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Original Research

Low Macular Pigment Optical Density Is Associated with Manifest Primary Open-Angle Glaucoma in Older Women☆

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A B S T R A C T

Background: Lower density of carotenoids lutein and zeaxanthin (L/Z) in the macula (i.e., macular pigment) has been linked to greater risk for age-related eye disease.

Objectives: We evaluated whether macular pigment optical density (MPOD) was associated with manifest primary open-angle glaucoma (POAG) among older women in the Carotenoids in Age-Related Eye Disease Study 2 (CAREDS2).

Methods: MPOD was measured with customized heterochromatic flicker photometry in women who attended CAREDS2 (2016–2019) and CAREDS1 (2001–2004) study visits. Manifest POAG at CAREDS2 was assessed using visual fields, disc photos, optical coherence tomography, and medical records. Age-adjusted linear and logistic regression models were used to investigate the cross-sectional association between POAG and MPOD at CAREDS2, and MPOD measured 15 years earlier at CAREDS1.

Results: Among 426 CAREDS2 participants (mean age: 80 y; range: 69–98 y), 26 eyes with manifest POAG from 26 participants were identified. Glaucomatous eyes had 25% lower MPOD compared to nonglaucomatous eyes [mean (SE): 0.40 (0.05) compared with 0.53 (0.01)] optical density units (ODU), respectively ($P = 0.01$). Compared with MPOD quartile 1, odds for POAG were lower for women in quartiles 2–4 (P-trend $= 0.01$). After excluding eyes with age-related macular degeneration, associations were similar but not statistically significant (P-trend $= 0.16$). Results were similar for MPOD measured at CAREDS1.

Conclusions: Our results add to growing evidence that low MPOD may be a novel glaucoma risk factor and support further studies to assess the utility of dietary interventions for glaucoma prevention.

Keywords: macular pigment, glaucoma, retina, ophthalmology, lutein, zeaxanthin

Introduction

Primary open-angle glaucoma (POAG) is a neurodegenerative condition characterized by retinal ganglion cell loss and visual field defects affecting over 44 million people worldwide and disproportionately affects women, Black, and Hispanic populations [1]. Interdisciplinary research is needed to target interventions for these high-risk populations. Currently, intraocular pressure (IOP) is the only known modifiable risk factor for POAG. However, some patients develop severe

Abbreviations: AMD, age-related macular degeneration; CAREDS, Carotenoids in Age-Related Eye Disease Study; IOP, intraocular pressure; L/Z, lutein and zeaxanthin; MPOD, macular pigment optical density; OCT, optical coherence tomography; POAG, primary open-angle glaucoma; RNFL, retinal nerve fiber layer; WHI, Women's Health Initiative.

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vision loss despite achieving significant IOP-lowering with medications and/or surgery [2]. Thus, there is an urgent need to identify novel modifiable glaucoma risk factors [3].

Emerging evidence suggests that low macular pigment optical density (MPOD), modifiable through dietary intake of carotenoids lutein and zeaxanthin (L/Z) [4], may lower risk for glaucoma. These carotenoids preferentially accumulate in the retina, including the retinal ganglion cell complex [5]. Carotenoids are powerful antioxidants, which may prevent the oxidative stress implicated in glaucoma pathogenesis [6]. Some small cross-sectional studies observed lower macular pigment levels in patients with glaucoma compared with age-matched controls [7–9], but others have observed no association [10,11]. Large cohort studies have also identified decreased glaucoma risk among participants reporting higher intake of foods rich in carotenoids [12–14]. Studies in large cohorts are needed to further assess the evidence of the association between macular pigment levels and manifest POAG.

The Carotenoids in Age-Related Eye Disease Study (CAREDS) is a 15-y prospective study conducted in 2001–2004 (CAREDS1) and 2016–2019 (CAREDS2) to evaluate the relationships between MPOD with age-related macular degeneration (AMD) and cataract among women from 3 clinical sites in the Women's Health Initiative (WHI) observational study [15,16]. CAREDS2 provided new outcome measures, including spectral-domain optical coherence tomography (OCT) and assessment of manifest POAG using visual field testing. We analyzed the cross-sectional association between manifest POAG and MPOD at CAREDS2, and the association between manifest POAG at CAREDS2 and MPOD measured ~15 years earlier at CAREDS1. We hypothesized that lower MPOD at both CAREDS2 and CAREDS1 would be associated with greater odds of having manifest POAG at CAREDS2.

Materials and Methods

CAREDS2 sample

Participants were recruited from Iowa City, IA; Portland, OR; and Madison, WI. A total of 2005 participants attended the CAREDS1 study (2001–2004). From this cohort, 685 participated in the CAREDS2 follow-up study (2016–2019) (Figure 1). Those who did not participate (n = 1320) were deceased (35.5%), had been lost to follow-up or declined contact in the WHI (35.8%), or were unable to be contacted or declined participation in CAREDS2 (15.7%). Among CAREDS2 participants, 71% (n = 487) participated through in-person examination and questionnaire, while 29% (n = 198) completed the questionnaire only. In total, 426 women were included in our analysis from among the 487 CAREDS2 participants who completed in-person study visits. We excluded 61 participants for the following reasons: *1*) did not complete MPOD testing at CAREDS2 (n = 50), *2*) manifest POAG status could not be adjudicated owing to insufficient or missing data (n = 4); or *3*) had a diagnosis of narrow angles or secondary glaucoma (i.e., angle-closure glaucoma and pseudoexfoliation glaucoma; n = 7) in ≥1 eye. All participants provided written informed consent. All research activities were approved by the University of Wisconsin-Madison Health Sciences institutional review board (ID#: 2015-1293) and were conducted in accordance with the tenets of the Declaration of Helsinki.

Assessment of MPOD

MPOD measurements were obtained at CAREDS1 and 2 using customized heterochromatic flicker photometry (Macular Metrics II), a validated and reproducible noninvasive, psychophysical technique [16]. The principles of customized heterochromatic flicker photometry have been described previously [16,17]. MPOD was measured in the eye with the better

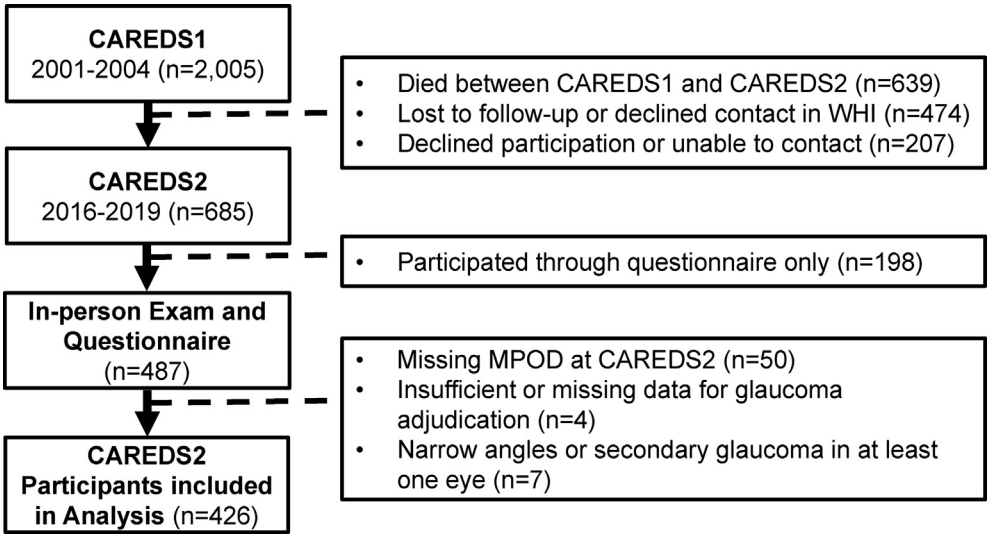

FIGURE 1. Flowchart of CAREDS2 participants included in the analysis (n = 426). CAREDS, Carotenoids in Age-Related Eye Disease Study; MPOD, macular pigment optical density; WHI, Women's Health Initiative.

best-corrected visual acuity. Testing was completed using a blue light–emitting diode with a peak wavelength of 460 nm, the maximum absorption spectrum for macular pigment. Measures were made at 0.5° from the foveal center, the location with the highest ratio of interindividual to intraindividual variability [16] and at 7° where the density of macular pigment is negligible [18]. MPOD at 0.5° was a mean of 5 separate determinations. The flicker rate for MPOD testing in CAREDS2 was adjusted using the critical flicker frequency at the foveal and parafoveal targets, which were determined for each participant before MPOD testing. Likewise, MPOD at the 0.5° target in the right and left eyes at CAREDS1 (2001–2004) was assessed as previously described [16].

Ocular examination and assessment of manifest POAG

Ocular characteristics and the presence of manifest POAG in CAREDS2 were assessed via in-person examinations conducted by trained examiners and medical records review. The CAREDS2 in-person study visit included IOP (Tono-Pen; Reichert), corneal thickness (PachPen; Accutome), and axial length (Gilras GRU-5000 A Biometer; US Ophthalmic) measured in both eyes. The presence of an intraocular lens implant was assessed via slit lamp examination. Stereoscopic 30° digital color photographs centered on the macula and the optic nerve (Topcon TRC-DX50) were obtained in both eyes by a certified photographer following pupil dilation with 2.5% phenylephrine and 1% tropicamide. A Wisconsin Reading Center-certified grader measured the vertical cup-to-disc ratio using IMAGEnet software (version 6; Topcon Healthcare) following a standard protocol [19]. Peripapillary retinal nerve fiber layer (RNFL) thickness was obtained using spectral-domain OCT (Heidelberg Spectralis; Heidelberg Engineering), with a quality score of 20 or above considered adequate for inclusion in our analysis. AMD was assessed from digital fundus photographs and classified according to the International Classification System for AMD (i.e., Beckman scale) [20].

We then obtained detailed medical records from the subset of CAREDS2 participants (n = 233) identified to have ≥1 of the following known glaucoma risk factors: self-reported glaucoma or self-reported glaucoma medication use, IOP ≥ 22 mm Hg, cup-to-disc ratio ≥ 0.6, cup-to-disc asymmetry ≥ 0.2, disc notching, disc hemorrhage, or RNFL thickness less than fifth percentile in the inferior or superior quadrants or for the mean of all quadrants in either eye. Medical records included clinic notes from eye care providers, visual field tests, optic nerve photos, and peripapillary RNFL OCT.

Participants who did not have recent reliable visual fields available for review in their medical records (i.e., visual fields last performed within 1 y with fixation losses ≤33%, false negatives ≤25%, and false positives ≤25%) and who did not have previous visual fields demonstrating reproducible glaucomatous defects were invited to obtain Humphrey visual field testing (Carl Zeiss Meditec) in each eye using the SITA (Swedish Interactive Threshold Algorithm)-Standard 24-2 testing algorithm. Visual field testing was performed sequentially in the right and then the left eye among 88 participants by trained technicians using the appropriate near refraction for each eye. If visual field testing in either eye was unreliable (>33% fixation losses, >25% false negatives or >25% false positives) or if the technician suspected a rim artifact, then the Humphrey visual field test was repeated in the unreliable eye(s).

Independent adjudication of manifest POAG at CAREDS2 was performed by 2 fellowship-trained glaucoma specialists (YL and CT) masked to participant MPOD using clinical data, visual field tests, optic disc photographs, and peripapillary RNFL OCT imaging from medical records and CAREDS2 in-person study visits. Manifest POAG was defined following criteria similar to that used in the Nurses' Health Study [21] based on the presence of glaucomatous visual field defects (i.e., nasal, paracentral, arcuate, or temporal defects) on reliable visual field testing. Defects were reproducible on ≥1 previous set of visual fields, unrelated to other eye conditions, and were consistent with the locations of optic nerve thinning from disc photographs and/or peripapillary RNFL OCT measurements. Disagreements regarding glaucoma diagnosis were resolved by achieving consensus between the 2 glaucoma specialists following repeat review of participant data.

Glaucoma measures, including visual field testing, were not obtained at CAREDS1, and thus, we were unable to ascertain manifest POAG status at CAREDS1. Nineteen CAREDS2 participants who self-reported glaucoma at CAREDS1 (3.6%) were retained in the analysis to avoid misclassification, as 30% of WHI participants who self-reported glaucoma were found not to have the condition in a previous study [22].

Statistical analysis

We compared the characteristics of participants with manifest POAG and participants without manifest POAG using age-adjusted linear and logistic regression models. Likewise, we compared the characteristics of participants included in the analysis with those who were excluded to determine the potential for survival and participation bias. Mean MPOD (± SE) at CAREDS2 in glaucomatous compared with nonglaucomatous eyes were analyzed using linear regression. Odds ratios with 95% CIs for manifest POAG by quartile of MPOD and per 1-SD increase (i.e., continuous exposure) were obtained using logistic regression. Sensitivity analyses were conducted to exclude participants who self-reported using L/Z supplements (≥1 mg/d) at CAREDS2 or who had intermediate or advanced AMD in the MPOD measured eye, as these characteristics may also influence the accumulation of macular pigment [23]. Similar regression models were developed using MPOD measured ~15 y earlier at CAREDS1 (using generalized estimating equations to account for intereye correlation), as well as separate models for the right and left eyes.

All associations were adjusted for age at the time of MPOD measurement. Additional covariates with known or biologically plausible associations with MPOD and glaucoma were sequentially added to the model to assess for evidence of significant confounding (i.e., change in the linear regression estimate of >10%), including waist circumference, BMI, diabetes, axial length, presence of an intraocular lens, and pack-years smoked (never smoker, <7 y, and ≥7 y). No evidence for significant confounding was observed for any covariates except for age. Consequently, we present results from the model adjusted for age only, as parsimony was favored to obtain reliable estimates. All statistical analyses were performed using SAS version 9.4. The threshold for statistical significance was set to $P \leq 0.05$.

Results

Sample characteristics

A total of 426 eyes from 426 participants who completed MPOD testing at CAREDS2 were included in the analysis. Participants had a mean age at CAREDS2 of 80.4 y (range, 69–98 y), were predominantly White (97%), and most had completed at least some college education (88%) (Table 1). Manifest POAG was present in 26 eyes (6.1%) and was associated with older age, self-reported glaucoma, self-reported glaucoma medication use, and larger cup-to-disc ratio ($P \leq 0.02$). MPOD was positively associated with L/Z supplement use (P-trend < 0.001), especially in the highest quartile, and negatively associated with larger waist circumference (P-trend < 0.03) (Supplemental Table 1). Excluded participants were slightly older, had lower education and income, had greater waist circumference and BMI, were more likely to self-report diabetes, and had slightly lower MPOD at CAREDS1 ($P \leq 0.02$) than those included in the analysis (Supplemental Table 2).

MPOD and manifest POAG at CAREDS2

Eyes with manifest POAG at CAREDS2 had 25% lower MPOD at CAREDS2 than nonglaucomatous eyes ($P = 0.01$) (Table 2). The odds of manifest POAG at CAREDS2 were lower for women in MPOD quartiles 2–4 compared with quartile 1 at CAREDS2 [odds ratio (95% CI): 0.25 (0.08–0.80); 0.12 (0.03-0.56); and 0.44 (0.17–1.17), respectively], although the association was not statistically significant for MPOD quartile 4.

In sensitivity analyses, the association between lower MPOD at CAREDS2 and manifest POAG at CAREDS2 remained significant after excluding eyes from participants using L/Z supplements ($n = 76$, 18%). In this subgroup, eyes with manifest POAG at CAREDS2 had 34% lower MPOD at CAREDS2 than nonglaucomatous eyes ($P = 0.01$). The odds of manifest POAG were lower for MPOD quartiles 2–4 compared with quartile 1 at CAREDS2, although the association was only significant for quartile 3 (Table 2). These associations were similar but nonsignificant after excluding eyes with intermediate or advanced AMD ($n = 106$, 25%; $P = 0.17$).

TABLE 1
Participant characteristics among those with and without manifest primary open-angle glaucoma (POAG) at CAREDS2 in either eye ($n = 426$).

Characteristics[1]	All participants ($n = 426$)	No manifest POAG ($n = 400$)	Manifest POAG ($n = 26$)	P
Age (y)—CAREDS2	80.4 ± 0.3	80.3 ± 0.26	82.7 ± 1.0	0.02
Race/ethnicity				0.96
Asian	6 (1)	5 (1)	1 (3)	
Black	3 (1)	3 (1)	0 (0)	
White	415 (97)	388 (98)	25 (97)	
>1 race	1 (0)	1 (0)	0 (0)	
Unknown/not reported	1 (0)	1 (0)	0 (0)	
Ethnicity				0.99
Non-Hispanic	424 (100)	396 (99)	26 (100)	
Hispanic	2 (0)	2 (1)	0 (0)	
Education				0.88
High school graduate or less	53 (12)	50 (13)	3 (8)	
Some college or vocational training	208 (49)	193 (49)	13 (49)	
Postcollege education	165 (39)	155 (39)	10 (43)	
Self-reported annual household income ≥$75,000—WHI baseline	110 (27)	106 (28)	4 (17)	0.21
Pack-years smoked—CAREDS1				0.41
Never smoker	247 (58)	228 (57)	18 (73)	
<7 pack-years	101 (24)	94 (24)	6 (21)	
≥7 pack-years	78 (18)	76 (19)	2 (6)	
Lutein and zeaxanthin supplement use—CAREDS2				0.26
<1 mg/d	350 (82)	330 (83)	19 (67)	
≥1 mg/d	76 (18)	68 (17)	7 (33)	
Self-reported diabetes—CAREDS2	38 (9)	37 (9)	1 (3)	0.36
BMI (kg/m^2)—CAREDS2	26.8 ± 0.3	26.9 ± 0.3	26.9 ± 1.0	0.94
Waist circumference (inches)—CAREDS2	35.8 ± 0.3	35.8 ± 0.3	36.1 ± 1.0	0.82
Self-reported glaucoma—CAREDS2	33 (8)	15 (4)	18 (65)	<0.001
Self-reported family history of glaucoma—CAREDS2	50 (13)	43 (12)	6 (23)	0.08
Self-reported glaucoma medication use—CAREDS2	22 (5)	6 (2)	15 (57)	<0.001
Cup-to-disc ratio—CAREDS2[2]	0.4 ± 0.0	0.4 ± 0.0	0.6 ± 0.0	<0.001
Intraocular pressure (mm Hg)—CAREDS2[2]	14.5 ± 0.2	14.5 ± 0.2	14.4 ± 0.7	0.95
Axial length (mm)—CAREDS2[2]	23.7 ± 0.1	23.7 ± 0.6	24.1 ± 0.2	0.09
Corneal thickness (μm)—CAREDS2[2]	557.9 ± 1.9	558.0 ± 1.9	554.1 ± 7.5	0.61
Age-related macular degeneration (intermediate/advanced)—CAREDS2[2]	98 (23)	91 (23)	7 (27)	0.81
Intraocular lens implant—CAREDS2[2]	261 (61)	238 (60)	22 (81)	0.06

Abbreviations: CAREDS, Carotenoids in Age-Related Eye Disease Study; ODU, optical density unit; POAG, primary open-angle glaucoma; WHI, Women's Health Initiative.

[1] Values are as age-adjusted mean ± SE for continuous variable and percentages for categorical variables.

[2] Eye-specific variables present data for the MPOD measured eye only.

TABLE 2
Mean[1] MPOD at CAREDS2 by manifest POAG status at CAREDS2 and odds ratios for manifest POAG at CAREDS2 by quartile of MPOD at CAREDS2.

	Full sample (n = 426)		
	No manifest POAG (n = 400)	Manifest POAG (n = 26)	β (SE), P
Mean MPOD	0.53 (0.01)	0.40 (0.05)	−0.13 (0.05), 0.01
MPOD by quartile	Eyes with manifest POAG/full sample	OR (95% CI)	P-trend
Q1 (0.00–0.32 ODU)	13/108	1.00	
Q2 (0.33–0.52 ODU)	4/110	0.25 (0.08–0.80)	
Q3 (0.53–0.69 ODU)	2/99	0.12 (0.03–0.56)	
Q4 (0.70–1.10 ODU)	7/107	0.44 (0.17–1.17)	
Per 1-SD increase	—	0.58 (0.37–0.90)	0.01
	No L/Z supplement use[2] (n = 350)		
	No manifest POAG (n = 331)	Manifest POAG (n = 19)	β (SE), P
Mean MPOD	0.50 (0.01)	0.33 (0.06)	−0.17 (0.06), 0.01
MPOD by quartile	Eyes with manifest POAG/full sample	OR (95% CI)	P-trend
Q1 (0.00–0.32 ODU)	10/95	1.00	
Q2 (0.33–0.52 ODU)	4/98	0.33 (0.10–1.11)	
Q3 (0.53–0.69 ODU)	2/85	0.16 (0.03–0.78)	
Q4 (0.70–1.10 ODU)	3/71	0.33 (0.09–1.27)	
Per 1-SD increase	—	0.44 (0.25–0.78)	0.01
	No AMD[3] (n = 320)		
	No manifest POAG (n = 301)	Manifest POAG (n = 19)	β (SE), P
Mean MPOD	0.51 (0.02)	0.43 (0.06)	−0.09 (0.06), 0.17
MPOD by quartile	Eyes with manifest POAG/full sample	OR (95% CI)	P-trend
Q1 (0.00–0.32 ODU)	8/83	1.00	
Q2 (0.33–0.52 ODU)	4/86	0.43 (0.12–1.51)	
Q3 (0.53–0.69 ODU)	2/80	0.19 (0.04–0.95)	
Q4 (0.70–1.10 ODU)	5/70	0.64 (0.19–2.09)	
Per 1-SD increase	—	0.69 (0.41–1.16)	0.16

Abbreviations: AMD, age-related macular degeneration; CAREDS, Carotenoids in Age-Related Eye Disease Study; L/Z, lutein and zeaxanthin; MPOD, macular pigment optical density; OR, odds ratio; POAG, primary open-angle glaucoma.
[1] Adjusted for age. Values are presented as mean (SE) optical density units.
[2] Excluding participants who self-reported using lutein and zeaxanthin supplements at CAREDS2 (≥1 mg/d).
[3] Excluding participants with intermediate or advanced AMD in the MPOD measured eye at CAREDS2.

MPOD at CAREDS1 and manifest POAG at CAREDS2

Eyes with manifest POAG compared with nonglaucomatous eyes at CAREDS2 had 21% lower MPOD at CAREDS1 (P = 0.04) (Table 3) with consistent results observed for the right and left eyes ($P \leq 0.05$) (Supplemental Tables 3 and 4). We also evaluated the relationship between MPOD at CAREDS1 and manifest POAG at CAREDS2 by quartile of MPOD. The odds of manifest POAG at CAREDS2 were lower for MPOD quartiles 2–4 than those for quartile 1 at CAREDS1, although the association was not statistically significant for quartile 3 (Table 3). Similar results were observed for the right and left eyes (Supplemental Tables 3 and 4).

In sensitivity analyses, the association between lower MPOD at CAREDS1 and manifest POAG at CAREDS2 remained significant after excluding eyes from participants (n = 14, 1.7%) using L/Z supplements at CAREDS1, with 21% lower MPOD among glaucomatous than that for nonglaucomatous eyes (P = 0.05). In this subgroup, the odds of manifest POAG at CAREDS2 were lower for MPOD quartiles 2–4 than those of quartile 1 at CAREDS1, although the association was not statistically significant for quartile 3 (Table 3). Similar results were observed for the right eye and left eye but were nonsignificant for the left eye and for quartile 3 of the right eye (Supplemental Tables 3 and 4).

The association between lower MPOD at CAREDS1 and manifest POAG at CAREDS2 were similar but did not achieve statistical significance after excluding eyes with intermediate or advanced AMD (n = 73, 8.8%), with 21% lower MPOD among glaucomatous than that for nonglaucomatous eyes (P = 0.06). Similar findings were observed for the right eye (P = 0.06) and left eye (P = 0.05).

Discussion

We contribute evidence of a protective association between macular pigment and manifest POAG in a sample of older women in CAREDS2. Eyes with manifest POAG had 25% lower MPOD than nonglaucomatous eyes at CAREDS2, and this finding was consistent after excluding participants using L/Z supplements (18% of sample). After excluding eyes with macular degeneration (25% of sample), results were similar but no longer statistically significant, which may have been due to limitations in sample size. Findings were similar for the associations observed between manifest POAG CAREDS2 and lower MPOD measured 15 y earlier at CAREDS1 among all eyes, as well as by eye laterality. Our study adds to growing evidence from cross-sectional, case–control studies that have reported associations between

TABLE 3
Mean[1] MPOD at CAREDS1 by manifest POAG status at CAREDS2 and odds ratios for manifest POAG at CAREDS2 by quartile of MPOD at CAREDS1.

	Full sample (n = 831)		
	No manifest POAG (n = 778)	Manifest POAG (n = 53)	β (SE), P
Mean MPOD	0.38 (0.01)	0.30 (0.04)	−0.08 (0.04), 0.04
MPOD by quartile	Eyes with manifest POAG/full sample	OR (95% CI)	P-trend
Q1 (0.00–0.23 ODU)	22/207	1.00	
Q2 (0.23–0.38 ODU)	10/208	0.41 (0.17–0.94)	
Q3 (0.38–0.50 ODU)	14/208	0.58 (0.25–1.37)	
Q4 (0.50–1.05 ODU)	7/208	0.27 (0.08–0.91)	
Per 1-SD increase	—	0.65 (0.42–1.02)	0.06
	No L/Z supplement use[2] (n = 817)		
	No manifest POAG (n = 764)	Manifest POAG (n = 53)	β (SE), P
Mean MPOD	0.38 (0.01)	0.30 (0.04)	−0.08 (0.04), 0.05
MPOD by quartile	Eyes with manifest POAG/full sample	OR (95% CI)	P
Q1 (0.00–0.23 ODU)	22/205	1.00	
Q2 (0.23–0.38 ODU)	10/202	0.41 (0.18–0.96)	
Q3 (0.38–0.50 ODU)	14/207	0.58 (0.25–1.36)	
Q4 (0.50–1.05 ODU)	7/203	0.27 (0.08–0.92)	
Per 1-SD increase	—	0.65 (0.42–1.02)	0.06
	No AMD[3] (n = 758)		
	No manifest POAG (n = 710)	Manifest POAG (n = 48)	β (SE), P
Mean MPOD	0.38 (0.01)	0.30 (0.04)	−0.08 (0.04), 0.06
MPOD by quartile	Eyes with manifest POAG/full sample	OR (95% CI)	P-trend
Q1 (0.00–0.23 ODU)	20/188	1.00	
Q2 (0.23–0.38 ODU)	8/192	0.35 (0.14–0.85)	
Q3 (0.38–0.50 ODU)	14/196	0.62 (0.26–1.46)	
Q4 (0.50–1.05 ODU)	6/182	0.26 (0.07–1.00)	
Per 1-SD increase	—	0.65 (0.40–1.05)	0.08

Abbreviations: AMD, age-related macular degeneration; CAREDS, Carotenoids in Age-Related Eye Disease Study; L/Z, lutein and zeaxanthin; MPOD, macular pigment optical density; OR, odds ratio; POAG, primary open-angle glaucoma.
[1] Adjusted for age. Values are presented as mean (SE) optical density units.
[2] Excluding participants who self-reported using lutein and zeaxanthin supplements at CAREDS1 (≥1 mg/d).
[3] Excluding participants with intermediate or advanced AMD in the MPOD measured eye at CAREDS1.

POAG and low MPOD at single time points [7–9]. The overall body of evidence supports the continued development of clinical trials to further investigate a possible protective role for macular pigment in manifest POAG.

We also observed a trend toward a nonlinear cross-sectional association between manifest POAG and the lowest quartile of MPOD at CAREDS2, which has not been previously reported. This is consistent with the saturability of enzymes that facilitate carotenoid absorption and localization in tissues [24]. Thus, our results suggest a threshold effect that provides important information for understanding dose–response relationships in the design of dietary interventions to determine whether increasing MPOD in patients with low MPOD reduces the risk for POAG incidence or progression [25]. There are ongoing randomized trials testing this hypothesis, including a recent trial that demonstrated an mean 60% increase in MPOD among participants with POAG who received L/Z supplementation (10 mg lutein, 2 mg zeaxanthin, and 10 mg meso-zeaxanthin) compared with placebo over 18 mo [26]. Furthermore, data from studies of AMD support the safety of L/Z supplementation ≤12 mg/d [27].

Our findings of a protective association between MPOD and manifest POAG at multiple time points in our cohort are consistent with earlier reports from small cross-sectional and case–control studies that only evaluated this association at a single time point. Igras et al. [7] reported 35% lower MPOD among POAG cases than that among controls, and similar results were reported by Ji et al. [9]. Siah et al. [8] reported that MPOD was 50% lower in patients with POAG and foveal ganglion cell complex thinning, and proposed that the association with MPOD may be specific to foveal-involved POAG [8]. However, other studies did not find an association between MPOD and POAG [10,11]. Small sample sizes and differences between the studied populations may have contributed to the heterogeneity of results in these previous small cross-sectional and case–control studies.

Large longitudinal studies have provided evidence for a protective effect of dietary carotenoids [21,28]. Lower dietary carotenoid intake was associated with greater risk for high-tension POAG in the Nurses' Health Study and Health Professionals Follow-up Study [21]. The same group later also reported a protective association between dietary nitrates and POAG [14]. Notably, nitrate-rich foods are also rich in carotenoids L/Z (e.g., green leafy vegetables) [29]. Greater consumption of green leafy vegetables was also associated with decreased risk for glaucoma in another longitudinal study [12,13]. It is possible that MPOD reflects the influence of several antioxidant nutrients in green leafy vegetables that may be protective against POAG. A major strength of our study is that MPOD is an objective measurement of ocular L/Z that does not rely on accurate dietary recall and accounts for variability in both carotenoid absorption and localization in the retina [30]. Moreover, MPOD reflects

dietary consumption of carotenoids over multiple years (rather than questionnaire-based dietary intake over the previous 3–12 mo) [30]. MPOD measurement is also noninvasive with high test/retest reliability [16], stability over months to years [31], and limited effects from age [32].

The potential biological mechanisms underlying the association between macular pigment and manifest POAG are incompletely understood. Carotenoids L/Z uniquely accumulate in brain and retinal neurons [33], serving as antioxidants and structural components that increase the rigidity of cell membranes [34]. Macular pigment is positively associated with the macular ganglion cell complex thickness [9,35], suggesting that macular pigment may prevent ganglion cell death in the macula (an early marker of glaucomatous neurodegeneration) [36]. A neuroprotective effect is also supported by epidemiologic studies demonstrating that greater exposure to dietary L/Z is associated with multiple markers of cognitive function [37,38] and lower risk for neurodegenerative conditions, including Alzheimer disease [39] and macular degeneration [23,40]. Recent evidence indicates that L/Z may help to maintain normal blood perfusion to the optic nerve head [41], an emerging glaucoma risk factor [42].

Limitations of this study include the inability to distinguish between incident and prevalent cases of POAG because visual field testing was not performed at CAREDS1. Using self-reported glaucoma in WHI to identify incident cases would have limited reliability [22] and a review of medical records and/or Medicare claims would undercount POAG cases given that approximately half of POAG cases are undiagnosed [43]. Furthermore, we cannot rule out the possibility that glaucomatous changes to the retina (e.g., thinning of the ganglion cell complex in the macula) reduced MPOD accumulation in POAG eyes (i.e., reverse causation) [44]. There was also significant loss to follow-up in our study owing to competing risks of mortality and nonparticipation, as has been observed in other longitudinal observational studies [28]. Importantly, the number of individuals who had POAG in the MPOD measured eye was limited ($n = 26$), which may have contributed to relatively imprecise estimates for the association with macular pigment, as well as limited the power to overcome the influence of AMD. We also observed greater use of L/Z supplements by participants with glaucoma and a significant increase in MPOD over 15 y for women who attended CAREDS2 follow-up study visits, which may have attenuated the association with POAG for MPOD measured at CAREDS1. Finally, our cohort was mostly comprised healthy non-Hispanic, White older women. Future large cohort or interventional studies would help assess the generalizability of our findings to men and to individuals from other racial and ethnic groups.

In conclusion, our study provides further evidence that low MPOD is associated with manifest POAG. Our results add to growing evidence that low MPOD may be a novel glaucoma risk factor and support further studies to assess the utility of dietary interventions for glaucoma prevention.

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Authors contributions

The authors' responsibilities were as follows—YL, JM: designed research; TL, YL, CT, ZL: conducted research; ZL, TL: analyzed data; YL, TL: wrote paper; ZL, BW, CT, RW, JM, TV, MN: edited and revised paper; YL: had primary responsibility for final content; and all authors: have read and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Data availability

Data are available on request to those who obtain the required approvals from the UW-Madison Health Sciences IRB and the Women's Health Initiative.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cdnut.2024.103789.

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