



## AREDS/AREDS2 Frequently Asked Questions

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### Taking the AREDS formulas

#### Are the AREDS vitamins right for me?

In clinical trials, the AREDS and AREDS2 formulas benefited people with intermediate or late AMD. There was no benefit for people with early AMD or for people who do not have AMD.

Your primary care physician or eye care provider is in the best position to advise you on how to treat your AMD. You may wish to discuss AREDS/AREDS2 supplements with your health care providers to decide which, if any, supplements are right for you.

#### Will taking the AREDS or AREDS2 supplements prevent AMD?

Nutritional supplements cannot prevent AMD. However, the AREDS/AREDS2 supplements may delay progression of intermediate to advanced AMD and may help you keep your vision longer. The participants in the AREDS trial have now been followed for more than 10 years, and the benefits of the AREDS formulation have persisted over this time.

#### Can I take a daily multivitamin if I am taking one of the AREDS/AREDS2 formulas?

Yes. The AREDS and AREDS2 formulas do not substitute for multivitamins. In AREDS, two-thirds of the study participants took multivitamins along with the AREDS formulation. In AREDS2, almost nine of ten participants took multivitamins.

#### Can a daily multivitamin alone provide the same vision benefits as the AREDS or AREDS2 formulas?

No. The vitamins and minerals tested in AREDS and AREDS2 trials were provided in much higher doses than what is found in multivitamins. Also, it is important to remember that most of the trial participants took multivitamins. Taking an AREDS formulation clearly provided a benefit over and above multivitamins.

### **Can diet alone provide the same levels of antioxidants and zinc as the AREDS or AREDS2 formulas?**

No. The high levels of vitamins and minerals are difficult to achieve from diet alone. However, previous studies have suggested that people who have diets rich in green, leafy vegetables—a good source of lutein and zeaxanthin—have a lower risk of developing AMD. In the AREDS2 trial, the participants who benefitted most from taking lutein + zeaxanthin were those who did not get much of these nutrients in their diet. Within this group, those who received lutein/zeaxanthin supplements had a 26% reduced risk of developing advanced AMD compared with those who did not receive the supplements.

### **Which AREDS/AREDS2 formula is right for me?**

Consult your doctor or eye care professional about which supplement, if any, is right for you.

#### **Commercially available formulas based on AREDS/AREDS2**

<b>Nutrient</b>	<b>AREDS formula*</b>	<b>AREDS2 fomula</b>
<b>Vitamin C</b>	500 mg	500 mg
<b>Vitamin E</b>	400 IU	400 IU
<b>Beta-carotene</b>	15 mg	-
<b>Copper (cupric oxide) **</b>	2 mg	2 mg
<b>Lutein</b>	-	10 mg
<b>Zeaxanthin</b>	-	2 mg
<b>Zinc</b>	80 mg	80 mg

\*Not recommended for current or former smokers

\*\*Added to avoid zinc-related copper deficiency

mg = milligrams

IU = international units

## **Why are the AREDS and AREDS2 formulas different?**

In the AREDS trial, taking the AREDS formula reduced the risk of advanced AMD by about 25% over a five-year period. In the AREDS2 trial, adding omega-3s or lutein + zeaxanthin to the 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 reduction in risk of advanced AMD, compared with those who took AREDS with beta-carotene. Also, for participants with very low levels of lutein and 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. (Please see below for [more details on the effects of lutein + zeaxanthin vs. beta-carotene \(https://nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/aredsareds2-frequently-asked-questions#section-id-14171\)](https://nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/aredsareds2-frequently-asked-questions#section-id-14171).) The investigators found no significant changes in the effectiveness of the formulation when they lowered zinc.

## **Where can I get the AREDS2 formula?**

The NEI does not produce the AREDS supplements. Bausch & Lomb produced the formulations for the AREDS and AREDS2 trials. The NEI cannot comment on the safety or effectiveness of any specific brand's formulations.

## **AREDS and AREDS2 formulation components**

### **What are lutein, zeaxanthin, and beta-carotene?**

Lutein, zeaxanthin, and beta-carotene belong to a family of nutrients known as carotenoids. Carotenoids are made by plants and are enriched in green leafy vegetables. They can be stored in animal tissues and are found at relatively low levels in animal-based foods. In the body, beta-carotene is used to make vitamin A, which is required by the retina to detect light and convert it into electrical signals. Beta-carotene itself is not found in the eye. In contrast, lutein and zeaxanthin are found in the retina and lens, where they may act as natural antioxidants and help absorb damaging, high-energy blue and ultraviolet light.

## How do lutein and zeaxanthin compare to beta-carotene?

During the AREDS trial, two large trials funded by the National Cancer Institute found that beta-carotene may increase lung cancer risk among people who smoke. Lutein and zeaxanthin are in the same family of nutrients as beta-carotene and are believed to have important functions in the retina. Lutein and zeaxanthin have not been associated with increased cancer risk.

Some studies prior to AREDS2 (references (<https://nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/aredsareds2-frequently-asked-questions#section-id-14196>), 1-7) found that dietary intake of lutein, zeaxanthin and omega-3 fatty acids is associated with a lower risk of developing advanced AMD. Analysis from the AREDS2 trial suggests that lutein + zeaxanthin offers similar or better protective benefits against advanced AMD compared with beta-carotene. In the trial, participants who took an AREDS formulation containing lutein + zeaxanthin lacking beta-carotene had an 18% lower risk of progressing to advanced AMD compared with those who took AREDS containing beta-carotene (no lutein or zeaxanthin). Among participants who had the lowest dietary intake of lutein and zeaxanthin, those who took AREDS with lutein + zeaxanthin had a 26% lower risk of progressing to advanced AMD compared to participants taking the original AREDS formula.

## What are omega-3s?

Omega-3 fatty acids are made by marine algae and 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 docosahexanoic acid (DHA) and its precursor eicosapentanoic acid (EPA). DHA is needed for the integrity of retinal cells and has been shown to promote retinal development and repair in prior studies.

## What is the function of copper in the AREDS/AREDS2 supplements?

In AREDS/AREDS2 trials, copper (as cupric oxide) was added to supplement formulas containing zinc. The goal was to reduce the risk of copper deficiency anemia, a condition associated with high levels of zinc intake. The studies showed clear benefits for patients who took an AREDS formula with zinc, with no evidence of anemia. There was no evidence that 2 mg copper was harmful, nor reason to suspect that it would be. So, in the AREDS investigators' hands, the use of copper was safe and may have helped balance the effects of zinc.

## **What is the basis for the concentration of zinc in the AREDS supplements? What concentration should I take?**

In the AREDS trial, the 80 mg zinc dose (alone or in combination with antioxidant vitamins) was found to be effective compared to a placebo. Although zinc was found to be an essential component of the AREDS formulation, some nutritional experts recommended a lower dose. In the AREDS2 trial, there was no placebo control. Instead, participants were given the option to take the original formula or to be randomly assigned to receive a modified version, such as a formula containing 25 mg zinc. The investigators did not find a difference in the effects of 80 mg vs. 25 mg zinc. Because AREDS2 did not include a placebo control, results from AREDS, placebo-controlled trial, are still considered the gold standard.

Zinc is found in vegetables, grains, and meat. Vegetables and grains contain other molecules that can prevent zinc absorption and thus reduce its bioavailability. Supplements contain purified zinc, without these competing molecules. Although the chemical form of zinc affects its rate of absorption in the stomach, it is not clear how this affects bioavailability (i.e., the amount of zinc that reaches the retina). For more on this topic, please see the .

## **Risks and side-effects**

### **What is the risk of lung cancer from taking beta-carotene?**

In the AREDS2 trial, 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% of participants who took an AREDS formulation with beta-carotene, compared with 0.9% of participants who took AREDS without beta-carotene. Across both groups, about 91% of participants who developed lung cancer were former smokers.

### **The dose of vitamin E in the AREDS formulation is higher than the recommended dietary allowance. Is this safe?**

The recommended dietary allowance (RDA) of vitamin E for adults over 14 years old is 22.4 IU; but it is not the maximum dose. Rather, it is the dose that nutrition experts have decided is sufficient for most people to remain healthy. The AREDS formula contains 400 IU to provide vitamin E beyond usual dietary intake.

The AREDS and AREDS2 trials found no adverse effects of 400 IU/day vitamin E. Other studies of adults taking more than 1,500 IU/day from natural vitamin E and 1,100 IU/day for synthetic vitamin E observed increased risk of bleeding, including brain bleeds. Most studies of vitamin E supplementation below these levels have shown beneficial or no effects on heart disease.

However, vitamin E can interact with some medications, including blood thinners, chemotherapeutic agents, and lipid-lowering drugs. NEI recommends consulting with a health care provider before taking vitamin E or other nutritional supplements.

For more information, please see the .

### **Do the AREDS/AREDS2 formulations interfere with other medications?**

High-dose nutritional supplements can sometimes interfere with medications and compete with other vital nutrients for absorption into the body. People who are considering taking an AREDS formulation should make a list of all the medications they take to share with their health care provider. The list should include supplements and over-the-counter drugs.

### **Does the high-dose vitamin E in the AREDS formulations affect the risk of prostate cancer?**

AREDS/AREDS2 found no effect of high-dose vitamin E on prostate cancer risk.

However, data from other studies on the relationship between vitamin E and prostate cancer conflict:

- In 1994, the Alpha-Tocopherol, Beta Carotene (ATBC) trial found a 35% *reduced* risk of prostate cancer in men taking 50 mg of vitamin E (synthetic, equivalent to 56 IU) daily for a follow-up of six years. (reference (<https://nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/aredsareds2-frequently-asked-questions#section-id-14196>). 8)
- In 2009, the Physicians Health Study II (PHS II) found that 400 IU of vitamin E every other day for a follow-up of eight years had no effect on the incidence of prostate cancer. (reference (<https://nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/aredsareds2-frequently-asked-questions#section-id-14196>). 9)

- In 2011, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) found a 17% increase in prostate cancer risk among men taking 400 IU of vitamin E daily for a follow-up of seven years. (reference (<https://nei.nih.gov/research/clinical-trials/age-related-eye-disease-studies-aredsareds2/aredsareds2-frequently-asked-questions#section-id-14196>). 10) That risk equates to 1-2 more prostate cancers per 1,000 patients who took high-dose vitamin E for one year. For unclear reasons, men who took both vitamin E and selenium did not have an increased rate of prostate cancer.

Many factors influence prostate cancer risk, including age, family history and race. Visit the National Cancer Institute web site for . NEI encourages men with concerns about taking vitamin E supplements to talk with their health care provider.

## **About the AREDS/AREDS2 trials**

### **Who conducted these studies and how were they funded?**

NEI funded AREDS and AREDS2. The lead investigator was Emily Chew, M.D., who is director of the NEI Division of Epidemiology and Clinical Applications and deputy clinical director of the NEI eye clinic at National Institutes of Health Clinical Research Center. Eleven clinical sites across the country participated in AREDS; 82 sites participated in AREDS2.

Additional support for AREDS2 was provided by the following NIH institutes and centers:

- NIH Office of Dietary Supplements
- National Center for Complementary and Alternative Medicine (now the National Center for Complementary and Integrative Health)
- National Institute on Aging
- National Heart, Lung and Blood Institute
- National Institute of Neurological Disorders and Stroke

The nutrients used in AREDS2 formulations were provided by Alcon, Bausch and Lomb, DSM Nutritional Products Inc., and Pfizer.

### **How many people participated in AREDS and AREDS2?**

The original AREDS trial involved 4,757 participants, ages 55-80 at the time of enrollment. Of 4,203 surviving participants, 3,549 (about 84%) took part in the follow-on AREDS2 trial.

AREDS2 enrolled 4,203 participants, ages 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.

### **Will the AREDS/AREDS2 formulations help prevent cataract?**

No. AREDS was designed to determine if daily intake of certain vitamins and minerals could reduce the risk of cataract and AMD. There was no effect on cataract. AREDS2 participants with the lowest level of dietary lutein and zeaxanthin, measured at enrollment, who took a formulation including those nutrients had on average a 32% reduction in progression to cataract surgery.

## **AREDS, AMD and genetic testing**

### **Should I have genetic testing to learn if AREDS/AREDS2 supplements are right for me?**

Data suggest that comprehensive dilated eye exams provide the best way to determine AMD risk. Genetic testing adds very little to fine tuning this estimate of AMD risk.

NEI analyses of AREDS and AREDS2 data indicate that AREDS/AREDS2 supplements are beneficial for patients of all tested genotypes. Based on the overall data, the American Academy of Ophthalmology also does not support the use of genetic testing to guide treatment for AMD.

### **Is genetic testing helpful for AMD? Are there drawbacks?**

Although genetic testing is important for research purposes, the NEI does not recommend genetic testing for AMD because results cannot guide prevention or treatment decisions. AMD is a complex disease, involving many known and yet undiscovered genetic risk factors. Even when testing results are weighed with other known risk factors, such as diet and smoking status, genetic status fails to reliably predict risk. Some people with low AMD genetic risk develop severe disease. Likewise, some people with high genetic risk never get AMD.



Drawbacks of genetic testing for AMD include possible increased anxiety. For example, results that indicate high risk could cause needless worry. By contrast, results indicating low AMD risk might discourage regular eye exams and that might catch early signs of disease.

## **Is genetic testing helpful for other eye diseases?**

Although not useful for AMD, genetic tests do help with the diagnosis and treatment of other eye diseases, such as Stargardt disease and von Hippel Lindau disease (VHL). In contrast to AMD, these diseases have a fixed pattern of inheritance, due usually to one faulty gene. AMD is considered complex, involving many genes and other factors. Stargardt disease is most commonly caused by mutations in a single gene called ABCA4. It can look like AMD but typically strikes at a younger age. Genetic testing can help diagnose the disease and potentially match patients to clinical trials. VHL disease can cause tumors in the eye but also in other areas, including the brain, spine, and kidney. Genetic testing for VHL disease is potentially lifesaving because a positive result strongly suggests the need for vigilant surveillance for cancer elsewhere in the body.

## **References**

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## Definitions

### AREDS

Age-Related Eye Disease Study

### AREDS2

Age-Related Eye Disease Study 2

### AMD

Age-related macular degeneration

### mg

milligrams

### IU

international units

## Formulation

In this document, a collection of vitamins and minerals given to participants as part of AREDS or AREDS2

## Formula

In this document, the collection of vitamins and minerals found to be effective for slowing progression to advanced AMD in AREDS and AREDS2

## Placebo

A pill given during a clinical trial that does not contain any active ingredients.

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## Additional Resources

### AREDS and AREDS2 Information

[Age-Related Eye Disease Studies](#)

[AREDS/AREDS2 - Background and Design](#)

[AREDS/AREDS2 Nutritional Supplements](#)

[AREDS/AREDS2 News](#)

### Information about AMD

[Age-Related Macular Degeneration](#)

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