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Association Between Dietary Supplement Use, Nutrient Intake, and Mortality Among US Adults: A Cohort Study

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Abstract

Background: The health benefits and risks of dietary supplementation use remain controversial.

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

Design: Prospective cohort study.

Setting: National Health and Nutrition Examination Survey (NHANES) 1999–2010 linked to National Death Index Mortality Data.

Patients: 30,899 US adults aged 20+ years who answered questions on dietary supplement use.

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

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Results: During a median follow-up of 6.1 years, a total of 3,613 total deaths occurred, including 945 CVD deaths and 805 cancer deaths. Ever use of dietary supplements was not associated with mortality outcomes. Adequate nutrient intake (≥ Estimated Average Requirement or Adequate Intake) of vitamin A, vitamin K, magnesium, and zinc was associated with reduced all-cause or CVD mortality, but the associations were confined to nutrient intake from foods not supplements. Excess nutrient intake (> Tolerable Upper Intake Level) of calcium was associated with an increased risk of cancer mortality (> vs. ≤ Tolerable Upper Intake Level: multivariable-adjusted mortality rate ratio = 1.62, 95% CI: 1.07, 2.45; multivariable-adjusted mortality rate difference = 1.7, 95% CI: −0.1, 3.5 per 1,000 person-years), and the association appeared to be related to calcium intake from supplements (≥1000 mg/d vs. non-users: multivariable-adjusted mortality rate ratio=1.53, 95% CI: 1.04, 2.25; multivariable-adjusted mortality rate difference = 1.5, 95% CI: −0.1, 3.1 per 1,000 person-years) not 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 US adults.

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Keywords

Dietary Supplement Use; Nutritional Intake; Adequate Intake; Excess Intake; Mortality; Estimated Average Requirement; Tolerable Upper Intake Level

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BACKGROUND

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

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

Using a nationally representative sample of US 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 US adults aged 20+ years who participated in the 6 cycles (from 1999–2000 to 2009–2010) of the National Health and Nutrition Examination Survey (NHANES) linked to mortality outcomes. Exclusion of pregnant or lactating women resulted in 30,958 participants, among which 30,899 provided completed information on dietary supplement use in the past 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 participants with 1 or 2 valid 24-hour diet recalls were included in the analysis of estimating nutrient intake from foods *versus* supplements and its association with mortality outcomes. NHANES was approved by the research ethic review board of the National Center for Health Statistics, and all participants provided written informed consent.

Dietary Supplement Use

NHANES participants were asked whether they used any dietary supplements in the past 30 days during an in-house interview. For those who reported supplement use, they were asked about the product name, and the frequency (e.g., how many times in a day), duration (e.g., how many days in the past 30 days), and serving form (e.g., capsules, tablets, pills, soft-gels, drops, or other forms). For each nutrient, the daily dose was calculated by combining the frequency (e.g., the number of capsules taken in each day) with the product information on ingredient (e.g., vitamin D, calcium), amount of ingredient per serving, and ingredient unit (e.g., IU, mg). Nutrient intake from each product was summed to estimate the total daily dose of each supplemental nutrient for each individual (eMethod 1).

Nutrient Intake from Foods

Nutrient intake from foods was assessed using 24-hour diet recalls conducted by trained interviewers. From 1999 to 2002, one diet recall was conducted in-person in the Mobile Examination Center; from 2003 to 2010, a second recall was added by telephone interview approximately 3–10 days after the first recall. Using the Automated Multiple Pass Method (AMPM), all foods and beverages consumed during the previous day were recorded. A standard set of measuring guides were used to help the respondent report the volume and dimensions of the food items consumed. Food intakes were coded and nutrient values were determined using the United States Department of Agriculture (USDA) Food and Nutrient Database for Dietary Studies (FNDDS), versions 1.0–5.0 (9).

Inadequate and Excess Nutrient Intake

Inadequate nutrient intake was defined as levels of total nutrient intake (foods + supplements) below the Estimated Average Requirement (EAR) or Adequate Intake according to Dietary Reference Intakes (DRIs) (10). Excess nutrient intake was defined as levels of nutrient intake above the Tolerable Upper Intake Level (UL).

Mortality

Mortality outcomes were obtained for each participant through linkage to the National Death Index through December 31, 2011 using a probabilistic match (11). The International Statistical Classification of Disease, 10^{th} Revision (ICD-10) was used to ascertain cause-specific death. Death from cardiovascular disease (CVD) was defined when I00-I09, I11, I13, I120-I51, I60-I69 were listed as the underlying cause of death; and death from cancer was defined when C00-C09 were listed as the underlying cause of death. Follow-up length was defined as the interval from the interview date to the date of death for participants who died or to the end of 2011 for participants who were censored.

Demographic, Lifestyle Factors, and Comorbidity Conditions

Demographic and lifestyle factors including age, sex, race/ethnicity, education, income, smoking, and physical activity were collected during household interviews. Alcohol intake, body 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, with former smokers defined as participants who reported smoking at least 100 cigarettes, but not currently smoking. Drinkers were defined as participants who drank at least 12 alcohol drinks in any given year. Moderate *versus* heavy drinkers were defined as participants who consumed <1 *versus* ≥1 drink/day for women and <2 *versus* ≥2 drinks/day for men. Participants who had at least 150 min moderate-to-vigorous physical activities per week were classified as being physically active, and physically inactive otherwise (12). Diet quality was assessed using the Healthy Eating Index-2015 that measures the adherence to the 2015 Dietary Guidelines for Americans (13). A higher score corresponds to a healthier diet. Comorbidity conditions, including cancer, congestive heart failure, coronary heart disease, heart attack, and stroke were defined if participants reported that they have ever been told by a doctor that they had such conditions, and/or if they have ever been told to take prescribed medicine or are currently taking prescribed medicine to treat high cholesterol, hypertension, or diabetes.

Statistical Analysis

We first estimated the prevalence of supplement use among US adults. Multivitamins-mineral (MVM) supplement use was defined as using a product formulated with 3+ vitamins with or without minerals (14). We then compared the distribution of demographic, lifestyle factors, and comorbidity conditions between individuals who used any dietary supplements and those who did not, using t-tests for continuous variables and chi-square tests for categorical variables. We further estimated total nutrient intake by summing the nutrient intake from foods and supplements and the percentage of US adults with inadequate or excess nutrient intake. To correct for measurement errors associated with dietary intake estimated using 1 or 2 days recalls, we used the National Cancer Institute method to adjust for usual intake estimates. It also corrects biases due to measure errors in evaluating associations between usual intake and health outcomes using regression calibration (eMethod 2) (15–17).

Next, we used Poisson regression models with robust standard errors to estimate mortality rates, mortality rate ratios (RR), and 95% confidence intervals (CIs) for associations between dietary supplement use, nutrient intake, and mortality. Two multivariable models were conducted: Model 1 was adjusted for age, sex, and race/ethnicity; and Model 2 was additionally adjusted for education, physical activity, cigarette smoking, alcohol drinking, diet quality, body mass index, and comorbidity conditions. Multiple imputation was conducted for variables with more than 5% missing values among the individuals who reported nutrient intake from both foods and supplements (i.e., 6.1% missing in alcohol). We further evaluated whether the association differed by nutrient intake from supplements *versus* foods, by including nutrient intake from supplements and foods as two separate variables in the same model. We also performed subgroup analysis among individuals with or without comorbidity conditions at baseline, and among individuals with high (≥ median) *versus* low (< 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 percentage of US adults with inadequate or excess intake were conducted using SAS version 9.4 (SAS Institute). The analyses for estimating mortality rates, RRs, and rate differences (RDs) were conducted using Stata version 15.1. $P < 0.05$ was considered statistically significant.

Role of the Funding Source

The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

RESULTS

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

The vitamin supplements commonly used by US adults were vitamin C (40.3%, 95% CI: 39.3–41.4%), vitamin E (38.6%, 95% CI: 37.6–39.6%), vitamin D (37.6%, 95% CI: 36.6–38.6%), and others. The mineral supplements commonly used by US adults were calcium (38.6%, 95% CI: 37.6–39.6%), zinc (34.5%, 95% CI: 33.5–35.4%), magnesium (33.3%, 95% CI: 32.3–34.3%), and others. 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 levels of nutrient intake from foods for 23 nutrients than nonusers (Table 2).

For vitamins and minerals, more than half of US adults had inadequate intake for vitamin D (67.4%, 95% CI: 65.7–69.1%), vitamin E (61.6%, 95% CI: 60.5–62.8%), choline (96.7%, 95% CI: 96.3–97.2%), vitamin K (62.2%, 95% CI: 60.9–63.5%), and potassium (99.1%, 95% CI: 99.0–99.3%). The prevalence of US adults with excess intake was low (<5%) for most nutrients except for niacin (7.1%, 95% CI: 6.5–7.6%) (Table 2).

During a median follow-up of 6.1 years, a total of 3,613 deaths occurred, including 945 CVD deaths and 805 cancer deaths. Supplement use of most individual nutrients (yes *versus* no) were associated with a lower risk of all-cause but not CVD or cancer mortality. However, all of the associations became statistically insignificant after multivariable adjustments except that lycopene supplement use (yes vs. no) was associated with a lower risk of all-cause mortality (RR=0.82, 95% CI: 0.60, 0.85) and cancer mortality (RR=0.66, 95% CI: 0.46–0.96) (Table 3, eTable 1).

Adequate nutrient intake of vitamin K (RR=0.79, 95% CI: 0.70, 0.90) and magnesium (RR=0.85, 95% CI: 0.74, 0.98) was each associated with a lower risk of all-cause mortality (Table 4). Adequate nutrient intake of vitamin A (RR=0.61, 95% CI: 0.43, 0.88), vitamin K (RR=0.68, 95% CI: 0.54, 0.86), and zinc (RR=0.50, 95% CI: 0.36, 0.71) was each associated with a lower CVD mortality (eTable 2). In contrast, excess nutrient intake of calcium was associated with a higher cancer mortality (RR=1.62, 95% CI: 1.07, 2.45) (eTable 3).

When sources of nutrient intake (foods *versus* supplements) were further evaluated, the lower all-cause mortality associated with adequate nutrient intake of vitamin K and magnesium were confined to nutrient intake from foods not supplements (vitamin K from foods: RR=0.79, 95% CI: 0.69, 0.92; RD per 1,000 person-years = −2.3, 95% CI: −3.7, −0.9; vitamin K from supplements: RR=0.96, 95% CI: 0.79, 1.17; RD per 1,000 person-years = −0.4, 95% CI: −2.4, 1.6; magnesium from foods: RR=0.78, 95% CI: 0.65, 0.93; RD per 1,000 person-years = −2.7, 95% CI: −4.5, −0.9; magnesium from supplements: RR=1.00, 95% CI: 0.87, 1.14 ; RD per 1,000 person-years=0.0, 95% CI: −1.6, 1.5) (Table 4). Similarly, the lower CVD mortality associated with adequate nutrient intake of vitamin A, vitamin K, and zinc were confined to nutrient intake from foods not supplements (eTable 2). On the other hand, the higher cancer mortality associated with excess calcium intake was attributable to high-dose calcium intake from supplements not foods. Calcium intake from supplements at ≥1000 mg/d was associated with an increased risk of cancer mortality (RR=1.53, 95% CI: 1.04, 2.25; RD per 1,000 person-years=1.5, 95% CI: −0.1, 3.1) (eTable 3, eFigure 1).

Similar associations were found among individuals with or without comorbidity conditions at baseline (eTables 4–6), and among individuals with high *versus* low baseline nutrient intake from foods (eTable 7). For vitamin D supplement use, stratified analysis revealed that supplement use was not associated with mortality among individuals with serum 25(OH)D <50 nmol/L; however, among individuals with serum 25(OH)D ≥50 nmol/L, vitamin D supplement use at >10 mcg/d was associated with an increased risk of all-cause mortality (RR=1.34, 95% CI: 1.00, 1.78; RD per 1,000 person-years =2.7, 95% CI: −0.2, 5.6) and cancer mortality (RR=2.11, 95% CI: 1.18, 3.77; RD per 1,000 person-years=1.6, 95% CI: 0.2, 3.1) (eTable 8, eFigures 2–3).

DISCUSSION

In a nationally representative sample of US adults, we found that dietary supplement use was not associated with mortality benefits. There were some suggestions that adequate nutrient intake from foods were associated with reduced mortality and excess nutrient intake from supplements could potentially be harmful.

We initially found that any supplement use, MVM supplement use, and supplement use of individual nutrients were all associated with a lower risk of all-cause mortality after adjusting for age, sex, and race/ethnicity. However, most of the associations became statistically insignificant after additional adjustments of 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. Indeed, our results along with those of others (18, 19) suggest that supplement users have higher levels of education and income and an overall healthier lifestyle (e.g., better diet quality, higher levels of physical activity, not smoking or drinking alcohol, and having a healthy weight) than nonusers. In addition, we and others (20, 21) found that supplement users, compared to nonusers, had higher levels of nutrient intake from foods alone. Thus, without additional nutrients from supplements, supplement users may have already had a lower prevalence of nutrient inadequacy that contributes to a 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 mortality among 23,943 participants in the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg) (22). Long-term multivitamin use was not associated with reduced incidence or mortality of stroke among 86,142 women in the Nurses' Health Study (23). Similarly, systematic review of cohort studies and intervention trials does not support the benefits for supplement use for primary prevention of CVD or cancer (3, 24). Although the use of lycopene supplement (yes vs. no) was associated with a lower risk of all-cause and cancer morality in our study, prior evidence from prospective cohort studies does not support that foods containing lycopene are associated with cancer risk (25). Evidence from RCTs also fails to support the chemoprevention role of lycopene supplements in prostate cancer (26, 27). Taken together, the totality of the current evidence does not support mortality benefits associated with the use of dietary supplements.

We also found that the mortality benefits associated with adequate intake of some nutrients (e.g., vitamin A, vitamin K, magnesium, and zinc) were confined to intake from foods and not supplements. There were also some suggestions that excess intake of some nutrients may have untoward effects. For example, a higher cancer mortality was observed in association with total calcium intake >UL. The potential harm of excess calcium intake has not been consistently reported (28), with some trials reporting reduced cancer risk associated with high intake (29–31) and others raising concerns about its safety (32–34). For example, the Health Professionals Follow-up Study reported total calcium intake ≥1500 mg/d was associated with an increased risk of 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 an increased risk of prostate cancer (RR=1.11, 95% CI: 1.02–1.20) and the association appeared stronger among those being followed for 10+ years (HR=1.22, 95% CI: 1.07–1.38) (36). The underlying mechanisms are unclear and may involve the 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 that the increased cancer mortality was only for high-dose calcium intake (at ≥1000 mg/d) from supplements not foods. These data are consistent with results from 59,744 male participants of the CPS-II Nutrition Cohort where lower supplemental doses (<1000 mg/d) or calcium intake from foods conferred no increased risk whereas higher supplemental doses of calcium (≥1000 mg/d) were associated with an increased all-cause mortality (8). The difference between the supplement *versus* food source of calcium may be explained by their different effects on circulating calcium: high calcium intake from foods can lead to reduced intestinal absorption and increased urinary excretion whereas long-term supplement use did not diminish circulating calcium levels (34).

There were some suggestions that vitamin D supplementation at >10 mcg/d might be associated with increased all-cause and cancer mortality among individuals with no vitamin D deficiency. It remains controversial whether vitamin D supplementation reduces premature death or prevents cancer. 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, the Vitamin D and Omega-3 Trial (VITAL), failed to detect an effect of vitamin D supplements at the dose of 2000 IU/day 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.

The strengths of our study include the use of a nationally representative sample of US adults, longitudinal study design, and collection of data using validated measures. However, there are some limitations that need to be considered. First, dietary supplement use was assessed in the previous 30 days, which may not reflect habitual supplement 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, the NHANES documented that the ingredient and dosage information were obtained from the bottles and nutrition fact labels at 80% of the time of interviews (43), which reduces the misclassification error due to recall bias. Second, self-reported dietary intake is also subject to measurement error. The NHANES incorporated one or two 24-hour diet recalls per person, which does not capture long-term intake due to large day-to-day variations in food intake. To improve the estimation on usual intake, we applied the National Cancer Institute method to reduce measurement errors associated with dietary intake estimated using diet recalls (44–46). The measurement errors cannot be ruled out, however, and are likely to be non-differential (i.e., independent of mortality), which attenuates the associations. Third, supplement use is highly correlated with participants' socioeconomic status and lifestyle factors such as education, cigarette smoking, body mass index, alcohol drinking, physical activity, and diet quality. Having chronic health conditions such as cancer, cardiovascular disease, hypertension, or diabetes may also motivate the initiation of dietary supplement use. To minimize the chance of residual confounding, we carefully adjusted for all these factors in the multivariable models. In addition, we stratified the association by presence or absence of comorbidity conditions at baseline and the associations remained similar. However, supplement use may be associated with factors that we haven't identified and adjusted, and residual confounding may still be present with the results. Forth, mortality outcomes were determined through linkage to the National Death Index through a probabilistic match (11) that may result in misclassification. A prior validation study has shown that the accuracy of the method was high, with 96.1% of the decedents and 99.4% of the living participants classified correctly (47). Fifth, due to limited sample size, we were unable to evaluate dietary supplement use with mortality from specific CVD conditions or cancer types, or mortality due to conditions other than CVD or cancer. Last, we have 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 shall be considered as exploratory and interpreted with cautions.

CONCLUSION

Use of dietary supplements was not associated with mortality benefits among US adults. While adequate nutrient intake from foods could contribute to a reduced risk of mortality, excess intake of nutrients from supplements might have an adverse effect on morality. The potential risks and benefits of dietary supplement use on health need to be further evaluated in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of US Adults by Dietary Supplement Use, NHANES 1999–2010 [*]

Characteristics	**Total Adults**	**Users of Dietary Supplements**	**Nonusers of Dietary Supplements**	***P*-value**
	(N=30,899)	**(N=14,763)**	**(N=16,136)**	
Age, *y*, mean (SE)	46.9 (0.2)	50.7 (0.3)	42.8 (0.2)	<0.001
Female, n (%)	15400 (50.9)	8156 (56.4)	7244 (45.1)	<0.001
Race/ethnicity, n (%)				
Non-Hispanic White	15295 (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 (%)				
Grades 0–12	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	13795 (54.7)	7919 (62.8)	5876 (46.2)	
Family Income to Poverty Ratio [†], n (%)				
<1.3	8287 (20.6)	2947 (14.3)	5340 (27.2)	<0.001
1.3–2.99	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 [‡], n (%)				
Non-smokers	15922 (51.4)	7816 (53.0)	8106 (49.7)	<0.001
Former smokers	8044 (24.8)	4571 (29.5)	3473 (19.8)	
Current smokers	6905 (23.9)	2368 (17.5)	4537 (30.5)	
Alcohol intake [§], n (%)				
Non-drinkers	11093 (35.7)	5455 (35.5)	5638 (35.8)	0.002
Moderate drinker	13573 (55.9)	6630 (56.8)	6943 (54.9)	
Heavy drinker	1933 (8.4)	820 (7.7)	1113 (9.2)	
HEI-2015 [//], mean (SE)	51.4 (0.2)	54.0 (0.3)	48.5 (0.2)	<0.001
HEI-2015 [//], n (%)				
Q1 (<41.8)	6462 (25.0)	2387 (19.2)	4075 (31.3)	<0.001
Q2 (41.8–50.5)	6900 (25.0)	3014 (22.8)	3886 (27.4)	
Q3 (50.6–60.0)	7147 (25.0)	3548 (26.0)	3599 (23.9)	
Q4 (>60.0)	7216 (25.0)	4432 (31.9)	2784 (17.5)	
Physical activity [¶], n (%)				
Active	14792 (53.1)	7422 (55.5)	7370 (50.5)	<0.001
Inactive	16095 (46.9)	7336 (44.5)	8759 (49.5)	
BMI [**], *kg/m*^{2}, mean (SE)	28.4 (0.1)	28.0 (0.1)	28.8 (0.1)	<0.001

Characteristics	Total Adults	Users of Dietary Supplements	Nonusers of Dietary Supplements	*P*-value
	(N=30,899)	(N=14,763)	(N=16,136)	
Weight status[**], n (%)				
BMI <25 kg/m[2]	8702 (33.3)	4401 (35.5)	4301 (30.9)	<0.001
BMI =25–29.9 kg/m[2]	9981 (34.0)	4862 (34.2)	5119 (33.7)	
BMI ≥30 kg/m[2]	9871 (32.8)	4388 (30.2)	5483 (35.5)	
Co-morbidities, 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	10617 (29.1)	5806 (33.0)	4811 (24.9)	<0.001
Diabetes	3618 (8.0)	1782 (8.3)	1836 (7.7)	0.09

Abbreviations: GED, General Equivalency Diploma; HEI, Healthy Eating Index; BMI, Body mass index; SE, standard error; NHANES, National Health and Nutrition Examination Survey

[*]Means and percentages were adjusted for survey weights of NHANES.

[†]Family income to poverty ratio represents the ratio of family income to the poverty threshold, adjusted for household size.

[‡]Cigarette smoking was defined as smoking at least 100 cigarettes during their lifetime, with former smokers defined as not currently smoking and current smokers defined as currently smoking.

[§]Alcohol drinking was defined as having at least 12 alcohol drinks in any given year. Moderate versus heavy alcohol drinkers were defined as participants who consumed <1 versus ≥ 1 drink/d for women and <2 versus ≥ 2 drinks/d for men.

[//]HEI-2015 was calculated to measure adherence to the 2015 Dietary Guidelines for Americans with a higher score corresponding to a higher-quality diet.

[¶]Participants who had at least 150 minutes per week of moderate-to-vigorous physical activity were classified as physically active according to the Center for Disease Control and Prevention (CDC) Physical Activity Guidelines for Americans.

[**]BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m[2]). Participants were classified as underweight (BMI<18.5 kg/m[2]), normal weight (BMI=18.5–24.9 kg/m[2]), overweight (BMI=25–29.9 kg/m[2]), and obese (BMI ≥30 kg/m[2]).

Table 2.

Prevalence of Dietary Supplement Use, Nutrient Intake Levels from Supplements *versus* Foods, and Percentages of Nutrient Intake < EAR or > UL among US Adults*

	Total Adults		Nonusers of Supplements	Users of Supplements			Total Adults	
	Supplement Use	Nutrient Intake (Foods + Supplements)	Nutrient Intake (Foods Alone)	Nutrient Intake (Foods Alone)†	Nutrient Intake (Supplements Alone)	Nutrient Intake (Foods + Supplements)‡	Nutrient Intake <EAR§	Nutrient Intake >UL§
	Prevalence (%) (95% CI)*	Mean ± SE*	Mean ± SE*	Mean ± SE*	Mean ± SE*	Mean ± SE*	Prevalence (%) (95% CI)*	Prevalence (%) (95% CI)*
Vitamin Supplement Use								
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)	---
Mineral Supplement Use								
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)

	Total Adults		Nonusers of Supplements	Users of Supplements			Total Adults	
	Supplement Use	Nutrient Intake (Foods + Supplements)	Nutrient Intake (Foods Alone)	Nutrient Intake (Foods Alone)†	Nutrient Intake (Supplements Alone)	Nutrient Intake (Foods + Supplements) ‡	Nutrient Intake <EAR§	Nutrient Intake >UL§
	Prevalence (%) (95% CI)*	Mean ± SE*	Mean ± SE*	Mean ± SE*	Mean ± SE*	Mean ± SE*	Prevalence (%) (95% CI)*	Prevalence (%) (95% CI)*
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 Supplement Use								
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	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		---

Abbreviations: EAR, Estimated Average Requirement; UL, Tolerable Upper Intake Level; AI, Adequate Intakes; RAE, retinal activity equivalent; DFE, dietary folate equivalent; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; SE, standard error; CI, confidence interval; NHANES, National Health and Nutrition Examination Survey

*The means and percentages were adjusted for survey weights of NHANES.

†Supplement users had significantly higher levels of nutrient intake from foods alone than non-users for 23 of the 25 nutrients examined (P values<0.05).

‡Among supplement users, levels of nutrient intake from both foods and supplements were significantly higher than levels of nutrient intake from foods alone for all 25 nutrients. Levels of total nutrient intake were significantly higher among supplement users than nonusers for all 25 nutrients (all P values<0.05).

§EAR and UL were based on DRIs. For nutrients that do not have EAR, AI was used to estimate the percentage of intake < AI (e.g., vitamin K, potassium, choline, and fiber) or < recommended intake (e.g., EPA+DHA). β-carotene, retinol, lutein, zeaxanthin, and lycopene have no EAR, AI, or recommended intake. UL for vitamin A applies to preformed vitamin A only. ULs for niacin and folate apply to synthetic forms obtained from supplements, fortified foods, or a combination of the two. UL for vitamin E applies to any form of supplemental α-tocopherol. UL for magnesium represents intake from a pharmacological 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.

The Association between Dietary Supplement Use (Users vs. Nonusers) and All-Cause Mortality among US Adults, NHANES 1999–2010

Supplements	Person-Years (Users / Nonusers)	All-Cause Mortality		
		Total Death (Users / Nonusers)	Model 1* RR (95% CI)	Model 2† RR (95% CI)
Any Supplement	90515 / 99288	2000 / 1613	0.85 (0.77, 0.94)	1.02 (0.92, 1.13)
MVM Supplement	66295 / 123508	1414 / 2199	0.85 (0.77, 0.94)	1.01 (0.91, 1.13)
Individual vitamin use				
Vitamin A	60556 / 129247	1254 / 2359	0.85 (0.77, 0.95)	1.00 (0.89, 1.13)
Beta-carotene	60440 / 129363	1254 / 2359	0.86 (0.77, 0.95)	1.01 (0.89, 1.14)
Retinol	56138 / 133664	1156 / 2457	0.86 (0.78, 0.96)	1.00 (0.89, 1.13)
Thiamin	61942 / 127860	1275 / 2338	0.87 (0.78, 0.97)	1.02 (0.90, 1.14)
Riboflavin	61733 / 128070	1280 / 2333	0.86 (0.78, 0.96)	1.01 (0.90, 1.14)
Niacin	62099 / 127704	1277 / 2336	0.86 (0.77, 0.96)	1.00 (0.90, 1.13)
Pantothenic Acid	59582 / 130221	1241 / 2372	0.85 (0.77, 0.94)	1.01 (0.90, 1.13)
Vitamin B_6	63528 / 126274	1321 / 2292	0.87 (0.78, 0.97)	1.02 (0.91, 1.15)
Folate	62799 / 127004	1294 / 2319	0.85 (0.76, 0.94)	0.99 (0.88, 1.12)
Vitamin B_{12}	64139 / 125663	1343 / 2270	0.85 (0.77, 0.94)	0.99 (0.89, 1.11)
Choline	9447 / 180355	125 / 3488	0.77 (0.60, 0.99)	0.97 (0.75, 1.25)
Vitamin C	69804 / 119998	1485 / 2128	0.88 (0.79, 0.98)	1.07 (0.94, 1.20)
Vitamin D	63794 / 126009	1304 / 2309	0.82 (0.74, 0.90)	0.96 (0.86, 1.07)
Vitamin E	68085 / 121718	1448 / 2165	0.81 (0.73, 0.89)	0.98 (0.89, 1.09)
Vitamin K	43823 / 145980	907 / 2706	0.81 (0.72, 0.90)	0.93 (0.82, 1.07)
Biotin	52670 / 137133	1101 / 2512	0.85 (0.76, 0.94)	1.00 (0.89, 1.13)
Individual mineral use				
Copper	52483 / 137319	1092 / 2521	0.84 (0.76, 0.92)	1.00 (0.89, 1.13)
Phosphorus	40657 / 149145	902 / 2711	0.88 (0.79, 0.98)	1.02 (0.89, 1.16)
Selenium	50953 / 138849	1075 / 2538	0.84 (0.76, 0.92)	0.99 (0.88, 1.11)
Boron	41529 / 148273	893 / 2720	0.86 (0.77, 0.96)	1.00 (0.88, 1.13)
Iodine	47219 / 142584	988 / 2625	0.86 (0.77, 0.96)	1.01 (0.89, 1.14)
Silicon	36105 / 153698	817 / 2796	0.88 (0.78, 0.98)	0.98 (0.86, 1.13)
Iron‡	43032 / 146771	822 / 2791	0.97 (0.86, 1.09)	1.02 (0.89, 1.19)
Magnesium	56881 / 132922	1118 / 2495	0.83 (0.75, 0.91)	0.97 (0.86, 1.09)
Calcium	66699 / 123103	1349 / 2264	0.81 (0.74, 0.89)	0.97 (0.88, 1.07)
Manganese	51182 / 138621	1037 / 2576	0.81 (0.73, 0.90)	0.96 (0.85, 1.08)
Tin	24321 / 165482	468 / 3145	0.97 (0.85, 1.11)	1.09 (0.92, 1.28)
Chromium	50575 / 139228	1008 / 2605	0.83 (0.74, 0.92)	0.97 (0.86, 1.10)
Molybdenum	44337 / 145466	957 / 2656	0.87 (0.78, 0.97)	1.01 (0.89, 1.15)
Vanadium	38418 / 151385	852 / 2761	0.87 (0.77, 0.98)	0.99 (0.86, 1.14)
Nickel	34572 / 155231	800 / 2813	0.89 (0.80, 0.99)	1.00 (0.88, 1.13)

Supplements	Person-Years (Users / Nonusers)	All-Cause Mortality		
		Total Death (Users / Nonusers)	Model 1* RR (95% CI)	Model 2† RR (95% CI)
Zinc	59276 / 130527	1209 / 2404	0.87 (0.78, 0.96)	1.02 (0.91, 1.15)
Potassium	46960 / 142843	1024 / 2589	0.90 (0.81, 1.00)	1.03 (0.92, 1.17)
Other supplements				
Lutein	29435 / 160368	710 / 2903	0.90 (0.80, 1.02)	1.00 (0.87, 1.15)
Lycopene	17989 / 171814	366 / 3247	0.72 (0.60, 0.85)	0.82 (0.68, 0.98)
Zeaxanthin	1397 / 188406	19 / 3694	0.66 (0.37, 1.18)	0.73 (0.38, 1.40)
Inositol	7835 / 181968	98 / 3515	0.74 (0.58, 0.95)	0.90 (0.68, 1.18)
Fiber	4468 / 185335	78 / 3535	0.79 (0.61, 1.04)	0.91 (0.65, 1.25)
Omega-3	7475 / 182328	115 / 3498	0.66 (0.47, 0.94)	0.82 (0.58, 1.17)
EPA	5934 / 183869	91 / 3522	0.63 (0.41, 0.97)	0.81 (0.53, 1.25)
DHA	6236 / 183567	96 / 3517	0.63 (0.42, 0.95)	0.81 (0.54, 1.21)
Omega-6	1994 / 187809	31 / 3582	0.79 (0.57, 1.10)	0.93 (0.67, 1.29)
Omega-9	1510 / 188293	25 / 3588	0.93 (0.59, 1.47)	1.06 (0.62, 1.80)

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MVM, multivitamins-mineral; NHANES, National Health and Nutrition Examination Survey; RR, rate ratio

*Model 1 was adjusted for age, sex, and race/ethnicity.

†Model 2 was additionally adjusted for education, physical activity, smoking, alcohol consumption, Healthy Eating Index-2015, body mass index, baseline comorbidity conditions, and survey weights of NHANES. Multiple imputation was conducted for covariate that has missing values for more than 5% (i.e., 6.1% missing in alcohol intake).

‡Model 2 for iron was additionally adjusted for anemia at baseline (yes vs. no).

Table 4.

Nutrient Intake from Foods *versus* Supplements in Association with All-Cause Mortality among US Adults

Nutrients	Total Nutrient Intake				Nutrient Intake from Foods			Nutrient Intake from Supplements[‡]		
	Person-years (≥EAR/<EAR)	N of Total Death (≥EAR/<EAR)	RR (95% CI)	RD (95% CI)	N of Total Death (≥EAR/<EAR)	RR (95% CI)	RD (95% CI)	N of Total Death (≥Median/ Nonusers)	RR (95% CI)	RD (95% CI)
Adequate Intake[*§]										
Vitamin A	78730 / 49313	1413 / 625	0.88 (0.74, 1.06)	−1.3 (−3.3, 0.6)	1270 / 768	0.87 (0.74, 1.01)	−1.5 (−3.2, 0.1)	523 / 1303	1.12 (0.94, 1.33)	1.2 (−0.7, 3.1)
Thiamin	170015 / 454	2835 / 10	0.65 (0.23, 1.87)	−6.2 (−24.8, 12.4)	2033 / 5	0.96 (0.21, 4.45)	−0.4 (−15.4, 14.7)	333 / 1860	1.09 (0.91, 1.32)	0.9 (−1.0, 2.8)
Riboflavin	169430 / 1039	2817 / 28	0.66 (0.33, 1.35)	−5.8 (−18.1, 6.4)	2816 / 29	0.72 (0.35, 1.48)	−4.4 (−15.8, 7.0)	873 / 1860	1.03 (0.90, 1.18)	0.3 (−1.3, 1.9)
Niacin	169990 / 480	2829 / 16	0.54 (0.27, 1.09)	−9.7 (−24.4, 5.0)	2829 / 16	0.60 (0.30, 1.21)	−7.5 (−20.6, 5.6)	827 / 1859	1.04 (0.91, 1.18)	0.4 (−1.1, 2.0)
Vitamin B_6	161408 / 9062	2557 / 288	1.00 (0.82, 1.21)	0.0 (−2.3, 2.2)	2461 / 384	0.95 (0.81, 1.13)	−0.6 (−2.5, 1.4)	593 / 1825	0.99 (0.85, 1.14)	−0.1 (−1.8, 1.5)
Folate	124006 / 4036	1941 / 97	0.88 (0.61, 1.25)	−1.5 (−5.7, 2.7)	1913 / 125	0.83 (0.61, 1.15)	−2.1 (−6.0, 1.9)	608 / 1301	1.00 (0.85, 1.19)	0.0 (−1.7, 1.8)
Vitamin B_{12}	169894 / 576	2830 / 15	0.89 (0.46, 1.75)	−1.4 (−10.0, 7.3)	2829 / 16	1.06 (0.54, 2.10)	0.7 (−6.7, 8.0)	544 / 1820	0.92 (0.80, 1.05)	−1.0 (−2.4, 0.5)
Choline	1585 / 54295	19 / 722	1.25 (0.74, 2.11)	2.1 (−3.5, 7.8)	9 / 732	1.47 (0.84, 2.59)	4.1 (−3.1, 11.3)	19 / 712	0.79 (0.39, 1.60)	−1.8 (−6.7, 3.0)
Vitamin C	131636 / 38833	2256 / 589	1.05 (0.86, 1.26)	0.5 (−1.6, 2.6)	2037 / 808	0.99 (0.86, 1.15)	−0.1 (−1.7, 1.6)	599 / 1703	1.10 (0.95, 1.29)	1.2 (−0.7, 3.0)
Vitamin D	8752 / 23148	132 / 271	1.01 (0.77, 1.33)	0.1 (−2.0, 2.2)	4 / 399	---	---	118 / 258	0.98 (0.74, 1.31)	−0.1 (−2.3, 2.1)
Vitamin E	58687 / 111783	1104 / 1741	0.99 (0.89, 1.09)	−0.2 (−1.3, 1.0)	48 / 2797	0.95 (0.66, 1.36)	−0.6 (−4.6, 3.3)	740 / 1713	0.97 (0.87, 1.09)	−0.3 (−1.6, 0.9)
Vitamin K	41693 / 86349	635 / 1403	0.79 (0.70, 0.90)	−2.3 (−3.5, −1.1)	504 / 1534	0.79 (0.69, 0.92)	−2.3 (−3.7, −0.9)	286 / 1506	0.96 (0.79, 1.17)	−0.4 (−2.4, 1.6)
Copper	167644 / 2826	2771 / 74	0.82 (0.56, 1.21)	−2.5 (−7.8, 2.9)	2758 / 87	0.81 (0.58, 1.13)	−2.6 (−7.3, 2.0)	667 / 1992	1.03 (0.88, 1.19)	0.3 (−1.4, 2.1)
Phosphorus	169960 / 510	2830 / 15	0.75 (0.34, 1.63)	−3.9 (−15.8, 8.1)	2830 / 15	0.76 (0.35, 1.66)	−3.6 (−15.4, 8.2)	365 / 2140	1.09 (0.92, 1.29)	1.0 (−1.0, 3.0)
Selenium	170323 / 146	2841 / 4	---	---	2841 / 4	---	---	324 / 2004	0.96 (0.82, 1.13)	−0.5 (−2.3, 1.3)

Nutrients	Total Nutrient Intake				Nutrient Intake from Foods			Nutrient Intake from Supplements[‡]		
	Person-years (≥EAR/<EAR)	N of Total Death (≥EAR/<EAR)	RR (95% CI)	RD (95% CI)	N of Total Death (≥EAR/<EAR)	RR (95% CI)	RD (95% CI)	N of Total Death (≥Median/ Nonusers)	RR (95% CI)	RD (95% CI)
Iron[//]	169684 / 785	2836 / 9	0.71 (0.29, 1.73)	−4.6 (−18.8, 9.6)	2835 / 10	0.66 (0.29, 1.51)	−5.8 (−20.1, 8.4)	433 / 2250	1.15 (0.99, 1.33)	1.7 (−0.3, 3.6)
Magnesium	75852 / 94618	994 / 1851	0.85 (0.74, 0.98)	−1.8 (−3.3, −0.2)	491 / 2354	0.78 (0.65, 0.93)	−2.7 (−4.5, −0.9)	776 / 1967	1.00 (0.87, 1.14)	0.0 (−1.6, 1.5)
Calcium	100797 / 69673	1205 / 1640	1.01 (0.89, 1.16)	0.1 (−1.4, 1.7)	742 / 2103	1.02 (0.90, 1.17)	0.3 (−1.3, 1.8)	522 / 1798	0.98 (0.85, 1.14)	−0.2 (−1.9, 1.5)
Zinc	162287 / 8183	2588 / 257	0.93 (0.74, 1.17)	−0.9 (−3.7, 2.0)	2539 / 306	0.91 (0.76, 1.09)	−1.2 (−3.5, 1.1)	750 / 1899	1.04 (0.91, 1.20)	0.5 (−1.1, 2.1)
Potassium	1196 / 169273	14 / 2831	1.12 (0.53, 2.37)	1.3 (−8.3, 10.9)	10 / 2835	1.01 (0.38, 2.64)	0.1 (−11.1, 11.2)	582 / 2056	1.03 (0.88, 1.21)	0.4 (−1.5, 2.3)
Fiber	4319 / 166150	64 / 2781	0.77 (0.54, 1.12)	−2.6 (−6.0, 0.8)	53 / 2792	0.84 (0.56, 1.27)	−1.8 (−5.9, 2.2)	38 / 2789	0.89 (0.61, 1.31)	−1.2 (−5.2, 2.8)
EPA+DHA	2527 / 167943	38 / 2807	0.89 (0.49, 1.62)	−1.2 (−7.3, 4.9)	0 / 2845	---	---	15 / 2815	0.95 (0.60, 1.49)	−0.6 (−5.5, 4.3)
Nutrients	**Person-years (>UL/≤UL)**	**N of Total Death (>UL/≤UL)**	**RR (95% CI)**	**RD (95% CI)**	**N of Total Death (>UL/≤UL)**	**RR (95% CI)**	**RD (95% CI)**	**N of Total Death (High dose / Nonusers)**	**RR (95% CI)**	**RD (95% CI)**
Excess Intake[†§]										
Vitamin A	948 / 127095	23 / 2015	1.54 (0.76, 3.12)	5.6 (−5.6, 16.7)	1 / 2037	---	---	261 / 1303	1.16 (0.97, 1.40)	1.7 (−0.5, 3.8)
Niacin	11415 / 159055	176 / 2669	1.00 (0.82, 1.21)	0.0 (−2.3, 2.2)	0 / 2845	---	---	236 / 1859	1.03 (0.86, 1.24)	0.4 (−1.8, 2.5)
Vitamin B6	2859 / 167610	62 / 2783	1.35 (0.98, 1.88)	4.0 (−1.0, 9.0)	0 / 2845	---	---	334 / 1825	1.07 (0.89, 1.28)	0.8 (−1.4, 3.0)
Folate	2859 / 167610	62 / 2783	1.21 (0.88, 1.67)	2.2 (−1.8, 6.1)	0 / 2038	---	---	146 / 1301	1.04 (0.82, 1.32)	0.4 (−2.1, 3.0)
Choline	38 / 55842	0 / 741	---	---	0 / 741	---	---	14 / 712	0.74 (0.38, 1.44)	−2.3 (−6.6, 2.0)
Vitamin C	1344 / 169126	30 / 2815	1.44 (0.82, 2.51)	5.0 (−4.2, 14.1)	0 / 2845	---	---	353 / 1703	1.15 (0.95, 1.39)	1.7 (−0.7, 4.0)
Vitamin D	103 / 31797	3 / 400	---	---	0 / 403	---	---	68 / 258	1.02 (0.74, 1.42)	0.2 (−2.5, 2.8)
Vitamin E	776 / 86394	24 / 1296	1.26 (0.89, 1.79)	3.0 (−2.0, 8.0)	0 / 2845	---	---	437 / 1713	0.99 (0.87, 1.13)	−0.1 (−1.7, 1.4)

Nutrients	Total Nutrient Intake				Nutrient Intake from Foods			Nutrient Intake from Supplements[‡]		
	Person-years (≥EAR/<EAR)	N of Total Death (≥EAR/<EAR)	RR (95% CI)	RD (95% CI)	N of Total Death (≥EAR/<EAR)	RR (95% CI)	RD (95% CI)	N of Total Death (≥Median/ Nonusers)	RR (95% CI)	RD (95% CI)
Copper	274 / 170196	5 / 2840	1.27 (0.58, 2.77)	3.1 (−8.3, 14.5)	0 / 2845	---	---	127 / 1992	1.14 (0.89, 1.46)	1.6 (−1.5, 4.8)
Phosphorus	96 / 170373	2 / 2843	---	---	0 / 2845	---	---	336 / 2140	1.12 (0.94, 1.35)	1.4 (−0.9, 3.7)
Selenium	1108 / 169362	15 / 2830	0.97 (0.46, 2.05)	−0.3 (−8.6, 8.0)	0 / 2845	---	---	177 / 2004	1.07 (0.86, 1.31)	0.8 (−1.8, 3.3)
Iron[//]	3834 / 166636	86 / 2759	1.25 (0.90, 1.74)	2.8 (−1.8, 7.5)	0 / 2845	---	---	123 / 2250	1.27 (0.99, 1.63)	3.1 (−0.5, 6.6)
Magnesium	4116 / 166353	72 / 2773	1.00 (0.70, 1.43)	0.0 (−4.1, 4.1)	0 / 2845	---	---	173 / 1967	1.01 (0.80, 1.28)	0.1 (−2.6, 2.9)
Calcium	5302 / 165167	124 / 2721	1.13 (0.87, 1.46)	1.4 (−1.8, 4.7)	4 / 2841	---	---	169 / 1798	1.05 (0.83, 1.34)	0.6 (−2.3, 3.5)
Zinc	6037 / 164433	142 / 2703	1.06 (0.87, 1.30)	0.7 (−1.7, 3.1)	0 / 2845	---	---	228 / 1899	1.11 (0.92, 1.33)	1.2 (−1.0, 3.4)

Abbreviations: AI, Adequate Intakes; CI, confidence interval; 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

[*] Adequate intake was defined as levels of nutrient intake ≥EAR. RRs, RDs, and 95% CIs correspond to the comparisons between individuals with total nutrient intake ≥EAR vs. <EAR. For choline, vitamin K, potassium, and fiber where EARs are not available, adequate intake was defined as intake ≥ AI; for EPA+DHA, adequate intake was defined as intake ≥ recommended intake by the Academy of Nutrition and Dietetic.

[†] Excess intake was defined as levels of nutrient intake >UL. RRs, RDs, and 95% CIs correspond to the comparisons between individuals with total nutrient intake >UL vs. ≤UL. There was no or very few of participants (< 0.1%) having excess intake of nutrients from food source only.

[‡] For nutrient intake from supplement source, the RRs, RDs, and 95% CIs for adequate intake correspond to the comparisons between individuals with supplemental intake ≥ median vs. nonusers. Median was defined as the median supplement dose reported by supplement users. The median dose was 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 for potassium, 2 g/d for fiber, and 600 mg for EPA+DHA. RRs, RDs, and 95% CIs for excess intake correspond to the comparison between individuals with supplemental intake at a high dose vs. nonusers. The high dose was determined by the commonly used dose at approximately 75th −85th percentile reported by supplement users. The high dose was 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, cigarette smoking, alcohol intake, Healthy Eating Index-2015, body mass index, baseline comorbidity conditions, and survey weights of NHANES. Models for two sources of intake (foods versus supplements) were adjusted for one another in the same model. Multiple imputation was conducted for covariate that has missing values for more than 5% (i.e., 6.1% missing in alcohol intake). RRs and RDs were not estimated for nutrients with deaths < 5 in any nutrient intake subgroups.

[//] Models for iron were additionally adjusted for anemia status at baseline (yes vs. no).