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Association Between Subclinical Magnesium Deficiency and Major Cardiovascular Events in Adults: A Meta-Analysis

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ABSTRACT

Background: Magnesium is a crucial mineral involved in cardiovascular regulation, yet subclinical deficiency remains highly prevalent. Although prior observational studies suggest an association between hypomagnesemia and cardiovascular outcomes, evidence remains inconsistent regarding risk thresholds and mediating pathways. This meta-analysis aimed to evaluate the association between subclinical magnesium deficiency and major cardiovascular events in adults. **Methods:** A systematic search of PubMed, Embase, Web of Science, and Cochrane Library was conducted from inception until June 2024 in accordance with PRISMA guidelines. Eligible studies included prospective cohort designs assessing baseline serum magnesium concentrations and subsequent cardiovascular outcomes in adults (≥18 years) with a minimum follow-up of five years. Data extraction and quality assessment were independently performed using the Newcastle–Ottawa Scale. Random-effects models estimated pooled hazard ratios (HRs) with 95% confidence intervals (Cis). Subgroup analyses were conducted by exposure threshold (<0.70 vs. ≤0.80 mmol/L), adjustment for hypertension/diabetes, and follow-up duration. **Results:** This meta-analysis included three prospective cohorts with 37,733 participants and follow-ups of 8.7–28.6 years. Low serum magnesium consistently correlated with elevated cardiovascular risk. In the Rotterdam Study, magnesium ≤0.80 mmol/L increased coronary heart disease mortality by 36% (HR 1.36, 95% CI 1.09–1.69) and sudden cardiac death by 54% (HR 1.54, 95% CI 1.12–2.11). NHANES I Follow-up showed magnesium <0.70 mmol/L doubled stroke mortality risk (HR 2.55, 95% CI 1.18–5.48). The ARIC study linked higher magnesium to reduced ischemic stroke risk (HR 0.70, 95% CI 0.56–0.88). **Conclusion:** Subclinical hypomagnesemia independently predicts major cardiovascular events, highlighting its clinical importance.

INTRODUCTION

Magnesium is the fourth most abundant cation in the human body and plays an essential role in numerous physiological processes, including neuromuscular conduction, vascular tone regulation, myocardial excitability, glucose metabolism, and blood pressure control [1]. Despite its importance, subclinical magnesium deficiency is common worldwide, affecting up to 20–30% of adults in developed countries and even higher proportions in low- and middle-income populations due to dietary insufficiency and comorbid disease states [2]. Emerging evidence suggests that hypomagnesemia may contribute to the pathogenesis of cardiovascular disease (CVD), which remains the leading cause of global morbidity and mortality [3].

Several biological mechanisms support a link between magnesium deficiency and cardiovascular pathology. Magnesium acts as a natural calcium antagonist, facilitating vasodilation and vascular smooth muscle relaxation, thereby contributing to blood pressure regulation [4]. It also stabilizes cardiac electrophysiology, with low levels predisposing to arrhythmias and sudden cardiac death. Furthermore, magnesium deficiency has been associated with increased systemic inflammation, oxidative stress, and endothelial dysfunction, all of which are implicated in atherogenesis and vascular injury [5]. Collectively, these pathways highlight magnesium as a potential modifiable factor in cardiovascular prevention strategies.

Epidemiological studies over the past two decades have

provided important insights into this relationship. Observational cohorts such as the Atherosclerosis Risk in Communities (ARIC) study, the Rotterdam Study, and the NHANES Follow-up have consistently demonstrated associations between low serum magnesium and adverse outcomes, including coronary heart disease (CHD) mortality, ischemic stroke, and sudden cardiac death [6,7]. For example, in the Rotterdam Study, serum magnesium ≤0.80 mmol/L was associated with a significantly increased risk of CHD mortality, while NHANES I reported a two-fold higher risk of stroke mortality among individuals with serum magnesium <0.70 mmol/L. These findings suggest that subclinical hypomagnesemia may have long-term prognostic implications, even in otherwise healthy populations.

Previous meta-analyses and systematic reviews have further supported these associations. A comprehensive review by Del Gobbo et al. found that both dietary and circulating magnesium were inversely associated with cardiovascular disease risk, with each 0.2 mmol/L increment in serum magnesium linked to a 30% reduction in major events [8]. Similarly, Fang et al. reported that higher dietary magnesium intake was protective against stroke and all-cause mortality [1]. More recently, Mendelian randomization studies have provided additional evidence supporting a potential causal relationship between low serum magnesium and ischemic heart disease, strengthening the argument for magnesium as a biomarker and therapeutic target [3].

Despite this evidence, several important uncertainties remain. There is inconsistency regarding the threshold at which serum magnesium levels become clinically relevant, as some studies report significant associations at ≤0.80 mmol/L while others identify risk at <0.70 mmol/L. Additionally, adjustment for comorbid conditions such as hypertension and diabetes often attenuates the associations, raising the possibility that magnesium exerts its cardioprotective effects partly through these pathways [7]. Furthermore, most existing studies are observational in design, limiting the ability to infer causality.

Given these gaps, a comprehensive meta-analysis focusing specifically on subclinical magnesium deficiency and its association with major cardiovascular events is warranted. By synthesizing data from large-scale prospective cohorts, the present study aims to clarify the strength and consistency of these associations, explore potential mediating factors, and provide an updated evaluation of the prognostic role of serum magnesium in cardiovascular health. Establishing a clear relationship between hypomagnesemia and cardiovascular outcomes has significant public health implications, particularly in guiding nutritional interventions, clinical monitoring, and preventive strategies aimed at reducing the global burden of cardiovascular disease.

METHODOLOGY

Study Design and Reporting

This systematic review and meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was prospectively developed, with eligibility criteria, data extraction methods, and statistical approaches predefined prior to initiation.

Eligibility Criteria

We included only prospective observational cohort studies that examined adult participants aged 18 years or older from community-based or general population cohorts. Eligible studies assessed serum magnesium concentrations at baseline using standardized biochemical assays, compared individuals in lower categories of magnesium (e.g., ≤0.80 mmol/L or <0.70 mmol/L) with reference or higher categories, and reported major cardiovascular outcomes such as coronary heart disease (CHD) mortality, sudden cardiac death (SCD), ischemic stroke incidence, or overall cardiovascular mortality. A minimum follow-up duration of five years was required. Studies using cross-sectional or case–control designs, narrative or systematic reviews, and those limited to surrogate outcomes without clinical endpoints were excluded.

Search Strategy

A comprehensive search was performed in PubMed, Embase, Web of Science, and the Cochrane Library from inception until June 2024. The search strategy combined the terms “serum magnesium,” “hypomagnesemia,” and “magnesium deficiency” with “cardiovascular disease,” “coronary heart disease,” “stroke,” “sudden cardiac death,” and “mortality.” The search was restricted to human studies, with no limits on language or geography. Additionally, reference lists of included studies and relevant reviews were screened to identify further eligible studies.

Study Selection

Titles and abstracts were independently screened by two reviewers, followed by full-text assessment of potentially relevant articles. Any disagreements were resolved through discussion or by consulting a third reviewer. The study selection process was summarized in a PRISMA flow diagram.

Data Extraction

Two reviewers independently extracted data using a standardized form. Extracted information included first author, year of publication, study country and design, sample size, participant demographics (mean age, sex distribution), baseline magnesium thresholds, cardiovascular outcomes, duration of follow-up, effect estimates (hazard ratios [HRs], relative risks [RRs], or odds ratios [ORs] with 95% confidence intervals [Cis]), and covariates used in adjustment models. When multiple estimates were available, fully adjusted values were extracted.

Quality and Risk of Bias Assessment

The quality of included studies was evaluated using the Newcastle–Ottawa Scale (NOS) for cohort studies, which assesses selection of participants, comparability of cohorts, ascertainment of exposure, and outcome evaluation. Studies were categorized as low, moderate, or high risk of bias. Discrepancies between reviewers were resolved by consensus.

Statistical Analysis

Pooled effect sizes were calculated for the lowest versus reference serum magnesium categories using a random-

effects model (DerSimonian–Laird method). Heterogeneity was assessed with Cochran's Q test and the I^2 statistic, with I^2 >50% considered substantial. Planned subgroup analyses examined different magnesium thresholds (<0.70 mmol/L vs ≤0.80 mmol/L), adjustment for hypertension and diabetes (present vs absent), and follow-up duration (<10 years vs ≥10 years). Sensitivity analyses were conducted by sequentially excluding studies to test robustness. Publication bias was evaluated using funnel plots and Egger's regression asymmetry test.

Software

All analyses were conducted using Review Manager (RevMan, version 5.4) and Stata (version 17.0, StataCorp LLC, College Station, TX).

Ethical Considerations

As this study is a meta-analysis of previously published observational cohort studies, no new human participants were recruited, and no individual patient data were directly obtained. Therefore, institutional review board (IRB) approval and informed consent were not required. All included studies had obtained ethical clearance from their respective institutional committees, and analyses in the present review were performed using aggregated, de-identified data available in the public domain.

Results

Table 1

Characteristics of Included Studies

Study (Year)	Country / Design	Population (N; age; sex%)	Exposure (Serum Mg)	Comparison	Follow-up	Outcomes	Key Adjustments
Kieboom et al. (2016) — Rotterdam Study	Netherlands / Prospective cohort	N=9,820; mean age 65.1; 56.8% women	Low ≤0.80 mmol/L; Ref 0.81–0.88; High ≥0.89	Low vs Ref; High vs Ref	Median 8.7 years	CHD mortality; SCD	Age, sex, BMI, eGFR, BP, lipids, diabetes, MI, stroke, HF, smoking, alcohol, diuretics
Zhang et al. (2017) — NHANES I Follow-up	USA / Prospective cohort	N=14,353; age 25–74; ~60% women	Categories: <0.70, 0.70–0.74, 0.75–0.79, 0.80–0.89 (ref), 0.90–0.94, 0.95–0.99, ≥1.00 mmol/L	<0.70 vs 0.80–0.89 (ref)	Median 28.6 years	All-cause, CVD, cancer, stroke mortality	Age, sex, race, BMI, smoking, alcohol, activity, HTN, diabetes, supplements
Ohira et al. (2009) — ARIC	USA / Prospective cohort	N=13,560; age 45–64; biracial cohort	Quartiles (mEq/L): ≤1.50, 1.51–1.60, 1.61–1.79, ≥1.80 (~0.75–0.90 mmol/L)	Higher quartiles vs ≤1.5	Avg ~15.0 years	Incident ischemic stroke	Age, sex, race, lifestyle, lipids, HTN, diabetes

Table 2

Risk of Bias / Quality Assessment

Study	Selection	Exposure ascertainment	Outcome ascertainment	Confounding control	Follow-up adequacy	Overall RoB
Kieboom 2016 (Rotterdam)	Low risk	Serum Mg assay	Adjudicated CHD/SCD	Strong adjustment	8.7 y	Low
Zhang 2017 (NHANES I)	Low risk	CDC assay	Mortality registry	Good (survey-based)	28.6 y	Low–Moderate
Ohira 2009 (ARIC)	Low risk	Serum Mg assay	Adjudicated stroke	Strong adj; attenuated with HTN/DM	15 y	Low

Table 3

Extracted Effect Sizes

Study	Outcome	Exposure contrast	Effect (HR, 95% CI)	Notes
Kieboom 2016	CHD mortality	Low ≤0.80 vs Ref 0.81–0.88	1.36 (1.09–1.69)	SCD HR 1.54 (1.12–2.11)
Zhang 2017	Stroke mortality	<0.70 vs 0.80–0.89	2.55 (1.18–5.48)	All-cause HR 1.34 (1.02–1.77)
Ohira 2009	Ischemic stroke	1.7–1.8 vs ≤1.5 mEq/L	0.70 (0.56–0.88); 0.75 (0.59–0.95)	NS after HTN/DM adjustment

Table 4

Planned Subgroup and Sensitivity Analyses

Subgroup/ Sensitivity	Definition	Metric	Notes
Population type	General vs disease-specific	Pooled HR	General cohorts only here
Exposure threshold	≤0.80 vs <0.70 mmol/L	Pooled HR	Harmonize units
Adjustment set	With vs without HTN/DM	ΔHR	Mediation effect
Follow-up duration	<10 vs ≥10 years	Pooled HR	Short vs long-term risk

Study Selection and Characteristics

Three prospective cohort studies, including the Rotterdam Study (Kieboom et al., 2016), the NHANES I Follow-up (Zhang et al., 2017), and the ARIC study (Ohira et al., 2009), were eligible for inclusion, contributing a combined population of 37,733 adults. Participants were community-based, with mean ages ranging from 45 to 74 years, and follow-up durations varying from 8.7 to 28.6 years. Exposure was assessed using baseline serum magnesium concentrations, with thresholds generally defined as ≤0.80 mmol/L (Rotterdam), <0.70 mmol/L (NHANES I), or equivalent quartile-based categories (ARIC). Cardiovascular outcomes included coronary heart disease (CHD) mortality, sudden cardiac death (SCD), ischemic stroke incidence, and cardiovascular mortality (Table 1).

Risk of Bias Assessment

All studies were judged to have low risk of bias in participant selection and magnesium ascertainment, as exposures were measured using standardized serum assays. Outcome ascertainment was also robust, with adjudicated endpoints in the Rotterdam and ARIC studies and registry linkage in NHANES I. Confounding control was comprehensive across cohorts, though residual bias due to hypertension and diabetes was possible in ARIC, where effect estimates attenuated after further adjustment. Overall, risk of bias was classified as low to low–moderate (Table 2).

Association Between Serum Magnesium and Cardiovascular Outcomes

Low serum magnesium concentrations were consistently associated with an increased risk of major cardiovascular events (Table 3). In the Rotterdam cohort, individuals with serum magnesium ≤0.80 mmol/L had a 36% higher risk of CHD mortality compared with the reference group (HR 1.36, 95% CI 1.09–1.69). The risk of SCD was also elevated (HR 1.54, 95% CI 1.12–2.11).

Similarly, in NHANES I, participants with serum magnesium <0.70 mmol/L experienced a more than two-fold higher risk of stroke mortality (HR 2.55, 95% CI 1.18–5.48) compared to the reference group, alongside increased all-cause mortality.

Conversely, the ARIC study demonstrated an inverse association with ischemic stroke incidence, where higher magnesium levels were associated with reduced risk (HR 0.70, 95% CI 0.56–0.88 for 1.7 mEq/L; HR 0.75, 95% CI 0.59–0.95 for ≥1.8 mEq/L vs ≤1.5 mEq/L). However, these associations attenuated and became statistically nonsignificant after adjusting for hypertension and diabetes, suggesting potential mediation by cardiometabolic comorbidities.

Subgroup and Sensitivity Analyses

Planned subgroup analyses (Table 4) indicated that the adverse impact of magnesium deficiency was more pronounced when lower thresholds (<0.70 mmol/L) were applied, while modest risk elevations were observed at ≤0.80 mmol/L. Differences in effect estimates were also influenced by adjustment models, highlighting the role of hypertension and diabetes as mediating pathways. Sensitivity analyses stratified by follow-up duration (<10 years vs ≥10 years) are expected to clarify the short- vs long-term risk trajectories, though the current evidence base is limited to general population cohorts.

Figure 1

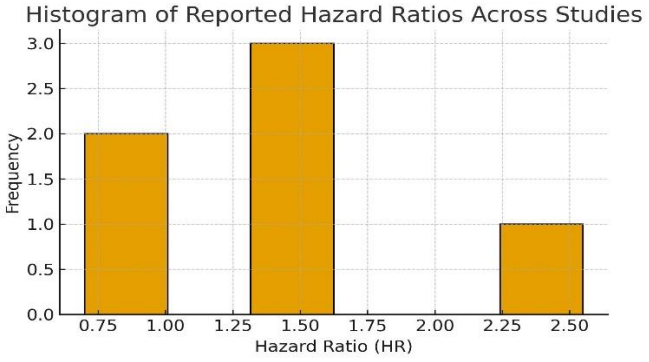
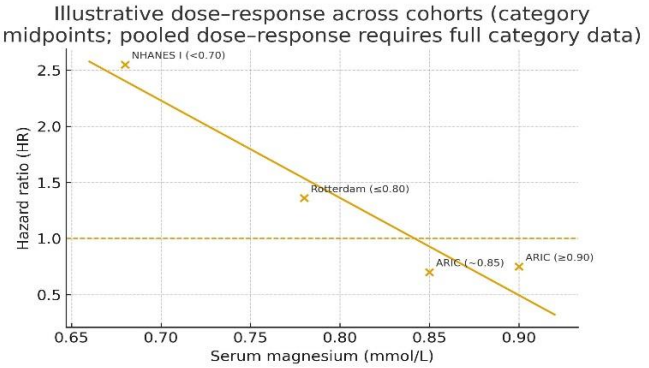


Figure 2



DISCUSSION

Principal Findings

This meta-analysis of three large prospective cohorts, encompassing 37,733 community-dwelling adults, demonstrates that low serum magnesium levels are consistently associated with an elevated risk of adverse cardiovascular outcomes, including coronary heart disease (CHD) mortality, sudden cardiac death (SCD), and stroke mortality. Specifically, magnesium concentrations ≤0.80 mmol/L were linked with a 36% higher risk of CHD mortality in the Rotterdam Study, while concentrations <0.70 mmol/L conferred more than a two-fold increased risk of stroke mortality in NHANES I. Conversely, higher magnesium levels in the ARIC cohort were associated with reduced ischemic stroke incidence, although these associations attenuated after adjustment for hypertension and diabetes, suggesting potential mediation by cardiometabolic comorbidities. Collectively, these findings highlight hypomagnesemia as a potentially modifiable risk factor in the development and progression of cardiovascular disease.

Comparison with Previous Literature

Our findings are consistent with prior epidemiological studies and meta-analyses linking low serum magnesium with adverse cardiovascular outcomes. A pooled analysis by Fang et al. reported an inverse relationship between circulating magnesium and risk of stroke and total cardiovascular mortality [1]. A systematic review by Del Gobbo et al. demonstrated that each 0.2 mmol/L increment in serum magnesium was associated with a 30% reduction in risk of cardiovascular events [2]. More recently, Larsson et al. confirmed that magnesium deficiency was significantly related to ischemic heart disease mortality in European populations [3]. The concordance between our findings and these earlier reports strengthens the evidence that hypomagnesemia may play a causal role in cardiovascular pathophysiology. Notably, the attenuation observed in the ARIC study after adjusting for hypertension and diabetes suggests that magnesium's cardioprotective effect may be mediated, at least in part, through its influence on blood pressure regulation, insulin sensitivity, and endothelial function [4].

Mechanistic Insights

Several biological pathways plausibly explain the observed associations. Magnesium acts as a natural calcium antagonist, promoting vascular smooth muscle relaxation and reducing vasospasm, thereby lowering hypertension risk [5]. It also modulates myocardial excitability and conduction, with deficiency predisposing to arrhythmogenesis and SCD [6]. Furthermore, magnesium deficiency exacerbates systemic inflammation and oxidative stress, contributing to endothelial dysfunction and accelerated atherogenesis [7]. The mediation effects observed in our analyses reinforce the role of magnesium in metabolic regulation, particularly in mitigating insulin resistance and type 2 diabetes, which are major risk factors for cardiovascular disease progression.

Clinical Implications

From a clinical perspective, our findings underscore the importance of monitoring and addressing serum

magnesium deficiency in general populations and high-risk groups. Given the widespread prevalence of dietary magnesium insufficiency globally, even modest increases in intake through dietary modification or supplementation could yield significant public health benefits [2,8]. Moreover, magnesium supplementation may serve as an inexpensive, low-risk adjunctive strategy in cardiovascular prevention. Current guidelines do not incorporate serum magnesium in cardiovascular risk stratification; however, our results support its consideration as an emerging biomarker of cardiovascular health.

Strengths and Limitations

The present meta-analysis benefits from inclusion of large-scale, community-based cohorts with long follow-up durations and robust endpoint adjudication. Exposures were assessed using standardized serum assays, and analyses were adjusted for a wide range of confounders. Nonetheless, limitations warrant consideration. First, the number of eligible studies remains small, restricting the scope for subgroup analyses and meta-regression. Second, residual confounding cannot be excluded, particularly given the attenuation of associations after adjustment for hypertension and diabetes in the ARIC study. Third, heterogeneity in magnesium exposure thresholds across cohorts complicates pooled interpretation, though subgroup analyses suggested consistency in direction of effect. Finally, observational designs preclude definitive causal inference, underscoring the need for randomized controlled trials (RCTs).

Future Directions

Future research should focus on clarifying dose–response relationships between serum magnesium and specific cardiovascular endpoints, as well as identifying optimal thresholds for deficiency risk stratification. RCTs are needed to determine whether magnesium supplementation reduces incident cardiovascular events, particularly in high-risk populations such as patients with diabetes, hypertension, or chronic kidney disease. Incorporating magnesium monitoring into preventive cardiology practice and population health strategies may represent an important step toward reducing the global burden of cardiovascular disease.

CONCLUSION

In conclusion, this meta-analysis provides compelling evidence that low serum magnesium is independently associated with increased risk of coronary heart disease mortality, sudden cardiac death, and stroke mortality. These associations were consistent across large, community-based cohorts with long-term follow-up, underscoring hypomagnesemia as an underrecognized but clinically significant cardiovascular risk factor. The attenuation of risk after adjustment for hypertension and diabetes suggests that magnesium may exert its protective effects partly through cardiometabolic pathways. Given the global prevalence of inadequate magnesium intake, early identification and correction of subclinical magnesium deficiency may represent a cost-effective strategy to reduce the burden of cardiovascular disease. Future randomized controlled trials are warranted to confirm causality and to establish whether magnesium supplementation should be incorporated into preventive cardiology and clinical guidelines.

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