Multivitamin use and the risk of myocardial infarction: a population-based cohort of Swedish women

Susanne Rautiainen, Agneta Åkesson, Emily B Levitan, Ralf Morgenstern, Murray A Mittleman, and Alicja Wolk

ABSTRACT

Background: Dietary supplements are widely used in industrialized countries.

Objective: The objective was to examine the association between multivitamin use and myocardial infarction (MI) in a prospective, population-based cohort of women.

Design: The study included 31,671 women with no history of cardiovascular disease (CVD) and 2262 women with a history of CVD aged 49–83 y from Sweden. Women completed a self-administered questionnaire in 1997 regarding dietary supplement use, diet, and lifestyle factors. Multivitamins were estimated to contain nutrients close to recommended daily allowances: vitamin A (0.9 mg), vitamin C (60 mg), vitamin D (5 μg), vitamin E (9 mg), thiamine (1.2 mg), riboflavin (1.4 mg), vitamin B-6 (1.8 mg), vitamin B-12 (3 μg), and folic acid (400 μg).

Results: During an average of 10.2 y of follow-up, 932 MI cases were identified in the CVD-free group and 269 cases in the CVD group. In the CVD-free group, use of multivitamins only, compared with no use of supplements, was associated with a multivariable-adjusted hazard ratio (HR) of 0.73 (95% CI: 0.57, 0.87). The use of multivitamins together with other supplements was 0.70 (95% CI: 0.57, 0.87). The HR for use of supplements other than multivitamins was 0.93 (95% CI: 0.81, 1.08). The use of multivitamins for ≥5 y was associated with an HR of 0.59 (95% CI: 0.44, 0.80). In the CVD group, use of multivitamins alone or together with other supplements was not associated with MI.

Conclusions: The use of multivitamins was inversely associated with MI, especially long-term use among women with no CVD. Further prospective studies with detailed information on the content of preparations and the duration of use are needed to confirm or refute our findings.


INTRODUCTION

The use of dietary supplements has substantially increased during the past decade, and in some populations nearly 50% of people report use of any kind of supplement (1, 2). Multivitamin and mineral supplements are the most frequently used preparations (1, 3), and a common belief is that they ensure an adequate nutrient intake that can help prevent coronary heart disease (CHD) (4). Multivitamins contain a wide spectrum of nutrients, such as antioxidant vitamins (5, 6), B vitamins (6, 7), and some supplements including minerals such as magnesium and selenium (8, 9), which all have been inversely related to CHD. Despite the widespread use of multivitamins, limited data are available on the relation of multivitamins to CHD incidence.

There is only one published randomized controlled trial (RCT) on low-dose multivitamin supplements (including vitamin C, vitamin E, β-carotene, selenium, and zinc) and incident CHD in women and men, which showed no effect (10). Observational studies on the other hand, have reported mixed results. Some studies found a statistically significant inverse association with the incidence of myocardial infarction (MI) (11–13), with CHD mortality, (14) and with cardiovascular disease (CVD) mortality (15), but others reported no association with MI incidence (16) or CHD mortality (17). The dose and the composition of ingredients vary in multivitamin supplements, both within and between countries, which may partly explain the inconsistent results. A recent Cochrane review reported that high-dose single supplements of vitamin A, β-carotene, or vitamin E used in different RCTs, which were expected to have beneficial effects on different health outcomes, were related to higher mortality (18).

In the current study, we evaluated the effect of multivitamins with and without minerals on the risk of MI in a prospective population-based cohort of women 48–83 y of age. Most Swedish multivitamin supplements include only essential vitamins and minerals with doses corresponding to recommended daily allowances.

SUBJECTS AND METHODS

The Swedish Mammography Cohort (SMC) was established between 1987 and 1990 in the Uppsala and Västmanland counties in central Sweden (19). A questionnaire concerning diet and other factors was mailed to all women born between 1914 and 1948, to which 74% responded. In 1997, to update and expand exposure data, a second questionnaire was mailed to all 56,030 cohort members that were alive and still living in the study area. Women were asked to fill in information on diet, history of vitamin

1 From the Divisions of Nutritional Epidemiology (SR, AA, and AW) and Biochemical Toxicology (RM), Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; the Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL (EBL); and the Cardiovascular Epidemiology Research Unit, Beth Israel Deaconess Medical Center, Boston, MA (MAM).

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3 Address correspondence to S Rautiainen, Institute of Environmental Medicine, Karolinska Institutet, Box 210, 171 77 Stockholm, Sweden. E-mail: susanne.rautiainen@ki.se.

supplement use, history of cigarette smoking and alcohol consumption, weight and height, physical activity, family history of MI before age of 60 y, educational level, use of certain medications (including postmenopausal hormones) and diagnosis of high cholesterol, hypertension, and diabetes (20). In the present study, the 1997 questionnaire, completed by 38,984 women (70%), was used as a baseline questionnaire because it included broad information on potential confounders and modifiers of the studied association.

We excluded 1741 women with a diagnosis of cancer (except nonmelanoma skin cancer) before baseline in 1997 and 1831 with missing information on dietary supplement use. We also excluded 1480 women with diabetes (self-reported and identified through linkage of the SM with the Swedish Hospital Discharge Registry) to avoid influence from changes in dietary habits and use of dietary supplements due to prevalent disease. The study cohort included 33,932 women at the start of follow-up in September 1997.

Assessment of dietary supplement use, diet, and other exposures

The questionnaire included predefined questions on the type and duration of use of multivitamins with or without minerals, vitamin E, calcium, and fish oil. It also included questions on the use of B vitamins, and magnesium. Multivitamins generally contain doses close to recommended daily allowances of vitamin A (0.9 mg), vitamin C (60 mg), vitamin D (5 μg), vitamin E (9 mg), thiamine (1.2 mg), riboflavin (1.4 mg), vitamin B-6 (1.8 mg), vitamin B-12 (3 μg), and folic acid (400 μg) (21). The minerals usually included are iron (10 mg), zinc (12 mg), copper (2 mg), calcium (120 mg), magnesium (50 mg), chromium (50 μg), selenium (40 μg), and iodine (150 μg). The sensitivity and specificity of self-reported multivitamin use in our questionnaire has been estimated to be 69% and 98%, respectively (22). The women also completed a 96-item food-frequency questionnaire (FFQ), on which they reported how often, on average, they consumed different foods or beverages during the last year by using 8 predefined response categories. Open-ended questions were used for foods consumed daily, including coffee, tea, and bread. We assessed diet quality by calculating a recommended food score based on dietary guidelines to distinguish healthy foods from less healthy foods (23). One point was added to the score when a subject reported ≥3 servings/mo of any of the following food items: fruit, vegetables, legumes, nuts, low-fat dairy products, whole-grain products, and fish. The maximum total score for a healthy diet that could be achieved was 25. Information on physical activity was collected by asking 5 questions relating to occupation, housework, walking or cycling, leisure-time exercise, and inactive leisure time (eg, watching television or reading). Physical activity levels for specific activities were estimated by multiplying reported duration (h/d) by absolute intensity defined as multiples of the metabolic equivalent (MET, kcal · kg⁻¹ · h⁻¹) of sitting quietly for 1 h. Physical activity has been validated against a 14-d activity diary in a group of Swedish men aged 44–78 y and was shown to estimate physical activity satisfactorily (24). Body mass index (BMI) was calculated as weight (in kg) divided with the square of the height (in m).

In the primary analyses we excluded 2262 women with a diagnosis of cardiovascular disorders (identified through the Swedish Hospital Discharge Registry, International Statistical Classification of Disease, 10th Revision, codes I20–25 and I60–69) (25). The CVD-free cohort included 31,670 women. We also performed separate analysis to examine the association between multivitamin use and MI among those 2262 women with history of CVD.

Case ascertainment and follow-up of the cohort 1997–2007

All women were followed from 15 September 1997 until the date of MI, death, or the end of follow-up (31 December 2007), whichever came first. The cases of MI (International Statistical Classification of Disease, 10th Revision, code I21) were ascertained through linkage via the personnel identification number to the Swedish Hospital Discharge Registry and the Cause of Death Registry. The registries for 1987 and 1995 were thoroughly validated and revealed high sensitivity (of 94) and positive predictive value (86%) for MI (26). We identified 932 cases of MI in the CVD-free subcohort and 269 cases of MI among women with a history of CVD during the follow-up from September 1997 to December 2007.

Statistical analyses

Women who reported using dietary supplements were categorized into users of multivitamins only, users of multivitamins in combination with other supplements, and users of supplements other than multivitamins. Nonsupplement users were the reference group. Differences in characteristics were analyzed with analysis of variance. Cox proportional hazard models were used to estimate relative risks as hazard ratios (HRs), with 95% CIs (26) by using the PHREG procedure in SAS (version 9.1; SAS Institute Inc, Cary, NC) was performed separately in women with no history of CVD and women with a history of CVD. In the multivariable analysis, the HRs were adjusted for established risk factors such as age (5-y age groups; ≤52, 53–57, 58–62, 63–67, 68–72, 73–77, or ≥78 y), smoking [never, past, current (≤10 or >10 cigarettes/d)], BMI (in kg/m²; <18.5, 18.5–24.9, 25–29.9, 30–34.9, or ≥35), physical activity (MET-h in tertiles), alcohol consumption (g/d in quartiles), family history of MI before the age of 60 y (yes or no), hypertension (yes or no), high cholesterol (yes or no), educational level (<10, 10–12, or >12 y), and tertiles of quality of diet score. The proportional hazard assumption was tested by entering the product of multivitamin use and the natural logarithm of time in the model; we found no evidence of violation of this assumption.

In the CVD-free group, the duration of multivitamin use was investigated by categorizing women into ≤5 y of use or ≥5 y of use. We applied Wald statistics to test for heterogeneity of risk estimates between categories of duration.

Furthermore, we investigated whether the association between multivitamin supplement use alone and MI differed by age (≤65 or ≥65 y), smoking status (never or ever), BMI (≤25 or ≥25), alcohol consumption [nondrinkers or current drinkers (≥1 drink/mo)], and hypertension (yes or no). We also investigated whether the association between multivitamin use and MI differed in by CVD status. We performed interaction tests on all categories with the Wald test. All P values shown are 2-sided.
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<0.05 were considered statistically significant. The Regional Ethical Board at Karolinska Institutet (Stockholm, Sweden) approved this investigation, and the self-administered questionnaire was considered to imply informed consent to participate in the study.

RESULTS

During the mean 10.2 y of follow-up, we identified 932 incident MI cases (775 nonfatal and 157 fatal) among women with no history of CVD at baseline and 269 cases (219 nonfatal and 50 fatal) among women with a history of CVD; 59% of women with no history of CVD and 59% of women with a history of CVD used any kind of supplements.

The characteristics of women in the SMC according to multivitamin use are shown in Table 1. In the group with no history of CVD, women using multivitamins alone compared with nonusers of any supplements were older, were more likely to have >12 y of education, were less likely to be current smokers, had slightly lower BMIs, were more likely to be current alcohol consumers, were more likely to be current users of postmenopausal hormones, had slightly higher quality of diet scores, were less physically active, and were less likely to have hypercholesterolemia and to be hypertensive. In the group with a history of CVD, women using multivitamins alone were younger, were more likely to have >12 y of education and a lower BMI, and were less physically active or less likely to be hypertensive.

In the multivariable analysis in women with no history of CVD, we observed that use of multivitamins alone, as compared with no use of supplements, was associated with a 27% (95% CI: 7%, 43%) lower risk of MI (Table 2). Women using multivitamins together with other supplements had a 30% (95% CI: 13%, 43%) lower risk of MI. Use of supplements other than multivitamins was not statistically significantly associated with MI. The associations were similar among regular and occasional users. Further adjustment for postmenopausal hormone use did not substantially change the results: the HR for use of only multivitamins was 0.73 (95% CI: 0.57, 0.94), and the HR for use of multivitamins in combination with other supplements was 0.71 (95% CI: 0.57, 0.88). The multivariable HR for a duration <5 y of multivitamin use was 0.82 (95% CI: 0.60, 1.12) compared with nonsupplement users. Use of multivitamins for ≥5 y before baseline was associated with an HR of 0.59 (95% CI: 0.43, 0.80).

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Age-standardized background characteristics of women in the Swedish Mammography Cohort1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No supplement use</td>
</tr>
<tr>
<td>No CVD history (n = 31,670)</td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>12,864</td>
</tr>
<tr>
<td>Myocardial infarction [n (%)]</td>
<td>403 (3.4)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60.2 ± 8.74</td>
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<tr>
<td>&gt;12 y of education (%)</td>
<td>17.3</td>
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<tr>
<td>Current smokers (%)</td>
<td>24.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2 ± 4.0</td>
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<tr>
<td>Ever alcohol drinkers (%)</td>
<td>81.8</td>
</tr>
<tr>
<td>Current HRT users (%)</td>
<td>31.1</td>
</tr>
<tr>
<td>Quality of diet score2</td>
<td>19.3 ± 4.0</td>
</tr>
<tr>
<td>Current total activity score (MET-h/d)</td>
<td>42.5 ± 4.8</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>19.1</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>6.6</td>
</tr>
<tr>
<td>Family history of MI (%)</td>
<td>1.9</td>
</tr>
<tr>
<td>CVD history (n = 2262)</td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>933</td>
</tr>
<tr>
<td>Myocardial infarction [n (%)]</td>
<td>118 (12.6)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>70.0 ± 8.0</td>
</tr>
<tr>
<td>&gt;12 y of education (%)</td>
<td>6.0</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>20.8</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>25.7 ± 4.3</td>
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<tr>
<td>Ever alcohol drinkers (%)</td>
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<tr>
<td>Current HRT users (%)</td>
<td>25.3</td>
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<tr>
<td>Quality of diet score2</td>
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<tr>
<td>Current total activity score (MET-h/d)</td>
<td>41.3 ± 1.2</td>
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<tr>
<td>Hypertension (%)</td>
<td>44.9</td>
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<tr>
<td>Hypercholesterolemia (%)</td>
<td>25.9</td>
</tr>
<tr>
<td>Family history of MI (%)</td>
<td>2.2</td>
</tr>
</tbody>
</table>

1 MET-h, metabolic equivalent task hours; MI, myocardial infarction; HRT, hormone replacement therapy; CVD, cardiovascular disease.
2 Multivitamins are estimated to contain recommended daily allowances of vitamin C (60 mg), vitamin E (9 mg), thiamine (1.2 mg), riboflavin (1.4 mg), vitamin B-6 (1.8 mg), vitamin B-12 (3 µg), and folic acid (400 µg).
3 Mean ± SD (all such values).
4 Significantly different from non–supplement users, P < 0.05 (ANOVA).
5 One point was added to the quality of diet score for consuming ≥3 servings/mo of one of the following items: fruit, vegetables, legumes, nuts, low-fat dairy products, and whole-grain products or fish. Maximum score possible was 25.
Multivitamins are estimated to contain recommended daily allowances of vitamin C (60 mg), vitamin E (9 mg), thiamine (1.2 mg), riboflavin (1.4 mg), vitamin B-6 (1.8 mg), vitamin B-12 (3 µg), and folic acid (400 µg).

In the group of women with a history of CVD, multivitamin use was associated with a statistically significant 34% lower risk of incident MI in a prospective cohort study of Dutch women and men (12). The Nurses’ Health Study reported that regular multivitamin use was associated with a 51% lower risk of incident MI in a prospective cohort study of 90,000 American women observed in a reverse association with incident MI (16) only among women using multivitamins containing vitamins and minerals > 200% of recommended daily allowances. Because of multiple comparisons, the authors interpreted the observed association as a chance finding. In another study of American men, no association was found between multivitamin use and CHD mortality (17). Moreover, the US Preventive Services Task Force has created clinical guidelines for the use of vitamin supplements, and they concluded that the evidence is insufficient to recommend for or against the use of supplements of vitamins A, C, and E; of multivitamins with folic acid; or of antioxidant combinations for the prevention of cancer or cardiovascular disease (28, 29).

### DISCUSSION

In this large, prospective cohort of women we observed a lower risk of MI among women with no history of CVD at baseline who were using either multivitamins alone or multivitamins in combination with other supplements. The association was stronger among women who used multivitamins for ≥5 y. The risk did not differ substantially when we stratified by factors such as age, smoking status, BMI, alcohol consumption, and hypertension. Among women with a history of CVD at baseline, multivitamin use alone or in combination with other supplements was not associated with MI.

From a public health point of view, it is important to evaluate whether multivitamins should be recommended to prevent MI. Only one RCT has studied the effect of low-dose multivitamin supplements (including 120 mg ascorbic acid, 30 mg vitamin E, 6 mg β-carotene, 100 µg Se, and 20 mg Zn) and incident CHD, and it showed no effect (10). Our results agree with some observational studies (11–15), but not with others (10, 16, 17). In one Swedish case-control study, use of multivitamin supplements was associated with a statistically significant 34% lower risk of incident MI in women and a 21% lower risk in men (11). Multivitamin use was associated with a statistically significant 51% lower risk of incident MI in a prospective cohort study of Dutch women and men (12). The Nurses’ Health Study reported that regular multivitamin use was associated with a 24% statistically significant lower risk of incident CHD (13). An American prospective study of women and men observed that combined use of multivitamins and supplements of vitamin A, C, or E was associated with a 25% lower risk of CHD mortality, and the effect was somewhat stronger for a duration of ≥5 y (14). Another American prospective study of women and men observed a 16% lower risk of CVD mortality (15). One recent prospective cohort study of >90,000 American women observed an inverse association with incident MI (16) only among women using multivitamins containing vitamins and minerals > 200% of recommended daily allowances. Because of multiple comparisons, the authors interpreted the observed association as a chance finding. In another study of American men, no association was found between multivitamin use and CHD mortality (17). Moreover, the US Preventive Services Task Force has created clinical guidelines for the use of vitamin supplements, and they concluded that the evidence is insufficient to recommend for or against the use of supplements of vitamins A, C, and E; of multivitamins with folic acid; or of antioxidant combinations for the prevention of cancer or cardiovascular disease (28, 29).
It may seem contradictory that our results do not agree with those of the RCT and some observational studies that evaluated the effects of multivitamin supplements on coronary events. The reason for this apparent contradiction may be that the dose and the composition of ingredients vary in multivitamin supplements used in different studies. In Sweden, multivitamins contain doses corresponding to recommended daily allowances; however, most other observational studies did not report doses of ingredients studied. It is important to point out that a recent Cochrane review of RCTs on supplements of vitamin B-6, B-9, or B-12 given alone or in combination, at any dosage, observed no effect on MI, stroke, or total mortality in participants at risk or with established CVD (30). RCTs of antioxidant supplements containing 1–3 compounds have failed to observe any benefit on CVD (31–36). Moreover, in another Cochrane review, high-dose and very-high-dose single supplements of vitamin A, β-carotene, or vitamin E used in different RCTs were associated with higher mortality (18). Another reason why RCTs have failed to observe any benefit from vitamin supplements on cardiovascular health may be that many RCTs were performed among participants with existing CVD, whereas observational studies are based mainly on healthy participants. We therefore, performed separate analyses in women with no history of CVD and women with a history of CVD and observed statistically significant associations only among the women with no history of CVD. However, the lack of inverse association among women with CVD at baseline may be due to limited statistical power in these analyses. Furthermore, the contradiction among studies may also be explained by the shorter follow-up in the majority of RCTs than in many observational studies. Our results were stronger among women who reported using multivitamins for ≥5 y than among women who reported using multivitamins for <5 y, which suggests that long-term use may be needed to achieve beneficial effects on MI.

The potential protective effects of multivitamins on MI may arise from antioxidant vitamins (5, 6), B vitamins (6, 7), and minerals if included (8, 9). Even if multivitamins contain low amounts of antioxidant vitamins such as vitamin C and vitamin E, they may be involved in mitigating the atherosclerotic process by scavenging free radicals (5). Reactive oxygen species in high amounts have been associated with the formation of atherosclerotic plaques that, if ruptured, can cause MI (37). B vitamins such as folate, B-6, and B-12 are involved in homocysteine metabolism, and deficiency of these vitamins has been associated with elevated homocysteine concentrations (38). Elevated homocysteine concentrations are suggested to increase the risk of CVD (39); however, homocysteine-lowering trials of supplements of folate, B-6, and vitamin B-12 to prevent CVD did not support such an association (39). Minerals may be protective in several ways. Magnesium may inhibit insulin resistance, decrease vascular tone, and inhibit pro-inflammatory changes and endothelial dysfunction. Enzymes such as glutathione peroxidases and thioredoxin reductases, which are involved in the protection against oxidative damage, require selenium (9).

Our study had several strengths, including the prospective population-based design and the practically complete follow-up by linkage to national registers. It minimized the concern that the findings were influenced by differential loss to follow-up. We also had access to detailed information on different potential confounders and CHD risk factors.

Our study may have had some limitations. We cannot exclude the possibility of exposure misclassification, which, however, is more likely to be nondifferential because of the prospective design. If exposure misclassification is present, it would tend to bias the results toward observing no association. Although we adjusted for several confounders in multivariable analysis, we cannot exclude the possibility of residual confounding. Furthermore, the observed inverse association between multivitamin use and MI could be due to a phenomenon that women who use dietary supplements are more health conscious and have other healthy behaviors. However, when adjusted for several potential confounders such as diet, physical activity, and educational level, the results remained unchanged. Moreover, we observed no inverse association among women who were users of dietary supplements other than multivitamins, which contradicts the theory that the observed association is an effect of healthy behavior in general. We could not evaluate the consumption of fortified foods, which might influence the effect of vitamin supplements. In Sweden there is a policy to add vitamin D to milk and to add vitamin A and D to butter and margarine (40, 41); however, there is no mandatory fortification policy for other vitamins and minerals, although some foods (eg, cereals and fruit juices) may be fortified with different vitamins and minerals. A bigger effect of multivitamins might be expected when the food supply was not already fortified.

In conclusion, we observed that multivitamin use is inversely associated with MI among women with no history of CVD. Further studies are needed to confirm or refute our findings and, if confirmed, to clarify what composition of multivitamins (doses and ingredients included) and duration of use is needed to observe beneficial effects on MI.

The authors’ responsibilities were as follows—SR, ÅÅ, EBL, RM, MAM, and AW: responsible for the study concept and design; AW: responsible for data collection; SR: responsible for data analysis; SR, ÅÅ, and AW: responsible for statistical analyses; AW, ÅÅ, EBL, MAM, and RM: provided expertise; SR: wrote the first draft of the manuscript; AW: obtained funding; and SR, ÅÅ, EBL, RM, MAM, and AW: reviewed and revised the manuscript. All authors reviewed the final manuscript. None of the authors had any personal or financial conflicts of interest.

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