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The Effect of Lutein, Zeaxanthin, and Meso-Zeaxanthin Supplementation on Visual Performance: A Systematic Review

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14. ABSTRACT

Objective: To determine whether nutritional supplementation with lutein (L), zeaxanthin (Z), and/or mesozeaxanthin (MZ) results in improved human visual performance. Method: A systematic literature search was performed on the effects of L, Z, and/or MZ supplementation on human visual performance. The databases which were queried were Pubmed and ScienceDirect. Results: A total of 19 studies were identified and analyzed. Combined analysis of all these studies revealed that 1) there were no safety concerns from L, Z, and MZ supplementation, and 2) with supplementation there was either improvement of visual performance or there was no change in visual performance. There were no studies in which visual performance decreased with supplementation. Several promising trends materialized from these studies: contrast sensitivity, glare disability, photostress recovery, critical flicker fusion frequency, and photophobia all showed general improvement with supplementation. Visual acuity and color vision, on the other hand, showed no improvement, or had inconclusive results.

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14. Abstract (continued)
Discussion/Conclusion: From a combined perspective, the data from literature indicates that supplementation with L, Z, and/or MZ improves certain visual performance tasks but not others. The recommendation from these emerging trends is to add antioxidant supplementation to the Warfighter's visual readiness toolkit for a tactical advantage.

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Introduction

Contemporary science often touts the panacea-like benefits of antioxidants, leading to their marketing as supplements for a variety of purposes, ranging from aiding in disease prevention to slowing of the aging process. However, despite the popularity of antioxidant supplementation, there is still a large medical and scientific community that questions the validity of these benefits. The diversity of claimed benefits of antioxidants stems from the fact that there is an abundance of antioxidant varieties, making the study of antioxidants and their benefits broad and overwhelming. To narrow the focus of the antioxidant debate to a workable thesis, this systematic review will focus only on ocular antioxidants and their visual performance benefits. In particular, this systematic literature review will only analyze the published works on supplementation with Lutein (L), Zeaxanthin (Z), and/or Meso-Zeaxanthin (MZ) and their effects on human visual performance.

Methods

The literature search was based on the following key words and concepts: Lutein, Zeaxanthin, Meso-Zeaxanthin, Visual Performance, Antioxidants, Supplementation, and Placebo-Controlled. Inclusion criteria for this systematic review were: 1) the study involved supplementation with one or more of the aforementioned macular pigment (MP) antioxidants, 2) the study was placebo-controlled, and 3) the study measured visual performance in some way. Exclusion criteria included all studies where supplementation did not occur, no placebo group was included, or no visual performance measures were studied. The databases searched were PubMed and Science Direct.

Non-parametric statistical analysis, in particular Fisher's Exact test, was performed to determine if there was a correlation between supplementation and improvement in the vision performance measures. A significance level of 0.05 was used for most of the hypothesis tests.

Results

In our search of the antioxidant literature, we reviewed over 100 articles, which were then filtered down to 14 pertinent articles that met our inclusion criteria. These studies' findings are summarized here. They varied in supplement formulation, duration, subject type, and aspect of visual performance assessed. Ten studies examined visual acuity, 10 examined contrast sensitivity (CS), 8 photostress recovery, 6 glare disability, 4 quality of life, 2 color vision, and 1 critical flicker fusion frequency (CFF). Subjects varied by pathology–1 study used subjects with age-related cataracts, 3 studies used subjects with age-related macular degeneration, and 10 studies used healthy subjects.

For ease of analysis, Tables 1, 3, 5, 7, 9, and 11 summarize the results of each of these 14 studies. Tables 2, 4, 6, 8, 10, 12, and 13 are the association tables constructed for the Fisher Exact test. The results are as follows, organized by aspect of visual performance investigated.

Visual Acuity

Visual acuity refers to the clarity of vision, and is the aspect of vision most known to the general population. Ten of the 14 studies included in the present paper investigated visual acuity. Summarized results of the ten studies that assessed the relationship between visual acuity and visual performance are shown in Table 1.

Table 1. Results of studies reviewed that included visual acuity

Visual Acuity														
Year	Study	# Subjects	Age (years)			Subgroups	Lutein Dosage (daily)	Zeaxanthin Dosage (daily)	Meso-Zeaxanthin Dosage (daily)	Study Duration	End of Study Results			
			Mean	SD	Range						Improved	Worsened	No Change	p-value
Healthy Subjects														
2008	*Bartlett, H. E., & Eperjesi, F. (2008). A randomised controlled trial investigating the effect of lutein and antioxidant dietary supplementation on visual function in healthy eyes. Clinical Nutrition, 27(2), 218-227.*	29	50	15.9	22 - 73	1	6 mg	0 mg	0 mg	18 months			✓	p > 0.05
						placebo	0 mg						✓	p > 0.05
2009	*Ma, L., Lin, X., Zou, Z., Xu, X., Li, Y., & Xu, R. (2009). A 12-week lutein supplementation improves visual function in Chinese people with long-term computer display light exposure. British Journal of Nutrition,102(02), 186. doi:10.1017/s0007114508163000*	37	24.2	1.6	N/A	1	6 mg	0 mg	0 mg	3 months			✓	p > 0.05
			24.2	1.2	N/A	2	12 mg	0 mg	0 mg				✓	p > 0.05
			25.7	2.1	N/A	placebo	0 mg						✓	p > 0.05
2011	*Nolan, J. M., Loughman, J., Akkali, M. C., Stack, J., Scanlon, G., Davison, P., & Beatty, S. (2011). The impact of macular pigment augmentation on visual performance in normal subjects: COMPASS. Vision Research, 51(5), 459-469.*	121	29	7	18 - 41	1	12 mg	1 mg	0 mg	12 months			✓	p > 0.05
						placebo	0 mg						✓	p > 0.05
2012	*Loughman, J., Nolan, J. M., Howard, A. N., Connolly, E., Meagher, K., & Beatty, S. (2012). The Impact of Macular Pigment Augmentation on Visual Performance Using Different Carotenoid Formulations. Investigative Ophthalmology & Visual Science, 53(12), 7871-7880.*	36	51	13	18 - 70	1	20 mg	2 mg	0 mg	6 months			✓	p > 0.05
						2	10 mg	2 mg	10 mg		✓			p = 0.008
						placebo	0 mg						✓	p > 0.05
2013	*Yao, Y., Qiu, Q., Wu, X., Cai, Z., Xu, S., & Liang, X. (2013). Lutein supplementation improves visual performance in Chinese drivers: 1-year randomized, double-blind, placebo-controlled study. Nutrition, 29(7-8), 958-964.*	120	36.5	1.6	25 - 47	1	20 mg	0 mg	0 mg	12 months			✓	p > 0.03
						placebo	0 mg						✓	p > 0.05
2016	*Nolan, J. M., Power, R., Stringham, J., Dennison, J., Stack, J., Kelly, D., . . . Beatty, S. (2016). Enrichment of Macular Pigment Enhances Contrast Sensitivity in Subjects Free of Retinal Disease: Central Retinal Enrichment Supplementation Trials – Report 1. Investigative Opthalmology & Visual Science, 57(7), 3429.*	105	44.83	11.46	N/A	1	10 mg	2 mg	10 mg	12 months			✓	p > 0.05
						placebo	0 mg						✓	p > 0.05
Subjects with AMD														
2004	*Richer, S., Stiles, W., Statkute, L., Pulido, J., Frankowski, J., Rudy, D., . . . Nyland, J. (2004). Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: The Veterans LAST study (Lutein Antioxidant Supplementation Trial). Optometry - Journal of the American Optometric Association, 75(4), 216-229.*	90	74.4	6.4	N/A	1	10 mg	0 mg	0 mg	12 months	✓			p = 0.01
			73.5	8.5	N/A	2	10 mg + other antioxidant	0 mg	0 mg		✓			p = 0.04
			76.1	6.4	N/A	placebo	0 mg						✓	p > 0.05
2013	*Murray, I. J., Makridaki, M., Rob L. P. Van Der Veen, Carden, D., Parry, N. R., & Berendschot, T. T. (2013). Lutein Supplementation over a One-Year Period in Early AMD Might Have a Mild Beneficial Effect on Visual Acuity: The CLEAR Study. Investigative Opthalmology & Visual Science, 54(3), 1781.*	72	70.5	8.7	N/A	1	10 mg	0 mg	0 mg	12 months			✓	p > 0.05
						placebo	0 mg					✓		p < 0.05
2015	*Huang, Y., Dou, H., Huang, F., Xu, X., Zou, Z., & Lin, X. (2015). Effect of Supplemental Lutein and Zeaxanthin on Serum, Macular Pigmentation, and Visual Performance in Patients with Early Age-Related Macular Degeneration. BioMed Research International, 2015, 1-8.*	112	69.7	8.3	N/A	1	10 mg	0 mg	0 mg	24 months			✓	p > 0.05
			69.3	6.9	N/A	2	20 mg	0 mg	0 mg				✓	p > 0.05
			68.5	6.9	N/A	3	10 mg	10 mg	0 mg				✓	p > 0.05
			69	7.5	N/A	placebo	0 mg						✓	p > 0.05
Subjects with Age-Related Cataracts														
2003	*Olmedilla, B., Granado, F., Blanco, I., & Vaquero, M. (2003). Lutein, but not α-tocopherol, supplementation improves visual function in patients with age-related cataracts: A 2-y double-blind, placebo-controlled pilot study. Nutrition, 19(1), 21-24.*	17	N/A	N/A	55 - 73	1	10 mg *	0 mg	0 mg	24 months	✓			p < 0.005
						2	0 mg + 100 mg α-tocopherol	0 mg	0 mg				✓	p > 0.05
						placebo	0 mg (placebo)						✓	p > 0.05

Of the 10 studies included, 3 showed improvement (in at least one supplementation group). One study showed improvement in visual acuity for all supplementation groups. This was the Richer et al. (2004) paper, which was conducted with subjects with atrophic age-related

macular degeneration (AMD). This suggests that the improvement in visual acuity observed, while an insignificant increase in healthy patients, was dramatic enough in the atrophic AMD patients that it was significant. Murray et al. (2013) was the only study in the present review to observe a decrease in visual acuity. This study showed that visual acuity of subjects with early AMD in the placebo group deteriorated during the study period, while visual acuity of those in the supplementation group had no change. This suggests that L and Z supplementation may be effective enough to halt the progression of visual acuity decline in AMD patients, even if it is not effective enough to improve visual acuity. Murray et al. (2013) also performed post hoc analysis in which the supplementation and placebo groups were split into subgroups based on visual acuity. The data of the subgroups with visual acuity worse than 20/320 was analyzed and it was found that the supplementation group showed a significant increase in visual acuity, while the placebo group showed no change.

In order to quantitatively summarize the data of Table 1, an association table, Table 2, was constructed and subjected to Fisher's Exact test. This resulted in a *p*-value of 0.043, allowing us to reject the null hypothesis. There is sufficient evidence to say that supplementation improves visual acuity.

Table 2. An association table for the Fisher Exact test analysis of visual acuity data

Visual Acuity		
	Improvement	No Improvement
Supplementation	4	6
Placebo	0	10
	$p = 0.0433$	

Note. Four of the 10 studies showed improvement (including the post hoc analysis done by Murray et al. (2013)). Fisher analysis of this data recommends rejecting the null hypothesis ($p = 0.0433$). It appears that supplementation improves visual acuity.

Contrast Sensitivity

Contrast can be defined by many different terms and formulas (e.g., Michelson contrast, root mean square (RMS) contrast, Weber contrast), and it can be measured in a variety of ways (e.g., the Pelli-Robinson chart, the VectorVision CSV 1000, the Optec500 Vision Tester, the Metropsis Visual Stimulus Generation Device, the CGT-2000). Contrast sensitivity can be measured under different lighting conditions, such as mesopic, photopic, and glare conditions). However, given these differences, most of the studies applied the same basic procedure. The test subject was asked to look at a target of a certain spatial frequency and orientation. The contrast of the target was adjusted until the subject was able to correctly assess the orientation of the target. This then became the threshold contrast and was taken as the subject's contrast sensitivity for that spatial frequency. Ten studies included in this literature review investigated contrast sensitivity.

The summarized results of the studies that assessed the relationship between contrast sensitivity and visual performance are shown in Table 3.

Table 3. Results of studies reviewed that included contrast sensitivity

Contrast Sensitivity														
Year	Study	# Subjects	Age (years)			Subgroups	Lutein Dosage (daily)	Zeaxanthin Dosage (daily)	Meso-Zeaxanthin Dosage (daily)	Study Duration	End of Study Results			
			Mean	SD	Range						Improved	Worsened	No Change	p-value
Healthy Subjects														
2006	*5. Kvansakul, J., Rodriguez-Carmona, M., Edgar, D. F., Barker, F. M., Kopcke, W., Schalch, W., & Barbur, J. L. (2006). Supplementation with the carotenoids lutein or zeaxanthin improves human visual performance. Ophthalmic and Physiological Optics, 26(4), 362-371.*	34	N/A	N/A	18 - 40	1	10 mg, 20 mg after 6 months	0 mg	0 mg	12 months	✓			p = 0.001
						2	0 mg	10 mg , 20 mg after 6 months	0 mg				✓	p > 0.05
						3	10 mg	10 mg	0 mg				✓	p > 0.05
						placebo	0 mg						✓	
2008	*Bartlett, H. E., & Eperjesi, F. (2008). A randomised controlled trial investigating the effect of lutein and antioxidant dietary supplementation on visual function in healthy eyes. Clinical Nutrition, 27(2), 218-227.*	29	50	15.9	22 - 73	1	6 mg	0 mg	0 mg	18 months			✓	p > 0.05
						placebo	0 mg				✓			**
2009	*Ma, L., Lin, X., Zou, Z., Xu, X., Li, Y., & Xu, R. (2009). A 12-week lutein supplementation improves visual function in Chinese people with long-term computer display light exposure. British Journal of Nutrition,102(02), 186. doi:10.1017/s0007114508163000*	37	24.2	1.6	N/A	1	6 mg	0 mg	0 mg	3 months	✓			p < 0.05
			24.2	1.2	N/A	2	12 mg	0 mg	0 mg		✓			p < 0.05
			25.7	2.1	N/A	placebo	0 mg						✓	p > 0.05
2011	*Nolan, J. M., Loughman, J., Akkali, M. C., Stack, J., Scanlon, G., Davison, P., & Beatty, S. (2011). The impact of macular pigment augmentation on visual performance in normal subjects: COMPASS. Vision Research, 51(5), 459-469.*	121	29	7	18 - 41	1	12 mg	1 mg	0 mg	12 months			✓	p > 0.05
						placebo	0 mg						✓	p > 0.05
2012	*Loughman, J., Nolan, J. M., Howard, A. N., Connolly, E., Meagher, K., & Beatty, S. (2012). The Impact of Macular Pigment Augmentation on Visual Performance Using Different Carotenoid Formulations. Investigative Ophthalmology & Visual Science, 53(12), 7871-7880.*	36	51	13	18 - 70	1	20 mg	2 mg	0 mg	6 months	✓			p < 0.05
						2	10 mg	2 mg	10 mg		✓			p < 0.05
						placebo	0 mg						✓	p > 0.05
2013	*Yao, Y., Qiu, Q., Wu, X., Cai, Z., Xu, S., & Liang, X. (2013). Lutein supplementation improves visual performance in Chinese drivers: 1-year randomized, double-blind, placebo-controlled study. Nutrition, 29(7-8), 958-964.*	120	36.5	1.6	25 - 47	1	20 mg	0 mg	0 mg	12 months	✓			p < 0.05
						placebo	0 mg						✓	p > 0.05
2016	*Nolan, J. M., Power, R., Stringham, J., Dennison, J., Stack, J., Kelly, D., . . . Beatty, S. (2016). Enrichment of Macular Pigment Enhances Contrast Sensitivity in Subjects Free of Retinal Disease: Central Retinal Enrichment Supplementation Trials – Report 1. Investigative Opthalmology & Visual Science, 57(7), 3429.*	105	44.83	11.46	N/A	1	10 mg	2 mg	10 mg	12 months	✓			p < 0.02
						placebo	0 mg						✓	p > 0.05
2017	*Stringham, J., Stringham, N., & O'Brien, K. (2017). Macular Carotenoid Supplementation Improves Visual Performance, Sleep Quality, and Adverse Physical Symptoms in Those with High Screen Time Exposure. Foods, 6(7), 47.*	48	21.2	N/A	18 - 25	1	19.9 mg	2.4 mg	1.7 mg	6 months	✓			p = 0.02
						placebo	0 mg						✓	p > 0.05
Subjects with AMD														
2004	*Richer, S., Stiles, W., Statkute, L., Pulido, J., Frankowski, J., Rudy, D., . . . Nyland, J. (2004). Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: The Veterans LAST study (Lutein Antioxidant Supplementation Trial). Optometry - Journal of the American Optometric Association, 75(4), 216-229.*	90	74.4	6.4	N/A	1	10 mg	0 mg	0 mg	12 months	✓			p < 0.05
			73.5	8.5	N/A	2	10 mg + other antioxidants	0 mg	0 mg		✓			p < 0.05
			76.1	6.4	N/A	placebo	0 mg						✓	p > 0.05
2015	*Huang, Y., Dou, H., Huang, F., Xu, X., Zou, Z., & Lin, X. (2015). Effect of Supplemental Lutein and Zeaxanthin on Serum, Macular Pigmentation, and Visual Performance in Patients with Early Age-Related Macular Degeneration. BioMed Research International, 2015, 1-8.*	112	69.7	8.3	N/A	1	10 mg	0 mg	0 mg	24 months	✓			p < 0.05
			69.3	6.9	N/A	2	20 mg	0 mg	0 mg		✓			p < 0.05
			68.5	6.9	N/A	3	10 mg	10 mg	0 mg				✓	p > 0.05
			69	7.5	N/A	placebo	0 mg						✓	p > 0.05

Table 3 reveals a convincing relationship between antioxidant supplementation and improved contrast sensitivity. For healthy subjects, Table 3 suggests that improvements seen in contrast sensitivity are commensurate with dosage. Early studies with relatively low supplementation dosages showed no improvement in CS. Later studies with greater than 12 mg/day of L, Z and/or MZ supplementation showed improvement in CS. However, note that subjects with AMD showed improved CS with relatively small supplementation dosages, possibly because their initial MPOD levels were so low that a small amount of supplementation magnified the effect.

Statistical analysis was performed to confirm a correlation between supplementation and improved CS. Table 4 is the association table constructed for CS data. Fisher's Exact test was performed, resulting in a *p*-value of 0.00027, allowing us to reject the null hypothesis. There is sufficient evidence to say that supplementation improves CS.

Table 4. An association table for the Fisher Exact test analysis of CS data

Contrast Sensitivity		
	Improvement	No Improvement
Supplementation	8	2
Placebo	1	9
	$p = 0.00027$	

Note. Fisher analysis of this data recommends rejecting the null hypothesis ($p = 0.00027$). There is sufficient evidence to suggest that supplementation improves CS.

Photostress Recovery Time

Photostress recovery time is defined as the time taken for visual resolution or sensitivity to return following a bleaching of the photoreceptors. Eight studies included in this literature review investigated photostress recovery time.

Photostress recovery time was measured with relatively the same method in all studies included in this review. However, there was a wide range of differences in terms of brightness, duration of the photostress stimulus, as well as the type of target stimulus used. Brightness ranged from dim to bright, duration of photostress stimulus ranged from 5 seconds to 1 minute, and the target stimulus varied from sine gratings, to lines of print, to flashing targets.

Subjects were first exposed to the photostress stimulus for the study's specified duration. After exposure to the photostress stimulus, subjects were asked to indicate when they were first able to distinguish the target stimulus. The time it took the subject to regain the ability to distinguish the target stimulus was recorded as their photostress recovery time. The results of these eight studies are shown in Table 5.

Table 5. Results of the studies reviewed that included photostress recovery time

Photostress Recovery														
Year	Study	# Subjects	Age (years)			Subgroups	Lutein Dosage (daily)	Zeaxanthin Dosage (daily)	Meso-Zeaxanthin Dosage (daily)	Study Duration	End of Study Results			
			Mean	SD	Range						Improved	Worsened	No Change	p-value
Healthy Subjects														
2008	*Bartlett, H. E., & Eperjesi, F. (2008). A randomised controlled trial investigating the effect of lutein and antioxidant dietary supplementation on visual function in healthy eyes. Clinical Nutrition, 27(2), 218-227.*	29	50	15.9	22 - 73	1	6 mg	0 mg	0 mg	18 months			✓	p > 0.05
						placebo	0 mg						✓	p > 0.05
2011	*Nolan, J. M., Loughman, J., Akkali, M. C., Stack, J., Scanlon, G., Davison, P., & Beatty, S. (2011). The impact of macular pigment augmentation on visual performance in normal subjects: COMPASS. Vision Research, 51(5), 459-469.*	121	29	7	18 - 41	1	12 mg	1 mg	0 mg	12 months			✓	p > 0.05
						placebo	0 mg						✓	p > 0.05
2012	*Loughman, J., Nolan, J. M., Howard, A. N., Connolly, E., Meagher, K., & Beatty, S. (2012). The Impact of Macular Pigment Augmentation on Visual Performance Using Different Carotenoid Formulations. Investigative Ophthalmology & Visual Science, 53(12), 7871-7880.*	36	51	13	18 - 70	1	20 mg	2 mg	0 mg	6 months			✓	p > 0.05
						2	10 mg	2 mg	10 mg				✓	p > 0.05
						placebo	0 mg						✓	p > 0.05
2014	*Hammond, B. R., Fletcher, L. M., Roos, F., Wittwer, J., & Schalch, W. (2014). A Double-Blind, Placebo-Controlled Study on the Effects of Lutein and Zeaxanthin on Photostress Recovery, Glare Disability, and Chromatic Contrast. Investigative Ophthalmology & Visual Science, 55(12), 8583-8589.*	115	23.7	4.61	18.6 - 40.6	1	10 mg	2 mg	0 mg	12 months	✓			p = 0.013
						placebo	0 mg						✓	p > 0.05
2016	*Nolan, J. M., Power, R., Stringham, J., Dennison, J., Stack, J., Kelly, D., . . . Beatty, S. (2016). Enrichment of Macular Pigment Enhances Contrast Sensitivity in Subjects Free of Retinal Disease: Central Retinal Enrichment Supplementation Trials – Report 1. Investigative Opthalmology & Visual Science, 57(7), 3429.*	105	44.83	11.46	N/A	1	10 mg	2 mg	10 mg	12 months			✓	p > 0.05
						placebo	0 mg						✓	p > 0.05
2017	*Stringham, J., Stringham, N., & O'Brien, K. (2017). Macular Carotenoid Supplementation Improves Visual Performance, Sleep Quality, and Adverse Physical Symptoms in Those with High Screen Time Exposure. Foods, 6(7), 47.*	48	21.2	N/A	18 - 25	1	19.9 mg	2.4 mg	1.7 mg	6 months	✓			p = 0.011
						placebo	0 mg						✓	p > 0.05
Subjects with AMD														
2004	*Richer, S., Stiles, W., Statkute, L., Pulido, J., Frankowski, J., Rudy, D., . . . Nyland, J. (2004). Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: The Veterans LAST study (Lutein Antioxidant Supplementation Trial). Optometry - Journal of the American Optometric Association, 75(4), 216-229.*	90	74.4	N/A	6.4	1	10 mg	0 mg	0 mg	12 months			✓	p > 0.05
			73.5	N/A	8.5	2	10 mg + other antioxidant	0 mg	0 mg				✓	p > 0.05
			76.1	6.4	N/A	placebo	0 mg						✓	p > 0.05
2015	*Huang, Y., Dou, H., Huang, F., Xu, X., Zou, Z., & Lin, X. (2015). Effect of Supplemental Lutein and Zeaxanthin on Serum, Macular Pigmentation, and Visual Performance in Patients with Early Age-Related Macular Degeneration. BioMed Research International, 2015, 1-8.*	112	69.7	8.3	N/A	1	10 mg	0 mg	0 mg	24 months	✓			p < 0.05
			69.3	6.9	N/A	2	20 mg	0 mg	0 mg		✓			p < 0.05
			68.5	6.9	N/A	3	10 mg	10 mg	0 mg				✓	p > 0.05
			69	7.5	N/A	placebo	0 mg						✓	p > 0.05

To quantitatively summarize the data of Table 5, an association table, Table 6, was constructed and subjected to Fisher's Exact test. This resulted in a *p*-value of 0.100. This is not less than 0.05, the traditional significance level used for hypotheses tests. However, level of significance, *p*-value, and confidence intervals (CIs) are a function of sample size, with *p*-value increasing (CI widening) with decreasing sample size. Since the sample size in this case is small (8 articles), we can reasonably increase the significance level in this case. Another factor that should be considered in choosing the significance level is the researcher's subjective assessment of the consequences of making a Type I error, that is, rejecting a null hypothesis that is true. In

our case, we need to consider the consequences of stating that supplementation improves vision when it is not the case. Since there was no evidence found in any of the studies that supplementation causes harm to the subjects, the risks associated with making a Type I error are small. Given the small sample size and the minimal risk associated with making a Type I error, it is reasonable to use $\alpha = 0.10$. Therefore, in the case of photostress recovery, we can tentatively reject the null hypothesis and conclude that supplementation likely has a positive effect on photostress recovery.

Table 6. An association table constructed for the Fisher Exact test analysis of photostress recovery data

	Photostress Recovery	
	Improvement	No Improvement
Supplementation	3	5
Placebo	0	8
	$p = 0.1000$	

Note. Fisher analysis of this data recommends rejecting the null hypothesis ($p = 0.1000$). There is sufficient evidence to suggest that supplementation improves photostress recovery.

Glare Disability

Glare is the sensation produced by luminance within the visual field that is sufficiently greater than the luminance to which the eyes are adapted to cause annoyance, discomfort, or loss in visual performance and visibility (Nadler, Miller, & Nadler, 1990). Glare disability is the loss in visual performance caused by glare. Five studies investigated glare disability.

Glare disability was measured using a variety of techniques (e.g., the brightness acuity test (BAT), the Functional Vison Analyzer, the CGT-2000 Contrast Glaretester, and some custom-made apparatuses). The procedures for all of the studies were similar and generally conformed. Target stimuli surrounded by a glare source were presented to the subject. Glare was adjusted, either by the subject or the experimenter, until the target could no longer be discerned. Glare disability was calculated as the glare and contrast at which a target stimuli was no longer detectable.

The results of the studies that investigated supplementation and glare disability are displayed in Table 7.

Table 7. Results of the studies reviewed that included glare disability

Glare Disability														
Year	Study	# Subjects	Age (years)			Subgroups	Lutein Dosage (daily)	Zeaxanthin Dosage (daily)	Meso-Zeaxanthin Dosage (daily)	Study Duration	End of Study Results			
			Mean	SD	Range						Improved	Worsened	No Change	p-value
Healthy Subjects														
2009	*Ma, L., Lin, X., Zou, Z., Xu, X., Li, Y., & Xu, R. (2009). A 12-week lutein supplementation improves visual function in Chinese people with long-term computer display light exposure. British Journal of Nutrition,102(02), 186. doi:10.1017/s0007114508163000*	37	24.2	1.6	N/A	1	6 mg	0 mg	0 mg	3 months			✓	p > 0.05
			24.2	1.2	N/A	2	12 mg	0 mg	0 mg				✓	p > 0.05
			25.7	2.1	N/A	placebo	0 mg						✓	p > 0.05
2011	*Nolan, J. M., Loughman, J., Akkali, M. C., Stack, J., Scanlon, G., Davison, P., & Beatty, S. (2011). The impact of macular pigment augmentation on visual performance in normal subjects: COMPASS. Vision Research, 51(5), 459-469.*	121	29	7	18 - 41	1	12 mg	1 mg	0 mg	12 months			✓	p > 0.05
						placebo	0 mg						✓	p > 0.05
2013	*Yao, Y., Qiu, Q., Wu, X., Cai, Z., Xu, S., & Liang, X. (2013). Lutein supplementation improves visual performance in Chinese drivers: 1-year randomized, double-blind, placebo-controlled study. Nutrition, 29(7-8), 958-964.*	120	36.5	1.6	25 - 47	1	20 mg	0 mg	0 mg	12 months	✓			p < 0.05
						placebo	0 mg						✓	p > 0.05
2014	*Hammond, B. R., Fletcher, L. M., Roos, F., Wittwer, J., & Schalch, W. (2014). A Double-Blind, Placebo-Controlled Study on the Effects of Lutein and Zeaxanthin on Photostress Recovery, Glare Disability, and Chromatic Contrast. Investigative Ophthalmology & Visual Science, 55(12), 8583-8589.*	115	23.7	4.61	18.6 - 40.6	1	10 mg	2 mg	0 mg	12 months			✓	p = 0.21
						placebo	0 mg						✓	p > 0.05
2017	*Stringham, J., Stringham, N., & O'Brien, K. (2017). Macular Carotenoid Supplementation Improves Visual Performance, Sleep Quality, and Adverse Physical Symptoms in Those with High Screen Time Exposure. Foods, 6(7), 47.*	48	21.2	N/A	18 - 25	1	19.9 mg	2.4 mg	1.7 mg	6 months	✓			p = 0.021
						placebo	0 mg						✓	p > 0.05
Subjects with Age-Related Cataracts														
2003	*Olmedilla, B., Granado, F., Blanco, I., & Vaquero, M. (2003). Lutein, but not α-tocopherol, supplementation improves visual function in patients with age-related cataracts: A 2-y double-blind, placebo-controlled pilot study. Nutrition, 19(1), 21-24.*	17	N/A	N/A	55 - 73	1	10 mg *	0 mg	0 mg	24 months			✓	p > 0.05
						2	0 mg + 100 mg α-tocopherol	0 mg	0 mg				✓	p > 0.05
						placebo	0 mg						✓	p > 0.05

To quantitatively summarize the data of Table 7, an association table, Table 8 was constructed and subjected to Fisher's Exact test. This resulted in a *p*-value of 0.500; the null hypothesis is retained. There is not sufficient evidence to say that supplementation improves glare disability.

Table 8. An association table for the Fisher Exact analysis of the glare disability data

Glare Disability		
	Improvement	No Improvement
Supplementation	1	5
Placebo	0	6
	$p = 0.5000$	

Note. Fisher analysis of this data recommends retaining the null hypothesis ($p = 0.5000$). There is not sufficient evidence to suggest that supplementation improves glare disability.

Vision Related Quality of Life

Vision Related Quality of Life (QOL) refers to the self-assessment of visual performance and is a subjective metric. Since 2004, we found 4 studies that looked at the relationship between supplementation and QOL. Vision related QOL was quantified using the National Eye Institute Visual Functioning Questionnaire 25 (NEI-VFQ-25) in Yao et al. (2013) and Huang et al. (2015). Nolan et al. (2011) devised their own non-validated visual function in normals questionnaire, and Richer et al. (2004) used a 4- to 20-point VFQ-14 rating system used by the National Eye Institute. Table 9 summarizes the results of the studies that involved vision related QOL results.

Table 9. Results of the studies reviewed that included vision related quality of life

Vision Related Quality of Life														
Year	**Study**	**# Subjects**	**Age (years)**			**Subgroups**	**Lutein Dosage (daily)**	**Zeaxanthin Dosage (daily)**	**Meso-Zeaxanthin Dosage (daily)**	**Study Duration**	**End of Study Results**			
			Mean	**SD**	**Range**						**Improved**	**Worsened**	**No Change**	**p-value**
Healthy Subjects														
2011	*Nolan, J. M., Loughman, J., Akkali, M. C., Stack, J., Scanlon, G., Davison, P., & Beatty, S. (2011). The impact of macular pigment augmentation on visual performance in normal subjects: COMPASS. Vision Research, 51(5), 459-469.*	121	29	7	18 - 41	1	12 mg	1 mg	0 mg	12 months	✓			$p < 0.03$
						placebo	0 mg						✓	$p > 0.05$
2013	*Yao, Y., Qiu, Q., Wu, X., Cai, Z., Xu, S., & Liang, X. (2013). Lutein supplementation improves visual performance in Chinese drivers: 1-year randomized, double-blind, placebo-controlled study. Nutrition, 29(7-8), 958-964.*	120	36.5	1.6	25 - 47	1	20 mg	0 mg	0 mg	12 months	✓			$p < 0.05$
						placebo	0 mg						✓	$p > 0.05$
Subjects with AMD														
2004	*Richer, S., Stiles, W., Statkute, L., Pulido, J., Frankowski, J., Rudy, D., . . . Nyland, J. (2004). Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: The Veterans LAST study (Lutein Antioxidant Supplementation Trial). Optometry - Journal of the American Optometric Association, 75(4), 216-229.*	90	74.4	6.4	N/A	1	10 mg	0 mg	0 mg	12 months			✓	$p > 0.05$
			73.5	8.5	N/A	2	10 mg + other antioxidant	0 mg	0 mg				✓	$p > 0.05$
			76.1	6.4	N/A	placebo	0 mg						✓	$p > 0.05$
2015	*Huang, Y., Dou, H., Huang, F., Xu, X., Zou, Z., & Lin, X. (2015). Effect of Supplemental Lutein and Zeaxanthin on Serum, Macular Pigmentation, and Visual Performance in Patients with Early Age-Related Macular Degeneration. BioMed Research International, 2015, 1-8.*	112	69.7	8.3	N/A	1	10 mg	0 mg	0 mg	24 months			✓	$p > 0.05$
			69.3	6.9	N/A	2	20 mg	0 mg	0 mg				✓	$p > 0.05$
			68.5	6.9	N/A	3	10 mg	10 mg	0 mg		✓			$p < 0.01$
			69	7.5	N/A	placebo	0 mg						✓	$p > 0.05$

To quantitatively summarize the data of Table 9, an association table, Table 10, was constructed and subjected to Fisher's Exact test. This resulted in a *p*-value of 0.2143; the null hypothesis is retained. There is not sufficient evidence to say that supplementation improves quality of life.

Table 10. An association table for the Fisher Exact analysis of quality of life data

Quality of Life		
	Improvement	No Improvement
Supplementation	2	2
Placebo	0	4
	$p = 0.2143$	

Note. Fisher analysis of this data recommends retaining the null hypothesis ($p = 0.2143$). There is not sufficient evidence to suggest that supplementation improves quality of life.

Color Vision

Two studies examined the relationship between color vision and supplementation using different methodology. Rodriguez-Carmona et al. (2006) determined color discrimination thresholds using the Color Assessment and Diagnosis (CAD) test. Hammond et al. (2014) studied chromatic contrast, which was determined using a Maxwellian-view optical system. The results of these studies are shown in Table 11.

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Table 11. Results of the studies reviewed that included color vision and critical flicker frequency threshold

Color Vision														
Year	Study	# Subjects	Age (years)			Subgroup Name	Lutein Dosage (daily)	Zeaxanthin Dosage (daily)	Meso-Zeaxanthin Dosage (daily)	Study Duration	End of Study Results			
			Mean	SD	Range						Improved	Worsened	No Change	p-value
Healthy Subjects														
2005	*Rodriguez-Carmona, M., Kvansakul, J., Harlow, J. A., Kopcke, W., Schalch, W., & Barbur, J. L. (2005). The effects of supplementation with lutein and/or zeaxanthin on human macular pigment density and colour vision. Ophthalmic and Physiological Optics, 26(2), 137-147.*	92	N/A	N/A	22 - 39	1	10 mg in first six months, then 20mg after 6 months.	10 mg in first six months, then 20mg after 6 months.	0 mg	16 months			✓	p > 0.05
						placebo	0 mg						✓	p > 0.05
2014	*Hammond, B. R., Fletcher, L. M., Roos, F., Wittwer, J., & Schalch, W. (2014). A Double-Blind, Placebo-Controlled Study on the Effects of Lutein and Zeaxanthin on Photostress Recovery, Glare Disability, and Chromatic Contrast. Investigative Ophthalmology & Visual Science, 55(12), 8583-8589.*	115	23.7	4.61	18.6 - 40.6	1	10 mg	2 mg	0 mg	12 months	✓			p = 0.03
						placebo	0 mg						✓	p > 0.05
Critical Flicker Fusion Threshold (CFF)														
Year	Study	# Subjects	Age (years)			Subgroups	Lutein Dosage (daily)	Zeaxanthin Dosage (daily)	Meso-Zeaxanthin Dosage (daily)	Study Duration	End of Study Results			
			Mean	SD	Range						Improved	Worsened	No Change	p-value
Healthy Subjects														
2017	*Stringham, J., Stringham, N., & O'Brien, K. (2017). Macular Carotenoid Supplementation Improves Visual Performance, Sleep Quality, and Adverse Physical Symptoms in Those with High Screen Time Exposure. Foods, 6(7), 47.*	48	21.2	N/A	18 - 25	1	19.9 mg	2.4 mg	1.7 mg	6 months	✓			p < 0.001
						placebo	0 mg						✓	p > 0.05

Rodriguez-Carmona et al. (2006) found no improvement in color vision with supplementation, while Hammond et al. (2014) found significant improvement.

To quantitatively summarize the data of Table 11, an association table, Table 12, was constructed and subjected to Fisher's Exact test. This resulted in a *p*-value of 0.500; the null hypothesis is retained. There is not sufficient evidence to say that supplementation improves color vision.

Table 12. An association table for the Fisher Exact analysis of color vision data

Color Vision		
	Improvement	No Improvement
Supplementation	1	1
Placebo	0	2
	$p = 0.5000$	

Note. Fisher analysis of this data recommends retaining the null hypothesis ($p = 0.5000$). There is not sufficient evidence to suggest that supplementation improves color vision.

Critical Flicker Fusion Frequency Threshold

The critical flicker fusion frequency (CFF) threshold is defined as the frequency at which a flickering light is indistinguishable from a steady, non-flickering light (Wells et al., 2001). There was only one study, Stringham et al. (2017), that assessed CFF.

To assess CFF, subjects were shown a short-wavelength, flickering stimulus. The presentation rate (flicker frequency) of the stimulus, delivered in square wave alternation (the light had 100% contrast between lightest and darkest and was merely turned on and off), was varied by the experimenter until the subject could no longer discern flickering (complete flicker fusion). This was taken as the subject's CFF threshold.

The results of Stringham et al. (2017) are shown in Table 11. This study found that supplementation with 24 mg of MP antioxidants over 6 months led to an improvement in CFF. This finding is promising and merits further investigation since this is the only placebo-controlled supplementation study thus far to examine CFF in relation to L, Z, and/or MZ supplementation.

To quantitatively summarize the data of Table 11, an association table for CFF, Table 13, was constructed and subjected to Fisher's Exact test. This resulted in a *p*-value of 0.500; the null hypothesis is retained. There is not sufficient evidence to say that supplementation improves CFF. However, note that this insignificant conclusion stems primarily from the fact that there was only one study performed.

Table 13. An association table for the Fisher Exact analysis of CFF data

CFF		
	Improvement	No Improvement
Supplementation	1	0
Placebo	0	1
	$p = 0.5000$	

Note. Fisher analysis of this data recommends retaining the null hypothesis ($p = 0.5000$).

Discussion

The ability to perform well under most conditions is dependent on the ability to see well under those same conditions. Thus, the benefits of having good visual performance often extend into good overall performance. It is important to note that good visual performance is more than just good visual acuity (i.e., seeing 20/20+). It is also the ability to perceive objects under low lighting and/or under low contrast conditions (such as fog or smog), the ability to quickly light- and dark-adapt to differing lighting conditions (such as moving from outdoor to indoor conditions), the ability to discriminate colors, and the ability to see through and/or tolerate glare (such as when driving or flying on sunny days). An inability to perform well under these adverse conditions can often lead to disastrous outcomes. Unfortunately, the military's helicopter crash rates over the past several wars in the Middle East illustrate this link between visual performance and overall performance. In these conflicts, it was found that just under half of rotary-wing

aircraft fatalities occurred in degraded visual environments whereby the aviator's visual perception was challenged and thus performance was degraded (Edens & Higginbotham, 2014). It can be hypothesized that had the aviators had better visual performance under these conditions, some of these outcomes could have been averted. From a preventative medicine perspective, the question then becomes, could the aviators' visual performance been improved and how could the improvement been achieved? Enter the antioxidant supplementation studies. Over the past several decades, there have been an abundance of studies on the benefits of antioxidants. However, after a careful literature search using our inclusion selection criteria, we were able to identify only 14 studies that investigated the connection between antioxidant supplementation and visual performance.

Within these studies we found three promising trends: visual acuity, CS, and photostress recovery all showed a tendency to improve with supplementation. On the other hand, glare disability, quality of life, color vision, and CFF showed no improvement, had inconclusive results, or had insufficient evidence to conclude. When we consider the mechanism of action of MP, these results can be explained. Macular pigment has two defining characteristics, which are also the mechanisms by which it might improve visual performance. First, it selectively filters short-wavelength light (the high energy portion of visible light), thereby improving visual performance by decreasing glare and scatter. Second, it is an antioxidant, which is theorized to reduce oxidative stress, improving the efficiency of the visual system.

Improvements in photostress recovery time are likely attributable to the filtering qualities of macular pigment, according to Stringham et al. (2017). Improvements seen in visual acuity and CS are likely attributable to both mechanisms of MP. Loughman et al. (2012) points out that visual acuity and CS depend on short wavelength glare phenomena and neurophysiologic aspects of vision. In other words, as Nolan et al. posit, improvements in CS could be the result of either MP's pre-receptoral filtering properties, or its antioxidant properties in action post-receptorally. Nolan et al. predict the latter is more likely because filtration would affect dark and light bars equally, thus not aiding in perceiving differences between them. Stringham et al. (2017) and Loughman et al. (2012) concur with this reasoning.

Improvements in visual acuity and CS caused by MP could be beneficial in everyday life. These two aspects of visual performance are vital to everyday tasks, like reading, driving, etc. Improvements in visual acuity and CS, or the maintenance of these aspects of visual performance, as seen in Murray et al. (2013), with the use of L, Z, and/or MZ supplementation has implications for productivity, safety, and quality of life.

Supplementation with Combinations of Lutein, Zeaxanthin, and Meso-Zeaxanthin

The studies detailed in this literature review vary in the combinations of L, Z, and/or MZ provided in their supplementation. This is because it has not yet been established what formulation of these ocular antioxidants is most beneficial to eye health and performance. It is important to note that antioxidants L, Z, and MZ are isomers, and that L can be isomerized into MZ. Furthermore, the three antioxidants tend to accumulate in different parts of the macula – L accumulates in the periphery, while Z and MZ accumulate foveally (Nolan et al., 2016). These properties of L, Z, and MZ are important considerations in formulating an ocular antioxidant supplement.

Toxicity

Supplementation with L, Z, and/or MZ has been investigated in placebo-controlled studies for about 15 years, and it appears these supplementations have no detrimental effects – none of the articles included in the present review showed decreases in visual performance, nor did they show any adverse effects. Additionally, toxicity studies of L, Z, and/or MZ using extraordinarily high dosages have found no harmful reactions. In one study using Wistar rats, the highest tested dosage level (400 mg/kg body weight/day) showed no observed adverse effect (Ravikrishnan et al., 2011). It is worth nothing that this dosage level is analogous to an 80kg adult taking over 1000 times the standard dosage in a single day, which is over 3 years' worth of supplements per day. Also, L and Z have also been given GRAS status by the U.S. Food and Drug Administration as food additives (GRAS Notices).

Conclusions

This systematic literature review has compiled the evidence and conclusions of the placebo-controlled L, Z, and/or MZ supplementation studies investigating human visual performance. We tentatively conclude that visual acuity, CS, and photostress recovery can be reasonably expected to improve with supplementation of L, Z, and/or MZ. In contrast, glare disability, quality of life, color vision, and CFF seem not to react to as well to the same supplementation. However, we recommend further research to solidify these conclusions. Specifically, we recommend several areas of potential future research: 1) CFF has been studied in only one placebo-controlled supplementation study (Stringham, Stringham, & O'Brien, 2017) , whereby CFF improved with supplementation. While this one study's conclusion was compelling, verification studies should be performed before final appraisal. 2) Color vision also merits further investigation, as the two studies included in this review had conflicting conclusions. 3) We recommend that placebo-controlled supplementation studies using L, Z, and/or MZ that test tasks such as marksmanship, aviation performance in degraded visual environments, vehicle operation, operations using night vision goggles, cognitive performance, and sleep quality, be performed. These studies would offer important practical information in deciding whether or not to incorporate L, Z, and/or MZ into military nutritional recommendations

Humans are expected to perform efficiently and effectively in a variety of degraded visual environments, such as dawn, dusk, rain, fog, and other sub-optimal visual conditions. Synthesizing the data collected in this systematic review, it suggests that humans could benefit from L, Z, and/or MZ supplementation in improving their visual performance under these austere visual conditions and possibly others. Depending on each person's baseline ocular health and physiology, the scale of improvement from supplementation varies. For example, night operations could be facilitated by improved CS and improved photostress recovery. Marksmanship could benefit from improved CS and glare disability. Driving performance could be improved with reduction in glare disability and improved photostress recovery time from oncoming lights. Aviator visual performance could be improved with increased ability to detect changes in contrast, particularly in low lighting.

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