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META-ANALYSIS

Total, dietary, and supplemental calcium intake and mortality from all-causes, cardiovascular disease, and cancer: A meta-analysis of observational studies

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Abstract *Aims:* This systematic review and meta-analysis of observational studies was conducted to summarize the evidence on the association between calcium intake and mortality.
Methods and results: PubMed, Institute for Scientific Information (ISI) (Web of Science), SCOPUS, SciRUS, Google Scholar, and Excerpta Medica dataBASE (EMBASE) were searched to identify related articles published through May 2014. We found 22 articles that assessed the association between total, dietary, and supplementary intake with mortality from all-causes, cardiovascular disease (CVD), and cancer. Findings from this meta-analysis revealed no significant association between total and dietary calcium intake and mortality from all-causes, CVD, and cancer. Subgroup analysis by the duration of follow-up revealed a significant positive association between total calcium intake and CVD mortality for cohort studies with a mean follow-up duration of >10 years (relative risk (RR): 1.35; 95% confidence interval (CI): 1.09–1.68). A significant inverse association was seen between dietary calcium intake and all-cause (RR: 0.84; 95% CI: 0.70–1.00) and CVD mortality (RR: 0.88; 95% CI: 0.78–0.99) for studies with a mean follow-up duration of ≤10 years. Although supplemental calcium intake was not associated with CVD (RR: 0.95; 95% CI: 0.82–1.10) and cancer mortality (RR: 1.22; 95% CI: 0.81–1.84), it was inversely associated with the risk of all-cause mortality (RR: 0.91; 95% CI: 0.88–0.94).
Conclusions: We found a significant relationship between the total calcium intake and an increased risk of CVD mortality for studies with a long follow-up time and a significant protective association between dietary calcium intake and all-cause and CVD mortality for studies with a mean follow-up of ≤10 years. Supplemental calcium intake was associated with a decreased risk of all-cause mortality.

Introduction

Findings from epidemiological studies have indicated an inverse association between dietary calcium intake and

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risk of hypertension, obesity, and type 2 diabetes [1,2]. In addition, calcium supplements are widely used in elderly population [3]. More than 50% of older men and almost 70% of older women in the United States used calcium supplements [4]. Although the role of calcium in the prevention and treatment of osteoporosis, normal growth, and development of the skeleton and teeth is well established, its effect on nonskeletal outcomes including cardiovascular events or cancers remains largely unknown [5–10]. High calcium intake has been suggested to increase fat excretion [11], which in turn might result in a decreased risk of cardiovascular disease (CVD). By contrast, calcium is present in atherosclerotic lesions, raising the possibility that an increased dietary and supplemental calcium intake may increase the risk of CVD [12,13].

Prior studies have examined the association between calcium intake from diet and supplements and all-cause mortality; however, findings were inconsistent [14–17]. Some prospective studies have reported an inverse association between dietary calcium intake and risk of mortality from CVD [18–20]. Others have shown that not only dietary but also supplemental calcium intake was inversely associated with deaths from CVD [17–21] and prostate cancer [22,23]. In a prospective cohort study, Van der Pols et al. [24] demonstrated that childhood calcium intake was inversely associated with stroke mortality. In another cohort study, calcium supplements, up to 1000 mg/d, and an increased dietary intake of calcium were associated with a reduced risk of mortality in women [17]. With increasing number of older men and women taking calcium supplements to avoid osteoporosis [25], examining the association between calcium intake and mortality is of great interest.

Although several studies have assessed the relationship between dietary and supplemental calcium intake and mortality, we are aware of no meta-analysis that summarized findings from previous publications. Given the inconsistent findings about the association between calcium intake and risk of all-cause mortality, this study aimed to systematically review the current evidence on the association between calcium intake and risk of all-cause, CVD, and cancer mortality, and to summarize the available findings in a meta-analysis, if possible.

Methods

Search strategy

A systematic search of the literature published earlier than May 2014 was conducted in PubMed, Institute for Scientific Information (ISI) (Web of Science), SCOPUS, SciRUS, Google Scholar, and Excerpta Medica dataBASE (EMBASE) by three independent investigators (Z.A., P.S., and S–S.S.) to identify related articles. The following keywords were used in our search strategy: “calcium” OR “milk” OR “dairy” in combination with “mortality” OR “fatal” OR “death” OR “survive.” All keywords were selected from the Medical Subject Headings (MeSH) database. In addition, a manual search of references of the published papers was performed to find other relevant articles. No language and time restrictions were applied. No attempt was made to include unpublished studies. Duplicate citations were then removed. The full text of related articles was obtained, in some cases, by contacting the corresponding author.

Eligibility criteria

The following inclusion criteria were adopted: (1) observational cohort or nested case–control studies that considered any source of calcium intake (total, dietary, or supplemental) and all-cause or specific cause of mortality; (2) publications that had provided estimates of relative risks (RRs) (odds ratios (ORs), hazard ratios (HRs), or rate ratios) with corresponding 95% confidence intervals (CIs). Studies that met these criteria were included in our analysis.

Excluded studies

Totally, 1522 articles were found in our initial search. We excluded 1428 articles through reading the title and abstract. The other 72 papers were excluded because of the following reasons: animal study ($n = 1$), studies that examined the effects of calcium plus vitamin D co-supplementation on mortality ($n = 3$), or assessed the relationship between serum calcium levels and mortality ($n = 45$) or reported the effects of dairy intake, not calcium separately, on mortality ($n = 23$). Finally, 22 prospective cohort studies [2,3,5,6,10,14–17,21,24,26–36] were included in this meta-analysis (Fig. 1). Out of these 22 studies, four studies had reported the association between total, dietary, and supplemental calcium intake with mortality [14,21,27,36], seven papers had assessed the association between total and dietary calcium intake and mortality [14,15,21,27,28,31,36], five studies had examined the association between total and supplemental calcium intake and mortality [14,21,27,32,36], and seven papers had reported the association between dietary and supplemental calcium intake, but not total calcium intake, with mortality [2,3,5,14,21,27,36]. When two studies had reported data for all-cause mortality from the same population [33,35], we only included the study with the larger sample size in the analysis [33], to avoid double-counting data [37,38]. We extracted the RRs for the highest versus the lowest calcium intake; however, in two articles the reference for comparisons was the subjects who had the highest intake of calcium [33,35]. Therefore, we converted the reported RRs and CIs in these two studies to obtain the RRs and CIs for subjects with the highest intake versus the subjects who had the lowest intake as reference. One study had nested the case–control design [10]. Due to the similarity of exposure assessment in such study designs to cohort studies, we included this publication in our analysis.