Nutrition Journal

RESEARCH

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Protective effect of serum carotenoids on mortality among metabolic syndrome patients: attenuated by lipid-lowering drugs

Chunxiang Li[1†], Yanlan Liang[1†], Qiuyuan Lu[1†], Yuanxin Lin[1], Shifeng Wen[1], Xiaoyu Luo[1], Shiping Huang[1], Xue Zhong[1], ZhangJian Xu[1] and Fei Wang[1*]

Abstract

Background Limited evidence exists about the relationship between serum carotenoid and mortality in metabolic syndrome (MetS) patients, and the effects of medication use on this association remains unclear.

Methods The study encompassed 2,521 MetS patients from the National Health and Nutrition Examination Survey (NHANES) 2001–2006 and 2017–2018. A total of 7 serum carotenoids were evaluated. Death data were sourced from the National Death Index, with causes assessed using ICD-10 codes. Bayesian kernel machine regression (BKMR) and random survival forest (RSF) were utilized to investigate serum carotenoid mixture on mortality and identify key carotenoids. "Qgcompint" R package was used to explore the modifying effects of medication use.

Results The serum carotenoid levels at baseline ranged from 0.04 to 1.37 μmol/L. During a follow-up of 15.1 years, there were 696 deaths (27.61%), with 247 (35.49%) by cardiovascular disease (CVD), 148 (21.26%) by cancer, and 301 (43.25%) by other diseases. Individual and combined serum carotenoids were negatively associated with all-cause mortality (HR range:0.70–0.88, 95%CI range:0.56–0.99, all $P < 0.05$). α-carotene (VIMP = 0.223 in RSF) and lutein/zeaxanthin (PIP = 1.000 in BKMR) emerged as the greatest contributors to all-cause mortality. Lipid-lowering drugs attenuate the negative effect of serum carotenoids on MetS patients' mortality ($P_{int} = 0.014$).

Conclusion The present study identified a protective effect of serum carotenoid on mortality in MetS patients, which was probably weakened by lipid-lowering drugs. Early dietary interventions for MetS patients taking lipid-lowering drugs, particularly those rich in carotenoids like α-carotene and lutein/zeaxanthin, could help reduce mortality.

Keywords Metabolic syndrome, Carotenoid, Mortality, Medication use, Lipid-lowing drugs, NHANES

[†]Chunxiang Li, Yanlan Liang and Qiuyuan Lu contributed equally to this work.

*Correspondence:
Fei Wang
wangfei18971630690@163.com
[1]Department of Occupational Health and Environmental Health, School of Public Health, Guangxi Medical University, Nanning, Guangxi, China

Introduction

Metabolic syndrome (MetS), affecting approximately 20%-25% of adults, was defined as a pathological condition characterized by abdominal obesity, insulin resistance, raised blood pressure and hyperlipidemia [1–3]. The prevalence of MetS in the United States has risen by 30% over the past three decades [4]. More importantly, MetS contributes to two-thirds of non-communicable disease mortality, particularly from cardiovascular disease (CVD) [5–7]. Furthermore, previous research shows that mortality in MetS patients may be influenced by variations in metabolic status, nutrient intake, and medication use [8, 9].

Carotenoids, such as α-carotene, β-carotene, lycopene, β-cryptoxanthin, lutein, zeaxanthin and other natural pigments, include essential nutrients for humans that are commonly from green vegetables, fruits and eggs [10]. Carotenoids are crucial for mitigating inflammation and oxidative stress by neutralizing reactive oxygen species (ROS) [11, 12]. A meta-analysis of 11 cross-sectional studies demonstrated that higher levels of serum carotenoids may be associated with slower progression of MetS [13]. In addition, several cohort studies have also shown an inverse correlation between serum carotenoid levels and MetS [14–16]. Furthermore, elevated serum carotenoid levels are associated with reduced mortality from cancer and CVD [17–19].

Previous studies have explored the association between serum carotenoids and mortality among patients with MetS, hypertension and diabetes patients, and the results remain controversial. Cohort Studies based on The National Health and Nutrition Examination Survey (NHANES) revealed that serum β-carotene did not significantly impact CVD mortality in hypertension (8,390 patients) and MetS (1,455 patients) [19, 20]. However, another cohort study of 4,323 individuals with type 2 diabetes (4,323 patients) found a negative relationship between serum β-carotene levels and CVD mortality [18]. The inconsistent findings may be due to interplay of diseases and failure to account for medication use in MetS.

Antihypertensive, hypoglycemic and lipid-lowering drugs were commonly used for MetS treatment [21, 22]. These medications may influence carotenoid levels. Epidemiological research suggests that statins, or other lipid-lowering medications, reduce blood levels of carotenoids such as α-carotene, β-carotenoids, lutein, and lycopene [23, 24]. However, antihypertensive drugs may increase carotenoid levels [22]. An experiment found that the co-administration of lycopene and metformin mitigates insulin resistance [25]. The potential mechanism involves medications influencing the transport of carotenoids in the bloodstream by modulating levels of high-density lipoproteins (HDL) or low-density lipoproteins (LDL) [26, 27]. HDL and LDL are major carriers of carotenoids in humans [28]. Statins and fibrates may lower carotenoid concentrations by reducing LDL levels [29, 30], while the antioxidant properties of metformin contribute to the stabilization of carotenoid concentrations and enhance their bioavailability [31]. Therefore, considering the potential effects of medication use is essential. However, limited research exists on the potential interaction effects between drug use and serum carotenoid levels (both individual and mixed) on mortality among MetS patients.

Based on the details above, a cohort study of 2,521 NHANES patients was conducted to investigate the individual and combined effects of serum carotenoids on mortality in MetS patients, along with the potential modification by medication use.

Methods

Study participants

NHANES serves as a comprehensive national survey that employs a stratified, multistage probability sampling methodology to procure representative samples throughout the United States. The participant flowchart is provided in Supplementary Fig. 1. The study focused on NHANES data from 2001 to 2006 and 2017 to 2018 ($n = 40{,}763$) with serum carotenoids, medication and death information. Following the exclusion of pregnant participants based on self-reporting ($n = 1{,}094$), individuals younger than 20 years old ($n = 19{,}610$), and those without MetS ($n = 17{,}199$), as well as subjects with missing data on serum carotenoids ($n = 335$), incomplete follow-up information ($n = 3$), or medication use data ($n = 1$), a total of 2,521 MetS patients were incorporated into study. The NHANES Ethics Review Committee granted ethical approval for this study, and all participants provided written informed consent.

Ascertainment of death

Mortality information in the NHANES database was linked to the National Death Index and tracked until December 31, 2019. Classification of death status was based on the International Classification of Diseases (ICD) 10th edition. Primary outcomes encompassed all-cause mortality, CVD mortality (I60-I69, I00-I09, I11, I13, I20-I51), cancer mortality (C00-C97) and other mortality. Other mortality mainly included the death of diabetes mellitus (E10-E14), chronic lower respiratory diseases (J40-J47), and Alzheimer's disease (G30) [32].

Definition of MetS

MetS was diagnosed by the criteria from the National Cholesterol Education Program Adult Treatment Panel III [33]. Participants were defined as MetS if they met any three or more of the following conditions: (1) waist

circumference ≥ 102 cm (men) or ≥ 88 cm(women), (2) Triglycerides ≥ 1.7mmol/L (150 mg/L) or drug treatment for elevated triglycerides, (3) HDL cholesterol < 1.0mmol/L(40 mg/dL)(men); < 1.3mmol/L(50 mg/dL) (women) or drug treatment for HDL cholesterol, (4) Fasting glucose > 5.6mmol/L(100 mg/dL) or drug treatment for elevated glucose. (5) Blood pressure ≥ 130/85mmHg or drug treatment for hypertension.

Assessment of serum carotenoids

The study included seven serum carotenoids. All detection rates exceeded 90%. α-carotene, trans β-carotene, lutein/zeaxanthin, β-cryptoxanthin and trans-lycopene were available from NHANES 2001–2006 and 2017–2018, except for total lycopene (unavailable in NHANES 2001–2002). Total serum carotenoid concentrations were the sum of the six carotenoids. Serum carotenoids were measured in NHANES 2001–2006 by using high-performance liquid chromatography (HPLC) and in NHANES 2017–2018 by using photodiode array detection methods (PDAD).

Assessment of covariates

The information on demographics and lifestyle, including age, gender, race, education, poverty-to-income ratio (PIR), body mass index (BMI), smoking, drinking, physical activity (PA), supplement use, comorbidity status, and medication use were collected by standardized questionnaires in NHANES. The level of education is divided into less than high school, high school or equivalent and over than high school. Smoking was classified as current, former, and never smoker [34]. Comorbidity status included hypertension, diabetes, and CVD [35–37]. PA was calculated by minutes of MET per week (MET-min/week) through the information of intensity, duration, and frequency of PA in a week [38]. The Healthy Eating Index (HEI) indicates overall diet quality; a higher total score reflects better diet quality [39]. Medication use included antihypertensive, hypoglycemic and lipid-lowering drugs. Combination drugs were defined as taking two or more drug types. All the drug names are shown in supplemental Table 1.

Statistical analysis

Serum carotenoid levels below the limit of detection (LOD) were imputed using LOD/√2. All serum carotenoid concentrations were transformed by the natural logarithm (ln) and categorized into quartiles.

The Kolmogorov-Smirnov test (K-S test) was used for normality testing. Continuous variables with a normal distribution are described using mean (standard error), while those with a non-normal distribution are described using median (interquartile range, IQR). Categorical variables are expressed as counts (percentages).

Multivariable-adjusted restricted cubic splines (RCS) model was used to show the dose-response relationship between serum carotenoids and mortality. The reference value (HR = 1) is set at the median and four nodes are placed at the 5th, 35th, 65th, and 95th percentile of ln-transformed concentration in RCS.

Three weighted Cox regression models were developed to explore the relationship between seven serum carotenoids and mortality in the MetS population. No covariate was adjusted in model 1. Model 2 was adjusted for age, gender, race and education, PIR, BMI, PA, smoking, drinking, HEI, comorbidity status, and supplement use. Model 3 adds the medication use confounder based on model 2. The reference group was created based on the results of the RCS analysis.

Bayesian kernel machine regression (BKMR) was used to explore the association between serum carotenoids mixture and mortality, while a random survival forest (RSF) (ntree = 1,000) was adopted to rank the importance of carotenoids. Total lycopene and total serum carotenoids were excluded from the mixed-level analysis due to a lack of data in NHANES 2001–2002.

To explore the potential modifying effects of medication use on the relationship serum carotenoid levels (both individual and mixed) and mortality, we applied multiplicative interaction analysis and the "qgcompint" package. Sensitivity analysis was conducted using a competitive risk model and stratified analysis. Moreover, we investigated the association between serum carotenoids and mortality in MetS patients with 3, 4, and 5 abnormal indicators.

All analyses were conducted by R software (version 4.2.2) with the packages "jomo" [40], "rms", "BKMR", "randomForestSRC" and "qgcompint" [41]. Statistical significance was set as $P < 0.05$.

Results

The baseline characteristics of participants

The study enrolled a total of 2521 participants, with an average age of 53.81 years and 51.7% being male. The median follow-up time was 15.1 years. As of December 31, 2019, there were 696 (27.61%) deaths, among which 247 (35.49%) were due to CVD, 148 (21.26%) were due to cancer and 301 (43.25%) were attributed to other diseases. The baseline characters categorized by survival outcome were displayed in Table 1. The death group has lower serum concentrations of lutein/zeaxanthin ($P < 0.001$), trans lycopene ($P < 0.001$), total lycopene ($P < 0.001$) and total carotenoid ($P = 0.015$), more likely to be taking medications for MetS ($P < 0.001$), including antihypertensive ($P < 0.001$), hypoglycemic ($P = 0.010$), lipid-lowering drugs ($P < 0.001$) and combination drugs ($P < 0.001$), and tended to be older ($P < 0.001$) and non-Hispanic white ($P = 0.01$). The survival group has higher

Table 1 Baseline characteristics of MetS patients in NHANES 2001–2006 and NHANES 2017–2018

Characters	Total	Survival	Mortality	*P*-value
	(*n* = 2521)	(*n* = 1825)	(*n* = 696)	
Age, years	53.81(0.40)	50.65(0.42)	65.69(0.83)	**< 0.001**
Gender, %				0.200
Female	1342(51.70)	1012(52.49)	330(48.72)	
Male	1179(48.30)	813(47.51)	366(51.28)	
Race, %				**0.010**
Mexican American	511(7.73)	397(8.60)	114(4.45)	
Non-Hispanic Black	441(9.51)	341(9.71)	100(8.74)	
Non-Hispanic White	1287(72.99)	838(70.98)	449(80.52)	
Other Race	282(9.77)	249(10.70)	33(6.28)	
Education, %				**< 0.001**
Less than high school	783(20.40)	521(18.18)	262(28.77)	
High school or equivalent	641(30.55)	453(30.49)	188(30.79)	
Over than high school	1097(49.04)	851(51.33)	246(40.43)	
PIR, %				**< 0.001**
<1.3	759(22.05)	517(20.36)	242(28.38)	
1.3–3.5	1036(39.48)	731(38.27)	305(44.03)	
≥3.5	726(38.47)	577(41.37)	149(27.59)	
Smoking, %				**< 0.001**
Current smoker	497(21.66)	369(21.22)	128(23.35)	
Former smoker	812(31.61)	519(29.39)	293(39.93)	
Never smoker	1212(46.73)	937(49.39)	275(36.73)	
Drinking, %				**0.020**
No	2125(84.43)	1555(85.44)	570(80.67)	
Yes	396(15.57)	270(14.56)	126(19.33)	
BMI, kg/m^2	32.68(0.25)	33.00(0.29)	31.47(0.31)	**< 0.001**
PA, MET-min/week	1418.38(109.50)	1619.96(135.76)	660.99(69.63)	**< 0.001**
HEI	49.01(0.43)	48.60(0.45)	50.55(0.69)	**0.010**
Comorbidity status, %				**< 0.001**
No	597(28.38)	533(33.17)	64(10.39)	
Yes	1924(71.62)	1292(66.83)	632(89.61)	
Supplement use, %				**< 0.001**
No	1408(56.01)	979(53.53)	429(65.31)	
Yes	1113(43.99)	846(46.47)	267(34.69)	
Medication use, %				**< 0.001**
No	892(39.46)	768(44.55)	124(20.30)	
Yes	1629(60.54)	1057(55.45)	572(79.70)	
Antihypertensive drugs, %				**< 0.001**
No	1037(45.72)	879(50.95)	158(26.04)	
Yes	1484(54.28)	946(49.05)	538(73.96)	
Lipid-lowering drugs, %				**< 0.001**
No	1766(70.18)	1324(72.57)	442(61.21)	
Yes	755(29.82)	501(27.43)	254(38.79)	
Antidiabetic drugs, %				**0.010**
No	1969(82.17)	1453(83.55)	516(76.99)	
Yes	552(17.83)	372(16.45)	180(23.01)	
Combination drugs, %				**< 0.001**
No	1636(67.91)	1255(71.00)	381(56.29)	
Yes	885(32.09)	570(29.00)	315(43.71)	
α-carotene, μmol/L	0.04(0.02,0.08)	0.04(0.02,0.08)	0.04(0.02,0.07)	0.154
Trans β-carotene, μmol/L	0.19(0.11,0.32)	0.18(0.11,0.31)	0.20(0.11,0.37)	0.161
Lutein/zeaxanthin, μmol/L	0.23(0.16,0.33)	0.24(0.17,0.33)	0.22(0.16,0.31)	**0.015**
β-cryptoxanthin, μmol/L	0.10(0.07,0.16)	0.10(0.07,0.16)	0.10(0.07,0.16)	0.561

Table 1 (continued)

Characters	Total	Survival	Mortality	*P*-value
	(*n* = 2521)	(*n* = 1825)	(*n* = 696)	
Trans lycopene, μmol/L	0.37(0.24,0.51)	0.38(0.26,0.53)	0.30(0.18,0.46)	**< 0.001**
Total lycopene, μmol/L	0.67(0.46,0.95)	0.70(0.49,0.96)	0.55(0.34,0.78)	**< 0.001**
Total carotenoid, μmol/L	1.33(0.95,1.83)	1.33(0.99,1.85)	1.21(0.86,1.74)	**0.016**

Note: Continuous variables with a normal distribution were presented as mean (standard error), those with a non-normal distribution as median (interquartile range), and categorical variables as counts (percentages). Other Race: including Multi-Racial and other Hispanics. PIR: poverty-to-income ratio. BMI: body mass index. PA: physical activity. HEI: healthy eating index

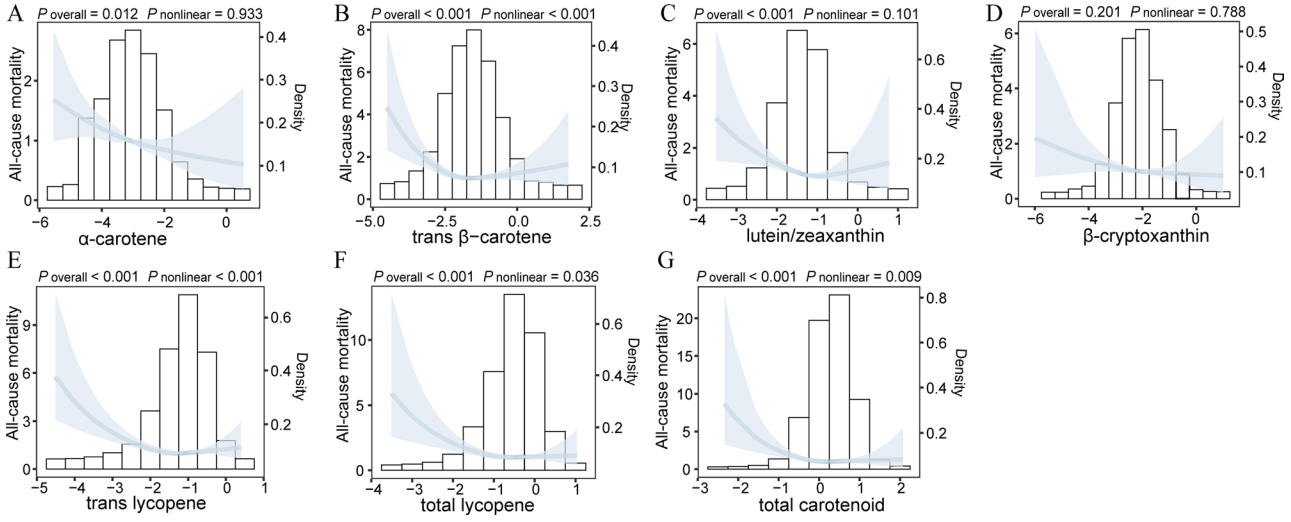

Fig. 1 Association between serum carotenoids with all-cause mortality among MetS patients in RCS. The reference value (HR = 1) is set at the median and four nodes are placed at the 5th, 35th, 65th, and 95th percentile of ln-transformed concentration in RCS. Adjusted for age, gender, race, BMI, PA, smoking, drinking, comorbidity status, HEI, supplement use, and medication use. BMI: body mass index. PA: physical activity. HEI: healthy eating index

levels of education ($P < 0.001$) and income ($P < 0.001$), engaged in more physical activity per week ($P < 0.001$), and were less likely to smoke ($P < 0.001$) and drink ($P = 0.020$). Additionally, the survival patients seemed to more often use dietary supplements and had a lower prevalence of comorbidity status (all $P < 0.001$), yet displayed a higher BMI and lower HEI scores (all $P < 0.05$).

Association between individual serum carotenoid level and both mortality in the MetS population

We observed the linear association between α-carotene ($P_{overall} = 0.012$, $P_{non\text{-}linear} = 0.093$), lutein/zeaxanthin ($P_{overall} < 0.001$, $P_{non\text{-}linear} = 0.101$), total lycopene ($P_{overall} < 0.001$ and $P_{non\text{-}linear} = 0.036$) and all-cause mortality (Fig. 1). Non-linear associations were found between trans β-carotene ($P_{overall} < 0.001$, $P_{non\text{-}linear} < 0.001$), trans lycopene ($P_{overall} < 0.001$, $P_{non\text{-}linear} < 0.001$), total carotene ($P_{overall} < 0.001$, $P_{non\text{-}linear} = 0.009$) and all-cause mortality (Fig. 1). Non-linear associations were also found between lutein/zeaxanthin ($P_{overall} = 0.003$, $P_{non\text{-}linear} = 0.020$), trans lycopene ($P_{overall} = 0.010$, $P_{non\text{-}linear} = 0.010$) and CVD mortality (Fig S2C&E), trans β-carotene and other mortality ($P_{overall} = 0.018$, $P_{non\text{-}linear} = 0.034$) (Fig S2P), while all serum carotenoids showed a linear association with cancer mortality (all $P_{non\text{-}linear} > 0.05$) (Fig S2H-N).

The weighted Cox regression analysis based on ln-transformed and quartiles of serum carotenoids after adjusting for included covariates were shown in Fig. 2 and Fig S3-6. β-cryptoxanthin (HR = 0.84, 95%CI: 0.75–0.95, $P = 0.008$), trans lycopene (HR = 0.49, 95%CI: 0.42–0.56, $P < 0.001$) and total lycopene (HR = 0.45, 95%CI: 0.42–0.56, $P < 0.001$) were associated with the higher prevalence of overall mortality in model 1 (Fig. 2). Following adjustments for demographic and lifestyle variables (model 2) as well as medication use (model 3), it was observed that elevated concentrations of 7 serum carotenoids were associated with a significant reduction in all-cause mortality (HR range:0.70–0.88, 95%CI range:0.56–0.99, all $P < 0.05$) (Fig. 2). Compared to the lowest quartiles in model 3, the highest quartiles of α-carotene (HR = 0.67, 95%CI: 0.50–0.89, $P = 0.005$) and lutein/zeaxanthin (HR = 0.68, 95%CI: 0.54–0.87, $P < 0.001$) were associated with 33% and 32% decreased hazards of all-cause mortality (Fig S3). The higher levels of serum trans lycopene (HR = 0.51, 95%CI: 0.39–0.67, $P < 0.001$) and total lycopene (HR = 0.53, 95%CI: 0.35–0.80, $P = 0.002$) had lower CVD mortality in the unadjusted

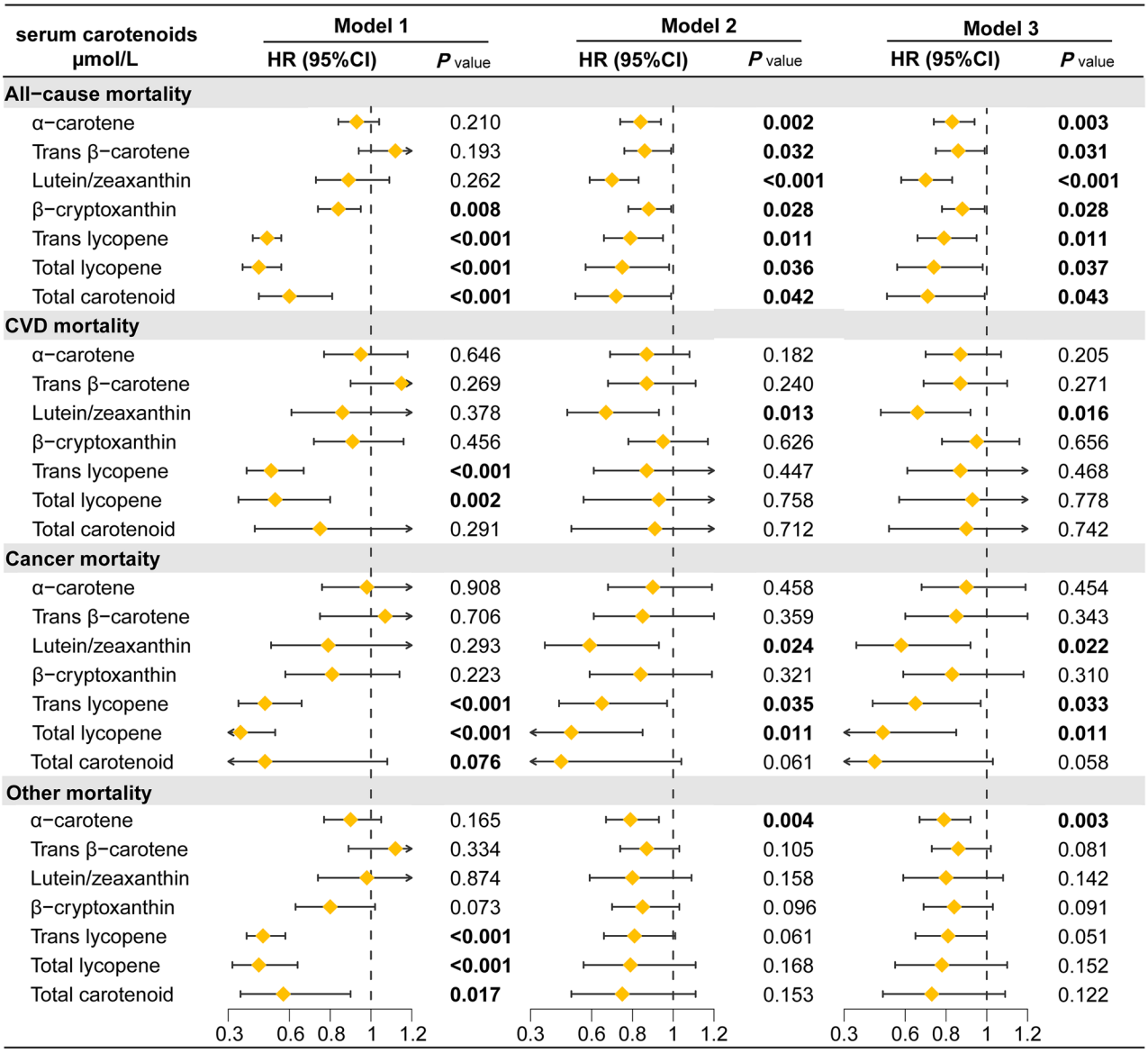

Fig. 2 Association between serum carotenoids with mortality among MetS patients in weighted cox regression model. Model 1: Unadjusted. Model 2: Adjusted for age, gender, race, BMI, PA, smoking, drinking, comorbidity status, HEI, and supplement use. Model 3: Adjusted for confounding factors in Model 2 and medication use. BMI: body mass index. PA: physical activity. HEI: healthy eating index

model (Fig. 2). After multivariable adjustment, a higher lutein/zeaxanthin was significantly associated with lower CVD mortality (HR = 0.67, 95%CI: 0.48–0.93, $P = 0.016$) (Fig. 2). Compared to the reference quartile(Q2) group, the multivariable-adjusted HRs (95% CIs) across quartiles of serum lutein/zeaxanthin concentrations were Q1: 1.20(0.79, 1.83), Q3: 0.61(0.39, 0.95), and Q4: 0.74(0.47–1.18) (P_{trend} = 0.042) (Fig S4). Besides, lutein/zeaxanthin (HR = 0.53, 95%CI: 0.34–0.81, $P = 0.022$), trans lycopene (HR = 0.62, 95%CI: 0.42–0.90, $P = 0.033$) and total lycopene (HR = 0.49, 95%CI: 0.29–0.83, $P = 0.011$) were negatively associated with cancer mortality (Fig. 2). Only α-carotene was negatively associated with other mortality (HR = 0.79, 95%CI: 0.67–0.92, $P = 0.003$) (Fig. 2). Furthermore, analogous findings were also discerned within the competitive risk model (Table S2). In addition, stratified analysis revealed that association in all-cause mortality was primarily observed among patients younger than 60 years (all $P < 0.003$) (Table S3).

Association between serum carotenoid mixture level and mortality in the MetS population and the key serum carotenoid

Total carotenoid was negatively associated with all-cause mortality in the weighted Cox regression model (HR = 0.71, 95%CI: 0.51–0.99, $P = 0.043$) (Fig. 2).

Elevated concentrations of the five serum carotenoids mixture (α-carotene, trans β-carotene, lutein/zeaxanthin, β-cryptoxanthin and trans-lycopene) were associated with lower mortality through the BKMR model (Fig. 3A-D). Upon fixing other serum carotenoids at specific percentiles, α-carotene and lutein/zeaxanthin exhibited a negative relationship with all-cause mortality, with lutein/zeaxanthin showing a dominant effect (PIP = 1.000) (Fig. 3E). Conversely, β-cryptoxanthin demonstrated a positive impact on all-cause mortality (PIP = 0.856) (Fig. 3E). For CVD mortality, lutein/zeaxanthin emerged as the primary influencing factor (PIP = 0.664) (Fig. 3F). Additionally, α-carotene had major protective effects against other mortality (PIP = 0.998) (Fig. 3H). Fixed the other four serum carotenoids at the median, α-carotene was significantly negatively correlated with both all-cause mortality and other mortality (Fig S7). Lutein/zeaxanthin and trans lycopene showed an inverse relationship with CVD mortality, and trans lycopene was also found to be negatively linked to cancer mortality (Fig S7). Additionally, β-cryptoxanthin exhibited an inverted U-shape association with all-cause mortality, suggesting that its impact may vary across different serum levels (Fig S7). Besides, β-cryptoxanthin may had possible synergistic or antagonistic effects with other serum carotenoids (Fig S8).

RSF was used to assess the importance of 5 serum carotenoids in our study. Figure 4 shows that α-carotene played the most important role in both all-cause mortality (VIMP = 0.223) and cancer mortality (VIMP = 0.947), while lutein/zeaxanthin ranked first in CVD mortality (VIMP = 0.028) and other causes of mortality (VIMP = 0.030). Notably, α-carotene and lutein/zeaxanthin contributed 83.28% of all serum carotenoids in reducing mortality risk in the MetS population.

Interactions of individual and mixed serum carotenoids, medication use, and mortality among MetS patients

Significant antagonistic action of medication use and lipid-lowering drugs were observed between all serum carotenoids and all-cause mortality (all $P_{int} < 0.02$) (Fig. 5). Moreover, medication use also had significant interactions with all serum carotenoids in CVD (except for trans lycopene) and cancer mortality (all $P_{int} < 0.05$) (Fig. S9). Lipid-lowering drugs had interactions with most of the serum carotenoids (except for trans lycopene and trans β-carotene) in CVD mortality (all $P_{int} < 0.05$) (Fig. S9). Notably, within the group without medication use for MetS, a notable inverse correlation was observed between serum carotenoids and mortality (HR range:0.22–0.62, 95%CI range:0.13–0.87, all $P < 0.05$) (Fig. 5). Moreover, medication use ($P_{int} < 0.001$), antihypertensive drugs ($P_{int} < 0.0001$), lipid-lowering drugs ($P_{int} = 0.002$), and combination drugs ($P_{int} = 0.025$) showed significant interactions with total carotenoid regarding all-cause mortality among MetS patients (Fig. 5).

A significant interaction was also observed between lipid-lowering drugs and the serum carotenoid mixture by "qgcompint" package ($P_{int} = 0.014$) (Fig. 6). Similarly, MetS patients not using lipid-lowering medication exhibited lower all-cause mortality with a 1-quartile increase in mixed serum carotenoids (psi1: -0.40, 95%CI: -0.58,

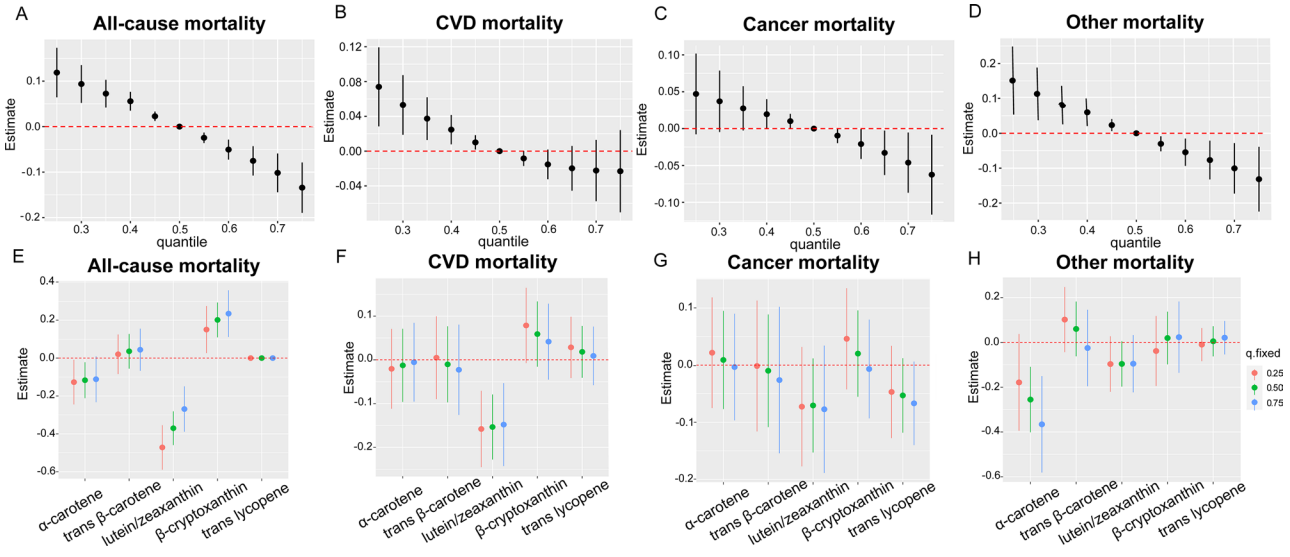

Fig. 3 Association between serum carotenoid mixtures with mortality among MetS patients in BKMR. Overall risk (95% CI) of serum carotenoid levels on all-cause (**A**), CVD (**B**), cancer (**C**), and other (**D**) mortality when comparing all the serum carotenoids at different percentiles with their median level. Univariate exposure of all-cause (**E**), CVD (**F**), cancer (**G**), and other (**H**) mortality at 95% confidence intervals comparing the changes in each exposure from the 25th, 50th, and 75th percentiles when the remaining exposures are fixed at the similar percentiles. Models were adjusted for age, gender, race, BMI, PA, smoking, drinking, comorbidity status, HEI, supplement use, and medication use. BMI: body mass index. PA: physical activity. HEI: healthy eating index

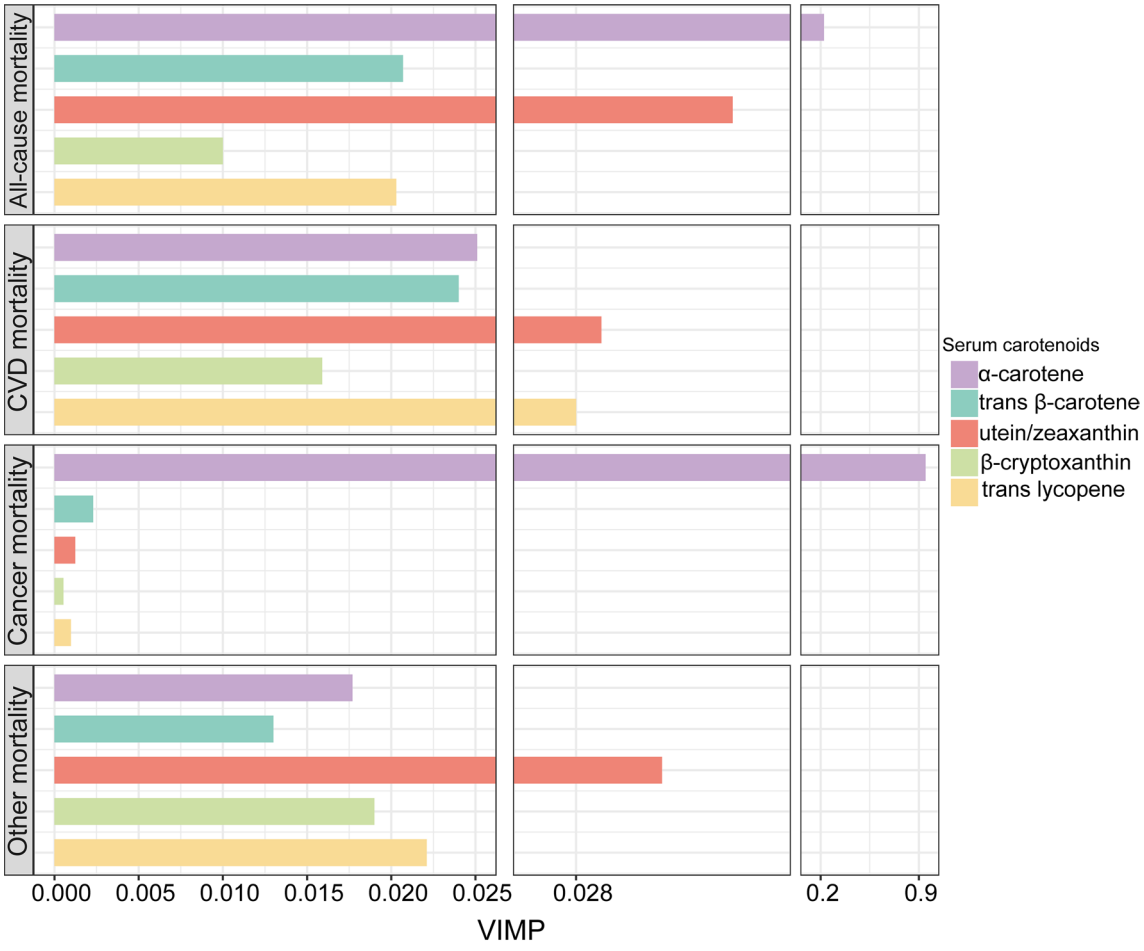

Fig. 4 Feature importance ranking plot for RSF in mortality. The entire dataset was split into training data (80%) and test data (20%). We set ntrees to 1,000 and obtained a C-index to evaluate model performance in the test data: 0.83 for all-cause mortality, 0.85 for CVD mortality, 0.98 for cancer mortality, and 0.79 for other mortality. VIMP: Variable importance

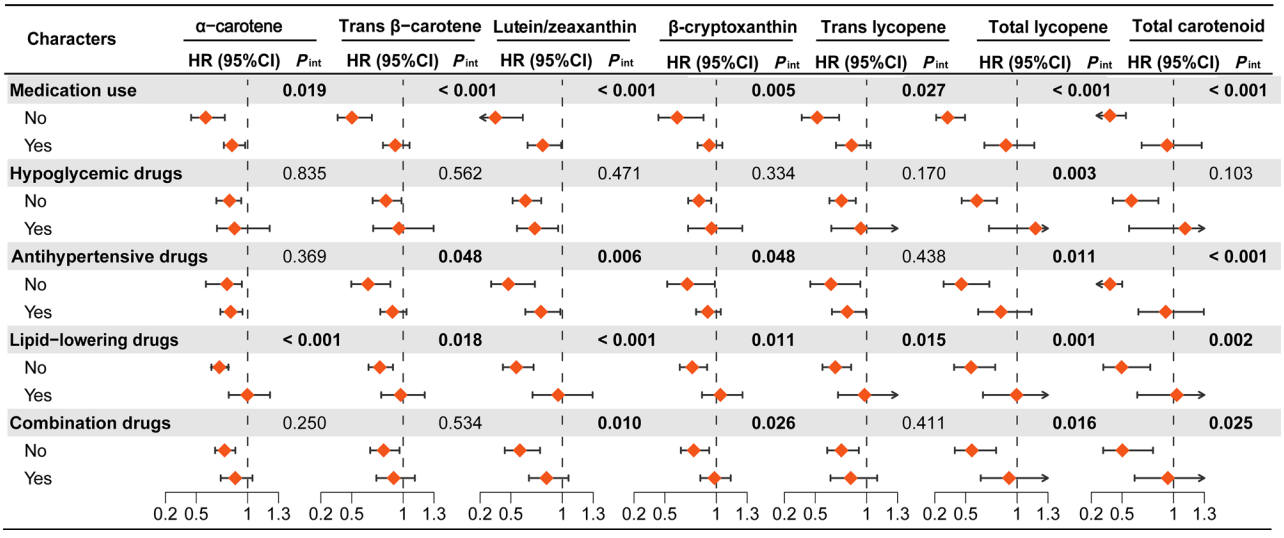

Fig. 5 Interaction analysis between drug use and serum carotenoids concerning all-cause mortality in MetS patients. Adjusted for age, gender, race, BMI, PA, smoking, drinking, comorbidity status, HEI, supplement use, and medication use.BMI: body mass index. PA: physical activity. HEI: healthy eating index

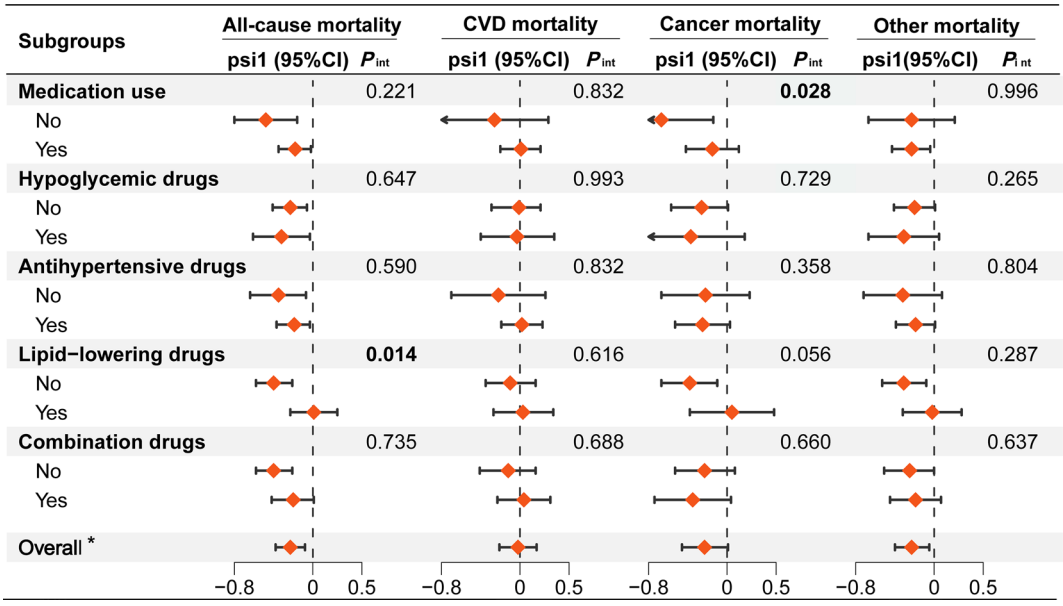

Fig. 6 The modifying effect of medication use on the association between mixed serum carotenoid and mortality in MetS patients. Overall indicates the association between mixed serum carotenoid levels and mortality using qgcomp model. Adjusted for age, gender, race, BMI, PA, smoking, drinking, comorbidity status, HEI, supplement use, and medication use. BMI: body mass index. PA: physical activity. HEI: healthy eating index. *: The qgcomp model to calculate the effect of mixed carotenoid levels on MetS patients' all-cause or cause-specific mortality

-0.21, $P<0.001$) (Fig. 6). Moreover, MetS patients without any medication use showed lower cancer mortality (psi1:-0.67, 95%CI: -1.20, -0.14, $P=0.013$) compared to those who were taking medications ($P_{int}=0.028$) (Fig. 6).

Sensitivity analysis

To enhance the robustness of our results, we further analyzed separate and combined level assessments of the relationship between serum carotenoids and all-cause mortality across subpopulations exhibiting 3, 4, and 5 abnormal indicators. After multivariate adjustments, α-carotene (HR = 0.83, 95%CI: 0.72–0.97, $P=0.016$), lutein/zeaxanthin (HR = 0.65, 95%CI: 0.49–0.87, $P=0.004$) and β-cryptoxanthin (HR = 0.76, 95%CI: 0.63–0.92, $P=0.006$) were negatively associated with all-cause mortality in the population exhibiting 3 abnormal indicators. There was no statistically significant association was observed in MetS patients with 4, and 5 abnormal indicators (all $P>0.05$) (Table S4).

In the BKMR model, for patients with 3 abnormal markers, higher levels of serum carotenoids showed a protective effect. Conversely, lower levels were found to be associated with all-cause mortality in MetS patients exhibiting 4, and 5 abnormal indicators (Fig S10).

During the interaction analysis, significant negative interactions were observed in lipid-lowering drugs exhibited with most of the serum carotenoids (except for β-cryptoxanthin) among patients with 3 abnormal indicators (all $P_{int}<0.05$) (Table S5). We also observed significant modifying effects of lipid-lowering drugs between mixed serum carotenoids and all-cause mortality in patients with 3 abnormal indicators ($P_{int}=0.029$), and of medication use in patients with more than 3 abnormal indicators ($P_{int}=0.021$) (Fig. S11). Significant negative associations were also found between the serum carotenoids mixture and mortality in the no lipid-lowering use among 3 abnormal indicators patients (psi1: -1.04, 95%CI: -1.83, -0.26, $P=0.009$) and no medication use groups (psi1: -0.40, 95%CI: -0.64, -0.15, $P=0.002$) among 3 abnormal indicators patients (Fig. S11).

Discussion

In the present longitudinal cohort study with 15.1 years of follow-up, our results revealed a negative association between serum carotenoids and mortality among MetS patients. Specifically, α-carotene and lutein/zeaxanthin were significant factors in reducing mortality among MetS patients. Noteworthy, the protective effect of serum carotenoids was attenuated by medication use, especially lipid-lowing drugs.

Both individual and combined levels of serum carotenoids were associated with reduced all-cause mortality in MetS patients, with α-carotene showing the most significant protective effects, followed by lutein/zeaxanthin. Our study generated findings that are consistent with previous research. For instance, based on a survey from NHANES III, elevated serum lycopene levels had significantly reduced mortality among MetS patients [42]. Some studies showed that α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene were

negatively associated with all-cause death [36–38]. Moreover, recent mixed-effects analyses of serum nutrients and mortality in MetS patients have highlighted the critical protective role of α-carotene [20]. Notably, α-carotene and lutein/zeaxanthin are natural lipid-soluble micronutrients obtained only from the diet [43]. Studies have indicated that a high intake of α-carotene- or lutein/zeaxanthin-rich food may be important for reducing the mortality risk [44]. In addition, a positive correlation between serum carotenoids and dietary carotenoids was found in the study, with a correlation range from 0.26 to 0.35 (Fig. S12). These findings suggested the importance of dietary interventions focused on increasing carotenoid intake.

However, existing evidence on the protective effect of lutein/zeaxanthin on CVD mortality remains controversial [45]. In the present study, lutein/zeaxanthin has been identified as a significant protective factor against CVD mortality. Due to the limited number of studies examining the relationship between serum carotenoids and mortality in individuals with MetS, direct comparisons with other findings are challenging. Nevertheless, a long-term repeated-measures study involving 3,116 participants over 25 years found that serum lutein/zeaxanthin exhibited a statistically significant protective effect against CVD mortality [46]. Additional evidence suggests that lutein/zeaxanthin may be associated with a reduced risk of CVD mortality in hypertensive adults [19]. Other studies have also suggested that higher serum levels of lutein/zeaxanthin may be associated with a reduced risk of MetS, diabetes, and obesity [47–49]. However, the study by Xinwei Peng et al [20]. (1455 MetS patients) found no significant association between lutein/zeaxanthin and CVD mortality. The observed differences may be attributed to the failure to account for the potential impact of medication use in patients with MetS and the limited sample size. In this study, we increased the sample size to 2,521 patients and identified an interaction between medication use, particularly lipid-lowering drugs, and the association between lutein/zeaxanthin levels and CVD mortality (all $P_{int} < 0.05$) (Fig. S9). Furthermore, by categorizing medications in this study, the utilized drugs group exhibited significantly increased lutein/zeaxanthin levels ($P = 0.008$) (Table S6).

Actually, the influence of drug use on human serum carotenoid levels remains unclear. Weber [50] et al. found that higher medication intake was associated with lower carotenoid levels (except for β-cryptoxanthin and lycopene). In contrast, a separate study discovered that simvastatin led to a significant increase in the concentrations of lutein, lycopene, α-carotene, and β-carotene [51]. In the present study, the protective effect of serum carotenoids may be diminished in individuals who take medication (lipid-lowering drugs) for MetS. Both individual and mixed serum carotenoids were negative associated with all-cause mortality among MetS patients with no lipid-lowering drugs. Furthermore, severity of the MetS also diminished the protective effect of serum carotenoids. The analysis revealed a negative association between most serum carotenoids and all-cause mortality in MetS patients with 3 abnormal indicators, but no significant association was found in those with 4 or 5 abnormal indicators. Besides, the concentrations of serum carotenoids were decreased with the severity of the MetS (Table S7). Therefore, the protective effect of serum carotenoids may be diminished in individuals who take medication for MetS, possibly due to the complexity of medication regimens and the severity of MetS in this population.

The potential underlying mechanism linking serum carotenoid levels to reduced mortality may be attributed to their antioxidant activity and anti-inflammatory effects [52, 53]. Insulin resistance, chronic inflammation, and oxidative stress are widely acknowledged as primary contributors to the development of MetS. Insulin resistance reduces glucose utilization in muscles and other tissues, thereby promoting the production of free fatty acids, which exacerbates MetS [9, 53]. This also results in increased reactive oxygen species (ROS), leading to oxidative stress and inflammation [54–56]. Oxidative stress can induce intracellular signaling changes in adipocytes, leading to adipocyte insulin resistance and increased secretion of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). This elevation in proinflammatory factors contributes to the progression and exacerbation of MetS [57]. Studies have shown that carotenoids and their carotenoid conversion products play a beneficial role in regulating adipocyte function by regulating cellular pathways associated with inflammation and oxidative stress responses, such as the nuclear factor-kB (NF-kB) and nuclear factor 2 associated factor 2 (Nrf2) pathways [58]. According to the most recent animal study, the administration of carotenoid-rich oil exhibited mitigating effects on insulin resistance in obese rats by enhancing anti-inflammatory and antioxidative mechanisms [59]. In addition, the negative association of total carotenoids, β-carotene and α-carotene with insulin resistance has also been confirmed in epidemiology [60]. Carotenoids represent a class of lipophilic pigments, characterized by their molecular structure into polar (including lutein, zeaxanthin, and β-cryptoxanthin) and non-polar (including α-carotene, β-carotene, and lycopene) [61]. Within the circulatory system, carotene predominantly associates with LDL, whereas lutein primarily binds to HDL [62, 63]. Lipid-lowering drugs reduce cholesterol synthesis and then up-regulate the LDL receptor on the cell surface, accelerate the serum LDL catabolism, and slightly increase the level of HDL [64]. This may affect serum

carotenoid concentration, thereby weakening its protective effect in MetS patients.

The present study offers several advantages. First, the cohort study featured a larger sample size than similar previous studies. Second, rigorously controlling for potential confounding variables improves the credibility of the findings. Third, various sensitivity analysis methods ensured the robustness of the results. Fourth, a novel exploration of the interaction effects of medication use on the association between serum carotenoid mixture and mortality. However, several limitations must to be acknowledged. Firstly, the current study participants were primarily from the US population, which limits the generalizability of the results to the Asian population. Second, serum carotenoids were assessed only at baseline. Not enough information to observe the impact of dynamic changes in carotenoids on MetS mortality. Furthermore, lacking information exists regarding the dosage and frequency of drug intake to evaluate its impact on serum carotenoids and MetS mortality.

Conclusion

Among MetS patients, serum carotenoid levels were negatively associated with mortality. Notably, α-carotene and lutein/zeaxanthin play important protective roles. However, the protective effect of serum carotenoids was diminished in MetS patients using medications, particularly lipid-lowering drugs. Therefore, dietary carotenoid supplementation in patients taking medication, especially in the early stages, may effectively lower the risk of mortality associated with MetS.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-025-01092-x .

Supplementary Material 1

Acknowledgements

We appreciate all the NHANES participants and staff for their invaluable efforts and contributions.

Author contributions

Chunxiang Li: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing. Yanlan Liang: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization. Qiuyuan Lu: Conceptualization, Methodology, Software, Visualization, Validation. Yuanxin Lin: Data curation, Methodology, Visualization. Shifeng Wen: Data curation, Investigation, Validation. Xiaoyu Luo: Data curation, Methodology, Validation. Shiping Huang: Data curation, Investigation. Xue Zhong: Data curation, Validation. ZhangJian Xu： Data curation. Fei Wang: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing - review & editing.

Funding

This study was supported by the National Natural Science Foundation of China (NSFC-42467058), Specific Research Project of Guangxi for Research Bases, and Talents (AD23026163); Research Basic Ability Improvement Project of Young and Middle-aged Teachers in Guangxi Universities (2023KY0093).

Data availability

The datasets analyzed during the current study are available on the NHANES website: https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate

The study involving human participants was rigorously reviewed and approved by the Research Ethics Review Board of the National Centre for Health Statistics (NCHS). All participants provided their written informed consent to take part in the research.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 24 October 2024 / Accepted: 12 February 2025
Published online: 19 February 2025

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