 values for mean Gaussian and Lorentzian fit functions were 0.89 and 0.95, respectively

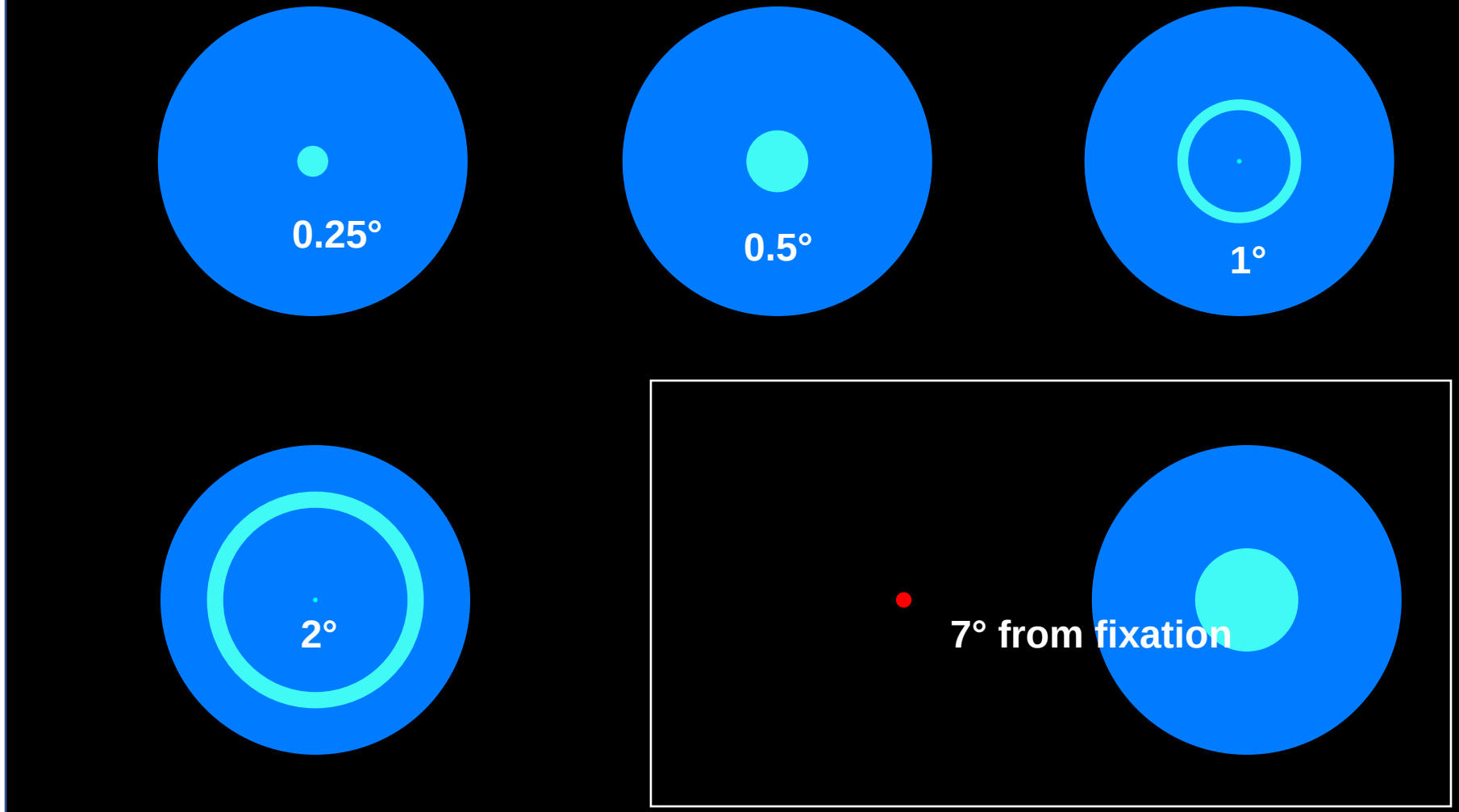
Conclusions:

Consistent with previous findings, the Lorentzian function provided a better description of MPOD spatial distribution

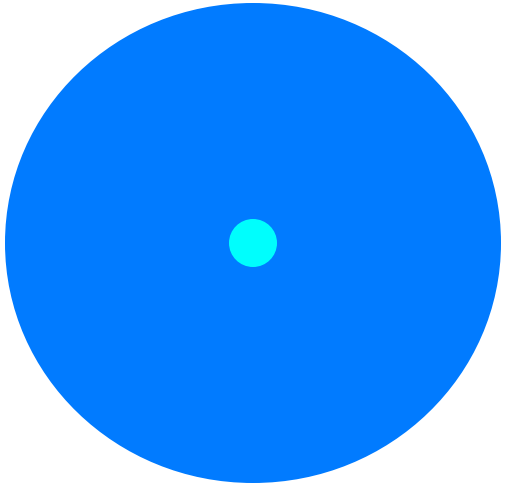
Kurtosis values may provide a separate metric for MPOD spatial distribution.

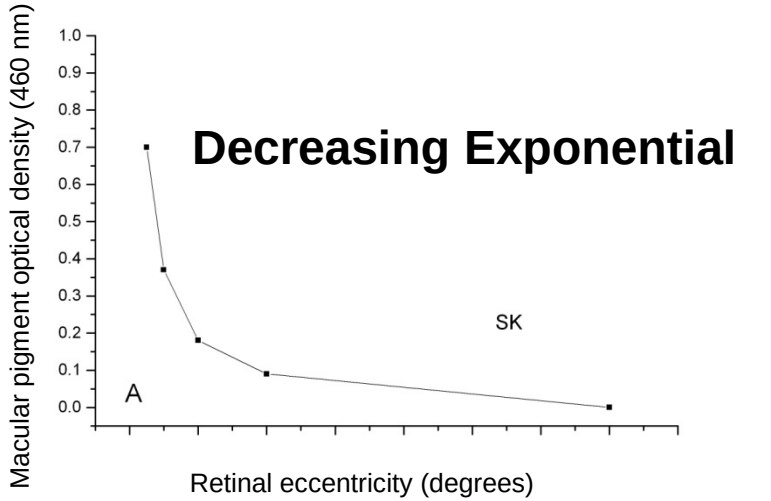
Does a broad base of MP provide better short wavelength, visible light filtration or enhanced anti-oxidant properties across the macula than a sharp, central peak?

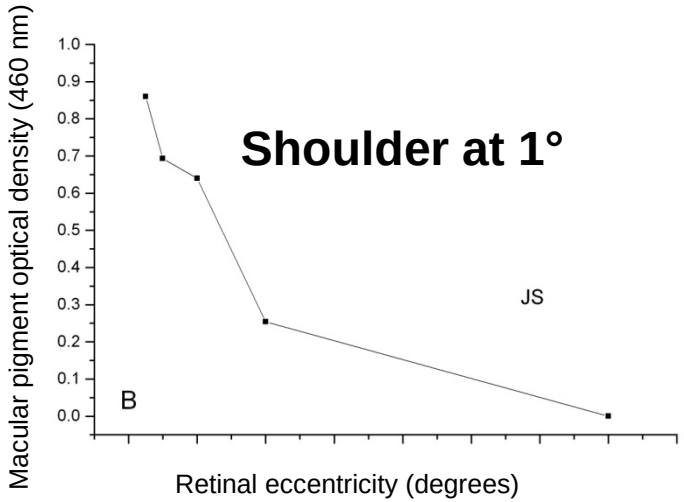
Retinal Locations for MP Measurements

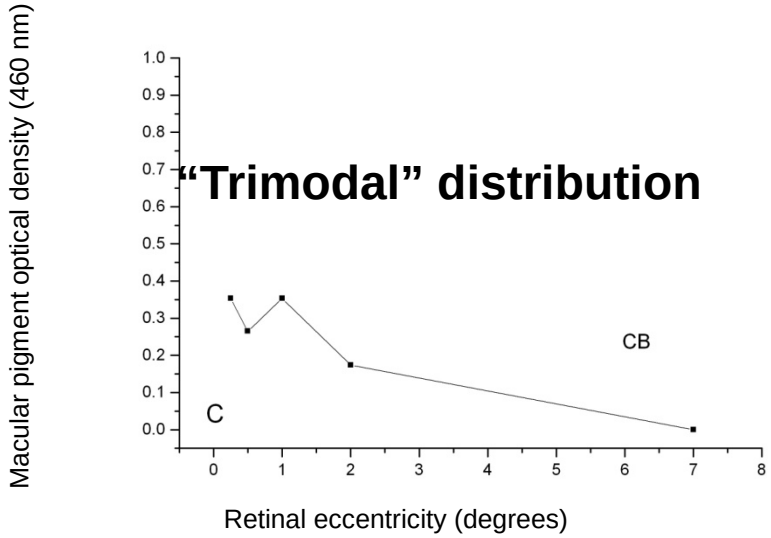


Variations of MPOD spatial profiles









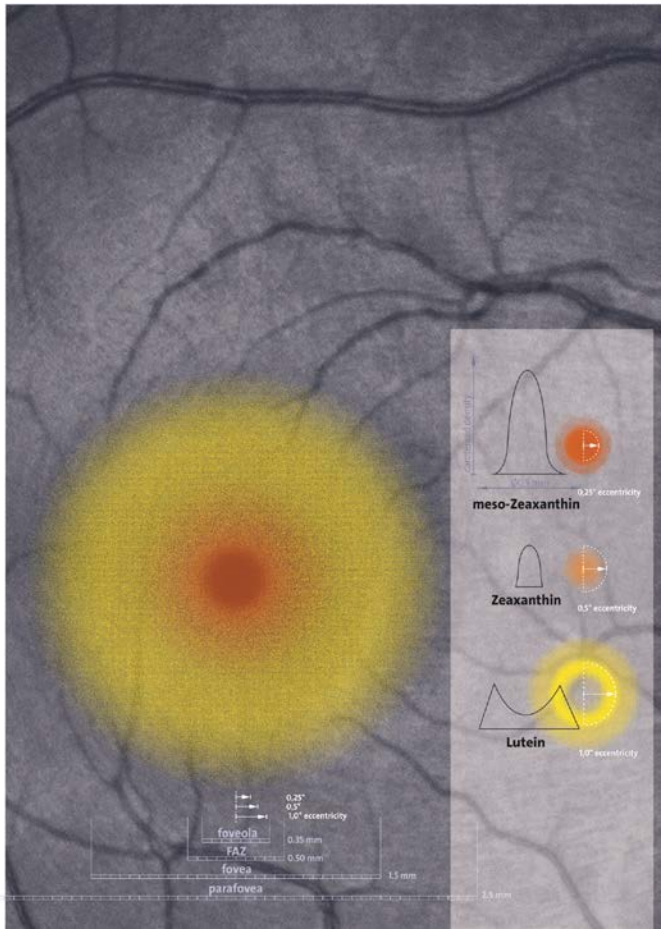


Figure Legend:

Distribution of MP's constituent carotenoids presented in scale onto a photograph of a healthy human retina. Figure courtesy of John Nolan, Robert Kuchling, and Kristiane Nöbel.

From: Enrichment of Macular Pigment Enhances Contrast Sensitivity in Subjects Free of Retinal Disease: Central Retinal Enrichment Supplementation Trials – Report 1

Invest. Ophthalmol. Vis. Sci.. 2016;57(7):3429-3439. doi:10.1167/iovs.16-19520

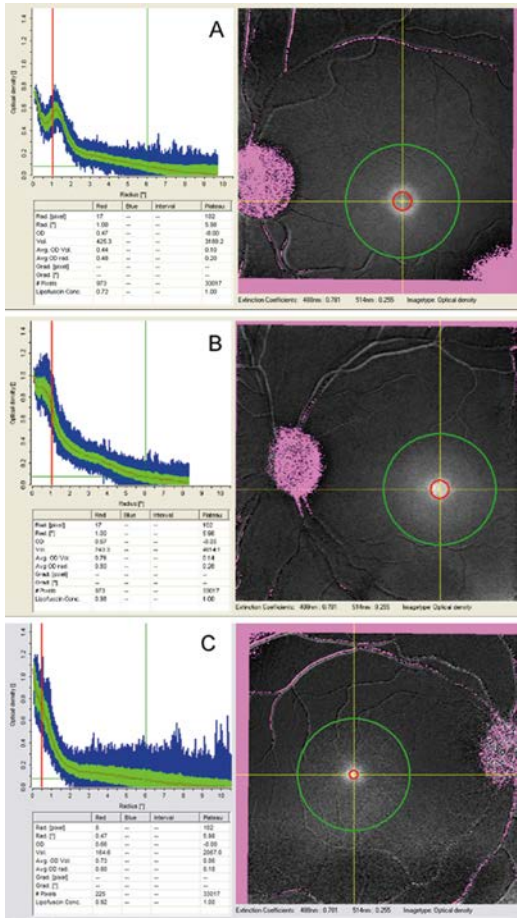


Figure Legend:

The three patterns of MPOD spatial distribution as obtained with the dual-wavelength technique. (A) ring-like profile, (B) intermediate profile, (C) no-ring profile.

From: Spatial Distribution of Macular Pigment in an Elderly French Population: The Montrachet Study
Invest. Ophthalmol. Vis. Sci.. 2016;57(10):4469-4475. doi:10.1167/iovs.16-19958

2. Visual Function: Contrast Sensitivity and Glare

I. Stringham, J. M., Garcia, P. V., Smith, P. A., McLin, L. N., & Foutch, B. K. (2011). Macular pigment and visual performance in glare: benefits for photostress recovery, disability glare, and visual discomfort. *Investigative Ophthalmology & Visual Science*, *52*(10), 7406-7415.

II. Putnam, C. M., & Bassi, C. J. (2015). Macular pigment spatial distribution effects on glare disability. *Journal of optometry*, *8*(4), 258-265.

III. Nolan JM, Power R, Stringham JM, Dennison J, Stack J, Kelly D, Beatty, S. Enrichment of Macular Pigment Enhances Contrast Sensitivity in Subjects Free of Retinal Disease: Central Retinal Enrichment Supplementation Trials–Report 1Central Retinal Enrichment Supplementation Trials. *Invest Ophthal Vis Sci*. 2016;*57*(7):3429-3439.

IV. Stringham JM, O'Brien KJ, Stringham NT Macular carotenoid supplementation improves disability glare performance and dynamics of photostress recovery. *Eye and Vision*. 2016;*3*(1):30.

Macular Pigment and Visual Performance: Benefits for Photostress Recovery, Disability Glare and Visual Discomfort

Investigative Ophthalmology and Visual Science (Sep 2011)

Retina

Macular Pigment and Visual Performance in Glare: Benefits for Photostress Recovery, Disability Glare, and Visual Discomfort

James M. Stringham,[1] Paul V. García,[1] Peter A. Smith,[1] Leon N. McLin,[2] and Brian K. Foutch[2]

Purpose. One theory of macular pigment's (MP) presence in the fovea is to improve visual performance in glare. This study sought to determine the effect of MP level on three aspects of visual performance in glare: photostress recovery, disability glare, and visual discomfort.

Methods. Twenty-six subjects participated in the study. Spatial profiles of MP optical density were assessed with heterochromatic flicker photometry. Glare was delivered via high-bright-white LEDs. For the disability glare and photostress recovery portions of the experiment, the visual task consisted of correct identification of a 1° Gabor patch's orientation. Visual discomfort during the glare presentation was assessed with a visual discomfort rating scale. Pupil diameter was monitored with an infrared (IR) camera.

Results. MP level correlated significantly with all the outcome measures. Higher MP optical densities (MPODs) resulted in faster photostress recovery times (average $P < 0.003$), lower disability glare contrast thresholds (average $P < 0.004$), and lower visual discomfort ($P = 0.002$). Smaller pupil diameter during glare presentation significantly correlated with higher visual discomfort ratings ($P = 0.037$).

Conclusions. MP correlates with three aspects of visual performance in glare. Unlike previous studies of MP and glare, the present study used free-viewing conditions, in which effects of iris pigmentation and pupil size could be accounted for. The effects described, therefore, can be extended more confidently to real-world, practical visual performance benefits. Greater iris constriction resulted (paradoxically) in greater visual discomfort. This finding may be attributable to the neurobiologic mechanism that mediates the pain elicited by light. (*Invest Ophthalmol Vis Sci.* 2011;52:7406–7415) DOI:10.1167/iovs.10-6699

Visual performance can be greatly compromised when glaring light enters the visual field. This is especially true of central vision, where intense light imaged onto the fovea tends to cause the most discomfort and disability, compared with the para- and perifoveal regions of the retina.[1–5] Intense, glaring lights in the periphery, however, can be strongly scattered by the ocular media over the fovea, which results in reduced contrast for objects viewed centrally.[2] This phenomenon is referred to as disability glare and is often experienced while viewing oncoming automobile headlights. Because the fovea yields the highest visual performance for nearly all parameters of vision, any factor that negatively impacts its function (i.e., glare) will result in noticeable decrements in visual performance. Conversely, any factor that promotes or protects foveal function would seemingly have noticeable visual performance benefits. Based on recent empiric evidence, it appears that the macular pigment (MP) could be such a factor.

The MP is a yellow, diet-derived pigment that is deposited anterior to the sensory retina, in the photoreceptor axon layer of the Henle and inner plexiform layers of the macula.[4] MP is distributed in a radially symmetric fashion about the center of the fovea, and, in most subjects, its optical density (MPOD) decreases exponentially with increasing eccentricity from the center of the fovea.[5,6] There are, however, exceptions.[7] MP is composed primarily of two dietary carotenoids: lutein (L) and zeaxanthin (Z).[8] In addition, meso-zeaxanthin (MZ), a stereoisomer of zeaxanthin that is converted from L in the retina,[9] makes up roughly 25% of the MP.[10] The molecular structures of L, Z, and MZ enable them to effectively protect biological tissue in two ways. First, by virtue of their carbon-conjugated double bonds, these carotenoids can quench the energy of damaging singlet oxygen and other free radical oxygen species.[11] Second, L, Z, and MZ (which are yellowish) selectively absorb high-energy, potentially damaging short-wavelength (blue) light.[12] On absorption, the energy is dissipated as heat. From the available data, the two roles (antioxidant and short-wave light filter) played by the retinal carotenoids appear to protect the macula from acute damage,[13] protect against cumulative damage resulting in age-related macular disease,[14] and maintain visual sensitivity over a lifetime.[15] L and Z are found in many colored fruits and vegetables, but tend to be most dense within leafy green vegetables such as spinach and kale.[16] Because of its exclusive dietary origin, MP density varies significantly among subjects: Those with diets rich in foods containing high amounts of L and Z tend to have higher densities of MP than do those with L- and Z-deficient diets.[17] The variation found among subjects in MP optical density (MPOD) is not trivial. Many studies have characterized samples in which subjects range from 0 to well over 1 log unit of MPOD.[5,18,19] Of the 20 or so carotenoids found circulating in human serum, only L and Z are found in the retina, and their concentration there is the highest level of carotenoid in any tissue in the body. In fact, the concentration of L and Z in the fovea is roughly 10,000 times greater than that of the blood,[10] which is indicative of active, continuous transport and deposition in retinal tissue.

The specificity of the location of L and Z in the fovea is conspicuous. As noted above, the fovea is critical for optimal visual performance, and so it makes sense that a substance

From [1]TASC, Incorporated, Brooks City-Base, Texas; and the [2]Air Force Research Laboratory, Brooks City-Base, Texas.

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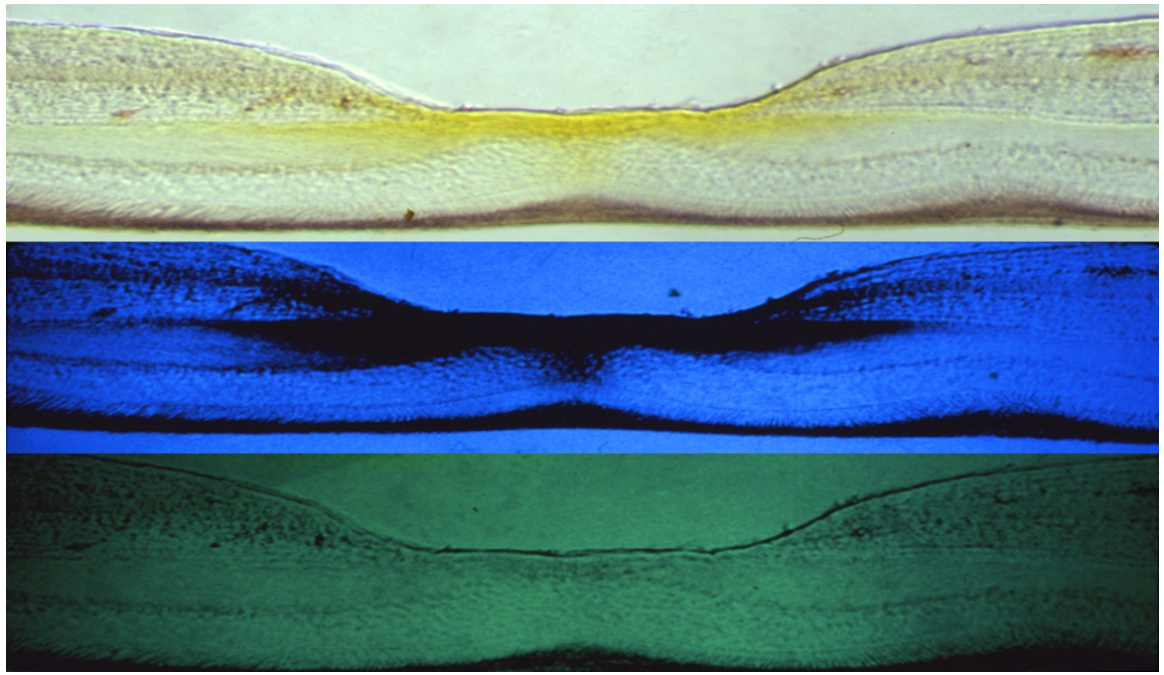
Disclosure: **J.M. Stringham**, None; **P.V. García**, None; **P.A. Smith**, None; **L.N. McLin**, None; **B.K. Foutch**, None

Corresponding author: James M. Stringham, Building 812, Brooks City-Base, TX 78235; james.stringham@brooks.af.mil.

Purpose

- One proposed function of macular pigment (MP) presence in the central retina is to improve visual performance under glare conditions

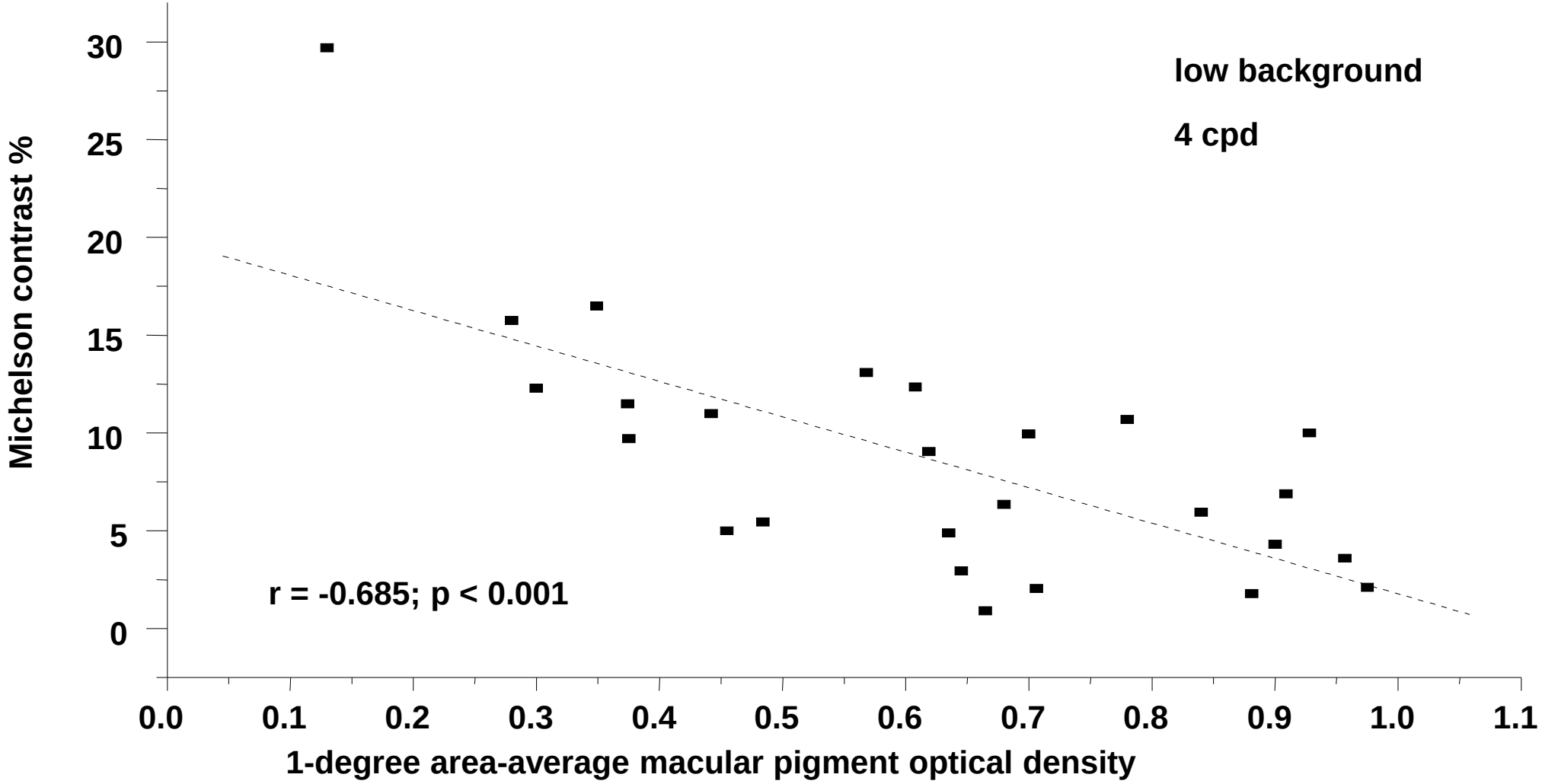
- This study evaluated the effect of MP levels on 3 aspects of visual performance under glare:
  1. Photostress recovery
  2. Disability glare
  3. Visual discomfort



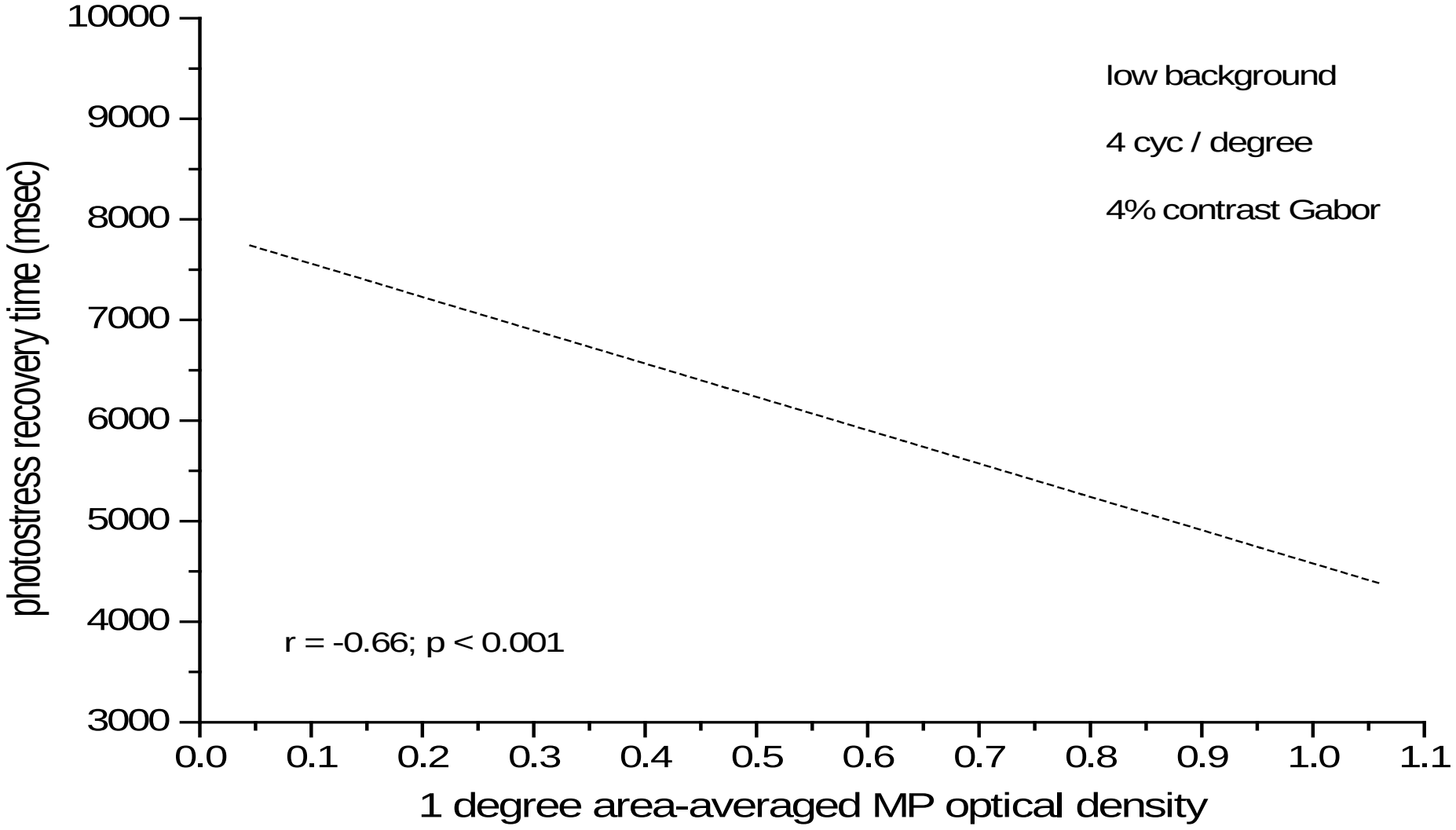
Methods

- Twenty-six (26) subjects
- Spatial profiles of MP optical density were assessed with heterochromatic flicker photometry
- Disability glare
  - Visual task consisted of correct identification of a 1^{o} Gabor patch's orientation
  - Glare was delivered dioptically via two high-bright white LEDs coupled with diffusers and focusing optics.
- Photostess recovery
  - Time to recovery of 1^{o} Gabor patch orientation after 5 second central glare exposure
- Visual discomfort
  - Assessed with a visual analog discomfort rating scale
- Pupil diameter was monitored with an IR camera, and pupils varied normally

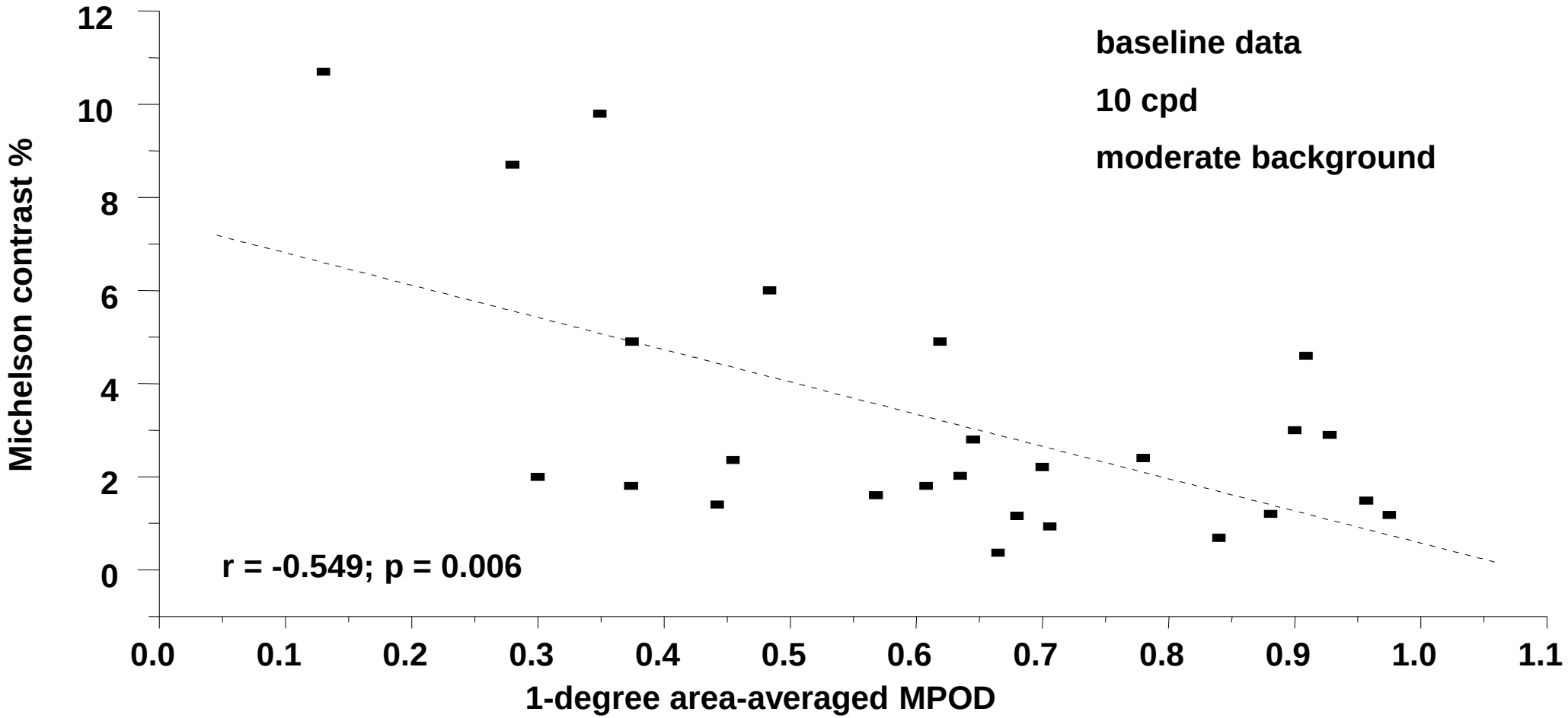
Contrast Thresholds and MPOD (without glare)



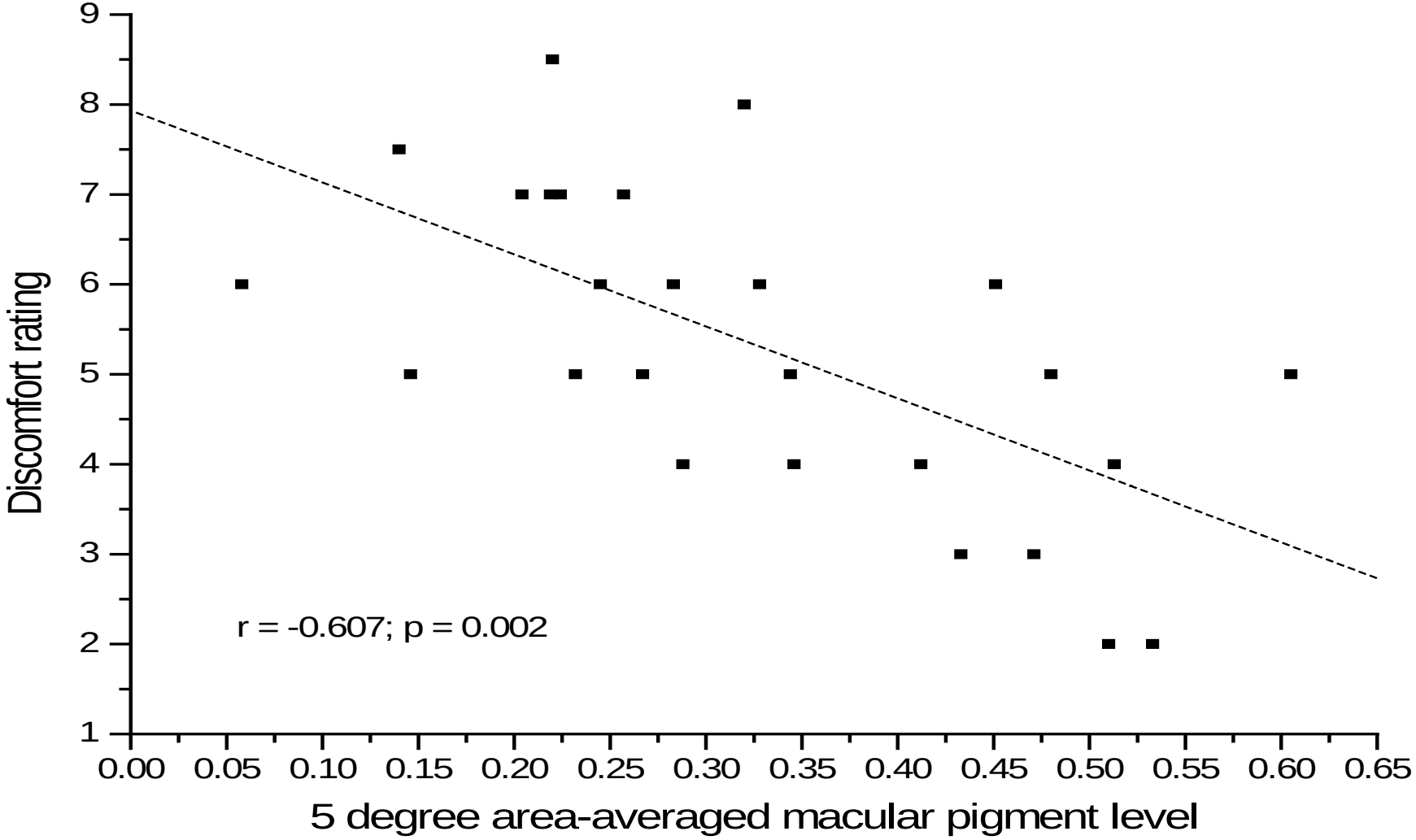
Photostress Recovery



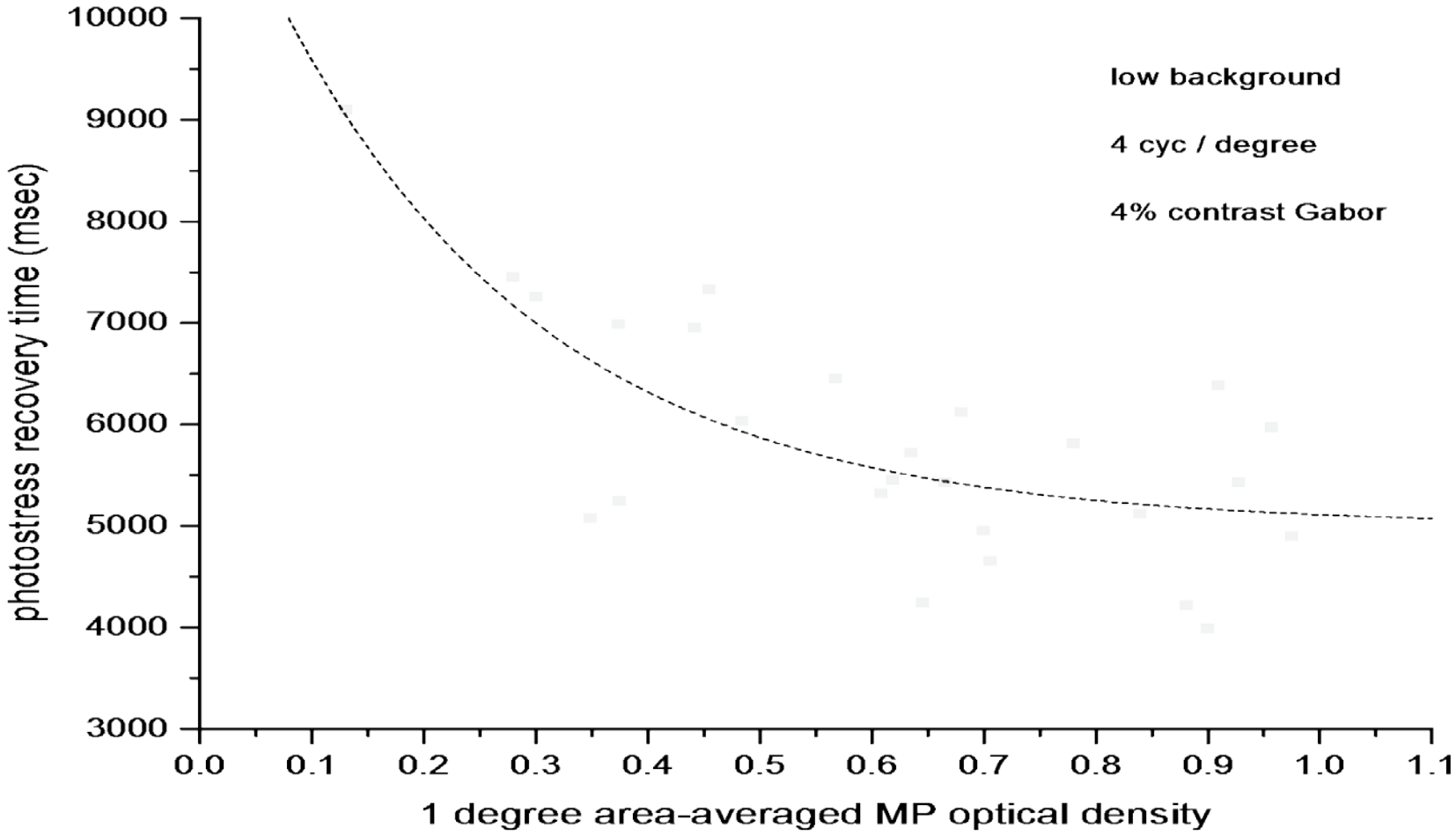
Disability Glare Thresholds and 1^0 area-averaged MPOD



Visual Discomfort Ratings and Central 5º Area-averaged MPOD



Photostress Recovery and MPOD Fit with Decreasing Exponential Function



****MPOD benefit for photostess recovery appears to asymptote**

MP and Visual Performance

Results:

- Higher MP values resulted in:
  - Faster photostress recovery times
  - Lower disability glare contrast thresholds
  - Lower visual discomfort

Conclusions:

- Higher MPOD is associated with improved visual performance in the presence of glare
- The study was performed under natural viewing conditions allowing results to have a greater extension into practical visual performance

Macular Pigment Spatial Distribution Effects on Glare Disability

Journal of Optometry (Feb 2015)

Journal of Optometry (2015) 8, 258–265

Journal of Optometry
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ORIGINAL ARTICLE

Macular pigment spatial distribution effects on glare disability

Christopher M. Putnam*, Carl J. Bassi

University of Missouri, St Louis College of Optometry, United States

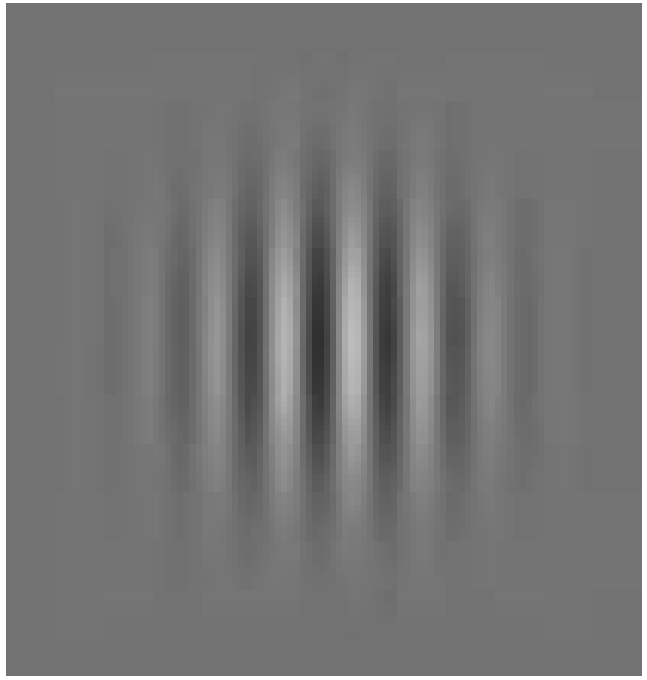
Received 15 October 2014; accepted 7 December 2014
Available online 16 February 2015

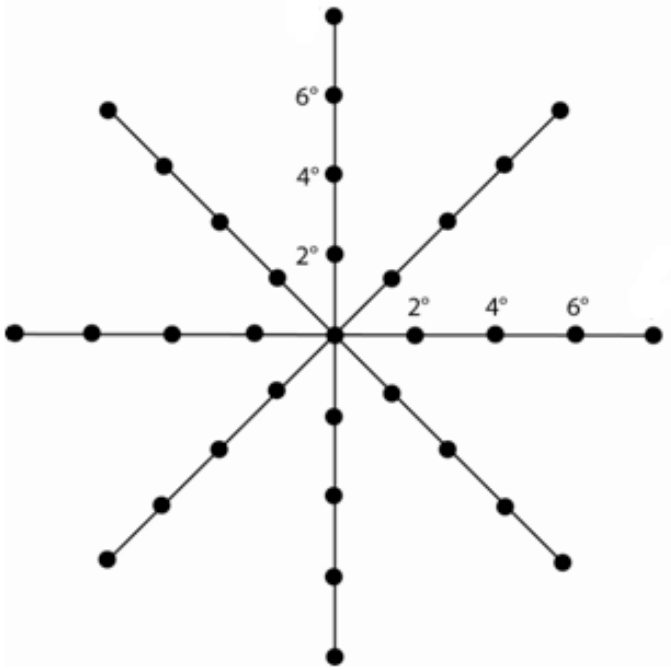
KEYWORDS
Macular pigment optical density;
Spatial distribution;
Glare disability

Abstract
Purpose: This project explored the relationship of the macular pigment optical density (MPOD) spatial profile with measures of glare disability (GD) across the macula.
Methods: A novel device was used to measure MPOD across the central 16° of retina along four radii using customized heterochromatic flicker photometry (cHFP)at eccentricities of 0°, 2°, 4°, 6° and 8°. MPOD was measured as discrete and integrated values at all measured retinal loci. GD was calculated as a difference in contrast sensitivity (CS) between no glare and glare conditions using identical stimuli presented at the same eccentricities. GD was defined as [(CSNo Glare – CSGlare)/CSNo Glare] in order to isolate the glare attenuation effects of MPOD by controlling for CS variability among the subject sample. Correlations of the discrete and integrated MPOD with GD were compared.
Results: The cHFP identified reliable MPOD spatial distribution maps demonstrating a 1st-order exponential decay as a function of increasing eccentricity. There was a significant negative correlation between both measures of foveal MPOD and GD using 6 cycles per degree (cpd) and 9 cpd stimuli. Significant correlations were found between corresponding parafoveal MPOD measures and GD at 2 and 4° of eccentricity using 9 cpd stimuli with greater MPOD associated with less glare disability.
Conclusions: These results are consistent with the glare attenuation effects of MP at higher spatial frequencies and support the hypothesis that discrete and integrated measures of MPOD have similar correlations with glare attenuation effects across the macula. Additionally, peak foveal MPOD appears to influence GD across the macula.

* Corresponding author at: 51MDG/SGPE, Osan AB 96266, Republic of Korea.
E-mail address: christopher.putnam@us.af.mil (C.M. Putnam).

http://dx.doi.org/10.1016/j.optom.2014.12.004
1888-4296/





Methods

Modulated sine grating patterns with spatial Gaussian envelope generated using Psykinematics (Kybervision, Montreal, Canada)

Target stimuli presented on a 19” CRT monitor with resolution set at 1600X1200 pixels

Non-linearities of luminance output were compensated for using gamma correction with a Spyder3 photometer (Datacolor, Lawrenceville, NJ)

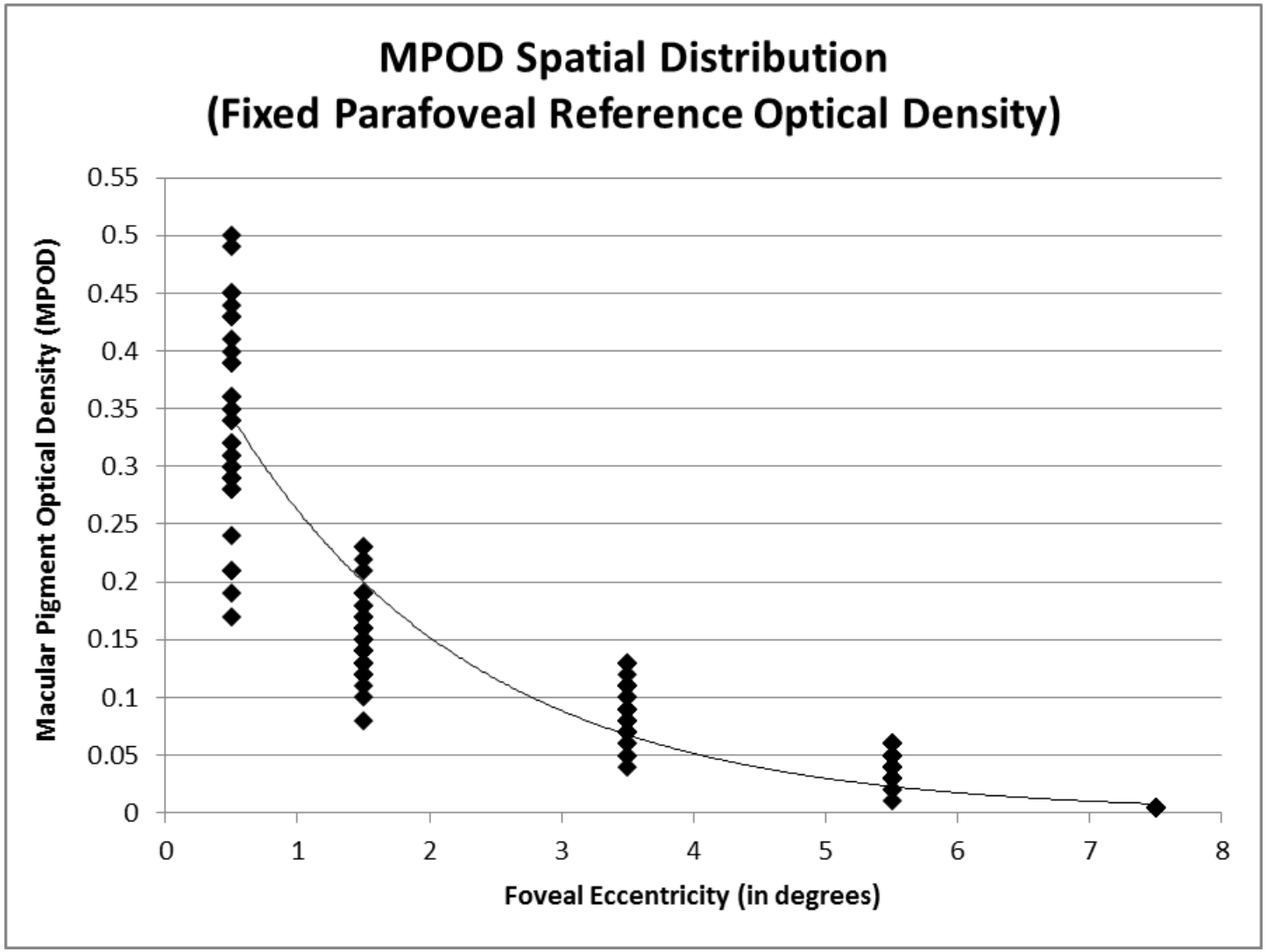


Figure 4
Best fitting 1st-order exponential decay function demonstrated by MPOD spatial distribution assuming a fixed, negligible parfoveal reference MPOD. The resulting exponential fit equation was $y = 0.451e^{-0.543x}$ with a covariance value of $r_2 = 0.912$.

Glare Disability Correlations with Foveal MPOD						
	Discrete Point			**1º Integrated Stimulus Area**		
	3cpd	*6cpd*	*9cpd*	*3cpd*	*6cpd*	*9cpd*
0º	-0.205	-0.401*	-0.491**	-0.206	-0.418*	-0.505**
2º	-0.235	-0.316*	-0.442**	-0.240	-0.315*	-0.421*
4º	-0.261	-0.291	-0.372*	-0.264	-0.284	-0.373*
6º	-0.283	-0.189	-0.168	-0.277	-0.173	-0.162

Table 2

Pearson correlation coefficients for glare disability and foveal MPOD measured as a discrete point and a 1◦ integrated stimulus area centered at 0^0, 2^0, 4^0, and 6◦ of eccentricity for 3, 6 and 9cpd grating targets.
(* $p \leq 0.05$ and **$p \leq 0.01$)

Macular Pigment Spatial Distribution Effects on Glare Disability

Results:

- Significant negative correlations between both foveal MPOD and glare disability using 6cpd and 9cpd stimuli
- Significant correlations were found between corresponding parafoveal MPOD measures and glare disability at 2^0 and 4^0 eccentricities using 9 cpd stimuli with greater MPOD associated with less glare disability

Conclusions:

- Glare attenuation effects of MP more pronounced at higher spatial frequencies
- Discrete and integrated measures of MPOD have similar glare attenuation effects across the macula.
- Peak foveal MPOD appears to be related to glare disability across the macula.

Foveal MPOD Predicts Parafoveal Glare Disability

Results:

Significant correlations between foveal MPOD and glare disability were found at 2^0 ($r=-0.49$, $p=0.03$) and 4^0 ($r=-0.41$, $p=0.05$) eccentricity using 9cpd stimuli

Near significant correlations between foveal MPOD and glare disability at 2^0 ($r=-0.58$, $p=0.07$) and 4^0 ($r=-0.42$, $p=0.09$) eccentricity using 6cpd stimuli and at 2^0 ($r=-0.33$, $p=0.08$) using 3cpd stimuli

Conclusions:

Higher levels of foveal MPOD correlated with decreased glare disability at 0^0, 2^0 and 4^0 eccentricity

Can Supplementation Improve Contrast Sensitivity?

Subjects (n=53) consumed daily a formulation containing 10mg lutein, 2mg zeaxanthin and 10mg meso-zeaxanthin or placebo for 12 months

Study visits were at baseline, 3, 6, and 12 months.

Primary outcome measure was contrast sensitivity at 6cpd

Secondary outcome measures included CS at other spatial frequencies, best-corrected visual acuity, glare disability, photostress recovery and light scatter.

MPOD was measured using dual-wavelength autofluorescence and serum carotenoid concentrations were analyzed using high performance liquid chromatography (HPLC).

Enrichment of Macular Pigment Enhances Contrast Sensitivity in Subjects Free of Retinal Disease: Central Retinal Enrichment Supplementation Trials – Report 1

Invest. Ophthalmol. Vis. Sci.. 2016;57(7):3429-3439. doi:10.1167/iovs.16-19520

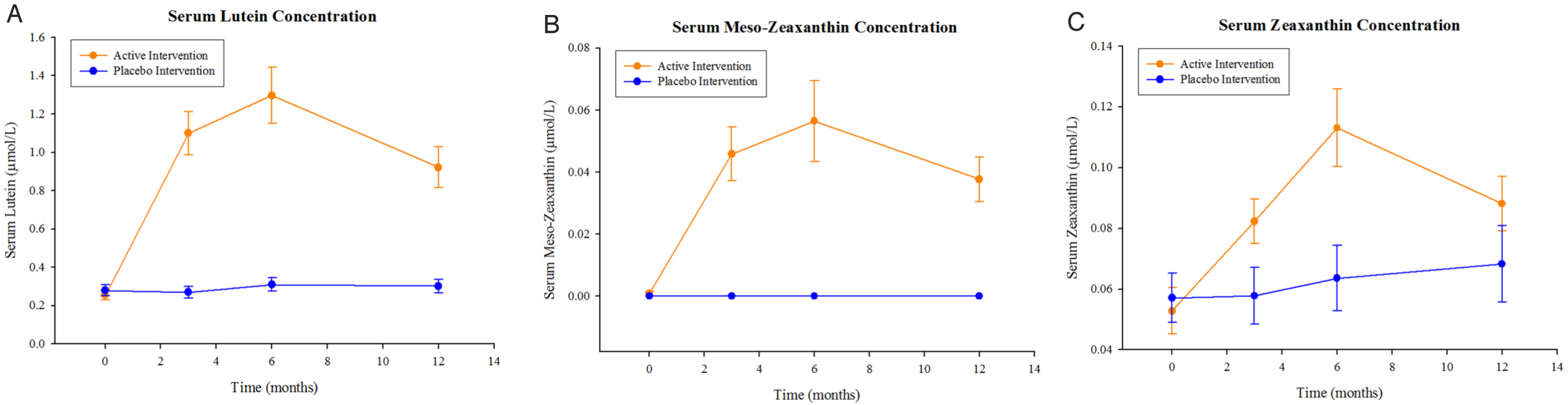


Figure Legend:

A) Serum L response for the active and placebo groups over the study period.
B) Serum MZ response for the active and placebo groups over the study period.
C) Serum Z response for the active and placebo groups over the study period.

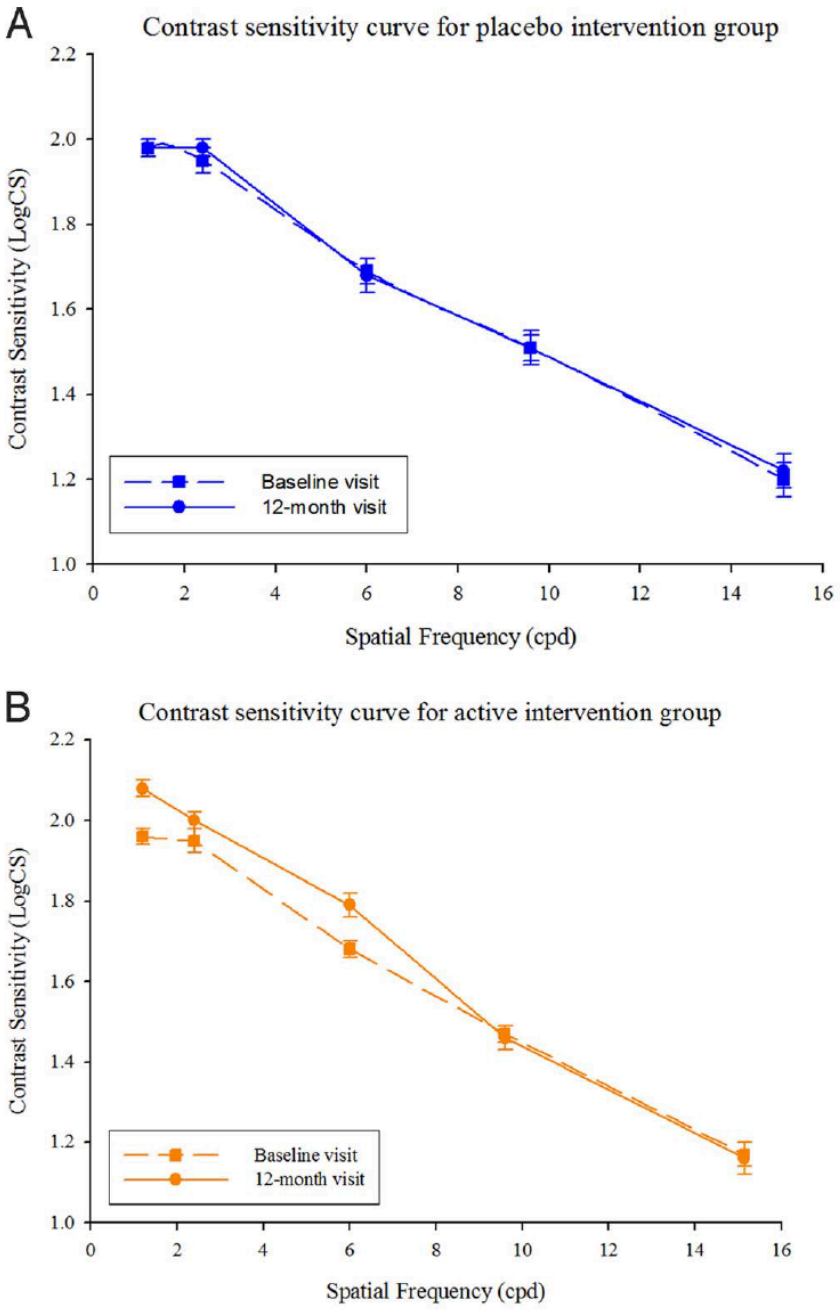


FIGURE 3. (A) Letter CS function for placebo intervention group. (B) Letter CS function for active intervention group.

Statistically significant improvements from baseline CS were detected at 6cpd ($p = 0.002$) and 1.2cpd ($p = 0.004$) in the treatment group.

Additionally, improvements in CS were commensurate with the observed increases in retinal concentrations of these carotenoids ($r = 0.342$, $p = 0.002$ at 6cpd).

Can Supplementation Improve Glare Disability?

A double-blind, placebo-controlled trial included 59 healthy volunteers (mean age = 21.7)

Subjects supplemented their daily diet for 12 months with:

A. 10mg L + 2mg total Z (1mg Z + 1mg MZ; n=24)

B. 20mg L + 4mg total Z (2mg Z + 2mg MZ; n=25)

C. placebo (n=10)

MPOD was assessed with customized heterochromatic flicker photometry.

PSR times for an 8 cycle /degree, 15 % contrast Gabor patch target were determined after each of five successive exposures to intense LED lights.

DG threshold was defined as the intensity of a ring of lights through which subjects were able to maintain visibility of the target.

Measures of all parameters were conducted at baseline, 6 months and 12 months

Macular carotenoid supplementation improves disability glare performance and dynamics of photostress recovery
***Eye and Vision*. 2016;*3*(1):30.**

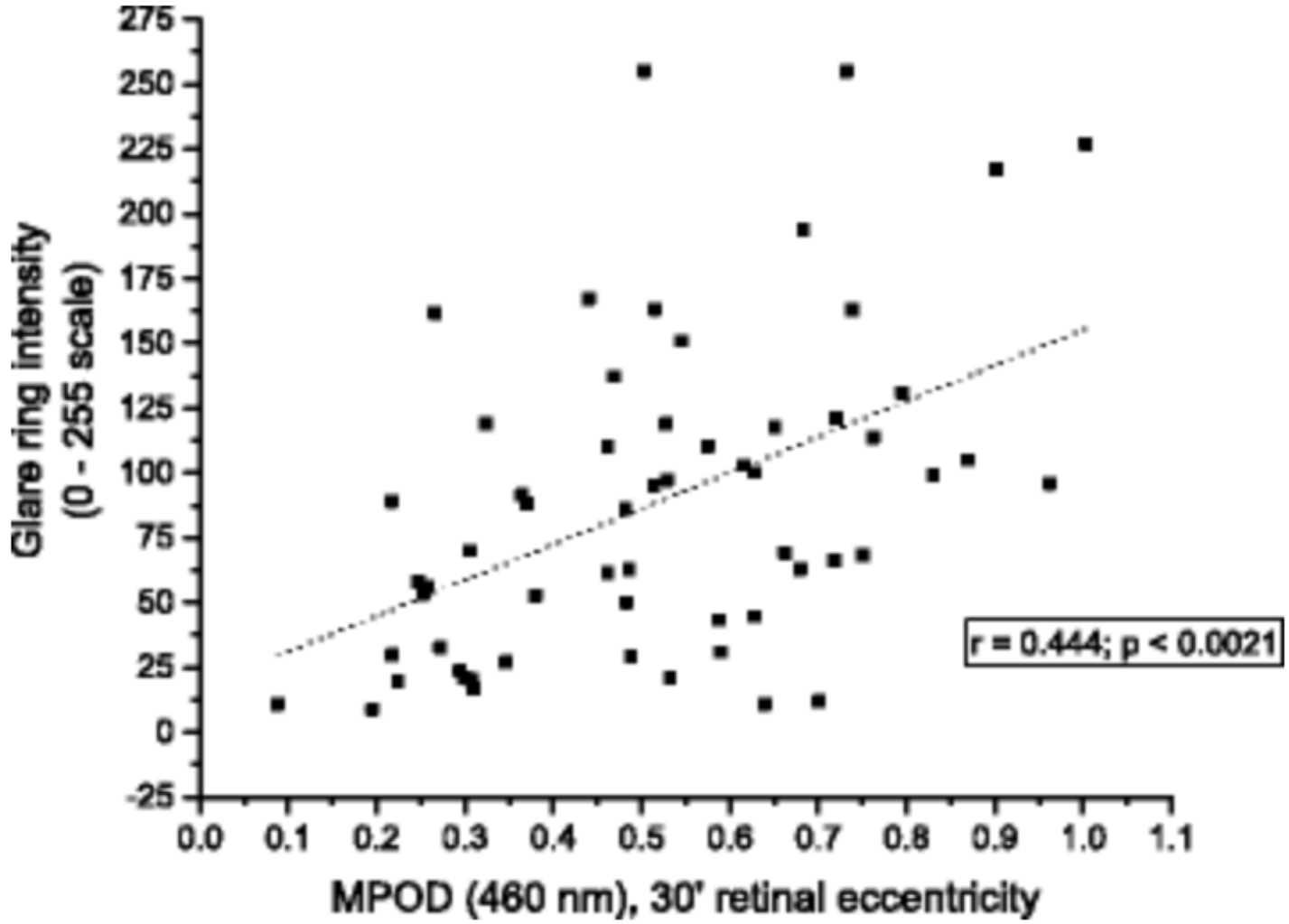


Fig. 2

Glare ring intensity setting as a function of MPOD, at baseline

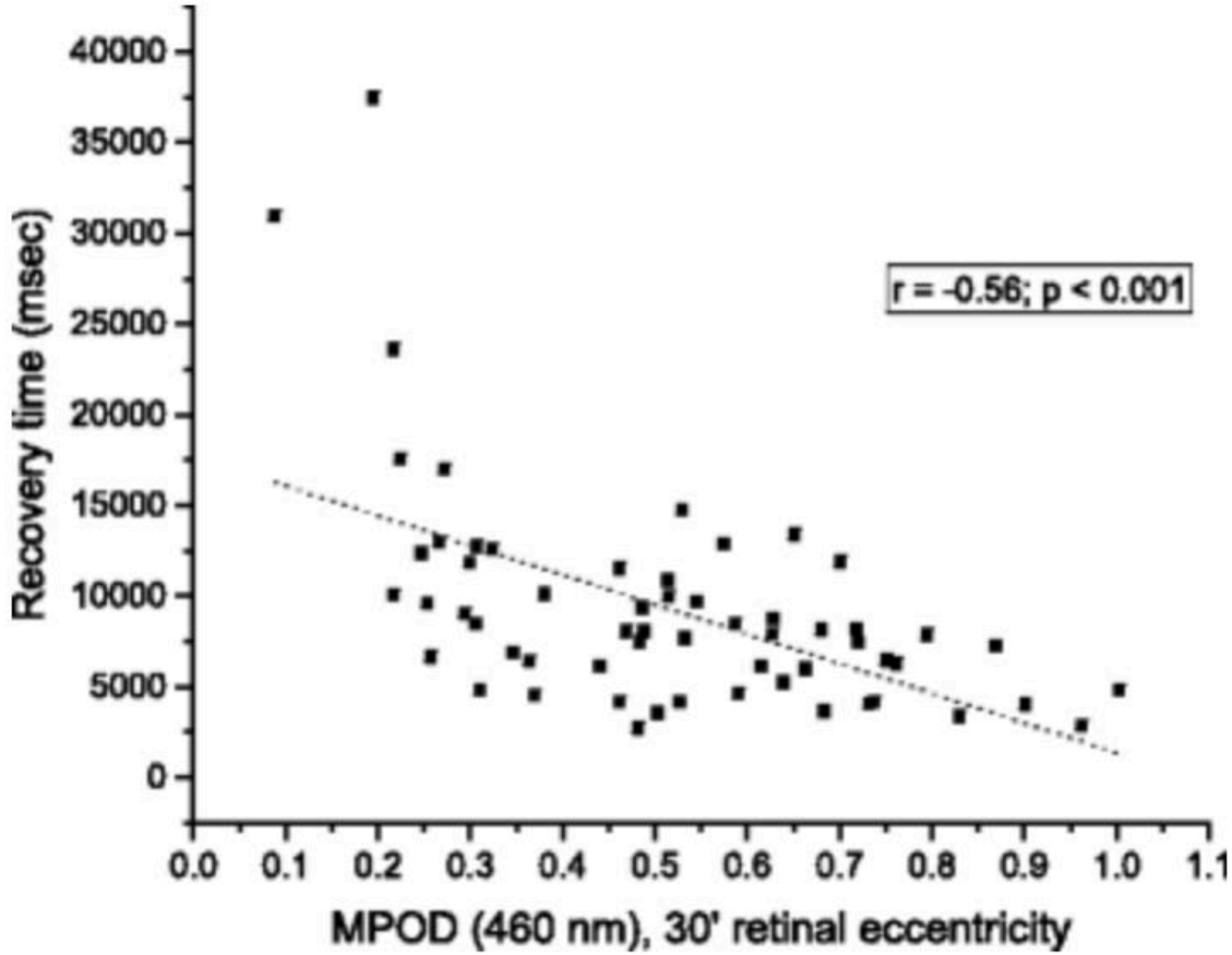


Fig. 3

PSR time as a function of MPOD, at baseline

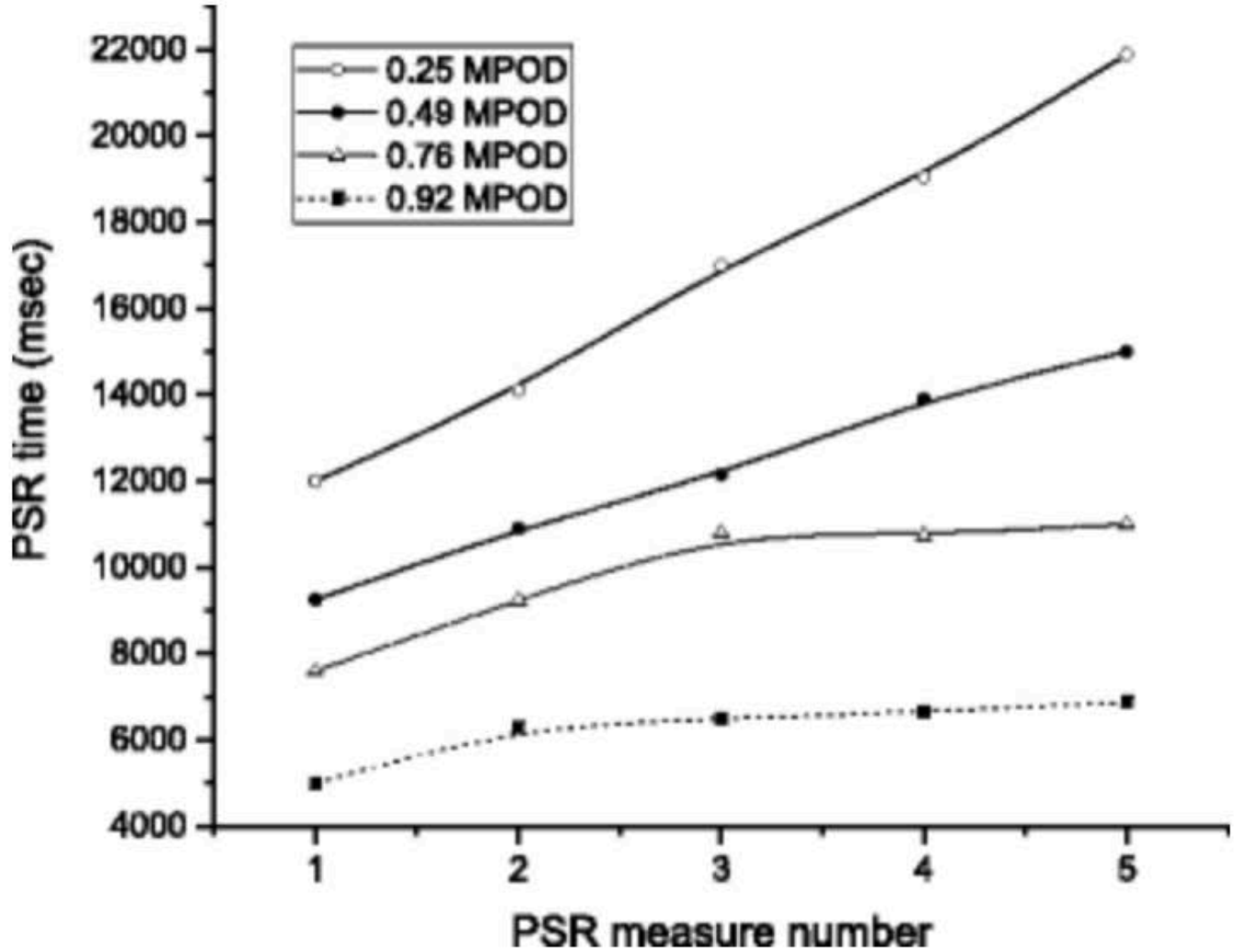


Fig. 5

PSR “fatigue functions” at baseline for four subjects with different MPOD.

Results:

At baseline, MPOD was significantly related to both DG thresholds ($r = 0.444$; $p = 0.0021$) and PSR times ($r = -0.56$; $p < 0.001$)

MPOD in both supplementation groups increased significantly versus placebo at both 6 and 12 month visits ($p < 0.001$ for all).

PSR times and DGthresholds improved significantly from baseline compared to placebo at 6 and 12 month visits ($p < 0.001$ for all)

As a function of MPOD, the repeated-exposure PSR curves became more asymptotic as opposed to linear.

Conclusions:

Increases in MPOD lead to significant improvements in PSR times and DG thresholds. The asymptotic shape of the repeated-exposure PSR curves suggests that increases in MPOD produce more consistent steady-state visual performance in bright light conditions. The mechanism for this effect may involve both the optical filtering and biochemical (antioxidant) properties of MP.

3. Intraocular Scatter and MPOD

I. Putnam, Christopher M., Pauline J. Bland, and Carl J. Bassi. "Influence of macular pigment optical density spatial distribution on intraocular scatter." *Journal of Optometry* (2015).

II. Beirne, Raymond O. "Macular pigment levels do not influence C-Quant retinal straylight estimates in young Caucasians." *Clinical and Experimental Optometry* 97.2 (2014): 171-174.

MPOD Spatial Distribution Influences on Higher-Order RMS Wavefront Error and Intraocular Scatter

Results:

Spatial mapping of MPOD was best-fit to a Lorentzian function

Discrete and integrated foveal MPOD was calculated

Inverse relationships between foveal MPOD and 3rd-4th order Zernike polynomials ($r=-0.35$, $p=0.11$) and forward intraocular scatter ($r=-0.39$, $p=0.07$) were demonstrated

Conclusions:

An inverse relationship may exist between MPOD and both HO RMS values and intraocular straylight

Influence of MPOD Spatial Distribution on Intraocular Scatter

Journal of Optometry (Nov 2015)

Journal of Optometry (2017) 10, 63–68

ELSEVIER

Journal of Optometry

www.journalofoptometry.org

ORIGINAL ARTICLE

Influence of macular pigment optical density spatial distribution on intraocular scatter

Christopher M. Putnam*, Pauline J. Bland, Carl J. Bassi

University of Missouri-St Louis, College of Optometry, United States

Received 5 July 2015; accepted 22 September 2015
Available online 24 November 2015

KEYWORDS
Macular pigment optical density;
Spatial distribution;
Intraocular scatter

Abstract
Purpose: This study evaluated the summed measures of macular pigment optical density (MPOD) spatial distribution and their effects on intraocular scatter using a commercially available device (C-Quant, Oculus, USA).
Methods: A customized heterochromatic flicker photometer (cHFP) device was used to measure MPOD spatial distribution across the central 16° using a 1° stimulus. MPOD was calculated as a discrete measure and summed measures across the central 1°, 3.3°, 10° and 16° diameters. Intraocular scatter was determined as a mean of 5 trials in which reliability and repeatability measures were met using the C-Quant. MPOD spatial distribution maps were constructed and the effects of both discrete and summed values on intraocular scatter were examined.
Results: Spatial mapping identified mean values for discrete MPOD [0.32 (s.d. = 0.08)], MPOD summed across central 1° [0.37 (s.d. = 0.11)], MPOD summed across central 3.3° [0.85 (s.d. = 0.20)], MPOD summed across central 10° [1.60 (s.d. = 0.35)] and MPOD summed across central 16° [1.78 (s.d. = 0.39)]. Mean intraocular scatter was 0.83 (s.d. = 0.16) log units. While there were consistent trends for an inverse relationship between MPOD and scatter, these relationships were not statistically significant. Correlations between the highest and lowest quartiles of MPOD within the central 1° were near significance.
Conclusions: While there was an overall trend of decreased intraocular forward scatter with increased MPOD consistent with selective short wavelength visible light attenuation, neither discrete nor summed values of MPOD significantly influence intraocular scatter as measured by the C-Quant device.

* Corresponding author at: UMSL College of Optometry, 417 Marillac Hall, 1 University Blvd, St Louis, MO 63121-4400, United States.
E-mail address: cmpyv6@umsl.edu (C.M. Putnam).

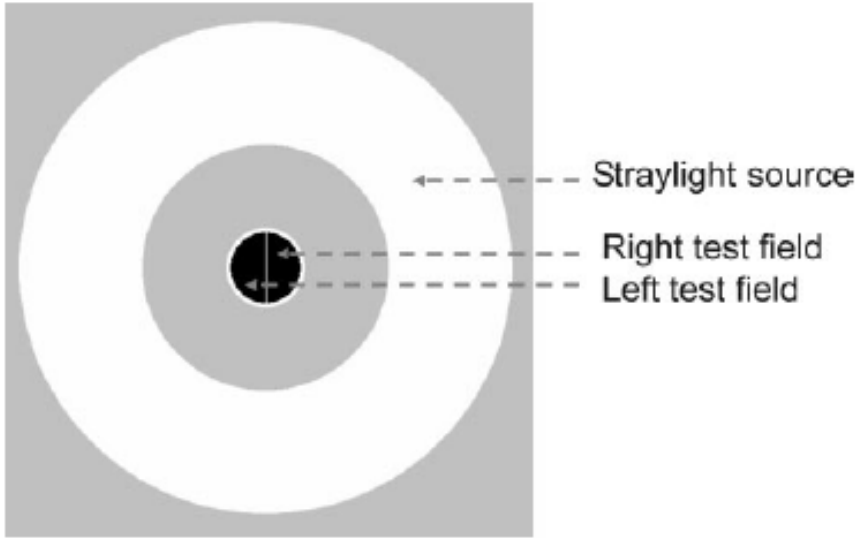
http://dx.doi.org/10.1016/j.optom.2015.10.001
1888-4296/

Methods

Subjects (n=33) with a mean age of 24.2 years (sd=2.7) underwent spatial MPOD testing using a cHFP technique. MPOD measurements were calculated for the following using OriginPro9 software:

1) Discrete foveal
2) across the central 1° diameter,
3) Across central 3.3° diameter
4) Across central 10° diameter
5) Across central 16° diameter of using

A mean intraocular scatter value was determined using the first 5 valid, repeatable measures as determined by the Oculus C-Quant.



Mean intraocular scatter was correlated with the five separate measures of MPOD corresponding to:

1) Stimulus area
2) Target area
3) Glare source area
4) MPOD across entire macula.

	Foveal MPOD Discrete Point	Integrated MPOD Across 1°	Integrated MPOD Across 3.3°	Integrated MPOD Across 10°	Integrated MPOD Across 16°
Mean	0.32	0.37	0.85	1.60	1.78
Std Dev	0.08	0.11	0.20	0.35	0.39

Table 1

Mean MPOD values for foveal MPOD measured as a discrete value, MPOD integrated across central 1°, MPOD integrated across central 3.3°, MPOD integrated across central10° and MPOD integrated across central 16°.

		Foveal MPOD Discrete Point	Integrated MPOD Across 1°	Integrated MPOD Across 3.3°	Integrated MPOD Across 10°	Integrated MPOD across 16°
Intraocular Scatter	Pearson Correlation	-0.311	-0.305	-0.296	-0.260	-0.261
	Sig. (2-tailed)	0.078	0.084	0.095	0.145	0.142

Table 2

Correlation coefficients for intraocular scatter thresholds and foveal MPOD measured as a discrete value, MPOD integrated across central 1°, MPOD integrated across central 3.3°, MPOD integrated across central 10° and MPOD integrated across central 16°.

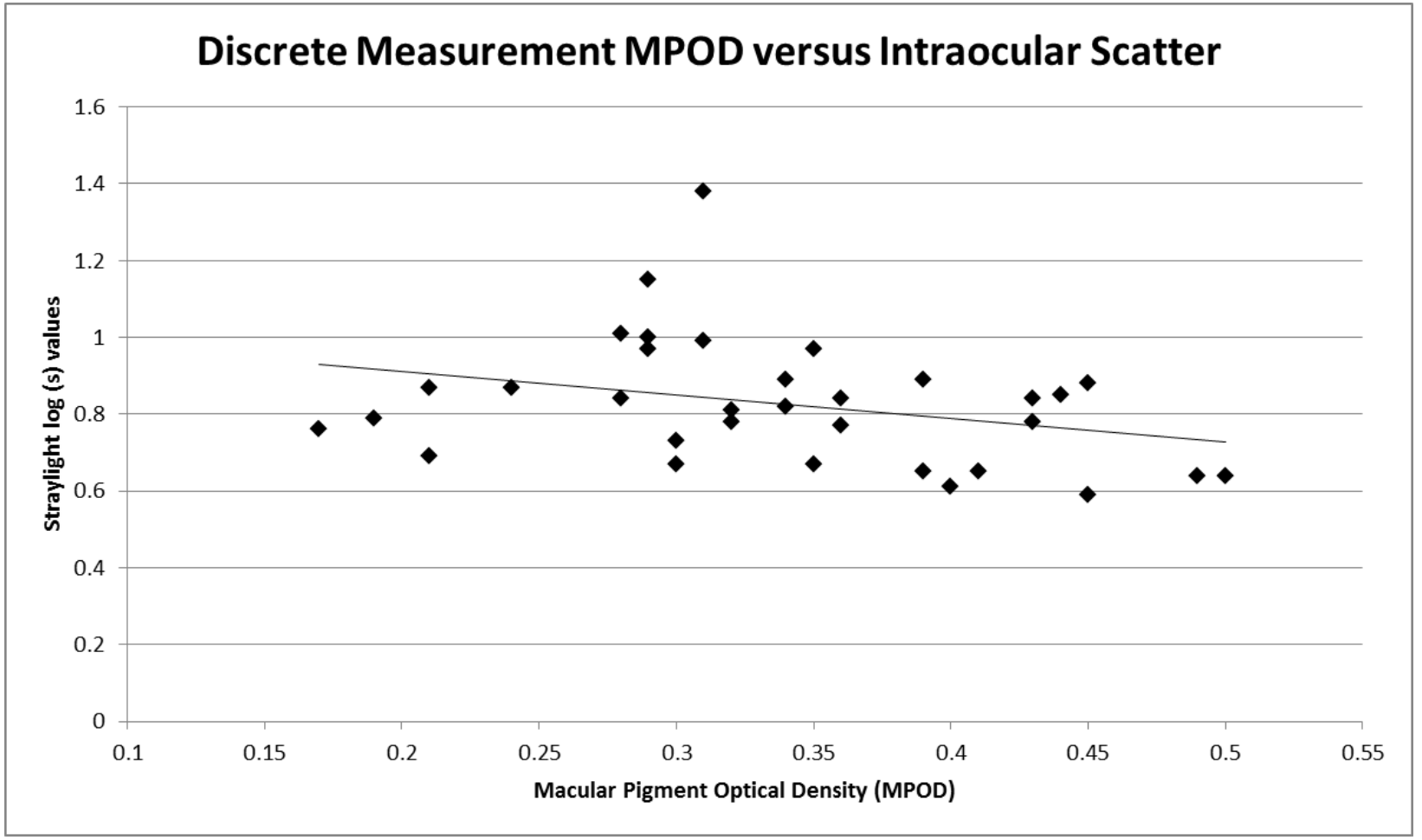


Figure 3

Scatterplot of discrete measurement MPOD versus intraocular scatter. The resulting linear regression fit equation was $y = -0.612x + 1.035$ with a covariance value of $r^2 = 0.097$.

Influence of MPOD Spatial Distribution on Intraocular Scatter

Results:

- An inverse relationship between MPOD and forward intraocular scatter demonstrated non-statistically significant relationships.

- Correlations between the highest and lowest quartiles of MPOD within the central 1◦ were near significance.

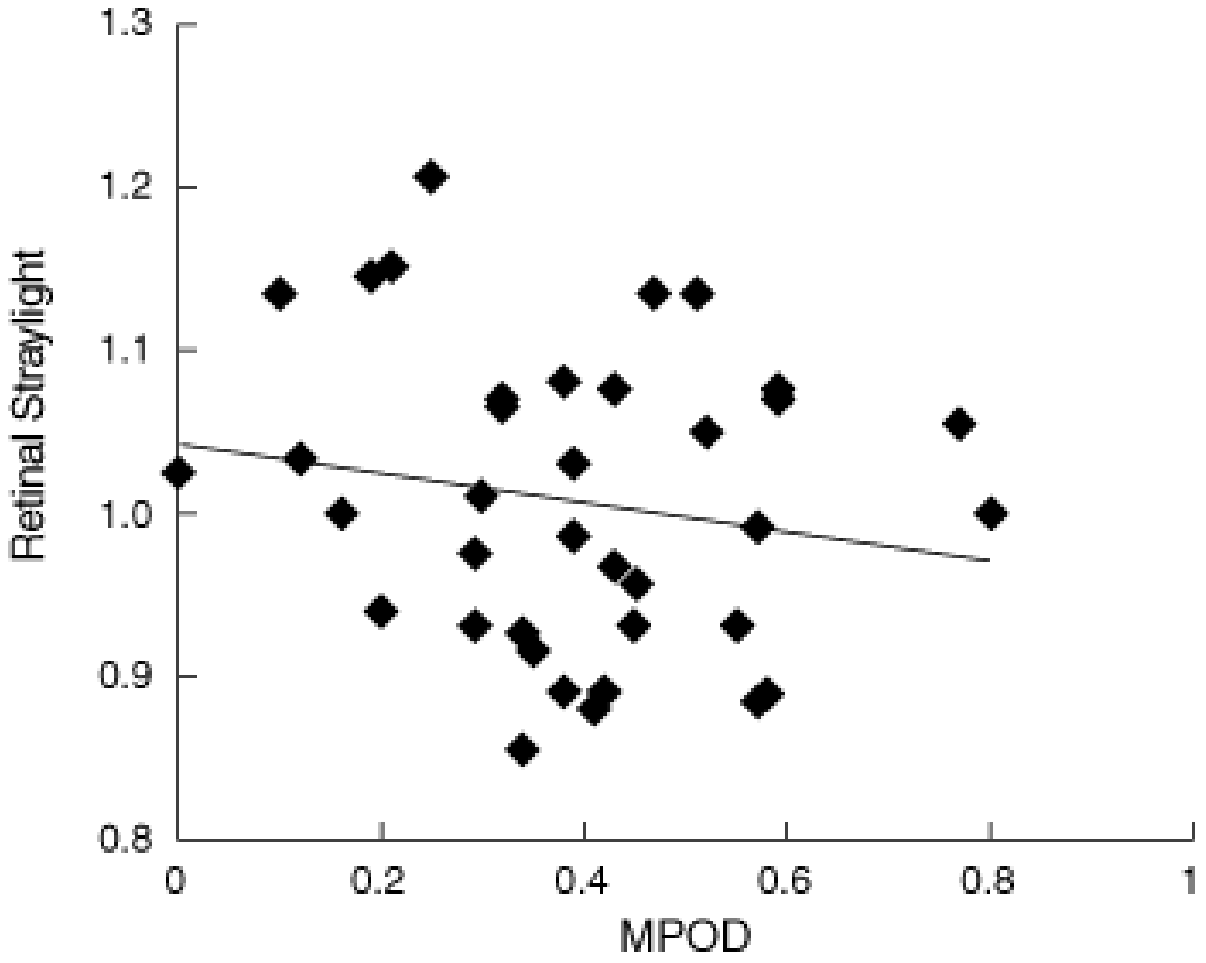
Conclusions:

- Overall trend of decreased intraocular forward scatter with increased MPOD consistent with selective short wavelength visible light attenuation.

- However, neither discrete nor summed values of MPOD significantly influence intraocular scatter as measured by the C-Quant device.

Macular pigment levels do not influence C-Quant retinal straylight estimates in young Caucasians (n=37)

-Beirne and Raymond (2014)



r=-0.17, p=0.30

Clinical and Experimental Optometry
http://onlinelibrary.wiley.com/doi/10.1111/cxo.12107/full#cxo12107-fig-0003

4. Eye Disease

I. Hogg RE, Woodside JV, McGrath A, Young IS, Vioque JL, Chakravarthy U, Tomazzoli L. Mediterranean Diet Score and Its Association with Age-Related Macular Degeneration: The European Eye Study. *Ophthalmology*. 2017;*124*(1):82-89.

II. Akuffo KO, Nolan JM, Peto T, Stack J, Leung I, Corcoran L, Beatty S. Relationship between macular pigment and visual function in subjects with early age-related macular degeneration. *British Journal of Ophthalmology*. 2016

III. Putnam CM, Kinerk WT, Bassi CJ. Central serous chorioretinopathy produces macular pigment profile changes. *Optometry & Vision Science*. 2013;*90*(7):e206-e212.

IV. Putnam CM, Bland PJ. Macular pigment optical density spatial distribution measured in a subject with oculocutaneous albinism. *Journal of optometry*. 2014;*7*(4):241-245.

Central Serous Chorioretinopathy Produces Macular Pigment Profile Changes

Optometry and Vision Science (Jul 2013)

1040-5488/13/9007-e206/0 VOL. 90, NO. 7, PP. e206–e212
OPTOMETRY AND VISION SCIENCE

CLINICAL CASE

Central Serous Chorioretinopathy Produces Macular Pigment Profile Changes

Christopher M. Putnam*, Wesley T. Kinerk†, and Carl J. Bassi‡

ABSTRACT

Purpose. Macular pigment (MP) is the collective name for three isomeric carotenoids: lutein, zeaxanthin, and meso-zeaxanthin. Macular pigment density is greatest in the central retina, peaking at the fovea and falling to negligible levels at 7 degrees of eccentricity from the fovea. Several studies have documented the interocular symmetry of MP optical density (MPOD) spatial distribution. The ongoing University of Missouri–St. Louis study uses a novel, customized heterochromatic flicker photometer to map the spatial distribution of MPOD up to 8 degrees of eccentricity relative to the fovea. Here, we report the MPOD measurements in a subject with resolved central serous chorioretinopathy (CSC) in the right eye.

Case Report. Two subjects performed the full MPOD spatial mapping. The test subject (WK) had a history of central serous CSC of the right eye. The control subject (CP) had an unremarkable ocular health history. Comprehensive exams were performed on each subject including Cirrus optical coherence tomography imaging and fundus photographs. Subject CP showed highly symmetric interocular MPOD profiles at the fovea and 2, 4, and 6 degrees of eccentricity. Subject WK showed interocular asymmetry at the fovea and at 2 degrees with relative symmetry at 4 and 6 degrees. A paired sample *t* test identified nonsignificant interocular values for subject CP and statistically significant differences of at 2 degrees for subject WK.

Conclusions. We hypothesize that subject WK's interocular MPOD spatial distribution asymmetry resulted from his history of resolved CSC. This asymmetry is statistically significant at 2 degrees of retinal eccentricity and corresponds to the extent of retinal pigment epithelium changes observed on the fundus photographs. These findings suggest that MP and retinal pigment epithelium changes after a CSC episode are comparable in the area of the retina affected. These disruptions may also be measureable in other macular conditions in which the sensory retina is affected (e.g., cystoid macular edema and clinically significant macular edema).

(Optom Vis Sci 2013;90:e206–e212)

Key Words: macular pigment, heterochromatic flicker photometry, macular pigment optical density, macular pigment spatial profile, central serous chorioretinopathy

Macular pigment (MP) is the collective name for three isomeric carotenoids: lutein, zeaxanthin, and meso-zeaxanthin. They are found in the greatest concentration within the photoreceptor axons (Henle fiber layer in macular region) and the inner plexiform layer.[1] Macular pigment density is greatest in the central retina, peaking at the fovea and falling to negligible levels at 7 degrees of eccentricity from the fovea.[2] Several studies have documented the interocular symmetry of MPOD spatial distribution using objective and subjective methods,[3] and biochemical methods.[4] The ongoing University of Missouri–St. Louis (UMSL) study is designed to assess the distribution of MP within and between eyes and its relationship to visual function.

The UMSL MP spatial distribution study is designed to evaluate the validity and reliability of a novel, customized heterochromatic flicker photometry (cHFP) device for the purpose of mapping the spatial distribution of MP optical density (MPOD) up to 8 degrees eccentricity relative to the fovea. The technique of cHFP has been used by several researchers currently studying MPOD and its relationship to visual function.[5–7]

The device used in the UMSL study is designed to create a spatial map of MPOD along eight meridians (0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315°) at 0-, 2-, 4-, 6-, and 8-degree foveal eccentricities using a 1-degree target of flickering, counterphased blue (460 nm) and green (564 nm) light matching the patient's critical flicker fusion threshold. The subject adjusts the luminance of the target until the absence of flicker (i.e., null point)

*OD, FAAO
†OD
‡PhD
University of Missouri–St. Louis College of Optometry, St. Louis, Missouri.

MPOD Spatial Distribution Measured in a subject with Oculocutaneous Albinism

Journal of Optometry (Jul 2014)

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OPTOM-100; No. of Pages 5 ARTICLE IN PRESS

Journal of Optometry (2014) xxx, xxx–xxx

Journal of Optometry

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CASE REPORT

Macular pigment optical density spatial distribution measured in a subject with oculocutaneous albinism

Christopher M. Putnam*, Pauline J. Bland

University of Missouri-St Louis College of Optometry, St. Louis, MO, United States

Received 10 February 2014; accepted 7 March 2014

KEYWORDS
Macular pigment optical density;
Oculocutaneous albinism;
Spatial distribution

Abstract
Purpose: Previous studies of macular pigment optical density (MPOD) distribution in individuals with oculocutaneous albinism (OCA) have primarily used objective measurement techniques including fundus reflectometry and autofluorescence. We report here on a subject with OCA and their corresponding MPOD distribution assessed through heterochromatic flicker photometry (HFP).
Methods: A subject with a history of OCA presented with an ocular history including strabismus surgery of the LE with persistent amblyopia and mild, latent nystagmus. Best corrected visual acuity was 20/25- RE and 20/40- LE. Spectral domain optical coherence tomography (SD-OCT) and fundus photography were also obtained. Evaluation of MPOD spatial distribution up to 8 degrees eccentricity from the fovea was performed using HFP.
Results: SD-OCT indicated a persistence of multiple inner retinal layers within the foveal region in the RE and LE including symmetric foveal thickening consistent with foveal hypoplasia. Fundus photography showed mild retinal pigmented epithelial (RPE) hypopigmentation and a poorly demarcated macula. OriginPro 9 was used to plot MPOD spatial distribution of the subject and a 33-subject sample. The OCA subject demonstrated a foveal MPOD of 0.10 with undetectable levels at 6 degrees eccentricity. The study sample showed a mean foveal MPOD of 0.34 and mean 6 degree eccentricity values of 0.03.
Conclusions: Consistent with previous macular pigment (MP) studies of OCA, overall MPOD is reduced in our subject. Mild phenotypic expression of OCA with high functional visual acuity may represent a Henle fiber layer amenable to additional MP deposition. Further study of MP supplementation in OCA patients is warranted.

* Corresponding author at: UMSL College of Optometry, 417 Marillac Hall, 1 University Blvd, St Louis, MO 63121-4400, United States.
E-mail address: cmpyv6@umsl.edu (C.M. Putnam).

http://dx.doi.org/10.1016/j.optom.2014.03.001
1888-4296/

Please cite this article in press as: Putnam CM, Bland PJ. Macular pigment optical density spatial distribution measured in a subject with oculocutaneous albinism. *J Optom.* (2014), http://dx.doi.org/10.1016/j.optom.2014.03.001

Hogg et al (2017)

Participants (n=4753) underwent a compehensive eye examination and digital retinal color photography.

Images were graded at a single center. Dietary intake during the previous 12 months was assessed by using a semi-quantitative food frequency questionnaire (FFQ).

Previously published Mediterranean Diet Score (MDS)was used to classify participants according to their responses on the FFQ.

Multivariable logistic regression was used to investigate the association of the MDS score and AMD, taking account of potential confounders and the multicenter study design.

Mediterranean Diet Scale

1. I eat at least 2 cups of vegetables every day.
2. I eat 2 or more pieces of fruit a day.
3. I eat 2 or more servings of whole grains a day.
4. I eat fish 2 or more times a week.
5. I eat beans or legumes 4 or more times a week.
6. I eat nuts or seeds almost every day.
7. I use olive oil as my main source of fat.
8. I drink a glass of red wine (but no more than 2) most days.
9. I eat red meat no more than once a week.

Scoring

If you scored 8 or 9, your diet is highly consistent with the ideal Mediterranean diet pattern.
If you scored 6-7, your diet has a lot in common with the ideal Mediterreanean diet pattern.
If you scored 4-5, your diet includes some elements of the ideal Mediterreanean diet pattern.
If you scored 0-3, your diet is not consistent with the ideal Mediterreanean diet pattern.

Table 2. Association of Mediterranean Diet Score and Neovascular Age-Related Macular Degeneration

	nvAMD	
	Unadjusted	*Adjusted**
MDS	OR (95% CI)	OR (95% CI)
≤4 (n = 808)	1 (reference)	1 (reference)
5 (n = 774)	0.88 (0.55–1.39)	0.83 (0.55–1.26)
6 (n = 536)	0.62 (0.33–1.16)	0.62 (0.39–1.00)
>6 (n = 201)	0.52 (0.29–0.93)	0.53 (0.27–1.04)
P trend	0.03	0.01

CI = confidence interval; MDS = Mediterranean Diet Score; nvAMD = neovascular age-related macular degeneration; OR = odds ratio.
*Adjusted for age, sex, country, education, smoking, drinking, self-reported history of cardiovascular disease, aspirin consumption, and diabetes.

MDS	All Early AMD (Grade 1–3)	
	Unadjusted	*Adjusted**
	OR (95% CI)	*OR (95% CI)*
≤4 (n = 1506)	1 (reference)	1 (reference)
5 (n = 1481)	0.99 (0.92–1.07)	1.01 (0.91–1.12)
6 (n = 1021)	0.98 (0.89–1.08)	1.01 (0.90–1.14)
>6 (n = 380)	0.94 (0.85–1.03)	0.96 (0.83–1.11)
P trend	0.4	0.9
	Large Drusen	
≤4 (n = 958)	1 (reference)	1 (reference)
5 (n = 936)	0.96 (0.83–1.11)	0.99 (0.80–1.21)
6 (n = 638)	0.89 (0.70–1.12)	0.90 (0.69–1.17)
≥6 (n = 238)	0.79 (0.65–0.97)	0.80 (0.65–0.98)
P trend	0.05	0.1

AMD = age-related macular degeneration; CI = confidence interval; MDS = Mediterranean Diet Score; OR = odds ratio.

*Adjusted for age, sex, country, education, smoking, drinking, self-reported history of cardiovascular disease, aspirin consumption, diabetes, and body mass index.

Macular Pigment
Associated AMD studies

Eye Disease Case Control Study
Age-Related Eye Disease Study I (AREDS I)
Age-Related Eye Disease Study II (AREDS II)

Eye Disease Case-Control Study

Design:

- 5 ophthalmology centers included:
  - 356 subjects (ages 55-80) with advanced AMD within 1-yr of enrollment
  - 520 control subjects
    - Frequency matched to cases of same age and sex

METHODS:

- Multiple Regression analysis controlled for smoking and other risk factors

RESULTS:

- Highest quintile dietary intake of carotenoids (specifically L and Z) showed 43% lower risk than lowest quintile in the development of advanced AMD
  - **Vit A, Vit C and Vit E showed no significant relationship to AMD development*

AREDS

- 5-year longitudinal, placebo-controlled study released in 2001

- 3640 subjects were divided into 4 groups:
  - 1) antioxidants+ zinc
  - 2) antioxidants ONLY
  - 3) zinc ONLY
  - 4) placebo

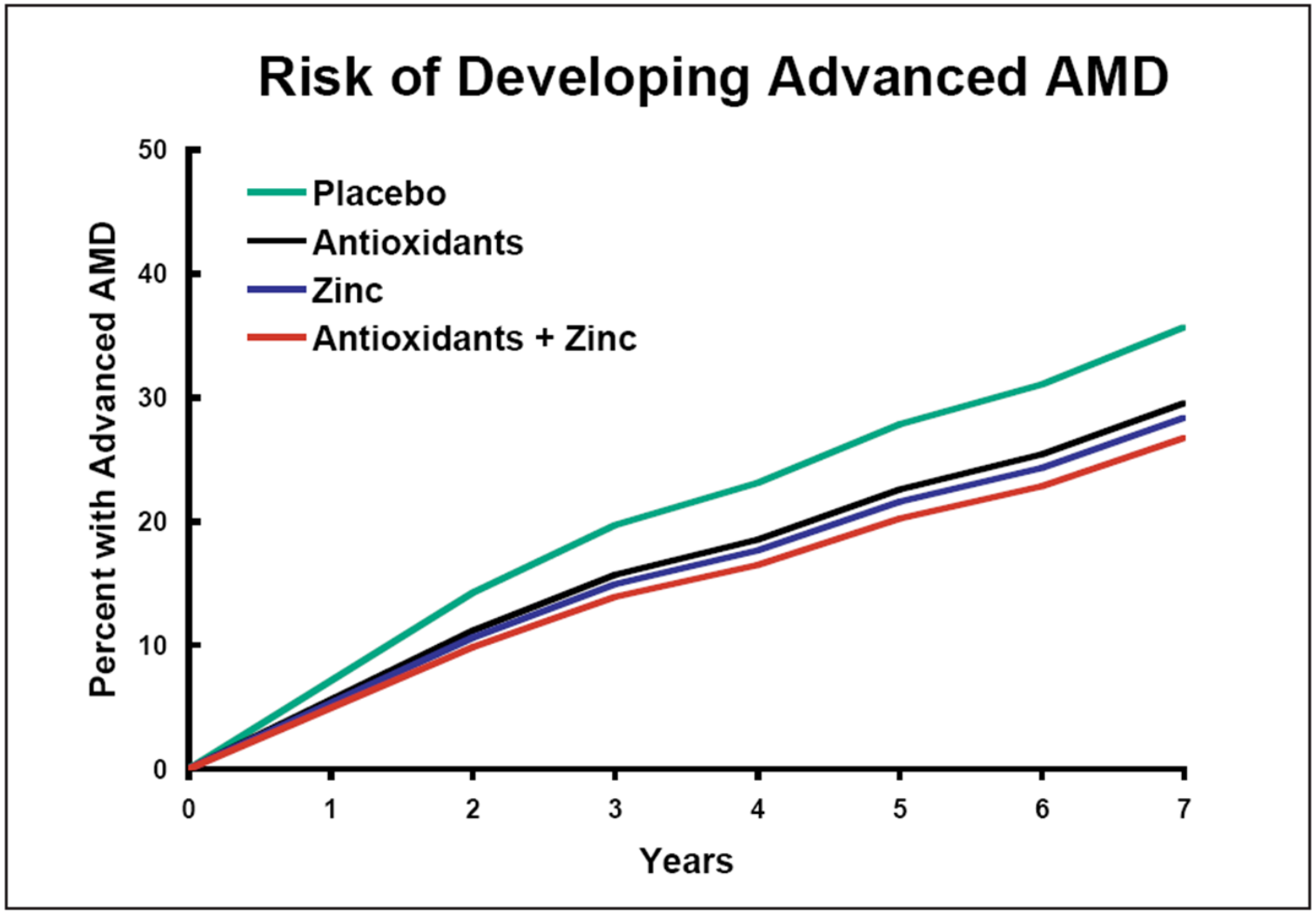
- **RESULTS:**

AREDS formulation reduced advanced AMD rate by 25% over a 5-year period
  - AREDS formulation DID NOT show prevention of early signs of AMD

- AREDS formula:
  - Vit A (15mg) / Vit C (500mg) / Vit E (400IU) / zinc (80mg) / copper (2mg)

12 year results still support antioxidant + zinc formulation

AREDS


Risk of Developing Advanced AMD
Placebo
Antioxidants
Zinc
Antioxidants + Zinc
Percent with Advanced AMD
50
40
30
20
10
0
0
1
2
3
4
5
6
7
Years

AREDS II

- 6 year longitudinal, placebo-controlled study released in May 2013

- 4203 men and women ages 50-85 were divided into 4 groups:
  - 1) 10mg L and 2mg Z + AREDS
  - 2) 350mg DHA and 650mg EPA + AREDS
  - 3) 10mg L and 2mg Z and 350mg DHA and 650mg EPA + AREDS
  - 4) control (AREDS formulation only) **No true placebo group**

- All participants were offered the
  - original AREDS formula (Standard of Care)
  - variation of the AREDS formulation (former smokers)

- In contrast to AREDS, AREDS II subjects were previously diagnosed with moderate to advanced ARM and/or AMD

AREDS II

L/Z plus AREDS formula:

- Reduced progression to advanced AMD 10% over AREDS formulation alone in total cohort
  - ✓*L/Z substitution for β-carotene resulted in a 18% risk reduction of advanced AMD within 5 years*
- Reduced progression to NV AMD by 11% of AREDS formulation alone in total cohort
  - ✓Reduced progression to NV AMD by 26% in subjects with lowest intake of L/Z
  - ✓*L/Z substitution for β-carotene resulted in a 22% risk reduction of NV AMD within 5 years*
- L/Z had no effect on cataract surgery or progression overall but lowered risk of progression by 30% in subjects with lowest dietary intake
- No apparent effect of β-carotene elimination or reduction of zinc to 25mg

5. Development of Myopia

a) Tong, N., Zhang, W., Zhang, Z., Gong, Y., Wooten, B., & Wu, X. (2013). Inverse relationship between macular pigment optical density and axial length in Chinese subjects with myopia. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *251*(6), 1495-1500.

b) Zheng, Wenjing, et al. "Macular pigment optical density and its relationship with refractive status and foveal thickness in Chinese school-aged children." *Current eye research* 38.1 (2013): 168-173.

c) Czepita, M., Karczewicz, D., Safranow, K., & Czepita, D. (2015). Macular Pigment Optical Density and Ocular Pulse Amplitude in Subjects with Different Axial Lengths and Refractive Errors. *Medical science monitor: international medical journal of experimental and clinical research*, *21*, 1716.

d) Williams, K. M., Bentham, G. C., Young, I. S., McGinty, A., McKay, G. J., Hogg, R., ... & Soubrane, G. (2017). Association Between Myopia, Ultraviolet B Radiation Exposure, Serum Vitamin D Concentrations, and Genetic Polymorphisms in Vitamin D Metabolic Pathways in a Multicountry European Study. *JAMA ophthalmology*, *135*(1), 47-53.

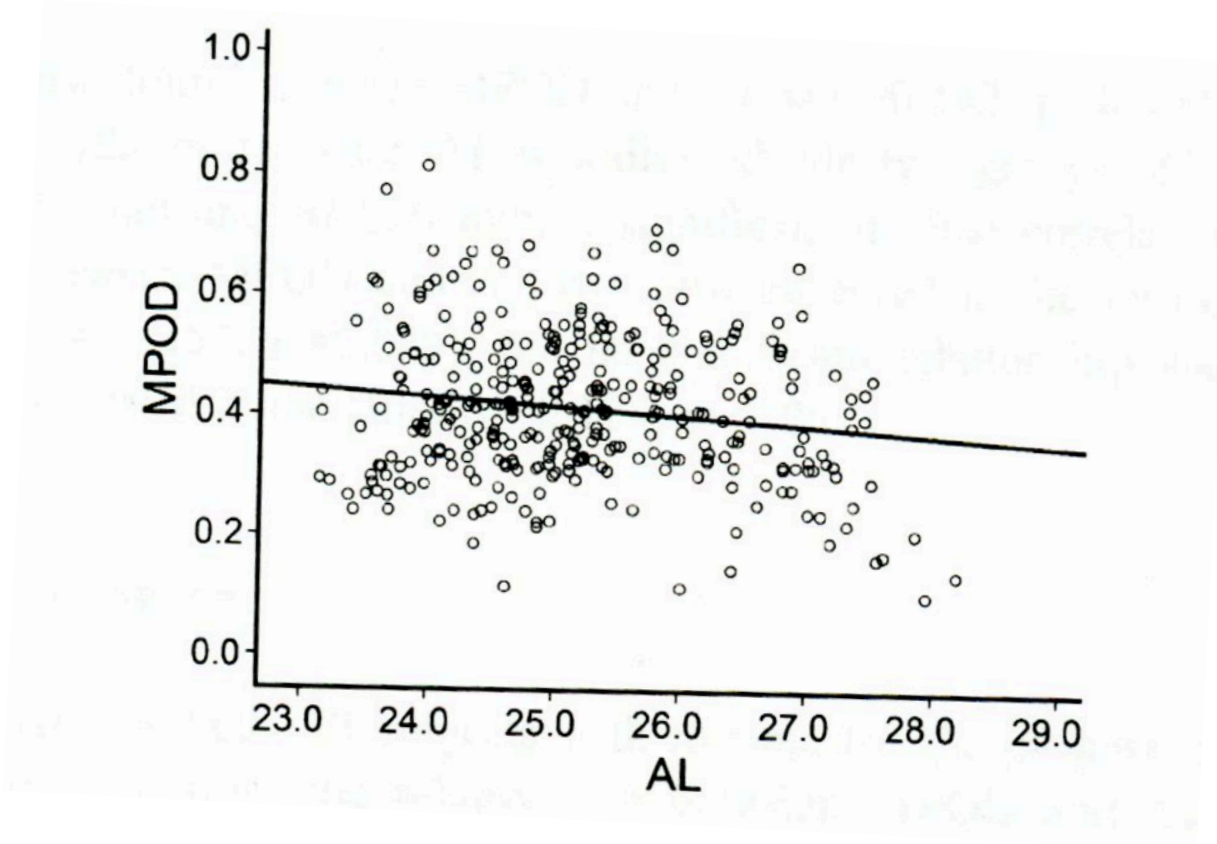
Tong et al, 2013

173 myopes (mean spherical equivalent [MSE]≤-1.00D) were recruited for this prospective study.

MPOD was measured in both eyes of each subject using a macular metrics densitometer.

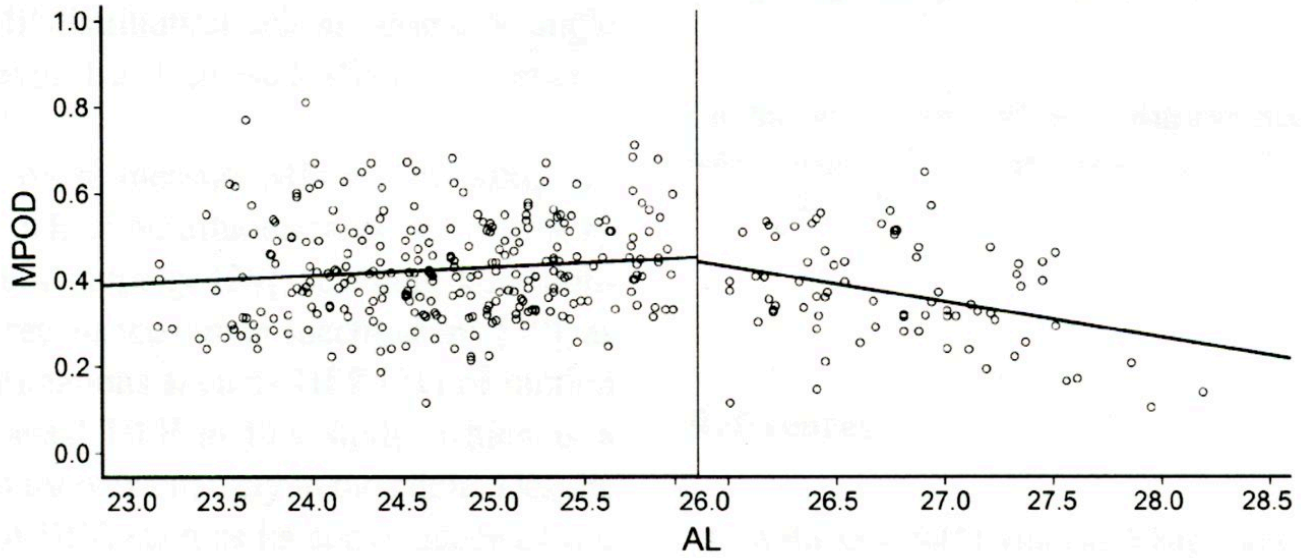
Axial length was measured in eyes using an IOL-Master

Overall Results



r = -.134, p=.012

High myopes (r = -0.348, p=.002) vs low myopes r= 0.117, p =.056



Zheng et al, 2013

94 Healthy children

Measured MPOD (Macular Metrics), spherical equivalent (auto refractor), IOP, choroidal thickness

TABLE 2 Correlations between MPOD and age, BMI, SE, IOP, MFT, and CFT.

	R	*p*
Age	0.02[a]	0.87[a]
BMI	0.03[b]	0.80[b]
SE	–0.03[c]	0.84[c]
IOP	0.21[d]	0.11[d]
MFT	0.08[e]	0.54[e]
CFT	–0.07[f]	0.61[f]

[a]Adjusted for BMI, SE, IOP, MFT, and CFT.
[b]Adjusted for age, SE, IOP, MFT, and CFT.
[c]Adjusted for age, BMI and IOP, MFT, and CFT.
[d]Adjusted for age, BMI and SE, MFT, and CFT.
[e]Adjusted for age, BMI, SE, IOP, and CFT.
[f]Adjusted for age, BMI, SE, IOP, and MFT.
p Values and correlation coefficients of partial correlation analysis.

Czepita et al 2015

140 eyes of 70 subjects

Ages 18 to 29 years (mean: 22.5 years; SD=2.8).

All underwent a thorough eye examination including: visual acuity, anterior segment and fundus examination, keratometry, auto-refractometry, and MPOD, OPA, AL, and IOP measurements.

Table 2. Refractive state, macular pigment optical density (MPOD), ocular pulse amplitude (OPA), and intraocular pressure (IOP).

Refractive state		MPOD (log units)		OPA (mmHg)		IOP (mmHg)	
		Mean	SD	Mean	SD	Mean	SD
Hyperopia		0.49	0.21	2.79	0.82	14.52	2.07
Emmetropia		0.49	0.21	2.64	0.72	14.89	2.13
Myopia	Low	0.55	0.25	2.33	0.79	14.21	2.64
	Medium	0.53	0.23	2.05	0.67	15.50	3.77
	High	0.50	0.21	1.86	0.46	17.12	2.03

Williams et al, 2017

A cross-sectional, population-based random sample of participants 65 years and older was chosen from 6 study centers from the European Eye Study.

4166 attended an eye examination including refraction, gave a blood sample, and were interviewed by trained fieldworkers using a structured questionnaire.

Myopia was defined as a mean spherical equivalent of −0.75 diopters or less.

Table 2. Association of Ultraviolet B Radiation Exposure, Education, Serum Vitamin D_3 Concentrations, and Lutein Concentrations With Myopia

Characteristic	Adjusted OR (95% CI)[a]	*P* Value[b]	Adjusted OR (95% CI)[c]	*P* Value[b]
UVB exposure (1 SD increase)	0.72 (0.56-0.93)	.01	0.75 (0.58-0.97)	.03
Years of education, median		.001		<.001
First tertile (7)	1 [Reference]	NA	1 [Reference]	NA
Second tertile (10)	1.26 (0.99-1.58)	.06	1.22 (0.96-1.57)	.10
Third tertile (14)	2.08 (1.41-3.06)	.001	2.04 (1.40-2.96)	.001
$25(OH)D_3$ concentrations (continuous)	0.99 (0.98-1.00)	.48	NA	NA
Quintiles of $25(OH)D_3$, median, nmol/L		.31		.31
First quintile (19.9)	1 [Reference]	NA	1 [Reference]	NA
Second quintile (33.1)	0.96 (0.79-1.31)	.78	0.95 (0.74-1.22)	.77
Third quintile (45.3)	0.87 (0.64-1.38)	.55	0.89 (0.59-1.36)	.62
Fourth quintile (58.9)	0.75 (0.47-1.20)	.24	0.78 (0.51-1.20)	.28
Fifth quintile (77.0)	0.87 (0.51-1.47)	.60	0.87 (0.56-1.38)	.59
Quintiles of plasma lutein, median, μmol/L		<.001		<.001
First quintile (0.03)	1 [Reference]	NA	1 [Reference]	NA
Second quintile (0.05)	0.93 (0.80-1.08)	.34	0.94 (0.81-1.10)	.48
Third quintile (0.11)	0.82 (0.55-1.20)	.30	0.83 (0.55-1.25)	.39
Fourth quintile (0.22)	0.89 (0.62-1.27)	.51	0.87 (0.63-1.19)	.41
Fifth quintile (0.48)	0.57 (0.46-0.72)	.001	0.59 (0.48-0.73)	<.001

Abbreviations: $25(OH)D_3$, serum 25-hydroxy vitamin D_3; NA, not applicable; OR, odds ratio; UVB, ultraviolet B radiation.

[a] Adjusted for age, sex, study center, and season for $25(OH)D_3$ and lutein concentrations.

[b] *P* value for effect of each variable on myopia.

[c] Adjusted for age, sex, study center, season, and all variables in the model (namely, UVB exposure, education, $25(OH)D_3$ concentrations, and plasma lutein concentrations).

Williams, K. M., Bentham, G. C., Young, I. S., McGinty, A., McKay, G. J., Hogg, R., ... & Soubrane, G. (2017). Association Between Myopia, Ultraviolet B Radiation Exposure, Serum Vitamin D Concentrations, and Genetic Polymorphisms in Vitamin D Metabolic Pathways in a Multicountry European Study. *JAMA ophthalmology*, *135*(1), 47-53.

6. Diabetes

a) Chous, A. P., Richer, S. P., Gerson, J. D., & Kowluru, R. A. (2015). The diabetes visual function supplement study (DiVFuSS). *British Journal of Ophthalmology*, bjophthalmol-2014.

b) Sahli, M. W., Mares, J. A., Meyers, K. J., Klein, R., Brady, W. E., Klein, B. E., ... & Millen, A. E. (2016). Dietary intake of lutein and diabetic retinopathy in the Atherosclerosis Risk in Communities Study (ARIC). *Ophthalmic epidemiology*, *23*(2), 99-108.

DiVFuSS

- **Diabetes Visual Function Supplement Study**
  - 6 month randomized, controlled clinical trial
  - 70 individuals with ≥ 5 years H/O DM1 or DM2 diagnosis and
  - No severe NPDR or PDR with BCVA 20/25 or better

- **Treatment Group**
  - 26 Female / 13 Male
  - Age 53.5±14.6
  - DM Duration 16±12.2 with HbA1c 7.1±1.0
  - 16 T1DM / 23 T2DM
  - 24 No DR / 10 Mild NPDR / 5 Moderate NPDR

- **Placebo Group**
  - 16 Female / 12 Male
  - Age 59.7±10.3
  - DM Duration 16.1±9.9 with HbA1c 7.3±1.1
  - 11 T1DM / 17 T2DM
  - 13 No DR / 14 Mild NPDR / 1 Moderate NPDR

DiVFuSS

DiVFuSS supplement (AREDS2 comparison)

Vit B12	6mcg
Vit C	**60mg (500mg)**
Vit D3	2000IU
Vit E	**60IU (400IU)**
Zinc	**15mg (80mg and 25mg)**
Ω-3	**240mg**
EPA 128mg / DHA	**96mg (EPA 650mg / DHA 350mg)**
α-lipoic	150mg
CoQ-10	20mg
Zeaxanthin	**8mg (2mg)**
Lutein	**4mg (10mg)**
Proprietary	530mg

Benfotiamine, N-acetyl cysteine, resveratrol, turmeric root extract, green tea leaf, French maritime extract

Placebo

Canola oil softgel

DiVFuSS

Measures of visual Function

CS at 1.5, 3, 6, 12 and 18 cycles/degree (M & S Technologies)
MPOD (QuantifEye)
Color Discrimination (L'Anthony Desaturated Cap)
5-2 Macular Threshold Perimetry (Kowa)

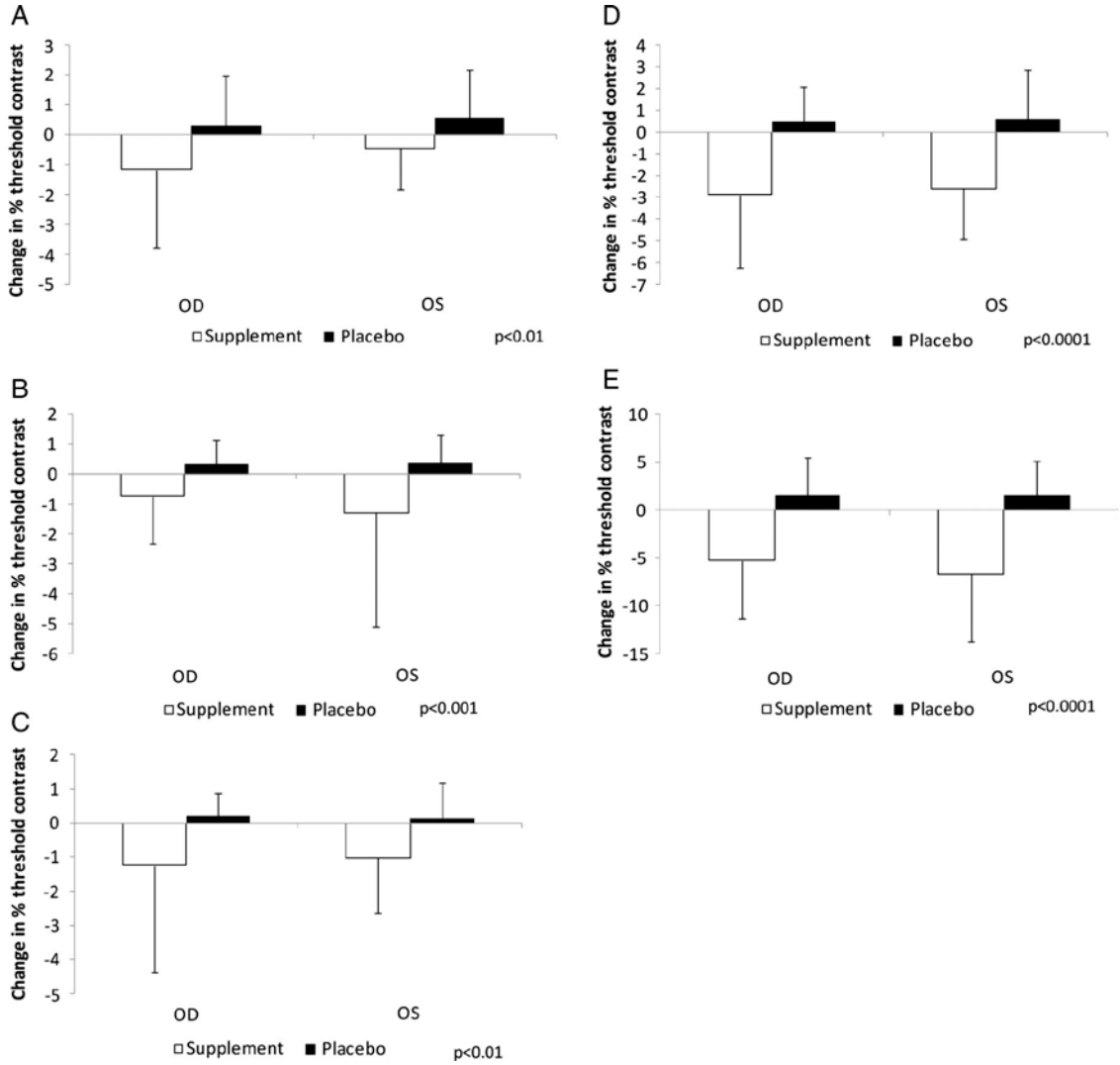
Retinal Evaluation

DFE including 3-field digital imaging
SD-OCT measures of mean foveal and RNFL thickness (Zeiss-Cirrus)

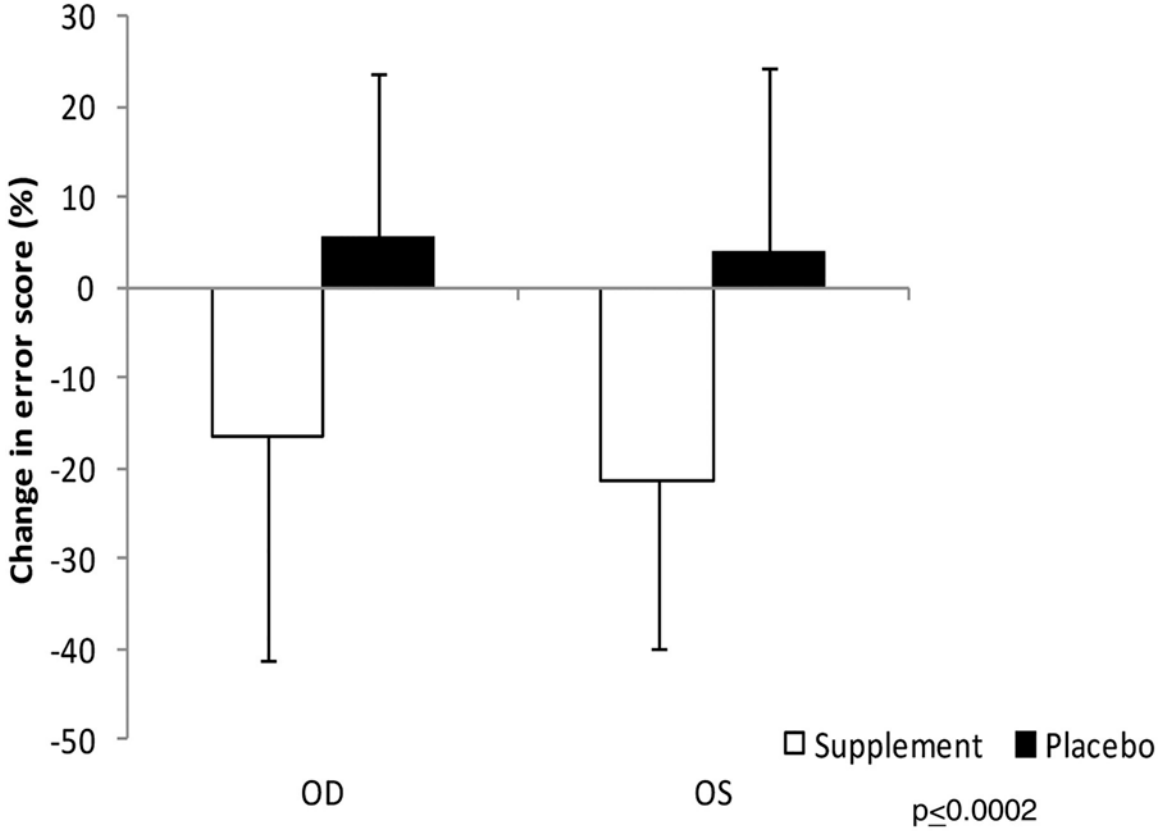
Serum Measures

HbA1c
LDL-C / HDL-C / Triglycerides / Total Cholesterol
D3
hsCRP
TNF-α

DiVFuSS: Change contrast sensitivity over 6 months

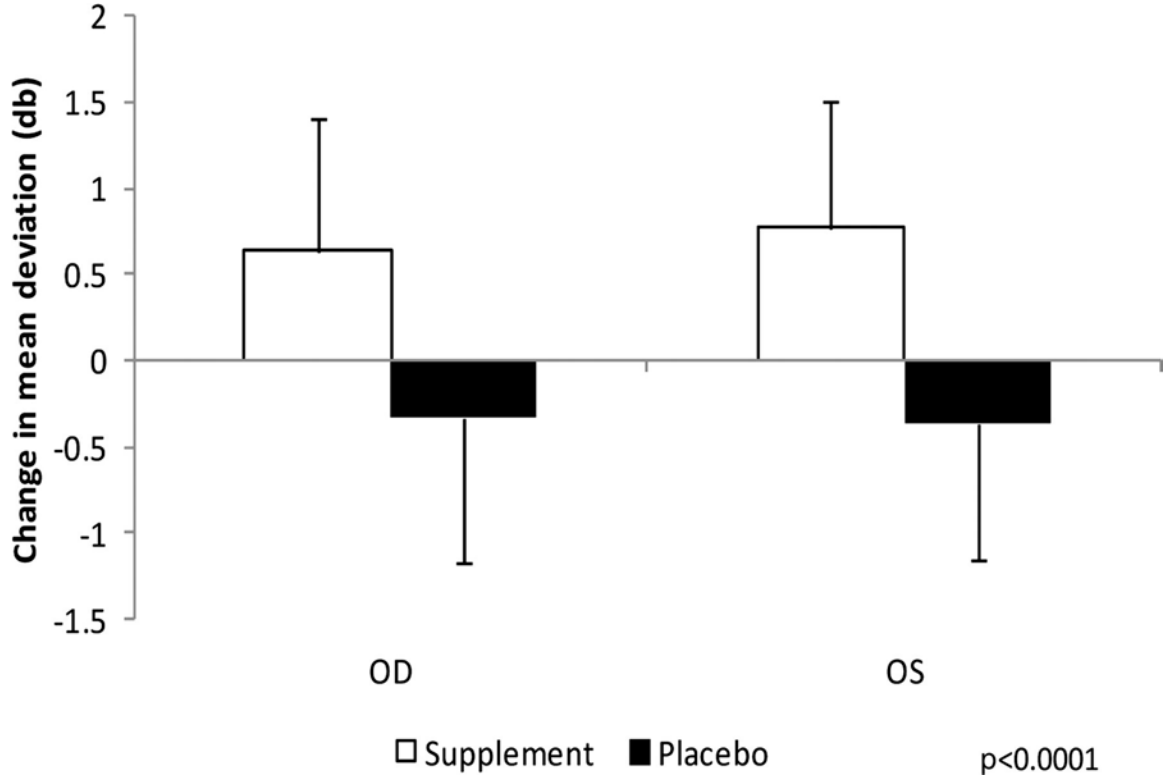


DiVFuSS Change color vision over 6 months

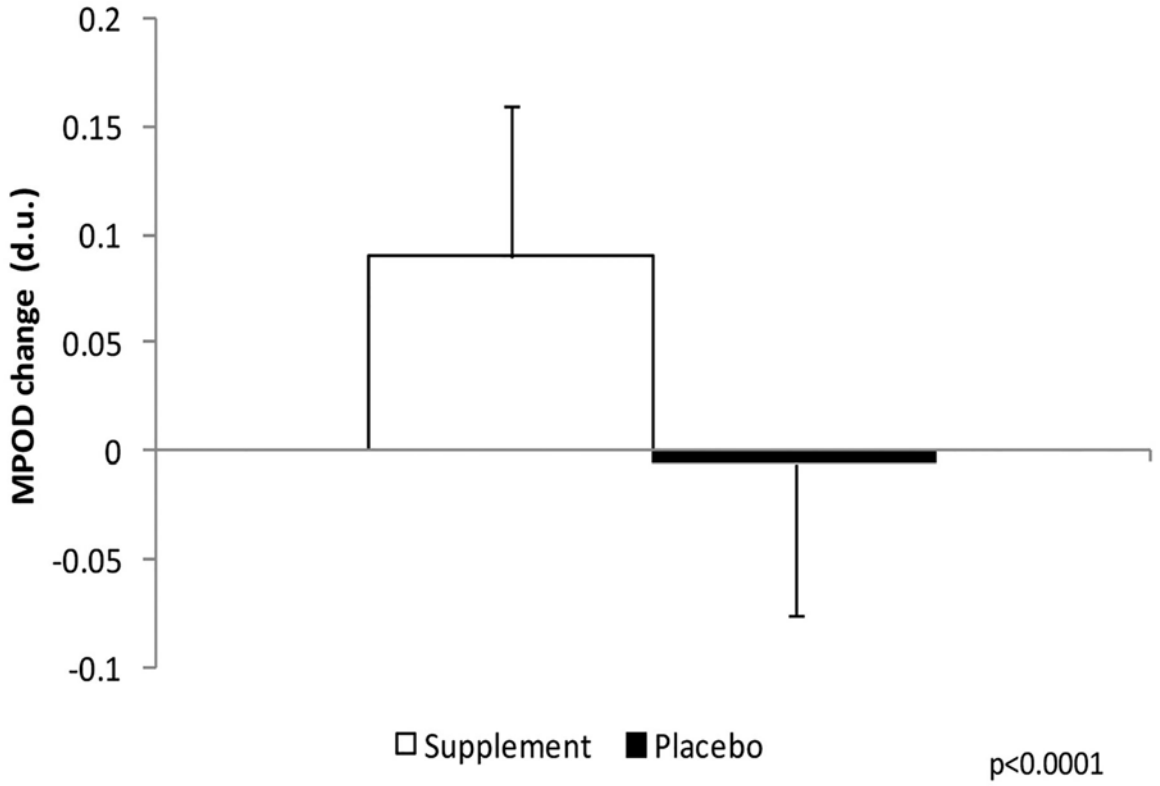


A higher color error score denotes less normal/more abnormal color discrimination

DiVFuSS Change visual field mean deviation over 6 months

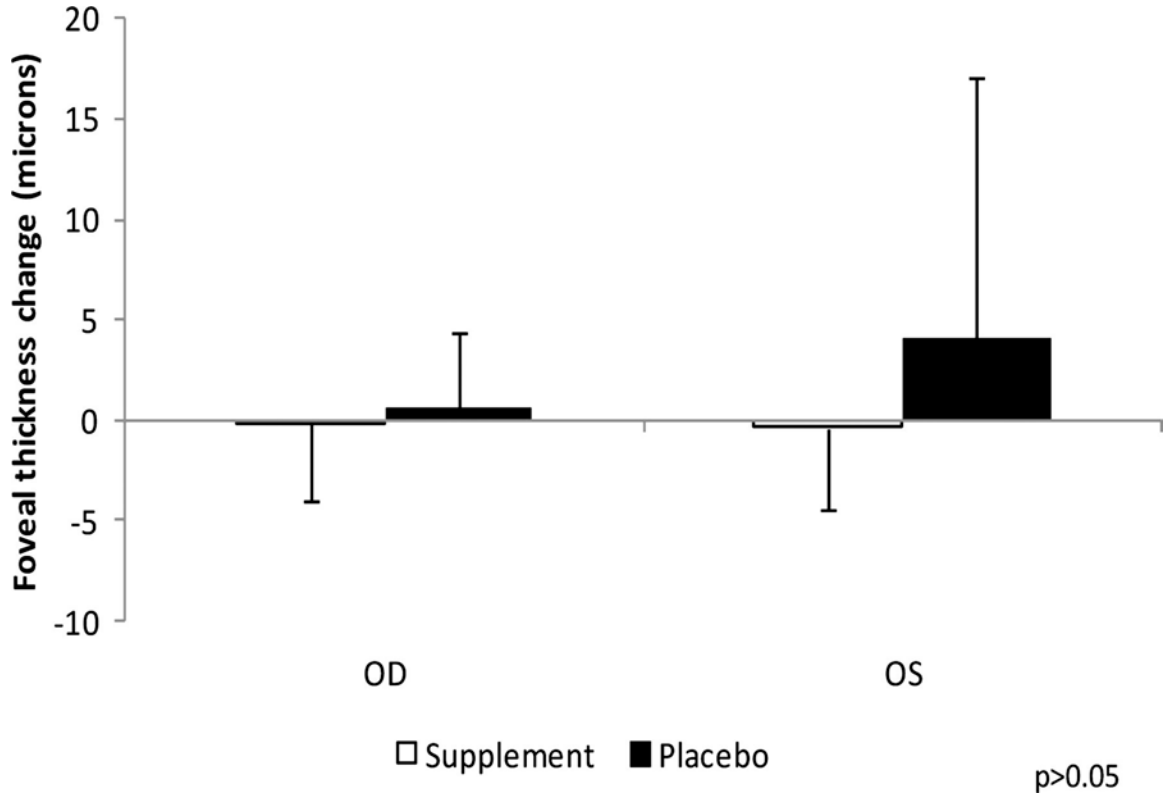


DiVFuSS Change MPOD over 6 months

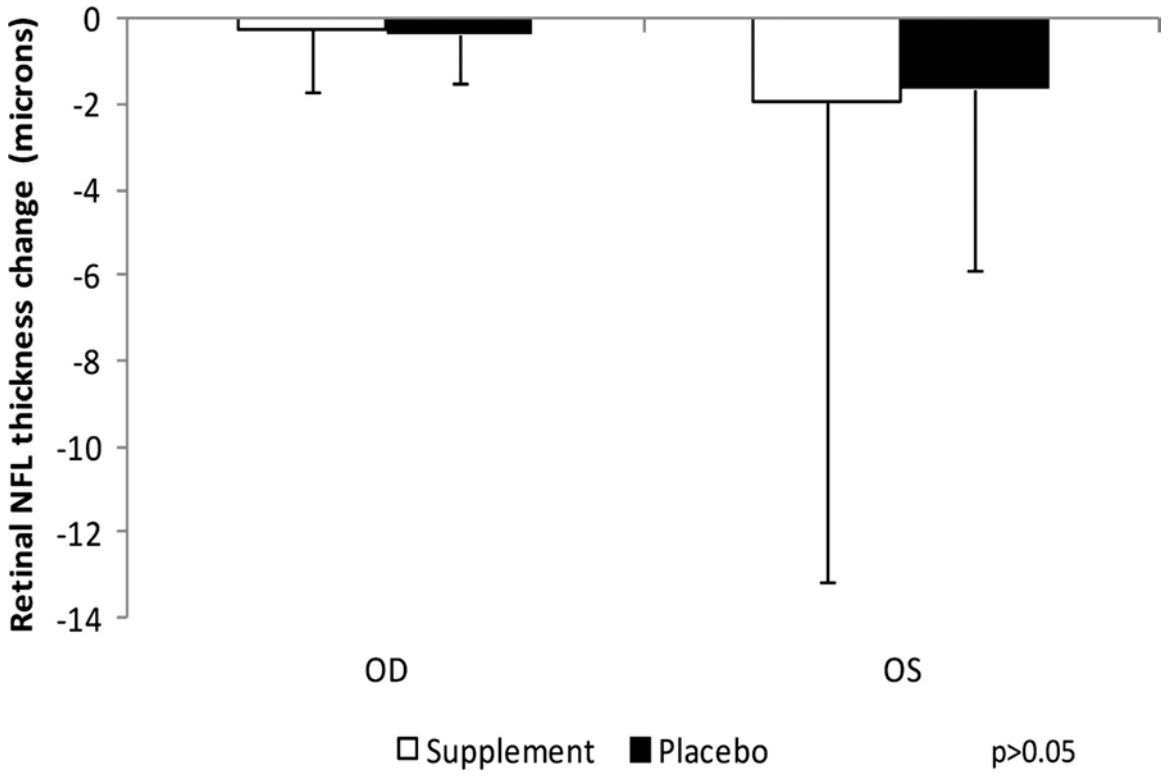


MPOD was measured in one eye at baseline and the same eye at trial completion

DiVFuSS Foveal thickness over 6 months



DiVFuSS


Retinal NFL thickness change (microns)
0
-2
-4
-6
-8
-10
-12
-14
OD
OS
Supplement
Placebo
p>0.05

DiVFuSS

Results at 6 months:

- **Measures of Visual Function**
  - Significant increase in MPOD
  - Significant improvements on CS at all spatial frequencies
  - Significant improvements color discrimination

- **Retinal Evaluation**
  - Near-significant (p=0.07) moderate NPDR downgraded to mild NPDR
  - Non-significant differences in SD-OCT foveal and RNFL thickness

- **Serum Measures**
  - Significant improvements in LDL-C, HDL-C and triglycerides
  - Significant improvement in D3 levels
  - Significant improvements in hsCRP
  - Non-significant findings for HbA1c, TNF-α, total cholesterol

Sahli et al, 2016

- Used logistic regression to examine the association between prevalent DR and energy-adjusted lutein intake by quartile (Q) using data collected from 1430 Atherosclerosis Risk in Communities Study (ARIC) participants with diabetes (n = 994 white, n = 508 black).
- DR was assessed from 45° non-mydriatic retinal photographs of one randomly chosen eye taken at visit 3.
- Dietary lutein intake was estimated using a 66-item food frequency questionnaire at visit 1

Sahli et al, 2016

Table 3. Association between dietary intake of lutein, assessed at visit 1 (1987–1989), and diabetic retinopathy among white and black Atherosclerosis Risk in Communities Study (ARIC) participants classified as having diabetes and having gradable eye photos at visit 3 (1993–1995), USA (N = 1430).

	Quartile energy-adjusted dietary intake of lutein (range in µg/1000 kcal)				
Group	Q1 (4–715)	Q2 (716–1359)	Q3 (1364–2590)	Q4 (2605–19,813)	p for trend[a]
Stratified by ethnicity					
Black (n = 473)					
n with DR/n in group	3/26	28/105	44/156	58/186	
Adjusted[b] OR	1	1.61	2.88	2.29	0.14
(95% CI)	(reference)	(0.37–7.06)	(0.65–12.67)	(0.53–9.86)	
White (n = 957)					
n with DR/n in group	48/331	42/253	40/202	35/171	
Adjusted[b] OR	1	1.17	1.32	1.36	**0.04**
(95% CI)	(reference)	(0.69–1.97)	(0.76–2.30)	(0.77–2.43)	
p for interaction					0.40
Stratified by HbA1c level[c]					
>7% (n = 629)					
n with DR/n in group	42/130	59/158	73/161	77/180	
Adjusted[b] OR	1	1.10	1.47	1.22	**0.04**
(95% CI)	(reference)	(0.65–1.87)	(0.85–2.53)	(0.71–2.13)	
≤7% (n = 801)					
n with DR/n in group	9/227	11/200	11/197	16/177	
Adjusted[b] OR	1	1.12	1.08	1.64	0.16
(95% CI)	(reference)	(0.44–2.83)	(0.41–2.87)	(0.65–4.15)	
p for interaction					0.47
Stratified by duration of diabetes					
<6 years (n = 636)					
n with DR/n in group	11/187	8/157	6/148	8/144	
Adjusted[b] OR	1	0.82	0.67	0.89	0.72
(95% CI)	(reference)	(0.31–2.16)	(0.22–2.04)	(0.31–2.50)	
≥6 years (n=794)					
n with DR/n in group	40/170	62/201	78/210	85/213	
Adjusted[b] OR	1	1.22	1.87	1.58	**0.01**
(95% CI)	(reference)	(0.71–2.08)	**(1.08–3.21)**	(0.91–2.75)	
p for interaction					0.20

[a]Calculated using energy-adjusted lutein as a continuous variable.
[b]All analyses adjusted for study center, total energy consumption, ethnicity, duration of diabetes and HbA1c levels, excluding the characteristic on which it is being stratified.
[c]Glucose control defined as adequate if HbA1c ≤7% and inadequate if HbA1c >7% according to recommendations by the American Diabetes Association.[36]
CI, confidence interval; OR, odds ratio; HbA1c, hemoglobin A1c; DR, diabetic retinopathy; Q, quartile.
Bolding denotes significant values.

The odds of higher lutein intake were greater among those with DR than those without DR. However, after adjusting for confounders, intake of lutein was not associated with DR.

7. Brain Function

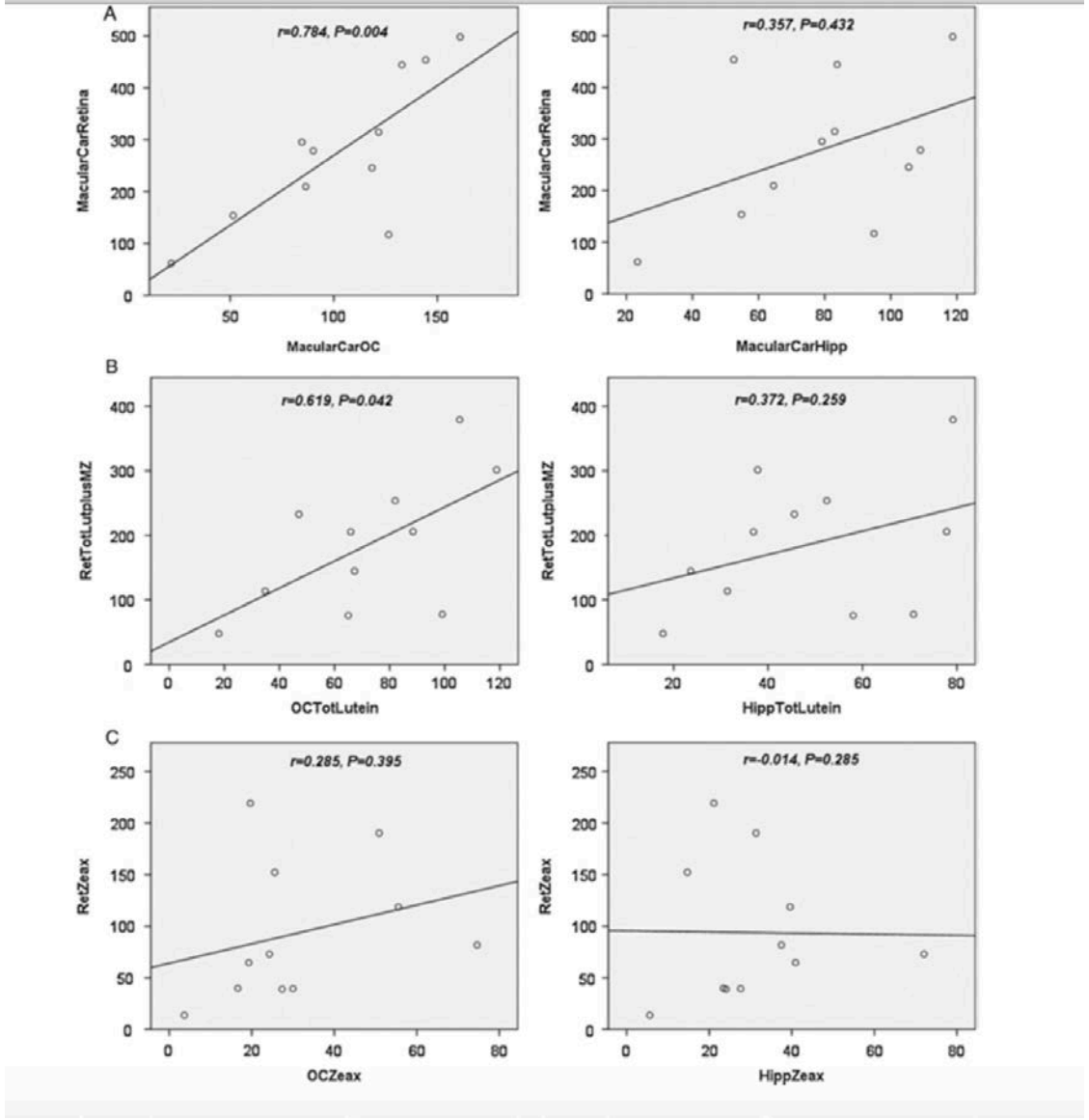
a) Vishwanathan, R., Schalch, W., & Johnson, E. J. (2016). Macular pigment carotenoids in the retina and occipital cortex are related in humans. *Nutritional neuroscience*, *19*(3), 95-101.

b) Lindbergh, Cutter A., et al. "Relationship of Lutein and Zeaxanthin Levels to Neurocognitive Functioning: An fMRI Study of Older Adults." *Journal of the International Neuropsychological Society* 22 (2016): 1-12.

c) Tanprasertsuk, J., Li, B., Bernstein, P. S., Vishwanathan, R., Johnson, M. A., Poon, L., & Johnson, E. J. (2016). Relationship between concentrations of lutein and stard3 among pediatric and geriatric human brain tissue. *PloS one*, *11*(5), e0155488.

Vishwanathan et al, 2016

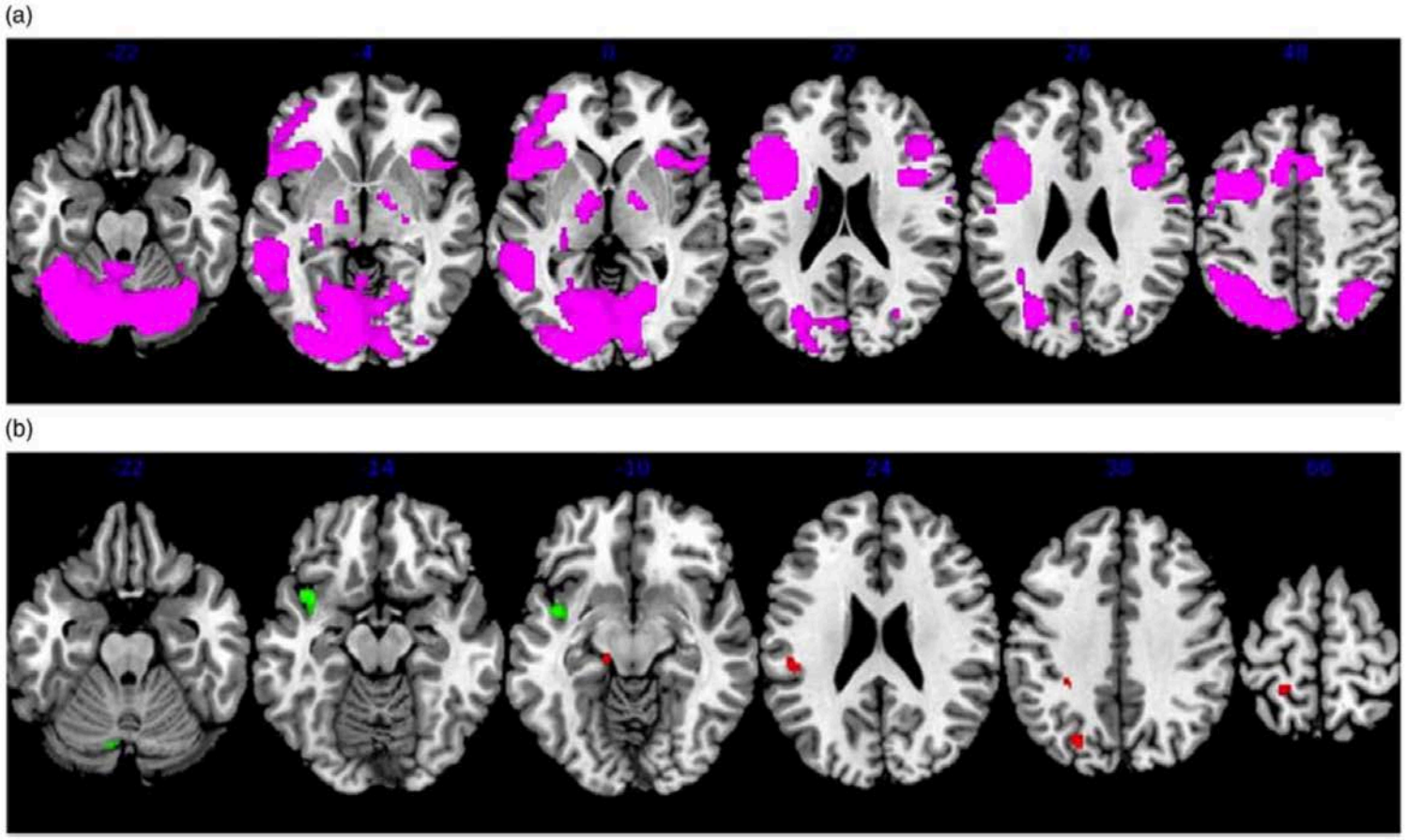
- Donated brain tissue (occipital cortex and hippocampus) was matched with retinal tissue were obtained from the National Disease Research Interchange.
- Decedents were men and women aged >50 years who either had normal cognitive function or Alzheimer's disease.
- Tissues were analyzed using standard lipid extractions followed by analysis on reverse-phase high performance liquid chromatography (HPLC) and normal- phase HPLC (for meso-zeaxanthin).



The graphs shown below depict the relationship between macular carotenoids (lutein, meso-zeaxanthin, and zeaxanthin in pmol/g) in the retina and the brain (n = 11) Macular carotenoids (lutein, meso-zeaxanthin, and zeaxanthin combined) in the retina (MacularCarRetina) were positively associated ($P < 0.05$) to their concentrations in the OC (MacularCarOC). No association was observed between macular carotenoids in the retina and the Hipp (MacularCarHipp). (B) Lutein plus meso-zeaxanthin in the retina (RetTotLutplusMZ) was positively associated ($P < 0.05$) with lutein in the OC (OCTotLutein) but not the Hipp (HippTotLutein). (C) No significant associations were observed between zeaxanthin in the retina (RetZeax) and the OC (OCZeax) and also between zeaxanthin in the retina and the Hipp (HippZeax).

Lindbergh et al, 2016

- Forty-three community-dwelling older adults (mean age = 72 years; 58% female; 100% Caucasian) were asked to learn and recall pairs of unrelated words in an fMRI-adapted paradigm.
- L and Z levels were measured in retina (macular pigment optical density) and serum using validated procedures (MacularMetrics, HPLC).



Panel (a) depicts whole-brain analyses of the encoding minus control contrast (independent of lutein and zeaxanthin levels) superimposed on a single-subject anatomical template Panel (b) displays brain activation significantly related to lutein and zeaxanthin concentrations during encoding. Areas in green represent increased activation associated with lower MPOD levels, while areas in red represent increased activation associated with lower serum lutein and zeaxanthin. Only six slices were selected based on largest extent activation to showcase the relation of lutein and zeaxanthin to brain activity and thus not every significant cluster is displayed.

Table 2. Relationship of lutein and zeaxanthin to brain activation during encoding ($N = 43$)

Region	*x*	*y*	*z*	Extent	*Z*-Score	Effect Size (*r*)
MPOD						
L insular cortex	−40	10	−14	99	3.03	0.45
L insular cortex	−42	0	−10	*	2.94	0.44
R middle temporal gyrus	62	−58	2	10	2.75	0.41
L cerebellum	−10	−76	−22	11	2.52	0.38
L supramarginal gyrus	−64	−34	26	3	2.44	0.37
Serum						
L lateral occipital cortex	−24	−74	38	45	2.96	0.44
L postcentral gyrus	−20	−44	66	31	2.90	0.43
L parietal operculum cortex	−48	−30	24	39	2.90	0.43
L precentral gyrus	−58	0	32	5	2.76	0.41
R lateral occipital cortex	36	−68	50	17	2.60	0.39
R lateral occipital cortex	26	−78	28	7	2.48	0.37

Note. The above table includes brain activity that was significantly and negatively associated with lutein and zeaxanthin levels during encoding of word pairs.
MPOD = macular pigment optical density. *x*, *y*, and *z* coordinates are in MNI space (mm). L = left and R = right.
* = cluster overlap with preceding row.

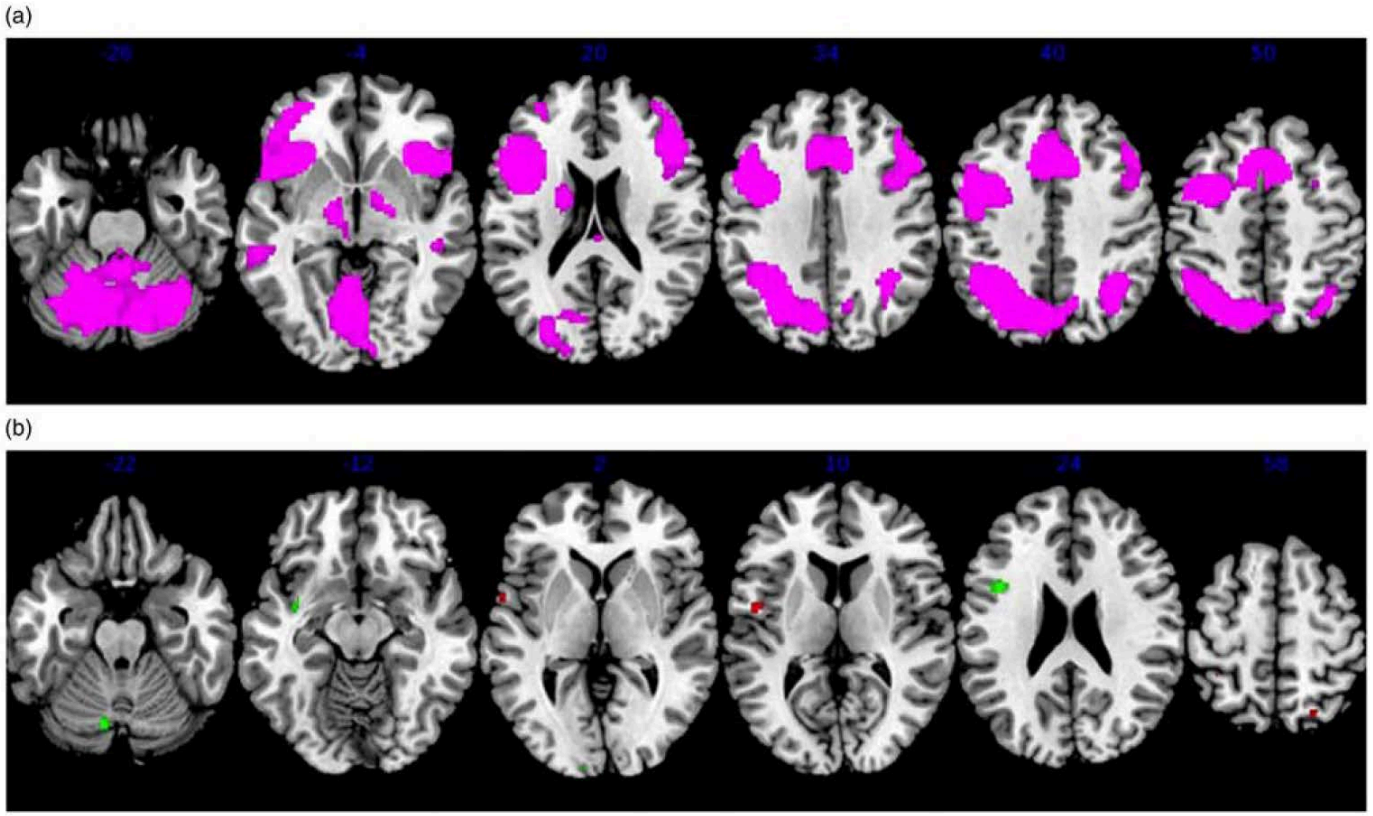


Fig. 3. Panel (**a**) depicts whole-brain analyses of the recall minus control contrast (independent of lutein and zeaxanthin levels) superimposed on a single-subject anatomical template in MNI space provided by MRIcron (http://www.mricro.com/mricron/install.html). To conserve space, only six slices were selected for visualization based on largest extent activation and thus not all significant voxel activity is represented. Panel (**b**) displays brain activation significantly related to lutein and zeaxanthin concentrations during retrieval. Areas in green represent increased activation associated with lower MPOD levels, while areas in red represent increased activation associated with lower serum lutein and zeaxanthin. Only six slices were selected based on largest extent activation to showcase the relation of lutein and zeaxanthin to brain activity and thus not every significant cluster is displayed.

Table 3. Relationship of lutein and zeaxanthin to brain activation during recall ($N = 43$)

Region	x	y	z	Extent	Z-Score	Effect size (r)
MPOD						
L inferior frontal gyrus	−42	8	24	48	3.10	0.46
L cerebellum	−10	−74	−22	24	2.96	0.44
L occipital pole	−12	−102	−2	9	2.78	0.41
L planum polare	−46	−4	−6	8	2.56	0.38
L insular cortex	−38	−4	−12	15	2.53	0.38
R middle frontal gyrus	46	34	18	7	2.47	0.37
R occipital pole	16	−96	12	2	2.40	0.36
Serum						
L central opercular cortex	−48	−4	10	21	3.36	0.49
R lateral occipital cortex	22	−68	58	9	2.56	0.38
L central opercular cortex	−58	2	2	7	2.48	0.37
L superior parietal lobule	−38	−42	60	4	2.45	0.37

Note. The above table includes brain activity that was significantly and negatively associated with lutein and zeaxanthin levels during retrieval of word pairs. x, y, and z coordinates are in MNI space (mm).
MPOD = macular pigment optical density. L = left and R = right.

Results: Following first-level contrasts of encoding and retrieval trials minus control trials ($p < .05$, family-wise error corrected, minimum voxel cluster = 8), L and Z were found to significantly and negatively relate to blood-oxygen-level-dependent signal in central and parietal operculum cortex, inferior frontal gyrus, supramarginal gyrus, planum polare, frontal and middle temporal gyrus, superior parietal lobule, postcentral gyrus, precentral gyrus, occipital cortex bilaterally, and cerebellar regions. The observed results suggest that L and Z promote cognitive functioning in old age by enhancing neural efficiency.

Tanprasertsuk et al 2016

- The objective of this study was to evaluate the cross-sectional relationship between concentrations of brain lutein and StARD3 (identified as its binding protein in retinal tissue) among three age groups: infants (1–4 months, n = 10), older adults (55–86 years, n = 8), and centenarians (98–105 years, n = 10).
- Brain lutein concentrations were analyzed by high-performance liquid chromatography and StARD3 levels were analyzed by Western Blot analysis.

Table 1. Subject characteristics

	Infants[b] (n = 10)	Older adults[b] (n = 8)	Centenarians[b] (n = 10)
Age[c]			
Mean (SEM)	95.6 (8.0)	76.4 (3.3)	100.2 (0.7)
Median	99.0	79.5	100.0
Range	31–123	55–86	98–105
Preterm, n (%)	2 (20%)	NA	NA
Sex			
Females, n (%)	4 (40%)	4 (50%)	10 (100%)
Race			
Caucasian, n (%)	8 (80%)	7 (87.5%)	8 (80%)
African American, n (%)	2 (20%)	0 (0%)	1 (10%)
Hispanic, n (%)	0 (0%)	1 (12.5%)	0 (0%)
Height, cm or m[d]			
Mean (SEM)	6.4 (0.4)	1.74 (0.02)	1.55 (0.02)
Median	6.1	1.73	1.57
Range	5.4–9.5	1.70–1.85	1.45–1.70
Weight, kg			
Mean (SEM)	6.4 (0.4)	81.0 (5.6)	55.6 (4.5)
Median	6.1	79.4	51.3
Range	5.4–9.5	52.2–97.5	33.6–77.1
BMI, kg/m^2			
Mean (SEM)	NA	26.86 (2.18)	22.75 (1.34)
Median		27.47	22.84
Range		15.27–33.73	16.01–29.10
Presence of disease, n (%)			
Alzheimer's disease	NA	3 (37.5%)	ND
MCI or dementia		ND	7 (70%)
Other		ND	9 (90%)
Cause of death			
SIDS, n (%)	4 (40%)	NA	NA
Others, n (%)	6 (60%)	8 (100%)	
Time interval between death and tissue collection, hours			
Mean (SEM)	16.8 (1.6)	13.9 (2.4)	ND
Median	17.5	11.0	
Range	9–23	7–24	
Brain tissue sample, n	17	16	15
Frontal cortex	10	0	9
Temporal cortex	0	0	6
Occipital cortex	0	8	0
Hippocampus	7	8	0

NA = not applicable

ND = no data available

[a]See S1–S3 Tables for more information

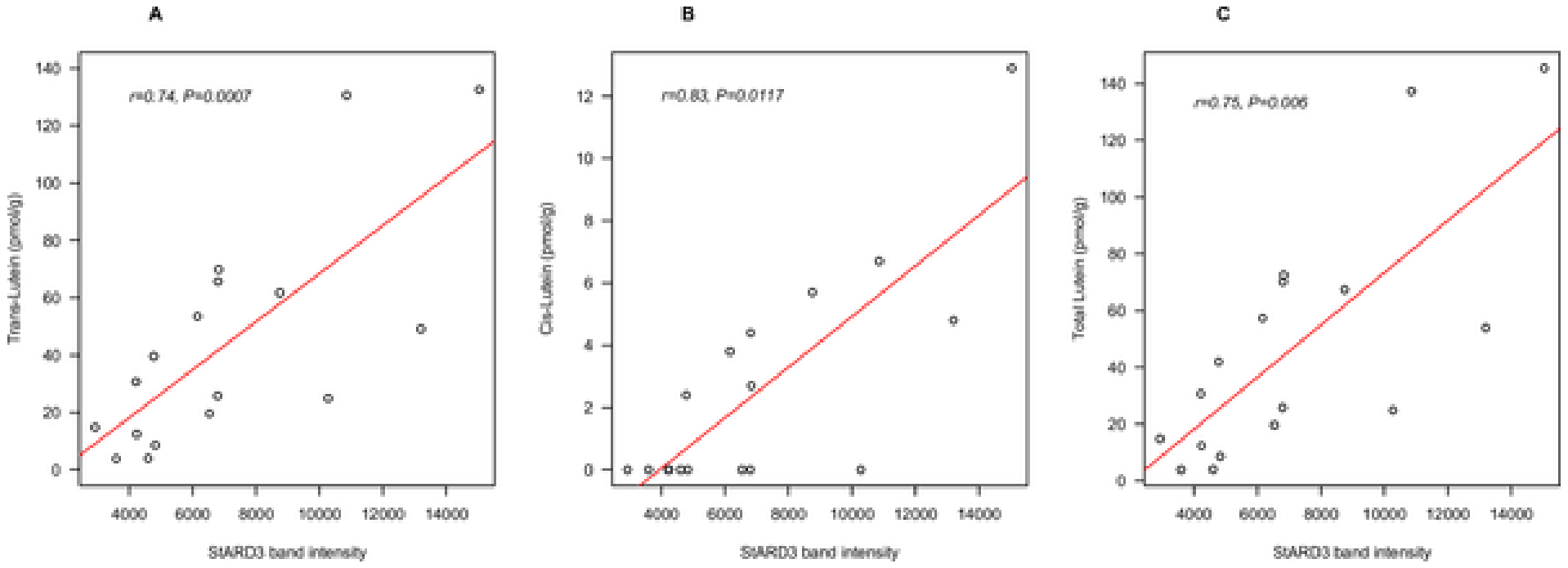
[b]One infant, one older adult, and one centenarian had no data for height and weight. One centenarian had no data for race.

[c]Age in days for infants, in years for older adults

[d]Height in centimeters for infants, in meters for older adults

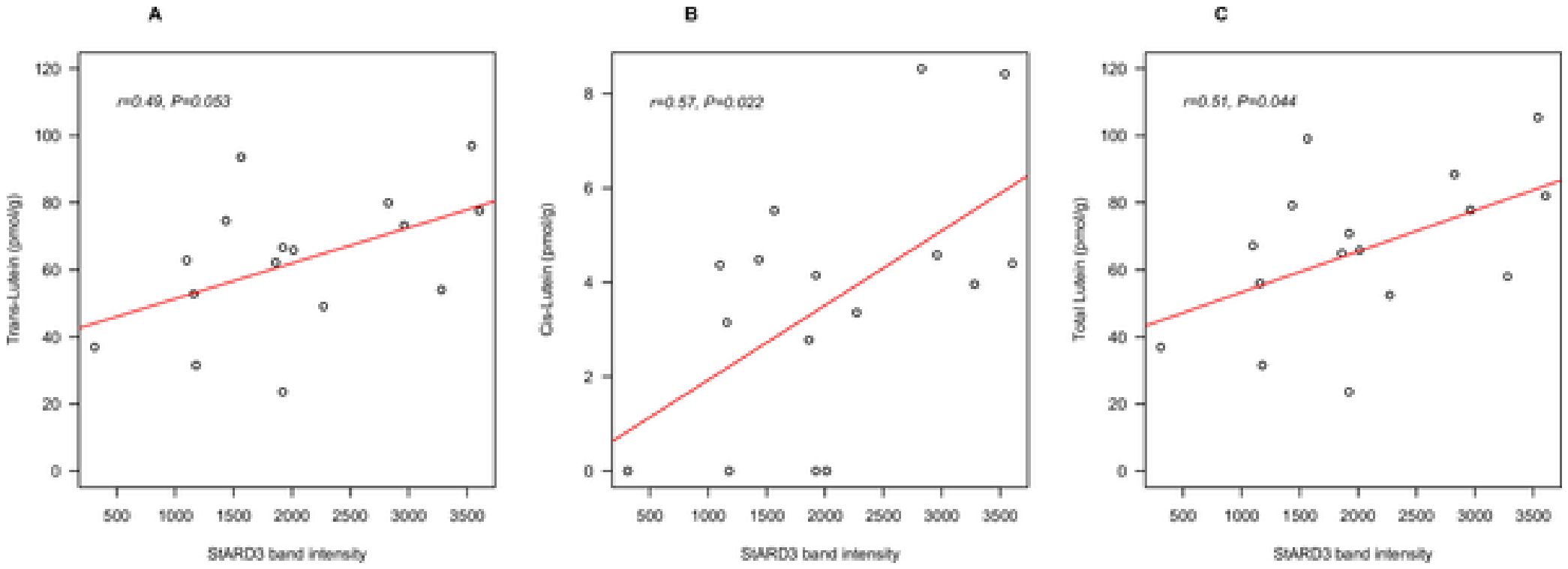
Tanprasertsuk J, Li B, Bernstein PS, Vishwanathan R, Johnson MA, et al. (2016) Relationship between Concentrations of Lutein and Stereoisomeric Zeaxanthins among Pediatric and Geriatric Human Brain Tissue. PLOS ONE 11(5): e0155488. doi:10.1371/journal.pone.0155488
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0155488

Fig 1.



Tanprasertsuk J, Li B, Bernstein PS, Vishwanathan R, Johnson MA, et al. (2016) Relationship between Concentrations of Lutein and StARD3 among Pediatric and Geriatric Human Brain Tissue. PLOS ONE 11(5): e0155488. doi:10.1371/journal.pone.0155488
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0155488

Fig 2.



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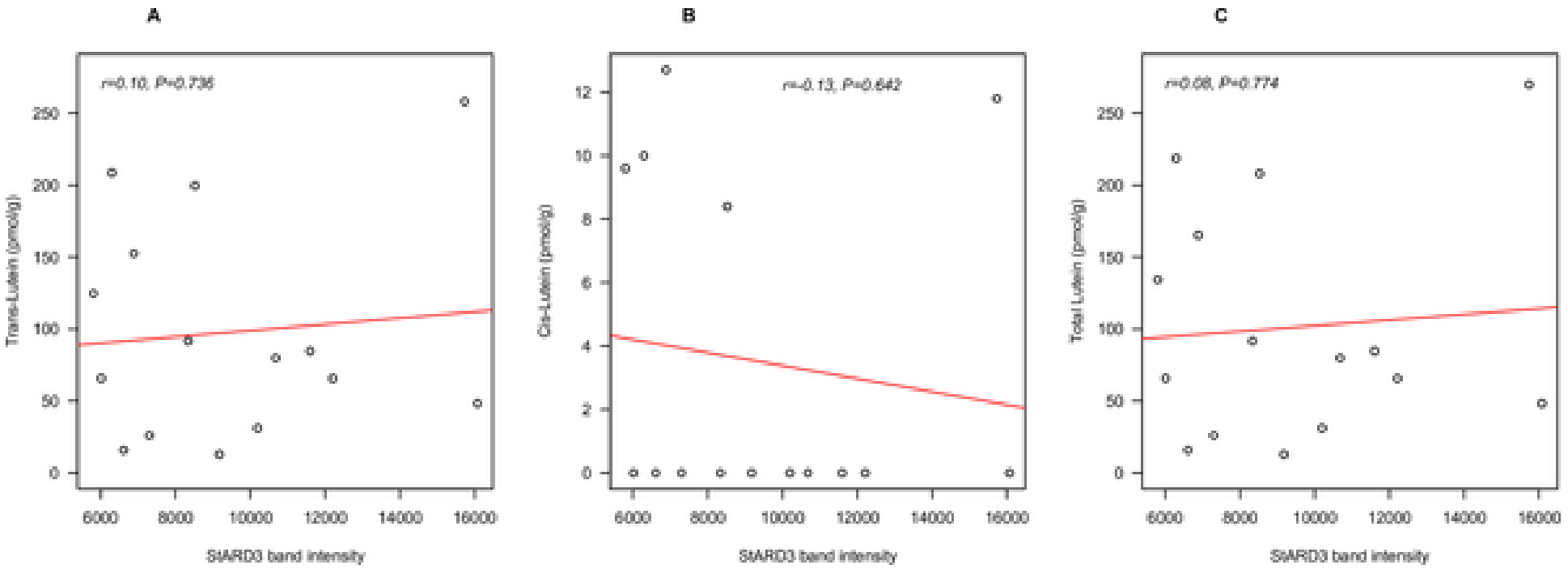
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0155488

Fig 3.



Tanprasertsuk J, Li B, Bernstein PS, Vishwanathan R, Johnson MA, et al. (2016) Relationship between Concentrations of Lutein and StARD3 among Pediatric and Geriatric Human Brain Tissue. PLOS ONE 11(5): e0155488. doi:10.1371/journal.pone.0155488
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0155488

The strong relationship in infant brains ($r = 0.75$, $P < 0.001$) suggests that lutein has a role in neural development. The relationship remained significant but weaker in older adults ($r = 0.51$, $P < 0.05$) and non-significant in centenarians ($r = 0.08$, $P > 0.05$), seven of whom had mild cognitive impairment (MCI) or dementia.

8. Cognitive Function

a) Kelly, D., Coen, R. F., Akuffo, K. O., Beatty, S., Dennison, J., Moran, R., ... & Nolan, J. M. (2015). Cognitive function and its relationship with macular pigment optical density and serum concentrations of its constituent carotenoids. *Journal of Alzheimer's Disease*, *48*(1), 261-277.

b) Zhou, Li-Xiao, et al. "Lower cognitive function in patients with age-related macular degeneration: a meta-analysis." *Clinical interventions in aging* 11 (2016): 215.

c) Nolan, J. M., Loskutova, E., Howard, A., Mulcahy, R., Moran, R., Stack, J., ... & Owens, N. (2015). The impact of supplemental macular carotenoids in Alzheimer's disease: a randomized clinical trial. *Journal of Alzheimer's Disease*, *44*(4), 1157-1169.

d) Chew, E. Y., Clemons, T. E., Agrón, E., Launer, L. J., Grodstein, F., & Bernstein, P. S. (2015). Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function: the AREDS2 randomized clinical trial. *Jama*, *314*(8), 791-801.

e) Renzi-Hammond, L. M., Miller, L. S., & Hammond, B. R. (2016). Oral Nutrient Supplementation and Cognitive Function. *Jama*, *315*(5), 515-516.

f) Hammond, B. R., & Renzi-Hammond, L. M. (2016). Perspective: a critical look at the ancillary age-related eye disease study 2: nutrition and cognitive function results in older individuals with age-related macular degeneration. *Advances in Nutrition: An International Review Journal*, *7*(3), 433-437.

Kelly et al 2015

Objective: To investigate the relationship between MP, serum concentrations of L and Z, and cognitive function in subjects free of

retinal disease with low MP (Group 1, n = 105) and in subjects with AMD (Group 2, n = 121).

Methods: MP was measured using customized heterochromatic flicker photometry and dual-wavelength autofluorescence;

cognitive function was assessed using a battery of validated cognition tests; serum L and Z concentrations were determined by

HPLC.

Table 3
Significant correlations between MP and cognitive scores in subjects free of retinal disease with low MP (Group 1) and subjects with early AMD (Group 2)

	Low MP group						AMD group					
	Densitometer				Spectralis		Densitometer				Spectralis	
	MP 0.25		MP 0.5		AF MP vol.		MP 0.25		MP 0.5		AF MP vol.	
Cognitive test	*r* value	*p* value	*r* value	*p* value	*r* value	*p* value	*r* value	*p* value	*r* value	*p* value	*r* value	*p* value
FAS test	0.072	0.476	0.116	0.248	0.002	0.982	**0.261**	**0.004**	**0.244**	**0.008**	0.160	0.083
Animal fluency	0.008	0.933	0.000	0.997	0.003	0.975	**0.186**	**0.044**	**0.188**	**0.042**	0.171	0.063
AST Congruency Cost	**–0.201**	**0.045**	–0.103	0.308	–0.063	0.530	0.122	0.188	0.127	0.173	0.091	0.325
AST Percent Correct	0.004	0.971	–0.004	0.972	0.091	0.364	**0.214**	**0.020**	**0.200**	**0.030**	0.111	0.230
PAL Total Errors	**–0.247**	**0.013**	–0.184	0.067	0.128	0.204	**–0.224**	**0.015**	–0.180	0.052	–0.030	0.744
PAL Total Errors Stage 6	**–0.273**	**0.006**	**–0.235**	**0.018**	0.181	0.071	**–0.183**	**0.047**	–0.145	0.117	–0.050	0.586
VRM Learning Slope	**0.258**	**0.009**	**0.290**	**0.003**	0.005	0.959	–0.079	0.397	–0.046	0.617	–0.025	0.786

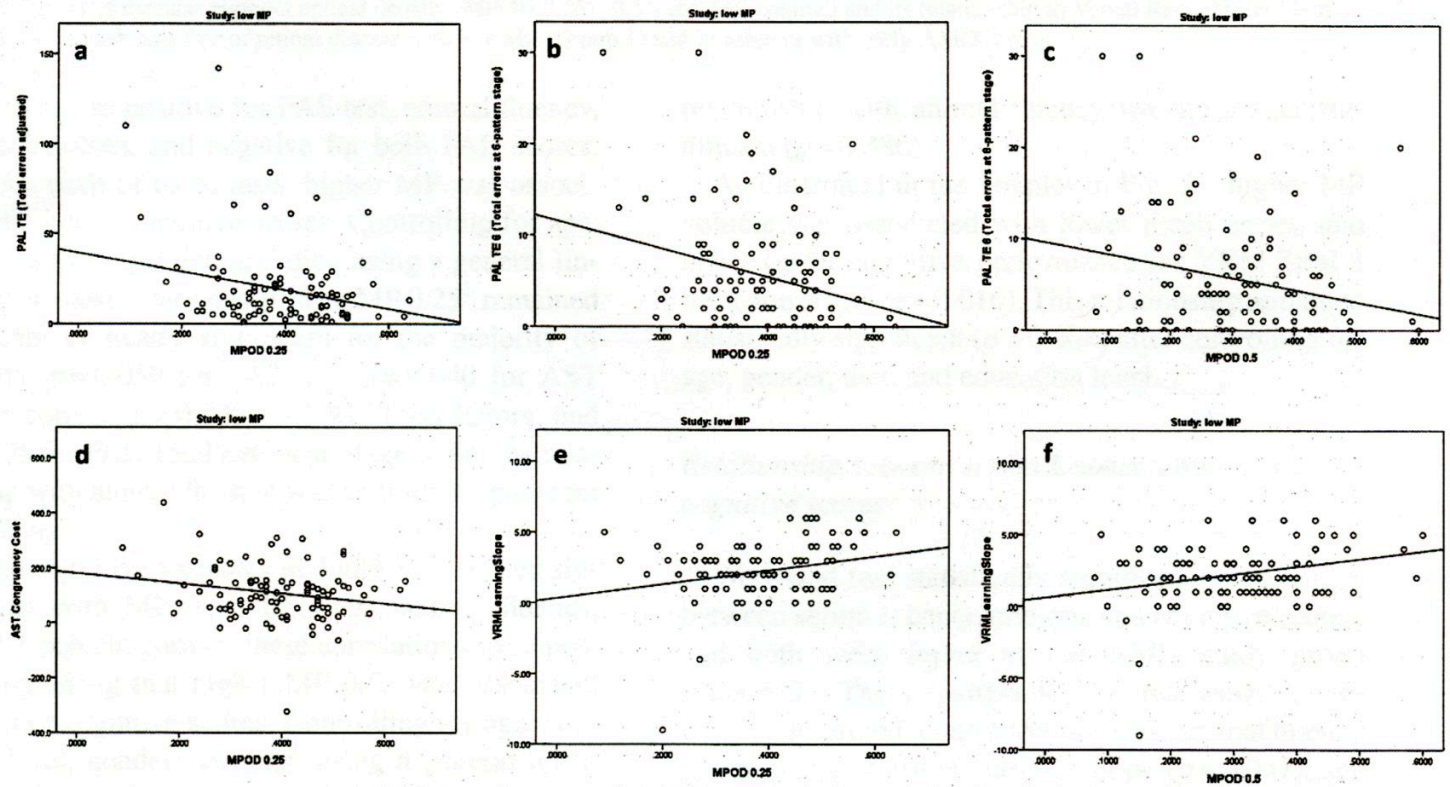


Fig. 1. Relationships between macular pigment optical density and cognitive scores in subjects free of retinal disease with low MP (Group 1).

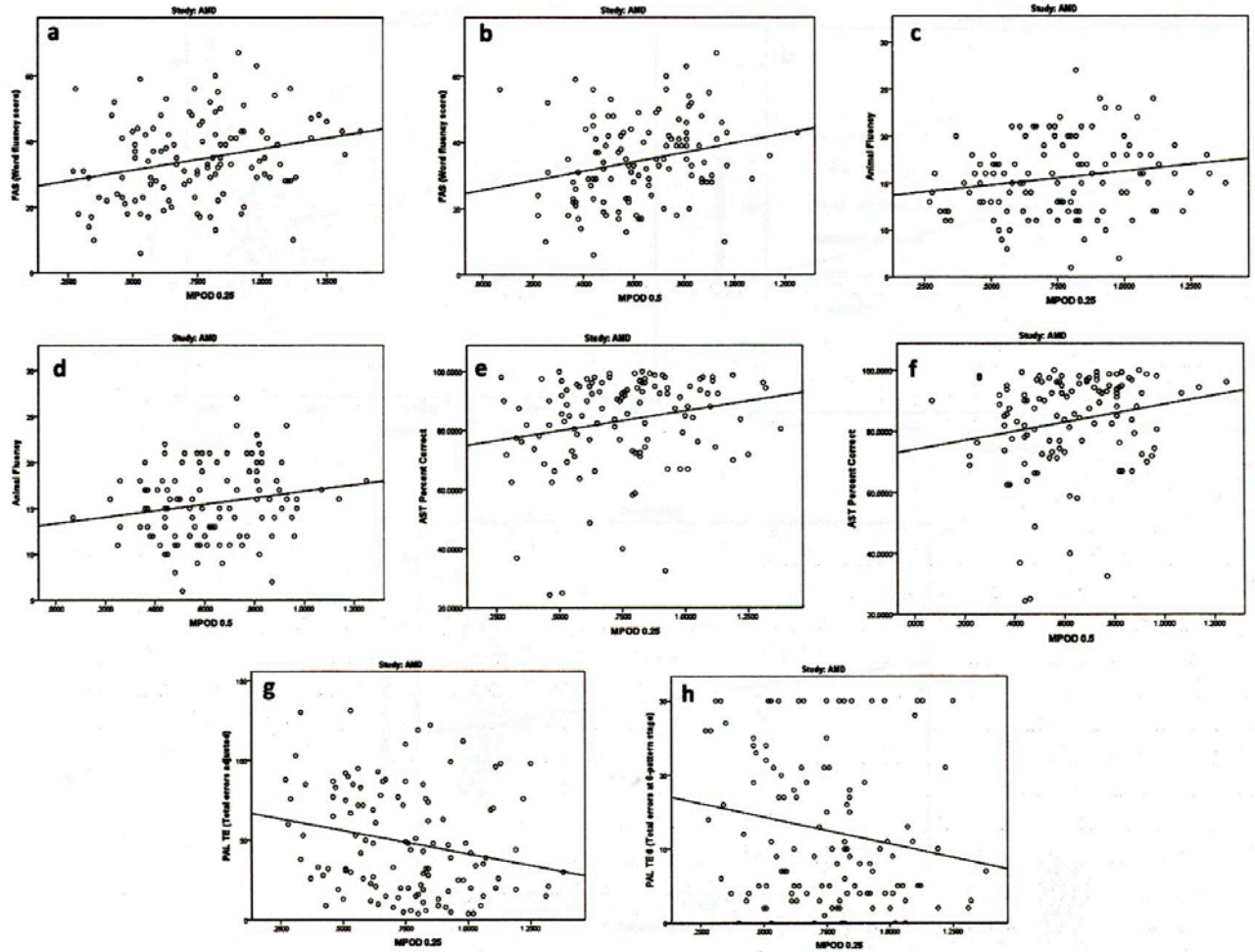


Fig. 3. Relationships between macular pigment optical density and cognitive scores in subjects with early AMD (Group 2).

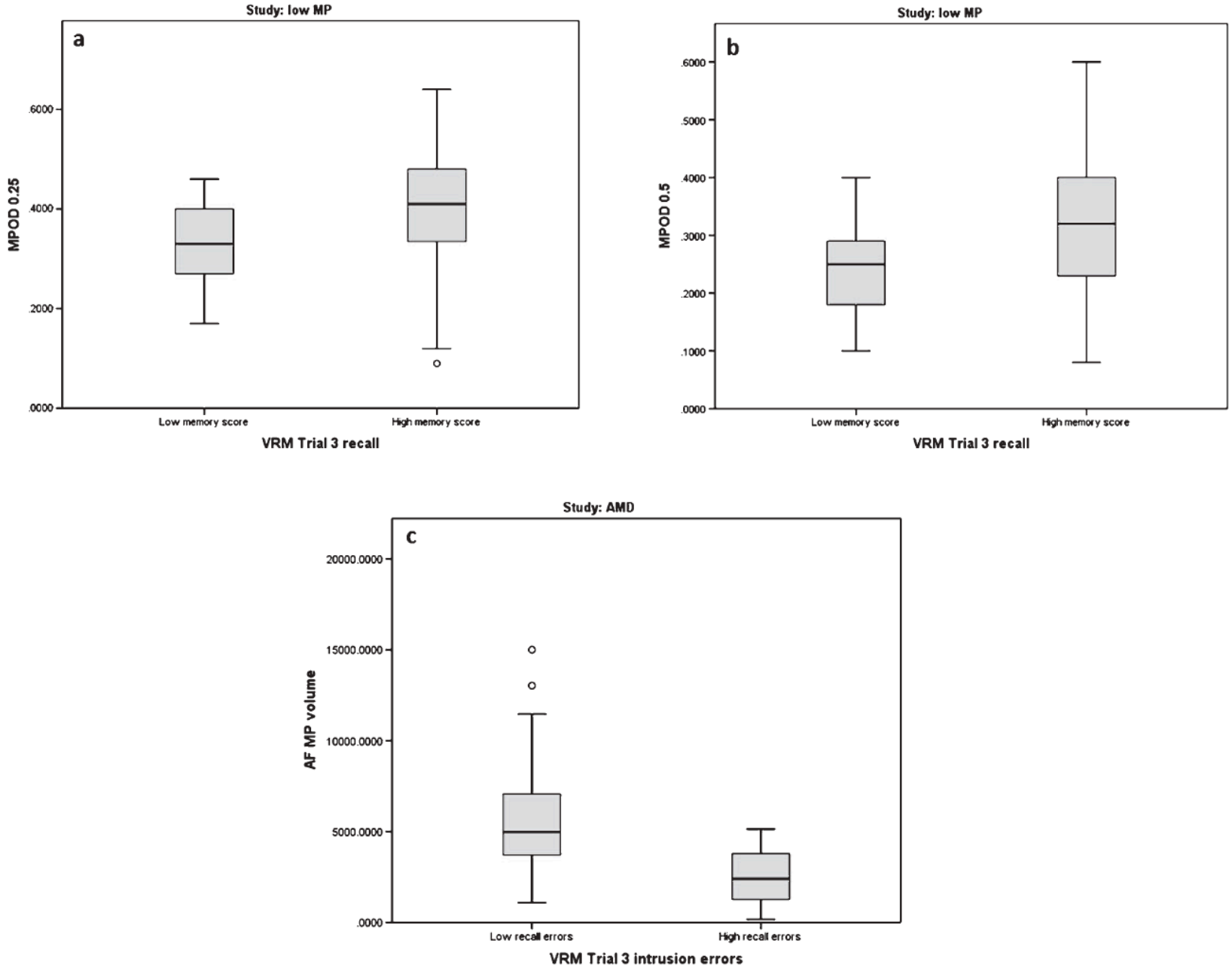


Fig. 2. Boxplots of macular pigment optical density (MPOD 0.25°, 0.5°, and MP volume) and its relationship to Verbal Recognition Memory (VRM) scores in subjects free of retinal disease with low MP (Group 1) and in subjects with early AMD (Group 2).

Kelly et al 2015

Results: Significant correlations were evident betweenMP and various measures of cognitive function in both groups ($r = –0.273$ to 0.261, $p \leq 0.05$, for all). Both serum L and Z concentrations correlated significantly ($r = 0.187$, $p \leq 0.05$ and $r = 0.197$, $p \leq 0.05$, respectively) with semantic (animal) fluency cognitive scores in Group 2 (the AMD study group), while serum L concentrations also correlated significantly with Verbal Recognition Memory learning slope scores in the AMD study group($r = 0.200$, $p = 0.031$).

Most of the correlations with MP, but not serum L or Z, remained significant after controlling for age,gender, diet, and education level.

Zhou et al, 2016

Of the initial 278 literatures, only six case–control and one RCT studies met all of the inclusion criteria. A total of 794 AMD patients and 1,227 controls were included in this study. Five studies were performed with mini-mental state examination (MMSE), two studies with animal fluency, two studies with trail making test (TMT)-A and -B, one study with Mini-Cog. Results of the meta-analysis revealed lower cognitive function test scores in patients with AMD, especially with MMSE and Mini-Cog test (*P*#0.001 for all).

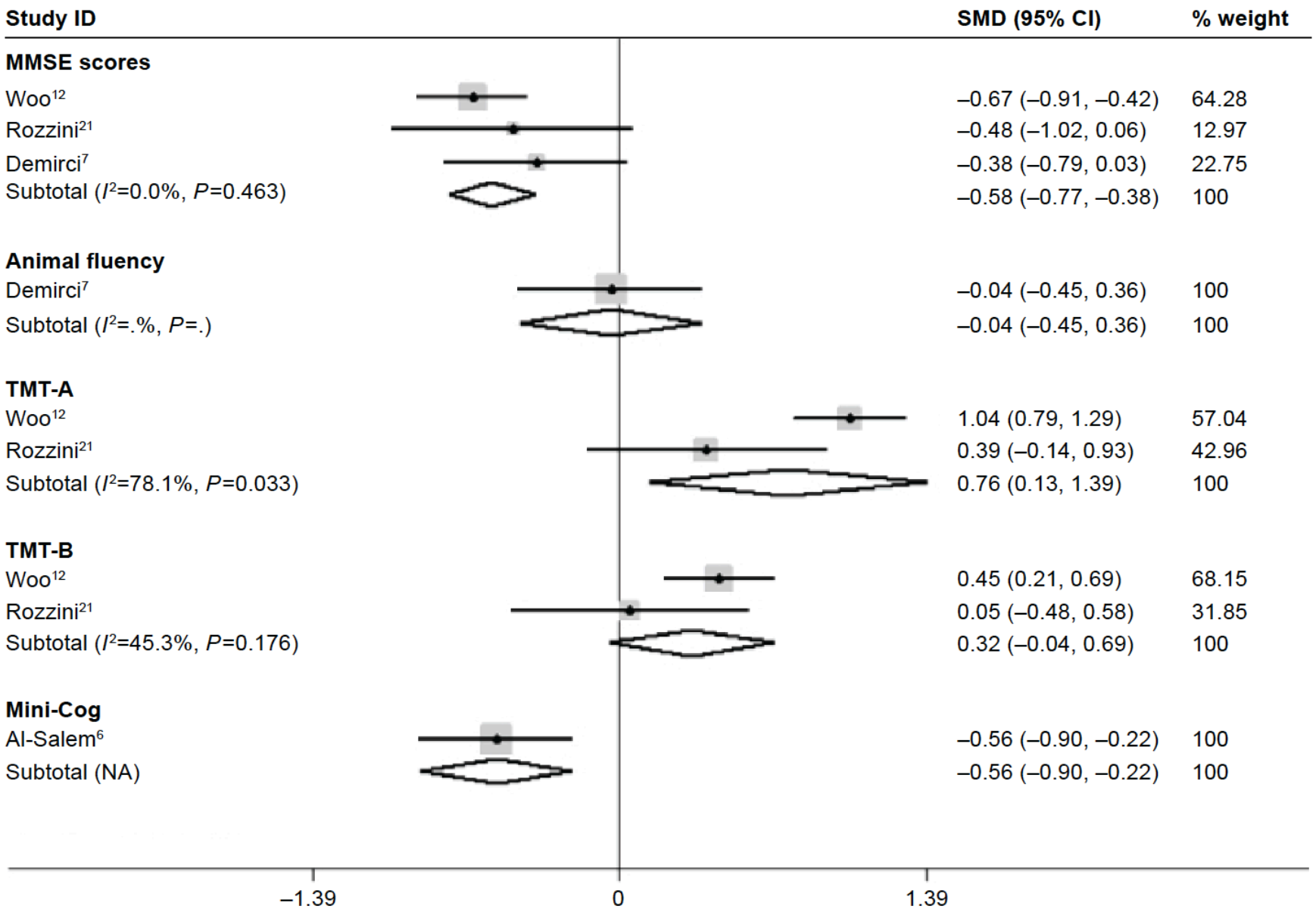


Figure 3 Meta-analysis of the cognitive function in wet-AMD patients and controls by MMSE, Animal fluency, Mini-Cog, TMT-A and -B.

Note: Weights are from random-effects analysis.

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; MMSE, mini-mental state examination; NA, not applicable; SMD, standard mean difference; TMT, trail making test.

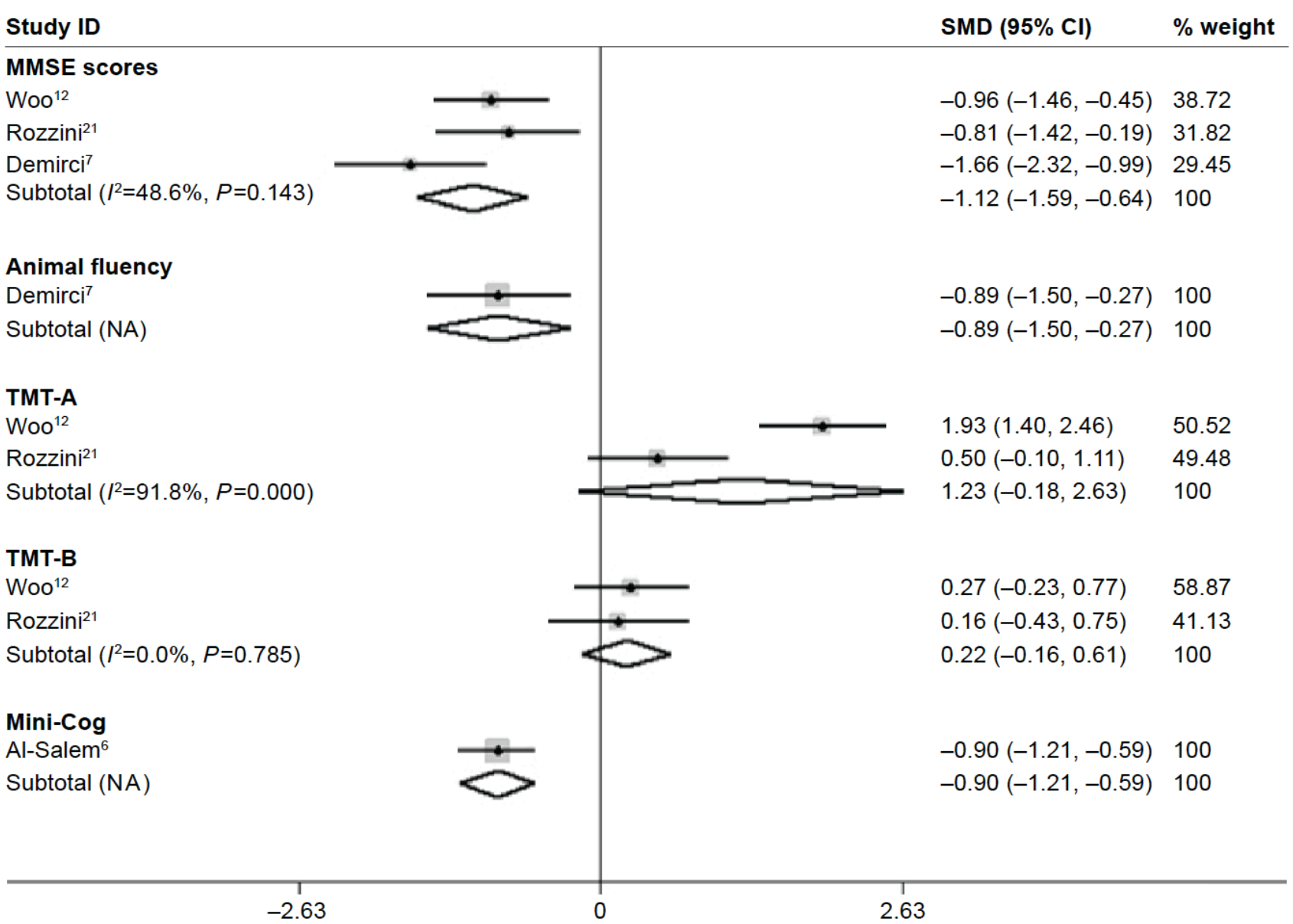


Figure 4 Meta-analysis of the cognitive function in dry-AMD patients and controls by MMSE, Animal fluency, Mini-Cog, TMT-A and -B.

Note: Weights are from random-effects analysis.

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; MMSE, mini-mental state examination; NA, not applicable; SMD, standard mean difference; TMT, trail making test.

Zhou et al, 2016

Results of the meta-analysis revealed lower cognitive function test scores in patients with AMD, especially with MMSE and Mini-Cog test ($P<0.001$ for all). The results also showed that differences in the TMT-A (except AMD [total] vs controls) and TMT-B test had no statistical significance ($P>0.01$).

This meta-analysis suggested lower cognitive function test scores in patients with AMD, especially with MMSE and Mini-Cog testing.

Nolan et al (2015)

Objective: To investigate supplementation with the macular carotenoids on MP, vision, and cognitive function in patients with AD versus controls.

Methods: A randomized, double-blind clinical trial with placebo and active arms. 31 AD patients and 31 age-similar control subjects were supplemented for six months with either Macushield (10 mg meso-zeaxanthin [MZ]; 10 mg lutein [L]; 2mg zeaxanthin [Z]) or placebo (sunflower oil). MP was measured using dual-wavelength autofluorescence (Heidelberg Spectralis®).

Serum L, Z, andMZwere quantified by high performance liquid chromatography. Visual function was assessed by best corrected visual acuity and contrast sensitivity (CS). Cognitive function was assessed using a battery of cognition tests, including theCambridge Neuropsychological Test Automated Battery (CANTAB).

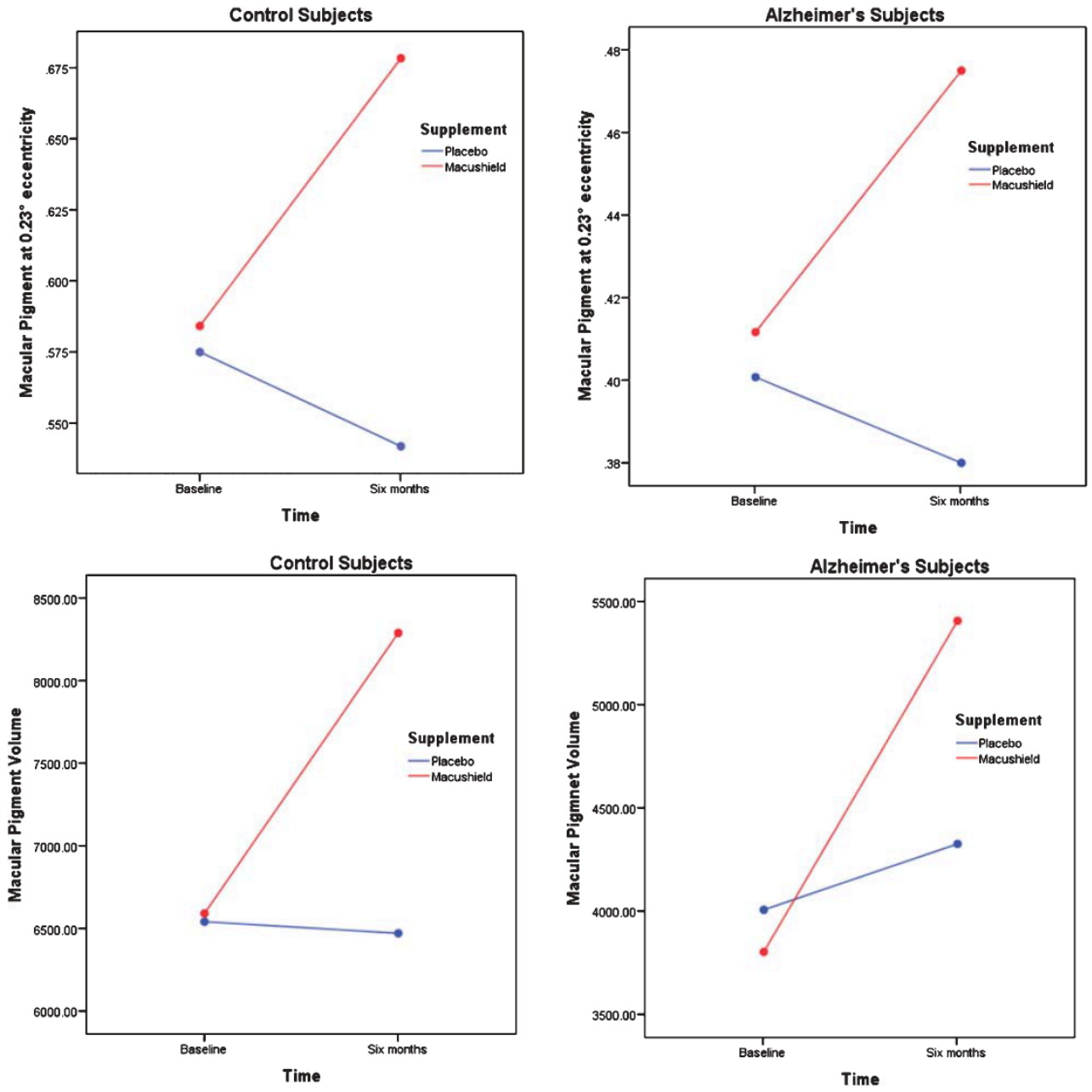


Fig. 2. Mean macular pigment at baseline and after six months of supplementation with either active supplement (Macushield) or placebo in subjects with Alzheimer's disease and control subjects.

Table 4
Contrast sensitivity at baseline and following six months of supplementation with either active or placebo intervention

Group	Intervention	Measurement	mean ± SD at baseline	mean ± SD at 6 months	% Change	Sig.
Control	placebo	CS at 1.2cpd	1.83 ± 0.154	1.82 ± 0.150	−0.01	0.84
Control	active	CS at 1.2cpd	1.76 ± 0.254	1.88 ± 0.249	*4.9*	**0.006**
AD	placebo	CS at 1.2cpd	1.51 ± 0.273	1.55 ± 0.320	2.9	0.108
AD	active	CS at 1.2cpd	1.47 ± 0.254	1.63 ± 0.237	*11*	**0.04**
Control	placebo	CS at 2.4cpd	1.81 ± 0.180	1.83 ± 0.185	1.1	0.6
Control	active	CS at 2.4cpd	1.73 ± 0.350	1.82 ± 0.290	5	**0.038**
AD	placebo	CS at 2.4cpd	1.47 ± 0.420	1.48 ± 0.402	0.7	0.461
AD	active	CS at 2.4cpd	1.48 ± 0.226	1.55 ± 0.241	*4.9*	**0.048**
Control	placebo	CS at 6.0cpd	1.37 ± 0.240	1.46 ± 0.205	3.3	0.275
Control	active	CS at 6.0cpd	1.57 ± 0.196	1.59 ± 0.161	0.3	0.687
AD	placebo	CS at 6.0cpd	1.34 ± 0.263	1.34 ± 0.309	0	0.785
AD	active	CS at 6.0cpd	1.17 ± 0.255	1.29 ± 0.303	*10*	0.16
Control	placebo	CS at 9.6cpd	1.16 ± 0.286	1.16 ± 0.350	0	0.919
Control	active	CS at 9.6cpd	1.27 ± 0.222	1.32 ± 0.171	4	0.38
AD	placebo	CS at 9.6cpd	1.03 ± 0.266	1.04 ± 0.300	0.9	0.84
AD	active	CS at 9.6cpd	0.87 ± 0.308	1.00 ± 0.340	*16*	**0.011**
Control	placebo	CS at 15.15cpd	0.89 ± 0.31	0.83 ± 0.32	−7	0.39
Control	active	CS at 15.15cpd	0.75 ± 0.36	0.88 ± 0.25	*16*	1.76
AD	placebo	CS at 15.15cpd	0.85 ± 0.16	0.79 ± 0.16	−7	0.471
AD	active	CS at 15.15cpd	0.68 ± 0.24	0.85 ± 0.24	*25*	**0.047**

Data displayed are mean ± standard deviation. Sig., the p value for paired-sample t testing between baseline and six months for each group split by intervention; CS, contrast sensitivity; cpd, cycles per degree; AD, Alzheimer's disease; active, Macushield^{TM}: 10 mg lutein, 10 mg meso-zeaxanthin, and 2 mg zeaxanthin; placebo, sunflower oil.

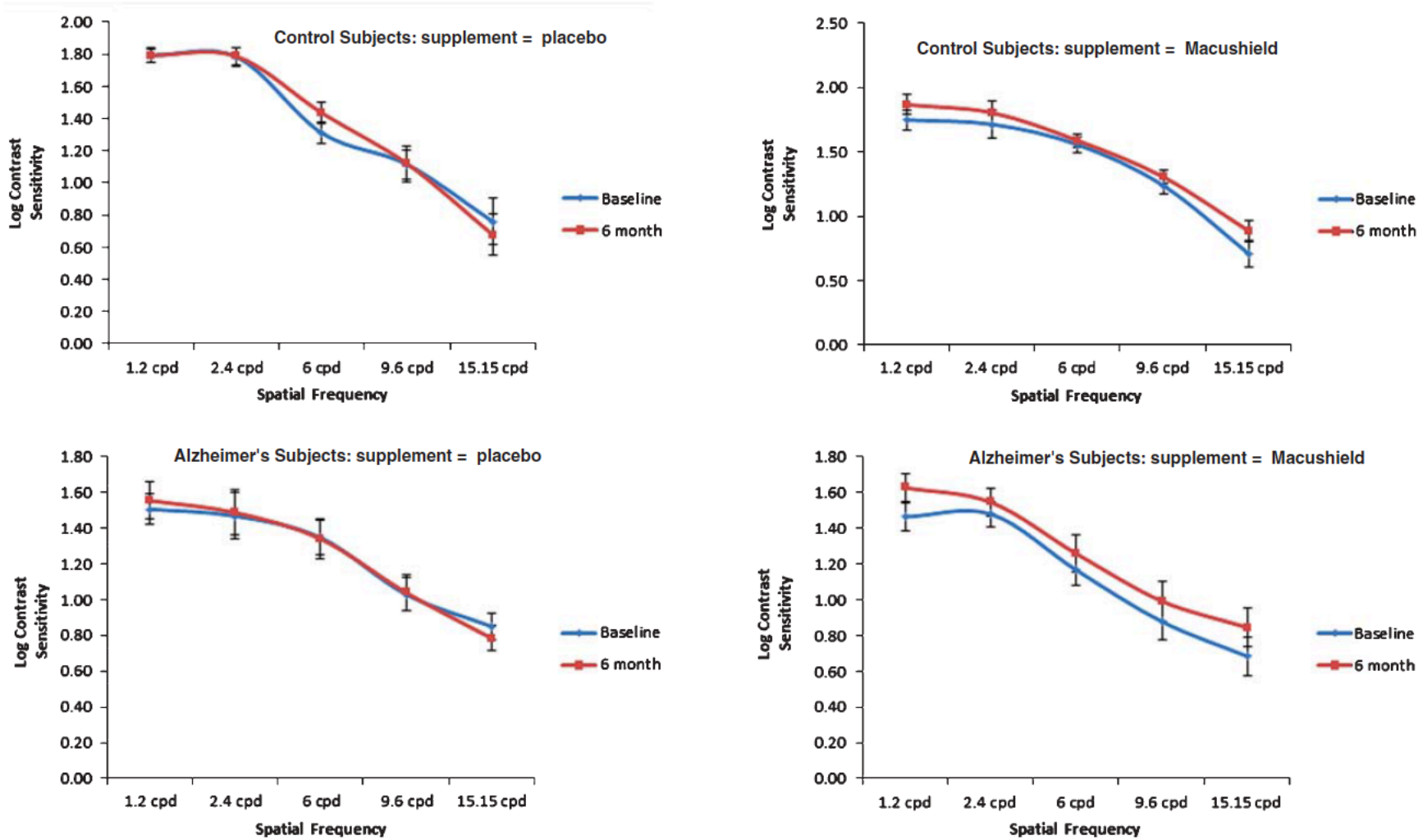


Fig. 3. Contrast sensitivity curve at baseline and after six months of supplementation with either active supplement (Macushield) or placebo in subjects with Alzheimer's disease and control subjects.

Nolan et al (2015)

Results: Subjects on the active supplement (for both AD and non-AD controls) exhibited statistically significant improvement in serum concentrations of L, Z, MZ, and MP ($p < 0.001$, for all) and also CS at ($p = 0.039$). Also, for subjects on the active supplement, paired samples t-tests exhibited four significant results (from five spatial frequencies tested) in the AD group, and two for the non-AD group, and all indicating improvements in CS. We found no significant changes in any of the cognitive function outcome variables measured ($p > 0.05$, for all).

Conclusion: Supplementation with the macular carotenoids (MZ, Z, and L) benefits patients with AD, in terms of clinically meaningful improvements in visual function and in terms of MP augmentation.

Chew et al 2015

OBJECTIVE To test the effects of oral supplementation with nutrients on cognitive function.
DESIGN, SETTING, AND PARTICIPANTS In a double-masked randomized clinical trial (the Age-Related Eye Disease Study 2 [AREDS2]), retinal specialists in 82 US academic andcommunity medical centers enrolled and observed participants who were at risk for developing late age-related macular degeneration (AMD). In addition to annual eye examinations, several validated cognitive function tests wereadministered via telephone by trained personnel at baseline and every 2 years during the5-year study.
INTERVENTIONS Long-chain polyunsaturated fatty acids (LCPUFAs) (1 g) and/or lutein(10mg)/zeaxanthin (2mg) vs placebo were tested in a factorial design. All participants were
also given varying combinations of vitamins C, E, beta carotene, and zinc.

Box. AREDS2 Cognitive Battery Tests by Order of Administration[a]

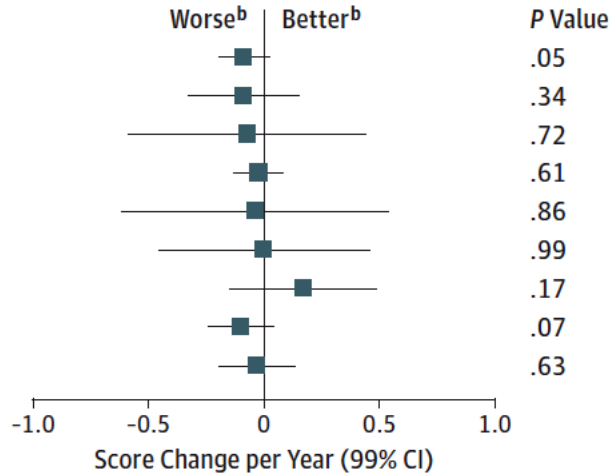
1. The Hearing Handicap Inventory[19] is given first because the interview is conducted by telephone
2. The Center for Epidemiologic Studies' Depression Scale (CES-D)[20] is designed to assess symptoms of depression in the general population
3. The Telephone Interview Cognitive Status-Modified (TICS-M)[21] is a version of the Mini Mental State Examination; TICS-M also includes 10 words that are given early and tested for immediate and delayed recall
4. The Animal Category[22] is used, together with the tests of letter fluency and alternating fluency (items 5 and 6), to assess language and executive function; participants are asked to name as many animals as possible within 1 minute
5. Letter Fluency[22] is used with animal and alternating fluency; participants are asked to name as many words starting with the letters *F*, *A*, and *S* as possible within 1 minute
6. Alternating Fluency[22] is used with animal and letter fluency; participants are instructed to alternately name a word beginning with the letter *C* and a food category in 1 minute
7. The Wechsler Memory Scale, Third Edition (WMS-III), Logical Memory Part I and Part II[23] measures both immediate and delayed recall of 2 stories; the test assesses 2 domains of cognitive function: attention and memory
8. Digits Backward[24] is a task used to test the speed of processing task, in which the participant is asked to count as fast as they can backward starting from 100 for 30 seconds
9. Delayed recall of the WMS-III Recall paragraph
10. TICS-M Recall consisted of recalling the 10 words initially read with the TICS

[a] Only test items 3 through 10 were used for scoring.

Figure 2. Results of the Mixed-Models Regression for the Change Per Year in Cognitive Function Test Scores From Baseline for Each of the Nutrients Tested

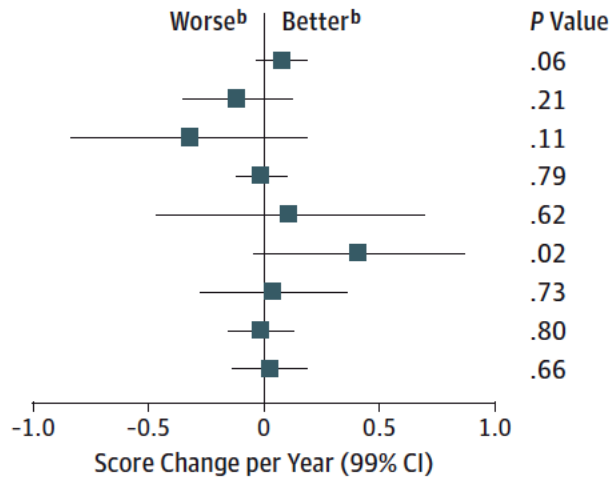
Omega-3 LCPUFA vs No Omega-3 LCPUFA[a]

Test	No. of Patients	Difference in Change in Score per Year (99% CI)	*P* Value
TICS word list recall[20]	2674	-0.08 (-0.19 to 0.03)	.05
Verbal fluency, animal[21]	2679	-0.09 (-0.33 to 0.15)	.34
Verbal fluency, letter[21]	2676	-0.07 (-0.59 to 0.44)	.72
Verbal fluency, alternating[21]	2665	-0.02 (-0.13 to 0.08)	.61
Wechsler logical memory I[22]	2682	-0.04 (-0.61 to 0.54)	.86
Wechsler logical memory II[22]	2675	0.00 (-0.46 to 0.46)	.99
Backwards counting[23]	2678	0.17 (-0.15 to 0.49)	.17
TICS total[c]	3063	-0.10 (-0.24 to 0.04)	.07
Composite score[d]	2636	-0.03 (-0.20 to 0.13)	.63



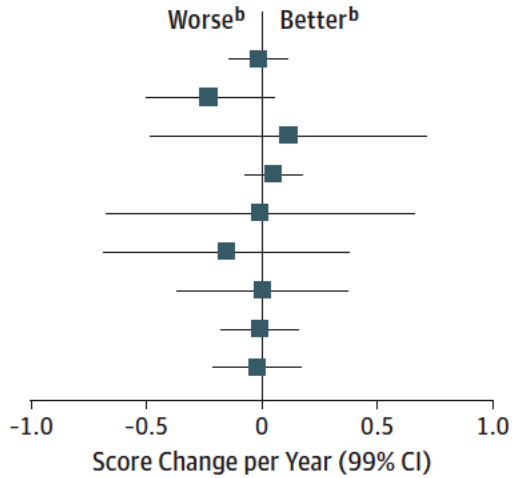
Lutein/Zeaxanthin vs No Lutein/Zeaxanthin[a]

Test	No. of Patients	Difference in Change in Score per Year (99% CI)	*P* Value
TICS word list recall[20]	2674	0.08 (-0.03 to 0.19)	.06
Verbal fluency, animal[21]	2679	-0.12 (-0.35 to 0.12)	.21
Verbal fluency, letter[21]	2676	-0.32 (-0.84 to 0.19)	.11
Verbal fluency, alternating[21]	2665	-0.01 (-0.12 to 0.09)	.79
Wechsler logical memory I[22]	2682	0.11 (-0.46 to 0.69)	.62
Wechsler logical memory II[22]	2675	0.41 (-0.05 to 0.87)	.02
Backwards counting[23]	2678	0.04 (-0.28 to 0.36)	.73
TICS total[c]	3063	-0.01 (-0.16 to 0.13)	.80
Composite score[d]	2636	0.03 (-0.14 to 0.19)	.66



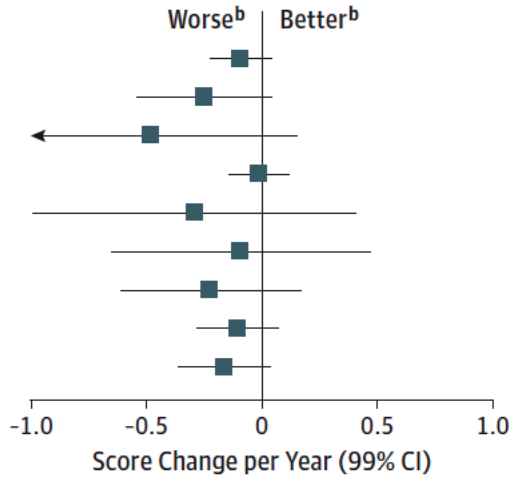
High Zinc vs Low Zinc[a]

Test	No. of Patients	Difference in Change in Score per Year (99% CI)	*P* Value
TICS word list recall[20]	2007	-0.02 (-0.14 to 0.11)	.74
Verbal fluency, animal[21]	2010	-0.23 (-0.50 to 0.05)	.04
Verbal fluency, letter[21]	2008	0.12 (-0.48 to 0.71)	.61
Verbal fluency, alternating[21]	2000	0.05 (-0.07 to 0.17)	.29
Wechsler logical memory I[22]	2009	-0.01 (-0.68 to 0.66)	.97
Wechsler logical memory II[22]	2006	-0.15 (-0.68 to 0.38)	.46
Backwards counting[23]	2007	0.00 (-0.36 to 0.37)	.98
TICS total[c]	2274	-0.01 (-0.18 to 0.16)	.89
Composite score[d]	1980	-0.02 (-0.21 to 0.17)	.77



Beta Carotene vs No Beta Carotene[a]

Test	No. of Patients	Difference in Change in Score per Year (99% CI)	*P* Value
TICS word list recall[20]	1795	-0.09 (-0.23 to 0.04)	.08
Verbal fluency, animal[21]	1798	-0.25 (-0.55 to 0.04)	.03
Verbal fluency, letter[21]	1796	-0.48 (-1.11 to 0.15)	.05
Verbal fluency, alternating[21]	1789	-0.01 (-0.14 to 0.12)	.83
Wechsler logical memory I[22]	1797	-0.29 (-0.99 to 0.41)	.28
Wechsler logical memory II[22]	1794	-0.09 (-0.65 to 0.46)	.67
Backwards counting[23]	1795	-0.22 (-0.61 to 0.17)	.14
TICS total[c]	2022	-0.11 (-0.28 to 0.07)	.12
Composite score[d]	1771	-0.16 (-0.36 to 0.04)	.04



LCPUFAs indicate long-chain polyunsaturated fatty acids.

[a] These analyses were adjusted for the following baseline covariates: age, sex, race, education, hypertension, baseline cognitive score, and baseline depression scale.

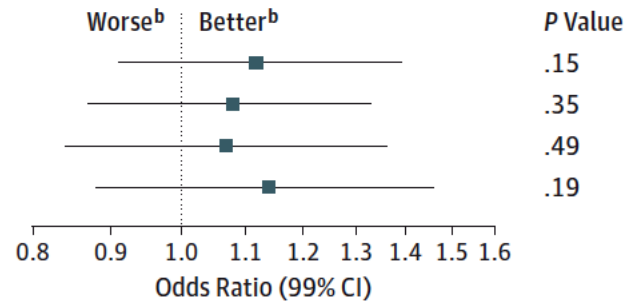
[b] Worse indicates a deterioration of the score for the tested nutrient (as indicated in each panel) and better means an improved score for participants randomized to receive the tested nutrient.

[c] The Telephone Interview Cognitive Status-Modified (TICS-M)[3] is a version of the Mini Mental State Examination (score range, 0-39 points; see eMethods [in Supplement 2] for explanation of scores for the other cognitive function tests).

[d] Composite scores were constructed by including the score of the cognitive tests, converting all test results into *z* scores, then adding the *z* scores. The composite score was computed to obtain an overall score for the battery of cognitive function tests, ranging from −22 to 17, with higher scores indicating better function.

Figure 3. Association of a TICS Score of Less Than 30 With Nutrient Intervention[a]

Nutrient	Score <30		Score ≥30		Odds Ratio (99% CI)	*P* Value
	No. of Patients	No. of Events	No. of Patients	No. of Events		
Omega-3 LCPUFA vs no omega-3 LCPUFA	1521	416	1503	397	1.12 (0.91-1.39)	.15
Lutein/zeaxanthin vs no lutein/zeaxanthin	1485	410	1539	403	1.08 (0.87-1.33)	.35
High zinc vs low zinc	1122	322	1123	303	1.07 (0.84-1.36)	.49
Beta carotene vs no beta carotene	999	289	996	261	1.14 (0.88-1.46)	.19



LCPUFAs indicate long-chain polyunsaturated fatty acids.

[a] Data were calculated using repeated-measures logistic regression. The Telephone Interview Cognitive Status-Modified (TICS-M)[3] is a version of the Mini Mental State Examination, (score range, 0-39 points). A dichotomous outcome from the TICS is defined as follows: (1) TICS total <30 points defines low cognitive function; and (2) TICS total ≥30 defines normal cognitive function. Models were adjusted for: baseline age, sex, race, history of hypertension, education, baseline cognitive score and baseline depression score.

[b] Worse indicates a deterioration of the TICS score (large proportion with low cognitive function) for that given nutrient and better indicates an improved TICS (smaller proportion with low cognitive function).

Chew et al 2015

Among older persons with AMD, oral supplementation with LCPUFAs or lutein/zeaxanthin had no statistically significant effect on cognitive function.

9. Traumatic Brain Injury

Brooke Army Medical Center

Identified need: Patient demographics include 290,000 diagnosed cases of mTBI from 2000-2015

Study included matched control of 100 acute, non-blast mTBI subjects with between ages 19-44 years

Results showed significant differences in pupillary light response (PLR), specifically dilation velocity and re-dilation recovery, suggesting possible damage to the sympathetic system

**King-Devick, Convernce Insufficiency Symptom Survey and NPC also demonstrated significant difference between matched controls and mTBI subjects

Review of Publications

Paucity of studies specifically focusing on photosensitivity phenomena within mTBI. Existing literature addresses photosensitivity as a general survey of overall sequelae, related factors and prevalence

2016 Dissertation study

Investigations into mTBI photosensitivity included:

1) Exploration of natural time course
2) Determination of associated factors
3) Assessment of current treatment

2016 Dissertation study

Aspects of photosensitivity:

1) ~85% of mTBI subjects reported stable photosensitivity within first 12 months
    1) ~50% of mTBI subjects reported decreased photosensitivty after 12 months
        1) Suggested mechanisms:
            1) Neural repair
            2) Neural habituation
            3) Compensatory mechanisms
        2) Of those reporting decreased photosensitivity:
            1) ~72% did NOT report wearing tinted lenses
            2) ~71% wore SCL

2016 Dissertation study

Remediation of photosensitivity

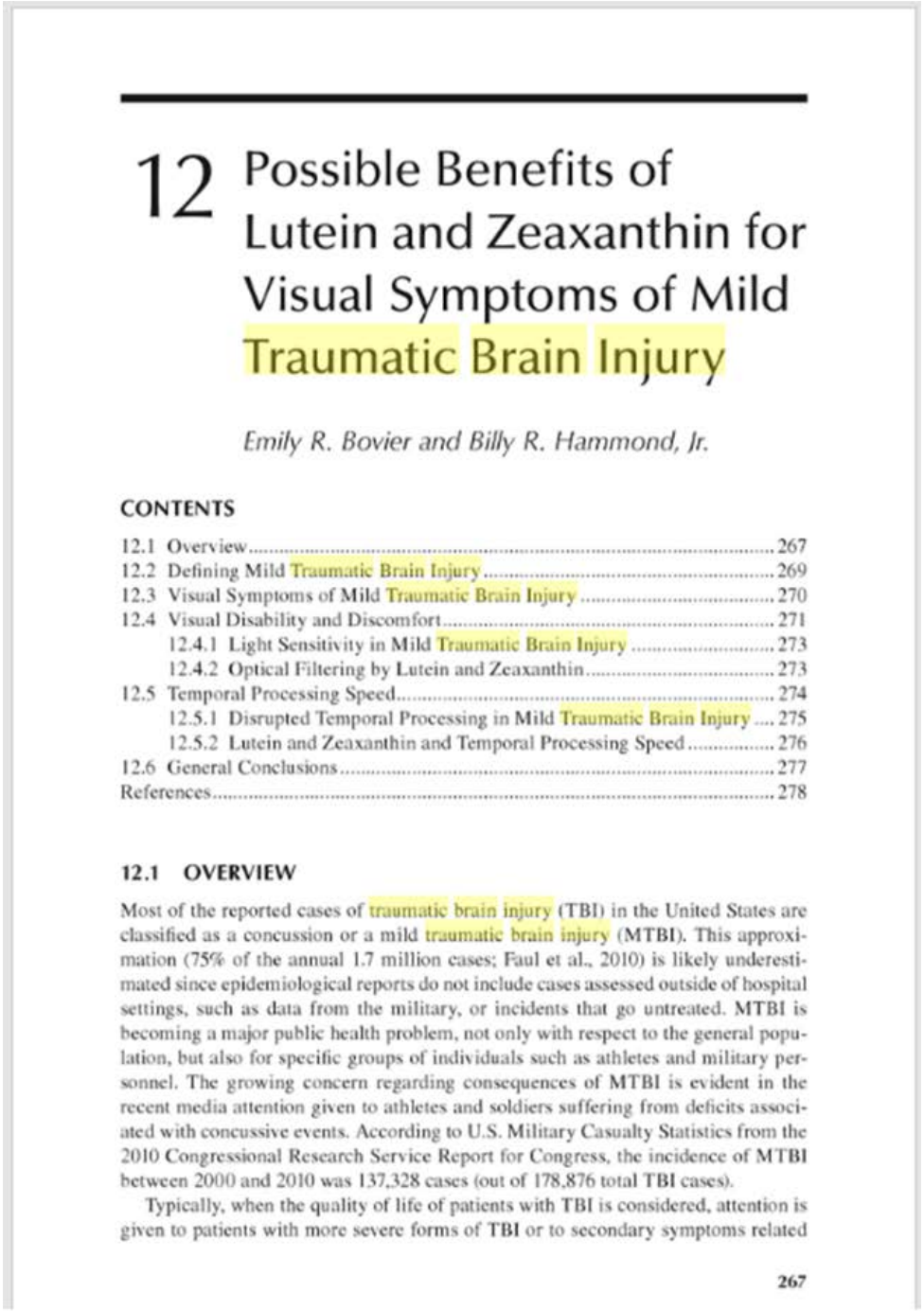
1) Habituation
2) Biomechanical adaptation of SCL wear through trigeminal desensitization

Dietary Supplements in Health Promotion

Published by CRC Press in 2015

Lutein and Zeaxanthin are found throughout retina and brain and may be uniquely suited to affecting processes initiated by concussive events including inflammatory stress. Secondary injury be immediately following impact in closed head injuries and is likely a contributor to neuronal dysfunction and loss.

Inflammation is an acute and chronic response to concussive head injury (Cederberg etal., 2010). Lutein has been shown to decrease the expression of COX-2 and reduce nNOS in a dose-dependent manner. Lutein and zeaxanthin also stabilize cell membranes along with omega-3 FAs reducing disruption of neuronal signaling.



12 Possible Benefits of Lutein and Zeaxanthin for Visual Symptoms of Mild Traumatic Brain Injury

Emily R. Bovier and Billy R. Hammond, Jr.

CONTENTS

12.1 OVERVIEW

Most of the reported cases of traumatic brain injury (TBI) in the United States are classified as a concussion or a mild traumatic brain injury (MTBI). This approximation (75% of the annual 1.7 million cases; Faul et al., 2010) is likely underestimated since epidemiological reports do not include cases assessed outside of hospital settings, such as data from the military, or incidents that go untreated. MTBI is becoming a major public health problem, not only with respect to the general population, but also for specific groups of individuals such as athletes and military personnel. The growing concern regarding consequences of MTBI is evident in the recent media attention given to athletes and soldiers suffering from deficits associated with concussive events. According to U.S. Military Casualty Statistics from the 2010 Congressional Research Service Report for Congress, the incidence of MTBI between 2000 and 2010 was 137,328 cases (out of 178,876 total TBI cases).

Typically, when the quality of life of patients with TBI is considered, attention is given to patients with more severe forms of TBI or to secondary symptoms related

AN Advances in Nutrition An International Review Journal

ω-3 Fatty Acid Supplementation as a Potential Therapeutic Aid for the Recovery from Mild Traumatic Brain Injury/Concussion[1,2]

Erin Gemkovich Barrett, Michael I. McBurney, and Eric D. Ciappio*

DSM Nutritional Products, Parsippany, NJ

ABSTRACT

Sports-related concussions or mild traumatic brain injuries (mTBIs) are becoming increasingly recognized as a major public health concern; however, no effective therapy for these injuries is currently available. ω-3 (n–3) fatty acids, such as docosahexaenoic acid (DHA), have important structural and functional roles in the brain, with established clinical benefits for supporting brain development and cognitive function throughout life. Consistent with these critical roles of DHA in the brain, accumulating evidence suggests that DHA may act as a promising recovery aid, or possibly as a prophylactic nutritional measure, for mTBI. Preclinical investigations demonstrate that dietary consumption of DHA provided either before or after mTBI improves functional outcomes, such as spatial learning and memory. Mechanistic investigations suggest that DHA influences multiple aspects of the pathologic molecular signaling cascade that occurs after mTBI. This review examines the evidence of interactions between DHA and concussion and discusses potential mechanisms by which DHA helps the brain to recover from injury. Additional clinical research in humans is needed to confirm the promising results reported in the preclinical literature. *Adv. Nutr. 5: 268–277, 2014.*

Mild Traumatic Brain Injury/Concussion

Concussion is a common injury among athletes, particularly those participating in contact sports such as football and hockey. Concussion, also referred to as mild traumatic brain injury (mTBI)[3], is defined by the CDC as "a complex pathophysiologic process affecting the brain, induced by traumatic biomechanical forces secondary to direct or indirect forces to the head" (1). This injury often results in impairments in memory and orientation and may be accompanied by a loss of consciousness (2). Approximately 1.5 million concussion-related emergency room visits are reported annually in the United States (3). Because many of these injuries go undiagnosed, it is estimated that up to 3.8 million individuals may be affected annually by sports-related concussions (3). Public awareness of concussion has grown in recent years, and, consequently, the incidence of diagnosed concussions has also displayed a dramatic increase, particularly among those aged ≤18 y. The incidence of concussions among minors increased 57% between 2008 and 2009 (4), and among high school athletes, the incidence has increased by 4.2-fold over an 11-y consecutive period beginning in 1998 (5). Conservative estimates of the combined direct and indirect annual cost of concussion are approximately $12 billion (6).

The short-term symptoms of concussions are variable depending on the severity of the injury. Symptoms often include headache, cognitive impairment (i.e., diminished reaction times, or "feeling foggy"), sensitivity to light and sound, irritability, sleep disturbances, and loss of consciousness (1,7). Symptoms typically resolve within 7–10 d for adults (7), but the presence of abnormal neurometabolic function may persist for up to 4 wk after injury (8). In children and adolescents, the recovery period from concussion may be longer (9,10); furthermore, children and adolescents may be at an increased risk of long-term cognitive impairments after injury because the developing brain is believed to be more vulnerable to insult as a result of injury (8,11). Postconcussion treatment and recovery is primarily limited to cognitive and physical rest until symptoms resolve. For athletes, returning to play after a concussion involves a

[1] Author disclosures: E. C. Barrett, M. I. McBurney, and E. D. Ciappio are employees of DSM Nutritional Products, a producer and seller of ω-3 FAs, including DHA.

[3] Abbreviations used: BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; LCPUFA, long-chain PUFA; mTBI, mild traumatic brain injury.

* To whom correspondence should be addressed. E-mail: eric.ciappio@dsm.com.

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J Neurosurg 121:42–54, 2014

Amelioration of oxidative stress and protection against early brain injury by astaxanthin after experimental subarachnoid hemorrhage

Laboratory investigation

Xiang-Sheng Zhang, M.D.,[1] Xin Zhang, M.D., Ph.D.,[1,2] Meng-Liang Zhou, M.D., Ph.D.,[2] Xiao-Ming Zhou, M.D.,[1] Ning Li, M.D.,[1] Wei Li, M.D.,[2] Zi-Xiang Cong, M.D.,[2] Qing Sun, M.D.,[2] Zong Zhuang, M.D.,[2] Chun-Xi Wang, M.D.,[2] and Ji-Xin Shi, M.D., Ph.D.[2]

[1]Department of Neurosurgery, Jinling Hospital, School of Medicine, Second Military Medical University, Shanghai, China; and [2]Department of Neurosurgery, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, Jiangsu Province, China

Object. Aneurysmal subarachnoid hemorrhage (SAH) causes devastating rates of mortality and morbidity. Accumulating studies indicate that early brain injury (EBI) greatly contributes to poor outcomes after SAH and that oxidative stress plays an important role in the development of EBI following SAH. Astaxanthin (ATX), one of the most common carotenoids, has a powerful antioxidative property. However, the potential role of ATX in protecting against EBI after SAH remains obscure. The goal of this study was to assess whether ATX can attenuate SAH-induced brain edema, blood-brain barrier permeability, neural cell death, and neurological deficits, and to elucidate whether the mechanisms of ATX against EBI are related to its powerful antioxidant property.

Methods. Two experimental SAH models were established, including a prechiasmatic cistern SAH model in rats and a one-hemorrhage SAH model in rabbits. Both intracerebroventricular injection and oral administration of ATX were evaluated in this experiment. Posttreatment assessments included neurological scores, body weight loss, brain edema, Evans blue extravasation, Western blot analysis, histopathological study, and biochemical estimation.

Results. It was observed that an ATX intracerebroventricular injection 30 minutes post-SAH could significantly attenuate EBI (including brain edema, blood-brain barrier disruption, neural cell apoptosis, and neurological dysfunction) after SAH in rats. Meanwhile, delayed treatment with ATX 3 hours post-SAH by oral administration was also neuroprotective in both rats and rabbits. In addition, the authors found that ATX treatment could prevent oxidative damage and upregulate the endogenous antioxidant levels in the rat cerebral cortex following SAH.

Conclusions. These results suggest that ATX administration could alleviate EBI after SAH, potentially through its powerful antioxidant property. The authors conclude that ATX might be a promising therapeutic agent for EBI following SAH.

(http://thejns.org/doi/abs/10.3171/2014.2.JNS13730)

Key Words • **astaxanthin** • **early brain injury** • **oxidative stress** • **subarachnoid hemorrhage** • **rat** • **rabbit** • **vascular disorders**

Subarachnoid hemorrhage (SAH) is one of the most life-threatening diseases, with high morbidity and mortality rates worldwide.[24] For the past decades, cerebral vasospasm has been regarded as the major cause of disastrous outcomes in patients who suffer an SAH. However, the success of therapies for SAH in reducing the incidence of cerebral vasospasm without improved long-term neurological outcome has been disappointing.[24] This fact suggests that cerebral vasospasm may not be the sole cause of poor outcomes after SAH. Recently, more and more studies have shown that early brain injury (EBI), which refers to the acute injuries to the whole brain within the first 72 hours following SAH, is the primary cause of death in patients with SAH.[3,22,24] Therefore, treatment of EBI has been considered to be the main goal in the management of patients with SAH. Although

Abbreviations used in this paper: ATX = astaxanthin; BBB = blood-brain barrier; DAB = 3,3'-diaminobenzidine; EB = Evans blue; EBI = early brain injury; GAPDH = glyceraldehyde-3-phosphate dehydrogenase; GSH = glutathione; H_2O_2 = hydrogen peroxide; MDA = malondialdehyde; PBS = phosphate-buffered saline; SAH = subarachnoid hemorrhage; SOD = superoxide dismutase; TBS-T = Tris-buffered saline with Tween 20.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

10. Military Applications

Macular Pigment and Visual Performance in Low Light Levels

Investigative Ophthalmology and Visual Science (Mar 2015)

Retina

Macular Pigment and Visual Performance in Low-Light Conditions

James M. Stringham,[1,2] Paul V. Garcia,[1] Peter A. Smith,[1] Paul L. Hiers,[1] Leon N. McLin,[3] Thomas K. Kuyk,[1] and Brian K. Foutch[3,4]

[1]TASC, Inc., JBSA Fort Sam Houston, Texas, United States
[2]Nutritional Neuroscience Laboratory, University of Georgia, Athens, Georgia, United States
[3]711th Human Performance Wing, Human Effectiveness Directorate, Bioeffects Division, Optical Radiation Bioeffects Branch, Air Force Research Laboratory, JBSA Fort Sam Houston, Texas, United States
[4]Rosenberg School of Optometry, University of the Incarnate Word, San Antonio, Texas, United States

Correspondence: James M. Stringham, Nutritional Neuroscience Laboratory, Department of Psychology, University of Georgia, Athens, GA 30602, USA;
psychjim@uga.edu.

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Purpose. By reducing rod intrusion and improving efficiency of neural signaling throughout the visual system, macular pigment (MP) could improve many aspects of visual performance in low-light level conditions. Our study examined this possibility for a variety of visual performance parameters, including spatial resolution, dark adaptation kinetics, and color detection.

Methods. Twenty-seven subjects participated in the study. Spatial profiles of MP optical density (MPOD) were determined by using heterochromatic flicker photometry. Mesopic- and scotopic-adaptation level experiments were conducted in Maxwellian view.

Results. Subjects with higher MPOD required significantly lower contrast to detect the mesopic-level resolution targets; this effect became stronger with increasing spatial frequency. Dark adaptation recovery times were significantly faster as a function of MPOD (by nearly 2 minutes for the lowest mesopic-level task [high versus low MPOD]; $P < 0.001$). Absolute scotopic thresholds were also significantly associated with MPOD ($P < 0.001$). Macular pigment optical density was inversely associated with detection of yellow ($P < 0.001$), and, paradoxically, approached a significant positive correlation with the detection of blue ($P = 0.06$).

Conclusions. Macular pigment appears to enhance visual function in low-light conditions. Based on the results of this study, it can be said that MP extends the range of foveal vision into lower light. Additionally, MP appears to enhance dark adaptation kinetics, which suggests that increased MPOD leads to more efficient photopigment regeneration. The findings of the color detection portion of the study are suggestive of an active compensatory mechanism that offsets absorption by MP in order to maintain normal color perception.

Keywords: macular pigment, lutein, visual performance, visual acuity, light/dark adaptation

The dietary carotenoids lutein (L) and zeaxanthin (Z), along with the zeaxanthin stereoisomer mesozeaxanthin (MZ, shown to be produced by conversion from L in the retina[1]), are found in their highest concentrations in the inner layers of the central macula of the primate fovea,[2–4] anterior to the photoreceptor outer segments. Here, the collective accumulation of L, Z, and MZ is referred to as macular pigment (MP). Macular pigment appears yellow in color, which affords it the ability to absorb high-energy, potentially damaging short-wavelength (SW, blue-appearing) light. In fact, MP is a relatively broadband filter, capable of absorbing light from 400 to 520 nm, with peak absorption at 460 nm.[5,6] Additionally, L, Z, and MZ are potent antioxidants,[7] a property that enables them to biochemically protect the tissue in which they are embedded. Because the fovea maintains an extremely high metabolism and concomitant oxygen tension,[8] L and Z are optimally positioned to quench singlet oxygen species (i.e., free radicals) before they can appreciably damage retinal tissue; this is the basis for MP's putative role in delaying the onset or retarding the progression of age-related macular degeneration (AMD).[9] In support of this function for MP, Weale[10] has suggested that the optical properties of MP are accidental, and that the biochemical properties of MP should be emphasized as the primary reason for its occurrence in the retina. This conclusion raises a few matters concerning the optical properties of MP. First, if not for optical reasons, why would MP be deposited in layers *anterior* to the photoreceptors, where it effectively screens high-energy SW light before it can photooxidize the vulnerable lipid-rich membranes in photoreceptor outer segments? Second, the broadband screening of photoreceptors from visible SW light must affect foveal vision in some way. From an evolutionary perspective, this effect must have promoted survival. Third, if the sole function of MP is to act as an antioxidant, then (in terms of AMD) how could human evolution select for a trait that protects against a disease that manifests well after the reproductive cycle? Clearly, the beneficial effects of MP on age-related macular disease are secondary to more immediate or acute stressors. Given this, we argue that both the optical and biochemical properties of MP are important to vision, and that neither is accidental.

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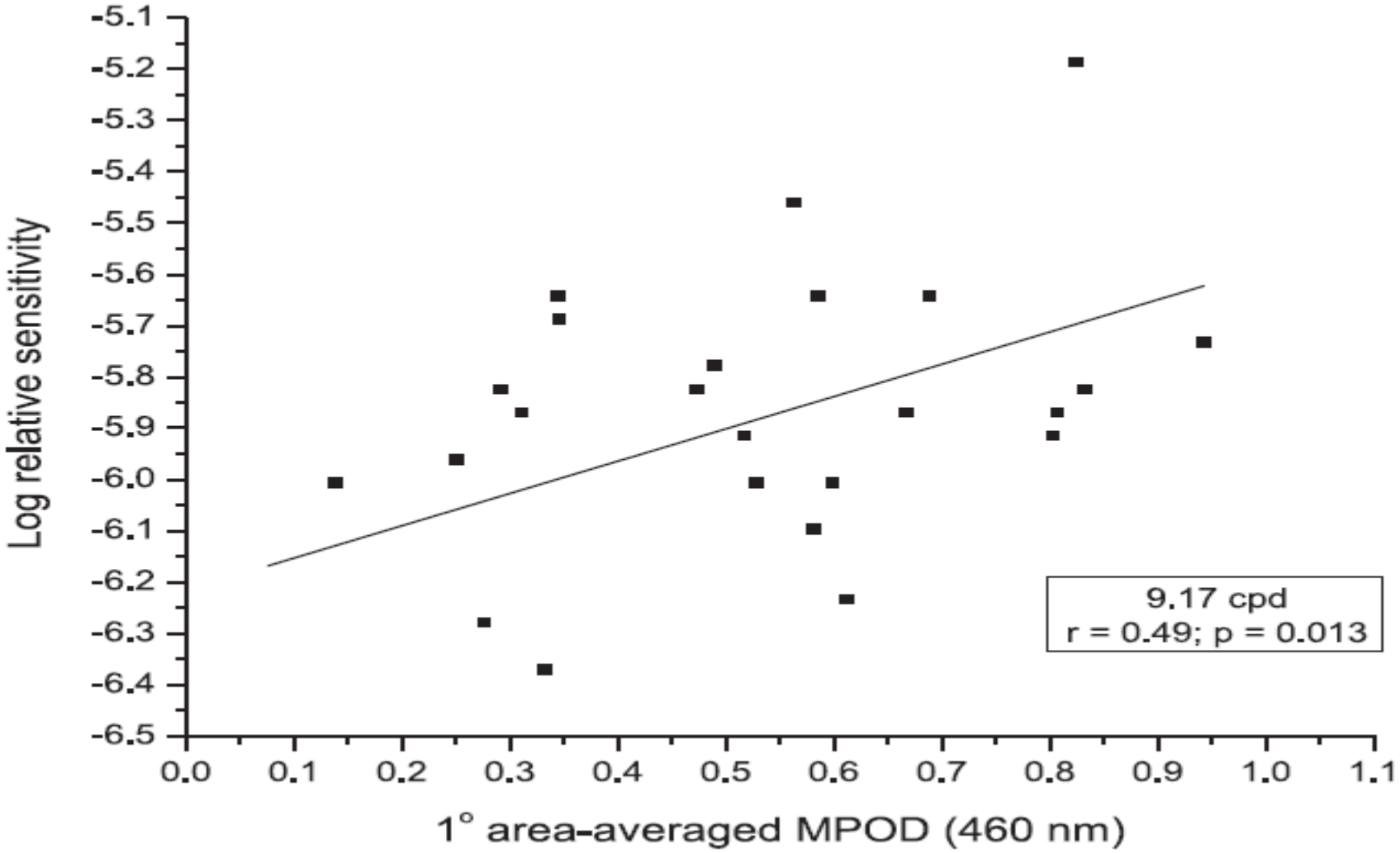
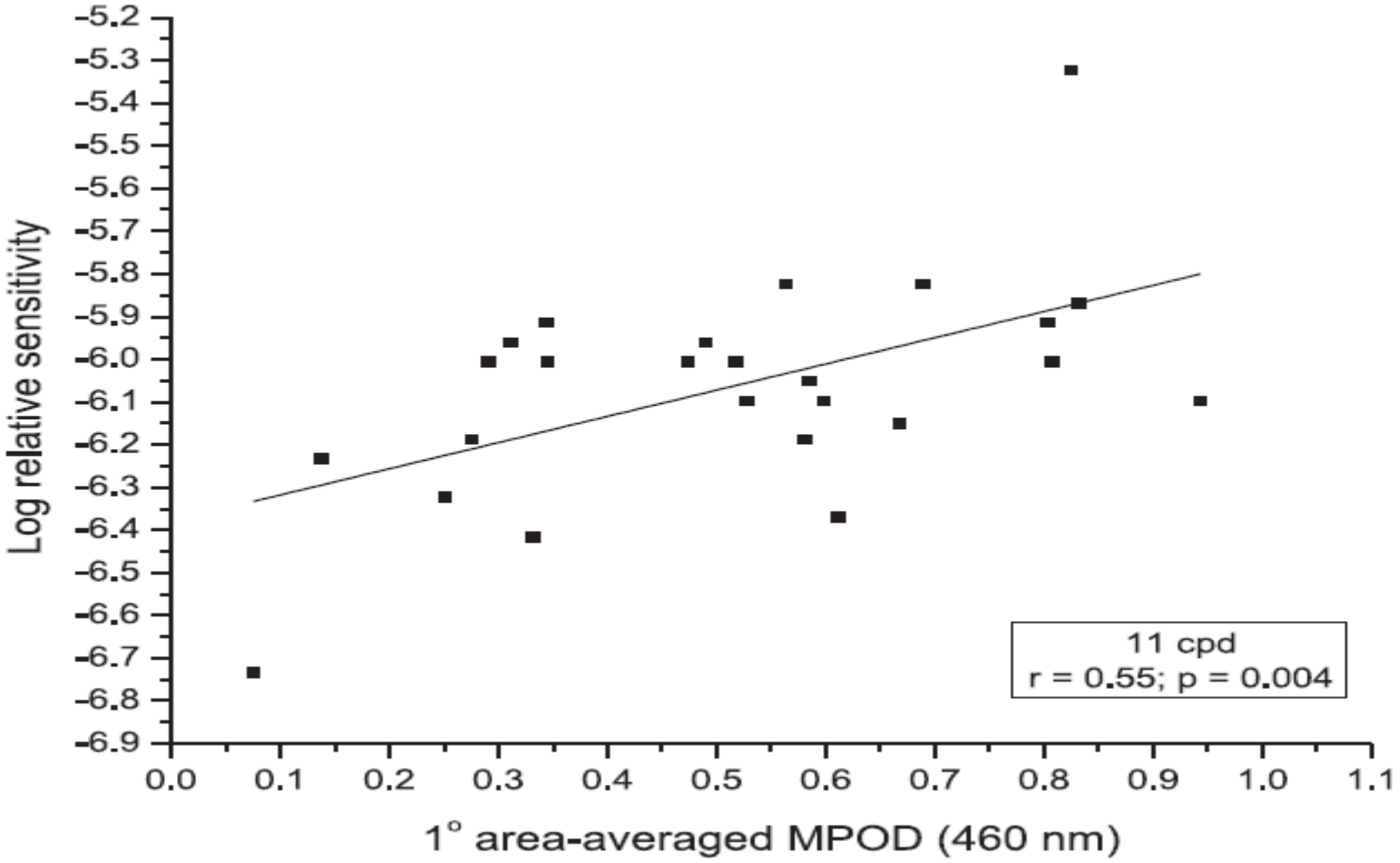
Investigative Ophthalmology & Visual Science

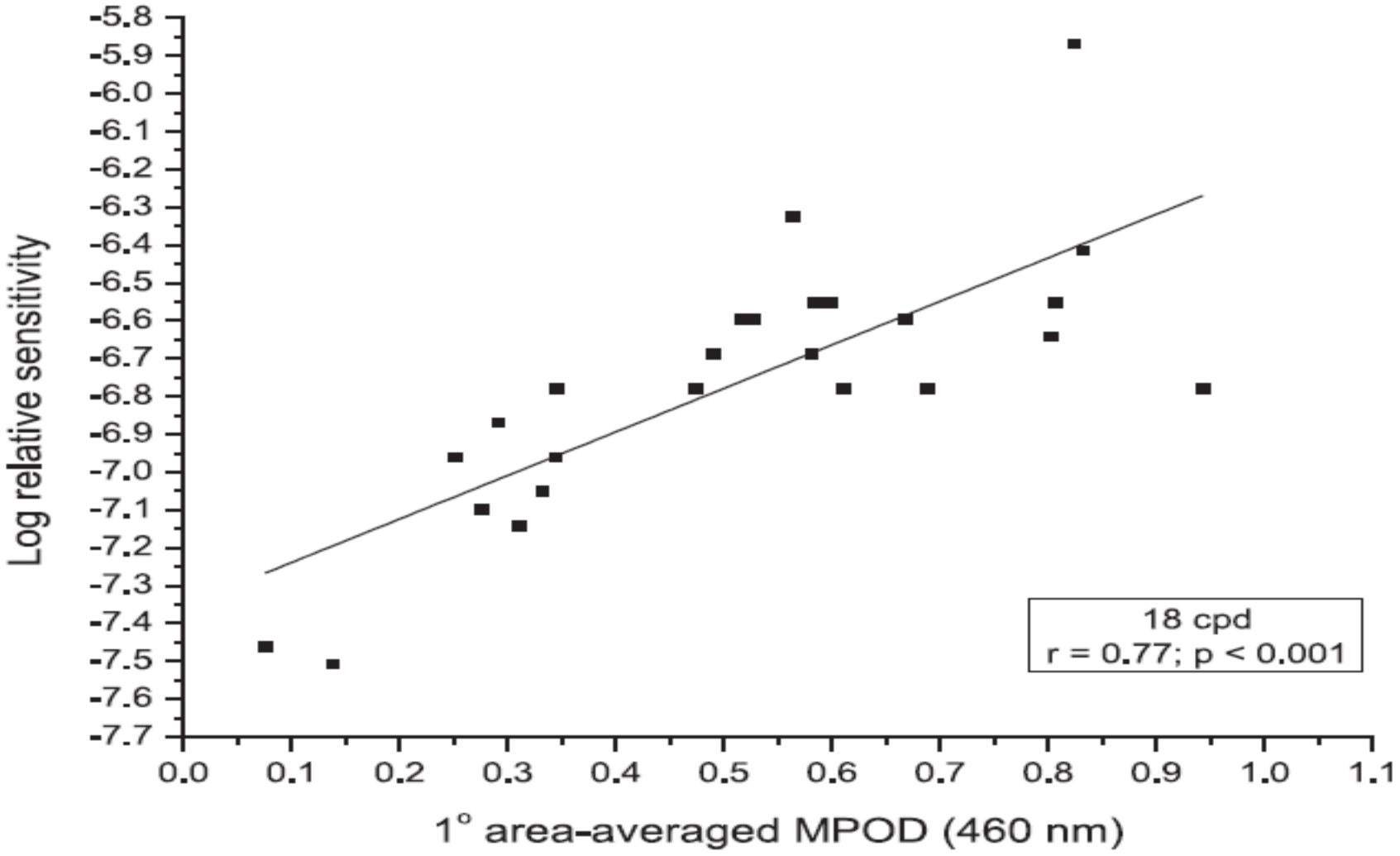
Log relative sensitivity as function of MPOD averaged over central 1^0



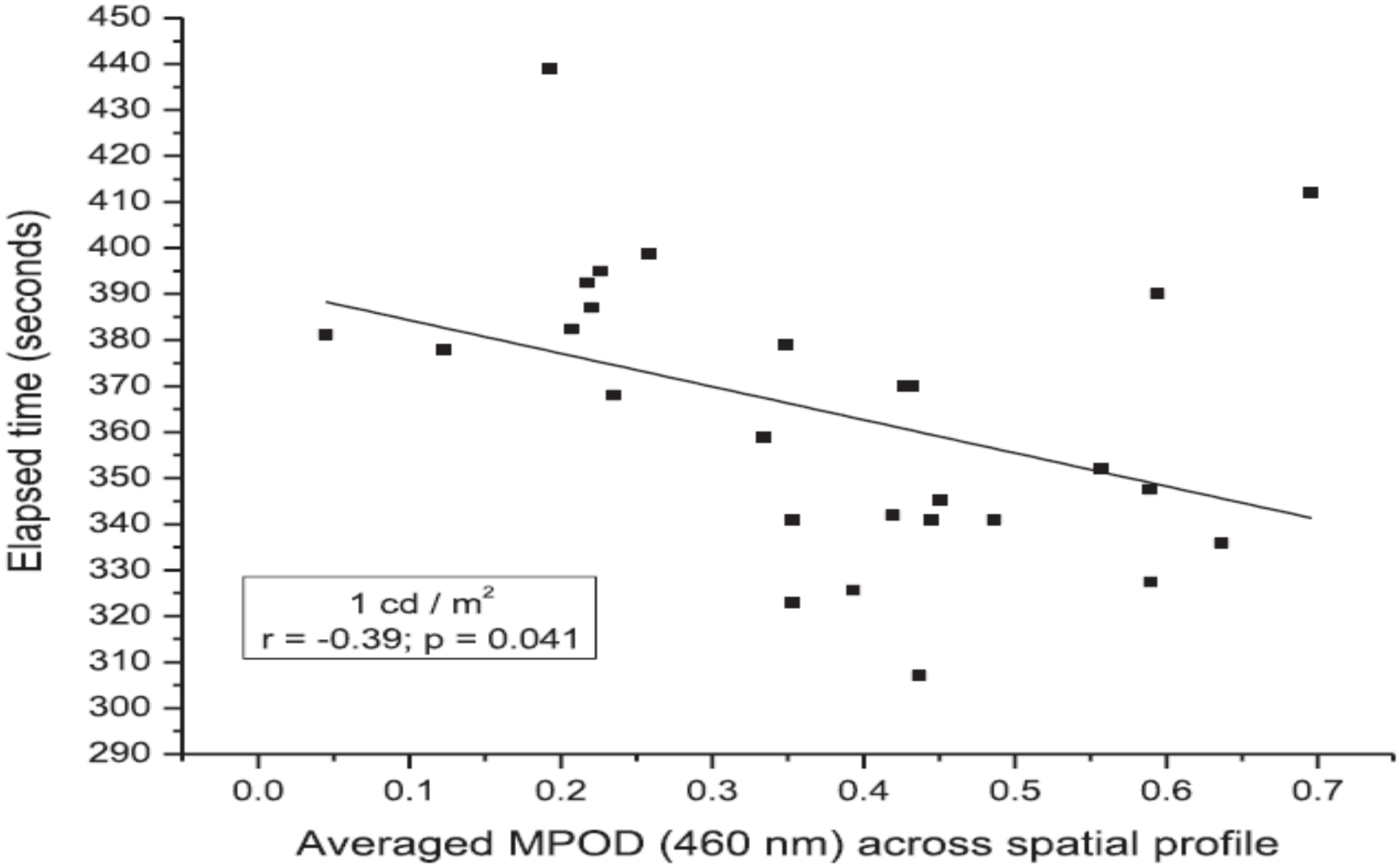
Log relative sensitivity as function of MPOD averaged over central 1^0



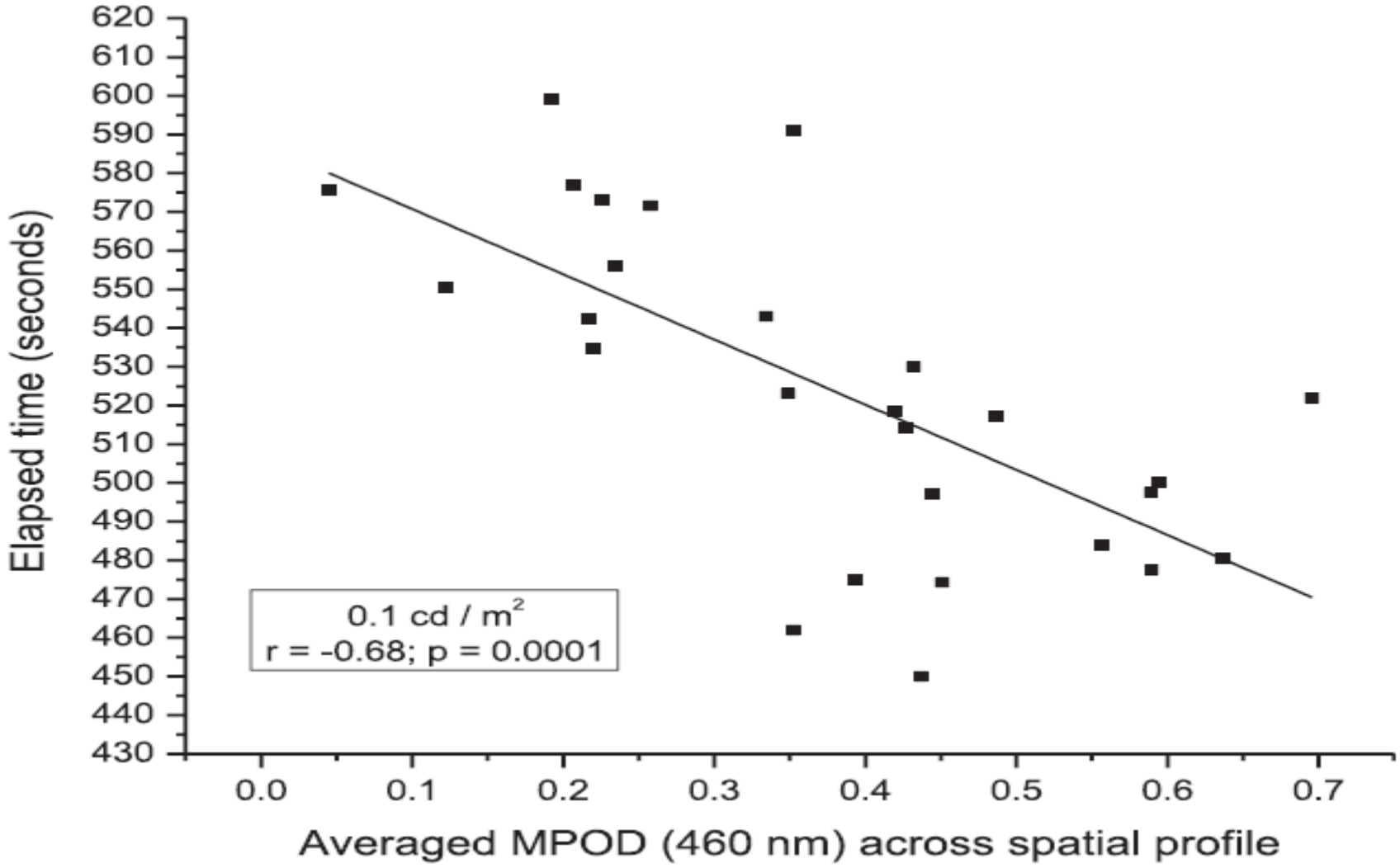
Log relative sensitivity as function of MPOD averaged over central 1^0



Time required to reach mesopic adaptation levels following 90% bleach as function of MPOD averaged over central 1^0



Time required to reach mesopic adaptation levels following 90% bleach as function of MPOD averaged over central 1^0



MP and Visual Performance in Low Light Conditions

Results:

- High MPOD associated with decreased mesopic thresholds
- Spatial frequency effects seen with mesopic thresholds
- Increased dark adaptation recovery

Conclusions:

- MP appears to be associated with dark adaptation kinetics
- MP may enhance visual function at low-light levels

How Much MP is Enough?

Results:

- **A critical value of MPOD near 0.60 was determined to provided maximal visual performance that encompassed photostress recovery, disability glare and high spatial frequency contrast sensitivity**

- **MPOD values >0.60 showed little to no improvement in glare reduction**

- **Glare discomfort showed an inverse, linear relationship to MPOD**

Macular Pigment
UMSL Graduate Program Work

Spatial Distribution Effects on Glare Disability

Influence of Spatial Distribution on Intraocular Scatter

Comparison of Methods to Describe Spatial Distribution

Foveal MPOD Predicts Parafoveal Glare Disability

Spatial Distribution Influences on Higher-Order RMS Wavefront Error and Intraocular Scatter

Macular Pigment
AFRL Future Directions

Work Cited

Sujak A. (2012). Exceptional molecular organization of canthaxanthin in lipid membranes. *Acta Biochimica Polonica*. 59(1): 31.

Hammond BR, Wooten BR, Engles M, Wong JC. (2012). The influence of filtering by the macular carotenoids on contrast sensitivity measured under simulated blue haze conditions. *Vision research*. 63: 58-62.

Stringham JM, Fuld K, Wenzel AJ. (2003). Action spectrum for photophobia. *J Opt Soc Am Image Sci Vis.* 20: 1852-1858.

Reading VM, Weale RA. (1974). Macular pigment and chromatic aberration. *JOSA*. 64(2): 231-234.

Bone RA, Landrum JT, Friedes LM, Gomez CM, Kilburn MD, Menendez E, Wang W. (1997). Distribution of lutein and zeaxanthin stereoisomers in the human retina. *Experimental eye research*. 64(2): 211-218.

Snodderly DM, Auran JD, Delori FC. (1984). The macular pigment. II. Spatial distribution in primate retinas. *Investigative ophthalmology & visual science*. 25(6): 674-685.

Subczynski, W. K., Wisniewska, A., & Widomska, J. (2010). Location of macular xanthophylls in the most vulnerable regions of photoreceptor outer-segment membranes. *Archives of biochemistry and biophysics*, *504*(1), 61-66.

Bone RA, Landrum JT, Cains A. (1992). Optical density spectra of the macular pigment in vivo and in vitro. *Vision research*. 32(1): 105-110.

Bernstein PS, Delori FC, Richer S, van Kuijk FJ, Wenzel AJ. (2010). The value of measurement of macular carotenoid pigment optical densities and distributions in age-related macular degeneration and other retinal disorders. *Vision research*. 50(7): 716-728.

Edge R, McGarvey DJ, Truscott TG. (1997). The carotenoids as anti-oxidants—a review. *Journal of Photochemistry and Photobiology B: Biology*. 41(3): 189-200.

Cantrell A, MacGarvey DJ, Truscott TG, Rancan F, Bohm F, (2003). *Arch Biochem Biophys.* 412: 47-54.

Okulski W, Sujak A, Gruszecki WI. (2000). Dipalmitoylphosphatidylcholine membranes modified with zeaxanthin: numeric study of membrane organisation. *Biochimica et Biophysica Acta (BBA)-Biomembranes*. 1509(1): 216-228.

Johnson EJ. (2012). A possible role for lutein and zeaxanthin in cognitive function in the elderly. *The American journal of clinical nutrition*. 96(5): 1161S-1165S.

Craft NE, Haitema TB, Garnett KM, Fitch KA, Dorey CK. (2012). Carotenoid, tocopherol, and retinol concentrations in elderly human brain. *J Nutr Health Aging*. 8(3): 156-162.

Johnson CA, Casson EJ. (1995). Effects of luminance, contrast, and blur on visual acuity. *OVS.* 72: 864-869.

Bone RA. (1976). Computer-enhanced resolution as an aid to identifying the macular pigment. *Vision research*. 16(10): 1191.