ORIGINAL INVESTIGATION

LESS IS MORE

Dietary Supplements and Mortality Rate in Older Women

The Iowa Women's Health Study

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Background: Although dietary supplements are commonly taken to prevent chronic disease, the long-term health consequences of many compounds are unknown.

Methods: We assessed the use of vitamin and mineral supplements in relation to total mortality in 38 772 older women in the Iowa Women's Health Study; mean age was 61.6 years at baseline in 1986. Supplement use was self-reported in 1986, 1997, and 2004. Through December 31, 2008, a total of 15 594 deaths (40.2%) were identified through the State Health Registry of Iowa and the National Death Index.

Results: In multivariable adjusted proportional hazards regression models, the use of multivitamins (hazard ratio, 1.06; 95% CI, 1.02-1.10; absolute risk increase, 2.4%), vitamin B_6 (1.10; 1.01-1.21; 4.1%), folic acid (1.15; 1.00-1.32; 5.9%), iron (1.10; 1.03-1.17; 3.9%), magnesium (1.08; 1.01-1.15; 3.6%), zinc (1.08; 1.01-1.15; 3.0%), and copper (1.45; 1.20-1.75; 18.0%) were associated with increased risk of total mortality when compared with corresponding nonuse. Use of calcium was inversely related (hazard ratio, 0.91; 95% confidence interval, 0.88-0.94; absolute risk reduction, 3.8%). Findings for iron and calcium were replicated in separate, shorter-term analyses (10-year, 6-year, and 4-year follow-up), each with approximately 15% of the original participants having died, starting in 1986, 1997, and 2004.

Conclusions: In older women, several commonly used dietary vitamin and mineral supplements may be associated with increased total mortality risk; this association is strongest with supplemental iron. In contrast to the findings of many studies, calcium is associated with decreased risk.

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IN THE UNITED STATES, THE USE OF dietary supplements has increased substantially during the past several decades,[1-3] reaching approximately one-half of adults in 2000, with annual sales of more than $20 billion.[1,3] Sixty-six percent of women participating in the Iowa Women's Health Study[2] used at least 1 dietary supplement daily in 1986 at an average age of 62 years; in 2004, the proportion increased to 85%. Moreover, 27% of women reported using 4 or more supplemental products in 2004.[2] At the population level, dietary supplements contributed substantially to the total intake of several nutrients, particularly in elderly individuals.[1,2]

Supplemental nutrient intake clearly is beneficial in deficiency conditions.[4] However, in well-nourished populations, supplements often are intended to yield benefit by preventing chronic diseases. Results of epidemiologic studies[5-9] assessing supplement use and total mortality risk have been inconsistent. Several randomized controlled trials (RCTs),[10,11] concentrating mainly on calcium and vitamins B, C, D, and E, have not shown beneficial effects of dietary supplements on total mortality rate; in contrast, some[12,13] have suggested the possibility of harm. Meta-analyses[14,15] concur in finding no decreased risk and potential harm. Supplements are widely used, and further studies regarding their health effects are needed. Also, little is known about the long-term effects of multivitamin use and less commonly used supplements, such as iron and other minerals.

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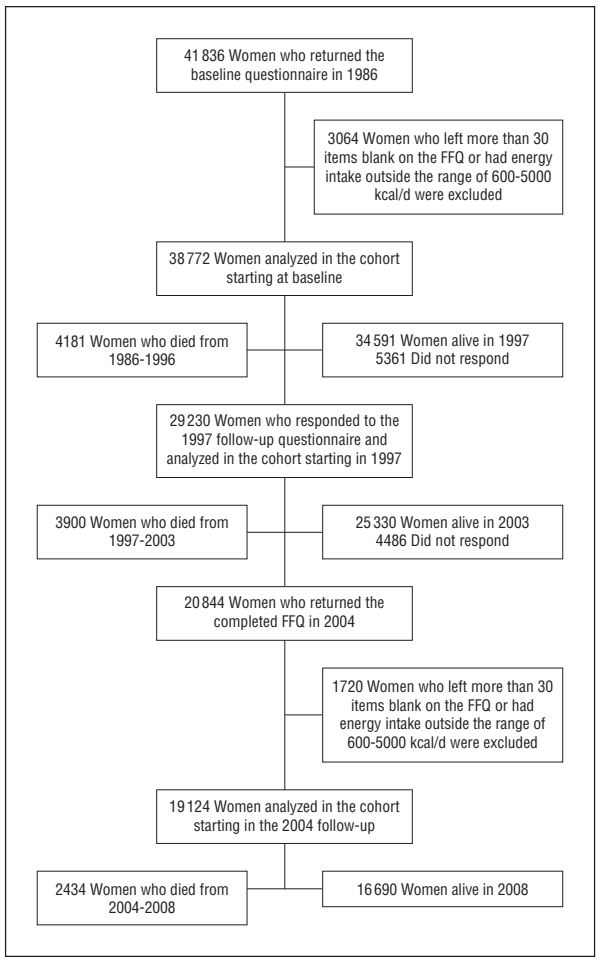

Figure. Flowchart for the Iowa Women's Health Study. FFQ indicates Food Frequency Questionnaire.

The aim of the present study was to assess the relationship between supplement use and total mortality rate in older women in the Iowa Women's Health Study. Our hypothesis, based on the findings of a previous study by some of us,[2] was that the use of dietary supplements would not be associated with a reduced rate of total mortality.

METHODS

The Iowa Women's Health Study[16] was designed to examine associations between several host, dietary, and lifestyle factors and the incidence of cancer in postmenopausal women. At the study baseline in 1986, a total of 41 836 women aged 55 to 69 years completed a 16-page self-administered questionnaire. Of these women, 99.2% were white and 98.6% were postmenopausal. Respondents were slightly younger, had lower body mass index (calculated as weight in kilograms divided by height in meters squared), and were more likely to live in rural areas compared with nonrespondents.[17] The Iowa Women's Health Study was approved by the University of Minnesota Institutional Review Board; return of the questionnaire was considered to indicate informed consent, concordant with prevailing practice in 1986.

We included 38 772 women, excluding from all analyses those who did not adequately complete a questionnaire including food frequency and supplement use at baseline in 1986.[2] For the analyses starting in 1997, a total of 29 230 women who filled out the supplement use questionnaire (diet data were not assessed) were included. In the 2004 starting analysis, 19 124 women were included. The study flow is shown in the **Figure**.

SUPPLEMENT USE AND DIETARY INFORMATION

Food intake was assessed at baseline and in the 2004 follow-up, using 2 nearly identical versions of the validated 127-food item Harvard Service Food Frequency Questionnaire.[18,19] Food composition values were obtained from the Harvard University Food Composition Database derived from US Department of Agriculture sources, supplemented with manufacturer information, and updated to reflect marketplace changes.

Supplement use was queried in 1986, 1997, and 2004 and included the 15 supplements assessed at all 3 surveys: multivitamins; vitamins A, beta-carotene, B_6, folic acid, B complex, C, D, and E; and minerals iron, calcium, copper, magnesium, selenium, and zinc. Different forms of vitamin D, cholecalciferol (D_3) or ergocalciferol (D_2), were not distinguished. At the baseline and 2004 follow-up surveys, the supplement-related questions were part of the Food Frequency Questionnaire. In the 1997 follow-up survey, the supplement questions were asked without querying regarding diet. Dose was assessed uniformly across 3 surveys for vitamins A, B_6, C, D, and E and for minerals calcium, iron, selenium, and zinc with 5 supplement-specific response options (no dose information was collected for vitamin B_6 at baseline or for vitamin D in 2004). Although the dietary supplement portion of the Food Frequency Questionnaire used in the study was not validated separately,[19] an evaluation[20] with similar instruments has reported validity correlations of approximately 0.8.

ASCERTAINMENT AND CLASSIFICATION OF MORTALITY

Deaths through December 31, 2008, were identified annually through the State Health Registry of Iowa or the National Death Index for participants who did not respond to the follow-up questionnaires or who had emigrated from Iowa. Underlying cause of death was assigned by state vital registries via the *International Classification of Diseases (ICD)*. We defined all cardiovascular disease (CVD) by ICD-9 codes 390-459 or ICD-10 codes I00-I99, cancer by codes 140-239 or C00-D48, and "other cause of death" for all other deaths, excluding 231 of those related to injury, accident, and suicide, because it is unlikely that supplement use would be causally related to these outcomes. Follow-up duration was calculated as the time from the baseline date to the date of death or to the last follow-up contact or December 31, 2008, whichever came first.

OTHER MEASUREMENTS

The baseline questionnaire included questions concerning potential confounders including age, height, educational level, place of residence (farm, rural area other than a farm, or city), diabetes mellitus, high blood pressure, weight, hormone replacement therapy, physical activity, and smoking status. As previously described,[2] physical activity was characterized as participating in moderate or vigorous activities less than a few times per month, a few times per month or once per week, or 2 or more times per week. Waist and hip circumferences were measured by each participant using a fixed protocol.[20]

The 1986 and 2004 questionnaires included the same questions and in a similar form except that educational level, place of residence, and waist and hip circumferences were not reassessed. The only questions that the 1997 questionnaire included

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Table 1. Characteristics of Women From the Iowa Women's Health Study Who Completed Questionnaires[a]

Characteristic	Baseline, 1986			Follow-up, 2004		
	Supplement Users (n=24 329)	Supplement Nonusers (n=14 443)	*P* Value[b]	Supplement Users (n=16 278)	Supplement Nonusers (n=2846)	*P* Value[b]
Age, mean (SD), y	61.6 (4.2)	61.5 (4.2)	.11	82.3 (3.9)	82.6 (4.0)	.004
Current smoker	14.0	17.1	<.001	3.3	4.8	<.001
Live on a farm[c]	18.1	21.0	<.001	21.1	21.7	.46
Current hormone replacement therapy use	13.5	7.2	<.001	9.7	4.8	<.001
Educational level, y[c]						
1-8	7.4	9.2	<.001	6.0	9.4	<.001
9-12	9.5	11.0		7.5	9.8	
High school graduate	41.0	43.9		41.3	43.4	
Beyond high school	42.1	36.0		45.2	37.5	
High blood pressure (hypertension)	35.7	38.6	<.001	43.7	43.9	.85
Diabetes mellitus	6.0	8.2	<.001	8.6	12.0	<.001
BMI, mean (SD)	26.9 (4.9)	27.5 (5.3)	<.001	26.6 (4.7)	27.6 (5.1)	<.001
Waist to hip ratio, mean (SD)[c]	0.83 (0.08)	0.85 (0.09)	<.001	0.82 (0.08)	0.84 (0.08)	<.001
Physical activity index						
<A few times/mo	17.9	25.5	<.001	26.3	40.1	<.001
A few times/mo or once/wk	26.6	29.5		18.8	19.1	
≥2 times/wk	55.5	45.1		55.0	40.7	
Diet						
Energy intake, kcal/d	1784 (579)	1883 (624)	<.001	1942 (708)	1925 (747)	.23
Protein (E%)	18.1 (3.2)	17.9 (3.2)	<.001	17.9 (3.4)	17.5 (3.3)	<.001
Carbohydrates, kcal/d (E%)	49.1 (7.7)	48.2 (7.7)	<.001	49.9 (8.3)	49.5 (8.2)	.02
Total fat, kcal/d (E%)	33.6 (5.8)	34.6 (5.7)	<.001	33.9 (6.4)	34.9 (6.5)	<.001
SAFA, kcal/d (E%)	11.7 (2.5)	12.2 (2.6)	<.001	11.6 (2.6)	12.0 (2.7)	<.001
MUFA, kcal/d (E%)	12.7 (2.5)	13.2 (2.5)	<.001	12.8 (2.7)	13.1 (2.8)	<.001
PUFA, kcal/d (E%)	6.1 (1.6)	6.0 (1.6)	<.001	6.0 (1.6)	5.9 (1.5)	.32
Alcohol, g/d	3.9 (8.9)	3.6 (8.9)	.004	2.3 (6.4)	1.7 (5.9)	<.001
Fruits, servings/d	2.7 (1.6)	2.5 (1.6)	<.001	3.1 (2.1)	2.8 (2.0)	<.001
Vegetables, servings/d	3.7 (2.2)	3.6 (2.1)	<.001	3.5 (2.3)	3.3 (2.4)	<.001
Whole grain, product servings/d	1.7 (1.3)	1.5 (1.2)	<.001	1.7 (1.3)	1.4 (1.2)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); E%, energy as a percentage of total energy intake; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SAFA, saturated fatty acid.

[a] Expressed as percentage except where indicated. Respondents in 1986 (n = 38 772) and in 2004 (n = 19 124) were included. Use of any of 15 supplements at the time of the given questionnaire was documented.

[b] Derived from results of the *t* test for continuous variables or from those of the χ^2 test for categorical variables.

[c] Baseline values.

in common with the 1986 and 2004 questionnaires were those regarding diabetes mellitus, weight, high blood pressure, hormone replacement therapy, and smoking status. Neither blood lipid levels nor blood pressure were measured in any survey.

DATA ANALYSES

Analyses were performed using statistical software (PC-SAS, version 9.2; SAS Institute, Inc, Cary, North Carolina). Continuous variables were compared using analysis of variance and categorical variables using χ^2 tests. Cumulative mortality rates by supplement use were examined. Absolute risk increase (ARI) and absolute risk reduction (ARR) were calculated by multiplying the absolute risk in the reference group by the multivariable-adjusted hazard ratio (HR) change in the comparison group. Cox proportional hazards regression analyses were used to explore the relationship between supplement use and outcomes. In the minimally adjusted model, we adjusted the association for age and energy intake; in multivariable adjusted model, version 1, we additionally adjusted for educational level, place of residence, diabetes mellitus, high blood pressure, body mass index, waist to hip ratio, hormone replacement therapy, physical activity, and smoking status. For multivariable adjusted model, version 2, we added intake of alcohol, saturated fatty acids, whole grain products, fruits, and vegetables.

Additional analyses were performed for shorter follow-up intervals; in each of the following periods, approximately 15% of deaths occurred: from 1986 until the end of 1996, from 1997 until the end of 2003, and from 2004 until the end of 2008. Data including supplement use from the corresponding interval questionnaire were used whenever available. Covariate adjustment was performed, as described in the previous paragraph. For analyses starting in 1997, current covariate data were available for diabetes mellitus, high blood pressure, body mass index, hormone replacement therapy, and smoking status. For analyses starting in 2004, current data were available for all covariates except educational level, place of residence, and waist to hip ratio. When current data were unavailable, information from 1986 was used.

RESULTS

Among the 38 772 women (mean [SD] age, 61.6 [4.2] years) followed up from the 1986 questionnaire data,

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Table 2. Adjusted HR (95% CI) for the Use of Supplements and Risk of Total Mortality in Women Aged 55-69 y at Baseline From the Iowa Women's Health Study[a]

	Cases/Total		HR (95% CI)		
Supplement	Users	Nonusers	Age and Energy Adjusted	Multivariable Adjusted, Version 1[b]	Multivariable Adjusted, Version 2[c]
Multivitamin	5218/12 769	10 161/25 474	1.02 (0.99-1.05)	1.06 (1.02-1.09)[d]	1.06 (1.02-1.10)[d]
Vitamin A	1159/2843	13 694/34 263	0.99 (0.93-1.05)	1.05 (0.98-1.11)	1.06 (0.99-1.13)
Beta-carotene	149/378	15 445/38 394	1.00 (0.85-1.17)	1.07 (0.91-1.26)	1.10 (0.93-1.30)
Vitamin B_6	530/1269	15 064/37 503	1.04 (0.95-1.13)	1.09 (1.00-1.19)	1.10 (1.01-1.21)
Folic acid	220/509	15 374/38 263	1.09 (0.95-1.24)	1.12 (0.98-1.29)	1.15 (1.00-1.32)
Vitamin B complex	1199/3174	14 395/35 598	0.93 (0.87-0.98)	0.99 (0.93-1.05)	1.00 (0.94-1.06)
Vitamin C	4293/10 905	10 812/26 806	0.96 (0.93-0.99)	1.01 (0.97-1.05)	1.01 (0.97-1.05)
Vitamin D	1575/4082	13 327/33 105	0.92 (0.87-0.96)[d]	1.00 (0.95-1.05)	1.00 (0.95-1.06)
Vitamin E	2125/5403	12 771/31 177	0.94 (0.90-0.99)	1.00 (0.95-1.05)	1.01 (0.96-1.05)
Calcium	6454/17 428	8847/20 735	0.83 (0.80-0.85)[d]	0.92 (0.89-0.95)[d]	0.91 (0.88-0.94)[d]
Copper	108/229	15 486/38 543	1.31 (1.08-1.58)[d]	1.42 (1.17-1.72)[d]	1.45 (1.20-1.75)[d]
Iron	1117/2738	13 801/34 443	1.03 (0.97-1.09)	1.09 (1.03-1.17)	1.10 (1.03-1.17)
Magnesium	568/1410	15 026/37 362	0.97 (0.91-1.03)	1.08 (0.99-1.18)	1.08 (1.01-1.15)
Selenium	490/1251	14 328/35 788	0.97 (0.89-1.06)	1.07 (0.97-1.17)	1.09 (0.99-1.19)
Zinc	1064/2635	13 790/34 398	0.97 (0.91-1.03)	1.05 (0.99-1.12)	1.08 (1.01-1.15)

Abbreviation: HR, hazard ratio.

[a] A total of 15 594 deaths in 38 772 women at risk; numbers differ resulting from missing information for specific supplements.

[b] Adjusted for age, educational level, place of residence, diabetes mellitus, high blood pressure, body mass index (calculated as weight in kilograms divided by height in meters squared), waist to hip ratio, hormone replacement therapy, physical activity, smoking status, and intake of energy.

[c] Adjusted for age; educational level; place of residence; diabetes mellitus; high blood pressure; body mass index; waist to hip ratio; hormone replacement therapy; physical activity; smoking status; and intake of energy, alcohol, saturated fatty acids, whole grain products, fruits, and vegetables.

[d] $P < .003$ (the P value that meets the Bonferroni criterion for 15 tests; overall significance level = .05).

15 594 deaths (40.2%) occurred during the mean follow-up time of 19.0 years. Mean body mass index was 27.0 (5.1); 36.8% of the respondents reported high blood pressure; 6.8%, diabetes mellitus; and 15.1%, current smoking status. At baseline, compared with nonusers, supplement users had a lower prevalence of diabetes mellitus, high blood pressure, and smoking status; a lower BMI and waist to hip ratio; and were less likely to live on a farm. Supplement users had a higher educational level, were more physically active, and were more likely to use estrogen replacement therapy (**Table 1**). Also, supplement users were more likely to have lower intake of energy, total fat, and monounsaturated fatty acids, saturated fatty acids and to have higher intake of protein, carbohydrates, polyunsaturated fatty acids, alcohol, whole grain products, fruits, and vegetables. Similar patterns were seen in the 2004 questionnaire among 19 124 women (Table 1) and for individual supplements (eg, iron and calcium) (eTable 1; http://www.internmed.com).

Self-reported use of dietary supplements increased substantially between 1986 and 2004.[2] In 1986, 1997, and 2004, 62.7%, 75.1%, and 85.1% of the women, respectively, reported using at least 1 supplement daily. The most commonly used supplements were calcium, multivitamins, vitamin C, and vitamin E (eTable 2); the most common supplement combinations were calcium and multivitamins; calcium, multivitamins, and vitamin C; and calcium and vitamin C.

At baseline, in Cox proportional hazards regression models with full follow-up time and adjusted for age and energy intake, self-reported use of vitamin B complex; vitamins C, D, and E; and calcium had significantly lower risk of total mortality compared with nonuse; copper was associated with higher risk (**Table 2**). With further adjustment (dose in multivariable adjusted model version 1), only the use of calcium retained a significantly lower risk of mortality (HR, 0.92; ARR, 3.5%); the other inverse associations were attenuated to nonsignificance. In contrast, further adjustment for nonnutritional factors strengthened several associations to significance that had HR higher than 1 in the minimal model: multivitamins (HR, 1.06; ARI, 2.2%), vitamin B_6 (1.09; 3.5%), and iron (1.09; 3.8%). Further adjustment for nutritional factors (version 2) affected the associations further: multivitamins (HR, 1.06; ARI, 2.4%), vitamin B_6 (1.10; 4.1%), folic acid (1.15; 5.9%), calcium (0.91; 3.8%), copper (1.45; 18.0%), iron (1.10; 3.9%), magnesium (1.08; 3.6%), and zinc (1.08; 3.0%).

In sensitivity analyses excluding women who had CVD or diabetes mellitus (n = 5772) or cancer (n = 3523) at baseline, the results were not materially changed. For example, for iron, the multivariable adjusted HR for total mortality was 1.13 (95% CI, 1.05-1.22). Parallel to the situation with total mortality rate, most supplements were unrelated to or showed higher cause-specific mortality rate in multivariable adjusted model version 2, although risk patterns varied across causes (**Table 3**).

In multivariable adjusted analyses across the shorter follow-up intervals, beginning with the baseline and each follow-up questionnaire (**Table 4**), the most consistent findings in multivariable adjusted model version 2 were for supplemental iron (HR, 1.20, 1.43, and 1.56; ARI, 2.2%, 5.5%, and 6.6%, respectively) and calcium (0.89, 0.90, and 0.88; ARR, 1.4%, 1.5%, and 1.8%, respectively). Supplemental folic acid tended toward higher risk, significant only in the last interval (HR, 1.28, 1.19, and 1.27; ARI, 3.0%, 2.6%, and 3.4%, respectively).

Dose-response associations could be computed for selected supplements. The inverse association with cal-

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Table 3. Adjusted HR (95% CI) for the Use of Supplements and Risk of Disease-Specific Mortality in Women Aged 55-69 y at Baseline From the Iowa Women's Health Study

Supplement	Cases/Total		HR (95% CI)	
	Users	Nonusers	Age and Energy Adjusted	Multivariable Adjusted[a]
		CVD Mortality		
Multivitamin	1864/12 769	3782/25 475	0.98 (0.92-1.03)	1.03 (0.97-1.09)
Vitamin A	406/2843	5027/34 263	0.94 (0.85-1.04)	1.02 (0.92-1.13)
Beta-carotene	54/378	5667/38 394	0.99 (0.76-1.29)	1.14 (0.87-1.50)
Vitamin B_6	189/1269	5532/37 503	1.01 (0.87-1.16)	1.07 (0.92-1.24)
Folic acid	85/509	5636/38 263	1.14 (0.92-1.41)	1.24 (0.99-1.54)
Vitamin B complex	405/3174	5316/35 598	0.85 (0.77-0.94)	0.91 (0.82-1.01)
Vitamin C	1518/10 905	4017/26 806	0.91 (0.86-0.97)	0.98 (0.92-1.04)
Vitamin D	577/4082	4890/33 105	0.90 (0.83-0.98)	0.99 (0.91-1.09)
Vitamin E	771/5403	4678/31 774	0.93 (0.86-1.00)	1.00 (0.92-1.08)
Calcium	2282/17 428	3319/20 735	0.78 (0.74-0.82)	0.87 (0.82-0.92)
Copper	39/229	5682/38 543	1.32 (0.96-1.81)	1.50 (1.09-2.06)
Iron	410/2738	5069/34 443	1.02 (0.92-1.13)	1.11 (1.00-1.23)
Magnesium	226/1410	5495/37 362	1.08 (0.94-1.23)	1.16 (1.01-1.34)
Selenium	171/1251	5249/35 788	0.93 (0.79-1.08)	1.03 (0.88-1.20)
Zinc	373/2635	5081/34 398	0.91 (0.82-1.01)	1.03 (0.92-1.14)
		Cancer Mortality		
Multivitamin	1749/12 769	3094/25 475	0.98 (0.92-1.04)	1.00 (0.94-1.07)
Vitamin A	349/2843	4324/34 263	1.10 (0.99-1.22)	1.16 (1.04-1.29)
Beta-carotene	42/378	4881/38 394	1.15 (0.87-1.50)	1.19 (0.89-1.58)
Vitamin B_6	167/1269	4756/37 503	1.06 (0.91-1.24)	1.14 (0.97-1.34)
Folic acid	68/509	4855/38 263	1.08 (0.85-1.38)	1.08 (0.84-1.40)
Vitamin B complex	389/3174	3174/35 598	0.99 (0.89-1.09)	1.06 (0.95-1.18)
Vitamin C	1406/10 905	3344/26 806	0.96 (0.90-1.02)	0.99 (0.93-1.06)
Vitamin D	477/4082	4208/33 105	0.95 (0.87-1.05)	1.03 (0.93-1.13)
Vitamin E	683/5403	4007/31 774	0.93 (0.85-1.01)	0.98 (0.90-1.07)
Calcium	2138/17 428	2690/20 735	0.81 (0.77-0.86)	0.89 (0.83-0.94)
Copper	31/229	4892/38 543	1.34 (0.96-1.87)	1.44 (1.02-2.01)
Iron	350/2738	4328/34 443	1.02 (0.91-1.14)	1.06 (0.95-1.19)
Magnesium	155/1410	4768/37 362	1.03 (0.89-1.20)	1.14 (0.98-1.33)
Selenium	151/1251	4506/35 788	1.02 (0.87-1.19)	1.12 (0.95-1.32)
Zinc	344/2635	4320/34 398	0.99 (0.89-1.11)	1.09 (0.97-1.22)
		Mortality From Other Causes[b]		
Multivitamin	1175/12 769	2078/25 475	1.12 (1.06-1.19)	1.17 (1.10-1.24)
Vitamin A	259/2843	2868/34 263	0.94 (0.84-1.05)	0.99 (0.89-1.11)
Beta-carotene	25/378	3284/38 394	0.89 (0.66-1.21)	0.99 (0.72-1.35)
Vitamin B_6	123/1269	3186/37 503	1.04 (0.89-1.21)	1.08 (0.92-1.27)
Folic acid	55/509	3254/38 263	1.06 (0.84-1.35)	1.11 (0.87-1.43)
Vitamin B complex	276/3174	3033/35 598	0.95 (0.86-1.06)	1.02 (0.92-1.14)
Vitamin C	952/10 905	2236/26 806	1.01 (0.95-1.08)	1.08 (1.01-1.15)
Vitamin D	340/4082	2800/33 105	0.87 (0.79-0.96)	0.96 (0.87-1.06)
Vitamin E	504/5403	2649/31 774	0.96 (0.89-1.04)	1.02 (0.94-1.11)
Calcium	1469/17 428	1772/20 735	0.90 (0.85-0.95)	1.00 (0.95-1.07)
Copper	24/229	3285/38 543	1.21 (0.85-1.73)	1.32 (0.92-1.90)
Iron	247/2738	2885/34 443	1.03 (0.92-1.14)	1.10 (0.98-1.23)
Magnesium	108/1410	3201/37 362	0.85 (0.73-1.00)	0.95 (0.80-1.12)
Selenium	116/1251	3009/35 788	0.95 (0.81-1.12)	1.08 (0.91-1.27)
Zinc	246/2635	2876/34 398	1.00 (0.89-1.11)	1.08 (0.97-1.22)

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio.

[a] Version 2; adjusted for age; educational level; place of residence; diabetes mellitus; high blood pressure; body mass index (calculated as weight in kilograms divided by height in meters squared); waist to hip ratio; hormone replacement therapy; physical activity; smoking status; and intake of energy, alcohol, saturated fatty acids, whole grain products, fruits, and vegetables.

[b] Causes other than injury, accident, or suicide.

cium was lost at its highest dose (**Table 5**). For supplemental iron, a dose-response relationship was observed in the full follow-up cohort starting in 1986. In the dose-response interval analyses, significantly increased risk was seen at progressively lower doses as the women aged through baseline in 1986, to baseline in 1997, to baseline in 2004. For vitamins A, C, D, and E, as well as minerals selenium and zinc, no dose-response association was found. These dose-response associations persisted after women with a history of CVD, diabetes mellitus, or cancer at baseline were excluded.

For supplemental iron, we also studied the consistency of reported use across surveys and total mortality among 16 841 women who completed all 3 question-

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Table 4. Adjusted HR (95% CI) for the Use of Supplements and Risk of Total Mortality Across 3 Separate Follow-up Periods in Women Aged 55-69 Years at Baseline From the Iowa Women's Health Study

	Cases/Total		HR (95% CI)	
Follow-up Period	Users	Nonusers	Age and Energy Adjusted	Multivariable Adjusted[a]
		Multivitamin		
1986-1996	1366/12 769	2764/25 474	0.98 (0.92-1.04)	1.02 (0.96-1.10)
1997-2003	1787/13 674	2005/14 174	0.91 (0.86-0.97)	0.97 (0.90-1.04)
2004-2008	1394/12 022	943/6577	0.83 (0.76-0.90)	0.94 (0.86-1.03)
		Vitamin A		
1986-1996	310/2843	3675/34 263	1.00 (0.89-1.12)	1.07 (0.95-1.21)
1997-2003	291/2218	3053/23 028	0.95 (0.84-1.08)	0.99 (0.87-1.13)
2004-2008	151/1126	2105/16 990	1.04 (0.87-1.23)	1.12 (0.94-1.34)
		Beta-carotene		
1986-1996	41/378	4140/38 394	1.02 (0.75-1.39)	1.09 (0.79-1.51)
1997-2003	159/1261	3741/27 143	0.93 (0.79-1.09)	1.02 (0.86-1.21)
2004-2008	47/469	2389/18 655	0.82 (0.61-1.09)	0.96 (0.72-1.29)
		Vitamin B_6		
1986-1996	140/1269	4041/37 503	1.02 (0.86-1.21)	1.14 (0.96-1.36)
1997-2003	364/2613	3000/22 723	1.02 (0.91-1.14)	1.05 (0.93-1.18)
2004-2008	156/1487	1487/16 525	0.83 (0.70-0.98)	0.87 (0.73-1.04)
		Folic Acid		
1986-1996	66/509	4115/38 263	1.21 (0.95-1.54)	1.28 (0.99-1.65)
1997-2003	146/951	3754/27 453	1.16 (0.98-1.37)	1.19 (0.99-1.42)
2004-2008	198/1321	2238/17 803	1.21 (1.04-1.41)	1.27 (1.09-1.50)
		Vitamin B Complex		
1986-1996	299/3174	3882/35 598	0.87 (0.77-0.98)	0.99 (0.87-1.11)
1997-2003	236/1791	3664/26 613	0.95 (0.83-1.08)	0.99 (0.86-1.14)
2004-2008	159/1421	2277/17 703	0.86 (0.73-1.02)	0.95 (0.80-1.13)
		Vitamin C		
1986-1996	1098/10 905	2949/26 806	0.91 (0.85-0.98)	0.99 (0.92-1.06)
1997-2003	1069/9016	2326/16 593	0.84 (0.78-0.91)	0.86 (0.79-0.93)
2004-2008	635/5640	1604/12 396	0.90 (0.82-0.99)	0.97 (0.88-1.07)
		Vitamin D		
1986-1996	401/4082	3594/33 105	0.88 (0.80-0.98)	1.01 (0.91-1.13)
1997-2003	379/3003	2976/22 231	0.95 (0.85-1.06)	1.02 (0.90-1.14)
2004-2008	258/2343	2178/16 781	0.83 (0.72-0.95)	0.90 (0.78-1.03)
		Vitamin E		
1986-1996	535/5403	3443/31 177	0.90 (0.82-0.98)	1.01 (0.92-1.11)
1997-2003	1064/8724	2379/17 074	0.88 (0.82-0.95)	0.92 (0.85-1.00)
2004-2008	680/6307	1596/11 910	0.83 (0.76-0.91)	0.94 (0.85-1.04)
		Calcium		
1986-1996	1600/17 428	2505/20 735	0.75 (0.71-0.80)	0.89 (0.83-0.95)
1997-2003	1743/14 248	1733/11 869	0.84 (0.78-0.89)	0.90 (0.83-0.97)
2004-2008	1289/11 600	1005/6785	0.77 (0.71-0.84)	0.88 (0.81-0.97)
		Copper		
1986-1996	30/229	4151/38 543	1.28 (0.89-1.83)	1.43 (0.98-2.07)
1997-2003	57/438	3843/27 966	0.93 (0.71-1.22)	1.02 (0.77-1.35)
2004-2008	24/255	2412/18 869	0.71 (0.47-1.08)	0.83 (0.55-1.27)
		Iron		
1986-1996	324/2738	3675/34 443	1.11 (0.99-1.24)	1.20 (1.07-1.35)
1997-2003	448/2395	2943/23 070	1.42 (1.28-1.57)	1.43 (1.28-1.59)
2004-2008	334/1645	1915/16 305	1.67 (1.48-1.89)	1.56 (1.38-1.77)
		Magnesium		
1986-1996	156/1410	4025/37 362	1.02 (0.87-1.20)	1.23 (1.04-1.45)
1997-2003	212/1606	2688/26 798	0.98 (0.85-1.13)	1.08 (0.93-1.25)
2004-2008	142/1273	2294/17 851	0.91 (0.77-1.09)	1.05 (0.88-1.25)
		Selenium		
1986-1996	127/1251	3834/35 788	0.94 (0.79-1.12)	1.11 (0.92-1.33)
1997-2003	205/1624	3157/23 711	0.97 (0.84-1.12)	1.09 (0.94-1.27)
2004-2008	94/913	2135/16 931	0.82 (0.67-1.02)	0.95 (0.76-1.18)
		Zinc		
1986-1996	279/2635	3705/34 398	0.96 (0.85-1.08)	1.11 (0.98-1.26)
1997-2003	353/2989	3023/22 433	0.85 (0.76-0.95)	0.90 (0.80-1.02)
2004-2008	190/1599	2034/16 247	0.93 (0.80-1.08)	1.03 (0.88-1.21)

Abbreviation: HR, hazard ratio.

[a]Version 2 adjusted for age; educational level; place of residence; diabetes mellitus; high blood pressure; body mass index (calculated as weight in kilograms divided by height in meters squared); waist to hip ratio; hormone replacement therapy; physical activity; smoking status; and intake of energy, alcohol, saturated fatty acids, whole grain products, fruits, and vegetables. Updated covariate data were used in the interval analyses if information was available. For the 1997 analyses, updated covariate data were available for diabetes mellitus, high blood pressure, body mass index, hormone replacement therapy, and smoking status; for the 2004 analyses, updated data were available for all covariates except educational level, place of residence, and waist to hip ratio.

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Table 5. Multivariable Adjusted HR (95% CI) for the Dose of Calcium and Iron Supplements and Risk of Total Mortality in Women Aged 55-69 y at Baseline From the Iowa Women's Health Study[a]

Follow-up Period	Dose									
	Cases	HR	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
	Calcium									
	Nonusers		>0-400 mg/d		>400-900 mg/d		>900-1300 mg/d		>1300 mg/d	
1986-2008	8847	1	1345	0.91 (0.85-0.96)	2973	0.91 (0.87-0.95)	1229	0.86 (0.81-0.91)	504	1.01 (0.92-1.11)
1986-1996	2505	1	323	0.84 (0.74-0.95)	709	0.83 (0.76-0.90)	304	0.84 (0.74-0.94)	137	1.03 (0.86-1.23)
1997-2003	1733	1	254	0.85 (0.73-0.98)	601	0.80 (0.72-0.89)	268	0.84 (0.73-0.97)	109	0.91 (0.74-1.12)
2004-2008	1003	1	98	0.88 (0.70-1.09)	520	0.83 (0.74-0.93)	309	0.83 (0.72-0.95)	111	0.92 (0.75-1.13)
	Iron									
	Nonusers		>0-50 mg/d		>50-200 mg/d		>200-400 mg/d		>400 mg/d	
1986-2008	13 801	1	527	1.02 (0.93-1.12)	222	1.08 (0.94-1.24)	118	1.35 (1.12-1.63)	47	1.57 (1.17-2.11)
1986-1996	3675	1	144	1.09 (0.92-1.30)	59	1.12 (0.86-1.46)	37	1.41 (1.01-1.96)	16	1.70 (1.02-2.83)
1997-2003	2943	1	115	1.13 (0.92-1.39)	74	1.69 (1.33-2.14)	59	1.30 (0.97-1.74)	14	1.91 (1.06-3.45)
2004-2008	1913	1	71	1.66 (1.28-2.14)	71	1.85 (1.43-2.39)	58	1.67 (1.25-2.22)	17	2.01 (1.19-3.40)

Abbreviation: HR, hazard ratio.

[a]Multivariable adjusted indicates model version 2. Adjusted for age; educational level; place of residence; diabetes mellitus; high blood pressure; body mass index (calculated as weight in kilograms divided by height in meters squared); waist to hip ratio; hormone replacement therapy; physical activity; smoking status; and intake of energy, alcohol, saturated fatty acids, whole grain products, fruits, and vegetables. Updated data covariates were used in the interval analyses if information was available. For 1997 analyses, updated covariate data were available for diabetes mellitus, high blood pressure, body mass index, hormone replacement therapy, and smoking status; for 2004 analyses, updated data were available for all covariates except educational level, place of residence, and waist to hip ratio.

naires. Compared with measures for nonusers, the multivariable adjusted HRs for users were 1.35 (95% CI, 1.20-1.52) for use reported at 1 survey, 1.62 (1.30-2.01) for use reported at 2 surveys, and 1.60 (1.04-2.46) for use reported at all 3 surveys.

COMMENT

In agreement with our hypothesis, most of the supplements studied were not associated with a reduced total mortality rate in older women. In contrast, we found that several commonly used dietary vitamin and mineral supplements, including multivitamins, vitamins B_6, and folic acid, as well as minerals iron, magnesium, zinc, and copper, were associated with a higher risk of total mortality. Of particular concern, supplemental iron was strongly and dose dependently associated with increased total mortality risk. Also, the association was consistent across shorter intervals, strengthened with multiple use reports and with increasing age at reported use. Supplemental calcium was consistently inversely related to total mortality rate; however, no clear dose-response relationship was observed.

Previous studies summarized in a systematic review[21] provide little support for our findings, suggesting beneficial effects of calcium on total mortality rate; in prospective cohorts and RCTs, vitamin D supplementation, but not calcium, was found to be associated with a nonsignificant reduction in CVD mortality. The pooled HR for the CVD risk in RCTs was 0.90 (95% CI, 0.77-1.05) for vitamin D and 1.14 (0.92-1.41) for calcium. We found no evidence for a benefit of vitamin D against total mortality.

The evidence regarding a possible harmful effect of supplemental iron is limited. Pocobelli et al[6] found that men in the highest category of average 10-year dose of supplemental iron had a 27% increased risk of total mortality compared with nonusers in age- and sex-adjusted models. The association was, however, attenuated after multivariable adjustment. High iron stores, measured as serum ferritin, have been found to be related to increased risk of CVD in 2 studies[22,23] but not in another.[24] Although we did not evaluate the possible mechanism, iron is suggested[25] to catalyze reactions that produce oxidants and thus promote oxidative stress. However, we cannot rule out the possibility that the increase in total mortality rate was caused by illnesses for which use of iron supplements is indicated. Chronic disease, major injury, and/or operations may cause anemia, which is then treated with supplemental iron. However, we could find no evidence for such reverse causality. Iron supplementation was related to future mortality rate even 19 years later in women free of CVD, diabetes mellitus, and cancer; baseline covariates of iron use were not greatly different from those of other supplements; and progressively lower doses were associated with excess risk as the women aged.

Increased blood homocysteine concentrations are considered to be a modifiable risk factor for CVD.[26] In RCTs,[14,27] folic acid, vitamin B_6, and vitamin B_{12} or their combinations have decreased blood homocysteine concentrations but failed to reduce the risk of CVD. In contrast, use of B vitamins has been found to be related to an increased risk of CVD in one study. Ebbing et al[13] found that the combination of folic acid and B_{12} supplementation increased the risk of mortality from all causes and from cancer in an RCT setting.

We are not aware of any long-term RCTs studying the effects of daily multivitamins on total mortality rate; epidemiologic studies[5,7-9] have not provided evidence of benefit. Observational findings regarding the antioxidant supplements selenium, beta-carotene, and vitamins A, C, and E and total mortality have been inconsistent,[5,6,9] al-

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though the use of vitamins C and E has been found to be related with reduced risk of all-cause mortality in 2 studies.[5,9] For supplemental vitamin A and beta-carotene, an observational study[6] has not provided evidence of benefit for total mortality rate. In RCTs,[10,11] supplementation with selenium, beta-carotene, or vitamins A, C, or E has not been found to be beneficial relative to total mortality rate in well-nourished populations, and some studies[12,13] have suggested this practice yields harm.

Strengths of the current study include the large sample size and longitudinal design. Also, the use of dietary supplements was queried 3 times: at baseline in 1986, 1997, and 2004. The use of repeated measures enabled evaluation of the consistency of the findings and decreased the risk that the exposure was misclassified.

Our study also has limitations. An intermediate event, such as CVD or cancer, can induce a change in supplement use and confound the exposure-outcome association. In our data, the use of supplements was not modified by a prebaseline diagnosis of CVD, diabetes mellitus, or cancer. Furthermore, intermediate cancer did not alter the supplement-taking pattern. It is possible that despite extensive adjustment, residual confounding remained. The use of dietary supplements is related to healthier lifestyle,[1,2] thus leading to apparently inverse associations with total mortality rate. The associations found after adjustment for lifestyle factors are more accurate from a perspective of a causal relationship. However, we cannot exclude the possibility that some supplements were taken for reasonable cause in response to symptoms or clinical disease. We did not have data regarding nutritional status or detailed information of supplements used. Also, the study population consisted only of white women; thus, generalization to other populations, ethnic groups, or men could be questioned. Because our primary hypothesis concerning supplement use and total mortality rate with covariate adjustment included 15 separate tests, a conservative Bonferroni approach would require a *P* value of .05/15.00 = .003. However, many of the additional statistical tests were confirmatory, strengthening confidence that findings were not explainable by chance.

Among the elderly population, the use of dietary supplements is widespread,[1-3] and supplements often are used with the intention of attaining health benefits by preventing chronic diseases. Although we cannot rule out benefits of supplements, such as improved quality of life, our study raises a concern regarding their long-term safety. Also, cumulative effects of widespread supplement use, together with food fortification, have raised concern regarding exceeding upper recommended levels and, thus, regarding long-term safety.[1] It is not advisable to make a causal statement of excess risk based on these observational data; however, it is noteworthy that dietary supplements, unlike drugs, do not require rigorous RCT testing, and observational studies are often the best-available method for assessing the safety of long-term use. Based on existing evidence, we see little justification for the general and widespread use of dietary supplements. We recommend that they be used with strong medically based cause, such as symptomatic nutrient deficiency disease.

In conclusion, in this large prospective cohort of older women, we found that most dietary supplements were unrelated to total mortality rate. However, several commonly used dietary vitamin and mineral supplements were associated with increased total mortality rate, most strongly supplemental iron; calcium showed some evidence of lower risk.

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Author Contributions: Dr Mursu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Jacobs. *Acquisition of data:* Robien, Harnack, and Jacobs. *Analysis and interpretation of data:* Mursu and Jacobs. *Drafting of the manuscript:* Mursu and Jacobs. *Critical revision of the manuscript for important intellectual content:* Mursu, Robien, Harnack, Park, and Jacobs. *Statistical analysis:* Mursu and Jacobs. *Obtained funding:* Robien, Harnack, and Jacobs. *Administrative, technical, and material support:* Robien, Harnack, and Jacobs.
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INVITED COMMENTARY

Vitamin and Mineral Supplement Use in Relation to All-Cause Mortality in the Iowa Women's Health Study

The beneficial influence of a proper diet on our health has been known since ancient times. Our diet provides a number of compounds that are essential for our health. Although a healthy diet provides a sufficient amount of vitamins and minerals, many individuals regularly take vitamin and mineral supplements hoping to further improve their health and prevent diseases. More than one-third of adults in high-income countries regularly take these supplements.[1]

Many studies have been conducted to verify the assumed beneficial effects of vitamin and mineral supplements. Although the results of epidemiologic observational studies almost uniformly have been positive, the results of individual randomized clinical trials undertaken to corroborate this hypothesis have remained largely inconclusive. Only through the systematic review of several randomized clinical trials have we gained the power and the precision to detect clinical harms and benefits.

In this issue of the *Archives*, Mursu and colleagues[2] report the results of the Iowa Women's Health Study. The authors assessed the use of vitamin and mineral supplements in relation to all-cause mortality in older women. The use of multivitamins, vitamin B_6, folic acid, magnesium, zinc, iron, and copper was individually statistically associated with increased risk of all-cause mortality when compared to nonuse.[2] After adjustment for multiplicity, only multivitamins and copper retained the significant association. The use of calcium and vitamin D was associated with a decreased risk of all-cause mortality when compared to nonuse before and after adjustment for multiplicity.[2] The Iowa Women's Health Study is observational; therefore, confounding by indication and by other such factors cannot be excluded. However, the study is large, well designed, and well conducted.

Mursu and colleagues add to the growing evidence demonstrating that certain antioxidant supplements, such as vitamin E, vitamin A, and beta-carotene, can be harmful.[3-5] Their results also concur with the findings of recent observational studies.[6,7] The belief that antioxidant supplements are beneficial seems likely to have resulted from a collective error. Perhaps oxidative stress is one of the keys to extension of our life span.[8]

The findings by Mursu and colleagues that calcium and vitamin D were associated with better survival also are interesting. Their results regarding calcium seem to contrast with those of a recent meta-analysis[9] of randomized trials that observed that calcium supplementation is associated with an increased risk of myocardial infarction and those of an observational study[10] that reported a 24% increase in coronary heart disease in Finnish postmenopausal women using calcium supplements. High intake of calcium also has been associated with an increased risk of prostate cancer.[11] Is taking only calcium supplements perhaps not a good idea? An intervention review published

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