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Early Childhood Lutein and Zeaxanthin Intake Is Positively Associated with Early Childhood Receptive Vocabulary and Mid-Childhood Executive Function But No Other Cognitive or Behavioral Outcomes in Project Viva

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ABSTRACT

Background: Lutein and zeaxanthin are carotenoids associated with better cognition in older adults. Recent evidence suggests that their dietary intake may also have cognitive implications in childhood.

Objective: The aim was to examine associations of early childhood lutein and zeaxanthin (L/Z) intake with cognition in early and mid-childhood.

Methods: Among 1378 children in Project Viva, a prospective cohort, mothers reported their child's dietary intake in early childhood (median: 3.2 y) using a food-frequency questionnaire. Child cognition and behavior were assessed at the same time point using the Peabody Picture Vocabulary Test (PPVT-III) and the Wide Range Assessment of Visual Motor Abilities (WRAVMA) and at mid-childhood (median: 7.7 y) using the Kaufman Brief Intelligence Test, the WRAVMA drawing subtest, the Wide Range Assessment of Memory and Learning, the Behavior Rating Inventory of Executive Function (BRIEF), and the Strengths and Difficulties Questionnaire.

Results: Children consumed a daily mean (SD) of 1.0 (0.4) mg L/Z in early childhood. Children in the third-quartile category of L/Z intake had a mean PPVT-III score 2.40 (95% CI: 0.27, 4.53) points higher than children in the lowest quartile category in early childhood, suggesting better receptive vocabulary. Children in the highest quartile category of L/Z intake had a parent-reported mean BRIEF Global Executive Composite score 1.65 (95% CI: −3.27, −0.03) points lower than children in the lowest quartile category in mid-childhood, indicating better executive function. We did not observe associations between L/Z intake and any of the other cognitive or behavioral outcomes assessed.

Conclusions: The overall findings do not provide strong evidence of an association between child L/Z intake and cognition and behavior. However, the positive associations found between early childhood L/Z intake and early childhood receptive vocabulary and mid-childhood executive function, in addition to previous evidence of neurodevelopmental benefit of L/Z intake, suggest that this relation deserves further investigation. *J Nutr* 2022;152:2555–2564.

Keywords: birth cohort, lutein and zeaxanthin, carotenoids, cognition, early life nutrition, early childhood development

Introduction

Lutein and zeaxanthin are xanthophyll carotenoids found in green leafy vegetables, brightly colored fruits, corn, and egg yolk (1). They preferentially accumulate in the human brain (2–4) and, along with meso-zeaxanthin, accumulate in the macula of the human retina where they form the macular pigment (5). Current evidence supports a role for lutein and zeaxanthin in the visual and cognitive health of older adults (6, 7). In adults, higher lutein and zeaxanthin status is related to better cognitive function (8–10) and lutein and zeaxanthin supplementation improves cognition (11–13). Emerging data also suggest a role for lutein and zeaxanthin in early neurodevelopment (14). Similar to older adults, in infant brain tissue, lutein is selectively taken up in comparison to other carotenoids that are predominant in the diet (4). Notably, the relative contribution of lutein to total carotenoids in the infant brain is twice that of older adults (3, 4). In addition, lutein was found to be the predominant carotenoid

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in mature breast milk (15), suggesting a need for lutein in early development.

Since the preferential deposition of lutein and zeaxanthin in the human retina and brain occurs early in life, and the first few years of life represent a critical period of brain development, evidence on the cognitive implications of greater lutein and zeaxanthin intake in children is warranted. Recent cross-sectional studies in pre-adolescents demonstrated that macular pigment optical density (MPOD), a noninvasive measure of carotenoids within retinal tissue and surrogate measure of brain lutein and zeaxanthin concentrations (16, 17), was associated with several aspects of cognitive function including academic math and written language achievement (18), relational memory performance (19), neural efficiency (20), and global intelligence, executive functioning, and visuo-spatial thinking abilities (21). Even though the density of the macular pigment may be augmented through dietary modification (22–25), the only study that, to our knowledge, evaluated the direct association between lutein and zeaxanthin status and cognition in children showed no associations between plasma concentrations and measures of sequential and simultaneous processing or receptive and expressive language (26). However, whether child dietary intake of lutein and zeaxanthin is associated with cognitive function has not been thoroughly investigated. Our own research found that higher maternal lutein and zeaxanthin intake during pregnancy was associated with better offspring verbal intelligence and behavior regulation in mid-childhood, independent of several maternal sociodemographic and dietary factors, suggesting a potential benefit in prenatal development (27).

Cognitive development in children predicts later school achievement and is linked to better jobs, higher incomes, and better access to health care in adulthood (28–32). The notion that dietary intake of lutein and zeaxanthin during childhood could be associated with cognitive function has great implications for the optimization of cognitive development, especially because dietary intake is a modifiable factor in early development. The objective of this study was to evaluate associations of early childhood intake of lutein and zeaxanthin with cognition in early and mid-childhood and executive function, behavior, and social-emotional development in mid-childhood.

Methods

Subjects

Participants were enrolled in Project Viva, a prospective cohort study investigating pre- and perinatal factors in relation to child health outcomes (33). Pregnant women were recruited between 1999 and 2002 at their first prenatal care visit from 8 offices of Atrius Harvard Vanguard Medical Associates, a multispecialty group practice in eastern Massachusetts. Exclusion criteria included multiple gestation, inability to answer questions in English, gestational age >22 wk at the time of the initial prenatal visit, and plans to move out of the area before delivery. Women who agreed to participate in the study (65% of those eligible) completed the first study visit after their obstetric appointment. The first visit was completed in the first trimester (median: 9.9 wk gestation), and the second visit was completed in the second trimester (median: 27.9 wk gestation). Detailed recruitment procedures were described previously (33). Offspring were followed up in early childhood (median age: 3.3 y) and mid-childhood (median age: 7.7 y). The institutional review boards of participating institutions authorized the study protocols. At each visit, mothers provided written informed consent and, beginning in mid-childhood, children provided verbal assent.

The Project Viva cohort consists of 2128 liveborn singleton infants and their mothers. Of the 1445 children who completed at least 1 cognitive test or behavioral questionnaire at early or mid-childhood, we included 1378 who completed an early childhood visit (**Figure 1**).

Measurements

Exposure: early childhood intake of lutein and zeaxanthin.

Mothers reported their children's dietary intake at the early childhood visit using a FFQ previously validated for use in preschool-aged children (34). The early childhood FFQ assessed intake of different foods using questions in the format "Please check the box that best represents how often your child eats each of the foods listed, on average, in the past month." The FFQ questions did not specify the portion size, so an endorsement of "one time" was categorized as 1 serving. Nutrient databases report lutein and zeaxanthin together; therefore, we assessed lutein and zeaxanthin combined as 1 exposure and refer to them as L/Z for the remainder of the article. We derived the L/Z content of each food from the Harvard nutrient composition database, which includes food-composition values from the USDA and is supplemented by additional published sources and communications with laboratories and manufacturers (35). We adjusted L/Z and other nutrient estimates for total energy intake using the nutrient residual method, to provide an estimate of nutrient effect independent of energy intake and to reduce the impact of measurement error (36).

Outcomes: child cognition and behavior.

Children underwent a series of standardized tests at the early and mid-childhood visits to evaluate several cognitive domains. All cognitive test scores used were selected a priori as primary outcomes. We used composite scores as our primary outcomes when available, except for the Kaufman Brief Intelligence Test, Second Edition (KBIT-II), where we used the individual KBIT-II scales to assess verbal and nonverbal intelligence as we were interested in both of these domains.

At the early childhood study visit (median age: 3.3 y; range: 2.8–6.2 y), trained research assistants administered the Peabody Picture Vocabulary Test–Third Edition (PPVT-III), a test of receptive language correlated with intelligence tests (37), and the Wide Range Assessment of Visual Motor Abilities (WRAVMA), including the pegboard, matching, and drawing subtests, to assess fine motor, visual spatial, and visual motor abilities, respectively (38). WRAVMA subtest scores were combined to generate a visual motor total composite score. The PPVT-III and WRAVMA are each scaled to a mean score of 100 (SD = 15).

At the mid-childhood study visit (median age: 7.7 y; range: 6.6–10.9 y), trained research assistants administered the KBIT-II to evaluate verbal and nonverbal global intelligence and the WRAVMA drawing subtest, to assess visual-motor integration (39). The KBIT-II (verbal and nonverbal) and WRAVMA are scaled to a mean score of 100 (SD = 15). In addition, the Wide Range Assessment of Memory and Learning (WRAML) design memory and picture memory subtests were

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Abbreviations used: BRIEF, Behavioral Rating Inventory of Executive Function; BRIEF GEC, Behavioral Rating Inventory of Executive Function–Global Executive Composite; KBIT-II, Kaufman Brief Intelligence Test, Second Edition; L/Z, lutein and zeaxanthin; MPOD, macular pigment optical density; PPVT-III, Peabody Picture Vocabulary Test, Third Edition; SDQ, Strengths and Difficulties Questionnaire; WRAML, Wide Range Assessment of Memory and Learning, Second Edition; WRAVMA, Wide Range Assessment of Visual Motor Abilities.

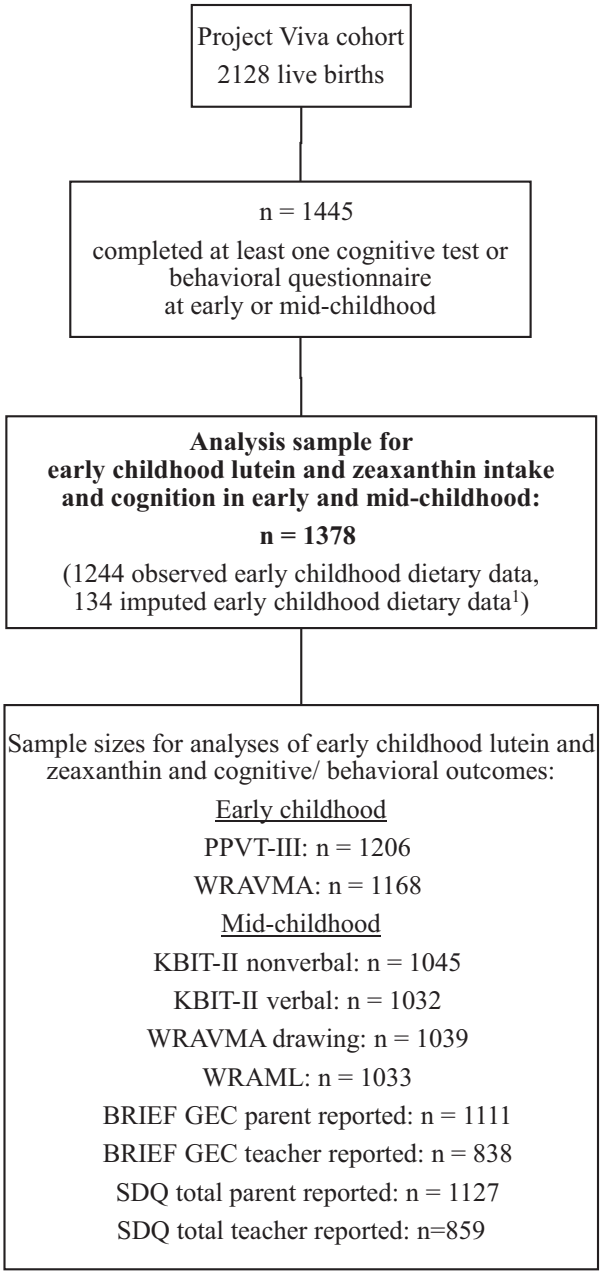

FIGURE 1 Flow diagram for inclusion in study population. [1]Exposure data were imputed for participants who had missing data but were eligible to complete the FFQ (i.e., completed the early childhood study visit but did not complete an FFQ). BRIEF GEC, Behavioral Rating Inventory of Executive Function–Global Executive Composite; KBIT-II, Kaufman Brief Intelligence Test, Second Edition; PPVT-III, Peabody Picture Vocabulary Test, Third Edition; SDQ, Strengths and Difficulties Questionnaire; WRAML, Wide Range Assessment of Memory and Learning, Second Edition; WRAVMA, Wide Range Assessment of Visual Motor Abilities.

used to assess memory and learning (40). The 2 WRAML subtests are scaled to a mean of 10 (SD = 3) and were summed to yield a total visual memory score. For all cognitive tests, we excluded results for which the administrator did not have confidence in the test performance (<1%).

At the mid-childhood study visit, parents and schoolteachers completed 2 behavioral questionnaires, the Behavioral Rating Inventory of Executive Function (BRIEF) and the Strengths and Difficulties Questionnaire (SDQ). The BRIEF is a validated 86-item questionnaire designed to assess executive function behaviors in home environments (41, 42) and includes the following subscales: inhibit, shift, emotional control, initiate, working memory, plan/organize, organization of materials, and monitor. The subscales form 2 indices: *1*) the Behavioral Regulation Index (BRIEF BRI), which reflects the ability of the child "to shift cognitive set and modulate emotions and behavior via appropriate inhibitory control," and *2*) the Metacognition Index (BRIEF MI), which indicates the child's ability to "initiate, plan, organize, and sustain future-oriented problem-solving in working memory." The BRIEF indices are each scaled to a mean of 50 (SD = 10). The Global Executive Composite (BRIEF GEC) combines the 2 indices and represents a summary measure of executive function. Higher BRIEF scores indicate worse executive function.

The SDQ is a validated 23-item questionnaire designed to assess social, emotional, and behavioral functioning (43). The SDQ is used extensively in clinical and research settings (44) and includes 5 subscales (prosocial behavior, hyperactivity/inattention, emotional symptoms, conduct problems, and peer relationship problems). Possible scores range from 0 to 40 points. Higher scores represent greater difficulties on all except the prosocial subscale, on which a higher score is more favorable. Normative data for the SDQ derive from a representative sample of US children (45).

Covariates.

Using a combination of self-administered questionnaires and interviews, Project Viva collected information on maternal age, education, household income, marital status, prepregnancy weight and height, parity, smoking history, and breastfeeding duration as well as the child's daily hours of television viewing/screen time and sleep (33). Data on maternal dietary intake were obtained from the FFQs (46, 47) administered at the early and mid-pregnancy visits. The child's sex, birth weight, and date of birth were obtained from hospital medical records. Mothers reported the best way to describe their child's race or ethnicity at the early childhood visit. We considered race and ethnicity in our analyses in an attempt to account for any other unmeasured social and environmental factors that might be associated with children's dietary intake (access to fresh fruits and vegetables and therefore L/Z intake) and cognitive/behavioral test scores. We calculated gestational age from the date of the last menstrual period or from the second-trimester ultrasound if the 2 differed by >10 d. We calculated sex-specific birth-weight-for-gestational-age z score using a US national reference (48). Maternal intelligence was evaluated using the PPVT-III administered at the early childhood visit and the composite KBIT-II at the mid-childhood visit. The Home Observation Measurement of the Environment short form (HOME-SF), completed by mothers at the mid-childhood visit, was used to assess the child's home environment for cognitive stimulation and emotional support (49).

Statistical analysis

All cognitive and behavioral outcomes were age- and sex-standardized except for the SDQ, and all were analyzed as continuous variables. We saw evidence of a nonlinear relation for some exposure–outcome associations; therefore, we modeled early childhood L/Z intake categorized into quartiles to allow a common analytical approach for all associations. We analyzed data using 3 sequential multivariable linear regression models for each child cognitive and behavioral outcome: model 0 adjusted for child age and sex, model 1 additionally adjusted for selected child characteristics (race/ethnicity, gestational age, birth-weight-for-gestational age z score, breastfeeding status at 6 mo, early childhood intake of vitamin B-12, daily hours of television viewing/screen time at early or mid-childhood, daily hours of sleep at early or mid-childhood), and model 2 additionally adjusted for selected maternal characteristics (marital status; household income; prepregnancy BMI; maternal PPVT-II or KBIT-III score; age; parity; education; smoking history; intake during pregnancy of L/Z, DHA, choline, and folate; and HOME score for mid-childhood outcomes). We selected covariates that we considered a priori to be confounders and that were associated with at least 1 child cognitive or behavioral

TABLE 1 Selected characteristics of included Project Viva mother–child pairs[1]

		Quartiles of early childhood lutein and zeaxanthin intake, mg/d			
	Overall	Q1: 0.40 (0.04–0.55)[2]	Q2: 0.69 (>0.55–0.84)	Q3: 1.00 (>0.84–1.18)	Q4: 1.52 (>1.18–4.12)
Maternal characteristics					
Age, mean (SD), y	32.3 (5.2)	32.2 (5.4)	32.4 (5.4)	32.4 (5.4)	32.3 (5.6)
Education, *n* (%)					
< College degree	409 (29.7)	101 (29.4)	95 (27.5)	106 (30.8)	107 (31.0)
4-y College or more	969 (70.3)	244 (70.6)	250 (72.5)	238 (69.3)	237 (69.0)
Annual household income, *n* (%)					
≤$70,000	518 (37.6)	116 (33.5)	120 (34.7)	131 (38.1)	152 (44.2)
>$70,000	860 (62.4)	229 (66.5)	225 (65.3)	213 (61.9)	192 (55.8)
Married or cohabitating, *n* (%)					
Yes	1283 (93.1)	325 (93.9)	328 (95.0)	317 (92.3)	313 (91.0)
No	95 (6.9)	21 (6.1)	17 (5.0)	26 (7.7)	31 (9.0)
Prepregnancy BMI (kg/m^2), *n* (%)					
<18.5 Underweight	42 (3.1)	9 (2.7)	8 (2.4)	11 (3.2)	14 (4.0)
18.5–24.9 Normal weight	845 (61.4)	224 (64.9)	217 (62.8)	218 (63.3)	187 (54.3)
25.0–29.9 Overweight	300 (21.8)	72 (20.9)	80 (23.0)	74 (21.5)	75 (21.7)
≥30 Obese	190 (13.8)	40 (11.5)	40 (11.7)	41 (12.1)	69 (20.0)
Parity, *n* (%)					
Nulliparous	664 (48.2)	175 (50.8)	152 (44.1)	163 (47.4)	174 (50.5)
Parity ≥1	714 (51.8)	170 (49.2)	193 (55.9)	181 (52.6)	170 (49.5)
Smoking status, *n* (%)					
Never	953 (69.2)	231 (66.9)	240 (69.5)	237 (69.0)	246 (71.4)
Former	278 (20.2)	74 (21.5)	67 (19.5)	74 (21.5)	63 (18.2)
During pregnancy	147 (10.6)	40 (11.6)	38 (11.0)	33 (9.6)	36 (10.4)
Maternal PPVT-III	105 (14.8)	105 (15.2)	105 (15.4)	107 (16.1)	104 (16.9)
Maternal KBIT-II	107 (17.1)	108 (15.6)	107 (16.7)	109 (16.1)	104 (16.7)
HOME-SF score	18.4 (2.2)	18.1 (2.4)	18.4 (2.6)	18.6 (2.2)	18.4 (2.4)
First–second- trimester dietary intake, mean (SD)					
Lutein and zeaxanthin, mg/d	2.7 (1.5)	2.1 (1.3)	2.5 (1.5)	2.7 (1.7)	3.3 (2.2)
DHA, mg/d	110 (96.1)	95.2 (82.8)	106 (98.8)	110 (87.7)	129 (104)
Folate, μg/d	1100 (335)	1080 (336)	1100 (335)	1100 (362)	1110 (357)
Choline, mg/d	329 (59)	317 (55.5)	326 (60.4)	330 (60.1)	341 (61.6)
Vitamin B-12, μg/d	10.7 (8.9)	10.1 (4.3)	10.4 (5.6)	11.1 (14.6)	11.1 (6.1)
Alcohol, servings/d	0.1 (0.0)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)
Total fruits, servings/d	3.0 (1.5)	2.6 (1.5)	3 (1.9)	3.2 (1.7)	3.3 (1.9)
Total vegetables, servings/d	2.9 (1.5)	2.5 (1.3)	2.8 (1.7)	3 (1.7)	3.3 (2)
Fish, servings/d	0.2 (0.4)	0.2 (0.2)	0.2 (0.2)	0.3 (0.2)	0.3 (0.2)
AHEI	60.7 (9.7)	58.2 (9.5)	59.8 (10)	62.1 (10.2)	62.6 (10.4)
Child characteristics					
Child sex, *n* (%)					
Male	703 (51.0)	195 (56.6)	179 (51.8)	171 (49.7)	158 (45.9)
Female	675 (49.0)	150 (43.4)	166 (48.2)	173 (50.3)	186 (54.1)
Race/ethnicity, *n* (%)					
White	923 (67.0)	263 (76.4)	241 (69.9)	233 (67.9)	185 (53.8)
Black	183 (13.3)	24 (7.1)	35 (10.3)	43 (12.4)	81 (23.4)
Asian	48 (3.5)	9 (2.6)	9 (2.5)	12 (3.4)	19 (5.5)
Hispanic	61 (4.4)	14 (4.2)	17 (4.9)	15 (4.4)	15 (4.3)
More than 1 race/ethnicity or other	163 (11.8)	34 (9.8)	43 (12.5)	41 (11.9)	45 (13.1)
Gestational length, mean (SD), wk	39.5 (1.9)	39.5 (1.9)	39.5 (2)	39.5 (1.9)	39.5 (1.9)
Birth weight, mean (SD), g	3490 (592)	3500 (597)	3506 (582)	3467 (580.6)	3454 (593)
Birth-weight-for-gestational age *z* score, mean (SD)	0.2 (1.1)	0.2 (0.9)	0.3 (0.9)	0.2 (0.9)	0.2 (0.9)
Breastfeeding duration, mean (SD), mo	6.3 (4.5)	5.8 (4.8)	6.3 (4.8)	6.9 (5)	6.4 (4.8)
Breastfeeding status at 6 mo, *n* (%)					
Formula only, never breastfed	144 (10.4)	44 (12.7)	41 (11.9)	37 (10.7)	22 (6.4)
Weaned	494 (35.9)	135 (39.0)	118 (34.2)	101 (29.5)	140 (40.7)
Mixed	365 (26.5)	83 (24.0)	103 (29.9)	90 (26.2)	89 (25.8)

(*Continued*)

TABLE 1 (*Continued*)

		Quartiles of early childhood lutein and zeaxanthin intake, mg/d			
	Overall	Q1: 0.40 (0.04–0.55)[2]	Q2: 0.69 (>0.55–0.84)	Q3: 1.00 (>0.84–1.18)	Q4: 1.52 (>1.18–4.12)
Breast milk only, no formula	375 (27.2)	84 (24.2)	83 (24.0)	115 (33.6)	93 (27.1)
Dietary intake in early childhood, mean (SD)					
Lutein and zeaxanthin, mg/d	1.0 (0.4)	0.4 (0.2)	0.7 (0.0)	1.0 (0.2)	1.7 (0.6)
DHA, mg/d	24.3 (31.9)	14.5 (29)	18.9 (27.7)	26.0 (34.5)	37.9 (51.8)
Folate, μg/d	210 (66.4)	177 (57.8)	206 (66.7)	221 (65.2)	237 (65.1)
Vitamin B-12, μg/d	4.1 (1.1)	4.2 (1.3)	4.2 (1.5)	4.0 (1.3)	3.9 (1.3)
Total fruits, servings/d	6.9 (3)	5.6 (3.2)	6.9 (3)	7.3 (2.8)	7.8 (2.6)
Total vegetables, servings/d	6.1 (3.7)	3.0 (2.2)	5.7 (2.4)	7.3 (2.4)	8.7 (2)
YHEI	54.8 (11.5)	49.1 (9.7)	53.8 (9.3)	56.7 (9.5)	59.6 (9.6)
Sleep in early childhood, h/d	11.2 (1.1)	11.1 (1.3)	11.2 (1.3)	11.2 (1.3)	11.1 (1.3)
Sleep in mid-childhood, h/d	9.9 (0.7)	9.9 (0.9)	9.9 (0.9)	9.9 (0.9)	9.8 (1.1)
TV in early childhood, h/d	1.7 (1.1)	1.8 (1.1)	1.7 (1.3)	1.6 (1.1)	1.5 (1.1)
Screen time in mid-childhood, h/d	3.4 (2.2)	3.7 (2.2)	3.4 (2.4)	3.3 (2.2)	3.4 (2.2)
Cognitive outcomes in early childhood,[3] mean (SD)					
PPVT-III	104 (14.4)	103 (14.1)	104 (14.6)	105 (14.1)	103 (14.6)
WRAVMA Total	102 (11.3)	101 (12.2)	103 (10.8)	102 (10.6)	102 (11.5)
Cognitive/behavioral outcomes in mid-childhood,[4] mean (SD)					
KBIT-II verbal	113 (14.8)	112 (14.5)	113 (14.7)	114 (13.7)	112 (16.0)
KBIT-II nonverbal	107 (16.9)	106 (16.4)	108 (16.6)	108 (16.1)	105 (18.2)
WRAVMA drawing	92.4 (16.6)	90.8 (16.6)	93.1 (17.0)	92.6 (16.4)	93.0 (16.5)
WRAML summary score	16.9 (4.4)	16.7 (4.4)	16.9 (4.3)	17.1 (4.6)	17.0 (4.1)
BRIEF GEC–parent reported	48.6 (9.1)	49.4 (9.5)	48.7 (9.3)	48.9 (9.3)	47.3 (8.3)
BRIEF GEC–teacher reported	50.8 (10.2)	50.4 (9.1)	50.0 (9.4)	51.2 (10.7)	51.3 (11.5)
SDQ total difficulties–parent reported	6.5 (4.7)	6.8 (5.0)	6.5 (4.8)	6.5 (4.7)	6.1 (4.5)
SDQ total difficulties–teacher reported	6.3 (5.8)	6.4 (5.3)	5.8 (5.3)	6.4 (6.2)	6.5 (6.2)

[1] $n = 1378$. AHEI, Alternate Healthy Eating Index; BRIEF GEC, Behavioral Rating Inventory of Executive Function–Global Executive Composite; HOME-SF, Home Observation Measurement of the Environment short form; KBIT-II, Kaufman Brief Intelligence Test, Second Edition; PPVT-III, Peabody Picture Vocabulary Test, Third Edition; Q, quartile; SDQ, Strengths and Difficulties Questionnaire; TV, television; WRAML, Wide Range Assessment of Memory and Learning, Second Edition; WRAVMA, Wide Range Assessment of Visual Motor Abilities; YHEI, Youth Healthy Eating Index.

[2] Median early childhood lutein and zeaxanthin intake (range), in mg/d for each quartile. Nutrient values were adjusted for total energy intake using the residual model. The maximum *n* in each of the quartile categories is as follows: Q1, 345; Q2, 345; Q3, 344; Q4, 344. The *n* in the quartile categories varies for different maternal and child characteristics because of missing data.

[3] Early childhood cognitive tests were administered at a median age of 3.2 y.

[4] Mid-childhood cognitive tests were administered at a median age of 7.7 y.

outcome in binary analyses. We present results from the 3 models to illustrate the extent to which addition of covariates changes effect estimates. We also considered adjustment for early childhood folate and DHA intake, as well as maternal vitamin B-12 intake. However, folate and L/Z are found in many of the same food sources and including folate in the model would adjust away some variability in L/Z, so we did not adjust for it in our models. Early childhood DHA and maternal vitamin B-12 were not associated with any of the child cognitive or behavioral outcomes in our dataset, so we did not include them in our models.

We used multiple imputation methods to impute missing data. We generated 50 imputed datasets using chained imputation, and combined estimates using Rubin's rules (50, 51). All 2128 participants were used in generating the imputed dataset, but analysis included only children who completed the early childhood visit and had available data from at least 1 cognitive test or behavioral questionnaire at early or mid-childhood. We used imputed values for all missing covariates. We imputed values of missing dietary intake in early childhood only for children who completed the early childhood visit. We did not impute missing cognitive or behavioral outcome data. The sample sizes for each exposure–outcome association varied depending on the cognitive or behavioral outcome. All analyses were performed using both original and imputed data, and results were similar. Therefore, we present results only from the imputed analysis throughout the article. We used SAS software, version 9.4 (SAS Institute), for all analyses.

Results

Participant characteristics

Characteristics of the included children and their mothers are shown in Table 1. Children in our eligible sample consumed a mean (SD) of 1.0 (0.4) mg L/Z/d in early childhood. Children were predominantly White (66%), born full term (92%), and breastfed for more than 6 mo (54%). Most mothers were college-educated (70%), married or living with a partner (93%), had a household income of more than $70,000 (62%), had a normal prepregnancy BMI (61%), and never smoked (69%).

Compared with the 750 children not included in this analysis, the 1378 included children were more likely to be White (67% vs. 57%, $P < 0.05$) and more likely to be exclusively breastfed at 6 mo (27% vs. 20%, $P < 0.001$). The mothers of included children were older in age (32 y vs. 31 y, $P < 0.001$), more likely to be college-educated

TABLE 2 Associations of intake of lutein and zeaxanthin with cognition in early childhood[1]

	Quartiles of early childhood lutein and zeaxanthin intake, mg/d			
Cognitive test and model[2]	Q1 (referent): 0.40 (0.04–0.55)[3]	Q2: 0.69 (>0.55–0.84)	Q3: 1.00 (>0.84–1.18)	Q4: 1.52 (>1.18–4.12)
PPVT-III ($n = 1206$)				
Model 0	0	0.72 (−1.73, 3.18)	2.05 (−0.39, 4.50)	0.20 (−2.25, 2.66)
Model 1	0	1.48 (−0.73, 3.70)	2.30 (0.08, 4.53)[4]	2.13 (−0.16, 4.41)
Model 2	0	1.58 (−0.53, 3.68)	2.40 (0.27, 4.53)[4]	1.82 (−0.45, 4.09)
WRAVMA total ($n = 1168$)				
Model 0	0	1.43 (−0.50, 3.37)	0.46 (−1.44, 2.36)	0.05 (−1.86, 1.96)
Model 1	0	1.50 (−0.37, 3.37)	0.39 (−1.47, 2.25)	0.74 (−1.17, 2.64)
Model 2	0	1.53 (−0.35, 3.40)	0.44 (−1.43, 2.31)	1.02 (−0.97, 3.02)

[1] Values are B (95% CI) and represent mean differences in cognitive scores from to the lowest quartile of early childhood lutein and zeaxanthin intake (referent). Q, quartile; PPVT, Peabody Picture Vocabulary Test; PPVT-III, Peabody Picture Vocabulary Test, Third Edition; WRAVMA, Wide Range Assessment of Visual Motor Abilities.
[2] Model 0: Adjusted for child age and sex. Model 1: model 0 adjusted for child characteristics: race/ethnicity, breastfeeding status at 6 mo, daily hours of television viewing in early childhood, intake of vitamin B-12, gestational age, birth-weight-for-gestational-age *z* score, daily hours of sleep in early childhood. Model 2: model 1 additionally adjusted for maternal characteristics: marital status; income; prepregnancy BMI; maternal PPVT; intake during pregnancy of lutein, DHA, choline, folate; age; parity; education; and smoking history.
[3] Median early childhood lutein and zeaxanthin intake (range), in mg/d. Nutrient values were adjusted for total energy intake using the residual model.
[4] 95% CI for the difference in mean cognitive/behavioral scores excludes zero.

(70% vs. 54%, $P < 0.001$) and married (93% vs. 88%, $P < 0.001$), more likely to have an annual household income of more than $70,000 (62% vs. 50%, $P < 0.001$) and a normal prepregnancy BMI (61% vs. 54%, $P < 0.05$), and had higher PPVT-III (105 vs. 101, $P < 0.001$) and KBIT-II scores (107 vs. 102, $P < 0.001$). Early childhood L/Z intake was the same among children included and excluded from our analysis.

Associations of child L/Z intake in early childhood with measures of cognition in early childhood

In the model adjusted for both child and maternal characteristics, children in the third-quartile category of L/Z intake had a mean PPVT-III score 2.40 (95% CI: 0.27, 4.53) points higher than children in the lowest quartile category. Child PPVT-III scores were higher with higher intake of L/Z, but the association did not appear linear, and intake in the fourth quartile was not associated with a significant difference in mean PPVT-III scores compared with the first quartile (**Table 2**). We did not observe associations between early childhood L/Z intake and WRAVMA total scores.

Associations of child L/Z intake in early childhood with measures of cognition and behavior in mid-childhood

Mid-childhood KBIT-II verbal and WRAVMA drawing scores were higher with higher early childhood L/Z intake, but the CIs for the mean differences in scores were wide and included the null (**Table 3**). We did not observe associations between early childhood L/Z intake and KBIT-II nonverbal, WRAML, or SDQ total (both parent- and teacher-reported) scores in mid-childhood (Table 3). In the model adjusted for both child and maternal characteristics, children in the highest quartile category of early childhood L/Z intake had lower parent-reported BRIEF GEC scores (−1.65 points; 95% CI: −3.27, −0.03) than children in the lowest quartile category, indicating better executive function with higher intake. We did not observe the same association with the teacher-reported BRIEF GEC (Table 3).

Discussion

In a prospective cohort study, we evaluated associations between early childhood intake of L/Z and measures of cognition and behavior. The overall findings do not provide strong evidence of a positive association of early childhood L/Z intake with cognition in early or mid-childhood, or with behavior in mid-childhood. However, these associations deserve further investigation as we observed positive associations of early childhood L/Z intake with early childhood verbal ability and mid-childhood executive function independently of multiple maternal and child sociodemographic, lifestyle, and dietary characteristics.

This study complements our previous findings in the same population that showed positive associations between maternal intake of L/Z during the first and second trimesters of pregnancy with offspring verbal intelligence and behavior regulation ability in mid-childhood (27). The differences in mean test scores that we found between the highest and lowest quartile category of L/Z intake, while modest, were similar to a previously published difference in mean scores between children at age 3 y who were ever breastfed and those who were never breastfed in the same cohort (52). Given the strong evidence that breast milk benefits neurodevelopment in children (53, 54), the differences appear to be clinically meaningful. Taken together, these results suggest a role for dietary L/Z in early neurodevelopment and subsequent cognitive function, especially verbal ability and executive function. We recognize that child and maternal dietary intake may be strongly associated and therefore we adjusted our models in the current analysis for maternal dietary intake of L/Z. Although slightly attenuated, the association between child L/Z and BRIEF GEC scores was robust to the adjustment for maternal L/Z intake, suggesting that child intake of L/Z may be associated with executive function independently of maternal intake.

Our findings are somewhat consistent with those of recent cross-sectional studies that evaluated associations of MPOD, a surrogate measure of lutein and zeaxanthin concentrations in the brain, with different domains of cognition and behavior in children and pre-adolescents. MPOD was positively associated with academic achievement, particularly math and written language in a study of 8–9-y-old children ($n = 56$) (18),

TABLE 3 Associations of early childhood lutein and zeaxanthin intake with cognition, executive function, behavior, and social-emotional development in mid-childhood[1]

	Quartiles of early childhood lutein and zeaxanthin intake, mg/d			
Cognitive/behavioral test and model[2]	Q1 (referent): 0.40 (0.04–0.55)[3]	Q2: 0.69 (>0.55–0.84)	Q3: 1.00 (>0.84–1.18)	Q4: 1.52 (>1.18–4.12)
KBIT-II verbal ($n = 1032$)				
Model 0	0	0.51 (−2.19, 3.22)	1.58 (−1.16, 4.33)	0.08 (−2.67, 2.82)
Model 1	0	0.32 (−2.02, 2.66)	1.32 (−1.05, 3.69)	1.31 (−1.09, 3.72)
Model 2	0	0.22 (−2.06, 2.50)	0.90 (−1.42, 3.22)	1.22 (−1.19, 3.63)
KBIT-II nonverbal ($n = 1045$)				
Model 0	0	1.44 (−1.62, 4.51)	1.94 (−1.14, 5.03)	−1.27 (−4.29, 1.75)
Model 1	0	1.38 (−1.60, 4.36)	1.75 (−1.27, 4.78)	−0.34 (−3.37, 2.69)
Model 2	0	1.21 (−1.77, 4.20)	1.46 (−1.58, 4.49)	−0.40 (−3.55, 2.74)
WRAVMA drawing ($n = 1039$)				
Model 0	0	2.54 (−0.44, 5.52)	1.80 (−1.17, 4.76)	1.99 (−0.95, 4.93)
Model 1	0	2.26 (−0.72, 5.24)	1.49 (−1.52, 4.50)	1.66 (−1.37, 4.69)
Model 2	0	2.11 (−0.89, 5.12)	1.36 (−1.69, 4.41)	2.03 (−1.13, 5.19)
WRAML ($n = 1033$)				
Model 0	0	0.14 (−0.65, 0.93)	0.17 (−0.62, 0.96)	0.25 (−0.53, 1.04)
Model 1	0	0.13 (−0.66, 0.92)	0.17 (−0.63, 0.97)	0.41 (−0.40, 1.21)
Model 2	0	0.11 (−0.68, 0.90)	0.17 (−0.63, 0.98)	0.53 (−0.31, 1.37)
BRIEF GEC–parent reported ($n = 1111$)				
Model 0	0	−0.76 (−2.38, 0.87)	−0.68 (−2.27, 0.90)	−1.94 (−3.52, −0.36)[4]
Model 1	0	−0.59 (−2.18, 1.00)	−0.67 (−2.24, 0.90)	−2.22 (−3.82, −0.62)[4]
Model 2	0	−0.11 (−1.68, 1.46)	−0.20 (−1.74, 1.34)	−1.65 (−3.27, −0.03)[4]
BRIEF GEC–teacher reported ($n = 838$)				
Model 0	0	−0.56 (−2.57, 1.45)	0.73 (−1.24, 2.69)	1.52 (−0.47, 3.51)
Model 1	0	−0.39 (−2.33, 1.55)	0.83 (−1.10, 2.76)	1.04 (−0.94, 3.02)
Model 2	0	−0.24 (−2.18, 1.69)	0.79 (−1.12, 2.71)	0.61 (−1.39, 2.61)
SDQ total–parent reported ($n = 1127$)				
Model 0	0	−0.09 (−0.93, 0.74)	−0.24 (−1.05, 0.57)	−0.32 (−1.14, 0.51)
Model 1	0	−0.05 (−0.86, 0.76)	−0.24 (−1.04, 0.55)	−0.51 (−1.34, 0.32)
Model 2	0	0.20 (−0.59, 1.00)	−0.03 (−0.81, 0.74)	−0.33 (−1.17, 0.51)
SDQ total–teacher reported ($n = 859$)				
Model 0	0	−0.54 (−1.66, 0.59)	0.14 (−0.96, 1.24)	0.46 (−0.65, 1.58)
Model 1	0	−0.55 (−1.64, 0.55)	0.07 (−1.01, 1.16)	0.24 (−0.88, 1.37)
Model 2	0	−0.38 (−1.48, 0.72)	0.13 (−0.95, 1.22)	0.16 (−0.98, 1.31)

[1] Values are β (95% CI) and represent mean differences in cognitive scores from to the lowest quartile of early childhood lutein and zeaxanthin intake (referent). BRIEF GEC, Behavioral Rating Inventory of Executive Function–Global Executive Composite; HOME-SF, Home Observation Measurement of the Environment short form; KBIT, Kaufman Brief Intelligence Test; KBIT-II, Kaufman Brief Intelligence Test, Second Edition; Q, quartile; SDQ, Strengths and Difficulties Questionnaire; WRAML, Wide Range Assessment of Memory and Learning, Second Edition; WRAVMA, Wide Range Assessment of Visual Motor Abilities.

[2] Model 0: Adjusted for child age and sex. Model 1: model 0 adjusted for child characteristics: race/ethnicity, breastfeeding status at 6 mo, daily hours of screen time in mid-childhood, intake of vitamin B-12 in early childhood, gestational age, birth-weight-for-gestational-age *z* score, daily hours of sleep in mid-childhood. Model 2: model 1 additionally adjusted for maternal characteristics: marital status; household income; prepregnancy BMI; maternal KBIT; intake during pregnancy of lutein, DHA, choline, folate; age; parity; education; smoking history;and HOME-SF score.

[3] Median early childhood lutein and zeaxanthin intake (range), in mg/d. Nutrient values were adjusted for total energy intake using the residual model.

[4] 95% CI for the difference in mean cognitive/behavioral scores excludes zero.

relational memory performance in a study of 7–10-y-old children ($n = 40$) (19), more efficient response to cognitive tasks in a study of 8–10-y-old children ($n = 49$) (20), and with measures of global intelligence, executive functioning, and visuo-spatial thinking abilities in a study of 7–13-y-old children ($n = 51$) (21). Additionally, a study of infants ($n = 55$) showed that higher concentrations of lutein and choline in breast milk collected at 3–4 mo postpartum were related to better infant recognition memory at 6 mo (55). However, a study of healthy 5–6-y-old children ($n = 160$) found no associations between intake or plasma concentrations of lutein and zeaxanthin and measures of sequential and simultaneous processing or receptive and expressive language (26). These discrepancies between associations with MPOD and diet/serum levels could be due to MPOD being a biomarker of brain concentrations of these carotenoids (16, 17), whereas diet/serum levels do not correlate as well with lutein concentrations in central nervous system tissues (22).

In addition to the evidence based on MPOD, a study of the distribution of carotenoids in infant brains found that lutein was the predominant carotenoid in all brain regions evaluated including the frontal cortex, which is associated with executive function (4). Lutein accumulation in this brain region may provide clues to its function. This is consistent with our finding of an association between early childhood intake of L/Z with executive function in mid-childhood. Our results are also consistent with other evidence showing that intake of healthier foods, including fruits and vegetables, is positively associated with executive function in children and adolescents (56).

This study has several strengths. Project Viva is a prospective cohort, and dietary intake was assessed during early childhood, a critical period for brain development (57, 58). We assessed different aspects of child cognition and behavior at early and mid-childhood using a battery of validated tests to give an overall picture of cognitive function in childhood. Given the novelty of our investigation, we did not have any a priori reason to select among the available cognitive/behavioral tests. We had assessed maternal L/Z intake in relation to the same outcomes in a previous analysis (27) and adjusted for maternal intake in this analysis.

This study has some limitations. First, measurement errors in dietary assessment are always a concern. The FFQ used to assess early childhood diet did not specify portion sizes. The actual amount eaten at each time of consumption may vary by participant. However, available data suggest that potential questions on portion size do not add substantially to the assessment of dietary intake (59, 60), and such random errors would lead to an underestimation of any associations. There is also the possibility of reporting bias for children's dietary consumption depending on the mother's perception of her child's development and awareness of which healthy foods should be consumed. However, the FFQ used in Project Viva was previously validated for use in preschool-aged children (34) and should reasonably rank children with regard to their L/Z intake after adjustment for total energy intake. Second, there is the possibility for measurement error in cognitive testing. However, trained research assistants administered the tests, we excluded results for which the administrator did not have confidence in the test performance, and any error in the dependent variable would have reduced the precision of our effect estimates, thus leading to more conservative findings. Third, both dietary intake and cognition were assessed concurrently at the early childhood visit. Although children's verbal intelligence and visual motor ability are not likely to impact their intake of L/Z-containing foods, there is still the possibility for reverse causality in the observed associations between L/Z intake and cognition in early childhood. Fourth, while we cannot rule out the possibility of residual confounding, we have made a substantial effort to address it by controlling for multiple potential confounders, including maternal socioeconomic status and intake of other nutrients that were shown to be related to neurodevelopment, as well as multiple child factors. Fifth, in mid-childhood models, we adjusted for child sleeping and screen time measured at mid-childhood. These factors could be on the causal pathway from exposure to outcome due to the timing of their assessment, but this is unlikely because, if they were true mediators, they would substantially weaken effect estimates, which was not observed for most of the mid-childhood outcomes. Last, the generalizability of our results is limited given that most children in Project Viva resided in eastern Massachusetts, had college-educated parents, and may consume more L/Z than the national average (61). Nevertheless, the few significant associations observed in this population suggest that small differences in early childhood L/Z intake may have implications for child verbal ability and executive function. The lack of detected associations with the other cognitive outcomes could be due to an absence of associations between L/Z and the cognitive domains assessed by the cognitive tests used, the tests not being sensitive enough to detect modest effect sizes, or our effect estimates underestimating the strength of the associations. It could also be due to our sample being at low risk of nutrient deficiencies or a compensation over time by the many factors, other than nutrition, that influence neurodevelopment. Like many food components, the effects of L/Z intake may be most apparent in children with the lowest intakes. Evaluating associations of dietary L/Z with cognition in populations from different settings and using other tools to assess L/Z status and cognitive and behavioral function is an important next step.

In conclusion, we found significant associations between higher early childhood L/Z intake and better performance on tests of verbal ability at early childhood and executive function in mid-childhood, but we did not find evidence of associations with other measures of cognition and behavior. Our findings complement those showing a benefit of L/Z intake on cognition at older age. Further evidence from prospective cohort and interventional studies is needed to provide stronger evidence in support of the presence or lack of these associations in early life, particularly among populations with lower L/Z intakes, to inform dietary recommendations for the optimization of cognitive development in children.

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Data Availablity

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

Conflict of interest

The author report no conflict of interest.

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