Multivitamin Supplements Are Inversely Associated with Risk of Myocardial Infarction in Men and Women—Stockholm Heart Epidemiology Program (SHEEP)[1]

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ABSTRACT Epidemiologic data relating multivitamin supplement use to the risk of cardiovascular disease are sparse and inconsistent. We examined the association between self-selected use of low dose multivitamin supplements and the risk of myocardial infarction (MI). Our results are based on data from a large population-based, case-control study of subjects aged 45–70 y residing in Sweden, a country in which consumption of fruits and vegetables is relatively low and foods are not fortified with folic acid. The study included 1296 cases (910 men, 386 women) with a first nonfatal MI and 1685 controls (1143 men, 542 women) frequency-matched to the cases by sex, age and hospital catchment area. Odds ratios (OR) and 95% CI were calculated from unconditional logistic regression models. Among controls, 57% of the women and 35% of the men used dietary supplements; corresponding figures for the cases were 42 and 27%, respectively. Of those taking supplements, 80% used multivitamin preparations. After adjustment for major cardiovascular risk factors, the OR of MI comparing regular users of supplements with nonusers were 0.79 (95% CI 0.63–0.98) for men and 0.66 (95% CI 0.48–0.91) for women. This inverse association was not modified by such healthy lifestyle habits as consumption of fruits and vegetables, intake of dietary fiber, smoking habits and level of physical activity, although never smoking appeared to outweigh the association in women. Findings from this study indicate that use of low dose multivitamin supplements may aid in the primary prevention of MI. J. Nutr. 133: 2650–2654, 2003.

KEY WORDS: • *antioxidants* • *cardiovascular disease* • *epidemiology* • *minerals* • *vitamins*

For many years, substantial interest has been focused on the role of various antioxidants in the prevention of cardiovascular disease (CVD).[3] Considerable evidence from epidemiologic studies indicates that a diet high in fruits and vegetables, rich sources of antioxidants, is inversely associated with risk of coronary heart disease (CHD), stroke and total cardiovascular morbidity or mortality (1–7). Although observational studies suggest an inverse association between intake of specific antioxidants and risk of CVD (1,8–12), intervention trials using high doses of antioxidant supplements have been largely disappointing (13–16). In two recent controlled clinical trials among high risk individuals, supplementation with high doses of a combination of vitamin C, vitamin E, β-carotene and in one trial also selenium, did not significantly reduce the incidence or mortality of CVD (17,18).

Folic acid and vitamins B-6 and B-12 are essential cofactors in the metabolism of homocysteine. Strong evidence indicates that moderately elevated plasma total homocysteine concentration is an independent modifiable risk factor for CVD (19,20). A meta-analysis by the Homocysteine Lowering Trialists' Collaboration demonstrated that supplementation with folic acid lowered plasma homocysteine levels by 25%; the addition of vitamin B-12 lowered homocysteine another 7%, but the addition of vitamin B-6 did not lead to any further reductions (21). The majority of epidemiologic studies report that subjects with higher plasma or serum concentrations of folic acid and vitamin B-6 have a lower risk of CVD (22).

Over the years, ample evidence has accumulated concerning the association of intakes and serum levels of specific antioxidants, folic acid, vitamin B-6 and vitamin B-12 with CVD risk. However, only three studies, all from the United States, have related self-selected multivitamin use to risk of CVD, and the results are inconsistent (23–25). Furthermore, two of these studies (24,25) were conducted in selected, highly educated populations of nurses and male physicians who may already have an adequate dietary intake of most micronutrients and might therefore not benefit from multivitamin use. To extend the knowledge of the role of dietary supplement use in prevention of MI, we investigated this issue in a large population-based, case-control study in Sweden, a country in which intake of fruits and vegetables is relatively low com-

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[3] Abbreviations used: CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; OR, odds ratio; PAI-1, plasminogen activator inhibitor 1; RR, relative risk; SHEEP, Stockholm Heart Epidemiology Program.

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pared with other populations, and foods are not fortified with folic acid.

SUBJECTS AND METHODS

Study population. Details of the Stockholm Heart Epidemiology Program (SHEEP), a population-based, case-control study, were described elsewhere (26). Briefly, the study base comprised all native Swedish residents of Stockholm County aged 45–70 y, without previous MI. Cases were identified from 1992 to 1993 and female cases also during 1994; they were recruited by discharge diagnosis from the computerized registers at the 10 acute hospitals of the region. In the present study, eligible cases were subjects with a first acute nonfatal MI who had survived for >28 d after the infarction (nonfatal MI represented 73% of the cases in the study base). Controls were randomly selected from a continuously updated computerized population register within 2 d from the case incidence (frequency matched to the cases by sex, age and hospital catchment area). Participation rates among male and female cases were 88 and 77% and among controls 75 and 69%, respectively, leaving 1296 MI cases (910 men, 386 women), and 1685 controls (1143 men, 542 women) for analyses. The study was approved by the Ethical Committee of Karolinska Institutet.

Data collection. Information on supplement use, diet, physical activity, smoking, hypertension, diabetes, job stress, previous diseases and use of medication was obtained through mailed questionnaires and, for some participants, through complementary telephone interviews. Physical activity was ascertained using seven questions about activity at home, leisure and work at different ages. Diet and supplement use were assessed with a food-frequency questionnaire that included questions about the brand and type of supplement used and the number of tablets taken per week. The time period covered for dietary intake and supplement use was the previous year before the MI for the cases or before a corresponding date for controls. The estimated mean content of a multivitamin/mineral preparation 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, 400 μg folic acid, and 40 μg selenium. For supplements containing only one specific nutrient, the estimated content was: 1000 mg vitamin C, 100 mg vitamin E and 50 μg selenium. B-vitamins were assumed to contain 2 mg thiamine, 2 mg riboflavin and 2 mg vitamin B-6.

All medical examinations and blood tests were completed ~3 mo after the incident of the MI, a time when metabolic stability was considered to have been regained (27,28). Analysis of serum total cholesterol, serum triglycerides, plasma fibrinogen and plasma plasminogen activator inhibitor 1 (PAI-1) was performed during the course of the study. The methods for blood sampling and blood chemical analyses were described previously (26,29).

Statistical analysis. Unconditional logistic regression models were used to estimate odds ratios (OR) with 95% CI. In multivariate analyses, we adjusted for age, hospital catchment area, smoking, job stress, BMI, physical inactivity, history of diabetes, hypertension, hypercholesterolemia, hypertriglyceridemia, PAI-1 and plasma fibrinogen. Prespecified cut-off levels were used for some of the covariates (high BMI, hypercholesterolemia and hypertriglyceridemia); for those without clinically accepted cut-off levels, we used values above the 75th percentile for the controls (high PAI-1 and high plasma fibrinogen). All tests of significance were two-sided and a P-value of <0.05 was considered significant. Data were analyzed using the statistical software program SAS (SAS Institute, Cary, NC).

RESULTS

There were no differences between cases and controls according to the levels of established cardiovascular risk factors for MI, including age, BMI, systolic and diastolic blood pressure, serum triglycerides, serum total cholesterol, plasma PAI-1 and plasma fibrinogen (data not shown). Among controls, 35% of the men and 57% of the women were regular or occasional users of dietary supplements; the corresponding figures among cases were 27 and 42%, respectively. The most commonly used preparations were multivitamin/minerals, comprising 80%; only 10% used separate vitamin C and 2% separate vitamin E supplements. For all micronutrients, intake was much higher from supplements (~2–7 times higher) than estimated intake from foods.

Dietary supplement use was significantly inversely associated with nonfatal MI among both men and women in models adjusted for age and hospital catchment area and in multivariate models further adjusted for major cardiovascular risk factors (**Table 1**). The association did not change appreciably after further controlling for consumption of fruits and vegetables and intake of dietary fiber; the OR of MI comparing regular users of supplements with nonusers were 0.78 (95% CI 0.62–0.97) for men and 0.67 (95% CI 0.49–0.93) for women.

To evaluate whether the association between dietary supplement use and MI does not differ across various health

TABLE 1

Odds ratios (OR) and 95% CI of nonfatal myocardial infarction for occasional and regular users of vitamin and mineral supplements among men and women[1]

	Men			Women		
	n cases/*n* controls	OR (95% CI)	*P*-value	*n* cases/*n* controls	OR (95% CI)	*P*-value
Nonusers	660/735	1.00		217/234	1.00	
Occasional or regular supplement users[2]						
Model 1[3]	910/1143	0.68 (0.57–0.83)	<0.01	386/542	0.58 (0.44–0.75)	<0.01
Model 2[4]	910/1143	0.77 (0.63–0.94)	0.01	386/542	0.71 (0.53–0.96)	0.03
Regular supplement users[2]						
Model 1[3]	861/1059	0.69 (0.56–0.85)	<0.01	343/483	0.53 (0.40–0.71)	<0.01
Model 2[4]	861/1059	0.79 (0.63–0.98)	0.03	343/483	0.66 (0.48–0.91)	0.01

[1] Values are OR and 95% CI from unconditional logistic regression models.

[2] The proportions of supplement users taking multivitamin/mineral supplements, separate vitamin C and separate vitamin E supplements were 80, 10 and 2%, respectively.

[3] Adjusted for age (5-y age groups) and hospital catchment area.

[4] Adjusted for age (5-y age groups), hospital catchment area, smoking (current, ex-smokers, never smokers), job stress (yes/no), high BMI (>28 kg/m^2), physical inactivity (yes/no), history of diabetes (yes/no), hypertension (yes/no), hypercholesterolemia (≥6.5 mmol/L or treatment with lipid lowering medications), hypertriglyceridemia (≥2.0 mmol/L), high plasma plasminogen activator inhibitor 1 (≥20 kU/L) and high plasma fibrinogen (≥4 g/L).

behaviors, we investigated this issue in subgroups stratified by such indicators of a healthy lifestyle as consumption of fruits and vegetables, intake of dietary fiber, smoking habits and level of physical activity (**Table 2**). The OR were quite similar in the subgroups defined by consumption of fruits and vegetables, intake of dietary fiber or level of physical activity. However, the observed inverse association between dietary supplement use and OR of MI was stronger among female current smokers than nonsmokers.

DISCUSSION

Our results are based on a large population-based, case-control study conducted in a population with a relatively low consumption of fruit and vegetables and without folic acid fortification of foods. Furthermore, Swedish multivitamin preparations are low dose, i.e., the content of one multivitamin/mineral tablet corresponds to the recommended daily dietary intakes. We observed that intake of multivitamin supplements in such relatively low doses is inversely associated with the risk of nonfatal MI. The association persisted after adjustments for major known risk factors for CHD and intakes of fruits, vegetables and dietary fiber, which may suggest an independent protective effect of vitamin and mineral supplements. Despite this, we cannot fully exclude the possibility that intake of supplements is associated with other unknown healthy lifestyle habits that may be related to the observed decreased risk of MI.

In multivitamin/mineral supplements there are several micronutrients with potentially protective effects on risk of MI, such as antioxidants, B-vitamins and some minerals. The strongest evidence for a protective effect on CVD is for the B-vitamins, particularly folic acid. Multiple lines of evidence support associations between folic acid intake, homocysteine levels and CVD. Folic acid, vitamin B-6 and vitamin B-12 are involved in the metabolism of homocysteine, and deficiency of these vitamins has been associated with higher plasma concentrations of total homocysteine (30). In a recent meta-analysis of 72 genetic and 20 prospective studies, Wald and colleagues demonstrated that the OR for a 5 μmol/L increase in serum homocysteine were on the order of 1.32 to 1.65 for CHD, deep vein thrombosis and stroke (19). Several observational studies also report an inverse association between multivitamin use and homocysteine levels (31–34). Moreover, a randomized, double-blind, placebo-controlled trial showed that multivitamin supplementation reduces total plasma homocysteine concentrations in healthy older adults consuming a folate-fortified diet (35). Another clinical trial also showed that supplementation with a combination of folic acid, vitamin B-6 and vitamin B-12 significantly decreased the incidence of major adverse events (including death, nonfatal MI and need for repeat revascularization) after percutaneous coronary intervention (36). Observational studies generally support a lower risk of CVD among individuals taking multivitamins (25) or among those with higher intakes of specific B-vitamins (22,25,37,38). Findings from the Kuopio Ischemic Heart Disease Risk Factor Study among men indicated that moderate-to-high dietary folic acid and vitamin B-12, but not vitamin B-6, were associated with a significantly decreased risk of CHD events (22). Two recent reports, one population-based cohort study of U.S. adults (38) and one case-control study in Spain (37), found that dietary intake of folic acid was significantly inversely related to risk of CVD (38). Similarly, in the large prospective Nurses Health Study, higher intakes of folic acid from either foods or supplements and vitamin B-6 from food and supplement sources combined, were associated with a reduced risk of CHD (25). The lowest risk of CHD was observed among women in the highest quintile of both folic acid and vitamin B-6 intake [relative risk (RR) = 0.57, 95% CI 0.40–0.82], suggesting an independent effect of these vitamins. The same study also showed that risk of CHD was reduced among women who regularly used multivitamins (RR = 0.76, 95% CI 0.65–0.90), which is consistent with our results. In contrast to the above-mentioned findings, results from the Physicians' Health Study (24) and the Cancer Prevention Study II (23) did not provide any clear association between multivitamin use and risk of CVD.

TABLE 2

Odds ratios (OR) and 95% CI of myocardial infarction for users of vitamin and mineral supplements (occasional or regular) vs. nonusers stratified by total consumption of fruits and vegetables, intake of dietary fiber, smoking status and physical activity among men and women[1]

		Men		Women	
		OR[2] (95% CI)	*P*-value	OR[2] (95% CI)	*P*-value
Total consumption of fruits and vegetables[3]	Low	0.76 (0.57–1.03)	0.08	0.67 (0.37–1.19)	0.17
	High	0.77 (0.58–1.02)	0.07	0.78 (0.55–1.13)	0.19
Dietary fiber intake[4]	Low	0.69 (0.50–0.94)	0.01	0.63 (0.41–0.96)	0.03
	High	0.80 (0.61–1.05)	0.10	0.84 (0.53–1.33)	0.45
Smoking status	Current	0.76 (0.53–1.11)	0.16	0.47 (0.27–0.83)	0.01
	Never	0.85 (0.56–1.30)	0.46	0.96 (0.57–1.62)	0.87
Physical activity[5]	Inactive	0.78 (0.50–1.19)	0.18	0.60 (0.38–0.95)	0.03
	Active	0.77 (0.58–1.02)	0.07	0.66 (0.41–1.06)	0.08

1 Values are OR and 95% CI from unconditional logistic regression models.

2 Adjusted for age (5-y age groups), hospital catchment area, smoking (current, ex-smokers, never smokers), job stress (yes/no), high BMI (>28 kg/m^2), physical inactivity (yes/no), history of diabetes (yes/no), hypertension (yes/no), hypercholesterolemia (≥6.5 mmol/L or treatment with lipid lowering medications), hypertriglyceridemia (≥2.0 mmol/L), high plasma plasminogen activator inhibitor 1 (≥20 kU/L), and high plasma fibrinogen (≥4 g/L).

3 The cut-off value for low and high consumption of total fruits and vegetables was 10 servings/wk (the median intake among men and women).

4 The cut-off value for low and high intake of dietary fiber was 14.9 g/d (the median intake among men and women).

5 Subjects who reported sedentary leisure time activities, including only occasional walks during the last 5–10 y, were classified as physically inactive.

Most studies to date have focused on the homocysteine-lowering effects of folic acid. However, folic acid may decrease the risk of CVD even by other potential mechanisms, such as antioxidant actions, stimulation of endothelial nitric oxide synthase or regeneration of the cofactor for this enzyme (39).

Several previous observational studies on the role of antioxidant vitamins have observed inverse relations between risk of CVD and dietary (1,9,12) and supplemental (8,10,11) intakes of vitamin C, vitamin E and β-carotene. Although inverse associations emerged between supplemental vitamin E and nonfatal MI in two randomized controlled trials (40,41), in other trials no or only marginally beneficial effects of supplementation with specific antioxidants were observed (13–17). However, there are some important differences between these trials and observational studies including ours. First, the doses of vitamins used in the controlled trials were higher than in our study, and experimental data suggest that prooxidant properties may occur at higher concentrations of vitamins (42–44). Hence, high doses of vitamins may attenuate potential beneficial effects and consequently could result in adverse effects on CVD outcomes. Furthermore, most of the clinical trials were conducted among high risk populations, and it has been suggested that antioxidants might be protective only before occlusive disease has developed (45,46). Similarly, most trials have included smokers only and the relation between smoking and oxidation is complex (47). Also, in some studies, only fatal CVD events and no effect on nonfatal MI or stroke were reported. Another important difference between clinical trials and our study concerns the potential beneficial effects of interaction between antioxidant vitamins and minerals. The great majority of supplement users in our study took multivitamin/mineral supplements, whereas almost all trials used separate vitamins or a combination of two. A combination of several antioxidants might provide synergistic effects against free radicals by regenerating each other from its radical form. Thus, a beneficial effect on CVD may be achieved only when balanced intakes of several antioxidant vitamins and minerals in low doses act in concert.

The strength of our study is that it is one of the largest observational studies on vitamins and minerals as they affect the number of nonfatal MI events, including both men and women. Furthermore, the study was population based and the participation rate was high for both cases and controls (26). In addition, detailed information on the contents of vitamins and minerals from supplements was based on objective data from pharmacies. A potential limitation of this study is the difficulty in separating beneficial effects of dietary supplementation from effects due to healthy lifestyle habits. However, even when we controlled for known cardiovascular risk factors and performed stratified analyses to evaluate the associations in subgroups with different health behaviors, the observed association persisted, although never smoking appeared to outweigh the inverse association in women. As in all case-control studies, we cannot exclude recall bias regarding self-reporting of dietary supplement intake. However, it is rather unlikely that cases would underestimate their use of dietary supplements or controls overestimate their use. The serum values registered for the cases at the examinations could also have been influenced by the disease and medication. In the SHEEP Study, however, the routine was to wait at least 3 mo after the MI event before blood sampling took place. The reason behind this is that earlier studies have showed that after three months MI-patients are stable in terms of metabolism and inflammation (27,28). Despite this, there is still a risk that the values recorded do not correspond fully with the status before the MI.

In conclusion, our results, based on a population in which consumption of fruits and vegetables is relatively low and foods are not fortified with folic acid, show that use of low dose multivitamin supplements is associated with a substantially lower risk of nonfatal MI. Although these results are promising, definitive proof that intake of low dose multivitamin supplements decreases CVD risk awaits the results from randomized, double-blind, placebo-controlled trials. If the association is confirmed, then multivitamin therapy may provide a cheap, safe and acceptable therapeutic option for the primary prevention of CVD.

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