Lutein across the Lifespan: From Childhood Cognitive Performance to the Aging Eye and Brain

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ABSTRACT
Lutein is a non-provitamin A dietary carotenoid found in dark green leafy vegetables, corn, eggs, and avocados. Among the carotenoids, lutein and its isomer, zeaxanthin, are the only 2 that cross the blood–retina barrier to form macular pigment in the retina. Lutein also preferentially accumulates in the human brain across multiple life stages. A variety of scientific evidence supports a role for lutein in visual as well as cognitive function across the lifespan. The purpose of this review is to summarize the latest science on lutein’s role in the eye and the brain across different ages. Curr Dev Nutr 2019;3:nzz066.

Introduction
Lutein is a non-provitamin A dietary carotenoid found in dark green, leafy vegetables, corn, eggs, and avocados (1). Originally understood to preferentially accumulate in the macula of the eye, the majority of research characterized the effects of lutein and its isomer zeaxanthin on eye health. Lutein has been strongly implicated in visual function (2) as well as being protective against age-related eye diseases, particularly age-related macular degeneration (AMD) and cataracts (3, 4). More recently, insights into the bioavailability and bioaccumulation of lutein have led researchers to consider a role for lutein in brain development and cognitive performance. The purpose of this review is to summarize the latest science on lutein’s role in the eye and the brain throughout the lifespan.

Effects of Lutein on Ocular Health and Visual Performance
The energy required for the countless physiological demands of the body is derived primarily from carbohydrates and lipids, composed of carbon and oxygen (4). In tissues with extremely high metabolism such as the retina (5) and brain (6), the instability of oxygen can cause devastating, often irreversible damage. Moreover, prolonged oxidative stress promotes proinflammatory responses (7), which can exacerbate damage and result in the creation of more reactive oxygen species (8). This positive feedback loop can result in the cumulative damage that is manifest in several age-related diseases, such as AMD (9, 10), atherosclerosis (11), and certain forms of cancer (12).

In the case of the retina, the metabolic rate is so exceedingly high that the body has prioritized a specific, nutrient-based strategy to help deal with the potential for oxidative stress. Namely, the carotenoids lutein and zeaxanthin accumulate in high densities in the region of the retina with the highest demand for oxygen, and therefore the highest risk of oxidative damage: the fovea (13). The fovea is extremely important to visual performance, because it mediates central vision and maintains the highest performance in terms of color discrimination, motion detection, contrast sensitivity, and acuity (14). Oxidative stress is not the only threat to the fovea, however—light...
energy incident on the retina can itself be damaging, whether via thermal- or photochemical-based lesions (15). This is especially true of short-wave visible light, which appears blue-violet in color. Owing to their yellow-orange coloration and location in the retina, lutein and zeaxanthin filter an appreciable amount of incident short-wave light before it reaches the photoreceptors of the sensory retina (16). Given their physical (light filtration) and biochemical (antioxidant) properties, lutein and zeaxanthin are ideally suited to protect the central retina and protect the lipid-dense retina from oxidation, and thereby facilitate good visual performance.

**Lutein and retinal development**

Despite the overwhelming focus on the association between relatively high levels of lutein in the diet/retina and a significant reduction in risk of developing AMD [e.g., (17, 18)], this relation is likely happenstance—adaptive pressures for accumulation of lutein in the retina would lead to survival advantages relatively early in life, and manifest before the reproductive cycle ends (not near the end of life). Indeed, there appears to be a significant role for lutein and zeaxanthin in the development of the retina. At the very earliest stages of retinal embryology (∼14 weeks of gestation), lutein and zeaxanthin begin to accumulate in the large fluid reservoir that makes up most of the globular shape of the eye—the vitreous humor. This accumulation peaks at 20–22 weeks of gestation, at which point the lutein is diverted out and into the retinal space (19). Interestingly, this time period corresponds to the development of key layers of the retina such as Bruch’s membrane, the plexiform layer, ganglion cell layer, nuclear layer, and photoreceptor layer (20).

The timing suggests that lutein plays a role in the development of the retina. Additional evidence to support a role for lutein in retinal development comes from a study of premature infants (born <33 weeks of gestation) in which infant formula fortified with lutein, β-carotene, and lycopene was compared with a control formula with no added carotenoids (21). After ∼4 mo of feeding with the respective formulas, electroretinography was performed to assess the status of retinal development. Overall, plasma lutein concentrations significantly correlated with the full-field electroretinogram response amplitude, and the supplemented group also showed greater rod photoreceptor sensitivity. In addition, the latency of light response was lower in the supplemented group, which indicates faster neural responses. These findings are suggestive of a significant and rapid contribution of lutein to retinal development. Lastly, it should be noted that lutein accumulates in the retina very early—perhaps in utero—at concentrations that are detectable with optical imaging techniques as early as 4 mo of age (22).

The early and very specific accumulation in the retina further bolsters the argument for lutein as a key component of retinal development.

**Lutein and visual performance**

The presence of lutein and zeaxanthin in the central (macular) retina yields a yellow pigmentation, termed “macular pigment” (MP). The concentration of MP is typically expressed in terms of optical density (MPOD) and can range among individuals from 0 to values as high as 1.60 (23). This range represents a dramatic difference in both carotenoid concentration and light filtration: a value of 1.60 MPOD means that only ∼2.5% of the short-wave visible light would penetrate through to the photoreceptors (compared with 100% for an individual with no MP). There have been several recent findings that indicate a significant contribution by lutein and zeaxanthin to visual performance. Generally, visual performance has been shown to improve as a function of MPOD. This has been found to be true for a variety of performance parameters, including speed of visual processing, which is related linearly to MPOD (24, 25). This speed advantage also translates into accuracy, whereby positional judgments of quickly moving objects are more precise with higher MPOD (26). Another clear visual performance advantage of higher MPOD is visual performance in bright light conditions (i.e., glare). Visual discomfort has been found to be significantly inversely correlated with MPOD (27–29)—participants are able to tolerate more light before squinting or averting their gaze due to discomfort. In addition, glare disability (the phenomenon where glare produces “washed out” vision due to scattered light within the eye) is significantly reduced as a function of MPOD (27, 28, 30) and can also be significantly reduced within individuals who supplement with lutein and zeaxanthin (31–33). Similarly, photostress recovery (the time required to recover visibility after a relatively bright flash of light) is significantly shorter both with higher MPOD (30) and within individuals who augment their MPOD via dietary supplementation with lutein and zeaxanthin (33).

**Mechanisms of action**

The aforementioned effects indicate the existence of several mechanisms of action for lutein and zeaxanthin in visual development and visual performance. The fact that these antioxidants confer protection to the retina—and thereby keep tissues healthy—accounts for at least some of these effects. In terms of visual performance in glare, short-wave light filtration would appear to be the most parsimonious explanation for performance enhancement. With regard to speed of visual processing and contrast sensitivity, light filtration cannot explain the significant enhancement seen in studies. Rather, these effects are most likely due to more efficient communication among visual neurons (41) and/or enhanced neurophysiological status in the retina and brain. Indeed, it was shown that MPOD is correlated significantly with a fundamental aspect of visual neurophysiology, called lateral inhibition (35).
Lutein and Cognition

Much of the early work on lutein and the central nervous system (CNS) focused on visual function/disease. This made sense because of the very high concentration of lutein and zeaxanthin in an area of the retina that is both critical to vision (cone-rich macula) and highly susceptible to disease (macular degeneration). It was not until relatively recently that some focus has turned to investigating the relation to other aspects of the CNS such as the brain. Recently, lutein has been observed to accumulate in the brain across multiple life stages ranging from infants to centenarians. Therefore, lutein may have an important role in the brain that is conserved across the lifespan. Lutein can be found in the circulation and throughout the human body where concentrations generally reflect intakes (44–48). Although lutein is not the major dietary carotenoid in the US diet for any age group (49), it is the carotenoid of highest concentration in human brain tissue (47, 50). This preferential accumulation in the brain is thought to occur owing to the presence of a specific lutein-binding protein present (51). In full-term human infants, lutein accounts for ~60% of total carotenoids in the brain despite survey data indicating lutein accounts for only ~12% of total carotenoids consumed in the diet in the first year of life (30). However, brain lutein content is significantly lower in preterm infants, who also have undetectable MPOD and very low concentrations of plasma carotenoids (52). Preferential accumulation of lutein in the brain is also observed at the opposite end of the lifespan, where lutein accounts for ~35% of total carotenoids in the centenarian brain despite making up only ~20% of the carotenoids in matched serum (47). Of interest is the suggestion that MPOD can serve as a biomarker of brain lutein concentrations. Certainly, this is plausible given that for lutein to be taken up in the retina it must cross the blood–brain barrier. Given this, MPOD measures might be a useful tool for cognitive studies testing the efficacy of lutein interventions. To test this, matched retina and brain sections from nonhuman primates (53) and humans (54) were analyzed for lutein. In nonhuman primates, lutein concentrations in the retina significantly correlated with lutein in the cerebellum, pons, and occipital cortex, and tended to correlate with concentrations in the frontal cortex. In humans, lutein in the retina was significantly related to lutein in the occipital cortex. These findings indicate that lutein accumulates up into the retina and multiple regions of the brain through similar mechanisms, thus supporting the use of MPOD as a biomarker of lutein and its isomer, zeaxanthin, in human brain tissue. Of note, although lutein is the major dietary carotenoid in both retinal and brain tissues, concentrations were found to be considerably greater in the retina.

Relation between brain concentrations of lutein and cognitive function

To further understand the relation between lutein status and cognitive function, the association between cognition and lutein concentrations in brain tissue of decedents >98 y at death and premortem measures of cognitive function were assessed. Subjects (n = 29) agreed to donate their brains upon death which were analyzed for carotenoids. Cognition measures included global cognition, primary degenerative dementia, delayed recall, delayed recognition, retention, intelligence quotient (IQ), and executive function (47). Among the carotenoids, brain lutein content was the most consistently related to cognitive test scores (47).
Lutein intervention and cognitive performance

Although the studies discussed to this point described compelling observational data on associations between lutein status and cognitive function in adults, the question remains, can lutein intake affect cognitive function? This question was examined in an intervention study involving a 4-mo, double-blind intervention trial of lutein and DHA (22:6n–3) supplementation (60). Forty-nine healthy women (60–80 y) were randomly assigned to receive lutein (12 mg/d) (n = 11), DHA (800 mg/d) (n = 14), a combination of lutein and DHA (n = 14), or placebo (n = 10). Cognitive tests including verbal fluency, memory, processing speed and accuracy, and self-reports of mood were performed at the study start and upon completion of the trial. After supplementation, verbal fluency scores improved significantly in the DHA-only, lutein-only, and combined treatment groups. Memory scores and rate of learning improved significantly in the lutein + DHA group, who also displayed a trend toward more efficient learning. This observation is consistent with findings from a study which reported a significant interaction between postmortem brain concentrations of lutein and DHA as a predictor of premortem cognitive test scores measuring verbal fluency, working memory, and dementia in centenarians (61). Combined lutein and DHA supplementation has also been shown to benefit younger adults (18–32 y old) (26). In this study, supplementation with lutein, zeaxanthin, and omega-3 fatty acids, including DHA, for 4 mo increased MP and improved neural processing speed. Collectively, these findings suggest that lutein may function in an additive/synergistic manner with DHA to influence cognitive function in older adults.

In a study involving older adults (mean age 63 y), a dietary intervention with avocados, a highly bioavailable food source of lutein, increased MPOD which was related to improved cognitive function (62). In other placebo-controlled intervention trials with older subjects (mean age 74 y), lutein/zeaxanthin supplements (12 mg/d for 1 y) resulted in cognitive improvements in older adults (mean age 74 y) (60, 63).

The influence of macular carotenoids on cognition in early life

Early work on lutein and the brain paralleled research on the visual system in that it tended to focus on older subjects and mechanisms that were mostly prophylactic. At first blush, it seems reasonable to infer that if lutein is influencing the cognitive function of subjects when they are older, it would also influence the cognition of subjects when they were younger. This inference is consistent with data showing that lutein/zeaxanthin supplementation improves the cognitive function of college students (64). Such generalizations, however, are not merited. Although much of the physical structure of the brain is complete by the age of 6 y (by some estimates, ~95%), modification of that structure continues until early adulthood. For instance, a second wave of synaptogenesis occurs near puberty (11–12 y) with significant pruning after that time (~1% of grey matter being lost every year between ~13–18 y) (65). The brain, like many biological systems, has a very close structure–function relation. Hence, significant maturational changes during adolescence mirror equally significant functional change. Because of such rapid change, the brain is particularly sensitive to exogenous input during adolescence. This has been shown very clearly by the extreme sensitivity of the adolescent brain to negative factors such as stress (66). The reverse implication, however, is also true: the brain may have an equally exquisite sensitivity to positive factors such as a good diet (67).

Studies on the role of the macular carotenoids in the brain function of children are quite recent. The ability to investigate this relation has benefited from the same advantage as the study of lutein in the brain of adults: namely, that retinal MP can be measured as a noninvasive biomarker for the amount of lutein in the brain (53, 54). The ability to measure a component of food, directly and nondestructively, in the very tissue that it could be affecting (the CNS) represents a powerful advantage. Concentrations of lutein when assessed in diet and serum are likely poor indicators of concentrations in the CNS. For example, Mulder et al. (48) measured lutein in the diet and serum of children in Canada and found that dietary intake (using the FFQ) only explained ~10% of the variation in serum lutein. This is similar to the type of correlations seen between serum lutein + zeaxanthin and MPOD measured in adults (correlations range around 0.30) (68). MPOD can, however, be reliably measured in preadolescent children (69) and, when used as a biomarker, provide more of a direct assessment of lutein’s influence on CNS tissue.

Using this technology, 4 recent cross-sectional studies have assessed the relation between MPOD and cognitive function in preadolescent children. The first was by Hassevoort et al. (70). In that study, 40 children aged 7–10 y had their MPOD, adiposity, and aerobic fitness measured and compared with their performance on a relational memory task. This task is known to be mediated by the hippocampi which are also known to preferentially accumulate lutein in infancy (71). Hassevoort et al. found that MPOD was negatively related to relational memory errors. The correlations remained even after adjustments for IQ and other health factors such as VO2 max. The next study (72), using fifty-six 8- to 9-y-olds, studied academic achievement directly. Since passage of the No Child Left Behind Act in 2001, academic progress has increasingly focused on standardized testing of basic scholastic skills. The comprehensive version of the Kaufman Test of Academic and Educational Achievement was used to assess such basic skills as reading, spelling, and mathematics. MPOD related to achievement (r = 0.40, P < 0.01), reading (r = 0.28, P < 0.05), math (r = 0.35, P < 0.01), and written language (r = 0.41, P < 0.01). Saint et al. (73), testing fifty-one 7- to 13-y-olds, found similar-sized correlations using the Woodcock-Johnson III (composite standard scores were obtained for Brief Intellectual Ability, Verbal Ability, Cognitive Efficiency, Processing Speed, and Executive Processes): MPOD was significantly related to Executive Processes (r = 0.29, P < 0.05) and Brief Intellectual Ability (r = 0.27, P < 0.05). The studies on children appear to be reflecting those on adults; lutein measured directly tends to explain ~10% of the variance in a range of cognitive functions.

The results on children are unique in that they de-emphasize the prophylactic function of the pigments. In other words, it seems less likely that the brain function of the children is being improved by preventing degenerative change (through, for instance, an antioxidant or anti-inflammatory mechanism). The multiple-regressional analyses by Hassevoort et al. (70) and Barnett et al. (72) further suggest that MPOD is not simply acting as a biomarker of improved health, IQ, or social economic status (SES). Walk et al. (74), using cognitive testing in conjunction with electroencephalography, and a matched case-control design (on variables like SES, age, and pubertal timing),
found that children with higher MPOD had lower brain activation when conducting the same cognitive tasks as children with lower MPOD. In other words, matched on a range of personal variables, children with lower MPOD had to use more brain to do the same task (decreased neural efficiency) and they made significantly more errors.

If these relations are not simply reflective of improved health, SES, and IQ, could MPOD be confounded with some other variables that relate to better cognition? Lieblein-Boff et al. (71) have shown that lutein relates to major amino acid neurotransmitters (like glutamate and γ-aminobutyric acid) that are well known to influence cognition. The fact that supplementing with lutein/zeaxanthin improves cognition in young adults, however, would suggest that, if this is the mechanism, then increasing lutein/zeaxanthin concentrations would also increase these neurotransmitters directly. This hypothesis can actually be tested because neurotransmitter levels in the brain can be measured noninvasively using available methods, e.g., Marsman et al. (75).

**Mechanism of action**

Despite consistent evidence of a beneficial relation of lutein with visual and cognitive function throughout the lifespan, the underlying mechanism of action remains unclear. It is speculated that some of the mechanisms by which lutein protects the retina from damage (antioxidant, anti-inflammatory) may also apply to the brain (76). The combination of high metabolic activity and rich PUFAs content in the brain makes this organ vulnerable to oxidative stress (77). Furthermore, elevated DHA oxidation has been observed in patients with dementia and cognitive impairment (78). Unlike nonpolar carotenoids, such as β-carotene and lycopene, lutein has polar groups at each end of the molecule, which is believed to cause the molecule to span the membrane in a perpendicular or semiperpendicular orientation to the membrane surface (79, 80). This, in combination with evidence demonstrating that lutein localizes to membrane domains rich in PUFAs (including DHA) (81, 82), suggests that lutein is well positioned in membranes to block oxidation of these vulnerable brain lipids. Inhibition of DHA oxidation not only helps to maintain membrane structure and fluidity but also preserves DHA so it remains available for cleavage and conversion into anti-inflammatory molecules (83). Although this potential lipid-protective action by lutein may, in part, explain the relation between lutein and neural function, it is possible that lutein may function through other independent mechanisms, including modulation of membrane stability and function, as well as communications between neurons (79, 84).

### Recommendations for Lutein Intake and Neural Health

#### Dietary sources

Rich food sources to consider are green leafy vegetables (spinach and kale), squash, broccoli, and corn (85, 86) (Table 1). Although eggs and avocados have relatively lower concentrations of lutein, both are considered highly bioavailable food sources of lutein, owing to their favorable fat profiles, and have been shown to increase MPOD and cognitive function in older adults (87–89).

| Food                          | Serving | Lutein + zeaxanthin (mg) |
|-------------------------------|---------|--------------------------|
| Spinach, frozen, cooked       | 1 cup   | 29.8                     |
| Kale, frozen, cooked          | 1 cup   | 25.6                     |
| Summer squash, cooked         | 1 cup   | 4.0                      |
| Peas, frozen, cooked          | 1 cup   | 3.8                      |
| Pumpkin, cooked               | 1 cup   | 2.5                      |
| Brussels sprouts, frozen, cooked | 1 cup | 2.4                     |
| Broccoli, frozen, cooked      | 1 cup   | 2.0                      |
| Sweet yellow corn, boiled     | 1 cup   | 1.5                      |
| Avocado, raw                  | 1 medium| 0.4                      |
| Egg yolk, raw                 | 1 large | 0.2                      |

#### Adults

It may be too early to make a recommendation for dietary intakes of lutein for promotion of cognitive health. However, intakes of ~6 mg/d have been related to a decreased risk of AMD (17), a disease which shares similar risk factors with age-related cognitive decline (90–92). Furthermore, the Age-Related Eye Disease Study 2 (AREDS2), a multicenter phase III randomized clinical trial, reported that in secondary analysis, lutein and zeaxanthin supplements (10 and 2 mg/d, respectively) on top of the AREDS supplement lowered the progression to advanced AMD in persons with low dietary lutein and zeaxanthin (93). And lastly, an intervention of 12 mg/d was found to improve cognition in older adults (60). Although these amounts (6–12 mg) can be achieved through proper dietary selections, the majority of the US adult population are not reaching these intakes (49, 94).

#### Infants and children

Similarly, it may be too soon to make recommendations for intakes of lutein in infants and children as it pertains to cognition. However, supplementation with lutein can increase lutein in breast milk and plasma of lactating mothers taking the supplement as well as corresponding plasma lutein concentrations in their infants (95). Furthermore, formulas supplemented with lutein enrich this bioactive in tissues, including retina and brain, compared with infants consuming lower amounts (96, 97). Therefore, higher intakes may be warranted to optimize brain development and cognition and recommendations for breastfeeding mothers may be necessary to ensure adequate lutein content in breast milk.

Dietary lutein appears to have an important role to play in the visual and cognitive development/optimization of children. If future intervention studies with children confirm these initial cross-sectional observations then they must also motivate the need to improve diet in early life. Lutein/zeaxanthin intake in American adults is low (~1–2 mg/d) but it tends to be even lower in early adolescence (~300–500 μg/d) (42). As with many aspects of diet, such deficits in childhood can start a cascade that simply amplifies with age. Interventions with children likely yield lifetime benefits.

#### Conclusions

To date, epidemiological evidence suggests that dietary lutein may be beneficial for visual and cognitive health across the lifespan.
may be due to its role as an antioxidant and anti-inflammatory agent. Among the carotenoids, lutein preferentially accumulates into the infant and adult brain. A variety of evidence including observational and intervention studies suggests a relation between lutein status and visual and cognitive function in younger and older adults, as well as preadolescent children. Based on lutein intakes being related to a decreased risk of AMD, which has similar risk factors to age-related cognitive decline, average lutein intakes are low for adults. The elderly may be a particularly vulnerable group owing to poor nutrition for reasons including economics, medication use, and decreased sense of taste and smell. More recent observational evidence indicates that lutein is likely also important for brain development and cognition in early life. Breast milk is the optimal source of lutein for infants; however, lutein content in breast milk is dependent on maternal intake. Lutein-supplemented formulas may be used as an alternative source of lutein in infants.

Lutein is not an essential nutrient. However, evidence is accumulating to suggest that lutein is important to optimize ocular and cognitive health. Although the precise mechanisms by which lutein may be influencing neural health across the lifespan remain to be investigated, efforts may be warranted to establish recommended intakes for this dietary bioactive given the sum of the evidence to date and the low dietary intake of lutein across all age groups (49, 50).

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