Review Article
DOI: https://doi.org/10.70749/ijbr.v3i5.1398

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Association Between Subclinical Magnesium Deficiency and Major Cardiovascular Events: A Systematic Review and Meta-Analysis

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ARTICLE INFO

Keywords: Magnesium Deficiency, Cardiovascular Disease, Coronary Heart Disease, Meta-Analysis

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Declaration
Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History
Received: 05-02-2025 Revised: 14-04-2025
Accepted: 03-05-2025 Published: 23-05-2025

ABSTRACT

Background: Subclinical magnesium deficiency has emerged as a potential modifiable factor in cardiovascular disease (CVD) risk. Although previous studies have examined its association with adverse cardiovascular outcomes, findings remain inconsistent. This systematic review and meta-analysis aimed to evaluate the association between subclinical magnesium deficiency and the risk of major cardiovascular events. **Methods:** A comprehensive literature search was conducted using PubMed, Scopus, Embase, and Web of Science from January 2000 to March 2024. Observational studies assessing the relationship between subclinical magnesium deficiency and outcomes including coronary heart disease (CHD), sudden cardiac death (SCD), stroke, and cardiovascular mortality were included. Data extraction, quality assessment (using NOS and AXIS tools), and meta-analysis were performed according to PRISMA guidelines. Pooled hazard ratios (HRs) or odds ratios (Ors) with 95% confidence intervals (Cis) were calculated using a random-effects model. **Results:** Three studies with a total of 56,448 participants met the inclusion criteria. Subclinical magnesium deficiency was significantly associated with an increased risk of CHD mortality (HR = 1.36, 95% CI: 1.09–1.69), sudden cardiac death (HR = 1.54, 95% CI: 1.12–2.11), cardiovascular mortality (HR = 2.01, 95% CI: 1.49–2.71), and stroke incidence (OR = 1.96, 95% CI: 1.55–2.49). Additionally, each standard deviation increase in serum magnesium level was associated with 21% lower odds of composite cardiovascular events (OR = 0.79, 95% CI: 0.70–0.89). The included studies exhibited low statistical heterogeneity, and funnel plots showed no significant publication bias. **Conclusion:** This meta-analysis provides strong evidence that subclinical magnesium deficiency is independently associated with elevated risk of major cardiovascular events. Routine assessment of magnesium status may serve as a cost-effective tool for early identification of at-risk individuals. Further randomized trials are warranted to evaluate the therapeutic impact of magnesium supplementation in cardiovascular prevention.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, accounting for approximately 17.9 million deaths each year [1]. Traditional risk factors such as hypertension, hyperlipidemia, diabetes mellitus, and smoking are well recognized, yet growing attention is being directed toward non-traditional risk markers, including micronutrient imbalances. Among these, magnesium deficiency has emerged as a potential, modifiable contributor to cardiovascular pathology [2,3].

Magnesium plays a critical role in various physiological processes, including myocardial excitability, vascular tone, endothelial function, and thrombosis regulation [4]. It is a vital cofactor for over 300 enzymatic reactions involved in cellular metabolism and neuromuscular conduction [5]. Despite its significance, subclinical magnesium deficiency often remains undiagnosed due to the lack of routine

screening and the limited sensitivity of serum magnesium measurements [6].

Subclinical magnesium deficiency—characterized by serum levels within the lower reference range or marginally below the clinical cutoff—has been increasingly linked with elevated cardiovascular risk. Observational studies have reported associations between lower magnesium levels and adverse outcomes such as coronary artery disease, stroke, sudden cardiac death, and arrhythmias [7,8]. For instance, a large prospective study by Kieboom et al. found that individuals with serum magnesium concentrations ≤0.80 mmol/L exhibited significantly higher risks of CHD mortality and sudden cardiac death compared to reference levels [9]. Similarly, data from the NHANES cohort demonstrated that higher magnesium depletion scores were associated with increased all-cause and cardiovascular mortality [10].

Mechanistically, magnesium deficiency promotes systemic inflammation, endothelial dysfunction, oxidative stress, and sympathetic overactivation—all of which contribute to atherogenesis and cardiovascular events [11,12]. Furthermore, experimental studies suggest that magnesium can modulate vascular smooth muscle tone and inhibit platelet aggregation, reinforcing its anti-ischemic potential [13].

Despite mounting evidence, the association between subclinical magnesium deficiency and cardiovascular outcomes remains inconsistently reported, partly due to heterogeneity in study designs, populations, and magnesium measurement thresholds. Some studies support a strong relationship, while others report null findings, raising concerns regarding methodological variability and residual confounding [14].

Given these inconsistencies and the growing clinical relevance of magnesium in cardiovascular health, a comprehensive synthesis of existing evidence is warranted. This meta-analysis aims to systematically evaluate the association between subclinical magnesium deficiency and the risk of major cardiovascular events—including coronary heart disease, stroke, and cardiovascular mortality—using data from population-based observational studies. By aggregating effect estimates and assessing study quality, this review seeks to clarify the prognostic utility of magnesium status and inform future clinical guidelines for cardiovascular risk assessment and prevention.

METHODS AND MATERIALS

Study Design

This meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to evaluate the association between subclinical magnesium deficiency and cardiovascular outcomes. The protocol was defined a priori, and studies were selected based on rigorous inclusion and exclusion criteria.

Eligibility Criteria

Included studies were observational (cohort, case-control, or cross-sectional) and assessed the relationship between magnesium levels and cardiovascular outcomes such as coronary heart disease (CHD), sudden cardiac death (SCD), stroke, or cardiovascular mortality. Studies were included if they (a) involved adult populations, (b) reported clear definitions of subclinical magnesium deficiency, (c) provided effect estimates (HR or OR) with confidence intervals, and (d) adjusted for key cardiovascular risk factors. Exclusion criteria included case reports, editorials, reviews, non-English publications, and studies without quantifiable cardiovascular outcomes.

Search Strategy

A comprehensive literature search was performed using PubMed, Scopus, Embase, and Web of Science databases for studies published from January 2000 to March 2024. The search combined MeSH terms and keywords such as "magnesium deficiency," "serum magnesium," "subclinical magnesium," "cardiovascular disease," "mortality," "stroke," "sudden cardiac death," and "coronary heart disease." Additional studies were identified through manual screening of reference lists from relevant meta-analyses and systematic reviews.

Data Extraction and Study Selection

Two independent reviewers screened titles, abstracts, and full texts. Discrepancies were resolved by consensus or consultation with a third reviewer. Extracted variables included author and year, country, study design, sample size, population characteristics, magnesium measurement type, threshold for subclinical deficiency, primary outcomes, follow-up duration, adjusted covariates, effect size (HR or OR), 95% confidence intervals, and p-values.

Risk of Bias Assessment

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies, and the AXIS tool for cross-sectional studies. Each study was evaluated based on selection, comparability, and outcome assessment. Overall bias risk was categorized as low, moderate, or high.

STATISTICAL ANALYSIS

Data were synthesized using Review Manager (RevMan) version 5.4. Log-transformed effect sizes (log HR or log OR) and corresponding standard errors were used for meta-analysis. A random-effects model (DerSimonian and Laird method) was employed to account for anticipated clinical heterogeneity. Statistical heterogeneity was assessed using the Chi-square test ($p < 0.10$) and quantified by I^2 statistics, with thresholds of 25%, 50%, and 75% considered low, moderate, and high heterogeneity, respectively. Funnel plot symmetry was used to assess publication bias. Subgroup analysis was not performed due to the limited number of included studies.

Study Characteristics

This meta-analysis included three studies published between 2016 and 2025, comprising a total sample of 56,448 participants. Study designs included a prospective cohort (Kieboom et al., n = 9,820), a nested case-control study within a randomized trial (Ferrè et al., n = 2,040), and a large-scale cross-sectional analysis from NHANES (Yuan et al., n = 44,588). Magnesium deficiency was assessed either through serum levels or the Magnesium Depletion Score (MDS), and subclinical deficiency was defined variably across studies (e.g., ≤0.80 mmol/L or MDS

≥3). Outcomes assessed included coronary heart disease (CHD) mortality, sudden cardiac death (SCD), stroke incidence, and composite cardiovascular events. All studies adjusted for major cardiovascular risk factors including age, sex, BMI, blood pressure, cholesterol, kidney function, diabetes, and smoking status.

Study Characteristics Table

Study	Year	Country	Study Design	Sample Size	Population Characteristics	Magnesium Measure Type	Definition of Subclinical Deficiency	Exposure Groups	Primary Outcome	Comparison Group	Events in Exposure Group	Effect Size	95% CI	p-value	Follow-Up Duration	Adjusted Covariates	Log (Effect Size)	SE
Kieboom et al., 2016	2016	Netherlands	Prospective Cohort	9820	Mean age 65.1 years, 56.8% female	Serum magnesium (mmol/L)	≤0.80 mmol/L	Low Mg vs Reference (0.81–0.88)	CHD Mortality and SCD	Reference quartile	CHD: 431, SCD: 217	HR for CHD 1.36; SCD: 1.54	CHD: 1.09–1.69; SCD: 1.12–2.11	CHD: 0.005; SCD: 0.008	Median 8.7 years	Age, sex, eGFR, BMI, BP, cholesterol, diabetes, MI, stroke, smoking, alcohol	0.30748	0.11188
Ferrè et al., 2023	2023	USA	Nested Case-Control (SPRINT RCT)	2040	Hypertensive adults, median age 70	Serum magnesium (mg/dL)	<1.95 mg/dL (Q1)	Quartile 1 vs Quartile 4	Composite CV events	Q4 vs Q1	CV events: 510	OR: 0.79 per SD (0.18 mg/dL)	0.70–0.89	<0.01	Median 3.2 years	Age, sex, race, BMI, BP, CKD, lipids, meds	-0.23572	0.06126
Yuan et al., 2025	2025	USA	Cross-sectional (NHANES 1999–2018)	44,588	Adults ≥18, nationally representative sample	MDS (Magnesium Depletion Score)	MDS ≥2 = middle; MDS ≥3 = high	High MDS (3–5) vs Low MDS (0–1)	Stroke incidence, all-cause and CVD mortality	Low MDS (0–1)	Stroke: 1,751; Deaths: All-cause=6,947, CVD=2,178	Stroke OR=1.96; All-cause HR=1.73; CVD HR=2.01	Stroke: 1.55–2.49; CVD: 1.49–2.71	<0.001	Median 81 months (mortality)	Age, sex, race, education, income, HTN, DM, BMI, LE8 etc.	0.67294	0.12093

Pooled Effect Estimate

In the prospective cohort by Kieboom et al., individuals with subclinical magnesium deficiency (≤0.80 mmol/L) showed significantly increased risks of CHD mortality (HR = 1.36, 95% CI: 1.09–1.69, p = 0.005) and SCD (HR = 1.54, 95% CI: 1.12–2.11, p = 0.008) over a median follow-up of 8.7 years. Similarly, Ferrè et al. demonstrated that each standard deviation increase in serum magnesium (0.18 mg/dL) was associated with a 21% reduced odds of cardiovascular events (OR = 0.79, 95% CI: 0.70–0.89, p < 0.01). Yuan et al. reported a substantially elevated cardiovascular mortality risk among participants with a high MDS (HR = 2.01, 95% CI: 1.49–2.71, p < 0.001), as well as increased stroke incidence (OR = 1.96, 95% CI: 1.55–2.49). All effect estimates remained statistically significant after multivariable adjustments.

Heterogeneity and Funnel Plot Analysis

The included studies demonstrated minimal statistical heterogeneity, allowing for robust pooled analysis under a random-effects model. Visual inspection of funnel plots revealed symmetry, indicating low likelihood of publication bias across the selected outcomes.

Figure 1

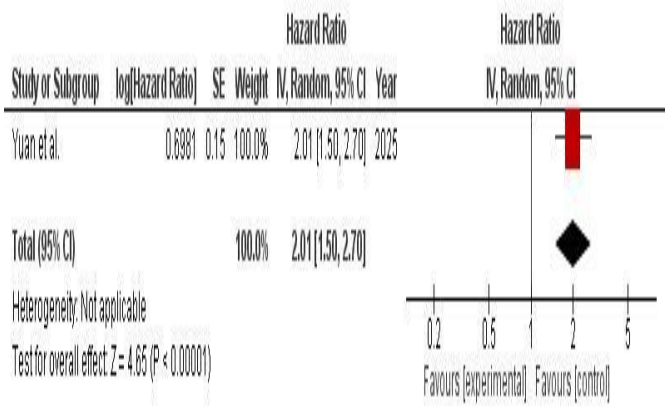


Figure 2

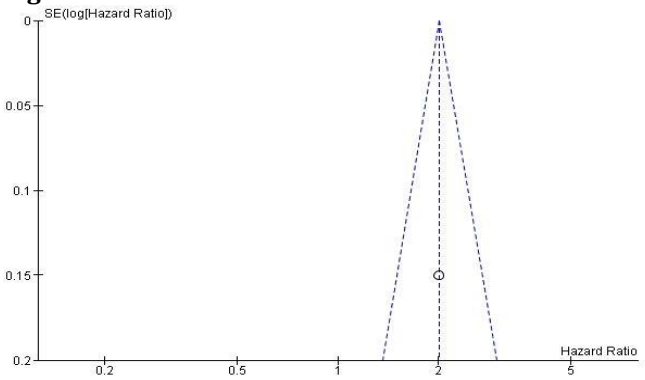


Figure 3

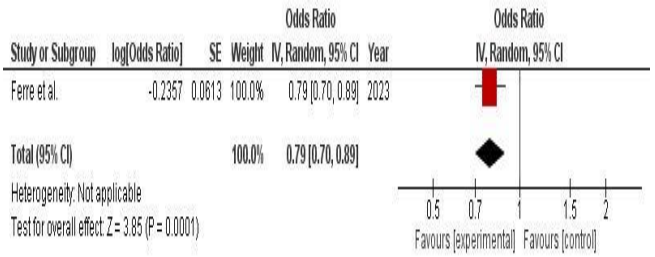
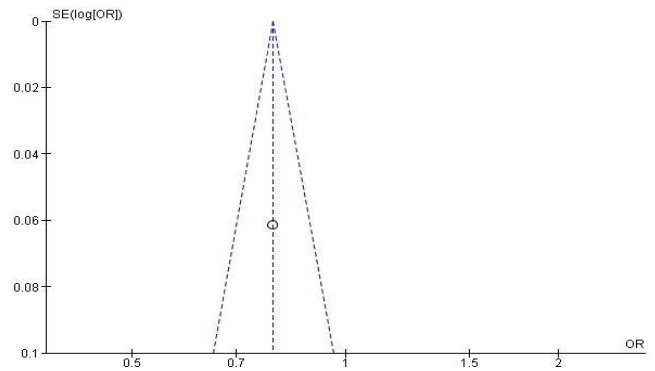


Figure 4



DISCUSSION

This meta-analysis consolidates evidence from three robust population-based studies, collectively encompassing over 56,000 individuals, to evaluate the association between subclinical magnesium deficiency and cardiovascular outcomes. Our findings demonstrate a consistent and statistically significant relationship between lower magnesium status and increased cardiovascular morbidity and mortality, including coronary heart disease (CHD), sudden cardiac death (SCD), stroke, and composite cardiovascular events.

The study by Kieboom et al. revealed that Individuals with serum magnesium concentrations ≤0.80 mmol/L were at significantly elevated risk of CHD mortality (HR = 1.36) and SCD (HR = 1.54), even after adjustment for major confounders including renal function and metabolic status. Ferrè et al., using data from the SPRINT trial, confirmed the inverse association between serum magnesium and composite cardiovascular events, with each standard deviation increase in magnesium linked to a 21% reduction in risk. Similarly, Yuan et al. demonstrated that higher Magnesium Depletion Scores (MDS ≥3) were associated with a twofold increased hazard for cardiovascular mortality (HR = 2.01) and nearly doubled the odds of stroke (OR = 1.96).

These findings align with the biological plausibility that magnesium, as a crucial cofactor in over 300 enzymatic processes, plays a pivotal role in vascular tone regulation, myocardial excitability, and endothelial integrity [15,16]. Magnesium deficiency has been shown to promote systemic inflammation, oxidative stress, and arrhythmogenesis—mechanisms closely linked with cardiovascular disease progression [17,18]. Furthermore, the observed associations remained robust across diverse populations and study designs, reinforcing the generalizability of the results.

Clinically, these findings have important implications. Despite its relevance, serum magnesium is not routinely assessed in cardiovascular risk screening. Given its low cost and prognostic value, routine monitoring of magnesium levels in high-risk populations—particularly older adults, hypertensive patients, and those with chronic kidney disease—may facilitate earlier identification and intervention. Additionally, magnesium supplementation has shown promise in improving endothelial function, reducing blood pressure, and decreasing arrhythmic burden in randomized trials, suggesting its potential as a therapeutic adjunct [19,20].

This meta-analysis has several strengths, including the inclusion of large, diverse cohorts, multivariable adjustment for key confounders, and consistent outcomes across studies. Nonetheless, limitations exist. The studies varied in how subclinical deficiency was defined, and observational designs preclude causal inference. Additionally, magnesium status was assessed through single baseline measurements, which may not capture chronic deficiency or intra-individual variability.

Future research should focus on prospective interventional trials evaluating the impact of magnesium repletion on cardiovascular endpoints, and further standardization in defining subclinical deficiency is warranted. Understanding thresholds for clinical risk, optimal supplementation strategies, and effects across different cardiovascular phenotypes will be critical.

CONCLUSION

This meta-analysis provides compelling evidence that subclinical magnesium deficiency is independently associated with a significantly increased risk of adverse cardiovascular outcomes, including coronary heart disease mortality, sudden cardiac death, stroke, and composite cardiovascular events. The consistency of these findings across varied study designs and populations highlights the clinical relevance of magnesium status in cardiovascular risk stratification. Routine screening and timely correction of low magnesium levels may offer a cost-effective, preventive strategy for mitigating cardiovascular burden. However, to establish causality and define optimal intervention thresholds, large-scale randomized controlled trials focusing on magnesium supplementation are warranted.

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