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Original Contribution

Use of Supplements of Multivitamins, Vitamin C, and Vitamin E in Relation to Mortality

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In this cohort study, the authors evaluated how supplemental use of multivitamins, vitamin C, and vitamin E over a 10-year period was related to 5-year total mortality, cancer mortality, and cardiovascular disease (CVD) mortality. Participants ($n = 77{,}719$) were Washington State residents aged 50–76 years who completed a mailed self-administered questionnaire in 2000–2002. Adjusted hazard ratios and 95% confidence intervals were computed using Cox regression. Multivitamin use was not related to total mortality. However, vitamin C and vitamin E use were associated with small decreases in risk. In cause-specific analyses, use of multivitamins and use of vitamin E were associated with decreased risks of CVD mortality. The hazard ratio comparing persons who had a 10-year average frequency of multivitamin use of 6–7 days per week with nonusers was 0.84 (95% confidence interval: 0.70, 0.99); and the hazard ratio comparing persons who had a 10-year average daily dose of vitamin E greater than 215 mg with nonusers was 0.72 (95% confidence interval: 0.59, 0.88). In contrast, vitamin C use was not associated with CVD mortality. Multivitamin and vitamin E use were not associated with cancer mortality. Some of the associations we observed were small and may have been due to unmeasured healthy behaviors that were more common in supplement users.

ascrobic acid; cohort studies; coronary disease; dietary supplements; mortality; neoplasms; vitamin E; vitamins

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; ICD-10, *International Classification of Diseases*, Tenth Revision; PHS, Physicians' Health Study; RR, relative risk; WACS, Women's Antioxidant Cardiovascular Study.

Free radicals are present in human cells both as a normal consequence of energy metabolism (1, 2) and as a consequence of exposure to exogenous factors such as cigarette smoke (1, 2). Laboratory studies have documented damage by free radicals, known as oxidative damage, to DNA (3, 4), proteins (5), and lipids (1). Because this type of damage is also associated with disease—for example, DNA damage (3, 4) and the occurrence of cancer (6) and lipid peroxidation (1) and the development of atherosclerosis (7)—attention has focused on the respective roles of free radicals and antioxidants in disease causation and prevention. Antioxidants, such as vitamins C and E, may be capable of preventing oxidative damage in human cells because they are strong electron donors and therefore are relatively quick to react with a free radical (1, 2).

Multivitamin and vitamin C and E supplements are commonly used in the United States (8). Whether or not use of these supplements is related to mortality is an important consideration in an evaluation of whether to initiate or continue their use. Currently, there is no clear evidence that taking multivitamins or vitamin C or E supplements delays mortality or, more specifically, reduces a person's risk of death from cardiovascular disease (CVD) or cancer. Findings from cohort studies of these associations are inconsistent (9–17), and findings from meta-analysis of randomized trials tend to show no benefit (18–22), although there are no published results from randomized trials of common multivitamin formulations and risk of death.

Randomized trials have the advantage of protecting against confounding by unmeasured variables, but their ability to detect an association may be limited by incomplete

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adherence in the study arms formed by randomization (23), a supplement dose that is not in the range needed (23), or a duration of use that is too short (23) to affect a person's risk of death.

In this cohort study, which was specifically designed to recruit supplement users and to measure their use of supplements, we evaluated the association between intake of multivitamins and vitamin C and E supplements in the 10 years before baseline and risk of total mortality, CVD mortality, and cancer mortality during the 5 years after baseline.

MATERIALS AND METHODS

Study population

The Vitamins and Lifestyle Study is a prospective study of men and women aged 50–76 years in western Washington State. The proposal for this study was approved by the institutional review board of the Fred Hutchinson Cancer Research Center (Seattle, Washington). The study's design was previously described in detail (24). Briefly, 364,418 persons identified from a commercial mailing list were mailed a cover letter that targeted supplement users and a 24-page sex-specific baseline questionnaire. Included in the cover letter was a statement that this was a study of how "vitamin supplements, certain foods, and physical activity can influence your risk of cancer," and in pilot testing, inclusion of this statement led to an increased frequency of participation by supplement users. Between October 2000 and December 2002, a total of 77,719 persons returned a questionnaire that passed eligibility and quality control checks. For the present analysis, we excluded 1 participant with no follow-up time and 45 participants who reported having a malabsorption condition (e.g., a prior gastroplasty) at baseline (these conditions are associated with decreased nutrient absorption); this left 77,673 participants.

Ascertainment of supplement use and potential confounders

Supplement use. For each type of supplement used, information was obtained on the duration, frequency, and dose per day on the days the supplement was taken. Ever use of a supplement was defined as use at least once per week, for a year, during the 10-year period before baseline.

A multivitamin was defined as a mixture containing at least 10 vitamins and/or minerals. Information was obtained on the brand of multivitamin currently used and the brand most commonly used in the past. Ten-year average frequency of multivitamin use (days/week) was computed as "duration (years)/10 (years) × frequency (days/week)."

We also computed 10-year average dose per day of vitamins C and E from single supplements (including mixtures other than multivitamins) plus multivitamins. To do so, we estimated the amounts of vitamins C and E in each subject's brand of multivitamin based on the *Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements 2002* (25) or the amount reported by the manufacturer or participant. Ten-year average doses of supplemental vitamin C and vitamin E (mg/day) were then computed as "duration (years)/10 (years) × frequency (days/week)/7 (days/week) × dose per day (mg/day)," summed over individual supplements and multivitamins.

Potential confounders. The following characteristics were considered a priori to be potential confounders because they might have been associated with supplement use and mortality: sex, age, race/ethnicity, marital status, education, recency/dose of smoking, alcohol intake, average physical activity in the 10 years before baseline (26), body mass index (weight (kg)/height $(m)^2$), age at menopause, estrogen therapy, estrogen plus progestin therapy, use of regular or extra-strength aspirin in the previous 10 years, use of other nonaspirin nonsteroidal antiinflammatory medication in the previous 10 years, current use of cholesterol-lowering medication, receipt of a prostate-specific antigen test in the previous 2 years, receipt of a mammogram in the previous 2 years, receipt of a sigmoidoscopy in the previous 10 years, self-rated health, health history (see below), mother's and father's ages at death, and diet (see below). For body mass index and alcohol intake, we adjusted for measures at 45 years of age rather than at baseline because the former were more strongly related to mortality.

Diet in the year before baseline was measured with a modified version of the food frequency questionnaire used in the Women's Health Initiative (27). Based on the components of diet recommended by the US Dietary Guidelines Advisory Committee (28), selected dietary variables were evaluated for their relation to mortality. The following variables were related to mortality and were included in the final statistical models: percentage of energy derived from *trans* fat, percentage of energy derived from saturated fat, daily number of servings of fruits, and daily number of servings of vegetables (excluding potatoes).

To adjust for health history at baseline, we created a morbidity score. Sex-specific age-adjusted Cox proportional hazards models (29) were used to determine the hazard ratio for death for each of 23 conditions for men and each of 27 conditions for women, modeled simultaneously (see footnote "c" in Table 1 for a list of the conditions). Using the coefficients from these models, we assigned each subject a morbidity score that was the natural logarithm of the hazard ratio for death based on his/her particular set of comorbid conditions as compared with persons with no comorbid conditions.

Ascertainment of death

We linked the cohort to the Washington State Death Certificate System to identify deaths occurring through December 31, 2006 (n = 3,535) (24). Additional deaths were identified from the Social Security Death Index (n = 37), linkage with the western Washington Surveillance, Epidemiology, and End Results cancer registry (n = 2), and notification by relatives (n = 3), for a total of 3,577 deaths (24).

The date of death was available for all deaths. Information on cause of death was available only for deaths identified through the Washington State Death Certificate System. It was determined from the underlying cause of death coded using the *International Classification of*

Table 1. Total Mortality Rates and Hazard Ratios for Total Mortality According to Participant Characteristics at Baseline, Vitamins and Lifestyle Study, Western Washington State, 2000–2006

Characteristic	No. of Subjects (n = 77,673)	%	Person-Years of Follow-up (n = 387,801)[a]	%	No. of Deaths (n = 3,577)	%	Mortality Rate[b]	Sex- and Age-Adjusted Hazard Ratio	95% Confidence Interval
Sex									
Female	40,308	52	202,169	52	1,514	42	7.49	1.00	Referent
Male	37,365	48	185,633	48	2,063	58	11.11	1.50	1.40, 1.60
Age at baseline, years									
50–54	17,952	23	91,245	24	263	7	2.88	1.00	Referent
55–59	17,566	23	87,978	23	419	12	4.76	1.65	1.42, 1.93
60–64	14,121	18	70,450	18	533	15	7.57	2.61	2.25, 3.02
65–69	12,834	17	63,647	16	789	22	12.40	4.26	3.71, 4.90
70–76	15,200	20	74,481	19	1,573	44	21.12	7.37	6.47, 8.40
Race/ethnicity									
White	71,096	92	355,127	92	3,276	92	9.22	1.00	Referent
Hispanic	669	1	3,330	1	16	0	4.80	0.70	0.42, 1.11
Black	990	1	4,872	1	61	2	12.52	1.39	1.08, 1.79
American Indian/Alaska Native	1,152	1	5,729	1	59	2	10.30	1.28	0.99, 1.65
Asian or Pacific Islander	1,937	2	9,751	3	66	2	6.77	0.78	0.61, 0.99
Other/missing data	1,829	2	8,992	2	99	3	11.01	1.06	0.86, 1.29
Marital status									
Married	57,212	74	286,458	74	2,390	67	8.34	1.00	Referent
Living with a partner	1,986	3	10,010	3	76	2	7.59	1.31	1.04, 1.64
Separated or divorced	8,943	12	12,521	11	442	12	9.99	1.54	1.39, 1.72
Widowed	5,570	7	44,250	7	469	13	17.07	1.46	1.32, 1.63
Never married	2,514	3	27,470	3	119	3	9.50	1.48	1.23, 1.78
Missing data	1,448	2	7,092	2	81	2			
Education	76,225								
Grade school/some high school	2,702	4	13,194	3	295	8	22.36	1.00	Referent
High school graduation/General Equivalency Diploma	12,747	16	63,471	16	825	23	13.00	0.75	0.66, 0.86
Some college/technical school	29,237	38	145,763	38	1,388	39	9.52	0.66	0.58, 0.75
College graduation	18,677	24	93,655	24	656	18	7.00	0.48	0.41, 0.55
Advanced degree	12,978	17	65,205	17	334	9	5.12	0.36	0.31, 0.42
Missing data	1,332	2	6,513	2	79	2			
Morbidity score[c]									
Level 1 ($\leq$0)	35,466	46	179,929	47	616	17	3.42	1.00	Referent
Level 2 ($>$0–$<$0.5)	27,916	36	139,999	36	1,015	29	7.25	1.70	1.54, 1.88
Level 3 (0.5–$<$1.0)	7,733	10	37,899	10	644	18	16.99	3.62	3.24, 4.05
Level 4 (1.0–$<$1.5)	3,978	5	18,827	5	586	16	31.13	6.13	5.46, 6.89
Level 5 (1.5–$<$2.0)	1,397	2	6,203	2	334	9	53.84	10.20	8.91, 11.69
Level 5 (2.0–$<$2.5)	503	1	2,116	1	157	4	74.20	14.09	11.80, 16.82
Level 6 (2.5–$<$3.0)	256	0	960	0	117	3	121.88	22.62	18.52, 27.62
Level 7 ($\geq$3.0)	192	0	715	0	89	3	124.48	23.41	18.71, 29.29
Missing data	232	0	1,153	0	19	1			

[a] Because of rounding, numbers of person-years for each variable do not always sum to exactly 387,801.

[b] Number of deaths per 1,000 person-years.

[c] 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's lymphoma, melanoma, prostate cancer, breast cancer, cervical cancer, uterine cancer, ovarian cancer, or all other cancers combined; coronary 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's disease; Parkinson's disease; and osteoporosis in women.

Diseases, Tenth Revision (ICD-10) (30). We classified deaths as being due to CVD (ICD-10 codes I00–I15, I20–I52, and I60–I99), cancer (ICD-10 codes C00–D48), or other causes.

Statistical analysis

Cox proportional hazards regression (29), with age as the time variable, was used to determine the hazard ratio for death (and 95% confidence interval) associated with supplement use, with adjustment for potential confounders. Participants were considered to be at risk for mortality from their age at completion of the baseline questionnaire through their age at death ($n = 3{,}577$) or age at censoring (withdrawal from the study ($n = 22$), moving out of Washington State ($n = 3{,}224$), or December 31, 2006 ($n = 70{,}850$)). We identified participants who had moved through linkage to the National Change of Address file, with follow-up by mail or phone (24).

To reduce the numbers of participants dropped from analyses because of missing data, we included a ''missing'' category for most confounders; nonetheless, 7%–12% of participants were excluded from each analysis because of missing data on exposure or confounding factors.

The statistical significance of the supplement variable was tested using a likelihood ratio test for trend with the exposure variable categorized in ordinal form. Because this test assumes a log-linear relation between the hazard ratio for mortality and the supplement use variable, we first tested for nonlinearity in this relation. To do so, we compared the model with the supplement variable categorized as a dummy variable with the model with the supplement variable categorized as an ordinal variable, and if they differed at a P value of 0.05, the test for trend was not conducted.

Statistical tests of interaction were performed using a likelihood ratio test comparing models with and without the interaction terms. The interaction terms were the products of the supplement use variable, coded as an ordinal variable, and the modifier variable, coded as a dummy variable.

We also determined the hazard ratios for death from CVD, cancer, and all other causes combined associated with supplement use. Analyses of death from CVD were stratified by history of CVD, and results were adjusted for potential confounders (see table footnotes). Analyses of death from cancer were stratified by history of cancer (excluding nonmelanoma skin cancer), and results were adjusted for potential confounders (see table footnotes).

RESULTS

During 387,801 person-years of follow-up, 3,577 deaths occurred among 77,673 participants (9.22 deaths per 1,000 person-years) (Table 1). Sixty-six percent of participants had ever used multivitamins, 47% had used a vitamin C supplement, and 48% had used a vitamin E supplement (Table 2). After multivariate adjustment, multivitamin use was not associated with risk of total mortality, whether evaluated by duration, frequency during period of use, or 10-year average frequency of use. Vitamin C use was associated with a small decreased risk of total mortality when evaluated by duration of use (P-trend = 0.019), average dose on days taken (P-trend = 0.023), and 10-year average daily dose (P-trend = 0.032). The hazard ratio comparing persons in the third tertile ($\geq$322.1 mg/day) of 10-year average daily dose with nonusers was 0.89 (95% confidence interval (CI): 0.81, 0.98). Vitamin E use was also associated with a small decreased risk of total mortality when it was evaluated by average dose on days taken (P-trend = 0.010) and 10-year average daily dose (P-trend = 0.008). The hazard ratio comparing persons in the third tertile ($\geq$215.1 mg/day) of 10-year average daily dose with nonusers was 0.89 (95% CI: 0.81, 0.98).

We also evaluated whether the hazard ratios for total mortality associated with 10-year average daily dose of vitamins C and E varied according to several participant characteristics (Table 3). Among never smokers, risk of total mortality was inversely related to use of supplemental vitamin C (hazard ratio = 0.76, 95% CI: 0.63, 0.92) and vitamin E (hazard ratio = 0.80, 95% CI: 0.66, 0.97) when comparing the highest tertile of use with nonuse, whereas there were no associations among current/recent smokers. Risk of total mortality was also inversely related to use of vitamins C and E among persons with a body mass index of 30 or greater; the respective hazard ratios were 0.76 (95% CI: 0.57, 1.01) and 0.78 (95% CI: 0.58, 1.04) when comparing the highest tertile of use with nonuse, whereas there were no associations among persons with a body mass index less than 25. Additionally, risk of total mortality was inversely related to use of vitamins C and E among persons who consumed less than the median daily number of servings of fruits and vegetables but not in persons who consumed at least the median number of servings per day. When results were stratified by age (data not shown), sex, alcohol use at age 45 years (data not shown), or morbidity score, the hazard ratios associated with increasing dose for both vitamin C and vitamin E did not vary markedly.

We also evaluated risk of death from CVD, cancer, and all other causes combined in relation to 10-year average daily dose of multivitamins, vitamin C, and vitamin E (Table 4). Multivitamin use was inversely associated with risk of CVD mortality (P-trend = 0.019) but not mortality from cancer or from all other causes combined. Overall, vitamin C use was not associated with CVD mortality, but it was inversely associated with risk among persons with a history of CVD at baseline (P-trend = 0.036). It was also associated with cancer mortality among persons in the third tertile of use ($\geq$322.1 mg/day) as compared with nonusers; however, there was no evidence of a dose-response relation. Vitamin E use was inversely related to risk of CVD mortality (P-trend = 0.001) only.

DISCUSSION

Our results should be interpreted in the context of several limitations. Although we adjusted for many factors associated with both supplement use and mortality, confounding by unmeasured factors may have occurred. For example, supplement users may be more likely than nonusers to participate in screening or comply with treatment for disease.

Table 2. Total Mortality Rates and Hazard Ratios for Total Mortality Associated With Supplement Use During the 10 Years Before Baseline, Vitamins and Lifestyle Study, Western Washington State, 2000–2006

Supplement	Subjects (n = 77,673)		Person-Years of Follow-up (n = 387,801)[a]		Deaths (n = 3,577)		Mortality Rate[b]	Sex- and Age-Adjusted HR	95% CI	Multivariate-Adjusted HR[c]	95% CI
	No.	%	No.	%	No.	%					
Multivitamins											
Duration of use, years											
None	25,759	33	128,786	33	1,266	35	9.83	1.00	Referent	1.00	Referent
1–3	9,009	12	45,148	12	388	11	8.59	1.02	0.91, 1.15	1.02	0.90, 1.14
4–6	8,931	11	44,619	12	372	10	8.34	0.92	0.82, 1.03	0.93	0.85, 1.09
7–9	6,337	8	31,522	8	306	9	9.71	1.00	0.88, 1.13	1.09	0.96, 1.24
≥10	24,471	32	121,960	31	1,091	31	8.95	0.83	0.77, 0.90	0.97	0.89, 1.06
Missing data	3,166	4	15,766	4	154	4	9.77				
P-trend								0.001		0.644	
Frequency of use during period of use, days/week											
None	25,759	33	128,786	33	1,266	35	9.83	1.00	Referent	1.00	Referent
1–2	1,675	2	8,398	2	74	2	8.81	0.98	0.77, 1.23	0.93	0.72, 1.20
3–4	3,190	4	15,999	4	102	3	6.38	0.80	0.65, 0.98	0.90	0.73, 1.12
5–6	7,911	10	39,792	10	214	6	5.38	0.66	0.57, 0.76	0.86	0.74, 1.00
7	34,000	4	169,285	44	1,650	46	9.75	0.93	0.86, 1.00	1.02	0.95, 1.11
Missing data	5,138	7	25,540	7	271	8	10.61				
P-trend								N/A[d]		0.690	
Ten-year average frequency of use, days/week											
None	25,759	33	128,786	33	1,266	35	9.83	1.00	Referent	1.00	Referent
>0–2	12,405	16	62,063	16	551	15	8.88	1.02	0.93, 1.13	1.02	0.92, 1.14
3–5	10,541	14	52,707	14	411	11	7.80	0.85	0.76, 0.95	0.94	0.83, 1.05
6–7	26,845	35	133,639	34	1,254	35	9.38	0.87	0.81, 0.94	1.00	0.92, 1.09
Missing data	2,123	3	10,606	3	95	3	8.96				
P-trend								0.001		0.873	
Vitamin C											
Duration of use[e], years											
None	41,490	53	206,723	53	2,063	58	9.98	1.00	Referent	1.00	Referent
1–3	6,906	9	34,617	9	294	8	8.49	0.95	0.84, 1.08	1.02	0.90, 1.16
4–6	6,344	8	31,815	8	262	7	8.24	0.89	0.78, 1.01	0.97	0.85, 1.11
7–9	4,296	6	21,540	6	165	5	7.66	0.77	0.65, 0.90	0.86	0.72, 1.01
≥10	15,366	20	76,722	20	647	18	8.43	0.77	0.70, 0.84	0.91	0.83, 1.00
Missing data	3,271	4	16,385	4	146	4	8.91				
P-trend								<0.001		0.019	
Dose[e] on days taken, mg/day											
None	41,490	53	206,723	53	2,063	58	9.98	1.00	Referent	1.00	Referent
60–250	4,385	6	21,848	6	209	6	9.57	0.93	0.80, 1.07	1.02	0.88, 1.19
500	14,850	19	74,418	19	590	16	7.93	0.75	0.69, 0.83	0.90	0.81, 0.99
1,000	11,768	15	59,080	15	448	13	7.58	0.80	0.72, 0.88	0.92	0.82, 1.02
1,500	2,484	3	12,397	3	104	3	8.39	0.91	0.75, 1.11	0.92	0.75, 1.13
Missing data	2,696	3	13,335	3	163	5	12.22				
P-trend								<0.001		0.023	

Table continues

Table 2. Continued

Supplement	Subjects (n = 77,673)		Person-Years of Follow-up (n = 387,801)[a]		Deaths (n = 3,577)		Mortality Rate[b]	Sex- and Age-Adjusted HR	95% CI	Multivariate-Adjusted HR[c]	95% CI
	No.	%	No.	%	No.	%					
Ten-year average dose[f], mg/day											
None	20,713	27	103,444	27	1,063	30	10.28	1.00	Referent	1.00	Referent
Tertile 1 (2.6–60.0)	19,334	25	96,195	25	925	26	9.62	0.92	0.84, 1.00	0.97	0.89, 1.07
Tertile 2 (60.1–322.0)	18,283	24	91,439	24	784	22	8.57	0.82	0.75, 0.90	0.97	0.88, 1.07
Tertile 3 (322.1–1,750.0)	18,710	24	93,613	24	762	21	8.14	0.73	0.66, 0.80	0.89	0.81, 0.98
Missing data	633	1	3,110	1	43	1	13.83				
P-trend								<0.001		0.032	
Vitamin E											
Duration of use[e], years											
None	40,445	52	201,496	52	2,030	57	10.07	1.00	Referent	1.00	Referent
1–3	9,680	12	48,914	13	354	10	7.24	0.77	0.69, 0.87	0.89	0.79, 1.00
4–6	8,490	11	42,505	11	322	9	7.58	0.74	0.65, 0.83	0.83	0.73, 0.94
7–9	4,704	6	23,470	6	205	6	8.73	0.80	0.69, 0.92	1.00	0.86, 1.16
≥10	11,501	15	57,137	15	530	15	9.28	0.74	0.67, 0.82	0.89	0.80, 0.99
Missing data	2,853	4	14,280	4	136	4	9.52				
P-trend								N/A		N/A	
Dose[e] on days taken, mg/day											
None	40,445	52	201,496	52	2,030	57	10.07	1.00	Referent	1.00	Referent
30–200	3,664	5	18,392	5	150	4	8.16	0.81	0.68, 0.95	0.85	0.71, 1.01
400	23,267	30	116,626	30	926	26	7.94	0.70	0.65, 0.76	0.88	0.81, 0.96
600–800	7,079	9	35,413	9	299	8	8.44	0.84	0.74, 0.95	0.91	0.80, 1.04
Missing data	3,218	4	15,874	4	172	5	10.84				
P-trend								N/A		0.010	
Ten-year average dose[f], mg/day											
None	20,259	26	101,130	26	1,050	29	10.38	1.00	Referent	1.00	Referent
Tertile 1 (1.3–42.0)	19,160	25	95,497	25	900	25	9.42	0.92	0.84, 1.01	0.97	0.88, 1.06
Tertile 2 (42.1–215.0)	18,916	24	94,984	24	757	21	7.97	0.74	0.68, 0.82	0.89	0.81, 0.98
Tertile 3 (215.1–1,000.0)	18,741	24	93,263	24	826	23	8.86	0.72	0.66, 0.79	0.89	0.81, 0.98
Missing data	597	1	2,927	1	44	1	15.03				
P-trend								<0.001		0.008	

Abbreviations: CI, confidence interval; HR, hazard ratio; N/A, not applicable.

[a] Because of rounding, numbers of person-years for each variable do not always sum to exactly 387,801.

[b] Number of deaths per 1,000 person-years.

[c] Adjusted for the following variables: sex; age; race/ethnicity; marital status; education; recency/dose of smoking; physical activity in the 10 years before baseline; estrogen therapy; estrogen plus progestin therapy; regular use of regular or extra-strength aspirin in the past 10 years; regular use of nonaspirin nonsteroidal antiinflammatory medication in the past 10 years; current use of cholesterol-lowering medication; prostate-specific antigen screening in the past 2 years; receipt of a mammogram in the past 2 years; sigmoidoscopy in the past 10 years; self-rated health; mother's and father's ages at death; body mass index at age 45 years; average alcohol intake at age 45 years; morbidity score; and the following variables, categorized in quartiles and a missing category: percentage of calories derived from *trans* fat; percentage of calories derived from saturated fat; number of servings per day of fruits; and number of servings per day of vegetables (excluding potatoes).

[d] *P*-trend is not applicable because the test for nonlinearity in the log hazard ratio was statistically significant at the 5% level.

[e] Of single supplements (and mixtures other than multivitamins).

[f] From single supplements (and mixtures other than multivitamins) plus multivitamins.

Although we adjusted for receipt of screening for several (but not all) cancers and for use of some medications that prevent CVD mortality, confounding by unmeasured healthy behaviors may have been present.

Table 3. Hazard Ratios for Total Mortality Associated With Use of Vitamin C and Vitamin E Supplements During the 10 Years Before Baseline, According to Participant Characteristics, Vitamins and Lifestyle Study, Western Washington State, 2000–2006

Characteristic	No. of Deaths in Reference Group (No Use)	Tertile 1			Tertile 2			Tertile 3		
		No. of Deaths	Multivariate-Adjusted HR[a]	95% CI	No. of Deaths	Multivariate-Adjusted HR[a]	95% CI	No. of Deaths	Multivariate-Adjusted HR[a]	95% CI
		Ten-Year Average Dose of Vitamin C[b], mg/day								
		2.6–60.0			60.1–322.0			322.1–1,750.0		
Sex										
Female	352	414	0.94	0.81, 1.10	378	1.02	0.87, 1.19	346	0.87	0.74, 1.03
Male	711	511	0.98	0.87, 1.11	406	0.91	0.80, 1.04	416	0.88	0.78, 1.01
P for interaction					0.685					
Smoking status										
Never smoker	301	275	0.91	0.77, 1.09	270	0.97	0.81, 1.16	211	0.76	0.63, 0.92
Former smoker; quit ≥10 years previously	404	381	1.04	0.90, 1.20	300	0.93	0.79, 1.09	322	0.91	0.77, 1.06
Current/recent smoker; quit <10 years previously	338	250	0.96	0.81, 1.15	188	1.00	0.83, 1.21	211	1.05	0.87, 1.27
P for interaction					0.143					
Body mass index[c] at age 45 years										
<25	479	445	0.96	0.84, 1.10	398	1.00	0.87, 1.15	409	0.94	0.81, 1.08
25–<30	326	271	1.04	0.88, 1.23	239	0.97	0.81, 1.17	219	0.91	0.76, 1.09
≥30	170	130	0.89	0.70, 1.14	93	0.87	0.67, 1.14	80	0.76	0.57, 1.01
P for interaction					0.771					
No. of servings of fruits and vegetables per day										
Less than median (0.0–3.1)	606	447	0.92	0.81, 1.05	348	0.94	0.82, 1.08	334	0.85	0.74, 0.98
Median or higher (3.2–26.4)	296	327	1.08	0.92, 1.28	322	1.02	0.87, 1.21	338	0.92	0.78, 1.09
P for interaction					0.740					
Morbidity score[d]										
No comorbid conditions	202	141	0.94	0.75, 1.18	129	0.91	0.71, 1.15	124	0.79	0.62, 1.01
≥1 comorbid condition	855	779	0.98	0.89, 1.09	649	0.98	0.80, 1.10	636	0.91	0.82, 1.02
P for interaction					0.238					
		Ten-Year Average Dose of Vitamin E[b], mg/day								
		2.3–42.0			42.1–215.0			215.1–1,000.0		
Sex										
Female	342	404	0.94	0.80, 1.09	345	0.91	0.78, 1.07	399	0.90	0.77, 1.05
Male	708	496	0.98	0.87, 1.11	412	0.86	0.76, 0.98	427	0.87	0.76, 0.99
P for interaction					0.474					
Smoking status										
Never smoker	287	271	0.92	0.77, 1.10	261	0.96	0.80, 1.15	235	0.80	0.66, 0.97
Former smoker; quit ≥10 years previously	398	344	0.96	0.83, 1.12	309	0.86	0.73, 1.00	360	0.89	0.77, 1.04
Current/recent smoker; quit <10 years previously	345	263	1.02	0.86, 1.21	166	0.83	0.68, 1.02	211	1.01	0.84, 1.22
P for interaction					0.570					

Body mass index at age 45 years											
<25	476	437	0.96	0.83, 1.10	364	0.87	0.75, 1.00	450	0.95	0.82, 1.09
25–<30	325	262	1.04	0.88, 1.23	236	0.96	0.80, 1.15	234	0.88	0.74, 1.06
≥30	162	126	0.85	0.67, 1.10	102	0.89	0.68, 1.16	83	0.78	0.58, 1.04
P for interaction					0.852					
No. of servings of fruits and vegetables per day										
Less than median (0.0–3.1)	609	446	0.94	0.82, 1.06	342	0.81	0.70, 0.93	337	0.82	0.71, 0.94
Median or higher (3.2–26.4)	286	298	1.00	0.84, 1.19	314	1.01	0.85, 1.20	314	1.00	0.85, 1.18
P for interaction					0.039					
Morbidity score[d]										
No comorbid conditions	205	143	0.89	0.71, 1.11	122	0.80	0.63, 1.02	128	0.86	0.68, 1.10
≥1 comorbid condition	839	749	0.99	0.89, 1.09	635	0.91	0.82, 1.02	694	0.90	0.81, 1.01
P for interaction					0.522					

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Reference category, no use. See Table 2, footnote "c," for adjustment factors.
[b] From single supplements (and mixtures other than multivitamins) plus multivitamins.
[c] Weight (kg)/height (m)^2.
[d] See Table 1, footnote "c," for the list of comorbid conditions.

Further, although participants reported their use of supplements during the 10 years before baseline and were followed for mortality for 5 years, this etiologic time window may be too short for some diseases. Additionally, the sensitivity of this study to detect an association between use of multivitamins and mortality may have been low because of the fortification of enriched grain products with folic acid, which became mandatory in the United States in 1998 (31).

Another concern is exposure measurement error. Although we obtained detailed information on the duration, frequency, and daily dose of supplements used, these self-reported measures are subject to error. However, in a validity study (32) conducted in the Vitamins and Lifestyle Study cohort, the reliability and validity of the measures of supplement use were found to be quite good. For the variable 10-year average dose, the intraclass correlation coefficient for test-retest reliability at baseline and after 3 months was 0.81 for multivitamins, 0.85 for vitamin C, and 0.87 for vitamin E. As compared with an interviewer's transcription of nutrient information on bottle labels, Pearson's correlation coefficient was 0.77 for current use of vitamin C and 0.81 for current use of vitamin E. As compared with vitamin nutrient levels in the blood, Pearson's correlation coefficient was 0.29 for intake of vitamin C from supplements and 0.69 for intake of vitamin E from supplements.

Below we compare our findings with findings from prior cohort studies and randomized trials of these associations.

Total mortality

Multivitamins. Our finding of no association between use of multivitamins and total mortality is consistent with the 2 prior cohort studies of this relation (10, 33). Although there are no published results from randomized trials of the common formulations of multivitamins, in 2 randomized trials of combinations of vitamins and minerals (the Linxian Trials (34) and the SU.VI.MAX Study (35)), small inverse associations were observed (relative risk (RR) = 0.87 (34) and RR = 0.77 (35)).

Vitamin C. Our finding of a decreased risk of total mortality associated with use of vitamin C supplements is consistent with some (11, 16) but not all (10) cohort studies; reported relative risks range from 0.85 to 1.09 (10, 11, 16). In a meta-analysis of 3 randomized trials of vitamin C supplement use and total mortality, the summary relative risk was 0.88 (95% CI: 0.32, 2.42) (20), and recent findings from 2 large randomized trials that were not included in the meta-analysis do not support an association. In one, the Women's Antioxidant Cardiovascular Study (WACS), which was conducted among 8,171 female health professional at elevated risk for cardiovascular events, the relative risk of total mortality associated with vitamin C supplement use (500 mg/day) was 1.03 during a mean follow-up period of 9 years (36). In the other, Physicians' Health Study (PHS) II, which was conducted among 16,641 male health professionals, the corresponding hazard ratio (500 mg of vitamin C per day) was 1.07 during a mean follow-up period of 8 years (37).

Vitamin E. Our finding of a decreased risk of total mortality is consistent with most (9, 10, 15, 17) but not all (11)

Table 4. Hazard Ratios for Cardiovascular Disease Mortality, Cancer Mortality, and Mortality From All Other Causes Combined Associated With Use of Vitamin Supplements During the 10 Years Before Baseline, Vitamins and Lifestyle Study, Western Washington State, 2000–2006

Cause of Death	No. of Deaths in Reference Group (No Use)	Tertile 1			Tertile 2			Tertile 3			*P* for Trend
		No. of Deaths	Multivariate-Adjusted HR[a]	95% CI	No. of Deaths	Multivariate-Adjusted HR[a]	95% CI	No. of Deaths	Multivariate-Adjusted HR[a]	95% CI	
		Ten-Year Average Frequency of Multivitamin Use, days/week									
		>0–2			3–5			6–7			
Cardiovascular disease											
Total[b]	350	140	1.00	0.81, 1.24	94	0.78	0.61, 1.00	285	0.84	0.70, 0.99	0.019
No history[c]	200	85	1.08	0.82, 1.41	51	0.72	0.52, 1.01	152	0.78	0.62, 0.98	0.012
History[c]	150	55	0.88	0.62, 1.24	43	0.84	0.58, 1.22	133	0.92	0.71, 1.19	0.498
Cancer											
Total[d]	578	271	1.07	0.92, 1.25	206	1.00	0.84, 1.18	609	1.06	0.94, 1.20	0.415
No history[e]	292	129	1.13	0.91, 1.41	104	1.05	0.82, 1.33	303	1.07	0.90, 1.28	0.517
History[e]	286	142	1.01	0.81, 1.23	102	0.94	0.74, 1.20	306	1.04	0.87, 1.25	0.705
All other causes (total)[f]	320	132	1.00	0.80, 1.23	105	0.93	0.73, 1.18	339	1.12	0.95, 1.32	0.233
		Ten-Year Average Dose of Vitamin C[g], mg/day									
		2.6–60.0			60.1–322.0			322.1–1,750.0			
Cardiovascular disease											
Total[b]	293	215	0.89	0.74, 1.08	179	0.81	0.66, 0.99	201	0.89	0.73, 1.08	0.147
No history[c]	165	114	0.82	0.64, 1.06	99	0.84	0.64, 1.10	120	1.00	0.77, 1.29	0.998
History[c]	128	101	0.95	0.72, 1.27	80	0.79	0.57, 1.08	81	0.75	0.55, 1.02	0.036
Cancer											
Total[d]	487	451	1.00	0.87, 1.15	399	1.07	0.93, 1.23	349	0.84	0.73, 0.98	N/A[h]
No history[e]	254	228	1.06	0.87, 1.28	175	0.90	0.74, 1.11	179	0.86	0.69, 1.05	0.076
History[e]	233	223	0.95	0.78, 1.16	224	1.20	0.98, 1.46	170	0.82	0.66, 1.02	N/A[h]
All other causes (total)[f]	267	244	1.03	0.86, 1.24	194	1.00	0.82, 1.22	200	1.01	0.82, 1.23	0.984
		Ten-Year Average Dose of Vitamin E[g], mg/day									
		1.3–42.0			42.1–215.0			215.1–1,000.0			
Cardiovascular disease											
Total[b]	300	201	0.79	0.64, 0.96	185	0.75	0.61, 0.92	203	0.72	0.59, 0.88	0.001
No history[c]	174	117	0.77	0.60, 0.99	107	0.79	0.61, 1.03	103	0.70	0.53, 0.91	0.012
History[c]	126	84	0.80	0.59, 1.09	78	0.70	0.51, 0.96	100	0.73	0.54, 0.99	0.027
Cancer											
Total[d]	476	445	1.02	0.89, 1.17	357	0.92	0.79, 1.06	410	0.93	0.81, 1.08	0.206
No history[e]	248	210	1.00	0.82, 1.22	172	0.86	0.70, 1.06	211	0.96	0.78, 1.17	0.422
History[e]	228	235	1.03	0.84, 1.25	185	0.95	0.77, 1.17	199	0.89	0.73, 1.11	0.235
All other causes (total)[f]	258	240	1.08	0.90, 1.31	204	0.99	0.81, 1.21	200	0.98	0.80, 1.20	0.679

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

[a] Reference category, no use.

[b] HR was adjusted for a history of cardiovascular disease at baseline (defined as a previous heart attack, coronary bypass surgery, angioplasty, a diagnosis of angina, or a previous stroke); use of blood pressure medication in the past 2 weeks; history of heart attack in a first-degree relative; and diabetes at baseline, in addition to all of the variables listed in footnote "c" of Table 2, except morbidity score, mother's age at death, and father's age at death.

[c] HR was adjusted for all of the variables specified in the above footnote within strata of history of cardiovascular disease.

[d] HR was adjusted for history of cancer and family history of cancer, in addition to the variables listed in footnote "c" of Table 2, except morbidity score, mother's age at death, and father's age at death.

[e] HR was adjusted for all of the variables specified in the above footnote within strata of history of cancer.

[f] HR was adjusted for all of the variables listed in footnote "c" of Table 2.

[g] From single supplements (and mixtures other than multivitamins) and multivitamins.

[h] *P*-trend is not applicable because the test for nonlinearity in the log hazard ratio was statistically significant at the 5% level.

cohort studies. Reported relative risks range from 0.73 to 1.44 (9–11, 15, 17); however, randomized trials do not support an association. In a meta-analysis of 24 randomized trials of vitamin E supplement use and total mortality, the summary relative risk was 1.02 (95% CI: 0.98, 1.05) (20). The relative risk of total mortality associated with use of vitamin E supplements was 1.00 in WACS (600 IU of vitamin E every other day) (36), and the hazard ratio was 1.07 in PHS II (400 IU of vitamin E every other day) (37).

Mortality from CVD and cancer

Multivitamins. Although in the present study there was a slightly decreased risk of CVD mortality associated with use of multivitamins, results from a prior cohort study suggested no association with coronary heart disease mortality (10). Risk of cerebrovascular disease mortality was evaluated in the Linxian Trials; the relative risk was 0.90 (34).

Our finding of no association between use of multivitamins and risk of cancer mortality is consistent with findings from a prior cohort study (10). The relative risk of cancer mortality was 0.87 in the Linxian Trials (34).

Vitamin C. Use of vitamin C supplements was associated with a decreased risk of coronary heart disease mortality in a 2004 pooled analysis of data from 4 cohort studies (RR = 0.76, 95% CI: 0.58, 0.99) (12). In the present study, overall, use of vitamin C was not associated with CVD mortality, although there was a slightly decreased risk among persons with a history of CVD at baseline. The association between vitamin C supplement use and CVD mortality was evaluated in 2 randomized trials (36, 37); the relative risk was 1.10 in WACS (36), and the hazard ratio was 1.02 in PHS II (37).

In the present study, use of vitamin C was associated with a slightly decreased risk of cancer mortality, although there was no dose-response trend. In a prior cohort study carried out among the elderly, the relative risk was 0.88 (10). However, no inverse association was observed in 2 randomized trials of the association between vitamin C use and cancer mortality; the relative risk was 1.28 in WACS (38), and the hazard ratio was 1.06 in PHS II (39).

Vitamin E. In the present study, use of vitamin E was associated with a decreased risk of CVD mortality. In a 2004 meta-analysis of results from 7 randomized trials on the association between vitamin E use and CVD mortality, Eidelman et al. (21) found a summary relative risk of 1.00 (95% CI: 0.94, 1.05). This finding is consistent with findings from another 2004 meta-analysis of 5 randomized trials (4 were included in the Eidelman et al. study) (18) and a pooled analysis of 4 cohort studies of coronary heart disease mortality (12).

Since 2004, there have been additional randomized trials. In the 2005 Women's Health Study, which included 39,876 women, risk of CVD mortality was lower among women in the vitamin E arm (600 IU every other day) relative to the placebo arm during a mean follow-up period of 10 years (RR = 0.76) (40). The duration of the vitamin E intervention was longer in that study than in previous trials (40). However, since the publication of the Women's Health Study results, vitamin E has been found to not be associated with CVD mortality in PHS II (RR = 1.07) (37) or WACS (hazard

ratio = 0.94) (36), and both of those studies had treatment durations almost as long as that of the Women's Health Study.

Use of vitamin E supplements was not associated with cancer mortality in the present study. This finding is consistent with that observed in a meta-analysis of 4 randomized trials (22). The relative risk was 0.87 in WACS (38), and the hazard ratio was 1.13 in PHS II (39). In a prior cohort study of elderly persons, the relative risk was 0.81 (10).

Associations stratified by potential modifiers

Our findings of stronger associations between total mortality risk and use of vitamins C and E among persons with greater body mass index and lesser fruit and vegetable consumption are consistent with the hypothesis that any impact of vitamins C and E on total mortality risk may be stronger among persons with greater levels of oxidative stress (1). On the other hand, the associations between use of vitamins C and E and total mortality risk were stronger among never smokers than among current/recent smokers, yet smoking is thought to increase oxidative stress (1). Notably, in a separate study, vitamin C and E supplements were associated with increased risks of total mortality among smokers but not among nonsmokers (13).

Summary

In the present study, we observed small decreased risks of total mortality associated with use of vitamin C and E supplements, but we found no association with multivitamins. In cause-specific analyses, multivitamin use and vitamin E use were associated with decreased risks of CVD mortality. Although the association between vitamin E use and CVD mortality was consistent with that observed in the Women's Health Study randomized trial, other findings were small in magnitude and should be interpreted cautiously because healthy behaviors tend to be more common in supplement users than in nonusers.

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