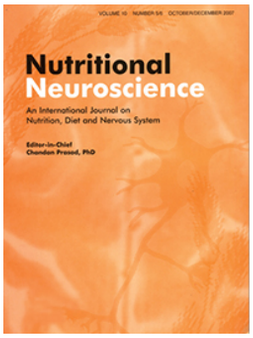

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REVIEW

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The influence of the macular carotenoids on women's eye and brain health

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ABSTRACT

Introduction: The mortality-morbidity paradox refers to the inconsistency in survival and disease between males and females: females live longer but tend to suffer greater age-related disease and disability. Many aspects of the latter can be targeted by lifestyle interventions, such as changes in dietary behavior.

Methods: The relevant literature is reviewed.

Conclusion: Dietary intake of the pigmented carotenoids appears to be particularly important for issues such as visual and cognitive loss. This may be due to the highly selective presence of a fraction of carotenoids, namely lutein (L) and zeaxanthin (Z), in specific tissues of the eye and brain. At those sites, L and Z have been shown to directly improve function and prevent central nervous system degeneration. On the palliative side, retinal LZ reduce glare disability, discomfort and photostress, improve chromatic contrast and visual range (e.g., the ability to see through blue atmospheric haze). These effects on input reflect changes in neural output such as improved visual processing speed, problem solving, memory and executive function (presumably due, also, to local effects in areas such as the hippocampus and frontal cortex). These effects on function throughout the central nervous system are mirrored by effects on disease progression. As potent antioxidants/anti-inflammatory agents, and "blue-blockers" within the retina, the pigments prevent loss that precedes neurodegenerative diseases such as age-related macular degeneration and some forms of dementia.

KEYWORDS

Sex differences; lutein; zeaxanthin; mortality-morbidity paradox; carotenoids; macular degeneration; macular pigment; Alzheimer's

I. Mortality-morbidity paradox

Humans are one of the only animal species where biological sex can confer both a distinct mortality advantage while simultaneously extracting a long-term cost of morbidity: females tend to live longer but often with higher rates of illness (see Table 1). There have been a number of speculative explanations for this strong sex difference in mortality-morbidity (reviewed by Austad and Fischer[10]) including endocrine differences, lack of genetic redundancy on the Y chromosome of males, inflammatory and oxidative stress differences, etc. Whatever the driver, there is clear evidence that the paradox exists.

One elegant example was provided in a demographic study of Icelanders between 1835 and 1920 [11]. This was a time period characterized by a number of natural catastrophes in Iceland (flooding, disease, famine, etc) with average lifespans changing concomitantly (to as low as 21 and as high as 69 years). Despite the trying nature of the period and lower life expectancy, however, and the strong homogeneity of the population, the large sex differences in survival was consistent (both at the beginning and end of life). This basic finding has been replicated often. For example, more male embryos are spontaneously aborted compared to female [12]. Younger males (ages 15–49 years) often die at a rate that is three times higher than females [13]. The average difference in life expectancy in developed countries favors females by about 7 years. No other current intervention in longevity research on humans can match this basic biological effect.

Despite such significant survival advantages, females are more vulnerable to a number of diseases and conditions that, while not always lethal, are significantly debilitating. For example, Jacobsen et al. [14], reviewing the incidence of 24 autoimmune diseases over the period of 1965–1995, noted that 80% of the affected were female. Sex differences in autoimmunity are reflected in some basic immune responses such as chronic inflammation [15]. Females may have a more robust immune response but then suffer from the long-term consequence such an enhanced response

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Table 1. Global sex differences on neurodegenerative disease and health focusing on areas influenced by carotenoid intake.

Variables	Effect
Morbidity	
Macular degeneration	70% prevalence in females [1]
Dementia	69% prevalence in females [2]
Parkinson's disease	54% prevalence in males [3]
Multiple sclerosis	Prevalence three times higher in females [4]
Cataracts	Global blindness due to cataract was 35.5% for females and 30.1% for males [5]
Osteoporosis	24.4% female, 20.5% male [6]
Mortality	
Life-span	74.2 years for females, 69.8 for males [7]
Cardiovascular disease/ stroke	A factor of 4–5 (30–64 years), less (two) at older age (65–89 years) [8]
All-cause cancer	19% higher in males than females (death rates 43% higher in males [9])

incurs (so called inflammaging) [16,17]. There also appear to be sex differences in exposure to oxidative stress that contribute to strong differences in neurodegenerative disease. These differences arise from both external (e.g. choice of profession) and internal sources (e.g. endocrine differences; [18]).

II. Sex differences in neurodegenerative disease

Although not as sexually dimorphic as many species, males in the USA (the difference is often muted in less wealthy countries [19]) tend to be about 8% taller and 15% heavier than females. These average differences in body size are reflected in differences in brain volume that are evident across the lifespan[20]. How these gross differences translate to finer differences in form and function is a current matter of debate[21]. Eliot et al, conducted a meta-analysis [22] of magnetic resonance imaging and post-mortem data and argued that, although larger, male and female brains are highly similar in form and function. Other meta-analyses of functional outcomes, however, favor the view that there are significant sex differences in the normal healthy brain [23]. Ultimately, relating a single binomial variable (sex, even without considering the continuum of gender) to a complex endpoint with large individual differences that change dynamically and systematically throughout life is a challenging task. What is clear, however, is that significant sex differences exist in susceptibility to neurodegenerative disease. There are neurodegenerative diseases whose incidence/prevalence is higher in males, most notably Parkinson's disease [24]. Many neurodegenerative diseases, however, tend to affect females more often and sooner than males. Even when correcting for differences in lifespan, females have higher incidence of dementias, notably Alzheimer's disease [25]. Detailed neuroimaging has shown that these differences tend to arise early [26]. The cumulative effects are not small. Women represent about 2/3rd of all cases of dementia. A similar prevalence is seen in other, often co-morbid, neurodegenerative conditions. Age-related macular degeneration (sometimes referred to as Alzheimer's of the eye [27]) is also about 70% female [1].

If oxidative and inflammatory stress are major drivers of age-related neurodegenerative disease, and this category of illness affects females more than males, one ameliorative and relatively benign approach would be to target antioxidants and anti-inflammatory elements of the diet. A recent meta-analysis of 29 outcomes in 24 systematic reviews [28] showed that higher intake of green leafy vegetables was strongly linked to reduced all-cause mortality (such as cancer rates): Increased intake of 100 g/day was linked to a 25% reduction in risk. Carotenoids, ubiquitously present in green leafy vegetables and colored fruits, are potent lipid-based antioxidants and are strongly anti-inflammatory [29] and are likely good candidates for intervention [30].

III. Surviving disabled: carotenoids target many morbidities that disproportionately impact females

Low bone mineral density (particularly trabecular for both males and females; [31]) precedes clinical manifestations of osteoporosis and can be detected in females as early as their 30s (particularly less active women; [32]) but then accelerates after menopause (resulting in about a 6% loss in height). Carotenoids have been shown to retard bone loss by preventing osteoclastic bone resorption and by promoting osteoblastic bone synthesis (both accelerated by oxidative stress; [33]). A number of studies have targeted lycopene (found in tomatoes) as a good candidate for intervention [34]. Beta-carotene [35], astaxanthin [36] and lutein/zeaxanthin [37] are also likely candidates.

Like early bone loss, the slow change in the optical density of the crystalline lens precedes cataract development [38]. Many years before an overt cataract, individuals suffer clinically significant visual loss due to an optically imperfect crystalline lens. This imperfection causes intraocular scattering and visual effects such as glare disability, visual spokes and haloing [39]. Cataract incidence (corrected for differences in life-span) is higher in females and, due to the associated visual loss, leads to many additional years of disability [5]. Higher lutein and zeaxanthin status (as measured in retinal tissue) is directly related to a clearer crystalline lens pre-cataract [40] and lower incidence and

prevalence of cataract including cataracts dense enough to require extraction [41].

A large body of empirical data has now linked higher intake of lutein and zeaxanthin with decreased risk of age-related macular degeneration [28,30]. This relation is clearly biologically feasible. In addition to affecting the oxidative and inflammatory mechanisms of the disease, L and Z in the macula strongly absorb the lower third of the visible spectrum effectively decreasing the 'blue' light hazard to the retina [42]. The short-wave portion of the visible spectrum also drives many deleterious aspects of visual function including limiting visual range (via blue haze; [43]), photophobia [44] and visual discomfort [45]. By filtering such light before it is incident on the foveal cones, visual function is improved [46]. AMD is a visual disease with visual symptoms that are exacerbated early in the course of the disease. Even if L and Z were not influencing the progression of the disease mechanistically, they would serve an important palliative function [47,48].

Parallel logic applies to dementia. About 20–25% of the oxygen from the lungs goes directly to the brain which has a very rich source of oxidizable fat (the brain is about 60% fat [49]). Peroxidation and chronic inflammation are strong drivers of degeneration of brain tissue [50]. L and Z (and a stereoisomer, meso-Z) are the only carotenoids in the retina and the primary carotenoids in the brain [51]. In the brain they are located in key information processing areas like hippocampus and occipital and frontal lobes [52]. Increasing evidence has suggested the possibility that LZ intake could be linked to the pathogenesis of Alzheimer's disease [53–56]. Yuan et al recently [57] showed that carotenoids may inhibit the deposition of brain β-amyloid and retard fibril formation.

Like with the eye, however, an important ancillary effect here might simply be palliative. Diseases of the brain most often manifest as losses in cognition. L and Z as neuro-pigments are thought to increase cellular efficiency [58] and improve cognitive function. A wide confluence of data, both cross-sectional [59] and interventional [60], has shown that L and Z improve critical aspects of cognition [61]. For example, the Nurse's Health Study (n = 49, 493) found that women in the highest quintile of LZ intake had a 24% reduced probability of reporting reduced cognitive function over a period of 22 years [57]. A similar finding was reported in a Chinese population (n = 16, 703) from Singapore [62]. Although it is common to isolate variables in dietary studies, it is likely the case that carotenoids are simply one part of an overall healthy eating pattern that can optimize cognition over the lifespan [63].

The confluence of evidence is important. Empirical data has now been collected on children [64], young adults [65], older adults [66] and adults with cognitive impairment [67]. The data has been based on results using questionnaires, psychophysical testing and a wide variety of neuroimaging [61]. All point to the same answer: increased intake leads to improved brain function.

IV. Carotenoids and body morphology

There appears to be a strong parallel between many aspects of central nervous system (CNS) function/disease and carotenoid intake. Should carotenoid interventions target women? In an early study [68], we found that females on average had about 38% lower retinal levels of L and Z compared to males (sex differences in retinal LZ has been found in some [69,70], but not all samples; [71]). This reduction was surprising in that females tend to have higher dietary intakes of L and Z compared males across ages ([72]; although some data suggest that even with lower dietary intake of carotenoids, plasma levels of carotenoids are higher in women compared to men;[73]). Carotenoids are lipid-soluble and stored in adipose tissue and females tend to have about 20% higher body fat compared to males (although this average varies across different ethnic groups [74]). Johnson et al. showed [75] that despite similarities in serum and dietary L and Z intake, the females in their sample had higher adipose levels of L and Z than the males. Increased storage can be an advantage in some situations (e.g. availability of carotenoid for breastmilk) but a disadvantage in others (less for retinal and brain tissue). Carotenoids in other species are often used for external coloration and sexual signaling [76]. Carotenoid metabolism in humans is also likely influenced by biology linked to reproduction [77]. It is that biology that can drive increased risk of disease (e.g. the number of pregnancies are directly related to Alzheimer's risk [78]). At the very least it emphasizes another reason why it might be important to target females: depletion due to caregiving.

V. Effects of LZ on reproductive biology and early development

In oviparous species, the yellow yolk of eggs serves as a visible reminder of the importance of carotenoids to prenatal development [79]. In humans, prematurity results in reduced LZ in retina [80] and brain [81]. Laie et al recently [82] studied the relation between myopia development and intake of L and Z during pregnancy. Myopia has become an important issue connected to modern life with some areas of the world approaching near total

prevalence [83]. Mothers in the highest quartile of L and Z intake (measured as plasma levels at delivery) had children with 38% less risk of poor acuity when assessed three years later. The visual system matures rapidly in the first few years of life [84]. Intake of L and Z is particularly low during that time (Johnson et al,). Developmental studies with Rhesus monkeys (raised LZ deficient and then compared to normal controls) has shown that RPE cells are negatively affected by the absence of L and Z [85]. Rubin et al. found [86] that pre-term human infants given a control formula without LZ and omega-fatty acids showed negative changes in evoked electrogram readings compared to supplemented formula. The reduction in carotenoid levels in preterm babies may be due, in part, to increases in oxidative stress (supplemental LZ improves their antioxidant status [87]). Lutein levels in arterial cord blood positively correlate with Activin A in preterms [88], a neuroprotein often used as biomarker for brain development. All of these results point, less to using L and Z as a treatment for preterms with disease [89], but rather highlights the importance of LZ intake for mothers to promote normal healthy development [90,91].

Infants are born with a very clear crystalline lens and high susceptibility to photo-oxidative insult [84]. Much of the aging of the retina may occur very early in life. It is likely for this reason that L and Z are so actively concentrated in colostrum and early breastmilk [92], likely drawing from the stores of the mother.

VI. Conclusion

There appears to be a strong link between morbid conditions affecting the central nervous system of females and conditions where L and Z appear to have a special prophylactic and palliative role. Lutein and Z are concentrated in retina and brain and are known to improve the fidelity of the eye's optics and the efficiency of critical neural pathways. This review focused on neurodegenerative disease but the linked effects are plethoric: higher levels of serum carotenoids have been associated with reduced risk of ovarian [93] and breast cancer [94], sarcopenia [95], skin wrinkling [96], inflammatory bowel disease [97] and multiple sclerosis [98]. The parallels between conditions that preferentially affect women and the link to carotenoids, especially L and Z is striking. Given the high probability of help and the low probability of harm, targeting the L and Z intake of women is a wise strategy.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Billy R. Hammond is a professor in the Brain and Behavioral Sciences program and the Principal investigator of the Vision Sciences Laboratory at the University of Georgia (UGA).

Lisa Renzi- Hammond is an associate professor in the Institute of Gerontology in UGAs college of Public Health. Both investigators have a long history in the study of the macular carotenoids.

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