Cross-Sectional Survey

Nonlinear Association Between Serum Lutein and Zeaxanthin Levels and Low Back Pain in US Adults: Results from the National Health and Nutrition Examination Survey

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Disclaimer: There was no external funding in the preparation of this article.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Article received: 01-05-2025
Revised article received: 03-30-2025
Accepted for publication: 04-10-2025

Free full article: www.painphysicianjournal.com

Background: Oxidative stress plays a critical role in the pathogenesis of low back pain. Higher serum levels of lutein and zeaxanthin are associated with reduced susceptibility to this disease due to their potent antioxidant properties.

Objectives: Our study aimed to assess the correlation between serum lutein and zeaxanthin levels and low back pain.

Study Design: This is a cross-sectional study based on publicly available data from the National Health and Nutrition Examination Survey.

Setting: The National Health and Nutrition Examination Survey employs a complex, multistage probability sampling design in order to select a nationally representative sample.

Methods: In our study, information was gathered from individuals who were 20 years old or older who took part in the National Health and Nutrition Examination Survey from 2001 through 2004. Detailed information was collected on low back pain, serum lutein and zeaxanthin levels, and various other crucial factors. Multivariable logistic regression and restricted cubic spline regression analyses were performed in order to investigate the relationship between serum lutein and zeaxanthin levels and the occurrence of low back pain.

Results: In our study 7,026 participants were included, of whom 38.21% (2,685 of 7,026) had low back pain. There was a nonlinear relationship ($P < 0.001$) between serum lutein and zeaxanthin levels and low back pain, depicted as a U-shaped curve in the restricted cubic spline. The occurrence rate for individuals with serum lutein and zeaxanthin levels below 25.3 nmol/dL was 0.975 (95% CI, 0.960–0.990; $P < 0.001$). In comparison, the occurrence rate for individuals with serum lutein and zeaxanthin levels exceeding 25.3 nmol/dL was 1.006 (95% CI, 1.000–1.013; $P = 0.043$).

Limitations: This is a cross-sectional study; therefore causality cannot be established.

Conclusion: A nonlinear association between serum lutein and zeaxanthin levels and the risk of low back pain was observed in US adults. The ideal serum lutein and zeaxanthin level that corresponds to the lowest risk of low back pain is approximately 25.3 nmol/dL.

Key words: Low back pain, serum lutein and zeaxanthin, cross-sectional study, NHANES

Pain Physician 2025: 28:439-448

Low back pain continues to be the leading cause of years lived with disability, affecting 619 million individuals globally in 2020; it is predicted to affect more than 800 million people by 2050 due to population growth and aging (1,2). Its wide-ranging prevalence and consequential disability have substantial negative effects not only on affected individuals but also on their families, colleagues, employers, and the society at large (3,4).

The pathophysiological mechanisms of low back pain are intricate; they include various factors, such as biophysical, psychological, social, and genetic factors, as well as comorbidities. Intervertebral disc degeneration is garnering increasing attention as a major cause of low back pain, which is responsible for approximately 40% of symptomatic low back pain (5,6). Increasing evidence suggests that oxidative stress plays a crucial role in the pathophysiology of intervertebral disc degeneration. Excessive reactive oxygen species levels will destroy nucleic acids, lipids, and proteins of nucleus pulposus cells; disrupt their cell activity and function; and eventually lead to cell senescence or death (7-9).

Lutein and zeaxanthin, both carotenoids, are found in various foods. Lutein is primarily found in green leafy vegetables, such as spinach, kale, and collard greens, as well as certain yellow or orange fruits and vegetables. Zeaxanthin is also found in yellow or orange fruits and vegetables, such as corn and citrus fruits (10). Both exhibit significant antioxidant characteristics, protecting cells from damage caused by free radicals. These antioxidants can mitigate oxidative stress, potentially reducing the risk of various diseases (11). Their frequent co-analysis reflects their combined presence, which synergistically enhances protective effects on the retina and macula (12). In our study, we also grouped lutein and zeaxanthin together, following the approach used in the National Health and Nutrition Examination Survey (NHANES) data analysis.

Due to the antioxidant and anti-inflammatory properties of lutein and zeaxanthin, aside from their beneficial effects on the eyes, they also offer other advantages to human health. An observational study reported that consuming diets high in lutein and zeaxanthin is associated with a lower occurrence of metabolic syndrome (13). Another study indicated increasing serum lutein and zeaxanthin levels were associated with a lower risk of all-cause and cardiovascular mortality in US adults with hypertension (14). A randomized controlled trial demonstrated that older men and women residing in the community from the Athens-Clarke County experienced enhanced cognitive function with lutein and zeaxanthin supplementation (15).

Although there has been extensive research into the positive effects of lutein and zeaxanthin on health, the association between serum lutein and zeaxanthin levels and low back pain remains unclear. Our hypothesis is that increased serum lutein and zeaxanthin levels have a negative association with the likelihood of experiencing low back pain. To examine this hypothesis, we carried out a study to explore the possible link between serum lutein and zeaxanthin levels and the occurrence of low back pain among US adults.

Methods

Study Population

This cross-sectional analysis made use of data that are publicly accessible from the NHANES. NHANES is a comprehensive series of studies designed to evaluate the health and nutritional well-being of individuals, both adults and children in the United States. Information was acquired from the website (http://www.cdc.gov/nchs/nhanes.htm).

Figure 1 illustrates the comprehensive procedure of participant inclusion and exclusion. We enrolled 10,452 participants aged ≥ 20 years who had completed the NHANES interview. Additionally, NHANES had data on both serum lutein and zeaxanthin levels and low back pain status recorded from 2001 through 2004. We excluded participants on the following grounds: pregnant women (n = 577), individuals with missing data on low back pain (n = 4), those with missing data on serum lutein and zeaxanthin levels (n = 1,212), and those with missing data on covariates (n = 1,633). Ultimately, 7,026 participants were included for further analysis.

The NHANES is sanctioned by the Ethics Review Committee of the National Center for Health Statistics (NCHS) (Protocol#98-12); all participants granted their consent in writing prior to their involvement (16). Additional approval from an Institutional Review Board was not necessary for the secondary analysis of deidentified NHANES data. Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (17), as well as all methods adhering to the Declaration of Helsinki and relevant guidelines and regulations.

Blood Lutein and Zeaxanthin Concentrations Assessment

NHANES data from 2001 through 2002 showed that serum lutein and zeaxanthin levels were measured using high-performance liquid chromatography. During the period of 2003 through 2004, the measurement of these lutein and zeaxanthin levels was conducted utilizing an equivalent high-performance liquid chromatography technique. To ensure uniformity, the data from NHANES 2003–2004 were converted to comparable lutein and zeaxanthin measurements by imple-

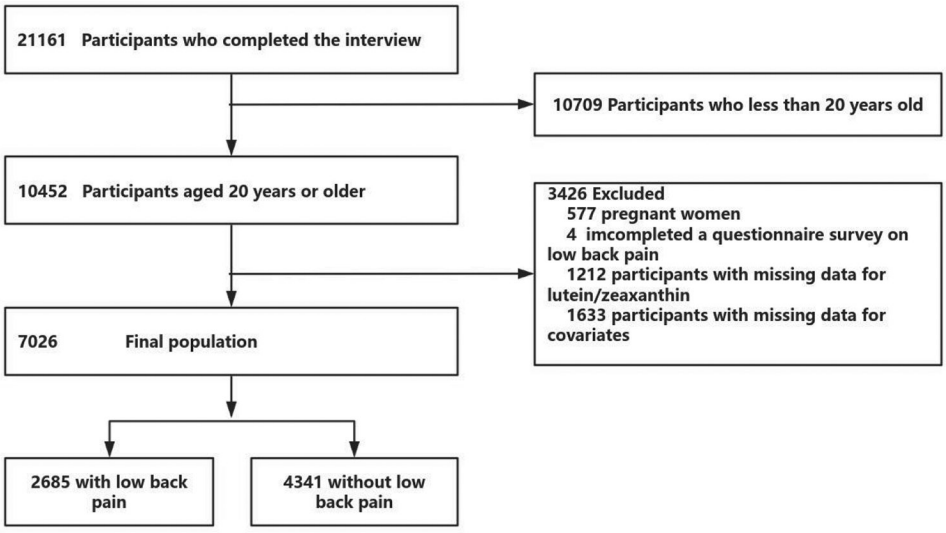

Fig. 1. *The study's flow diagram.*

menting a regression method. This approach ensured consistency in lutein and zeaxanthin measurements across cycles. Previously, there have been descriptions of laboratory protocols and quality assurance techniques for measuring serum lutein and zeaxanthin at the NHANES website: https://wwwn.cdc.gov/Nchs/Nhanes/2001-2002/L06VIT_B.htm and https://wwwn.cdc.gov/Nchs/Nhanes/2003-2004/L45VIT_C.htm.

Low Back Pain Definition

Identifying low back pain in participants was based on their responses to the miscellaneous pain survey (variable LBQ070), which inquired if they had experienced low back pain within the previous 3 months. Low back pain was considered present if the participants answered "yes" to the question (18).

Covariate Analysis

The covariates considered in our study included age, gender, body mass index (BMI [kg/m^2]), marital status, race, education level, family poverty-income ratio, physical activity, smoking habits, alcohol intake, analgesic user, and presence of hypertension, diabetes, or osteoporosis, as stated in the available literature.

We obtained information according to standardized questionnaires from the NHANES. Race was divided into non-Hispanic White, non-Hispanic Black, Mexican American, or other races (19). Marital status was divided into married and living with a partner, or living alone (19). Educational level was divided into less than high school, high school, and more than high school (20). Family income was divided into 3 groups based on poverty-income ratio (< 1.3, 1.3–3.5, > 3.5) (18,19). Smoking habits was were classified as never smoked, current smoker, and former smoker (19). Physical activity was classified as sedentary, moderate, or vigorous (19). Alcohol intake was defined as having consumed at least 12 alcoholic drinks within one year (21). According to 2 sections of the NHANES interview: Analgesic Medications and Prescription Medications, analgesic use was defined as both having taken over-the-counter or prescription pain medications every day for as long as a month and having taken any prescription medications during the past month (22). Hypertension, diabetes, and osteoporosis were determined according to participants' responses to NHANES inquiries about whether a physician had diagnosed one or more of these diseases.

Statistical Analysis

For this research, we conducted a secondary analysis of openly available datasets. We represent continuous variables that follow a normal distribution as means with SDs; variables that do not follow a normal distribution as medians with interquartile ranges (IQR); and categorical variables as percentages (%). The distribution of serum lutein and zeaxanthin levels was used to determine the quartiles. To compare differences

across groups, various statistical tests were employed: one-way analysis of variance (ANOVA, for variables that follow a normal distribution); Kruskal-Wallis (for variables that do not follow a normal distribution); and χ^2 tests (for categorical variables).To evaluate the association between serum lutein and zeaxanthin and low back pain, logistic regression models were utilized, which provided odds ratios and 95% CIs.

Previous literature reports that advanced age, being a woman, having a low education level, and being obese are all associated with chronic low back pain risk (23,24).

Marital status, race, and family income may influence eating habits and thus blood vitamin levels, so we took those demographic variables into account when adjusting Model 1. Physical activity, smoking, drinking alcohol, using analgesics, and other lifestyle habits have long been considered to be closely related to health and disease. Yoshimoto, et al (25) reported that smoking and alcohol consumption are risk factors for low back pain, therefore we adjusted for these lifestyle factors in Model 2. Additionally, comorbidities such as hypertension, diabetes, and osteoporosis are associated with low back pain risk (26,27), therefore we adjusted for them in Model 3.

We conducted restricted cubic spline regression with 4 knots at the 5th, 35th, 65th, and 95th percentiles of serum lutein and zeaxanthin in order to evaluate the linearity and the dose-response relationship between serum lutein and zeaxanthin and low back pain, while accounting for the variables in Model 3.

Moreover, potential effect modifications of the relationship between serum lutein and zeaxanthin and low back pain were assessed for variables such as age (20–64 or ≥ 65 years); gender; BMI (healthy:18.5–-24.9 or unhealthy); race (non-Hispanic, White, or other races); education level (less than high school, high school diploma or equivalent, or postsecondary education); poverty-income ratio (< 1.3, 1.3–3.5, > 3.5); marital status (married and living with a partner or single); activity level (sedentary, moderate, or vigorous activity); alcohol intake (yes or no); smoking status (yes or no); analgesic user (yes or no); hypertension (yes or no); diabetes (yes or no); and osteoporosis (yes or no). Multivariate logistic regression and likelihood ratio tests were used to examine the interactions between the subgroups and serum lutein and zeaxanthin levels.

In order to evaluate the validity of our results, we conducted several sensitivity analyses. First, in order to mitigate the effect of missing covariates, we conducted sensitivity analyses that included the missing data. Second, dietary lutein and zeaxanthin intake was additionally adjusted. In addition, we further adjusted for other biomarkers, including dietary niacin, dietary calcium, dietary magnesium, dietary iron, and dietary zinc).

Since the sample size was determined solely based on the given data, no preliminary statistical power estimates were acquired. R 3.3.2 (The R Foundation) and Free Statistics software (Version 1.7, Beijing, China, http://www.clinicalscientists.cn/freestatistics) were used for all statistical analyses (28). We utilized a 2-tailed test and deemed a P value < 0.05 as having statistical significance.

Results

Study Participants Characteristics

Among the 7,026 enrolled participants (mean age, 50.7 years; 51.9% men), the median (interquartile range) serum concentrations were 25.3 (18.5 – 35.0) nmol/dL for lutein and zeaxanthin. Table 1 provides a summary of baseline characteristics of the participants based on quartiles of serum lutein and zeaxanthin levels. Individuals with higher serum lutein and zeaxanthin concentrations tended to be older, have a normal BMI, are non-Hispanic Black, live alone, have a higher educational level, come from a higher-income family, engage in vigorous activity, and never smoked.

Associations Between Serum Lutein and Zeaxanthin Levels and Low Back Pain

A Univariate analysis revealed significant associations between low back pain and various factors, such as gender, race, educational level, family income, activity, smoking, hypertension, diabetes, and osteoporosis (Supplementary Table S1).

Table 2 presents the association between serum lutein and zeaxanthin levels and low back pain according to lutein and zeaxanthin quartiles. After fully adjusting for possible confounding factors, compared to individuals with serum lutein and zeaxanthin levels in the middle quartile (18.53–25.30 nmol/dL), those in the low quartile (≤ 18.51nmol/dL) and high quartile (25.32–34.95 nmol/dL) exhibited adjusted odds ratios for serum lutein and zeaxanthin levels and low back pain of 1.27 (95% CI, 1.12 – 1.44; P < 0.001) and 1.14 (95% CI, 1.01–1.29; P = 0.038), respectively.

There was a nonlinear relationship between serum lutein and zeaxanthin levels and low back pain (P for

Table 1. *Study population characteristics.*

Variables	Serum lutein and zeaxanthin levels (nmol/dL)				*P*
	Total (n = 7,026)	Q1 (n =2,340) (≤ 20.69)	Q2 (n = 2,338) (20.7-31.08)	Q3 (n =2,348) (≥ 31.10)	
Age (yrs), Mean ± SD	50.7 ± 18.5	47.8 ± 18.5	50.4 ± 18.6	53.8 ± 17.9	< 0.001
Gender, n (%)					0.167
Men	3,643 (51.9)	1176 (50.3)	1,232 (52.7)	1,235 (52.6)	
Women	3,383 (48.1)	1,164 (49.7)	1,106 (47.3)	1,113 (47.4)	
BMI, n (%)					< 0.001
< 18.5	101 (1.4)	36 (1.5)	32 (1.4)	33 (1.4)	
18.5-24.9	2,104 (29.9)	603 (25.8)	688 (29.4)	813 (34.6)	
25-25.9	2,580 (36.7)	749 (32)	877 (37.5)	954 (40.6)	
> 25.9	2,241 (31.9)	952 (40.7)	741 (31.7)	548 (23.3)	
Race/ethnicity, n (%)					< 0.001
Non-Hispanic White	3,837 (54.6)	1,440 (61.5)	1,250 (53.5)	1,147 (48.9)	
Non-Hispanic Black	1,294 (18.4)	385 (16.5)	431 (18.4)	478 (20.4)	
Mexican American	1,435 (20.4)	389 (16.6)	514 (22)	532 (22.7)	
Other Race	460 (6.5)	126 (5.4)	143 (6.1)	191 (8.1)	
Education level, n (%)					< 0.001
Less Than High School	1,989 (28.3)	666 (28.5)	669 (28.6)	654 (27.9)	
High School Diploma	1,715 (24.4)	667 (28.5)	558 (23.9)	490 (20.9)	
Postsecondary	3,322 (47.3)	1,007 (43)	1,111 (47.5)	1,204 (51.3)	
Marital status, n (%)					< 0.001
Married or living with a partner	2,615 (37.2)	947 (40.5)	857 (36.7)	811 (34.5)	
Living alone	4,411 (62.8)	1,393 (59.5)	1,481 (63.3)	1,537 (65.5)	
Family PIR, n (%)					< 0.001
<1.3	1,859 (26.5)	727 (31.1)	615 (26.3)	517 (22)	
1.3-3.5	2,769 (39.4)	958 (40.9)	912 (39)	899 (38.3)	
>3.5	2,398 (34.1)	655 (28)	811 (34.7)	932 (39.7)	
activity, n (%)					< 0.001
Sedentary	2,831 (40.3)	1,032 (44.1)	974 (41.7)	825 (35.1)	
Moderate	2,136 (30.4)	709 (30.3)	700 (29.9)	727 (31)	
Vigorous	2,059 (29.3)	599 (25.6)	664 (28.4)	796 (33.9)	
Alcohol intake, n (%)	4,921 (70.0)	1,615 (69)	1,648 (70.5)	1,658 (70.6)	0.415
Smoking, n (%)					< 0.001
Not at all	3,770 (53.7)	1,111 (47.5)	1,280 (54.7)	1,379 (58.7)	
Every day	1,326 (18.9)	659 (28.2)	410 (17.5)	257 (10.9)	
Some days	1,930 (27.5)	570 (24.4)	648 (27.7)	712 (30.3)	
Analgesic user, n (%)	1,544 (22.0)	541 (23.1)	507 (21.7)	496 (21.1)	0.235
Hypertension, n (%)	3,082 (43.9)	1,001 (42.8)	1,024 (43.8)	1,057 (45)	0.302
Diabetes, n (%)	959 (13.6)	331 (14.1)	323 (13.8)	305 (13)	0.494
Osteoporosis, n (%)	463 (6.6)	145 (6.2)	141 (6)	177 (7.5)	0.074
Low back pain, n (%)	2,685 (38.2)	1,027 (43.9)	822 (35.2)	836 (35.6)	< 0.001

Q, quartiles; SD, standard deviation; PIR, poverty-income ratio (ratio of family income to poverty threshold); BMI, body mass index (kg/m^2)

Table 2. *Association between serum lutein and zeaxanthin (nmol/dL) and low back pain.*

Variable	OR (95%CI)								
	N event%	Crude	*P*-Value	Model One	*P*-Value	Model 2	*P*-Value	Model 3	*P*-Value
Q1 (n =2340) (≤ 20.69)	1027 (43.9)	1.44 (1.28–1.62)	< 0.001	1.32 (1.17–1.49)	< 0.001	1.27 (1.13–1.44)	< 0.001	1.27 (1.12–1.44)	< 0.001
Q2 (n = 2338) (20.7-31.08)	822 (35.2)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q3 (n =2348) (≥ 31.1)	836 (35.6)	1.02 (0.9–1.15)	0.749	1.09 (0.96–1.23)	0.182	1.14 (1.01–1.29)	0.035	1.14 (1.01–1.29)	0.038

Q, quartiles; OR, odds ratio; Ref, reference.
Model One was adjusted for sociodemographic variables (age, gender, body mass index, race/ethnicity, education level, family income, marital status,).
Model 2 was adjusted for Model 1, activity level, alcohol intake, smoking status, and analgesic use.
Model 3 was adjusted for Model 2, hypertension, diabetes, and osteoporosis.

nonlinearity, < 0.001), which is depicted as a U-shaped curve in restricted cubic spline regression (Fig. 2). The occurrence rate of participants with serum lutein and zeaxanthin levels below 25.3 nmol/dL experiencing low back pain was 0.975 (95% CI, 0.960 – 0.990; *P* <0.001) (Table 3). This suggests that the likelihood of suffering from low back pain is reduced by 2.5% for every one nmol/dL rise in serum lutein and zeaxanthin levels. In comparison, the occurrence rate of individuals with serum lutein and zeaxanthin levels exceeding 25.3 nmol/dL who experience low back pain was 1.006 (95% CI, 1.0 – 1.013; *P* = 0.043) (Table 3). This suggests that the likelihood of experiencing low back pain rises by 0.6% for every one nmol/dL increase in serum lutein and zeaxanthin levels.

We conducted stratified analyses in order to assess the potential effects of various modifiers on the relationship between serum lutein and zeaxanthin levels and low back pain across different subgroups. There were no significant interactions in any subgroups after stratification according to age (20 – 64 or ≥ 65 years); gender; BMI (normal: 18.5 – 24.9 or abnormal); race (non-Hispanic white or other races); education level (less than high school, high school diploma, or post-secondary); poverty to income ratio (< 1.3, 1.3–3.5, > 3.5); marital status (married and living with a partner or single); activity level (sedentary, moderate, or vigorous activity); alcohol intake (yes or no); smoking status (yes or no); analgesic use (yes or no); hypertension (yes or no); diabetes (yes or no); and osteoporosis (yes or no) (all interaction *P* values were > 0.05) (Table 4).

In sensitivity analyses, the nonlinear association between serum lutein and zeaxanthin levels and low back pain persisted consistently, even after including participants with missing data (Supplementary Table S2, Supplementary Fig. S1). Furthermore, adjustments for dietary lutein and zeaxanthin did not alter the results (Supplementary Table S3). Additionally, after further adjusting for other biomarkers such as dietary niacin, calcium, magnesium, iron, and zinc, the results remained stable (Supplementary Table S4).

Discussion

As far as we know, this is the first time research exploring the association between serum lutein and zeaxanthin and low back pain. According to our research, there was a nonlinear relationship (*P* < 0.001) between serum lutein and zeaxanthin levels and low back pain, which was depicted as a U-shaped curve in restricted cubic spline regression. The ideal serum lutein and zeaxanthin level that corresponds to the lowest risk of low back pain is approximately 25.3 nmol/dL. Serum lutein and zeaxanthin levels were negatively associated with low back pain when the level is below 25.3 nmol/dL; levels above 25.3 nmol/dL are associated with low back pain.

Previous research has found that increased levels of serum lutein and zeaxanthin in the blood are associated with a reduced likelihood of several chronic conditions, such as age-related macular degeneration, metabolic syndrome, and cognitive decline (13-15). However, there have been no previous studies on the association between serum lutein and zeaxanthin levels and low back pain. In our large-sample study, we explored the associations between serum lutein and zeaxanthin levels and the risk of low back pain using multivariable logistic regression models and restricted cubic spline regression. After adjusting for various possible confounding factors, we found a nonlinear relationship between serum lutein and zeaxanthin levels and low back pain. This suggests that appropriate serum lutein and zeaxanthin levels may offer potential benefits for individuals with low back pain. More attention should be paid to serum lutein levels in patients

with low back pain; US adults should avoid lutein and zeaxanthin level deficiency and overdose. The consistency of this association is further supported by various stratified and sensitivity analyses, which confirm the validity of our results. Our findings provide new evidence for the link between antioxidants and low back pain.

The biological mechanisms linking serum lutein and zeaxanthin with low back pain are unclear, but they might be associated with the following mechanisms. Firstly, oxidative stress is a complex process associated with the pathogenesis of low back pain because excessive free radicals can damage vital biomolecules and cellular structures (29). Serum lutein and zeaxanthin might provide a defense against oxidative stress and consequently lower the likelihood of experiencing low back pain due to their strong antioxidant characteristics. Secondly, neurogenic inflammation, a key element in low back pain development, involves the release of neuropeptides like substance P and calcitonin gene-related peptide from the trigeminal nerve, leading to arterial vasodilation, extravasation of plasma proteins, and mast cell degranulation (12-14). Previous studies have shown serum lutein and zeaxanthin levels are inversely associated with inflammatory markers related to chronic disease (30,31). Therefore, it is suggested that the antioxidant and anti-inflammatory properties of serum lutein and zeaxanthin may contribute to its beneficial effects on low back pain. However, further longitudinal studies with larger sample sizes are needed to delve deeper into the correlation between serum lutein and zeaxanthin levels and low back pain.

It is crucial to recognize the limitations of our research. First, low back pains were based on self-reports; we were unable to differentiate between the various types of low back pain. Furthermore, because of our study's observational design, it was not possible to establish causality; longitudinal studies are needed for additional confirmation. Furthermore, low back pain data was restricted to the years 2000 through 2004, thereby constraining our ability to verify our findings with NHANES data from varying timeframes. Moreover, our results are based on adults in the United States, potentially limiting their generalizability to other populations. Ultimately, it is not possible to eliminate the chance of lingering and unidentified confounding variables.

In conclusion, a nonlinear association between serum lutein and zeaxanthin levels and the risk of low back pain was observed in United States adults. The ideal serum lutein and zeaxanthin level that corresponds to the lowest risk of low back pain is approximately 25.3 nmol/dL. Further studies are needed to confirm our findings.

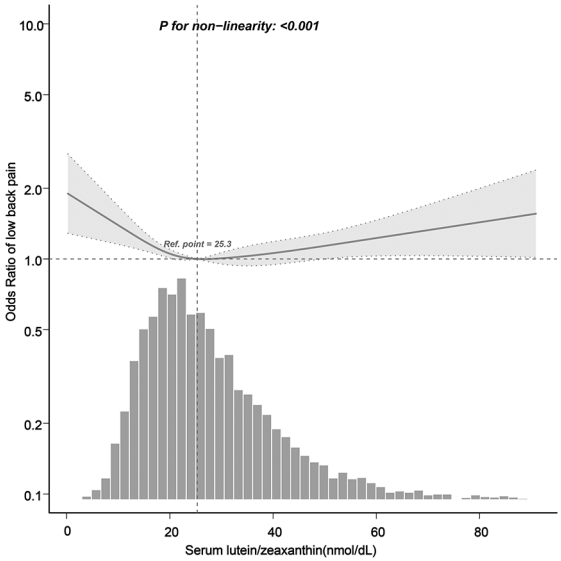

Fig. 2. *Association between serum lutein and zeaxanthin levels and low back pain in restricted cubic spline regression. Solid lines represent the predicted value; dash lines, 95% CI. A serum lutein and zeaxanthin level of 25.3 nmol/dL was used as the reference to estimate all odds ratios. Adjustments made for age, gender, body mass index, race/ethnicity, education level, family income, marital status, activity level, alcohol use, smoking status, analgesic use , hypertension, diabetes, and osteoporosis . Only 99.5% of the data is displayed.*

Table 3. *Threshold effect analysis of the relationship of serum lutein and zeaxanthin (nmol/dL) with low back pain.*

Serum Lutein/zeaxanthin levels(nmol/L)	Adjusted Model	
	OR (95% CI)	
< 25.3	0.975 (0.96–0.99)	0.001
≥ 25.3	1.006 (1–1.013)	0.043
Log-likelihood ratio test		<0.001

OR, odds ratio. Adjustments made for age, gender, body mass index, race/ethnicity, education level, family income, marital status, activity level, alcohol intake, smoking status, analgesic use , hypertension, diabetes, and osteoporosis . Only 99.5% of the data is displayed.

Acknowledgments

We thank Dr. Liu Jie (People's Liberation Army of China General Hospital, Beijing, Peoples Republic of China), Dr. Liu Huanxian(People's Liberation Army of China General Hospital, Beijing, Peoples Republic of China) and Dr. Yang Qilin (The Second Affiliated Hos-

Table 4. *Stratified analyses of the associations between serum lutein and zeaxanthin levels (nmol/dL) and low back pain.*

Subgroup	Change in serum lutein and zeaxanthin (nmol/dL), OR (95% CI)			*P* for interaction
	Q1 (≤ 18.51)	Q2(18.53–25.30)	Q3 (≥ 34.98)	
Age(years)				0.088
20-64	1.36 (1.18–1.57)	1(Ref)	1.09 (0.94-1.26)	
≥65	1.08 (0.84-1.38)	1(Ref)	1.19 (0.95-1.51)	
Gender				0.258
Men	1.25 (1.06-1.49)	1(Ref)	1.17 (0.99–1.39)	
Women	1.3 (1.09–1.55)	1(Ref)	1.11 (0.92–1.32)	
BMI				0.519
Normal	1.29 (1.02–1.64)	1(Ref)	1.02 (0.81–1.27)	
Abnormal	1.28 (1.11–1.48)	1(Ref)	1.19 (1.02–1.38)	
Race				0.397
Non-Hispanic White	1.16 (0.99–1.37)	1(Ref)	1.16 (0.98–1.38)	
Others Race	1.54 (1.14–2.07)	1(Ref)	1.15 (0.86–1.54)	
Education				0.815
Less Than High School	1.14 (0.9–1.43)	1(Ref)	1.1 (0.87–1.39)	
High School Diploma	1.2 (0.95–1.53)	1(Ref)	1.19 (0.91–1.55)	
Postsecondary	1.39 (1.16–1.67)	1(Ref)	1.16 (0.97–1.39)	
Married				0.882
Married or living with a partner	1.3 (1.06–1.59)	1(Ref)	1.18 (0.95–1.45)	
Living alone	1.27 (1.08–1.48)	1(Ref)	1.12 (0.96–1.31)	
Family_PIR				0.71
< 1.3	1.4 (1.11–1.77)	1(Ref)	1.2 (0.93–1.54)	
1.3-3.5	1.19 (0.98–1.44)	1(Ref)	1.11 (0.91–1.36)	
> 3.5	1.25 (1–1.55)	1(Ref)	1.15 (0.93–1.41)	
Activity				0.281
Sedentary	1.29 (1.07–1.55)	1(Ref)	1.36 (1.12–1.66)	
Moderate	1.27 (1.02–1.59)	1(Ref)	1.14 (0.91–1.44)	
Vigorous	1.22 (0.96–1.55)	1(Ref)	0.91 (0.72–1.14)	
Analgesic use				0.15
No	1.27 (1.1–1.46)	1(Ref)	1.16 (1.01–1.34)	
Yes	1.25 (0.96–1.62)	1(Ref)	1.05 (0.81–1.37)	
Alcohol				0.684
No	1.26 (1–1.57)	1(Ref)	1.09 (0.87–1.38)	
Yes	1.27 (1.1–1.47)	1(Ref)	1.16 (1–1.35)	
Smoker				0.247
Not at all	1.25 (1.05–1.49)	1(Ref)	1.04 (0.88–1.23)	
Every day	1.36 (1.04–1.77)	1(Ref)	1.03 (0.74–1.44)	
Some days	1.24 (0.97–1.57)	1(Ref)	1.4 (1.11–1.76)	

pital of Guangzhou Medical University, Guangzhou, Guangdong, Peoples Republic of China) for helping in this revision.

Ethics Declarations

Ethical review and approval were not required for this study, since our secondary analysis did not necessitate additional Institutional Review Board oversight.

Informed Consent Statement

NHANES was authorized by the National Center for Health Statistics Ethics Review Committee. All participants provided written informed consent prior to participation.

Availability of Data and Materials

The datasets analyzed for this study are available from the corresponding author upon reasonable request.

Consent for Publication

This manuscript has been reviewed and approved for publication by all authors.

Table 4 cont. *Stratified analyses of the associations between serum lutein and zeaxanthin levels (nmol/dL) and low back pain.*

Subgroup	Change in serum lutein and zeaxanthin (nmol/dL), OR (95% CI)			*P* for interaction
	Q1 (≤ 18.51)	Q2(18.53–25.30)	Q3 (≥ 34.98)	
Hypertension				0.505
No	1.32 (1.12–1.55)	1(Ref)	1.05 (0.89–1.25)	
Yes	1.22 (1.01–1.47)	1(Ref)	1.25 (1.04–1.5)	
Diabetes				0.333
No	1.31 (1.15–1.49)	1(Ref)	1.18 (1.03–1.35)	
Yes	1.1 (0.79–1.53)	1(Ref)	0.95 (0.68–1.34)	
osteoporosis				0.403
No	1.3 (1.15–1.47)	1(Ref)	1.16 (1.02–1.31)	
Yes	0.86 (0.51–1.46)	1(Ref)	1.03 (0.63–1.68)	

Q, quartiles; OR, odds ratio; Ref, reference. Adjustments made for age, gender, body mass index, race/ethnicity, education level, family income, marital status, activity level, alcohol intake, smoking status, analgesic user, hypertension, diabetes, osteoporosis. The strata variable was not included in the model when stratifying by itself.

Supplemental material available at www.painphysicianjournal.com

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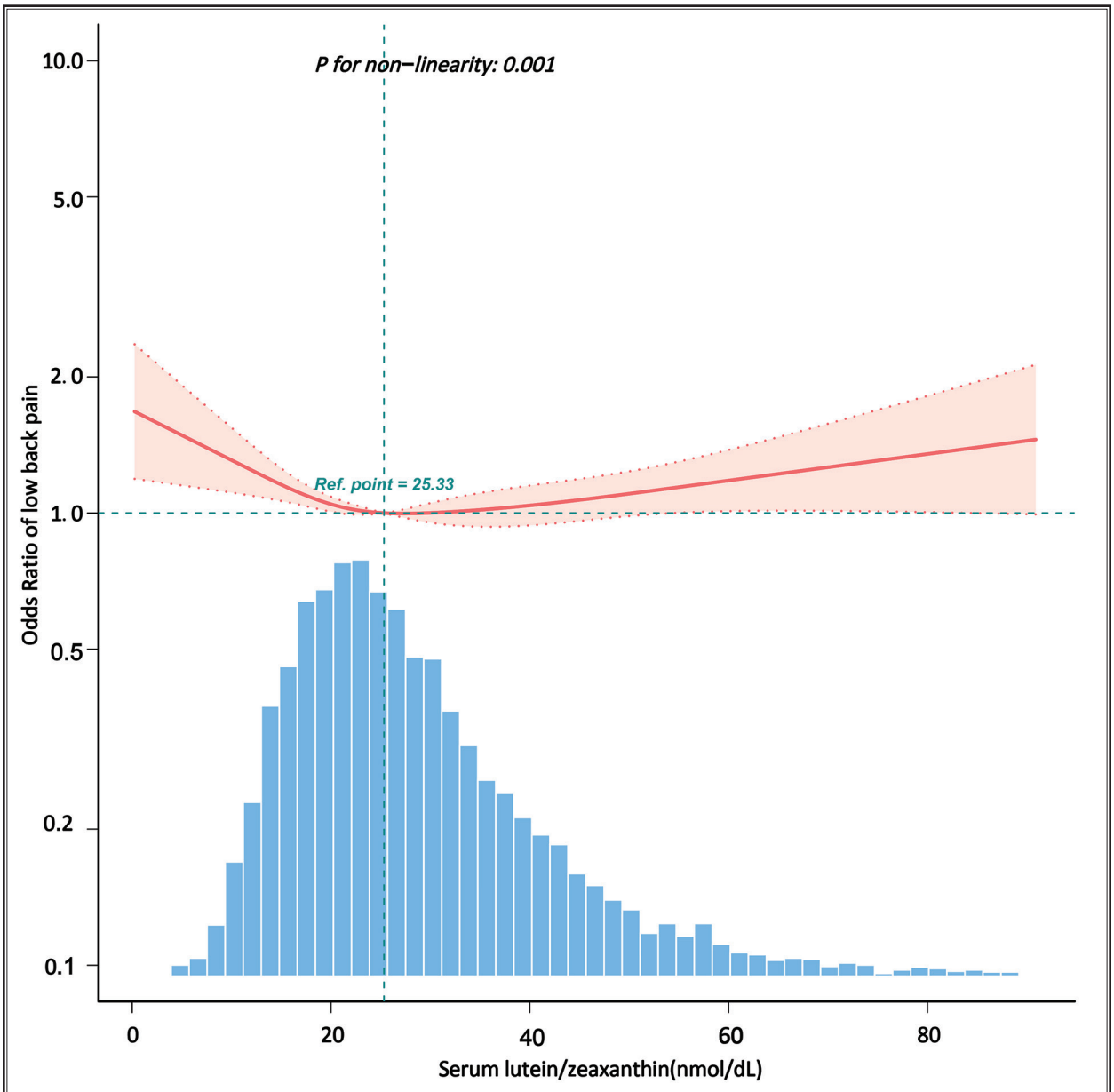

Supplemental Fig. 1. *Association between serum lutein and zeaxanthin levels and low back pain in restricted cubic spline regression after including the missing data. Solid lines represent the predicted value; dash lines, 95% CI. A serum lutein and zeaxanthin level of 25.3 nmol/dL was used as the reference to estimate all odds ratios. Adjustments made for age, gender, body mass index, race/ethnicity, education level, family income, marital status, activity level, alcohol use, smoking status, analgesic use, hypertension, diabetes, and osteoporosis . Only 99.5% of the data is displayed.*

Supplementary Table S1. *Association of covariates and low back pain risk*.

Variable	OR_95 CI	*P*_value
Age(years)	1 (1.00–1.00)	0.572
Gender, n(%)		
Men	1 (reference)	
Women	1.2 (1.09–1.32)	< 0.001
Body mass index (kg/m^2)		
< 18.5	1 (reference)	
18.5-24.9	0.78 (0.52–1.17)	0.226
25-25.9	0.87 (0.58–1.3)	0.491
> 25.9	1.08 (0.72–1.63)	0.694
Race/ethnicity, n (%)		
Non-Hispanic White	1 (reference)	
Non-Hispanic Black	0.83 (0.73–0.94)	0.004
Mexican American	0.7 (0.61–0.79)	< 0.001
Others Race	0.92 (0.76–1.12)	0.414
Education level, n (%)		
Less Than High School	1 (reference)	
High School Diploma	1.02 (0.89–1.16)	0.813
Postsecondary	0.79 (0.71–0.89)	< 0.001
Marital status, n (%)		
Married or living with a partner	1 (reference)	
Living alone	0.98 (0.89–1.09)	0.735
Analgesic user, n (%)		
No	1 (reference)	
Yes	1.65 (1.47–1.85)	< 0.001
Family income, n (%)		
< 1.3	1 (reference)	
1.3-3.5	0.84 (0.75–0.95)	0.004
> 3.5	0.69 (0.61–0.78)	< 0.001
Activity level		
Sedentary	1 (reference)	
Moderate	0.81 (0.72–0.91)	< 0.001
Vigorous	0.67 (0.6–0.76)	< 0.001
Alcohol intake		
No	1 (reference)	
Yes	0.95 (0.85–1.05)	0.294
Smoking, n (%)		
Not at all	1 (reference)	
Every day	1.54 (1.35–1.74)	< 0.001
Some days	1.21 (1.08–1.35)	0.001
Osteoporosis, n (%)		
No	1 (reference)	
Yes	1.97 (1.63–2.38)	< 0.001
Hypertension		
No	1 (reference)	
Yes	1.23 (1.12–1.36)	< 0.001
Diabetes		
No	1 (reference)	
Yes	0.79 (0.67–0.93)	0.004
Lutein and zeaxanthin	0.99 (0.99–1.00)	< 0.001

Supplementary Table S2. *Association between serum lutein and zeaxanthin (nmol/dL)and low back pain after including the missing data.*

Variable	OR (95% CI)								
	n event_%	Crude	*P* value	Model One	*P* value	Model 2	*P* value	Model 3	*P* value
Q1 (n =2,872) (≤ 20.69)	1,240 (43.2)	1.4 (1.26–1.56)	<0.001	1.31 (1.17–1.46)	<0.001	1.25 (1.12–1.39)	<0.001	1.24 (1.11–1.39)	< 0.001
Q2 (n = 2,893) (20.7-31.08)	1,018 (35.2)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q3 (n =2,894) (≥ 31.1)	1,043 (36)	1.04 (0.93–1.16)	0.499	1.09 (0.97–1.21)	0.137	1.14 (1.02–1.27)	0.021	1.14 (1.02–1.27)	0.025

Q, quartiles; OR, odds ratio; Ref, reference.
Model 1 was adjusted for sociodemographic variables (age, gender, body mass index, race/ethnicity, education level, family income, and marital status).
Model 2 was adjusted for Model 1, activity level, alcohol intake, smoking status, and analgesic use.
Model 3 was adjusted for Model 2, hypertension, diabetes, and osteoporosis.

Supplementary Table S3. *Association between serum lutein/zeaxanthin (nmol/dL)and low back pain after further adjusted for dietary lutein/zeaxanthin.*

Variable	OR (95%CI)					
	n total	n event_%	crude OR (95%CI)	crude *P* value	adj OR (95%CI)	adj *P* value
Q1 (n =2340) (≤ 20.69)	2340	1027 (43.9)	1.44 (1.28~1.62)	< 0.001	1.27 (1.12~1.43)	< 0.001
Q2 (n = 2338)(20.7-31.08)	2338	822 (35.2)	1 (Ref)		1 (Ref)	
Q3 (n =2348) (≥ 31.1)	2348	836 (35.6)	1.02 (0.9~1.15)	0.749	1.14 (1.01~1.3)	0.034

Q, quartiles; OR, odds ratio; CI, confidence interval; Ref: reference.adjusted for sociodemographic variables (age, gender, marital status, body mass index, race/ethnicity, education level, family income).activity level, alcohol, smoking status, analgesic user, hypertension, diabetes, osteoporosis, and dietary lutein/zeaxanthin.

Supplementary Table S4. *Association between serum lutein and zeaxanthin (nmol/dL) and low back pain after further adjustment for other biomarkers.*

Variable	OR (95% CI)					
	n total	n event_%	crude OR (95% CI)	crude. *P* value	adj OR (95% CI)	adj *P* value
Q1(n =2340) (≤ 20.69)	2340	1027 (43.9)	1.44 (1.28–1.62)	<0.001	1.27 (1.12–1.43)	<0.001
Q2(n = 2338) (20.7-31.08)	2338	822 (35.2)	1(Ref)		1(Ref)	
Q3(n =2348) (≥ 31.1)	2348	836 (35.6)	1.02 (0.9–1.15)	0.749	1.14 (1.01–1.3)	0.034

Q, quartiles; OR, odds ratio; Ref, reference. Adjusted for sociodemographic variables (age, gender, marital status, body mass index, race/ethnicity, education level, family income), activity level, alcohol use, smoking status, analgesic use, hypertension, diabetes, osteoporosis, dietary lutein and zeaxanthin, dietary energy intake, dietary protein intake, dietary carbohydrate intake, and dietary fiber intake.