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Review

Effect of macular pigment carotenoids on cognitive functions: A systematic review

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ABSTRACT

Lutein and zeaxanthin—xanthophyll carotenoids with antioxidant and anti-inflammatory characteristics—are present in the retina and the brain. High concentrations of these carotenoids have been positively related to cognitive performance. Therefore, this systematic review analyses the relationship between macular pigment density and cognitive functions.

Most relevant databases were scoured for studies on healthy people relating cognitive functions to macular pigment optical density (MPOD). There were no age, sex, or race limitations. PROSPERO registration: CRD42021254833.

Nineteen studies were included, seven randomized controlled trials (RCT) and eleven observational studies. The general aim of the studies was to examine the association between carotenoids (lutein, meso-zeaxanthin and zeaxanthin) and cognitive function. Most observational studies correlates MPOD levels with cognitive function or brain activity. Besides, RCTs compared the cognitive function and/or brain activity after increasing lutein and zeaxanthin intake though dietary supplementation or avocado consumption. Dietary lutein and zeaxanthin intake increased MPOD in six of the seven clinical trials and significantly improved most of the cognitive functions studied. A wide variety of test and methodologies for measuring cognitive functions were observed. Memory, processing speed, attention and reasoning were the cognitive function significantly related to MPOD levels in adults. Brain activity also was related to MPOD, but the results were inconsistent. Only four of the eleven observational studies were based on young people and all studies showed a significant relationship between MPOD and cognitive functions.

This systematic review showed a direct relationship among cognitive functions, macular pigment and the intake of lutein and zeaxanthin.

1. Introduction

Carotenoids are natural plant pigments commonly found in human diet, mainly in green leafy vegetables, bright-coloured fruits and eggs [1]. Lutein (L) and zeaxanthin (Z) are oxygenated carotenoids or xanthophylls, which are accumulated in the macula lutea, a 5–6mm-diameter area of the retina responsible for central vision [2]. Unlike L and Z, which are entirely of dietary origin, meso-zeaxanthin (MZ) is formed in the macula from L in a 1:1 ratio [3]. L, Z, and MZ are collectively referred to as macular pigment (MP) and protect the retina from short-wavelength blue light and oxidative stress [4].

Higher intake of these nutrients, either through diet or

Abbreviations: AD, Alzheimer's disease; AMD, age-related macular degeneration; BIA, brief intellectual ability; BVRT, Benton Visual Retention Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; CF, cognitive functions; CNS, central nervous system; CNSVS, CNS Vital Signs; FCSRT, Free and Cued Selective Reminding Test; IQ, Intelligent quotient; IST 15, Isaacs Set Test; KBIT-2, Kaufman Brief Intelligence Test Second Edition; K-TEA, Kaufman Test of Educational Achievement; L, Lutein; MP, macular pigment; MPD, macular pigment density; MPOD, macular pigment optical density; MZ, meso-zeaxanthin; PS, Processing Speed; RCI, Reliable Change Index; RCT, Randomised Controlled Trials; WJ-III, Woodcock-Johnson III; WTAR, Wechsler Test of Adult Reading; Z, zeaxanthin.

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supplementation, has been associated with an increase in MP [5]. There is evidence that they may improve vision in individuals with the early form of age-related macular degeneration (AMD) [6]—a leading cause of vision-loss among older adults—and retard the progression of this disease [7].

IBased on our understanding of how L and Z benefit neural health of the retina, these carotenoids may prevent age-related cognitive decline, mainly with the areas of spatial memory, reasoning, complex attention and attributable also to young and pediatric people through their strong antioxidant and anti-inflammatory properties [8-10]. The retina is a component of the central nervous system (CNS), where carotenoids are found in the hippocampus, the occipital lobe, and the frontal cortex of the brain [11]. This knowledge has stimulated research on their potential cognitive benefits. A growing body of literature indicates that in older adults, MP positively correlate with a range of cognitive functions (CF), including visuospatial skills, learning, memory, language abilities, executive functions, processing speed, and global cognition [12,13], which are affected by dietary habits and nutrition [14]. There is also a corpus of evidence suggesting that good nutrition is important for optimal cognition [15], and it is also associated with a reduced risk of Alzheimer's disease (AD)—the most common form of dementia—in later life [16].

To assess cognitive performance in individuals, a variety of cognitive batteries or assessments are employed, such as the Cambridge Neuropsychological Test Automated Battery (CANTAB) [17]—one of the most widely used— or the Woodcock-Johnson III (WJ-III), which is a set of standardised tests of cognitive skills, such as short intellectual ability, verbal ability, cognitive efficiency, processing speed, and decisional performance processes [18].

At least two of the three macular carotenoids are found in the brain [19] in concentrations proportional to that in the retina [20]. Therefore, macular pigment density (MPD) likely reflects L and Z brain concentrations. Given that concentration levels of these carotenoids relate positively to cognitive performance in both cognitively impaired [21] and cognitively intact individuals [22], the potential role of these dietary compounds (L and Z) in optimizing and maintaining cognition warrants study [23]. This may explain the epidemiological evidence of a significant relationship between MPOD and cognitive health in two cross-sectional studies [21,24]. So, MPOD could likely be just a biomarker for the effects of L-Z in brain. While it is true that the underlying mechanisms in vivo of L-Z in the brain are unclear, there are different possibilities about the mechanism that may influence latent physio-neurological mechanisms in cognitive or visual functions. A presumed indicator is increased brain perfusion in prefrontal regions, improving the potential neuronal mechanism over the course of cognitive performance. Another could be related to pathologies that may affect the brain such as oxidative, inflammatory or cardiometabolic stress [25]. This study analyses the relationship between MPD and cognitive capacity in healthy people, based on the scientific evidence presented in previous research, employing a systematic review.

2. Experimental section

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations [26] and was registered with the PROSPERO International Prospective Registry (record CRD42021254833).

2.1. Search strategy

A systematic search based on population, intervention, comparison, and outcome strategy was performed between 1 December 2020 and 1 February 2021. The study population consisted of healthy individuals (non-AMD), without restriction by age, gender, or weight. Intervention with L and/or Z through diet and/or dietary supplementation was evaluated and compared to placebo groups. The relationship between macular pigment optical density (MPOD) and CF was investigated.

Three databases namely, PubMed, Scopus, and Web of Science were scoured for articles published between 1 November 2015 and 1 January 2021. The following search terms were used: macular pigment, lutein, zeaxanthin, xanthophyll, carotenoids, cognition function, neural efficiency, memory, cognition diseases, intellectual ability, cognitive performance, and neurocognitive functioning. Considering the format differences for each database, the combination of keywords was the same in all of them: (Macular pigment OR MPOD OR Lutein OR Zeaxanthin OR carotenoids OR xanthophyll) AND (cognition function OR Neural Efficiency OR Memory OR cognition diseases OR intellectual ability OR cognitive performance OR Neurocognitive Functioning).

2.2. Study selection

The studies were evaluated by two independent reviewers and any disagreement was resolved by a third reviewer.

First, studies searched were imported to Mendeley and duplicates were removed. Later, titles and abstracts were evaluated according to inclusion and exclusion criteria. Finally, full texts identified were screened.

2.3. Inclusion and exclusion criteria

Inclusion criteria: (1) scientific articles with experimental studies (clinical trials) and observational studies (cross-sectional, case-control, cohort study designs) published in peer-review journals; (2) human studies; (3) MPOD and CF should be studied; and (4) dietary supplementation with L and/or Z as intervention.

Exclusion criteria: (1) studies without MP or cognitive function analysis; (2) studies of psychosis and mental illness; (3) studies of possibility or risk of developing AD and dementia; and (4) animal trials.

2.4. Data analysis and study quality

Two reviewers performed data analysis and study quality assessment independently. A third reviewer was consulted when disagreements arose.

Recorded data included: (1) study design (type, purpose, duration); (2) inclusion and exclusion criteria; (3) sample characteristics, including age, race, and body mass index (BMI); (4) sample size (number of patients, percentage of males, groups); (5) MPOD assessment (basal value, change post-treatment); (6) L and Z concentrations in blood serum (basal value, change post-treatment); (7) CF evaluation (cognitive test battery, task for calculating the index score); and (8) relationship between MPOD and CF. The data were expressed as mean±SD.

Studies based on children and pre-adolescents were analysed separately from studies on adults (that is, studies on people more than 18 years of age). A qualitative synthesis of the results was performed to determine the relationship between MPOD and CF. The impact of carotenoid supplementation was evaluated first on MPOD and then on brain activity and/or cognitive ability. We considered $p < 0.05$ as statistically significant.

The quality of studies was evaluated using the National Institutes of Health (NIH)'s tool for 'Quality Assessment of Controlled Intervention Studies' and the 'Quality Assessment Tool for Observational Cohort and Cross-sectional Studies' [27]. Studies with low, medium and high risks of bias were considered of good, fair and poor qualities, respectively.

3. Results

3.1. Flow diagram

Fig. 1 shows the selection process in this systematic review and Table 1 presents the characteristics of both the samples and the studies included.

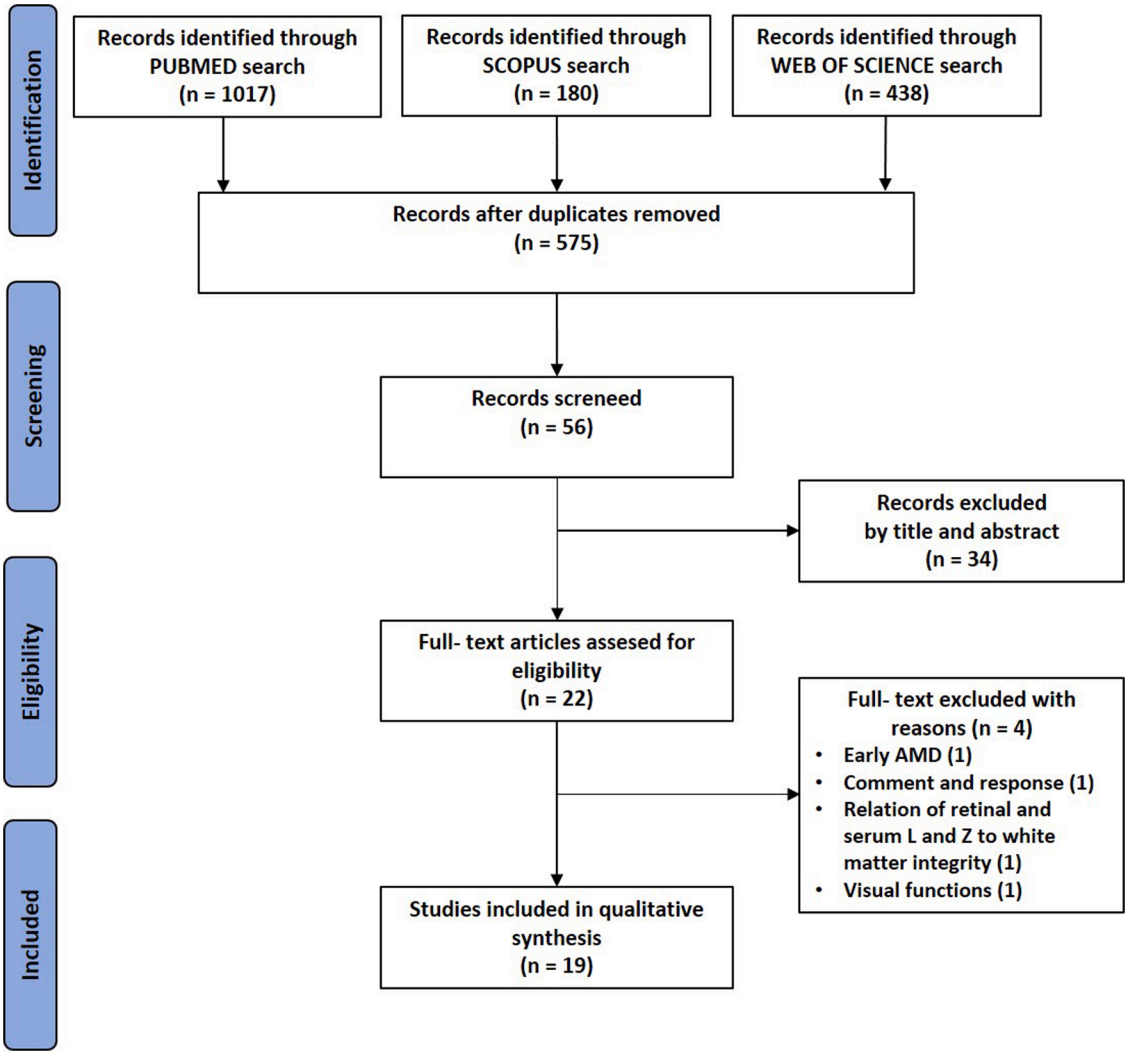

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram for this systematic review [26].

3.2. Characteristics of the studies included and their sample

Nineteen studies were included in this systematic review (Table 1). A total of 1371 subjects (19.39% [35] –57% [29] male) were analysed, of whom, 420 were participants in clinical trials (active groups: $n = 264$; control group: $n = 156$) [11,23,28–32]. The age range of the sample was from 7 to 86 years. Four studies included only children, aged between 7 and 13 years [18,33–35]; two studies analysed young adults, that is, those aged between 18 and 30 years [28,29]; five studies selected adults aged between 25 and 45 years [31,36–39]; and six included older adults [11,24,32,40,41]

Race was reported in seven studies, with 88.19% being Caucasian; 3.77% Asian; 0.86% Hispanic; 3.99% African–American or Black; and 3.15% of other races [18,24,29,32,39,41,42]. The BMI $\geq$ 25.0 kg/m^2 or obesity was the inclusion criterion in four studies [31,36,37,39].

The general objective of the studies analysed was to examine the association between carotenoids (L, MZ, and Z) and CF (Table 1).

All studies correlated MP levels with CF [11,18,23,24,28–31,33–40] or brain activity [32,41,42]. Clinical trials compared CF after increasing carotenoids intake through dietary supplementation [11,23,28,29] or avocado consumption [30,31]. In the RCT conducted by Scott et al. [28] subjects in the treatment group ingested 0.40 $\pm$ 0.01 mg/100 g (edible portion) of lutein respect to $<$ 0.1 mg in the control group. In the RCT conducted by Edwards et al. [29] the lutein/zeaxanthin content was 3 times higher in the intervention meals as it was in the control meals (treatment group Female: 561 mcg, Male: 701mcg; control group Female: 164 mcg, Male: 205mcg).

3.3. MPOD

MPOD was measured by heterochromatic flicker photometry at 0.5° of retinal eccentricity in most of the analysed studies [11,18,24,28–31,33–37,39,41]. Only two studies measured MP by dual-wavelength auto-fluorescence method [23,40]. Ajana et al. measured MPOD at 0.5° and 1° eccentricity [40], while Power et al. showed MP volume out to 7° eccentricity [23]. Table 2 shows MPOD data.

The MPOD at 0.5° eccentricity [11,18,36,37,39–41,24,28–31,33–35] ranged from 0.34 [24] to 0.70 [40]. The studies with pediatric population showed a mean MPOD of 0.598 $\pm$ 0.08 (ranging from 0.48 to 0.66) [18,33–35], and the studies with adult population showed a mean MPOD of 0.472 $\pm$ 0.08 (ranging from 0.38 to 0.70) [11,28–31,36–42].

The effect of dietary xanthophyll supplementation on MPOD was analysed in five studies [11,28–31].

An active supplement containing 10 mg L and 2 mg Z (DSM Nutritional Product, Kaiseraugst, Switzerland) was used in 2 studies for 12-months [11,29]. The authors found a significant increase in MPOD in both older [11] and younger [29] adults. Stringham et al. used two amounts of daily macular Xanthophyll supplements (a 13 mg supplement containing 10.86 mg L and 2.27 mg Z isomers versus a 27 mg supplement containing 22.33 mg L and 4.70 mg Z) for 6-months in

Table 1
Types of included studies and characteristics of their samples.

First author, year	Study Desing, Duration (months)	Inclusion Criteria	Exclusion Criteria	Purpose of study	Sample size (*n* (% male)) Groups: n	Age (mean ± SD)	Race (n)	BMI (kg/m2) (mean ± SD)
Saint, 2018	Observational study (Cross-sectional)	7–13 years of age	NR	Relationship between MPOD to CF	51 (51%)	9.14 (± 1,86)	White (Non-Hispanic) (39) Hispanic (1) >1 Race Listed (11)	NR
Barnett, 2018	Observational study (Cross-sectional)	Normal VA or CVA	ND, PD and psychoactive medication status.	Relationship between L and Z intake, MPOD values to academic performance	56 (30%)	8.8 (± 0,1)	NR	18.7 ± 0.4
Hassevoort, 2017	Observational study (Cross-sectional)	Fitness Improves Thinking in Kids (FITKids) Trial (ClinicalTrials.gov: NCT01619826)	ND or AD, PD and psychoactive medication status	Relationship between MPOD, aerobic fitness, and central adiposity to memory	40 (37%)	8.8 (± 0.11)	NR	19.0 ± 0.50
Walk, Khan, et al., 2017	Observational study (Cross-sectional)	Completed two pre-testing sessions	≤60% correct on flanking trials	Relationship between MPOD to CF	49 (19.39%)	8.69 (± 0.08)	NA	NA
Stringham, 2019	Controlled-trial. Double-blind. Randomised. (6-month)	Healthy students at the University of Georgia, non-smokers, with UCVA or CVA ≥ 20/20 and no history of OP	Current or previous supplementation with L and/or Z	Relationship between dietary carotenoids to CF	59 (45.8%) Placebo: 10 13 mg: 24 27 mg: 25	21,5	NR	18.5–27
Hammond, 2017	Controlled-trial. Double-blind. Randomised. (12-month)	Good overall health; no xanthophyll supplementation in the previous 6 months; BCVA ≥ 20/40; no ND to impair CF; absence of GC to impair absorption of NS	NR	Relationship between *L* + *Z* supplementation to CF in older adults.	51 (41,18%) Active: 36 Placebo: 15	Total: 73.74 (± 8.20) Active:72.51 (± 6.24) Placebo: 70.93 (± 5.70)	NR	NR
Renzi-Hammond, 2017	Controlled-trial. Double-blind. Randomised. (12-months)	Good overall and ocular health, BCVA≥20:40 and no NS use in the previous six months	NA	Relationship between *L* + *Z* supplementation to CF in young, healthy adults	51 (57%) Active: 37 Placebo: 14	21.21 (±2.52) Active:NR Placebo: NR	White (40), Black (6) Pan-Asian (3) Latino (2)	NR
Scott, 2017	Controlled-trial. Randomised. (6-month)	Low intakes of lutein-rich foods	History of liver, kidney or pancreatic disease; anemia; active bowel disease or resection; bleeding disorders; some food allergies; Some medications	Relationship between intake of avocado to cognition	40 (37.5%) Active: 20 Placebo: 20	Active: 63.3 (±11.1) Placebo: 62.5 (±9.2)	NR	Active: 24.15 ± 3.86 Placebo: 23.03 ± 3.98
Power, 2018	Controlled-trial. Double-blind. Randomised. (12-months)	Low MP; ≥18 years; BCVA ≥ 6/6; ≤ 5 D of SE; no DM; no ocular pathology; and no previous consumption of NS with L and/or Z and/or MZ	NR	Relationship between *L* + *Z* supplementation to CF in healthy individuals with low MP levels	91 (51.6%) Active: 45 Placebo: 46	45.42 (± 12.40)	NR	Active: 27.34 ± 4.72 Placebo: 26.22 ± 4.67
Edwards, 2020	Controlled-trial. Randomised. (12-week)	Aged 25–45 years with a BMI ≥ 25.0 kg/m2	BMI < 25 kg/m2, pregnancy or lactation, history of ND or MD, non-normal VA and food allergies or intolerances	Relationship between avocado consumption to CF in overweight and obesity adults	84 (43%) Active: 47 Placebo: 37	Placebo: 34.0 (±6.2) Active: 34.6 (±5.7)	NR	Control goup: 31.31 ± 5.49 Avocado group: 32.49 ± 5.83
Lindbergh, 2018	Controlled-trial. Randomised. (12-months)	Initial phone screening, more thorough medical history review	Left-handedness, TBI, AMD, GD to interfere with supplement absorption, CVA 〈 20/40, MRI incompatibility, GDS total score 〉 19, or ND	Relationship between *L* + *Z* to brain activity	44 (40.9%) Active: 30 Placebo: 14	Placebo: 70.43 (±5.43) Active: 72.43 (±6.48)	Caucasian (44)	NR
Vishwanathan, 2014	Observational study (Cross-sectional)	NR	NR	Relationships between serum *L*+ Z and MPOD with	108 (49.1%)	77.6 (± 0,3)	Black (33)	26.9 ± 0.4

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Table 1 (*continued*)

First author, year	Study Desing, Duration (months)	Inclusion Criteria	Exclusion Criteria	Purpose of study	Sample size (*n* (% male)) Groups: n	Age (mean ± SD)	Race (n)	BMI (kg/m2) (mean ± SD)
				cognition in healthy older adults				
Ajana, 2018	Observational study (Cross-sectional)	≥ 65 years from 3 French cities	Developed late AMD; incomplete data for tests and missing information	Relationship between MPOD, *L* + *Z* plasma concentrations to CF	184 (31,5%)	82,3 (±4,3)	NR	NA
Cannavale, 2019	Observational study (Cross-sectional)	Aged 25–45 years, BMI ≥ 25 kg/m2, and no history of metabolic or gastrointestinal disease, or ND or CD	Use of tobacco products	Relationship between carotenoids in diet, serum, and the MPOD to memory in overweight or obese adults	94 (54.46%)	34.9 (±6.1)	NR	33.3 ± 6.6
Khan, 2018	Observational study (Cross-sectional)	Aged 25–45 years with BMI > 25.0 kg/m2	Pregnant, history of ND, used anti-psychotic or anti-anxiety medication, history of MD, or had non-normal VA	Relationship between MPOD to IQ, in overweight and obesity adults	114 (39%)	34.6 (± 6.1)	Caucasian (91)	Khan, 2018
Edwards, 2019	Observational study (Cross-sectional)	Aged 25–45 years with BMI > 25.0 kg/m2	BMI < 25 kg/m2, pregnancy, history ND, history of MD or non-normal VA	Relationship between MPOD to CF in overweight and obesity adults	101 (30.7%)	34.98 (± 5.85)	NR	32.78 ± 5.46
Walk, Edwards, et al., 2017	Observational study (Cross-sectional)	Aged 25 to 45 years, complete KBIT, a measure of IQ, readable EEG recording, normal VA or CVA, no ND	Not complete all relevant aspects of testing, not in the selected age range, pregnant or nursing, or taking certain medications	Relationship between age, MPOD, and neuro-cognitive indices.	60 (29%)	33.8 (± 5.7)	NA	NA
Mewborn, 2018	Observational study (Cross-sectional)	Community-dwelling older adults	Left-handedness, history of OP, CVA < 20/40, AMD in either eye, GD to interfere with L and Z absorption, MRI incompatibility, or history of TBI, dementia, or other ND	Relationship between *L* + *Z* to brain activity	51 (41.2%)	71.75 (± 6.16)	Caucasian (51)	NR
Lindbergh, 2017	Observational study (Cross-sectional)	Community-dwelling older adults (65–86 years)	Left-handedness, TBI, AMD in either eye, GD to interfere with L/Z absorption, CVA < 20/40, MRI incompatibility, and/or evidence of dementia or other ND	Relationship between *L* + *Z* to brain activity	43 (41.86%)	71.55 (±5.84)	Caucasian (43)	NA

AD: Attentional Disorders; AMD: Age-related Macular Degeneration; BCVA: Best Corrected Visual Acuity; BMI: Body Mass Index;; CD: Cognitive Disorders; CF: Cognitive Function; CVA: Corrected Visual Acuity; DM: Diabetes Mellitus; ERP: Event related potential; GC: Gastric Conditions; GDS: Geriatric Depression Scale; IQ: Intelligence Quotient; KBIT: the Kaufman Brief Intelligence Test; L: Lutein; MD: Metabolic Diseases; MP: Macular Pigment; MPOD: Macular Pigment Optical Density; ND: Neurological Disorders; NS: Nutritional Supplements; OP: Ocular Pathology; PD: Physical Disabilities; SE: Spherical Equivalence; TBI: Traumatic Brain Injury; UCVA: Uncorrected Visual Acuity; VA: Visual Acuity; Z: Zeaxanthin;.

young adults. Both supplements induced a significant increase in the MPOD, but there are no differences between supplement types [28]. All studies were controlled by a placebo group that showed no significant change in MPOD after follow-up.

Power et al. also evaluated the impact of daily dietary supplementation containing 10 mg L, 10 mg MZ and 2 mg Z for 12-months in adults, but the effect was measured on MP volume. The authors found a significant increase of MP volume in active supplementation group (+64%) while placebo group showed no significant change [23].

Xanthophyll supplementation through avocado daily consumption was evaluated in two studies with contrary results [30,31]. While Scott et al., found a significant increase in MPOD after 6-months in healthy adults [30], Edwards et al., did not present significant changes in MPOD after 3-months in overweight adults [31].

3.4. Blood serum

L and Z concentrations in blood serum were evaluated in eleven studies [11,23,42,24,28–31,36,40,41]. All authors used the same analysis method (high performance liquid chromatography), but the units of measurement presented were different. Table 2 shows the data obtained in each study.

All controlled-trial found a significant increase in serum L and Z after 6–12 months of xanthophyll supplementation [11,23,28,29], or after 3–6 months of avocado consumption [30,31]. However, Scott et al. also observed a significant increase in serum L in their placebo group [30].

Only six studies analysed the correlation between MP and carotenoids in blood serum [11,28–31,36]. A significant direct relationship between both parameters was observed in all of them.

Table 2
Studies reporting xanthophyll carotenoids in retina and/or blood serum.

First author, year	Population Age (mean ± SD)	Sex (% female)	Retinal concentrations MPOD Basal value (mean ± SD)	Change post-treatment (time, mean change, p)	Blood serum concentrations L basal value (mean ± SD)	Z basal value (mean ± SD)	*L*+*Z* basal value (mean ± SD)	Change post-treatment (time, mean change, p)
Saint, 2018	10(±4.26)	45.5%	0.476 ± 0.167	NA	NR	NR	NR	NA
Barnett, 2018	8.8 (± 0.1)	70%	0.640 ± 0.030	NA	NR	NR	NR	NA
Hassevoort, 2017	8.8 (± 0.11)	63%	0.660 ± 0.030	NA	NR	NR	NR	NA
Walk, Khan, et al., 2017	8.69 (± 0,08)	80.61%	0.610 ± 0.030	NA	NR	NR	NR	NA
Stringham, 2019	21.5	54.20%	NR	6-months Active groups *13 mg/day:* **+0.106*** ($p<0.05$) *27 mg/day:* **+0.120*** ($p<0.05$) Placebo: +0.026 (NR)	Active groups: 0.210 ± 0.111 µg/mL Placebo: 0.237 ± 0.141 µg/mL	Active groups: 0.210 ± 0.111 µg/mL Placebo: 0.052 ± 0.034 µg/Ml	NR	6-months Active groups: ***L*+ 1.040*** µg/mL ($p<0.05$) ***Z*+ 0.152*** µg/mL ($p<0.05$) Placebo: L −0.015 µg/mL (NR) Z −0.002 µg/mL (NR)
Hammond, 2017	Total: 73.74 (± 8.20) Active:72.51 (± 6.24) Placebo: 70.93 (± 5.70)	58.82% Active: 52.77% Placebo: 73.33%	Active group 0.520 ± 0.19 Placebo: 0.420 ± 0.16	12-months: Active group **+0.070** ($p<0.03$) Placebo: +0.050 (NR)	Active group 0.150 ± 0.080 ng/µL Placebo: 0.150 ± 0.060 ng/µL	Active group 0.030 ± 0.020 ng/µL Placebo: 0.030 ± 0.020 ng/µL	Active group: 0.180 ± 0.110 ng/µL Placebo: 0.180 ± 0.070 ng/µL	12-months: Active group: ***L*+ 0.440*** ng/µL ($p<0.05$) ***Z*+ 0.100*** ng/µL ($p<0.05$) **L-*Z*+ 0.540*** ng/µL ($p<0.05$) Placebo: L −0.001 ng/µL ($p>0.05$) Z −0.000 ng/µL ($p>0.05$) L-Z −0.001 ng/µL ($p>0.05$)
Renzi-Hammond, 2017	21.21 (±2.52)	43% Active: 43.24% Placebo: 42.85%	Active group 0.470 ± 0.18 Placebo: 0.400 ± 0.12	12-months: Active group **+0.090** ($p<0.001$) Placebo: +0.040 ($p>0.05$)	Active group 0.110 ± 0.070 ng/µL Placebo: 0.100 ± 0.03 ng/µL	Active group 0.030 ± 0.020 ng/µL Placebo: 0.030 ± 0.020 ng/µL	Active group: 0.140 ± 0.080 ng/µL Placebo: 0.130 ± 0.040 ng/µL	12-months: Active group: *L*+ 0.270* ng/µL (NR) *Z*+ 0.050* ng/µL (NR) L-*Z*+ 0.320* ng/µL (NR) Placebo: *L*+ 0.090 ng/µL (NR) *Z*+ 0.010 ng/µL (NR) L-*Z*+ 0,100 ng/µL (NR)
Scott, 2017	Active: 63.3 (±11.1) Placebo: 62.5 (±9.2)	62,5% Active: 70% Placebo: 55%	Active groups: 0.393 ± 0.142 Placebo: 0.380 ± 0.141	6-months Active groups **+0.101** ($p = 0.001$) Placebo: +0.044 ($p>0.05$)	Active groups: 0.330 ± 0.139 nmol/L Placebo: 0.322 ± 0.134 nmol/L	Active groups: 0.067 ± 0.017 nmol/L Placebo: 0.065 ± 0.033 nmol/L	NR	6-months Active groups: ***L*+ 0.084** nmol/L ($p = 0.001$) Z −0.060 nmol/L ($p>0.05$) Placebo: ***L*+ 0.049** nmol/L ($p = 0.03$) *Z*+ 0.013 nmol/L ($p = 0.004$)
Power, 2018	45.42 (± 12.40)	48.4% Active: NR %	Active groups: MP volume 3982 ± 1337	12-months Active groups MP volume	Active groups: 0.249 ± 0.134 µmol/L	Active groups: 0.052 ± 0.042 µmol/L	NR	12-months Active groups: ***L*+ 0.647***

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Table 2 (*continued*)

First author, year	Population Age (mean ± SD)	Sex (% female)	Retinal concentrations MPOD Basal value (mean ± SD)	Change post-treatment (time, mean change, p)	Blood serum concentrations L basal value (mean ± SD)	Z basal value (mean ± SD)	*L+Z* basal value (mean ± SD)	Change post-treatment (time, mean change, p)
		Placebo: NR%	Placebo: 4026 ± 1758	**+2558*** (*p*<0.001) Placebo: MP volume −151 (NR)	Placebo: 0.283 ± 0.133 μmol/L	Placebo: 0.058 ± 0.037 μmol/L		μmol/L (*p*<0.001) ***Z*+ 0.034** μmol/L (*p* = 0.016) Placebo: L −0.011 μmol/L (*p*>0.05) *Z*+ 0.005 μmol/L (*p*>0.05)
Edwards, 2020	Placebo: 34.0 (±6.2) Active: 34.6 (±5.7)	57% Active: 48.93% Placebo: 48.64%	Active groups: 0.470 ± 0.220 Placebo: 0.470 ± 0.190	3-months Active groups +0.020 (*p*>0.05) Placebo: +0.020 (*p*>0.05)	Active groups: 0.120± 0.060 μmol/L Placebo: 0.140 ± 0.070 μmol/L	NR	NR	3-months Active groups: ***L*+ 0.040*** μmol/L (*p*<0.01) Placebo: L −0.005 μmol/L (*p*>0.05)
Lindbergh, 2018	Placebo: 70.43 (±5.43) Active: 72.43 (±6.48)	59.1% Active: 53.33% Placebo: 71.43%	Active groups: 0.540 ± 0.190 Placebo: 0.440 ± 0.140	3-months Active groups **+0.070*** (*p* = 0.016) Placebo: +0.000 (*p*>0.05)	NR	NR	NR	NA
Vishwanathan, 2014	77.6 ± 0,3	50.9%	0.343 (±0,018)	NA	NR	NR	494 ± 27 nmol/l.	NA
Ajana, 2018	82.3 (±4,3)	68.5%	0.700 ± 0.200	NA	NR	NR	0.400 ± 0.200 μM	NA
Cannavale, 2019	34.9 (±6.1)	45.54%	0.438 ± 0.200	NA	0.129 ± 0.06 μmol/L	NR	NR	NA
Khan, 2018	34.6 (± 6.1)	61%	0.460 ± 0.210	NA	NR	NR	NR	NA
Edwards, 2019	34.98 (± 5,85)	69.30%	0.480 ± 0.260	NA	NR	NR	NR	NA
Walk, Edwards, et al., 2017	33.8 (± 5.7)	71%	0.490 ± 0.250	NA	NR	NR	NR	NA
Mewborn, 2018	71.75 (± 6.16)	58,8%	Younger adults 0.426 ± 0.160 Older adults 0.496 ± 0.170	NA	NR	NR	Younger adults 0.247 ± 0.120 μmol/L Older adults 0.308 ± 0.670 μmol/L	NA
Lindbergh, 2017	71.55 (±5,84)	58.14%	0.510 ± 0.180	NA	NR	NR	0.310 ± 0.170 μmol/L	NA

MPOD Macular Pigment Optical Density; *L* = Lutein; *Z* = Zeaxanthin; NA = Not applicated; NR = Not reported.
Bolded data show significant changes over time ($p < 0.05$).
* Data significantly different from placebo group ($p < 0.05$).

3.5. CF and MPOD

Table 3 summarises the relationship between MPOD and CF.

3.5.1. Cognitive functions in preadolescent children – childhood

The CF analysed were: academic achievement (mathematics, written language composite standard scores and reading) [33]; accurate performance [35]; brief intellectual ability (BIA), cognitive efficiency, visual-auditory learning, spatial relations [18]; and relational memory [34].

Intelligent quotient (IQ) was studied by four authors using the WJ [33,34] or Kaufman Test of Educational Achievement (K-TEA) [33,35]. Furthermore, different cognitive abilities were analysed with the WJ-III Tests: BIA, Verbal Ability, Cognitive Efficiency, Processing Speed (PS), and Executive Processes [18] or cognitive test battery (memory task) [34] . Data are showed in Table 3.

MPOD was significantly related ($p < 0.05$) to executive processes, BIA, the spatial relations subtest [18], academic achievement, mathematics (math concepts and computation), written language composite standard scores (written expression and spelling) [33], memory [34], and accurate performance [35].

3.5.2. Cognitive functions in adults

Psychomotor and PS [28], verbal and visual memory, CF in the reasoning and executive processes [11], visual memory, reasoning ability and complex attention [29], spatial working memory and efficiency in approaching a problem [30], verbal and visual memory [23], verbal and visual memory, verbal abilities [24,40], PS, attentional

Table 3
Relationship between MPOD and Cognitive Function considering different tests.

First author, year	Age (mean ± SD)	Sex (% female)	TEST Battery	CF (task for calculating the index score)	Relationship between MPOD and CF
Saint, 2018	10(±4.26)	45.5%	WJ-III	Brief Intellectual Ability (BIA) Verbal Ability Cognitive Efficiency Processing Speed Executive Processes Visual-Auditory Learning Spatial Relations	WJ-III Composite Scores: MPOD vs *BIA $r = 0.268$ ($p<0.05$) Verbal Ability $r = 0.159$ ($p>0.05$) *Cognitive Efficiency $r = 0.206$ ($p \leq 0.10$)) Processing Speed $r = 0.099$ ($p>0.05$) Executive Processes $r = 0.288$ ($p < 0.05$) Select WJ-III Subtests considering sex differences): *Visual-Auditory Learning $r = 0.236$ ($p \leq 0.10$) *Spatial Relations $r = 0.299$ ($p<0.05$))
Barnett, 2018	8.8 (± 0,1)	70%	WJ KTEA	IQ (WJ) Academic performance: math concepts, letter and word recognition, reading comprehension, word recognition fluency, written expression, listening comprehension (KTEA)	MPOD vs *academic achievement ($R^2 = 0.10$. $P < 0.01$) *mathematics ($R^2 = 0.07$. $P= 0.02$) *math concepts ($R^2 = 0.05$. $P= 0.04$) *math computation ($R^2 = 0.09$. $P= 0.02$) *written language composite standard scores ($R^2 = 0.15$. $P < 0.01$) * written expression ($R^2 = 0.11$. $P= 0.008$) *spelling ($R^2 = 0.13$. $P= 0.004$) *reading or reading fluency improve ($p<0.05$) listening comprehension did not improve
Hassevoort, 2017	8.8 (± 0,11)	63%	WJ	IQ Memory performance (WJ-)	MPOD improve IQ ($p>0.05$) *relational memory ($p<0.05$)
Walk, Khan, et al., 2017	8.69 (± 0,08)	80.61%	K-TEA EEG	IQ Educational achievement (K-TEA)	Higher MPOD improve *accurate performance: (higher MPOD group: $M = 82.242$) vs (lower MPOD group: $M = 75.545$) -for congruent trials ($F= 0.566$. $p= 0.456$. ηp 2 = 0.012). -*for incongruent trials ($F= 4.623$. $p= 0.037$. ηp 2 = 0.091) Reaction times revealed no significant effects involving MPOD. Lower MPOD improve *P3 amplitudes: (higher MPOD: $M = 14.247$) vs (lower MPOD: $M = 18.535$) -(F (1. 46) = 5.287. $p= 0.026$. ηp 2 = 0.103)
Stringham, 2019	21.5	54.20%	CNSVS	Composite memory (N/R) Verbal memory (N/R) Visual memory (N/R) Working memory (N/R) Psychomotor Speed (N/R) Processing speed (N/R) Attention (N/R) Reasoning (N/R) Executive function (N/R) Cognitive flexibility (N/R) Social acuity (N/R) Reaction time (N/R)	MPOD vs memory ($p>0.05$) *psychomotor speed ($r = 0.38$; $p = 0.003$) *processing speed ($r = 0.35$; $p = 0.007$) MPOD vs the rest of cognitive functions N/R
Hammond, 2017	Total: 73.74 (± 8.20) Active:72.51 (± 6.24) Placebo: 70.93 (± 5.70)	58.82% Active: 52.77% Placebo: 73.33%	CNSVS	Verbal Memory (Verbal Memory Test) Visual Memory (Visual Memory Test) Psychomotor Speed (FTT, SDC) Attention (ST, SAT, CPT) Reasoning (NVRT) Executive function (SAT) Cognitive flexibility (SAT, ST)	MPOD vs *Verbal Memory ($r= 0.31$. $p= 0.07$) *Visual Memory ($r= 0.24$. $p= 0.09$) Psychomotor Speed (N/R) *Reasoning ($r= 0.45$. $p= 0.04$) *Executive function (errors of attention) ($r = -0.18$. $p= 0.08$) Cognitive flexibility ($r= 0.20$. $p= 0.10$) Neurocognitive Index (N/R)
Renzi-Hammond, 2017	21.21 (±2.52)	43% Active: 43.24% Placebo: 42.85%	CNSVS	Verbal Memory (Verbal Memory Test) Visual Memory (Visual Memory Test) Psychomotor Speed (FTT, SDC) Attention (ST, SAT, CPT) Reasoning (NVRT) Executive function (SAT)) Cognitive flexibility (SAT, ST)	MPOD improvements in: Verbal memory ($p>0.05$) *Visual memory ($p < 0.05$) *Complex attention ($p < 0.04$) *Reasoning ability ($p < 0.05$) Executive function ($p>0.05$) Cognitive flexibility ($p>0.05$)

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Table 3 (*continued*)

First author, year	Age (mean ± SD)	Sex (% female)	TEST Battery	CF (task for calculating the index score)	Relationship between MPOD and CF
Scott, 2017	Active: 63.3 (±11.1) Placebo: 62.5 (±9.2)	62,5% Active: 70% Placebo: 55%	CANTAB	Memory (PAL) Spatial Working Memory (SWM) Processing speed Attention Delayed Match to Sample (DMS) Spatial Span (SSP) Spatial Span Reverse (SSP-R)	MPOD vs Memory (Avocado group): *Spatial Working Memory (r= 0.46. p= 0.041) *Efficiency in approaching a problem (r= 0.47. p= 0.036) Processing speed N/R Attention N/R Delayed Match to Sample N/R Spatial Span N/R Spatial Span Reverse N/R
Power, 2018	45.42 (± 12.40)	48.4% Active: NR % Placebo: NR%	CANTAB	Verbal Memory (VRM) Visual memory (PAL) Processing speed = Comprehension (MOT) Phonemic fluency and semantic fluency ("FAS" and "Animal" tests) Executive function (AST)	MPOD vs *Verbal Memory (reduction in intrusion errors)(r= –0.306; p= 0.033) * Visual memory (reduction in total errors) (r= –0.342; p= 0.005) Processing speed = Comprehension N/R Phonemic fluency and semantic fluency N/R Executive function N/R
Edwards, 2020	Placebo: 34.0 (±6.2) Active: 34.6 (±5.7)	57% Active: 48.93% Placebo: 48.64%	KBIT-2 EEG	IQ Processing speed Attention (Flanker task, Oddball task) Inhibition (Nogo task) (EEG)	MPOD vs cognition: No relationship (p>0.05)
Lindbergh, 2018	Placebo: 70.43 (±5.43) Active: 72.43 (±6.48)	59.1% Active: 53.33% Placebo: 71.43%	WTAR fMRI - adapted task	Memory (WTAR) Neural mechanisms (fMRI)	MPOD vs estimated intellectual functioning (memory) No relation (p>0.05)
Vishwanathan, 2014	77.6 ± 0,3	50.9%	3MS SRT: learn SRT: delayed recall Reaction time Verbal fluency Digit-symbol substitution task Box drawing task Pattern comparison task	Attention, language and orientation (3MS) Verbal learning and memory (SRT) Reaction time Verbal fluency Speed and associative learning ability (Digit-symbol substitution task) Sensory motor speed (Box drawing task) Perceptual speed (Pattern comparison task)	Relationship between cognitive function measures and MPOD: 3MS: 0.269 ($P\leq$ 0.05) SRT: learn: 0.263 ($P\leq$ 0.05) SRT: delayed recall: 0.220 ($P\leq$ 0.05) Reaction time: −0.059 Verbal fluency: 0.249 ($P\leq$ 0.05) Digit-symbol substitution task: 0.249 ($P\leq$ 0.05) Box drawing task: 0.154 Pattern comparison task: 0.195 ($P\leq$ 0.05)
Ajana, 2018	82.3 (±4,3)	68.5%	MMSE FCSRT BVRT IST15	Global cognitive functioning (MMSE) Memory performance and verbal learning (FCSRT) Visual memory and visual perception (BVRT) Verbal fluency abilities and speed of verbal production (IST15)	MPOD improvements in : *Memory performance and verbal learning (β= 0.15, p<0.05) * Visual memory and visual perception (β= 0.39, p<0.05) * Verbal fluency abilities and speed of verbal production (β= 1.16, p<0.05)
Cannvavale, 2019	34.9 (±6.1)	45.54%	KBIT-2	IQ (KBIT-2) Memory ability (Computerized spatial reconstruction task)	MPOD and Memory: 0.438 ± 0.20 (p> 0.05) Misplacement: −0.110 (p > 0.05) Object-Location Binding: 0.083 (p > 0.05)
Khan, 2018	34.6 (± 6.1)	61%	KBIT	IQ (KBIT-2) Fluid and crystallized intelligence	MPOD vs *IQ (β = 0.20, p= 0.04) * Fluid intelligence (β = 0.20, p= 0.03) Crystallized intelligence (β = 0.11, p= 0.25)
Edwards, 2019	34.98 (± 5,85)	69.30%	KBIT-2 EEG	IQ (KBIT-2) Processing speed Attention (Oddball task) (EEG)	MPOD improve IQ: r = 0.18 (p>0.05) and *Processing speed (p<0.05) MPOD was inversely related to *Attention (attentional demands) (p<0.05)
Walk, Edwards, et al., 2017	33.8 (± 5.7)	71%	KBIT EEG	IQ (KBIT) Cognitive Tasks: Attentional inhibition Selective attention (oddball task) Inhibition (A go/no-go task) (EEG)	MPOD vs *IQ: the response accuracy to standard stimuli (r= 0.342. p= 0.007) reaction time to target stimuli (r= 0.468. $p\leq$ 0.001). Cognitive Tasks: *Attentional inhibition: incongruent trials (r = –0.306. p= 0.018) peak amplitude for incongruent trials (r= 0.259. p= 0.045) *Selective attention:

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Table 3 (*continued*)

First author, year	Age (mean ± SD)	Sex (% female)	TEST Battery	CF (task for calculating the index score)	Relationship between MPOD and CF
					reaction time (r= 0.366. p= 0.004) inverse efficiency (r= 0.257. p= 0.047) Inhibition (A go/no-go task) N/R.
Mewborn, 2018	71.75 (± 6.16)	58,8%	JLO fMRI	Visual–spatial processing and decision-making	Lower MPOD was associated with greater brain activity (i.e."neural inefficiency") (p<0.05) in regions associated with: *visual–spatial performance * decision-making
Lindbergh, 2017	71.55 (±5,84)	58.14%	WTAR fMRI (adapted task)	Memory (WTAR) Neural mechanisms (fMRI)	Lower MPOD levels were associated with greater brain activity (i.e.. neural inefficiency) (p<0.05) in regions associated with: *verbal learning

Note: WJ: The Woodcock-Johnson tests. KTEA: Kaufman Test of Academic and Educational Achievement II. EEG (electroencephalographic) modified version of the Eriksen flanker task. CNSVS: CNS Vital Signs; Morrisville, NC, Computerized test battery. CANTAB: Cambridge Neuropsychological Test Automated Battery. MMSE: Mini-Mental State Examination. FCSRT: Free and Cued Selective Reminding Test. BVRT: the Benton Visual Retention Test. IST15: the Isaacs Set Test. KBIT: The Kaufman Brief Intelligence Test, (KBIT-2) Second Edition. JLO: a judgment of line orientation task. fMRI: a functional magnetic resonance imaging scan. WTAR: Wechsler Test of Adult Reading. FTT: Finger Tapping Test. SDC: Symbol-Digit Coding Test. ST: Stroop Test. CPT): Continuous Performance Task. NVRT: Non-Verbal Reasoning Test. SAT: Shifting Attention Test. MOT: Motor screening task. AST: attention switching task. IQ: Intelligent quotient. (* p<0.05).

demands [37], attentional inhibition and selective attention [38] were analysed in adults. Besides, MPOD values were also related to brain activity [41,42].

Memory was analysed in nine studies [11,23,28-30,32,36,40,42] (Table 3) using the CANTAB [23,30], the CNS Vital Signs (CNSVS; Morrisville, NC) [11,28,29], and the Kaufman Brief Intelligence Test Second Edition (KBIT-2) [36].

The Teng Modified Mini-Mental State Examination (3MS) was a global measure of attention, language and orientation and the Buschke selective reminding test (SRT) was used to study verbal learning and memory [24]. Memory performance was studied using the Free and Cued Selective Reminding Test (FCSRT) and visual memory was studied using the Benton Visual Retention Test (BVRT) [40]. Finally, the Wechsler Test of Adult Reading (WTAR) was employed to analyze memory [32,42].

Statistically significant correlations between MPOD and memory were reported [11,23,29,30,40]. Higher MPOD values at 1° were significantly associated with higher visual memory scores [40]. On the contrary, two studies demonstrated that MPOD was not statistically correlated with memory ($p > 0.05$) [28,36].

PS was analysed in six studies using the KBIT [31,37], the Isaacs Set Test (IST 15) [40], the CNSVS [28], and the CANTAB [23,30]; it improved significantly with MPOD ($p < 0.05$) in four of them [28,31,37,40].

Attention was studied in several academic works [11,24,28–31,37,38]. However, only five reported statistically significant correlations of MPOD with attention [24,37], reaction time and inverse efficiency [38], executive function [11,24], and complex attention [29]. The other studies did not provide results. It was observed that learning ability and MOPD values had statistically significant correlations (p<0.05)[24].

Two studies analysed measurements relative to inhibition using the oddball task, the Eriksen flanker task, and the go/no-go task [31,38]. Correlation between changes in MPOD and inhibition was not reported [31,38].

Reasoning outcome was measured in three studies [11,28,29], which used the CNSVS. MPOD was significantly related to performance in the reasoning domain (r= 0.45, p= 0.04) [11]. The Reliable Change Index (RCI) was higher for people who improved their MPOD than those who did not (0.94 and 0.18, respectively, $p < 0.05$) [29]. A correlation was not reported by Stringham (2019) [28].

Cognitive flexibility was analysed in three studies, using CNSVS [11,28,29]. Stringham (2019) did not report relation between MPOD and cognitive flexibility [28]; however, Hammond (2017) and Renzi-Hammond (2017) observed an improvement although not statically significant ($p > 0.05$) in this executive function [11,29].

3.5.3. *Brain activity and MPOD*

Brain activity was analysed in six studies [31,32,37,38,41,42]. The WTAR was employed to estimate intellectual functioning [32,42]. Although lower MPOD levels were associated with significantly higher brain activity in several regions related to verbal learning ($p < 0.01$) [42], MPOD values were not significantly related to estimate intellectual functioning or brain activation in any study [32]. Visual-spatial performance and decision-making were measured by Mewborn (2018) using the judgment of line orientation (JLO) task, which is conceptually based on the Benton JLO task. Brain activity in regions associated with visual-spatial performance and decision-making were predicted by MPOD [41]. Walk (2017), Edward (2020), and Edward (2019) analysed neural mechanisms using electroencephalographic activity [31,37,38]. Lindbergh (2017), Lindbergh (2018) and Mewborn (2018) considered fMRI, through MRI compatible goggles (verbal learning task [42,32] or JLO task [41] with functional scans, from the brainstem to the top of the head).

3.6. *Quality assessment*

Table 4 shows the quality assessment of all included studies, both the seven Randomized Controlled Trials (RCT) and the twelve observational studies. In two studies [29,32], some of the authors received fees from Abbott Nutritional Products and three studies [11,29,32], were funded by the same laboratory. Because cross-sectional design was present in most of the studies, the evidence provided to justify the causal relationship between MPOD and CF is weaker than that provided by other observational studies and RCTs.

4. Discussion

The xanthophyll carotenoids L and Z have antioxidant and anti-inflammatory characteristics. It is well-known that both can traverse the blood-brain barrier to produce important health effects in the brain as well as in the retina.

This systematic review aims to show the relationship between MP and cognitive capacity. That is why we have included the most recent 19 articles that discuss this issue—including studies on children.

Several methodologies have been tried to establish a relationship between MP and CF. Most studies show the correlation between MPOD

Table 4
Quality Assessment by National Institutes of Health (NIH)'s tool for 'Quality Assessment of Controlled Intervention Studies' and the 'Quality Assessment Tool for Observational Cohort and Cross-sectional Studies' [27].

First Author (year)	Study Quality Assessment Tools Questions															
CONTROLLED INTERVENTION STUDIES (RCT)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Total x/14	Quality Assessment
Hammond (2017)	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	13	Fair
Renzi-Hammond (2017)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	NO	YES	NO	11	Poor
Scott (2017)	YES	YES	YES	NA	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	12	Fair
Lindbergh (2018)	YES	YES	YES	YES	YES	YES	NO	NR	YES	YES	YES	YES	YES	NO	11	Poor
Power (2018)	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	13	Fair
Stringham (2019)	YES	YES	YES	YES	YES	YES	NO	NR	YES	YES	YES	YES	YES	NO	11	Poor
Edwards (2020)	YES	YES	YES	NR	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	13	Good
Total score across studies	7	7	7	5	7	7	5	4	7	7	7	6	7	1	—-	
OBSERVATIONAL COHORT AND CROSS-SECTIONAL STUDIES	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**	**Q12**	**Q33**	**Q14**	**Total x/ 14**	**Quality Assessment**
Vishwanathan (2014)	YES	YES	NR	YES	NO	NO	NO	YES	YES	NO	YES	NR	NA	YES	7	Fair
Walk, Khan, et al., (2017)	YES	YES	YES	YES	NO	YES	NO	NA	YES	YES	YES	NR	NA	NR	8	Good
Walk, Edwards, et al., (2017)	YES	YES	NR	YES	NO	YES	NO	NA	YES	NO	YES	NR	NA	NR	6	Fair
Hassevoort (2017)	YES	YES	NR	YES	NO	YES	NA	NA	YES	NO	YES	NR	NA	YES	7	Fair
Lindbergh (2017)	YES	YES	YES	YES	NO	NO	NO	NA	YES	NO	YES	NR	NA	YES	7	Fair
Khan (2018)	YES	YES	NR	YES	NO	NO	NO	NA	YES	NO	YES	NR	NA	NR	5	Poor
Mewborn (2018)	YES	YES	YES	YES	NO	YES	NA	NA	YES	NO	YES	NR	YES	YES	9	Good
Barnett (2018)	YES	YES	YES	YES	NO	YES	NA	NA	YES	NO	YES	NR	NA	YES	8	Fair
Ajana (2018)	YES	YES	NR	NO	NO	NO	NO	YES	YES	YES	YES	NR	NA	YES	6	Poor
Saint (2018)	YES	YES	YES	YES	NO	NO	NO	NR	YES	NO	YES	NR	YES	YES	8	Fair
Cannavale (2019)	YES	NO	NR	NR	NO	YES	NR	NR	YES	NA	YES	NR	NA	YES	5	Poor
Edwards (2019)	YES	YES	NR	YES	NO	NO	NO	NR	YES	NR	YES	NR	NA	YES	6	Poor
Total score across studies	12	11	5	10	0	6	0	2	12	3	12	0	2	9	—	

Note: Q1: Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?; Q2: Was the method of randomization adequate (i.e., use of randomly generated assignment)?; Q3: Was the treatment allocation concealed (so that assignments could not be predicted)?; Q4: Were study participants and providers blinded to treatment group assignment?; Q5: Were the people assessing the outcomes blinded to the participants' group assignments?; Q6: Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?; Q7: Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?; Q8: Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?; Q9: Was there high adherence to the intervention protocols for each treatment group?; Q10: Were other interventions avoided or similar in the groups (e.g., similar background treatments)?; Q11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?; Q12: Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?; Q13: Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?; Q14: Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?; NR: not reported; CD: cannot determine; NA: not applicable.

Note: Q1: Was the research question or objective in this paper clearly stated? Q2: Was the study population clearly specified and defined? Q3: Was the participation rate of eligible persons at least 50%?; Q4: Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? Q5. Was a sample size justification, power description, or variance and effect estimates provided? Q6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?; Q7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?; Q8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?; Q9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; Q10: Was the exposure(s) assessed more than once over time?; Q11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; Q12: Were the outcome assessors blinded to the exposure status of participants?; Q13: Was loss to follow-up after baseline 20% or less? Q14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome (s)? NR: not reported; CD: cannot determine; NA: not applicable.

levels and CF or brain activity. Besides, seven RCT compared the increase in MP after daily macular carotenoids consumption to CF and/or brain activity.

As seen in RCT, dietary intake of macular xanthophyll carotenoids supplements appears to increase their levels in blood serum [11,23,28–31] and MPOD [11,23,28–30]. However, Edwards et al. did not observe any significant increase in MPOD after 12 weeks of avocado consumption in overweight adults [31]. This result could be motivated by three factors: first, an insufficient quantity of xanthophyll supplement with avocado—however, Scott et al. found a significant increase in MPOD after six months of avocado consumption in healthy normo-weight adults [30]. Second, an insufficient time period—Edwards et al. analysed MPOD changes after only three months, whereas other studies showed changes from six months onwards. Finally, the population was different from other studies—Edward et al. analysed overweight and obese patients whereas most other studies found a significant improvement of MPOD in healthy adults. The intake of L and Z into the bloodstream sparks a competition of sorts among different tissues—including the adipose tissue—to acquire these xanthophylls. Therefore, when the adipose tissue is large (overweight), it contains more L and Z and, thus, fewer carotenoids are free to reach the MP [19].

RCTs were not performed on children. Despite this, MPOD values appear to be higher in children than in adults—with two exceptions. Saint et al. showed a mean of MPOD value (0.476) in their children population similar to the MPOD average in the adult population of this review (0.472). Additionally, the MPOD mean reported by Saint et al. (2018) was lower than that in other studies on children (> 0.600) [33–35]. Perhaps, slightly higher mean age in Saint et al.'s study than in the other studies could influence this result (9.1 years [18] versus 8.7 [35] and 8.8 years [33,34], respectively). Alternatively, Ajana et al. showed the highest mean MPOD of this review (0.700) in an older adult population (mean age 82.3 years). This value did not agree with the other values presented in this review. Curiously, Ajana et al. measured MPOD by dual-wavelength auto-fluorescence rather than by heterochromatic flicker photometry, as was performed in most of the analysed studies [40].

MPOD increase via supplement intake may decrease with age. MPOD is modified by L and Z intake and agents that produce oxidation and inflammation, such as alcohol, smoke, or blue-light exposure [43]. The oxidative processes in the retina tissue have a cumulative effect with the manifestation of residue deposits (drusen) [44]. In this way, under similar conditions of carotenoids intake and exposure to oxidative agents, it would be logical to assume that younger people have higher MPOD than older people. L and Z levels in the blood are not analysed in children. Given that a direct relationship between MP and L and Z levels in blood has been demonstrated, MPOD measurement could be sufficient to establish carotenoids levels, avoiding invasive techniques such as blood extraction.

In order to measure CF, numerous methods were found in this review. The discrepancies among the abilities measured, the tests performed, and the analysis methods hindered the comparison of studies. To summarize the relation between MP and CF, this study describes studies on children, analyses randomized controlled trials and finishes with observational studies. To conclude, the risk-of-bias study is considered.

The participants of studies in children were of a similar age and showed a significant relation between MPOD and CF [18,33–35]. IQ (brief intellectual ability, academic performance, or educational achievement) and MPOD relation was found [18,33,35]. Saint et al. showed the lowest mean MPOD value (0.476±0.167), but also found significantly better memory when MPOD levels were increased [34]. Furthermore, children can build a cognitive map in absence of visual information [45] thus L and Z levels could be essential to brain development.

Six of the seven controlled trials reviewed showed an improvement in several CF after MPOD increase [11,23,28–32]. The participants in active groups (n = 20–49) were in 3 age grouping of 21.21±2.52 - 21.5 years [28,29], 34.60±5.70 - 45.42±12.40 years [23,31], and 63.30 ±11.10 - 72.51±6.24 years [11,30,32]. MP improved in all active groups. MPOD values were observed in four of them [11,29–31] whereas Power et al. showed MP measurement as Macular Pigment Optical Volume [23] and Stringham (2019) omitted MPOD mean value [28]. Finally, in Lindbergh (2018) study was not observed significant relation among CF and MPOD [11,23,28–32].

The CFs that showed a significant increment with MPOD increase are detailed below.

Memory was analysed in nine studies. Visual memory [11,23,29–32] and verbal memory [11,23,24,40] showed a significant relation with MP levels, even though neither Stringham (2019) nor Cannavale (2019) observed this relation [28,36]. We do not know the MPOD mean value of Stringham (2019) but Cannavale (2019)'s population showed a MPOD value (0.438±0.200) lower than the MPOD average value in the adult population of this review (0.472). This could be because Cannavale included overweight people. However, even when MP is similar among people, who may or may not be overweight, CF is lower when the bodyweight is not within the normal range [46]. The results of Lindbergh's studies are not shown [32,42].

Reasoning ability [11,29] and efficiency in approaching a problem [30] were also analysed, and they were found to improve when MPOD increased.

Attention was studied in eight publications, but only five of them shared their results. Executive function [11,24] and complex attention [24,29,37,38] were the CF that improved with MPOD increase.

PS was analysed in five studies, showing an improvement of this CF with an increase in MPOD value ($p < 0.05$) [28,37,40]. Scott et al. and Power et al. did not share their PS results [23,30].

When brain activity is studied [31,32,37,38,41,42], a lower MPOD value is associated with neural inefficiency ($p < 0.05$) [41,42]. L and Z have beneficial effects that can traverse the blood-brain barrier and manifest as improved brain functioning [47]. Therefore, a MP study would be useful to analyze brain conditions. Nowadays, degenerative disorders such as AD or Parkinson's disease are being studied in the context of macular carotenoids ingestion [48,49].

In this systematic review, no studies have been excluded because of a poor-quality rating. Only Edwards et al. [31] performed an intention-to-treat (ITT) analysis in their RCT. Justification for sample size or description of study potency was not provided by any of the observational studies.

This systematic review of the 19 publications about MPOD and CF could have been enough to conclude. However, the differences between the studies analysed limited the findings. The studies reviewed consider different cognitive capacities using different tasks which complicates the comparison of results. For this reason, the relation between MPOD and CF shown in this review was based on the significant test results (p-value < 0.05), regardless of the reliability of each test (based on its specificity and repeatability). Additionally, a lot of the CF analysed are not reported, holding back data on the correlation between MPOD and CF. It is therefore necessary to standardize the description of test results, even if they are not significant, in order to be able to compare studies. In addition, the range of effect sizes on main dependent CF measurements could be an important date to analyze correlations and the sample sizes.

This review highlights the need to standardize the assessment of CF. In this respect, the knowledge of MPOD levels could be of great value in the context of both adults and children. The direct relationship observed in this review between MP and the cognitive abilities of subjects may facilitate the assessment of individuals when their collaboration in cognitive tests is limited. Additionally, the study of MPOD could be easier and quicker than the measurement of CF. Moreover, when MPOD is lower than media levels, diet should be examined, and intake of eggs, fruits, and vegetables should be increased [50]. Thus, to follow up on the state of CF, it would be necessary to undergo an initial test and then

continue with MPOD measurement.

In the other hand, a positive association among wider retinal vessel caliber and higher L and Z concentrations in serum and retina has also been demonstrated [51]. In the same way, cerebral blood flow could be associated with cognitive function [52]. However, factors such as the vascular function or lipids ingested are not been considered in the studies reviewed.

5. Concluding remarks

This systematic review showed a direct relationship between CF and MP. Many CF's improve when MP increases in children and healthy adults without overweight. However, repeatable and standardised methods to measure CF are needed to confirm the influence of MPOD values on each cognitive ability.

CRediT authorship contribution statement

Marta-C. García-Romera: Conceptualization, Methodology, Validation, Investigation, Supervision, Writing – original draft, Visualization, Writing – review & editing, Project administration. **María-Carmen Silva-Viguera:** Investigation, Writing – original draft. **Inmaculada López-Izquierdo:** Investigation, Writing – original draft. **Alfredo López-Muñoz:** Investigation, Writing – original draft. **Raúl Capote-Puente:** Writing – original draft. **Beatriz Gargallo-Martínez:** Investigation, Writing – original draft, Supervision, Writing – review & editing.

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Data availability

Data will be made available on request.

References

[1] R. Estévez-Santiago, B. Olmedilla-Alonso, B. Beltrán-de-Miguel, C. Cuadrado-Vives, Lutein and zeaxanthin supplied by red/orange foods and fruits are more closely associated with macular pigment optical density than those from green vegetables in Spanish subjects, Nutr. Res. 36 (11) (2016) 1210–1221. Available at: https://www.sciencedirect.com/science/article/pii/S0271531716304365 [Accessed February 11, 2021].

[2] S.S. Ahmed, M.N. Lott, D.M Marcus, The macular xanthophylls, Surv. Ophthalmol. 50 (2) (2005) 183–193. Available at: https://www.sciencedirect.com/science/article/pii/S0039625704001894 [Accessed February 9, 2021].

[3] M. Neuringer, M.M. Sandstrom, E.J. Johnson, D.M. Snodderly, Nutritional manipulation of primate retinas, I: effects of lutein or zeaxanthin supplements on serum and macular pigment in xanthophyll-free Rheus monkeys, Invest. Ophthalmol. Vis. Sci. 45 (9) (2004) 3234–3243. Available at: https://tvst.arvojournals.org/article.aspx?articleid=2123938 [Accessed February 9, 2021].

[4] F.M. Barker, D.M. Snodderly, E.J. Johnson, W. Schalch, W. Koepcke, J. Gerss, et al., Nutritional manipulation of primate retinas, V: effects of lutein, zeaxanthin, and n-3 fatty acids on retinal sensitivity to blue-light-induced damage, Invest. Ophthalmol. Vis. Sci. 52 (7) (2011) 3934–3942. Available at: https://iovs.arvojournals.org/article.aspx?articleid=2187033 [Accessed February 9, 2021].

[5] D.I. Thurnham, J.M. Nolan, A.N. Howard, S. Beatty, Macular response to supplementation with differing xanthophyll formulations in subjects with and without age-related macular degeneration, Graefe's Arch. Clinic. Experiment. Ophthalmol. 253 (8) (2015) 1231–1243. Available at: http://isrctn.org [Accessed February 11, 2021].

[6] K.O. Akuffo, J.M. Nolan, A.N. Howard, R. Moran, J. Stack, R. Klein, et al., Sustained supplementation and monitored response with differing carotenoid formulations in early age-related macular degeneration, Eye 29 (7) (2015) 902–912. Available at: http://www.nature.com/articles/eye201564 [Accessed February 11, 2021].

[7] E.Y. Chew, T.E. Clemons, J.P. SanGiovanni, R.P. Danis, F.L. Ferris, M.J. Elman, et al., Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression AREDS2 report no. 3, JAMA Ophthalmol. 132 (2) (2014) 142–149.

[8] D.A. Butterfield, M.L. Bader Lange, R. Sultana, Involvements of the lipid peroxidation product, HNE, in the pathogenesis and progression of Alzheimer's disease, Biochim. Biophys. Acta 1801 (8) (2010) 924–929.

[9] Y. Sawikr, N.S. Yarla, I. Peluso, M.A. Kamal, G. Aliev, A. Bishayee, Neuroinflammation in Alzheimer's Disease, Elsevier., 2017, pp. 33–57. Available at: https://www.sciencedirect.com/science/article/pii/S1474442215700165 [Accessed February 9, 2021].

[10] D. Gazzolo, S. Picone, A. Gaiero, M. Bellettato, G. Montrone, F. Riccobene, et al., Early pediatric benefit of lutein for maturing eyes and brain-an overview, Nutrients 13 (9) (2021).

[11] B.R. Hammond, L.S. Miller, M.O. Bello, C.A. Lindbergh, C. Mewborn, L.M. Renzi-Hammond, Effects of lutein/zeaxanthin supplementation on the cognitive function of community dwelling older adults: a randomized, double-masked, placebo-controlled trial, Front. Aging Neurosci. 9 (AUG) (2017). Available at: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00254/full [Accessed January 12, 2021].

[12] J. Feeney, C. Finucane, G.M. Savva, H. Cronin, S. Beatty, J.M. Nolan, et al., Low macular pigment optical density is associated with lower cognitive performance in a large, population-based sample of older adults, Neurobiol. Aging 34 (11) (2013) 2449–2456, https://doi.org/10.1016/j.neurobiolaging.2013.05.007. Available at:.

[13] L.M. Renzi, A. Iannaccone, E. Johnson, S. Kritchevsky, The relation between serum xanthophylls, fatty acids, macular pigment and cognitive function in the Health ABC Study, FASEB J. 22 (1 Supplement) (2008), 877.5-877.5. Available at: https://faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fasebj.22.1_supplement.877.5 [Accessed February 9, 2021].

[14] S.J. Spencer, A. Korosi, S. Layé, B. Shukitt-Hale, R.M. Barrientos, Food for thought: how nutrition impacts cognition and emotion, npj Sci. Food 1 (1) (2017). Available at: https://www.nature.com/articles/s41538-017-0008-y [Accessed February 9, 2021].

[15] C. Valls-Pedret, A. Sala-Vila, M. Serra-Mir, D. Corella, R. De La Torre, MÁ Martínez-González, et al., Mediterranean diet and age-related cognitive decline: a randomized clinical trial, JAMA Intern. Med. 175 (7) (2015) 1094–1103. Available at: https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2293082 [Accessed February 9, 2021].

[16] A. Otaegui-Arrazola, P. Amiano, A. Elbusto, E. Urdaneta, P. Martínez-Lage, Diet, cognition, and Alzheimer's disease: food for thought, Eur. J. Nutr. 53 (1) (2014) 1–23.

[17] R. Nouchi, T. Suiko, E. Kimura, H. Takenaka, M. Murakoshi, A. Uchiyama, et al., Effects of lutein and astaxanthin intake on the improvement of cognitive functions among healthy adults: a systematic review of randomized controlled trials, Nutrients 12 (3) (2020).

[18] S.E. Saint, L.M. Renzi-Hammond, N.A. Khan, C.H. Hillman, J.E. Frick, B. R. Hammond, The macular carotenoids are associated with cognitive function in preadolescent children, Nutrients 10 (2) (2018). Available at: www.mdpi.com/journal/nutrients [Accessed March 15, 2021].

[19] E.J. Johnson, R. Vishwanathan, M.A. Johnson, D.B. Hausman, A. Davey, T. M. Scott, et al., Relationship between serum and brain carotenoids, α -tocopherol, and retinol concentrations and cognitive performance in the oldest old from the georgia centenarian study, J. Aging Res. 2013 (2013) 1–13. Available at: http://www.hindawi.com/journals/jar/2013/951786/ [Accessed February 11, 2021].

[20] R. Vishwanathan, W. Schalch, E.J. Johnson, Macular pigment carotenoids in the retina and occipital cortex are related in humans, Nutr. Neurosci. 19 (3) (2016) 95–101.

[21] L.M. Renzi, M.J. Dengler, A. Puente, L.S. Miller, B.R. Hammond, Relationships between macular pigment optical density and cognitive function in unimpaired and mildly cognitively impaired older adults, Neurobiol. Aging 35 (7) (2014) 1695–1699.

[22] J. Feeney, C. Finucane, G.M. Savva, H. Cronin, S. Beatty, J.M. Nolan, et al., Low macular pigment optical density is associated with lower cognitive performance in a large, population-based sample of older adults, Neurobiol. Aging 34 (11) (2013) 2449–2456.

[23] R. Power, R.F. Coen, S. Beatty, R. Mulcahy, R. Moran, J. Stack, et al., Supplemental retinal carotenoids enhance memory in healthy individuals with low levels of macular pigment in a randomized, double-blind, placebo-controlled clinical trial, J. Alzheimer's Dis. 61 (3) (2018) 947–961. Available at: https://www.medra.org/servlet/aliasResolver?alias=iospress&doi=10.3233/JAD-170713 [Accessed December 10, 2020].

[24] R. Vishwanathan, A. Iannaccone, T.M. Scott, S.B. Kritchevsky, B.J. Jennings, G. Carboni, et al., Macular pigment optical density is related to cognitive function in older people, Age Ageing 43 (2) (2014) 271–275. Available at: http://www.epuap.org/gltreatment.

[25] E.T.M. Leermakers, S.K.L. Darweesh, C.P. Baena, E.M. Moreira, D.M. Van Lent, M. J. Tielemans, et al., The effects of lutein on cardiometabolic health across the life course: a systematic review and meta-analysis, Am. J. Clin. Nutr. 103 (2) (2016) 481–494.

[26] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, BMJ 339 (7716) (2009) 332–336. Available at: https://pubmed.ncbi.nlm.nih.gov/19622551/ [Accessed June 2, 2021].

[27] National Heart L and BI (NIH) website. No Title: quality Assessment Tools of Intervention Controlled Studies and for Observational Cohort and Cross-sectional Studies. Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

[28] N.T. Stringham, P.V. Holmes, J.M. Stringham, Effects of macular xanthophyll supplementation on brain-derived neurotrophic factor, pro-inflammatory cytokines, and cognitive performance, Physiol. Behav. (2019) 211.
[29] L. Renzi-Hammond, E. Bovier, L. Fletcher, L. Miller, C. Mewborn, C. Lindbergh, et al., Effects of a lutein and zeaxanthin intervention on cognitive function: a randomized, double-masked, placebo-controlled trial of younger healthy adults, Nutrients. 9 (11) (2017) 1246. Available at: http://www.mdpi.com/2072-6643/9/11/1246 [Accessed December 10, 2020].
[30] T.M. Scott, H.M. Rasmussen, O. Chen, E.J. Johnson, Avocado consumption increases macular pigment density in older adults: a randomized, controlled trial, Nutrients 9 (9) (2017) 919. Available at: http://www.randomization.com/ [Accessed January 12, 2021].
[31] C.G. Edwards, A.M. Walk, S.V. Thompson, G.E. Reeser, J.W. Erdman, N.A. Burd, et al., Effects of 12-week avocado consumption on cognitive function among adults with overweight and obesity, Int. J. Psychophysiol. 148 (2020) 13–24. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0167876019305598 [Accessed January 12, 2021].
[32] C.A. Lindbergh, L.M. Renzi-Hammond, B.R. Hammond, D.P. Terry, C.M. Mewborn, A.N. Puente, et al., Lutein and zeaxanthin influence brain function in older adults: a randomized controlled trial, J. Int. Neuropsychol. Soc. 24 (1) (2018) 77–90, https://doi.org/10.1017/S1355617717000534. Available at:[Accessed January 13, 2021].
[33] S.M. Barnett, N.A. Khan, A.M. Walk, L.B. Raine, C. Moulton, N.J. Cohen, et al., Macular pigment optical density is positively associated with academic performance among preadolescent children, Nutr. Neurosci. 21 (9) (2018) 632–640.
[34] K.M. Hassevoort, S.E. Khazoum, J.A. Walker, S.M. Barnett, L.B. Raine, B. R. Hammond, et al., Macular carotenoids, aerobic fitness, and central adiposity are associated differentially with hippocampal-dependent relational memory in preadolescent children, J. Pediatr. 183 (2017), 108–114.e1.
[35] A.M. Walk, N.A. Khan, S.M. Barnett, L.B. Raine, A.F. Kramer, N.J. Cohen, et al., From neuro-pigments to neural efficiency: the relationship between retinal carotenoids and behavioral and neuroelectric indices of cognitive control in childhood, Int. J. Psychophysiol. 118 (2017) 1–8, https://doi.org/10.1016/j.ijpsycho.2017.05.005. Available at:[Accessed January 12, 2021].
[36] C.N. Cannavale, K.M. Hassevoort, C.G. Edwards, S.V. Thompson, N.A. Burd, H. D. Holscher, et al., Serum lutein is related to relational memory performance, Nutrients 11 (4) (2019).
[37] C.G. Edwards, A.M. Walk, C.N. Cannavale, S.V. Thompson, G.E. Reeser, H. D. Holscher, et al., Macular xanthophylls and event-related brain potentials among overweight adults and those with obesity, Mol. Nutr. Food Res. 63 (15) (2019), 1801059. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/mnfr.201801059 [Accessed December 10, 2020].
[38] A.M. Walk, C.G. Edwards, N.W. Baumgartner, M.R. Chojnacki, A.R. Covello, G. E. Reeser, et al., The role of retinal carotenoids and age on neuroelectric indices of attentional control among early to middle-aged adults, Front. Aging Neurosci. 9 (JUN) (2017).
[39] N.A. Khan, A.M. Walk, C.G. Edwards, A.R. Jones, C.N. Cannavale, S.V. Thompson, et al., Macular Xanthophylls Are Related to Intellectual Ability Among Adults With Overweight and Obesity, MDPI AG, 2018.
[40] S. Ajana, D. Weber, C. Helmer, B.M. Merle, W. Stuetz, J.F. Dartigues, et al., Plasma concentrations of lutein and zeaxanthin, macular pigment optical density, and their associations with cognitive performances among older adults, Invest. Ophthalmol. Vis. Sci. 59 (5) (2018) 1828–1835.
[41] C.M. Mewborn, C.A. Lindbergh, T.L. Robinson, M.A. Gogniat, D.P. Terry, K.R. Jean, et al., Lutein and zeaxanthin are positively associated with visual–spatial functioning in older adults: an fMRI study, Nutrients 10 (4) (2018).
[42] C.A. Lindbergh, C.M. Mewborn, B.R. Hammond, L.M. Renzi-Hammond, J. M. Curran-Celentano, L.S. Miller, Relationship of lutein and zeaxanthin levels to neurocognitive functioning: an fMRI study of older adults, J. Int. Neuropsychol. Soc. 23 (1) (2017) 11–22, https://doi.org/10.1017/S1355617716000850. Available at:.
[43] U. Chakravarthy, T.Y. Wong, A. Fletcher, E. Piault, C. Evans, G. Zlateva, et al., Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis, BMC Ophthalmol. 10 (1) (2010) 31. Available at: http://www.biomedcentral.com/1471-2415/10/31.
[44] C.C. Birda, N.M.M. Bressler, S.B.B. Bressler, I.H.H. Chisholm, G. Coscas, M.D. D. Davis, et al., An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group, Surv. Ophthalmol. 39 (5) (1995) 367–374. Available at: http://www.uc.pt/en/fmuc/phdhs/Courses/translationalresearchinretinaldegenerativediseases/5_Bird_A_et_al.CLASSIFICACAO_INTERNACIONAL_Am_J_Ophthalmol_2009.pdf [Accessed February 5, 2019].
[45] M. Bostelmann, P. Lavenex, P. Banta Lavenex, Children five-to-nine years old can use path integration to build a cognitive map without vision, Cognit. Psychol. 121 (May) (2020), 101307, https://doi.org/10.1016/j.cogpsych.2020.101307. Available at:.
[46] J.M. Kronschnabl, T. Kneip, L.M. Weiss, M. Bergmann, Bodyweight change and cognitive performance in the older population, PLoS One 16 (4 April) (2021).
[47] E.J. Johnson, A possible role for lutein and zeaxanthin in cognitive function in the elderly, Am. J. Clin. Nutr. 96 (5) (2012). Available at: https://pubmed.ncbi.nlm.nih.gov/23053547/ [Accessed May 17, 2021].
[48] C. Yuan, H. Chen, Y. Wang, J.A. Schneider, W.C. Willett, M.C. Morris, Dietary carotenoids related to risk of incident Alzheimer dementia (AD) and brain AD neuropathology: a community-based cohort of older adults, Am. J. Clin. Nutr. 113 (1) (2021) 200–208.
[49] J. Lakey-Beitia, D. Jagadeesh Kumar, M.L. Hegde, K.S Rao, Carotenoids as novel therapeutic molecules against neurodegenerative disorders: chemistry and molecular docking analysis, Int. J. Mol. Sci. 20 (22) (2019). Available at: https://pubmed.ncbi.nlm.nih.gov/31703296/ [Accessed June 2, 2021].
[50] B. Olmedilla-Alonso, B. Beltrán-De-Miguel, R. Estévez-Santiago, C. Cuadrado-Vives, Markers of lutein and zeaxanthin status in two age groups of men and women: dietary intake, serum concentrations, lipid profile and macular pigment optical density, Nutr. J. 13 (1) (2014). Available at: https://pubmed.ncbi.nlm.nih.gov/24889185/ [Accessed May 11, 2021].
[51] T. Lawler, J. Korger, Y. Liu, Z. Liu, J.W. Pak, N. Barrett, et al., Serum and macular carotenoids in relation to retinal vessel caliber fifteen years later, in the second carotenoids in age-related eye disease study, Invest. Ophthalmol. Vis. Sci. 62 (9) (2021).
[52] S. Ogoh, Relationship between cognitive function and regulation of cerebral blood flow, J. Physiol. Sci. 67 (3) (2017) 345–351.