



Association between Dietary Lutein/Zeaxanthin Intake and Metabolic Syndrome among US Females: An Analysis of National Health and Examination Surveys 2015–2018

Yanqi Zhang, Linda L Knol, and Libo Tan 

Department of Human Nutrition, University of Alabama, Tuscaloosa, AL, USA

ABSTRACT

The prevalence of metabolic syndrome (MetS) is greater among US females than males, mainly due to higher risks of dyslipidemia and hyperglycemia. Lutein and zeaxanthin (L/Z) are carotenoids that can alter the composition of lipoproteins, which may affect components of MetS. However, little is known about the association between L/Z intake and MetS, especially in females. The purpose of this study was to explore the relation between dietary L/Z or dietary plus supplemental L/Z intakes and MetS in women ($n = 630$), aged 20–50 y, participating in the NHANES 2015–2018. Compared with the lowest quartile, women in the highest quartile of dietary L/Z intake had significantly lower risk of MetS after adjusting for confounders (OR = 0.46; 95% CI: 0.21, 0.98). No significant relation was noted between dietary plus supplemental L/Z intake and MetS. Future cohort studies should investigate the effects of L/Z on MetS development in women. *Curr Dev Nutr* 2021;5:nzab123.

Keywords: carotenoids, lutein, zeaxanthin, metabolic syndrome, females, NHANES

© The Author(s) 2021. Published by Oxford University Press on behalf of the American Society for Nutrition. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Manuscript received July 31, 2021. Initial review completed September 11, 2021. Revision accepted September 21, 2021. Published online October 6, 2021.

The authors reported no funding received for this study.

Author disclosures: The authors report no conflicts of interest.

Address correspondence to LT (e-mail: ltan@ches.ua.edu).

Abbreviations: L/Z, lutein/zeaxanthin; MetS, metabolic syndrome.

Introduction

Metabolic syndrome (MetS) is characterized by a cluster of cardiovascular disease risk factors that occur simultaneously, including central adiposity, elevated levels of blood pressure, fasting glucose and triglyceride, and lower HDL cholesterol concentrations (1). MetS is positively associated with risk of chronic diseases, including stroke, type II diabetes, and certain types of cancers (2–4). In 2016, 36.9% of the adult population (aged ≥ 20 y) in the USA had MetS (5). The prevalence of MetS in American females was greater than in males, mainly due to higher rates of dyslipidemia, elevated fasting glucose, and waist circumference (6–8). Between 2011 and 2016, the increase in the prevalence of MetS was more pronounced in women than in men in the USA (a significant 4.9%, $P < 0.05$ compared with a nonsignificant 3.9%, $P = 0.19$) (5). Although MetS is less prevalent in younger people, a significantly higher increase in its prevalence was found in adults aged 20–39 y, compared with adults aged 60 and older (5.1% compared with 3.8%, $P < 0.05$) (5). A cross-sectional study showed a significant increase in the prevalence of central obesity in women aged under 50 y, whereas this MetS risk factor decreased significantly in women over 50 (9). As such, US females aged 20–50 y were chosen as the target population in the present study.

Phytochemicals with antioxidant functionality are highly researched in nutrition for the prevention and treatment of various diseases, in-

cluding cardiovascular diseases, obesity, and diabetes (10). Lutein (L) and its isomer zeaxanthin (Z) are carotenoids that are commonly found in dark leafy vegetables, such as kale and spinach. The typical American dietary intake concentration of L/Z is ~ 1 –2 mg/d, with the amount of L/Z in cooked spinach and kale being 12.8 mg and 8.88 mg per 100 g serving, respectively (11). L/Z are potent scavengers of free radicals due to their polarity and extended conjugated double bonds, thus retarding the development of metabolic diseases by increasing the mRNA expression of antioxidant enzymes and decreasing proinflammatory cytokines (12). Furthermore, as polar carotenoids, lutein and zeaxanthin are primarily transported by HDL particles, and research shows that they are correlated with the size and concentration of “good cholesterol” (13–15). Previous observational and interventional studies suggested that L/Z intakes were positively correlated with serum HDL cholesterol, but negatively correlated with serum LDL cholesterol and serum triglyceride (16, 17). Two cross-sectional studies indicated an inverse relation between serum L/Z concentration and risk of elevated waist circumference, hypertriglyceridemia, and hypertension in adults (18, 19). A few studies reported that serum L/Z concentrations were significantly and inversely related to MetS (18, 20, 21). However, little is known about whether dietary L/Z intake is associated with the prevalence of MetS, especially in young and middle-aged females.

TABLE 1 Study characteristics by MetS in US females ($n = 630$)¹

Group	Overall n (weighted percentage)	No MetS Mean/percentage mean (SE)	MetS Mean/percentage mean (SE)	P value ²
N	630	475	155	
Age, y	—	33 (0.48)	36 (0.76)	<0.01**
Race/ethnicity, %				0.10
Mexican American	175 (18.4%)	68.8 (4.09)	31.2 (4.09)	
Non-Hispanic white	192 (56.8%)	79.3 (3.07)	20.7 (3.07)	
Non-Hispanic black	133 (12.4%)	83.8 (3.21)	16.2 (3.21)	
Other Hispanic/multiracial	130 (12.4%)	73.1 (4.40)	26.9 (4.40)	
Smoking status, %				<0.05*
Never	461 (69.3%)	81.2 (2.56)	18.9 (2.56)	
Former	77 (15.4%)	66.1 (4.85)	33.9 (4.85)	
Current	92 (15.3%)	70.8 (4.89)	29.2 (4.89)	
Total energy intake (kcal/d)	—	1804.13 (34.2)	1832.59 (44.3)	0.60
Dietary L/Z				0.17
Quartile 1 (low)	163 (24.3%)	73.9 (4.96)	26.2 (4.96)	
Quartile 2	146 (24.5%)	75.4 (4.49)	24.6 (4.49)	
Quartile 3	176 (26.4%)	73.3 (3.42)	26.7 (3.42)	
Quartile 4 (high)	145 (24.8%)	86.3 (3.48)	13.7 (3.48)	
Dietary + supplemental L/Z				0.34
Quartile 1 (low)	164 (24.5%)	77.7 (1.99)	22.8 (1.99)	
Quartile 2	145 (24.1%)	77.4 (4.12)	22.6 (4.12)	
Quartile 3	182 (27.5%)	74.3 (3.27)	25.7 (3.27)	
Quartile 4 (high)	139 (23.9%)	84.2 (3.42)	15.8 (3.42)	

¹Values are mean (SE) or percentage (SE), $n = 630$. This analysis was done among participants with complete data for MetS screening using the National Cholesterol Education Program Adult Treatment Panel III criteria. L/Z, lutein/zeaxanthin; MetS, metabolic syndrome.

²P value was based on a t-test when the dependent variable is continuous and χ^2 test when the dependent variable is categorical. * $P < 0.05$, ** $P < 0.01$.

Therefore, in this study, we aimed to explore the association between dietary as well as dietary plus supplemental L/Z intake and MetS in US females, aged 20–50 y using a national survey dataset. It was hypothesized that a higher L/Z intake is inversely associated with the prevalence of MetS among young and middle-aged US females.

Methods

Database and sample

A sample of women was selected from the NHANES 2015–2018. NHANES is a cross-sectional study that provides representative data for the noninstitutionalized US population. Detailed information regarding study design and data collection is available (https://www.cdc.gov/nchs/data/series/sr_02/sr02-184-508.pdf). Participants complete surveys, a physical exam, laboratory data collection, 2 d of 24-h dietary recalls, and 2 d of dietary supplement use recalls (21).

This study's sample ($n = 630$) included premenopausal women, aged between 20 and 50 y. As changes in estrogen may affect MetS risk factors, women who were pregnant, breastfeeding, menopausal, and posthysterectomy were excluded from the overall sample ($n = 9779$) (22). In addition, women with a diagnosis of type II diabetes were not included. Participants who had any of the MetS criteria data missing were also excluded.

Dependent variable of interest

According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and Joint Interim Statement (22), MetS was defined as the presence of 3 or more of the following 5 criteria for fe-

males: elevated waist circumference (≥ 88 cm), elevated serum triglyceride concentrations (≥ 150 mg/dL), low HDL cholesterol serum concentrations (< 50 mg/dL), elevated blood pressure (systolic ≥ 130 and/or diastolic ≥ 85 mm Hg), or elevated fasting glucose serum concentrations (≥ 100 mg/dL). Blood pressure measure was calculated based on the mean of 3 systolic and diastolic measures.

Independent variable of interest

Using the USDA's Food and Nutrient Database for Dietary Studies (FNDDS) 2015–2018, the intakes of dietary or supplemental L/Z were calculated based on the mean of total L/Z intake from two nonconsecutive 24-h food recalls and two 24-h dietary supplement use recalls, respectively. Because L/Z intakes were not normally distributed, both dietary L/Z and dietary plus supplemental L/Z intakes were divided into 4 quartiles according to the weighted distribution of intake.

Covariates

Age, race (Mexican American, non-Hispanic white, non-Hispanic black, and other races), and smoking status (never, former, and current smokers) were chosen as covariates based on evidence that they are risk factors or health disparities of MetS (23). People with or without MetS in this study had a similar total energy intake ($P = 0.60$, Table 1), thus this variable was not adjusted in the analysis.

Statistics analysis

SAS 9.4 (SAS Institute) and SUDAAN release 11.0.3 (Research Triangle Institute) were used for the data analysis. Final analyses were completed using SUDAAN to compute inferential statistics and account for the multistage probability design of NHANES, oversampling

TABLE 2 The association (OR, 95% CI)¹ between the quartiles of dietary lutein/zeaxanthin (L/Z) intake, or quartiles of dietary and supplemental L/Z intake, and MetS in US females (n = 630)

Group	Dietary L/Z intake		Dietary + supplemental L/Z intake	
	Crude OR (95% CI) ²	Adjusted OR (95% CI) ³	Crude OR (95% CI)	Adjusted OR (95% CI)
Age, y	1.04 (1.01, 1.07)	—	1.04 (1.01, 1.08)	—
Race				
Mexican American	1.97 (1.13, 3.45)	—	2.00 (1.14, 3.50)	—
Non-Hispanic white	Referent	—	Referent	—
Non-Hispanic black	0.80 (0.42, 1.52)	—	0.79 (0.42, 1.52)	—
Other Hispanic/multiracial	1.66 (0.80, 3.47)	—	1.64 (0.77, 3.50)	—
Smoking status, %				
Never	Referent	—	Referent	—
Former	2.29 (1.17, 4.48)	—	2.36 (1.23, 4.52)	—
Current	1.91 (0.97, 3.78)	—	1.93 (0.99, 3.78)	—
Dietary L/Z, range (mg/d)				
Quartile 1, 0.006–0.48	Referent	Referent	—	—
Quartile 2, 0.49–0.81	0.83 (0.44, 1.55)	0.87 (0.54, 1.39)	—	—
Quartile 3, 0.82–1.72	0.90 (0.52, 1.56)	0.93 (0.62, 1.39)	—	—
Quartile 4, 1.73–51.7	0.38 (0.15, 0.97)	0.46 (0.21, 0.98)	—	—
Dietary + supplemental L/Z, range (mg/d)				
Quartile 1, 0.006–0.49	—	—	Referent	Referent
Quartile 2, 0.50–0.81	—	—	0.71 (0.36, 1.42)	0.77 (0.46, 1.30)
Quartile 3, 0.82–1.74	—	—	0.82 (0.44, 1.52)	0.86 (0.54, 1.36)
Quartile 4, 1.75–51.7	—	—	0.42 (0.17, 1.01)	0.49 (0.24, 1.00)

¹Calculated by logistic regression analysis.

²Crude (nonadjusted) regression analysis.

³Adjusted regression analysis. Model: age, race, and smoking status were adjusted.

of low-income households, and sampling weights. Both dietary L/Z intake and dietary plus supplemental L/Z were coded as categorical variables (quartiles) by determining their weighted distribution. The differences in means of continuous and categorical variables across the MetS and non-MetS groups were tested by a t-test and χ^2 test, respectively. Binary logistic regressions were conducted to test the association between dietary L/Z intake, dietary plus supplemental L/Z intake, and MetS outcomes, before and after adjusting for the covariates of age, race, and smoking status. An a priori $\alpha < 0.05$ was defined as statistically significant.

Results

Among the 630 participants aged 20–50 y, ~24.6% had MetS (Table 1). Participants with MetS were significantly older than those without MetS (36 versus 33 y, $P < 0.01$). Among participants who did not smoke, 18.9% had MetS. However, among previous or current smokers, the rates increased to 33.9% and 29.2%, respectively ($P < 0.05$). In univariate analyses, race, total energy intake, quartile of dietary L/Z intake, and quartile of dietary plus supplemental L/Z intake were not significantly different among people with or without MetS. As age increased, the risk of MetS also increased (OR = 1.04; 95% CI: 1.01, 1.07). Additionally, Mexican Americans were more likely to have MetS than non-Hispanic whites (OR = 1.97; 95% CI: 1.13, 3.45). The odds of having MetS were 2.29 times higher for former smokers than those who had never smoked (OR = 2.29; 95% CI: 1.17, 4.48).

Mean dietary L/Z intakes by quartiles 1, 2, 3, and 4, respectively, were 0.30 ± 0.01 mg, 0.64 ± 0.01 mg, 1.16 ± 0.02 mg, and 4.56 ± 0.49 mg (data not shown in the table). After adjusting for age, race, and smoking

status, quartile 4, representing the highest intake of dietary L/Z (ranging from 1.73 to 51.70 mg/d), was associated with significantly lower odds of MetS compared to the lowest intake (OR = 0.46; 95% CI: 0.21, 0.98) (Table 2).

Mean dietary intake plus supplemental L/Z intakes were 0.33 ± 0.01 mg, 0.64 ± 0.01 mg, 1.20 ± 0.02 mg, and 4.73 ± 0.52 mg, in quartiles 1, 2, 3, and 4, respectively (data not shown in the table). No statistically significant relations were found between the quartiles of dietary plus supplemental L/Z intake and the odds of developing MetS (Table 2).

Discussion

Among US females aged 20–50 y, participants with the highest intake (quartile) of dietary L/Z had significantly reduced odds of MetS than those with the lowest intake (quartile). The results suggested that only intakes of >1.73 mg/d were related to a reduced risk. Although an inverse association between total carotenoids intake and the prevalence of MetS was reported in previous research, few studies have focused on L/Z intake and MetS (24, 25). A previous cross-sectional study by Sluijs et al. showed no relation between dietary L/Z intake and MetS in Dutch males aged 40–80 y (24). The inconsistency between their finding and ours may be due to different populations and small variation of L/Z intake in their study (i.e., Dutch males in quartile 4 consumed only twice as much L/Z as those in quartile 1) (24). In our study, the mean intake of dietary L/Z for women in quartile 4 (4.56 ± 0.49 mg/d) was 15 times higher than that for women in quartile 1. This average daily L/Z intake in quartile 4 is also much higher than the national average of 1–2 mg (26). After exploring the individual food files, we found

that some women in quartile 4 had high intakes of kale, spinach, and romaine lettuce. Women in the highest quartile may consume a diet that contains higher intakes of L/Z, such as leafy greens, which are also high in other carotenoids such as β -cryptoxanthin and α - and β -carotene, that may also be beneficial for people with MetS (27, 28). This study did not suggest significant relations between MetS and dietary L/Z intakes in quartiles 2 and 3. Given the low absorption rate of lutein, it is plausible that the intakes of L/Z in these 2 quartiles were not high enough for optimal bioavailability and functionality (29).

In this group of US women, there was no significant association between MetS and dietary intake plus supplemental L/Z in combination. One possible explanation is that the intake of supplemental L/Z in this young population is low. Supplements containing L/Z are usually found in multivitamin and mineral preparations formulated for the older adult. The assumption is confirmed by the data, as the average consumption of dietary and supplemental L/Z did not change much compared with dietary L/Z alone, and participants in quartile 4 of dietary plus supplemental L/Z intake only showed a mean increase of 0.17 mg in supplemental L/Z compared with quartile 1.

This study has multiple strengths. First, NHANES 2015–2018 is a recent national dataset representing the prevalence of MetS and L/Z intake in the US population. Secondly, the study was the first that examined the association between L/Z intake and risk of MetS in females, who tend to have lower serum HDL cholesterol, higher serum triglycerides and blood fasting glucose, and increased waist circumference compared with males (6, 7). As L/Z has been shown to affect lipid metabolism and body fat accumulation, examining the relation between L/Z and MetS in females is much needed (16, 17). Thirdly, the study focused on the young and middle-aged population. Exploring preventative strategies for MetS at an early age would be important for reducing the occurrence of the disease later in life. The study has a few limitations that should also be noted. First, the use of 2-d, self-reported 24-h recalls and 24-h dietary supplement use recalls may not truly reflect usual dietary intakes. Secondly, due to the nature of a cross-sectional study, the causality of L/Z intake and MetS cannot be determined. However, the promising findings will inform future interventional studies. Thirdly, although the main covariates (age, race, and smoking status) were adjusted in the analysis, other unknown confounding factors may exist. Further studies are needed to investigate the relation between other modifiable habits and MetS, such as physical activity, alcohol intake, and other dietary components in both women and men.

In conclusion, compared with young and middle-aged females with the lowest intake of dietary L/Z, those in the highest quartile of intake had a significantly reduced prevalence of MetS. The relation between L/Z intake and other diseases, especially MetS-related diseases, warrants further research.

Acknowledgments

The authors' contributions were as follows—YZ and LT: designed the research; YZ and LLK: analyzed data; YZ: wrote the manuscript; LLK and LT: reviewed and edited the manuscript; LT: had primary responsibility for final content; and all authors: read and approved the final manuscript.

Data Availability

The data underlying this article are available in the National Health and Nutrition Examination Survey database, at <https://www.cdc.gov/nchs/nhanes/index.htm>.

References

- Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart J, James WP, Loria CM, Smith SC, Jr. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120(16):1640–5.
- Björge T, Lukanova A, Jonsson H, Tretli S, Ulmer H, Manjer J, Stocks T, Selmer R, Nagel G, Almquist M. Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. *Cancer Epidemiol Biomarkers Prev* 2010;19(7):1737–45.
- Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care* 2005;28(7):1769–78.
- Engin A. The definition and prevalence of obesity and metabolic syndrome. *Adv Exp Med Biol* 2017;960:1–17.
- Hirode G, Wong RJ. Trends in the prevalence of metabolic syndrome in the United States, 2011–2016. *JAMA* 2020;323(24):2526–8.
- Cohen E, Margalit I, Goldberg E, Krause I. Gender as an independent risk factor for the components of metabolic syndrome among individuals within the normal range of body mass index. *Metab Syndr Relat Disord* 2018;16(10):537–42.
- Pradhan AD. Sex differences in the metabolic syndrome: implications for cardiovascular health in women. *Clin Chem* 2014;60(1):44–52.
- Campbell B, Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Females, Hispanics and older individuals are at greatest risk of developing metabolic syndrome in the U.S. *Diabetes Metab Syndr* 2016;10(4):230–3.
- Lee SE, Han K, Kang YM, Kim S-O, Cho YK, Ko KS, Park JY, Lee KU, Koh EH. Trends in the prevalence of metabolic syndrome and its components in South Korea: findings from the Korean National Health Insurance Service Database (2009–2013). *PLoS One* 2018;13(3):e0194490.
- Zhang YJ, Gan RY, Li S, Zhou Y, Li AN, Xu DP, Li HB. Antioxidant phytochemicals for the prevention and treatment of chronic diseases. *Molecules* 2015;20(12):21138–56.
- Eisenhauer B, Natoli S, Liew G, Flood VM. Lutein and zeaxanthin-food sources, bioavailability and dietary variety in age-related macular degeneration protection. *Nutrients* 2017;9(2):120.
- Pap R, Pandur E, Jánosa G, Sipos K, Agócs A, Deli J. Lutein exerts antioxidant and anti-inflammatory effects and influences iron utilization of BV-2 microglia. *Antioxidants* 2021;10(3):363.
- DiMarco DM, Norris GH, Millar CL, Blesso CN, Fernandez ML. Intake of up to 3 eggs per day is associated with changes in HDL function and increased plasma antioxidants in healthy, young adults. *J Nutr* 2017;147(3):323–9.
- Waters D, Clark RM, Greene CM, Contois JH, Fernandez ML. Change in plasma lutein after egg consumption is positively associated with plasma cholesterol and lipoprotein size but negatively correlated with body size in postmenopausal women. *J Nutr* 2007;137(4):959–63.
- Wang Y, Chung SJ, McCullough ML, Song WO, Fernandez ML, Koo SI, Chun OK. Dietary carotenoids are associated with cardiovascular disease risk biomarkers mediated by serum carotenoid concentrations. *J Nutr* 2014;144(7):1067–74.
- Blesso CN, Andersen CJ, Bolling BW, Fernandez ML. Egg intake improves carotenoid status by increasing plasma HDL cholesterol in adults with metabolic syndrome. *Food Funct* 2013;4(2):213–21.

17. Xu XR, Zou ZY, Xiao X, Huang YM, Wang X, Lin XM. Effects of lutein supplement on serum inflammatory cytokines, ApoE and lipid profiles in early atherosclerosis population. *J Atheroscler Thromb* 2013;20(2):170–7.
18. Beydoun MA, Shroff MR, Chen X, Beydoun HA, Wang Y, Zonderman AB. Serum antioxidant status is associated with metabolic syndrome among U.S. adults in recent national surveys. *J Nutr* 2011;141(5):903–13.
19. Sugiura M, Nakamura M, Ogawa K, Ikoma Y, Matsumoto H, Ando F, Shimokata H, Yano M. Associations of serum carotenoid concentrations with the metabolic syndrome: interaction with smoking. *Br J Nutr* 2008;100(6):1297–306.
20. Liu J, Shi WQ, Cao Y, He LP, Guan K, Ling WH, Chen YM. Higher serum carotenoid concentrations associated with a lower prevalence of the metabolic syndrome in middle-aged and elderly Chinese adults. *Br J Nutr* 2014;112(12):2041–8.
21. Beydoun MA, Canas JA, Beydoun HA, Chen X, Shroff MR, Zonderman AB. Serum antioxidant concentrations and metabolic syndrome are associated among U.S. adolescents in recent national surveys. *J Nutr* 2012;142(9):1693–704.
22. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112(17):2735–52.
23. Moore JX, Chaudhary N, Akinyemiju T. Metabolic syndrome prevalence by race/ethnicity and sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. *Prev Chronic Dis* 2017;14(E24):287.
24. Sluijs I, Beulens JW, Grobbee DE, van der Schouw YT. Dietary carotenoid intake is associated with lower prevalence of metabolic syndrome in middle-aged and elderly men. *J Nutr* 2009;139(5):987–92.
25. Ahn S, Jun S, Kang M, Shin S, Wie G-A, Baik HW, Joung H. Association between intake of antioxidant vitamins and metabolic syndrome risk among Korean adults. *J Nutr Health* 2017;50(4):313–24.
26. Monsen ER. Dietary reference intakes for the antioxidant nutrients: vitamin C, vitamin E, selenium, and carotenoids. *J Am Diet Assoc* 2000;100(6):637–40.
27. Sugiura M, Nakamura M, Ogawa K, Ikoma Y, Yano M. High serum carotenoids associated with lower risk for the metabolic syndrome and its components among Japanese subjects: Mikkabi cohort study. *Br J Nutr* 2015;114(10):1674–82.
28. Al-Delaimy W, Slimani N, Ferrari P, Key T, Spencer E, Johansson I, Johansson G, Mattisson I, Wirfalt E, Sieri S, et al. Plasma carotenoids as biomarkers of intake of fruits and vegetables: ecological-level correlations in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Eur J Clin Nutr* 2005;59(12):1397–408.
29. Zhang Y, Kong L, Tan L. Effectiveness of nanoscale delivery systems on improving the bioavailability of lutein in rodent models: a systematic review. *Crit Rev Food Sci Nutr* 2020;1–16. (Epub ahead of print; doi: 10.1080/10408398.2020.1853035).