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Dietary supplement use and mortality in a cohort of Swedish men

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The use of dietary supplements has increased substantially in most industrialized countries. The aim of this study was to prospectively examine the association between use of dietary supplements and all-cause mortality, cancer mortality and CVD mortality in men. We used the population-based prospective cohort of 38 994 men from central Sweden, 45–79 years of age, with no cancer or CVD at baseline and who completed a self-administered FFQ including questions on dietary supplement use and life-style factors in 1997. During average 7.7 years of follow-up, 3403 deaths were ascertained; among them, 771 due to cancer and 930 due to CVD (during 5.9 years of follow-up). In multivariate adjusted models including all men there was no association observed between use of any dietary supplement or of multivitamins, vitamin C, vitamin E or fish oil specifically and all-cause mortality, cancer or CVD mortality. Among current smokers, regular use of any supplement was associated with statistically significant increased risk of cancer mortality: relative risk (RR) 1·46 (95 % CI 1·06, 1·99). Among men reporting an inadequate diet at baseline (assessed by Recommended Food Score), there was a statistically significant inverse association between use of any dietary supplement and CVD mortality (RR 0·72; 95 % CI 0·57, 0·91), no associations were observed among men with adequate diets. In conclusion, we cannot exclude that the use of dietary supplements is harmful for smokers. On the other hand, among men with an insufficient diet, the use of supplements might be beneficial in reducing CVD mortality.

Dietary supplements: Vitamins: All-cause mortality: Cancer mortality: Cardiovascular mortality: Prospective studies

Over the last decades the use of dietary supplements has increased substantially in most industrialized countries[1,2]. The users are paying significant amounts of money in expectation to decrease their morbidity and mortality, but there is little evidence of such effects.

A few randomized controlled supplementation trials have shown decreased cancer incidence and all-cause mortality in European[3] and Chinese populations[4], but baseline micronutrients status was considered suboptimal in the study participants. In general, the conducted randomized trials show little support of a preventive effect of dietary supplement use on cancer and CVD development[5–8] and even increased mortality has been reported in certain high-risk groups such as smokers and exposed workers[9–11]. Randomized controlled trials may, however, be too short to detect any effects, particularly regarding the incidence of cancer. In addition, with few exceptions, trials tend to use relatively high dosages of a few agents and focus on persons with high risk for disease or those with existing disease and therefore are not necessarily valid for the effects of long-term, low doses of several agents in the general population[12].

Observational studies offer the possibility to investigate the effect on mortality of the long-term use of low doses of several different micronutrients. The results from prospective cohort studies are, however, inconsistent. Absence of any association between use of specific dietary supplements and mortality was observed in several cohort studies[13–16], while others suggested an inverse association between use of single or combinations of vitamins and/or multivitamins and all-cause mortality[17,18], CVD mortality[18–21] and cancer mortality[22–24]. Inconsistent results may in part be explained by the fact that the use of dietary supplements is often associated with other lifestyle factors that may predict the risk of disease[25–28]. In addition, there is a need for observational studies exploring the association between supplement use and mortality taking into account diet adequacy/deficiency.

In the present study we explored the association between use of dietary supplements and mortality in relation to diet quality in a prospective population-based cohort of Swedish middle-aged and elderly men, taking lifestyle factors such as self-perceived health status into consideration.

Methods

A population-based prospective cohort of Swedish men (COSM), living in central Sweden (Västmanland and Örebro Counties), was established during the autumn of 1997. All men 45–79 years of age, living in the area (identified in the population register; *n* 100 303) received a mailed FFQ, and 48 850 responded. The COSM study well represents the Swedish male population with regard to age distribution, relative weight and educational level as compared with representative

Abbreviations: RR, relative risk.

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data from Statistics Sweden[29]. Men with a previous cancer diagnosis other than non-melanoma skin cancer (*n* 2592) identified by linkage to the National Swedish Cancer Registry, and a history of CVD according to the International Classification of Diseases (*n* 5069), identified by linkage to the National Hospital Discharge Registry, were excluded. We also excluded men with missing or incorrect national identification numbers, participants returning their questionnaires empty or with incomplete data regarding dietary supplement use, leaving 38,994 men at baseline. The regional Ethical Review Board at Karolinska Institutet approved the study.

The use of dietary supplements was self-reported to be either regular, occasional or no use[30]. Regular and occasional users further specified what kind of predefined supplement (multivitamins, vitamin C, vitamin E and fish oil) they used. The estimated mean content of a multivitamin preparation used in the study population was 60 mg vitamin C, 9 mg vitamin E, 1·2 mg thiamine, 1·4 mg riboflavin, 1·8 mg vitamin B_6, 3 μg vitamin B_{12} and 400 mg folic acid. For supplements containing only one specific nutrient the estimated content was: 1000 mg vitamin C, 100 mg vitamin E. The mean content of fish oil was 500 mg (18 % EPA and 12 % docosapentaenoic acid, respectively). Sensitivity and specificity of self-reported use of any dietary supplement in the FFQ was 78 and 93 %, respectively[31].

The FFQ contained questions on food frequencies including alcoholic beverages (ninety-six items), sociodemographic data, height, weight, smoking status, physical activity (time spent on walking/bicycling and exercising), self-perceived health status, hypertension, high cholesterol levels and diabetes. The validity of the FFQ in comparison to fourteen 24 h recalls in 248 men varied between (Spearman correlation coefficient; *r*) 0·38 and 0·81 (mean 0·62) for total micronutrients (including supplements)[30,32]. The FFQ was used to define diet according to recommended food scores which is a simple way to define the quality by separating 'healthy' from 'less healthy' foods, based on current knowledge and dietary guidelines[33]. Such a score has been shown to be highly predictive of mortality[33,34]. The recommended food scores included fruits, vegetables, legumes, nuts, low-fat dairy products, whole-grain products and fish. Each food with a consumed frequency of at least one to three times/month, was assigned a food score of one. This added up to a maximum of 25 for the recommended food score. We considered those who scored in the lowest quintile (scores <16) of the recommended food score as having an inadequate diet, while the other (scores 16–25) were considered to have an adequate diet.

Date of death was ascertained through linkage of the cohort to the Swedish Death Registry at Statistics Sweden. The follow-up period for all-cause mortality extended from 1998 to 2005 (8 years), while specified causes of death extended to 2003 (6 years), ascertained through linkage to the Swedish Registry of Causes of Death at the National Board of Health and Welfare. This registry is considered almost 100 % complete. We classified cause of death according to the International Classification of Diseases 10 (CVD codes I00–I79 and cancers codes C00–C97).

Relative risk (RR) and 95 % CI were estimated using the Cox proportional hazards models. Follow-up was censored at date of death or end of follow-up period, whichever occurred first. RR values were adjusted for age (continuous), BMI (<20, 20–25, 25–30 or >30), smoking status (never smoker, former smoker, current smoker), education (≤ 9 years, 10–12 years, ≥ 12 years), marital status (single, married, divorced, widowed), physical activity (≤ 30, 30–68 and ≥ 68 min/d), self-perceived health status (five categories), recommended food score (tertiles), hypertension (yes/no), high cholesterol (yes/no) and diabetes (yes/no).

Results

Among the 38 994 men in the cohort, 13 295 (34 %) reported any use of dietary supplements. Out of the users, 6049 (15 %) reported regular use and 7246 (19 %) reported occasional use of one or more dietary supplements. Among the different supplements, multivitamins were used by 5530 (14 %), vitamin C by 4328 (11 %), vitamin E by 1593 (4 %) and fish oil by 1869 (5 %) men in the cohort. Compared to men who did not use supplements, users tended to be older, more educated, more physically active and more seldom current smokers (Table 1).

During 300 725 person-years (mean 7.7 years) of follow-up from 1998 to 2005 for all-cause mortality, 3403 deaths were ascertained. During the cause-specific mortality follow-up from 1998 to 2003 of 228 270 person-years (mean 5.9

Table 1. Age-standardized baseline characteristics of a cohort of 38 994 Swedish men, aged 45–79 years, stratified by use of any dietary supplements, presented as mean or percentage (*n* 38 994)

Characteristics	Non-users	Users
No. of subjects	25 699	13 295
% of total subjects	66	34
Age (years)		
Mean	58·5	60·5
SD	9·2	9·7
BMI (kg/m^2)		
Mean	25·9	25·4
SD	3·3	3·2
Smoking status (%)		
Never smokers	36·6	38·8
Former smokers	37·4	39·3
Current smokers	26	21·9
Education (%)		
Less than high school	70·1	62·4
High school	14·0	16·0
University	15·9	21·6
Married (%)	83·5	81·9
Physical activity (min/d)*		
Mean	55·2	58
SD	44·0	43·4
Self-perceived health status (%)		
Very good	23·7	22·50
Good	55·5	55·0
Average	19·0	20·3
Bad	1·6	2·0
Very bad	0·3	0·3
Recommended food score†		
Mean	18·3	19·0
SD	4·4	4·4
Hypertension (%)	20·0	20·2
High cholesterol levels (%)	11·0	11·8
Diabetes mellitus (%)	5·6	5·2

*Time spent on walking/bicycling and exercising.
†Each point refers to the consumption of fruits, vegetables, legumes, nuts, low-fat dairy products, whole-grain products and fish at least one to three times per month (maximum 25).

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years), 771 deaths occurred due to cancer and 930 due to CVD.

There was no association between the overall use of dietary supplements and risk of all-cause mortality, CVD or cancer mortality in age-adjusted models or after adjustment for relevant covariates (Table 2). The risk estimates remained the same after further adjustment for alcohol consumption (g ethanol/d). In order to minimize a possible impact on the associations by subjects starting to take supplements because of a not yet diagnosed morbidity, we stratified the analyses by time of follow-up. There were no significant associations between regular users of any supplement and all-cause mortality, cancer mortality and CVD mortality after exclusion of the first 3 years of follow-up (Table 2). There were no associations between the use of any specific supplement (multivitamins, vitamin C, vitamin E or fish oil) and risk of all-cause mortality, CVD or cancer mortality (data not shown).

In analyses stratified by smoking status we observed, among current smokers, a statistically significant positive association corresponding to 46 % increased risk (95 % CI, 6, 99) between regular use of any dietary supplement and cancer mortality in comparison to no use (Table 3). This association persisted even after exclusion of the first 3 years of follow-up (RR 1·48; 95 % CI 1·01, 2·16). There were, however, no associations between supplement use and CVD mortality or all-cause mortality. Among never smokers, there was a tendency of a statistically significant inverse association between regular use of any supplement and cancer mortality (RR 0·68; 95 % CI, 0·46, 1·01).

To assess whether a deficient diet may affect the association between use of supplements and risk of mortality, we stratified the diet according to inadequate (the lowest quintile of recommended food score) and adequate intake (quintiles 2–5). Men who reported an inadequate diet and used dietary supplements had a 28 % statistically significant lower risk of CVD mortality (95 % CI 9, 43) compared to never users (Table 4). This association was not observed among those with an adequate diet. After exclusion of the first 3 years of follow-up, the RR of CVD mortality was 0·76 (95 % CI 0·56, 1·01). There was a non-significant inverse association between supplement use and cancer mortality (RR 0·88; 95 % CI 0·67, 1·16).

Discussion

In this large population-based prospective cohort of middle-aged and elderly Swedish men, we found no association between use of any dietary supplement or of multivitamins, vitamin C, vitamin E or fish oil specifically and all-cause mortality, cancer or CVD mortality in all men. We observed, however, that among current smokers, regular use of any supplement was associated with 46 % increased risk of death due to cancer. In addition, among men with an inadequate diet there was a statistically significant inverse association, corresponding to 28 % decreased risk, between combined occasional and regular supplement use and CVD mortality.

The present results of an inverse association between the use of any supplement and decreased risk of CVD mortality taking into account quality of diet are in agreement with those observed in randomized trials from the Linxian Province in China, a rural area with a chronically low intake of several nutrients. Men, but not women, had after a 6-year multivitamin/mineral supplement trial a 58 % decreased CVD mortality (95 % CI 7, 81)[35]. Another trial performed in the same area showed a similar reduction in CVD mortality among men[36]. A lower cancer incidence restricted to men in the SU.VI.MAX randomized trial in France was suggested to be caused by a lower baseline antioxidant status in men than in women[3]. These results are in agreement with the present findings for men with inadequate diet. Among observational studies that have not considered adequacy of diet, some have reported inverse associations between the use of single or combinations of vitamins and/or multivitamins and all-cause mortality[17,18], CVD mortality[18–21] and cancer mortality[22–24].

In analyses stratified by smoking status, we found a statistically significant increased risk between regular use of any supplement and cancer mortality among current smokers. This agrees with results from a large prospective cohort study, showing an increased cancer mortality rate among smokers who used multivitamin supplements[17] and a suggested

Table 2. Relative risk (RR) of all-cause mortality, cancer mortality and CVD mortality according to non-specific supplement use in a cohort of 38 994 Swedish men

Use of supplements	No. of deaths	RR*	95 % CI	RR†	95 % CI	No. of deaths‡	RR†	95 % CI
All-cause mortality								
No use	2102	1§		1§		1591	1§	
Occasional	631	0·93	0·85, 1·02	0·94	0·85, 1·02	480	0·94	0·85, 1·04
Regular	670	1·00	0·91, 1·09	1·04	0·95, 1·13	487	1·00	0·90, 1·11
Cancer mortality								
No use	479	1§		1§		319	1§	
Occasional	140	0·92	0·76, 1·11	0·93	0·77, 1·12	85	0·85	0·67, 1·09
Regular	152	1·02	0·85, 1·23	1·07	0·89, 1·29	103	1·10	0·88, 1·38
CVD mortality								
No use	582	1§		1§		355	1§	
Occasional	163	0·85	0·71, 1·01	0·86	0·72, 1·02	98	0·84	0·67, 1·06
Regular	185	0·95	0·80, 1·11	1·00	0·85, 1·19	104	0·93	0·74, 1·16

* Adjusted for age.
† Fully adjusted model (adjusted for age, BMI, smoking status, education, marital status, physical activity, self-perceived health and recommended food score, hypertension, high cholesterol levels and diabetes).
‡ The first 3 years of follow-up excluded (follow-up comprises 2001–2005 for all-cause and 2001–2003 for cause-specific mortality).
§ Reference group.

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Table 3. Relative risk (RR) of all-cause mortality, cancer mortality and CVD mortality in relation to use of non-specific supplements, stratified by smoking status in a cohort of Swedish men*

	Never smokers			Former smokers			Current smokers		
Use of supplements	No. of deaths	RR	95 % CI	No. of deaths	RR	95 % CI	No. of deaths	RR	95 % CI
All-cause mortality									
No	601	1·00†		731	1·00†		730	1·00†	
Occasional	192	0·91	0·77, 1·07	227	0·99	0·85, 1·15	197	0·63	0·79, 1·09
Regular	188	0·91	0·77, 1·08	267	1·10	0·96, 1·27	202	1·14	0·97, 1·34
Cancer mortality									
No	134	1·00†		172	1·00†		164	1·00†	
Occasional	47	0·98	0·70, 1·37	45	0·85	0·61, 1·18	47	1·01	0·73, 1·40
Regular	31	0·68	0·46, 1·01	64	1·14	0·85, 1·52	55	1·46	1·06, 1·99
CVD mortality									
No	156	1·00†		213	1·00†		205	1·00†	
Occasional	44	0·79	0·56, 1·11	65	0·97	0·73, 1·28	51	0·83	0·61, 1·13
Regular	55	1·00	0·73, 1·36	77	1·09	0·83, 1·41	49	0·90	0·65, 1·25

* Each stratified model is adjusted for age, BMI, education, marital status, physical activity, self-perceived health, recommended food score, hypertension, high cholesterol levels and diabetes.
† Reference group.

increased mortality rate among elderly smokers from eleven European countries (the SENECA study) who used supplements[37]. Increased mortality was also reported in two intervention trials among high-risk individuals (smokers and workers exposed to asbestos) taking high dosage of β-carotene[9,10]. It was suggested that β-carotene affected the growth of preclinical tumours rather than the induction of tumours[38]. The free radical-rich environment produced by cigarette smoke and the resultant inflammatory response in the lung may combine to induce oxidation of some antioxidants, resulting in a pro-oxidant effect[39–41].

Strengths of the present study are the population-based and prospective design and the practically complete follow-up of the study population through linkage with computerized registers. We were also able to perform separate analyses among smokers and among men considered to have a deficient diet while controlling for several potential confounders. As a more frequent use of dietary supplements has been associated with low self-perceived health[27,28], there is a risk of reverse causality in cohort studies, especially during a short follow-up. In the present study, we were able to control for the responders' self-perceived health status and exclusions of possible not yet diagnosed diseases during the first 3 years of follow-up did not alter our conclusion.

On the other hand, if supplement use is assessed only at baseline, a longer follow-up will increase the risk of exposure misclassification attenuating the observed estimates, given that the use of these preparations varies over time. Although the sensitivity and the specificity of the self-reported supplement use in the present study were satisfactory[31], the main limitation associated with present study may be that the use of supplements was assessed only at baseline. Thus, there is a potential risk that the absence of statistically significant association between supplement use and mortality in some of the analyses in the data could be due to measurement error.

In conclusion, although present study results need to be confirmed by other studies, they suggest that supplement use may have a harmful effect among smokers and a beneficial effect when the diet is inadequate.

Table 4. Relative risk (RR) of all-cause mortality, cancer mortality and CVD mortality in relation to any use (occasional or regular) of non-specific supplements, stratified by diet quality in a cohort of Swedish men*

	Inadequate diet (21 %)†			Adequate diet (79 %)		
		Any use			Any use	
Use of supplement	No. of deaths	RR	95 % CI	No. of deaths	RR	95 % CI
All-cause mortality						
No	740	1·00‡		1360	1·00‡	
Yes	399	0·94	0·83, 1·06	901	1·01	0·92, 1·10
Cancer mortality						
No	157	1·00‡		322	1·00‡	
Yes	77	0·88	0·67, 1·16	215	1·04	0·87, 1·24
CVD mortality						
No	235	1·00‡		346	1·00‡	
Yes	103	0·72	0·57, 0·91	245	1·07	0·91, 1·27

* Adjusted for age, BMI, smoking status, education, marital status, physical activity, self-perceived health, recommended food score, hypertension, high cholesterol levels and diabetes.
† Classified as the lowest quintile of recommended food score (scores < 16).
‡ Reference group.

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