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## Original Contribution

# Antioxidant Vitamin Intake and Mortality

## The Leisure World Cohort Study

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To assess the relationship between antioxidant vitamin intake and all-cause mortality in older adults, we examined these associations using data from the Leisure World Cohort Study, a prospective study of residents of the Leisure World retirement community in Laguna Hills, California. In the early 1980s, participants (who were aged 44–101 years) completed a postal survey, which included details on use of vitamin supplements and dietary intake of foods containing vitamins A and C. Age-adjusted and multivariate-adjusted (for factors related to mortality in this cohort—smoking, alcohol intake, caffeine consumption, exercise, body mass index, and histories of hypertension, angina, heart attack, stroke, diabetes, rheumatoid arthritis, and cancer) hazard ratios for death were calculated using Cox regression for 8,640 women and 4,983 men (median age at entry, 74 years). During follow-up (1981–2013), 13,104 participants died (median age at death, 88 years). Neither dietary nor supplemental intake of vitamin A or vitamin C nor supplemental intake of vitamin E was significantly associated with mortality after multivariate adjustment. A compendium that summarizes previous findings of cohort studies evaluating vitamin intake and mortality is provided. Attenuation in the observed associations between mortality and antioxidant vitamin use after adjustment for confounders in our study and in previous studies suggests that such consumption identifies persons with other mortality-associated lifestyle and health risk factors.

adults; aging; antioxidants; cohort studies; longevity; mortality; risk factors; vitamins

Abbreviations: CI, confidence interval; IU, international units; RAE, retinol activity equivalents; RR, risk ratio.

Oxidative stress has been suggested to increase the incidence of chronic disease and mortality. The oxidative-modification hypothesis regarding atherosclerosis suggests that antioxidants may inhibit the oxidation of low-density lipoprotein cholesterol, hindering its ability to clog the coronary arteries and preventing cardiovascular disease (1, 2). Increasing evidence suggests that oxidative stress is also involved in cerebral aging, cognitive impairment, and dementia (3, 4). In addition, antioxidants may prevent cancer by inhibiting the formation of carcinogenic nitrosamines, protecting DNA from oxidative damage, and enhancing immune function (5). Thus, dietary and supplemental intake of antioxidant vitamins may help reduce the incidence of cardiovascular disease, cancer, and dementia and thereby reduce mortality.

However, few studies have examined the possible protective association for dietary and supplemental intake of vitamins A, C, and E together in the same population group.

In 1981, we undertook a prospective cohort study of nearly 14,000 elderly men and women with the aim of studying factors, especially modifiable lifestyle practices, associated with longevity and successful aging. We report here the associations between antioxidant vitamin intake (dietary and supplemental) and all-cause mortality after 32 years of follow-up.

### METHODS

The Leisure World Cohort Study was established in the early 1980s, when 13,978 (8,877 female and 5,101 male)

residents of a California retirement community (Leisure World Laguna Hills) aged 44–101 years completed a postal health survey. The Leisure World population and the cohort are predominantly Caucasian, well-educated, and upper middle-class. The baseline health survey asked for information about demographic factors (birth date, sex, marital status, number of children, height, weight); medical history (high blood pressure, angina, heart attack, stroke, diabetes, rheumatoid arthritis, fractures after age 40 years, cancer, gallbladder surgery, glaucoma, cataract surgery); medication use (hypertensive medication, digitalis, nonprescription pain medication); personal habits (cigarette smoking, exercise, alcohol drinking); beverage intake (coffee, tea, milk, carbonated soda); use of vitamin supplements; and usual frequencies of consumption of foods that are common sources of dietary vitamins A and C.

### Estimation of vitamin intake

Information on the brand, formulation, and intake frequency of any vitamin supplements containing vitamin A, C, or E was obtained. Participants were asked, “Are you **currently** taking any vitamin supplements (include cod liver oil)?” and “You will need to get the vitamin bottle(s) or container(s) to complete the next group of questions. *First*, please list the brand name of each vitamin you are currently taking and indicate the number of times per week you take this vitamin. *Second*, please check the ingredient section of the label of each type of vitamin. We would like to know the vitamin A, vitamin C, and vitamin E content of each type of vitamin. For vitamin A, this is probably listed in International Units (IU), for vitamin C in milligrams (mg), and for vitamin E in milligrams (mg) or International Units (IU).” From this information we calculated the daily dosage of each of these vitamins. This information on vitamin supplement use was also obtained on a follow-up questionnaire administered in 1985.

The food frequency portion of the questionnaire, designed to estimate intakes of vitamins A and C, asked about the participant’s usual consumption of 56 foods or food groups (6, 7) within the last 12 months. Frequency of consumption was a multiple-choice item with the following choices: rarely or never, a few times per year, about monthly, a few times per month, a few times per week, and daily or almost daily. These responses were converted to 0, 0.01, 0.03, 0.10, 0.50, and 1.0 times per day, respectively. Seasonal use was taken into account based on the number of months in which fresh fruits and vegetables were available in the marketplace. For example, for a vegetable that is in season 6 months a year and is consumed a few times per week when in season, intake data were converted to a frequency of 0.25 times daily. On the basis of the US Department of Agriculture tables of food values (1976–1984) for the standard portion size of each item (8), we estimated average daily dietary intakes of vitamins A and C by summing the products of the nutrient content of each food item and the frequency with which it was eaten.

Dietary and supplemental intakes were summed to obtain total intakes of vitamins A and C. Vitamin A from diet and supplements included  $\beta$ -carotene. Participants were classified into thirds based on tertile values for dietary and total vitamin intakes for men and women in the total cohort.

### Determination of outcome

The vital status of cohort members was determined through periodic contact and resurvey, searches of death indexes, and death certificates. Participants were followed until death or December 31, 2013, whichever came first. To date, 35 cohort members have been lost to follow-up. Previous reports present details of data collection (7, 9–11).

### Statistical analysis

Hazard ratios for the association between vitamin intake and mortality were calculated separately for men and women, using Cox regression analysis (12) with age as the time scale. Participants contributed person-years from their age at the baseline survey (delayed entry) to their age at death or December 31, 2013, whichever occurred first. To control for potential confounders, we performed analysis adjusting for factors previously found to be related to mortality in this cohort: smoking (never, past, or current smoking), alcohol intake (0,  $\leq 1$ , 2–3, or  $\geq 4$  drinks/day), caffeine intake ( $< 50$ , 50–99, 100–199, 200–399, or  $\geq 400$  mg/day), exercise (0,  $\frac{1}{4}$ ,  $\frac{1}{2}$ ,  $\frac{3}{4}$ – $1\frac{3}{4}$ , or  $\geq 2$  hours/day), body mass index (weight (kg)/height (m)<sup>2</sup>; underweight, normal-weight, overweight, or obese), and histories of hypertension, angina, heart attack, stroke, diabetes,

**Table 1.** Baseline Characteristics of Participants in the Leisure World Cohort Study, 1981–2013

Characteristic	Men (n = 4,983)		Women (n = 8,640)	
	Mean (SD)	%	Mean (SD)	%
Age at baseline, years	74.3 (7.1)		73.2 (7.4)	
Age at last follow-up, years	86.0 (7.1)		88.4 (7.3)	
Duration of follow-up, years	11.7 (7.6)		15.2 (8.1)	
Body mass index <sup>a</sup>	24.2 (2.9)		23.1 (3.5)	
Exercise, hours/day	1.1 (1.3)		0.9 (1.1)	
Alcohol, drinks/day	1.6 (1.5)		1.2 (1.2)	
Caffeine, mg/day	176 (172)		168 (166)	
Vitamin supplement use <sup>b</sup>		61		68
History of disease				
High blood pressure		36		41
Angina		15		9.4
Heart attack		17		6.6
Stroke		7.1		3.7
Cancer		9.4		13
Diabetes		8.3		5.0
Rheumatoid arthritis		4.4		6.8
Cigarette smoking				
Never smoker		33		55
Past smoker		58		33
Current smoker		9		12
Alive on December 31, 2013		2.1		4.8

Abbreviation: SD, standard deviation.

<sup>a</sup> Weight (kg)/height (m)<sup>2</sup>.

<sup>b</sup> Use of any vitamin supplement.

**Table 2.** Hazard Ratio for Death According to Vitamin Intake Among Men, Leisure World Cohort Study, 1981–2013

Vitamin Intake	No. of Subjects	No. of Deaths	Model 1 <sup>a</sup>		Model 2 <sup>b</sup>	
			HR	95% CI	HR	95% CI
Tertile of dietary vitamin A						
Low (<6,667 IU/day)	1,762	1,719	1.00	Referent	1.00	Referent
Medium	1,614	1,593	0.94	0.87, 1.00	1.00	0.93, 1.07
High (≥15,333 IU/day)	1,607	1,566	0.93	0.87, 1.00	1.00	0.93, 1.07
Tertile of dietary vitamin C						
Low (<145 mg/day)	1,947	1,901	1.00	Referent	1.00	Referent
Medium	1,716	1,680	1.00	0.94, 1.07	1.05	0.98, 1.12
High (≥210 mg/day)	1,320	1,297	1.00	0.94, 1.08	1.05	0.98, 1.13
Supplemental vitamin A						
No	2,907	2,845	1.00	Referent	1.00	Referent
Yes	2,076	2,033	0.95	0.89, 1.00	0.96	0.91, 1.02
Supplemental vitamin C						
No	2,109	2,064	1.00	Referent	1.00	Referent
Yes	2,874	2,814	0.96	0.90, 1.01	0.98	0.92, 1.04
Supplemental vitamin E						
No	2,533	2,479	1.00	Referent	1.00	Referent
Yes	2,450	2,399	0.96	0.91, 1.02	0.98	0.92, 1.04
Tertile of total vitamin A						
Low	1,792	1,747	1.00	Referent	1.00	Referent
Medium	1,630	1,604	0.98	0.91, 1.04	1.03	0.96, 1.10
High	1,561	1,527	0.94	0.88, 1.01	1.00	0.93, 1.08
Tertile of total vitamin C						
Low	1,920	1,879	1.00	Referent	1.00	Referent
Medium	1,598	1,564	0.98	0.92, 1.05	1.02	0.95, 1.09
High	1,465	1,435	0.96	0.90, 1.03	1.00	0.93, 1.07

Abbreviations: CI, confidence interval; HR, hazard ratio.

<sup>a</sup> Results were adjusted for age.

<sup>b</sup> Results were adjusted for age, smoking, body mass index, exercise, alcohol intake, caffeine consumption, and histories of hypertension, angina, heart attack, stroke, diabetes, rheumatoid arthritis, and cancer.

rheumatoid arthritis, and cancer. To account for the possibility that recent disease development may have altered intakes of the vitamins under study as well as be related to mortality, we repeated the analyses after excluding the first 5 years of follow-up. We also repeated the analysis using only the first 15 years of follow-up. Additionally, we compared hazard ratios for persistent supplement users (users at both baseline and follow-up) with hazard ratios for persons who did not report supplement use at either baseline or follow-up. Statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina). All tests were 2-sided, and no adjustment of the *P* values was made for multiple comparisons.

This study was approved by the institutional review boards of the University of Southern California (Los Angeles, California) and the University of California, Irvine (Irvine, California).

### Compendium of previous studies

For comparison purposes, we compiled a compendium of previous prospective cohort studies that evaluated vitamin

intake and mortality. A search of the literature (PubMed) was supplemented by review of references in identified papers. Details on numbers of subjects and deaths, ages of participants, study dates, vitamins studied, risk estimates and 95% confidence intervals, and adjustment variables were abstracted. Results are presented in Web Table 1 (available at <http://aje.oxfordjournals.org/>).

### RESULTS

After exclusion of 237 women and 118 men with missing information on the variables of interest or potentially confounding variables, data on 13,623 participants (8,640 women and 4,983 men) were analyzed. At study entry, the participants ranged in age from 44 years to 101 years (median age, 74 years). By December 31, 2013, a total of 13,104 participants (96%) had died at ages 59–110 years (median age at death, 88 years).

Table 1 presents selected characteristics of the participants by sex. Men were, on average, older than women at study entry (74 years vs. 73 years), and a greater proportion had

**Table 3.** Hazard Ratio for Death According to Vitamin Intake Among Women, Leisure World Cohort Study, 1981–2013

Vitamin Intake	No. of Subjects	No. of Deaths	Model 1 <sup>a</sup>		Model 2 <sup>b</sup>	
			HR	95% CI	HR	95% CI
Tertile of dietary vitamin A						
Low (<8,000 IU/day)	2,852	2,718	1.00	Referent	1.00	Referent
Medium	2,906	2,761	0.92	0.87, 0.97	0.97	0.92, 1.03
High (≥16,333 IU/day)	2,882	2,747	0.91	0.86, 0.96	0.99	0.93, 1.04
Tertile of dietary vitamin C						
Low (<155 mg/day)	2,773	2,637	1.00	Referent	1.00	Referent
Medium	2,956	2,818	0.92	0.87, 0.97	0.96	0.91, 1.01
High (≥225 mg/day)	2,911	2,771	0.90	0.85, 0.95	0.97	0.92, 1.02
Supplemental vitamin A						
No	4,663	4,465	1.00	Referent	1.00	Referent
Yes	3,977	3,761	0.96	0.92, 1.01	0.97	0.93, 1.02
Supplemental vitamin C						
No	3,085	2,952	1.00	Referent	1.00	Referent
Yes	5,555	5,274	0.96	0.92, 1.01	0.98	0.93, 1.02
Supplemental vitamin E						
No	3,944	3,783	1.00	Referent	1.00	Referent
Yes	4,696	4,443	0.97	0.92, 1.01	0.99	0.94, 1.03
Tertile of total vitamin A						
Low	2,864	2,738	1.00	Referent	1.00	Referent
Medium	2,869	2,717	0.93	0.88, 0.99	0.99	0.94, 1.04
High	2,907	2,771	0.89	0.85, 0.94	0.96	0.91, 1.01
Tertile of total vitamin C						
Low	2,670	2,545	1.00	Referent	1.00	Referent
Medium	3,020	2,888	0.95	0.90, 1.01	0.98	0.93, 1.04
High	2,950	2,793	0.96	0.91, 1.02	1.01	0.95, 1.06

Abbreviations: CI, confidence interval; HR, hazard ratio.

<sup>a</sup> Results were adjusted for age.

<sup>b</sup> Results were adjusted for age, smoking, body mass index, exercise, alcohol intake, caffeine consumption, and histories of hypertension, angina, heart attack, stroke, diabetes, rheumatoid arthritis, and cancer.

died by the end of follow-up (98% vs. 95%). Men also had, on average, a greater body mass index, exercised more, and consumed more alcohol and caffeine than women, but smaller proportions currently smoked and took vitamin supplements. Sixty-six percent of participants took vitamin supplements at baseline: 44% took vitamin A, 62% took vitamin C, and 52% took vitamin E.

Hazard ratios for mortality according to vitamin intake are shown in Table 2 for men and in Table 3 for women. Medium and high intakes of dietary vitamins A and C and total vitamin A in women were significantly associated with decreased mortality. However, the mortality reductions were attenuated and no longer significant after adjustment for potential confounders, although the confounding factors remained significantly related to mortality. Similar results were found in the analysis of men and women combined using sex-specific cut-points for the vitamins.

The hazard ratios for vitamin intake changed little within smoking or body mass index categories. For total vitamin C

intake among men, hazard ratios for smoking categories were 1.00 (reference) for low intake/never smoker, 0.98 for medium intake/never smoker, 1.01 for high intake/never smoker, 1.21 for low intake/past smoker, 1.20 for medium intake/past smoker, 1.20 for high intake/past smoker, 1.96 for low intake/current smoker, 2.20 for medium intake/current smoker, and 1.90 for high intake/current smoker. The same pattern was observed for total vitamin A in men and total vitamins C and A in women. Likewise, within body mass index categories, the hazard ratios for vitamin intake were similar.

Exclusion of the first 5 years of follow-up (including 852 deaths in men and 1,007 deaths in women) did not substantially change the findings. Neither did limiting the analysis to the first 15 years of follow-up. Additionally, risk of death was not different in persistent supplement users (those who reported taking supplements at both baseline and the 1985 follow-up) and persons who did not take supplements at either baseline or follow-up.

## DISCUSSION

In this study, we found that the modestly decreased risks of death associated with antioxidant intake (dietary and supplemental) were attenuated and no longer significant after adjustment for potential confounders. Vitamin consumption might be indicative of groups of people with different lifestyles and different disease states that are also related to mortality. Although differences between users and nonusers of vitamin supplements in this study were not great, vitamin supplement users had lower (though not statistically significant) prevalences of several diseases, especially high blood pressure, heart attack, stroke, and diabetes. Still, some persons may have taken supplements because of their underlying diseases. However, we found that exclusion of the first 5 years of follow-up did not appreciably change the vitamin-mortality associations. The associations found after adjustment for lifestyle factors and disease status are more accurate from the perspective of a causal relationship.

Another explanation for the lack of association between vitamin intake and mortality may be that our cohort members were well fed. The median intake of vitamin A from food sources was 17,206 IU. More than 95% of participants received the 1980 Recommended Dietary Allowance specified by the National Research Council (13) for vitamin A (5,000 IU for males; 4,000 IU for females) from food sources alone. Therefore, most cohort members, even in the lowest third, did not have a low absolute nutrient intake. Dietary vitamin intake was generally more than adequate to meet participants' minimum dietary requirements, but it provided the opportunity to examine the impact of high levels of nutrients. Nonetheless, we cannot rule out the possibility of an association with high vitamin intake as compared with low absolute intake.

### Previous studies of vitamins and mortality

As shown in Web Table 1, some large, prospective cohort studies have found significantly lower mortality with vitamin intake (supplemental C (14), supplemental E (14), supplemental E/C (15), supplemental A, C, or E in women (16), supplemental antioxidants (17), dietary C (18, 19), dietary A or  $\beta$ -carotene (18, 19), and total C (20)). However, most studies have not (supplemental A or  $\beta$ -carotene (21–23), supplemental C (21–24), supplemental E (21–27), multivitamins or multivitamins/minerals (14, 15–17, 22, 24, 25, 28–30), regular supplement use (31), dietary vitamin A or  $\beta$ -carotene (20, 23, 32, 33), dietary C (23, 32, 33), dietary E (19, 23, 32, 33), total C (34), and total E (20)). Many of these studies, which were carried out in diverse populations (United States, United Kingdom, Europe, Sweden, Japan), in both men and women, and in both younger and older adults, included adjustment for various potential confounders. Generally such adjustment attenuated the risks of all-cause mortality observed with only age and sex adjustment. These studies and ours suggest that confounders or chance might account for the positive associations between vitamin intake and decreased mortality observed in some previous prospective studies.

Although many cohort studies did not find a reduced risk of death in vitamin supplement users, the continued use of

vitamin supplements by a large proportion of the population and the presumed safety of antioxidant supplementation prompted the study of antioxidant vitamins in randomized clinical trials. Generally, these studies too have shown no beneficial association of vitamins with mortality at various doses (35–38). Several recent meta-analyses of these randomized trials even suggested a small but significant increase in mortality with antioxidant vitamins in general (risk ratio (RR) = 1.03, 95% confidence interval (CI): 1.01, 1.05 (38)) and specifically with  $\beta$ -carotene (RR = 1.07, 95% CI: 1.04, 1.11 (35) and RR = 1.05, 95% CI: 1.01, 1.09 (38)) and vitamin E (RR = 1.04, 95% CI: 1.00, 1.05 (38) and RR = 1.04, 95% CI: 1.01, 1.07 (36)).

### Strengths and limitations

Our data on vitamin intake were self-reported using a mailed questionnaire. Conclusions regarding dietary vitamin intakes are limited by the crudeness with which intake was estimated—self-reported frequencies of consumption of selected food items which were translated into nutrient intakes by reference to US Department of Agriculture food consumption tables. Difficulties with these methods have been enumerated (39, 40). Although assessing the true level of intake is difficult, self-reported consumption is suitable for ranking of individuals.

To validate the information on vitamin supplement use in this study, we previously compared data collected on our mail questionnaire with data collected by personal interview 15 months later (6). Current supplement use as ascertained by the 2 methods was comparable, with 84% agreement. However, changes over time in vitamin intake may have affected our outcomes. Previous analyses in our cohort compared use of vitamin A supplements 2 and 4 years after baseline with baseline use (41). When vitamin A supplement use was divided into 3 groups (none, low, and high), the agreement between baseline and the 2 later time periods was 72% and 63%, respectively, with  $\kappa$  statistics of 0.53 and 0.38, indicating moderate-to-good agreement. Similar comparisons for dietary  $\beta$ -carotene consumption divided into thirds (low, medium, high) yielded lower  $\kappa$  statistics (0.25 and 0.27). Disagreement between the questionnaires represents a combination of real changes in vitamin use and dietary habits, lack of precision in the questions, and nonreliability of the responses to specific questions. Although self-reported supplement use was somewhat consistent over time, our data demonstrate that misclassification in food frequency questionnaires represents a substantial problem in trying to detect small differences in risk due to nutrient intake.

Vitamin A comprises a group of fat-soluble compounds that includes preformed vitamin A (retinol and retinyl esters) and provitamin A carotenoids (including  $\beta$ -carotene) (42). Preformed vitamin A is found in foods from animal sources (including dairy products, liver, and fish) and from fortified cereals. Provitamin A comes from plants, especially leafy green and orange/yellow vegetables and fruits. To account for the different bioactivities of retinol and provitamin A carotenoids, amounts of vitamin A are expressed in micrograms of retinol activity equivalents (RAE). Because the body converts all dietary sources of vitamin A into retinol, 1  $\mu$ g of

physiologically available retinol is equivalent to 1 µg of retinol, 12 µg of β-carotene, and 24 µg of α-carotene or β-cryptoxanthin. From supplements, the body converts 2 µg of β-carotene to 1 µg of retinol. Our study collected vitamin A data in the form of IU, the standard measure in the 1980s. Today vitamin A is still listed in IU on food and supplement labels, even though nutrition scientists prefer RAE. Rates for conversion between µg RAE and IU are: 1 IU retinol = 0.3 µg RAE, 1 IU β-carotene from supplements = 0.15 µg RAE, 1 IU β-carotene from food = 0.05 µg RAE, and 1 IU α-carotene or β-cryptoxanthin = 0.025 µg RAE.

Another limitation was our lack of dietary vitamin E data. Vitamin E comprises a group of fat-soluble compounds that include both tocopherols and tocotrienols (43). Numerous foods provide vitamin E. Nuts, seeds, and vegetable oils are the best sources of α-tocopherol, and significant amounts are available in green leafy vegetables and fortified cereals. Most vitamin E in the US diet is in the form of γ-tocopherol from soybean oil, canola oil, corn oil, and other vegetable oils. We did not ask about intake of most of these foods on our questionnaire.

We were also unable to adjust our findings for energy or fat intake, because we had collected dietary information related only to vitamins A and C. Researchers in some previous studies adjusted for energy or fat intake in their vitamin analysis (14, 17–19, 22, 25, 29, 30, 32–34). Energy adjustment, in general, reduces measurement error for all nutrients in food frequency questionnaire data (44).

We analyzed men and women separately. We did this for comparison with other studies reporting sex-specific results, because of differences between men and women in baseline characteristics and mortality rates, and due to the possibility of differential accuracy of self-reported dietary information between men and women (44). Men tend to underreport their dietary intake when it is ascertained through a food frequency questionnaire (45). Women might recall dietary habits better, on average, than men, given their traditional role in buying food and preparing meals. With our inability to adjust for energy intake, this appeared to be particularly important. Additionally, men might have undergone greater dietary changes following retirement in comparison with women, and thus we were unable to capture “true” long-term exposure status in men (46).

Our study had the advantages of a prospective design, a large size, long and essentially complete follow-up, detailed dosage information on both dietary and supplemental intakes of vitamins A, C, and E, and the capability to control for numerous potentially confounding factors. Still, our investigation is an observational study, not a randomized trial. It does, however, suggest that confounders might account for the positive associations between vitamin intake and lower risk of death in some previous prospective studies. In the general population, health-promoting habits often cluster, resulting in 2 extreme groups: the health-conscious, who have multiple health-promoting habits, and those with no such habits. For example, persons taking vitamin supplements may differ from nonusers in terms of their smoking, exercise habits, and medical history, as well as in unmeasured ways that influence longevity, leading to apparently inverse associations with total mortality rate.

## Conclusions

Results observed in this large cohort study with long follow-up are not consistent with any substantial relationship between antioxidant vitamin intake (supplemental, dietary, or total) and mortality. Based on existing evidence, we see no justification for the general and widespread intake of supplemental vitamins A, C, and E to increase longevity among persons with a nutritionally adequate diet.

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## REFERENCES

1. Diaz MN, Frei B, Vita JA, et al. Antioxidants and atherosclerotic heart disease. *N Engl J Med*. 1997;337(6):408–416.
2. Steinberg D, Witztum JL. Is the oxidative modification hypothesis relevant to human atherosclerosis? Do the antioxidant trials conducted to date refute the hypothesis? *Circulation*. 2002;105(17):2107–2111.
3. Deschamps V, Barberger-Gateau P, Peuchant E, et al. Nutritional factors in cerebral aging and dementia: epidemiological arguments for a role of oxidative stress. *Neuroepidemiology*. 2001;20(1):7–15.
4. Berr C. Cognitive impairment and oxidative stress in the elderly: results of epidemiological studies. *Biofactors*. 2000; 13(1-4):205–209.
5. van Poppel G, van den Berg H. Vitamins and cancer. *Cancer Lett*. 1997;114(1-2):195–202.
6. Gray GE, Paganini-Hill A, Ross RK, et al. Assessment of three brief methods of estimation of vitamin A and C intakes for a prospective study of cancer: comparison with dietary history. *Am J Epidemiol*. 1984;119(4):581–590.
7. Paganini-Hill A. Risk factors for Parkinson's disease: the Leisure World Cohort Study. *Neuroepidemiology*. 2001;20(2): 118–124.
8. US Department of Agriculture. *Composition of Foods*. (USDA Handbook no. 8, versions 1–14). Washington, DC: US Government Printing Office; 1976–1984.
9. Paganini-Hill A, Ross RK, Henderson BE. Prevalence of chronic disease and health practices in a retirement community. *J Chronic Dis*. 1986;39(9):699–707.

10. Paganini-Hill A, Chao A, Ross RK, et al. Exercise and other factors in the prevention of hip fracture: the Leisure World Study. *Epidemiology*. 1991;2(1):16–25.
11. Paganini-Hill A, Hsu G, Chao A, et al. Comparison of early and late respondents to a postal health survey questionnaire. *Epidemiology*. 1993;4(4):375–379.
12. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc B Methodol*. 1972;34(2):187–220.
13. Food and Nutrition Board, Institute of Medicine; and National Research Council. *Recommended Dietary Allowances*. 9th ed. Washington, DC: National Academy Press; 1980.
14. Pocobelli G, Peters U, Kristal AR, et al. Use of supplements of multivitamins, vitamin C, and vitamin E in relation to mortality. *Am J Epidemiol*. 2009;170(4):472–483.
15. Losonczy KG, Harris TB, Havlik RJ. Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the Established Populations for Epidemiologic Studies of the Elderly. *Am J Clin Nutr*. 1996; 64(2):190–196.
16. Watkins ML, Erickson JD, Thun MJ, et al. Multivitamin use and mortality in a large prospective study. *Am J Epidemiol*. 2000;152(2):149–162.
17. Li K, Kaaks R, Linseisen J, et al. Vitamin/mineral supplementation and cancer, cardiovascular, and all-cause mortality in a German prospective cohort (EPIC-Heidelberg). *Eur J Nutr*. 2012;51(4):407–413.
18. Pandey DK, Shekelle R, Selwyn BJ, et al. Dietary vitamin C and beta-carotene and risk of death in middle-aged men. The Western Electric Study. *Am J Epidemiol*. 1995;142(12):1269–1278.
19. Agudo A, Cabrera L, Amiano P, et al. Fruit and vegetable intakes, dietary antioxidant nutrients, and total mortality in Spanish adults: findings from the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain). *Am J Clin Nutr*. 2007;85(6):1634–1642.
20. Sahyoun NR, Jacques PF, Russell RM. Carotenoids, vitamins C and E, and mortality in an elderly population. *Am J Epidemiol*. 1996;144(5):501–511.
21. Brzozowska A, Kaluza J, Knoop KT, et al. Supplement use and mortality: the SENECA Study. *Eur J Nutr*. 2008;47(3):131–137.
22. Mursu J, Robien K, Harnack LJ, et al. Dietary supplements and mortality rate in older women: the Iowa Women's Health Study. *Arch Intern Med*. 2011;171(18):1625–1633.
23. Roswall N, Olsen A, Christensen J, et al. Micronutrient intake in relation to all-cause mortality in a prospective Danish cohort. *Food Nutr Res*. 2012;56:5466.
24. Iso H, Kubota Y. Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev*. 2007;8(suppl):35–80.
25. Stampfer MJ, Hennekens CH, Manson JE, et al. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med*. 1993;328(20):1444–1449.
26. Hayden KM, Welsh-Bohmer KA, Wengreen HJ, et al. Risk of mortality with vitamin E supplements: the Cache County Study. *Am J Med*. 2007;120(2):180–184.
27. Dietrich M, Jacques PF, Pencina MJ, et al. Vitamin E supplement use and the incidence of cardiovascular disease and all-cause mortality in the Framingham Heart Study: Does the underlying health status play a role? *Atherosclerosis*. 2009; 205(2):549–553.
28. Kim I, Williamson DF, Byers T, et al. Vitamin and mineral supplement use and mortality in a US cohort. *Am J Public Health*. 1993;83(4):546–550.
29. Park SY, Murphy SP, Wilkens LR, et al. Multivitamin use and the risk of mortality and cancer incidence: the Multiethnic Cohort Study. *Am J Epidemiol*. 2011;173(8): 906–914.
30. Neuhauser ML, Wassertheil-Smoller S, Thomson C, et al. Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. *Arch Intern Med*. 2009;169(3):294–304.
31. Messerer M, Håkansson N, Wolk A, et al. Dietary supplement use and mortality in a cohort of Swedish men. *Br J Nutr*. 2008; 99(3):626–631.
32. Todd S, Woodward M, Tunstall-Pedoe H, et al. Dietary antioxidant vitamins and fiber in the etiology of cardiovascular disease and all-causes mortality: results from the Scottish Heart Health Study. *Am J Epidemiol*. 1999;150(10):1073–1080.
33. Genkinger JM, Platz EA, Hoffman SC, et al. Fruit, vegetable, and antioxidant intake and all-cause, cancer, and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. *Am J Epidemiol*. 2004;160(2): 1223–1233.
34. Enstrom JE, Kanim LE, Klein MA. Vitamin C intake and mortality among a sample of the United States population. *Epidemiology*. 1992;3(3):194–202.
35. Vivekananthan DP, Penn MS, Sapp SK, et al. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet*. 2003; 361(9374):2017–2023.
36. Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*. 2005;142(1):37–46.
37. Bjelakovic G, Nikolova D, Simonetti RG, et al. Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. *Lancet*. 2004;364(9441): 1219–1228.
38. Bjelakovic G, Nikolova D, Gluud LL, et al. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev*. 2012;3:CD007176.
39. Hankin JH, Rawlings V, Nomura A. Assessment of a short dietary method for prospective study on cancer. *Am J Clin Nutr*. 1978;31(2):355–359.
40. Hankin JH, Kolonel LN, Hinds MW. Dietary history methods for epidemiologic studies: application in a case-control study of vitamin A and lung cancer. *J Natl Cancer Inst*. 1984;73(6): 1417–1422.
41. Paganini-Hill A, Chao A, Ross RK, et al. Vitamin A, beta-carotene, and the risk of cancer: a prospective study. *J Natl Cancer Inst*. 1987;79(3):443–448.
42. Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academy Press; 2001.
43. Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington, DC: National Academy Press; 2000.
44. Subar AF, Thompson FE, Kipnis V, et al. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires: the Eating at America's Table Study. *Am J Epidemiol*. 2001;154(12):1089–1099.
45. Gnardellis C, Boulou C, Trichopoulou A. Magnitude, determinants and impact of under-reporting of energy intake in a cohort study in Greece. *Public Health Nutr*. 1998;1(2):131–137.
46. Chung S, Popkin BM, Domino ME, et al. Effect of retirement on eating out and weight change: an analysis of gender differences. *Obesity (Silver Spring)*. 2007;15(4):1053–1060.