

Review Article

Calcium intake and hip fracture risk: a meta-analysis of prospective cohort studies

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Abstract: It has been suggested that the amount of calcium intake may influence hip fracture incidence. However, the results of the researches in this regard are inconsistent. We performed this meta-analysis to estimate the association between calcium intake and hip fracture risk. Prospective cohort studies on calcium intake and hip fracture risk were identified by searching databases from the period 1960 to 2014. Results from individual studies were synthetically combined using STATA 11 software. The results indicated that a total of 8 prospective cohort studies were included in our meta-analysis, involving 2,435 cases and 267,759 participants. The combined relative risk (RR) of hip fracture for highest compared with lowest amount calcium intake was 0.97 (95% confidence interval [CI]: 0.89-1.07). Little evidence of publication bias was found. In conclusion, this meta-analysis provides evidence of no association between calcium intake and hip fracture risk. However, this finding is based on only a limited number of included studies.

Keywords: Calcium, hip fracture, prospective cohort study, meta-analysis

Introduction

Hip fractures are the most severe and frequent fractures in old population [1, 2], because they almost always result in hospitalization, lead to permanent disability in about half of patients, and are fatal in approximately 20% of patients [3]. It is suggested that the consumption of calcium-rich foods such as milk may slow down bone loss and reduce the risk of hip fracture. These recommendations are primarily based on evidence from observational studies and randomized controlled trials (RCTs) [4, 5]. However, in 2011, the result of a prospective cohort study suggested that gradual increases in dietary calcium intake in female population were not associated with further reductions in fracture risk [6]. Moreover, in 2004 a meta-analysis of fifteen RCTs including more than 1,800 participants suggested that for postmenopausal women, with supplementation of 500-2000 mg Calcium per day provided only a modest benefit for bone density: 2.05% for total-body bone density, 1.66% for lumbar

spine bone density, 1.60% for hip bone density, and 1.91% for the distal radius [7]. In this research, the authors concluded that calcium supplementation alone plays only a small positive effect on bone density.

Consequently, different recommended daily intakes of calcium exist in different countries which show the uncertainty regarding optimal amount of calcium intake. For instance, it is recommended that, for adults more than 50 years old, the daily adequate intake of calcium is 1200 mg per day in the United States and 700 mg per day in the United Kingdom [8]. Several meta-analyses have assessed the effect of calcium plus vitamin D in RCTs, and their result suggested a small but significant reduction in hip fracture risk [9, 10], but in these studies, the benefit of calcium supplementation was not tested alone. Considering the fact that only increasing calcium intake is also a recommended strategy for preventing fractures [11], the assessment of calcium intake and its effect on hip fracture risk reduction is of clinical and public health importance.

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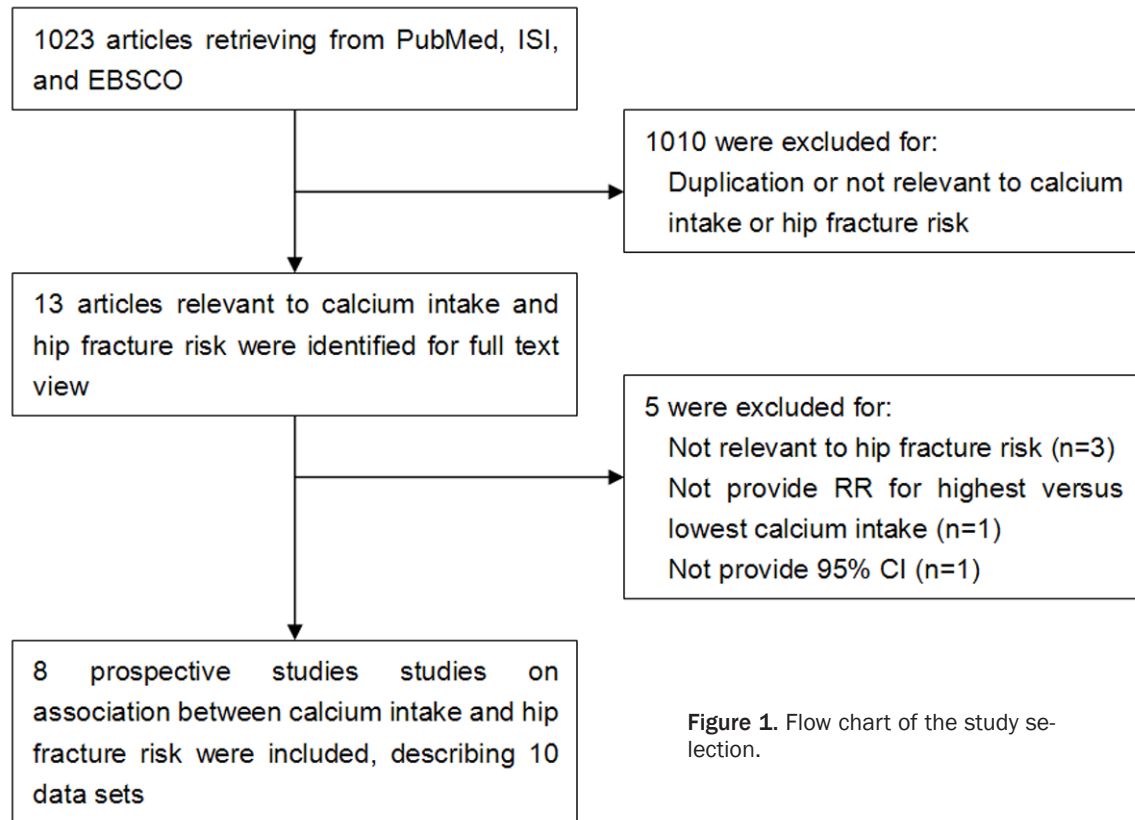


Figure 1. Flow chart of the study selection.

Given the inconsistency of existing literature and the insufficient statistical power of primary studies, we conducted this meta-analysis on prospective cohort studies, which may provide reliable evidence useful in primary prevention of hip in relation to calcium intake and less susceptible to selection and recall biases than are case-control studies.

Methods and materials

Data source

Three databases were electronically searched to retrieve prospective cohort studies on association between calcium intake and hip fracture risk until 31 Jan 2014, including PubMed, EBSCO and ISI web of knowledge. Searching terms were: “calcium”, combined with “fracture” or “hip fracture”, and combined with “cohort studies” or “prospective studies”. Moreover, we checked the reference lists of retrieved articles to identify more studies.

Inclusion and exclusion criteria

We first performed initial screening of titles and abstracts. A second screening was based on full-texts review. Studies were considered eligi-

ble if they meet the following criteria: 1) It was a prospective cohort study in design. 2) The exposure of interest was calcium intake. 3) The endpoint of interest was hip fracture risk. 4) The documents accessed reported the measures on quality control and provided completely original data. The outcomes of the studies reported in the original articles could be expressed as relative risks (RRs), hazard ratios (HRs) or odds ratios (ORs), and their 95% confidence intervals (CIs). Moreover, in the original papers the consensus confounding factors (e.g., age, body mass index, alcohol, smoking, physical activity, etc) were controlled; and (5) when there were several reports concerning the same cohort we included only the last one in the meta-analysis. Accordingly, the following exclusion criteria were carried out: Papers were not taken into consideration when: (1) there were no original data or the original literature could not be accessed; (2) cohorts were based on people with other specific diseases; and (3) in the case of duplication of previously published data.

Data extraction

Two reviewers independently searched and selected literatures, then extracted relevant

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Table 1. Characteristics of prospective cohort studies of calcium intake and hip fracture risk

| Study | Location, period | | Age (years) at enrollment | Length (years of follow up) | Number of cases/size of cohort | Calcium assessment | Adjusted relative risk (95% CI) | Adjusted factors |
|----------------------------|--|---|---------------------------|-----------------------------|-----------------------------------|--------------------|--|--|
| Paganini-Hill et al., 1991 | California retirement community | USA | 73 | 6.8 | Men: 50/2966 Women: 216/5752 | FFQ | Men: 1.11 (0.76-6.46) Women: 1.05 (0.66-1.59) | Age |
| Looker et al., 1993 | NHANES I follow-up study | USA | 50-74 | 16 | Men: 44/2116 Women: 122/2226 | 24-h recall | Men: 0.53 (0.2-1.2) Women: 0.72 (0.4-1.3) | Alcohol, smoking, physical activity, BMI, HRT use |
| Owusu et al., 1997 | Health Professionals Follow-up Study | USA | 54 (40-75) | 8 | Men: 56/43063 | FFQ | Men: 1.19 (0.42-3.35) | Age, BMI, smoking, physical activity, total energy, alcohol, vitamin D intake |
| Cumming et al., 1997 | Study of Osteoporotic Fractures | USA | 71 | 6.6 | Women: 306/9704 | FFQ | Women: 0.9 (0.5-1.7) | Age, clinic, weight, history of fracture since age 50 y, fall in past 12 mo, protein intake, caffeine intake, recreational physical activity, walking for exercise, use of vitamin D supplements and Tums antacids |
| Meyer et al., 1997 | National Health Screening Norway | Norway | 47.1 (40-53) | 13.8 | Men: 49/20035 Women: 154/19752 | FFQ | Men: 0.64 (0.28-1.45) Women: 0.67 (0.42-1.08) | Age, height, BMI, physical activity, DM, disability pension, marital status, smoking |
| Feskanich et al., 2003 | Nurses' Health Study | USA | 34-59 | 18 | Women: 603/72337 | FFQ | Women: 0.90 (0.67-1.21) | Protein intake, retinol intake, total vitamin D intake, age, BMI, postmenopausal hormone use, physical activity, smoking, calcium supplement use, multivitamin use, vitamin K, vitamin A intake, total energy intake, alcohol use, caffeine intake |
| Benetou et al., 2010 | European Prospective Investigation into Cancer and nutrition study | Italy, The Netherlands, Greece, Germany, Sweden | 64.3 (60-86) | 8 | Men: 53/10538 Women: 222/18584 | FFQ | 1.02 (0.91-1.13) | Sex, age, BMI, height, educational level, smoking status, physical activity at leisure, supplement use, history of diabetes at enrolment and total energy intake. |

CI, confidence interval; NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; HRT, hormone replacement therapy; FFQ, food-frequency questionnaire; DM, diabetes mellitus.

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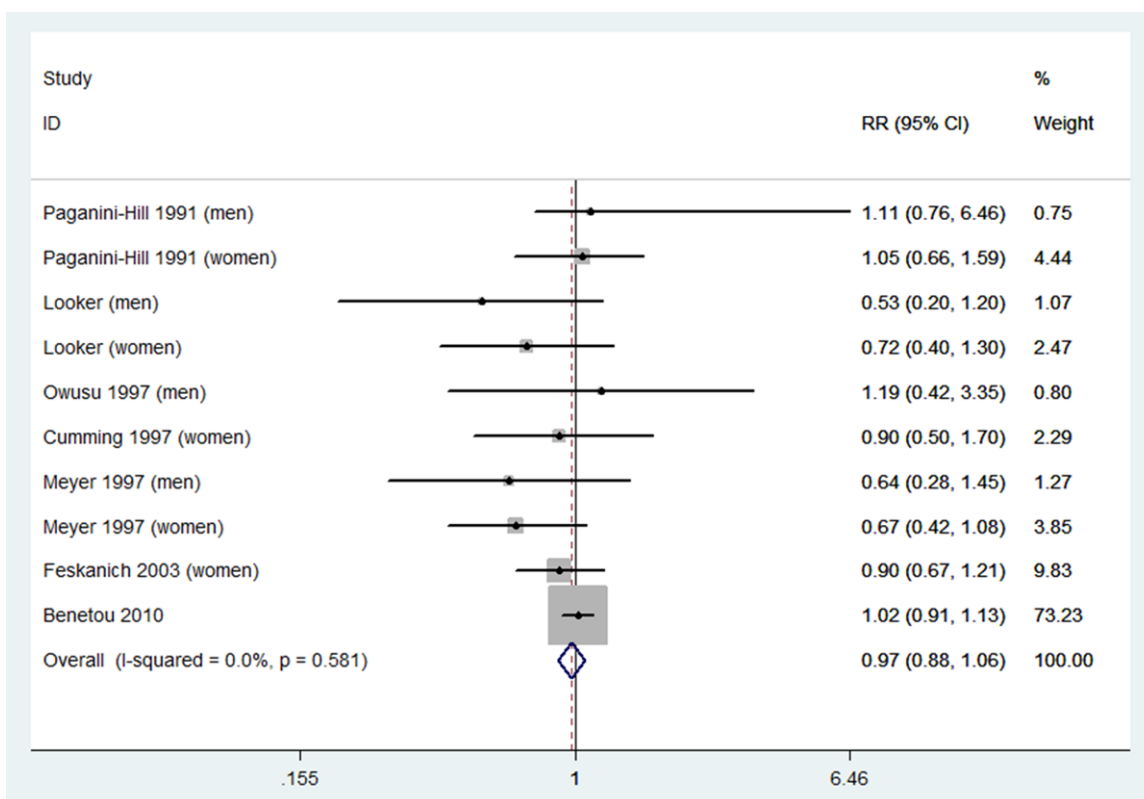


Figure 2. Fix-effects meta-analysis of prospective cohort studies that examined calcium intake and the risk of hip fracture (RR, relative risk; CI, confidence interval).

Table 2. Combined relative risks of hip fracture risk related to calcium intake by characteristics of population and study design

| Group | No. of studies | RR (95% CI) | P-heterogeneity | I ² |
|-----------------------------------|----------------|------------------|-----------------|----------------|
| Total | 10 | 0.97 (0.89-1.07) | 0.58 | 0.0% |
| Gender | | | | |
| Men | 4 | 0.77 (0.48-1.23) | 0.58 | 0.0% |
| Women | 5 | 0.86 (0.71-1.05) | 0.68 | 0.0% |
| Both men and women | 1 | 1.02 (0.92-1.14) | - | - |
| Geographic area | | | | |
| Europe | 3 | 0.99 (0.89-1.10) | 0.84 | 50.0% |
| USA | 7 | 0.90 (0.74-1.10) | 0.14 | 0.0% |
| Length of follow-up | | | | |
| ≤ 8 | 5 | 1.02 (0.92-1.13) | 0.99 | 0.0% |
| > 8 | 5 | 0.78 (0.63-0.97) | 0.68 | 0.0% |
| Adjustment of confounding factors | | | | |
| Age only | 2 | 1.06 (0.71-1.59) | 0.93 | 0.0% |
| Multivariate adjusted | 8 | 0.97 (0.88-1.06) | 0.39 | 4.7% |

data according to data extraction form. Disagreements were solved by discussion. The extracted data including: the first author, year of publication, name of the cohort, age of population at enrollment, length of follow-up, number of cases, size of cohort, calcium intake

assessment methods, and adjusted factors. For outcome statistics, we extracted RRs, ORs or HRs and their 95% CIs of the most fully adjusted model which reported hip fracture incidence in highest calcium intake group compared with lowest calcium intake group.

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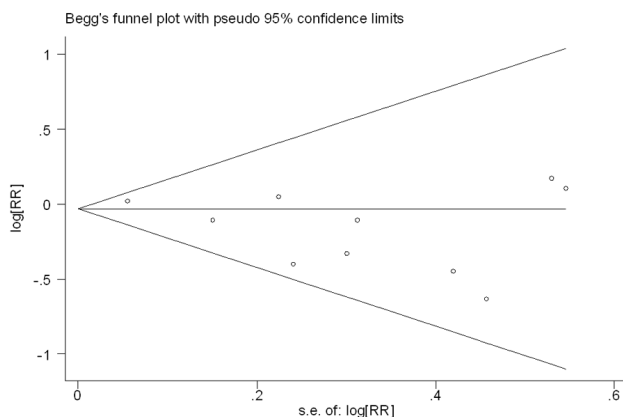


Figure 3. Begg's funnel plot of prospective cohort studies that examined calcium intake and the risk of hip fracture.

Instead of providing aggregate scores, the quality of individual studies was assessed by reporting the key components of cohort design, including characteristics of population, cohort information, and statistical control for potential confounding factors.

Statistical analysis

ORs and their corresponding 95% CI were used to evaluate the strength of association between calcium intake and hip fracture risk. Heterogeneity among included studies was checked by chi-square-based Q test and I^2 test. If the data showed no heterogeneity ($P > 0.10$, $I^2 < 50\%$), Mantel-Haenszel fixed effect model was used, otherwise DerSimonian-Laird random effect model was used. Because characteristics of the population, length of follow-up and adjustments for confounding factors were not consistent among studies, we further conducted subgroup analysis according to these factors to explore the potential differences in these subgroups and possible explanations for heterogeneity. Then, we conducted sensitivity analysis to investigate the influence of any single study on the overall risk estimate by omitting one study in turn. Publication bias was quantitatively assessed by Egger's linear regression test [12] and visual inspection of Begg's funnel plots [13]. Data were analyzed using STATA 11.0 (Stata Statistical Software, College Station, TX, USA, www.stata.com) software.

Results

We initially identified 1023 potentially eligible studies, but most were excluded because they

were not prospective cohort studies or the exposure or endpoint was irrelevant. After assessing the full texts of 13 potentially relevant articles, we identified eight eligible researches, including ten data sets, 2,435 cases and 267,762 participants. A flow chart showing the study selection process is presented in **Figure 1**.

Study characteristics

The characteristics of the included studies are presented in **Table 1**. Of them, five cohorts were conducted in USA, and three in Europe (Italy, the Netherlands, Greece, Germany, Sweden and Norway). Cohort size ranged from 4,342 to 72,337. The duration of follow-up ranged from 6.6 to 18 years, with a median of 10.5 years. In three studies, all participants were women, in one study, all participants were men, and in four studies, both men and women were included. Most original studies measured calcium intake by using a food frequency questionnaire, while in one study, calcium intake was measured by 24-hour food recall. Case ascertainment was not consistent across studies, with some using postcard or telephone interview, and others using medical record. One study only adjusted for age, whereas another seven studies adjusted for a wide range of potential confounders for hip fracture including age, BMI, smoking, alcohol consumption, physical activity, vitamin D intake etc.

Main analysis

The multivariable-adjusted RRs for each study and the combined RR for highest calcium intake level compared with lowest calcium intake level are presented in **Figure 2**. Of the ten data sets, three showed that higher level of calcium intake is associated with higher hip fracture risk, but none of them is statistically significant. The RRs of the association varied from 0.53 to 1.11 across studies. Overall, the combined RR of hip fracture in highest level of calcium intake compared with lowest level of calcium intake was 0.97 (0.89-1.07). Substantial heterogeneity was not observed ($P = 0.58$, $I^2 = 0.0\%$).

Subgroup and sensitivity analysis

The results of subgroup analyses are presented in **Table 2**. The result was not significantly modified when stratified by gender, geographic

area, and adjustment of confounding factors. However, in subgroup analysis stratified by length of follow-up, we found when the length of follow-up is more than eight years, the risk of hip fracture decreases significantly 0.78 (0.63-0.97). Then, sensitivity analysis was conducted to investigate the influence of a single study on the overall risk, estimated by omitting one study in turn. The results showed that no single study did materially alter.

Publication bias

Visual inspection of the Begg's funnel plot did not identify substantial asymmetry (**Figure 3**). The Begg's rank correlation test and Egger linear regression test also indicated no evidence of publication bias among studies assessing whether different level of calcium intake influenced the risk of hip fracture (Begg, $P = 0.85$; Egger, $P = 0.06$).

Discussion

The interest in the association between calcium intake and the risk of hip fracture has existed for a long time. Our meta-analysis of eight prospective cohort studies including 10 data sets shows that no association is related to calcium intake and hip fracture risk. However, in our study, the subgroup analysis stratified by length of follow-up showed that if continuously take high amount of calcium for more than eight years, the risk of hip fracture will be significantly reduced (RR = 0.78, 95% CI: 0.63-0.97).

Our study has some important strength. Comparing with meta-analysis, individual studies usually have insufficient statistical power. Thus, our meta-analysis of eight prospective cohort studies involving nearly 270,000 participants increased the power to detect a potential association and provided more reliable estimates. All the included studies are prospective cohort studies in design, which greatly reduced the likelihood of recall- and selection biases. Moreover, the association between calcium intake and the risk of hip fracture remained unchanged in the sensitivity analysis. In addition, we found a significant relation between calcium intake and hip fracture intake in cohorts with more than eight years of follow-up, which was not pointed out by other studies.

Potential limitations of this meta-analysis should also be considered. Firstly, prospective cohort studies may still be susceptible to bias, including residual confounding factors and loss to follow-up. Secondly, in many included studies, the calcium intake from supplements was not assessed separately from dietary sources, which may influence the results, although heterogeneity was not found between studies assessing calcium intake alone and those from both dietary and supplement sources. Thirdly, in included researches, the information of phosphate intake, physical activity, and baseline 25-hydroxyvitamin D concentrations were insufficient, but these factors may also influence the associations between calcium intake and hip fracture risk [14-16], which is also one of the limitations of our study. Fourthly, a conservative bias to our assessment may be introduced due to misclassification of participants according to the amount of calcium intake. Fifthly, a potential publication bias might influence the findings due to our relatively strict inclusion criteria, although little evidence of publication bias was observed. Finally, the current analysis was only based on studies carried out in European and USA. Therefore, additional research in other populations, especially African and Asian is needed to generalize the findings.

Several reasons may explain the outcome of no association between calcium intake and hip fracture risk. First of all, the amount of calcium intake may be overestimated in some studies which used food frequency questionnaire to assess the amount of calcium intake [17], and this measurement bias, though maybe non-differential, could also mislead the real calcium effect in relation to hip fracture risk. Nonetheless, the correlations between 24-hour diet records and food-frequency questionnaires were high [18] and also in some studies, the validity of calcium intake estimations were measured by comparing with more detailed method [19, 20]. This measurement error may lead to a conservative bias, but with the large number of include cases and total participants, important associations should not have been missed. Furthermore, some of studies that assessed hip fracture data also reported that dietary calcium intake has been inversely associated with colon cancer susceptibility [21], and kidney stones susceptibility [19, 22]. The

results of these studies showed that these calcium intake measures should be accurate enough to detect relations if there is any. Another possible explanation for the negative result is that doctors usually advised patients with recognized osteoporosis to increase calcium intake, which may conceal the inverse association between calcium intake and fracture risk [23]. However, in the Nurses' Health Study, though excluded those women with a history of diagnosed osteoporosis, its negative findings did not significantly change [24, 25].

In addition to the variables we examined, other dietary factors, like the amount of vitamin D intake, protein intake and coffee consumption may influence the effect of calcium on fracture risk. Thus, future studies of the prevention of hip fracture as well as any non-vertebral fracture should not only consider dietary calcium intake or calcium supplementation alone but should also focus on the optimal combination of calcium plus vitamin D, protein and other dietary factors.

In conclusion, this meta-analysis provides evidence of no association between calcium intake and hip fracture risk. More studies, with a sufficiently long follow-up period, are needed to investigate the distinct role of different dietary components including calcium and its interaction with other dietary factors. The overall risks of calcium related outcomes in populations with different prevalence of health problems should also be investigated.

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Disclosure of conflict of interest

None.

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