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INPLASY

# Zinc Supplementation and Systemic Inflammation in Aging: A Systematic Review and Meta-Analysis of Effects on Immune Biomarkers in Older Adults

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## ADMINISTRATIVE INFORMATION

**Support -** None.

**Review Stage at time of this submission -** Data analysis.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202620017

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 4 February 2026 and was last updated on 23 October 2026.

## INTRODUCTION

**Review question / Objective** The objective of this systematic review and meta-analysis is to synthesize evidence from randomized controlled trials (RCTs) regarding the impact of zinc supplementation on immune biomarkers in older adults. The study aims to clarify the effects of zinc on key markers of inflammation and cellular immunity, providing a stronger evidence base to inform clinical and public health strategies for promoting healthy immune aging.

**Rationale** The global population is aging rapidly, with a significant increase in the proportion of older adults who are more susceptible to infectious diseases and age-related chronic conditions due to immunosenescence and inflammaging [1-3]. Zinc, an essential micronutrient for immune function, is often deficient in this demographic [4, 5]. While previous research has explored the role of zinc, existing systematic reviews have often included broader adult populations or have not focused specifically on the comprehensive panel of inflammatory and cellular biomarkers relevant to immunosenescence in older adults [6]. This review addresses this gap by focusing on this vulnerable population to provide a more precise understanding of zinc's role in modulating the immune response during aging.

**Condition being studied** The review focuses on older adults and examines the impact of zinc supplementation on cellular immunity and inflammatory biomarkers in this population.

## METHODS

**Search strategy** A systematic literature search was conducted in January 2025 across multiple databases, including PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy employed a combination of keywords and MeSH terms related to zinc supplementation, immune function, inflammatory biomarkers, and older adults.

**Participant or population** The review includes studies involving elderly human participants with a mean age greater than 55 years.

**Intervention** Oral zinc intervention in any form or dosage.

**Comparator** The control arm used either a placebo, no intervention, or standard care as the comparator.

**Study designs to be included** The review is limited to Randomized Controlled Trials (RCTs).

**Eligibility criteria** Inclusion criteria: Studies were included if they were full-text, randomized controlled trials involving elderly humans (mean age > 55 years), investigated oral zinc supplementation, had a control arm (placebo, no intervention, or standard care), reported at least one immune or inflammatory biomarker with pre- and post-intervention data, and were published in English.
Exclusion criteria: Studies were excluded if they were not RCTs, involved non-elderly populations, used non-oral zinc interventions, or did not report on relevant immune or inflammatory biomarkers.

**Information sources** The information sources for this review are the published full-text articles identified through the systematic search of the PubMed, Scopus, and CENTRAL databases.

**Main outcome(s)** The primary outcomes of interest are the changes from baseline to post-intervention in key biomarkers reflecting systemic inflammation and cellular immunity within both the intervention and control groups, including:
High-sensitivity C-reactive protein (hs-CRP) or CRP
Total leukocyte count
Total neutrophil count
Total lymphocyte count.

**Additional outcome(s)** Secondary outcomes include additional immune and inflammatory markers, provided sufficient data are available to conduct a meta-analysis, such as:
• Pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β)
• T-cell subsets (e.g.,CD3+, CD4+, CD8+)
• CD4/CD8 ratio
• Natural Killer (NK) cells
• T-cell proliferation
If sufficient numerical data are not available, a qualitative summary will be generated.

**Data management** Data were extracted from the included studies by a reviewer using a standardized form and were verified three times on different occasions to ensure accuracy. The extracted information included study characteristics, participant demographics, intervention details, control group type, and outcome data (mean and standard deviation for both intervention and control groups at baseline and post-intervention).

**Quality assessment / Risk of bias analysis** The methodological quality of the included RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [7].

**Strategy of data synthesis** The meta-analysis was conducted using a random-effects model with the Hedges' estimator. The effect of zinc supplementation was estimated using the Standardized Mean Difference (SMD) with Hedges' g correction to account for small sample bias and differences in measurement scales. A difference-in-differences approach was used to calculate the net change between the intervention and control groups. Statistical heterogeneity was assessed using the $I^2$ and $\tau^2$ statistics. All analyses were performed using the Jamovi software (version 2.3.28). This systematic review and meta-analysis was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [8].

**Subgroup analysis** If the number of eligible studies permits, we will conduct subgroup analyses based on participants' general health status, zinc dose, and duration of the intervention.

**Sensitivity analysis** A leave-one-out sensitivity analysis was conducted to evaluate the influence of individual studies on the pooled estimate.

**Language restriction** English.

**Country(ies) involved** Saudi Arabia.

**Keywords** zinc supplementation, immunosenescence, inflammaging, older adults, elderly, immune biomarkers, hs-CRP, C-reactive protein, meta-analysis, systematic review, randomized controlled trial.

**Dissemination plans** The findings of this systematic review and meta-analysis will be disseminated through publication in a peer-reviewed journal.

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## Contributions of each author

Author 1 - Abdullah Alhewiti - Abdullah Alhewiti was responsible for conceptualization, methodology, literature search and study selection, data extraction, risk of bias assessment, formal analysis and data synthesis, interpretation of findings, drafting of the manuscript, and writing the final version.
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