Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Lutein and Zeaxanthin

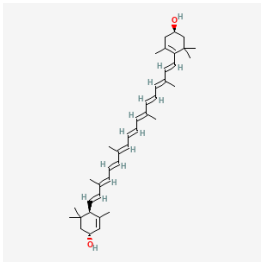
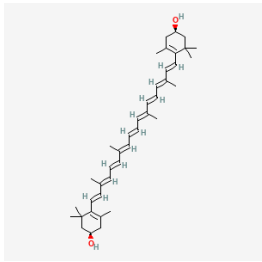
Evidence Summary

Higher levels of lutein and zeaxanthin are associated with lower incidence of several diseases, including dementia. Clinical trials show benefit for AMD and suggest benefit for other conditions.

Neuroprotective Benefit: Epidemiological evidence suggests a link between higher levels of lutein and/or zeaxanthin and brain health. Some clinical trial evidence supports a neuroprotective role.

Aging and related health concerns: Combination supplements containing lutein and zeaxanthin can help prevent progression to late AMD. Lutein and zeaxanthin may have benefits for overall eye health or other disorders.

Safety: Lutein and zeaxanthin are allowed food additives. There are no known safety signals for lutein and/or zeaxanthin within the typical dosing ranges. Large studies with follow-ups of 5 to 10 years have not identified long-term safety concerns.

Availability: In food or as an OTC supplement	**Dose**: Many studies and supplements use 10 mg/day of lutein and/or 2 mg/day of zeaxanthin.	**Lutein:** **Chemical formula:** $C_{40}H_{56}O_2$ **MW**: 568.9 g/mol  Source: PubChem **Zeaxanthin:** **Chemical formula:** $C_{40}H_{56}O_2$ **MW**: 568.9 g/mol  Source: PubChem
Half-life: Lutein: 76 days Zeaxanthin: 38 days	**BBB**: Penetrant	
Clinical trials: The largest clinical trial enrolled over 4,000 participants.	**Observational studies**: A systematic review and meta-analysis of dietary intake, serum levels, and/or supplementation with lutein included more than 387,000 individuals.	

What is it?

There are more than a thousand known carotenoids, which are yellow, orange, and red organic pigments produced by plants and other kingdoms of living organisms. Carotenoids absorb certain wavelengths of light for photosynthesis and also assist in photoprotection in conditions of too much light (Hashimoto et al., 2016). Carotenoids can be divided into xanthophylls or carotenes, which either do or do not have oxygen, respectively (Thomas & Johnson, 2018). Lutein and zeaxanthin are two xanthophyll carotenoids; they are isomers of one another (Mares et al., 2016).

Lutein is found in many fruits and vegetables – notably leafy green vegetables such as kale and spinach – and also in eggs (Ranard et al., 2017). Notable sources of zeaxanthin include corn, peppers, goji berries, and eggs (Tudor & Pintea, 2020). For humans and other animals, these compounds must be obtained from the diet.

Carotenoids absorb specific wavelengths of light such as high-energy blue light. They are also antioxidants that can capture reactive oxygen species. These actions both protect plants from damage as well as expand the absorption ability of plants for photosynthesis (Flieger et al., 2024). In humans, lutein and zeaxanthin both accumulate in the retina – in particular, in a part of the retina known as the macula lutea, or fovea. Together, lutein and zeaxanthin and their metabolites form what is known as macular pigment, and levels can be measured in the retina by measuring macular pigment optical density (MPOD) (Bernstein et al., 2016). The macula is largely responsible for the sharp, detailed central vision of objects directly in front of you (Medline). The retina is also particularly prone to oxidative damage, given the exposure to visible light as well as the high levels of oxygen and polyunsaturated fats present in the tissue (Tudor & Pintea, 2020). In the macula, lutein and zeaxanthin act as antioxidants, quenching reactive oxygen species (ROS) that can form in the eye after absorption of UV or blue light. Lutein and zeaxanthin can also scavenge free radicals. By neutralizing these sources of oxidative stress, lutein and zeaxanthin can mitigate or prevent damage (Bernstein et al., 2016).

Lutein and zeaxanthin may also play a more direct role in visual performance through their light filtering activities that may reduce the effects of glare and optimize contrast sensitivity. Supplementation with these two xanthophylls has thus been of interest for visual function, as well as against diseases of the eye such as age-related macular degeneration (AMD) and cataracts (Bernstein et al., 2016). Diets with high intake of vegetables and fruits rich in lutein and zeaxanthin have been associated with lower incidence of many disorders, including AMD, cardiovascular disease, and cancer (Thomas & Johnson, 2018). Untreated vision loss is a risk factor for dementia (Livingston et al., 2024). Lutein and zeaxanthin have thus been of interest for cognitive health, given their antioxidant function as well as their potential ability to reduce risk factors for cognitive decline.

Neuroprotective Benefit: Epidemiological evidence suggests a link between higher levels of lutein and/or zeaxanthin and brain health. Some clinical trial evidence supports a neuroprotective role.

Types of evidence:

- 11 meta-analyses or systematic reviews
- 10 clinical trials
- 10 observational studies
- 2 reviews
- 2 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:
Lutein and/or zeaxanthin have been tested in clinical trials for cognitive benefits in a variety of populations. Observational studies have also assessed dietary intake of foods rich in these compounds and/or levels of these compounds in the body and looked to see whether there was a statistical association between intake and/or levels and cognitive function, cognitive decline, or incidence of dementia.

A 2021 meta-analysis assessed randomized controlled trials (RCTs) that looked at lutein supplementation, including foods rich in lutein, and the effects of cognitive function. The seven included studies ranged in length from 3 months to 5 years and mostly enrolled healthy adults over a wide range from 18 to 70 years of age. The studies were also heterogenous in what assessment they used to measure particular domain(s) of cognition. Overall, the authors concluded that there was a trend towards improvement in complex attention, executive function, and memory with lutein supplementation compared to placebo treatment, but these results were not statistically significant. However, when they looked at the change from baseline for the placebo and treatment groups in these studies, they found that some – though not all – studies reported significant improvement or prevention of decline in the treatment group, whereas there was no effect in placebo group or decline. The authors hypothesized that supplementation with lutein may prevent decline rather than improving existing cognitive function, particularly in the executive function domain. They also theorized that study lengths of at least 4 months were necessary to observe changes in lutein levels, and called for larger, longer studies to fully assess the role of lutein in cognition (Li & Abdel-Aal, 2021).

It is worth noting that the largest, longest study included in the meta-analysis did not report benefit of lutein and zeaxanthin. A study known as Age-Related Eye Disease Study (AREDS) found that a combination of vitamin C, vitamin E, copper, zinc, and beta-carotene was beneficial for some patients with age-related macular degeneration (AMD). A follow-up study known as the Age-Related Eye Disease Study 2 (AREDS2) tested whether omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) and/or lutein + zeaxanthin added additional benefits in participants at high risk of developing late age-related macular degeneration (AMD). The 4,203 people in AREDS2 therefore all could take the original AREDS vitamin combination and were randomized to placebo, LCPUFAs, lutein + zeaxanthin, or LCPUFAs + lutein + zeaxanthin. Patients could opt into a secondary randomization of different dosing of the original AREDS formulation. The dosing in AREDS2 lasted for 5 years, and the average age of the participants was 73 years. Of these 4,203 participants, approximately 3,000 consented to be in an ancillary study of cognition and had at least one cognitive function test and one follow-up assessment. When the authors compared those who received lutein + zeaxanthin to those who had not, they found no difference in change in overall cognition or individual domains. Whether this reflects a lack of efficacy of lutein and zeaxanthin, that the intervention was started too late, that the dose was not appropriate, or that the study population was too well-nourished and highly educated to have a benefit, is not clear. The study design also cannot rule out the possibility that there were cognitive benefits in all groups, as all groups received some form of supplementation (Chew et al., 2015).

A 2020 systematic review of xanthophyll carotenoids, including of lutein, included five studies. This systematic review included only healthy adults free from retinal disease; thus, there was significant but not complete overlap between their included studies and that of Li & Abdel-Aal, 2021. The conclusion of the systematic review was that three of five studies of lutein reported significant benefit on different domains of cognitive function, particularly for visual episodic memory and inhibition. The included studies were all small, with a wide range of ages included in the studies (Nouchi et al., 2020).

Other RCTs have been published since the publication of these systematic reviews and/or meta-analyses. A 2022 study randomized 60 healthy older adults to receive either placebo or a combination supplement of omega-3 fatty acids, vitamin E, lutein (10 mg), zeaxanthin (2 mg), and meso-zeaxanthin (10 mg). Dosing lasted for 24 months. The researchers looked at changes in cognitive function as well as tissue concentrations of carotenoids and omega-3 fatty acids. They found significant improvements in working memory in the intervention group compared to the placebo group at 24 months; the intervention group made 26% to 38% fewer errors than baseline, depending on the specific assessment, whereas the placebo group had a 1% decline or up to a 14% increase in errors over the course of the

trial. Interestingly, those who had greater changes in any of the compounds had better cognitive performance compared to those who had smaller changes in tissue concentration of the compounds (Power et al., 2022).

One study by Sueyasu et al., 2023 reports on a two-stage RCT in healthy older adults with memory complaints but without dementia. In the first stage, known as Trial 1, they randomized 120 adults to receive either long-chain polyunsaturated fatty acids (LCPUFAs) such as arachidonic acid (ARA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) and an undisclosed compound or LCPUFAs and lutein (10 mg) + zeaxanthin (2 mg) or placebo daily. Dosing lasted for 24 weeks. After assessing results from Trial 1, the researchers randomized 192 participants to either placebo or LCPUFA + lutein + zeaxanthin at the same dosage for 12 weeks to confirm results of Trial 1. In the overall trials, the researchers did not find a difference in cognitive function between groups. However, when they looked just at participants with MoCA scores less than 23, they did report a significant improvement in memory in those who received LCPUFA + lutein + zeaxanthin compared to placebo.

Studies in children have also found that compared to placebo, supplementation with lutein and zeaxanthin was associated with improved cognitive performance in a variety of domains (Parekh et al., 2024).

An analysis from the Mediterranean DASH Intervention for Neurodegeneration Delay (MIND) trial found that plasma lutein and zeaxanthin levels were associated with higher scores for semantic memory (Liu et al., 2021). A preliminary analysis of 123 participants ages 65+ in the CogLife 2.0 study found that plasma levels of lutein were significantly correlated with semantic fluency (Pickert et al., 2024).

Supplementation with, intake of, or circulating levels of lutein and / or zeaxanthin have also been associated with benefits to brain health as measured by neuroimaging. A systematic review looked at RCTs and cohort studies in healthy older adults that either supplemented participants with lutein and/or looked at circulating lutein levels, respectively. The systematic review reported that multiple RCTs reported increases in brain activity in certain regions, increased functional connectivity, and increased gray matter volume in the lutein supplemented group compared to placebo (Yagi et al., 2021).

Epidemiological studies have also looked at levels of intake and/or circulating levels of lutein and/or zeaxanthin and cognition performance. In the approximately 4,000 adults 50 and older in the Irish Longitudinal Study on Aging, higher plasma lutein and zeaxanthin levels were associated with higher

scores on global cognition, memory, and executive function; zeaxanthin level alone was associated with better processing speed (Feeney et al., 2017). A longitudinal study in France comprising approximately 3,000 middle aged adults found that consumption of a carotenoid-rich diet in mid-life was strongly associated with serum lutein levels and also with cognitive function after adjusting for lifestyle, health, and sociodemographic factors (Kesse-Guyot et al., 2014). Similarly, an observational study of approximately 6,390 older adults in the US also found that participants who had the highest intake of lutein and zeaxanthin had significantly greater working memory function as compared to those in the lowest intake group (Zuniga et al., 2021). A study assessing samples from the Georgia Centenarian Study reported that serum lutein and zeaxanthin were consistently significantly related to better cognition in both their whole population of octogenarians (n=78) and centenarians (n=220), as well as in centenarians alone (Johnson et al., 2013).

While some studies look at serum levels of lutein and/or zeaxanthin, others look at macular pigment optical density (MPOD), which is linearly related to the concentration of macular pigment in the retina. (Bernstein et al., 2010). Supplementation with lutein and zeaxanthin with sufficient dosing and duration increases MPOD (Wilson et al., 2021). Increased MPOD may correlate with better vision and/or eye health, and may be a prognostic marker for certain eye diseases such as AMD and/or cataracts (Hu et al., 2023; Hu et al., 2024). A systematic review of observational studies and RCTs in healthy individuals found that in six of the seven included clinical trials, increasing intake of lutein and zeaxanthin resulted in increased MPOD and there were improvements in cognitive function, though the types of tests and domains tested varied across studies (García-Romera et al., 2022).

Several epidemiological studies have found inverse associations between intake and/or circulating levels of lutein and/or zeaxanthin and incidence of dementia. One observational study of over 7,000 participants with a mean follow-up of 16 to 17 years found that serum lutein and zeaxanthin levels were associated with significantly lower incidence of all-cause dementia, whether adjusted for lifestyle (HR=0.93; 95% CI 0.87 to 0.99; p=0.037) or for socioeconomic status (HR=0.92; 95% CI 0.86 to 0.93; p=0.013) (Beydoun et al., 2022). A study of 927 participants in the Rush Memory and Aging Project who were free from AD at baseline and followed for a mean of 7 years found that those in the highest quintile of intake of lutein and zeaxanthin had significantly lower incidence of dementia (HR=0.57; 95% CI 0.37 to 0.87; p-trend=0.02) (Yuan et al., 2021). It should be noted that not all observational studies find statistical associations between levels of lutein and/or zeaxanthin and incidence of dementia (reviewed in Firozjae et al., 2024).

A characterization study looked at data containing cognitive, brain imaging, and blood-biomarker levels of diet and nutrition in a sample of 100 older adults and found that higher levels of specific nutrients including lutein and zeaxanthin were associated with a delayed brain aging phenotype. This association was specific to certain nutrient compounds, and the associations were not due to differences in sex, education, income, body measurements, or physical activity (Zwilling et al., 2024).

Lutein and zeaxanthin have also been explored as risk or protective factor for Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Higher dietary intake of lutein was associated with lower incidence of ALS in a study that pooled results from 5 cohort studies comprising over a million participants (Fitzgerald et al., 2013). Interestingly, a systematic review and meta-analysis of observational studies reported a higher incidence of PD in those with higher lutein intake (OR=1.86; 95% CI 1.20 to 2.88) in the case-control studies (n=1,303) but no association between lutein intake and PD incidence (RR=1.00; 95% CI 0.82 to 1.21) in cohort studies (n=189,671) (Talebi et al., 2022).

Taken together, there is epidemiological evidence that higher intake and/or higher circulating levels of lutein and zeaxanthin is associated with either better cognitive function or lower incidence of cognitive decline and/or dementia, with more evidence supporting a role of these antioxidants in preventing decline as opposed to improving existing function. Some evidence from randomized controlled trials supports these findings, though the existing evidence is hampered by smaller studies with heterogeneous study conditions. It may also be possible that lutein and zeaxanthin must be used in combination with other nutrients for a benefit, or that they are beneficial only in some patient populations, or that they are beneficial only in the context of lutein and/or zeaxanthin deficiency. Robust trials with large sample sizes and supplementation for extended durations in different populations are necessary to fully elucidate the effects of lutein and zeaxanthin supplementation on cognitive health.

Human research to suggest benefits to patients with dementia:

A 2015 study enrolled 31 patients with AD and 31 similarly aged cognitively intact controls and randomized them to either placebo treatment or a macular pigment supplement of lutein (10 mg), zeaxanthin (2 mg) and meso-zeaxanthin (10 mg) daily. Dosing lasted for 6 months. Both healthy and AD participants who received the intervention had significant increases in serum concentrations of all three macular pigments at the end of the trial. Both healthy and AD participants in the intervention group also had significant improvements in visual function. The AD participants had similar responses to cognitively

intact participants, suggesting that uptake of these xanthophylls may not be compromised in AD. The authors did not detect improvements in cognitive function in the timeframe of this trial, which the authors did not find surprising; they hypothesize that lutein and zeaxanthin, as antioxidants, play more of a preventive role than an improvement role, especially on a relatively short time scale (Nolan et al., 2015).

Nolan et al., 2018 tested two combinations of supplements. One, termed Formulation 1, was the same formulation used in Nolan et al., 2015: lutein (10 mg), zeaxanthin (2 mg), and meso-zeaxanthin (10 mg). Another, termed Formulation 2, was the same xanthophyll combination plus 1 g of fish oil containing 430 mg docosahexaenoic acid (DHA) and 90 mg eicosapentaenoic acid (EPA) daily. In the study, 12 patients with AD received Formulation 1 and 13 patients with AD received Formulation 2; both groups of AD patients received the supplements for 18 months. The participants with AD who received Formula 1 had been previously enrolled in Nolan et al., 2015, and the participants with AD who received Formulation 2 had been previously enrolled in an unpublished study assessing the impact of xanthophylls plus fish oil on phospholipid profiles in patients with AD. The researchers found that the blood xanthophyll levels increased more in the group who received Formulation 2 compared to Formulation 1, and that those who received Formulation 2 appeared to have significantly less AD progression than those who received Formulation 1, with progression defined as stage of AD. This was a small study, and the researchers caution it should be taken as preliminary, particularly as they did not have specific measurements of functional or cognitive ability beyond classification of participants as having mild, moderate, or severe AD. The study was also not placebo controlled.

Nolan et al., 2022 then ran another RCT in patients with mild to moderate AD. Their daily supplement in this study contained lutein (10 mg), zeaxanthin (2 mg), meso-zeaxanthin (10 mg), 1 g fish oil (500 mg DHA and 150 mg EPA), and vitamin E (15 mg). The study intended to enroll a total of 120 participants and run for 24 months but had to be amended due to the COVID-19 pandemic. The researchers enrolled 77 participants to either active intervention (n=50) or placebo (n=27) treatment for 12 months. At the end of the study, patients in the intervention group had significant increases in levels of carotenoids in both skin and in blood, and in DHA, EPA, and vitamin E in blood. There were trends towards greater declines on MMSE in the placebo group. There was a significant difference between the intervention and placebo in terms of clinical collateral memory score, with more individuals in the intervention group improving or remaining unchanged whereas more of the placebo group declined. It should be noted that the clinical collateral memory score was developed for this study and was based on information from

the primary caregiver of the patient.

Several epidemiological studies have reported inverse correlations of either intake of or serum/plasma levels of lutein and/or zeaxanthin and dementia. A 2021 systematic review and meta-analysis assessed plasma/serum carotenoid levels and dementia status. The study comprised 10,633 participants and found that there were significantly lower levels of lutein (SMD=-0.86; 95% CI -1.67 to -0.05, p=0.04) and zeaxanthin (SMD=-0.59; 95% CI -1.12 to -0.06, p=0.03) in patients with AD compared to cognitively intact controls. There was no significant association between AD status and levels of other carotenoids (Qu et al., 2021). Other systematic reviews and/or meta-analyses have also found that patients with AD have significantly lower blood lutein and/or zeaxanthin than cognitively intact controls (Mullan et al., 2018; Wang et al., 2023). An observational study of approximately 7,000 adults reported that high levels of lutein and zeaxanthin were associated with lower incidence of AD mortality compared to lower levels; the results were specific to specific carotenoids, as other carotenoids did not show any significant association with AD mortality (Min & Min, 2014).

More research is needed to parse whether supplementation in patients with dementia can be beneficial, and whether benefit is dependent on supplementing a particular patient population, or supplementing in combination with other compounds, or over a minimum timeframe.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

There are both indirect and direct putative mechanisms of action for neuroprotection for lutein and zeaxanthin.

Untreated vision loss is a recognized modifiable risk factor for dementia (Livingston et al., 2024). As lutein and zeaxanthin may help prevent or slow vision loss or even potentially improve visual acuity, it is possible that these two antioxidants are neuroprotective by reducing a risk factor for neurological harm (National Eye Institute / National Health Institute; Hu et al., 2023; Hu et al., 2024).

Oxidative stress is thought to play a significant role in AD (Qu et al., 2021). As antioxidants and free radical scavengers capable of crossing the blood-brain barrier and found in the brain, lutein and zeaxanthin may also have a direct neuroprotective role by reducing oxidative stress. By removing oxidative stressors, antioxidants such as lutein and zeaxanthin can prevent lipid peroxidation, DNA damage, mitochondrial damage, and other cellular harm in the brain (Flieger et al., 2024).

Epidemiological studies in human participants have found that higher intake of lutein and zeaxanthin is associated with lower global levels of AD pathology in the brain, along with lower AD diagnostic scores, severity of neuritic plaques, and density and severity of tau tangles (Yuan et al., 2021). Studies have also found that levels of lutein and/or zeaxanthin are significantly lower in brains from AD patients as compared to brains from cognitively intact controls (Dorey et al., 2023). Animal studies also suggest that lutein and/or zeaxanthin can reduce oxidative stress, improve learning and memory, and may also be anti-amyloidogenic (Flieger et al., 2024; Ye et al., 2024). Lutein and zeaxanthin can also play an anti-inflammatory role, which could reduce neuronal harm (Ye et al., 2024).

It may be that lutein and zeaxanthin are only neuroprotective in certain populations, such as those who are deficient in these compounds. For instance, one study found that supplementing lutein with or without a green tea extract for 16 weeks resulted in higher serum levels of lutein, but did not change body antioxidant status or oxidative stress level in well-nourished adults (Li et al., 2010).

APOE4 interactions:

It is not yet known whether lutein and/or zeaxanthin supplementation interact with APOE status.

An animal study suggested that APOE variations may affect the metabolism of carotenoids in some tissues, though whether this would translate into any clinical significance is not clear (Huebbe et al., 2016). A study of 188 healthy Finnish volunteers did not find a difference in carotenoid levels based on APOE genotype (Leskinen et al., 2021). Further work is needed to explore whether there is an interaction between APOE status and the effects of lutein and/or zeaxanthin.

Aging and related health concerns: Combination supplements containing lutein and zeaxanthin can help prevent progression to late AMD. Lutein and zeaxanthin may have benefits for overall eye health or other disorders.

Types of evidence:

- 8 meta-analyses or systematic reviews
- 4 clinical trials
- 2 observational studies
- 2 professional resources

- 1 scoping review

Age-related macular degeneration: AS A COMBINATION SUPPLEMENT, BENEFIT FOR INTERMEDIATE AMD

Age-related macular degeneration (AMD) is a common cause of blindness. This condition involves deterioration of the fovea, which is the area of the retina where lutein and zeaxanthin accumulate. The Age-Related Eye Disease Study (AREDS) and Age-Related Eye Disease Study 2 (AREDS2) assessed the effect of various vitamin supplements on the progression of AMD and vision loss. AREDS tested a combination of vitamin C, vitamin E, copper, and zinc, and AREDS2 tested those compounds plus lutein and zeaxanthin or omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) (Ruia & Kaufman, 2023). Together, the studies comprised over 4,000 patients and found that the combination of vitamin C, vitamin E, copper, lutein, zeaxanthin, and zinc may delay progression of intermediate to advanced AMD. There is no effect on prevention of early to intermediate AMD. The original formulation in AREDS contained beta-carotene, but it was found that former smokers who took beta-carotene had significantly higher incidence of lung cancer than those who did not receive beta-carotene. Lutein and zeaxanthin replaced beta-carotene (National Eye Institute / National Health Institute).

In the 2013 publication at the end of the 5-year AREDS 2, participants who received lutein + zeaxanthin did not have further reduced risk of progression compared to those who did not receive lutein + zeaxanthin. However, subgroup analyses of quintiles of lutein + zeaxanthin intake showed that for patients in the lowest quintile, treatment with lutein + zeaxanthin significantly lowered the risk of progression to advanced AMD compared to those who did not receive lutein + zeaxanthin (HR=0.74; 95% CI, 0.59 to 0.94; p=0.01) (AREDS2 Research Group). A follow-up study assessed an additional 5-year period for a total of 10 years of follow-up. The original 5-year period was an RCT; the second 5-year period was an extension where all participants were offered, but not required, to take the AREDS 2 supplement. When they compared those who had been originally randomized to receive lutein + zeaxanthin vs. no lutein + zeaxanthin, they found that there was a significantly lower risk of progression to advanced AMD in those who received lutein + zeaxanthin (HR=0.91; 95% CI 0.84 to 0.99; p=0.02). The researchers estimated that the original AREDS formula had a relative 25% beneficial effect of reducing risk of progression to late AMD over the course of 5 years; they stated that there may be an additional relative 10% to 20% beneficial effect of lutein + zeaxanthin, though it is not possible to fully assess because it would not be ethical to assign patients to true placebo treatment at this time (Chew et al., 2022).

Multiple observational studies have found that lutein and/or zeaxanthin intake is associated with lower incidence of AMD and/or delayed progression of AMD (Ye et al., 2024).

Cataracts: AS A COMBINATION SUPPLEMENT, BENEFIT IN POTENTIALLY DEFICIENT POPULATIONS

Lutein and zeaxanthin supplementation have been assessed for other ocular conditions, including cataracts. Intake or circulating levels of lutein and/or zeaxanthin have been associated with lower incidence of cataracts in meta-analyses of observational studies (Liu et al., 2014).

AREDS2 also assessed the impact of supplementation with various vitamin combinations on the development of cataracts. They found that overall, there was no impact on the probability of requiring cataract surgery based on whether the participants supplement contained lutein + zeaxanthin or not. However, when they looked at subgroup analyses of dietary intake of lutein and zeaxanthin, they found a significantly lower risk of progression to cataract surgery in those who were lutein + zeaxanthin supplemented compared to those who were not (HR=0.68; 95% CI 0.48 to 0.96; p=0.03) (AREDS2 Study Group 2013).

Overall Aging: THEORETICAL BUT NO PROVEN BENEFIT

One theory of many is that aging is mediated at least in part by oxidative stress and/or free radial damage. As lutein and zeaxanthin are antioxidant and thus can counter these cellular insults, there has been interest in whether either or both of these compounds may play a role in general aging processes. Higher dietary intake of lutein and/or zeaxanthin has been associated with lower incidence of a number of age-related diseases as well as certain biomarkers of aging, such as longer telomere length (Ye et al., 2024).

Lower levels of lutein and/or zeaxanthin in blood may be associated with higher incidence of frailty and cognitive frailty, respectively (Rietman et al., 2019; Khalid et al., 2022; Zupo et al., 2022). Several studies suggest that lutein levels, intake, and/or supplementation may be beneficial for inflammatory profiles (Leermakers et al., 2016). An RCT randomized 80 individuals to either placebo (n=14) or intervention (n=66); the intervention group received a supplement with lutein (10 mg), zeaxanthin (2 mg), and meso-zeaxanthin (10 mg) daily for 6 months. Compared to the placebo group, the intervention group had

statistically significant reductions in the inflammatory cytokines IL-1β, TNF-α, and OxLDL (Stringham et al., 2024).

Cardiometabolic Disease and Health: POTENTIAL FOR BENEFIT BUT MORE RESEARCH NEEDED

A systematic review and meta-analysis of clinical trials and observational studies assessed the association between lutein blood concentrations, intake, or supplementation and cardiometabolic outcomes. The 71 included studies had a total of 387,569 participants. The meta-analyses pooled results from dietary intake and blood level studies and found that there was lower incidence of coronary heart disease (pooled RR=0.88; 95% CI 0.80 to 0.98) and stroke (pooled RR=0.82; 95% CI 0.72 to 0.93) in those with the highest tertile of lutein levels or intake compared to the lowest tertile. There was also a significant association between higher lutein and lower incidence of metabolic syndrome (pooled RR=0.75; 95% CI 0.60 to 0.92). The researchers reported that there was no significant heterogeneity in results. They performed subgroup analyses to compare results from dietary intake and blood concentration and found no differences in results; the study design (prospective, cross-sectional, or case-control) also did not influence results (Leermakers et al., 2016). Mechanistically, lutein and/or zeaxanthin supplementation may have anti-inflammatory actions that are beneficial for cardiovascular health and may also have positive effects on endothelial function (Hajizadeh-Sharafabad et al., 2019).

The AREDS2 study described above also contained an ancillary study called the Cardiovascular Outcome Study (COS). COS reported that there was no reduction in risk of cardiovascular disease or secondary cardiovascular disease outcome in participants who received lutein and zeaxanthin, nor those who received LCPUFAs, in addition to the other vitamin supplements in AREDS (AREDS Research Group, 2014).

Other trials have reported benefits of lutein and/or zeaxanthin on different measures of cardiovascular health. For instance, an 8-week study of 28 middle aged men with obesity in Japan found that supplementation with lutein and lycopene reduced visceral fat and waist circumference (Takagi et al., 2020). Another trial of 117 participants with obesity tested supplementation with lutein or placebo for 32 weeks. At the end of the study, those who received lutein had significant reductions in total cholesterol, LDL-c, and malonaldehyde levels – the latter being a marker of lipid peroxidation and thus oxidative stress (Zhou et al., 2025). It should be noted though that there are conflicting results in the literature regarding the effect, if any, of lutein on lipid profiles and adiposity, as well as on insulin resistance and blood pressure (Leermakers et al., 2016) and a meta-analysis found that lutein and

zeaxanthin supplementation did not affect total cholesterol or LDL-c, but might significantly increase HDL-c levels in older adults (Ghasemi et al., 2023).

There have been inconsistent findings on whether there is an association between intake or levels of lutein and/or zeaxanthin and type 2 diabetes. Some systematic reviews and meta-analyses such as Leermakers et al., 2016 find no association; others, such as Jiang et al., 2021 do report significant inverse associations between intake and levels of lutein and incidence of type 2 diabetes.

Overall, there is some evidence that suggest lutein and/or zeaxanthin may have benefits for cardiometabolic disease, but much of it is observational. More work is needed to identify whether there is a real biological benefit that is clinically meaningful and due to the compound(s) themselves rather than confounding factors.

Other Age-Related Diseases:

Multiple studies have reported that either dietary intake of or circulating levels of lutein and/or zeaxanthin are associated with lower incidence of specific cancers, such as breast cancer (Dehnavi et al., 2024) and gastric cancer (Han et al., 2024). Lutein and zeaxanthin intake has also been associated with better bone density, lower incidence of wrist or hip fractures, and potentially a lower incidence of osteoporosis (Ye et al., 2024). Whether these findings are correlational or causational requires future work.

Safety: Lutein and zeaxanthin are allowed food additives. There are no known safety signals for lutein and/or zeaxanthin within the typical dosing ranges. Large studies with follow-ups of 5 to 10 years have not identified long-term safety concerns.

Types of evidence:

- 3 clinical trials
- 1 case report
- 1 professional resource
- 8 reviews

Both lutein and zeaxanthin are generally recognized as safe (GRAS) when consumed as food or food additive by the FDA, and also allowed by the EU (Bernstein et al., 2016). Overall, the existing data has strong support for safety up to 20 mg/day for lutein and 2 mg/day for zeaxanthin, with some data suggesting that higher doses may also be well within safe ranges (Shao & Hathcock, 2006; Bernstein et al., 2016; Edwards, 2016).

The Age-Related Eye Disease Study 2 (AREDS2) was a study of different supplement combinations in 4,203 participants ages 50 to 85; median follow-up time was 5 years. All participants received the original AREDS formulation of vitamin C, vitamin E, cooper, zinc, and beta-carotene. The participants were randomized to receive either lutein (10 mg/day) + zeaxanthin (2 mg/day), omega-3 LCPUFAs consisting of EPA (650 mg/day) + DHA (350 mg/day), both lutein + zeaxanthin and LCPUFAs, or placebo. All participants were also offered a secondary randomization to one of 4 variations of the original AREDS formulation. There were no clinically or statistically significant differences in reported rates of serious adverse events in any of the primary randomization groups (AREDS2 Research Group). Small RCTs in children have also reported no adverse events related to lutein or zeaxanthin treatment (Parekh et al., 2024).

One case report from Choi et al., 2016 details a 60-year-old woman with bilateral 'foveal sparkles' with no visual complaints or deficits in visual acuity. The woman had an atypically high level of lutein consumption from both diet as well as lutein supplementation, and several measures of carotenoid levels indicated the patient's carotenoid levels were 2 to 3 times higher than the average unsupplemented population of the clinic that the patient was referred to. On the advice of the medical team, she discontinued the lutein supplement, and the foveal crystals were resolving 7 months later; her carotenoid levels also decreased closer to the population mean.

Drug interactions:

The supplement-drug interactions of lutein and zeaxanthin are not well characterized.

Co-administration of lutein and beta-carotene may lead to reduced absorption of both carotenes (Drugs.com). Lutein may affect absorption of vitamin E (Medline). According to WebMD, zeaxanthin may interact with drugs that lower blood sugar, as zeaxanthin may lower blood sugar (WebMD). As always, it is best to have a thorough discussion with your medical provider about all of your medications and supplements before adding a new supplement.

Lutein and zeaxanthin are best absorbed with a high-fat meal (Medline).

Research underway:

There are 11 ongoing studies registered on clinicaltrials.gov that involve supplementation with lutein (clinicaltrials.gov), zeaxanthin (clinicaltrials.gov), or both. These trials are assessing a variety of patient populations from infants to older children to adults with type 2 diabetes. They also explore several conditions, including tinnitus, visual function, or retinal health. One study is assessing zeaxanthin in patients with metastatic cancer (NCT05232409).

NCT06489873 is an ongoing study that aims to enroll 80 healthy adult participants. The participants will be randomized to receive either a supplement containing lutein, zeaxanthin, and fish oil or a matching placebo; dosing will last for 6 months. The primary outcome measures are change in cognitive function over the course of the trial, bone density, and macular pigment optical density (MPOD). The study is estimated to complete in May 2025.

Two studies are RCTs assessing cognitive or developmental outcomes in infants (NCT03838536) or children (NCT05177679) after 3 to 9 months of supplements containing lutein and/or zeaxanthin.

Search terms:
Pubmed, Google: lutein, zeaxanthin

- Cognition, dementia, AD, AMD, vision, eye health, safety, drug interactions

Websites visited for lutein and zeaxanthin:

- Clinicaltrials.gov: Lutein; Zeaxanthin
- Examine.com: Lutein; Zeaxanthin
- Drugs.com: Lutein; Zeaxanthin (0)
- WebMD.com: Lutein; Zeaxanthin
- PubChem: Lutein; Zeaxanthin
- DrugBank.ca: Lutein; Zeaxanthin
- ConsumerLab.com: Lutein; Zeaxanthin

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.