**Egg Antioxidants - Lutein and Zeaxanthin:**
**An overview of current evidence and opportunities in Cognitive Health**

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The aim of this project was to undertake a broad, desktop review of the current evidence supporting a possible relationship between lutein and zeaxanthin intake and/or status and cognition.

## Lutein and Zeaxanthin

Lutein and zeaxanthin (L/Z) are the main antioxidants in eggs. They belong to a group of compounds known as 'xanthophyll carotenoids'. L/Z are naturally present in food, especially in dark green leafy vegetables, such as spinach and kale, as well as eggs – in the egg yolk. While plants contain higher levels of L/Z than eggs, the L/Z in eggs has been shown to be highly bioavailable – i.e. the body absorbs and uses the L/Z from eggs efficiently[1,2].

Results from the USDA nutrient database (see Table 1) report eggs (raw) contain approximately 500 µg L/Z per 100g. These results are similar to the 2007 results obtained from testing Australian eggs (510µg per 100g) but more recent testing in 2018 from National Measurement Institute (NMI) indicated raw eggs contain less than previously indicated at an average of 291µg per 100g. The L/Z content of eggs is dependent largely on the composition of hen feed as well as the duration of feeding[3]. Changes to hen feed or feeding protocols may have affected the L/Z levels reflected in the 2018 results. Further investigation into the reasons for the change in L/Z levels may be required. As L/Z are also responsible for the colour of the egg yolk it is in the best interest of Australian Eggs and their consumers, from both an aesthetic as well as a health perspective to maintain higher levels of L/Z where possible.

**Table 1: Lutein and Zeaxanthin Content of Common Foods[4]**

| Food | Lutein and zeaxanthin (µg/100g) |
|---|---|
| Kale, cooked | 18246 |
| Spinach, raw | 12197 |
| Spinach, cooked | 11308 |
| Parsley | 5562 |
| Peas, green (boiled) | 2593 |
| Pistachio nuts, raw | 1404 |
| Egg yolk, raw | 1094 |
| Broccoli (cooked) | 1079 |
| Asparagus, cooked | 771 |
| Frozen corn (boiled from frozen) | 684 |
| Egg whole, raw | 504 |
| Egg whole, cooked (hard-boiled) | 353 |

In the body, L/Z have been shown to accumulate in both the retina of the eye (suggesting eye health benefits) and the brain (suggesting cognitive health benefits)[5]. Because of the accumulation in the brain and given that the eye is an extension of the neural system, L/Z is increasingly recognized as having a possible role in cognitive function[6].

**Cognition**

Cognition (also referred to as 'cognitive health', 'cognitive performance' or 'cognitive function') refers to the health of the brain and its overall function.

The area of nutrition and cognition is wide-ranging as it can involve individuals across the lifespan from brain development during pregnancy, cognitive development and function in infants, cognition in childhood and adulthood, all the way to preventing cognitive decline in older adults. Cognitive health enables most aspects of productivity such as employment, social engagement and disease self-management at all ages. Maintaining cognition and preventing cognitive decline is therefore an important aspect of the overall health of Australians.

Measuring the cognitive benefits of foods and/or nutrients can be complex given a range of factors, including diet and lifestyle, impact cognition and because there are a variety of tools that can be used to measure different aspects of cognition in different population groups. For example, the commonly used Mini Mental State Examination (MMSE) is a set of 30 questions used by doctors and other healthcare professionals to check for cognitive impairment. Mainly used in older adults, this examination includes a range of aspects of cognition including short- and long-term memory, attention span, concentration, language and communication skills, ability to plan and ability to understand instructions. Whereas, cognition in children is more likely to be measured using a range of cognitive assessments aimed at this age-group and assess outcomes such as IQ, academic performance, memory and attention.

The report is set out under the original aims of this review (as outlined in original project brief):

- *Understand the current, available research base supporting a role for lutein and zeaxanthin in cognition*
- *Identify key population groups most likely to benefit from increased lutein and zeaxanthin intake*
- *Identify key research gaps where there may be opportunities to fund further research studies*
- *Develop evidence based key messages for marketing and communication in areas of research where enough research currently exists*

**Summary of the current, available research base supporting a role for lutein and zeaxanthin in cognition**

Four systematic reviews summarizing the current available research regarding lutein and zeaxanthin and cognitive function have been published in the last six years (2012, 2014, 2017, 2018)[6-9]. Nine complementary studies conducted in 2017 and 2018 were also located in the PubMed database which provide a broader understanding of the current evidence on the effects of lutein and zeaxanthin in cognition (4 RCTs[10-13], 1 cohort[14] and 4 cross sectional studies[15-18]). Further evidence may be available by searching other databases and/or contacting key researchers working in this space.

Research to date demonstrates lutein consistently associates with a wide range of cognitive measures that include executive function, language, learning and memory, while there is sparse evidence for a relationship between zeaxanthin and cognition. The beneficial effects of lutein are thought to be due to its antioxidant and anti-inflammatory properties and the current rationale supporting a role for lutein in cognitive function is based on the following observations: 1) lutein is the predominant carotenoid in human brain tissue in early as well as late life; 2) primate retinal lutein concentrations, i.e., macular pigment density in animal models are related to brain lutein levels; 3) macular pigment density is related to cognitive function in adults; 4) lutein supplementation in adults improves cognitive function.

The Macular Pigment Optical Density (MPOD) has been found to be a reliable biomarker of brain levels of lutein and zeaxanthin, and is currently used as a direct reflection of lutein and zeaxanthin in the neural tissue[9].

Consistent evidence suggests there is a relationship between higher MPOD and a range of cognitive measures in children, young and older adults[6-9,16-18]. A range of suggested improvements include academic achievement, language scores, executive processes and intellectual ability in children, attention in young adults and global cognitive function in older adults[6,7,9,18].

Further to this, three RCTs demonstrate the possible beneficial effects of supplemental lutein and zeaxanthin in increasing MPOD and positively effecting attention and memory in young and older adults[11-13].

Dietary intake and blood levels of lutein have been frequently, but not always consistently, correlated with better cognitive performance. For example, significant beneficial effects of higher lutein intake or blood levels have been found in older adults with Alzheimer's Disease (AD) and mild cognitive impairment [6,8,9]. A risk reduction of 19% and 24% have been suggested in all-cause dementia and AD, repectively.

Limited research demonstrates a relationship between dietary intake and blood levels of lutein with measures of cognition in children and young adults, although this may be due to difficulties in studying these population groups.

In Infants, the majority of the studies focus on the brain level of lutein, which accounts for more than half of the total carotenoids, and is twice that found in adults (59 vs 31% respectively)[7-9]. A preferential uptake of lutein into infant neural tissue from foods has also been suggested when compared to other carotenoids[7]. These findings suggest that lutein may play a major role in neuronal development.

The effect of zeaxanthin on cognition is inconclusive due to the limited investigation in this area. However an overall positive relationship of lutein and zeaxanthin supplements, MPOD and cognitive functions merits further investigation.

Overall, the evidence to date is strongest in older adults including adults with Alzheimers Disease and mild cognitive impairment. The relationship between L/Z and cognition is biologically plausible but further quality intervention studies measuring cognitive outcomes would strengthen this evidence base.

**Key population groups most likely to benefit from increased lutein and zeaxanthin intake**

**Pregnancy and Infancy:**
Lutein accounts for more than half of infant brain carotenoids, suggesting it may play a major role in brain development. Evidence suggests that the infant brain needs large amounts of antioxidants because of its high metabolic rate. A preferential uptake of dietary lutein into infant neural tissue has also been reported when compared to other carotenoids. While further, direct evidence is needed in this group it is likely that they would benefit from increased intakes of lutein and zeaxanthin.

**Childhood:**
While there is some evidence suggesting that higher MPOD (which increases with higher intakes of L/Z) improves the cognition of children including overall acadamic achievement, language scores, executive processes and intellectual ability, no direct association has been found between dietary/supplemental intake and blood levels of lutein with measures of cognition in this age group. Further scientific investigation would be required to conclude the benefits of lutein and zeaxanthin intake on cognition in children.

**Young Adulthood:**
Overall, there is limited research in young adults from two recent RCTs. While these two studies found positive results, the effects of lutein and zeaxanthin on cognitive function in this age group is inconclusive.

**Mid-Older Adulthood:**
Recent evidence indicates the benefits of lutein on cognition in mid-older adults. Compared to other carotenoids, lutein is consistently associated with a wide range of cognitive measures that include executive function, language, learning and memory, particularly in older adults. While higher MPOD, blood and dietary levels of L/Z have been related to better cognition in healthy individuals, positive effects have also been demonstrated in people with Alzheimer's Disease (AD) or mild cognitive impairment. This suggests a critical role of lutein in age-related cognitive health – showing a possible protection against age-related cognitive decline. Although a minority of the studies to date have focused on the effects of zeaxanthin, evidence suggests a positive relationship between blood levels of lutein and zeaxanthin and MPOD with cognitive functions.

**Adults with (or at risk of) mild cognitive impairment or Alzheimer's Disease:**
Alzheimer's Disease (AD) is a neurodegenerative disease. It is the most common form of dementia in Australia and accumulating evidence suggests that oxidative stress plays an important role in this condition. One study has shown that antioxidant-rich food reduces the risk of AD by inhibiting oxidative stress. Furthermore, a review study has suggested that lutein and zeaxanthin are depleted both in individuals with Mild Cognitive Impairment (MCI) and in those with Alzheimer disease. Significant beneficial effects of higher dietary lutein intake or blood levels have been found in older adults with AD and a cohort study showed that higher blood lutein levels decreased the risk of all-cause dementia and AD by 19% and 24%, respectively. However, the AREDS 2 study, in older adults, showed no effect of LZ supplementation on cognitive function.

One egg-specific study suggested moderate egg intake may have a beneficial association with certain areas of cognitive performance[19]. Overall the recent evidence supports the health benefits of lutein and zeaxanthin in people with mild cognitive impairment and Alzheimer's Disease.

**Key gaps where there may be opportunities to fund further research studies**

- **General** – *further understanding of neural mechanisms – how is L/Z playing a role in cognition?*
- Further intervention studies are needed to better understand the specific ways L/Z is impacting cognitive function. Researchers have suggested that studies across all age-groups using more novel measures of brain health such as fMRI scans – 'functional magnetic resonance imaging' would assist in better understanding the mechanisms at play.

- **Pregnancy –** *is L/Z intake or status during pregnancy related to cognitive performance in pregnant women and/or their offspring?*
- There is a lack of research investigating the possible benefits of L/Z intake or status (measured by MPOD) during pregnancy and possible effects on cognition. A research study could therefore be conducted which quantifies intake levels of L/Z in Australian pregnant women (or women of child-bearing age) and ascertains whether those with higher L/Z intakes perform better on cognitive tests compared to those with lower L/Z intakes.

- **Children –** *can higher diet quality (including adequate L/Z intake) contribute to academic performance?*
- Specific interventions with L/Z in children may be difficult (ie compliance may be difficult in a trial that asks children to increase their L/Z intake or take an L/Z supplement) but a study which assesses overall diet quality (and L/Z's or eggs' overall contribution to this) with markers of cognition (using specific cognitive tests or academic achievement) may provide useful information.

- **Older Australians** – *can L/Z intake help protect against cognitive decline in older Australians?*
- Evidence in an Older Australian population. Cohort studies linking LZ intake or blood levels of L/Z to cognitive function have been conducted in older adults in countries including Ireland, France and the USA but we are unaware of similar studies in Australia.
    - This may entail linking in with a large cohort such as the Blue Mountains Eye Study and running some cognitive function questionnaires and seeing if LZ intake, LZ blood levels or MPOD are associated with cognition in this group of older Australians.
    - Outcomes of this type of study include providing some information as to whether L/Z intake may be associated with protecting against cognitive decline in Australian older adults.

- **Alzheimers' Disease or mild-cognitive impairment** - Further studies could be conducted in groups such as those with Alzheimer's Disease and individuals with mild-cognitive impairment to confirm previous findings that increasing L/Z delays the progression of cognitive decline in these specific groups.

Other possible opportunities:

- Link in with organisations which have a focus on 'cognitive health' such as Alzheimer's Australia (now Dementia Australia: https://www.dementia.org.au/ ) – the opportunity may be to provide information and/or recipes around eggs and the beneficial nutrients they contain for cognitive health or to co-fund more specifc research in this space.

**Eggs and cognition - more than just lutein and zeaxanthin**

While this review of evidence has focused on the possible role of the antioxidants lutein and zeaxanthin, it is important to remember that eggs contain other nutrients which have (or likely have) cognitive benefits. A further understanding of how these nutrients work together to impact cognitive health is also of interest.

These nutrients include some which FSANZ have alreaady pre-approved food-health relationships related to cognition and cognitive health which could be used by Australian Eggs to communicate benefits in this area. Table 2 outlines nutrients in eggs which meet the conditions for using the pre-approved food-health relationships related to cognition.

Table 2: Nutrients in eggs with cognitive functions

| **Nutrient** | **Amount in Eggs** | **Pre-approved food-health relationships for General Level Health Claims related to Cognition** |
|---|---|---|
| Iron | 1.7mg per serve (14% RDI) | “Necessary for normal neurological development in the foetus”<br>“Contributes to normal cognitive function”<br>In children: “Contributes to normal cognitive development” |
| Iodine | 43µg per serve (29% RDI) | “Necessary for normal neurological function”<br>“Contributes to normal cognitive function” |
| Folate | 97µg per serve (49% RDI) | “Contributes to normal psychological function” |
| Vitamin B1 (Thiamin) | 0.12mg (11% RDI) | “Contributes to normal psychological function” |
| Vitamin B2 (Riboflavin) | 0.5mg (29% RDI) | “Contributes to normal functioning of the nervous system” |
| Vitamin B5 (Pantothenic Acid) | 2.1mg per serve (42% RDI) | “Contributes to normal mental performance” |
| Vitamin B12 | 0.8µg per serve (40% RDI) | “Necessary for normal neurological structure and function”<br>“Contributes to normal psychological function” |

Other nutrients in eggs including choline and omega-3 fatty acids also have some evidence which supports a role for them in brain development and/or cognition[9,20].

Given this wide array of nutrients in eggs which are involved in congition, FNA suggest it may be worth considering research project opporutnities that focus on eggs as a whole rather than limiting only to the antioxidants lutein and zeaxanthin.

**Key messages for marketing and communication in areas of research where enough research currently exists**

Given the evidence base for lutein/zeaxanthin and cognition is still building, there is limited opportunity for communication currently in this space.

Examples of key messages/facts for Australian Eggs:

- Eggs contain the antioxidants lutein and zeaxanthin.
- Lutein and zeaxanthin accumulate in the brain, suggesting they may play an important role in cognitive function.
- Lutein accounts for more than half of all carotenoids found in the infant brain, suggesting a unique role in brain development.
    - The infant brain needs large amounts of antioxidants (such as lutein and zeaxanthin found in eggs) because of its high metabolic rate.

- Eggs contain a variety of nutrients necessary for cognition including iron, iodine, folate and B-vitamins.

*Note: the above messages may require modification of wording pending their usage.*

**Main Researchers in this space**

**Carotenoid/Antioxidant specific Research:**

**Elizabeth J Johnson –**

http://hnrca.tufts.edu/research/labs/antioxidants/elizabeth-j-johnson-ph-d/

Antioxidants Research Laboratory, Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Gerald J. & Dorothy Friedman School of Nutrition Science and Policy, Tufts University, Boston, Massachusetts, USA.

**Cognitive Research:**

**Centre of Research Excellence in Cognitive Health – Australian National University**

http://cognitivehealth.anu.edu.au/

The Centre for Research Excellence in Cognitive Health was launched in June 2016 and conducts research to optimize cognitive health and prevent cognitive decline. The CRE Cognitive Health is a collaboration between Chief and Associate Investigators from the Australian National University, University of Melbourne, University of New South Wales, Australian Catholic University, Baker IDI Heart and Diabetes Institute and University of Exeter.

Members of the Diet and Cognitive Health team include:

- Professor Kaarin Anstey (Principal Investigator)
- Associate Professor Nicolas Cherbuin
- Professor Nicola Lautenschlager
- Professor Perminder Sachdev
- Associate Professor Jonathan Shaw

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