Total mortality risk in relation to use of less-common dietary supplements[1–3]

Gaia Pocobelli, Alan R Kristal, Ruth E Patterson, John D Potter, Johanna W Lampe, Ann Kolar, Ilonka Evans, and Emily White

ABSTRACT

Background: Dietary supplement use is common in older US adults; however, data on health risks and benefits are lacking for a number of supplements.

Objective: We evaluated whether 10-y average intakes of 13 vitamin and mineral supplements and glucosamine, chondroitin, saw palmetto, *Ginko biloba*, garlic, fish-oil, and fiber supplements were associated with total mortality.

Design: We conducted a prospective cohort study of Washington State residents aged 50–76 y during 2000–2002. Participants (n = 77,719) were followed for mortality for an average of 5 y.

Results: A total of 3577 deaths occurred during 387,801 person-years of follow-up. None of the vitamin or mineral 10-y average intakes were associated with total mortality. Among the nonvitamin-nonmineral supplements, only glucosamine and chondroitin were associated with total mortality. The hazard ratio (HR) when persons with a high intake of supplements (≥4 d/wk for ≥3 y) were compared with nonusers was 0.83 (95% CI: 0.72, 0.97; P for trend = 0.009) for glucosamine and 0.83 (95% CI: 0.69, 1.00; P for trend = 0.011) for chondroitin. There was also a suggestion of a decreased risk of total mortality associated with a high intake of fish-oil supplements (HR: 0.83; 95% CI: 0.70, 1.00), but the test for trend was not statistically significant.

Conclusions: For most of the supplements we examined, there was no association with total mortality. Use of glucosamine and use of chondroitin were each associated with decreased total mortality. *Am J Clin Nutr* 2010;91:1791–800.

INTRODUCTION

Routine use of vitamin, mineral, and other nonvitamin-nonmineral dietary supplements is common among older persons in the United States (1). An estimated one-half of persons 57–85 y of age take a dietary supplement regularly (at least once per week) (1). Users tend to be motivated by the putative health benefits (2–4), but there is no clear evidence that the use of the most-common dietary supplements (eg, multivitamins) affects mortality, and there are few or no studies of mortality risk in relation to the use of many of the less-common dietary supplements. Evidence of efficacy is not required before a dietary supplement is marketed to the public (5) and, until December 2007 (6) there was no requirement for manufacturers of dietary supplements to include contact information on their products or to report the occurrence of adverse events that may be related to their use to the US Food and Drug Administration (7). The VITamin and Lifestyle (VITAL) Study was implemented to assess whether the use of dietary supplements was related to the occurrence of various health outcomes. We (8) previously reported on associations between the use of the most-common dietary supplements (multivitamins, vitamin C, and vitamin E) and mortality. In the current study we evaluated associations between the use of 20 less-common dietary supplements and total mortality.

SUBJECTS AND METHODS

Study population

Men and women who were 50–76 y of age between October 2000 and December 2002 and lived in a 13-county area of western Washington State were eligible to participate in this cohort study. The study proposal was approved by the institutional review board of the Fred Hutchinson Cancer Research Center. The methods of recruitment of participants, data collection, and follow-up for outcomes were described previously (9). Briefly, 364,418 individuals, who were identified from a purchased commercial mailing list, were sent a cover letter and a 24-page questionnaire to be self-administered. With the goal of encouraging supplement users to participate in the study, the cover letter described the study as one on supplement use and cancer risk. Between October 2000 and December 2002, 79,300 questionnaires were returned, and among them, 77,719 met eligibility and quality-control checks. Characteristics of the participants were described previously (9). For the current analysis we excluded one participant who died before his questionnaire reached the study center and 45 participants who reported having a malabsorption condition at baseline that may have impaired their ability to absorb nutrients. A total of 77,673 participants remained for analysis.

[1] From the Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA (GP, ARK, REP, JDP, JWL, and EW), and the Cancer Prevention Program, Fred Hutchinson Cancer Research Center, Seattle, WA (GP, ARK, REP, JDP, JWL, AK, IE, and EW).

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[3] Address correspondence to G Pocobelli, Department of Epidemiology, School of Public Health, University of Washington, Box 357236, Seattle, WA 98195. E-mail: gpocobel@u.washington.edu.

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Supplement use

A participant was classified as a user of an individual supplement or multivitamin if she or he reported use at least once per week for ≥1 y during the previous 10 y; all other participants were classified as nonusers of the individual supplement or multivitamin. For each vitamin, mineral, and nonvitamin-nonmineral, we ascertained intake from single supplements (including mixtures other than multivitamins (eg, a supplement of B vitamins)] and multivitamins, including the duration and frequency of use of each individual supplement during the previous 10 y, and for vitamins and minerals only, we ascertained the average dose per day. Information was also obtained on the duration and frequency of multivitamin use and the current brand and the most commonly used past brand of multivitamin. The amount of each vitamin or mineral contained in the multivitamin was obtained from the *Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements 2002* (10), from the manufacturer (for the 16 multivitamin brands listed in the questionnaire), or from the amount reported by the participant (if the multivitamin was not one of the 16 brands listed).

The 10-y average daily intake of each vitamin and mineral was then computed as the duration (y) ÷ 10 y × frequency (d/wk) ÷ 7 d/wk × dose per day (U/d) and summed over the individual supplement and multivitamin. Each user of a vitamin and mineral supplement was categorized into one of the following 3 groups of 10-y average daily intake (U/d): *1*) the first tertile, *2*), more than the first tertile up to the amount of that nutrient that would be obtained from a 10-y daily use of the multivitamin pill Centrum Silver (Wyeth, Madison NJ), or *3*) more than the amount of that nutrient that would be obtained from a 10-y daily use of the multivitamin pill Centrum Silver (Wyeth). Therefore, only participants who used an individual supplement of that nutrient or a multivitamin with a relatively high amount of that nutrient could be classified into the highest-intake group. Individuals who only consumed that supplemental nutrient via 10 y of daily use of a standard multivitamin could not be classified into the highest-intake group. Because the amount of iron varies considerably in different formulations of multivitamins, and the amount that would be obtained from daily use of Centrum Silver (4.0 mg/d; Wyeth) is relatively low, we defined the highest category of iron-supplement use as greater than the amount that would be obtained from daily use of several common multivitamin pills (18.0 mg/d; [eg, Centrum (Wyeth)].

Each user of a nonvitamin-nonmineral supplement was categorized into 1 of 2 groups of 10-y intake: *1*) a low-use category based on a duration of use of <3 y or a frequency of use of <4 d/wk, or *2*) a high-use category based on a duration of use ≥3 y and a frequency of use during that time of ≥4 d/wk. A few brands of multivitamins contain saw palmetto, *Ginko biloba*, and/or garlic but in doses of 10–50% of the amount in individual supplements. Therefore, individuals who only obtained these compounds from one of those brands of multivitamins were classified into the low-use category.

Potential confounders

The following variables were identified as potential confounders because of their association with total mortality and their potential to be associated with supplement use: age, sex, race-ethnicity, marital status, education, recency of smoking/pack-years of smoking, average physical activity in the 10 y before baseline (11), estrogen-therapy use, estrogen plus progestin–therapy use, use of regular strength or extra strength aspirin in the previous 10 y, use of nonaspirin nonsteroidal antiinflammatory medications (NSAIDS) in the previous 10 y, current use of cholesterol-lowering medication, prostate specific antigen test in the previous 2 y, mammogram in the previous 2 y, sigmoidoscopy in the previous 10 y, self-rated health, health history, ages at death of mother and father, body mass index (BMI; in kg/m^2) at age 45 y, alcohol intake at age 45 y, and diet (*see* below). We used a participant's recall of their BMI at age 45 y and alcohol intake at age 45 y rather than at baseline because the measures at 45 y of age were more strongly related to mortality.

A morbidity score was created to adjust for health history at baseline. To do so, sex-specific and age-adjusted Cox proportional hazards models were used to determine the hazard ratio (HR) for death associated with 23 conditions in men, modeled simultaneously, and 27 conditions in women, modeled simultaneously (**Table 1**). Each participant was assigned a morbidity score that was based on the coefficients for their set of conditions.

Diet in the year before baseline was measured by using a modified version of the food-frequency questionnaire used in the Women's Health Initiative (12). On the basis of recommendations of the US Dietary Guidelines Advisory Committee for specific components of diet (13), selected diet variables were evaluated for their relation to mortality. Among them, the following variables were related to mortality and were included in the final statistical models: percentage energy from *trans* fat, percentage energy from saturated fat, daily servings of fruits, and daily servings of vegetables (excluding potatoes).

Ascertainment of death

Among the 77,673 participants, 3577 deaths were identified from the start of follow-up through 31 December 2006 (9). A total of 3535 deaths were identified from the Washington State Center for Health Statistics, which has records of deaths of Washington State residents, including those that occurred outside of the state (14). An additional 37 deaths were identified from the Social Security Death index, 2 deaths were identified from the Western Washington Surveillance Epidemiology and End Results cancer registry, and 3 deaths were identified from notification by relatives. The date of death was available for all deaths.

Statistical analyses

For each supplement, the HR of death, which compared each category of users with nonusers, and the associated 95% CIs were measured by using Cox proportional hazards regression (15) with age as the time variable. Person-years were accrued from participants' age at completion of the baseline questionnaire through their age at death (n = 3577) or censoring [withdrew from the study (n = 22), moved out of Washington State (n = 3224), or 31 December 2006 (n = 70,850)]. Participants who moved out of state were identified mainly by annual linkage to the National Change of Address system (9).

TABLE 1
Total mortality rates by baseline participant characteristics, western Washington, 2000–2006[1]

Characteristic	Subjects (n = 77,673)		Person-years (n = 387,801)[2]		Deaths (n = 3577)		No. of deaths/1000 person-years
	n	Percentage	n	Percentage	n	Percentage	
Sex							
F	40,308	52	202,169	52	1514	42	7.49
M	37,365	48	185,633	48	2063	58	11.11
Age at baseline							
50 to <55 y	17,952	23	91,245	24	263	7	2.88
55 to <60 y	17,566	23	87,978	23	419	12	4.76
60 to <65 y	14,121	18	70,450	18	533	15	7.57
65 to <70 y	12,834	17	63,647	16	789	22	12.40
70 to <77 y	15,200	20	74,481	19	1573	44	21.12
Race-ethnicity							
White	71,096	92	355,127	92	3276	92	9.22
Hispanic	669	1	3330	1	16	0	4.80
Black	990	1	4872	1	61	2	12.52
American Indian/Alaska Native	1152	1	5729	1	59	2	10.30
Asian or Pacific Islander	1937	2	9751	3	66	2	6.77
Other/missing	1829	2	8992	2	99	3	11.01
Marital status							
Married	57,212	74	286,458	74	2390	67	8.34
Living with a partner	1986	3	10,010	3	76	2	7.59
Separated or divorced	8943	12	12,521	3	442	13	9.99
Widowed	5570	7	44,250	11	469	13	17.07
Never married	2514	3	27,470	7	119	3	9.50
Missing	1448	2	7092	2	81	2	11.42
Education							
Grade school/some high school	2702	3	13,194	3	295	8	22.36
High school or GED	12,747	16	63,471	16	825	23	13.00
Some college/technical school	29,237	38	145,763	38	1388	39	9.52
College graduate	18,677	24	93,655	24	656	19	7.00
Advanced degree	12,978	17	65,205	17	334	9	5.12
Missing	1332	2	6513	2	79	2	12.13
Cigarette smoking							
Nonsmoker	39,041	50	196,707	51	1071	30	5.44
Current smoker							
1 to <20 y	1261	2	6314	2	48	1	7.60
20 to <40 y	2047	3	10,195	3	131	4	12.85
≥40 y	3177	4	14,912	4	422	12	28.30
Former smoker							
Quit <10 y ago							
1 to <20 y	597	1	3010	1	23	1	7.64
20 to <40 y	1693	2	8446	2	79	2	9.35
≥40 y	2843	4	13,748	4	294	8	21.38
Quit ≥10 y ago							
1 to <20 y	15,080	19	75,575	19	534	15	7.07
20 to <40 y	7655	10	38,031	10	453	13	11.91
≥40 y	3327	4	15,930	4	439	12	27.56
Missing	1012	1	4933	1	83	2	16.83
Physical activity in the 10 y before baseline							
None	11,500	15	56,917	15	816	23	14.34
Quartile 1: >0–3.0 MET-h	16,325	21	81,248	21	881	25	10.84
Quartile 2: 3.1–8.1 MET-h	16,406	21	81,943	21	700	20	8.54
Quartile 3: 8.2–17.8 MET-h	16,117	21	80,656	21	612	17	7.59
Quartile 4: 17.9–157.3 MET-h	16,234	21	81,677	21	500	14	6.12
Missing	1091	1	5361	1	68	2	12.68

(Continued)

TABLE 1 (*Continued*)

Characteristic	Subjects (n = 77,673)		Person-years (n = 387,801)[2]		Deaths (n = 3577)		No. of deaths/1000 person-years
	n	Percentage	n	Percentage	n	Percentage	
Self-rated health							
Excellent	11,279	15	57,249	15	149	4	2.60
Very good	29,273	38	147,832	38	685	19	4.63
Good	27,395	35	136,902	35	1302	36	9.51
Fair	8212	11	39,450	10	977	27	24.77
Poor	1514	2	6369	2	464	13	72.86
Morbidity score[3]							
Level 1 (≤0)	35,466	46	179,929	46	616	17	3.42
Level 2 (>0–0.5)	27,916	36	139,999	36	1015	29	7.25
Level 3 (>0.5–1.0)	7733	10	37,899	10	644	18	16.99
Level 4 (>1.0–1.5)	3978	5	18,827	5	586	16	31.13
Level 5 (>1.5–2.0)	1397	2	6203	2	334	9	53.85
Level 5 (>2.0–2.5)	503	1	2116	1	157	4	74.18
Level 6 (>2.5–3.0)	256	0	960	0	117	3	121.87
Level 7 (>3.0)	192	0	715	0	89	3	124.47
Missing	232	0	1153	0	19	1	16.48

[1] GED, general equivalency diploma; MET-h, metabolic equivalent task hours.
[2] Because of rounding, the numbers of person-years across strata of a variable do not always sum to 387,801.
[3] By using Cox regression, the following conditions, categorized as yes or no, were modeled simultaneously in sex-specific and age-adjusted models to obtain the morbidity score: current use of medication for depression or anxiety; current use of blood pressure medication; a history of lung cancer, colon cancer, bladder cancer, leukemia, pancreatic cancer, non-Hodgkin lymphoma, melanoma, prostate cancer, breast cancer, cervical cancer, uterine cancer, ovarian cancer, and all other cancers combined; ischemic heart disease (defined as a previous heart attack), coronary bypass surgery, angioplasty, or diagnosis of angina; stroke; congestive heart disease; rheumatoid arthritis; diabetes; viral hepatitis; cirrhosis of the liver; other chronic liver disease; emphysema, chronic bronchitis, or chronic obstructive pulmonary disease; kidney disease; ulcerative colitis or Crohn disease; Parkinson disease; and osteoporosis in women.

We included a missing category for most confounders to reduce the number of participants excluded from each analysis. Even so, in the analyses shown in **Tables 2–4**, the percentages of participants dropped from each analysis because of missing data were 6–8%.

All analyses were adjusted for age and sex. For selected supplements, in the order of the variables listed above (under Potential confounders), each was entered into the model and only those that changed the HR by ≥5% were retained in the model. Nearly all of the same variables were retained in each of the selected supplement-mortality models. Therefore we adjusted each supplement-mortality model for every variable that was identified as a confounder in any of the selected models. The covariates included in the final model were, age, sex, education,

TABLE 2
Total mortality rates and hazard ratios (HRs) of total mortality in relation to use of vitamin supplements during the 10 y before baseline, western Washington, 2000–2006

10-y Average daily supplement use[1]	Subjects (n = 77,673)		Person-years (n = 387,801)[2]		Deaths (n = 3577)		No. of deaths/1000 person-years	Sex- and age-adjusted		Multivariate-adjusted[3]	
	n	Percentage	n	Percentage	n	Percentage		HR	95% CI	HR	95% CI
Retinol											
None	25,207	32	126,008	32	1234	34	9.79	1.00	Reference	1.00	Reference
19.3–510.0 μg/d	17,306	22	86,554	22	724	20	8.36	0.96	0.88, 1.05	0.98	0.89, 1.08
510.1–1200.0 μg/d	26,181	34	130,574	34	1172	33	8.98	0.85	0.79, 0.93	0.96	0.89, 1.05
1200.1–8790.0 μg/d[4]	7701	10	38,396	10	356	10	9.27	0.88	0.78, 0.99	1.00	0.88, 1.13
Missing	1278	2	6270	2	91	3	14.51				
P for trend									<0.001		0.600
β-Carotene											
None	26,589	34	132,889	34	1305	36	9.82	1.00	Reference	1.00	Reference
6.4–377.0 μg/d	16,515	21	82,526	21	742	21	8.99	0.99	0.90, 1.08	1.00	0.91, 1.09
377.1–600.0 μg/d	10,953	14	54,751	14	500	14	9.13	0.88	0.79, 0.97	0.95	0.86, 1.06
600.1–13,554.0 μg/d[4]	22,669	29	112,982	29	966	27	8.55	0.83	0.76, 0.90	0.94	0.86, 1.02
Missing	947	1	4654	1	64	2	13.75				
P for trend									<0.001		0.116

(Continued)

TABLE 2 (*Continued*)

10-y Average daily supplement use[1]	Subjects (n = 77,673)		Person-years (n = 387,801)[2]		Deaths (n = 3577)		No. of deaths/1000 person-years	Sex- and age-adjusted		Multivariate-adjusted[3]	
	n	Percentage	n	Percentage	n	Percentage		HR	95% CI	HR	95% CI
Vitamin D											
None	24,648	32	123,180	32	1222	34	9.92	1.00	Reference	1.00	Reference
0.2–5.0 μg/d	22,010	28	110,111	28	916	26	8.32	0.92	0.84, 1.00	0.96	0.88, 1.05
5.1–10.0 μg/d	25,024	32	124,797	32	1107	31	8.87	0.83	0.76, 0.90	0.96	0.88, 1.04
10.1–30.0 μg/d[4]	5128	7	25,500	7	253	7	9.92	0.94	0.82, 1.06	1.02	0.88, 1.18
Missing	863	1	4214	1	79	2	18.75				
P for trend								Not applicable[5]		0.645	
Thiamine											
None	25,509	33	127,610	33	1262	35	9.89	1.00	Reference	1.00	Reference
0.032–0.750 mg/d	18,310	24	91,426	24	786	22	8.60	0.95	0.87, 1.04	0.97	0.88, 1.06
0.751–1.50 mg/d	19,498	25	97,081	25	897	25	9.24	0.85	0.78, 0.93	0.97	0.89, 1.06
1.51–104.65 mg/d[4]	13,748	18	68,729	18	571	16	8.31	0.86	0.78, 0.95	0.98	0.89, 1.09
Missing	608	1	2956	1	61	2	20.64				
P for trend								<0.001		0.785	
Niacin											
None	25,233	32	126,200	33	1257	35	9.96	1.00	Reference	1.00	Reference
0.4–10.0 mg/d	20,808	27	104,042	27	884	25	8.50	0.94	0.86, 1.02	0.97	0.87, 1.06
10.1–20.0 mg/d	23,966	31	119,474	31	1089	30	9.11	0.85	0.78, 0.92	0.97	0.89, 1.06
20.1–1024.0 mg/d[4]	7047	9	35,074	9	293	8	8.35	0.80	0.70, 0.90	0.91	0.80, 104
Missing	619	1	3012	1	54	2	17.93				
P for trend								<0.001		0.225	
Vitamin B-6											
None	24,734	32	123,689	32	1228	34	9.93	1.00	Reference	1.00	Reference
0.04–1.40 mg/d	17,513	23	87,587	23	731	20	8.35	0.93	0.85, 1.02	0.96	0.87, 1.05
1.41–3.00 mg/d	20,207	26	100,560	26	972	27	9.67	0.87	0.79, 0.95	0.98	0.90, 1.07
3.01–270.00 mg/d[4]	14,650	19	73,206	19	595	17	8.13	0.86	0.79, 0.95	0.97	0.87, 1.07
Missing	569	1	2759	1	51	1	18.48				
P for trend								<0.001		0.568	
Vitamin B-12											
None	24,724	32	123,647	32	1226	34	9.92	1.00	Reference	1.00	Reference
0.1–5.0 μg/d	18,249	23	91,283	24	754	21	8.26	0.93	0.85, 1.02	0.98	0.89, 1.07
5.1–25.0 μg/d	25,756	33	128,428	33	1176	33	9.16	0.85	0.79, 0.93	0.95	0.87, 1.03
25.1–300.0 μg/d[4]	8262	11	41,089	11	369	10	8.98	0.89	0.79, 1.00	1.01	0.89, 1.14
Missing	682	1	3355	1	52	1	15.50				
P for trend								<0.001		0.526	
Folic acid											
None	24,749	32	123,801	32	1234	34	9.97	1.00	Reference	1.00	Reference
8.6–200.0 μg/d	21,809	28	109,033	28	929	26	8.52	0.93	0.86, 1.02	0.96	0.88, 1.05
200.1–400.0 μg/d	24,865	32	124,007	32	1117	31	9.01	0.83	0.77, 0.90	0.95	0.87, 1.03
400.1–1400.0 μg/d[4]	5686	7	28,207	7	251	7	8.90	0.86	0.75, 0.99	0.97	0.84, 1.12
Missing	564	1	2753	1	46	1	16.71				
P for trend								<0.001		0.286	

[1] From single supplements (and mixtures other than multivitamins) plus multivitamins.
[2] Because of rounding, the numbers of person-years across strata of a variable do not always sum to 387,801.
[3] Cox regression analysis adjusted for the following variables: sex, age, education, recency of smoking/dose of smoking, physical activity in the 10 y before baseline, self-rated health, and morbidity score.
[4] Greater than amount of that nutrient that could be obtained from a 10-y daily use of one pill of the multivitamin Centrum Silver (Wyeth, Madison, NJ).
[5] Not applicable because the test for nonlinearity in the log-hazard ratio was significant at $\alpha = 0.05$.

recency of smoking/dose of smoking, average physical activity in the 10 y before baseline, self-rated health, and morbidity score. These variables were categorized as shown in Table 1, except for age, which was adjusted for as a continuous variable. To control for confounding by indication we also adjusted for indications for use of supplements that are typically taken for a specific condition: a history of anemia in the year before baseline (yes/no) was included in the model of iron use, a previous diagnosis of benign prostatic hyperplasia (yes/no) was included in the model of saw palmetto use, and joint pain or a history of osteoarthritis (yes/no) was included in the models of glucosamine and chondroitin use.

In separate analyses we adjusted each model for all of the potential confounders (listed in Potential confounders) determined a priori. After doing so, we did not detect any association that was not present in the more parsimonious models, and

TABLE 3
Mortality rates and hazard ratios (HRs) of total mortality in relation to use of mineral supplements during the 10 y before baseline, western Washington, 2000–2006[1]

10-y Average daily supplement use[2]	Subjects (n = 77,673)		Person-years (n = 387,801)[3]		Deaths (n = 3577)		No. of deaths/1000 person-years	Sex- and age-adjusted		Multivariate-adjusted[4]	
	n	Percentage	n	Percentage	n	Percentage		HR	95% CI	HR	95% CI
Iron (mg/d)											
None	27,541	35	137,722	36	1328	37	9.64	1.00	Reference	1.00[5]	Reference
0.1–4.0 mg/d	16,404	21	81,738	21	774	22	9.47	0.97	0.89, 1.06	0.98[5]	0.89, 1.07
4.1–18.0 mg/d	29,502	38	147,439	38	1225	34	8.31	0.87	0.81, 0.94	0.95[5]	0.88, 1.03
18.1–68.0 mg/d[6]	3069	4	15,230	4	165	5	10.83	1.27	1.08, 1.50	1.13[5]	0.95, 1.34
Missing	1157	1	5672	1	85	2	14.98			—	
P for trend									NA[7]		0.729
Magnesium											
None	25,758	33	128,748	33	1288	36	10.00	1.00	Reference	1.00	Reference
1.1–50.0 mg/d	21,096	27	105,413	27	898	25	8.52	0.94	0.86, 1.02	0.96	0.87, 1.04
50.1–100.0 mg/d	23,493	30	116,927	30	1057	30	9.04	0.84	0.77, 0.91	0.95	0.87, 1.03
100.1–500.0 mg/d[6]	6752	9	33,920	9	278	8	8.20	0.82	0.72, 0.94	0.92	0.80, 1.06
Missing	574	1	2795	1	56	2	20.04				
P for trend									<0.001		0.145
Zinc											
None	25,558	33	127,780	33	1273	36	9.96	1.00	Reference	1.00	Reference
0.32–7.50 mg/d	20,271	26	101,283	26	873	24	8.62	0.96	0.88, 1.04	0.98	0.90, 1.07
7.51–15.0 mg/d	21,171	27	105,462	27	961	27	9.11	0.86	0.79, 0.93	0.96	0.88, 1.05
15.1–130.00 mg/d[6]	10,098	13	50,490	13	415	12	8.22	0.76	0.68, 0.85	0.92	0.81, 1.03
Missing	575	1	2786	1	55	2	19.74				
P for trend									<0.001		0.154
Selenium											
None	26,822	35	134,203	35	1322	37	9.85	1.00	Reference	1.00	Reference
0.21–10.10 μg/d	16,797	22	83,868	22	768	21	9.16	1.02	0.93, 1.11	1.00	0.91, 1.10
10.11–20.00 μg/d	15,235	20	75,825	20	700	20	9.23	0.88	0.81, 0.97	0.95	0.86, 1.04
20.10–400.00 μg/d[6]	18,363	24	91,685	24	747	21	8.15	0.78	0.71, 0.85	0.96	0.88, 1.06
Missing	456	1	2219	1	40	1	18.02				
P for trend									<0.001		0.284
Chromium											
None	27,455	35	137,298	35	1349	38	9.83	1.00	Reference	1.00	Reference
0.2–34.0 μg/d	16,730	22	83,637	22	747	21	8.93	1.02	0.93, 1.11	1.01	0.92, 1.11
34.1–130.0 μg/d	30,486	39	152,044	39	1317	37	8.66	0.84	0.78, 0.91	0.95	0.88, 1.03
130.1–393.0 μg/d[6]	2535	3	12,556	3	125	3	9.96	0.91	0.76, 1.10	1.03	0.85, 1.24
Missing	467	1	2266	1	39	1	17.21				
P for trend									NA[7]		0.317

[1] NA, not applicable.
[2] From single supplements (and mixtures other than multivitamins) plus multivitamins.
[3] Because of rounding, the numbers of person-years across strata of a variable do not always sum to 387,801.
[4] Cox regression analysis adjusted for the following variables: sex, age, education, recency of smoking/dose of smoking, physical activity in the 10 y before baseline, self-rated health, and morbidity score.
[5] Additionally adjusted for self-report at baseline of anemia in the previous year.
[6] Greater than the amount of that nutrient that could be obtained from daily use of one pill of the multivitamin Centrum (Wyeth, Madison, NJ).
[7] NA because the test for nonlinearity in the log-hazard ratio was significant at $\alpha = 0.05$.

we did not fail to detect any association that was present in the parsimonious models. The results of the parsimonious models are shown in Tables 2–4.

The statistical significance of each supplement variable was tested by using a likelihood-ratio test for trend with the variable categorized in ordinal form. Because this test assumes a log-linear relation between the HR for death and the supplement variable, we first tested for nonlinearity in this relation. To do so, we computed a likelihood-ratio test and compared the model with supplement use categorized as a dummy variable to the model with supplement use categorized as an ordinal variable. If the models differed at $P = 0.05$, the test for trend was not computed. All analyses were conducted with Stata/SE 10.1 (StataCorp LP, College Station, TX).

RESULTS

Among the 77,673 participants, 3577 deaths occurred during 387,801 person-years of follow-up (9.22 deaths/1000 person-years). Participants who were relatively more likely to die were men, older, black or American Indian/Alaska Native, and not married or living with a partner, had less education, were current cigarette smokers and smokers for longer durations, and had lower physical activity levels in the 10 y before baseline and

TABLE 4
Mortality rates and hazard ratios (HRs) of total mortality in relation to use of nonvitamin-nonmineral supplements during the 10 y before baseline, western Washington, 2000–2006[1]

10-y Average supplement use[2]	Subjects (n = 77,673)		Person-years (n = 387,801)[3]		Deaths (n = 3577)		No. of deaths/1000 person-years	Sex- and age-adjusted		Multivariate-adjusted[4]	
	n	Percentage	n	Percentage	n	Percentage		HR	95% CI	HR	95% CI
Fiber[5]											
None	65,919	85	329,435	85	2925	82	8.88	1.00	Reference	1.00	Reference
Low	6619	9	32,883	9	360	10	10.95	1.14	1.02, 1.27	0.90	0.80, 1.00
High	3480	5	17,260	5	200	6	11.59	1.06	0.92, 1.22	0.97	0.84, 1.13
Missing	1655	2	8223	2	92	3	11.19				
P for trend									0.078		0.172
Glucosamine[6]											
None	61,769	80	308,451	80	3021	84	9.79	1.00	Reference	1.00[7]	Reference
Low	10,023	13	50,348	13	342	10	6.79	0.69	0.62, 0.78	0.92[7]	0.82, 1.04
High	5606	7	27,650	7	191	5	6.91	0.63	0.54, 0.72	0.83[7]	0.72, 0.97
Missing	275	0	1353	0	23	1	17.01				
P for trend									NA[8]		0.009
Chondroitin[6]											
None	66,976	86	334,521	86	3214	90	9.61	1.00	Reference	1.00[7]	Reference
Low	6793	9	34,054	9	223	6	6.55	0.67	0.58, 0.76	0.88[7]	0.77, 1.02
High	3686	5	18,141	5	126	4	6.95	0.63	0.53, 0.75	0.83[7]	0.69, 1.00
Missing	218	0	1085	0	14	0	12.90				
P for trend									NA[8]		0.011
Saw palmetto (men only)[6]											
None	33,187	89	164,816	89	1881	53	11.41	1.00	Reference	1.00[9]	Reference
Low	2166	6	10,872	6	87	2	8.00	0.67	0.54, 0.83	0.87[9]	0.70, 1.09
High	1936	5	9578	5	86	2	8.98	0.63	0.51, 0.78	0.93[9]	0.74, 1.16
Missing	76	0	367	0	9	0	24.55				
P for trend									0.140		0.280
Ginko biloba[6]											
None	66,825	86	333,356	86	3192	89	9.58	1.00	Reference	1.00	Reference
Low	6854	9	34,594	9	223	6	6.45	0.77	0.67, 0.88	0.84	0.73, 0.97
High	3691	5	18,352	5	139	4	7.57	0.78	0.65, 0.92	0.96	0.81, 1.15
Missing	303	0	1499	0	23	1	15.34				
P for trend									<0.001		0.102
Garlic[6]											
None	68,273	88	340,755	88	3139	88	9.21	1.00	Reference	1.00	Reference
Low	4899	6	24,527	6	221	6	9.01	1.03	0.90, 1.18	1.02	0.88, 1.17
High	4188	5	20,932	5	194	5	9.27	0.86	0.74, 1.00	0.89	0.76, 1.03
Missing	313	0	1558	0	23	1	14.77				
P for trend									0.097		0.177
Fish oil[6]											
None	69,857	90	348,950	90	3247	91	9.31	1.00	Reference	1.00	Reference
Low	4234	5	21,091	5	172	5	8.16	0.97	0.84, 1.14	1.03	0.88, 1.21
High	3331	4	16,505	4	139	4	8.42	0.84	0.71, 1.00	0.83	0.70, 1.00
Missing	251	0	1256	0	19	1	15.13				
P for trend									0.051		0.097

[1] NA, not applicable.
[2] From single supplements (and mixtures other than multivitamins) plus multivitamins.
[3] Because of rounding, the numbers of person-years across strata of a variable do not always sum to 387,801.
[4] Cox regression analysis adjusted for the following variables: sex, age, education, recency of smoking/dose of smoking, physical activity in the 10 y before baseline, self-rated health, and morbidity score.
[5] The low-use category included those with a 10-y average frequency of use of <3 d/wk; the high use category includes those with a 10-y average frequency of use of ≥3 d/wk.
[6] The low-use category included those with a duration of use of <3 y or a frequency of use <4 d/wk; the high-use category that included those with a duration of use ≥3 y and a frequency of use during that time of ≥4 d/wk.
[7] Additionally adjusted for a composite variable that categorized participants as having either nonrheumatoid arthritis or chronic neck, back, or joint pain or as having neither condition.
[8] NA because the test for nonlinearity in the log-hazard ratio was significant at $\alpha = 0.05$.
[9] Additionally adjusted for a previous diagnosis of benign prostatic hyperplasia.

poorer self-rated health (Table 1). By design, the morbidity score was strongly related to total mortality (Table 1).

After multivariate adjustment there were no associations between the 10-y average daily intake of any of the vitamins (Table 2) or minerals (Table 3) and total mortality. Among the nonvitamin-nonmineral supplements, 10-y average daily intakes of glucosamine and chondroitin were each associated with decreased risks of total mortality (Table 4). For glucosamine the HR was 0.92 (95% CI: 0.82, 1.04) for low use and 0.83 (95% CI: 0.72, 0.97) for high use (P for trend = 0.009). For chondroitin the HR was 0.88 (95% CI: 0.77, 1.02) for low use and 0.83 (95% CI: 0.69, 1.00) for high use (P for trend = 0.011).

To explore the possibility that these inverse associations were due to uncontrolled confounding that was present as a result of unmeasured healthy behavior being more common in glucosamine and chondroitin users, we evaluated these associations among nonusers of NSAIDs in the previous 10 y and in women who never used hormone replacement therapy (HRT). We expected the prevalence of the unmeasured healthy behavior to be lower in nonusers of NSAIDs and in women who never used HRT. The HR associated with glucosamine use did not become less strong when the analysis was restricted to nonusers of NSAIDs (adjusted HRs for low and high use were 0.88 and 0.62, respectively) or when restricted to women who never used HRT (adjusted HRs for low and high use were 0.79 and 0.83, respectively). Similarly, the HR associated with chondroitin use did not become less strong when restricted to nonusers of NSAIDs (adjusted HRs for low and high use were 0.83 and 0.51, respectively); however, the HR for high use of chondroitin was slightly less strong when restricted to women who never used HRT (adjusted HRs for low and high use were 0.87 and 0.91, respectively).

No other nonvitamin-nonmineral supplement was associated with mortality, although there was a suggestion of an inverse association between a high use of fish-oil supplements and total mortality risk (HR: 0.83; 95% CI: 0.70, 1.00), but the test for trend was not statistically significant (P for trend = 0.097). None of the HRs were appreciably changed when we omitted the morbidity score from the multivariate-adjusted models.

DISCUSSION

Among the vitamin supplements we examined, some were evaluated previously in randomized trials for their relation to total mortality. However, comparisons across studies are limited by differences in the duration and dose of supplement use, in the lengths of follow-up, and the underlying health status of participants. β-Carotene–supplement use was associated with a modestly increased risk of total mortality in a meta-analysis of 6 randomized trials (relative risk: 1.06; 95% CI: 1.01, 1.11) (16). Vitamin A–supplement use was not associated with total mortality in a meta-analysis of 2 randomized trials (HR: 1.18; 95% CI: 0.84, 1.68) (16). In the current study β-carotene use and retinol-supplement use were not associated with total mortality.

In a 2007 meta-analysis of 4 randomized trials, vitamin D–supplement use was not associated with total mortality (relative risk: 0.97; 95% CI: 0.92, 1.02) (17). This finding was consistent with that from the Women's Health Initiative trial (18) of calcium plus vitamin D supplementation (HR: 0.91; 95% CI: 0.83, 1.01). In the current study there was also no association between vitamin D–supplement use and total mortality. Our findings of no association between use of any of the vitamin B supplements and risk of total mortality is generally consistent with previous studies (19–21).

There is a paucity of published studies of total mortality risk in relation to use of the mineral supplements listed in Table 3; an exception is selenium, which has antioxidant properties (22). In a 2007 meta-analysis of 3 randomized trials, the use of selenium supplements was not associated with total mortality risk (HR: 0.85; 95% CI: 0.68, 1.07) (23). In the current study use of selenium supplements was also not associated with total mortality.

Previously published studies of the relation between the use of iron supplements and risk of death were mainly conducted among those at an increased risk of iron deficiency, including infants, children, and pregnant women. However, associations between iron concentrations in the body (serum ferritin or serum transferrin-iron saturation) and mortality were examined in cohort studies conducted in general adult populations (24–26) and in older adult populations (27, 28). The results from these studies (24–28) are mixed, possibly because of an inability to distinguish the effect of iron from the effect of an underlying health condition that may be related to iron concentrations in the body and the risk of death (28).

Among the nonvitamin-nonmineral supplements we examined, only glucosamine and chondrotin were associated with total mortality; the use of each was associated with a 17% reduced risk of death. Glucosamine and chondroitin are commonly taken together (29) and are marketed as beneficial to the normal functioning of joints. Among older adults in the United States, glucosamine, with or without chondroitin, is the most commonly used nonvitamin-nonmineral supplement; the prevalence of regular use is estimated to be7% in persons 57–85 y of age (1).

Findings from a 2000 (30) and 2003 (31) meta-analysis of randomized trials are consistent with a positive association between the use of glucosamine and chondroitin and improvement in symptoms of osteoarthritis. However, in a 2007 meta-analysis (32) of randomized trials of chondroitin for treatment of osteoarthritis, there was no effect on osteoarthritis symptoms after the analysis was restricted to 3 trials that used the intent-to-treat principle.

Little is known about the effect of glucosamine or chondroitin on other conditions. Satia et al (33) recently reported that the use of glucosamine or chondroitin in the 10 y before baseline was associated with a reduced risk of lung and colorectal cancer in the same (VITAL) cohort that we report on in the current study. Animal studies suggested that both glucosamine (34, 35) and chondroitin (36) impede the progression of cardiovascular disease and that both glucosamine (37) and chondroitin (38) have therapeutic effects in colitis.

Proposed mechanisms by which chondroitin may provide symptomatic relief in patients with osteoarthritis include the reduction of proinflammatory factors, modification of apoptotic pathways, and improvement in the anabolic/catabolic balance of extracellular cartilage matrix (39, 40). Accumulating experimental evidence indicates that chondroitin and glucosamine may inhibit nuclear transcription factor κB–dependent pathways. Abnormal regulation of nuclear transcription factor κB has been linked to inflammatory diseases and cancer (41).

Although, to our knowledge, there have been no previous studies of glucosamine or chondroitin in relation to mortality,

other antiinflammatory drugs have been associated with reduced total mortality. Our results for glucosamine and chondroitin are similar to the finding in the Iowa Women's study (42) of an 18% reduction in total mortality associated with aspirin use.

We also observed a borderline statistically significant decreased risk of total mortality associated with the high use of fish-oil supplements (HR: 0.83; 95% CI: 0.70, 1.00). In a 2009 meta-analysis (43) of randomized controlled trials, the use of fish-oil supplements was not associated with total mortality risk (HR: 0.92; 95% CI: 0.91, 1.28; $n = 11$ studies) but was associated with a decreased risk of cardiovascular disease mortality (HR: 0.80; 95% CI: 0.69, 0.92; $n = 11$ studies).

The limitations of the current study should be considered in the interpretation of our results. The generalizability of our results may be limited to the extent that characteristics that modify the associations differ in the broader population compared with the VITAL cohort (44). Further, although the HRs were adjusted for many factors associated with supplement use and mortality, confounding by unmeasured factors may be present. If this confounding was due to unmeasured healthy behaviors being more common in supplement users than nonusers, this bias would cause the HRs to be spuriously low (ie, the estimated benefit would be spuriously great). Another concern is that we adjusted for health conditions that could be on the pathway between supplement use and risk of death. However, because these conditions could have been a reason for supplement use, we choose to adjust for them. In sensitivity analyses, we observed that our risk estimates were not appreciably affected by adjustment for the morbidity score. Further, although participants were instructed to report their use of supplements during the 10 y before baseline, this time window may have been too recent to include the etiologically relevant period for some deaths. In addition, the time period during which exposure information was ascertained overlapped with the period that enriched grain products were fortified with folic acid in the United States, which became mandatory in 1998 (45). Nonusers of folic-acid supplements would have had some supplementation, and therefore, the sensitivity of this study to detect an association with folic acid–supplement use may be low.

Although detailed information was obtained on supplement use, exposure measurement error is a concern because we relied on participants to accurately report their 10-y intake, which likely varied during this period. A validity study (46) was conducted in the VITAL cohort of most of the vitamin and mineral supplements examined in the current study. The reliability and validity of the exposure measures were shown to be good. For the variable 10-y average daily dose, the intraclass correlation coefficient$r$ for test-retest reliability at baseline and after 3 mo varied between 0.69 for β-carotene and 0.84 for folic acid and vitamin B-12. This measurement error is likely nondifferential in this cohort study and would attenuate our risk estimates toward HR = 1.

Some supplements may contain a mixture of more than one nutrient, which makes it difficult to separate their independent effects. For example, different vitamins and minerals may be taken in the form of a single multivitamin, different B vitamins may be taken in the form of a B-vitamin-complex pill, and glucosamine and chondroitin are often taken together in a single pill. Therefore, our results for glucosamine and chondroitin are not independent, and only one of these agents may have driven the results. For vitamins and mineral supplements, we attempted to separate associations with the use of specific supplemental nutrients from those of multivitamin use only by restricting the highest category of users to participants with a 10-y average dose that was greater than one that could be achieved from 10 y of daily use of a common multivitamin formulation.

In conclusion, in the current study there were few associations between use of any of the supplements and total mortality. There was a suggestion of a decreased risk associated with fish oil–supplement use at a high amount ($\geq$4 d/wk for $\geq$3 y). The strongest associations we observed were between glucosamine and chondroitin use and total mortality; the use of each was associated with decreased risks of total mortality. Glucosamine and chondroitin may have antiinflammatory properties, and future studies that evaluate risk of death separately for those diseases with and without a chronic inflammatory cause, and with longer durations of follow-up and possibly functional studies, may increase our understanding of any potential benefit of glucosamine- and chondroitin-supplement use.

The authors' responsibilities were as follows—ARK, REP, JDP, and EW: study concept and design and obtaining funding; ARK, REP, JDP, AK, IE, and EW: acquisition of data; GP, ARK, REP, JDP, JWL, and EW: analysis and interpretation of data; GP and EW: drafting of the manuscript and statistical analysis; EW, AK, and IE: study supervision; and all authors: critical revision of the manuscript for important intellectual content and administrative, technical, or material support. GP and EW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. None of the authors reported a conflict of interest.

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