Nutritional supplements for age-related macular degeneration
Nupura Krishnadev, Annal D. Meleth and Emily Y. Chew

Introduction
Age-related macular degeneration (AMD) is the leading cause of visual loss in older adults in the USA and developed countries [1]. Epidemiological studies over the last two decades have provided insights into the risk factors associated with AMD, including age, sex, diet, nutritional status, smoking, hypertension, and genetic markers. Although antivascular endothelial growth factor agents have resulted in a remarkable beneficial effect in reducing the risk of moderate vision loss in patients with neovascular AMD [2,3], a large proportion of patients with AMD still continue to lose vision and there is no effective treatment available for the atrophic form of AMD. Therapies that focus on prevention through optimization of modifiable risk factors such as diet and nutritional status are key approaches to reducing the burden of disease. Methods that help to prevent development or progression of AMD through nutritional supplementation will become especially important as our population increases in longevity and the number of individuals affected with AMD continues to rise.

Purpose of review
Age-related macular degeneration (AMD), a leading cause of visual loss in older adults, has limited therapeutic options. This review describes the current literature on the role of nutritional supplementation in primary and secondary prevention of AMD.

Recent findings
Many observational studies have explored the association between diet, nutrient intake, and AMD. In particular, high dietary intakes of ω-3 fatty acids, and macular xanthophylls lutein and zeaxanthin have been associated with a lower risk of prevalent and incident AMD. However, the Age-Related Eye Disease study (AREDS) is the only large-scale randomized controlled clinical trial to show a 25% beneficial effect of nutritional supplementation in reducing the risk progression to advanced AMD in patients with intermediate AMD or with advanced AMD in one eye at 5 years of follow-up. On the basis of the results of AREDS, these patients are recommended to take AREDS formulation of vitamins C, E, β-carotene, and zinc with copper.

Summary
At the present time, there is insufficient evidence in the literature to recommend routine nutritional supplementation in healthy adults for primary prevention of AMD. However, patients with intermediate risk of AMD or advanced AMD in one eye should consider taking AREDS-type supplements. Observational studies have also suggested benefit from increased dietary intake of macular xanthophylls and ω-3 fatty acids. These are currently being evaluated prospectively in a randomized controlled clinical trial, the AREDS2.

Keywords
age-related macular degeneration, antioxidant vitamins, lutein, ω-3 fatty acids, zeaxanthin
vitamins C, E, β-carotene, and zinc with copper. In particular, macular xanthophylls and long-chain fatty acids have received significant attention in the literature since the last review on this subject in this journal in 2007 [4].

**Age-Related Eye Disease Study and Age-Related Eye Disease study-type formulations**

AREDS was the first large-scale randomized controlled clinical trial to demonstrate the benefit of vitamin and mineral supplementation in preventing progression to advanced AMD. The AREDS formulation of vitamin C 500 mg, vitamin E 400 IU, β-carotene 15 mg, and zinc (zinc oxide 80 mg and cupric oxide 2 mg) showed a 25% risk reduction in progression to advanced AMD over 5 years in patients with intermediate AMD (extensive intermediate drusen in one or both eyes, one or more large drusen in at least one eye, or nonsubfoveal geographic atrophy in one eye) or advanced AMD (subfoveal geographic atrophy or choroidal neovascular membrane) in one eye [5]. The risk of losing vision of three or more lines (doubling of the visual angle) also was reduced by 19% with this combination treatment. In fact, when available nutritional studies were reviewed by the Cochrane collaboration, the main evidence regarding the effectiveness of vitamin supplementation in preventing AMD progression was attributed as deriving primarily from AREDS [6].

A recent report from the Blue Mountain Eye study [7], a population-based study, supported the AREDS finding of a beneficial effect of zinc in AMD progression. Of the original cohort, 2454 patients were re-examined with stereoscopic fundus photography 5 and 10 years after initial study enrollment, and energy-adjusted nutrient intakes were assessed. In threshold analyses, patients in the top decile of total zinc intake (≥15.8 mg/day) were significantly less likely to develop any AMD (relative risk [RR] 0.56; 95% confidence interval [CI] 0.32–0.97) or early AMD (RR 0.54; 95%CI 0.30–0.97) when compared with the remaining population. Unlike AREDS, however, the Blue Mountain Eye study also found that higher β-carotene intake was associated with an increased risk of neovascular AMD, even after adjusting for smoking status. The authors suggested that this result be taken with caution, as the cause for this negative association is not known. It is also important to note that this was an observational study and that the number of patients with advanced AMD was limited.

Although the AREDS demonstrated protective benefits of supplementation in delaying AMD progression, the role of vitamins and minerals in the primary prevention of AMD is more difficult to ascertain. The AREDS formulation showed no effect in preventing the development of large drusen in participants who had small drusen at baseline, and the incidence of advanced AMD in this group was exceedingly low (<1%). In 2005, the Rotterdam study [8] suggested that high dietary intake of β-carotene, vitamins C and E, and zinc was associated with a 35% reduction in incident AMD risk in elderly persons. More recently, the Women’s Health study randomized 39,876 women to low-dose aspirin and vitamin E. After 10 years of treatment and follow-up, aspirin therapy had no large beneficial or harmful effect on risk of AMD [9], with 111 cases of AMD in the aspirin group and 134 cases in the placebo group (hazard ratio 0.82; 95%CI 0.64–1.06).

The Physicians Health study II may provide some further insights into the role of vitamin C, E, and β-carotene supplementation in preventing AMD. In this study, 14,642 men were randomized to one of 16 possible combinations of vitamin C (500 mg), vitamin E (400 IU), β-carotene (50 mg), and a multivitamin to assess their role in the primary prevention of cardiovascular disease, cancer, cataract, and AMD [10]. Follow-up was completed in December 2007 and data analysis is in progress.

Despite these results, a recent Cochrane library review [11] of three large-scale clinical trials randomizing 23,000 patients did not show a benefit of supplementation with β-carotene or vitamin E in preventing AMD. The review concluded that there was insufficient evidence to recommend routine supplementation with antioxidant vitamins or minerals in healthy adults to delay or prevent AMD onset.

**ω-3 long-chain polyunsaturated fatty acids**

ω-3 polyunsaturated fatty acids include ω-3 linolenic acid (short chain), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) (both long chain). Diet is the only source of these fatty acids, as they cannot be synthesized by humans de novo. DHA is present in high concentrations in the outer segments of photoreceptors, which are constantly shed and turned over during the visual cycle. Both ω-3 linolenic acid and EPA are dietary precursors to DHA. Deficiencies of DHA have been implicated in AMD onset [12], and long-chain ω-3 fatty acids may also help to prevent the oxidative, inflammatory, and age-related retinal damage that occurs during AMD development [13].

Several epidemiological studies have suggested an inverse relationship between dietary ω-3 long-chain polyunsaturated fatty acid or fish intake and risk of AMD. In the Blue Mountain Eye study [14], one serving of fish per week was associated with reduced 10-year risk of incident early AMD (RR 0.69; 95%CI 0.49–0.98). This benefit was primarily among participants with less than
the median baseline α-linoleic acid consumption. Another large Australian cohort study also showed that higher ω-3 fatty acid intake was inversely associated with early AMD when the highest and lowest quartiles were compared [odds ratio (OR) 0.85; 95%CI 0.71–1.02] [15].

In the AREDS population, higher intakes of DHA and EPA were associated with a lower risk of progression to advanced AMD, independent of AREDS supplementation [16], AREDS participants with highest intake of ω-3 long-chain polyunsaturated fatty acids were approximately half as likely to have neovascular AMD at baseline (OR 0.61; 95%CI 0.41–0.90) or to progress over a 6-year period from bilateral drusen to central geographic atrophy (OR 0.44; 95%CI 0.23–0.87) when compared with those who had the lowest intake (AREDS report no. 20 and 23) [17,18*]. In addition, a nested cohort study of AREDS participants at moderate-to-high risk of advanced AMD demonstrated a 12-year incidence of advanced AMD that was 30% lower in patients reporting the highest consumption of ω-3 fatty acids [19].

A recent meta-analysis by Chong et al. [20*] reviewed nine studies with a total sample of 88974 people, including 3205 AMD cases (1847 early and 1356 late AMD cases). A high dietary intake of ω-3 fatty acids was associated with a 38% reduction in the risk of advanced AMD (pooled OR 0.62; 95%CI 0.48–0.82). A minimum bi-weekly fish intake was associated with a reduced risk of both early AMD and late AMD. On the basis of observational data reviewed, the authors concluded that consumption of ω-3 fatty acids may be associated with a lower risk of AMD but that there was insufficient evidence to recommend ω-3 fatty acid supplementation for AMD prevention in the general population. However, randomized trials are needed to test the efficacy of this nutritional factor.

**Lutein and zeaxanthin**

Macular pigment is composed primarily of the xanthophylls lutein and zeaxanthin, also members of the carotenoid family. Their antioxidant properties, as well as their ability to filter short-wavelength light, may help to protect the outer retina and retinal pigment epithelium from oxidative stress and aid in cell membrane stability [21]. Interestingly, Parisi et al. [22] noted improvement in multifocal electroretinogram results in 15 AMD patients given oral supplementation with lutein and zeaxanthin as compared to age-matched controls.

The association between AMD risk and lutein and zeaxanthin supplementation has been explored in several large-scale epidemiological studies. The Eye Disease Case Control study found that the risk for advanced AMD was reduced by 43% in participants in the highest quintile of dietary carotenoid intake, when compared with those in the lowest quintile (OR 0.57; 95%CI 0.35–0.92) [23]. In 2006, the Carotenoids in Age-Related Eye Disease study (CAREDS) concluded that lutein-rich and zeaxanthin-rich diets may protect against intermediate AMD in female patients less than 75 years of age [24]. More recently, the Blue Mountain Eye study [7] reported that higher dietary lutein and zeaxanthin intake reduced the risk of incident AMD over 5 and 10 years. Participants in the top tertile of intake (≥942 μg/day) had a decreased risk of incident neovascular AMD (RR 0.35; 95%CI 0.13–0.92), and those with above median intakes (743 μg) had a reduced risk of indistinct soft or reticular drusen when compared with the remaining population. In AREDS, dietary lutein/zeaxanthin intake (as determined by a food frequency questionnaire at enrollment) was inversely associated with prevalent neovascular AMD (OR 0.65; 95%CI 0.45–0.93), geographic atrophy (OR 0.45; 95%CI 0.24–0.86), and large or extensive intermediate drusen (OR 0.73; 95%CI 0.56–0.96) when the highest versus lowest quintiles were compared [25].

Measurement of macular pigment optical density (MPOD) provides a noninvasive measurement of retinal lutein and zeaxanthin. This measurement may be helpful in evaluating the association of the macular pigment with various aspects of the serum carotenoids, though the causal relationship may be difficult to elucidate. Although studies have shown that MPOD is related to dietary intake or serum levels of lutein and zeaxanthin [26], the results relating MPOD to AMD have been inconsistent across populations and are influenced by the many factors that affect uptake and distribution of these carotenoids in the body. A recent report from the CAREDS group could not find a consistent cross-sectional association between MPOD and AMD [21] and suggested that prospective studies were needed to further explore this relationship.

**B vitamins**

Homocysteine is an intermediary amino acid formed during metabolism of the essential amino acid methionine. Hyperhomocysteinemia, defined as a plasma homocysteine concentration of greater than 2.0 mg/l or 15 μmol/l, is thought to induce vascular endothelial dysfunction, a process that has also been implicated in neovascular AMD [27]. Cross-sectional and case–control studies in the last few years suggest an association exists between elevated serum homocysteine levels and the risk of AMD [28–30]. In the Blue Mountain Eye study [28], serum homocysteine greater than 15 μmol/l was associated with an increased likelihood of AMD in participants less than 75 years of age, and in patients with serum homocysteine of 15 mmol/l or less, low serum B12 was associated with nearly four-fold higher odds of AMD.
Vitamin B12 and folic acid act as essential coenzymes during homocysteine metabolism; treatment with folic acid, vitamin B6 (pyridoxine hydrochloride), and vitamin 12 (cyanocobalamin) has shown to reduce homocysteine levels [31]. The Women’s Antioxidant and Folic Acid Cardiovascular study (WAFACS), a randomized trial, assessed whether treatment with vitamins B6 and B12 and folic acid could prevent cardiovascular events in women with preexisting cardiovascular disease or multiple risk factors [32]. Although no benefit was found in terms of cardiovascular disease reduction, the study provided an opportunity to evaluate AMD risk. Of the 5442 participants enrolled in the study, 5205 did not have a baseline diagnosis of AMD and were included in the AMD analysis. The results, based on an average of 7.3 years of treatment and follow-up, indicate that those assigned to active treatment had a statistically significant 35–40% decreased risk of developing AMD. However, the authors suggest that the results be interpreted cautiously, as AMD diagnosis was self-reported, and that findings in this group of women at increased risk of cardiovascular disease may not be applicable to the general population. Although there were only a small number of cases of advanced AMD (19 cases; 17 exudative in nature and two with geographic atrophy), this randomized trial does suggest that further investigation into the role of B vitamins in AMD risk is warranted.

### Future directions

The available observational and small trial data are compelling, and further research with large-scale prospective randomized controlled trials is needed to examine the role of nutritional supplementation in AMD. The National Eye Institute developed the AREDS2 trial, a multicenter, randomized trial, to assess the effects of daily oral supplementation of lutein, zeaxanthin, and/or DHA and EPA on the progression to advanced AMD, as compared to placebo (Table 1). More than 4000 participants aged 50–85 years were enrolled and will be followed for 5 years. Included are participants with bilateral large drusen or large drusen in one eye with advanced AMD (neovascular AMD or central geographic atrophy) in the fellow eye at baseline. The primary outcome is the development of advanced AMD with secondary outcome of moderate visual acuity loss.

In addition, AREDS2 provides an opportunity to further refine the original AREDS formulation by eliminating β-carotene and lowering the dose of zinc. β-Carotene is not found in the eye but was thought to be important as a systemic antioxidant in the original AREDS formulation. Two large controlled randomized trials demonstrated an increased risk of lung cancer in smokers taking β-carotene. The high doses of zinc may not be necessary, as recent data have suggested that the systemic absorption of zinc is limited to about 25 mg per day. For these reasons, the AREDS formulation will be tested in a secondary randomization by assigning consenting participants to one of these four formulations (Table 2).

The socioeconomic benefits of primary and secondary prevention of AMD are enormous. In 2004, the direct medical cost of AMD treatment was estimated at US$575 million in the USA, excluding nursing home and home healthcare costs, and productivity losses [33]. This figure will only continue to rise, as the number of individuals affected with AMD increases in parallel with the aging population and as the expense of therapies such as antivascular endothelial growth factor (anti-VEGF) treatments for neovascular AMD increases. It has been reported that the projected increases in cases of visual impairment and blindness from AMD by the year 2050 may be lowered by 17.6% if vitamin prophylaxis at early AMD presentation is given in addition to standard neovascular AMD treatment (laser or anti-VEGF injections), when compared with neovascular AMD treatment alone [34*]. At an approximate cost of US$100 per patient per year, supplementation with vitamins and minerals may be a cost-effective method of therapy for patients with AMD to reduce future impairment and disability.

### Table 1 Nutrients and doses to be tested in the primary randomization of the Age-Related Eye Disease study 2 trial

<table>
<thead>
<tr>
<th>Randomization agents</th>
<th>Daily dose</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>–</td>
</tr>
<tr>
<td>Lutein/zeaxanthin</td>
<td>10/2 mg</td>
</tr>
<tr>
<td>DHA/EPA</td>
<td>350/650 mg</td>
</tr>
<tr>
<td>Lutein/zeaxanthin + DHA/EPA</td>
<td>10/2 mg + 350/650 mg</td>
</tr>
</tbody>
</table>

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

### Table 2 Four alternative Age-Related Eye Disease study formulations being tested in the secondary randomization of Age-Related Eye Disease study 2

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Vitamin C (mg)</th>
<th>Vitamin E (IU)</th>
<th>β-Carotene (mg)</th>
<th>Zinc oxide (mg)</th>
<th>Cupric oxide (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>500</td>
<td>400</td>
<td>15</td>
<td>80</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>500</td>
<td>400</td>
<td>0</td>
<td>80</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>500</td>
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<td>15</td>
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<td>500</td>
<td>400</td>
<td>0</td>
<td>25</td>
<td>2</td>
</tr>
</tbody>
</table>
Conclusion

At the present time, there is insufficient evidence in the literature to recommend routine nutritional supplementation for primary prevention of AMD. However, patients with intermediate risk of AMD or advanced AMD in one eye are recommended to take AREDS-type supplements, as this formulation has been proven to reduce the risk of progression to advanced AMD by 25% over 5 years. Many observational studies have also suggested benefit from increased dietary intake of additional nutrients such as carotenoids and ω-3 fatty acids. These supplements are currently being evaluated in the AREDS2 trial, a randomized controlled clinical trial testing the effects of lutein and ω-3 fatty acids on rates of the progression to advanced AMD. Although vitamin B supplementation appears to be potentially beneficial in the treatment of AMD in a randomized trial, no recommendations can be made until further studies are conducted. The cost-effectiveness of prevention with oral supplements has been demonstrated in the AREDS study. The results of AREDS2 and other studies may provide further insight into the prevention of progression to advanced AMD.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this (pp. 239–240).


This review assesses all the available, clinical trials on nutritional supplementation in the primary prevention of AMD, concluding that there is insufficient evidence to recommend routine supplementation in healthy adults to prevent AMD.


The results of this study from the AREDS group suggest that dietary ω-3 fatty acid intake is associated with a decreased risk of progression from bilateral drusen to central geographic atrophy.


This detailed meta-analysis suggests that consumption of fish and foods rich in ω-3 fatty acids may be associated with a lower risk of AMD.


Using statistical models based on current knowledge and trends, this report forecasts AMD and its consequences in the USA through the year 2050 with different treatment scenarios, concluding that prevalence of AMD will increase substantially by 2050, but the use of new therapies may mitigate its effects.
Nutritional supplementation in age-related macular degeneration
Hanna Coleman and Emily Chew

Purpose of review
This review assesses the current status of the knowledge of
the role of nutrition in age-related macular degeneration – a
leading cause of vision loss in the persons with European ancestry.

Recent findings
We will evaluate the different nutritional factors and both
observational and interventional studies used to assess the
association of nutrition with age-related macular
degeneration. Persons with intermediate risk of age-related macular
degeneration or advanced age-related macular
degeneration in one eye are recommended to take the
formulation proven in the Age-Related Eye Disease Study
(AREDS) to be successful in preventing the development of advanced age-related macular degeneration by 25%. The
formulation consists of vitamins C, E, beta-carotene and zinc. In addition, observational data suggest that high
dietary intake of macular xanthophylls lutein and zeaxanthin
are associated with a lower risk of advanced age-related macular degeneration. Similarly, long-chain
polyunsaturated fatty acids derived from fish consumption
are also associated with a decreased risk of advanced age-
related macular degeneration.

Summary
Persons with intermediate age-related macular
degeneration or advanced age-related macular
degeneration (neovascular or central geographic atrophy)
in one eye should consider taking the AREDS-type
supplements. Further evaluation of nutritional factors,
specifically, lutein/zeaxanthin and omega 3 fatty acids will
be tested in a multicenter controlled, randomized trial – the
Age-Related Eye Disease Study 2 (AREDS2).

Keywords
age-related macular degeneration, antioxidant vitamins,
long-chain polyunsaturated fatty acids, lutein/zeaxanthin,
macular edema, zinc

Abbreviations
AMD  age-related macular degeneration
AREDS  Age-Related Eye Disease Study
DHA  docosahexaenoic acid

Introduction
Age-related macular degeneration (AMD) is the leading
cause of visual loss in the United States in older persons
and has limited therapeutic options. Risk factors associ-
ated with AMD include sex, iris color, heredity, cardio-
vascular health, nutrient status, body mass index, age, and
smoking. Prevention of modifiable risk factors such as the
nutrient status is a promising approach to reducing the
burden of AMD. These studies may provide clues to
nutritional factors that may be tested as preventive
therapy of AMD. This is particularly important as the
estimated numbers of persons with AMD will double in the
year 2030.

Systematic review of the literature
We attempted to review and synthesize the relevant
literature published in the last 12 months on the efficacy
of nutritional supplements in the prevention of advanced
AMD. The bulk of the literature analysed the intake
effect, whether by diet or supplementation, of the macular
xanthophylls lutein and zeaxanthin and the omega 3 fatty
acids and the effect of antioxidant vitamins and mineral
found in the Age-Related Eye Disease Study (AREDS)
formulation. The AREDS formulation includes vitamins
C, E, beta-carotene and zinc with copper.

The literature search to support this review was con-
All searches were limited to articles with a publication
date of 2006, and where offered, the search was limited
to studies with human subjects and those published in
English. The following databases were searched: Medline
and Medline in-process (PubMed), Scopus, Embase.com,
Web of Knowledge, The Cochrane Library, Natural Standard
and Google Scholar.

AREDS and AREDS-like formulations
The Cochrane review [1*] summarized the findings of the
available nutritional studies and found eight pertinent
randomized clinical trials. It reported that the existing
evidence as to the effectiveness of antioxidant vitamin
and mineral supplementation in retarding the progression
of AMD is derived mainly from the AREDS (Table 1) [2]. The AREDS results showed a beneficial effect of antioxidant supplementation (15 mg of beta-carotene, 500 mg of vitamin C and 400 IU of vitamin E and 80 mg zinc plus 2 mg copper) on retarding the progression to advanced AMD. The other trials had, in general, small sample size with shorter duration of follow-up and the results were inconsistent across these studies. The review concluded, however, that the generalizability of the AREDS findings to other populations with different nutritional status is unknown and that the long-term effect from supplementation cannot be determined without conducting further large randomized controlled trials in other populations.

The results of the Rotterdam Study (1990–1993) were published at the end of 2005 [3]. The study investigated whether regular dietary intake of antioxidants was associated with a lower risk of incident AMD in over 4000 persons aged 55 years or older in a middle-class suburb of Rotterdam, The Netherlands. In this study, a high dietary intake of beta-carotene, vitamins C and E, and zinc was also associated with a substantially reduced risk of AMD in elderly persons. The Reykjavik Eye Study evaluated the 5-year risk factors for incident AMD in a random sample of individuals 50 years and older. It found that current alcohol consumption decreased the risk for drusen and consuming dietary fiber-rich vegetables was also protective for the development of drusen formation. Eating meat and meat products once a week or less compared with those who eat it more frequently decreased the risk of pigmentary abnormalities [4]. An interesting aspect of this study is that the development of advanced AMD of geographic atrophy outnumbered the neovascular form (5:1) but a small number of incident cases of advanced AMD developed in this cohort over the course of 5 years.

Chiu and Taylor [5] reviewed the epidemiological literature on the roles of vitamins C and E and carotenoids as well as the effect of dietary carbohydrate intake. They found that while data from the observational studies generally support a protective role for antioxidants intake, results from intervention trials, with the exception of AREDS, are less encouraging with respect to limiting the risk of AMD. They postulated that given the many insults associated with aging, proper nutrition early in life, possibly including use of antioxidant supplements, may control or prevent some of these insults resulting in extended function later in life thus providing the least costly means of delaying AMD [5].

**Lutein and zeaxanthin**

Oxidative stress is thought to play a significant role in the pathogenesis of AMD due to combined exposures of the retina to light and oxygen. The possibility that the antioxidant balance can be altered by diet or nutritional supplementation has created much interest. Of particular interest is the effect on macular pigment which are composed principally of the carotenoids lutein and zeaxanthin.

The existence of the macula lutea of the human retina has been known for decades. Lutein and zeaxanthin give it the yellow appearance. The antioxidant capabilities of these xanthophylls combined with their ability to filter short-wavelength light could protect the outer retina, retinal pigment epithelium, and choriocapillaris from oxidative damage [6].

Mares et al. [7] found that macular pigment optical density, measured by heterochromatic flicker photometry, is directly related to dietary intake of lutein and zeaxanthin but even more strongly to serum concentrations, which may reflect unmeasured physical and medical factors that influence the uptake, distribution, and utilization of lutein and zeaxanthin. They also found that higher abdominal body fat and diabetes are related to lower macular pigment optical density [7].

The observational study, Carotenoids in Age-Related Eye Disease (CAREDS), concluded that diets rich in lutein plus zeaxanthin may protect against intermediate AMD in healthy women younger than 75 years [8]. The population-based Pathologies Oculaires Liees – a l’Age (POLA) study – also was strongly suggestive of a protective role of the xanthophylls, in particular zeaxanthin, for the protection against AMD and cataract [9*]. On the other hand, the US Food and Drug Administration recently reviewed intervention and observational studies that evaluated the role of lutein and zeaxanthin in reducing the risk of AMD and cataracts and concluded that no credible evidence exists for a health claim about the intake of lutein or zeaxanthin (or both) and the risk of AMD or cataracts [10], and the US National Institutes of Health [11] performed a broader review of the efficacy and safety of multivitamin and mineral supplement use to prevent cancer and chronic disease in adults and concluded that the evidence is insufficient to prove the

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**Table 1** Recommendation for AREDS-type supplement intermediate AMD (extensive intermediate drusen, large drusen, and no advanced AMD) advanced AMD (neovascular AMD or central geographic atrophy) in one eye

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Amount</th>
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<tbody>
<tr>
<td>Vitamin C</td>
<td>500 mg</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400 IU</td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>15 mg</td>
</tr>
<tr>
<td>Zinc oxide</td>
<td>80 mg</td>
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presence or absence of benefits from use of multivitamin and mineral supplements to prevent cancer and chronic disease.

**Fatty acids**

Long-chain polyunsaturated fatty acids are classified based on their chemical structure into two groups: omega-3 fatty acids and omega-6 fatty acids. The omega-3 notation means that the first double bond is three carbons from the methyl end of the molecule. The long chain fatty acid docosahexaenoic acid (DHA) is in high concentrations in the photoreceptor outer segments and is constantly shed and turned over during the normal visual cycle. A deficiency of DHA might therefore impair retinal function and promote AMD [12]. In fact, several previous epidemiologic studies and clinical trials suggest that high dietary intake of fat is associated with a higher prevalence or incidence of early or late AMD whereas higher intakes of fish or n-3 fatty acids were associated with lower rates of AMD [13,14]. The available results are inconsistent, however. While the US Twin Study of Age-Related Macular Degeneration provided evidence that cigarette smoking increases risk while fish consumption and omega-3 fatty acid intake reduce risk of AMD [15*], a review performed by Hodge et al. [16] of the available literature on the efficacy of omega-3 fatty acids in preventing AMD concluded that although very high levels of the omega-3 fatty acid DHA are naturally present in the retina in the disk membranes of photoreceptor cells’ outer segments, dietary supplementation was neither clearly supported nor refuted by the available world literature and further studies were needed.

Based on all of the current nutritional data and given the need of further compelling evidence, the National Eye Institute developed the AREDS2 study – a randomized controlled clinical trial which started enrolling in the fall of 2006. Its primary objective is to determine whether oral supplementation with macular xanthophylls (lutein at 10 mg/day + zeaxanthin at 2 mg/day) or omega-3 long-chain polyunsaturated fatty acids (LCPUFAs; DHA + eicosapentaenoic acid at a total of 1 g/day) will decrease the risk of progression to advanced AMD, as compared with placebo. It will also study the effects of these nutritional supplements on moderate vision loss and on the development of cataracts. This objective will be accomplished by collecting and assessing the data on approximately 4000 participants aged 50–85 years, who, at the time of enrollment, have sufficiently clear lenses for quality fundus photographs and have either bilateral large drusen or large drusen in one eye and advanced AMD (neovascular AMD or central geographic atrophy) in the fellow eye. Of the primary randomization agents, one quarter of the patients will be assigned placebo, another quarter to lutein/zeaxanthin, one quarter to omega-3 LCPUFAs, and the final quarter to the combination of the two.

This provides an opportunity to further refine the AREDS-type supplements by eliminating beta-carotene, which increases the risk of lung cancer in patients who are smokers. Zinc administered as 80 mg of zinc oxide was considered by the zinc experts to be too high and lower levels may be sufficient because only 25 mg will be absorbed the the body. These two factors in the AREDS-type supplements will be evaluated specifically in the secondary randomization. These agents (AREDS-Type Supplement) formulations are divided into the four inclusion groups listed in Table 2.

It is estimated that about 55 million people in the United States may be at risk for AMD. Of these, eight million are at high risk, and are thus likely to benefit from the current combination of zinc and antioxidant therapy. If all eight million people at high risk for AMD took the supplement therapy, more than 300 000 of them could be saved from advanced AMD in the next 5 years.

The economic benefit associated with the prevention of and progression to advanced AMD in even a small proportion of cases is significant and will result in major cost savings to individuals and society at large. The evidence that diet and nutrition play crucial roles in the pathogenesis of early AMD and its progression to AMD is now compelling; further studies are essential in order to find the key micronutrient ingredients that will fully change our treatment and prevention of AMD in the future.

**Conclusion**

For persons with intermediate risk of AMD (bilateral large drusen) or advanced AMD (unilateral neovascular AMD or geographic atrophy involving the center of fovea), the AREDS-type supplements are recommended because they are proven to reduce the risk of developing advanced AMD by 25%. The public health impact of such supplements is potentially enormous. Since observational data suggest additional nutritional factors such as lutein/zeaxanthin and omega-3 long-chain polyunsaturated fatty acids may also play important roles in the prevention of advanced AMD, they are currently evaluated in a controlled clinical trial AREDS2. This study will evaluate these factors as potential further preventive therapy of AMD.

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<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>Vitamin C</td>
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<td>500 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400 IU</td>
<td>400 IU</td>
<td>400 IU</td>
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<tr>
<td>Beta-carotene</td>
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<td>0 mg</td>
<td>0 mg</td>
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<td>Zinc oxide</td>
<td>80 mg</td>
<td>80 mg</td>
<td>25 mg</td>
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<tr>
<td>Cupric oxide</td>
<td>2 mg</td>
<td>2 mg</td>
<td>2 mg</td>
</tr>
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Table 2 The four AREDS formulations to be tested in the second randomization of AREDS2
References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 251).

1. Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age related macular degeneration. Cochrane Database of Syst Rev 2006; (2):CD000254. This review article assesses the different clinical trials conducted for age-related macular degeneration. It gives a broad and unbiased view of the results of the various studies.


