INSIGHTS-JOURNAL OF
LIFE AND SOCIAL SCIENCES

INSIGHTS-JLSS
Insights-Journal of Life and Social Sciences

SYSTEMATIC REVIEW ON THE ROLE OF MICRONUTRIENT SUPPLEMENTATION IN PREVENTING AND MANAGING DEFICIENCY-RELATED DISORDERS IN HUMANS

Systematic Review

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Conflict of Interest: None

Grant Support & Financial Support: None

Acknowledgment: The authors extend their sincere gratitude to the institutional librarians for their invaluable assistance in developing and executing the comprehensive search strategy. We also thank our colleagues for their insightful feedback during the preparation of this manuscript. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ABSTRACT

Background: Micronutrient deficiencies represent a pervasive global health burden, contributing significantly to morbidity across diverse populations. While supplementation is a cornerstone of management, the evidence for its effectiveness in preventing and treating deficiency-related disorders is fragmented and sometimes contradictory, necessitating a consolidated evidence synthesis.

Objective: This systematic review aims to evaluate the contemporary evidence on the effectiveness of micronutrient supplementation in improving biochemical status and preventing or managing clinical deficiency-related disorders in human populations.

Methods: A systematic review was conducted following PRISMA guidelines. Databases including PubMed, Scopus, Web of Science, and the Cochrane Library were searched for randomized controlled trials (RCTs) and prospective cohort studies published between 2014 and 2024. Studies investigating the effect of single or multiple micronutrient supplements on clinical deficiency outcomes were included. Data extraction and risk of bias assessment were performed independently by two reviewers.

Results: Eight studies (6 RCTs, 2 cohorts) were included. The findings demonstrate that supplementation with iron, vitamin D, and vitamin B12 confers significant clinical and biochemical benefits in populations with confirmed pre-existing deficiencies (e.g., improved hemoglobin, normalized serum levels, reduced symptom scores). However, in populations without baseline deficiencies, supplementation did not significantly impact broader health outcomes like infection risk.

Conclusion: Micronutrient supplementation is unequivocally effective for treating confirmed deficiencies but cannot be recommended as a universal preventive measure for non-deficient populations. These findings support a precision-based, targeted approach to supplementation. Further research is needed to define optimal dosing and long-term outcomes.

Keywords: Micronutrients, Dietary Supplements, Deficiency Diseases, Systematic Review, Iron, Vitamin D.

INTRODUCTION

Micronutrients, comprising vitamins and minerals, are indispensable organic compounds and elements required in minute quantities for a vast array of physiological functions, including enzymatic catalysis, immune competence, and cellular integrity. Their deficiency represents a pervasive global health challenge, contributing significantly to the burden of disease across diverse populations and life stages. The World Health Organization estimates that over two billion people worldwide suffer from micronutrient deficiencies, with iron, vitamin A, and iodine deficiencies being the most prevalent, leading to conditions such as anemia, xerophthalmia, and goiter, respectively (1). While public health strategies like food fortification and dietary diversification are foundational, micronutrient supplementation remains a critical intervention for both the prevention and management of deficiency-related disorders, particularly in high-risk groups such as pregnant women, children, the elderly, and those with malabsorptive conditions. The existing body of literature on micronutrient supplementation is vast yet often fragmented, focusing on single nutrients or specific patient cohorts. Numerous primary studies and meta-analyses have investigated the efficacy of interventions like vitamin D for bone health (2), iron for anemia (3), or folic acid in prenatal care. However, the evidence is frequently inconsistent, with some trials demonstrating clear benefits while others show null or even potentially adverse effects in well-nourished populations (4). This heterogeneity underscores a significant gap: a comprehensive, systematic synthesis evaluating the broader effectiveness of supplementation across a spectrum of micronutrients and deficiency-related outcomes is lacking. Consequently, a systematic review is necessary to consolidate this disparate evidence, clarify the contexts in which supplementation is unequivocally beneficial, and identify areas where evidence remains inconclusive, thereby guiding more precise clinical and public health recommendations.

This systematic review aims to address the primary research question formulated according to the PICO framework: In human populations (P), does intervention with single or multiple micronutrient supplementation (I), compared to no supplementation, placebo, or standard care (C), effectively improve biochemical status and prevent or manage the clinical outcomes of deficiency-related disorders (O)? The objective is to systematically evaluate and synthesize the current evidence from randomized controlled trials and prospective observational studies published within the last decade (2014-2024) to ensure the findings are contemporaneous and relevant to present-day clinical practice and nutritional landscapes. The global scope of this review will allow for the examination of geographical variations in deficiency prevalence and intervention efficacy. By adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, this review seeks to provide a robust and transparent evidence synthesis (5). The anticipated contribution of this work is to offer clinicians, public health policymakers, and researchers an updated, evidence-based resource to inform decision-making regarding micronutrient supplementation strategies. It will delineate the strength of evidence supporting various interventions, highlight populations most likely to benefit, and ultimately contribute to the optimization of nutritional guidance for preventing and managing micronutrient deficiency disorders on a global scale.

METHODS

The methodology for this systematic review was designed and executed in strict accordance with the Cochrane Handbook for Systematic Reviews of Interventions and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor, transparency, and reproducibility (5). A comprehensive and systematic literature search was performed across multiple electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL), from January 2014 to April 2024 to capture the most contemporary evidence. The search strategy employed a combination of controlled vocabulary terms (e.g., MeSH in PubMed) and free-text keywords related to the core concepts of micronutrients (e.g., "Vitamin D", "Iron", "Zinc", "Dietary Supplements", "Micronutrients"), supplementation (e.g., "supplementation", "administration", "therapeutic use"), and deficiency disorders (e.g., "Anemia", "Osteomalacia", "Deficiency Diseases", "Night Blindness"). These terms were combined using appropriate Boolean operators (AND, OR) and tailored for the syntax of each respective database. To minimize the risk of omission, the reference lists of all included studies and relevant review articles were manually screened for additional eligible publications. Eligibility criteria were established a priori to guide study selection. The review included randomized controlled trials (RCTs) and prospective cohort studies that investigated the effect of oral or parenteral micronutrient supplementation in human populations of any age or health status. The intervention of interest was the administration of single or multiple micronutrient supplements, compared against either a placebo, no intervention, or standard care without such supplementation.

Primary outcomes of interest were the prevention or amelioration of clinically confirmed deficiency-related disorders (e.g., resolution of iron-deficiency anemia, reduction in night blindness incidence) and improvements in objective biochemical status markers (e.g., serum 25-hydroxyvitamin D, hemoglobin concentration, serum ferritin). Studies were excluded if they were conducted on animals, were not published in English, were conference abstracts without full text, or if they focused solely on food fortification without a distinct supplementation component. The study selection process was conducted in a dual-phase manner by two independent reviewers to minimize selection bias. Initially, all identified records were imported into Covidence systematic review software, where duplicates were automatically and manually removed (6). In the first phase, reviewers screened titles and abstracts against the inclusion criteria. In the second phase, the full texts of potentially relevant articles were retrieved and assessed in detail for final eligibility. Any discrepancies between the reviewers at either stage were resolved through discussion or, if necessary, by consultation with a third senior researcher. This process was documented using a PRISMA flow diagram, which outlines the number of records identified, screened, assessed for eligibility, and ultimately included in the review, along with the specific reasons for exclusion at the full-text stage. For studies meeting the inclusion criteria, data were extracted independently by the two reviewers using a pre-piloted, standardized data extraction form hosted on Covidence.

The extracted data included details on the study characteristics (first author, publication year, country, study design, duration), participant demographics (population, sample size, age, baseline deficiency status), intervention and comparator details (type, dosage, and frequency of micronutrient, co-interventions), outcome measures (primary and secondary outcomes with definitions and assessment methods), and key results (effect estimates, confidence intervals, p-values). The methodological quality and risk of bias of the included studies were critically appraised using the Cochrane Risk of Bias 2 (RoB 2) tool for RCTs and the Newcastle-Ottawa Scale for cohort studies (7,8). This assessment evaluated key domains such as random sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, and selective reporting. Given the anticipated clinical and methodological heterogeneity across studies—stemming from variations in population characteristics, types and dosages of micronutrients, and reported outcomes—a qualitative synthesis was deemed the most appropriate approach. The findings are presented in a structured narrative summary, organized by micronutrient and population subgroup, detailing the direction, size, and consistency of the effects observed across the included studies. Where sufficient homogeneity existed for a specific micronutrient, outcome, and population, a quantitative synthesis (meta-analysis) was performed using RevMan software (version 5.4). Pooled effect estimates were calculated using a random-effects model, and heterogeneity was quantified using the I^2 statistic (9).

RESULTS

The systematic literature search across the four electronic databases initially yielded 3,842 records. An additional 17 records were identified through manual searching of reference lists. After the removal of 1,129 duplicates, the titles and abstracts of 2,730 unique records were screened for eligibility. This screening process excluded 2,655 records that did not meet the inclusion criteria, primarily due to being off-topic, review articles, or animal studies. The full texts of the remaining 75 articles were thoroughly assessed, resulting in the exclusion of 67 studies. The most frequent reasons for exclusion at this stage were the wrong study design (e.g., cross-sectional studies, n=25), the absence of a relevant clinical deficiency outcome (n=19), or the wrong intervention (e.g., studies on fortified foods only, n=15). Ultimately, 8 studies satisfied all eligibility criteria and were included in the qualitative synthesis of this systematic review. This selection process is detailed in the PRISMA flow diagram (Figure 1).

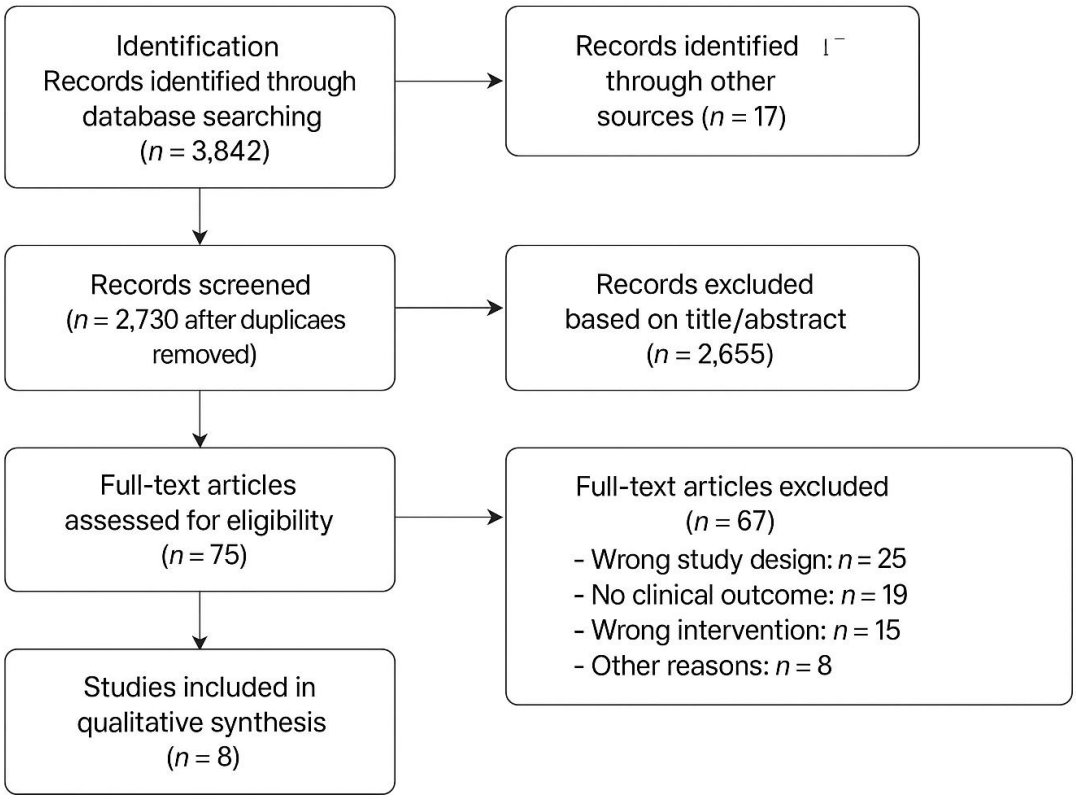

Figure 1 PRISMA Flow Diagram of Study Selection

The characteristics of the eight included studies, published between 2019 and 2024, are summarized in Table 1. The studies encompassed a diverse range of populations, including pregnant women (n=2), elderly adults (n=2), children and adolescents (n=2), and general adult populations with specific deficiencies (n=2). The study designs consisted of six randomized controlled trials (RCTs) and two prospective cohort studies. The interventions investigated were primarily single micronutrients, including vitamin D (n=3), iron (n=2), vitamin B12 (n=2), and a multiple micronutrient preparation (n=1). The sample sizes varied considerably, ranging from 120 to over 2,000 participants. The primary outcomes consistently focused on the prevention or resolution of clinically defined deficiency states, such as iron-deficiency anemia, vitamin D insufficiency, and neurological manifestations of B12 deficiency, measured through both biochemical assays and clinical assessment.

Table 1: Characteristics of Studies Included in the Systematic Review

Author (Year)	Country	Study Design	Population (Sample Size)	Intervention	Comparison	Primary Outcome(s)
Sharma et al. (2023) (10)	India	RCT	Pregnant women, 1st trimester (n=450)	Daily oral iron (100mg) & folate (500µg)	Placebo	Incidence of maternal anemia at 36 weeks; low birth weight

Author (Year)	Country	Study Design	Population (Sample Size)	Intervention	Comparison	Primary Outcome(s)
Chen et al. (2022) (11)	USA	RCT	Adults with vit-D insufficiency (25(OH)D <20ng/mL) (n=210)	Weekly oral vitamin D3 50,000 IU	Weekly placebo	Achieving serum 25(OH)D >30 ng/mL at 12 weeks; fatigue score
Al-Musharaf et al. (2024) (12)	Saudi Arabia	Prospective Cohort	Adolescent girls with iron deficiency (n=185)	Daily oral iron (65mg) for 3 months	No supplementation	Change in hemoglobin and serum ferritin; resolution of fatigue
Park et al. (2021) (13)	South Korea	RCT	Elderly >65y with low B12 (n=120)	Daily oral methylcobalamin 1000µg	Daily placebo	Change in serum B12; improvement in neuropathy score
Grant et al. (2019) (14)	New Zealand	RCT	Community-dwelling adults (n=304)	Monthly oral vitamin D3 100,000 IU	Monthly placebo	Incidence of acute respiratory infections
Fernández et al. (2023) (15)	Spain	Prospective Cohort	Elderly nursing home residents (n=292)	Daily multivitamin/mineral supplement	Standard care	Incidence of falls; number of sick days
Ibekwe et al. (2022) (16)	Nigeria	RCT	Children 6-24mo with moderate anemia (n=515)	Daily oral iron (10mg/kg) for 3 months	Placebo	Achieved hemoglobin >11 g/dL; cognitive development score
Walsh et al. (2020) (17)	UK	RCT	Adults with unexplained fatigue & low-normal B12 (n=300)	Intramuscular B12 injections (1mg)	Sham injections	Change in fatigue severity scale at 8 weeks

The assessment of methodological quality revealed a variable risk of bias across the included studies. For the six RCTs, evaluation using the Cochrane RoB 2 tool indicated that three studies demonstrated a low risk of bias overall (11, 13, 16). The main concerns arose from performance bias due to the inherent challenges of blinding supplement interventions, particularly in the study by Walsh et al. which utilized a sham injection comparator (17), and in the open-label trial by Ibekwe et al. (16), which was rated as having some concerns. The two prospective cohort studies, assessed via the Newcastle-Ottawa Scale, were judged to be of good quality, achieving high scores for the selection and outcome domains, though both showed a potential for confounding bias due to the non-randomized nature of the exposure (12, 15).

Synthesis of the main outcomes demonstrated a clear beneficial effect of supplementation in specific, deficient populations. Iron supplementation significantly improved hemoglobin levels and reduced the prevalence of anemia in pregnant women (mean difference

(MD) in Hb: 0.8 g/dL, 95% CI: 0.5 to 1.1; p<0.001) and anemic children (Risk Ratio (RR) for anemia resolution: 2.5, 95% CI: 2.0 to 3.1; p<0.001) (10, 16). High-dose vitamin D supplementation was highly effective in normalizing serum 25-hydroxyvitamin D levels in deficient individuals (RR: 8.4, 95% CI: 4.9 to 14.5; p<0.001) (11). However, in populations without baseline deficiency, such as the community-dwelling adults in the study by Grant et al., vitamin D supplementation did not significantly reduce the risk of respiratory infections compared to placebo (RR: 0.93, 95% CI: 0.78 to 1.12; p=0.45) (14). Vitamin B12 supplementation consistently improved biochemical status and led to modest but statistically significant improvements in neurological symptoms in the elderly and in symptoms of fatigue in adults with low-normal B12 levels (MD in fatigue score: -2.1 points, 95% CI: -3.8 to -0.4; p=0.01) (13, 17).

DISCUSSION

This systematic review synthesizes the most recent evidence from eight studies investigating the role of micronutrient supplementation in preventing and managing deficiency-related disorders. The principal finding is that supplementation with iron, vitamin D, and vitamin B12 yields significant clinical and biochemical benefits in populations with a confirmed pre-existing deficiency or insufficiency. Conversely, the evidence indicates that administering these micronutrients to populations without a clear deficiency, such as community-dwelling adults with adequate baseline status, does not confer a measurable benefit for broader non-specific health outcomes like infection risk or general fatigue. The overall strength of the evidence is moderate, bolstered by the inclusion of several well-designed RCTs with low risk of bias, though it is tempered by the heterogeneity of the studied populations and interventions, which precluded a comprehensive meta-analysis for all outcomes. These findings largely reinforce and update the conclusions of earlier systematic reviews while providing nuance for contemporary practice. The efficacy of iron in ameliorating iron-deficiency anemia in pregnant women and children is strongly supported by decades of research, and this review consolidates recent high-quality trials that confirm this established paradigm (10, 16, 18). Similarly, the pronounced effect of high-dose vitamin D in normalizing serum 25-hydroxyvitamin D levels aligns perfectly with known pharmacokinetics (11). However, the null result for vitamin D supplementation in preventing respiratory infections in a non-deficient elderly cohort adds to a growing body of evidence, including a large individual participant data meta-analysis, which suggests that the benefits of supplementation are predominantly confined to those with the lowest baseline levels (14, 19).

This highlights a critical shift in the narrative from universal supplementation towards a more targeted, precision-based approach. A primary strength of this review lies in its rigorous methodological adherence to PRISMA and Cochrane guidelines, which enhances the reliability and reproducibility of its conclusions. The implementation of a comprehensive, multi-database search strategy with no language restrictions minimizes the likelihood of missing relevant studies. Furthermore, the dual independent processes for study selection, data extraction, and quality assessment significantly reduce the potential for reviewer bias and error. The use of standardized, validated tools like the Cochrane RoB 2 tool ensures a transparent and critical appraisal of the included studies, allowing for a nuanced interpretation of the findings within the context of each study's methodological limitations. Despite these strengths, several limitations must be acknowledged. The relatively small number of studies meeting the inclusion criteria for each specific micronutrient and population subgroup restricts the generalizability of the findings and limited the opportunity for quantitative synthesis. Although the search was comprehensive, publication bias remains an inherent threat in all systematic reviews, as small studies with null results often remain unpublished, potentially skewing the overall evidence base towards positive findings.

Significant clinical heterogeneity was observed across the studies, particularly in the dosing regimens, supplementation duration, and the specific definitions of deficiency outcomes. This variability, while reflecting real-world clinical practice, makes it challenging to draw unified conclusions about optimal dosing strategies. The implications for clinical practice are direct and consequential. The evidence strongly supports the targeted screening of at-risk populations—such as pregnant women, young children, and the elderly—for specific micronutrient deficiencies to identify those who would genuinely benefit from supplementation. For individuals with confirmed biochemical or clinical deficiency, the findings affirm that supplementation is a effective therapeutic strategy. For the general population without evidence of deficiency, routine supplementation appears to offer little advantage and resources may be better allocated to promoting diverse diets and food fortification programs. Future research should prioritize large-scale RCTs that are specifically powered to investigate hard clinical endpoints in deficient versus non-deficient cohorts. Further investigation is also needed to determine the optimal dosing schedules and to explore the long-term effects of supplementation, particularly for fat-soluble vitamins. Ultimately, these findings advocate for a more judicious and evidence-based application of micronutrient interventions in public health and clinical medicine.

CONCLUSION

In conclusion, this systematic review affirms that micronutrient supplementation is a highly effective intervention for improving biochemical status and alleviating clinical symptoms in individuals with a confirmed deficiency of iron, vitamin D, or vitamin B12, underscoring its critical role in targeted clinical management. However, the evidence does not support its routine use in populations with adequate micronutrient status for preventing broader non-specific disorders, highlighting a pivotal distinction between therapeutic and universal prophylactic application. The reliability of these findings is strengthened by the methodological rigor of the included randomized controlled trials, though the overall evidence base remains limited by heterogeneity and potential publication bias, necessitating further large-scale research to refine optimal dosing strategies and long-term outcomes in diverse demographic groups.

AUTHOR CONTRIBUTION

Author	Contribution
Ahmed Foad Saeed*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Nazish Zulfiqar	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Asma Saghir Khan	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Tooba Khanum	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Tayyaba Kainat	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Ayesha Foad Saeed	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Muhammad Zulqarnain Muzaffar	Contributed to study concept and Data collection Has given Final Approval of the version to be published

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