Calcium and cardiovascular disease

ORIGINAL ARTICLE

Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg)

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ABSTRACT

Background It has been suggested that a higher calcium intake might favourably modify cardiovascular risk factors. However, findings of an ultimately decreased risk of cardiovascular disease (CVD) are limited. Instead, recent evidence warns that taking calcium supplements might increase myocardial infarction (MI) risk.

Objective To prospectively evaluate the associations of dietary calcium intake and calcium supplementation with MI and stroke risk and overall CVD mortality.

Methods Data from 23 980 Heidelberg cohort participants of the European Prospective Investigation into Cancer and Nutrition study, aged 35–64 years and free of major CVD events at recruitment, were analysed. Multivariate Cox regression models were used to estimate HRs and 95% CIs.

Results After an average follow-up time of 11 years, 354 MI and 260 stroke cases and 267 CVD deaths were documented. Compared with the lowest quartile, the third quartile of total dietary and dairy calcium intake had a significantly reduced MI risk, with a HR of 0.69 (95% CI 0.50 to 0.93), respectively. Associations for stroke risk and CVD mortality were overall null. In comparison with non-users of any supplements, users of calcium supplements had a statistically significantly increased MI risk (HR=1.86; 95% CI 1.17 to 2.96), which was more pronounced for calcium supplement only users (HR=2.39; 95% CI 1.12 to 5.12).

Conclusions Increasing calcium intake from diet might not confer significant cardiovascular benefits, while calcium supplements, which might raise MI risk, should be taken with caution.

INTRODUCTION

Epidemiological studies have consistently reported inverse associations between dietary calcium intake and the risk of hypertension, obesity and type 2 diabetes,1–8 suggesting that a reasonably higher intake of this mineral might ultimately decrease the occurrence of cardiovascular events. Such a plausible health benefit has indeed been shown by several epidemiological studies. In three prospective studies, dietary calcium intake was significantly inversely associated with the ischaemic stroke risk.9–11 A fourth study also found a statistically significant inverse association between dietary calcium intake and mortality from ischaemic heart disease.12 In a Swedish male cohort, the association between dietary calcium intake and overall cardiovascular disease (CVD) mortality was inverse and of borderline statistical significance.13 However, except for these supportive findings, the majority of observational studies reported null associations.14–21

Calcium supplements, which are commonly recommended to elderly people, particularly post-menopausal women, to maintain their bone health, have also been suggested as beneficial agents to improve serum cholesterol profiles22–24 and to control hypertension.25 However, no strong epidemiological evidence suggests that calcium supplementation might provide cardiovascular benefits.10 12 14 16 Instead, two recent meta-analyses of clinical trials have prompted a warning that calcium supplements might increase a person’s risk of having myocardial infarction (MI).26 27

In this study, we aimed to prospectively examine the associations of dietary calcium intake, in total or separated from dairy sources and from non-dairy sources and calcium supplementation with MI and stroke risk and overall CVD mortality in a German cohort.

METHODS

Study population

The Heidelberg cohort is one of the two German cohorts participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. In 1994–8, the EPIC-Heidelberg cohort recruited 25 540 local residents, who were then aged 35–64 years. A detailed description of the recruitment procedures has been published elsewhere.20 The ethics committee of the Heidelberg University Medical School approved the study protocol and all participants provided informed consent. In this study, we excluded participants who had a diagnosis of MI, stroke, or transient ischaemic attack at baseline (n=1522). We also excluded participants whose daily energy intake fell into the top or the bottom 0.5 centile (men: <887>/5582 kcal/day;
Assessment of dietary calcium intake and calcium supplementation

A self-administered food frequency questionnaire (FFQ), which had been validated using 12 24 h dietary recalls in a subsample of 104 participants from the two German cohorts, was used to assess consumption of 148 food items in the 12 months before the date of recruitment. Dietary calcium intake was derived using the German Nutrient Database BSL, version II.3. Within the entire EPIC-Germany, dairy foods and non-alcoholic beverages were the main sources of dietary calcium, providing 39.9% and 28.2% of the daily intake, respectively. The Spearman correlation coefficient between the FFQ and the mean of the 12 24-h dietary recalls was 0.58 for dairy foods and 0.70 for non-alcoholic beverages.

In a baseline interview and follow-up questionnaire surveys, participants were asked if they had regularly taken vitamin/mineral supplements in the past 4 weeks, where ‘regularly’ was defined as daily use for at least 1 week or non-daily use of at least five doses on a regular basis. Self-reported supplements were coded using the Anatomical Therapeutic Chemical classification system. Data on dosage were not collected. In this study, we separated cohort participants into users of calcium supplements (Anatomical Therapeutic Chemical code A12A), users of other supplements (containing users of unspeciﬁed supplements) and non-users of any supplements. Users of calcium supplements were also separated into calcium supplement only users and users of calcium supplements plus other vitamins/minerals.

Incident cardiovascular outcomes

Incident cardiovascular events during follow-up were reported by participants or their next of kin in follow-up surveys. Reported cardiovascular events were veriﬁed by tracking medical records or ofﬁcial death certiﬁcates. In this study, cardiovascular events of interest, which were coded using the International Classiﬁcation of Diseases 10th version (ICD-10), were incident MI (ICD-10 codes I21–I25), incident stroke (ICD-10 codes I60–I69) and overall CVD mortality (ICD-10 codes I00–I99).

Statistical analysis

Dietary intakes of calcium and other nutrients were adjusted for total energy intake of 2200 kcal/day for men and 1700 kcal/day for women using the residual method. Residuals were obtained from sex-speciﬁc linear regressions of the log-transformed calcium intake on the log-transformed total energy intake. The energy-adjusted nutrient intakes were categorised into quartiles using sex-speciﬁc cut-off points. The lowest quartiles were used as reference groups.

Age- and sex-adjusted baseline characteristics of participants across quartiles of energy-adjusted total dietary calcium intake and across calcium supplementation status were compared using analysis of covariance for continuous variables and logistic regression for binary variables. Multivariate Cox regressions were performed to estimate HRs and 95% CIs. To avoid violation of the proportionality assumption, all models were stratified by the rounded age at recruitment (1-year category). The following potential confounders were adjusted for in the analyses of dietary calcium intake: sex, age at recruitment, the highest educational level (no/primary school, secondary/technical school and university), physical activity (inactive, moderately inactive, moderately active and active), body mass index (BMI, kg/m²), smoking categories (never smoker; former smoker, quit ≥10 years and quit <10 years, current smoker, ≤10, 11–20 and >20 cigarettes/day), lifetime alcohol intake (g/day), total energy intake (kcal/day), energy-adjusted dietary intakes of vitamin D (µg/day), saturated fatty acids (g/day) and total protein (g/day), self-reported diabetes mellitus at recruitment and use of calcium supplements. Other baseline characteristics, including dietary intakes of ﬁbre, vitamin C and folate acid, self-reported hypertension, hyperlipidaemia and regular use of antihypertensive drugs, lipid-lowering drugs and non-steroidal anti-inﬂammatory drugs only slightly affected the HRs and therefore they were not included in the ﬁnal models. Mutual adjustment for dairy and non-dairy calcium intakes was made when they were analysed separately. Linear trends were examined using the likelihood ratio test, in which the median intakes of quartiles were modelled as a continuous variable.

Multivariate Cox models that examined the effects of calcium supplementation also adjusted for total dietary calcium intake, self-reported hyperlipidaemia and use of non-steroidal anti-inﬂammatory drugs, as they appreciably affected the risk estimates. In addition to examining the effect of calcium supplementation at baseline, extended Cox regression models were ﬁtted to examine the effects of the most recent and the cumulative calcium supplementation by using the data on supplement use collected during the follow-up. All analyses were repeated after exclusion of CVD events that occurred in the ﬁrst 2 years of follow-up.

All statistical tests were two-sided, with p<0.05 being considered statistically signiﬁcant. SAS software (V9.2; SAS Institute) was used to perform all statistical analyses.

RESULTS

Table 1 shows the baseline characteristics of participants by quartiles of the energy-adjusted total dietary calcium intake and by calcium supplementation status. A higher dietary calcium intake was mainly associated with favourable factors, including younger age, higher likelihood of having a university degree and being physically active, less likelihood of being overweight/obese (BMI ≥25 kg/m²) and current smokers and an average shorter smoking duration and lower lifetime alcohol consumption. Dietary calcium intake was also positively associated with dietary vitamin D, saturated fatty acid and total protein intake and the likelihood of taking calcium supplements. Compared with non-users, users of calcium supplements were more likely to be women, physically more active and less likely to be overweight/obese. On the other hand, users of calcium supplements had an older age, an overall lower educational level and a longer duration of smoking.

After an average follow-up time of 11 years, 354 MI cases, 260 stroke cases and 267 CVD deaths were documented. After adjustment for potential confounders, a statistically signiﬁcant inverse association was only found between total dietary calcium intake and MI risk for the third quartile compared with the lowest quartile (HR=0.69; 95% CI 0.50 to 0.94; table 2). Compared with the lowest quartile, the second quartile of total calcium intake had a statistically signiﬁcantly increased stroke risk (1.50; 95% CI 1.06 to 2.11), which became non-signiﬁcant after exclusion of the ﬁrst 2 years of follow-up. For source-speciﬁc calcium intake, the previously observed reduction of MI risk in the third quartile of total calcium intake remained in the third quartile of dairy calcium intake (HR=0.68; 95% CI 0.50 to 0.93; table 3). None of the linear trend tests was statistically signiﬁcant. Further exclusion of supplement users from analyses did not substantially change the risk estimates for total and source-speciﬁc dietary calcium intakes (data not shown).
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As shown in table 4, users of calcium supplements had a statistically significantly increased MI risk in comparison with non-users of any supplements (HR=1.26; 95% CI 1.17 to 2.96). This association was more pronounced for calcium supplement users than non-users of any supplements (HR=1.86; 95% CI 1.17 to 2.96).

In this prospective cohort study, total, dairy, or non-dairy calcium intake did not have an overall statistically significant inverse association with cardiovascular risk, except for a likely reduction of MI risk associated with a moderately higher dairy calcium intake. However, this study also suggests that MI risk might be substantially increased by taking calcium supplements.

The association between dietary calcium intake and MI risk has been rarely reported. In our cohort, a moderately higher dietary calcium intake (the third quartile, mean=820 mg/day) was statistically significantly associated with a 50% lower MI risk. However, this inverse association became non-significant for men (HR=0.80; 95% CI 0.56 to 1.14) but more significant for women (HR=0.43; 95% CI 0.22 to 0.82).

Table 1 Multivariate HRs and 95% CIs for MI and stroke incidence and CVD mortality by quartile of total dietary calcium intake, the EPIC-Heidelberg cohort, 1994—2010

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total dietary calcium intake in quartiles*</th>
<th>Calcium supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile</td>
<td>1 (low) 2 3 4 (high)</td>
<td>Calcium supplements</td>
</tr>
<tr>
<td>Non of participants†</td>
<td>5986 5983 5998 6003</td>
<td>Other supplements</td>
</tr>
<tr>
<td>Total mortality</td>
<td>513 675 820 1130‡</td>
<td>No supplements used</td>
</tr>
<tr>
<td>MI incidence</td>
<td>188 330 466 780‡</td>
<td></td>
</tr>
<tr>
<td>Stroke incidence</td>
<td>324 345 353 351‡</td>
<td></td>
</tr>
<tr>
<td>CVD mortality</td>
<td>3.0 3.2 3.3 3.4‡</td>
<td></td>
</tr>
<tr>
<td>Diet intake of saturated fatty acids* (g/day)</td>
<td>30.0 30.8 31.3 32.3‡</td>
<td></td>
</tr>
<tr>
<td>Diet intake of total protein* (g/day)</td>
<td>65.2 67.3 69.5 74.5‡</td>
<td></td>
</tr>
<tr>
<td>Use of anti-hypertensive drugs (%)</td>
<td>13.0 13.2 13.3 13.4</td>
<td></td>
</tr>
<tr>
<td>Use of calcium supplements (%)</td>
<td>3.1 3.2 3.3 3.4</td>
<td></td>
</tr>
<tr>
<td>Use of NSAIDs (%)</td>
<td>3.5 3.6 3.7 3.8</td>
<td></td>
</tr>
<tr>
<td>Use of antioxidants (%)</td>
<td>3.9 4.0 4.1 4.2</td>
<td></td>
</tr>
<tr>
<td>Use of vitamin D (%)</td>
<td>4.3 4.4 4.5 4.6</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for total energy intake using the residual method. The cut-off points were 603, 748 and 924 mg/ day for men and 610, 738 and 898 mg/day for women.
†Participants with a diagnosis of myocardial infarction, stroke, or transient ischaemic attack at recruitment and participants whose total energy intake fell into the top or bottom 0.5 sex-specific centile (men: <887/5582 kcal/day; women: <703/4381 kcal/day) were excluded.
‡p<0.05. Values are either percentages or means.
§Self-reported.
BMI, body mass index; EPIC, European Prospective Investigation into Cancer and Nutrition; NSAIDS, non-steroidal anti-inflammatory drugs.

DISCUSSION

In this prospective cohort study, total, dairy, or non-dairy calcium intake did not have an overall statistically significant inverse association with cardiovascular risk, except for a likely reduction of MI risk associated with a moderately higher dairy calcium intake. However, this study also suggests that MI risk might be substantially increased by taking calcium supplements.

The association between dietary calcium intake and MI risk has been rarely reported. In our cohort, a moderately higher dietary calcium intake (the third quartile, mean=820 mg/day) was statistically significantly associated with a 50% lower MI risk. However, this inverse association became non-significant for men (HR=0.80; 95% CI 0.56 to 1.14) but more significant for women (HR=0.43; 95% CI 0.22 to 0.82). A possible explanation for this gender-related disparity might be, if we assume that the observed inverse association was false, that a higher dietary calcium intake was associated with certain uncontrolled confounders in women but not in men. In a cohort study of middle-aged and elderly US male health professionals, which has perhaps been the only large-scale study reporting this association so far, no significant results were found, even in participants who had a history of myocardial infarction.
who had similar calcium intakes for which the association was statistically significant in this study. In our cohort, the inverse association was only confined to dairy calcium intake, suggesting a possibility that the inverse association might be caused by other unknown nutrients coexisting in milk products. For instance, three case-control studies have reported an inverse association between dairy fat biomarkers (pentadecanoic and heptadecanoic acid) and the risk of a first-ever MI or cardiovascular risk factors.

Our finding of an overall null association between total, dairy, or non-dairy calcium intake and stroke risk is consistent with the majority of previous findings, although two studies of Japanese/Japanese immigrants and one study of US women observed a statistically significant inverse association. An easy interpretation of this inverse association is that the potential anti-hypertensive effect of calcium might cause an ultimate reduction in ischaemic stroke risk. However, none of these three studies reported a similar reduced risk of haemorhagic stroke, which is equally likely to be caused by hypertensive.
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Table 4  Multivariate HRs and 95% CIs for MI and stroke incidence and CVD mortality by calcium supplementation status, the EPIC-Heidelberg cohort, 1994—2010

<table>
<thead>
<tr>
<th>Supplements</th>
<th>No of cases</th>
<th>HR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Model A</td>
</tr>
<tr>
<td>MI incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-use of any supplements</td>
<td>256</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Calcium</td>
<td>20</td>
<td>1.86 (1.17 to 2.96)</td>
</tr>
<tr>
<td>Calcium only*</td>
<td>7</td>
<td>2.39 (1.12 to 5.12)</td>
</tr>
<tr>
<td>Calcium plus others †</td>
<td>13</td>
<td>1.66 (0.95 to 2.93)</td>
</tr>
<tr>
<td>Other supplements</td>
<td>78</td>
<td>0.75 (0.58 to 0.97)</td>
</tr>
<tr>
<td>Stroke incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-use of any supplements</td>
<td>179</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Calcium</td>
<td>10</td>
<td>1.05 (0.55 to 1.99)</td>
</tr>
<tr>
<td>Calcium only*</td>
<td>1</td>
<td>0.34 (0.05 to 2.47)</td>
</tr>
<tr>
<td>Calcium plus others †</td>
<td>9</td>
<td>1.35 (0.69 to 2.66)</td>
</tr>
<tr>
<td>Other supplements</td>
<td>71</td>
<td>0.87 (0.56 to 1.66)</td>
</tr>
<tr>
<td>CVD mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-use of any supplements</td>
<td>184</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Calcium</td>
<td>9</td>
<td>1.02 (0.51 to 2.00)</td>
</tr>
<tr>
<td>Calcium only*</td>
<td>3</td>
<td>1.20 (0.38 to 3.78)</td>
</tr>
<tr>
<td>Calcium plus others †</td>
<td>6</td>
<td>0.94 (0.41 to 2.15)</td>
</tr>
<tr>
<td>Other supplements</td>
<td>74</td>
<td>0.94 (0.71 to 1.24)</td>
</tr>
</tbody>
</table>

Model A: adjusted for sex, age at recruitment, educational level, physical activity, BMI, smoking categories, lifetime alcohol intake, energy-adjusted total dietary calcium, vitamin D, saturated fatty acid and total protein intake, total energy intake and self-reported hyperlipidaemia and diabetes mellitus at recruitment and use of NSAIDs.

Model B: excluded cardiovascular events that occurred in the first 2 years of follow-up.

Model C: the effects of the most recent supplementation.

Model D: the effects of the cumulative supplementation. The HRs indicate the relative risks for each self-report of supplementation.

*Model: n=236.
†n=695.
BMI, body mass index; CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; MI, myocardial infarction; NSAIDS, non-steroidal anti-inflammatory drugs.

achieve a better understanding of the mechanisms behind the adverse cardiovascular effect of calcium supplementation, its interactions with of parathyroid hormone should be investigated.

Our study has several strengths, such as its prospective design, relatively large sample size and an average follow-up time of more than 10 years. However, this study also has several important limitations.

First, our dietary data contained measurement errors, which are unavoidable in application of a FFQ. In addition, one single measure of dietary nutrient intakes at baseline apparently could not capture the long-term variation, as we know that individuals might modify their diet after onset of certain diseases or enhancement of health consciousness. The same problem also stands for those modifiable lifestyle confounders.

Second, this study only excluded pre-existing MI, stroke and transient ischaemic attack. Failing to exclude individuals with other pre-existing CVD subtypes might attenuate an inverse association with CVD mortality if they were more likely to have a calcium-rich diet than relatively healthy individuals, or the other way round. However, the influence of this incomplete exclusion should be minor, as MI and stroke together account for the vast majority of CVD. There is also no evidence suggesting that individuals with pre-MI conditions are more likely to take calcium supplements. On the contrary, the positive association between calcium supplementation and MI risk was strengthened by exclusion of the first 2-year follow-up.

Third, in most of the clinical trials included in the above-mentioned meta-analyses,26 27 calcium in elemental form was administered at ≥1000 mg/day. Therefore, whether a lower dosage will still pose an extra MI risk should be examined. Unfortunately, this study could not answer this question owing to lack of detailed data.

Lastly, it needs to be noted that 44.5% of vitamin/mineral users in this study did not report the names of their supplements and we therefore only identified a limited number of calcium supplement users, who accounted for 3.6% of all cohort participants. This prevalence is lower than that observed in a small German elderly population (about 8% in men and 27% in women).23 It is also lower than the prevalence (11.0%) reported by a US national survey.25 It is possible that the unreported calcium supplementation would affect the accuracy of our results if identified calcium supplement users had a different cardiovascular risk profile than unidentified calcium supplement users.

In conclusion, this study suggests that increasing dietary calcium intake from diet might not confer significant cardiovascular benefits, while calcium supplements, which might raise MI risk, should be taken with caution.

Acknowledgements The authors thank all cohort participants for their consistent participation. We are also grateful to our colleagues, Marie-Luise Groß, Jutta Schmitt and Dorothee Zoller, for their work in disease verification and data preparation.

Contributors KL: data analysis, result interpretation and manuscript writing. JL, RK and SR: reviewed and commented on the manuscript. RK: administrative and financial support.

Funding This work was supported by the Deutsche Krebshilfe [grant-No 70-488-Ha I] and the Graduiertenkolleg 793: Epidemiology of communicable and chronic non-communicable disease and their inter-relationships.

Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was provided by the ethics committee of the Heidelberg University Medical School.

Provenance and peer review Not commissioned; internally peer reviewed.

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Heart: first published as 10.1136/heartjnl-2011-301345 on 23 May 2012. Downloaded from http://heart.bmj.com/ on May 12, 2022 by guest. Protected by copyright.
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