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Association Among Dietary Supplement Use, Nutrient Intake, and Mortality Among U.S. Adults

A Cohort Study

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Background: The health benefits and risks of dietary supplement use are controversial.

Objective: To evaluate the association among dietary supplement use, levels of nutrient intake from foods and supplements, and mortality among U.S. adults.

Design: Prospective cohort study.

Setting: NHANES (National Health and Nutrition Examination Survey) data from 1999 to 2010, linked to National Death Index mortality data.

Participants: 30 899 U.S. adults aged 20 years or older who answered questions on dietary supplement use.

Measurements: Dietary supplement use in the previous 30 days and nutrient intake from foods and supplements. Outcomes included mortality from all causes, cardiovascular disease (CVD), and cancer.

Results: During a median follow-up of 6.1 years, 3613 deaths occurred, including 945 CVD deaths and 805 cancer deaths. Ever-use of dietary supplements was not associated with mortality outcomes. Adequate intake (at or above the Estimated Average Requirement or the Adequate Intake level) of vitamin A, vitamin K, magnesium, zinc, and copper was associated with reduced all-cause or CVD mortality, but the associations were restricted to nutrient intake from foods. Excess intake of calcium was associated with increased risk for cancer death (above vs. at or below the Tolerable Upper Intake Level: multivariable-adjusted rate ratio, 1.62 [95% CI, 1.07 to 2.45]; multivariable-adjusted rate difference, 1.7 [CI, −0.1 to 3.5] deaths per 1000 person-years), and the association seemed to be related to calcium intake from supplements (≥1000 mg/d vs. no use: multivariable-adjusted rate ratio, 1.53 [CI, 1.04 to 2.25]; multivariable-adjusted rate difference, 1.5 [CI, −0.1 to 3.1] deaths per 1000 person-years) rather than foods.

Limitations: Results from observational data may be affected by residual confounding. Reporting of dietary supplement use is subject to recall bias.

Conclusion: Use of dietary supplements is not associated with mortality benefits among U.S. adults.

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A recent study found that more than half of U.S. adults reported use of dietary supplements in the previous 30 days (1). Whether dietary supplement use is associated with health benefits or risks is controversial. The overall evidence suggests no benefits or harms, but a few randomized controlled trials have reported adverse outcomes associated with dietary supplement use, especially at high doses (2, 3). For example, the ATBC (Alpha-Tocopherol, Beta-Carotene Cancer Prevention) study and CARET (Beta-Carotene and Retinol Efficacy Trial) found that β-carotene supplements (20 or 30 mg/d) increased risk for lung cancer among smokers (4, 5), and SELECT (Selenium and Vitamin E Cancer Prevention Trial) reported that supplemental use of vitamin E (400 IU/d) increased risk for prostate cancer among men (6).

Although randomized controlled trials usually assess dietary supplement use at a specific dose, prospective cohort studies allow for evaluation of dose dependence versus threshold effects and potential heterogeneous effects of nutrient intake from supplements versus foods (7). For example, the CPS-II (Cancer Prevention Study II) Nutrition Cohort found that higher doses of supplemental calcium (≥1000 mg/d) were associated with increased risk for all-cause death in men, but lower doses (<1000 mg/d) or calcium intake from foods were not associated with mortality outcomes (8). Therefore, both the dose of the supplement and the nutrient source (foods vs. supplements) can play critical roles in determining the benefits or risks of nutrient intake.

Using a nationally representative sample of U.S. adults, we evaluated the association between dietary supplement use and mortality from all causes, cardiovascular disease (CVD), and cancer. We further assessed whether adequate or excess nutrient intake was associated with mortality and whether the associations differed by nutrient intake from foods versus supplements.

METHODS

Study Design and Population

We used data from U.S. adults aged 20 years or older who participated in 6 cycles (1999–2000 to 2009–2010) of NHANES (National Health and Nutrition Examination Survey). Exclusion of pregnant or lactating women resulted in 30 958 participants, among whom 30 899 provided complete information on dietary supplement use in the previous 30 days. Those who responded "refused" or "don't know" or did not answer the questions on dietary supplement use were excluded (*n* = 59). Among the 30 899 participants who provided information on dietary supplement use, 27 725 with 1 or 2 valid 24-hour diet recalls were included in the analysis that estimated nutrient intake from foods versus supplements and its association with mortality outcomes. NHANES was approved by the research ethics review board of the National Center for Health Statistics, and all participants provided written informed consent.

Dietary Supplement Use

NHANES participants were asked during an in-house interview whether they had used any dietary supplements in the previous 30 days. Those who reported supplement use were asked about the product name, frequency (for example, how many times each day), duration (for example, how many days in the previous 30 days), and serving form (for example, capsules, tablets, pills, softgels, or drops). For each nutrient, the daily dose was calculated by combining the frequency (for example, the number of capsules taken each day) with the product information on the ingredient (for example, vitamin D or calcium), the amount per serving, and the units (for example, international units or milligrams). Nutrient intake from each product was summed to estimate the total daily dose of each supplemental nutrient for each participant (**Appendix 1**, available at Annals.org).

Nutrient Intake From Foods

Nutrient intake from foods was assessed using 24-hour diet recalls conducted by trained interviewers. One diet recall was done in person at the Mobile Examination Center; from 2003 to 2010, a second recall was added by telephone interview approximately 3 to 10 days after the first one. Using the Automated Multiple-Pass Method, all foods and beverages consumed the previous day were recorded. A standard set of measuring guides was used to help the respondent report the volume and dimensions of the items consumed. Food intakes were coded and nutrient values were determined using the U.S. Department of Agriculture Food and Nutrient Database for Dietary Studies (FNDDS), versions 1.0 to 5.0 (9).

Inadequate and Excess Nutrient Intake

Inadequate nutrient intake was defined as levels of total nutrient intake (foods plus supplements) below the Estimated Average Requirement or the Adequate Intake level specified in the Dietary Reference Intakes (10). Excess nutrient intake was defined as levels above the Tolerable Upper Intake Level.

Mortality

Mortality outcomes were obtained for each participant through linkage to the National Death Index through 31 December 2011 using a probabilistic match (11). The International Classification of Diseases, 10th Revision (ICD-10), was used to ascertain cause-specific death. Death due to CVD was defined as ICD-10 codes I00 to I09, I11, I13, I20 to I51, or I60 to I69 being listed as the underlying cause of death, and death due to cancer was defined as codes C00 to C97 being listed as the underlying cause. Follow-up length was defined as the interval from the interview date to the date of death or to the end of 2011 for those who were censored.

Demographic Characteristics, Lifestyle Factors, and Comorbid Conditions

Demographic characteristics and lifestyle factors, including age, sex, race/ethnicity, education, income, smoking, and physical activity, were collected during household interviews. Alcohol intake, weight, and height were obtained during physical examinations at the Mobile Examination Center. Smokers were defined as participants who reported smoking at least 100 cigarettes during their lifetime, and former smokers were defined as those who reported smoking at least 100 cigarettes but were not currently smoking. Drinkers were defined as participants who consumed at least 12 alcoholic drinks in a given year. Moderate versus heavy drinkers were defined as participants who consumed fewer than 1 versus 1 or more drinks per day (women) or fewer than 2 versus 2 or more drinks per day (men). Participants were classified as physically active if they had at least 150 minutes of moderate to vigorous physical activity per week and were classified as physically inactive otherwise (12). Diet quality was assessed using the Healthy Eating Index-2015, which measures adherence to the 2015–2020 Dietary Guidelines for Americans (13). A higher score corresponds to a healthier diet. Comorbid conditions, including cancer, congestive heart failure, coronary heart disease, myocardial infarction, and stroke, were defined if participants reported having ever been told by a physician that they had these conditions and/or if they had ever been told to take or were currently taking prescription medication to treat high cholesterol, hypertension, or diabetes.

Statistical Analysis

We first estimated the prevalence of supplement use among the participants. Multivitamin and mineral (MVM) supplement use was defined as use of a product formulated with 3 or more vitamins with or without minerals (14). We then compared the distribution of demographic characteristics, lifestyle factors, and comorbid conditions between participants who used any dietary supplements and those who did not, using *t* tests for continuous variables and χ^2 tests for categorical variables. We further estimated total nutrient intake by summing intake from foods and supplements and the percentage of participants with inadequate or excess intake. To correct for measurement error associated with use of 1- or 2-day recalls to estimate dietary intake, we used the National Cancer Institute (NCI) method to adjust for usual intake estimates. The method also uses regression calibration to correct for bias due to measurement error in evaluating associations between usual intake and health outcomes (**Appendix 2**, available at Annals.org) (15–17).

Next, we used Poisson regression models with robust SEs to estimate mortality rates, mortality rate ratios (RRs), and 95% CIs for associations among dietary supplement use, nutrient intake, and mortality. Two multivariable models were used. Model 1 was adjusted for age, sex, and race/ethnicity, and model 2 was also adjusted for education, physical activity, smoking, alcohol intake, diet quality, body mass index, and comorbid

Table 1. Characteristics of Study Participants, by Dietary Supplement Use*

Characteristic	All Participants (*n* = 30 899)	Dietary Supplement Users (*n* = 14 763)	Dietary Supplement Nonusers (*n* = 16 136)	*P* Value
Mean age (±SE), *y*	46.9 ± 0.2	50.7 ± 0.3	42.8 ± 0.2	<0.001
Female, *n* (%)	15 400 (50.9)	8156 (56.4)	7244 (45.1)	<0.001
Race/ethnicity, *n* (%)				
Non-Hispanic white	15 295 (70.7)	8826 (78.6)	6469 (62.6)	<0.001
Non-Hispanic black	6169 (11.1)	2304 (7.8)	3865 (14.5)	
Hispanic	8169 (12.7)	3016 (8.4)	5153 (17.2)	
Other	1266 (5.5)	617 (5.3)	649 (5.7)	
Education, *n* (%)				
Less than high school	9672 (20.0)	3356 (13.6)	6316 (26.7)	<0.001
High school graduate/GED	7369 (25.3)	3459 (23.6)	3910 (27.1)	
Some college or above	13 795 (54.7)	7919 (62.8)	5876 (46.2)	
Family income–poverty ratio, *n* (%)†				
<1.30	8287 (20.6)	2947 (14.3)	5340 (27.2)	<0.001
1.30–2.99	9167 (29.2)	4302 (27.2)	4865 (31.4)	
3.00–4.99	5659 (25.1)	3093 (26.9)	2566 (23.3)	
≥5.00	4982 (25.1)	3169 (31.6)	1813 (18.2)	
Smoking status, *n* (%)‡				
Nonsmoker	15 922 (51.4)	7816 (53.0)	8106 (49.7)	<0.001
Former smoker	8044 (24.8)	4571 (29.5)	3473 (19.8)	
Current smoker	6905 (23.9)	2368 (17.5)	4537 (30.5)	
Alcohol intake, *n* (%)§				
None	11 093 (35.7)	5455 (35.5)	5638 (35.8)	0.002
Moderate	13 573 (55.9)	6630 (56.8)	6943 (54.9)	
Heavy	1933 (8.4)	820 (7.7)	1113 (9.2)	
Mean Healthy Eating Index-2015 score (±SE)‖	51.4 ± 0.2	54.0 ± 0.3	48.5 ± 0.2	<0.001
Quartile of Healthy Eating Index-2015 score, *n* (%)				
1 (<41.8)	6462 (25.0)	2387 (19.2)	4075 (31.3)	<0.001
2 (41.8–50.5)	6900 (25.0)	3014 (22.8)	3886 (27.4)	
3 (50.6–60.0)	7147 (25.0)	3548 (26.0)	3599 (23.9)	
4 (>60.0)	7216 (25.0)	4432 (31.9)	2784 (17.5)	
Physical activity, *n* (%)¶				
Active	14 792 (53.1)	7422 (55.5)	7370 (50.5)	<0.001
Inactive	16 095 (46.9)	7336 (44.5)	8759 (49.5)	
Mean BMI (±SE), *kg/m²*	28.4 ± 0.1	28.0 ± 0.1	28.8 ± 0.1	<0.001
Weight category, *n* (%)				
Underweight or normal-weight (BMI <25 kg/m²)	8702 (33.3)	4401 (35.5)	4301 (30.9)	<0.001
Overweight (BMI 25–29.9 kg/m²)	9981 (34.0)	4862 (34.2)	5119 (33.7)	
Obese (BMI ≥30 kg/m²)	9871 (32.8)	4388 (30.2)	5483 (35.5)	
Comorbid conditions, *n* (%)				
Cancer	2964 (8.8)	1915 (11.7)	1049 (5.7)	<0.001
Congestive heart failure	1118 (2.4)	578 (2.5)	540 (2.3)	0.20
Coronary heart disease	1408 (3.5)	817 (4.1)	591 (2.8)	<0.001
Myocardial infarction	1503 (3.5)	789 (3.8)	714 (3.2)	0.006
Stroke	1277 (2.8)	688 (3.1)	589 (2.5)	0.008
High cholesterol	9067 (29.1)	5336 (35.1)	3731 (22.9)	<0.001
Hypertension	10 617 (29.1)	5806 (33.0)	4811 (24.9)	<0.001
Diabetes	3618 (8.0)	1782 (8.3)	1836 (7.7)	0.091

BMI = body mass index; NHANES = National Health and Nutrition Examination Survey.
* Means and percentages were adjusted for NHANES survey weights.
† Ratio of family income to the poverty threshold, adjusted for household size.
‡ Smokers were defined as participants who had smoked ≥100 cigarettes in their lifetime.
§ Drinkers were defined as participants who consumed ≥12 alcoholic drinks in a given year. Moderate versus heavy drinkers were defined as those who consumed <1 versus ≥1 drink per day (women) or <2 versus ≥2 drinks per day (men).
‖ Calculated to measure adherence to the 2015–2020 Dietary Guidelines for Americans. A higher score indicates a higher-quality diet.
¶ Participants who had ≥150 min of moderate to vigorous physical activity per week were classified as physically active according to the Centers for Disease Control and Prevention Physical Activity Guidelines for Americans.

conditions. Multiple imputation was done for alcohol intake (6.1% missing values), the only variable missing more than 5% of values among participants who reported nutrient intake from both foods and supplements. We further evaluated whether the association differed by nutrient intake from supplements versus foods by including intake from both sources as separate variables in the same model. We also performed subgroup analysis among participants with or without comorbid conditions at baseline and among those with high (at or above the median) versus low (below the median) nutrient intake from foods at baseline.

Sampling weights were adjusted in all analyses to account for unequal probabilities of sample selection due to complex sample design and oversampling of certain subgroups. The analyses for estimating nutrient intake from foods and supplements and the percentage of participants with inadequate or excess intake were conducted using SAS, version 9.4 (SAS Institute), and the analyses for estimating mortality rates, RRs, and rate differences (RDs) were done using Stata, version 15.1 (StataCorp). A *P* value less than 0.05 was considered statistically significant.

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RESULTS

More than half of participants (51.2%) reported use of dietary supplements in the previous 30 days, and 38.3% reported use of MVM supplements. Compared with nonusers, supplement users were older and were more likely to be female and non-Hispanic white, have higher levels of education and family income, eat a healthy diet, and be physically active. They were also less likely to be current smokers, heavy drinkers, or obese but reported a higher prevalence of comorbid conditions at baseline (Table 1).

The most commonly used vitamin supplements were vitamin C (40.3% [95% CI, 39.3% to 41.4%]), vitamin E (38.6% [CI, 37.6% to 39.6%]), and vitamin D (37.6% [CI,

Table 2. Prevalence of Dietary Supplement Use, Nutrient Intake Levels From Supplements Versus Foods, and Percentages of Nutrient Intake Below the EAR or Above the UL*

Supplement	All Participants		Mean Nutrient Intake (Foods Only)± SE Among Nonusers of Supplements	Dietary Supplement Users			All Participants	
	Prevalence of Supplement Use (95% CI), %	Mean Nutrient Intake (Foods + Supplements) ± SE		Mean Nutrient Intake (Foods Only) ± SE†	Mean Nutrient Intake (Supplements Only) ± SE	Mean Nutrient Intake (Foods + Supplements) ± SE‡	Prevalence of Nutrient Intake Below EAR (95% CI), %§	Prevalence of Nutrient Intake Above UL (95% CI), %§
Vitamins								
Vitamin A (RAE mcg/d)	35.3 (34.3-36.3)	953.2 ± 10.4	583.3 ± 3.4	704.0 ± 3.6	973.2 ± 24.7	1612.0 ± 20.3	32.2 (30.9-33.4)	0.7 (0.6-0.9)
β-Carotene (RAE mcg/d)	35.2 (34.2-36.2)	250.2 ± 5.2	150.5 ± 1.2	199.7 ± 1.6	239.7 ± 12.3	428.3 ± 13.1	–	–
Retinol (RAE mcg/d)	32.4 (31.5-33.4)	680.6 ± 6.9	415.4 ± 3.0	478.5 ± 3.0	800.3 ± 17.6	1224.1 ± 12.9	–	–
Vitamin C (mg/d)	40.3 (39.3-41.4)	220.8 ± 6.4	82.1 ± 0.7	96.7 ± 0.7	321.9 ± 13.8	418.6 ± 13.9	23.6 (22.5-24.8)	0.9 (0.7-1.1)
Vitamin D (mcg/d)	37.6 (36.6-38.6)	12.1 ± 0.5	4.5 ± 0.04	5.1 ± 0.04	13.5 ± 0.5	24.7 ± 1.3	67.4 (65.7-69.1)	0.6 (0.4-0.8)
Vitamin E (mg/d)	38.6 (37.6-39.6)	71.0 ± 2.4	7.1 ± 0.03	8.0 ± 0.04	161.4 ± 5.3	169.4 ± 5.3	61.6 (60.5-62.8)	0.8 (0.6-1.0)
Thiamin (mg/d)	35.8 (34.8-36.8)	6.7 ± 0.3	1.7 ± 0.01	1.9 ± 0.01	13.6 ± 0.6	15.5 ± 0.6	0.2 (0.1-0.2)	–
Riboflavin (mg/d)	35.8 (34.8-36.7)	6.6 ± 0.2	2.1 ± 0.01	2.3 ± 0.01	12.0 ± 0.6	14.3 ± 0.6	0.5 (0.4-0.6)	–
Niacin (mg/d)	36.0 (35.0-37.0)	39.5 ± 0.7	24.5 ± 0.1	25.1 ± 0.1	40.5 ± 1.8	65.6 ± 1.8	0.2 (0.2-0.3)	7.1 (6.5-7.6)
Vitamin B_6 (mg/d)	36.9 (35.9-37.9)	7.8 ± 0.3	1.9 ± 0.01	2.0 ± 0.01	15.5 ± 0.6	17.6 ± 0.6	3.9 (3.6-4.3)	1.8 (1.5-2.0)
Folate (DFE mcg/d)	36.6 (35.6-37.6)	813.9 ± 7.9	524.8 ± 2.5	561.3 ± 2.5	734.7 ± 12.0	1300.7 ± 13.5	2.5 (2.2-2.8)	3.1 (2.7-3.5)
Vitamin B_{12} (mcg/d)	37.3 (36.3-38.3)	38.0 ± 1.9	5.3 ± 0.03	5.6 ± 0.03	86.1 ± 4.8	91.7 ± 4.8	0.3 (0.2-0.4)	–
Choline (mg/d)	5.4 (4.9-5.9)	348.5 ± 4.2	333.4 ± 1.3	340.9 ± 4.9	301.7 ± 41.4	616.5 ± 78.2	96.7 (96.3-97.2)	0.1 (0.01-0.2)
Vitamin K (mcg/d)	26.0 (25.1-26.8)	101.9 ± 0.6	89.7 ± 0.5	106.0 ± 0.8	29.6 ± 0.8	135.8 ± 1.2	62.2 (60.9-63.5)	–
Minerals								
Calcium (mg/d)	38.6 (37.6-39.6)	1115.1 ± 7.2	898.1 ± 4.4	970.0 ± 4.5	479.2 ± 10.8	1449.2 ± 11.3	32.4 (31.2-33.6)	3.9 (3.5-4.3)
Selenium (mcg/d)	29.7 (28.8-30.7)	130.5 ± 0.8	109.8 ± 0.3	112.8 ± 0.4	65.2 ± 2.0	178.0 ± 2.0	0.1 (0.0-0.2)	0.9 (0.7-1.1)
Magnesium (mg/d)	33.3 (32.3-34.3)	338.8 ± 2.7	280.0 ± 1.3	307.3 ± 1.5	146.8 ± 5.8	454.1 ± 6.4	49.7 (48.4-51.0)	2.6 (2.3-2.9)
Potassium (mg/d)	26.5 (25.6-27.4)	2719.3 ± 9.2	2626.7 ± 9.0	2888.8 ± 14.3	82.5 ± 2.5	2971.3 ± 14.8	99.1 (99.0-99.3)	–
Phosphorus (mg/d)	22.5 (21.7-23.4)	1363.6 ± 4.6	1327.6 ± 4.3	1387.4 ± 6.6	97.9 ± 4.2	1485.3 ± 8.0	0.3 (0.2-0.4)	0.1 (0.01-0.1)
Iron (mg/d)	24.5 (23.6-25.4)	19.8 ± 0.1	15.4 ± 0.1	16.1 ± 0.1	17.0 ± 0.3	33.1 ± 0.3	0.4 (0.3-0.5)	2.5 (2.2-2.7)
Zinc (mg/d)	34.5 (33.5-35.4)	18.2 ± 0.2	11.9 ± 0.04	12.4 ± 0.05	17.6 ± 0.4	30.0 ± 0.4	3.1 (2.9-3.4)	4.1 (3.7-4.4)
Copper (mg/d)	30.7 (29.8-31.6)	1.9 ± 0.02	1.3 ± 0.01	1.4 ± 0.01	1.8 ± 0.04	3.2 ± 0.04	1.3 (1.1-1.6)	0.3 (0.2-0.3)
Other								
Lutein + zeaxanthin (mcg/d)	17.1 (16.3-17.9)	1535.1 ± 27.6	1279.4 ± 8.8	1566.0 ± 13.1	1106.0 ± 139.3	2630.9 ± 134.4	–	–
Lycopene (mcg/d)	13.1 (12.4-13.8)	5737.2 ± 27.2	5608.6 ± 24.2	5697.6 ± 54.5	859.5 ± 128.3	6432.7 ± 75.1	–	–
Fiber (g/d)	2.6 (2.3-2.9)	16.1 ± 0.1	15.9 ± 0.1	18.0 ± 0.3	4.7 ± 0.3	22.7 ± 0.5	97.2 (96.8-97.5)	–
EPA (mg/d)	5.2 (4.6-5.8)	48.8 ± 1.8	30.0 ± 0.2	32.2 ± 0.5	336.3 ± 25.6	368.4 ± 25.7	–	–
EPA + DHA (mg/d)	–	–	–	–	–	–	97.8 (97.5-98.1)	–
DHA (mg/d)	5.3 (4.8-5.9)	91.6 ± 1.2	79.1 ± 0.5	83.9 ± 1.1	214.4 ± 13.2	298.3 ± 13.4	–	–

DFE = dietary folate equivalent; DHA = docosahexaenoic acid; EAR = Estimated Average Requirement; EPA = eicosapentaenoic acid; NHANES = National Health and Nutrition Examination Survey; RAE = retinal activity equivalent; UL = Tolerable Upper Intake Level.
* Means and percentages were adjusted for NHANES survey weights.
† Supplement users had significantly higher levels of nutrient intake from foods only than nonusers ($P < 0.05$) for all nutrients except choline and lycopene.
‡ Among supplement users, levels of nutrient intake from both foods and supplements were significantly higher than intake from foods only for all 25 nutrients. Levels of total nutrient intake were significantly higher among supplement users than nonusers for all 25 nutrients ($P < 0.05$ for all).
§ EAR and UL were based on Dietary Reference Intakes. For nutrients with no EAR, the Adequate Intake level (vitamin K, potassium, choline, and fiber) or the recommended intake (EPA + DHA) was used to estimate prevalence of inadequate intake. *β*-Carotene, retinol, lutein, zeaxanthin, and lycopene have no EAR, Adequate Intake level, or recommended intake. The UL for vitamin A applies to preformed vitamin A only. The ULs for niacin and folate apply to synthetic forms obtained from supplements, fortified foods, or a combination of the two. The UL for vitamin E applies to any form of supplemental *α*-tocopherol. The UL for magnesium represents intake from a pharmacologic agent only and does not include intake from food and water. ULs are not available for *β*-carotene, retinol, thiamin, riboflavin, vitamin B_{12}, vitamin K, potassium, lutein, zeaxanthin, lycopene, fiber, EPA, and DHA.

Table 3. Association of Dietary Supplement Use With All-Cause Mortality

Supplement	Person-Years (Users/Nonusers)	Total Deaths (Users/Nonusers), *n*	RR (95% CI)	
			Model 1*	Model 2†
Any	90 515/99 288	2000/1613	0.85 (0.77–0.94)	1.02 (0.92–1.13)
MVM	66 295/123 508	1414/2199	0.85 (0.77–0.94)	1.01 (0.91–1.13)
Individual vitamins				
Vitamin A	60 556/129 247	1254/2359	0.85 (0.77–0.95)	1.00 (0.89–1.13)
β-Carotene	60 440/129 363	1254/2359	0.86 (0.77–0.95)	1.01 (0.89–1.14)
Retinol	56 138/133 664	1156/2457	0.86 (0.78–0.96)	1.00 (0.89–1.13)
Thiamin	61 942/127 860	1275/2338	0.87 (0.78–0.97)	1.02 (0.90–1.14)
Riboflavin	61 733/128 070	1280/2333	0.86 (0.78–0.96)	1.01 (0.90–1.14)
Niacin	62 099/127 704	1277/2336	0.86 (0.77–0.96)	1.00 (0.90–1.13)
Pantothenic acid	59 582/130 221	1241/2372	0.85 (0.77–0.94)	1.01 (0.90–1.13)
Vitamin B_6	63 528/126 274	1321/2292	0.87 (0.78–0.97)	1.02 (0.91–1.15)
Folate	62 799/127 004	1294/2319	0.85 (0.76–0.94)	0.99 (0.88–1.12)
Vitamin B_{12}	64 139/125 663	1343/2270	0.85 (0.77–0.94)	0.99 (0.89–1.11)
Choline	9447/180 355	125/3488	0.77 (0.60–0.99)	0.97 (0.75–1.25)
Vitamin C	69 804/119 998	1485/2128	0.88 (0.79–0.98)	1.07 (0.94–1.20)
Vitamin D	63 794/126 009	1304/2309	0.82 (0.74–0.90)	0.96 (0.86–1.07)
Vitamin E	68 085/121 718	1448/2165	0.81 (0.73–0.89)	0.98 (0.89–1.09)
Vitamin K	43 823/145 980	907/2706	0.81 (0.72–0.90)	0.93 (0.82–1.07)
Biotin	52 670/137 133	1101/2512	0.85 (0.76–0.94)	1.00 (0.89–1.13)
Individual minerals				
Copper	52 483/137 319	1092/2521	0.84 (0.76–0.92)	1.00 (0.89–1.13)
Phosphorus	40 657/149 145	902/2711	0.88 (0.79–0.98)	1.02 (0.89–1.16)
Selenium	50 953/138 849	1075/2538	0.84 (0.76–0.92)	0.99 (0.88–1.11)
Boron	41 529/148 273	893/2720	0.86 (0.77–0.96)	1.00 (0.88–1.13)
Iodine	47 219/142 584	988/2625	0.86 (0.77–0.96)	1.01 (0.89–1.14)
Silicon	36 105/153 698	817/2796	0.88 (0.78–0.98)	0.98 (0.86–1.13)
Iron	43 032/146 771	822/2791	0.97 (0.86–1.09)	1.02 (0.89–1.19)‡
Magnesium	56 881/132 922	1118/2495	0.83 (0.75–0.91)	0.97 (0.86–1.09)
Calcium	66 699/123 103	1349/2264	0.81 (0.74–0.89)	0.97 (0.88–1.07)
Manganese	51 182/138 621	1037/2576	0.81 (0.73–0.90)	0.96 (0.85–1.08)
Tin	24 321/165 482	468/3145	0.97 (0.85–1.11)	1.09 (0.92–1.28)
Chromium	50 575/139 228	1008/2605	0.83 (0.74–0.92)	0.97 (0.86–1.10)
Molybdenum	44 337/145 466	957/2656	0.87 (0.78–0.97)	1.01 (0.89–1.15)
Vanadium	38 418/151 385	852/2761	0.87 (0.77–0.98)	0.99 (0.86–1.14)
Nickel	34 572/155 231	800/2813	0.89 (0.80–0.99)	1.00 (0.88–1.13)
Zinc	59 276/130 527	1209/2404	0.87 (0.78–0.96)	1.02 (0.91–1.15)
Potassium	46 960/142 843	1024/2589	0.90 (0.81–1.00)	1.03 (0.92–1.17)
Other				
Lutein	29 435/160 368	710/2903	0.90 (0.80–1.02)	1.00 (0.87–1.15)
Lycopene	17 989/171 814	366/3247	0.72 (0.60–0.85)	0.82 (0.68–0.98)
Zeaxanthin	1397/188 406	19/3694	0.66 (0.37–1.18)	0.73 (0.38–1.40)
Inositol	7835/181 968	98/3515	0.74 (0.58–0.95)	0.90 (0.68–1.18)
Fiber	4468/185 335	78/3535	0.79 (0.61–1.04)	0.91 (0.65–1.25)
Omega-3	7475/182 328	115/3498	0.66 (0.47–0.94)	0.82 (0.58–1.17)
EPA	5934/183 869	91/3522	0.63 (0.41–0.97)	0.81 (0.53–1.25)
DHA	6236/183 567	96/3517	0.63 (0.42–0.95)	0.81 (0.54–1.21)
Omega-6	1994/187 809	31/3582	0.79 (0.57–1.10)	0.93 (0.67–1.29)
Omega-9	1510/188 293	25/3588	0.93 (0.59–1.47)	1.06 (0.62–1.80)

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; MVM = multivitamin and mineral; NHANES = National Health and Nutrition Examination Survey; RR = rate ratio.
* Adjusted for age, sex, and race/ethnicity.
† Adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, presence of comorbid conditions at baseline, and NHANES survey weights. Multiple imputation was done for alcohol intake.
‡ Also adjusted for presence of anemia at baseline (yes vs. no).

36.6% to 38.6%]). The most commonly used mineral supplements were calcium (38.6% [CI, 37.6% to 39.6%]), zinc (34.5% [CI, 33.5% to 35.4%]), and magnesium (33.3% [CI, 32.3% to 34.3%]). Levels of total nutrient intake were higher among supplement users than nonusers for all 25 nutrients. When nutrient intake from supplements was not accounted for, supplement users still had higher intake levels from foods for 23 nutrients (Table 2).

More than half of participants had inadequate intake of vitamin D (67.4% [CI, 65.7% to 69.1%]), vitamin E (61.6% [CI, 60.5% to 62.8%]), choline (96.7% [CI, 96.3% to 97.2%]), vitamin K (62.2% [CI, 60.9% to 63.5%]), and potassium (99.1% [CI, 99.0% to 99.3%]). The prevalence of participants with excess intake was less than 5% for all nutrients except niacin (7.1% [CI, 6.5% to 7.6%]) (Table 2).

During a median follow-up of 6.1 years, 3613 deaths occurred, including 945 CVD deaths and 805 cancer deaths. Supplemental use of most individual nutrients was associated with lower risk for all-cause death but not CVD or cancer death. However, all of the associations were statistically insignificant after multivariable adjustment, except that lycopene supplement use was associated with lower risk for all-cause death (RR, 0.82 [CI, 0.68 to 0.98]) and cancer death (RR, 0.66 [CI, 0.46 to 0.96]) (Table 3; Appendix Table 1, available at Annals.org).

Adequate intake of vitamin K (RR, 0.79 [CI, 0.70 to 0.90]) and magnesium (RR, 0.85 [CI, 0.74 to 0.98]) was associated with lower risk for all-cause death (Table 4). Adequate intake of vitamin A (RR, 0.61 [CI, 0.43 to 0.88]), vitamin K (RR, 0.68 [CI, 0.54 to 0.86]), copper (RR, 0.29 [CI, 0.17 to 0.51]), and zinc (RR, 0.50 [CI, 0.36 to 0.71]) was associated with lower CVD mortality (Appendix Table 2, available at Annals.org). Excess intake of calcium was associated with higher cancer mortality (RR, 1.62 [CI, 1.07 to 2.45]) (Appendix Table 3, available at Annals.org).

When sources of nutrient intake were further evaluated, the lower all-cause mortality associated with adequate intake of vitamin K and magnesium was restricted to intake from foods (vitamin K from foods: RR, 0.79 [CI, 0.69 to 0.92]; RD, −2.3 [CI, −3.7 to −0.9] deaths per 1000 person-years; vitamin K from supplements: RR, 0.96 [CI, 0.79 to 1.17]; RD, −0.4 [CI, −2.4 to 1.6] deaths per 1000 person-years; magnesium from foods: RR, 0.78 [CI, 0.65 to 0.93]; RD, −2.7 [CI, −4.5 to −0.9] deaths per 1000 person-years; magnesium from supplements: RR, 1.00 [CI, 0.87 to 1.14]; RD, 0.0 [CI, −1.6 to 1.5] deaths per 1000 person-years) (Table 4). Similarly, the lower CVD mortality associated with adequate intake of vitamin A, vitamin K, zinc, and copper was restricted to intake from foods (Appendix Table 2). However, the higher cancer mortality associated with excess calcium intake was attributable to high doses from supplements rather than foods. Supplemental calcium intake of 1000 mg/d or higher was associated with increased risk for cancer death (RR, 1.53 [CI, 1.04 to 2.25]; RD, 1.5 [CI, −0.1 to 3.1] deaths per 1000 person-years) (Appendix Table 3 and Appendix Figure 1, available at Annals.org).

Similar associations were found among participants with or without comorbid conditions at baseline (Appendix Tables 4 to 6, available at Annals.org) and those with high versus low nutrient intake from foods at baseline (Appendix Table 7, available at Annals.org). Stratified analysis revealed that vitamin D supplement use was not associated with mortality among participants with serum 25-hydroxyvitamin D levels less than 50 nmol/L; however, among those with levels of 50 nmol/L or higher, vitamin D supplement use at more than 10 mcg/d was associated with increased risk for all-cause death (RR, 1.34 [CI, 1.00 to 1.78]; RD, 2.7 [CI, −0.2 to 5.6] deaths per 1000 person-years) and cancer death (RR, 2.11 [CI, 1.18 to 3.77]; RD, 1.6 [CI, 0.2 to 3.1] deaths per 1000 person-years) (Appendix Table 8 and Appendix Figures 2 and 3, available at Annals.org).

DISCUSSION

We found that dietary supplement use was not associated with mortality benefits in a nationally representative sample of U.S. adults. The evidence suggests that adequate nutrient intake from foods was associated with reduced mortality and excess intake from supplements could be harmful.

We initially found that any supplement use, MVM supplement use, and supplemental use of individual nutrients were each associated with lower risk for all-cause death after adjustment for age, sex, and race/ethnicity. However, most of the associations became statistically insignificant after additional adjustment for education and lifestyle factors. These results suggest that supplement use itself does not have direct health benefits. The apparent association between supplement use and lower mortality may reflect confounding by higher socioeconomic status and healthy lifestyle factors that are known to reduce mortality. Our results and those of others (18, 19) suggest that supplement users have higher levels of education and income and a healthier lifestyle overall (for example, better diet, higher levels of physical activity, no smoking or alcohol intake, and healthy weight) than nonusers. In addition, we and others (20, 21) found that supplement users had higher levels of nutrient intake from foods alone than nonusers. Thus, supplement users may have already had lower prevalence of nutrient inadequacy that contributed to lower mortality.

Our null findings are consistent with those from other recent cohort studies. For example, dietary supplement use was not associated with all-cause, CVD, or cancer death among 23 943 participants in the EPIC-Heidelberg (European Prospective Investigation into Cancer and Nutrition) study (22). Long-term multivitamin use was not associated with reduced incidence of or death due to stroke among 86 142 women in the NHS (Nurses' Health Study) (23). Similarly, systematic review of cohort studies and intervention trials does not support the benefits of supplement use for primary prevention of CVD or cancer (3, 24). Although use of lycopene supplements was associated with lower risk for all-cause and cancer death in our study, prior evidence from prospective cohort studies does not support an association between lycopene-containing foods and cancer risk (25). Evidence from randomized controlled trials also does not support the chemopreventive role of lycopene supplements in prostate cancer (26, 27). Overall, the current evidence does not support mortality benefits associated with use of dietary supplements.

We found that the mortality benefits associated with adequate intake of some nutrients, such as vitamin A, vitamin K, magnesium, zinc, and copper, were restricted to intake from foods. There was also evidence that excess intake of some nutrients may have adverse effects. For example, we found higher cancer mortality with total calcium intake above the Tolerable Upper Intake Level. The potential harm of excess calcium intake has not been consistently reported (28), with some trials reporting reduced cancer risk with high intake (29–

Table 4. Nutrient Intake From Foods Versus Supplements and Association With All-Cause Mortality

Nutrient	Person-Years (≥EAR/<EAR)	Total Nutrient Intake			Nutrient Intake From Foods		
		Total Deaths (≥EAR/<EAR), *n*	RR (95% CI)†	RD (95% CI)†	Total Deaths (≥EAR/<EAR), *n*	RR (95% CI)†	RD (95% CI)†
Adequate intake‡							
Vitamin A	78 730/49 313	1413/625	0.88 (0.74 to 1.06)	−1.3 (−3.3 to 0.6)	1270/768	0.87 (0.74 to 1.01)	−1.5 (−3.2 to 0.1)
Thiamin	170 015/454	2835/10	0.65 (0.23 to 1.87)	−6.2 (−24.8 to 12.4)	2835/10	0.70 (0.24 to 2.00)	−5.0 (−22.4 to 12.4)
Riboflavin	169 430/1039	2817/28	0.66 (0.33 to 1.35)	−5.8 (−18.1 to 6.4)	2816/29	0.72 (0.35 to 1.48)	−4.4 (−15.8 to 7.0)
Niacin	169 990/480	2829/16	0.54 (0.27 to 1.09)	−9.7 (−24.4 to 5.0)	2829/16	0.60 (0.30 to 1.21)	−7.5 (−20.6 to 5.6)
Vitamin B_6	161 408/9062	2557/288	1.00 (0.82 to 1.21)	0.0 (−2.3 to 2.2)	2461/384	0.95 (0.81 to 1.13)	−0.6 (−2.5 to 1.4)
Folate	124 006/4036	1941/97	0.88 (0.61 to 1.25)	−1.5 (−5.7 to 2.7)	1913/125	0.83 (0.61 to 1.15)	−2.1 (−6.0 to 1.9)
Vitamin B_{12}	169 894/576	2830/15	0.89 (0.46 to 1.75)	−1.4 (−10.0 to 7.3)	2829/16	1.06 (0.54 to 2.10)	0.7 (−6.7 to 8.0)
Choline	1585/54 295	19/722	1.25 (0.74 to 2.11)	2.1 (−3.5 to 7.8)	9/732	1.47 (0.84 to 2.59)	4.1 (−3.1 to 11.3)
Vitamin C	131 636/38 833	2256/589	1.05 (0.86 to 1.26)	0.5 (−1.6 to 2.6)	2037/808	0.99 (0.86 to 1.15)	−0.1 (−1.7 to 1.6)
Vitamin D	8752/23 148	132/271	1.01 (0.77 to 1.33)	0.1 (−2.0 to 2.2)	4/399	–	–
Vitamin E	58 687/111 783	1104/1741	0.99 (0.89 to 1.09)	−0.2 (−1.3 to 1.0)	48/2797	0.95 (0.66 to 1.36)	−0.6 (−4.6 to 3.3)
Vitamin K	41 693/86 349	635/1403	0.79 (0.70 to 0.90)	−2.3 (−3.5 to −1.1)	504/1534	0.79 (0.69 to 0.92)	−2.3 (−3.7 to −0.9)
Copper	167 644/2826	2771/74	0.82 (0.56 to 1.21)	−2.5 (−7.8 to 2.9)	2758/87	0.81 (0.58 to 1.13)	−2.6 (−7.3 to 2.0)
Phosphorus	169 960/510	2830/15	0.75 (0.34 to 1.63)	−3.9 (−15.8 to 8.1)	2830/15	0.76 (0.35 to 1.66)	−3.6 (−15.4 to 8.2)
Selenium	170 323/146	2841/4	–	–	2841/4	–	–
Iron§	169 684/785	2836/9	0.71 (0.29 to 1.73)	−4.6 (−18.8 to 9.6)	2835/10	0.66 (0.29 to 1.51)	−5.8 (−20.1 to 8.4)
Magnesium	75 852/94 618	994/1851	0.85 (0.74 to 0.98)	−1.8 (−3.3 to −0.2)	491/2354	0.78 (0.65 to 0.93)	−2.7 (−4.5 to −0.9)
Calcium	100 797/69 673	1205/1640	1.01 (0.89 to 1.16)	0.1 (−1.4 to 1.7)	742/2103	1.02 (0.90 to 1.17)	0.3 (−1.3 to 1.8)
Zinc	162 287/8183	2588/257	0.93 (0.74 to 1.17)	−0.9 (−3.7 to 2.0)	2539/306	0.91 (0.76 to 1.09)	−1.2 (−3.5 to 1.1)
Potassium	1196/169 273	14/2831	1.12 (0.53 to 2.37)	1.3 (−8.3 to 10.9)	10/2835	1.01 (0.38 to 2.64)	0.1 (−11.1 to 11.2)
Fiber	4319/166 150	64/2781	0.77 (0.54 to 1.12)	−2.6 (−6.0 to 0.8)	53/2792	0.84 (0.56 to 1.27)	−1.8 (−5.9 to 2.2)
EPA + DHA	2527/167 943	38/2807	0.89 (0.49 to 1.62)	−1.2 (−7.3 to 4.9)	0/2845	–	–
	Person-Years (>UL/≤UL)	**Total Nutrient Intake**			**Nutrient Intake From Foods**		
		Total Deaths (>UL/≤UL), *n*	**RR (95% CI)†**	**RD (95% CI)†**	**Total Deaths (>UL/≤UL), *n***	**RR (95% CI)†**	**RD (95% CI)†**
Excess intake‖							
Vitamin A	948/127 095	23/2015	1.54 (0.76 to 3.12)	5.6 (−5.6 to 16.7)	1/2037	–	–
Niacin	11 415/159 055	176/2669	1.00 (0.82 to 1.21)	0.0 (−2.3 to 2.2)	0/2845	–	–
Vitamin B_6	2859/167 610	62/2783	1.35 (0.98 to 1.88)	4.0 (−1.0 to 9.0)	0/2845	–	–
Folate	2859/167 610	62/2783	1.21 (0.88 to 1.67)	2.2 (−1.8 to 6.1)	0/2038	–	–
Choline	38/55 842	0/741	–	–	0/741	–	–
Vitamin C	1344/169 126	30/2815	1.44 (0.82 to 2.51)	5.0 (−4.2 to 14.1)	0/2845	–	–
Vitamin D	103/31 797	3/400	–	–	0/403	–	–
Vitamin E	776/86 394	24/1296	1.26 (0.89 to 1.79)	3.0 (−2.0 to 8.0)	0/2845	–	–
Copper	274/170 196	5/2840	1.27 (0.58 to 2.77)	3.1 (−8.3 to 14.5)	0/2845	–	–
Phosphorus	96/170 373	2/2843	–	–	0/2845	–	–
Selenium	1108/169 362	15/2830	0.97 (0.46 to 2.05)	−0.3 (−8.6 to 8.0)	0/2845	–	–
Iron§	3834/166 636	86/2759	1.25 (0.90 to 1.74)	2.8 (−1.8 to 7.5)	0/2845	–	–
Magnesium	4116/166 353	72/2773	1.00 (0.70 to 1.43)	0.0 (−4.1 to 4.1)	0/2845	–	–
Calcium	5302/165 167	124/2721	1.13 (0.87 to 1.46)	1.4 (−1.8 to 4.7)	4/2841	–	–
Zinc	6037/164 433	142/2703	1.06 (0.87 to 1.30)	0.7 (−1.7 to 3.1)	0/2845	–	–

DFE = dietary folate equivalent; DHA = docosahexaenoic acid; EAR = Estimated Average Requirement; EPA = eicosapentaenoic acid; NHANES = National Health and Nutrition Examination Survey; RAE = retinal activity equivalent; RD = rate difference; RR = rate ratio; UL = Tolerable Upper Intake Level.

* For nutrient intake from supplements, the RRs, RDs, and 95% CIs for adequate intake correspond to comparisons between participants with supplemental intake at or above the median versus nonusers. The median was defined as the median supplement dose reported by supplement users. Median doses were 820 RAE mcg/d for vitamin A, 1.5 mg/d for thiamin, 1.7 mg/d for riboflavin, 18 mg/d for niacin, 2 mg/d for vitamin B_6, 600 DFE mcg/d for folate, 12 mcg/d for vitamin B_{12}, 25 mg/d for choline, 90 mg/d for vitamin C, 9 mcg/d for vitamin D, 45 mg/d for vitamin E, 20 mcg/d for vitamin K, 1.8 mg/d for copper, 55 mg/d for phosphorus, 20 mcg/d for selenium, 16 mg/d for iron, 50 mg/d for magnesium, 200 mg/d for calcium, 14 mg/d for zinc, 80 mg/d for potassium, 2 g/d for fiber, and 600 mg/d for EPA + DHA. RRs, RDs, and 95% CIs for excess intake correspond to comparisons between participants with supplemental intake at a high dose versus nonusers. The high dose was determined by the commonly used dose at approximately the 75th to 85th percentile reported by supplement users. High doses were 1050 RAE mcg/d for vitamin A, 20 mg/d for niacin, 3 mg/d for vitamin B_6, 680 DFE mcg/d for folate, 50 mg/d for choline, 500 mg/d for vitamin C, 10 mcg/d for vitamin D, 100 mg/d for vitamin E, 2 mg/d for copper, 100 mg/d for phosphorus, 70 mcg/d for selenium, 18 mg/d for iron, 100 mg/d for magnesium, 1000 mg/d for calcium, and 15 mg/d for zinc.

† RRs, RDs, and 95% CIs were adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, presence of comorbid conditions at baseline, and NHANES survey weights. In models that included intake from both foods and supplements, each source was adjusted for the other. Multiple imputation was done for alcohol intake. RRs and RDs were not estimated for nutrients with <5 deaths in any intake subgroup.

‡ Adequate intake was defined as levels of nutrient intake at or above the EAR. RRs, RDs, and 95% CIs correspond to the comparisons between participants with total nutrient intake at or above versus below the EAR. For choline, vitamin K, potassium, and fiber, EARs were not available, so adequate intake was defined as intake at or above the Adequate Intake level. For EPA + DHA, adequate intake was defined as intake at or above that recommended by the Academy of Nutrition and Dietetics.

§ Models were also adjusted for presence of anemia at baseline (yes vs. no).

‖ Excess intake was defined as levels of nutrient intake above the UL. RRs, RDs, and 95% CIs correspond to comparisons between participants with total nutrient intake above versus at or below the UL. Few participants (<0.1%) had excess intake of nutrients from foods only.

Table 4–Continued

Total Deaths (≥Median/Nonusers), *n*	RR (95% CI)†	RD (95% CI)†
	Nutrient Intake From Supplements*	
523/1303	1.12 (0.94 to 1.33)	1.2 (−0.7 to 3.1)
333/1860	1.11 (0.95 to 1.31)	1.3 (−0.7 to 3.3)
873/1860	1.03 (0.90 to 1.18)	0.3 (−1.3 to 1.9)
827/1859	1.04 (0.91 to 1.18)	0.4 (−1.1 to 2.0)
593/1825	0.99 (0.85 to 1.14)	−0.1 (−1.8 to 1.5)
608/1301	1.00 (0.85 to 1.19)	0.0 (−1.7 to 1.8)
544/1820	0.92 (0.80 to 1.05)	−1.0 (−2.4 to 0.5)
19/712	0.79 (0.39 to 1.60)	−1.8 (−6.7 to 3.0)
599/1703	1.10 (0.95 to 1.29)	1.2 (−0.7 to 3.0)
118/258	0.98 (0.74 to 1.31)	−0.1 (−2.3 to 2.1)
740/1713	0.97 (0.87 to 1.09)	−0.3 (−1.6 to 0.9)
286/1506	0.96 (0.79 to 1.17)	−0.4 (−2.4 to 1.6)
667/1992	1.03 (0.88 to 1.19)	0.3 (−1.4 to 2.1)
365/2140	1.09 (0.92 to 1.29)	1.0 (−1.0 to 3.0)
324/2004	0.96 (0.82 to 1.13)	−0.5 (−2.3 to 1.3)
433/2250	1.15 (0.99 to 1.33)	1.7 (−0.3 to 3.6)
776/1967	1.00 (0.87 to 1.14)	0.0 (−1.6 to 1.5)
522/1798	0.98 (0.85 to 1.14)	−0.2 (−1.9 to 1.5)
750/1899	1.04 (0.91 to 1.20)	0.5 (−1.1 to 2.1)
582/2056	1.03 (0.88 to 1.21)	0.4 (−1.5 to 2.3)
38/2789	0.89 (0.61 to 1.31)	−1.2 (−5.2 to 2.8)
15/2815	0.95 (0.60 to 1.49)	−0.6 (−5.5 to 4.3)

Total Deaths (High Dose/Nonusers), *n*	RR (95% CI)†	RD (95% CI)†
	Nutrient Intake From Supplements*	
261/1303	1.16 (0.97 to 1.40)	1.7 (−0.5 to 3.8)
236/1859	1.03 (0.86 to 1.24)	0.4 (−1.8 to 2.5)
334/1825	1.07 (0.89 to 1.28)	0.8 (−1.4 to 3.0)
146/1301	1.04 (0.82 to 1.32)	0.4 (−2.1 to 3.0)
14/712	0.74 (0.38 to 1.44)	−2.3 (−6.6 to 2.0)
353/1703	1.15 (0.95 to 1.39)	1.7 (−0.7 to 4.0)
68/258	1.02 (0.74 to 1.42)	0.2 (−2.5 to 2.8)
437/1713	0.99 (0.87 to 1.13)	−0.1 (−1.7 to 1.4)
127/1992	1.14 (0.89 to 1.46)	1.6 (−1.5 to 4.8)
336/2140	1.12 (0.94 to 1.35)	1.4 (−0.9 to 3.7)
177/2004	1.07 (0.86 to 1.31)	0.8 (−1.8 to 3.3)
123/2250	1.27 (0.99 to 1.63)	3.1 (−0.5 to 6.6)
173/1967	1.01 (0.80 to 1.28)	0.1 (−2.6 to 2.9)
169/1798	1.05 (0.83 to 1.34)	0.6 (−2.3 to 3.5)
228/1899	1.11 (0.92 to 1.33)	1.2 (−1.0 to 3.4)

31) and others raising concerns about its safety (32–34). For example, the HPFS (Health Professionals Follow-up Study) reported that total calcium intake of 1500 mg/d or higher was associated with increased risk for advanced or fatal prostate cancer among 47 750 men in the cohort (35). In a recent systematic review of 11 cohort studies, high total calcium intake was associated with increased risk for prostate cancer (relative risk, 1.11 [CI, 1.02 to 1.20]), and the association seemed stronger among persons followed for 10 or more years (relative risk, 1.22 [CI, 1.07 to 1.38]) (36). The underlying mechanisms are unclear and may involve stimulation of calcium-sensing receptors to promote secretion of parathyroid hormone–related protein, which could subsequently inhibit cell differentiation and alter proliferation (37). We further evaluated calcium intake from foods versus supplements and found increased cancer mortality only for high doses (≥1000 mg/d) from supplements rather than foods. These data are consistent with results from 59 744 men in the CPS-II Nutrition Cohort, where lower supplemental doses (<1000 mg/d) or calcium intake from foods did not increase risk, whereas higher supplemental doses (≥1000 mg/d) were associated with increased all-cause mortality (8). The difference between calcium from supplements versus foods may be explained by the different effects on circulating calcium: High intake from foods can lead to reduced intestinal absorption and increased urinary excretion, whereas long-term supplement use does not diminish circulating calcium levels (34).

We found that vitamin D supplementation at doses above 10 mcg/d might be associated with increased all-cause and cancer death among persons without vitamin D deficiency. Whether vitamin D supplementation reduces premature death or prevents cancer is controversial. Prior meta-analysis of intervention trials suggests that vitamin D supplements may modestly reduce all-cause and cancer mortality (38), but recent trials did not support its role in preventing cancer or CVD (39–41). The most recent trial, VITAL (Vitamin D and Omega-3 Trial), did not detect an effect of vitamin D supplements at a dose of 2000 IU/d on reducing cancer or CVD incidence among 25 817 participants during a median follow-up of 5.3 years (42). Potential benefits or harms of vitamin D supplement use need to be further evaluated.

Strengths of our study include use of a nationally representative sample of U.S. adults, longitudinal study design, and collection of data using validated measures. However, several limitations must be considered. First, dietary supplement use was assessed in the previous 30 days, which may not reflect habitual use or capture changes in use after baseline assessment. Prevalence and dosage of supplement use were based on self-report and so are subject to recall bias. However, NHANES documented that the ingredient and dosage information were obtained from the bottles and nutrition fact labels at the time of the interview 80% of the time (43), which reduces misclassification error due to recall bias.

Second, self-reported dietary intake is also subject to measurement error. NHANES incorporated one or two 24-hour diet recalls per person, which does not capture long-term intake because of large day-to-day variations in food intake. To improve the estimation of usual intake, we applied the NCI method to reduce measurement error associated with dietary intake estimated using diet recalls (44–46). Measurement error cannot be ruled out, however, and is likely to be nondifferential (independent of mortality), which attenuates the associations.

Third, supplement use is highly correlated with participants' socioeconomic status and lifestyle factors, such as education, smoking, body mass index, alcohol intake, physical activity, and diet quality. Having chronic health conditions, such as cancer, CVD, hypertension, or diabetes, may also motivate initiation of dietary supplement use. To minimize the chance of residual confounding, we adjusted for all of these factors in the multivariable models. In addition, we stratified participants by presence of comorbid conditions at baseline, and the associations remained similar. However, supplement use may be associated with factors that we have not identified and adjusted for, and residual confounding may still be present.

Fourth, mortality outcomes were determined through linkage to the National Death Index via a probabilistic match (11), which may have resulted in misclassification. A prior validation study showed that the method was highly accurate, with 96.1% of the decedents and 99.4% of the living participants classified correctly (47).

Fifth, given the limited sample size, we were unable to evaluate dietary supplement use and mortality from specific CVD conditions or cancer types or mortality due to conditions other than CVD or cancer.

Finally, we evaluated multiple nutrients, which can lead to spurious findings due to multiple comparisons. Humans consume foods and nutrients that are highly correlated. The complex interactions among nutrients are likely to play a more important role in determining health outcomes than individual nutrients. Thus, our findings on individual nutrients should be considered exploratory and interpreted with caution.

In conclusion, use of dietary supplements was not associated with mortality benefits among a nationally representative sample of U.S. adults. Although adequate nutrient intake from foods could contribute to reduced risk for death, excess intake from supplements might increase mortality. The potential risks and benefits of dietary supplement use for health need to be further evaluated in future studies.

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Reproducible Research Statement: *Study protocol and data set:* Not available. *Statistical code:* Available from Dr. Zhang (e-mail, fang_fang.zhang@tufts.edu).

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Appendix 1: Methods of Estimating Daily Dosage of Dietary Supplements

Data on dietary supplement use were obtained from 6 cycles of NHANES (1999–2000 to 2009–2010). At each cycle, participants were asked during the household interview whether they had used any vitamins, minerals, or other dietary supplements in the previous 30 days. If the answer was yes, they were asked to show the containers to the interviewers, who recorded the product information, including the brand name and the product form (for example, tablets or capsules). If the participants could not show the containers, they were asked to recall the product information. More than 75% of the production information was recorded on the basis of information from the containers. Participants were then asked to report the number of days they took the product in the previous 30 days and the number of servings (for example, tablets, capsules, or drops) they usually took on days when they took it (48).

Data on supplement use are available from the following NHANES data files: 30-day total dietary supplement use, 30-day individual dietary supplement use, product information, ingredient information, and blend information. The first 2 files contain information on use of dietary supplements in the previous 30 days reported by each participant, and the last 3 contain information on the supplement brands, ingredients, amounts of the ingredients, and blends.

To estimate the daily dose of dietary supplements for each participant, we first estimated the number of different products used by each participant by multiplying the number of days by the number of serving size units used in the previous 30 days. We then associated each product in the product information data file with the ingredient in the information data file to identify the amount of vitamins, minerals, and nutrients in each serving size unit for each product. For proprietary blends, we used the blend information data file to disaggregate the ingredients.

To estimate the daily dose of nutrients that each participant received from multiple products, we summed the amount of each nutrient consumed from different products by multiplying the number of serving size units in the previous 30 days by the amount of nutrient per serving size for each product. We then divided the total amount by 30 days to estimate the daily dose of each supplemental nutrient taken by each participant. For example, for a participant who reported daily use of one 600-mg tablet of a single-ingredient calcium supplement for 20 days and 1 capsule of an MVM supplement containing 200 mg of calcium for 15 days, the total daily dose of supplemental calcium intake in the previous 30 days for that participant was estimated to be 500 mg/d in the past 30 days.

$$\frac{1\text{ tablet} \times 600\,\frac{\text{mg}}{\text{tablet}} \times 20\text{ d} + 1\text{ capsule} \times 200\,\frac{\text{mg}}{\text{capsule}} \times 15\text{ d}}{30\text{ d}} = 500\text{ mg/d}$$

This process was repeated for each ingredient of interest to estimate the daily nutrient intake from supplements for each participant.

Appendix 2: Methods of Estimating Usual Intake of Nutrients From Foods

Nutrient intake from foods among NHANES participants was assessed using 24-hour diet recalls conducted by trained interviewers. One 24-hour diet recall was done in person at the Mobile Examination Center; from 2003 to 2010, a second recall was added by telephone interview approximately 3 to 10 days after the first recall. To estimate nutrient intake from foods, all foods and beverages reported in diet recalls were coded, and their nutrient values were determined using FNDDS, versions 1.0 to 5.0 (9).

Dietary data from one or two 24-hour diet recalls may not represent a person's usual intake because of substantial within-person variability due to day-to-day variations in food intake. To correct for measurement error, we applied the NCI method to estimate usual intake of nutrients from foods (49). As documented in prior literature, the NCI method is the preferred method for estimating usual intake distribution from 24-hour diet recalls (17). It also uses regression calibration to correct for bias caused by measurement error in evaluating associations between usual intake and health outcomes (50).

We used a 2-step approach to estimate usual intake in the NCI method. The first step modeled the probability of consuming a given food or nutrient and the amount for foods or nutrients that are not consumed daily by most persons. Because most nutrients are consumed daily by nearly everyone, the amount-only model was used in the first step (MIXTRAN macro) for most nutrients. For nutrients that are episodically consumed, with more than 5% of the participants reporting zero intake on a given day (17), such as lycopene, eicosapentaenoic acid, docosahexaenoic acid, and added vitamin E, we used a 2-part model that estimated the probability of consumption and the amount.

The second step of the NCI method involves estimating usual intake with parameters estimated from the first step using mixed-effect linear regression on a transformed scale with a person-specific effect (INDIVINT macro) (49). The NCI method requires that some of the participants have multiple days of nutrient intake to estimate and separate within- and between-person variation (51). In our study, 17 189 also provided a second valid diet recall (62% of the 27 725 participants who provided a first valid recall). For each nutrient, the following covariates were specified for estimation of usual intake: an indicator of first- versus second-day diet recall, day of the week when recall occurred (weekday vs. weekend), use of dietary supplements (yes vs. no), age group (20 to 34, 35 to 49, 50 to 64, and ≥65 years), sex, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other). For the association analysis, we also included education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, and presence of comorbid conditions at baseline.

To estimate the percentage of U.S. adults with adequate or excess nutrient intake, we compared the estimated usual intake with a predefined threshold, such as the Estimated Average Requirement or the Tolerable Upper Intake Level specified in the Dietary Reference Intakes (10). As expected, the SEs associated with the estimated mean intake decreased after adjustment using the NCI method. Because the NCI method produces adjusted usual intake that is shrunk toward the sample mean, the estimated percentage of participants with nutrient intake below the Estimated Average Requirement or above the Tolerable Upper Intake Level was also smaller than that estimated without the NCI method. The associations between adequate or excess nutrient intake and mortality outcomes were largely similar before and after adjustment using the NCI method.

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Appendix Table 1. Association of Dietary Supplement Use With CVD and Cancer Mortality							
Supplement	**Person-Years (Users/Nonusers)**	**CVD Mortality**			**Cancer Mortality**		
		CVD Deaths (Users/ Nonusers), *n*	**RR (95% CI)**		**Cancer Deaths (Users/ Nonusers), *n***	**RR (95% CI)**	
			Model 1*	**Model 2†**		**Model 1***	**Model 2†**
Any	90 515/99 288	528/417	0.90 (0.74–1.09)	1.04 (0.84–1.31)	439/366	0.92 (0.76–1.13)	1.00 (0.80–1.25)
MVM	66 295/123 508	373/572	0.86 (0.73–1.01)	1.03 (0.85–1.25)	313/492	0.91 (0.74–1.12)	1.00 (0.80–1.26)
Individual vitamins							
Vitamin A	60 556/129 247	324/621	0.83 (0.70–0.98)	0.98 (0.81–1.18)	287/518	0.97 (0.80–1.18)	1.08 (0.87–1.35)
β-Carotene	60 440/129 363	324/621	0.83 (0.70–0.98)	0.98 (0.81–1.18)	287/518	0.97 (0.80–1.18)	1.09 (0.87–1.35)
Retinol	56 138/133 664	296/649	0.84 (0.71–1.00)	0.96 (0.79–1.16)	262/543	1.02 (0.84–1.25)	1.11 (0.88–1.39)
Thiamin	61 942/127 860	334/611	0.90 (0.76–1.07)	1.06 (0.87–1.30)	279/526	0.90 (0.72–1.11)	0.96 (0.76–1.22)
Riboflavin	61 733/128 070	334/611	0.88 (0.74–1.05)	1.03 (0.84–1.26)	283/522	0.92 (0.74–1.15)	1.00 (0.78–1.27)
Niacin	62 099/127 704	334/611	0.90 (0.75–1.08)	1.06 (0.87–1.29)	282/523	0.91 (0.73–1.13)	0.98 (0.77–1.25)
Pantothenic acid	59 582/130 221	324/621	0.90 (0.75–1.07)	1.05 (0.86–1.29)	276/529	0.91 (0.73–1.14)	0.99 (0.78–1.26)
Vitamin B_6	63 528/126 274	345/600	0.90 (0.75–1.07)	1.06 (0.87–1.29)	293/512	0.92 (0.74–1.14)	0.98 (0.78–1.24)
Folate	62 799/127 004	340/605	0.89 (0.74–1.06)	1.04 (0.85–1.28)	284/521	0.86 (0.70–1.06)	0.94 (0.74–1.19)
Vitamin B_{12}	64 139/125 663	346/599	0.87 (0.73–1.03)	1.00 (0.82–1.21)	294/511	0.88 (0.71–1.11)	0.95 (0.75–1.22)
Choline	9447/180 355	32/913	0.74 (0.42–1.30)	0.89 (0.47–1.70)	29/776	1.04 (0.69–1.55)	1.30 (0.85–2.00)
Vitamin C	69 804/119 998	391/554	0.88 (0.75–1.04)	1.08 (0.89–1.32)	328/477	0.94 (0.77–1.14)	1.03 (0.84–1.27)
Vitamin D	63 794/126 009	336/609	0.80 (0.68–0.95)	0.91 (0.76–1.10)	300/505	0.96 (0.78–1.18)	1.07 (0.85–1.35)
Vitamin E	68 085/121 718	383/562	0.82 (0.70–0.96)	1.02 (0.84–1.23)	316/489	0.83 (0.68–1.01)	0.94 (0.76–1.16)
Vitamin K	43 823/145 980	229/716	0.80 (0.67–0.96)	0.89 (0.72–1.10)	211/594	0.93 (0.75–1.15)	0.99 (0.76–1.30)
Biotin	52 670/137 133	281/664	0.87 (0.72–1.05)	1.02 (0.82–1.28)	245/560	0.90 (0.72–1.12)	1.00 (0.77–1.29)
Individual minerals							
Copper	52 483/137 319	285/660	0.84 (0.70–1.01)	0.99 (0.81–1.23)	248/557	0.88 (0.71–1.10)	1.02 (0.79–1.30)
Phosphorus	40 657/149 145	232/713	0.85 (0.69–1.05)	0.96 (0.76–1.22)	209/596	1.00 (0.80–1.26)	1.09 (0.83–1.43)
Selenium	50 953/138 849	277/668	0.83 (0.69–0.99)	0.95 (0.77–1.18)	245/560	0.93 (0.74–1.17)	1.04 (0.80–1.34)
Boron	41 529/148 273	224/721	0.81 (0.67–0.99)	0.88 (0.71–1.11)	206/599	1.02 (0.82–1.26)	1.12 (0.87–1.44)
Iodine	47 219/142 584	253/692	0.85 (0.70–1.03)	0.98 (0.78–1.22)	223/582	0.93 (0.74–1.16)	1.03 (0.80–1.33)
Silicon	36 105/153 698	210/735	0.84 (0.68–1.04)	0.90 (0.71–1.14)	188/617	1.01 (0.81–1.26)	1.07 (0.83–1.40)
Iron	43 032/146 771	208/737	0.96 (0.78–1.17)	1.02 (0.80–1.30)‡	190/615	1.02 (0.79–1.31)	1.02 (0.78–1.35)‡
Magnesium	56 881/132 922	288/657	0.82 (0.69–0.97)	0.93 (0.75–1.14)	253/552	0.92 (0.74–1.14)	1.04 (0.82–1.32)
Calcium	66 699/123 103	345/600	0.76 (0.64–0.91)	0.89 (0.73–1.07)	303/502	0.90 (0.73–1.10)	0.99 (0.78–1.25)
Manganese	51 182/138 621	266/679	0.80 (0.66–0.97)	0.92 (0.74–1.15)	240/565	0.90 (0.73–1.12)	1.01 (0.80–1.30)
Tin	24 321/165 482	121/824	1.03 (0.84–1.25)	1.11 (0.90–1.37)	115/690	1.15 (0.86–1.54)	1.20 (0.84–1.70)
Chromium	50 575/139 228	253/692	0.81 (0.68–0.98)	0.94 (0.76–1.16)	230/575	0.93 (0.75–1.15)	1.02 (0.80–1.30)
Molybdenum	44 337/145 466	248/697	0.86 (0.71–1.03)	0.95 (0.76–1.19)	220/585	0.98 (0.79–1.23)	1.06 (0.82–1.38)
Vanadium	38 418/151 385	215/730	0.82 (0.67–1.01)	0.89 (0.70–1.12)	201/604	1.05 (0.84–1.31)	1.14 (0.87–1.49)
Nickel	34 572/155 231	205/740	0.87 (0.71–1.07)	0.94 (0.74–1.20)	188/617	1.08 (0.86–1.35)	1.14 (0.87–1.50)
Zinc	59 276/130 527	317/628	0.86 (0.73–1.03)	1.01 (0.83–1.24)	270/535	0.90 (0.73–1.11)	1.00 (0.78–1.28)
Potassium	46 960/142 843	270/675	0.92 (0.77–1.10)	1.01 (0.82–1.24)	231/574	0.99 (0.80–1.23)	1.06 (0.83–1.36)
Other							
Lutein	29 435/160 368	187/758	0.89 (0.71–1.11)	0.98 (0.77–1.24)	166/639	1.06 (0.82–1.36)	1.16 (0.89–1.51)
Lycopene	17 989/171 814	96/849	0.68 (0.51–0.91)	0.77 (0.57–1.02)	75/730	0.61 (0.43–0.87)	0.66 (0.46–0.96)
Zeaxanthin	1397/188 406	5/940	1.21 (0.40–3.71)	1.43 (0.52–3.94)	4/801	0.41 (0.09–1.86)	0.55 (0.12–2.53)
Inositol	7835/181 968	23/922	0.71 (0.40–1.27)	0.80 (0.40–1.60)	21/784	0.76 (0.50–1.14)	0.93 (0.61–1.41)
Fiber	4468/185 335	16/929	0.62 (0.37–1.04)	0.70 (0.30–1.65)	16/789	0.78 (0.39–1.57)	0.84 (0.38–1.84)
Omega-3	7475/182 328	27/918	0.57 (0.35–0.90)	0.65 (0.38–1.09)	30/775	0.78 (0.48–1.27)	1.03 (0.64–1.66)
EPA	5934/183 869	23/922	0.63 (0.37–1.09)	0.74 (0.40–1.36)	24/781	0.73 (0.41–1.31)	1.00 (0.57–1.77)
DHA	6236/183 567	24/921	0.64 (0.38–1.07)	0.76 (0.43–1.35)	25/780	0.80 (0.45–1.41)	1.08 (0.62–1.88)
Omega-6	1994/187 809	7/938	1.12 (0.49–2.57)	1.05 (0.45–2.43)	12/793	0.99 (0.54–1.81)	1.26 (0.64–2.47)
Omega-9	1510/188 293	5/940	0.72 (0.29–1.76)	0.52 (0.19–1.41)	8/797	0.99 (0.46–2.10)	1.24 (0.54–2.85)

CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; MVM = multivitamin and mineral; NHANES = National Health and Nutrition Examination Survey; RR = rate ratio.
* Adjusted for age, sex, and race/ethnicity.
† Adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, and presence of comorbid conditions at baseline. Multiple imputation was done for alcohol intake. RRs and 95% CIs were adjusted for NHANES survey weights.
‡ Also adjusted for presence of anemia at baseline (yes vs. no).

Appendix Table 2. Association of Nutrient Intake From Foods Versus Supplements and CVD Mortality

Nutrient	Person-Years (≥EAR/<EAR)	Total Nutrient Intake			Nutrient Intake From Foods			Nutrient Intake From Supplements*		
		CVD Deaths (≥EAR/<EAR), *n*	RR (95% CI)†	RD (95% CI)†	CVD Deaths (≥EAR/<EAR), *n*	RR (95% CI)†	RD (95% CI)†	CVD Deaths (≥Median/Nonusers), *n*	RR (95% CI)†	RD (95% CI)†
Adequate intake‡										
Vitamin A	78 730/49 313	342/172	0.61 (0.43 to 0.88)	−1.3 (−2.5 to −0.2)	299/215	0.51 (0.36 to 0.73)	−1.8 (−3.0 to −0.7)	145/323	1.22 (0.94 to 1.59)	0.5 (−0.2 to 1.2)
Thiamin	170 015/454	720/4	–	–	720/4	–	–	92/467	1.28 (0.94 to 1.73)	0.7 (−0.2 to 1.6)
Riboflavin	169 430/1039	713/11	0.29 (0.08 to 1.04)	−6.2 (−17.4 to 5.0)	713/11	0.31 (0.08 to 1.15)	−5.6 (−16.1 to 4.9)	233/469	1.05 (0.86 to 1.30)	0.1 (−0.4 to 0.7)
Niacin	169 990/480	718/6	0.19 (0.06 to 0.60)	−10.6 (−25.3 to 4.2)	718/6	0.21 (0.07 to 0.67)	−9.3 (−22.8 to 4.1)	220/467	1.10 (0.89 to 1.36)	0.2 (−0.3 to 0.8)
Vitamin B_6	161 408/9062	646/78	0.78 (0.52 to 1.17)	−0.7 (−2.0 to 0.6)	620/104	0.75 (0.51 to 1.09)	−0.8 (−2.1 to 0.4)	155/458	1.06 (0.82 to 1.37)	0.2 (−0.5 to 0.8)
Folate	124 006/4036	488/26	0.54 (0.28 to 1.02)	−2.0 (−4.8 to 0.7)	480/34	0.57 (0.29 to 1.10)	−1.8 (−4.5 to 0.9)	163/323	1.09 (0.84 to 1.40)	0.2 (−0.4 to 0.8)
Vitamin B_{12}	169 894/576	718/6	0.44 (0.18 to 1.10)	−3.2 (−8.4 to 2.1)	718/6	0.53 (0.20 to 1.39)	−2.3 (−6.9 to 2.4)	128/461	0.87 (0.66 to 1.15)	−0.3 (−1.0 to 0.3)
Choline	1585/54 295	5/184	0.39 (0.09 to 1.67)	−1.3 (−2.6 to 0.0)	2/187	–	–	6/181	0.93 (0.29 to 3.02)	−0.1 (−2.5 to 2.2)
Vitamin C	131 636/38 833	570/154	1.09 (0.77 to 1.54)	0.2 (−0.6 to 1.1)	515/209	1.06 (0.82 to 1.38)	0.2 (−0.5 to 0.8)	166/424	1.11 (0.86 to 1.43)	0.3 (−0.4 to 0.9)
Vitamin D	8752/23 148	28/68	0.66 (0.39 to 1.13)	−0.7 (−1.7 to 0.2)	1/95	–	–	27/64	0.63 (0.37 to 1.09)	−0.8 (−1.9 to 0.2)
Vitamin E	58 687/111 783	296/428	1.09 (0.89 to 1.32)	0.2 (−0.3 to 0.7)	10/714	0.90 (0.38 to 2.13)	−0.3 (−2.2 to 1.7)	198/425	1.04 (0.83 to 1.30)	0.1 (−0.5 to 0.7)
Vitamin K	41 693/86 349	153/361	0.68 (0.54 to 0.86)	−0.9 (−1.4 to −0.3)	119/395	0.66 (0.49 to 0.89)	−0.9 (−1.5 to −0.3)	69/382	1.02 (0.75 to 1.39)	0.0 (−0.7 to 0.8)
Copper	167 644/2826	693/31	0.29 (0.17 to 0.51)	−5.9 (−10.4 to −1.5)	690/34	0.32 (0.19 to 0.53)	−5.3 (−9.1 to −1.5)	173/502	1.01 (0.79 to 1.28)	0.0 (−0.6 to 0.6)
Phosphorus	169 960/510	716/8	0.28 (0.07 to 1.18)	−6.4 (−19.2 to 6.4)	716/8	0.28 (0.07 to 1.20)	−6.3 (−19.0 to 6.3)	96/542	1.11 (0.87 to 1.42)	0.3 (−0.4 to 1.0)
Selenium	170 323/146	722/2	–	–	722/2	–	–	81/510	0.95 (0.70 to 1.30)	−0.1 (−0.9 to 0.7)
Iron§	169 684/785	721/3	–	–	721/3	–	–	119/567	1.24 (0.93 to 1.66)	0.6 (−0.3 to 1.5)
Magnesium	75 852/94 618	249/475	0.83 (0.63 to 1.11)	−0.5 (−1.2 to 0.2)	112/612	0.73 (0.51 to 1.03)	−0.7 (−1.5 to 0.0)	204/497	0.93 (0.74 to 1.17)	−0.2 (−0.7 to 0.4)
Calcium	100 797/69 673	291/433	0.96 (0.73 to 1.28)	−0.1 (−0.8 to 0.6)	168/556	1.11 (0.82 to 1.50)	0.3 (−0.5 to 1.1)	130/457	0.93 (0.72 to 1.19)	−0.2 (−0.8 to 0.4)
Zinc	162 287/8183	636/88	0.50 (0.36 to 0.71)	−2.4 (−4.1 to −0.7)	627/97	0.56 (0.40 to 0.78)	−1.9 (−3.3 to −0.5)	199/475	1.06 (0.84 to 1.34)	0.2 (−0.5 to 0.8)
Potassium	1196/169 273	3/721	–	–	2/722	–	–	150/517	0.96 (0.75 to 1.25)	−0.1 (−0.7 to 0.5)
Fiber	4319/166 150	9/715	0.49 (0.24 to 1.02)	−1.3 (−2.3 to −0.3)	8/716	0.64 (0.29 to 1.41)	−0.9 (−2.3 to 0.4)	5/715	0.42 (0.14 to 1.27)	−1.5 (−2.7 to −0.3)
EPA + DHA	2527/167 943	11/713	0.95 (0.45 to 2.01)	−0.1 (−2.0 to 1.7)	0/724	–	–	4/718	–	–

Nutrient	Person-Years (>UL/≤UL)	Total Nutrient Intake			Nutrient Intake From Foods			Nutrient Intake From Supplements*		
		CVD Deaths (>UL/≤UL), *n*	RR (95% CI)†	RD (95% CI)†	CVD Deaths (>UL/≤UL), *n*	RR (95% CI)†	RD (95% CI)†	CVD Deaths (High Dose/Nonusers), *n*	RR (95% CI)†	RD (95% CI)†
Excess intake‖										
Vitamin A	948/127 095	4/510	–	–	0/514	–	–	71/323	1.30 (0.92 to 1.83)	0.7 (−0.3 to 1.8)
Niacin	11 415/159 055	47/677	1.15 (0.80 to 1.64)	0.4 (−0.7 to 1.4)	0/724	–	–	58/467	1.18 (0.82 to 1.70)	0.5 (−0.6 to 1.5)
Vitamin B_6	2859/167 610	15/709	1.60 (0.86 to 2.99)	1.5 (−1.0 to 4.0)	0/724	–	–	83/458	1.19 (0.87 to 1.63)	0.5 (−0.4 to 1.4)
Folate	2859/167 610	15/709	1.25 (0.64 to 2.44)	0.6 (−1.4 to 2.6)	0/514	–	–	38/323	1.07 (0.66 to 1.74)	0.2 (−1.1 to 1.4)
Choline	38/55 842	0/189	–	–	0/189	–	–	4/181	–	–
Vitamin C	1344/169 126	5/719	1.14 (0.39 to 3.34)	0.4 (−2.7 to 3.5)	0/724	–	–	97/424	1.22 (0.90 to 1.66)	0.5 (−0.3 to 1.4)
Vitamin D	103/31 797	0/96	–	–	0/96	–	–	16/64	0.68 (0.37 to 1.23)	−0.7 (−1.8 to 0.3)
Vitamin E	776/86 394	6/345	1.31 (0.68 to 2.52)	0.8 (−1.4 to 2.9)	0/724	–	–	125/425	1.13 (0.83 to 1.55)	0.3 (−0.5 to 1.2)
Copper	274/170 196	1/723	–	–	0/724	–	–	33/502	1.20 (0.68 to 2.12)	0.5 (−1.2 to 2.2)
Phosphorus	96/170 373	0/724	–	–	0/724	–	–	87/542	1.12 (0.84 to 1.48)	0.3 (−0.5 to 1.1)
Selenium	1108/169 362	3/721	–	–	0/724	–	–	41/510	1.15 (0.73 to 1.82)	0.4 (−1.0 to 1.7)
Iron§	3834/166 636	26/698	1.59 (0.83 to 3.05)	1.5 (−1.1 to 4.1)	0/724	–	–	37/567	1.55 (0.91 to 2.64)	1.4 (−0.6 to 3.4)
Magnesium	4116/166 353	16/708	1.05 (0.54 to 2.02)	0.1 (−1.6 to 1.9)	0/724	–	–	39/497	0.91 (0.56 to 1.49)	−0.2 (−1.4 to 0.9)
Calcium	5302/165 167	29/695	1.18 (0.77 to 1.81)	0.5 (−0.8 to 1.7)	1/723	–	–	41/457	1.09 (0.73 to 1.64)	0.2 (−0.9 to 1.4)
Zinc	6037/164 433	37/687	0.99 (0.61 to 1.62)	0.0 (−1.3 to 1.2)	0/724	–	–	58/475	0.93 (0.62 to 1.38)	−0.2 (−1.1 to 0.8)

CVD = cardiovascular disease; DFE = dietary folate equivalent; DHA = docosahexaenoic acid; EAR = Estimated Average Requirement; EPA = eicosapentaenoic acid; NHANES = National Health and Nutrition Examination Survey; RAE = retinal activity equivalent; RD = rate difference; RR = rate ratio; UL = Tolerable Upper Intake Level.

* For nutrient intake from supplements, the RRs, RDs, and 95% CIs for adequate intake correspond to the comparisons between participants with supplemental intake at or above the median versus nonusers. The median was defined as the median supplement dose reported by supplement users. Median doses were 820 RAE mcg/d for vitamin A, 1.5 mg/d for thiamin, 1.7 mg/d for riboflavin, 18 mg/d for niacin, 2 mg/d for vitamin B_6, 600 DFE mcg/d for folate, 12 mcg/d for vitamin B_{12}, 25 mg/d for choline, 90 mg/d for vitamin C, 9 mcg/d for vitamin D, 45 mg/d for vitamin E, 20 mcg/d for vitamin K, 1.8 mg/d for copper, 55 mg/d for phosphorus, 20 mcg/d for selenium, 16 mg/d for iron, 50 mg/d for magnesium, 200 mg/d for calcium, 14 mg/d for zinc, 80 mg/d for potassium, 2 g/d for fiber, and 600 mg/d for EPA + DHA. RRs, RDs, and 95% CIs for excess intake correspond to the comparison between participants with supplemental intake at a high dose versus nonusers. The high dose was determined by the commonly used dose at approximately the 75th to 85th percentile reported by supplement users. High doses were 1050 RAE mcg/d for vitamin A, 20 mg/d for niacin, 3 mg/d for vitamin B_6, 680 DFE mcg/d for folate, 50 mg/d for choline, 500 mg/d for vitamin C, 10 mcg/d for vitamin D, 100 mg/d for vitamin E, 2 mg/d for copper, 100 mg/d for phosphorus, 70 mcg/d for selenium, 18 mg/d for iron, 100 mg/d for magnesium, 1000 mg/d for calcium, and 15 mg/d for zinc.

† RRs, RDs, and 95% CIs were adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, presence of comorbid conditions at baseline, and NHANES survey weights. In models that included intake from both foods and supplements, each source was adjusted for the other. Multiple imputation was done for alcohol intake. RRs and RDs were not estimated for nutrients with <5 deaths in any intake subgroup.

‡ Adequate intake was defined as levels of nutrient intake at or above the EAR. RRs, RDs, and 95% CIs correspond to the comparisons between participants with total nutrient intake at or above versus below the EAR. For choline, vitamin K, potassium, and fiber, EARs were not available, so adequate intake was defined as intake at or above the Adequate Intake level. For EPA + DHA, adequate intake was defined as intake at or above that recommended by the Academy of Nutrition and Dietetics.

§ Models were also adjusted for presence of anemia at baseline (yes vs. no).

‖ Excess intake was defined as levels of nutrient intake above the UL. RRs, RDs, and 95% CIs correspond to the comparisons between participants with total nutrient intake above versus at or below the UL. Few participants (<0.1%) had excess intake of nutrients from foods only.

Appendix Table 3. Association of Nutrient Intake From Foods Versus Supplements and Cancer Mortality

Nutrient	Person-Years (≥EAR/<EAR)	Total Nutrient Intake			Nutrient Intake From Foods			Nutrient Intake From Supplements*		
		Cancer Deaths (≥EAR/<EAR), *n*	RR (95% CI)†	RD (95% CI)†	Cancer Deaths (≥EAR/<EAR), *n*	RR (95% CI)†	RD (95% CI)†	Cancer Deaths (≥Median/Nonusers), *n*	RR (95% CI)†	RD (95% CI)†
Adequate intake‡										
Vitamin A	78 730/49 313	319/158	0.95 (0.66 to 1.37)	−0.1 (−1.1 to 0.8)	284/193	0.88 (0.61 to 1.25)	−0.3 (−1.3 to 0.6)	114/309	1.26 (0.89 to 1.79)	0.6 (−0.4 to 1.6)
Thiamin	170 015/454	664/2	–	–	664/2	–	–	72/440	0.84 (0.59 to 1.19)	−0.5 (−1.4 to 0.4)
Riboflavin	169 430/1039	660/6	0.80 (0.21 to 3.04)	−0.7 (−5.6 to 4.1)	660/6	0.89 (0.24 to 3.34)	−0.4 (−4.7 to 3.9)	196/437	1.00 (0.78 to 1.30)	0.0 (−0.7 to 0.8)
Niacin	169 990/480	662/4	–	–	662/4	–	–	185/437	1.01 (0.77 to 1.31)	0.0 (−0.7 to 0.8)
Vitamin B_6	161 408/9062	595/71	0.87 (0.59 to 1.27)	−0.4 (−1.7 to 0.8)	575/91	0.87 (0.60 to 1.25)	−0.4 (−1.6 to 0.7)	136/429	0.88 (0.64 to 1.21)	−0.3 (−1.2 to 0.5)
Folate	124 006/4036	445/32	0.73 (0.44 to 1.21)	−0.9 (−2.6 to 0.8)	442/35	0.83 (0.51 to 1.36)	−0.5 (−2.0 to 1.0)	131/312	1.03 (0.75 to 1.41)	0.1 (−0.8 to 0.9)
Vitamin B_{12}	169 894/576	662/4	–	–	662/4	–	–	127/429	0.91 (0.67 to 1.24)	−0.3 (−1.1 to 0.6)
Choline	1585/54 295	2/182	–	–	0/184	–	–	5/176	1.14 (0.41 to 3.15)	0.3 (−2.2 to 2.8)
Vitamin C	131 636/38 833	513/153	1.02 (0.74 to 1.40)	0.0 (−0.9 to 1.0)	466/200	1.06 (0.79 to 1.42)	0.2 (−0.7 to 1.0)	143/401	1.17 (0.91 to 1.48)	0.5 (−0.3 to 1.2)
Vitamin D	8752/23 148	41/66	1.27 (0.85 to 1.89)	0.5 (−0.4 to 1.3)	1/106	–	–	35/65	1.11 (0.71 to 1.72)	0.2 (−0.7 to 1.1)
Vitamin E	58 687/111 783	248/418	0.93 (0.74 to 1.15)	−0.2 (−0.8 to 0.4)	9/657	0.54 (0.26 to 1.12)	−1.3 (−2.5 to −0.1)	162/410	0.95 (0.75 to 1.20)	−0.1 (−0.8 to 0.5)
Vitamin K	41 693/86 349	152/325	0.92 (0.70 to 1.21)	−0.2 (−0.9 to 0.5)	125/352	1.05 (0.77 to 1.42)	0.1 (−0.7 to 0.9)	58/355	0.77 (0.48 to 1.23)	−0.6 (−1.6 to 0.4)
Copper	167 644/2826	650/16	1.28 (0.67 to 2.46)	0.6 (−0.8 to 2.1)	649/17	1.30 (0.70 to 2.41)	0.7 (−0.7 to 2.0)	150/467	1.06 (0.80 to 1.40)	0.2 (−0.7 to 1.0)
Phosphorus	169 960/510	664/2	–	–	664/2	–	–	84/498	1.20 (0.85 to 1.69)	0.5 (−0.6 to 1.7)
Selenium	170 323/146	665/1	–	–	665/1	–	–	77/468	1.03 (0.74 to 1.43)	0.1 (−0.9 to 1.0)
Iron§	169 684/785	663/3	–	–	663/3	–	–	99/523	1.13 (0.83 to 1.55)	0.4 (−0.6 to 1.4)
Magnesium	75 852/94 618	240/426	0.97 (0.74 to 1.28)	−0.1 (−0.9 to 0.7)	124/542	0.71 (0.51 to 0.99)	−0.9 (−1.7 to −0.1)	176/460	1.09 (0.84 to 1.42)	0.3 (−0.5 to 1.0)
Calcium	100 797/69 673	303/363	1.07 (0.84 to 1.36)	0.2 (−0.5 to 0.9)	202/464	0.97 (0.71 to 1.32)	−0.1 (−1.0 to 0.8)	130/422	1.16 (0.86 to 1.56)	0.5 (−0.5 to 1.4)
Zinc	162 287/8183	609/57	0.99 (0.61 to 1.59)	0.0 (−1.4 to 1.4)	596/70	0.92 (0.60 to 1.41)	−0.3 (−1.6 to 1.1)	168/449	1.04 (0.80 to 1.37)	0.1 (−0.7 to 0.9)
Potassium	1196/169 273	3/663	–	–	3/663	–	–	133/481	1.12 (0.85 to 1.48)	0.3 (−0.5 to 1.2)
Fiber	4319/166 150	13/653	0.62 (0.27 to 1.41)	−1.1 (−2.6 to 0.4)	11/655	0.64 (0.24 to 1.68)	−1.0 (−2.8 to 0.8)	9/650	0.96 (0.41 to 2.28)	−0.1 (−2.5 to 2.3)
EPA + DHA	2527/167 943	9/657	1.24 (0.55 to 2.81)	0.7 (−2.2 to 3.6)	0/666	–	–	4/655	–	–

Nutrient	Person-Years (>UL/≤UL)	Total Nutrient Intake			Nutrient Intake From Foods			Nutrient Intake From Supplements*		
		Cancer Deaths (>UL/≤UL), *n*	RR (95% CI)†	RD (95% CI)†	Cancer Deaths (>UL/≤UL), *n*	RR (95% CI)†	RD (95% CI)†	Cancer Deaths (High Dose/Nonusers), *n*	RR (95% CI)†	RD (95% CI)†
Excess intake‖										
Vitamin A	948/127 095	4/473	–	–	1/476	–	–	53/309	1.40 (0.92 to 2.14)	1.0 (−0.4 to 2.3)
Niacin	11 415/159 055	35/631	0.88 (0.60 to 1.28)	−0.4 (−1.3 to 0.6)	0/666	–	–	53/437	0.87 (0.59 to 1.28)	−0.4 (−1.4 to 0.6)
Vitamin B_6	2859/167 610	18/648	1.62 (0.88 to 2.96)	1.7 (−1.0 to 4.4)	0/666	–	–	83/429	0.95 (0.67 to 1.35)	−0.1 (−1.1 to 0.8)
Folate	2859/167 610	18/648	0.74 (0.34 to 1.60)	−0.6 (−2.1 to 0.8)	0/477	–	–	29/312	1.01 (0.71 to 1.42)	0.0 (−0.9 to 0.9)
Choline	38/55 842	0/184	–	–	0/184	–	–	4/176	–	–
Vitamin C	1344/169 126	10/656	2.08 (0.76 to 5.66)	3.0 (−2.8 to 8.9)	0/666	–	–	87/401	1.32 (1.00 to 1.74)	0.9 (−0.1 to 1.9)
Vitamin D	103/31 797	1/106	–	–	0/107	–	–	25/65	1.50 (0.83 to 2.71)	0.9 (−0.6 to 2.4)
Vitamin E	776/86 394	4/312	–	–	0/666	–	–	91/410	0.92 (0.70 to 1.21)	−0.2 (−1.0 to 0.5)
Copper	274/170 196	0/666	–	–	0/666	–	–	33/467	1.30 (0.76 to 2.24)	0.9 (−1.1 to 2.8)
Phosphorus	96/170 373	0/666	–	–	0/666	–	–	77/498	1.24 (0.87 to 1.78)	0.7 (−0.6 to 1.9)
Selenium	1108/169 362	1/665	–	–	0/666	–	–	44/468	1.10 (0.75 to 1.62)	0.3 (−0.9 to 1.5)
Iron§	3834/166 636	20/646	1.20 (0.73 to 1.98)	0.6 (−1.1 to 2.3)	0/666	–	–	31/523	1.18 (0.78 to 1.79)	0.5 (−0.9 to 1.9)
Magnesium	4116/166 353	21/645	1.67 (0.93 to 2.98)	1.9 (−0.8 to 4.5)	0/666	–	–	46/460	1.41 (0.96 to 2.09)	1.2 (−0.3 to 2.7)
Calcium	5302/165 167	35/631	1.62 (1.07 to 2.45)	1.7 (−0.1 to 3.5)	0/666	–	–	51/422	1.53 (1.04 to 2.25)	1.5 (−0.1 to 3.1)
Zinc	6037/164 433	35/631	1.34 (0.92 to 1.95)	0.9 (−0.4 to 2.3)	0/666	–	–	59/449	1.27 (0.92 to 1.76)	0.8 (−0.3 to 1.9)

DFE = dietary folate equivalent; DHA = docosahexaenoic acid; EAR = Estimated Average Requirement; EPA = eicosapentaenoic acid; NHANES = National Health and Nutrition Examination Survey; RAE = retinal activity equivalent; RD = rate difference; RR = rate ratio; UL = Tolerable Upper Intake Level.

* For nutrient intake from supplements, the RRs, RDs, and 95% CIs for adequate intake correspond to the comparisons between participants with supplemental intake at or above the median versus nonusers. The median was defined as the median supplement dose reported by supplement users. Median doses were 820 RAE mcg/d for vitamin A, 1.5 mg/d for thiamin, 1.7 mg/d for riboflavin, 18 mg/d for niacin, 2 mg/d for vitamin B_6, 600 DFE mcg/d for folate, 12 mcg/d for vitamin B_{12}, 25 mg/d for choline, 90 mg/d for vitamin C, 9 mcg/d for vitamin D, 45 mg/d for vitamin E, 20 mcg/d for vitamin K, 1.8 mg/d for copper, 55 mg/d for phosphorus, 20 mcg/d for selenium, 16 mg/d for iron, 50 mg/d for magnesium, 200 mg/d for calcium, 14 mg/d for zinc, 80 mg/d for potassium, 2 g/d for fiber, and 600 mg/d for EPA + DHA. RRs, RDs, and 95% CIs for excess intake correspond to the comparison between participants with supplemental intake at a high dose versus nonusers. The high dose was determined by the commonly used dose at approximately the 75th to 85th percentile reported by supplement users. High doses were 1050 RAE mcg/d for vitamin A, 20 mg/d for niacin, 3 mg/d for vitamin B_6, 680 DFE mcg/d for folate, 50 mg/d for choline, 500 mg/d for vitamin C, 10 mcg/d for vitamin D, 100 mg/d for vitamin E, 2 mg/d for copper, 100 mg/d for phosphorus, 70 mcg/d for selenium, 18 mg/d for iron, 100 mg/d for magnesium, 1000 mg/d for calcium, and 15 mg/d for zinc.

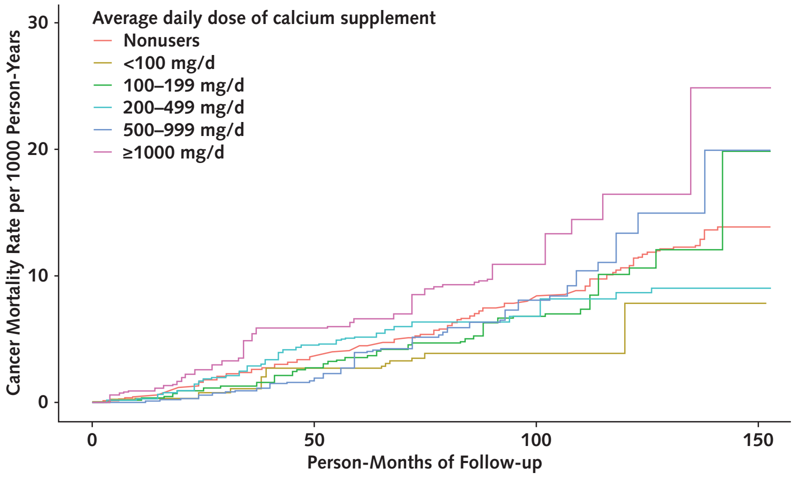
† RRs, RDs, and 95% CIs were adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, presence of comorbid conditions at baseline, and NHANES survey weights. In models that included intake from both foods and supplements, each source was adjusted for the other. Multiple imputation was done for alcohol intake. RRs and RDs were not estimated for nutrients with <5 deaths in any intake subgroup.

‡ Adequate intake was defined as levels of nutrient intake at or above the EAR. RRs, RDs, and 95% CIs correspond to the comparisons between participants with total nutrient intake at or above versus below the EAR. For choline, vitamin K, potassium, and fiber, EARs were not available, so adequate intake was defined as intake at or above the Adequate Intake level. For EPA + DHA, adequate intake was defined as intake at or above that recommended by the Academy of Nutrition and Dietetics.

§ Models were also adjusted for presence of anemia at baseline (yes vs. no).

‖ Excess intake was defined as levels of nutrient intake above the UL. RRs, RDs, and 95% CIs correspond to the comparisons between participants with total nutrient intake above versus at or below the UL. Few participants (<0.1%) had excess intake of nutrients from foods only.

Appendix Figure 1. Association of calcium supplement use with cancer mortality.



At risk, *n*	0	50	100	150
Nonusers	18 182	11 704	5882	374
<100 mg/d	1499	1016	412	17
100–199 mg/d	2133	1577	787	63
200–499 mg/d	2783	1651	647	44
500–999 mg/d	1724	1118	491	33
≥1000 mg/d	1373	904	385	28

Cumulative mortality curves were adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, presence of comorbid conditions at baseline, and NHANES survey weights. NHANES = National Health and Nutrition Examination Survey.

Appendix Table 4. Association of Dietary Supplement Use With Mortality, by Presence of Comorbid Conditions at Baseline

Supplement	All-Cause Mortality				CVD Mortality				Cancer Mortality			
	Participants With Comorbid Conditions		Participants Without Comorbid Conditions		Participants With Comorbid Conditions		Participants Without Comorbid Conditions		Participants With Comorbid Conditions		Participants Without Comorbid Conditions	
	Deaths (Users/ Nonusers), *n*	RR (95% CI)*	Deaths (Users/ Nonusers), *n*	RR (95% CI)*	Deaths (Users/ Nonusers), *n*	RR (95% CI)*	Deaths (Users/ Nonusers), *n*	RR (95% CI)*	Deaths (Users/ Nonusers), *n*	RR (95% CI)*	Deaths (Users/ Nonusers), *n*	RR (95% CI)*
Any	1670/1236	0.97 (0.87–1.09)	330/377	1.16 (0.90–1.51)	455/338	0.98 (0.78–1.23)	73/79	1.42 (0.88–2.28)	366/276	1.07 (0.84–1.36)	73/90	1.11 (0.72–1.69)
MVM	1185/1721	1.01 (0.91–1.13)	229/478	0.94 (0.67–1.31)	327/466	1.01 (0.82–1.24)	46/106	0.83 (0.47–1.48)	259/383	1.10 (0.89–1.37)	54/109	0.86 (0.49–1.52)
Individual vitamins												
Vitamin A	1039/1867	0.98 (0.86–1.12)	215/492	1.04 (0.76–1.44)	283/510	0.94 (0.76–1.17)	41/111	0.81 (0.43–1.51)	235/407	1.14 (0.90–1.45)	52/111	1.12 (0.65–1.90)
Retinol	960/1946	0.98 (0.86–1.12)	196/511	1.05 (0.76–1.44)	259/534	0.94 (0.76–1.17)	37/115	0.81 (0.43–1.52)	214/428	1.15 (0.91–1.45)	48/115	1.12 (0.66–1.91)
β-Carotene	1039/1867	0.97 (0.85–1.12)	215/492	1.07 (0.79–1.44)	283/510	0.96 (0.77–1.18)	41/111	0.74 (0.38–1.43)	235/407	1.15 (0.90–1.47)	52/111	1.31 (0.76–2.25)
Thiamin	1062/1844	1.01 (0.89–1.14)	213/494	1.00 (0.72–1.39)	291/502	1.02 (0.82–1.26)	43/109	0.93 (0.52–1.68)	228/414	1.03 (0.82–1.30)	51/112	0.97 (0.57–1.65)
Riboflavin	1068/1838	1.01 (0.89–1.14)	212/495	0.97 (0.70–1.33)	291/502	0.98 (0.79–1.23)	43/109	0.91 (0.50–1.65)	233/409	1.09 (0.86–1.38)	50/113	0.93 (0.54–1.62)
Niacin	1064/1842	1.00 (0.88–1.13)	213/494	0.99 (0.71–1.38)	292/501	1.02 (0.83–1.26)	42/110	0.92 (0.51–1.67)	231/411	1.06 (0.84–1.34)	51/112	0.94 (0.55–1.63)
Pantothenic acid	1035/1871	1.00 (0.88–1.13)	206/501	0.91 (0.66–1.23)	282/511	1.00 (0.80–1.25)	42/110	0.92 (0.51–1.67)	227/415	1.07 (0.85–1.35)	49/114	0.95 (0.55–1.64)
Vitamin B_6	1105/1801	1.02 (0.90–1.16)	216/491	0.96 (0.69–1.33)	301/492	1.03 (0.83–1.27)	44/108	0.90 (0.49–1.63)	242/400	1.08 (0.87–1.35)	51/112	0.90 (0.52–1.56)
Folate	1088/1818	1.00 (0.87–1.14)	206/501	0.92 (0.67–1.27)	198/495	1.01 (0.81–1.26)	42/110	0.87 (0.47–1.60)	235/407	1.01 (0.81–1.27)	49/114	0.92 (0.52–1.60)
Vitamin B_{12}	1119/1787	0.99 (0.88–1.11)	224/483	0.96 (0.70–1.31)	301/492	0.99 (0.79–1.22)	45/107	0.87 (0.48–1.58)	240/402	1.02 (0.80–1.29)	54/109	0.97 (0.56–1.68)
Choline	100/2806	1.01 (0.80–1.29)	25/682	0.86 (0.46–1.62)	27/766	0.95 (0.50–1.83)	5/147	0.45 (0.15–1.35)	25/617	1.55 (0.99–2.40)	4/159	0.62 (0.13–2.94)
Vitamin C	1237/1669	1.02 (0.91–1.14)	248/459	1.13 (0.84–1.53)	337/456	0.96 (0.78–1.19)	54/98	1.39 (0.81–2.40)	270/372	1.09 (0.88–1.36)	58/105	1.10 (0.69–1.76)
Vitamin D	1085/1821	0.94 (0.83–1.06)	219/488	1.01 (0.76–1.34)	293/500	0.90 (0.73–1.11)	43/109	0.82 (0.46–1.47)	249/393	1.13 (0.89–1.43)	51/112	1.04 (0.61–1.78)
Vitamin E	1207/1699	0.93 (0.84–1.03)	241/466	1.05 (0.79–1.39)	332/461	0.94 (0.77–1.15)	51/101	0.91 (0.53–1.56)	261/381	0.94 (0.75–1.18)	55/108	1.09 (0.70–1.69)
Vitamin K	761/2145	0.89 (0.77–1.03)	146/561	0.97 (0.72–1.30)	197/596	0.85 (0.67–1.07)	32/120	1.02 (0.54–1.94)	176/466	1.01 (0.76–1.34)	35/128	1.20 (0.69–2.07)
Biotin	922/1984	1.00 (0.87–1.14)	179/528	0.90 (0.67–1.22)	244/549	0.99 (0.79–1.25)	37/115	0.80 (0.42–1.54)	202/440	1.06 (0.83–1.36)	43/120	1.03 (0.60–1.78)
Individual minerals												
Copper	911/1995	0.98 (0.86–1.11)	181/526	0.93 (0.70–1.24)	248/545	0.96 (0.77–1.20)	37/115	0.84 (0.45–1.58)	206/436	1.07 (0.84–1.38)	42/121	0.97 (0.56–1.68)
hosphorus	751/2155	0.99 (0.85–1.14)	151/556	0.99 (0.72–1.34)	200/593	0.94 (0.74–1.19)	32/120	0.83 (0.41–1.70)	172/470	1.11 (0.83–1.47)	37/126	1.32 (0.76–2.29)
Selenium	897/2009	0.96 (0.85–1.09)	178/529	0.93 (0.69–1.26)	240/553	0.93 (0.75–1.16)	37/115	0.84 (0.46–1.54)	204/438	1.11 (0.86–1.44)	41/122	0.97 (0.56–1.69)
Boron	746/2160	0.96 (0.84–1.11)	147/560	1.07 (0.78–1.48)	194/599	0.88 (0.69–1.12)	30/122	0.89 (0.46–1.74)	170/472	1.16 (0.90–1.48)	36/127	1.33 (0.76–2.32)
Iodine	824/2082	1.00 (0.87–1.15)	164/543	0.93 (0.68–1.27)	218/575	0.94 (0.75–1.19)	35/117	0.92 (0.50–1.72)	184/458	1.09 (0.85–1.40)	39/124	1.09 (0.62–1.90)
Silicon	680/2226	0.94 (0.81–1.10)	137/570	1.11 (0.81–1.54)	182/611	0.90 (0.71–1.14)	28/124	0.85 (0.40–1.78)	155/487	1.07 (0.81–1.42)	33/130	1.49 (0.85–2.61)
Iron†	674/2232	1.00 (0.85–1.17)	148/559	1.25 (0.90–1.74)	183/610	0.95 (0.75–1.20)	25/127	1.07 (0.49–2.31)	150/492	1.04 (0.76–1.41)	40/123	1.45 (0.87–2.44)
Magnesium	933/1973	0.99 (0.88–1.11)	185/522	0.83 (0.61–1.13)	246/547	0.91 (0.74–1.11)	42/110	0.97 (0.55–1.73)	210/432	1.13 (0.89–1.43)	43/120	0.90 (0.52–1.54)
Calcium	1124/1782	0.95 (0.85–1.06)	225/482	0.96 (0.72–1.27)	297/496	0.85 (0.70–1.04)	48/104	0.84 (0.47–1.50)	254/388	1.09 (0.86–1.38)	49/114	0.88 (0.51–1.53)
Manganese	864/2042	0.94 (0.83–1.07)	173/534	0.90 (0.65–1.24)	228/565	0.88 (0.70–1.11)	38/114	0.94 (0.51–1.72)	200/442	1.09 (0.85–1.39)	40/123	1.00 (0.58–1.72)
Tin	378/2528	1.02 (0.84–1.24)	90/617	1.36 (0.95–1.94)	109/684	1.06 (0.86–1.30)	12/140	1.05 (0.37–3.03)	89/553	1.14 (0.76–1.70)	26/137	2.08 (1.24–3.51)
Chromium	841/2065	0.94 (0.82–1.08)	167/540	0.99 (0.74–1.32)	217/576	0.86 (0.68–1.09)	36/116	1.17 (0.65–2.12)	191/451	1.09 (0.85–1.39)	39/124	1.02 (0.59–1.77)
Molybdenum	800/2106	0.98 (0.86–1.13)	157/550	0.98 (0.70–1.36)	215/578	0.95 (0.76–1.20)	33/119	0.88 (0.46–1.69)	182/460	1.12 (0.86–1.45)	38/125	1.15 (0.66–2.00)
Vanadium	714/2192	0.95 (0.82–1.11)	138/569	1.09 (0.80–1.49)	187/606	0.89 (0.70–1.13)	28/124	0.78 (0.38–1.64)	166/476	1.15 (0.87–1.52)	35/128	1.46 (0.83–2.54)
Nickel	671/2235	0.94 (0.82–1.08)	129/578	1.18 (0.86–1.63)	178/615	0.93 (0.73–1.19)	27/125	0.87 (0.41–1.85)	156/486	1.14 (0.86–1.50)	32/131	1.61 (0.92–2.82)
Zinc	1004/1902	1.02 (0.90–1.14)	205/502	0.99 (0.74–1.33)	274/519	1.01 (0.82–1.23)	43/109	0.87 (0.47–1.59)	226/416	1.10 (0.86–1.40)	44/119	0.86 (0.50–1.50)
Potassium	857/2049	1.02 (0.90–1.17)	167/540	1.00 (0.72–1.37)	237/556	1.07 (0.85–1.33)	33/119	0.70 (0.34–1.42)	193/449	1.13 (0.88–1.46)	38/125	1.15 (0.66–2.01)
Other												
Lutein	600/2306	0.96 (0.82–1.12)	110/597	1.13 (0.83–1.54)	160/633	0.89 (0.69–1.16)	27/125	1.26 (0.65–2.46)	137/505	1.16 (0.89–1.52)	29/134	1.36 (0.73–2.55)
Lycopene	317/2589	0.81 (0.67–0.97)	49/658	0.82 (0.53–1.28)	86/707	0.72 (0.53–0.97)	10/142	1.00 (0.45–2.23)	64/578	0.66 (0.47–0.93)	11/152	0.77 (0.31–1.94)
Zeaxanthin	18/2888	1.03 (0.61–1.74)	1/706	0.10 (0.01–0.65)	5/788	1.63 (0.56–4.80)	0/152	–	4/638	0.66 (0.14–2.99)	0/163	–
Inositol	77/2829	0.93 (0.73–1.19)	21/686	0.86 (0.47–1.60)	18/775	0.87 (0.43–1.76)	5/146	0.60 (0.20–1.82)	18/624	1.15 (0.74–1.78)	3/160	0.28 (0.06–1.28)
Fiber	61/2845	0.87 (0.65–1.16)	17/690	1.19 (0.62–2.28)	13/780	0.66 (0.37–1.16)	3/149	1.25 (0.33–4.71)	13/629	1.05 (0.49–2.24)	3/160	0.49 (0.13–1.79)
Omega-3	99/2807	0.79 (0.57–1.08)	16/691	1.02 (0.49–2.15)	24/769	0.74 (0.45–1.21)	3/149	0.22 (0.05–1.06)	29/613	1.11 (0.69–1.80)	1/162	0.41 (0.05–2.99)
EPA	77/2829	0.70 (0.48–1.01)	14/693	1.38 (0.62–3.08)	20/773	0.81 (0.46–1.43)	3/149	0.33 (0.07–1.59)	23/619	0.96 (0.55–1.68)	1/162	0.60 (0.08–4.46)
DHA	82/2824	0.72 (0.51–1.03)	14/693	1.19 (0.53–2.68)	21/772	0.84 (0.49–1.44)	3/149	0.28 (0.06–1.35)	24/618	1.08 (0.62–1.88)	1/162	0.51 (0.07–3.82)
Omega-6	28/2878	1.13 (0.82–1.56)	3/704	0.51 (0.14–1.77)	7/786	1.55 (0.70–3.46)	0/152	–	12/630	1.65 (0.86–3.15)	0/163	–
Omega-9	23/1883	1.29 (0.80–2.10)	2/705	0.58 (0.12–2.78)	5/788	0.94 (0.38–2.31)	0/152	–	8/634	1.61 (0.73–3.58)	0/163	–

CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; MVM = multivitamin and mineral; NHANES = National Health and Nutrition Examination Survey; RR = rate ratio.
* RRs and 95% CIs were adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, and NHANES survey weights. Multiple imputation was done for alcohol intake. RRs and 95% CIs for CVD and cancer mortality were not estimated for zeaxanthin, omega-6, and omega-9 because no CVD deaths or cancer deaths occurred for supplement users without comorbid conditions.
† Also adjusted for presence of anemia at baseline (yes vs. no).

Appendix Table 5. Association of Adequate Nutrient Intake (at or Above the EAR) With Mortality, by Presence of Comorbid Conditions at Baseline

Nutrient, by Intake Level	All-Cause Mortality				CVD Mortality				Cancer Mortality			
	Participants With Comorbid Conditions		Participants Without Comorbid Conditions		Participants With Comorbid Conditions		Participants Without Comorbid Conditions		Participants With Comorbid Conditions		Participants Without Comorbid Conditions	
	Deaths (≥EAR/<EAR), *n*	RR (95% CI)*	Deaths (≥EAR/<EAR), *n*	RR (95% CI)*	Deaths (≥EAR/<EAR), *n*	RR (95% CI)*	Deaths (≥EAR/<EAR), *n*	RR (95% CI)*	Deaths (≥EAR/<EAR), *n*	RR (95% CI)*	Deaths (≥EAR/<EAR), *n*	RR (95% CI)*
Intake of vitamin ≥EAR vs. <EAR												
Vitamin A	1184/492	0.86 (0.70–1.05)	229/133	0.99 (0.64–1.52)	296/136	0.58 (0.41–0.81)	46/36	1.00 (0.50–2.00)	265/124	0.97 (0.66–1.42)	54/34	1.03 (0.56–1.89)
Thiamin	2301/7	1.03 (0.23–4.64)	534/3	0.50 (0.19–1.34)	602/3	1.31 (0.20–8.36)	118/1	0.18 (0.05–0.60)	530/2	0.33 (0.05–2.04)	134/0	–
Riboflavin	2287/21	0.56 (0.27–1.19)	530/7	1.42 (0.36–5.65)	596/9	0.18 (0.05–0.60)	117/2	0.84 (0.16–4.27)	528/4	0.87 (0.19–3.97)	132/2	4.50 (0.37–54.94)
Niacin	2293/15	0.45 (0.24–0.83)	536/1	2.21 (0.47–10.36)	600/5	0.20 (0.07–0.59)	118/1	0.38 (0.07–1.99)	528/4	0.25 (0.07–0.93)	134/0	–
Vitamin B_6	2068/240	1.03 (0.85–1.25)	489/48	0.97 (0.60–1.57)	538/67	0.74 (0.49–1.12)	108/11	0.84 (0.35–2.03)	474/58	0.84 (0.58–1.21)	121/13	1.20 (0.45–3.23)
Folate	1593/83	0.75 (0.52–1.08)	348/14	1.22 (0.45–3.26)	408/24	0.43 (0.23–0.79)	80/2	0.79 (0.14–4.57)	363/26	0.55 (0.35–0.89)	82/6	2.75 (0.83–9.08)
Vitamin B_{12}	2294/14	0.60 (0.33–1.12)	536/1	4.42 (0.45–43.53)	599/6	0.17 (0.07–0.41)	119/0	–	529/3	0.56 (0.10–3.13)	133/1	1.02 (0.09–12.09)
Choline†	13/608	1.04 (0.60–1.83)	6/114	2.16 (0.96–4.88)	2/160	0.36 (0.07–1.76)	3/24	2.42 (0.67–8.75)	2/151	0.64 (0.09–4.63)	0/31	–
Vitamin C	1845/463	0.98 (0.81–1.18)	411/126	1.20 (0.80–1.80)	478/127	0.89 (0.62–1.28)	92/27	1.52 (0.80–2.91)	412/120	0.97 (0.68–1.39)	101/33	1.21 (0.71–2.07)
Vitamin D	111/222	0.97 (0.76–1.22)	21/49	1.01 (0.41–2.48)	24/58	0.71 (0.38–1.32)	4/10	0.27 (0.07–1.09)	32/54	1.03 (0.66–1.59)	9/12	3.36 (1.19–9.52)
Vitamin E	922/1386	0.93 (0.83–1.03)	182/355	1.01 (0.76–1.33)	257/348	0.98 (0.79–1.21)	39/80	0.91 (0.54–1.56)	205/327	0.94 (0.74–1.19)	43/91	0.91 (0.54–1.53)
Vitamin K†	541/1135	0.82 (0.73–0.93)	94/268	0.69 (0.48–0.98)	130/302	0.65 (0.50–0.83)	23/59	0.79 (0.45–1.40)	132/257	1.03 (0.79–1.33)	20/68	0.64 (0.32–1.29)
Intake of mineral ≥EAR vs. <EAR												
Copper	2249/59	0.83 (0.54–1.29)	522/15	0.94 (0.38–2.29)	579/26	0.25 (0.14–0.45)	114/5	0.58 (0.17–1.96)	518/14	1.04 (0.55–1.99)	132/2	8.08 (0.94–69.06)
Phosphorus	2295/13	0.57 (0.29–1.13)	535/2	0.67 (0.19–2.42)	598/7	0.16 (0.05–0.48)	118/1	0.26 (0.06–1.05)	530/2	0.63 (0.15–2.57)	134/0	–
Selenium	2304/4	0.65 (0.25–1.69)	537/0	–	603/2	0.20 (0.07–0.61)	119/0	–	531/1	0.48 (0.05–4.40)	134/0	–
Iron‡	2303/5	1.00 (0.21–4.71)	533/4	0.57 (0.22–1.46)	603/2	1.31 (0.21–8.09)	118/1	0.19 (0.06–0.63)	530/2	0.30 (0.06–1.40)	133/1	1.16 (0.13–10.56)
Magnesium	806/1502	0.86 (0.75–1.00)	188/349	0.72 (0.53–0.98)	208/397	0.76 (0.58–1.01)	41/78	1.02 (0.60–1.74)	195/337	1.07 (0.82–1.40)	45/89	0.72 (0.38–1.35)
Calcium	938/1370	0.93 (0.83–1.05)	267/270	1.01 (0.77–1.33)	235/370	0.81 (0.64–1.04)	56/63	1.32 (0.81–2.17)	236/296	1.00 (0.80–1.26)	67/67	1.05 (0.64–1.74)
Zinc	2096/212	0.86 (0.69–1.07)	492/45	1.76 (1.07–2.91)	526/79	0.42 (0.29–0.60)	110/9	1.79 (0.50–6.48)	490/42	0.91 (0.56–1.49)	119/15	1.49 (0.75–2.95)
Potassium†	12/2296	1.28 (0.65–2.52)	2/535	0.71 (0.16–3.08)	3/602	2.62 (0.84–8.16)	0/119	–	3/529	0.60 (0.16–2.34)	0/134	–
Intake of other nutrients at or above AI level or recommended intake vs. less than AI level or recommended intake												
Fiber†	50/2258	0.75 (0.52–1.06)	14/523	0.62 (0.25–1.54)	7/598	0.38 (0.18–0.82)	2/117	0.73 (0.13–4.25)	12/520	0.66 (0.28–1.56)	1/133	0.11 (0.01–0.87)
EPA + DHA†	31/2277	0.77 (0.46–1.29)	7/530	1.59 (0.54–4.70)	9/596	0.90 (0.39–2.06)	2/117	0.21 (0.03–1.64)	8/524	1.00 (0.42–2.36)	1/133	1.37 (0.17–10.73)

AI = Adequate Intake; CVD = cardiovascular disease; DHA = docosahexaenoic acid; EAR = Estimated Average Requirement; EPA = eicosapentaenoic acid; NHANES = National Health and Nutrition Examination Survey; RR = rate ratio.

* RRs and 95% CIs were adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, and NHANES survey weights. Multiple imputation was done for alcohol intake. RRs and 95% CIs were not estimated for several nutrients because no deaths occurred among participants without comorbid conditions with nutrient intakes at or above the EAR or below the EAR.

† The classifications of choline, vitamin K, potassium, and fiber were based on AI level (at or above vs. below the AI level). The classification of EPA + DHA was based on daily intake recommended by the Academy of Nutrition and Dietetics (at or above vs. below the recommended intake).

‡ Also adjusted for presence of anemia at baseline (yes vs. no).

Appendix Table 6. Association of Excess Nutrient Intake (Above the UL) With Mortality, by Presence of Comorbid Conditions at Baseline

Nutrient, by Intake Level	All-Cause Mortality				CVD Mortality				Cancer Mortality			
	Participants With Comorbid Conditions		Participants Without Comorbid Conditions		Participants With Comorbid Conditions		Participants Without Comorbid Conditions		Participants With Comorbid Conditions		Participants Without Comorbid Conditions	
	Deaths (>UL/≤UL), *n*	RR (95% CI)*	Deaths (>UL/≤UL), *n*	RR (95% CI)*	Deaths (>UL/≤UL), *n*	RR (95% CI)*	Deaths (>UL/≤UL), *n*	RR (95% CI)*	Deaths (>UL/≤UL), *n*	RR (95% CI)*	Deaths (>UL/≤UL), *n*	RR (95% CI)*
Intake of vitamin >UL vs. ≤UL												
Vitamin A†	17/1659	1.12 (0.47–2.68)	6/356	1.63 (0.61–4.31)	3/429	1.06 (0.16–7.15)	1/81	–	3/386	1.65 (0.29–9.42)	1/87	1.23 (0.17–8.86)
Niacin‡	147/2161	1.00 (0.81–1.22)	29/508	0.82 (0.49–1.38)	42/563	1.20 (0.84–1.70)	5/114	0.38 (0.13–1.09)	29/503	1.01 (0.68–1.50)	6/128	0.25 (0.09–0.76)
Vitamin B_6	54/2254	1.27 (0.87–1.84)	8/529	0.92 (0.41–2.04)	13/592	1.48 (0.78–2.83)	2/117	0.42 (0.10–1.74)	17/515	1.64 (0.88–3.06)	1/133	0.57 (0.08–4.22)
Folate‡	54/2254	1.33 (0.91–1.93)	8/529	0.49 (0.19–1.25)	13/592	1.28 (0.60–2.76)	2/117	0.42 (0.10–1.84)	17/515	0.80 (0.35–1.84)	1/133	0.11 (0.01–0.81)
Choline	0/621	–	0/120	–	0/162	–	0/27	–	0/153	–	0/31	–
Vitamin C	24/2284	1.36 (0.84–2.19)	6/531	1.91 (0.73–4.96)	3/602	1.11 (0.29–4.22)	2/117	1.18 (0.60–2.34)	9/523	2.04 (0.73–5.66)	1/133	2.32 (0.22–24.02)
Vitamin D	3/330	2.46 (0.85–7.09)	0/70	–	0/82	–	0/14	–	1/85	3.91 (0.62–24.47)	0/21	–
Vitamin E§	22/1089	1.58 (1.01–2.45)	2/207	0.68 (0.23–2.04)	5/293	0.96 (0.36–2.61)	1/52	1.16 (0.09–14.73)	3/260	0.80 (0.12–5.31)	1/52	1.71 (0.34–8.61)
Intake of mineral >UL vs. ≤UL												
Copper	4/2304	1.28 (0.55–2.94)	1/536	0.27 (0.05–1.39)	1/604	2.62 (0.68–10.19)	0/119	–	0/532	–	0/134	–
Phosphorus	2/2306	1.78 (0.34–9.40)	0/537	–	0/605	–	0/119	–	0/532	–	0/134	–
Selenium	9/2299	0.94 (0.42–2.12)	6/531	0.82 (0.28–2.40)	2/603	1.20 (0.26–5.56)	1/118	–	1/531	1.22 (0.16–9.29)	0/134	–
Iron‖	76/2232	1.48 (1.07–2.05)	10/527	1.22 (0.59–2.50)	21/584	1.65 (0.92–2.95)	5/114	2.96 (0.88–9.93)	19/513	1.56 (0.90–2.70)	1/133	0.18 (0.02–1.40)
Magnesium¶	58/2250	1.06 (0.77–1.45)	14/523	0.76 (0.33–1.75)	12/593	1.08 (0.56–2.07)	4/115	1.23 (0.28–5.46)	17/515	1.62 (1.01–2.60)	4/130	1.46 (0.31–6.97)
Calcium	102/2206	1.02 (0.79–1.32)	22/515	1.15 (0.62–2.15)	26/579	1.17 (0.76–1.80)	3/116	0.39 (0.12–1.34)	29/503	1.53 (1.03–2.27)	6/128	1.94 (0.58–6.45)
Zinc	119/2189	0.96 (0.78–1.18)	23/514	1.11 (0.68–1.82)	32/573	0.95 (0.58–1.56)	5/114	0.64 (0.23–1.73)	31/501	1.44 (0.99–2.10)	4/130	0.40 (0.13–1.22)

CVD = cardiovascular disease; NHANES = National Health and Nutrition Examination Survey; RR = risk ratio; UL = Tolerable Upper Intake Level.
* RRs and 95% CIs were adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, and NHANES survey weights. Multiple imputation was done for alcohol intake. RRs and 95% CIs were not estimated for several nutrients because 1 or no deaths occurred among participants (with and/or without comorbid conditions) with nutrient intakes above the UL.
† UL applies to preformed vitamin A only.
‡ UL applies to synthetic forms obtained from supplements, fortified foods, or a combination of the two.
§ UL applies to any form of supplemental α-tocopherol.
¶ UL represents intake from a pharmacologic agent only and does not include intake from food and water.

Appendix Table 7. Association of Dietary Supplement Use With Mortality, by Level of Nutrient Intake From Food at Baseline

Supplement	All-Cause Mortality				CVD Mortality				Cancer Mortality			
	Dietary Intake at or Above Median		Dietary Intake Below Median		Dietary Intake at or Above Median		Dietary Intake Below Median		Dietary Intake at or Above Median		Dietary Intake Below Median	
	Deaths (Users/ Nonusers), *n*	RR (95% CI)*	Deaths (Users/ Nonusers), *n*	RR (95% CI)*	Deaths (Users/ Nonusers), *n*	RR (95% CI)*	Deaths (Users/ Nonusers), *n*	RR (95% CI)*	Deaths (Users/ Nonusers), *n*	RR (95% CI)*	Deaths (Users/ Nonusers), *n*	RR (95% CI)*
Individual vitamins												
Vitamin A	571/642	1.03 (0.90–1.17)	186/639	1.04 (0.76–1.43)	145/147	1.05 (0.76–1.45)	49/173	1.21 (0.79–1.87)	128/149	1.13 (0.84–1.51)	46/154	1.25 (0.73–2.14)
Thiamin	528/740	1.03 (0.88–1.21)	515/1062	1.01 (0.85–1.20)	133/180	0.92 (0.63–1.34)	139/272	1.26 (0.98–1.63)	131/180	0.97 (0.70–1.33)	106/249	0.99 (0.69–1.42)
Riboflavin	573/768	1.04 (0.90–1.20)	470/1034	0.99 (0.83–1.18)	133/188	0.88 (0.61–1.29)	137/266	1.26 (0.95–1.67)	136/191	0.99 (0.72–1.36)	104/235	1.03 (0.74–1.43)
Niacin	405/625	1.04 (0.86–1.25)	639/1176	0.98 (0.84–1.15)	97/148	0.92 (0.63–1.35)	175/304	1.14 (0.89–1.47)	105/155	1.04 (0.72–1.49)	135/271	0.96 (0.69–1.35)
Vitamin B_6	531/687	1.07 (0.92–1.25)	552/1075	0.99 (0.84–1.16)	139/164	1.15 (0.81–1.61)	144/277	1.02 (0.79–1.33)	121/168	0.89 (0.62–1.29)	128/249	1.10 (0.82–1.48)
Folate	380/476	1.00 (0.82–1.23)	408/774	1.07 (0.89–1.27)	98/115	0.81 (0.52–1.26)	109/192	1.46 (1.06–1.99)	90/124	0.98 (0.68–1.40)	85/178	1.04 (0.72–1.51)
Vitamin B_{12}	589/787	1.06 (0.91–1.23)	504/965	0.90 (0.76–1.08)	146/203	0.89 (0.64–1.23)	135/240	1.14 (0.88–1.48)	139/197	1.06 (0.76–1.48)	109/221	0.85 (0.61–1.20)
Choline	13/330	0.68 (0.30–1.54)	15/383	1.09 (0.67–1.78)	4/75	1.74 (0.42–7.14)	4/106	1.07 (0.22–5.26)	2/90	0.35 (0.05–2.68)	6/86	2.87 (1.09–7.53)
Vitamin C	770/742	1.14 (0.98–1.32)	440/893	1.00 (0.82–1.22)	193/179	1.15 (0.83–1.58)	121/231	1.08 (0.79–1.49)	184/157	1.39 (1.05–1.84)	95/230	0.81 (0.54–1.21)
Vitamin D	101/130	1.01 (0.73–1.39)	51/121	0.79 (0.50–1.24)	20/31	0.76 (0.35–1.62)	15/30	0.55 (0.22–1.35)	28/34	1.15 (0.65–2.02)	14/31	0.88 (0.35–2.25)
Vitamin E	607/574	1.07 (0.92–1.25)	571/1093	0.94 (0.80–1.09)	147/145	0.98 (0.69–1.40)	163/269	1.13 (0.86–1.49)	141/148	0.88 (0.64–1.22)	127/250	1.02 (0.74–1.39)
Vitamin K	332/670	0.90 (0.76–1.08)	210/826	1.01 (0.77–1.33)	75/164	0.72 (0.48–1.06)	58/217	1.19 (0.85–1.67)	85/156	1.01 (0.68–1.49)	39/197	0.80 (0.50–1.30)
Individual minerals												
Copper	425/703	0.97 (0.83–1.15)	463/1254	1.05 (0.89–1.25)	111/173	0.98 (0.67–1.43)	120/320	0.99 (0.75–1.30)	107/170	1.08 (0.77–1.51)	100/289	1.01 (0.70–1.46)
Phosphorus	304/749	1.01 (0.82–1.25)	430/1362	1.03 (0.87–1.21)	73/180	0.82 (0.54–1.25)	118/353	1.06 (0.81–1.39)	80/188	0.98 (0.67–1.43)	94/304	1.22 (0.85–1.75)
Selenium	345/713	0.94 (0.78–1.14)	530/1257	1.02 (0.86–1.21)	82/166	0.87 (0.55–1.37)	141/335	1.02 (0.80–1.30)	86/190	0.84 (0.57–1.25)	119/271	1.22 (0.89–1.69)
Iron†	317/912	1.01 (0.83–1.23)	340/1276	1.05 (0.84–1.30)	83/219	1.06 (0.73–1.55)	86/336	1.02 (0.71–1.48)	77/224	0.98 (0.65–1.48)	81/284	1.09 (0.71–1.66)
Magnesium	422/697	1.00 (0.84–1.18)	493/1233	0.99 (0.85–1.16)	110/167	1.01 (0.68–1.49)	130/317	0.90 (0.70–1.15)	109/171	1.04 (0.72–1.49)	106/280	1.09 (0.79–1.53)
Calcium	491/603	0.96 (0.81–1.14)	614/1137	0.99 (0.88–1.11)	114/144	0.85 (0.57–1.25)	167/299	0.96 (0.76–1.22)	115/148	0.99 (0.70–1.39)	142/261	1.02 (0.73–1.43)
Zinc	444/729	1.05 (0.87–1.25)	545/1127	1.01 (0.86–1.18)	111/179	0.98 (0.69–1.38)	147/287	1.02 (0.80–1.29)	107/181	0.98 (0.71–1.36)	122/256	1.05 (0.72–1.53)
Potassium	467/837	1.09 (0.94–1.27)	364/1177	1.00 (0.83–1.20)	121/196	1.12 (0.81–1.54)	99/308	0.94 (0.73–1.22)	126/209	1.18 (0.86–1.63)	68/263	0.89 (0.60–1.32)
Other												
Fiber	41/1230	0.90 (0.60–1.34)	22/1552	1.00 (0.58–1.72)	7/310	0.46 (0.17–1.26)	6/401	1.35 (0.35–5.18)	9/309	0.58 (0.23–1.51)	7/341	1.30 (0.40–4.16)
EPA + DHA	36/1243	0.89 (0.53–1.49)	44/1522	0.73 (0.46–1.15)	4/308	0.46 (0.14–1.59)	17/395	1.01 (0.51–2.00)	12/296	1.49 (0.74–3.01)	10/348	0.71 (0.32–1.56)

CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; NHANES = National Health and Nutrition Examination Survey; RR = rate ratio.
* RRs and 95% CIs were adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, presence of comorbid conditions at baseline, and NHANES survey weights. Multiple imputation was done for alcohol intake.
† Also adjusted for presence of anemia at baseline (yes vs. no).

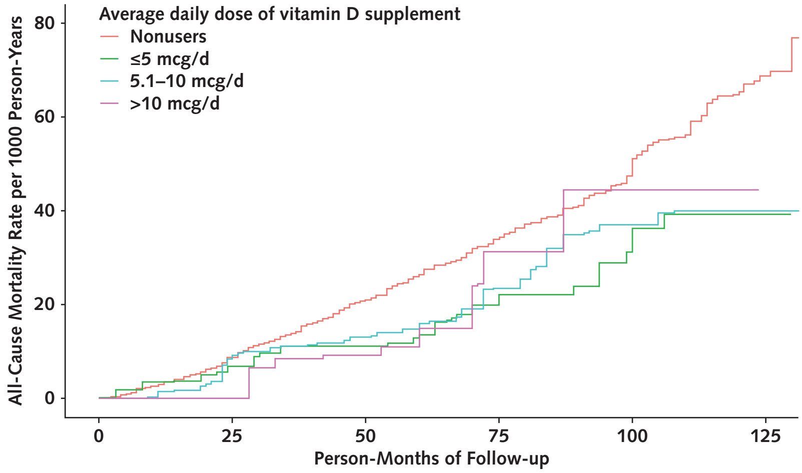
Appendix Table 8. Association of Vitamin D Supplement Use With Mortality, by Baseline Level of Serum 25-(OH)D

Vitamin D Supplement Use, by Mortality Type	Serum 25-(OH)D Level <50 nmol/L			Serum 25-(OH)D Level ≥50 nmol/L		
	Deaths/ Person-Years, *n*	RR (95% CI)*	RD per 1000 Person-Years (95% CI)*	Deaths/ Person-Years, *n*	RR (95% CI)*	RD per 1000 Person-Years (95% CI)*
All-cause mortality						
Nonusers	646/36 160	1 (reference)	0 (reference)	492/41 857	1 (reference)	0 (reference)
≤5 mcg/d	38/3146	0.58 (0.36 to 0.94)	−6.5 (−11.1 to −1.8)	83/6384	1.04 (0.77 to 1.41)	0.3 (−2.2 to 2.8)
5.1–10 mcg/d	79/4679	0.73 (0.52 to 1.03)	−4.1 (−8.3 to 0.1)	316/17 436	1.13 (0.95 to 1.34)	1.0 (−0.5 to 2.5)
>10 mcg/d	16/1199	0.72 (0.36 to 1.47)	−4.3 (−12.3 to 3.7)	169/8335	1.34 (1.00 to 1.78)	2.7 (−0.2 to 5.6)
CVD mortality						
Nonusers	156/36 160	1 (reference)	0 (reference)	135/41 857	1 (reference)	0 (reference)
≤5 mcg/d	7/3146	0.49 (0.14 to 1.72)	−1.7 (−3.8 to 0.5)	22/6384	1.05 (0.53 to 2.09)	0.1 (−1.5 to 1.7)
5.1–10 mcg/d	22/4679	0.94 (0.53 to 1.68)	−0.2 (−2.0 to 1.6)	90/17 436	1.06 (0.74 to 1.50)	0.1 (−0.7 to 0.9)
>10 mcg/d	5/1199	2.07 (0.77 to 5.57)	3.5 (−3.2 to 10.2)	39/8335	0.86 (0.57 to 1.31)	−0.3 (−1.1 to 0.5)
Cancer mortality						
Nonusers	162/36 160	1 (reference)	0 (reference)	100/41 857	1 (reference)	0 (reference)
≤5 mcg/d	8/3146	0.40 (0.16 to 0.98)	−2.3 (−4.0 to −0.7)	20/6384	1.31 (0.62 to 2.78)	0.5 (−0.9 to 1.8)
5.1–10 mcg/d	18/4679	0.86 (0.41 to 1.80)	−0.6 (−3.0 to 1.9)	62/17 436	1.32 (0.75 to 2.33)	0.5 (−0.5 to 1.5)
>10 mcg/d	1/1199	0.28 (0.04 to 2.05)	−2.7 (−5.0 to −0.5)	42/8335	2.11 (1.18 to 3.77)	1.6 (0.2 to 3.1)

25-(OH)D = 25-hydroxyvitamin D; CVD = cardiovascular disease; NHANES = National Health and Nutrition Examination Survey; RD = rate difference; RR = rate ratio.
* RRs, RDs, and 95% CIs were adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, presence of comorbid conditions at baseline, and NHANES survey weights. Multiple imputation was done for alcohol intake.

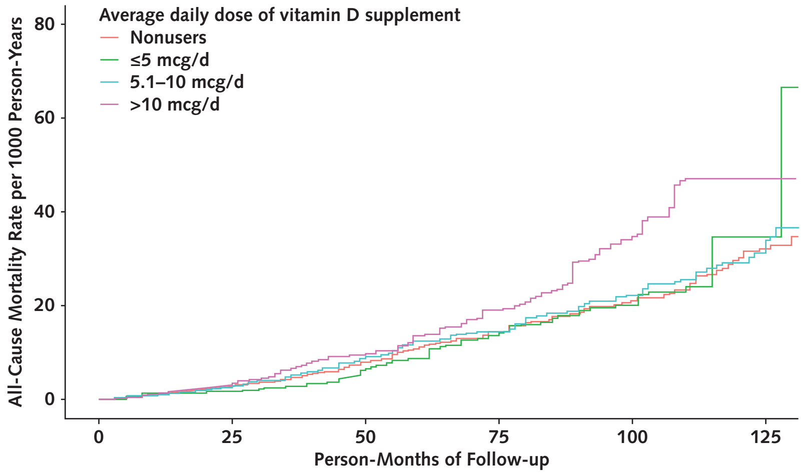
Appendix Figure 2. Association of vitamin D supplement use with all-cause mortality, by baseline serum level of 25-(OH)D.

Baseline Serum 25-(OH)D Level <50 nmol/L



At risk, *n*						
Nonusers	6505	5590	4037	2644	1595	404
≤5 mcg/d	531	475	371	238	148	17
5.1–10 mcg/d	739	670	550	386	227	48
>10 mcg/d	236	202	128	71	46	7

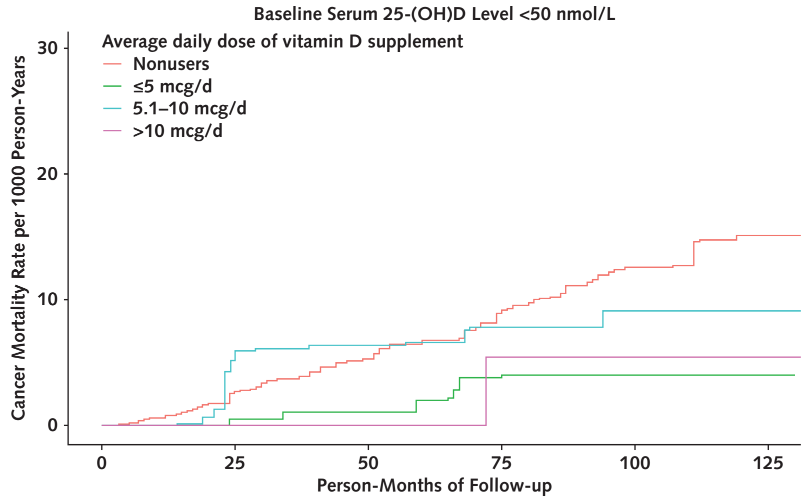
Baseline Serum 25-(OH)D Level ≥50 nmol/L



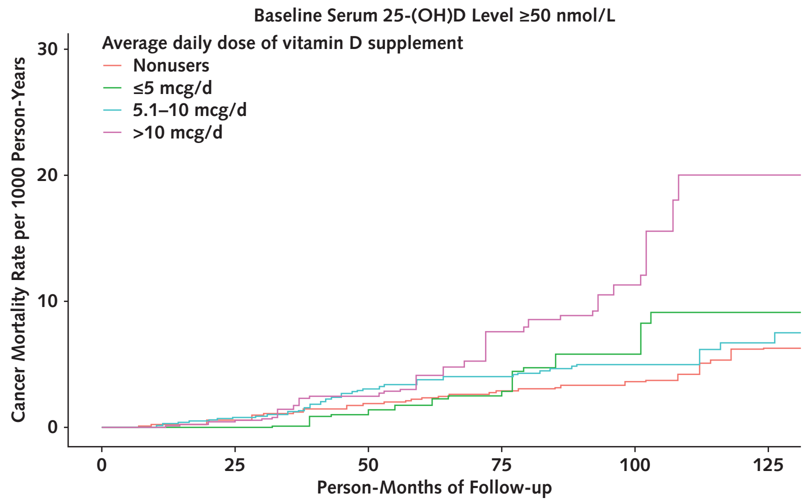
At risk, *n*						
Nonusers	7776	6593	4618	3137	1653	380
≤5 mcg/d	1126	1003	748	501	254	36
5.1–10 mcg/d	2942	2631	2059	1430	730	163
>10 mcg/d	2020	1460	804	479	241	48

Cumulative mortality curves were adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, presence of comorbid conditions at baseline, and NHANES survey weights. 25-(OH)D = 25-hydroxyvitamin D; NHANES = National Health and Nutrition Examination Survey.

Appendix Figure 3. Association of vitamin D supplement use with cancer mortality, by baseline serum level of 25-(OH)D.



At risk, *n*	0	25	50	75	100	125
Nonusers	6505	5590	4037	2644	1595	404
≤5 mcg/d	531	475	371	238	148	17
5.1–10 mcg/d	739	670	550	386	227	48
>10 mcg/d	236	202	128	71	46	7



At risk, *n*	0	25	50	75	100	125
Nonusers	7776	6593	4618	3137	1653	380
≤5 mcg/d	1126	1003	748	501	254	36
5.1–10 mcg/d	2942	2631	2059	1430	730	163
>10 mcg/d	2020	1460	804	479	241	48

Cumulative mortality curves were adjusted for age, sex, race/ethnicity, education, physical activity, smoking, alcohol intake, Healthy Eating Index-2015 score, body mass index, presence of comorbid conditions at baseline, and NHANES survey weights. 25-(OH)D = 25-hydroxyvitamin D; NHANES = National Health and Nutrition Examination Survey.