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Total carotenoid intake is associated with reduced loss of grip strength and gait speed over time in adults: The Framingham Offspring Study

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ABSTRACT

Background: Lower antioxidant serum concentrations have been linked to declines in lean mass and physical function in older adults. Yet population data on the effect of dietary antioxidants on loss of muscle strength and physical function are lacking.

Objective: We sought to determine the association of antioxidant intake [vitamin C, vitamin E, and total and individual carotenoids (α -carotene, β -carotene, β -cryptoxanthin, lycopene, and lutein + zeaxanthin)] with annualized change in grip strength and gait speed in adults from the Framingham Offspring study.

Methods: This prospective cohort study included participants with a valid FFQ at the index examination and up to 2 prior examinations and at ≥ 2 measures of primary outcomes: grip strength ($n = 2452$) and/or gait speed ($n = 2422$) measured over 3 subsequent examinations. Annualized change in grip strength (kg/y) and change in gait speed (m/s/y) over the follow-up period were used. Linear regression was used to calculate β coefficients and P values, adjusting for covariates.

Results: Mean $\pm$ SD age of participants was 61 ± 9 y (range: 33–88 y). Median intakes (IQR, mg/d) of vitamin C, vitamin E, and total carotenoid across available examinations were 209.2 (133.1–394.2), 27.1 (7.4–199.0), and 15.3 (10.4–21.3), respectively. The mean follow-up time was $\sim 12 \pm 2$ y (range: 4.5–15.4 y). In the sex-combined sample, higher intakes of total carotenoids, lycopene, and lutein + zeaxanthin were associated with increased annualized change in grip strength [β (SE) per 10-mg higher intake/d, range: 0.0316 (0.0146) to 0.1223 (0.0603) kg/y]. All antioxidants except for vitamin C were associated with faster gait speed [β (SE) per 10-mg higher intake/d, range: 0.00008 (0.00004) to 0.0187 (0.0081) m/s/y].

Conclusions: Higher antioxidant intake was associated with increase in grip strength and faster gait speed in this cohort of adults. This finding highlights the need for a randomized controlled trial of dietary antioxidants and their effect on muscle strength and physical function. *Am J Clin Nutr* 2021;113:437–445.

Keywords: muscle strength, physical function, aging, nutrition, diet, epidemiology, community-based, sarcopenia, prospective cohort study, food frequency questionnaire

Introduction

Sarcopenia is defined as the presence of age-related declines in muscle strength, muscle quantity/quality, and physical performance (1). Sarcopenia contributes to reduced mobility, disability,

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Data sharing: Data described in the manuscript, code book, and analytic code will be made available upon request pending application to and approval by the Framingham Heart Study.

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Abbreviations used: CHS, Cardiovascular Health Study; CRP, C-reactive protein; FHS, Framingham Heart Study Offspring Cohort; InCHIANTI, Invecchiare in Chianti; IRB, institutional review board; WHAS, Women's Health and Aging Studies.

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and institutionalization, and the care of patients with sarcopenia places considerable economic burden on the US healthcare system (2). Age-related declines in muscle mass and strength are accompanied by declines in physical function (3, 4) that is further associated with cardiovascular disease, impaired mobility, and mortality (5, 6). The cause of age-related declines in muscle strength and physical function is multifactorial, yet mechanisms are not well understood. As the number of older adults is projected to increase >60% in the next 15 y (7), an improved understanding of the determinants of loss of muscle and physical function is essential to develop novel interventions for prevention and treatment.

Although lifestyle factors could be key in the prevention and treatment of muscle loss and functional decline, the focus of research as it relates to age-related loss of muscle and physical function has been relegated mostly to exercise, vitamin D, and dietary protein (8–11). Mechanistic studies suggest that oxidative stress could be a central mechanism of age-related decline in muscle mass and function (12, 13). Therefore, aspects of diet may reduce oxidative stress and play important roles in age-related loss of muscle and physical function. Dietary antioxidants inhibit or delay oxidation, and carotenoids, in particular, quench free radicals, reduce damage from oxygen species, and modulate redox-sensitive transcription factors (such as NF- κ B) that are involved in upregulation of IL-6 and other proinflammatory cytokines. Cross-sectional studies report that low antioxidant status is independently associated with impairments in physical performance (14) and muscle strength (14, 15) and may contribute to frailty (16). Prospective cohort studies have reported that serum total carotenoid concentrations (measured at the baseline) are protective against declines in muscle strength and physical function in older adults (17–20). Serum concentrations of antioxidants at 1 time point do not capture chronic exposure, and data on dietary intake of carotenoids or other key antioxidants, such as vitamin C and E, are still lacking. Therefore, in this prospective cohort study, we determined whether cumulative intake of antioxidants in the diet across several years can delay age-related loss of physical function in older adults from the Framingham Heart Study Offspring cohort (FHS). We hypothesized that higher intake of vitamin C, vitamin E, and total and individual carotenoids (α -carotene, β -carotene, β -cryptoxanthin, lycopene, and lutein + zeaxanthin) would be associated with reduced loss of grip strength and gait speed over time in adult males and females. We further analyzed data from the Cardiovascular Health Study (CHS) to validate findings in the FHS.

Methods

Study population

Study participants included participants in the FHS. From 1971 to 1975, 5124 male and female study participants were enrolled (age range at enrollment: 5–70 y) and subsequently examined at approximately 4-y intervals to investigate familial risk factors for cardiovascular disease among the adult offspring, and their spouses, of the population-based Framingham Original Cohort (21). The current study included participants with a valid dietary assessment [defined as questionnaires with ≤ 12 food items left blank or energy intakes of ≥ 600 or ≤ 4000 kcal/d

(females) and ≤ 4200 kcal/d (males)] at the index examination (either 1998–2001 or 2005–2008), ≥ 2 prior dietary assessments (either 1995–1998 and 1991–1995 or 1998–2001 and 1995–1998) and ≥ 1 measure of our primary outcomes: either grip strength in 1999–2005, 2005–2008, and 2011–2013 or gait speed in 1999–2005, 2005–2008, and 2011–2013. For the analysis of grip strength, participants were excluded because of missing physical activity, height, vitamin C, vitamin E, and smoking. For the analysis of gait speed, participants were excluded because of missing data for physical activity, height, vitamin C, vitamin E, and smoking.

Validation of findings in the CHS

To validate the results observed in the FHS, we first analyzed data from the CHS. CHS is a population-based longitudinal cohort established in 1989–1990 to study coronary heart disease and stroke in 5201 adults aged ≥ 65 y (22). All participants underwent health evaluations per standardized protocols, and details of the CHS study methodology have been published elsewhere (22). The current study included CHS participants with dietary information available at the baseline examination (1989) and ≥ 2 grip strength or gait speed measurements at baseline and 2 follow-up examinations. We included 3801 and 3770 participants for analyses of grip strength and gait speed, respectively.

This study was approved by the institutional review board (IRB) at Hebrew SeniorLife (IRB protocol number 2014-29) and Boston University, and informed consent was obtained from all participants. All relevant institutional committees on human research approved the CHS study, and all participants gave informed consent.

Antioxidant intake

In the FHS, at the index examination (either 1998–2001 or 2005–2008) and up to 2 prior examinations (either 1995–1998 and 1991–1995 or 1998–2001 and 1995–1998), usual dietary intake was assessed with the semiquantitative, 126-item Willett FFQ (23). The FFQ was mailed to study participants, who were asked to complete the questionnaire based on their food intake over the previous year and to bring it to the exam site, where it was reviewed by clinic staff. Questionnaires with >12 food items left blank or extreme energy intakes were considered invalid and excluded. The Willett FFQ has been validated for several micronutrients, including carotenoids, vitamin C, and vitamin E, against biochemical indicators of nutrient status (24–26). Intake of vitamin C, vitamin E, and individual carotenoids (mg/d) was calculated using the food list section as well as supplemental intakes of these nutrients at each examination. Total carotenoid intake was calculated as the sum of intakes of individual carotenoids (α - and β -carotene, β -cryptoxanthin, lutein + zeaxanthin, and lycopene) at each examination. Not all participants had dietary information available at all 3 examinations. Therefore, each of the antioxidant variables was calculated as an average intake over the index examination and up to 2 prior examinations for each participant to maximize the use of data. For example, average of dietary intake in 1998–2001, 1995–1998, and 1991–1995 was used to predict changes in outcome from 1998–2001 onward. Similarly, average of dietary intake in 2005–2008, 1998–2001, and 1995–1998 was

used to predict changes in outcome from 2005–2008 onward. If intake on ≥ 1 questionnaires was missing, the cumulative average intake was calculated by averaging the intakes at each examination when available.

In the CHS, usual dietary intake was assessed at baseline using a version of the National Cancer Institute FFQ that was administered to 4643 male and female study participants (27, 28). Participants were asked to indicate how often, on average, they had consumed specific foods during the past year as “almost every day or at least 5 times per week,” “about 1 to 4 times per week,” “about 1 to 3 times per month,” “5 to 10 times per year,” or “never.” This self-administered FFQ provided pictures of the foods to simplify identification of the frequency of consumption of each food item to minimize staff time in administering the questionnaire. Nutrient intakes such as dietary vitamin C and β -carotene were estimated from the questionnaire responses. Dietary supplements were not assessed with this questionnaire. The validity of this method was evaluated against 24-h dietary recalls (27, 29). Because of the brief nature of this FFQ, only dietary intakes of vitamin C and β -carotene were available for the validation study.

Annualized change in grip strength

In the FHS, at the baseline (1999–2005) and the 2 follow-up examinations (2005–2008 and 2011–2014), grip strength (kg) was measured using an adjustable isometric hand-held dynamometer. Participants were asked to maximally squeeze the dynamometer for 3 s. Three trials were attempted on each hand for a total of up to 6 trials, and the maximum value among all trials, regardless of side (left or right), was used for the current study (30).

In the CHS, grip strength was measured at every clinic visit starting in 1989, except the first follow-up in 1990–1991. Annualized change in grip strength (kg/y) was calculated by subtracting baseline grip strength from the follow-up grip strength, divided by the follow-up time in years.

Annualized change in gait speed

In the FHS, for gait speed, the faster of 2 consecutive trials on a 4-m course walked at usual pace was recorded in meters per second. At the baseline (1999–2005) examination, gait time was recorded to the nearest second, whereas at the 2 follow-up examinations (2005–2008 and 2011–2014), it was recorded to the nearest hundredth of a second. The faster of the 2 recorded gait speeds was included in the analyses.

In the CHS, gait speed [4.57 m (15 feet), expressed in m/s] was measured at every clinic visit (annually from 1989–1990 to 1998–1999, and in 2005–2006). Annualized change in gait speed (m/s) was calculated by subtracting baseline gait speed from the follow-up gait speed, divided by follow-up time in years.

Other variables

Covariate information was obtained from measures collected closest to the time of the baseline dietary exam and included sex, age, height, energy intake, BMI (kg/m^2), physical activity, current smoking, and multivitamin use. Height without shoes (inches) was measured to the nearest quarter inch with a stadiometer and converted to meters. Weight (pounds), in light clothing, was measured with a standardized balance-beam scale

and converted to kg. BMI was computed using measured height and weight at baseline. Physical activity level was assessed by the PASE (Physical Activity Scale for the Elderly) score, a validated questionnaire of self-reported activity over the past 7 d (31). The smoking status of the participants was assessed via questionnaire as current cigarette smoker (smoked regularly in the past year), former smoker, or never smoker; former and never smokers were combined into the group “noncurrent smokers.” Energy intake (kcal/d) and multivitamin use (yes/no) were calculated from the food list section of the FFQ.

In the CHS, sex, age, height, weight, current smoking, and physical activity (total kilocalories expended in physical activity) were obtained at the baseline. BMI was computed using measured height and weight at baseline. Energy intake was estimated from the FFQ.

Statistics

We conducted separate analyses for the 2 outcome measures of annualized change in grip strength and annualized change in gait speed. A Student 2-sample *t* test was used to estimate differences in means between male and female participants, and a chi-square test was used for categorical variables. These tests were also used to estimate differences between male and female study participants who were excluded due to missing covariates (height, physical activity, vitamin C, vitamin E, or smoking status) compared with those who were retained in the final analytic sample. Pearson's correlation coefficients were calculated for gait speed measured over 3 examinations. Over the follow-up period, the maximum time between outcome measurements was used to calculate each of the changes. The intake of each antioxidant (vitamin C, vitamin E, total carotenoids, and individual carotenoids) was modeled as a continuous variable. To estimate the associations between each antioxidant measure with annualized change in grip strength and gait speed, linear regression models were used to calculate changes in annualized change in grip strength and gait speed associated with a 10-mg higher average intake/d of the antioxidant. β coefficients calculated from these linear regression models should be interpreted as follows: on average, in participants with an annual decline in grip strength or gait speed, a positive β coefficient indicates that increases in the antioxidant are associated with less decline per year. On average, in participants with an annual increase in grip strength or gait speed, a positive β coefficient indicates that increases in the antioxidant are associated with greater increases per year.

Crude models were initially adjusted for age and sex. Final models were further adjusted for baseline grip strength or gait speed, height, BMI, energy (residual method), physical activity, current smoking, and multivitamin use. Each antioxidant (vitamin C, E, and total carotenoids) model included adjustment for the other antioxidants. Each individual carotenoid was adjusted for vitamin C and vitamin E in the same model. To determine whether possible associations of dietary antioxidants and muscle strength and physical function differed by sex and age groups, we tested for interaction of the antioxidants with sex and age. We further tested the interaction between vitamin C and E because these vitamins interact synergistically such that vitamin C can regenerate α -tocopherol and inhibit α -tocopheroxyl radical-mediated propagation (32). Interactions

FIGURE 1 Flow chart showing total number of participants enrolled in the Framingham Offspring Study and the final number of participants included in the analyses.

were considered significant for $P < 0.05$. Subgroup analyses were performed by sex or by age groups (age <60 compared with ≥ 60 y) if interactions were significant.

Validation of findings in the CHS

Analyses in the CHS cohort utilized the same statistical methods used in the FHS. Primary exposures included dietary intake of vitamin C and β -carotene in milligrams per day. Final models were adjusted for age, height, BMI, current smoking, total energy intake, physical activity, and baseline gait speed or grip strength. We tested for interaction between the antioxidants and sex. Interactions were considered significant for $P < 0.05$. Subgroup analysis was performed by sex if interactions were significant. Because all study participants were aged >60 y (mean age: 72 y), we did not conduct analyses stratified by age.

A nominal 2-sided P value of 0.05 was considered statistically significant for all analyses. All analyses were conducted using SAS software version 9.4 (SAS Institute Inc.).

Results

FHS

This study included 2452 and 2422 participants for analyses of grip strength and gait speed, respectively (Figure 1). In total, 196 participants were excluded due to missing covariates ($n = 94$ men and 102 women). Men who were excluded had shorter height (mean $\pm$ SD: 68.1 ± 2.5 inches), lower baseline grip strength (40.7 ± 9.4 kg), and shorter follow-up time for grip strength and gait speed (10.8 ± 2.9 y for both) than those in the study sample (P range: 0.004–0.04). Women excluded due

to missing covariates included significantly higher percentages of current smokers [$n = 24$ (25.3%)], lower baseline gait speed (1.2 ± 0.2 m/s), greater changes in annualized change in gait speed (-0.01 ± 0.03 m/s/y), and shorter follow-up times for grip strength and gait speed (10.5 ± 2.7 y for both) than those in the study sample (P range: <0.0001 – 0.009).

The mean age was 61 ± 9 y in males and in females (range: 33–88 y, Table 1). The median (IQR) intakes of vitamin C, vitamin E, and total carotenoids were 188.5 (121.8–349.1), 20.0 (6.5–159.4), and 14.1 (9.5–19.8) mg/d, respectively, in males and 228.3 (143.8–424.9), 35.7 (9.4–224.8), and 15.9 (11.3–22.4) mg/d, respectively, in females. Eleven percent of males and 59% of females used multivitamin supplements. Over the mean follow-up of ~ 12 y (range: 4.5–15.4 y), the annualized change in grip strength was -0.6 ± 0.8 kg/y in males and -0.3 ± 0.6 kg/y in females, and the annualized change in gait speed was -0.01 ± 0.03 m/s in males and -0.02 ± 0.03 m/s in females.

In males, baseline gait speed was moderately correlated with gait speed at subsequent examinations in 2005–2008 ($r = 0.36$, $P < 0.0001$) and in 2011–2014 ($r = 0.33$, $P < 0.0001$). Gait speed at the 2 subsequent examinations showed stronger correlations ($r = 0.56$, $P < 0.0001$), which could be due to recording of gait speed at baseline to the nearest second compared with to the nearest hundredth of a second at the 2 subsequent examinations. Similarly, in females, baseline gait was correlated with gait speed at subsequent examinations in 2005–2008 ($r = 0.42$, $P < 0.0001$) and in 2011–2014 ($r = 0.36$, $P < 0.0001$), whereas gait speed at the 2 subsequent examinations showed stronger correlations ($r = 0.57$, $P < 0.0001$).

TABLE 1 Characteristics of participants from the Framingham Offspring Study ($n = 2452$)¹

	All ($n = 2452$)	Male ($n = 1103$)	Female ($n = 1349$)	<i>P</i> value
Age, y (range: 33–88 y)	61.0 $\pm$ 9.2	61.1 $\pm$ 9.1	61.0 $\pm$ 9.2	0.81
BMI, kg/m ²	28.2 $\pm$ 5.4	28.9 $\pm$ 4.6	27.6 $\pm$ 5.9	<0.0001
Height, m	1.7 $\pm$ 0.1	1.8 $\pm$ 0.1	1.6 $\pm$ 0.1	<0.0001
Weight, kg	79.4 $\pm$ 17.8	88.8 $\pm$ 15.3	71.9 $\pm$ 15.9	<0.0001
Physical activity index	37.3 $\pm$ 6.2	37.8 $\pm$ 6.9	36.9 $\pm$ 5.5	0.0002
Current smokers, <i>n</i> (%)	261 (10.6)	116 (10.5)	145 (10.8)	0.85
Multivitamin supplement users, <i>n</i> (%)	1234 (53.9)	481 (47.3)	752 (59.3)	<0.0001
Vitamin C, mg/d	209.2 (133.1–394.2)	188.5 (121.8–349.1)	228.3 (143.8–424.9)	<0.0001
Vitamin E, mg/d	27.1 (7.4–199.0)	20.0 (6.5–159.4)	35.7 (9.4–224.8)	<0.0001
Total carotenoids, mg/d	15.3 (10.4–21.3)	14.1 (9.5–19.8)	15.9 (11.3–22.4)	<0.0001
α -carotene, mg/d	0.8 $\pm$ 0.6	0.7 $\pm$ 0.6	0.9 $\pm$ 0.7	<0.0001
β -carotene, mg/d	4.7 $\pm$ 2.8	4.1 $\pm$ 2.3	5.2 $\pm$ 3	<0.0001
Lutein + zeaxanthin, mg/d	3.4 $\pm$ 2.3	3.0 $\pm$ 2.1	3.7 $\pm$ 2.4	<0.0001
Lycopene, mg/d	8.9 $\pm$ 4.9	9.1 $\pm$ 5.2	8.8 $\pm$ 4.6	0.1716
Energy, kcal/d	1869 $\pm$ 537	2005 $\pm$ 568	1754 $\pm$ 475	<0.0001
Protein, g/d	80 $\pm$ 23	82 $\pm$ 24	78 $\pm$ 22	<0.0001
Baseline grip strength, kg	33.1 $\pm$ 12.5	43.4 $\pm$ 9.9	24.6 $\pm$ 6.7	<0.0001
Annualized change in grip strength, kg/y	−0.4 $\pm$ 0.7	−0.6 $\pm$ 0.8	−0.3 $\pm$ 0.6	<0.0001
Mean follow-up time for grip strength (y, range: 4.5–15.4)	11.5 $\pm$ 2.3	11.5 $\pm$ 2.3	11.6 $\pm$ 2.2	0.27
Baseline gait speed	1.3 $\pm$ 0.3	1.3 $\pm$ 0.3	1.3 $\pm$ 0.3	0.79
Annualized change in gait speed ²	−0.02 $\pm$ 0.03	−0.01 $\pm$ 0.03	−0.02 $\pm$ 0.03	0.0042
Mean follow-up time for gait speed (y, range: 4.5–15.4) ²	11.5 $\pm$ 2.3	11.4 $\pm$ 2.3	11.5 $\pm$ 2.2	0.28

¹ Values are presented as means $\pm$ SDs, *n* (%), or medians (IQRs) unless otherwise indicated. Means $\pm$ SDs were compared using Student's 2 sample *t* test.

² For gait speed analyses, $n = 2422$ participants (1095 males and 1327 females).

There were no statistically significant interactions of antioxidants with sex (*P* range: 0.76–0.84 for change in grip strength and 0.74–0.91 for change in gait speed). Although the correlation between vitamins C and E was 0.60 ($P < 0.0001$), there were no statistically significant interactions between vitamins C and E ($P = 0.09$ for change in grip strength and 0.29 for change in gait speed); thus, results of analyses with sexes combined are presented.

Annualized change in grip strength

In crude models, higher intake of vitamin C was associated with a larger change in grip strength per year ($\beta \pm$ SE per 10-mg higher intake/d = 0.0014 $\pm$ 0.0006, $P = 0.02$, [Table 2](#)). However, no statistically significant associations were observed for vitamin E and total carotenoids ($\beta \pm$ SE per 10-mg higher intake/d = −0.0017 $\pm$ 0.0011, $P = 0.10$, and $\beta \pm$ SE per 10-mg higher intake/d = 0.0163 $\pm$ 0.0144, $P = 0.26$, respectively). In subsequent models, adjusted for age and sex, associations for vitamin C remained significant ($\beta \pm$ SE per 10-mg higher intake/d = 0.0011 $\pm$ 0.0006, $P = 0.05$), and associations for total carotenoid intake also became significant ($\beta \pm$ SE per 10-mg higher intake/d = 0.0277 $\pm$ 0.0134, $P = 0.04$) such that higher intake of total carotenoids was associated with a larger change in grip strength per year. In fully adjusted models, only the association of total carotenoid intake remained significant ($\beta \pm$ SE per 10-mg higher intake/d = 0.0316 $\pm$ 0.0146, per 10-mg higher intake/d, $P = 0.03$).

In analyses of individual carotenoids, crude models revealed that only lycopene was associated with larger annualized change in grip strength ($\beta \pm$ SE per 10-mg higher intake/d = 0.1117 $\pm$ 0.0275, $P < 0.01$, [Table 2](#)). In fully

adjusted models, both lutein + zeaxanthin ($\beta \pm$ SE per 10-mg higher intake/d = 0.1223 $\pm$ 0.0603, $P = 0.04$) and lycopene ($\beta \pm$ SE per 10-mg higher intake/d = 0.0873 $\pm$ 0.0284, $P < 0.01$) were statistically significant, whereas β -carotene trended toward significance ($\beta \pm$ SE per 10-mg higher intake/d = 0.0920 $\pm$ 0.0542, $P = 0.09$). The strongest association was observed for lutein + zeaxanthin intake.

Annualized change in gait speed

In crude models, higher intake of total carotenoids was associated with a larger change in gait speed per year ($\beta \pm$ SE per 10-mg higher intake/d = 0.0016 $\pm$ 0.0006, $P < 0.01$, [Table 3](#)). However, no significant associations were observed for vitamin C and E ($P = 0.47$ and 0.95, respectively). In subsequent models, adjusted for age and sex, associations for total carotenoids remained significant ($\beta \pm$ SE per 10-mg higher intake/d = 0.0023 $\pm$ 0.0005, $P < 0.01$), whereas vitamin E became significant ($\beta \pm$ SE per 10-mg higher intake/d = 0.00009 $\pm$ 0.00004, $P = 0.02$) such that higher intake of total carotenoids was associated with a larger change in gait speed per year. In fully adjusted models, both vitamin E and total carotenoids remained significant ($\beta \pm$ SE per 10-mg higher intake/d = 0.00008 $\pm$ 0.00004, $P = 0.04$ and $\beta \pm$ SE per 10-mg higher intake/d = 0.0021 $\pm$ 0.0005, $P < 0.01$, respectively).

In analyses of individual carotenoids ([Table 3](#)), all 4 carotenoids were associated with a larger annualized change in gait speed in crude and fully adjusted models. The largest association was observed for α -carotene intake ($\beta \pm$ SE per 10-mg higher intake/d 0.0187 $\pm$ 0.0081, $P = 0.02$).

TABLE 2 Association of vitamins C and E and total and individual carotenoid intake (for 10-mg higher intake/d) with annualized change in grip strength (kg/y) in 2452 males and females from the Framingham Offspring Study

Antioxidants	Crude model			Age- and sex-adjusted model			Fully adjusted model ¹		
	β^2	SE	P value	β	SE	P value	β	SE	P value
Vitamin C	0.0014	0.0006	0.02	0.0011	0.0006	0.05	0.0008	0.0006	0.21
Vitamin E	-0.0017	0.0011	0.10	0.0003	0.0010	0.79	0.0008	0.0011	0.44
Total carotenoids	0.0163	0.0144	0.26	0.0277	0.0134	0.04	0.0316	0.0146	0.03
α -carotene	-0.1804	0.2157	0.40	0.0981	0.2018	0.63	0.0363	0.2195	0.87
β -carotene	-0.0081	0.0524	0.88	0.0928	0.0492	0.06	0.0920	0.0542	0.09
Lycopene	0.1117	0.0275	<0.01	0.0676	0.0258	<0.01	0.0873	0.0284	<0.01
Lutein + zeaxanthin	0.0731	0.0594	0.22	0.1209	0.0556	0.03	0.1223	0.0603	0.04

¹Linear regression models were adjusted for age, sex, height, BMI, physical activity, energy intake (residual method), current smoking, and multivitamin supplement use and baseline grip strength. Antioxidant groups under study were adjusted for each other in the models; individual carotenoids were adjusted for vitamin C and vitamin E.

² β coefficients were calculated per 10-mg higher intake/d.

Stratified analyses by age in the FHS

For analysis of grip strength, interaction by age was not significant for vitamin C ($P = 0.27$), vitamin E ($P = 0.19$), and total carotenoids ($P = 0.09$). For analysis of gait speed, interaction by age was significant for vitamin E ($P = 0.04$) but not for vitamin C ($P = 0.12$) or total carotenoids ($P = 0.08$). Stratified analyses by age (<60 y compared with ≥ 60 y) showed that the association of vitamin E with annualized change in gait speed seemed to be largely driven by associations in adults aged ≥ 60 y ($\beta \pm$ SE per 10-mg higher intake/d = 0.00001 ± 0.00005 , $P = 0.79$ in those aged less than 60 y and $\beta \pm$ SE per 10-mg higher intake/d = 0.0001 ± 0.00006 , $P = 0.08$ in those aged ≥ 60 y). However, the associations within the subgroups did not reach statistical significance.

Validation of findings in CHS

The mean age of males and females was 73 ± 5.5 y and 72 ± 5.1 y, respectively (range: 65–95 y). Mean $\pm$ SD intake for dietary vitamin C (mg/d) was 185.0 ± 87 (males) and 210 ± 94 (females). Mean $\pm$ SD for dietary β -carotene (mg/d) was 5.2 ± 3.4 (males) and 5.8 ± 3.5 (females). Mean $\pm$ SD of baseline grip strength (kg) was 40.2 ± 8.8 (males) and 24.0 ± 6.0 (females), and mean $\pm$ SD of baseline gait speed was 0.9 m/s (0.2 for both males and females). Over the mean follow-up of ~ 7.2 y (range:

1.9–9.8 y), annualized change in grip strength in kg/y was -0.9 ± 1.5 in males and -0.4 ± 1.0 in females. Over the mean follow-up of ~ 5.5 y (range: 0.9–7.8 y), annualized change in gait speed in m/s was -0.02 ± 0.09 in males and -0.01 ± 0.08 in females.

No significant associations were observed for β -carotene intake and change in grip strength or gait speed (Table 4). There was no statistically significant interaction of β -carotene with sex (P range: 0.45 for change in grip strength and $P = 0.06$ for change in gait speed). Higher dietary intake of vitamin C was associated with greater loss of grip strength ($\beta \pm$ SE per 10-mg higher intake/d = -0.00530 ± 0.00247 , $P = 0.03$) but trended to be associated with reduced loss of gait speed ($\beta \pm$ SE per 10-mg higher intake/d = 0.00033 ± 0.00017 , $P = 0.06$). There was a significant interaction between vitamin C and sex in the analyses of grip strength ($P = 0.04$), but not in the analyses of gait speed ($P = 0.67$). Upon stratification, higher dietary vitamin C was associated with greater loss of grip strength in males ($\beta \pm$ SE per 10-mg higher intake/d = -0.01270 ± 0.00498 , $P = 0.01$), but not in females.

Discussion

In this community-based cohort of adults from the FHS, higher intakes of total carotenoids, lycopene, and lutein + zeaxanthin were associated with increase in grip strength. Higher intake

TABLE 3 Association of vitamins C and E and total and individual carotenoid intake (for 10-mg higher intake/d) with annualized change in gait speed (m/s per year) in 2422 males and females from the Framingham Offspring Study

Antioxidant intake (mg/d)	Crude model			Age- and sex-adjusted model			Fully-adjusted model ¹		
	β^2	SE	P value		SE	P value	β	SE	P value
Vitamin C	0.00002	0.00002	0.47	0.000009	0.00002	0.97	-0.00001	0.00002	0.56
Vitamin E	0.000003	0.00004	0.95	0.00009	0.00004	0.02	0.00008	0.00004	0.04
Total carotenoids	0.0016	0.0006	<0.01	0.0023	0.0005	<0.01	0.0021	0.0005	<0.01
α -carotene	0.0162	0.0084	0.05	0.0273	0.0077	<0.01	0.0187	0.0081	0.02
β -carotene	0.0048	0.0020	0.02	0.0091	0.0019	<0.01	0.0080	0.0020	<0.01
Lycopene	0.0063	0.0011	<0.01	0.0043	0.0010	<0.01	0.0043	0.0010	<0.01
Lutein + zeaxanthin	0.0073	0.0023	<0.01	0.0095	0.0021	<0.01	0.0084	0.0023	<0.01

¹Linear regression models were adjusted for age, sex, height, BMI, physical activity, energy intake (residual method), current smoking, and multivitamin supplement use and baseline grip strength. Antioxidant groups under study were adjusted for each other in the models; individual carotenoids were adjusted for vitamin C and vitamin E.

² β coefficients were calculated per 10-mg higher intake/d.

TABLE 4 Association of vitamin C and β -carotene intake (for 10-mg higher intake/d) with annualized change in grip strength (kg/y) and gait speed (m/s/y) in sex-combined and sex-stratified analyses in males and female participants from the CHS

Sensitivity analyses	Grip strength				Gait speed			
	<i>n</i>	$\beta^{1,2}$	SE	<i>P</i> value	<i>n</i>	β	SE	<i>P</i> value
Total vitamin C	3801	−0.00530	0.00247	0.03	3770	0.00033	0.00017	0.06
Total β -carotene	3801	0.00006	0.00007	0.33	3770	−0.00001	0.00001	0.59

¹ β coefficients were calculated per 10-mg higher intake/d.

²Linear regression models were adjusted for sex, age, height, BMI, smoking, total energy intake, physical activity.

of all antioxidants except for vitamin C was associated with increased gait speed for each antioxidant. The high amounts of total carotenoid intake in the current study (~20–22 mg/d) can be obtained by consuming 3–4 medium carrots, which will provide ~22–29 mg/d of total carotenoids.

In a cross-sectional study of 986 older Italians from the Invecchiare in Chianti (InCHIANTI) study, plasma concentrations of α - and γ -tocopherol and dietary vitamin C and β -carotene were associated with higher physical performance and knee strength. Similarly, among 669 older females from the WHAS (Women's Health and Aging Studies) I and II, low concentrations of total serum carotenoids were associated with poor grip, hip, and knee strength, whereas α -tocopherol was associated with lower grip and knee strength (15). Prospective cohort studies from the InCHIANTI study have reported that participants in the lowest quartile of total plasma carotenoids at baseline were at higher risk of developing poor hip, knee, or grip strength over 6 y compared with those in the highest quartile (19). Further, higher total plasma carotenoids were associated with a lower risk of developing severe walking disability and slowing of 4-m walking speed over 6 y (18).

Although these studies build a strong case for carotenoids, they only examined baseline serum concentrations of carotenoids. Serum antioxidant concentrations vary over time and use of a single measurement does not capture chronic exposure to nutrients. Intakes of vitamin C and carotenoids are prone to seasonal variation (33), and interpretation of plasma α -tocopherol is confounded by blood lipid concentrations (34). Additionally, studies of individual carotenoids are lacking.

Overall, the results for total carotenoids from the current study are consistent with those of the previous InCHIANTI studies. However, our study extends these previous findings by further reporting on individual carotenoids, with the strongest associations for lycopene, lutein + zeaxanthin (grip strength), and α -carotene (gait speed). Although vitamin E was protective against loss of gait speed but not grip strength, the association with gait speed was weak. Vitamin C was not associated with grip strength or gait speed, which was inconsistent with previous findings from the InCHIANTI study. Compared with the InCHIANTI study, vitamin C intakes in this study were more than double in males and more than triple in females. Further, the mean intakes of vitamin C and E in this study were higher than the recommended dietary allowance of these nutrients (35), which could explain the weak associations for these nutrients at such high intakes.

Unexpectedly, the results from the validation study in CHS did not yield the same results as in the FHS. In the CHS, higher dietary vitamin C trended to be associated with reduced loss of

gait speed. Sex modified the association of dietary vitamin C and grip strength. Higher dietary vitamin C was associated with greater loss of grip strength in males, but not in females. β -carotene intake was not related to either of the outcome variables. Use of different diet questionnaires and differences in age and follow-up times across the 2 cohorts could have contributed to these discrepant findings. Further, the CHS questionnaire only assessed dietary intake and not supplements. The FFQ used in the FHS has demonstrated Pearson's correlations of vitamin C and individual carotenoids with 24-h dietary recalls (*r* range: 0.11–0.28), with 7-d diet records (*r* range: 0.23–0.57) (36), and with strong correlations with circulating concentrations of biomarkers of vitamin C and E (24, 34, 37, 38). The FFQ used in the CHS has demonstrated Pearson's correlations for β -carotene and vitamin C with 6 monthly 24-h dietary recalls in a subset of participants (range: 0.24–0.51) (27), but similar validation against circulating concentrations of antioxidants is unavailable. Finally, the shorter time interval between repeated measures of grip strength and gait speed in CHS may have affected the precision of the estimate of change per year.

Although a few studies have examined associations of serum concentrations with muscle strength and physical function, a focus on dietary intakes may provide more information. A recent epidemiological study shows that a higher intake of fruits and vegetables (major sources of carotenoids) is associated with a lower risk of disability (39). Further, several studies have linked adherence to a Mediterranean diet (rich in fruits and vegetables) with faster walking speed (40, 41) and slower decline of mobility (42) over time, suggesting a long-term effect of diet on physical function.

Antioxidants inhibit or delay oxidative stress, a mechanism that is central to age-related loss of muscle and physical function. Previous studies suggest that older adults with low serum/plasma carotenoid concentrations are at a higher risk of developing elevations in IL-6 over time (43, 44). These higher concentrations of IL-6 and C-reactive protein (CRP) have been shown to increase the risk of muscle strength loss. Similarly, serum protein carbonyls, markers of oxidative protein damage caused by oxidative stress may be an independent predictor of low grip strength (12), decrease in walking speed, and progression to severe walking disability among older females (45). Lutein has been associated with higher physical activity (46) and lower sedentary time. Although the mechanisms for these associations are unclear, it has been proposed that lutein can cross the blood–brain barrier and may influence brain centers that regulate physical activity (47, 48).

This study included large numbers of male and female participants from 2 community-based cohorts. FHS included a

wide age range across the spectrum of adulthood. The prospective cohort designs in FHS and CHS established a temporal relation between antioxidant intake and changes in grip strength and gait speed. Both the cohorts are well characterized, enabling us to account for several potential confounding variables. However, this study has some limitations. FFQs used in both cohorts are prone to measurement errors due to recall bias. FFQs do not measure absolute intakes but can effectively rank individuals' dietary intakes when used in large epidemiologic studies (23, 24, 34, 37, 38). Our findings could be influenced by other factors, such as sedentariness, a separate construct impacting muscle mass and function, changes in diet over follow-up, overall healthier dietary pattern, and competing risk of mortality. Attrition in cohort studies with long-term follow-up is inevitable and can introduce bias. Finally, the FHS is composed of participants of European ancestry, thus limiting generalizability to other races and ethnic groups. However, CHS is more racially diverse.

In conclusion, intake of total carotenoid, lycopene, and lutein + zeaxanthin was associated with reduced loss of grip strength over time after taking into account intake of vitamin C and E in this cohort of adult males and females. Higher intake of all antioxidants except for vitamin C was associated with increased gait speed. The effect of carotenoids seems to be modest; however, over many years these small differences can be clinically meaningful. With expected misclassification of carotenoids, the association could be substantially stronger. It is possible that unmeasured factors related to carotenoid intake may delay the loss of grip strength or gait speed with age. However, we were unable to replicate these findings in the CHS, our validation cohort. Overall, these findings highlight the protective effect of dietary antioxidants in attenuating loss of muscle and physical function in older adults, important aspects of health with aging. These findings highlight the need for a study to replicate these findings before undertaking a randomized control trial of dietary antioxidants and their effect on muscle strength and physical function.

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