

Evaluation of Cardiovascular Risks Associated with Calcium Use: A Systematic Review and Meta-Analysis

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Abstract

Background: Calcium plays vital roles in both physiological and pathological processes, and its use as a therapeutic agent is primarily indicated for osteoporosis and osteopenia. It may increase cardiovascular risk, thereby increasing cardiovascular morbidity and mortality.

Objective: To synthesize the available evidence on cardiovascular risks in patients using calcium-based medications and supplements.

Methods: This systematic review and meta-analysis utilized three major international databases and included intervention studies and comparative observational studies with data on the intake of calcium-based medications or supplements in adult populations and associated cardiovascular outcomes. A p-value < 0.05 was considered for all analyses, and the certainty of evidence was assessed using the GRADE approach.

Results: A total of fourteen articles were included: three pivotal intervention studies, four post hoc analyses, and seven observational studies. The outcomes assessed were mortality from cardiovascular events, myocardial infarction, stroke, and coronary artery disease. Although an increased incidence of coronary artery disease was observed among users of calcium-based medications or supplements when considering only observational studies (RR 1.08; 95% CI 1.02–1.15), this finding was not confirmed in interventional studies. Therefore, further investigation is warranted. No increased risk of cardiovascular mortality, myocardial infarction, or stroke was observed. The quality of the evidence was considered low or very low for all outcomes due to the risk of bias and limitations inherent to the meta-analyses themselves.

Conclusions: Caution is recommended when interpreting the results, particularly in the development of clinical protocols. The importance of pharmacotherapeutic monitoring for patients using these medications is emphasized, and further research to explore additional outcomes is suggested.

Keywords: Calcium; Calcium Compounds; Heart Disease Risk Factors; Systematic Review.

Introduction

Calcium is the most abundant mineral in the human body.¹ The biochemical and metabolic processes that regulate calcium ion concentrations are complex and involve the gastrointestinal, renal, and skeletal systems. These systems maintain calcium concentrations in extracellular and circulating fluids at constant levels through transport mechanisms.¹ Regulation of these processes involves the action of hormones, notably parathyroid hormone (PTH), vitamin D, calcitonin, and estrogens (such as estriol and estradiol), which are primarily used in women.^{1,2}

Calcium is widely prescribed or recommended as a therapeutic agent or dietary supplement. Furthermore, calcium is included in clinical protocols and therapeutic guidelines for certain health conditions, particularly osteoporosis, osteopenia, and the reduction of fracture incidence.^{3,4}

It is important to note that access to calcium-based medications and supplements in Brazil is relatively easy and inexpensive, with free distribution through the Unified Health System (SUS). This expanded access allows a greater number of individuals to benefit from supplementation, particularly at-risk groups such as older adults and postmenopausal women. Conversely, there is evidence demonstrating an increased cardiovascular risk in patients using calcium-based medications or supplements. The focus is on the association between calcium and vascular calcification and atherosclerosis, potentially leading to increased cardiovascular morbidity and mortality.^{2,5,6}

In this context, the aim of this study was to synthesize the available evidence regarding the presence of cardiovascular risks in patients using calcium-based medications and supplements.

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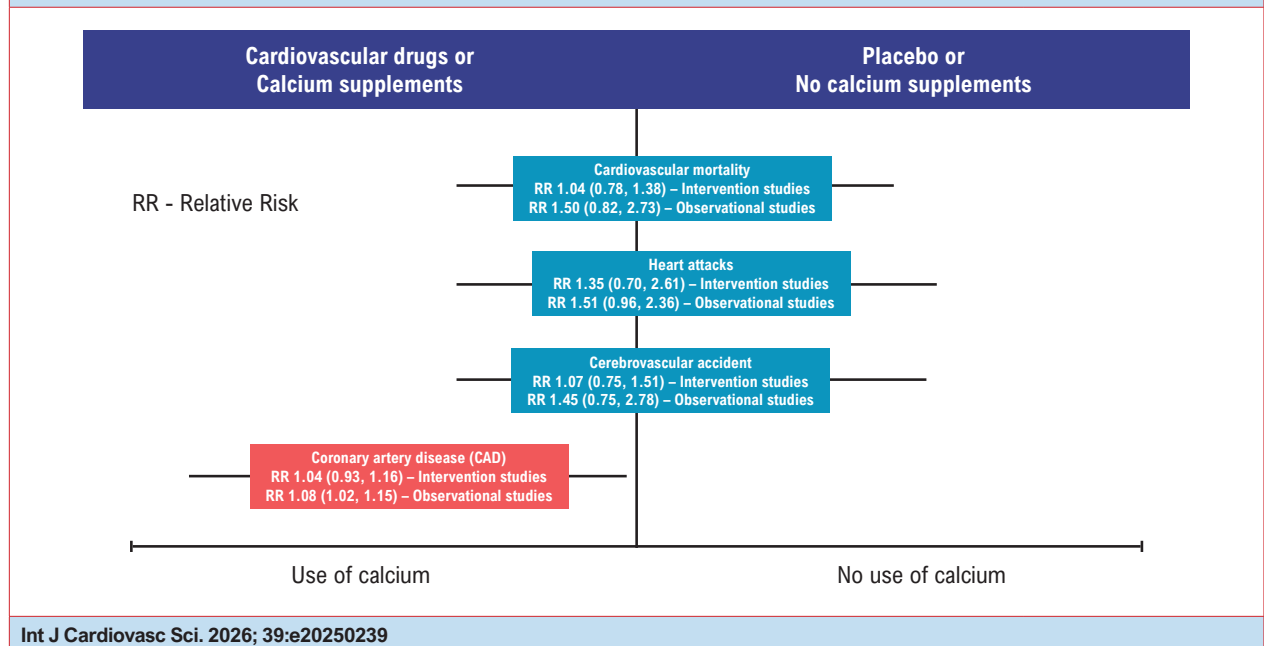
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Manuscript received October 27, 2025; revised manuscript March 10, 2026; accepted March 24, 2026.

Editor responsible for the review: Glaucia Maria Moraes de Oliveira

DOI: <https://doi.org/10.36660/ijcs.20250239>

Central Illustration: Evaluation of Cardiovascular Risks Associated with Calcium Use: A Systematic Review and Meta-Analysis

Int J Cardiovasc Sci. 2026; 39:e20250239

Methods

Study design

This systematic literature review with meta-analysis was conducted in accordance with the methodological guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and reported in accordance with the PRISMA⁷ recommendations (Table S1 – Supplementary Material). The study protocol was registered on the PROSPERO platform on June 17, 2023 (CRD42023429824).

Search strategy

The research question was based on the PICOS framework - population (P), intervention (I), comparator (C), outcomes (O), and study design (S) - which were defined as follows:

- P:** Adult individuals.
- I:** Use of calcium-based medications or supplements (with or containing calcium).
- C:** Any other active treatment; use of any type of supplement; placebo; no treatment.
- O:** Mortality from cardiovascular events or any other cardiovascular event or associated risk.
- S:** Interventional studies and observational studies with a comparator.

Searches were conducted in the PubMed, EMBASE, and LILACS databases between July 1, 2022, and April 30, 2025. The search strategy included descriptors related to calcium-based medications and supplements and cardiovascular risks, which were combined using the Boolean operators OR and AND. Details

of the search strategies used for each database are available in the supplementary material (Table S2).

In addition, a manual search of the bibliographic references of the selected studies was performed.

Inclusion criteria

Primary observational and interventional studies that assessed cardiovascular risk in individuals using calcium-based medications or supplements were included.

The inclusion of both interventional and observational studies was justified by the interest in evaluating outcomes in controlled clinical settings through interventional studies, as well as in real-world settings, where patients were embedded in their social and healthcare contexts, through observational studies.

In addition, post hoc analyses of previously published pivotal studies were included, even if not specified in the protocol. This decision was made by mutual agreement among all members of the research team, as it was noted during the eligibility stage that several post hoc analyses met the research criteria and were therefore included in the study.

Exclusion criteria

Articles published in non-Roman scripts (e.g., Chinese, Japanese) were excluded, as were studies in which the target population was not adults and/or in which the medication and/or supplement was administered via a route other than oral.

Identification and selection of studies

Articles identified through the searches were exported to EndNote[®] software, where duplicates were removed.

Subsequently, the records were uploaded to the Rayyan® platform. Two authors independently selected the studies, following these steps: (1) screening (review of titles and abstracts) and (2) eligibility (full-text review). Any disagreements between the authors were resolved by consensus, and a third reviewer was involved when necessary.

Data extraction

The following study characteristics were extracted:

Regarding the study: study design and type, year of publication, country in which the study was conducted, and number of participants.

Regarding participant characteristics: data such as age, sex, ethnicity, comorbidities, type of therapy used and evaluated (medication or supplement use), as well as dosage, regimen, and duration of follow-up.

Regarding outcomes: associated cardiovascular risk, method used to assess cardiovascular risk, any other significant health conditions, and main study conclusions.

The data extraction process was performed independently by two authors, and discrepancies were resolved by a third reviewer. Microsoft Excel was used for data recording, extraction, and management.

Risk of bias analysis

The risk of bias assessment of the included studies was performed independently by two reviewers, with a consensus meeting held to compare and reconcile the assessments. Discrepancies were resolved by a third reviewer.

Primary observational studies were assessed using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool, and interventional studies were assessed using the Risk of Bias Tool for Randomized Trials (RoB 2.0).

Analysis of the quality of evidence

To assess the quality of the evidence, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was applied to each included outcome. The assessment was performed by two independent authors, and discrepancies were resolved through discussion with a third reviewer.

Statistical analysis

Statistical analysis (meta-analysis) was conducted using Review Manager® (RevMan) software, based on data extracted from the studies.

Analyses were performed using a random-effects model, applying the Mantel–Haenszel method for dichotomous outcomes. The effect measure used was relative risk (RR) with a 95% confidence interval (CI) and a significance level of 0.05. Heterogeneity was analyzed using the I^2 value, and sensitivity was explored in analyses in which the I^2 value was above 50%, which is considered a high level of heterogeneity.⁷

These decisions were made and agreed upon by all researchers to standardize the analyses and reduce the risk of bias by proportionally weighting the contribution of each study

to the meta-analysis, considering differences in populations and outcomes across studies.

Subgroup analysis

Subgroup analyses were performed in populations specified in the protocol and included patients using calcium with or without vitamin D, as well as female patients.

Results

Study Identification and Selection

The database search identified 3,276 records, of which 46 were duplicates, resulting in a total of 3,230 records. No eligible studies were identified through the manual search. None of the retrieved records was excluded due to non-Roman characters. After the screening process, 95 studies were selected for full-text review, of which 79 were excluded based on the eligibility criteria (Table S3 – Supplementary Material), and 2 were not available in the databases. At the end of the selection process, 14 studies were included for qualitative analysis as well as quantitative analysis (meta-analysis) (Figure 1).

Characteristics and Main Findings of the Included Studies

Regarding interventional studies, seven articles were included, corresponding to three studies (Table S4 – Supplementary Material).

All seven were double-blind randomized clinical trials (RCTs), in which the interventions compared calcium in specific molecular forms with placebo.

All RCTs evaluated only female patients, with Bolland et al., 2008,⁸ Boursiquot et al., 2009,⁹ Cauley et al., 2013,¹⁰ and Hsia et al., 2007¹¹ restricting the population to postmenopausal women, that is, women in whom this condition had already been established and was present at the time of the study.

Regarding potential conflicts of interest, only the study by Hsia et al., 2007¹¹ reported receiving funding from a pharmaceutical company. The other studies reported no such funding.

The studies by Lewis et al., 2011,¹² Bolland et al., 2008,⁸ and Hsia et al., 2007¹¹ are pivotal studies, whereas the studies by Boursiquot et al., 2009,⁹ Cauley et al., 2013,¹⁰ Kato et al., 2023,¹³ and Prentice et al., 2013¹⁴ are post hoc studies related to the study by Hsia et al., 2007.¹¹

A 0.05 significance level was adopted for all included studies.

Regarding observational studies, seven articles were included (Table S5 – Supplementary Material).

The study by Godinho et al., 2021¹⁵ was the only Brazilian study and also the only cross-sectional study. The methodology was based on collecting data from women using calcium-based medications or supplements at the time of the study and whether they had reported the outcomes assessed. Because the data were collected at a specific point in the evaluation timeline, the study was included; however, it was not possible to perform a meta-analysis with the data obtained.

All six other studies were cohort studies, with Harvey et al., 2018,¹⁶ Li et al., 2012,¹⁷ and Pentti et al., 2009¹⁸ being prospective

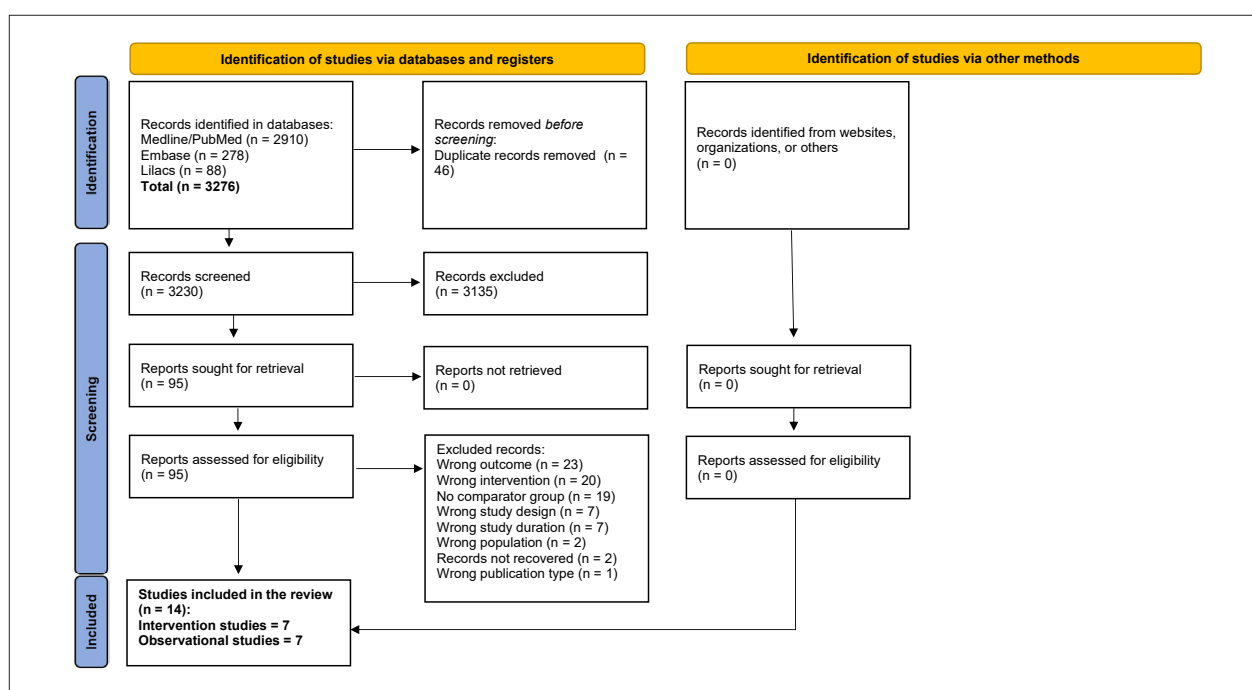


Figure 1 – PRISMA flowchart for article selection. Source: The author, 2024

cohorts, and Kassis et al., 2022,¹⁹ Kim et al., 2022,²⁰ and Park et al., 2022²¹ being retrospective cohorts.

Three studies evaluated calcium in combination with vitamin D: Godinho et al., 2021,¹⁵ Kassis et al., 2022,¹⁹ and Kim et al., 2022.²⁰ The remaining studies did not mention the possibility of combining vitamin D in the supplements administered to participants.

The studies by Godinho et al., 2021¹⁵ and Pentti et al., 2009¹⁸ were the only ones to evaluate women exclusively, whereas the others evaluated both men and women.

Regarding potential conflicts of interest, only researchers in the study by Harvey et al., 2018¹⁶ declared having received funding from different pharmaceutical companies. The other studies reported not having received any.

A 0.05 significance level was adopted for all included studies.

Risk of Bias in Included Studies

The reported data were correlated with the outcome data analyzed in this review, and the final results are presented in the supplementary material (Tables S6 and S7).

For interventional studies, the main concern was related to domain 5, which refers to bias in the selection of reported outcomes. No studies were penalized for the other domains.

Regarding the risk of bias analysis for observational studies, penalties occurred in domains 1, 3, 5, and 6, referring, respectively, to bias due to confounding, bias in the classification of interventions, bias due to missing data, and bias in the measurement of outcomes.

Meta-analyses

Among the outcomes eligible for meta-analysis, four were included: mortality from cardiovascular events, occurrence

of heart attacks, occurrence of strokes (ischemic stroke), and occurrence of CAD.

The meta-analyses were stratified according to study design. A subgroup analysis was performed including patients using calcium combined with vitamin D. The analysis of pre-established health conditions, as proposed in the protocol, was not performed due to a lack of available data in the included studies.

Furthermore, in meta-analyses involving interventional studies, priority was given to including only the pivotal study rather than post hoc analyses, whenever possible, in accordance with studies derived from the same pivotal study.

The results obtained are presented in Figure 2 (interventional studies) and Figure 3 (observational studies).

A meta-analysis was also performed considering only the subgroup of observational studies in which the intervention evaluated was the use of calcium-based supplements combined with vitamin D, as shown in Figure 4. Two studies were evaluated, which demonstrated no difference between the group of patients using calcium-based and vitamin D supplements and those not using supplements (RR 1.30; 95% CI [0.46; 3.67]), although with high heterogeneity ($I^2 = 93\%$; $p = 0.0002$). Sensitivity analyses were not possible because only two studies were analyzed.

It was possible to perform three sensitivity analyses in meta-analyses presenting high heterogeneity ($I^2 > 50\%$), namely: (i) the outcome of cardiovascular event mortality in interventional studies, (ii) the outcome of cardiovascular event mortality in observational studies, and (iii) the outcome of myocardial infarction occurrence in observational studies.

Among these, for outcome (ii), the removal of the study by Kim et al.,²⁰ 2022 was identified as responsible for the observed heterogeneity value. The study was reviewed to investigate

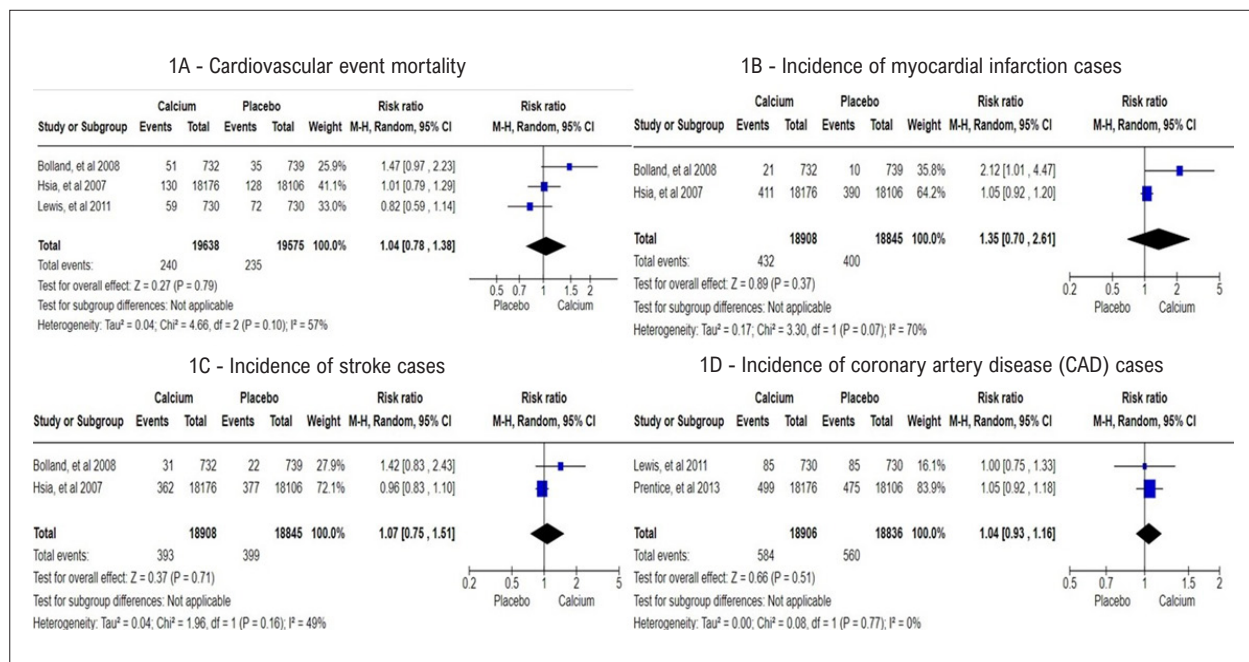


Figure 2 – Outcomes Assessed – Intervention studies. SOURCE: The author, 2025. CI: confidence interval; M-H: Mantel-Haenszel analysis; RR: risk ratio; CAD: Coronary Artery Disease.

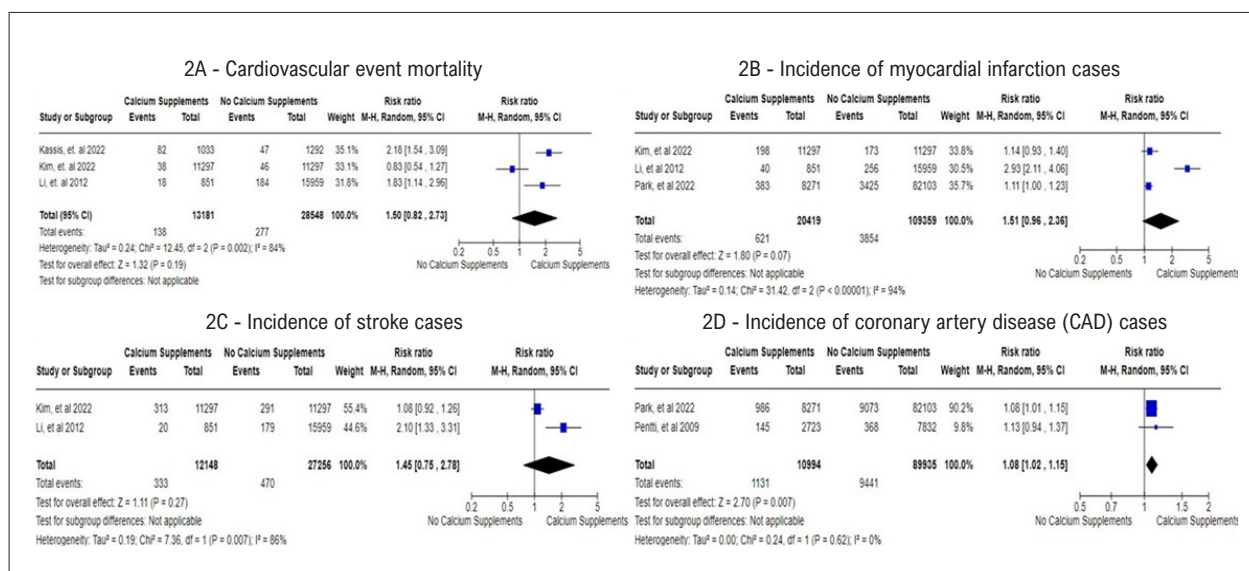


Figure 3 – Outcomes Assessed – Observational studies. SOURCE: The author, 2025. CI: confidence interval; M-H: Mantel-Haenszel analysis; RR: risk ratio; CAD: Coronary Artery Disease.

potential clinical, methodological, and/or statistical variability, and one possible difference identified was that the study population was of Asian origin, whereas the remaining studies primarily included Caucasian populations. No other relevant differences were identified upon review of the study.

For outcome (iii), the study by Li et al., 2012,¹⁷ was identified as responsible for the observed heterogeneity. The study was reviewed to assess potential clinical, methodological, and/or

statistical variability, and one possible difference was that the study population was of Caucasian origin, whereas the other two studies primarily included Asian populations. No additional differences were identified during the review of the study.

Furthermore, additional subgroup analyses or sensitivity analyses were not feasible due to the insufficient number of records (more than one) required to support the development of statistical analyses.

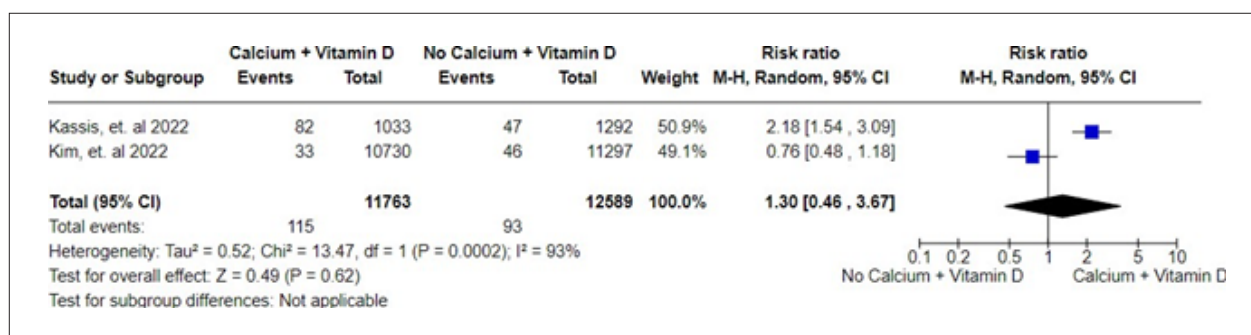


Figure 4 – Mortality due to Cardiovascular Events – Observational studies – Calcium + vitamin D subgroup. Source: The author (2025). CI: confidence interval; M-H: Mantel-Haenszel analysis; RR: risk ratio.

Assessment of the quality of evidence (GRADE)

The results of the quality of evidence assessment generated using the GRADE tool²² were grouped and are presented in Table S8 for intervention studies and Table S9 for observational studies, available in the supplementary material.

Penalties occurred in three of the tool's domains: (i) related to risk of bias: a severe penalty was applied due to studies included in the outcomes presenting bias in at least one assessment domain; (ii) related to inconsistency: the outcomes were penalized for presenting heterogeneity, considering high I² values and statistically significant p values, as well as studies that did not share a CI with the diamond; and (iii) related to imprecision: a penalty was applied for CIs greater than or less than 50% of the baseline and for non-symmetry of the final results of the diamonds obtained.

The central figure represents a summary of the main findings of this article.

Discussion

Calcium, essential for various physiological functions, is widely used as a supplement, particularly in the prevention and treatment of osteoporosis and fractures. In Brazil, its easy access and free distribution through the SUS primarily benefit older adults and postmenopausal women. However, recent studies have highlighted potential cardiovascular risks associated with its use, particularly due to its association with vascular calcification and atherosclerosis. Therefore, investigating these potential adverse effects is essential to guide safe and effective clinical practice.

The data statistically demonstrated a higher incidence of CAD in patients using calcium-based medications or supplements compared with the control group in observational studies. However, this was not observed in the meta-analysis of the RCTs. Observational studies may be susceptible to residual confounding; therefore, these findings should be interpreted with caution, and further studies are required for this assessment. Considering the other three main outcomes evaluated in the meta-analyses, aside from the occurrence of CAD in observational studies, no higher incidence of cardiovascular events associated with the use of calcium-based medications or supplements was found (Central Illustration).

Considering other published studies addressing the topic in a similar manner, three systematic reviews with meta-analyses

were identified, with results that may be useful and comparable to this study.

The study by Yang et al., 2020,²³ performed a meta-analysis of prospective cohort studies on the relationship between dietary calcium intake and mortality from cardiovascular events. That study found no association between the amount of calcium intake and an increased risk for a given outcome. Although that study only considered calcium intake through diet, it is possible to establish a reasonable correlation between its findings and those obtained in the present meta-analysis. This is because the calcium doses evaluated by Yang et al., 2020,²³ ranged from 250 to 1600 mg of calcium per day, in populations of both male and female participants, and the data collection and follow-up periods ranged from 5.5 to 28 years, all of which were also represented in the present meta-analysis.

It is important to highlight that, in this meta-analysis, the primary objective was to analyze calcium in the form of medications or supplements. However, studies in which dietary calcium was combined with the medications and supplements evaluated were permitted. In all studies in which this combination was permitted and reported, no differentiation was made between events occurring in patients using only the medication or supplement and those using them in combination with dietary calcium, which may introduce some limitations to the data obtained and analyzed.

In the study by Asemi et al., 2015,²⁴ the association between calcium and the occurrence of total mortality, cancer mortality, or cardiovascular events was also statistically evaluated in observational studies. The authors found no statistically significant evidence of an association between cardiovascular mortality and any of the three groups evaluated, whether considering calcium intake from supplements, food, or total intake from both calcium sources.

Finally, the study by Chung et al., 2016,²⁵ evaluated the risk of mortality due to cardiovascular events, such as CAD and stroke, in comparison with populations using calcium from diet or supplements and control groups. Although no statistically significant evidence of an increased occurrence of any of the evaluated outcomes was found among the population groups assessed, the authors emphasized caution in the interpretation of these results. This caution was mainly attributed to four factors: the possibility of publication bias related to language, since only studies published in English were included; the lack of data on

total calcium intake, particularly from dietary sources; the lack of data on events occurring in populations exposed to higher-than-usual daily calcium doses; and, finally, the substantial variability in statistical methods used across the included studies, which limited comparability and the ability to perform meta-analytic statistical analyses that could reduce biases arising from this heterogeneity.

No systematic reviews with meta-analyses were found that evaluated cardiovascular outcomes such as CAD, myocardial infarction, and ischemic stroke in intervention studies, nor specifically the myocardial infarction outcome assessed in the present study, either in intervention or observational studies. Therefore, the first and main strength of the present study was the performance of a meta-analysis of the included intervention studies for the four evaluated outcomes, including three that had not been previously analyzed. Furthermore, it was also possible to extract results for the myocardial infarction outcome in both intervention and observational studies. These analyses provided new data on the occurrence of previously unclarified cardiovascular outcomes, contributing to the investigation of their occurrence in the evaluated population.

It is also worth noting that no study presented results for the evaluated outcomes considering subgroups of patients with any type of reported comorbidity. When considering the evaluated outcomes, it would be important to assess results for this subgroup of patients, since the presence of comorbidities could influence the final results. Since this was not possible, there is no way to accurately account for comorbidities in the occurrence of the analyzed outcomes.

Regarding the risk of bias assessments of the studies, it is noteworthy that, of all studies included in the qualitative and quantitative analyses, only three studies did not receive any type of penalty in the domains of the tools used. This information demonstrates the need for greater rigor and methodological control in the conduct and publication of studies, as this directly affects the analyses performed in systematic reviews with or without meta-analyses.

A large proportion of patients using calcium are predominantly female, often using medications or supplements for preventive or therapeutic purposes due to age and health status. Therefore, the results of this study contribute to decision-making in the development, management, and maintenance of clinical protocols involving the use of calcium, with essential pharmacotherapeutic monitoring in the prescription and use of medications or supplements.

Regarding potential limitations of this study, the low number of studies in which meta-analyses could be performed should be highlighted, considering both the main analyses and the only subgroup that could be analyzed, which was the use of calcium in association with vitamin D, evaluated only for the outcome of mortality due to cardiovascular events. In other words, it is not possible to determine, based on a high level of evidence, the degree of impact of vitamin D on the analyzed outcomes.

Considering the high degree of heterogeneity observed in some meta-analyses, the level of evidence obtained through the GRADE approach, and the hierarchical classification of the analyzed studies, comprising both interventional and observational designs, extreme caution is required when interpreting the results and attempting to apply them in evidence-based clinical practice.

Furthermore, periodic updating of this meta-analysis is warranted, not only to incorporate updated data for the evaluated outcomes but also to enable the inclusion of new studies that may emerge.

Conclusion

Based on the results of this study, particularly the meta-analyses, although an increase in CAD cases was observed in patients using calcium-based medications or supplements compared with those in the control group, this finding was observed only in observational studies, and no difference between groups was identified in the RCTs. Therefore, these findings should be interpreted with caution and further investigated in future studies. For the other outcomes, no statistically significant evidence was found associating the use of calcium in medications or supplements with a higher risk of mortality from cardiovascular events, myocardial infarction, or ischemic stroke. These findings indicate that, based on the data analyzed, calcium does not appear to increase the risk of these conditions.

Furthermore, as a perspective for future research in this area, it would be possible to conduct and develop meta-analyses including other outcomes related to the topic that have not yet been evaluated in this or other studies, as well as to monitor new intervention or observational studies that could be included to update the data from the present study.

Author Contributions

Conception and design of the research, statistical analysis, writing of the manuscript and critical revision of the manuscript for intellectual content: Gouveia PH, Souza AW; acquisition of data and analysis and interpretation of the data: Gouveia PH, Guimarães JS, Souza AW.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Gouveia PH, from Universidade Federal do Paraná (UFPR).

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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*Supplemental Materials

For additional information, please click here.



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