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# Lutein/Zeaxanthin for the Treatment of Age-Related Cataract

## AREDS2 Randomized Trial Report No. 4

The Age-Related Eye Disease Study 2 (AREDS2) Research Group; Emily Y. Chew, MD<sup>1</sup>; John Paul SanGiovanni, ScD<sup>1</sup>; [et al](#)

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Interviews

## Abstract

**Importance** Age-related cataract is a leading cause of visual impairment in the United States. The prevalence of age-related cataract is increasing, with an estimated 30.1 million Americans likely to be affected by 2020.

**Objective** To determine whether daily oral supplementation with lutein/zeaxanthin affects the risk for cataract surgery.

**Design, Setting, and Patients** The Age-Related Eye Disease Study 2

(AREDS2), a multicenter, double-masked clinical trial, enrolled 4203 participants, aged 50 to 85 years, at risk for progression to advanced age-related macular degeneration.



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to daily placebo; polyunsaturated fatty acids, 1 g; or a combination to evaluate the effects on the primary outcome of progression to advanced age-related macular degeneration.

**Main Outcomes and Measures** Cataract surgery was documented at annual study examination with the presence of pseudophakia or aphakia, or reported during telephone calls at 6-month intervals between study visits. Annual best-corrected visual acuity testing was performed. A secondary outcome of AREDS2 was to evaluate the effects of lutein/zeaxanthin on the subsequent need for cataract surgery.

**Results** A total of 3159 AREDS2 participants were phakic in at least 1 eye and 1389 of 6027 study eyes underwent cataract surgery during the study, with median follow-up of 4.7 years. The 5-year probability of progression to cataract surgery in the no lutein/zeaxanthin group was 24%. For lutein/zeaxanthin vs no lutein/zeaxanthin, the hazard ratios for progression to cataract surgery was 0.96 (95% CI, 0.84-1.10;  $P = .54$ ). For participants in the lowest quintile of dietary intake of lutein/zeaxanthin, the hazard ratio comparing lutein/zeaxanthin vs no lutein/zeaxanthin for progression to cataract surgery was 0.68 (95% CI, 0.48-0.96;  $P = .03$ ). The hazard ratio for 3 or more lines of vision loss was 1.03 (95% CI, 0.93-1.13;  $P = .61$  for lutein/zeaxanthin vs no lutein/zeaxanthin).

**Conclusions and Relevance** Daily supplementation with lutein/zeaxanthin had no statistically significant overall effect on rates of cataract surgery or vision loss.

**Trial Registration** [clinicaltrials.gov](https://clinicaltrials.gov) Identifier: [NCT00345176](https://clinicaltrials.gov/ct2/show/study/NCT00345176).



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Age-related cataract, the leading cause of blindness worldwide, is a leading cause of visual impairment in the United States.<sup>1-3</sup> The prevalence of age-related cataract is increasing, with an estimated 30.1 million Americans likely to be affected by 2020, escalating the already large public health and economic burden of the disease.<sup>4</sup> Numerous observational studies have reported inverse relationships between various dietary micronutrients and the development of age-related cataract or the occurrence of cataract surgery.<sup>5-10</sup> Of greatest interest have been micronutrients with antioxidant capabilities because of the importance of oxidative damage in cataract formation. In the absence of any consensus about the importance of specific micronutrients, several controlled clinical trials have tested whether selected micronutrients with antioxidant characteristics or multivitamins affect cataract development.<sup>11-17</sup> Because of variable results, no clear treatment recommendation has resulted from the trials conducted to date. This includes the Age-Related Eye Disease Study (AREDS), which tested a formulation containing vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg; as well as the minerals zinc (as zinc oxide), 80 mg, and copper (as cupric oxide), 2 mg, for both age-related macular degeneration (AMD) and cataract.<sup>18</sup> Although AREDS showed a 25% beneficial effect for reducing the risk for developing advanced AMD, it showed no statistically significant effect of the AREDS formulation on the progression of lens opacities.

The AREDS2 randomized clinical trial was designed to evaluate whether oral supplementation with lutein/zeaxanthin and/or omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) might affect development of advanced AMD. A secondary goal was to evaluate the effect of lutein/zeaxanthin on the progression of age-related cataract. A rationale for examining the im-

pect of lutein/zeaxanthin comes from observational data collected in AREDS, other epidemiologic studies, and animal studies.<sup>19</sup> Lutein and zeaxanthin, xanthophylls with antioxidant capabilities, are the only carotenoids detected in the human lens.<sup>20</sup> Observational studies have demonstrated an



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blood levels of

particularly the nuclear

form and cataract surgery.<sup>21-24</sup> AREDS2 provided an opportunity to examine the effect that daily dietary supplementation with lutein/zeaxanthin had on age-related cataracts in a randomized clinical trial. The primary cataract outcome in AREDS2 was cataract surgery, with the secondary outcomes of progression of lens opacities or change in visual acuity. Clinical trial results for the AMD component of AREDS2 are presented elsewhere.

## Methods

Details of the AREDS2 study design described in a previous report<sup>25</sup> are briefly summarized here. Eighty-two retinal specialty clinics enrolled 4203 participants, aged 50 to 85 years, from October 2006 through September 2008. Institutional review boards at the clinical sites approved the AREDS2 research protocol, and participants provided written informed consent. Recruitment of participants was based on retinal findings of bilateral large drusen or large drusen in 1 eye and advanced AMD in the fellow eye. At least 1 eye of each participant was free of advanced AMD. There were no specific inclusion criteria regarding lens opacity status other than the need for sufficiently clear media to allow quality fundus photographs. There was also no specific eligibility criterion for visual acuity.

A run-in phase using study placebo and the AREDS formulation tested the participants' likely ability to adhere to the study regimen. Participants were eligible for enrollment at their randomization visit if they took at least 75% of the run-in medications and if they agreed to take the AREDS2 supplements and stop current use of supplements containing lutein, zeaxanthin, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), vitamin C, vitamin E, beta carotene, zinc, or copper, unless supplied by AREDS2. They could not have other ocular diseases that might confound assessment of the ocular outcomes or other systemic diseases including lung cancer or other diseases associated with poor 5-year survival. Participants with previous cataract surgery were excluded only if the surgery was less than 3 months prior to enrollment.

## Study Design

AREDS2 is a randomized, double-masked, placebo-controlled, 2 × 2 factorial trial evaluating the risks and benefits of adding lutein/zeaxanthin, 10



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plements daily: (1) placebo; (2) lutein/zeaxanthin; (3) DHA/EPA; or (4) lutein/zeaxanthin and DHA/EPA. This article evaluates the role of lutein/zeaxanthin for the treatment of age-related lens opacities, specifically for progression to cataract surgery. Components of the AREDS2 formulation, donated by DSM Nutritional Products, include lutein/zeaxanthin supplied as water soluble triglyceride compounds and omega-3 LCPUFA formulation supplied in ethyl ester form as Ropufa 75 n-33 EE.

A second randomization was conducted for the AMD component of the trial. Because of evidence that beta carotene may increase the risk for lung cancer in cigarette smokers and the AREDS formulation may contain more zinc than can be absorbed,<sup>26</sup> we tested the effect of eliminating beta carotene and reducing the dosage of zinc in the AREDS formulation (not displayed in the consort diagram in [Figure 1](#)). These nutrients were considered only important for the treatment of AMD but they need to be considered for potential interaction with the primary randomization.

Centrum Silver (Pfizer Inc) was offered to all study participants to standardize multivitamin intake. Participants and study personnel were masked to all treatment assignments.

## Follow-up and Adherence

Follow-up study visits were conducted annually. Telephone contacts were scheduled 3 months after randomization and at 6 months between study visits to collect information about compliance with study medication, AMD treatment, cataract surgery, and occurrence of adverse events. Best-corrected visual acuity was obtained annually using a standardized protocol. Certified photographers obtained red reflex lens photographs at baseline and annually. The photographs were assessed by masked graders for the severity of cortical and posterior subcapsular cataract (PSC) lens opacities at the University of Wisconsin Fundus Photograph Reading Center, Madison, Wisconsin.

Adherence to the treatment regimen was assessed by pill count at each annual study visit. Serum levels of lipids, lutein/zeaxanthin, fat soluble vitamins, zinc, and copper were measured at baseline and years 1, 3, and 5 in 545 participants from a subset of clinics. Participants were followed up until 4.7 years (interquartile



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## Outcome Measures

The study examined the effects of lutein/zeaxanthin on progression to cataract surgery with data collected during regular telephone contacts and the annual study visits. A study ophthalmologist examined the anterior segment using slitlamp biomicroscopy at the annual visit to diagnose or confirm the presence of pseudophakia or aphakia. The severity and progression of cortical and PSC opacities on the red reflex lens photographs and the presence of pseudophakia or aphakia were graded at the reading center.

The primary outcome of the cataract clinical trial was progression to cataract surgery. Other outcomes included (1) progression to cataract surgery or an absolute increase in opacity size (area) within the central 5 mm of the lens or 10% for cortical or 5% for PSC opacities; (2) progression to cataract surgery or a 20% absolute increase in the area of either opacity within the central 5 mm of the lens; and (3) a reduction in visual acuity of 15 or more letters from baseline. Safety outcomes included mortality.

## Statistical Analyses

The unit of analysis for ophthalmic outcomes was by eye. The lens efficacy outcome, the time to progression to cataract surgery, was assessed with a Cox proportional hazards model using the Wei, Lin, and Weissfeld method for obtaining robust variance estimates, allowing for dependence among multiple event times (1 or 2 study eyes).<sup>27</sup> The models were run with and without stratification by the secondary randomization. Patients lost to follow-up or who died during the course of the study were censored at the time of the last contact. Hazard ratios (HRs) and 95% CIs of the lutein main effect were computed. Additional analyses and subgroup analyses were analyzed in the same fashion as the primary lens efficacy outcome. All analyses were conducted following the intention-to-treat principle and using SAS software version 9.2 (SAS Institute Inc).

## Results

AREDS2 enrolled 4203 people with a mean (SD) age of 73.1 (7.7) years. Bilateral pseudophakia was present in 1044 participants who were excluded from the study (25% of participants). The remaining 3159 participants (75%) were randomized to the primary randomization evaluating modifications to the AREDS supplements. Nearly all of the remaining participants (98.2%) chose to take the commercial AREDS formulation (Figure 1). Baseline characteristics were comparable across the 4 treatment groups in the primary randomization (Table). Of the randomized participants, 96% were white and 55% were female. A large percentage of participants (89%) requested Centrum Silver at study entry. At baseline, 2878 participants were bilaterally phakic, while 281 were pseudophakic in 1 eye. At baseline, 1239 of 2943 participants (42%) had cortical cataract and 229 of 2941 (8%) had PSC cataract. Baseline cataract status was comparable across the 4 treatment groups.

About 7% of the primary study cohort permanently stopped their study medications but were still followed up. About 3% of participants began taking lutein/zeaxanthin in both treatment arms; approximately 19% of these participants stopped their study medications permanently. Approximately 80% of the participants took the study medications at least 75% of the time, as assessed by pill count. There were no differences in adherence among the treatment groups.

### Follow-up

Of the 3159 randomized participants, 104 (3%) were lost to follow-up and 204 (6%) died. Distributions were similar across the 4 treatment groups.

### Data Quality

Masked duplicate photographic gradings were conducted every month on 5% of eyes randomly selected from the previous month's evaluations, resulting in 1293 eyes that had repeat gradings between 2009 and 2012. Of these, 777 eyes were phakic. Duplicate gradings of the red reflex lens photographs demonstrated 93% agreement for the presence of cortical opacities and 97% agreement for the presence of PSC. The mean difference between the 2 grades was 0.03 mm<sup>2</sup> (95% CI, -5.31 to 5.25) for cortical and 0.03

mm<sup>2</sup> (95% CI, -0.7 to 0.81) for PSC opacities.

## Dietary and Serum Levels of Lutein/Zeaxanthin

... of the study nutrients, excluding the supplements, ... ent groups. Dietary intake was similar to that of participants in the Women's Health Study of female health professionals, a highly educated and well-nourished group.<sup>27</sup> Both the AREDS2 and the Women's Health Study evaluated dietary intake with the Harvard Semi-Quantitative Assessment Food Frequency Questionnaire.<sup>28</sup>

### Serum Levels

Serum levels of the study nutrients were balanced across treatment groups at baseline. Median baseline serum levels of lutein in participants randomized to lutein increased by 191% to 215% at years 1, 3, and 5, while those randomized to placebo showed minimal changes. Although not statistically significant, mean percentage increase in serum levels of lutein/zeaxanthin in those randomized to lutein/zeaxanthin and beta carotene were lower than those randomized to lutein/zeaxanthin alone at year 5 (171% vs 270%, respectively;  $P = .08$ ).

### Outcomes

#### Progression to Cataract Surgery

Of the 6027 study eyes, 1389 study eyes (23%; 876 participants) underwent cataract surgery during the study. The number of eyes and Kaplan-Meier probabilities (N[%]) of progression to cataract surgery by 5 years for study eyes randomized to lutein/zeaxanthin or no lutein/zeaxanthin were 681 eyes (24%) and 708 eyes (24%), respectively (Figure 2). A comparison of lutein/zeaxanthin to no lutein/zeaxanthin for progression to cataract surgery resulted in a HR of 0.96 (95% CI, 0.84-1.10;  $P = .54$ ) (Figure 3). Subgroup analyses restricted to quintiles of dietary lutein/zeaxanthin intake resulted in HRs for the first and fifth quintiles of 0.68 (95% CI, 0.48-0.96;  $P = .03$ ) and 1.27 (95% CI, 0.91-1.79;  $P = .16$ ), respectively (Figure 4). Results for quintiles 2 through 4, also displayed in Figure 4, were greater than quintile 1 and less than quintile 5. A test of interaction between treatment and the quintile groups showed a  $P$  value of .006.



Although there was no scientific rationale to consider omega-3 LCPUFAs to be important in reducing the progression to cataract surgery, this analysis was conducted for completeness. Comparison of omega-3 LCPUFAs vs no omega-3 LCPUFAs resulted in a nonstatistically significant HR of 1.01 (95%



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### Development of Any Cataract

Of the 6027 study eyes, 1833 (30%) had an outcome defined as any cataract. For this outcome, the comparison of lutein/zeaxanthin vs no lutein/zeaxanthin yielded a HR of 0.93 (95% CI, 0.83-1.04;  $P = .20$ ) (Figure 3). In subgroup analyses restricted to quintiles of dietary lutein/zeaxanthin intake, HRs for the first and fifth quintiles were 0.70 (95% CI, 0.53-0.94;  $P = .02$ ) and 1.15 (95% CI, 0.86-1.54;  $P = .36$ ), respectively, for the lutein/zeaxanthin vs no lutein/zeaxanthin comparison (Figure 4). The results for quintiles 2 through 4 were in between the values for quintiles 1 and 5. A test of interaction between treatment and the quintile groups showed a  $P$  value of .01.

### Development of Any Severe Cataract

Of the 6027 eligible eyes, 1504 (25%) had an outcome defined as severe cataract. For lutein/zeaxanthin vs no lutein/zeaxanthin, the HR for progression to severe cataract was 0.94 (95% CI, 0.83-1.07;  $P = .33$ ). For the same outcome, in subgroup analyses by quintiles of lutein/zeaxanthin intake, a comparison of lutein/zeaxanthin vs no lutein/zeaxanthin resulted in HRs of 0.64 (95% CI, 0.46-0.89;  $P = .008$ ) and 1.26 (95% CI, 0.91-1.75;  $P = .17$ ) for the lowest and highest quintiles of dietary lutein/zeaxanthin, respectively. A test of interaction between treatment and the quintile groups had a  $P$  value of .003.

### Visual Acuity

None of the nutrients studied affected rates of moderate or worse vision loss, defined as a loss of 15 or more letters from baseline. The HR for the development of moderate vision loss was 1.03 (95% CI, 0.93-1.13;  $P = .59$ ; Figure 3) for the lutein/zeaxanthin vs no lutein/zeaxanthin comparison. Subgroup analyses restricted to quintiles of dietary lutein/zeaxanthin intake resulted in nonstatistically significant HRs from the first through fifth quintiles (data not shown).

### Safety Outcomes

No clinically or statistically significant serious adverse effect was associated with the treatments. Oral supplementation daily with lutein/zeaxanthin, DHA/EPA, or the modifications of the AREDS formulation had no effect on mortality. The HR for lutein/zeaxanthin vs no lutein/zeaxanthin for mortality



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## DISCUSSION

AREDS reported that use of oral supplements containing vitamin C, vitamin E, and beta carotene, as well as the minerals zinc and copper, did not affect the progression of lens opacities.<sup>18</sup> In AREDS2, we found neither beneficial nor harmful effects on the rates of cataract surgery or moderate vision loss when lutein/zeaxanthin was added to the AREDS formulation. No statistically significant effect was noted for any or severe cataract, defined as cataract surgery or specific levels of progression of cortical or PSC opacities.

Interpreting the cataract findings, particularly those for lutein/zeaxanthin, requires consideration of the AREDS2 study design and study population. AREDS2 volunteers were generally better educated and better nourished than the general population, with higher dietary intake levels of lutein/zeaxanthin and omega-3 LCPUFAs. AREDS2 participants in the lowest quintile of dietary intake of lutein/zeaxanthin showed some evidence of a beneficial effect of lutein/zeaxanthin supplementation on the progression to the cataract outcomes. Vitamin supplementation in a relatively undernourished population in China reduced the risk for progression of lens opacities.<sup>13</sup> Whether there is a subgroup of persons who are relatively less well nourished that would benefit from lutein/zeaxanthin supplementation to slow the progression of lens opacities remains uncertain.

A second consideration is that a large proportion of AREDS2 participants (89%) elected to take Centrum Silver supplements, which contain a small amount of lutein, 250 µg, along with other carotenes and other antioxidants that may affect cataract development. AREDS2 was designed to test large doses of lutein/zeaxanthin, 10mg/2mg, against near dietary levels of intake. However, a previous randomized clinical trial<sup>17</sup> and observational data from AREDS<sup>29,30</sup> suggested that use of multivitamins, such as Centrum, might retard cataract development. The effect of Centrum use on our results cannot be determined because nearly all participants took the supplement.

The possible effect of competitive absorption of carotenoids, which has been demonstrated in other human studies<sup>31,32</sup> and in animal studies,<sup>33</sup> also needs consideration. About half of the AREDS2 cohort who consented to the secondary study randomization were assigned to take high doses of beta



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carotenoids. Some participants received both carotenoids, while others received lutein/zeaxanthin alone. The reduction in the serum levels of lutein/zeaxanthin in those participants who received both carotenoids may be the result of the apparent systemic competitive absorption of carotenoids.

An additional consideration in interpreting the results is the timing and duration of the use of the supplements. The mean age of AREDS2 participants at enrollment into the follow-up study was 72 years. At that time, 42% already had some cortical opacities and 8% had some PSC opacities. Given the advanced age of participants, cataracts may have already begun to develop in many who had no apparent opacities at the start of the study. Perhaps the intervention was too late or of insufficient duration to affect the outcomes.

AREDS2 was conducted at 82 retinal specialty clinics and the primary focus was on the retinal outcomes. Although the optimal approach to assessing the lens outcome, using specialized lens photography, was beyond the scope possible for AREDS2 whose investigators were all retinal specialists without such equipment, we were able to incorporate red reflex lens photographs for grading the severity of cortical and PSC lens opacities. Assessing nuclear opacities requires specialized slitlamp photography, which was not readily available in a retinal practice, so that information on nuclear cataract was incomplete. Because of the missing information on all subtypes, we used a clinically important outcome, cataract surgery, as our primary outcome. The absence of an effect of the interventions on the rates of cataract surgery may indicate an absence of an effect on nuclear and/or PSC opacities, which are the subtypes most likely to affect vision and by far the most common causes of the need for cataract surgery.<sup>34-36</sup> Nuclear and PSC opacities have been reported in 65% and 61% of surgical cases, respectively.<sup>36</sup> Cortical opacities alone are an uncommon cause of cataract surgery.

Strengths of the study include 5-year follow-up, low losses to follow-up, standardized data collection, and good compliance with the treatment regimen. The adherence data are further supported by data showing that serum

levels of nutrients were elevated throughout the study, on average, in participants assigned to the medications. The primary outcome, cataract surgery, is a clinically important and an easily verified outcome.



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higher dietary intake or have a protective effect on the development of cataract, this randomized, placebo-controlled trial did not find an effect of supplementation with lutein/zeaxanthin on cataract surgery, cortical or PSC lens opacity progression, or vision loss. Whether supplementation would be beneficial for less well-nourished populations requires further study.

## Article Information

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**AREDS2 Research Group Writing Team:** The AREDS2 Research Group is found online in the [Supplement](#) (eAppendix).

**Corresponding Author:** Emily Y. Chew, MD, National Eye Institute, National Institutes of Health, Bldg 10, CRC Rm 3-2531, 10 Center Dr, MSC 1204, Bethesda, MD 20892-1204 ([echew@nei.nih.gov](mailto:echew@nei.nih.gov)).

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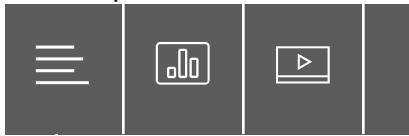
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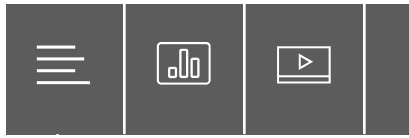
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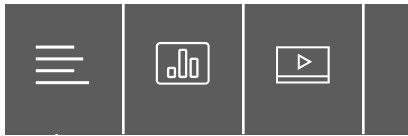
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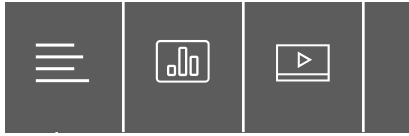
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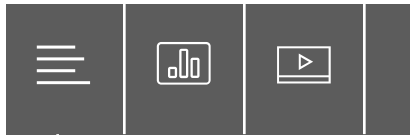
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