

Original Communication

Egg Consumption Alters Lutein Transport in the Circulation and Enhances Macular Pigment Density in Older Adults

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Abstract

Background: Lutein, a dietary carotenoid, is selectively taken up into the retina (measured as macular pigment optical density, MPOD) and brain. Thus, MPOD and brain lutein content are positively associated with cognition in older adults. However, the relationship between serum lutein and cognition is inconsistent. Therefore, serum lutein, which is carried primarily by high-density lipoproteins (HDLs) and to a lesser extent by low-density lipoproteins (LDLs) and very low-density lipoproteins (VLDLs), may not accurately reflect neural lutein levels. Eggs, which modulate circulating lipoproteins, are particularly effective at enriching lutein in neural tissue even when the serum lutein response is small. **Methods:** This study conducted post hoc analyses of a randomized controlled trial to test the effects of consuming 2 eggs vs. 4 oz. of egg whites daily for 6 months on lutein transport in the circulation, and the subsequent relationship to MPOD and cognitive function in older adults (50–85 years old; 20 women, 21 men). The primary outcome of determine the relationship between lutein contained in HDL and MPOD. A secondary outcome evaluated the relationship between HDL-contained lutein and cognitive function. Blood draws, MPOD measurements, and cognitive assessments were performed at baseline and after 6 months. **Results:** The change from baseline for MPOD was significant for the egg group ($p < 0.05$) but not for the egg white group (0.09 ± 0.04 OD vs. 0.02 ± 0.05 OD, respectively). Similarly, the change in the proportion of serum lutein carried by the HDL (LDL+VLDL) was significant in the egg group ($59 \pm 11\%$ to $67 \pm 18\%$; $p < 0.05$) but not in the egg white group (67 ± 22 to $60 \pm 24\%$) after 6 months. However, there were no significant differences between groups. When evaluating only participants who increased the proportion of serum lutein carried by HDL in response to egg consumption ($n = 14$), a trend between this proportion and MPOD was observed ($p = 0.07$). An increase in the proportion of serum lutein on the HDL was also associated with improved visual memory and learning ($p < 0.04$). **Conclusions:** In this study, the relative distribution of serum lutein between the HDL and LDL reflected lutein accumulation in neural tissue and cognitive status in older adults. Thus, further investigation into the effects of eggs on promoting cognitive health by enhancing lutein delivery to the brain is warranted. **Clinical Trial Registration:** This study was registered at ClinicalTrials.gov (NCT01621646, <https://clinicaltrials.gov/study/NCT01621646>).

Keywords: lutein; eggs; high-density lipoprotein; cognition; macular pigment; older adults

1. Introduction

Lutein is a fat-soluble dietary carotenoid found in a variety of fruits and vegetables, including broccoli, green peas, and dark green leafy vegetables [1]. Lutein selectively accumulates in the primate retina and brain. In the retina, lutein and its isomer zeaxanthin form macular pigment (MP), which filters harmful blue light and plays a critical role in visual function [2]. Randomized controlled trials have reported that dietary sources of lutein significantly increase macular pigment optical density (MPOD) [3]. MPOD is positively correlated with concentrations of lutein in the brain and is used as a biomarker of lutein content in neural tissue [4]. Cognition studies consistently report a positive association between MPOD, brain lutein concentrations, and cognitive performance in younger and

older adults [5]. However, increasing serum lutein concentration through increased dietary or supplemental intake does not consistently enhance MPOD or cognitive function [6].

Lutein is mainly transported in the circulation on high-density lipoproteins (HDL) [7]. Serum HDL is correlated with MPOD in humans [8], and HDL deficiency impairs neural lutein accumulation in chicks [9]. These findings suggest a role for HDL in transporting lutein to neural tissue. Thus, dietary sources of lutein that also modulate circulating lipoproteins, particularly HDL, may enhance lutein deposition in neural tissue and benefit visual function and cognition.

Egg yolks are a dietary source of lutein, and moderate egg consumption has been linked to better cognition in



older adults [10]. Despite containing modest levels of lutein (0.5 mg/egg), consumption of eggs has a striking effect on MPOD [11]. Given extensive evidence demonstrating that eggs modify blood lipoproteins, we sought to explore whether the distribution of lutein among serum lipoproteins mediates neural lutein accumulation, i.e., MPOD. Our primary outcome was to determine the impact of eggs on the transport of lutein on lipoproteins on MPOD. A secondary outcome was to evaluate the relationship between lutein contained in HDL and cognitive function. This exploratory study used a post-hoc analysis to investigate the effects of consuming whole eggs versus egg whites for 6 months on serum lutein transport and MPOD. We then assessed the relationship between change in serum lutein transport and cognitive performance.

2. Materials and Methods

2.1 Subjects

Forty-three healthy, non-smoking men and women (50–85 years old; 20 women, 21 men) were recruited from the general population from July 2012 through May 2015. All subjects completed the study by November 2015. Subjects underwent a screening examination that included medical history, physical examination, and routine blood clinical chemistry profile. Inclusion criteria included low intake of lutein-rich foods. Exclusion criteria included egg allergy and history of liver, kidney, or pancreatic disease, anemia, active bowel disease or resection, and bleeding disorders. Individuals taking medications interfering with fat absorption were also excluded. Other exclusion criteria included current use of steroids, antipsychotic, antitmanic, monoamine inhibitors, or dementia medications. Additionally, use of any nutrient supplement for the previous 2 months was an exclusion. Aspirin and non-steroidal anti-inflammatory drugs were not considered exclusions.

2.2 Experimental Design

The study was conducted using a post-hoc analysis of a previously conducted randomized controlled trial [12] which was approved by the Human Investigative Review Committee of Tufts University and was carried out in accordance with the guidelines of the Declaration of Helsinki. Informed consent was obtained from all subjects. This study was registered at ClinicalTrials.gov (NCT01621646).

2.3 Study Protocol

Details of the study protocol have been described previously [12]. Briefly, upon enrollment, the research dietitian randomized subjects to either the egg or egg white group using a randomization plan generator (<https://randomizer.org>). At baseline, 3 months, and 6 months, subjects provided a fasting blood sample. Serum was separated from red blood cells via centrifugation ($880 \times g$, 10 min, 4°C) and were stored at -80°C until analysis. MPOD and cognitive function measurements were also performed at these

visits. A food frequency questionnaire was administered [13] and analyzed by the research dietitian. Subjects were instructed to not change their dietary habits throughout the study period.

Subjects visited the study center monthly to pick up supplies of either: (1) 100 g of eggs (equal to 2 large eggs containing 0.5 mg lutein), or (2) egg whites (4 oz. pasteurized, homogenized liquid egg whites) containing no lutein. Subjects were also given recipes for incorporation of eggs/egg whites into their daily meals. If a subject requested hard-boiled eggs, they were given 1 dozen cooked eggs at a time. At monthly visits, compliance was monitored by an interview—the dietitian would ask specific questions on the daily intake of intervention foods and review compliance calendars. Twice-monthly telephone monitoring occurred to check on subjects' food supplies and to query them for any situation that may have occurred with food products. Subjects were encouraged to contact the kitchen laboratory or the dietitian if there was any question about the quality or amount of food supplies they received.

2.4 Serum Lutein and Lipoprotein Analysis

Serum lutein was extracted and analyzed in the primary study by high performance liquid chromatography using a previously described method [14]. The method yields adequate separation of all-trans lutein, cis lutein, all-trans-zeaxanthin, cis-zeaxanthin, cryptoxanthin, alpha-carotene, 13-cis-beta-carotene, all-trans-beta-carotene, and 9-cis-beta-carotene, as well as four geometrical isomers of lycopene (15-cis, 13-cis, 9-cis, and all-trans lycopenes). Carotenoids were quantified at 455 nm by determining peak areas in the high performance liquid chromatography (HPLC). Concentrations were corrected for extraction and handling losses by monitoring the recovery of the echinenone internal standard. The lower limit of detection with this method is 0.2 pmol for each carotenoid. Serum HDL, LDL, and triglycerides (used to determine very low-density lipoprotein (VLDL)) were measured using a Beckman Coulter AU400 (Beckman Coulter Life Sciences, Indianapolis, IN, USA) standard operating procedure.

2.5 Carotenoid Quantification on Serum Lipoproteins

Removal of apolipoprotein (apo) B-containing lipoproteins (LDL and VLDL) from serum was performed using a MgCl_2 (#M8266, Sigma-Aldrich, St. Louis, MO, USA)/phosphotungstic acid (#455970, Sigma-Aldrich, St. Louis, MO, USA) precipitation method, producing pure HDL in serum [15]. Carotenoids in HDL were extracted from serum using a modified Folch method [16] and quantified using reverse-phase HPLC [14]. Lutein in HDL is expressed as a concentration ($\mu\text{mol/L}$) and as a percentage of the total amount of lutein in serum. To confirm clean separation of HDL from LDL and VLDL and estimate HDL recovery, serum Apo A and Apo

Table 1. Cognitive test battery.

Domain	Cognitive test	Description
Attention Tests	Choice Reaction Time	2-choice reaction time test with two possible stimuli and two possible responses
	Rapid Visual Information Processing	Tests sustained attention
Visual Memory Tests	Delayed Match to Sample	Test of simultaneous and delayed matching to sample
	Paired Associate Learning	Assess visual memory and new learning
Executive Function, Working Memory, Planning Tests	Spatial Span	Memory Assesses Working
	Spatial Span Reverse	Memory Assesses Working Memory
	Spatial Working Memory	Tests ability to retain spatial information and manipulate items in working memory
	Stockings of Cambridge	Test of spatial planning and spatial working memory

B concentrations (mg/dL) were determined before and after precipitation using an enzymatic colorimetric assay according to manufacturer's instructions (Beckman Coulter AU 400 system) [17]. Apo A recovery was ~97%, while Apo B was not detectable after precipitation. For each carotenoid, recovery was calculated as the sum of each in HDL and Apo B lipoprotein fractions divided by the serum total value of that carotenoid multiplied by 100. The average recovery of each carotenoid was >90%. The recovery of lutein was $92.9 \pm 7.2\%$.

2.6 MPOD Measurement

MPOD was measured in the primary study using heterochromatic flicker photometry [18]. Measurements were conducted using a macular densitometer (Macular Metrics Corp, Rehoboth, MA, USA) that has been simplified and modified for practical clinical use. MPOD at 0.5° eccentricity was assessed. This MPOD measurement protocol is reliable and safe in older adults [19].

2.7 Cognitive Tests

Cognitive performance was assessed in the primary study using a computerized battery of tests designed to evaluate multiple cognitive domains—memory, processing speed, and attention (Table 1, CANTAB, Cambridge Cognition)—and has been described elsewhere [20]. Subjects performed each test with a touch-screen tablet. Standardized, scripted instructions were provided for each test.

2.8 Sample Size Calculation

Standard sample size calculation procedures for the study estimated that 20/group gives an 80% chance that a 0.05 level test of significance will find a significant difference in MPOD. This was based on a previous study that reported a significant increase in MPOD with one egg/day for 12 weeks [21]. However, because this was a post hoc analysis, no sample size calculation was performed.

2.9 Statistical Analyses

The egg and egg white groups were compared for possible differences in characteristics (i.e., age, sex, education, body mass index (BMI, kg/m²) and HDL-associated lutein (as a concentration and as a percentage of serum total lutein)) at baseline using independent *T*-tests or Chi-Square for categorical variables. In all participants, baseline serum HDL and Apo B lipoprotein fractions were compared to determine differences in carotenoid concentrations using paired *T*-tests. One-way analysis of variance (ANOVA) with Tukey's Honestly Significant Difference was performed to determine carotenoid distribution within each lipoprotein fraction. Pearson's correlation was used to evaluate associations between HDL-associated lutein, MPOD, or serum total lutein and cognitive test scores at baseline. Correlations were adjusted for age and education.

Differences in serum lutein (total and HDL-associated), lipoproteins, and MPOD before and after each intervention were determined using paired *T*-tests. Pearson's correlation was used to examine associations between changes in HDL-associated lutein and changes in MPOD. We adjusted for age and baseline MPOD as both may be associated with change in MPOD [22,23]. In this study, BMI was not associated with MPOD changes, so we did not adjust for it. Pearson's correlation was also used to determine associations between change in HDL-associated lutein and change in cognitive test scores, adjusting for age, education, and baseline cognitive test score. To determine whether change in HDL-associated lutein is an independent predictor of change in cognitive test scores, multiple linear regression was performed. The model included age, education, and baseline cognitive test scores as covariates. For all analyses, significance was set at the 0.05 level. The *p* values for non-significant results >0.1 are not reported. Given the exploratory nature of this study, no adjustment of *p* values for type I errors due to multiple comparisons was performed. Correlations with *p* < 0.1 are mentioned but not considered statistically significant. SAS 9.4 (SAS products, Cary, NC, USA) was used for data analysis.

3. Results

3.1 Baseline Characteristics and Carotenoid Profile in Lipoproteins

Forty-one subjects completed the study (95% of enrolled). Two subjects dropped out due to non-compliance to the study protocol. No adverse events were reported. There were no significant differences between the egg and egg white groups in baseline measures of age, sex, BMI, and education (Table 2). Compliance for the study intervention was 96% (egg white group: 98%; egg 94%).

Table 2. Baseline characteristics of participants, mean (SD).

	Egg (n = 21)	Egg white group (n = 20)
Age (years)	63.4 (11.6)	61.2 (8.1)
Sex (female/male)	9/12	11/9
Education (0–5 scale)*	4.0 (0.9)	3.6 (0.9)
BMI (kg/m ²)	24.2 (3.1)	24.8 (2.6)

*0, 0–8th grade; 1, high school; 2, high school graduate; 3, some college (includes associate's degree, technical degree, and apprenticeship); 4, college graduate (4-year degree); 5, graduate degree. BMI, body mass index; SD, standard deviation.

To characterize the carotenoid content in both HDL and Apo B (LDL, VLDL) lipoproteins, we analyzed the carotenoid profiles in a subset of subjects at baseline (10 subjects randomly selected from each intervention group). Serum carotenoid profiles in HDL and Apo B lipoprotein fractions are shown in Fig. 1 (expressed as $\mu\text{mol/L}$) and Fig. 2 (for each carotenoid, expressed as % of total concentration). Lutein concentration and percent of total lutein in serum were significantly greater in HDL compared to the Apo B lipoprotein fraction ($p < 0.001$), while zeaxanthin and cryptoxanthin content were similar between the two fractions, whereas the percent contribution of cryptoxanthin was significant. The more non-polar carotenoids (alpha-carotene, beta-carotene, lycopene) were significantly greater in the Apo B lipoprotein fraction compared to the HDL fraction ($p < 0.001$). Within the Apo B lipoprotein fraction, lycopene was significantly greater than all other carotenoids, while lutein content was significantly lower than all carotenoids except zeaxanthin ($p < 0.05$). In the HDL fraction, lutein was significantly greater than all carotenoids except zeaxanthin. Lycopene was significantly lower than all other carotenoids ($p < 0.05$). These results are consistent with a previous study that used differential centrifugation to separate serum lipoproteins for carotenoid analysis [24].

3.2 Effect of Eggs and Egg Whites on Serum Lutein, Lutein Transport, and MPOD

The effect of consuming eggs vs egg whites for 6 months on serum lutein, lipoproteins, and MPOD is shown in Table 3. Measures of lutein content in HDL and total lutein in serum did not differ between intervention groups

at baseline. In the egg group, total lutein concentrations in serum slightly increased after 6 months, but this was not statistically significant. Lutein concentrations in the HDL fraction of serum significantly increased by 26%, and the percentage of serum lutein on HDL increased by 14% ($p < 0.05$ for both). In the egg white group, lutein concentration in the HDL fraction of serum, and the percent of serum lutein on HDL decreased over 6 months ($p < 0.05$). Total serum lutein did not change in response to egg white intake. Egg, but not egg white, consumption increased the ratio of HDL to LDL and VLDL in serum. MPOD increased significantly from baseline in the egg group by 21% ($p < 0.05$), but no significant baseline-to-6-month change was observed in the egg white group. No significant between-group difference was detected. Collectively, these results suggest that eggs enhance the amount of lutein on HDL, the proportion of serum lutein on HDL, and lutein accumulation in neural tissue, however, given the lack of a between group difference, this would require further testing.

3.3 Relationship Between Change in HDL-Associated Lutein and Change in MPOD

Next, we assessed whether the observed increases in MPOD and HDL-associated lutein in response to egg intake are related. The relationship between change in MPOD and change in serum lutein or HDL-associated lutein in subjects from the egg and egg white groups are reported in Table 4. None of the circulating lutein measures were associated with MPOD when all subjects were included. This is consistent with other carotenoid intervention studies, which have observed little to no serum response to a lutein intervention despite responses in MPOD [11,21]. Interestingly, when we analyzed only those subjects who increased circulating lutein content (any change >0) in response to egg consumption, we observed a non-significant trend between percent serum lutein on HDL and MPOD ($p = 0.07$). This suggests that individuals who increase the proportion of serum lutein on HDL in response to egg intake tend to have increased lutein accumulation in neural tissue.

The correlation between change in percent serum lutein on HDL and MPOD in this subset of egg group participants exhibits an abnormal pattern: two distinct linear correlations (Fig. 3A). To investigate this further, we evaluated the characteristics of subjects within each correlation group. Subjects within the top correlation (re-illustrated in Fig. 3B) had significantly higher baseline MPOD and change in MPOD compared to subjects in the bottom correlation. Other factors, such as BMI, oxidized LDL, and baseline HDL and LDL did not differ between correlation groups. When the two correlation groups were analyzed separately, we observed a significant correlation ($r = 0.87$, $p = 0.02$) between change in percent lutein on HDL and MPOD in subjects who had higher baseline MPOD and change in MPOD (Fig. 3B), which likely drove this correlation.

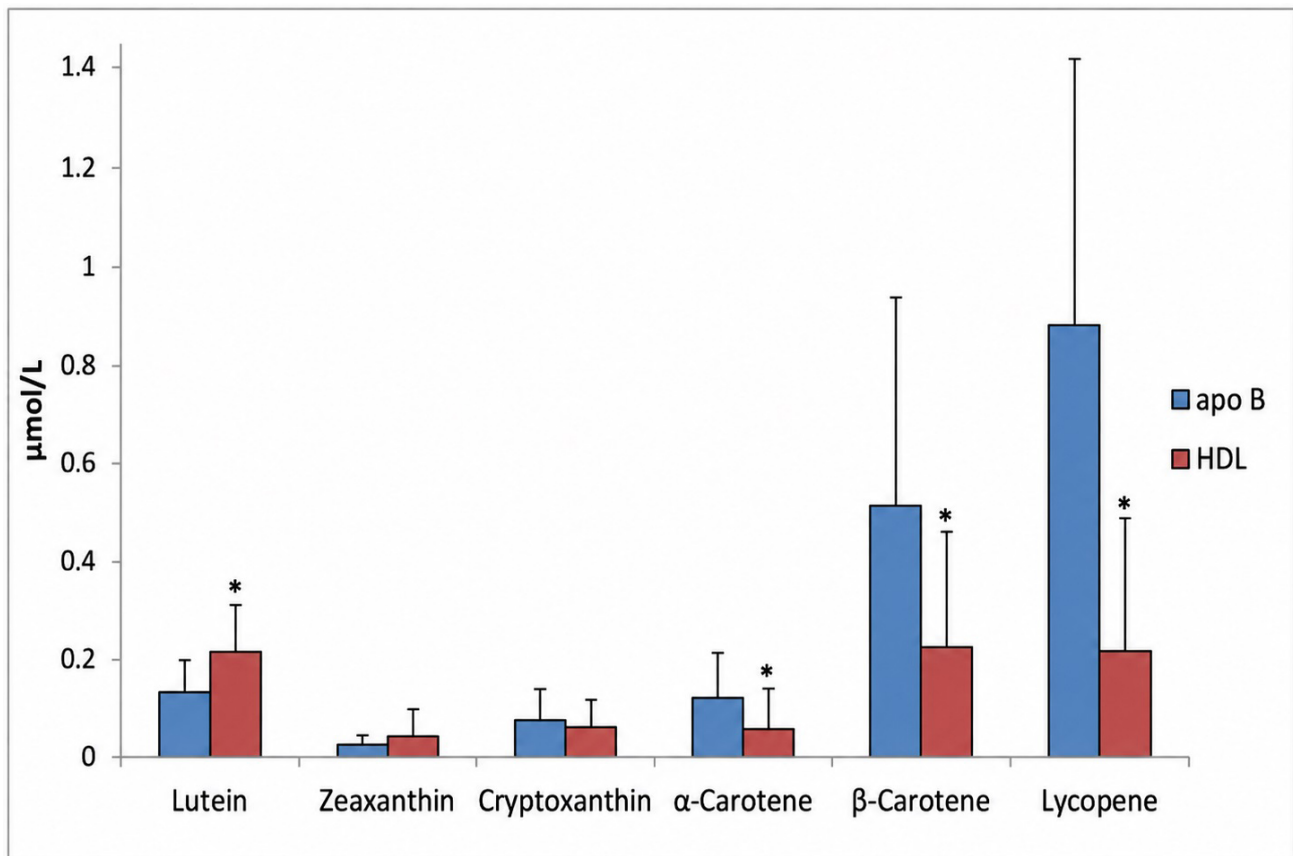


Fig. 1. Baseline carotenoid profile in serum Apo B lipoprotein and HDL (μmol/L, Mean ± SD) in older adults (n = 20). HDL, high-density lipoproteins. Significantly different from Apo B lipoprotein fractions (Paired *T* test, * *p* < 0.05).

Table 3. Effect of 2 eggs vs. 4 oz. egg whites on serum lutein, lipoproteins, and MPOD.

	Egg group (n = 21)		Egg white group (n = 20)	
	Baseline	6 months	Baseline	6 months
Serum Lutein (μmol/L)	0.31 ± 0.11	0.35 ± 0.12	0.31 ± 0.12	0.27 ± 0.12
HDL Lutein (μmol/L)	0.19 ± 0.08	0.24 ± 0.10*	0.21 ± 0.10	0.17 ± 0.10*
% Lutein on HDL	59 ± 11	67 ± 18*	67 ± 22	60 ± 24*
HDL/(LDL+VLDL)	0.51 ± 0.19	0.59 ± 0.23*	0.53 ± 0.23	0.59 ± 0.25
MPOD (OD)	0.42 ± 0.12	0.51 ± 0.15*	0.41 ± 0.14	0.43 ± 0.15

*Significantly different from baseline (Paired *T*-test, *p* < 0.05). MPOD, macular pigment optical density; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

Table 4. Relationship between change in biomarkers of circulating lutein and change in macular pigment optical density in adults consuming either eggs or egg whites.

	Egg group		Egg white group	
	All (n = 21)	Subset ^a (n = 12)	All (n = 20)	Subset ^a (n = 6)
Serum Lutein	-0.12	-0.40	0.05	-0.24
HDL Lutein	-0.06	-0.28	-0.05	--
% Lutein in HDL	-0.14	0.57 ^b	-0.14	0.03

^aPearson's correlation coefficient, adjusted for age and baseline MPOD. Participants who increased serum lutein; HDL lutein (egg: n = 13, egg white: n = 3); % Lutein in HDL (egg: n = 14, egg white: n = 6).

^b*p* = 0.07.

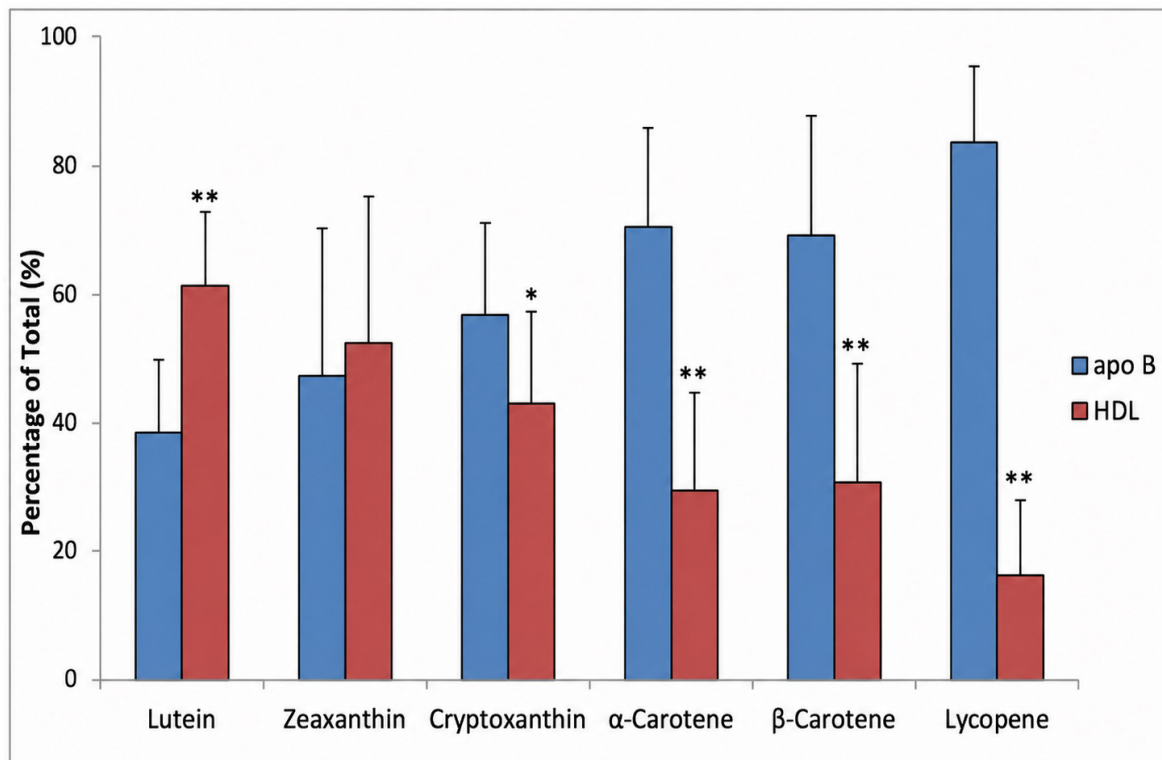


Fig. 2. Baseline carotenoid profiles in serum Apo B lipoprotein and HDL (for each carotenoid, % of total serum concentration, Mean $\pm$ SD) in older adults (n = 20). Significantly different from Apo B lipoprotein fractions (Paired *T* test, * $p < 0.05$, ** $p < 0.01$).

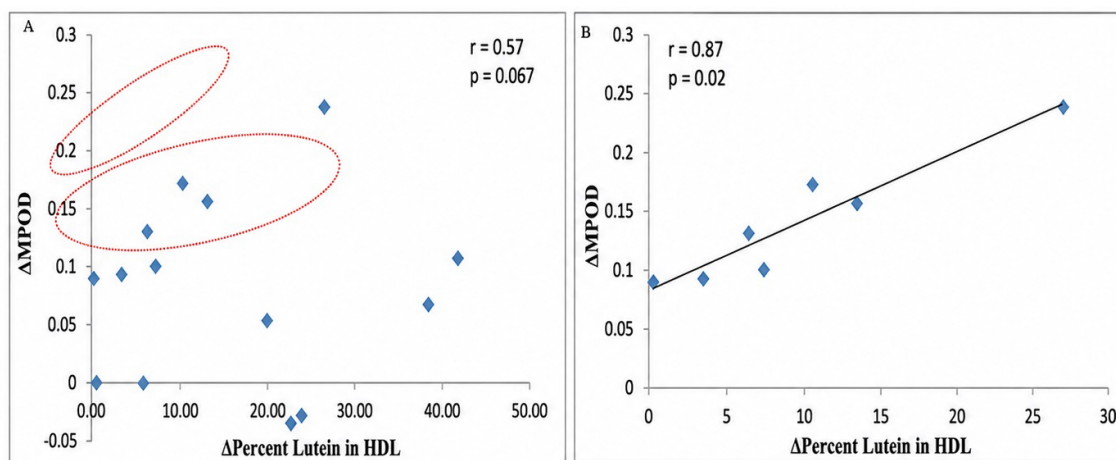


Fig. 3. Relationship between change in percent lutein in HDL and MPOD. (A) Relationship between change in percent lutein in HDL and MPOD participants who improved percent lutein in HDL in response to egg intake (n = 14). (B) Reillustration of top ellipse from (A) (see top dashed ellipse).

3.4 Relationship Between Proportion of Lutein on HDL and Cognitive Performance in Older Adults

We next assessed whether increasing the percentage of serum lutein on HDL relates to improvements in cognitive function. First, we report the relationships between baseline percent lutein on HDL, MPOD, and cognitive test scores in all subjects (Table 5). MPOD ($p = 0.07$) and percent serum lutein on HDL ($p = 0.04$) were moderately inversely associated with the total number of errors on a

measure of visual memory and learning—paired associates learning (PAL). MPOD also tended to be associated with a measure of sustained attention—Rapid Visual Information Processing (RVP) ($p = 0.04$). Serum lutein was not related to cognition. The relationship between change in percent serum lutein on HDL and change in cognitive performance is shown in Table 6.

In exploratory, unadjusted analyses, changes in the percentage of serum lutein on HDL were associated with

Table 5. Baseline correlations between MPOD, % lutein in HDL, or serum total lutein and cognition (n = 41).

	MPOD	% Lutein in HDL	Serum Lutein
CRT, mean latency	0.03	0.08	−0.02
DMS, percent correct	−0.10	0.22	0.07
SSP, forward	0.04	0.10	0.21
SSP, reverse	0.01	−0.03	0.10
PAL, total errors	−0.30 ($p = 0.07$)	−0.34 ($p = 0.04$)	−0.23
PAL, stages completed	0.22	0.20	0.24
SWM, between errors	−0.16	0.01	0.07
SWM, strategy	0.07	−0.05	0.08
RVP A	0.34 ($p = 0.04$)	−0.09	0.28
RVP B	0.12	0.11	0.29
SOC, number problems solved	0.10	0.04	0.06

R value represents partial Pearson's correlation coefficient, adjusted for age and education.

p values for non-significant results >0.1 are not reported.

CRT, choice reaction time; DMS, delayed matching to sample; SSP, spatial span; PAL, paired associates learning; SWM, spatial working memory; RVP, rapid visual information processing; SOC, stockings of cambridge.

Table 6. The relationship between changes in the percentage of lutein in HDL and changes in cognition in older adults (n = 41).

	R value	p value	Beta-coefficient	p value
CRT, mean latency	−0.17	0.33	−0.07	0.36
DMS, percent correct all	0.37	0.03	1.10	0.01
SSP, forward	0.09	0.63	−0.0001	0.99
SSP, reverse	0.09	0.60	0.001	0.85
PAL, total errors	−0.20	0.24	−0.10	0.36
PAL, stages completed	0.47	0.005	0.01	0.008
SWM, between errors	0.29	0.09	0.23	0.08
SWM, strategy	−0.09	0.62	−0.02	0.59
RVP A	−0.17	0.33	−0.001	0.29
RVP B	−0.19	0.29	−0.001	0.41
SOC, # problems solved	−0.21	0.23	−0.02	0.19

R value represents partial Pearson's correlation coefficient, adjusted for age, education, baseline cognitive test score. Beta-coefficient was generated using multiple linear regression with age, education, and baseline cognitive test score included in the model. CRT, choice reaction time; DMS, delayed matching to sample; SSP, spatial span; PAL, paired associates learning; SWM, spatial working memory; RVP, rapid visual information processing; SOC, stockings of cambridge.

changes in selected visual memory outcomes for two visual memory tests—delayed match to sample (DMS) and PAL. MPOD also tended to be related to improved PAL scores (fewer total errors ($r = 0.29$, $p = 0.09$; $\beta = 40.1$, $p = 0.09$)). Change in serum total lutein was not related to change in cognition. To determine whether our cognitive findings regarding HDL-associated lutein could be attributed to choline content in eggs, serum choline was ana-

lyzed in a subset of subjects ($n = 22$) [25]. We then added this variable to our linear regression model. For DMS and PAL (stages completed), the beta-coefficients for percent serum lutein on HDL remained significant. Moreover, for PAL (total errors), the beta-coefficient for percent serum lutein on HDL became significant ($\beta = -0.27$, $p = 0.048$).

4. Discussion

This exploratory study investigated how eggs enrich lutein in neural tissue, and how this change relates to short-term cognitive health in older adults. We report that consumption of 2 eggs per day for 6 months alters lutein transport in the circulation by increasing the proportion of lutein on HDL. Increasing the proportion of lutein on HDL is related to increased lutein in neural tissue and improved cognitive performance.

4.1 Eggs Alter Circulating Lutein Transport and Enhance Neural Lutein Accumulation

Our findings that daily egg consumption increases MPOD are consistent with previous short-term (<6 month) intervention studies in adults [11,21]. Also similar to our results, these studies found that serum lutein increased to a lesser extent than MPOD in response to either 2–4 eggs per day for 5 weeks [11] or did not change in response to 6 eggs/week for 12 weeks [21]. Our study suggests that modulation of serum lipoproteins, particularly increasing the ratio of HDL to LDL and VLDL, may partially explain the observed enhancement in MPOD in response to eggs.

Previous evidence suggests HDL may be important for delivering lutein to neural tissue [9]. Egg consumption is consistently shown to increase serum lipoproteins [26]. However, the degree of this increase and the relative change of HDL to LDL and VLDL depend on several factors like

age, genetics (e.g., polymorphisms in ATP-binding cassette transporter: *ABCG5*), and “dose” of egg. Indeed, an increase in serum HDL was observed in response to 2 or 4 eggs per day [11]. By contrast, a lower dose of eggs (6 per week, or <1 per day) did not result in serum lipoprotein changes [21]. Interestingly, two interventions in which egg consumption (one per day for 2 or 3 months) increased serum lutein but not HDL, did not enhance MPOD in adults [27,28]. Our results suggest that increasing the proportion of circulating lutein on HDL in response to egg intake may increase MPOD in some individuals. Thus, delivery of lutein to neural tissue appears to depend on the partitioning of serum lutein to HDL relative to LDL and VLDL. The mechanism by which lutein on HDL preferentially delivers to neural tissue remains unknown. However, *in vitro* studies investigating alpha-tocopherol delivery to the brain suggest that scavenger receptor class B, type I (SR-BI) at the blood-brain barrier facilitates preferential uptake of this fat-soluble nutrient from HDL [29].

The relationship between the proportion of serum lutein on HDL and MPOD may depend on a number of factors. Given that a significant association was only observed in participants with higher baseline MPOD and a greater change in MPOD in response to eggs, it is possible that some individuals may be predisposed to take up more lutein into neural tissue and may be more sensitive to dietary lutein interventions with regard to lutein transport on HDL and MPOD response. A number of genetic variants, including lipoprotein-related genes, have been identified as independent predictors of MPOD [30]. Future studies should investigate the effect of these genetic variants on delivery of HDL-associated lutein to neural tissue.

The effect of eggs on particular subclasses of HDL and LDL has been investigated. In young healthy adults, consuming eggs increases large HDL and LDL particles [31], as opposed to small HDL and LDL. Whether specific subclasses of HDL differentially deliver lutein to neural tissue remains unknown. Future studies should investigate the relationship between MPOD, and the proportion of serum lutein carried on subclasses of HDL and LDL.

4.2 Enhancing the Proportion of Serum Lutein on HDL is Related to Improved Cognitive Function

We found that increasing the proportion of serum lutein on HDL is related to improved cognition, particularly visual recognition memory and learning. MPOD, but not serum lutein, is consistently related to cognitive performance [32,33,34,35,36], with a notable exception in a centenarian population in which serum lutein was related to brain lutein concentration and cognitive test scores [37]. While the mechanism of the benefits of neural lutein on cognition remain unclear, lutein may inhibit lipid peroxidation [38,39], modulate brain membrane properties, or alter synaptic membrane function [40].

The observed relationship between lutein on HDL and cognition is novel. Our study found that both the proportion of serum lutein on HDL and MPOD were associated with the same cognitive tests. While this observation could be attributed to these tests being more sensitive than the others, this result lends support to the hypothesis that the relative distribution of serum lutein on HDL reflects lutein accumulation in neural tissue, and thus cognitive status in older adults. The use of this biochemical measure in future lutein-cognition studies may be warranted.

4.3 Limitations

A limitation of this study is that eggs are nutrient-dense foods and likely influence cognition through the actions of multiple nutrients important for the brain (e.g., choline, vitamin B12). While we attempted to account for the effects of choline in our analyses, given the small sample size of this study, it was not possible to adjust for all factors in our regression model. Given that this study was explorative, a sample size was not determined, and we did not conduct multiple comparison analyses; the results should be interpreted as being modest. Another limitation is the method used for the separation of lipoproteins. While the ultracentrifugation method is preferred, we were limited to sampling archived samples. Studies have noted that freezing prior to ultracentrifugation can decrease measurable HDL free cholesterol compared to fresh serum [41]. Our findings provide rationale for future studies that can create a more comprehensive model to tease out the effects of eggs on lutein transport to neural tissue and cognition in adults. Another limitation of this study is that it was conducted over a relatively short period of time. Studies of longer duration must be performed to determine long-term effects of incorporating eggs into a healthy diet on lutein content in HDL, MPOD, and cognitive function in older adults.

5. Conclusions

A dietary intervention with eggs effectively modulates lutein transport in the circulation by enhancing the relative amount of serum lutein carried on HDL. This effect is related to enhanced MPOD and cognitive function in older adults. However, these results are an association and not a cause/effect. Further studies are needed to evaluate the mechanisms by which lutein transport into neural tissue the effects visual and cognitive function. Our findings have important implications for incorporating eggs into a healthy diet to promote age-related cognitive health.

Availability of Data and Materials

Data described in the manuscript, code book and analytic code will be made available upon request pending application and approval.

Author Contributions

The clinical study was conducted and supervised by EJJ and HMR. TMS was responsible for the clinical testing. All authors (EMH, TMS, HMR, EJJ) helped draft the manuscript and revise it critically for important intellectual content. Data analysis was conducted by EMH. All authors (EMH, TMS, HMR, EJJ) approved the final version. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Human Investigative Review Committee of Tufts University and was carried out in accordance with the guidelines of the Declaration of Helsinki. Informed consent was obtained from all subjects. This study was registered at ClinicalTrials.gov (NCT01621646, <https://clinicaltrials.gov/study/NCT01621646>).

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Conflicts of Interest

The authors declare no conflicts of interest. John Nolan served as a Guest Editor of the Special Issue but had no involvement in the selection of reviewers, peer-review process, or editorial decision-making for this article because of a potential conflict of interest with the corresponding author. Full responsibility for the editorial process for this article was delegated to Torsten Bohn.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/IJVN50298>.

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