Dietary Calcium and Magnesium Intake and Mortality: A Prospective Study of Men

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The authors examined the association of dietary calcium and magnesium intake with all-cause, cardiovascular disease (CVD), and cancer mortality among 23,366 Swedish men, aged 45–79 years, who did not use dietary supplements. Cox proportional hazards regression models were used to estimate the multivariate hazard ratios and 95% confidence intervals of mortality. From baseline 1998 through December 2007, 2,358 deaths from all causes were recorded in the Swedish population registry; through December 2006, 819 CVD and 738 cancer deaths were recorded in the Swedish cause-of-death registry. Dietary calcium was associated with a statistically significant lower rate of all-cause mortality (hazard ratio (HR) = 0.75, 95% confidence interval (CI): 0.63, 0.88; \( P_{\text{trend}} < 0.001 \)) and a nonsignificantly lower rate of CVD (HR = 0.77, 95% CI: 0.58, 1.01; \( P_{\text{trend}} = 0.064 \)) but not cancer mortality (HR = 0.87, 95% CI: 0.65, 1.17; \( P_{\text{trend}} = 0.362 \)) when the highest intake tertile (mean = 1,953 mg/day; standard deviation (SD), 334) was compared with the lowest (990 mg/day; SD, 187). Dietary magnesium intake (means of tertiles ranged from 387 mg/day (SD, 31) to 523 mg/day (SD, 38) was not associated with all-cause, CVD, or cancer mortality. This population-based, prospective study of men with relatively high intakes of dietary calcium and magnesium showed that intake of calcium above that recommended daily may reduce all-cause mortality.

calcium; dietary supplements; eating; magnesium; men; mortality

Although the role of calcium and magnesium in homeostasis has been examined extensively, the optimal intake of the nutrients and balance between them is not clear. Calcium and magnesium may antagonize each other in terms of absorption and metabolism, particularly when intake of one is significantly higher than intake of the other (1, 2). Associations between intakes of these 2 micronutrients and incidence of major chronic diseases such as hypertension, type 2 diabetes, cardiovascular disease (CVD), and specific cancers have been investigated in many epidemiologic studies (2–12). However, the association of calcium intake with mortality has been addressed in few investigations, with no consistent inverse associations observed with CVD mortality (13–15) and an adverse association observed with prostate cancer mortality (16, 17); to our knowledge, there are no studies of dietary magnesium intake and mortality. Most studies were limited to only drinking water as a source of calcium and magnesium when evaluating the association with CVD (18–21) or cancer (22–24) mortality.

Therefore, we conducted a prospective study of dietary intakes of calcium and magnesium in relation to all-cause mortality as an ultimate outcome, taking into account both potentially protective and potentially harmful health effects of the 2 micronutrients. We analyzed data from 23,366 participants in the population-based Cohort of Swedish Men, which we followed for 10 years. We also examined whether the observed associations of each of the micronutrients with all-cause mortality depend on the level of the other one. Furthermore, we examined the associations of dietary calcium and magnesium more specifically with CVD and cancer mortality.
MATERIALS AND METHODS

Study population

The Cohort of Swedish Men was established in central Sweden (Västmanland and Örebro Counties) in 1997–1998. A questionnaire was sent to all men (n = 100,303) aged 45–79 years living in the study area, and 48,645 men answered. For the analysis, we excluded those who returned a blank questionnaire (n = 92); those who died before January 1, 1998 (n = 55); those with a previous cancer diagnosis other than nonmelanoma skin cancer (n = 2,592); those with a history of CVD (n = 5,069) or diabetes (n = 3,204); those with extreme energy intake estimates (i.e., 3 standard deviations from the mean value for log-transformed energy); and those who reported use of any types of dietary supplements (n = 14,267). Men who consumed dietary supplements were excluded because there was not sufficient information on supplement composition to estimate calcium and magnesium intake from these sources. After these exclusions, the study cohort comprised 23,366 men. There were no differences in mortality rates between users (12%) and nonusers (11%) of dietary supplements during 10 years of follow-up of the cohort.

Assessment of diet and other exposures

Food frequency questionnaires (FFQs) were used to assess dietary intake during the previous year before cohort entry. The FFQ contained questions on 96 food items, which included the most commonly consumed foods in the study population as well as foods with high concentrations of some nutrients and/or bioactive substances. Frequency of consumption was reported according to 8 predefined categories: never/seldom, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, once/day, 2 times/day, and ≥3 times/day. Intakes of calcium, magnesium, and other nutrients were calculated by multiplying the frequency of consumption of each food item by the nutrient content of appropriate age-specific portion sizes from the Swedish National Food Administration Database (25).

Validity of the FFQ has been evaluated among 248 men by using 14 24-hour recall telephone interviews spread over a whole year (26). The Spearman correlation coefficients (ρ) between energy-adjusted calcium and magnesium intake assessed by the FFQ and by 24-hour recalls were 0.77 and 0.73, respectively.

Sociodemographic data, waist and hip circumferences, total physical activity, self-perceived health status, smoking history, and alcohol drinking habits were collected by using a self-administered questionnaire. The questionnaire also included information about hypertension and hypercholesterolemia.

Follow-up of the cohort and ascertainment of cases

Dates of death or migration from the study area were obtained from the Swedish Death and Population Registers at Statistics Sweden through December 31, 2007. Detailed information on causes of death was available from the Swedish Register of Death Causes at the National Board of Health and Welfare through December 31, 2006, because there is up to a 1-year delay in completion of these register data. Deaths from cardiovascular (codes 100–179) and cancer (codes C00–C97) causes were classified according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. Completeness of the registers is nearly 100%.

Statistical analysis

Cox proportional hazards regression models were used to estimate the hazard ratios and 95% confidence intervals of all-cause, CVD, and cancer mortality among men. Survival time was calculated as the time from study entry until death; migration; December 31, 2007 (for analysis of all-cause mortality); or December 31, 2006 (for cause-specific mortality analysis), whichever was earlier.

Multivariate hazard ratio estimates were adjusted for age (continuous variable); marital status (single, married, divorced or widowed); education (less than high school, high school or university); total physical activity (≤40.9 metabolic equivalent task hours × hours/day (median), >40.9 metabolic equivalent task hours × hours/day) (27); self-perceived health status (very good, good, average, bad, or very bad); waist-to-hip ratio (≤0.94 (median), >0.94); smoking status (never, former, or current); alcohol consumption (≤5 g ethanol/day, >5 g ethanol/day); and intakes of dietary fiber (quartiles), saturated fatty acids (quartiles), vitamin D (quartiles), and phosphorus (quartiles). Intakes of nutrients were adjusted for energy intake of 2,600 kcal/day by using the residual method (28). Multivariate hazard ratio estimates for tertiles of intake of calcium and magnesium were mutually adjusted. Including 4 categories (quartiles) for waist-to-hip ratio, alcohol consumption, and total physical activity did not materially alter the results.

We checked whether the proportional hazards assumption was reasonable in the multivariate models. Scaled Schoenfeld’s residuals were regressed against survival time. There was no evidence of departure from the assumption.

To calculate P values for trend, the median values of tertiles of calcium and magnesium intake were used as a continuous variable. Using the likelihood ratio test, we tested statistical interactions between calcium and magnesium intake in predicting mortality. All statistical analyses were performed with Stata, version 10, software (StataCorp, College Station, Texas). All reported P values are 2-sided; P values ≤0.05 were considered statistically significant.

RESULTS

The baseline characteristics of the study population, by tertiles of energy-adjusted calcium and magnesium intake, are shown in Table 1. Mean dietary calcium intake increased 2-fold between the lowest tertile (990 mg/day (standard deviation, 187)) and the highest tertile (1,953 mg/day (standard deviation, 334)). The main sources of this nutrient in the diet were milk and milk products (68.5%) and cereal products (8.4%). Compared with men in the lowest tertile of calcium intake, those in the highest tertile had higher intakes of protein, fat, and phosphorus and lower intakes of alcohol,
carbohydrates, and dietary fiber. Intake of magnesium was generally high in the study population and ranged from 387 mg/day (standard deviation, 31) in the lowest tertile to 523 mg/day (standard deviation, 38) in the highest tertile. Only 5% of men had a magnesium intake of less than 314 mg/day. Thirty-three percent of magnesium was obtained from bread and cereal products, 17.5% from milk and dairy products, and 11.9% from vegetables. Among men in the lowest tertile of magnesium intake, dietary fiber, calcium, and phosphorus intake was lower and fat intake was higher than among men in the highest tertile. Men in the lowest tertile also had a lower educational level, and more of them were smokers.

The Pearson’s correlation between calcium and magnesium intake was 0.18.

During an average of 10 years of follow-up (224,206 person-years, 1998–2007), 2,358 deaths from all causes were registered. From baseline 1998 through December 2006 (203,036 person-years), 819 CVD deaths and 738 cancer deaths were registered.

We observed inverse associations between energy-adjusted calcium intake and risk of all-cause and CVD mortality (Table 2). Compared with men in the lowest tertile of calcium intake, those in the highest tertile had a 25% (95% confidence interval: 0.63, 0.88; \( P_{\text{trend}} < 0.001 \)) lower risk of all-cause mortality and a 23% (95% confidence interval: 0.58, 1.01; \( P_{\text{trend}} = 0.064 \)) lower risk of CVD mortality, although the latter association was not statistically significant at the 0.05 level. Further adjustment of CVD mortality for hypertension and high cholesterol did not change the risk estimates.

We found no association between calcium intake and cancer mortality. In multivariate analyses, we did not observe associations between magnesium intake and all-cause, CVD, or cancer mortality.

Exclusion of the first 2 years of follow-up did not substantially change the observed risk estimates. Men in the highest, compared with the lowest, tertile of dietary calcium intake had a 24% lower mortality rate from all causes.

### Table 1. Age-standardized Baseline Characteristics of a Cohort of 23,366 Swedish Men Aged 45–79 Years by Tertiles of Energy-adjusted Dietary Calcium and Magnesium Intake, 1998

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Calcium Intake, mg/day</th>
<th>Magnesium Intake, mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1,230 (n = 7,786)</td>
<td>1,230–1,598 (n = 7,788)</td>
</tr>
<tr>
<td>Calcium, mg/day</td>
<td>990 (187)</td>
<td>1,408 (105)</td>
</tr>
<tr>
<td>Magnesium, mg/day</td>
<td>443 (65)</td>
<td>454 (60)</td>
</tr>
<tr>
<td>Age, years</td>
<td>57.6 (9.0)</td>
<td>58.1 (9.0)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.94 (0.08)</td>
<td>0.94 (0.07)</td>
</tr>
<tr>
<td>Total physical activity, MET × hours/day</td>
<td>41.6 (5.0)</td>
<td>41.7 (4.9)</td>
</tr>
<tr>
<td>University education &gt;12 years</td>
<td>17.2</td>
<td>17.6</td>
</tr>
<tr>
<td>Married</td>
<td>83.0</td>
<td>84.8</td>
</tr>
<tr>
<td>Health status very good or good</td>
<td>79.0</td>
<td>82.4</td>
</tr>
<tr>
<td>Smoking</td>
<td>35.5</td>
<td>37.5</td>
</tr>
<tr>
<td>Energy from diet, kcal/day</td>
<td>2,608 (791)</td>
<td>2,715 (742)</td>
</tr>
<tr>
<td>Alcohol consumption, g/day</td>
<td>13.1 (11.5)</td>
<td>10.7 (9.3)</td>
</tr>
<tr>
<td>Adjusted daily intake of energy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total protein, g</td>
<td>91 (13)</td>
<td>101 (9)</td>
</tr>
<tr>
<td>Total fat, g</td>
<td>86 (15)</td>
<td>91 (13)</td>
</tr>
<tr>
<td>Saturated</td>
<td>36.9 (7.8)</td>
<td>41.6 (7.7)</td>
</tr>
<tr>
<td>Monounsaturated</td>
<td>30.3 (5.4)</td>
<td>30.8 (4.6)</td>
</tr>
<tr>
<td>Polysaturated</td>
<td>12.5 (2.7)</td>
<td>11.9 (2.1)</td>
</tr>
<tr>
<td>Total carbohydrates, g</td>
<td>339 (39)</td>
<td>323 (33)</td>
</tr>
<tr>
<td>Dietary fiber, g</td>
<td>31.2 (8.5)</td>
<td>30.2 (7.4)</td>
</tr>
<tr>
<td>Vitamin D, μg</td>
<td>6.2 (2.3)</td>
<td>6.3 (2.1)</td>
</tr>
<tr>
<td>Phosphorus, mg</td>
<td>1,754 (223)</td>
<td>2,016 (178)</td>
</tr>
</tbody>
</table>

Abbreviation: MET, metabolic equivalent task hours.

a Values are expressed as mean (standard deviation) or percentage.

b Energy adjusted to 2,600 kcal/day by using the residual method (28). The 5th–95th percentiles were 798–2,258 mg/day for calcium and 355–561 mg/day for magnesium.

† Self-reported.
DISCUSSION

In this population-based, prospective cohort study of men not taking dietary supplements, we found that dietary calcium intake was inversely associated with mortality from all causes. Men in the highest, compared with the lowest, tertile of calcium intake had a statistically significant 25% lower rate of mortality from all causes. Cardiovascular mortality was decreased by 23% when we compared the highest with the lowest tertiles of calcium intake, although this reduction was not statistically significant. We did not observe an...
association between calcium intake and cancer mortality. Dietary magnesium intake was not associated with all-cause, cardiovascular, or cancer mortality.

Our findings for calcium are in line with results from the Women’s Health Initiative randomized trial, in which calcium plus vitamin D supplementation was associated with a nonsignificant decrease in all-cause mortality (14). They are also in line with results from a prospective cohort study of 34,486 postmenopausal US women, in which the highest versus the lowest quartiles of dietary and total (diet + supplements) calcium intake were associated with statistically significant 37% and 33% lower mortality from ischemic heart disease, respectively (13). Similarly, in an ecologic study, a high level of calcium in drinking water (94–146 mg/day) was associated with a statistically significant lower risk of noncerebrovascular (10%) and cerebrovascular (14%) causes of death among elderly people from the southwest of France (29). Dairy products as a source of calcium were considered in a prospective study of a Japanese population (46,465 men and 64,327 women aged 40–79 years) with a generally low dietary calcium intake (15). The risk of mortality for men in the highest versus the lowest quintile of dairy calcium intake was 47% lower for total stroke, 54% lower for hemorrhagic stroke, and 47% lower for ischemic stroke, and the associations were statistically significant; corresponding risk estimates for women were 43%, 49%, and 50% lower. However, there was an internal inconsistency in that study because total calcium intake was nonsignificantly associated with stroke mortality.

Adjustment for hypertension and high cholesterol did not change the estimates of risk of CVD mortality associated with calcium intake. This finding may be because both blood pressure and cholesterol levels have a graded, continuous association with CVD mortality and our study assessed them as only dichotomous variables or because the pathways are not the most important in cardiovascular death. An alternate explanation that cannot be ruled out is confounding by factors associated with dietary calcium intake that were not measured in this study.

The beneficial effect of calcium intake on mortality could be explained by a positive influence of calcium on blood pressure, serum cholesterol level, and blood glucose. Results of a meta-analysis of randomized controlled trials indicated a statistically significant decrease in systolic blood pressure with calcium supplementation (30). Calcium supplement intake (mean dose = 1,200 mg/day) was associated with reduced systolic blood pressure, and the effect was greater for people with a relatively low dietary calcium intake (<800 mg/day). It was also reported that a high-calcium diet was associated with significantly reduced total cholesterol and low density lipoprotein cholesterol and did not change high density lipoprotein cholesterol in serum (31). During a weight-loss intervention among women, a significantly greater decrease in low density lipoprotein cholesterol was observed in the group with calcium and vitamin D supplementation than in the placebo group (32). Dietary calcium has also been associated with lower risk of diabetes mellitus, which increases the risk of all-cause and CVD mortality (33).

An inverse association between magnesium concentration in drinking water and CVD mortality was observed for women from southern Sweden (19) and in a French population (29). To the best of our knowledge, there are no studies of dietary and total magnesium intake and mortality. A dietary deficiency of magnesium and abnormalities in magnesium metabolism are often associated with an imbalance of calcium, sodium, and potassium (34). Magnesium deficiency plays an important role in heart diseases, such as ischemic heart disease, congestive heart failure, sudden cardiac death, atherosclerosis, and a number of cardiac arrhythmias (34).

We did not observe an association between dietary magnesium intake and mortality in the present study. However, note that, compared with other populations, ours had, in general, a high magnesium intake (mean = 450 mg/day, 5th percentile = 355 mg/day) and a high calcium intake (mean = 1,400 mg/day, 5th percentile = 798 mg/day). For example, in the US National Health and Nutrition Examination Survey, mean intake of magnesium was less than 300 mg/day among middle-aged and older men who did not use supplements (35). Among 51,529 US men aged 40–75 years included in the Health Professionals Follow-up Study, the

<table>
<thead>
<tr>
<th>Calcium Intake, mg/day&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. of Deaths</th>
<th>HR</th>
<th>95% CI</th>
<th>No. of Deaths</th>
<th>HR</th>
<th>95% CI</th>
<th>No. of Deaths</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1,230</td>
<td>395</td>
<td>1.00</td>
<td></td>
<td>236</td>
<td>1.07</td>
<td>0.90, 1.27</td>
<td>152</td>
<td>0.95</td>
<td>0.76, 1.17</td>
</tr>
<tr>
<td>1,230–1,598</td>
<td>272</td>
<td>0.85</td>
<td>0.72, 0.99</td>
<td>307</td>
<td>0.99</td>
<td>0.84, 1.17</td>
<td>183</td>
<td>0.86</td>
<td>0.69, 1.07</td>
</tr>
<tr>
<td>≥1,599</td>
<td>222</td>
<td>0.70</td>
<td>0.57, 0.86</td>
<td>288</td>
<td>0.74</td>
<td>0.60, 0.91</td>
<td>303</td>
<td>0.85</td>
<td>0.67, 1.07</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

<sup>a</sup> Multivariate hazard ratios and 95% confidence intervals adjusted for age, marital status, education, self-reported health status, smoking status, physical activity, waist-to-hip ratio, alcohol consumption, energy-adjusted dietary fiber, saturated fatty acid, vitamin D, and phosphorus intake. The interaction between calcium or magnesium intake was not statistically significant (P = 0.148).

<sup>b</sup> Energy-adjusted to 2,600 kcal/day by using the residual method (28). The 5th–95th percentiles were 798–2,258 mg/day for calcium and 355–561 mg/day for magnesium.

Table 3. Multivariate-adjusted Hazard Ratios and 95% Confidence Intervals<sup>a</sup> for All-cause Mortality Among 23,366 Swedish Men by Energy-adjusted Dietary Intake of Calcium and Magnesium, 1998–2007
median of the lowest quintile of magnesium intake (diet and supplements) was 243 mg/day and in the highest quintile was 452 mg/day; the medians of calcium intake were 500 mg/day and 1,400 mg/day, respectively (36). In other words, it seems that there were no magnesium-deficient participants in our study population, which could explain the overall lack of association with magnesium. Further studies are needed in other populations with lower dietary magnesium intakes to address this issue.

Strengths of our study include the population-based, prospective design and detailed information on diet. The prospective design and practically complete cohort follow-up minimized the possibility of recall bias and bias caused by loss to follow-up. The extensive data on possible risk factors for mortality allowed comprehensive adjustment of confounders. Although the FFQ-based estimates of dietary calcium and magnesium intake had relatively high validity, some misclassification of calcium and magnesium intake is inevitable. Measurement error in assessing dietary intake in a prospective setting leading to nondifferential misclassification would have likely attenuated rather than exaggerated the true associations. Furthermore, it is not known whether participants’ diet during the baseline year reflected their diet during the biologically relevant period.

Moreover, we did not have data about calcium and magnesium intake from drinking water, which could be a relevant source of these minerals, and men who consumed these nutrients in dietary supplements were excluded because of lack of information on the composition of the supplements. In Sweden, dietary supplement use is associated with higher education, lower body weight, more physical activity, and worse subjective health (37). Exclusion of supplement users could result in a loss of generalizability if they were different from the analytical cohort in terms of occurrence of death. However, we found that users and nonusers of dietary supplements had very similar mortality rates. We cannot rule out the possibility that some unmeasured confounders or residual confounding accounted for the observed associations.

In conclusion, the findings from this prospective cohort study of men support an inverse association between dietary calcium intake and all-cause mortality. The inverse association between dietary calcium intake and CVD mortality was not statistically significant, and there was no apparent relation between magnesium and all-cause, CVD, or cancer mortality. However, these results have to be considered in the context of the study population with relatively high intakes of dietary calcium and magnesium. Future studies should examine intake of calcium and magnesium from diet, from drinking water, and from dietary supplements in relation to all-cause and specific causes of mortality, especially in populations in which potential deficiency of these minerals is suspected.

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