Qi et al. Nutrition Journal (2025) 24:9
https://doi.org/10.1186/s12937-025-01079-8

Nutrition Journal

RESEARCH Open Access

Dietary carotenoid intakes and biological aging among US adults, NHANES 1999–2018

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Abstract

Background Carotenoids have been shown to have multiple health benefits, including antioxidant and anti-inflammatory. The data for the effect of dietary specific carotenoids on biological aging is limited. Our study aims to examine the association between dietary carotenoid intake levels and biological aging.

Methods This cross-sectional study was performed among 27,338 adults from NHANES 1999–2018. Dietary intake was assessed through two 24-hour dietary recall interviews. Biological aging indices included allostatic load (AL), homeostatic dysregulation (HD), Klemera-Doubal method (KDM), and phenoAge (PA). Multiple linear regression, weighted quantile sum (WQS) regression and quantile g-computation (QG-comp) were used to explore the associations of single carotenoid and mixed carotenoids with biological aging.

Results Associations between dietary carotenoid intake levels and biological aging indices were significant among adults across the United States. Multiple linear regression showed that most carotenoids were significantly negatively correlated with AL (β = -0.017 - -0.011), HD (β = -0.045 - -0.032), KDM (β = -0.984 - -0.471), and PA (β = -0.975 - -0.539). Subgroup analysis indicated that male, older individuals, smokers, alcohol drinkers, and less physically active individuals are particularly sensitive populations. Meanwhile, WQS regression and QG-comp analyses consistently indicated a negative association between mixed carotenoids exposure and four biological aging indices, highlighting that lutein/zeaxanthin and β-carotene were responsible for the outcomes.

Conclusions Increased dietary intakes of various carotenoids were associated with lower biological aging indices, which was possibly and mainly driven by lutein/zeaxanthin and β-carotene.

Keywords Dietary carotenoids, Biological age, National health and nutrition examination survey (NHANES), Mixed exposure

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Introduction

Aging is a complex and unavoidable process in which various deleterious changes gradually accumulate in cells and tissues, ultimately leading to weakness, lack of resilience, and increased risk for several major chronic diseases [1–3], including cancer [4], cardiovascular disease [5], metabolic disorders [2], diabetes [6], and neurodegenerative diseases [7]. In turn, the rate or process of aging can be equally influenced by disease, but also by other factors [8], such as diet [9, 10], health status, etc [11]. Because of the complexity of aging, biological age estimation facilitates the combining of multiple biomarkers into a single latent variable, which can better explain the aging process [12]. To date, a variety of biologic age based on clinical phenotypic metrics, molecular biology metrics, or composite metrics has emerged. Algorithms that incorporate information from standard clinical parameters have been shown to be among the most accurate in predicting biological aging and the risk of age-related diseases [13, 14], such as allostatic load (AL) [15], homeostatic dysregulation (HD) [16], Klemera-Doubal method (KDM) [17], and phenoAge (PA) [18].

Carotenoids are typically colorful C40 tetra-terpenoid pigments produced by a variety of plants, bacteria, and fungi, but are not synthesized in animals [19, 20]. Although more than 1,100 carotenoids are found in nature, only a very small number of carotenoids play a role in the human diet [21, 22]. The six major carotenoids that are most abundant in the diet are α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin, and account for 95% of the carotenoids found in American blood and brain [23, 24]. It has been suggested that these carotenoids contribute to optimizing healthy lifespan: Low intake of these carotenoids has been associated with all-cause mortality [25], cardiovascular disease [26], oxidative DNA damage [27, 28], inflammation, and immune decline [29]. Carotenoids are involved in increasing long-term health [24]. However, large population-based studies on the effect of intake levels of dietary carotenoids on biological aging are still limited. Our study provides new evidence for a more comprehensive and accurate assessment of the relationship between the nutritional status of various carotenoids and aging.

To clarify the specific effects of different carotenoid intake on biological aging, we investigated the association of total carotene, α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein with zeaxanthin (combined) with several biological aging indices including AL, HD, KDM, and PA in the 1999–2018 National Health and Nutrition Examination Survey (NHANES).

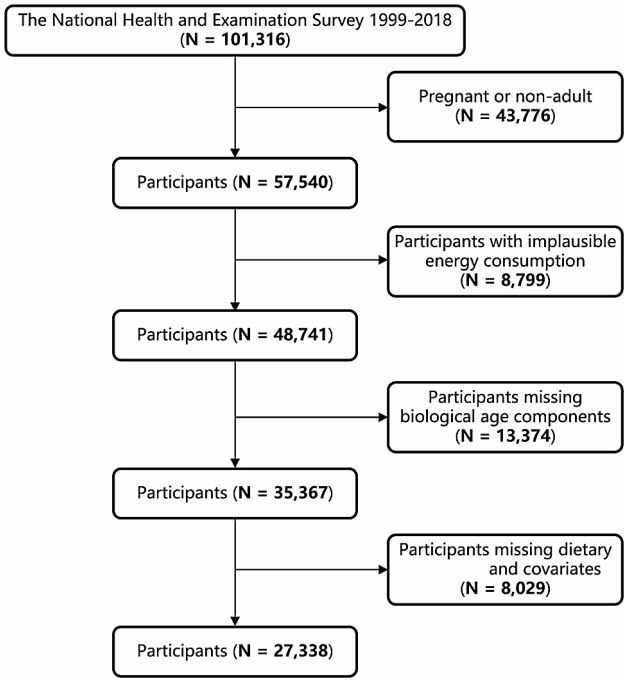

Fig. 1 Flowchart depicting the participants' selection

Materials & methods

Study population

As previously documented and disclosed, NHANES is an extensive, nationwide survey performed by the National Center for Health Statistics (NCHS), utilizing stratified, multistage methodologies to capture exact analysis of the health and nutritional state of Americans [30]. We utilized cross-sectional data from NHANES 1999–2018 that encompassed 27,338 individuals who satisfied the following criteria: non-pregnant adults ($n = 57,540$), standard daily energy intake (800–4200 kcal/d for male and 500–3500 kcal/d for female) ($n = 48,741$) [31], possess all the components of biological ages ($n = 35,367$), dietary and covariates are complete ($n = 27338$) (Fig. 1). Before the survey, ethical clearance was obtained from the Institutional Review Board of NCHS, and all participants provided the informed consent by signing the necessary documents.

Assessment of dietary carotenoids

Two 24-hour dietary recall questionnaires were administered by NHANES, the first by face-to-face collection at MEC, and the second by telephone collection 3 to 10 days later. Dietary carotenoid intakes used in this study including α-carotene (mcg/day), β-carotene (mcg/day), β-cryptoxanthin (mcg/day), lycopene (mcg/ day), and lutein + zeaxanthin (mcg/day) were calculated using the average of two 24-hour recalls or the reported value for participants who completed one 24-hour interview. Finally, the total carotene intake was determined by summing up the intake of α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein + zeaxanthin.

Construction of biological aging indices

Biological aging indices were employed to utilize different calculation methods and incorporate twelve different blood chemistry parameters to measure biological aging, including albumin, alkaline phosphatase, C-reactive protein, total cholesterol, creatinine, glycated hemoglobin, systolic blood pressure, uric acid, lymphocyte percent, white blood cell count, blood urea nitrogen and mean (red) cell volume (Additional file 1: Table S1) [12, 32–34]. AL consists of the combined effects of long-term stress and life events on an individual's physiological health and is determined by assessing the proportion of biomarker values that increase an individual's risk [15]. In our study, the level of risk was determined by considering individuals in the highest quartile of the distribution of 11 of the 12 biomarkers for a given biomarker [35–37]. For the biomarker albumin, albumin in the lowest quartile was considered to be at risk based on previous studies [38]. The resulting AL values range of 0 to 1 was defined as the proportion of biomarkers considered 'at risk' among the 12 biomarkers selected. HD, KDM, and PA were initially trained on blood chemistry-derived indices using NHANES 1988–1994 (NHANES III) data, employing the methodology originally outlined by Hastings et al. [33], Klemera et al. [17], and Levine et al. [34]. The R package 'BioAge' provides access to the corresponding algorithms and R code at https://github.com/dayoonkwon/BioAge. In brief, HD is calculated based on the Mahalanobis distance of a set of biomarkers relative to a reference sample, which can be interpreted as the deviation of human physiology from a healthy sample of NHANES III participants aged 20–30 years [16]. KDM was calculated from a series of biomarker regressions of chronological age and can be interpreted as the age at which the average physiology of NHANES III matches that of a person [32]. PA was developed through the analysis of multiple factors associated with mortality risks using elastic-net Gompertz regression to estimate the risk of death [12]. To measure changes in biological aging, the higher the AL or HD, the higher the risk of dysregulation of homeostasis and physiological health load in an individual, and individuals with higher AL or HD were considered to be experiencing accelerated aging. Participants with KDM or PA values higher than their actual age were considered to be aging faster. All of the above methods have been proven to predict disease, disability, and mortality [37, 39–41].

Assessment of covariates

Potential covariates of our study included age (years), sex (male/female), race (Mexican American/non-Hispanic White/non-Hispanic Black/other), NHANES cycle (year), body mass index (BMI, kg/m^2), smoking (yes/no), drinking (yes/no), physical activity status (yes/no), education level (below high school/high school/above high school), annual household income (< $20,000/$20,000-$55,000/> $55,000), daily energy intake (kcal/d), diet condition assessed by Alternative Healthy Eating Index (AHEI), retinol intake status (mcg/d), nutrient supplement use status (yes/no), self-reported cancer (yes/no), cardiovascular diseases (CVD) (yes/no), hypertension (yes/no), and diabetes (yes/no). AHEI was derived from the original Healthy Eating Index and took into account eleven different food components, which were identified through a thorough review of studies [42]. All other covariates were gathered from the NHANES questionnaires, as well as through laboratory tests and physical examinations. More details on the measurement of covariates can be found on the NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm).

Statistical analysis

All analyses were performed with R (version 4.3.1), and considered sample weights, stratification, and clustering for the complex survey design. All carotenoid intakes were log-transformed to achieve a normal distribution [43]. Participants' characteristics were shown as means (95% CI) for continuous variables and percentages (95% CI) for categorical variables, respectively. Multivariate linear regression models were utilized to analyze the associations of total carotene, α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein with zeaxanthin (combined) with biological aging indices, and we have predefined four models. Model 1 was adjusted for age, sex, race, and year. Model 2 adjusted for age, sex, race, year, BMI, smoking, drinking, exercise, education level, and income. Model 3 adjusted for the same variables as Model 2 and for energy intake, AHEI, retinol intake, and nutritional supplements. Model 4 adjusted for the same variables as Model 3 and for self-reported cancer, self-reported CVD, self-reported hypertension, and self-reported diabetes.

Subsequently, the best-fitting dose-response curves of the associations of carotenoids with biological aging indices were subsequently shaped by restricted cubic spline (RCS) regression with four knots based on the 5th, 35th, 65th and 95th percentiles of log-transformed dietary carotenoids intake with the median as the reference in the model 4.

Moreover, multiple stratified analyses were applied to evaluate the possible modifying effects of the following factors: age (≥ 60/60), sex (male/female), race (non-Hispanic white/others), BMI (< 30/30), smoking (yes/no), drinking (yes/no), exercise (yes/no), education (below high school/high school/above high school), income (< $20,000/$20,000-$55,000/> $55,000), AHEI (divided into three groups based on tertiles), retinol (divided into three

groups based on tertiles), nutrient supplement (yes/no), hypertension (yes/no).

Lastly, the weighted quantile sum (WQS) regression and quantile g-computation (QG-comp) models were used to assess the associations of the carotenoid mixture [α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein with zeaxanthin (combined)] with biological aging indices [44, 45]. The WQS model integrates the effects of multiple chemicals into a mixture index through quantile scoring and weighting methods, thereby facilitating the tests for the association between the mixture index and a certain outcome. WQS model applied 1000 bootstrap samples as the parameter to produce stable estimates [44]. The QG-computation analysis extends WQS regression by integrating it with g-computation, offering the explanatory simplicity and computational convenience of WQS regression while avoiding the homogeneity assumption regarding the directionality of exposure-outcome associations [46]. A P value < 0.05 was considered statistically significant, and all statistical tests were two-sided.

Results

Basic characteristics of participants according to the quartiles of log-transformed total carotene

The characteristics of the participants according to the quartiles of log-transformed total carotene are shown in Table 1. Participants with higher total carotene levels were more likely to be male, older, and drinkers, have higher physical activity levels, socioeconomic status, energy intake levels, AHEI score, and retinol intake levels, as well as have lower BMI, the prevalence of hypertension, CVD, and diabetes, AL, HD, KDM, and PA.

Relationship between total carotene, α-carotene, β-carotene, β-cryptoxanthin and lutein/zeaxanthin and biological aging indices

Figure 2 shows the relationship of total carotene and various carotenoids with biological age indicators of AL, HD, KDM, and PA, we processed the original data of carotenoids by log-transformation, and the results indicated that total carotene and various carotenoids were significantly correlated with biological aging indices, except for HD, which showed no significant correlation with α-carotene and β-cryptoxanthin.

For total carotene, participants in quartile 4 were more likely to have lower AL (β: -0.016, *P*<0.001),

Table 1 Baseline characteristics according to log-transformed total carotene quartiles: NHANES, 1999-2018[a]

Variables	Total carotene (*N* = 27338)				*P*
	≤ 3.46 *N* = 6835	3.46–3.80 *N* = 6835	3.80–4.08 *N* = 6835	>4.08 *N* = 6834	
Age, years	42.73(42.07,43.39)	45.58(44.93,46.24)	49.76(49.08,50.43)	49.50(48.73,50.27)	0.045
Male, %	44.20(42.60,45.70)	46.20(44.50,47.90)	49.20(47.70,50.70)	53.40(51.70,55.00)	< 0.001
Non-Hispanic white, %	65.70(62.00,69.20)	69.10(66.20,71.80)	70.40(67.50,73.10)	72.20(69.50,74.70)	0.334
BMI, kg/m^2	28.98(28.73,29.23)	28.94(28.71,29.18)	28.89(28.61,29.16)	28.43(28.14,28.72)	< 0.001
Smoke, %	49.10(47.30,50.90)	45.30(43.20,47.30)	43.40(41.80,45.10)	42.30(40.70,43.90)	0.235
Drink, %	70.30(68.60,72.00)	73.70(71.80,75.50)	74.20(72.40,75.90)	76.70(75.00,78.30)	< 0.001
Regular exercise, %	35.10(33.70,36.60)	39.10(37.40,40.90)	41.20(39.40,43.10)	41.90(39.90,44.00)	< 0.001
College graduate or above, %	47.00(44.80,49.20)	56.90(54.50,59.30)	62.10(60.10,64.10)	65.80(63.80,67.70)	< 0.001
> 55,000 annual household income, %	34.50(32.30,36.80)	43.10(40.70,45.60)	47.60(45.70,49.60)	48.30(46.10,50.40)	< 0.001
Daily energy intake, kcal/d	1818.05(1794.15,1841.95)	1991.63(1969.03,2014.23)	2123.14(2098.85,2147.43)	2289.52(2264.18,2314.86)	< 0.001
Dietary supplements use, %	45.70(43.50,47.80)	53.40(51.40,55.30)	56.20(54.20,58.10)	58.30(56.50,60.10)	< 0.001
AHEI score	29.11(28.75,29.47)	30.81(30.43,31.18)	32.89(32.53,33.25)	33.71(33.24,34.19)	< 0.001
Retinol, mcg	389.67(378.37,400.97)	433.24(417.11,449.36)	430.37(416.68,444.06)	440.27(428.38,452.17)	< 0.001
Self-reported cancer, %	9.10(8.10,10.20)	10.00(9.00,11.20)	9.50(8.60,10.60)	9.50(8.70,10.40)	< 0.001
Self-reported hypertension, %	32.30(30.60,34.00)	30.90(29.50,32.40)	29.30(27.70,30.90)	30.50(28.80,32.30)	0.007
Self-reported cardiovascular diseases, %	9.90(8.90,11.00)	8.30(7.50,9.20)	7.40(6.60,8.40)	7.70(7.00,8.50)	< 0.001
Self-reported diabetes, %	9.50(8.70,10.40)	9.30(8.50,10.20)	9.10(8.10,10.20)	8.40(7.40,9.40)	0.589
Allostatic Load	0.28(0.27,0.28)	0.27(0.26,0.27)	0.26(0.25,0.26)	0.26(0.25,0.26)	< 0.001
Homeostatic Dysregulation	1.63(1.61,1.66)	1.58(1.56,1.60)	1.56(1.54,1.58)	1.54(1.51,1.56)	< 0.001
Klemera-Doubal Method	40.06(39.45,40.67)	39.77(39.23,40.31)	39.31(38.69,39.92)	39.19(38.55,39.83)	< 0.001
phenoAge	45.98(45.28,46.68)	45.96(45.31,46.61)	45.63(44.92,46.34)	45.75(44.98,46.53)	< 0.001

[a]Continuous variables were listed as weighted mean (95% CI). Categorical variables were listed as weighted percentage (95% CI). After adjusting for age, general linear models and chi-square tests were conducted to compare continuous and categorical baseline characteristics, respectively

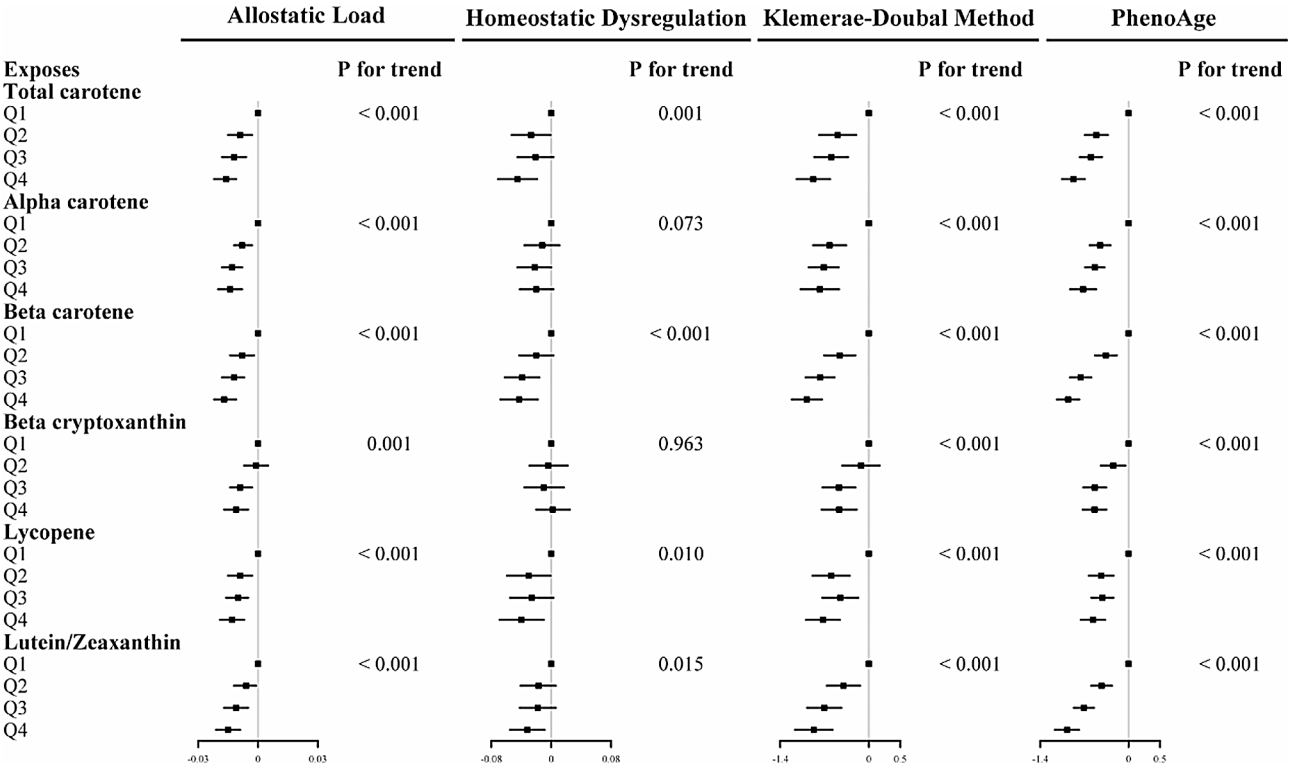

Fig. 2 Forest plot of the association of log-transformed total carotene, α-carotene, β-carotene, β-cryptoxanthin, and lutein/ zeaxanthin with biological aging indices. The adjustments involved the covariables selected in the model 4 of multiple linear regression model

HD (β: -0.045, $P=0.003$), KDM (β: -0.882, $P<0.001$) and PA (β: -0.875, $P<0.001$). Participants in the highest quartile of α-carotene had significantly lower AL (β: -0.014, $P<0.001$), KDM (β: -0.778, $P<0.001$) and PA (β: -0.720, $P<0.001$) compared with those in quartile 1. For β-carotene, as well as had significantly lower AL (β: -0.017, $P<0.001$), HD (β: -0.043, $P=0.003$), KDM (β: -0.984, $P<0.001$) and PA (β: -0.959, $P<0.001$) compared with those in quartile 1. For β-cryptoxanthin, participants had significantly lower AL (β: -0.011, $P=0.001$), KDM (β: -0.471, $P=0.002$) and PA (β: -0.539, $P<0.001$) compared with those in quartile 1. For lycopene, participants had significantly lower AL (β: -0.013, $P<0.001$), HD (β: -0.040, $P=0.025$), KDM (β: -0.728, $P<0.001$) and PA (β: -0.563, $P<0.001$) compared with those in quartile 1. Similarly, for lutein/zeaxanthin, participants in the highest quartile had AL (β: -0.015, $P<0.001$), HD (β: -0.032, $P=0.024$), KDM (β: -0.873, $P<0.001$) and PA (β: -0.975, $P<0.001$) were significantly lower than quartile 1. (Supplementary Material 1: Tables S2-S7)

RCS analysis investigating the relationship between total carotene, α-carotene, β-carotene, β-cryptoxanthin, and lutein/zeaxanthin and biological aging indices

For total carotene, α-carotene, β-carotene, β-cryptoxanthin, and lutein/zeaxanthin, the linearities and dose-response as sociations with biological aging indices were flexibly modeled by conducting RCS regression models (Fig. 3). After multivariate adjustment, total carotene exhibited linear relationships with lower AL ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.107$) and KDM ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.090$), except for PA ($P_{overall} <0.001$, $P_{nonlinearity} =0.025$). Monotonic and linear relationships were observed between α-carotene and AL ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.150$), HD ($P_{overall} = 0.006$, $P_{nonlinearity} = 0.158$), and PA ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.077$), with the exception of KDM ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.002$). β-carotene showed linear relationships with AL ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.378$), HD ($P_{overall} = 0.002$, $P_{nonlinearity} = 0.415$), and KDM ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.053$), except for PA ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.009$). Monotonic and linear relationships were found between lycopene and lower AL ($P_{overall} < 0.001$, $P_{nonlinearity} =0.402$), KDM ($P_{overall} <0.001$, $P_{nonlinearity} =0.077$), and PA ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.077$). With the exception of KAM ($P_{overall} < 0.001$, and $P_{nonlinearity} = 0.031$) and PA ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.021$), lutein/zeaxanthin demonstrated monotonic and linear relationships with AL ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.378$) following multivariate adjustment. On the other hand, β-cryptoxanthin exhibited non-linear relationships with AL ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.107$), KDM ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.049$), and PA ($P_{overall} < 0.001$, $P_{nonlinearity} = 0.026$).

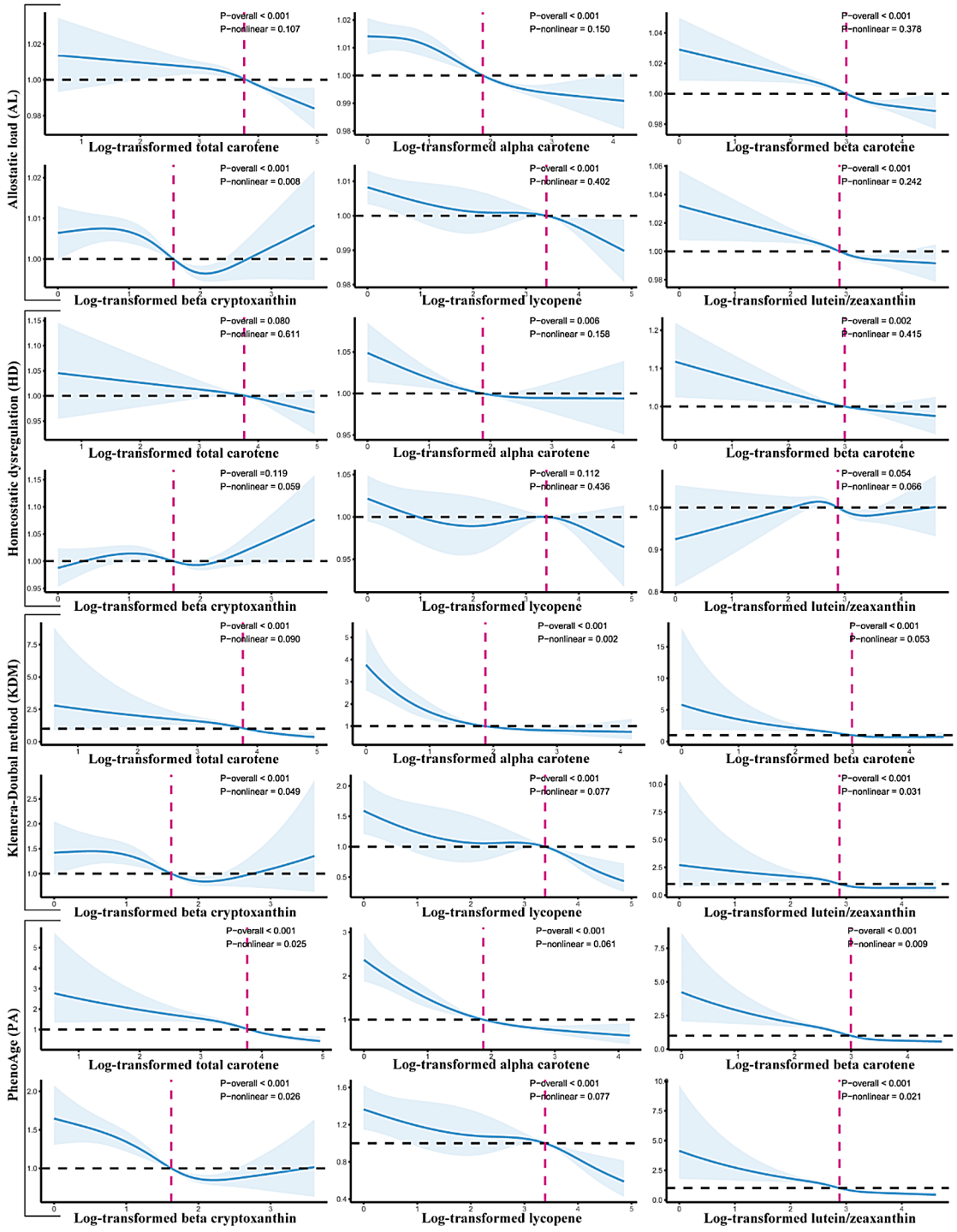

Fig. 3 Associations between log-transformed total carotene, α-carotene, β-carotene, β-cryptoxanthin and lutein/zeaxanthin with biological aging indices were evaluated by RCS. The adjustments involved the covariables selected in the model 4 of multiple linear regression model. The pink dotted lines indicate the median, the solid blue lines correspond to the central estimates, and the bluish-shaded regions indicate the 95% confidence intervals

Stratification of total carotene, α-carotene, β-carotene, β-cryptoxanthin, and lutein/ zeaxanthin in relation to biological aging indices

Similar associations were found when extensive stratified analyses were conducted based on the variables of interest after controlling for variables. It is noteworthy that among participants who were older than 60 years of age, male, white, non-obese, smokers, alcohol drinkers, less physically active, more highly educated, used supplements, and had lower AHEI scores, the results were

closely related to our main findings. (Additional file 1: Tables S8-S31)

Associations of the carotenoid mixtures with biological aging indices

WQS regression and QG-computation models were applied to investigate the associations between carotenoid mixtures and biological aging indices AL, HD, KDM, and PA. Contrary to the QG-computation model, the WQS regression model requires the assumption for the direction of associations. Therefore, based on the observation of the multiple linear regression model, the negative models of AL, HD, KDM, and PA were constructed. As shown in Fig. 4 (A), all four biological aging indices were significantly negatively correlated with carotenoid mixtures in two models. In WQS regression model as AL (β: -0.205, $P<0.001$), HD (β: -0.233, $P=0.019$), KDM (β: -1.548, $P<0.001$) and PA (β: -1.585, $P<0.001$), and QG-computation model as AL (β: -0.010, $P<0.001$), HD (β: -0.016, $P=0.013$), KDM (β: -0.550, $P<0.001$) and PA (β: -0.503, $P<0.001$).

In the WQS regression (Fig. 4.B), lutein/zeaxanthin and α-carotene emerged as the top two key contributors significantly influencing both AL and KDM. For HD, β-carotene and lycopene were identified as the top two carotenoids making the most substantial contributions, respectively. And for PA, lutein/zeaxanthin and β-carotene are considered the top two contributors. The weights of each carotenoid determined by QG- computation calculations differed from the WQS regression results (Fig. 4.C). The two carotenoids that contributed most to AL acceleration were α-carotene and lycopene. The two carotenoids that contributed most to HD acceleration were β-carotene and lycopene. The two carotenoids that contributed most to KDM were β-carotene and α-carotene. The two carotenoids that contributed most to PA were β-carotene and lutein/zeaxanthin.

Discussion

The present study examined the relationship between dietary carotenoids and biological aging in the general adult population using nationally representative data from NHANES. Our preliminary findings showed that total carotene, α-carotene, β-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein/zeaxanthin were significantly negatively correlated with AL, HD, KDM, and PA, except for HD, which showed no significant correlation with α-carotene and β-cryptoxanthin. Furthermore, similar trends were found in subsequent stratification analyses. Similarly, both mixed models consistently indicate that carotenoid mixtures have a significant negative correlation with the combined effect on biological aging, and highlight that high levels of lutein/zeaxanthin and β-carotene intake may play a crucial role in reducing biological aging indices.

Collectively, carotenoids perform a multitude of vital biological functions, with antioxidant activity being of particular significance for human health [47]. As antioxidants, carotenoids are thought to help protect the body from oxidative damage caused by free radicals and reactive oxygen species, which accumulate over time and contribute to age-related diseases [48, 49]. Existing evidence suggests a correlation between carotenoid intake and reduced oxidative stress [50]. Several of our previous studies have found that individuals whose diets are rich in antioxidant and anti-inflammatory foods not only show a reduced risk of all-cause, cardiovascular disease, and cancer deaths, but also are less susceptible to aging [51, 52]. A study of 3660 participants from the NHANES cohort observed a significant association between total serum α-carotene, β-carotene, and β-cryptoxanthin and leukocyte telomere length (LTL): the higher the concentration of carotenoids in the blood, the longer the telomeres [53]. This result was replicated in a larger setting of the same cohort, where serum carotenoids were usually positively correlated with LTL [54]. Another cross-sectional study of the relationship between dietary carotenoid intake and Soluble Klotho (S-Klotho) plasma levels in older adults showed that total carotene intake was associated with an increase in S-Klotho levels and that there was a significant positive correlation between α-carotene, β-carotene and lutein/zeaxanthin intake and S-Klotho levels [55]. However, large population-based studies on the effect of intake levels of dietary carotenoids on biological aging are still limited. To date, this study presents a groundbreaking investigation that provides new evidence for the link between dietary carotenoid intake levels and human aging. Similarly, consistent results obtained by stratified analyses considering confounders support the reliability and strength of our findings.

In our baseline observations, we found that participants with higher total carotene levels were more likely to be male and older, have higher physical activity levels, higher income, and education levels, as well as lower BMI. This phenomenon is quite interesting. We speculate that older individuals may have changing nutritional needs and absorption capacities, slower metabolism, and a higher risk of chronic diseases, which could lead them to pay more attention to healthy eating [56]. Additionally, the higher proportion of males with high intake levels may be due to metabolic and physiological differences between genders, which could affect the absorption and utilization of carotenoids. Furthermore, individuals with higher economic status may be more able to focus on and practice healthy lifestyles, such as balanced nutrition, more regular exercise, and reduced smoking.

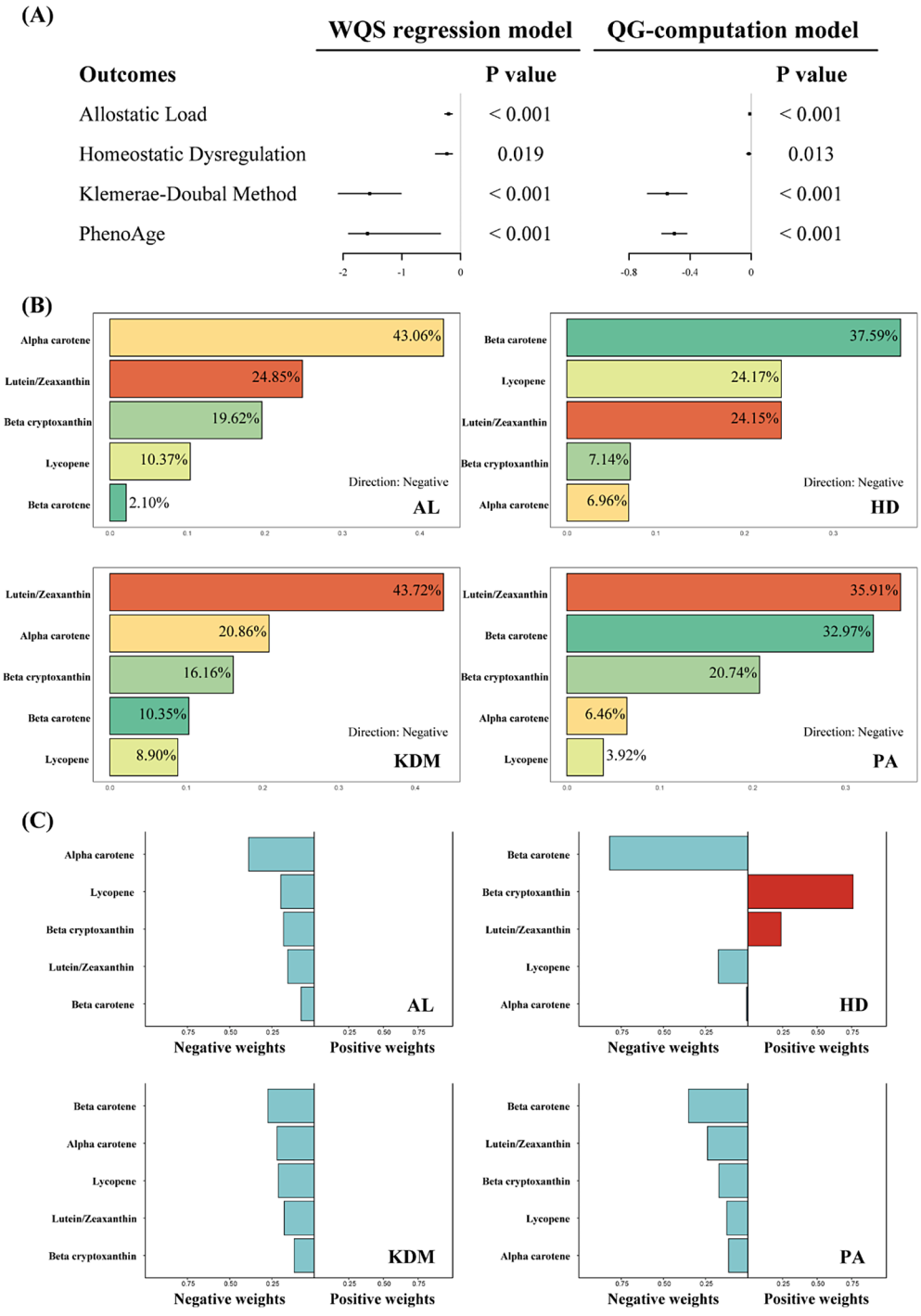

Fig. 4 Forest plot for the associations of the carotenoid mixtures with biological aging indices in the WQS regression and QG-computation models (**A**), and the estimated weights in the WQS regression (**B**) and QG-computation models (**C**). Carotenoids were log-transformed and introduced into the model, and the adjusted covariates involved the covariates selected for model 4 in the multiple linear regression model

Not only in the single carotenoid model, our study found that α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein/zeaxanthin were all negatively associated with lower biological aging indices, but mixed exposure analyses presented consistent results. Interestingly, for the first time in our study, lutein/zeaxanthin and β-carotene were found to be the main contributors. Meanwhile, as two mixed exposure analysis models consistently indicate that α-carotene is the primary contributor to AL, demonstrating that α-carotene also plays

an important role in reducing biological aging indices. Lutein and zeaxanthin are usually considered to be associated with visual and cognitive functions. They can be taken up by the retina at high concentrations and bind to lutein and zeaxanthin proteins, resulting in the formation of macular pigment [57]. Whereas lutein and zeaxanthin levels in the retina are known to be highly correlated with levels of lutein and zeaxanthin in the brain (especially in the occipital region), like the retina, the brain is actively accumulating lutein [58]. Our present study may provide new evidence for the discovery of its potential biological function. It is worth noting that lutein/zeaxanthin intake has been decreasing in the United States. According to NHANES, the average intake of lutein/zeaxanthin decreased from 2.15 mg/d for men and 2.21 mg/d for women in 1987 to 1.58 mg/d for men and 1.76 mg/d for women in 2013 [59]. β-carotene is a precursor of vitamin A and an antioxidant that inhibits the development and progression of cancer. It also exhibits anti-inflammatory effects in various animal and cellular models and has demonstrated a protective effect against the development of a wide range of diseases [60–62]. While previous research has indicated that β-carotene may increase the risk of lung cancer in certain populations [63], our study offers new evidence suggesting that β-carotene could play a potential role in biological aging. α-carotene also as the main precursor of vitamin A in the human body. Several studies have suggested that α-carotene may have more important antioxidant properties than other types of carotenoids [64, 65]. Thus, we speculate that the significant role of α-carotene in driving lower biological aging indices may be attributed to its greater potential antioxidant properties.

In addition, in stratified analyses, most of our results showed that preliminary findings observed in participants who were older than 60 years, male, white, non-obese, smokers, alcohol drinkers, less physically active, highly educated, used supplements, and had lower AHEI scores were strongly associated with outcomes. This is consistent with the results of another study comparing α-carotene, β-carotene, and lutein/zeaxanthin with S-Klotho levels [55]. However, we considered a richer set of indicators for evaluating biological aging. Previous studies have shown that dietary carotenoid intake is negatively associated with obesity [66]. Thus, our study further emphasizes the importance of increasing dietary carotenoid intake for health.

The mechanisms by which dietary carotenoids influence biological aging are unknown. Although chronic diseases such as cancer, diabetes, and cardiovascular disease affect aging, the underlying association between dietary carotenoid levels and aging did not change after adjustment for these chronic diseases. Therefore, it is not possible to explain this negative association in terms of other chronic diseases. Carotenoids have been extensively studied as antioxidants, anti-inflammatory agents, immunoprotectors, immunomodulators, cell membrane stabilizers, and regulators of apoptosis, as well as cell cycle and angiogenesis controllers [67]. In particular, the scavenging capacity of carotenoids reduces reactive oxygen species, promotes DNA repair, negatively regulates oncogenic transcription, and stimulates some key genes encoding antioxidant enzymes [68]. Also carotenoids, as lipophilic antioxidants, can avoid iron-dependent lipid peroxidation, thus alleviating programmed cell death caused by iron death [69]. Although dietary carotenoids from fruits and vegetables are partially converted to vitamin A by the enzyme BCO1, a large portion is transferred to several tissues and biological fluids. In these tissues and fluids, carotenoids exert direct antioxidant functions based on their intrinsic structure or indirect antioxidant functions after oxidative modification by BCO2 and other enzymatic or non-enzymatic actions [21]. In addition, it has also been shown that carotenoid intake can promote gut health by regulating the balance of gut flora, thus having a beneficial effect on the whole, which may be related to its systemic anti-inflammatory and antioxidant properties [70].

This study has several strengths. The first is the large sample size and rich information on covariates. Second, the use of a sophisticated multistage probability sampling method ensured that the participants in this study were a true reflection of the general population, allowing the findings to be generalized across the United States. We also considered multiple clinical indicators such as AL, HD, KDM, and PA, and used an integrated approach to understand the effects of biological aging. In addition, multiple potential confounders were carefully adjusted for, including lifestyle, dietary factors, and prevalence. Finally, multiple statistical models were used in this study, which greatly improved the reliability of the conclusions. Nevertheless, we recognize some limitations of this study. Firstly, this was a cross-sectional observational study, and therefore directional causality could not be established. Second, important biomarkers of aging, including LTL, were not included in this study, and it remains highly likely that some confounding factors have not yet been considered. Third, although the present study assessed total food intake in a detailed manner using two non-consecutive 24-hour dietary recalls, day-to-day variability and recall bias were unavoidable. Fourth, lack of an independent population to validate the current findings. Finally, intake levels do not equal serum and brain levels because provitamin A carotenoids are converted to the corresponding retinoid metabolites and absorbed.

Conclusion

Our study indicated a significant association between various dietary carotenoids and biological aging. Higher intake levels of dietary carotenoids were found to be associated with lower biological aging indices. Among them, lutein/zeaxanthin and β-carotene were the major contributors, suggesting that further studies on the biological functions of lutein/zeaxanthin and β-carotene are worthwhile. These findings provide additional scientific evidence for the relationship between dietary carotenoids and biological aging. Further prospective and experimental studies are urgently needed to validate our results and explore possible molecular biological mechanisms.

Abbreviations

AL	Allostatic load
HD	Homeostatic dysregulation
KDM	Klemera-Doubal method
PA	PhenoAge
WQS	Weighted quantile sum
QG-comp	Quantile g-computation
NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
CVD	Cardiovascular diseases
BMI	Body mass index
AHEI	Alternative Healthy Eating Index
RCS	Restricted cubic spline
LTL	Leukocyte telomere length
S-Klotho	Soluble Klotho

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-025-01079-8.

Supplementary Material 1

Acknowledgements

All authors expressed their gratitude to the participants involved in NHANES 1999–2018 for their priceless contributions.

Author contributions

X.Q., X.W. and Y.L. were responsible for the design of the study, offered statistical assistance, drafted the manuscript, and assumed primary accountability for the final content. X.Q., L.C., Y.L. and K.D. were involved in the preparation and analysis of the data, as well as the visualization of the results. S.Y., Y.W., R.Z. and C.Z. performed a thorough repetition and validation of the statistical analysis. All authors actively participated in the research process, made significant contributions to manuscript revisions, and carefully reviewed and approved the final version of the manuscript.

Funding

All authors received financial support from the National Key Research and Development Program of China (grant number 2022YFC2010105) and the Heilongjiang Province Key R&D Plan Project (grant number 2022ZX02C26), with funding specifically allocated to Ying Li.

Data availability

The datasets supporting the conclusions of this study are available from the NHANES database (https://www.cdc.gov/nchs/nhanes/).

Declarations

Ethics approval and consent to participate

The National Center for Health Statistics (NCHS) Research Ethics Review Board approved the research protocols, and all participants provided written informed consent. All the methods included in this study are in accordance with the declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 22 July 2024 / Accepted: 8 January 2025
Published online: 16 January 2025

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