For the Media:
Questions and Answers about AREDS2

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What are AREDS and AREDS2?

The Age-Related Eye Disease Study (AREDS) was designed to determine if daily intake of certain vitamins and minerals could reduce the risk of cataract and advanced age-related macular degeneration (AMD). The study included a placebo-controlled trial, launched in 1992, to evaluate a combination of vitamins E and C, beta-carotene, and zinc—known as the AREDS formulation. In 2001, the investigators reported that the AREDS formulation reduced the risk of advanced AMD by about 25 percent over a five-year period. There was no effect on cataract. After completion of the AREDS trial, all participants were given the option to receive the AREDS formulation as part of a five-year follow-up study.

In 2006, the investigators began a separate clinical trial called AREDS2. The primary goal was to determine if adding omega-3 fatty acids or the antioxidants lutein and zeaxanthin to the original AREDS formulation would make it more effective for reducing the risk of advanced AMD or cataract. In prior observational studies, increased dietary intake of some or all of these nutrients had been linked to a reduced risk of advanced AMD and cataract. The omega-3 fatty acids tested in AREDS2 were docosahexanoic acid (DHA) and its precursor eicosapentanoic acid (EPA). There were four main treatment arms to the trial: (1) control/AREDS formulation only, (2) lutein/zeaxanthin added to the formulation, (3) DHA/EPA added, (4) lutein/zeaxanthin and DHA/EPA added.

A secondary goal of the AREDS2 trial was to determine if changing beta-carotene and zinc levels in the original AREDS formulation would affect the risk of advanced AMD. The investigators tested the effects of eliminating beta-carotene, which some studies have shown may increase the risk of lung cancer in smokers. Only participants who were non-smokers or formers smokers were eligible to receive beta-carotene in AREDS2. The investigators also tried lowering the dose of zinc. In the original AREDS study, the dose was set high because a previous small trial had found that high-dose zinc was beneficial for AMD. However, some nutritionists were concerned the dose was too high.

What are the latest results?

AREDS and AMD

After the original trial ended, the investigators followed the AREDS participants for an additional five years. By the end of this 10-year period, about 70 percent of participants were taking the AREDS formulation. The investigators found that participants who had been assigned to the AREDS formulation in the original trial were 25-30 percent less likely to develop advanced AMD than those who had originally been assigned to placebo. Among participants at the highest risk for AMD, 34 percent who had taken the

AREDS formulation in the trial progressed to advanced AMD, compared to 44 percent who had taken the placebo.

AREDS2 and AMD
In the AREDS2 trial, adding DHA/EPA or lutein/zeaxanthin to the original AREDS formulation (containing beta-carotene) had no additional overall effect on the risk of advanced AMD. However, trial participants who took AREDS containing lutein/zeaxanthin and no beta-carotene had a slight reduction in the risk of advanced AMD, compared to those who took AREDS with beta-carotene. Also, for a subgroup of participants with very low levels of lutein/zeaxanthin in their diet, adding these supplements to the AREDS formulation helped lower their risk of advanced AMD. Finally, former smokers who took AREDS with beta-carotene had a higher incidence of lung cancer. The investigators found no significant changes in the effectiveness of the formulation when they removed beta-carotene or lowered zinc.

AREDS2 and cataract
Neither omega-3 fatty acids nor lutein/zeaxanthin, when added to the original AREDS formulation, had any overall effect on the need for cataract surgery. However, when the participants were ranked into five equal-sized groups according to their dietary lutein/zeaxanthin intake, supplementation with lutein/zeaxanthin appeared to make a difference for the group with the lowest dietary levels. Within that group, lutein/zeaxanthin was associated with a 32 percent reduction in progression to cataract surgery.

What are the implications for preventing advanced AMD?
The AREDS formulation is the only treatment known to reduce the risk of advanced AMD. The AREDS follow-up study found that taking the AREDS formulation has a persistent benefit for reducing the risk of advanced AMD.

Despite prior evidence that dietary intake of the omega-3 fatty acids DHA and EPA seem to play important roles in visual health, taking them as supplements did not reduce the risk of advanced AMD in the AREDS2 trial. Lutein/zeaxanthin also had no overall effect on the risk of advanced AMD. However, there may be benefits to substituting lutein/zeaxanthin for beta-carotene in the original AREDS formulation, especially for current and former smokers, and for people who do not eat enough green leafy vegetables. Because these benefits are based on subgroup analyses, they should be interpreted with caution.

How common are cataract and AMD?
AMD and cataract are major causes of visual disability in the United States. It is estimated that 24.4 million Americans over age 40 have cataracts, or have had surgery to treat them. About 2 million people in the U.S. age 50 and over have vision loss

caused by advanced AMD. About four times as many people have an intermediate stage of AMD, with or without vision loss.

What is AMD?
AMD involves damage to the macula, a region of the retina that is packed with light-sensing cells called photoreceptors. The macula is important for central, high-resolution vision that is needed for tasks such as reading, driving, and recognizing faces. People with AMD lose this sharp vision and eventually may become blind.

The causes of AMD are not fully understood, but it is associated with several risk factors besides aging. It has a genetic component, often runs in families, and is most common among people of European descent. Variation in specific genes has been shown to increase the risk of developing AMD. Other risk factors for AMD include high blood pressure, cardiovascular disease, obesity, smoking, and a diet high in fats and low in green leafy vegetables and fish.

What is cataract?
A cataract is a clouding of the lens in the eye, most commonly associated with aging. Cataract can be treated by surgically removing the cloudy lens and replacing it with an artificial lens. Each year, the cost of outpatient, inpatient and prescription drug services related to cataract treatment totals about $6.8 billion in the U.S.

What are lutein and zeaxanthin?
Lutein and zeaxanthin, along with beta-carotene, belong to a family of organic pigments known as carotenoids. Carotenoids are made by plants and are especially enriched in green leafy vegetables. They can be stored in animal tissues and are found at relatively low levels in animal food products. Beta-carotene is an orange pigment. In the body, it is used to make Vitamin A, which is required by the retina to detect light and convert it into electrical signals. Lutein and zeaxanthin are yellow pigments and are responsible for the yellow color of corn, marigolds, egg yolks and animal fat. Lutein/zeaxanthin are also found in the human retina and lens, where they may act as natural antioxidants and help absorb damaging, high-energy blue and ultraviolet light.

What are omega-3 fatty acids?
Omega-3 fatty acids are made by marine algae and are enriched in fish oils; they are believed to be responsible for the health benefits associated with regularly eating fish, including lower rates of cardiovascular disease. The AREDS2 study focused on the omega-3 fatty acids DHA and its precursor EPA. DHA is needed for the integrity of retinal cells, and has been shown to promote retinal development and repair in prior studies.

How is AMD diagnosed and what are its stages?

AMD diagnosis and staging depend largely on changes within the eye that can only be seen during an eye exam. These may include pigmentary changes in the retina and the presence of drusen, which are yellow deposits under the retina that contain cholesterol and cellular debris. Most people develop some very small drusen as a normal part of aging. Researchers and clinicians generally recognize three stages of AMD.

1. Early AMD is characterized by the development of medium-sized drusen about 63-125 microns across, close to the width of an average human hair. Early AMD does not cause vision loss.
2. Intermediate AMD is characterized by large drusen (bigger than 125 microns) along with pigmentary changes in the retina. Intermediate AMD usually causes little or no vision loss.
3. In addition to drusen, advanced AMD is characterized by either:
    - A gradual breakdown of the central retinal area, called dry AMD or geographic atrophy
    - Abnormal and fragile blood vessels under the retina that can leak blood and damage the retina, called wet or neovascular AMD.

There are treatments to slow vision loss from neovascular AMD, including drugs that inhibit a protein called vascular endothelial growth factor (VEGF). When injected into the eye, these drugs can reduce the growth of abnormal blood vessels. *As reported in 2001, the AREDS formulation does not benefit people who have early AMD, or no AMD. It can slow the progression of intermediate AMD to advanced AMD*.

What were the subgroup effects of lutein/zeaxanthin on advanced AMD?

In the AREDS2 trial, lutein/zeaxanthin appeared to have some benefits for reducing the risk of developing advanced AMD in two subgroups: participants with low levels of these two antioxidants in their diets and participants taking AREDS without beta-carotene.

Diet

In a subgroup analysis, participants were ranked into five equal-sized groups according to their dietary lutein/zeaxanthin levels (measured through blood analysis and the Harvard semi-quantitative food frequency questionnaire). Within the group that had the lowest dietary levels of lutein/zeaxanthin, those who received lutein/zeaxanthin supplements had a 26 percent reduced risk of developing advanced AMD compared with those who did not receive the supplements. Within the other groups, there were no significant differences in developing advanced AMD between participants who received the lutein/zeaxanthin supplements and those who did not. The investigators noted that overall, AREDS2 participants tended to have higher dietary levels of lutein/zeaxanthin and other nutrients compared with the general population.

Lutein/zeaxanthin vs. beta-carotene

Because lutein, zeaxanthin and beta-carotene are all carotenoids, they compete with each other for absorption in the body. This could explain, in part, why lutein/zeaxanthin had no overall effect. Among the participants taking the original AREDS formulation, the beta-carotene within it would have been expected to limit absorption of lutein/zeaxanthin. This was confirmed by blood analysis. When beta-carotene was removed from the formulation, the researchers found evidence that lutein/zeaxanthin can slow progression to advanced AMD. Compared with participants who took AREDS containing beta-carotene (no lutein/zeaxanthin), those who took AREDS containing lutein/zeaxanthin (no beta-carotene) had an 18 percent lower risk of progressing to advanced AMD.

What were the subgroup effects of beta-carotene on cancer risk?

About 50 percent of the participants in AREDS2 were former smokers, and another seven percent were smokers at the time of the study. Since prior studies have linked beta-carotene to increased lung cancer risk among smokers, current smokers or those who had quit smoking less than a year before enrollment were excluded from receiving beta-carotene. Despite this precaution, lung cancers were observed in 2 percent of participants who took AREDS containing beta-carotene, compared to 0.9 percent of participants who took AREDS without beta-carotene. Across both groups, about 91 percent of participants who developed lung cancer were former smokers.

Who conducted these studies and how were they funded?

The lead investigator was Emily Chew, M.D., who is deputy director of the Division of Epidemiology and Clinical Applications and deputy clinical director at the National Eye Institute (NEI), part of the National Institute of Health. AREDS and the follow-up study were conducted at 11 clinical sites. AREDS2 was conducted at 82 sites.

The AREDS study and follow-up were supported by NEI. The AREDS2 trial was supported by NEI, and by other NIH components, including the Office of Dietary Supplements, the National Center for Complementary and Alternative Medicine (NCCAM), the National Institute on Aging (NIA), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Neurological Disorders and Stroke (NINDS). The supplements used in AREDS2 were provided by Alcon, Bausch and Lomb, DSM, and Pfizer.

What was the study population in the AREDS follow-up?

The original AREDS trial involved 4757 participants, age 55-80 at the time of enrollment. Of 4203 surviving participants, 3549 (about 84 percent) took part in the follow-up study.

What was the study population in AREDS2?
AREDS2 enrolled 4203 participants, age 50-85. Because the original AREDS trial established that the formulation does not benefit people with no AMD or early AMD, the AREDS2 trial was limited to people with intermediate AMD in both eyes, or intermediate AMD in one eye and advanced AMD in the other eye.

What is the original AREDS formulation?
- 500 milligrams (mg) of vitamin C
- 400 international units of vitamin E
- 15 mg beta-carotene
- 80 mg zinc as zinc oxide
- 2 mg copper as cupric oxide

What modifications were tested in AREDS2?
- 10 mg lutein and 2 mg zeaxanthin
- 350 mg DHA and 650 mg EPA
- No beta-carotene
- 25 mg zinc

How were these modifications tested in AREDS2?
All participants were offered the AREDS formulation. The overall effects lutein/zeaxanthin and DHA/EPA were evaluated by randomly assigning (randomizing) participants to one of four treatment groups: (1) control, i.e., AREDS formulation only, (2) lutein/zeaxanthin added, (3) DHA/EPA added, (4) lutein/zeaxanthin and DHA/EPA added. The treatment status of the participants was not revealed to them or to the researchers who analyzed the data until completion of the study.

The effects of adjusting beta-carotene and zinc levels were evaluated in a secondary randomization. Participants who chose to take AREDS (all but 19) were given the option to keep taking the original formulation or be randomly assigned to receive (1) the original formulation, (2) AREDS without beta-carotene, (3) AREDS with low zinc, or (4) AREDS with low zinc and no beta-carotene. For participants who consented to the randomization, their treatment status was not revealed to them or to the researchers who analyzed the data until completion of the study.

Progression to advanced AMD was determined by retinal photographs and by treatment for neovascular AMD after study enrollment (e.g., with VEGF inhibitors). Data on cataract surgeries were collected through regular phone calls to participants and annual study visits.

Where can I get more information?
AREDS follow-up study

- Chew *et al*. “Long-Term Effects of Vitamins C, E, Beta-Carotene and Zinc on Age-Related Macular Degeneration.” Ophthalmology, published online April 11, 2013.

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- AREDS2 Research Group. “Lutein/Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration. The Age-Related Eye Disease Study 2 (AREDS2) Controlled Randomized Clinical Trial.” JAMA, published online May 5, 2013.
- AREDS2 Research Group. “Lutein/Zeaxanthin for the Treatment of Age-Related Cataract.” JAMA Ophthalmology, published online May 5, 2013.

For more background on AREDS, AMD and cataract, please visit http://www.nei.nih.gov/amd/.