Original Article

Associations of dietary and plasma lutein + zeaxanthin with depression in US adults: findings from NHANES

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Background and Objectives: Evidence regarding the relationship between dietary and plasma lutein + zeaxanthin (L + Z) levels and the risk of depression is scarce. This study aimed to investigate the associations of dietary consumption of L + Z and plasma L + Z level with risk of depression in adult of United States by using data from National Health and Nutrition Examination Survey (NHANES). **Methods and Study Design:** A total of 7,829 and 7,324 individuals aged ≥ 20 years were included from the NHANES to analyze the relationship between dietary L + Z and depression, as well as plasma L+ Z levels with the risk of depression, separately. Multivariable logistic regression analyses were used. Subsequently, the dose-response relationships were conducted using restricted cubic splines. **Results:** In the multivariable model, the highest quartile of dietary L + Z intake was associated with a significantly lower risk of depression compared to the lowest quartile (OR = 0.68, 95%CI: 0.52, 0.89, $p < 0.01$). Similarly, the highest quartile of plasma L + Z levels was linked to a reduced risk of depression compared to the lowest quartile (OR = 0.58, 95%CI: 0.44, 0.76, $p < 0.001$). **Conclusions:** This study suggests that an appropriate increase in dietary L + Z intake and higher plasma L + Z levels are associated with a lower risk of depression. These results should be confirmed by randomized controlled trial (RCTs) to explore the effects of supplementing L + Z on depression.

Key Words: dietary intake of lutein + zeaxanthin, plasma lutein + zeaxanthin level, depression, US adults, NHANES

INTRODUCTION

Depression is a pervasive psychiatric disorder that is defined by persistent melancholy, despair, lack of value, and a weakened tendency towards previously enjoyable activities, which seriously hinders an individual's psychosocial function and reduces their standard of living.[1] About 280 million people worldwide suffer from a depressive disorder.[2] Daily depression affects one-sixth of the population in the United States. According to epidemiological research, depression affects 25% of women and 6% of men at some point in their life, with young individuals being more likely to suffer from the condition.[3] Research shows that in 2019, 7.8% of American adults experienced at least one severe depressive episode.[4] An increasing body of research shows that depressive emotions might be a contributing factor to the development of certain physical disorders,[5–8] and depressed individuals are at a higher risk than non-depressed individuals of worsening the course of their illness.[9,10] Owing to its high incidence and severe illness burden, depression has emerged as a major public health concern on a global scale.

Depression is a result of the complex interaction between biological, social, and psychological variables. Research has shown that biologically related depression can be regulated through diet.[11] Lutein and zeaxanthin (L + Z) belong to the carotenoid family and are present in egg yolks and a variety of dark green leafy vegetables.[12] In the human body, L + Z both act as antioxidants and free radical scavengers for photoreceptors. The compounds are widely present in natural plants such as spinach, kiwifruit, and corn. Moreover, carotenoids are bioactive and have therapeutic benefits on mental health; previous research has reported a negative correlation between carotenoids and depression.[13] Meanwhile, low plasma carotenoid concentrations have been linked to clinical features of depression in the elderly and can predict the onset of new depression symptoms.[14] Dietary consumption and plasma levels of L + Z are hypothesized to be associated with the risk of depression. Nonetheless, only a few studies have comprehensively explored the relationship between dietary consumption of L + Z and depression. Studies have revealed a strong negative link between L + Z in food and the incidence of depression in individuals with cardiometabolic disorders.[15] However, other studies have demonstrated that lutein/zeaxanthin is not significantly linked to depressive symptoms in American adults.[16] Still, the linear link between the depression risk and plasma L + Z levels remains unexplored.

Thus, our research investigated the relationship between dietary intake and plasma level of L + Z and

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risk of depression in US adults by analyzing data from the 2005–2006 and 2017-2018 National Health and Nutrition Examination Survey (NHANES).

METHODS

Demographic information

Figure 1 shows the sample selection process flowchart. Considering that plasma L + Z data were only available from NHANES 2005–2006 and 2017-2018, only the data from these two time periods were used in this study. NHANES 2005–2006 and 2017-2018 included a total of 19,602 participants. Among these participants, the present study included 10,548 individuals aged 20 years or older, and those missing full depression data (n = 1381) were excluded. The relationship between dietary intake and plasma L + Z levels with the risk of depression was analyzed separately. A total of 379 and 655 individuals with missing data were removed from the corresponding groups. During the two dietary recall interviews, 959 and 1188 respondents were further removed due to missing data on energy or total fat. In the end, a total of 7,829 and 7,324 individuals were included to analyze the relationship between L + Z in food and plasma L + Z levels and risk of depression separately. The National Center for Health Statistics Research Ethics Review Board approved the NHANES protocols, and all participants provided written informed permission throughout the survey.

Evaluation of dietary and plasma lutein + zeaxanthin levels

Dietary consumption data was used to estimate the kind and amount of food and beverages consumed in the 24 h prior to the interview. In addition, the amount of energy, nutrients, and other ingredients in these foods and drinks were also estimated. In this research, two dietary recall interviews were conducted to evaluate dietary L + Z consumption, energy, and total fat. Our analysis of dietary intake is based on the average of two 24-h dietary recall interviews, as conducted by the NHANES. The dietary intake data were processed using the U.S. Department of Agriculture (USDA) Food and Nutrient Database for Dietary Studies (FNDDS), which ensures accurate estimation of food and nutrient intake.

The specific laboratory protocols for plasma L + Z were described in full in the NHANES publication. Photodiode array detection and HPLC were performed to determine the serum levels of L + Z. A small volume (100 μL) of serum was mixed with an ethanol solution containing two internal standards, retinyl butyrate and nonapreno-beta-carotene (C45). Subsequently, the micronutrients were extracted from the aqueous phase using vacuum drying and were deposited in hexane. The extract was resolved in ethanol and acetonitrile and then filtered to remove insoluble particles. Equal portions of the filtrate were infused into a C18 reverse column, and the mixture was eluted with an equal flow of ethanol. These chemicals' absorbance in the solution was directly correlated with their concentration. Three wavelengths—300, 325, and 450 nm—were detected while chromatograms were recorded, which roughly correlated to the maximum absorption.

Outcome definition

The Patient Health Questionnaire (PHQ-9) is an assessment method which is a self-reported instrument used to diagnose depression based on nine clinical features.[17] The tool includes nine categories for symptom response and reactions on a 4-point scale: 0 (not at all), 1 (a few days), 2 (more than half the days), and 3 (nearly every day), was employed to evaluate depression signs and symptoms

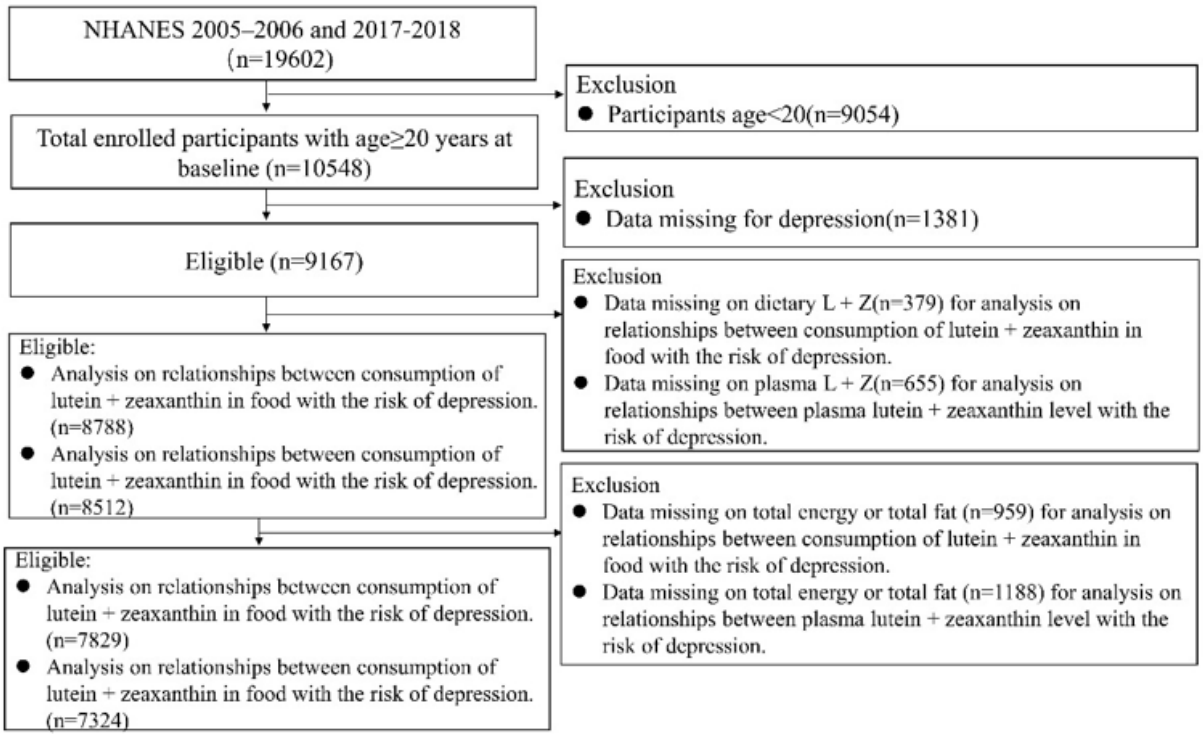

Figure 1. Flow chart of participant selection for the study population, NHANES 2005–2006 and 2017-2018.

over the two weeks preceding the study. The final score is obtained by adding all the scores and ranges from 0 to 27. As in previous studies, a PHQ-9 total score of greater than 10 was used to identify depression in this investigation.[18,19]

Statistical analysis

Continuous variables conforming to a normal distribution were presented as the mean and standard deviation (SD), whereas categorical variables were expressed as numbers and percentages to depict the characteristics of the research population. Chi-square tests were performed to analyze categorical variables, while analysis of variance (ANOVA) was used to examine variations between means. In addition, the relationship between the levels of L + P in food and plasma with depression risk was determined by estimating the odds ratios (OR) and 95% confidence intervals using multiple logistic regression. The multivariable adjusted models were adjusted for gender (male or female), race (Mexican-American, non-hispanic white, black, other hispanic, other race/ ethnicity), age (continuous), education level (less than high school, high school, college graduate or above or missing), marriage status (married, widowed, divorced, separated, living with partner, never married or missing), the family income to poverty ratio (<2.34, ≥2.34 or missing), body mass index(BMI) (<25, ≥25 kg/m^2, or missing), smoking status (never, past, current, or missing), alcohol status (yes, no), leisure-time physical activity (unit: metabolic equivalents/week; <500, 500 to <1000, ≥1000, or missing), consumption of energy through food (continuous), dietary intake of fat (continuous), hypertension (yes, no, or missing), diabetes (yes, no, or missing), and coronary heart disease (yes, no, or missing). Thereafter, the dose-response relationships between dietary and plasma L + Z and depression risk were examined by fitting restricted cubic splines. A two-sided *p* value of less than 0.05 was deemed statistically significant in all analyses, which were carried out with R software 3.6.2.

RESULTS

Participant characteristics

Table 1 and 2 show the study population's characteristics from NHANES 2005–2006 and 2017-2018, divided into the plasma L + Z level group and the dietary L + Z consumption group. A total of 7,829 individuals (3,736 males and 4,093 females) were included in the dietary L + Z consumption group, with a mean age of 49.88 ± 17.94 years. The plasma L + Z level group comprised of 7,324 (3,489 males and 3,835 females), with a mean age of 49.95 ± 17.91 years. The two groups were divided into quartiles based on the L + Z levels. Individuals with higher dietary consumption of L + Z tend to be older, have a lighter weight, have higher levels of leisure exercise time, achieved a college graduate or above education level, never smoked, and had a higher intake of energy and fat. Individuals with greater plasma levels of L + Z tend to be older, female, have college graduate or above education level, richer, lighter weight, never smoked, and had a lower intake of energy and fat.

Analysis of multivariate logistic regression for the relationships between dietary and plasma lutein + zeaxanthin levels with the risk of depression

The adjusted multivariable analysis revealed associations of the dietary consumption of L + Z in food and plasma L + Z levels with the risk of depression, as displayed in Table 3. The unadjusted model showed a negative association between dietary and plasma L + Z levels and the risk of depression. Compared with the lowest quartile, the highest quartile of dietary L + Z was associated with a decreased rate of depression (OR = 0.52, 95%CI: 0.41, 0.67, $p < 0.001$). Meanwhile, the highest quartile of plasma L + Z levels was associated with a lower risk of depression compared to the lowest quartile (OR = 0.38, 95%CI: 0.30, 0.49, $p < 0.001$). Model I was adjusted for sex, age, ethnicity, educational level, and marriage status, showing a negative association between both dietary and plasma L + Z levels and the risk of depression. Compared to the lowest quartile, the highest quartile of dietary L + Z consumption was associated with a reduced incidence of depression (OR = 0.59, 95%CI: 0.46, 0.76, $p < 0.001$). Moreover, the highest quartile of plasma L + Z levels was linked to a reduced risk of depression compared to the lowest quartile (OR = 0.40, 95%CI: 0.30, 0.52, $p <0.001$). Model II was further adjusted, including BMI, smoking status, leisure exercise time, family income to poverty ratio, alcohol status, energy, total fat, hypertension, diabetes, and coronary heart disease. Similarly, the results revealed a negative relation between both dietary and plasma L + Z levels with the risk of depression. The highest quartile of dietary L + Z intake was related to decreased risk of depression compared to the lowest quartile (OR = 0.68, 95%CI: 0.52, 0.89, $p < 0.01$). Meanwhile, the highest quartile of plasma L + Z levels was associated with a decreased risk of depression compared with the lowest quartile (OR = 0.58, 95%CI: 0.44, 0.76, $p < 0.001$). As the quartiles of plasma and dietary L + Z levels increased, participants exhibited a lower tendency for depression (all p for trend < 0.01). The results showed that per 1-SD increase in dietary or plasma L + Z levels were associated with decreased risk of depression (all $p < 0.05$). Moreover, the dose-response relationships were analyzed using restricted cubic splines. As shown in Figure 2, the association between dietary L + Z intake and risk of depression showed a U-shaped trend, indicating that an appropriate increase in the intake of dietary L + Z was associated with decreased risk of depression. Furthermore, the association between plasma L + Z level and the risk of depression showed a linear downward trend, and a lower risk of depression was observed as plasma L + Z levels increased (Figure 3).

Table 1. General characteristics of the study population in the dietary lutein + zeaxanthin analysis

	Dietary lutein and zeaxanthin (μg)				
	Q1 (0.00-454.50)	Q2 (455.00-820.50)	Q3 (821.00-1548.50)	Q4 (1549.50-57188.00)	*p*-value[§]
N	1957	1955	1958	1959	
Age, years[†]	47.4 ± 18.1	48.7 ± 18.4	51.3 ± 18.0	52.2 ± 16.9	<0.001
Gender[‡]					0.052
Male	900 (45.99%)	929 (47.52%)	984 (50.26%)	923 (47.12%)	
Female	1057 (54.01%)	1026 (52.48%)	974 (49.74%)	1036 (52.88%)	
Race					<0.001
Non-Hispanic white	865 (44.20%)	897 (45.88%)	851 (43.46%)	864 (44.10%)	
Black	481 (24.58%)	424 (21.69%)	414 (21.14%)	494 (25.22%)	
Other Hispanic	115 (5.88%)	128 (6.55%)	111 (5.67%)	115 (5.87%)	
Mexican American	313 (15.99%)	352 (18.01%)	357 (18.23%)	219 (11.18%)	
Other race/ ethnicity	183 (9.35%)	154 (7.88%)	225 (11.49%)	267 (13.63%)	
Education level					<0.001
Less than high school	223 (11.40%)	189 (9.67%)	154 (7.87%)	111 (5.67%)	
High school	853 (43.61%)	768 (39.30%)	696 (35.55%)	521 (26.62%)	
College graduate or above	880 (44.99%)	997 (51.02%)	1108 (56.59%)	1325 (67.71%)	
Marital status					<0.001
Married	955 (48.82%)	1033 (52.84%)	1130 (57.71%)	1082 (55.32%)	
Widowed	133 (6.80%)	166 (8.49%)	159 (8.12%)	143 (7.31%)	
Divorced	214 (10.94%)	191 (9.77%)	177 (9.04%)	253 (12.93%)	
Separated	81 (4.14%)	78 (3.99%)	64 (3.27%)	47 (2.40%)	
Never married	374 (19.12%)	322 (16.47%)	262 (13.38%)	286 (14.62%)	
Living with partner	199 (10.17%)	165 (8.44%)	166 (8.48%)	145 (7.41%)	
The ratio of family income to poverty	2.39 ± 1.54	2.55 ± 1.57	2.76 ± 1.59	3.04 ± 1.63	<0.001
BMI, kg/m^2	29.7 ± 7.32	29.5 ± 6.90	29.8 ± 7.00	29.1± 6.97	<0.05
Leisure exercise time, MET/week	1094 ± 3702	1115 ± 1854	1175 ± 2180	1629 ± 13712	0.127
Drinking					<0.001
No	1555 (79.46%)	1490 (76.21%)	1515 (77.37%)	1442 (73.61%)	
Yes	402 (20.54%)	465 (23.79%)	443 (22.63%)	517 (26.39%)	
Smoking status					<0.001
Never	993 (50.82%)	1053 (53.89%)	1102 (56.31%)	1134 (57.92%)	
Past	418 (21.39%)	495 (25.33%)	546 (27.90%)	558 (28.50%)	
Current	543 (27.79%)	406 (20.78%)	309 (15.79%)	266 (13.59%)	

MET (Metabolic Equivalent of Task) represents the amount of energy expended during physical activity. One MET is the amount of energy expended while sitting quietly. MET/week refers to the metabolic equivalents expended through physical activity in a week.

[†]Data are expressed as mean + standard deviation (SD)

[‡]n (%).

[§]*p* values indicate significant differences between the groups by ANOVA or chi-square tests.

Table 1. General characteristics of the study population in the dietary lutein + zeaxanthin analysis (cont.)

	Dietary lutein and zeaxanthin (μg)				
	Q1 (0.00-454.50)	Q2 (455.00-820.50)	Q3 (821.00-1548.50)	Q4 (1549.50-57188.00)	*p*-value[§]
Hypertension					0.054
No	1288 (66.12%)	1277 (65.42%)	1230 (62.88%)	1228 (62.75%)	
Yes	660 (33.88%)	675 (34.58%)	726 (37.12%)	729 (37.25%)	
Diabetes					0.215
No	1676 (87.70%)	1661 (86.83%)	1623 (85.42%)	1648 (86.33%)	
Yes	235 (12.30%)	252 (13.17%)	277 (14.58%)	261 (13.67%)	
Coronary heart disease					0.434
No	1864 (95.59%)	1873 (96.20%)	1861 (95.34%)	1861 (95.19%)	
Yes	86 (4.41%)	74 (3.80%)	91 (4.66%)	94 (4.81%)	
Depression					<0.001
No	1759 (89.88%)	1785 (91.30%)	1826 (93.26%)	1850 (94.44%)	
Yes	198 (10.12%)	170 (8.70%)	132 (6.74%)	109 (5.56%)	
Energy (kcal)	1765± 736	2049 ± 771	2181± 840	2222 ± 920	<0.001
Total fat (g)	66.9 ± 33.4	79.8 ± 36.1	86.4 ± 39.4	87.4 ± 43.7	<0.001

MET (Metabolic Equivalent of Task) represents the amount of energy expended during physical activity. One MET is the amount of energy expended while sitting quietly. MET/week refers to the metabolic equivalents expended through physical activity in a week.
[†]Data are expressed as mean + standard deviation (SD)
[‡]n (%).
[§]p values indicate significant differences between the groups by ANOVA or chi-square tests.

Table 2. General characteristics of the study population in the plasma lutein + zeaxanthin analysis

	Plasma levels of lutein and zeaxanthin (u mol /L)				
	Q1 (0.030-0.195)	Q2 (0.197-0.283)	Q3 (0.285-0.399)	Q4 (0.401-3.270)	*p*-value[§]
N	1793	1863	1830	1838	
Age, years[†]	48.4 ± 18.0	49.0 ± 18.3	50.0 ± 18.1	52.4 ± 17.0	<0.001
Gender[‡]					<0.05
Male	854 (47.63%)	918 (49.28%)	891 (48.69%)	826 (44.94%)	
Female	939 (52.37%)	945 (50.72%)	939 (51.31%)	1012 (55.06%)	
Race					<0.001
Non-Hispanic white	1085 (60.51%)	863 (46.32%)	701 (38.31%)	628 (34.17%)	
Black	343 (19.13%)	457 (24.53%)	448 (24.48%)	409 (22.25%)	
Other Hispanic	77 (4.29%)	100 (5.37%)	126 (6.89%)	130 (7.07%)	
Mexican American	184 (10.26%)	295 (15.83%)	365 (19.95%)	352 (19.15%)	
Other race/ ethnicity	104 (5.80%)	148 (7.94%)	190 (10.38%)	319 (17.36%)	

MET (Metabolic Equivalent of Task) represents the amount of energy expended during physical activity. One MET is the amount of energy expended while sitting quietly. MET/week refers to the metabolic equivalents expended through physical activity in a week.
[†]Data are expressed as mean + standard deviation (SD)
[‡]n (%).
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	Q1 (0.030-0.195)	Q2 (0.197-0.283)	Q3 (0.285-0.399)	Q4 (0.401-3.270)	*p*-value[§]
Education level					<0.001
Less than high school	100 (5.58%)	139 (7.47%)	204 (11.15%)	194 (10.57%)	
High school	814 (45.40%)	713 (38.29%)	604 (33.01%)	512 (27.89%)	
College graduate or above	879 (49.02%)	1010 (54.24%)	1022 (55.85%)	1130 (61.55%)	
Marital status					<0.001
Married	873 (48.72%)	955 (51.26%)	1011 (55.28%)	1117 (60.84%)	
Widowed	131 (7.31%)	132 (7.09%)	157 (8.58%)	139 (7.57%)	
Divorced	213 (11.89%)	211 (11.33%)	164 (8.97%)	189 (10.29%)	
Separated	69 (3.85%)	68 (3.65%)	61 (3.34%)	48 (2.61%)	
Never married	340 (18.97%)	318 (17.07%)	267 (14.60%)	224 (12.20%)	
Living with partner	166 (9.26%)	179 (9.61%)	169 (9.24%)	119 (6.48%)	
The ratio of family income to poverty	2.38 ± 1.52	2.58 ± 1.58	2.75 ± 1.59	3.06± 1.64	<0.001
BMI, kg/m^2	31.4± 8.42	30.0 ± 7.13	28.9 ± 6.48	27.8 ± 5.44	<0.001
Leisure exercise time, MET/week	994 ± 1930	1226 ± 2501	1595 ± 14600	1272 ± 3518	0.215
Drinking					<0.01
No	1422 (79.31%)	1439 (77.24%)	1364 (74.54%)	1389 (75.57%)	
Yes	371 (20.69%)	424 (22.76%)	466 (25.46%)	449 (24.43%)	
Smoking status					<0.001
Never	823 (45.95%)	952 (51.13%)	1042 (57.00%)	1191 (64.83%)	
Past	421 (23.51%)	500 (26.85%)	503 (27.52%)	471 (25.64%)	
Current	547 (30.54%)	410 (22.02%)	283 (15.48%)	175 (9.53%)	
Hypertension					<0.001
No	1078 (60.26%)	1228 (66.02%)	1195 (65.44%)	1208 (65.87%)	
Yes	711 (39.74%)	632 (33.98%)	631 (34.56%)	626 (34.13%)	
Diabetes					<0.001
No	1468 (83.98%)	1610 (88.56%)	1547 (86.38%)	1560 (87.49%)	
Yes	280 (16.02%)	208 (11.44%)	244 (13.62%)	223 (12.51%)	
Coronary heart disease					<0.01
No	1681 (94.02%)	1774 (95.58%)	1749 (95.99%)	1770 (96.51%)	
Yes	107 (5.98%)	82 (4.42%)	73 (4.01%)	64 (3.49%)	
Depression					<0.001
No	1574 (87.79%)	1732 (92.97%)	1707 (93.28%)	1745 (94.94%)	
Yes	219 (12.21%)	131 (7.03%)	123 (6.72%)	93 (5.06%)	
Energy (kcal)	2028 ± 856.	2089 ± 841	2071 ± 858	2022 ± 773	<0.05
Total fat (g)	79.3 ± 39.7	82.0 ± 38.7	80.1 ± 40.2	78.6 ± 37.1	<0.05

MET (Metabolic Equivalent of Task) represents the amount of energy expended during physical activity. One MET is the amount of energy expended while sitting quietly. MET/week refers to the metabolic equivalents expended through physical activity in a week.

[†]Data are expressed as mean + standard deviation (SD)

[‡]n (%).

[§]*p* values indicate significant differences between the groups by ANOVA or chi-square tests.

Table 3. Multivariate regression for associations of dietary consumption of lutein + zeaxanthin and plasma lutein + zeaxanthin level with risk of depression

Exposure	Non-adjusted[†]		Adjust I[‡]		Adjust II[§]	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Dietary lutein and zeaxanthin						
Per 1 SD increase	0.80 (0.70, 0.91)	<0.001	0.83 (0.73, 0.94)	<0.01	0.88 (0.78, 0.99)	<0.05
Q1	Reference (1.00)		Reference (1.00)		Reference (1.00)	
Q2	0.85 (0.68, 1.05)	0.128	0.90 (0.73, 1.12)	0.361	0.94 (0.75, 1.18)	0.600
Q3	0.64 (0.51, 0.81)	<0.001	0.73 (0.58, 0.93)	<0.01	0.79 (0.62, 1.01)	0.065
Q4	0.52 (0.41, 0.67)	<0.001	0.59 (0.46, 0.76)	<0.001	0.68 (0.52, 0.89)	<0.01
p for trend	<0.001		<0.001		<0.01	
Plasma Lutein and zeaxanthin (nmol/L)						
Per 1 SD increase	0.61 (0.53, 0.70)	<0.001	0.62 (0.54, 0.71)	<0.001	0.74 (0.65, 0.85)	<0.001
Q1	Reference (1.00)		Reference (1.00)		Reference (1.00)	
Q2	0.54 (0.43, 0.68)	<0.001	0.55 (0.43, 0.69)	<0.001	0.62 (0.49, 0.79)	<0.001
Q3	0.52 (0.41, 0.65)	<0.001	0.53 (0.42, 0.67)	<0.001	0.68 (0.53, 0.88)	<0.01
Q4	0.38 (0.30, 0.49)	<0.001	0.40 (0.30, 0.52)	<0.001	0.58 (0.44, 0.76)	<0.001
p for trend	<0.001		<0.001		<0.001	

L+P, lutein + zeaxanthin; OR, odds ratio; 95% CI, 95% confidence intervals
[†]The non-adjusted model was not adjusted for any factor
[‡]Model I was adjusted for age, gender, race, education level, and marital status
[§]Model II was adjusted for age, gender, race, education level, energy, marital status, total fat, BMI, Smoking status, leisure exercise time, hypertension, diabetes, coronary heart disease, the ratio of family income to poverty, and drinking.

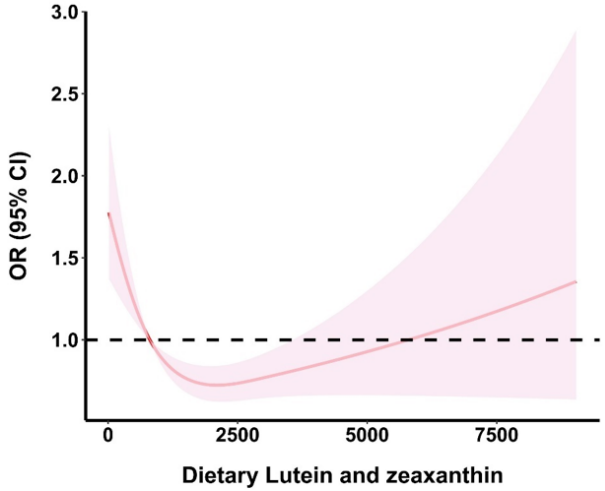

Figure 2. The dose-response association between dietary lutein + zeaxanthin intake and depression

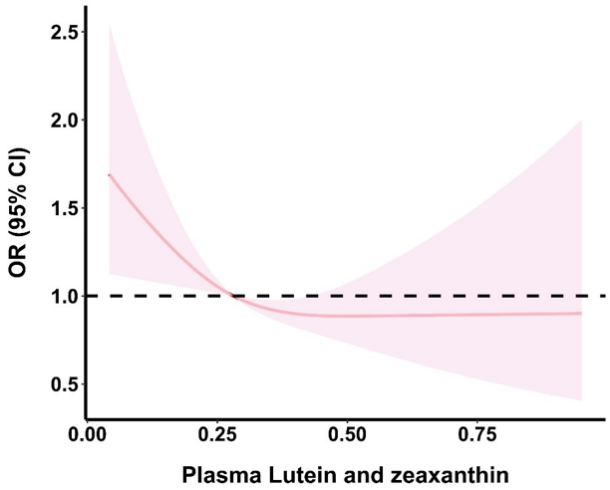

Figure 3. The dose-response association between plasma lutein + zeaxanthin level and depression

Subgroup analyses

Tables 4 and 5 show the associations between dietary L + Z consumption and plasma L + Z level and the risk of depression in different subgroups. Subgroup analysis was conducted and the participants were stratified by age, total energy, total fat, marriage status, gender, race, household income to poverty ratio, educational level, and BMI.

The findings demonstrated that the highest quartile of dietary L + Z consumption (Q2-Q4) was associated with lower OR for the risk of depression in nearly all subgroups when compared with the lowest quartile. The findings indicated no significant interaction between dietary consumption of L + Z and risk of depression among most of the stratification factors (all p for interaction > 0.05), with the exception of total fat-based subgroup analysis (p for interaction <0.05). For participants with an average daily total fat intake of < 75 g/day, the relationship between dietary L + Z levels and depression was significant, but not for participants with an average daily total fat intake of ≥ 75 g/day.

The results revealed that although the relationships were not statistically significant in certain categories, greater plasma L + Z levels (Q2-Q4) tend to be related to lower ORs for depression in most subgroups compared to the lowest quartile. The findings provided by the interaction test indicated no significant interaction between the levels of plasma L + Z and the other hierarchical factors (all p for interaction > 0.05), except for gender and total fat (p for interaction <0.05). In female individuals, the relationship between plasma L + Z levels and depression was more significant compared to males. For participants with an average daily total fat intake of < 75 g/day, the relationship between plasma L + Z levels and depression was more significant than for participants with an average daily total fat intake of ≥ 75g/day.

DISCUSSION

The relationship between L + Z and depression has not been extensively studied. However, available evidence suggests that these carotenoids may exert protective effects on mental health. A recent systematic review and meta-analysis indicated a significant inverse association between dietary carotenoid intake, particularly L + Z, and depressive symptoms.[20] Additionally, other studies have provided evidence supporting the neuroprotective role of L + Z, showing their potential to improve cognitive function and brain health, which may indirectly contribute to lowering the risk of depression.[21] These findings suggested that maintaining adequate levels of these carotenoids through diet could be an effective strategy in the prevention of depression. Further research is warranted to confirm these effects in diverse populations. In this community-based investigation, the relationship between plasma and dietary levels of L + Z with the risk of depression was analyzed in US adults. Results from this study demonstrated that an appropriate increase in dietary L + Z intake and higher plasma L + Z levels are associated with a lower risk of depression. Notably, these associations were maintained when the participants were sub-grouped by age, marital status, educational level, ethnicity, and the ratio of family income to the poverty level. Meanwhile, the results of our study showed that a variety of variables may affect the relationship between plasma and dietary intake of L + Z with the risk of depression. Nonetheless, the impact of energy and fat intake on depression should be further explored, as this could provide a more comprehensive understanding of the mechanism underlying the inhibitory effects of increasing dietary L + Z against depression. For instance, a higher intake of energy and fat might be linked to better overall dietary habits, potentially benefiting mental health. Conversely, a lower intake of energy and fat could reflect a healthier lifestyle, which may also be associated with a reduced risk of depression. Therefore, investigating the interaction between these nutritional factors and depression risk could offer valuable insights for developing dietary recommendations aimed at preventing and treating depression. Collectively, our results highlight the need to maintain high plasma levels of L + Z by consuming an appropriate amount of L + Z to prevent depression. This study provides new insights into the relationship between nutrition and mental health, particularly concerning the potential role of L + Z in preventing and treating depression. The strong negative association observed between these carotenoids and depression risk highlights the potential for dietary

Table 4. Association between dietary lutein + zeaxanthin intake and depression across different subgroups

	Dietary lutein and zeaxanthin (μg)				*p* for trend	*p* for interaction
	Q1 (0.00-454.50)	Q2 (455.00-820.50)	Q3 (821.00-1548.50)	Q4 (1549.50-57188.00)		
Age						0.152
<60	Reference (1.00)	1.06 (0.81, 1.38) 0.661	0.75 (0.55, 1.02) 0.064	0.74 (0.54, 1.02) 0.067	<0.05	
≥60	Reference (1.00)	0.77 (0.50, 1.19) 0.234	0.90 (0.59, 1.37) 0.614	0.59 (0.36, 0.94) <0.05	0.067	
Gender						0.836
Male	Reference (1.00)	0.98 (0.69, 1.41) 0.925	0.90 (0.62, 1.31) 0.591	0.67 (0.44, 1.03) 0.068	0.076	
Female	Reference (1.00)	0.98 (0.73, 1.31) 0.881	0.75 (0.54, 1.04) 0.087	0.71 (0.50, 0.99) <0.05	<0.05	
Race						0.159
Non-Hispanic white	Reference (1.00)	0.99 (0.71, 1.38) 0.962	0.65 (0.44, 0.96) <0.05	0.61 (0.40, 0.93) <0.05	<0.01	
Others	Reference (1.00)	0.95 (0.69, 1.29) 0.732	0.94 (0.68, 1.30) 0.722	0.76 (0.54, 1.07) 0.119	0.147	
Education level						0.607
Less than high school	Reference (1.00)	1.06 (0.53, 2.14) 0.865	1.02 (0.46, 2.27) 0.966	0.91 (0.38, 2.14) 0.823	0.829	
High school	Reference (1.00)	1.09 (0.78, 1.53) 0.623	0.95 (0.65, 1.37) 0.773	0.80 (0.52, 1.22) 0.296	0.293	
College graduate or above	Reference (1.00)	0.84 (0.59, 1.18) 0.316	0.66 (0.46, 0.96) <0.05	0.56 (0.39, 0.82) <0.01	<0.01	
Marital status						0.341
Married/ Living with partner	Reference (1.00)	0.88 (0.64, 1.20) 0.417	0.81 (0.58, 1.13) 0.211	0.53 (0.35, 0.78) <0.01	<0.01	
Widowed/ Divorced/ Separated	Reference (1.00)	1.10 (0.72, 1.67) 0.652	0.97 (0.62, 1.53) 0.911	0.93 (0.59, 1.46) 0.751	0.663	
Never married	Reference (1.00)	1.00 (0.59, 1.68) 0.992	0.54 (0.28, 1.04) 0.065	0.85 (0.47, 1.52) 0.575	0.266	
BMI						0.716
<25	Reference (1.00)	0.78 (0.48, 1.25) 0.294	0.72 (0.43, 1.23) 0.232	0.68 (0.39, 1.21) 0.188	0.159	
≥25	Reference (1.00)	1.03 (0.79, 1.33) 0.835	0.84 (0.63, 1.11) 0.214	0.70 (0.52, 0.94) <0.05	<0.05	
The ratio of family income to poverty						0.778
<2.34	Reference (1.00)	0.98 (0.74, 1.30) 0.888	0.81 (0.60, 1.11) 0.197	0.60 (0.42, 0.85) <0.01	<0.01	
≥2.34	Reference (1.00)	0.84 (0.54, 1.30) 0.424	0.82 (0.52, 1.29) 0.390	0.73 (0.46, 1.16) 0.182	0.198	
Total energy (kcal)						0.193
<2000	Reference (1.00)	1.01 (0.76, 1.34) 0.932	0.69 (0.49, 0.97) <0.05	0.64 (0.45, 0.92) <0.05	<0.01	
≥2000	Reference (1.00)	0.99 (0.67, 1.46) 0.970	1.00 (0.68, 1.48) 0.993	0.81 (0.53, 1.24) 0.332	0.358	
Total fat (g)						<0.01
<75	Reference (1.00)	1.11 (0.83, 1.49) 0.465	0.61 (0.42, 0.90) <0.05	0.67 (0.46, 0.98) <0.05	<0.01	
≥75	Reference (1.00)	0.88 (0.61, 1.27) 0.487	1.02 (0.72, 1.47) 0.897	0.74 (0.50, 1.09) 0.126	0.239	

Adjusted for age, gender, race, education level, energy, marital status, total fat, BMI, Smoking status, leisure exercise time, hypertension, diabetes, coronary heart disease, the ratio of family income to poverty, and drinking.

Table 5. Association between plasma levels of lutein and zeaxanthin and depression across different subgroups

	plasma levels of lutein and zeaxanthin (μmol /L)				*p* for trend	*p* for interaction
	Q1 (0.030-0.195)	Q2 (0.197-0.283)	Q3 (0.285-0.399)	Q4 (0.401-3.270)		
Age						0.842
<60	Reference (1.00)	0.60 (0.45, 0.80) <0.001	0.73 (0.54, 0.98) <0.05	0.59 (0.42, 0.83) <0.01	<0.01	
≥60	Reference (1.00)	0.69 (0.44, 1.07) 0.097	0.63 (0.39, 1.00) <0.05	0.58 (0.36, 0.93) <0.05	<0.05	
Gender						<0.05
Male	Reference (1.00)	0.80 (0.56, 1.15) 0.224	0.53 (0.34, 0.80) <0.01	0.67 (0.44, 1.04) 0.077	<0.05	
Female	Reference (1.00)	0.52 (0.38, 0.72) <0.001	0.80 (0.58, 1.10) 0.165	0.54 (0.38, 0.78) <0.001	<0.01	
Race						0.078
Non-Hispanic white	Reference (1.00)	0.77 (0.55, 1.08) 0.128	0.55 (0.36, 0.85) <0.01	0.46 (0.28, 0.77) <0.01	<0.001	
Others	Reference (1.00)	0.55 (0.39, 0.77) <0.001	0.76 (0.55, 1.04) 0.088	0.63 (0.44, 0.89) <0.01	0.059	
Education level						0.754
Less than high school	Reference (1.00)	0.73 (0.29, 1.80) 0.494	0.67 (0.29, 1.58) 0.363	0.69 (0.29, 1.63) 0.396	0.444	
High school	Reference (1.00)	0.62 (0.43, 0.89) <0.05	0.82 (0.56, 1.20) 0.310	0.71 (0.46, 1.10) 0.128	0.153	
College graduate or above	Reference (1.00)	0.60 (0.42, 0.84) <0.01	0.62 (0.43, 0.89) <0.05	0.45 (0.30, 0.68) <0.001	<0.001	
Marital status						0.667
Married/ Living with partner	Reference (1.00)	0.70 (0.50, 0.98) <0.05	0.70 (0.49, 1.00) <0.05	0.54 (0.37, 0.81) <0.01	<0.01	
Widowed/ Divorced/ Separated	Reference (1.00)	0.57 (0.37, 0.89) <0.05	0.80 (0.51, 1.24) 0.308	0.60 (0.37, 0.98) <0.05	0.082	
Never married	Reference (1.00)	0.62 (0.36, 1.06) 0.082	0.54 (0.28, 1.03) 0.062	0.82 (0.43, 1.56) 0.539	0.256	
BMI						0.453
<25	Reference (1.00)	0.59 (0.36, 0.96) <0.05	0.49 (0.28, 0.83) <0.01	0.43 (0.24, 0.77) <0.01	<0.01	
≥25	Reference (1.00)	0.60 (0.45, 0.79) <0.001	0.72 (0.54, 0.96) <0.05	0.63 (0.46, 0.87) <0.01	<0.01	
The ratio of family income to poverty						0.683
<2.34	Reference (1.00)	0.65 (0.48, 0.88) <0.01	0.72 (0.52, 1.00) <0.05	0.65 (0.45, 0.93) <0.05	<0.05	
≥2.34	Reference (1.00)	0.60 (0.38, 0.94) <0.05	0.67 (0.43, 1.04) 0.071	0.44 (0.27, 0.73) <0.01	<0.01	
Total energy (kcal)						0.427
<2000	Reference (1.00)	0.54 (0.39, 0.74) <0.001	0.69 (0.50, 0.96) <0.05	0.58 (0.41, 0.83) <0.01	<0.01	
≥2000	Reference (1.00)	0.74 (0.51, 1.06) 0.103	0.65 (0.43, 0.96) <0.05	0.57 (0.37, 0.89) <0.05	<0.01	
Total fat (g)						<0.05
<75	Reference (1.00)	0.48 (0.34, 0.68) <0.001	0.71 (0.51, 1.00) <0.05	0.53 (0.36, 0.77) <0.01	<0.01	
≥75	Reference (1.00)	0.81 (0.57, 1.13) 0.2086	0.59 (0.41, 0.87) <0.01	0.66 (0.44, 0.99) <0.05	<0.05	

Adjusted for age, gender, race, education level, energy, marital status, total fat, BMI, Smoking status, leisure exercise time, hypertension, diabetes, coronary heart disease, the ratio of family income to poverty, and drinking.

interventions as a non-invasive and accessible means of improving mental health outcomes. Future public health strategies could benefit from incorporating recommendations for increased consumption of L + Z-rich foods, particularly for populations at higher risk of depression.

Both a rise in oxidative stress and a fall in the levels of circulating antioxidants have been linked to depression. About a quarter of depression patients exhibit mild inflammation, and more than half of patients exhibit mildly elevated CRP levels.[22,23] Many people suffering from depression may have inflammation as a contributing factor.[23] Some biological and physical mechanisms may link dietary and plasma L + Z levels with depression. Carotenoids represent bioactive dietary ingredients that have aroused contemporary interest in their therapeutic effects on psychological well-being and the quality of sleep.[24] Numerous studies have investigated the relationship between L + Z and cancer, revealing that they may have antioxidant properties that help control apoptotic cellular processes.[25,26] Antioxidants can terminate neuronal damage by inhibiting hydroxyl radicals and limiting lipid peroxidation to reduce oxidative damage.[27] Earlier research reported that lower levels of carotenoids are linked to an increase in depression symptoms.[28] Moreover, carotenoids can alter biological activities, exhibiting anti-inflammatory and antioxidant properties.[29] Two preclinical investigations indicated that supplementary β-carotene or zeaxanthin reduced inflammatory biomarkers such as tumor necrosis factor-α and interleukin-6, improving depressive-like traits in rats or mice with diabetes.[30,31] Additionally, other research have demonstrated a decrease in antioxidant activity and depressive-like behavior in rodents: oxidative stress was lessened by supplemental β-carotene therapy by reducing plasma nitrite levels.[32] The above arguments imply that depressive symptoms decrease as lutein/zeaxanthin increases. However, further study is urgently required to explore the underlying mechanism. Nevertheless, human trial data remains lacking. Hence, the conclusion of L + Z reducing depression should be interpreted with caution until human trials are conducted.

The relationship between lutein/zeaxanthin and depression has not been extensively studied in the past. A previous study reported a negative relation between the amount of plasma carotenoids level and the risk of developing depression or depression symptoms.[14] In addition, a previous investigation has demonstrated a substantial negative relation between the risk of depression in participants with cardiovascular metabolic illnesses and the consumption of L + Z.[15] However, lutein/zeaxanthin did not appear to be linked to depression symptoms in a cross-sectional study conducted among adult Americans.[16] This is inconsistent with the research results of this study. This disparity may be attributed to differences in sample size and moderating variables. When further exploring the relationship between plasma and dietary L + Z with depression, the results indicated stable outcomes regardless of subgroup analysis for age, ethnicity, education level, marital status, BMI, total energy and household income. However, the subgroup analysis revealed that gender showed a significant interaction with plasma L + Z levels. The relationship between plasma L + Z and depression was more significant in female participants compared to males. Females are influenced by certain proteins in the process of regulating depressive emotions. These biological processes are related to immune inflammation control. However, men are more prone to experiencing imbalances during these processes.[33] Meanwhile, the subgroup analysis revealed that total fat showed a significant interaction with dietary L + Z levels. For participants with an average daily total fat intake of < 75 g/day, the relationship between dietary L + Z levels and depression was significant, but not for participants with an average daily total fat intake of ≥ 75 g/day. The reason may be related to the impact of fat type and concentration on the absorption of carotenoids. Multiple validations have confirmed that dietary fat promotes the absorption of carotenoids through an *in vitro* model.[34] Fat may also decrease the concentration of carotenoids through biological processes.[35] However, this result still requires further intervention experiments in the future to explore and confirm.

Our study has several advantages. First, this study examined the link between plasma L + Z levels and depression risk in the US population. Secondly, it is the first research to explore the linear relationship between plasma and dietary levels of L + Z with the risk of depression. Prior research has investigated the connection between depression in American adults and dietary L + Z. However, the studies' sample sizes were not as large as ours. Second, our work used a sample approach to investigate the well-characterized NHANES datasets, allowing us to extrapolate our findings to the whole US population. Third, the linear associations between depression and plasma and dietary levels of lutein and zeaxanthin were investigated using a restricted cubic spline, which provides an excellent estimate of the actual link between exposure and the accompanying results since it is adept at finding linear correlations. Nevertheless, the limitations of the study should also be acknowledged. Firstly, the cross-sectional research approach limits the observation to the target population's health condition at a particular moment in time, and causality cannot be determined. Second, residual confounders, such as geographic location, socioeconomic position, and medication usage, may also have had an impact on our findings.

Conclusion

The present results demonstrate the associations of higher dietary and plasma L + Z levels with lower depression risk. The findings offer insights into how L + Z can possibly be leveraged to reduce a person’s risk of depression and improve health. However, our findings must be validated by multicenter, prospective, and large-scale studies. RCTs are still needed in the future to explore the effects of supplementing lutein + zeaxanthin on depression. We should aim for a healthy and balanced diet in terms of nutritional supplementation.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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