REVIEW

The Effect of Lutein/Zeaxanthin Intake on Human Macular Pigment Optical Density: A Systematic Review and Meta-Analysis

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ABSTRACT

Lutein, zeaxanthin, and meso-zeaxanthin are the only carotenoids found in the human macula and may have a role in visual function. These carotenoids are reported to protect the retina, and thus vision, as antioxidants and by acting as a blue light filter. Our objective was to determine a minimum concentration of lutein/zeaxanthin intake that is associated with a statistically significant and/or clinically important change in macular pigment optical density (MPOD) among adults with healthy eyes. We searched Ovid MEDLINE, CENTRAL, and the Commonwealth of Agriculture Bureau for English-language studies through to July 2020. Two reviewers screened results to identify studies that evaluated supplements or dietary sources of lutein/zeaxanthin on MPOD among adults with healthy eyes. One reviewer extracted data and assessed strength of evidence, which was confirmed by a second reviewer. Two independent reviewers assessed the risk of bias. Meta-analyses were stratified by total lutein/zeaxanthin dose. We included 46 studies ($N = 3189$ participants; mean age = 43 y; 42% male). There was no statistically significant change in MPOD among studies evaluating <5 mg/d of total lutein/zeaxanthin intake which primarily assessed dietary interventions for 3–6 mo (pooled mean difference, 0.02; 95% CI: −0.01 to 0.05). The pooled mean increase in MPOD was 0.04 units (95% CI: 0.02 to 0.07) among studies evaluating 5 to <20 mg/d of lutein/zeaxanthin and was 0.11 units (95% CI: 0.06 to 0.16) among studies evaluating ≥20 mg/d of lutein/zeaxanthin for 3–12 mo. MPOD increased with lutein/zeaxanthin intake, particularly at higher doses, among adults with healthy eyes. The effects of lutein/zeaxanthin intake at doses <5 mg/d or from dietary sources is less clear. Increased lutein/zeaxanthin intake can help with maintaining ocular health. Future research is needed to determine the minimum dose and duration of lutein/zeaxanthin intake that is associated with a clinically important change in MPOD or visual function. *Adv Nutr* 2021;00:1–11.

Statement of Significance: We conducted a systematic review to determine the quantities of lutein/zeaxanthin intake from either dietary or supplemental sources that are associated with macular pigment optical density (MPOD) among adults with healthy eyes. We concluded that >10 mg/d of lutein/zeaxanthin can increase MPOD, but the effects at doses <5 mg/d or from dietary sources are less clear and there are no studies evaluating doses of 5 to <10 mg/d of lutein/zeaxanthin.

Keywords: lutein, zeaxanthin, meso-zeaxanthin, macular pigment optical density, systematic review, meta-analysis

Introduction

Lutein and zeaxanthin are xanthophyll carotenoids. Humans cannot synthesize lutein and zeaxanthin and must obtain these from their diet. Sources of lutein and zeaxanthin include green leafy vegetables, egg yolks, corn, and squash (1). It has been estimated that American adults consume 1–2 mg of lutein/zeaxanthin per day from dietary sources (2). Of the >1000 carotenoids found in nature, only lutein and zeaxanthin and their metabolites are present in the human macula (3). Collectively, lutein, zeaxanthin, and meso-zeaxanthin (an isomer of zeaxanthin) comprise the macular pigment. These carotenoids are reported to protect the retina, and thus vision, as antioxidants and by acting as a blue light filter (4).

Macular pigment optical density (MPOD) is a measure of the concentrations of lutein/zeaxanthin in the macula (4). MPOD is measured in optical density units and ranges between 0 and 1. A recent systematic review reported a

positive association between MPOD and visual function, including correlations with contrast sensitivity, photostress recovery, and glare disability (5).

A systematic review conducted in 2016 evaluated the effects of lutein supplementation on MPOD in patients with age-related macular degeneration and in healthy subjects (6). This review included only randomized placebo-controlled trials of supplements. Ma et al. concluded that lutein/zeaxanthin supplements can increase MPOD in patients with age-related macular degeneration as well as in healthy subjects and reported a dose-response relation. Our review expands the scope of this review by including dietary sources of lutein and/or zeaxanthin, including other study designs in addition to randomized controlled trials (RCTs), and evaluating additional subgroups. Additionally, several new studies have been published in recent years, particularly studies with a longer duration of follow-up or larger sample sizes (7–12).

Currently, there are no dietary recommendations on the daily intake of lutein and zeaxanthin. The overall aim of this systematic review is to inform guidance on dietary recommendations for lutein/zeaxanthin intake to achieve optimal ocular health among adults with healthy eyes. Our specific objectives were to determine if there is a minimum or incremental concentration of lutein/zeaxanthin intake that is associated with a statistically significant and/or clinically important change in MPOD and to assess the dose-response relation between lutein/zeaxanthin intake and MPOD. Additionally, we sought to assess if results vary by age, sex, study location, risk of bias, source of lutein/zeaxanthin (food versus supplement), and the type of supplement (e.g., with or without meso-zeaxanthin and with or without other substances).

Methods

This systematic review followed guidelines from the Cochrane Handbook for Systematic Reviews (13) and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (14). We registered the protocol at PROSPERO as CRD42020197594.

Literature search

We updated the search strategy from an existing scoping review on lutein/zeaxanthin intake and visual outcomes (15). With the assistance of a librarian, we restricted searches by date and English language, and we adapted the search syntax for Ovid MEDLINE, Cochrane Central Register of Studies, and Commonwealth of Agriculture Bureau (**Supplemental Table 1**). We conducted the search in July 2020. We also hand searched the reference lists of eligible studies.

Selection of studies

We included studies assessing the effect of lutein/zeaxanthin supplements or dietary sources of lutein/zeaxanthin on MPOD in the general adult population with healthy eyes. We included interventions that lasted for ≥3 wk. We included RCTs, controlled clinical trials, comparative studies, evaluation studies, follow-up studies, prospective studies, crossover studies, case-control studies, matched-pair analyses, and cross-sectional studies. We did not limit studies based on setting or location. We excluded studies that included populations with age-related macular disease, diabetic retinopathy, diabetes, populations with children (aged <18 y), pregnant or breastfeeding women, and excluded animal and in vitro studies. We also excluded studies if we were unable to determine the lutein/zeaxanthin dose, and if an outcome of interest was not reported. We excluded reports with no original data (e.g., reviews, commentaries), case reports, studies with <10 subjects, and non-English language publications.

Studies with mixed populations (i.e., those with eye disease and not; those aged under 18 and aged 18 y and older; pregnant and not pregnant) were excluded unless data were presented separately for the population of interest.

We first rescreened studies identified in the scoping review to determine their eligibility for this review. Results from the updated search were then screened. For this review, we had 1 screener and a second screener verify or screen excluded studies. Screening first considered title/abstracts and then the full text of articles. We tracked and resolved all differences between reviewers through consensus. We used DistillerSR (Evidence Partners) to manage the screening process.

Data extraction

One reviewer extracted data and a second reviewer checked the extraction. For all articles, we extracted information on general study characteristics (e.g., study design, study period, length of follow-up, location, sample size), study participants (e.g., age, sex, BMI, per cent smokers), interventions (e.g., supplement versus dietary intervention, other nutrients, dose, frequency, duration), comparisons, and outcomes (e.g., results, measures of variability, and methods of ascertainment).

Risk of bias assessment

Cochrane risk of bias tool for trials (16) and Risk Of Bias In Nonrandomized Studies of Interventions tool (ROBINS-I) (17) were used to assess the quality of the included studies. Two team members independently completed each assessment.

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Supplemental Figures 1–3 and Supplemental Tables 1–7 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: HFP, heterochromatic flicker photometry; MPOD, macular pigment optical density; RCT, randomized controlled trial.

Data synthesis for statistical analysis

We conducted a qualitative synthesis for all questions and conducted meta-analysis where studies were sufficiently similar with respect to key variables [e.g., population, type of intervention (food versus supplement), outcome definition, study duration]. RCTs and cohort studies were meta-analyzed separately. We did not pool studies that used different methods for ascertaining MPOD because there is poor agreement between the different methods (18, 19).

Statistical heterogeneity among the trials considered for quantitative pooling was tested using a standard chi-squared test with a significance level of $\alpha \leq 0.10$. We also examined heterogeneity among studies using the I-squared statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance. A value >50% was considered to indicate substantial heterogeneity (20).

For continuous outcomes, we calculated a mean difference by using a random-effects model with the DerSimonian and Laird formula in settings of low heterogeneity (21).

Where there were ≥10 studies, we performed a meta-regression analysis with different doses of lutein/zeaxanthin and outcomes of interest. If studies provided sufficient information, we conducted stratified or subgroup analyses by: study location/country, risk of bias, supplements with or without meso-zeaxanthin, lutein/zeaxanthin supplements with or without other substances (e.g., zinc, ω-3, and PUFAs).

Publication bias was examined using Begg's test and Egger's test, including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes for which meta-analyses are conducted and there are ≥10 studies (22, 23). Publication bias was also qualitatively considered as part of the strength of evidence determination.

STATA statistical software (Intercooled, version 14.2, StataCorp) was used for all meta-analyses.

Strength of evidence

At the completion of our review, we graded the strength of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework (24). One investigator graded the evidence, and a second investigator confirmed the grading. We applied evidence grades for each dosing strata (i.e., <5 mg/d, 5 to <20 mg/d, and ≥20 mg/d).

Limitations to individual study quality (using individual risk of bias assessments), consistency, directness, precision, and publication bias were assessed. We classified evidence into 4 categories: (1) "high" grade (indicating we are very confident that the true effect lies close to that of the effect estimate); (2) "moderate" grade (indicating we are moderately confident in the effect estimate); (3) "low" grade (indicating our confidence in the effect estimate is limited); and (4) "very low" grade (indicating very little confidence in the effect estimate).

Role of the funding source

The International Life Sciences Institute North America (now the Institute for the Advancement of Food and Nutrition Sciences) provided the review question and reviewed the protocol and report but did not participate in the literature search, determination of study eligibility, analysis, interpretation of findings, or preparation of the manuscript for publication.

Results

Search results

We retrieved 401 unique citations; 46 studies, published in 49 articles, met our eligibility criteria, including 34 RCTs, 6 non-RCTs, and 6 single-arm studies (**Figure 1**). **Supplemental Tables 2** and **3** detail the trial and participant characteristics of the RCT and nonrandomized studies, respectively. Six studies evaluated dietary interventions (25–30), 38 evaluated supplements (7–12, 31–62), and 2 compared a dietary intervention with a supplement (63, 64) (**Table 1**). Study duration ranged from 5 wk to 24 mo. Known confounders, such as BMI, smoking status, and diabetes, were often not controlled for or reported on in the studies. BMI was reported in 31 studies (7–9, 11, 12, 25–35, 40, 42–44, 46–49, 53, 56, 57, 59, 60, 63), smoking status was reported in 26 studies (8, 9, 12, 25, 27, 29–32, 34–36, 40, 42–44, 46–50, 54, 59, 60, 63, 64), and diabetes was reported in 10 studies (25, 30, 38, 40, 42, 49, 57, 59, 63, 64).

Supplemental Figures 1–3 provide a summary of the risk of bias assessment. Most of the RCTs had an unclear or high risk of bias and most of the nonrandomized studies had at least a moderate risk of bias.

Concentration of lutein/zeaxanthin intake and MPOD

We stratified the syntheses based on the total daily dose of lutein/zeaxanthin. Within each dose strata, we present the results for MPOD at 0.5° eccentricity, the results for MPOD measured using heterochromatic flicker photometry (HFP), and then additional results that were not included in our meta-analysis.

Dose <5 mg/d.

Three randomized placebo-controlled trials evaluated the effects of <5 mg/d of lutein/zeaxanthin daily intake on MPOD at 0.5° eccentricity (26–28). All 3 of these trials used a dietary intervention with 0.5 to 4.5 mg/d of lutein/zeaxanthin and followed participants for 3 to 6 mo. All 3 trials had a high risk of bias due to lack of masking. There was a nonstatistically significant increase in MPOD at 0.5° eccentricity (mean difference, 0.02; 95% CI: −0.005 to 0.05; **Figure 2**). Including an additional trial (25) that evaluated eggs enriched with lutein or zeaxanthin (0.66–1.31 mg/d) and measured MPOD using HFP did not change the results (mean difference, 0.02; 95% CI: −0.01 to 0.04; **Supplemental Table 4**).

We did not include 3 trials in the meta-analysis; 1 trial did not provide sufficient data to be included (36) and the other trials were not randomized (30, 62). Results from these

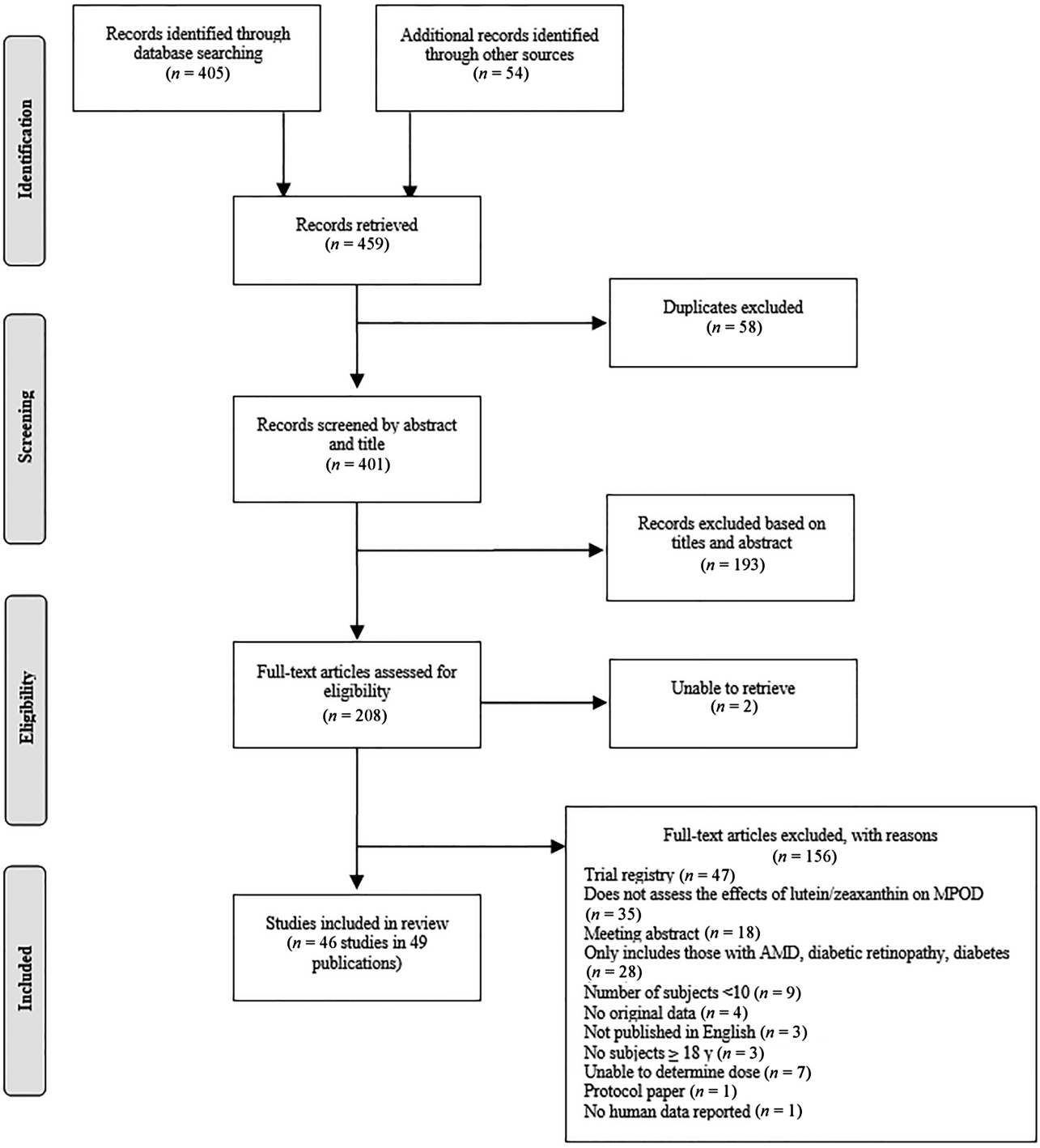

FIGURE 1 PRISMA diagram for studies that evaluate the effects of lutein/zeaxanthin intake on MPOD among adults with healthy eyes. AMD, age-related macular degeneration; MPOD, macular pigment optical density; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

trials suggest an increase in MPOD after supplementation with lutein/zeaxanthin (**Supplemental Tables 5–7**).

Lutein/zeaxanthin intake at <5 mg/d may increase MPOD but our confidence in these results is very low because of the concerns with the study limitations and the imprecise results (**Table 2**).

Dose 5 mg/d to <20 mg/d.

Six placebo-controlled trials evaluated a supplement with 5 to <20 mg/d of lutein/zeaxanthin and reported on MPOD with 0.5° eccentricity and followed participants for 3–12 mo (10, 11, 32, 42, 43, 47). Two of the trials had an unclear risk of bias (42, 43) and 4 trials were considered to have a high

TABLE 1 Characteristics of included studies that evaluated the effect of lutein/zeaxanthin intake on MPOD among adults with healthy eyes

	RCTs ($N = 34$)	Nonrandomized controlled trials ($N = 6$)	Single-arm trials ($N = 6$)
Comparison, *n*			
Dietary intervention vs. placebo	4	2	—
Supplement vs. placebo	23	—	—
Dietary intervention vs. supplement	1	1	—
Supplement vs. supplement	6	3	—
Supplement	—	—	6
Mean (range) of follow-up	6.7 mo (2 to 24 mo)	5.8 mo (2 to 12 mo)	5.2 mo (5 wk to 8 mo)
Location			
USA	16	4	3
Europe	13	2	2
Asia	5	0	1
Reported details on known confounders, *n*			
BMI	25	3	3
Smoking	20	4	2
Diabetes	6	2	2
MPOD Assessment,[1] *n*			
HFP	28	6	4
Autofluorescence	3	1	2
Raman spectrometry	3	0	0
Reflectometry	0	0	1
Not reported	1	0	0
Overall risk of bias (RCTs), *n*			
Low	8	—	—
High	14	—	—
Unclear	12	—	—
Overall risk of bias (nonrandomized studies), *n*			
Low	—	0	1
Moderate	—	3	4
Serious	—	1	0
Critical	—	2	1

[1] Some studies used >1 method to assess MPOD.
HFP, heterochromatic flicker photometry; MPOD, macular pigment optical density; RCT, randomized controlled trial.

risk of bias, mainly due to high loss to follow-up (10, 11, 32, 47). Pooling these trials in a meta-analysis demonstrated a statistically significant increase in MPOD of 0.04 (95% CI: 0.02 to 0.07; Figure 2).

There were 2 additional trials that assessed MPOD using HFP, but did not report the eccentricity (7, 38). Including these 2 trials in the meta-analysis increased the change in MPOD (mean difference, 0.06; 95% CI: 0.03 to 0.09; Supplemental Table 4).

Seven randomized placebo-controlled trials were not included in the meta-analysis because they did not report sufficient information (8, 12, 35, 37, 44) or because they used autofluorescence to measure MPOD (9, 34). Results from these studies are generally consistent with the conclusion that intake of lutein/zeaxanthin, especially at higher doses, increases MPOD in the fovea (Supplemental Table 5).

Five RCTs of supplements (49–53), 2 non-RCTs (54, 64), and 2 single-arm trials (58, 59) evaluated a daily supplement with 5 to <20 mg of lutein/zeaxanthin in ≥1 of their study arms. In these studies, MPOD either remained steady or significantly increased compared with baseline MPOD after 5 wk to 6 mo of lutein/zeaxanthin supplementation (Supplemental Tables 6, 7).

Daily doses of lutein/zeaxanthin between 5 and <20 mg increased MPOD by 0.04 units (95% CI: 0.02 to 0.07) among adults with healthy eyes (moderate strength of evidence; **Table 3**).

Dose ≥ 20 mg/d.

Five placebo-controlled trials evaluated a supplement with ≥20 mg/d of lutein/zeaxanthin and reported MPOD with 0.5° eccentricity and followed participants for 3–12 mo (33, 39, 43, 45, 47). One study had a low risk of bias (45), 2 studies had an unclear risk of bias (39, 43), and 2 studies had a high risk of bias because of a lack of blinding (33) or a high loss to follow-up (47). We pooled these 5 trials and found that MPOD increased by 0.11 units after lutein/zeaxanthin supplementation compared with placebo (95% CI: 0.06 to 0.16; Figure 2). The interpretations from the meta-analysis do not change when we include the studies that used heterochromatic flicker but did not report the eccentricity (33, 39–41, 43, 45–47) (Supplemental Table 4).

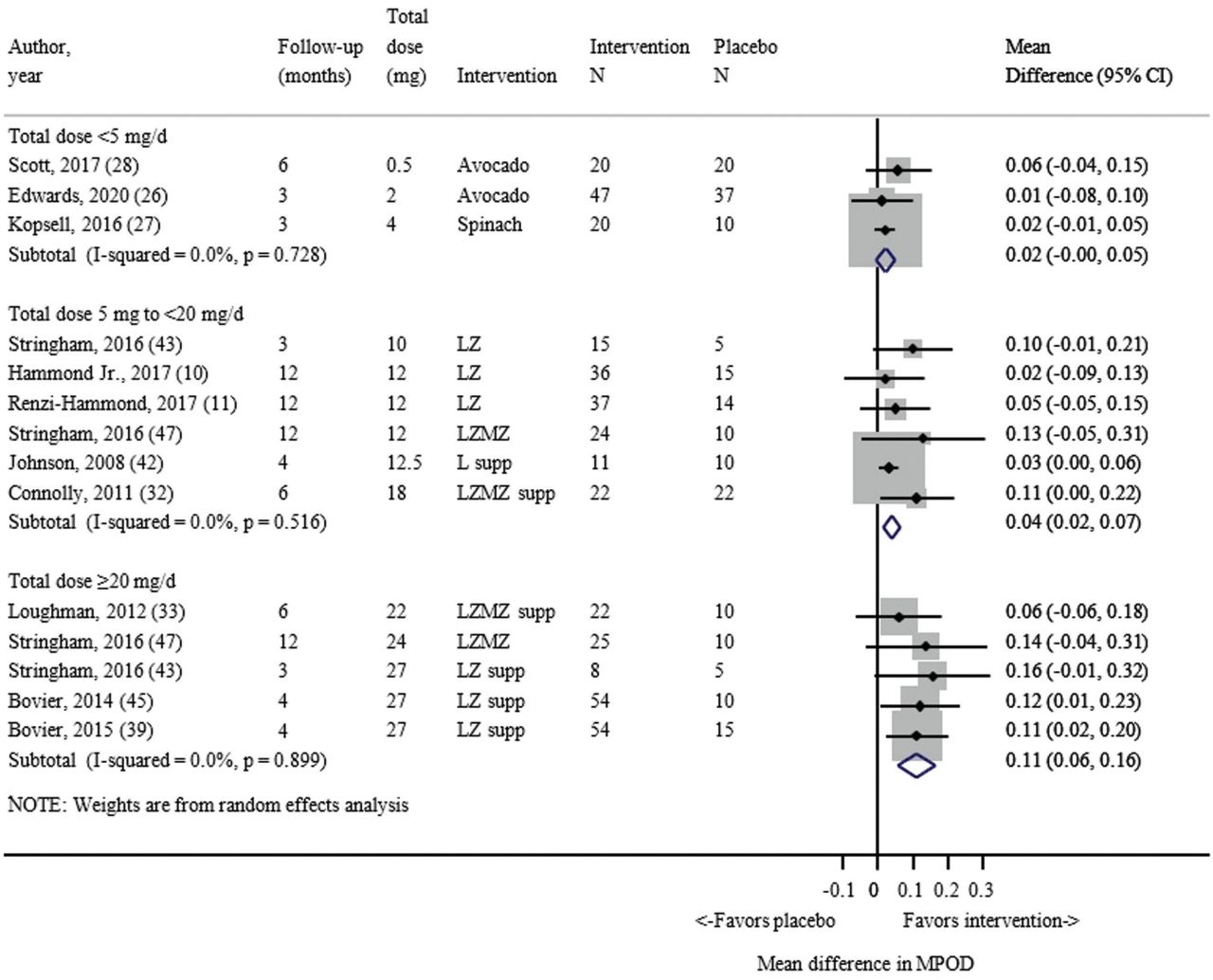

FIGURE 2 Meta-analysis of the effects of lutein/zeaxanthin intake on MPOD among adults with healthy eyes. L, lutein; MPOD, macular pigment optical density; MZ, meso-zeaxanthin; Z, zeaxanthin.

Three randomized placebo-controlled trials were not included in the meta-analysis because they did not report sufficient data to be included (12, 31, 44). All 3 trials reported statistically significant increases in MPOD after 6 to 12 mo of lutein/zeaxanthin supplementation.

Two RCTs of supplements (48, 50), 4 non-RCTs (54–56, 64), and 3 single-arm trials (57, 60, 61) evaluated a supplement with ≥20 mg/d of lutein/zeaxanthin in ≥1 of their study arms. Follow-up in these trials ranged between 2 and 12 mo. These trials generally support the conclusion that supplementation with ≥20 mg of lutein/zeaxanthin daily increases MPOD (Supplemental Tables 6–7).

Daily doses of lutein ≥20 mg increase MPOD by 0.11 units (95% CI: 0.06 to 0.16) among adults with healthy eyes (moderate strength of evidence; Table 3).

Dose-response relation

We included 18 randomized placebo-controlled trials with 3–12 mo of follow-up that assessed the effects of lutein/zeaxanthin intake on MPOD using HFP in a metaregression to assess the dose-response relation (7, 10, 11, 25–28, 32, 33, 38–43, 45–47). Based on the results of this metaregression, MPOD is expected to increase by 0.003 optical density units (95% CI: 0.001 to 0.006) per 1 mg increase of the total daily intake of lutein/zeaxanthin (Table 3). The effect on MPOD was significantly greater among studies that used a total daily dose of lutein/zeaxanthin ≥5 mg compared with those that used a dose <5 mg (0.051; 95% CI: 0.006 to 0.095). There were no studies that assessed the effects on MPOD and used a total daily dose of lutein/zeaxanthin between 5 and 10 mg.

Dietary sources

We conducted a metaregression including 4 studies that used a dietary intervention (25–28) and 14 that used a supplement (7, 10, 11, 32, 33, 38–43, 45–47). Dietary source is strongly tied to lutein/zeaxanthin dose: the total daily dose of lutein/zeaxanthin was <5 mg in all the studies that used

TABLE 2 Strength of the evidence and conclusions of the effect of lutein/zeaxanthin intake on MPOD among adults with healthy eyes

Dose	Number and type of studies (participants)	Strength of evidence	Conclusion
<5 mg/d	5 RCTs (25–28, 36) ($N = 284$ participants) and 1 non-RCT (30) ($N = 24$ participants)	Very low[1,2]	Unable to draw a conclusion
5 mg/d to <20 mg/d	20 RCTs (7–12, 32, 34, 35, 37, 38, 42–44, 47, 49–53) ($N = 1285$ participants), 2 non-RCTs (54, 64) ($N = 103$ participants), and 2 single-arm trials (58, 59) ($N = 79$ participants)	Moderate[3]	Daily doses of lutein between 5 and <20 mg may increase MPOD by 0.04 units[4] among adults with healthy eyes
≥20 mg/d	13 RCTs (12, 31, 33, 39–41, 43–48, 50) ($N = 628$ participants), 4 non-RCTs (54–56, 64) ($N = 253$ participants), and 3 single-arm trials (57, 60, 61) ($N = 350$ participants)	Moderate[3]	Daily doses of lutein ≥20 mg may increase MPOD by 0.11 units[5] among adults with healthy eyes

[1]Evidence downgraded due to very serious limitations.
[2]Evidence downgraded due to imprecise results.
[3]Evidence downgraded due to serious study limitations.
[4]Estimate based on a meta-analysis of 6 RCTs ($n = 221$ study participants).
[5]Estimate based on a meta-analysis of 5 RCTs ($n = 213$ study participants).
MPOD, macular pigment optical density; RCT, randomized controlled trial.

a dietary intervention and was ≥12 mg in all the studies that used a supplement. Supplements had a greater effect on MPOD than dietary interventions (0.051; 95% CI: 0.006 to 0.095; Table 3).

Additionally, there were 2 studies that compared a supplement to a dietary intervention (63, 64). Franciose et al. (63) randomly assigned 48 participants to a capsule with 6 mg/d of lutein/zeaxanthin, a tablet with 4 mg/d of lutein/zeaxanthin, or a diet with green, yellow, orange, and red fruits and vegetables (estimated 6.6 mg of lutein/zeaxanthin). After 12 wk of supplementation, there were no statistically significant differences in MPOD for any of the interventions. Bone et al. (64) was a nonrandomized study that compared a supplement with 12 mg/d of lutein/zeaxanthin with a liquid supplement with 28 mg/d of lutein/zeaxanthin/meso-zeaxanthin. After 24 wk, MPOD significantly increased in the liquid supplement group, but remained unchanged in the supplement group.

Elements of supplements

We conducted a metaregression of 5 studies that used a supplement that contained meso-zeaxanthin (32, 33, 43, 46, 47) and 9 studies that used a supplement that did not contain meso-zeaxanthin (7, 10, 11, 38–42, 45). The dose of meso-zeaxanthin in these supplements ranged from 0.53 mg to 10.6 mg/d. Supplements with meso-zeaxanthin did not significantly change the effect of lutein/zeaxanthin intake on MPOD (mean difference, 0.040; 95% CI: −0.027 to 0.106; Table 3).

Additionally, 3 RCTs (9, 34, 48) and 2 non-RCTs (55, 64) compared a supplement with meso-zeaxanthin to placebo or another supplement without meso-zeaxanthin. The interventions in these trials were very heterogenous, and the results of these trials were mixed. Both Nolan 2016 et al. and Nolan 2015 et al. compared a daily supplement with 10 mg lutein, 2 mg zeaxanthin, and 10 mg meso-zeaxanthin to placebo and reported a statistically significant increase in MPOD with the supplement (9, 34). Thurnham et al. (48) evaluated 3 daily supplements with a total 22 mg of lutein, zeaxanthin, and meso-zeaxanthin, but the amounts of lutein and meso-zeaxanthin varied. After 2 mo of supplementation, there were no significant differences in MPOD between the 3 supplements. Bone et al. (64) compared a daily liquid supplement with 15 mg lutein, 3 mg zeaxanthin, and 10 mg of meso-zeaxanthin to a daily gel capsule supplement with 10 mg lutein and 2 mg zeaxanthin and reported a statistically significant increase in MPOD among participants who received the liquid supplement compared with the participants who received the gel capsule supplement. Bone et al. (55) compared a daily supplement with 9.1 mg of lutein, 9.1 mg of zeaxanthin, and 1.8 mg of meso-zeaxanthin to a daily supplement with 19 mg of lutein and 1 mg of zeaxanthin. There was a significant change in MPOD among older adults, but not among younger adults.

In the metaregression, 2 studies evaluated supplements with substances other than lutein/zeaxanthin (38, 42) and 12 studies evaluated supplements with only lutein/zeaxanthin (7, 10, 11, 32, 33, 39–41, 43, 45–47). Johnson et al. (42) evaluated a supplement with lutein plus DHA and Berrow et al. (38) evaluated a supplement with lutein and zeaxanthin plus vitamin C, vitamin E, zinc, copper, and ω-3 fatty acids. Based on the results of the metaregression, supplements with substances other than lutein/zeaxanthin did not change the effect of lutein/zeaxanthin intake on MPOD (mean difference, −0.029; 95% CI: −0.077 to 0.019).

An additional 6 RCTs compared supplements with substances other than lutein/zeaxanthin to either a placebo or a substance with only lutein/zeaxanthin (8, 35–37, 52, 53). In addition to lutein and/or zeaxanthin, the supplements contained vitamin C, vitamin E, and α-lipoic acid (36); vitamin C, vitamin E, zinc, and selenium (35); vitamin C and vitamin E (37); DHA, γ-linolenic acid, vitamins, and zinc (8); DHA (52), and anthocyanines (53). The results from these studies were mixed, with some showing a significant increase

in MPOD after supplementation (35, 36) and others showed no statistically significant effect (8, 52, 53).

Subgroups

Two studies reported their results by age group (55, 59). Bone et al. (55) was a nonrandomized trial that recruited younger (aged 18–30 y) and older (aged ≥50 y) adults and compared 2 supplements with varying amounts of lutein, zeaxanthin, and meso-zeaxanthin. This study reported that the change in MPOD was greater among those who received the supplement with lutein, zeaxanthin, and meso-zeaxanthin than those who received the supplement with only lutein and zeaxanthin, but the results were significant only for the older adults. Cardinault et al. (59) was a single-arm trial that recruited adults aged 20–35 y and adults aged 60–75 y. After 5 wk of treatment with a daily supplement containing 9 mg of lutein and 0.45 mg of zeaxanthin, there were no significant differences in MPOD for both younger and older adults.

Two studies conducted a subgroup analysis by gender (25, 60). Kelly et al. (25) was an RCT that evaluated an unmodified diet, a diet with lutein-enriched eggs, zeaxanthin-enriched eggs, or a lutein egg beverage. This study did not report any differences by gender. Iannaccone et al. (60) was a single-arm trial where participants received a daily 20 mg supplement of zeaxanthin for 4 mo followed by a 4-mo washout period. After 4 mo of supplementation, MPOD increased significantly in both males and females. However, the increase in MPOD was not sustained for males during the washout period.

We conducted a metaregression of 11 studies conducted in the USA (10, 11, 26, 27, 39, 41–43, 45–47) and 8 studies conducted outside the USA (7, 28, 32, 33, 38, 40, 42). We did not find any significant differences on the effects on MPOD among studies conducted in the USA versus those conducted outside the USA (–0.021; 95% CI: –0.062 to 0.020; Table 3).

Finally, we compared studies that were considered to have a low compared with unclear compared with high overall risk of bias in a metaregression. The overall risk of bias did not significantly change the effect of lutein/zeaxanthin intake on MPOD (mean difference, –0.018; 95% CI: –0.048 to 0.012; Table 3).

Discussion

Our systematic review of 46 randomized and nonrandomized trials suggests that lutein and zeaxanthin intake at doses over 5 mg/d for ≥3 mo can increase MPOD concentrations among adults with healthy eyes by 0.4 to 0.11 units. There appears to be a dose-response relation, with greater effects on MPOD with higher doses of lutein/zeaxanthin. However, based on currently available evidence, it remains unclear if these increases in MPOD correspond to improvements in visual function.

The effects of lutein and zeaxanthin at doses <5 mg/d are less clear. Most of the trials of low doses of lutein or zeaxanthin evaluated dietary interventions, making it difficult to disentangle the effects of dose and the effects of dietary source. We found 2 studies that evaluated a supplement with a dietary intervention, but the results from these studies were conflicting (63, 64).

We found no difference in the effect on MPOD between supplements with and without meso-zeaxanthin and between supplements with and without other substances. Our results could have been limited by the heterogeneity in the dose of meso-zeaxanthin and in the types of substances used in the supplements; future studies will need to confirm this.

Our findings are mostly consistent with a prior systematic review (6). We have expanded on the prior review by including both dietary interventions and supplements and by including study designs other than randomized placebo-controlled trials. In addition, we included 11 randomized placebo-controlled trials that were published after the prior review (7, 8, 10–12, 38, 40, 43, 44, 46, 47), including 5 trials with ≥1 y of follow-up (8, 10–12, 47).

Our review had several limitations, including the possibility of publication and reporting biases. Our review may have missed unpublished studies or studies that were published in languages other than English. We were unable to include

TABLE 3 Metaregression results of studies that evaluate the effect of lutein/zeaxanthin intake on macular pigment optical density among adults with healthy eyes

Variable	Number of studies	Mean difference (95% CI)	*P*
Total dose	18	0.003 (0.001 to 0.006)	0.004
Dose ≥10 mg/d vs. <10 mg/d	18	0.051 (0.006 to 0.095)	0.028
Dose ≥15 mg/d vs. <15 mg/d	18	0.053 (0.011 to 0.095)	0.016
Dose ≥20 mg/d vs. <20 mg/d	18	0.048 (0.003 to 0.093)	0.040
Supplement vs. dietary intervention	18	0.051 (0.006 to 0.095)	0.028
Supplements with meso-zeaxanthin vs. supplements without meso-zeaxanthin	14	0.040 (–0.027 to 0.106)	0.221
Supplements with substances other than lutein/zeaxanthin vs. supplements with only lutein/zeaxanthin	14	–0.029 (–0.077 to 0.019)	0.212
US vs. non-US countries	18	–0.021 (–0.062 to 0.020)	0.298
Risk of bias	18	–0.018 (–0.048 to 0.012)	0.413

many studies in our meta-analyses because of incomplete outcome reporting. Furthermore, the heterogeneity in the study designs, interventions, comparisons, and outcome assessments limited our ability to include additional studies in the meta-analysis. Because many studies were excluded from the meta-analysis and the metaregressions, our analyses may not have been adequately powered to detect a difference in MPOD for supplements with meso-zeaxanthin or other substances. Many of the studies included in our review were short-term studies with small sample sizes. All studies were conducted for ≥3 wk, per our eligibility criteria. However, most (74%) of the studies lasted for 6 mo or shorter. Masking of the intervention was not always feasible in many of the studies, particularly those evaluating a dietary intervention. The lack of masking may be less relevant for objective assessments of MPOD, such as with autofluorescence or Raman spectroscopy. It is unclear if study participants may have changed behavior, including adherence, if unmasked. Many studies had high losses to follow-up and not all studies controlled for potential confounders, such as smoking status, BMI, and diabetes.

In conclusion, among adults with healthy eyes, lutein/zeaxanthin intake increases MPOD, particularly at doses >10 mg/d. The effects of lutein/zeaxanthin intake at doses <5 mg/d or from dietary sources is less clear. We found no studies that assessed the effects of 5 to 10 mg/d of lutein/zeaxanthin on MPOD. Increased lutein/zeaxanthin intake can help with maintaining ocular health. However, future research is needed to determine the minimum dose and duration of lutein/zeaxanthin intake that is associated with a clinically important change in MPOD or visual function.

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Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request.

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