Abstract: Purpose: Scientific evidence suggests a role for lutein and zeaxanthin, in visual function. The purpose of this research was to summarize the data related to lutein/zeaxanthin intake and visual outcomes in adults with healthy eyes using evidence mapping methods and to describe the research to date that would be useful in guiding future research priorities, systematic reviews, and meta-analyses. Design: A search of Medline®, Cochrane Central, and CAB databases was performed for studies of all designs published from 1946 to October 2016. Our search strategy included lutein, zeaxanthin, meso-zeaxanthin, xanthophylls and carotenoids as well as visual outcomes to include macular pigment density (MPD). Results: Forty-seven studies published in English language were identified and mapped. Most research was conducted in controlled parallel trials (77%) using lutein/zeaxanthin supplements. Studies evaluated effects of lutein/zeaxanthin supplementation (66%) or lutein/zeaxanthin in combination with other nutrients (17%); or evaluated foods rich in lutein/zeaxanthin (17%). MPD (89%) was the most common outcome measure studied. Additional outcome measures included in 47 studies were visual acuity (23%), contrast sensitivity (17%), glare sensitivity (13%), and photostress recovery (11%). Conclusions: This study using evidence mapping found that studies evaluating lutein/zeaxanthin supplementation or intake and visual outcomes had MPD as the most common outcome. We conclude that there is sufficient research to...
warrant a future systematic review/meta-analysis evaluating the role of lutein/zeaxanthin and visual outcomes in participants with healthy eyes. Of interest would be a systematic review of the studies that evaluated both MPD and visual function to determine the strength of the relationship between these two outcomes in healthy adults.

**Subjects:** Nutrition; Complementary and Integrative Medicine; Aging

**Keywords:** lutein; zeaxanthin; visual function; macular pigment

### 1. Introduction

Extensive epidemiological observation indicates that fruits and vegetables rich in carotenoids provide a variety of health benefits including prevention of chronic diseases, such as heart disease, cancer, stroke, diabetes, Alzheimer’s disease, cataracts, and age-related macular degeneration (Hu, Huang, Wang, Zhang, & Qu, 2014; Lamport, Saunders, Butler, & Spencer, 2014; Liu, 2013). The relationship between lutein and zeaxanthin, dietary xanthophyll carotenoids, and visual function is particularly compelling because of the more than 600 carotenoids found in nature, they are taken up selectively into the macula (Bernstein et al., 2001; Bone, Landrum, & Tarsis, 1985). In the macula, lutein and zeaxanthin are thought to provide protection through their roles as blue light filters, antioxidants and anti-inflammatory agents (Johnson, 2014). In addition, there may be a structural role for these compounds to modulate functional properties of synaptic membranes (Gruszecki, 2004; Gruszecki, Sujak, Strzalka, Radunz, & Schmid, 1999). Lutein has also been shown to enhance gap junctional communication (Stahl & Sies, 2001), which, in the retina, is important for light processing and may be important for the development of neural circuitry in the visual system. Given this, lutein and zeaxanthin have been proposed to be of benefit to ocular health. In fact, a 2012 meta-analyses have reported that an increase in the intake of these carotenoids may be protective against late age-related macular degeneration (AMD) (Ma et al., 2012) and a statistically significant inverse association was observed between lutein and zeaxanthin intake and neovascular AMD risk (Liu et al., 2014). Additionally, a 2014 meta-analysis that evaluated the relationship between blood lutein and zeaxanthin concentrations and the risk of age-related cataract reported that high concentrations were significantly associated with a decrease in the risk of nuclear cataract (Liu et al., 2014). While a role for lutein and zeaxanthin has been systematically evaluated in age-related eye disease, such a systematic evaluation has not yet been performed to evaluate a role for lutein/zeaxanthin in visual outcomes among adults with healthy eyes. The overall objective was to identify if there is sufficient evidence to date to support initiating a future full systematic review to evaluate the role of lutein/zeaxanthin on visual outcomes. Through evidence mapping, we determined the extent of the evidence base related to lutein/zeaxanthin on visual outcomes among adults with healthy eyes.

### 2. Methods

#### 2.1. Description of evidence mapping

Evidence mapping is a tool used to systematically identify, organize and summarize the scientific evidence on a broad subject (Althuis & Weed, 2013). The steps include a comprehensive literature search strategy, establishing study eligibility criteria and a systematic study selection process, extracting data, developing outcome groups and tabulating data using descriptive analyses. An evidence map is the first step in conducting a broad systematic review. However, unlike a systematic review, evidence mapping does not require an evaluation for risk-of-bias of the included studies or an extraction and synthesis of the studies’ findings. Rather, an evidence map summarizes the characteristics of existing literature and determines where there is sufficient evidence to identify research gaps as well as research areas where systematic reviews can be performed. Therefore, evidence mapping can be used to plan more focused questions for a systematic review and meta-analysis. Evidence mapping can be a cost-effective methodology to facilitate evidence-based decision-making.
This evidence mapping summarizes the data related to lutein/zeaxanthin intake and visual outcomes among adults with healthy eyes using the generic analytic framework that was developed for dietary reference values (Russell et al., 2009). We applied the steps involved in a prior evidence mapping (Wang, Shams-White, Bright, Parrott, & Chung, 2016) to construct the lutein/visual outcome evidence-map database: 1) identify the scope of the evidence map; 2) define the roles and responsibilities of the parties (stakeholder panel and research team); 3) develop a comprehensive search strategy; 4) establish study eligibility criteria and systematic study selection process; 5) carry out abstract screening and selection; 6) carry out data extraction and 7) classify outcome categories. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Liberati et al., 2009) was used to depict the flow of retrieved records through the phases of screening and inclusion.

We reviewed published papers. Therefore, it was not necessary to include a statement regarding adherence to the guidelines of the Declaration of Helsinki and Institutional Review Board approval was not needed.

2.2. Identification of the scope
The guiding key question for this project was to determine if higher compared to lower lutein/zeaxanthin intake was associated with normal healthy eye structure (including macular pigment density, MPD) and visual function with the goal of summarizing the extent and distribution of the evidence.

2.3. Stakeholder panel and research team responsibilities
In order to gain an understanding of the most important clinical uncertainties, patterns of use, and technical details about this topic, we interviewed a selected number of Key Informants (KIs). When identifying KIs, we aimed for a diverse and representative group that was likely to generate a broad range of perspectives on carotenoid metabolism and biology, visual function and ocular structure. KIs included a nutritionist, ophthalmologist, and a dietician.

At the beginning of the project KIs helped finalize the literature search strategy and guiding key questions.

2.4. Systematic search
A protocol was developed according to the methodology outlined in standard systematic review methods (Agency for Healthcare Research and Quality, 2010; Eden, Levit, & Morton, 2011; Moher, Liberati, Tetzlaff, & Altman, 2009). We conducted an electronic search on Medline®, Commonwealth Agricultural Bureau (CAB), Cochrane Central Register of Controlled trials, and bibliography searches of prior systematic reviews and eligible studies that examine lutein/zeaxanthin and visual outcomes. The search terms are tabulated in Supplemental Table S1. Searches spanned the time period from 1946—October 2016 and were limited to adults (>18 years). Other inclusion and exclusion criteria applied during citation and full-text screenings are given in Table 1.

Table 1. Study eligibility criteria

| Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| • Published 1946—October 2016                                                     | • Reviews, bibliographies, case reports                                           |
| • Published in English                                                             | • Cross-sectional studies                                                          |
| • Study designs: randomized controlled trials; controlled clinical trials; other control trials, including random allocation, masked, or blinded; comparative studies; evaluation studies; follow-up studies; prospective studies; cross-over studies; case-control studies; matched-pair analyses; intervention studies | • Populations with children (<18 years), pregnant or breastfeeding women           |
|                                                                                   | • Number of subjects <10                                                           |
|                                                                                   | • Lutein/zeaxanthin dose not clearly reported (amount not provided)                |
|                                                                                   | • An outcome of interest is not reported                                          |
|                                                                                   | • Animal studies                                                                   |
|                                                                                   | • In vitro studies                                                                 |

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In step 1, we performed title and abstract screening, in duplicate. We collected pertinent data from qualifying primary studies to determine the scope of the existing literature: 1) Population; 2) Intervention; 3) Control; 4) Outcomes; 5) Study design (e.g., randomized parallel trials, cross-over trials); 6) Duration of follow-up; and 7) Number of participants per group of intervention. One reviewer extracted information and a second reviewer verified the data entries for accuracy and thoroughness. This first step is intended to inform on the current state of research that could be used to make a recommendation on whether there is sufficient evidence to warrant a systematic review. Systematic Review Data Repository was used as a tool for the extraction and management of data for the evidence mapping (srdr.ahrq.gov). All analyses and charting were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and Microsoft Excel 2013.

3. Results
The results of a search for publication (1946—October 2016) that assessed the relationship between lutein/zeaxanthin intake and visual outcomes and met the search criteria are listed in Figure 1. The electronic search identified 2545 abstracts. After removal of duplicates (n = 500), potentially eligible publications (n = 176) that assessed the relation between lutein/zeaxanthin intake and visual outcomes were identified for full text review. The first author and year of publication of the eligible primary research studies and the source by which they were identified are detailed elsewhere (Supplemental Table S2). A total of 47 studies in 46 publications that received a full text review were found to be eligible (Figure 1). The references of included studies

![Figure 1. Study flow diagram depicting the review process](https://example.com/image.png)
are listed in the Supplemental Table S3. Descriptive analyses of the data were used to identify potential gaps and future research directions.

### 3.1. Study design characteristics

Of 47 studies evaluated, 36 were controlled parallel trials, 8 were single arm studies (without a comparator or control group), 3 were observational supplement studies (2 cohort studies and 1 was a case-control study). Thirty-one of 36 trials were randomized and 5 were controlled trials without randomization (Table 2). Of 36 controlled trials, 22 were double-blind (i.e., both patients and outcome assessors were blinded) trials, two were single-blind (i.e., only outcome assessors were blinded) trials, and 12 did not report on blinding.

### 3.2. Study characteristics

Although we searched the literature between 1946 and 2016, the 47 eligible studies were published between 1997 and 2016. The sample size of these studies ranged from 10 to 396 and the study duration ranged from 28 days to 1.5 years. The majority of these studies were conducted in the USA followed by Ireland and the United Kingdom. Other study sites included Japan, China, England, Italy, Germany, France and the Netherlands (Figure 2).

### 3.3. Population characteristics

The age distribution among eligible studies was somewhat evenly distributed among the decades, however 16 studies did not report age (Figure 3). Thirty-seven percent of the studies were composed of 25–49% male subjects and 25% of the studies consisted of 50–75% male subjects. The remainder of the studies consisted of mostly women (>75%, n = 6 studies) or men (>75%, n = 4 studies). Nine studies (18% of the studies) did not specify the gender (Table 3). The majority of the

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**Table 2. Study design characteristics**

| Study Design                  | N (%) | Randomization   | N (%) | Blindness          | N (%) |
|-------------------------------|-------|-----------------|-------|-------------------|-------|
| Controlled trials, parallel   | 36 (77)| Randomized      | 31 (67)| Double-blind<sup>a</sup> | 22 (46)|
|                               |       | Not randomized  | 5 (11) | Single blind<sup>b</sup> | 2 (4) |
|                               |       |                 |       | No blinding/unspecified | 12 (26)|
| Single arm<sup>c</sup>        | 8 (17) | Not applicable  |       | Not reported       |       |
| Cohort                        | 2 (4)  | Not applicable  |       | Not reported       |       |
| Case-control                  | 1 (2)  | Not applicable  |       | Not reported       |       |

<sup>a</sup>Both investigators and subjects are blinded to the group assignment; <sup>b</sup>Investigators or outcome assessors are blinded to the group assignment, but the subjects are not blinded to the group assignment; <sup>c</sup>Single arm studies have only intervention group without a comparator, therefore randomization was not applicable.

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![Figure 2. Study characteristics.](image)

- N=49
- Years of Publication: 1997 – 2016
- Sample Size: 10-396
- Duration Range: 28 days – 1.5 years

![Sample Size N (%)](image)

- 10-25: 10 (20.4%)
- 26-49: 17 (34.7%)
- 50-99: 13 (26.5%)
- ≥ 100: 9 (18.4%)
studies (n = 28, 58%) did not specify the body mass index of the study population, 13 studied subjects with normal weight (27%) and 8 studies evaluated overweight subjects. None of the studies had obese subjects (Table 3).

### 3.4. Lutein/zeaxanthin interventions

Of 47 eligible studies, 66% evaluated supplementation with lutein and/or zeaxanthin (n = 31); 8 studies (17%) involved lutein/zeaxanthin supplementation in combination with other nutrients such as multivitamins, carotene, docosahexaenoic acid, and others, and 8 (17%) studies evaluated interventions with foods containing lutein/zeaxanthin. The most common foods tested included eggs (3 studies), spinach (2 studies), and corn, increased fruits and vegetables, and goji berries in 1 study each. In 6 studies, the food was distributed to participants and intake was confirmed using diary, diet records, and food frequency questionnaire and 2 studies provided no information.

### 3.5. Types of outcomes

Among the 47 studies, 42 (89%) reported MPD outcomes. MPD was most commonly assessed using the following methods: heterochromatic flicker photometry (n = 33), autofluorescence (n = 4), and Raman spectroscopy (n = 3). Other visual outcomes included contrast sensitivity (n = 11), visual acuity (n = 8), glare sensitivity (n = 6), photostress recovery (n = 5), and 6 studies had other, varied visual outcomes (Figure 4). Across studies, the follow-up of outcomes varied and ranged from 4 to 76 weeks.
3.6. Adverse effects
Six of 47 studies reported adverse effects and all 6 studies concluded that adverse effects were not attributable to lutein/zeaxanthin supplementation. The remaining 41 studies did not report any data on adverse effects.

3.7. Research-dense areas and gaps
A bubble plot was used to identify relationships or patterns among the study interventions, study type and visual outcomes (Figure 4). The bubble plot used data in the lutein/zeaxanthin evidence-map database and a study was included multiple times if multiple outcomes of interest were reported. The bubble plot is plotted in a two dimensional grid according to outcome categories and study design. Each data point is placed in the appropriate grid location (by study design and outcome), the size of which is relative to the subject number and the color of which refers to the intervention type (lutein/zeaxanthin supplement with or without other nutrients, lutein/zeaxanthin contained in food). From this visual representation of the studies evaluated it is clear that controlled parallel trials evaluating lutein/zeaxanthin interventions (alone or in combination with other nutrients, foods) is where the majority of the research has been conducted with macular pigment being the primary outcome of interest followed by contrast sensitivity and visual acuity. Similarly, in studies of other design, MPD was the outcome most studied. There is a lack of cohort studies examining the association between intake of lutein/zeaxanthin and visual outcomes. Among interventional trials, there is also sparsity of data on visual outcomes other than MPD.

4. Discussion
This study using evidence mapping found that studies evaluating lutein/zeaxanthin supplementation or intake and visual outcomes among healthy adults had MPD as the most common outcome. Most research was conducted in controlled parallel trials (77%) using lutein/zeaxanthin supplements. Studies evaluated effects of lutein/zeaxanthin supplementation (66%) or lutein/zeaxanthin in combination with other nutrients (17%); or evaluated foods rich in lutein/zeaxanthin (17%). MPD (89%) was the most common outcome measure studied. Additional outcome measures included in 47 studies were visual acuity, contrast sensitivity, glare sensitivity, and photostress recovery.

Lutein and zeaxanthan have been long recognized as providing protection against age-related eye disease (Abdel-Aal, Akhtar, Zaheer, & Ali, 2013; Renzi & Johnson, 2007). In fact, two recent meta-analyses have reported a relationship between lutein/zeaxanthin intake and a decreased risk of early age-related macular degeneration and cataracts (Liu et al., 2014; Ma et al., 2012). The recent meta-analysis examining the relationship between lutein/zeaxanthin intake and a decreased risk of early age-related macular degeneration included only 11 studies with healthy participants (Stahl & Sies, 2001). To the best of our knowledge, a comprehensive systematic
review of the literature on a role for lutein/zeaxanthin and visual outcomes among healthy eyes has not been conducted.

Several important outcomes in vision for these carotenoids have been proposed. Lutein and zeaxanthin, as macular pigment, filter significant amounts of short-wave energy (Snodderly, Brown, Delori, & Auran, 1984), thus protecting the photoreceptors from light damage. Given their roles as antioxidants, lutein and zeaxanthin may also provide protection by inactivating highly reactive free radicals and oxygen triplicates that result from light-induced cellular activity (Hammond & Fletcher, 2012). Thus, there is biologically plausibility to lutein/zeaxanthin providing benefit in visual function.

Regardless of the study design, MPD was the most studied visual outcome. Macular pigment is considered to have a structural function in vision due to its properties as a short-wavelength (blue) light filter (Bone, Landrum, & Cains, 1992) and as a strong antioxidant (Khachik, Bernstein, & Garland, 1997), both of which provide protection from damaging light. Also, it has been suggested that macular pigment, through its light filtering properties, may enhance visual function and comfort by attenuation of the effects of chromatic aberration and light scatter (Nussbaum, Pruett, & Delori, 1981). Our results suggest that there is a large enough body of evidence to conduct a systematic review/meta-analysis of the results from the controlled trials that looked at macular pigment among healthy adults. This could help us quantify the lutein dose required to reach optimal MPD in the eyes of healthy people. Additionally, studies also looked at other measures of visual outcomes such as contrast sensitivity, visual acuity, glare sensitivity, and photostress recovery, the relationship between these outcome measures could be more fully explored in a systematic review/meta-analysis.

We identified that there is a lack of cohort studies examining visual outcomes. We also identified potential challenges in conducting a future systematic review and meta-analysis. The MPD data, as well as the measures of visual outcomes were reported heterogeneously and they were not consistently reported among studies. Furthermore, 17% of the lutein/zeaxanthin interventions involved co-interventions with other nutrients or another 17% of studies included interventions with foods rich in lutein/zeaxanthin, thus potentially making it difficult to tease out the role of lutein/zeaxanthin.

To date, there has been no systematic evaluation of the overall strength of the evidence to support a role for lutein/zeaxanthin in visual outcomes among participants with healthy eyes. This evidence map is the first step in such an evaluation. It is important to note that this evidence map does not include an assessment of risk of bias or the direction of the effect. Therefore, this evidence map is not able to determine the quality or consistency of the research that has been conducted to date.

5. Conclusion
Evidence mapping is an important and useful tool in defining research gaps as well as well-investigated research areas. In our analysis, the majority of the studies evaluating lutein/zeaxanthin intake and visual outcomes had MPD as the measure of interest. However, there are a number of studies with other outcome measures of interest (contrast sensitivity, glare sensitivity, photostress recovery, visual acuity) suggesting that there is sufficient research to date to warrant a systematic review and meta-analysis evaluating the role of lutein/zeaxanthin and visual outcomes among healthy individuals. However, co-interventions and consistency of the data reported would need to be considered in a future systematic review. Of interest for a future review of studies that evaluate the association between macular pigment and visual function. A systematic review and meta-analysis, which would evaluate the quality of the research studies as well as the direction of effect, would provide more conclusive evidence on the role of lutein/zeaxanthin and visual outcomes among healthy adults.
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Supplementary material

Supplemental data for this article can be accessed here.

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