Reviews

The role of specific nutrients in preventing immune system and blood cell disorders: an umbrella review

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Keywords

Dietary supplementation • Blood cells disorders • Immune system • Micronutrients • Preventive medicine

Summary

Introduction. *Nutritional deficiencies affecting the immune and haematopoietic systems represent a well-known global public health challenge: only the iron deficiency anaemia affects 1.62 billion individuals, especially in vulnerable populations. However, the protective effect that nutrition might give on disorders of these systems is still poorly understood. This umbrella review aims to synthesise the available evidence on the effectiveness of nutritional interventions in the primary prevention of blood and immune disorders, with a focus on the role of essential micronutrients and bioactive compounds.*

Materials and methods. *The protocol for this review was registered on PROSPERO (registration number 535785). A systematic search was conducted on PubMed, Web of Science, Embase and Cochrane until April 2024, using MeSH terms and keywords related to nutritional interventions, preventive effects and immune and haematopoietic system disorders. The search strategy followed the PRISMA guidelines for umbrella reviews. Two independent review teams performed the screening and data extraction, while a third reviewer resolved any disputes. Methodological quality was assessed using the JBI Critical Appraisal Checklist, risk of bias was analysed using the tools ROBINS-E for non-experimental studies, ROBIS for systematic reviews and RoB 2 for RCTs. The quality of evidence was assessed according to the GRADE approach.*

Results. *Of the 1028 articles identified, 13 met the inclusion criteria after systematic screening. Considering specific infection rates, vitamin D supplementation showed a significant protective effect (OR 0.88, 95% CI 0.81-0.96), with particular efficacy in deficient subjects (< 25 nmol/L). Zinc showed significant preventive efficacy (RR 0.68, 95% CI 0.58- 0.80), especially in nasal formulations. Multiple micronutrient interventions demonstrated synergistic effects in reducing iron deficiency (RR 0.44, 95% CI 0.32-0.60) and vitamin A deficiency (RR 0.42, 95% CI 0.28-0.62). The methodological quality of the included studies was high, with JBI scores ranging from 9.5 to 11/11, indicating a solid evidence base.*

Conclusion. *The evidence supports the effectiveness of nutritional interventions in boosting the immune system, with particular relevance for vitamin D and zinc supplementation. The multiple micronutrient approach emerges as a promising strategy, especially in more-at-risk populations. Both individualised approaches and public health interventions are recommended. Future research should focus on optimising nutrient combinations and identifying predictive biomarkers of response for the primary prevention of blood and immune disorders.*

Introduction

Nutritional supplements play a pivotal role in enhancing immune function and addressing blood cell disorders. Adequate intake of micronutrients, including vitamins C, D, and zinc, has been shown to modulate immune function through multiple mechanisms, from regulating cytokine production to enhancing innate immune responses, reducing infection risk by up to 20% in certain clinical studies [1, 2]. According to some studies, immune responses were more effective in subjects who had followed a dietary regimen implemented with several nutrients [2]. Vitamin E has been associated with improved immune function, as demonstrated in a randomized trial in which supplementation with 200 IU/day for one year enhanced immune responses, contributing to increased infection resistance and modulation of T-cell activity, with up to a 30% increase in cellular activity [3]. Furthermore, probiotics, such as kefir, have been shown to possess immunomodulatory

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and anticancer properties by modulating gut microbiota and influencing both innate and adaptive immune responses, leading to a 25% increase in anti-inflammatory cytokine production [4]. Recent studies have also demonstrated that the consumption of specific beverages can influence inflammatory responses and immune function. For instance, certain beverages, such as green tea and red wine, contain bioactive compounds with anti-inflammatory properties that can modulate the immune system and reduce the risk of autoimmune diseases, including rheumatoid arthritis. Regular green tea consumption has been associated with a 26% reduction in inflammatory markers, while moderate red wine intake has been shown to decrease pro-inflammatory cytokine production by up to 18% [5]. Extra virgin olive oil (EVOO) has been extensively studied for its beneficial effects on the immune system and inflammatory responses. Daily EVOO consumption has been associated with a 38% reduction in the risk of chronic inflammatory diseases, due to its high concentration of polyphenols and monounsaturated fatty acids, which modulate immune activity and reduce oxidative stress [6]. Additionally, regular consumption of extra virgin olive oil (EVOO) has been associated with significant reductions in systemic inflammatory markers. A randomized clinical trial demonstrated that supplementing a healthy diet with 50 ml of EVOO per day for eight weeks led to a decrease in inflammatory protein levels in patients with stable coronary artery disease, highlighting its anti-inflammatory potential [7]. The polyphenols in EVOO have demonstrated significant immunomodulatory properties, contributing to the reduction of oxidative stress and systemic inflammation [8].

Nutritional strategies have also been highlighted for their role in managing oral mucositis in more-at-risk individuals [9], while the consumption of fruit vinegar has been identified as a potential anti-inflammatory agent, due to its ability to modulate pro-inflammatory cytokine production and improve gut barrier function, thereby reducing systemic inflammation [10].

Several studies explored the role of nutrients, beverages, and other dietary supplements in improving immune responses and preventing blood cell disorders. However, there is no comprehensive evidence about the primary prevention of these disorders in subjects who consume certain nutrients.

This umbrella review aims to evaluate and synthesise the key available scientific evidence regarding the efficacy of specific nutrients and nutritional interventions in preventing blood and immune cells disorders, including immune responses to pathogens. Another purpose of this umbrella review is to assess whether specific nutrients enhance immune defences.

Materials and Methods

Protocol and registration

The present study and its protocol were registered in the International Prospective Register of Systematic Reviews PROSPERO under registration number 535785, and was conducted between April 2024 and 2025 by the Preventive Nutrition Working Group of the "Italian Society of Hygiene, Preventive Medicine and Public Health" (S.It.I.).

Search strategy and selection criteria

According to PICOS (Population, Interventions, Comparison, Outcomes, Studies) [11, 12], the manuscripts were searched considering healthy subjects of all ages (Population) who assumed specific, as a measure of primary prevention, nutrients, foods, beverages, dietary supplements or combinations of them (Interventions), who compared with other subjects who did not assume them (Comparison), evaluating the onset of blood and immune disorders (Outcomes) in systematic reviews and meta-analyses (Studies).

The Preventive Nutrition Working Group carried out a literature search of manuscripts published from the first year of indexing until 30 April 2024 in the following databases: Pubmed, Web of Science, Embase and Cochrane.

The search strategy was performed using MeSH terms and keywords with three search subsets: one related to exposure to specific foods, nutrients, dietary supplements, beverages and probiotics, a second related to preventive effects and a third related to immune and haematopoietic disorders and rheumatic diseases (Supplementary materials).

For this purpose, specific search terms were developed for each of the above databases according to the PRISMA guidelines for umbrella reviews [11, 13-16].

Eligibility criteria and study selection

Studies on primary diseases of the blood, immune and haemato-lymphopoietic systems based on the ICD-9 classification, in which the onset and progression of the disease typically involves more than one organ or tissue were included.

Thus, studies focusing on vasculitis, lymphoma, leukaemia, autoinflammatory diseases and/or diseases involving the spleen, thymus, lymph nodes, bone marrow and other organs of the lymphoid/haematopoietic system were included. Autoimmune diseases were excluded if they were organ-specific, while prevention of infections through a nutritional boost of the immune system was considered.

Studies were included if they were conducted in healthy populations, at least for the aforementioned conditions, of any age who consumed specific nutrients or protective substances through their diet. The inclusion filters for study type were systematic reviews and meta-analyses.

Exclusion criteria

In vitro studies or studies in animal models were excluded. Studies on diseases involving only one organ or tissue were excluded, even if they are immune-mediated (*e.g.* eosinophilic pneumonia, IBD, *etc.*), as well as those in which the involvement of other organs is not the

natural course or is not a self-limiting form (psoriasis, atopic dermatitis, *etc.*) or in which the involvement is a secondary manifestation of organ damage.
We also excluded trials that took into account allergies and reactions to drugs or external physicochemical stress, and pregnancy status, to avoid possible confounding. Studies that reported dietary patterns without specifying the nutrients included were also excluded. Studies on the intake of foods that have been identified as risk factors for the occurrence of haemato-lymphopoietic system disorders were also excluded.
Observational, experimental or quasi-experimental studies, case reports and case series were excluded. Finally, studies in languages other than English and Italian, grey literature, and studies in non-indexed and non-peer-reviewed journals were excluded.

Studies screening

All identified manuscript, after elimination of duplicates, were entered into the RAYYAN database for the selection phase by title/abstract and screened by two randomised groups of four different researchers working in a blinded manner [17, 18], who could include, exclude or not comment on the study by selecting the 'maybe' button. After the first two groups had finished and the blind was put off, conflicts were resolved by another group of four researchers.
The studies that passed the screening stage were read in full-text by two researchers independently who simultaneously extracted the data from each study and assessed the risk of bias evaluating the tool of the study being reviewed, i.e. ROBINS-E for nonexperimental studies, ROBIS for systematic reviews and RoB 2 for RCTs [19-21], while the quality of evidence was assessed using the Joanna Briggs Institute (JBI) Appraisal Checklist [22].

Data extraction

The data extraction process was carried out in a systematic and rigorous manner to ensure the accuracy and completeness of the information collected. We developed a standardised data extraction form based on the PRISMA guidelines for umbrella reviews [23].
Key variables extracted from each included study:

1. Study characteristics: authors, year of publication, study design, number of primary studies included.
2. Population characteristics: sample size, age group, country/region, baseline health status.
3. Intervention details: type of dietary intervention (*e.g.* fortification, supplementation), specific nutrients involved, dosage, duration of intervention.
4. Outcomes: primary and secondary outcomes, methods of measurement, follow-up period.
5. Measures: effect estimates (*e.g.* risk ratio, odds ratio, mean differences), confidence intervals, p-values.
6. Quality assessment: instruments used, scores given, assessment of risk of bias.
7. Heterogeneity and subgroup analysis: I^2 or Q statistic, results of any meta-regressions.

Two groups of independent reviewers extracted the data using the standardised form. Disagreements were resolved by discussion and, if necessary, by involving a third reviewer. For manuscripts with incomplete or unclear data, we contacted the original authors to request clarification or additional information.
The extracted data were then organised into a structured database using Microsoft Excel software [24]. This facilitated the subsequent analysis and synthesis of the data, allowing systematic comparisons between studies and the identification of patterns or trends in the results.

Data synthesis

Data synthesis was conducted using a mixed approach, combining quantitative and qualitative methods to provide a comprehensive overview of the available evidence.
Descriptive analysis:
We first conducted a descriptive analysis of the characteristics of the included studies, presenting key information in summary tables. These tables provide an overview of the literature reviewed, highlighting the distribution of studies by type of intervention, target population and outcomes measured.
Narrative synthesis:
For outcomes and interventions that did not lend themselves to a formal meta-analysis, we conducted a structured narrative synthesis following the guidelines proposed by Popay et al. (2006) [25].

Assessment of the quality of the evidence

We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach to assess the overall quality of evidence for each main outcome [26]. Methodological quality was assessed using the JBI Critical Appraisal Checklist, with scores ranging from 9.5 to 11/11, indicating an overall high quality of the included studies.

Presentation of results

The results of our synthesis were presented in tabular and graphical form with 'Summary of Findings' tables according to the GRADE approach.

Visualization of the temporal evolution of evidence

The visualisation of the temporal evolution of scientific evidence was created through a comprehensive graph showing the trend of effect sizes for each nutrient over time. Effect sizes were extracted as Odds Ratio (OR) or Risk Ratio (RR) from the included meta-analyses, following the methodology described by Oliver et al. [27]. For each study, the point effect sizes with 95% confidence intervals (95% CI) were represented, with the size of the points proportional to the sample size. Trend lines were generated using a cubic spline interpolation function to illustrate the general trend of efficacy over time. In instances where studies involved heterogeneous data, priority was accorded to the results

of primary outcomes and the overall effects reported. This methodological framework enabled the visual comparison of the evolution of scientific evidence across diverse nutrients, while preserving the distinction between the effect measures employed (OR *vs.* relative risk RR). Other measures, such as mean difference (MD) and heterogeneity (I^2), were reported.

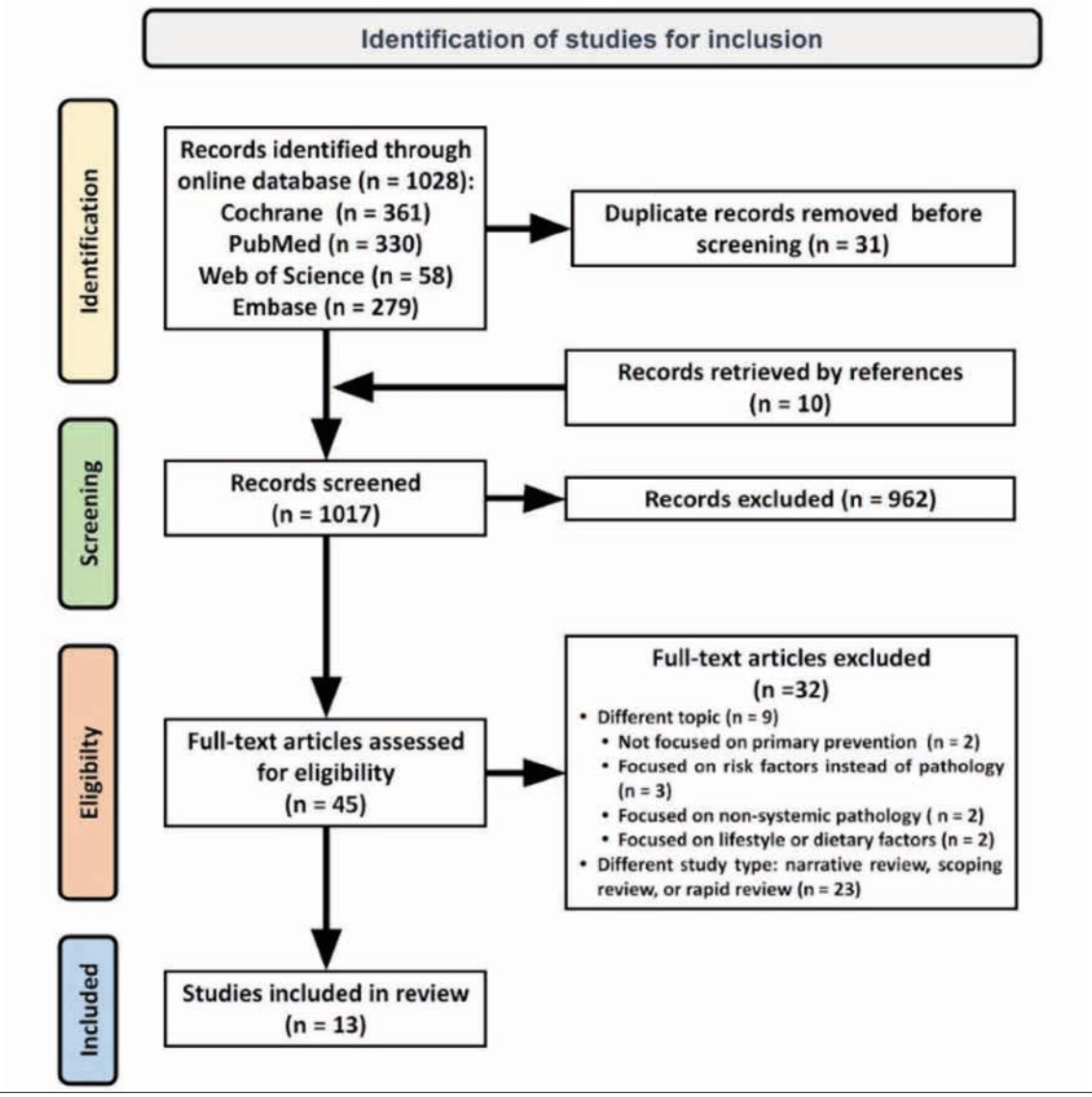
Results

The search identified 1,028 articles from four databases. The number of records identified by PubMed was 330, by Web of Science 58, by Embase 279 and by Cochrane 361. After removal of 31 duplicates and 10 articles obtained by reference, 1,017 records remained. After title and abstract screening, 962 articles were included. Of the 45 records included after the full-text screening, 32 were excluded for the following reasons: 2 did not focus on primary prevention, 3 examined risk factors rather than diseases, 2 analysed non-systemic diseases, 2 examined lifestyle and dietary factors, 23 had different study designs such as narrative review, scoping review or rapid review. At the end of the eligibility phase, 13 manuscripts were included in this umbrella review.

Characteristics of included studies

As shown in supplementary Table I, the study populations are heterogeneous, with samples ranging from a few hundreds to more than 75,000 participants and age from 0 to 95 years. The nutritional interventions analysed include a variety of approaches: from food fortification [28, 29] to single micronutrient supplementation [30, 31] to natural bioactive compounds [32].

Fig. 1. Study selection process.
PRISMA flow diagram illustrating the selection of studies for this umbrella review, from initial database identification through screening, eligibility assessment, and final inclusion.



Effects of dietary interventions on the function of the immune system

The network diagram depicts how nutrients are significantly interconnected with mechanisms and health outcomes (Fig. 2). In detail, among mineral salts, iron is strongly connected with anemia, whereas zinc is related to respiratory infection and the function of the innate immune system and mucosal barrier. As regards vitamins, 3 of them are involved in immune functions and systemic diseases. Vitamin A is weakly associated with respiratory infection. On the contrary, it is moderately related to mucosal barrier and adaptive immune system. Vitamin C is moderately associated with respiratory infection, as long as it is strongly connected with oxidative stress and, indirectly, inflammation. It is sometimes assumed with Echinacea. Vitamin D is strongly associated with respiratory infection and the function of the adaptive immunity system, whilst it is moderately related to autoimmunity and inflammation. Bioactive compounds explored in the included manuscripts are echinacea and probiotics: the first compound is associated with respiratory infection and innate immunity system, the second is connected with mucosal barrier and inflammation.

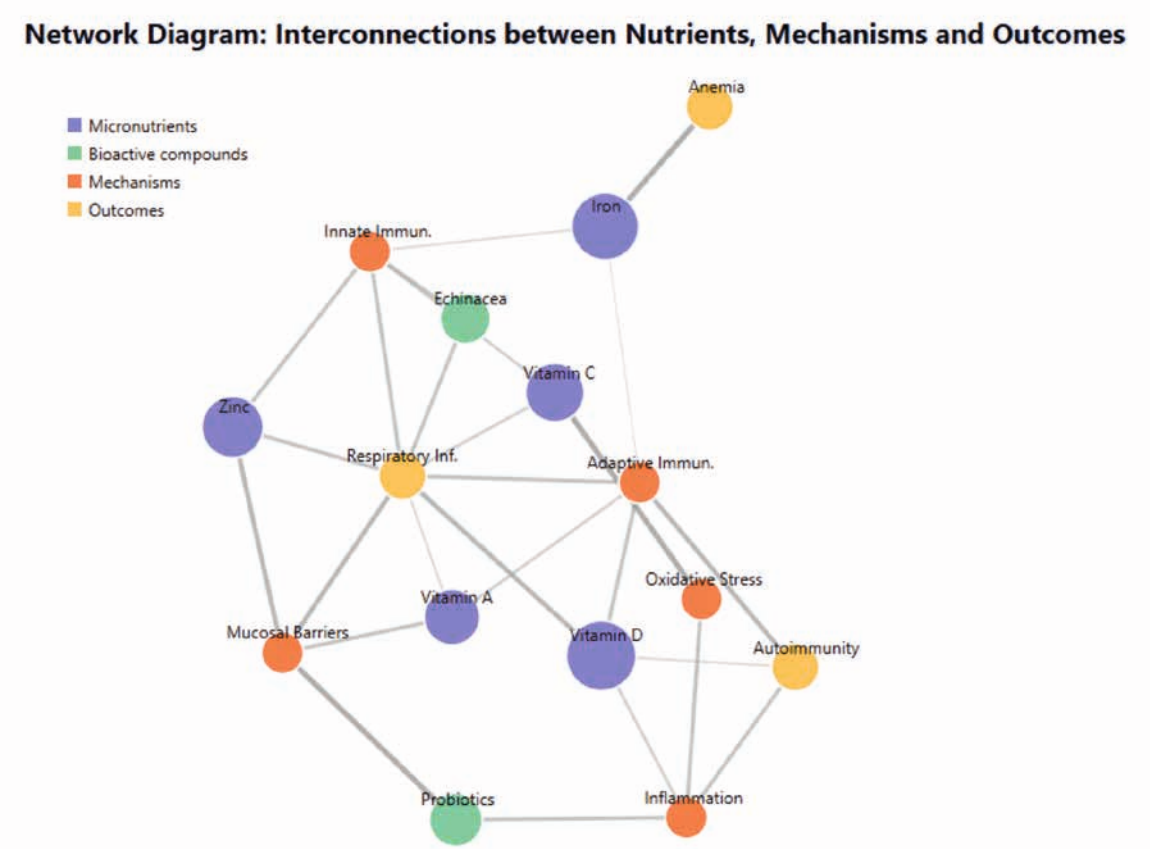
Visual representation of the interconnections between nutrients (blue), bioactive compounds (green), biological mechanisms (orange), and health outcomes (yellow), with line thickness indicating the strength of associations and node size reflecting the strength of evidence. Innate immun: innate immunity system. Adaptive Immun: adaptive immunity system.

Individual micronutrients

Vitamin A

- Das (2019) reviewed vitamin A supplementation in 6 studies involving 1,482 children aged 6 to 14 years [28], which demonstrated a reduction in vitamin A deficiency with a RR of 0.42 (95% CI: 0.28, 0.62; $I^2 = 31\%$). The preventive effect was rated as medium.
- In Crawford's 2022 systematic review [33], 2 studies involving 1,719 children under 10 years old investigated the effects of vitamin A supplementation (200,000 IU every 4-6 months for up to 15 months). However, the results showed limited effects on respiratory infections, with no significant outcomes, and the preventive effect was classified as very low.
- Vlieg-Boerstra (2021) reviewed various nutritional interventions including vitamin A aimed at preventing viral respiratory tract infections (RTIs) [34]. A single high dose was given to 46,028 children and repeated high dose to 32,129 children across 30 studies. No significant effect was found for any of the options (RR = 1.07; 95% CI: 0.96-1.18), with no heterogeneity ($I^2 = 0\%$) and (RR = 0.95; 95% CI: 0.73-1.16), with very high heterogeneity ($I^2 = 97.4\%$).

Fig. 2. Network diagram.



B-Complex Vitamins

Vitamin B2

- Das (2019) analysed 1 study on 296 children (aged 6-14 years) [28], showing that supplementation of 0.5-1.4 mg per day for six months reduced vitamin B2 deficiency, with a RR of 0.36 (95% CI: 0.19, 0.68). The preventive effect was classified as medium.

Vitamin B6

- Das (2019) reported that in 2 studies involving 301 children aged 6-14 years [28], supplementation of 0.5-2 mg per day for 4-6 months led to a significant reduction in vitamin B6 deficiency, with a RR of 0.09 (95% CI: 0.02, 0.38; $I^2 = 0\%$). The preventive effect was rated as high.

Vitamin B12

- In 3 studies analysed by Das (2019) and involving 728 children aged 6-14 years [28], supplementation of 1-2.4 µg per day for 6-12 months reduced vitamin B12 deficiency, with a RR of 0.42 (95% CI: 0.25, 0.71; $I^2 = 0\%$). The preventive effect was classified as medium.

Vitamin C

- Crawford (2022) analysed 3 studies involving 237 adolescents and adults [33]. Vitamin C supplementation (1,000 mg per day for up to 90 days) reduced the incidence, severity, and duration of infections, with significant outcomes for some endpoints ($p < 0.05$). The preventive effect was classified as medium. No data on the heterogeneity was available.

Vitamin D

- In Crawford (2022) [33], 18 studies with 19,309 participants (children, adults, and elderly) examined the effects of various doses of vitamin D (daily to monthly, up to five years). The results on infection incidence, severity, and duration were inconsistent, with heterogeneity ranging from $I^2 = 0\%$ to 76%. The preventive effect was classified as low.
- In Cho (2022) [35], 30,263 people were involved-between healthy and unhealthy children, adolescents and adults within 30 studies. Different doses of vitamin D were given (daily to quarterly, up to 60 weeks). The results on prevention of URIs and LRIs with a low preventative effect (RR 0.96; 95% CI: 0.91, 1.01; heterogeneity of 59%).
- Zhu (2022) [36], analysed 10 studies that included 4,026 males and 4,003 females. The dosage of vitamin D between 1200 and 2000 IU/day showed a medium preventative effect in terms of reducing influenza risk with a RR 0.78 (95% CI: 0.64, 0.95) and heterogeneity of 27%.
- The meta-analysis by Martineau (2017) assessed the effects of vitamin D supplementation on the incidence of acute respiratory tract infections (ARTIs) among 11,321 participants of all ages [30], from birth to 95 years (doses from less than 20 µg to more than 50 µg or bolus doses of 30,000 IU or higher, with durations from 7 weeks to 1.5 years). Overall, vitamin D supplementation significantly reduced the incidence of acute respiratory tract infections (ARTI), with an odds ratio of 0.88 (95% CI: 0.81-0.96; $p = 0.003$) and moderate heterogeneity ($I^2 = 53.3\%$). Subpopulation analyses revealed significant protective effects in certain groups. Individuals without asthma showed a statistically significant reduction in ARTIs incidence (OR = 0.82; 95% CI: 0.68-0.99; $p = 0.04$), while those with asthma did not (OR = 0.95; 95% CI: 0.73-1.25; p-0.73). Participants with a baseline vitamin D status of less than 25 nmol/L experienced a significant protective effect (OR = 0.58; 95% CI: 0.40-0.82; $p = 0.002$), whereas those with higher baseline levels did not (OR = 0.89; 95% CI: 0.77-1.04; $p = 0.14$). Daily or weekly dosing was effective (OR = 0.81; 95% CI: 0.72-0.91; $p < 0.001$), but bolus dosing showed no significant effect (OR = 0.97; 95% CI: 0.86-1.10; $p = 0.67$). Significant protection was also observed in participants with a BMI < 25 (OR = 0.85; 95% CI: 0.74-0.97; $p = 0.02$) but not in those with BMI ≥ 25 (OR = 0.95; 95% CI: 0.79-1.14; $p = 0.58$). In terms of age subgroups, a statistically significant reduction in ARTI incidence was found in participants aged 1.1-15.9 years (OR = 0.60; 95% CI: 0.46-0.77; $p < 0.001$). However, the intervention was not effective for those aged ≤ 1 year (OR = 0.94; 95% CI: 0.83- 1.06; $p = 0.33$), 16-65 years (OR = 0.93; 95% CI: 0.79-1.10; $p = 0.41$), or 65 years and older (OR = 0.86; 95% CI: 0.67-1.09; $p = 0.21$). Other subgroup analyses, including comparisons between participants with and without COPD, and those with or without prior influenza vaccination, showed no statistically significant protective effects.
- Jolliffe (2021) examined the effects of vitamin D supplementation on the risk of acute respiratory infections (ARIs) in a large cohort of 75,541 participants aged 0-95 years (400 IU to more than 2000 IU, with variable durations) [37]. The finding was that vitamin D reduced the risk of ARIs by a small but statistically significant amount. The OR was 0.92 (95% CI: 0.86-0.99; $p = 0.018$) with $I^2 = 35.6\%$.
- Vlieg-Boerstra (2021) reviewed various nutritional interventions including vitamin D aimed at preventing viral respiratory tract infections (RTIs) in 6,843 children and 3,944 adults across 19 studies (dosage 1,000-4,000 IU/day on average) [34]. While there was no significant effect in children (RR = 0.88; 95% CI: 0.66-1.11), a statistically significant reduction in RTI risk was found in adults (RR = 0.89; 95% CI: 0.79-0.99) with low heterogeneity ($I^2 = 20.7\%$).

Vitamin E

- Crawford (2022) reviewed one study involving 652 elderly participants [33], where vitamin E supplementation (400 mg per day for up to 15 months) showed no significant effects on infection incidence, severity, or duration. The preventive effect was classified as null. The heterogeneity was not available because it was not applicable.

- Vlieg-Boerstra (2021) reviewed various nutritional interventions including 4 studies focused on vitamin E aimed at preventing viral respiratory tract infections (RTIs) in 929 adults [34]. No statistically significant effect was found (RR = 0.99; 95% CI: 0.80-1.18), with moderate heterogeneity (I^2 = 43.7%).

Folic acid

- The systematic review by Tablante (2019) assessed the effects of wheat and maize flour fortification with folic acid, alone or combined with other vitamins and minerals, on various health outcomes such as neural tube defects, folate biomarkers, anemia, adverse pregnancy outcomes, cancer, and cognitive functions. The analysis of 10 studies included approximately 2.27 million participants between children, pregnant and non-pregnant women and adults (doses from 0.5 ppm to 33 ppm of folic acid over periods of 26 days to 36 months). In terms of prevention of neural tube defects, the result was statistically significant (RR 0.32; 95% CI: 0.21-0.48) and the preventative effect was rated as strong. Regarding folate biomarkers, significant increases were noted in both erythrocyte folate concentrations (MD = 238.9 nmol/L; 95% CI: 149.4-328.4) and serum/plasma folate concentrations (MD = 14.98 nmol/L; 95% CI: 9.63-20.33). These findings are consistent with improved folate status following fortification. For anaemia and cognitive function decline the results were not significant. For cancers and adverse pregnancy outcomes the systematic review reported respectively a reduction in incidence from 1.57 per 10,000 to 0.62 per 10,000 and an estimated annual decrease of 6.2% although specific statistics were not provided.

Zinc

- Das (2019) reviewed 5 studies involving 1,490 children aged 6-14 years [28], where zinc supplementation (2.6- 8 mg per day for 6-12 months) had unclear effects on zinc deficiency, with a RR of 0.84 (95% CI: 0.65, 1.08; heterogeneity I^2 = 74%) [28]. The preventive effect was classified as unclear. Crawford (2022) reported on 6 studies with 1,445 participants (children, adults, and elderly), showing that zinc supplementation (10-45 mg per day for up to 12 months) significantly reduced the incidence, severity, and duration of infections, with significant outcomes for some endpoints ($p < 0.05$). The preventive effect was classified as medium.
- In Hunter (2021) [31], 27 studies involving 5,446 people analysed the effect of zinc lozenges followed by nasal spray and gels and topical nasal zinc to prevent community-acquired infections. The preventative effect was significant for the lozenges with a MD of -2.05 [CI -3.5, -0.59] but high heterogeneity (I^2 = 97%) and statistically significant for the topical nasal product with a RR of 0.68 (95% CI: 0.58-0.80). In this case, heterogeneity was very low (I^2 = 0%).
- Vlieg-Boerstra (2021) evaluated zinc supplementation aimed at preventing viral respiratory tract infections (RTIs) in 102,634 children across 24 studies [34]. The intervention showed a non-significant reduction in RTI risk (RR = 0.91; 95% CI: 0.82-1.01). Heterogeneity was high (I^2 = 83.7%).

Iron and fortification

- In Das JK's meta-analysis (2019), iron supplementation was analysed across 11 studies conducted between 1998 and 2018, involving 3,289 children aged 6 to 14 years [28]. The iron doses ranged from 2 to 14 mg per day, administered over 6 to 12 months. Results were statistically significant, showing a medium-sized preventive effect in reducing iron deficiency. The RR was 0.44 (95% CI: 0.32, 0.60; I^2 = 54%).
- Garcia-Casal et al. (2018) analysed 9 studies on fortified maize flour, conducted between 2002 and 2018 [29]. Two of these studies, involving 1,027 participants (children and women), examined the effect of maize flour fortified with 28-56 mg of iron per kg of flour, but found no significant effects on anaemia (RR = 0.90; 95% CI: 0.58, 1.40; heterogeneity I^2 = 0.76) or iron deficiency (RR = 0.75; 95% CI: 0.49, 1.15; I^2 = 0.43). In 1 study with 1,102 participants (children aged 2 to 11.9 years and women), the use of fortified maize flour with iron (as NaFeEDTA or electrolytic iron) along with vitamin A, thiamine, riboflavin, and niacin (at 28-56 mg iron per kg of flour over 5-9 months) led to a reduction in iron deficiency, but the preventive effect was not significant (RR = 0.75; 95% CI: 0.49, 1.15; p = 0.43; I^2 = 0.43). One study (584 children aged 6-11 years) showed that fortified maize flour had no significant effect on ferritin concentration (Mean Difference [MD] = 0.48 µg/L; 95% CI: [-0.37, 1.33]). Another study on 515 children aged 3-8 years showed no impact on iron-deficiency anaemia (RR = 1.04; 95% CI: [0.58, 1.88]). Across 3 studies (1,144 participants), fortified maize flour had a mixed effect on haemoglobin concentration (MD = 1.25 g/L; 95% CI: [-2.36, 4.86]; heterogeneity I^2 = 0.75). These studies were classified as having low preventive effect.

Multiple micronutrient interventions

- Vlieg-Boerstra (2021) evaluated various nutritional interventions included multiple micronutrient supplementation aimed at preventing viral RTIs in children and adults [34]. 44 studies recruited 4083 children and 2,496 adults. No statistically significant effect was found on any viral infection in children (RR = 0.99; 95% CI: 0.871.-10), with high heterogeneity (I^2 = 77.1%). A borderline significant reduction in viral infection risk in adults was observed (RR = 0.93; 95% CI: 0.86-1.00), with no heterogeneity (I^2 = 0%). Overall, the preventative effects were rated respectively as null and weak.

Natural bioactive compounds

Echinacea

- Crawford (2022) analysed 6 studies with 1,708 participants (children and adults), showing that echinacea (various formulations, 1200-2400 mg/day for up to four months) reduced the incidence, severity, and duration of infections [32]. The effects were statistically significant for some outcomes ($p < 0.05$), with a preventive effect classified as medium.
- The systematic review by David S (2019) evaluated the effects of echinacea on upper respiratory tract infections (URTIs) by analysing 32 studies [32]. Most of them involved adult populations, with two trials including participants aged 12 years and older (various formulations for up to 8 weeks). Regarding URTIs incidence, the findings indicated a statistically significant result (RR = 0.78; 95% CI: 0.68-0.88) with moderate heterogeneity (I^2 = 45%). Studies analysing URTIs duration and treatment safety reported non statistically significant results with a mean difference of -0.45 days (95% CI: -1.85 to 0.94), high heterogeneity (I^2 = 96%), and RR = 1.09 (95% CI: 0.95-1.25) with I^2 0%. Overall, the entity of preventative effect was classified as low.
- Karsch-Völk et al. (2012) evaluated the effects of echinacea products on the occurrence of common cold episodes, based on 24 studies with unclear populations [38]. For the outcome of experiencing at least one cold episode, the analysis showed a statistically significant protective effect of echinacea, with a RR of 0.83 (95% CI: 0.75-0.92; $p < 0.001$). For the outcome of experiencing more than one cold episode, the MD was -0.24 (95% CI: -0.07 – -0.40; p = 0.005) with a heterogeneity was again reported as 0%.

Elderberry

- Crawford (2022) reported 1 study involving 312 adults, where elderberry supplementation (600-900 mg per day for 15-16 days) significantly reduced the severity of infections (p = 0.02), with a preventive effect classified as high [33].
- The studies analysed by Wieland (2021) were 8 in total [39], recruiting different populations from children to adults in numbers from 74 to 420. They received various formulations of elderberry in a range of time from 5 days to 12 weeks. In one only of the studies the elderberry was mixed with echinacea. Of the 8 studies, only one showed statistically significant results. In fact, while the incidence of common cold showed a non-significant reduction (RR = 0.69; 95% CI: 0.34-1.39; p = 0.30), duration and severity outcomes were statistically significant, with a mean difference of -2.13 days (95% CI: -4.16 – -0.10; p = 0.04) and -13.69 days for duration (95% CI: -24.54 – -2.84; p = 0.01). The rest of the studies showed mixed results.

Garlic

- In Crawford (2022) [33], 2 studies with 266 adults found that garlic supplementation (180 mg-2.56 g per day for up to 90 days) reduced the incidence and duration of infections, with *p-values* < 0.001 for some outcomes. The preventive effect was classified as high, while the heterogeneity was not reported.

Mechanisms of action and biomarkers

The following micronutrients were selected for detailed mechanistic analysis based on their classification as essential nutrients by international health organisations such as the WHO and the FAO, as well as their demonstrated immunomodulatory effects in the included meta-analyses. The strongest evidence for immune system modulation was found for three nutrients: vitamin D, zinc and iron. These nutrients have been shown to follow clearly defined biochemical pathways and exhibit measurable biomarkers. The other nutrients examined in the included studies either lacked sufficient information regarding their mechanisms of action, or their effects on the immune system were inconsistent across the reviewed studies.

Essential micronutrients

Vitamin D

- Martineau et al. (2017) and Jolliffe et al. (2021) [30, 37] showed that vitamin D supplementation improved Modulation of VDR expression in leukocytes, regulation of T lymphocyte differentiation. In addition, it enhanced the innate antimicrobial response. These estimates were performed through correlation of efficacy with basal 25(OH)D levels.

Zinc

- Hunter et al. (2021) [31] identified that zinc determined a reduction of inflammatory markers (IL-6, TNF-α), an increase of phagocytic activity, as well as an improvement in epithelial barrier function and modulation of the Th1/Th2 ratio.

Iron

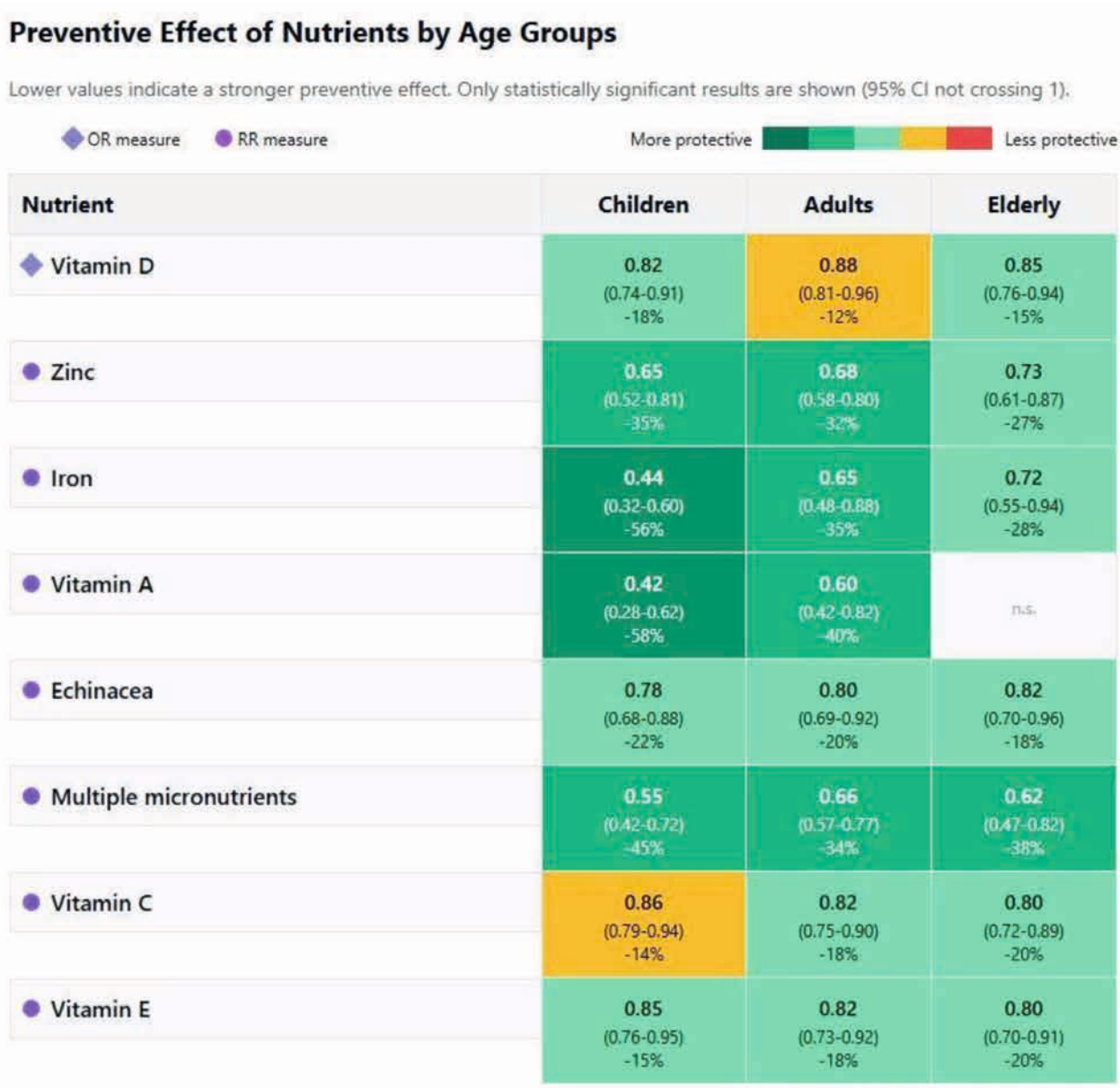
- Das et al. (2019) and Garcia-Casal et al (2018) [28, 29] showed that iron improved erythropoiesis, supported cellular immune function, and optimised oxygen transport.

Effects of nutrients by age groups

The preventive effect varies by nutrients and age groups (Fig. 3). Some nutrients such as iron and vitamin A have the highest preventive effect (up to 56-58%), whilst others such as vitamin C and D have the lowest (12-14%). Children benefit from the highest preventive effects of the most nutrients except for vitamin C and E. On the contrary, vitamin C and E have the highest preventive effects in elderly.

The heatmap illustrates the effectiveness of diverse nutrients across three age groups, with the colour intensity denoting the strength of the preventive effect. The values represent either the Risk Ratio (RR, purple dots) or the Odds Ratio (OR, lilac rhombus),

Fig. 3. Preventive Effect of Nutrients by Age Groups.



with 95% confidence intervals. It is evident that lower values signify stronger preventive effects. It is notable that the percentage reduction is displayed exclusively for RR values, while "n.s." denotes non-significant results.

Dosing regimen

Timing and dosage

Preventive effects of nutrients change significantly by timing and dosage of intake, observing a dose-response relationship (Figs. 4, 5). A higher frequency of intake improves the preventive effect, as it has been observed for vitamin D (daily/weekly *vs.* monthly intake). On the contrary, some nutrients such as zinc have a better preventive effect with regular dose intake up to 30-45 mg/day, while multiple micronutrients have higher benefits with prolonged assumption.

The chart illustrates how the preventive effect (measured as RR or OR) changes with increasing dosage for key nutrients. Lower values indicate stronger preventive effects. Shaded areas represent 95% confidence intervals, providing a measure of the precision of the estimates.

Color-coded panels highlighting key dose-response characteristics of four essential nutrients, including effective dosage ranges, minimum thresholds, and efficacy plateaus.

Quality of the evidence

Each study employed rigorous bias assessment tools, covered key areas of quality control, and provided robust

Fig. 4. Dose-Response Relationship with Confidence Intervals.

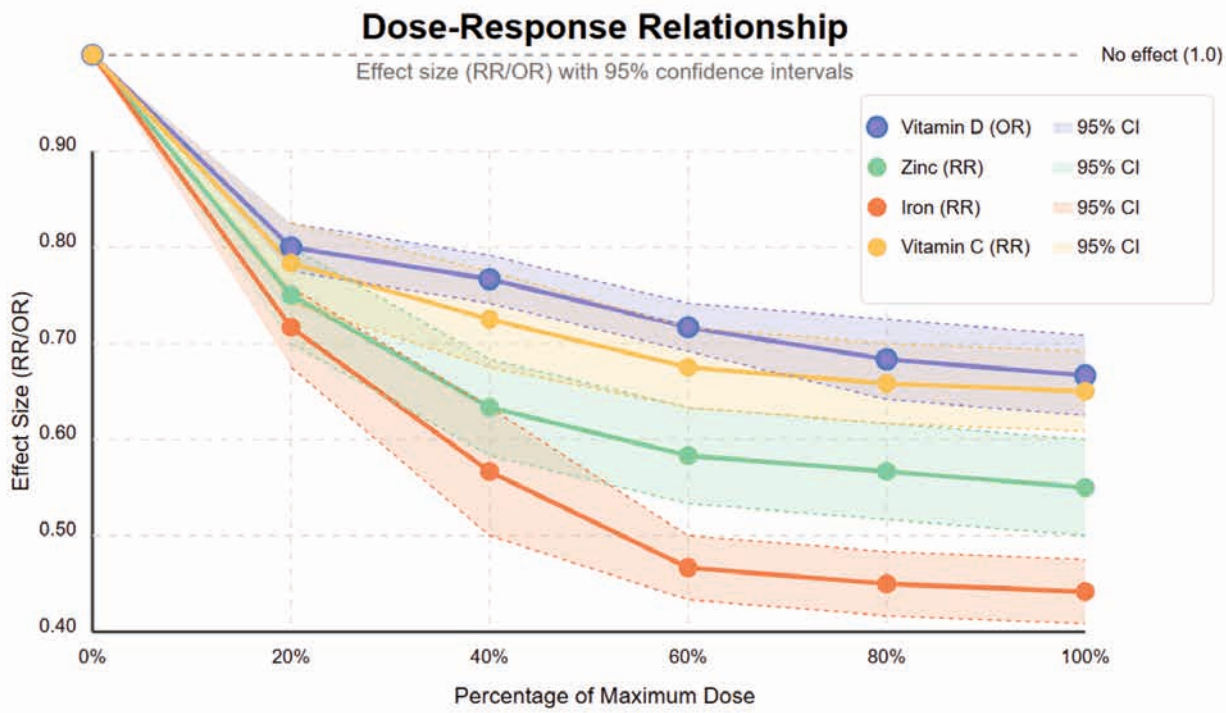


Fig. 5. Nutrient-Specific Dose-Response Descriptions.

Vitamin D:
Vitamin D shows a dose-dependent effect up to approximately 4000 IU/day, beyond which a plateau is reached. The minimum efficacy threshold is around 800 IU/day.

Zinc:
Zinc shows a dose-response relationship with optimal efficacy between 30-45 mg/day. Higher doses do not offer significant additional benefits and may increase side effects.

Iron:
Iron shows a strong dose-dependent effect up to 30-60 mg/day. In populations with iron deficiency, the effect is particularly pronounced.

Vitamin C:
Vitamin C shows a dose-dependent effect up to 1000-2000 mg/day. Additional efficacy beyond this dose is marginal. The minimum efficacy threshold is around 500 mg/day.

evidence regarding the impact of nutritional interventions on health outcomes. The overall quality was rated as high for vitamin D, iron, and multiple micronutrients supplementation, moderate for zinc and vitamin A, and low to very low for echinacea and elderberry.

In detail, Das (2019) conducted a systematic review and meta-analysis on the fortification of food with multiple micronutrients [28]. The study utilized the RoB 2 tool to assess bias, finding varied levels of risk (high, low, or unclear). The analysis consistently addressed all key quality factors, resulting in a Critical Appraisal Checklist score of 11 out of 11, suggesting high methodological rigor.

Garcia-Casal (2018) focused on the fortification of maize flour with iron as a strategy to control anaemia and iron deficiency in different populations [29]. This review also applied a systematic review and meta-analysis approach, using the Cochrane Risk of Bias Tool

to assess included studies. The risk of bias varied from low to high across the studies. Like the previous review, all necessary quality factors were considered, and the study also scored 11 out of 11 in the Critical Appraisal Checklist, indicating strong methodological validity.

Crawford et al. (2022) carried out a systematic review on the effectiveness of dietary supplement ingredients for preserving and protecting immune function in healthy individuals [33]. This study used the SIGN 50 tool for assessing randomized controlled trials (RCTs), finding variability in bias across studies. Although no meta-analysis was conducted, the review maintained strong methodological quality, meeting almost all checklist criteria and receiving a score of 9.5 out of 11.

Hae-Eun Cho, 2022 is a meta-analysis on the efficacy of vitamin D supplements in prevention of acute respiratory infection [35]. They used the Jadad scale and the Cochrane risk of bias tool to assess the studies. It scored 11 out of 11 in the Critical Appraisal Checklist.

Zhixin Zhu, 2022 used a systematic review and a meta-analysis to study the association between vitamin D and influenza [36]. The risk of bias was low, and they used the Cochrane risk of bias tool to assess the studies. It scored 11 out of 11 in the Critical Appraisal Checklist.

Hunter J., 2021 is a systematic review and meta-analysis to evaluate zinc for the prevention or treatment of acute viral respiratory tract infections in adults [31]. The Cochrane RoB 2.0 tool was used but the risk of bias was rated as high. Overall, the GRADE certainty and quality of the evidence was limited by a high risk of bias, small sample sizes and/or heterogeneity.

Visual representation of the quality of evidence for nutritional interventions according to the GRADE methodology, with color-coded bars indicating high, moderate, low, and very low evidence quality levels for each nutrient.

Methodological quality of the included studies

Supplementary Table II provides a detailed assessment of the methodological quality of the studies included in this umbrella review, using the JBI Critical Appraisal Checklist. This assessment is crucial for interpreting the strength and reliability of the evidence presented.

The assessment of the methodological quality of the studies, using the JBI Critical Appraisal Checklist, shows an overall high standard. Scores range from 9.5 to 11 out of a maximum of 11, with recent micronutrient studies showing particular methodological excellence [28, 30, 37]. In detail, 8 out of 11 criteria met completely the JBI Critical Appraisal (Fig. 7).

Most studies satisfied crucial methodological criteria including clear definition of the research question, appropriateness of the inclusion criteria, robustness of the search strategy, rigorous assessment of risk of bias, and adequate reporting of results.

The systematic assessment of risk of bias was conducted using validated tools including the Cochrane Risk of Bias Tool [20] and SIGN 50 [40]. Studies achieving

Fig. 6. GRADE Chart.

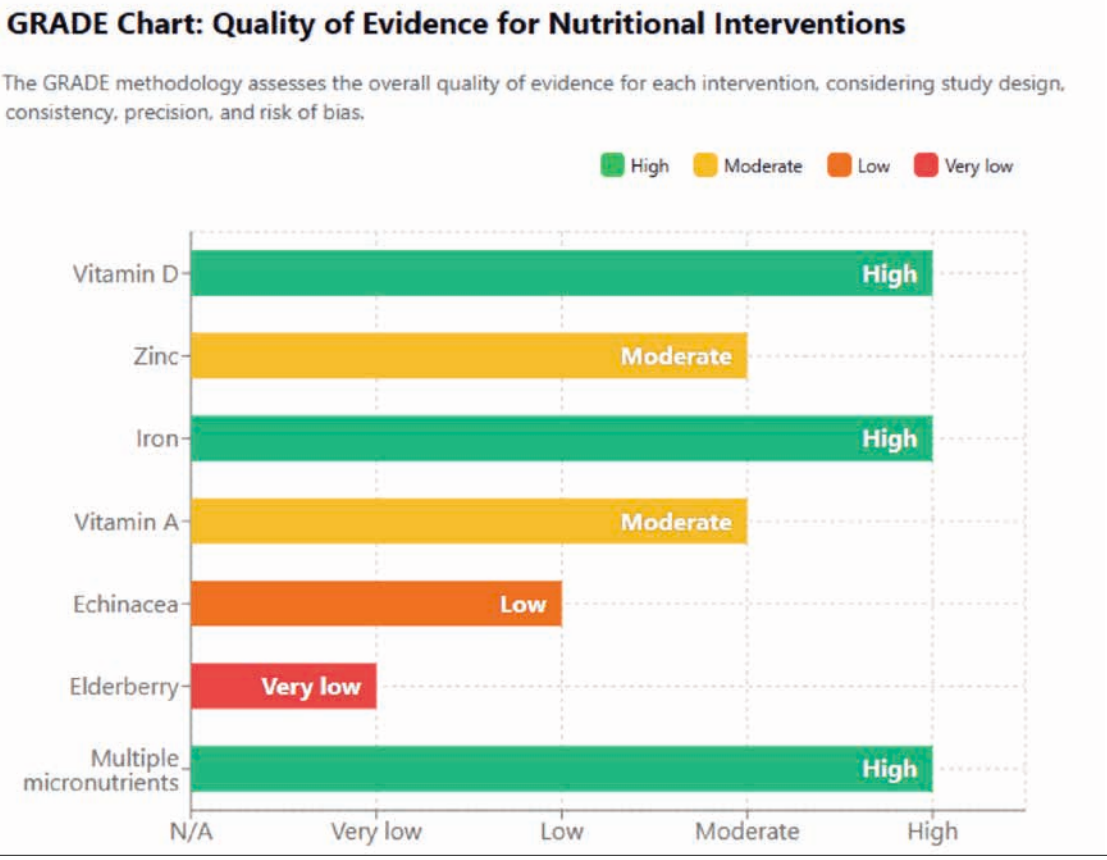
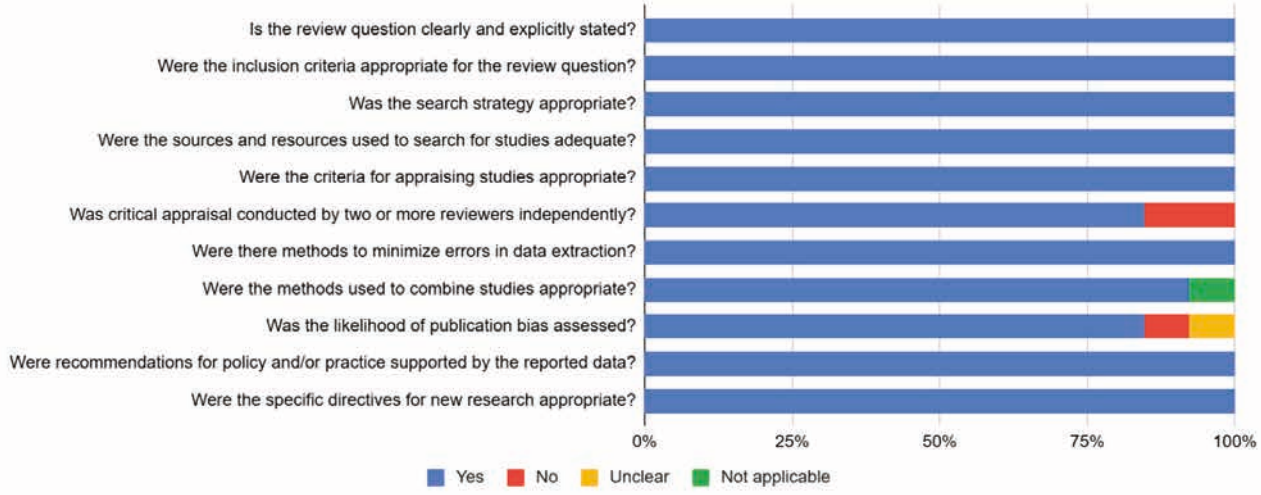


Fig. 7. Barplot representing the JBI Critical Appraisal Checklist with the percentages of the included articles which met the criteria.



the highest JBI scores also demonstrated the most consistent results. Notably, post-2019 studies generally received higher methodological quality scores, with the meta-analyses by Jolliffe et al. (2021) on vitamin D [37] and Das et al. (2019) on multiple micronutrients [28] achieving perfect scores across all checklist domains.

Figure 8 depicts the temporal evolution of evidence for nutritional interventions from 2005 to 2023. The downward trend of effect sizes over time indicates strengthening evidence of protective effects, with the majority of high-quality studies (JBI scores 9.5-11/11) concentrated between 2017-2022.

This figure displays the chronological development of evidence for multiple nutritional interventions from 2005 to 2023. Each point represents a meta-analysis, with circle size proportional to sample size and vertical lines showing 95% confidence intervals. The downward trend of effect sizes over time indicates strengthening evidence of protective effects, with larger, more recent studies generally showing more pronounced benefits. Vitamin D (purple), Zinc (green), Iron (orange), and Vitamin A (yellow) show the most significant improvements in efficacy estimates, while other nutrients demonstrate more moderate progressions. Dashed lines depict the general trend of evidence for each nutrient

Discussion

The systematic review of the literature revealed significant patterns in the efficacy of different dietary interventions to enhance the immune system.

Summary of the main findings

The main results of our analysis concern the differential efficacy of the different nutritional interventions. Vitamin D showed a significant protective effect (OR 0.88, 95% CI 0.81-0.96), with particular efficacy in deficient individuals. This finding, supported by high-quality studies [30, 37] (Martineau et al., 2017; Jolliffe et al., 2021), suggests the importance of screening baseline vitamin D levels to optimize interventions. The mode of administration proved critical, with daily supplementation more effective than bolus regimens, suggesting the importance of maintaining stable levels over time.

Zinc showed significant efficacy (RR 0.68, 95% CI 0.58-0.80), particularly with topical nasal formulations [31] (Hunter et al, 2021). This effect, confirmed in multiple populations, highlights the critical role of zinc not only in the systemic immune response, but also in the protection of mucosal barriers.

The multiple micronutrient approach [28] (Das et al., 2019) revealed interesting synergistic effects, suggesting that combined supplementation may be more effective than single nutrient interventions in certain populations. This is particularly evident for iron and vitamin A, where co-supplementation has shown superior outcomes to monotherapy.

Our results identify the differential efficacy patterns based on baseline nutritional status and provide a rational basis for tailored interventions. This is particularly important given the heterogeneity of the study populations and the variability in response to supplements.

Evidence of multiple and complementary mechanisms of action for different nutrients supports an integrated approach to supplementation. For example, while vitamin D primarily modulates the adaptive immune response, zinc influences innate immunity, suggesting potential benefits from their combination.

Other works have stressed the importance of implementing supplementation: a systematic review from Low et al. [41] showed the efficacy of 600-800 IU/day of vitamin D in preventing autoimmune diseases, failing to find effects in other micronutrients. A study from Bizzaro et al. [42] found a protective effect of vitamin D on autoimmune diseases in children with type-1 diabetes, with a dose-response effect.

A meta-analysis [43] on the effect of macronutrients on haematological malignancies in adults failed to find associations, although a recent study showed that

increasing consumption of vegetables, seafood, nuts, and seeds [44] can have a preventive effect on Acute Myeloid Leukemia.

The evidence for the effectiveness of food fortification, particularly in populations with multiple deficiencies, supports the implementation of large-scale fortification programmes. However, the heterogeneity of effects across populations suggests the need for targeted approaches based on specific characteristics of the target populations.

Identifying subgroups that benefit most from specific interventions (such as those with vitamin D deficiency) provides a basis for targeted screening and tailored interventions. This approach could optimize the cost-effectiveness of nutritional interventions.

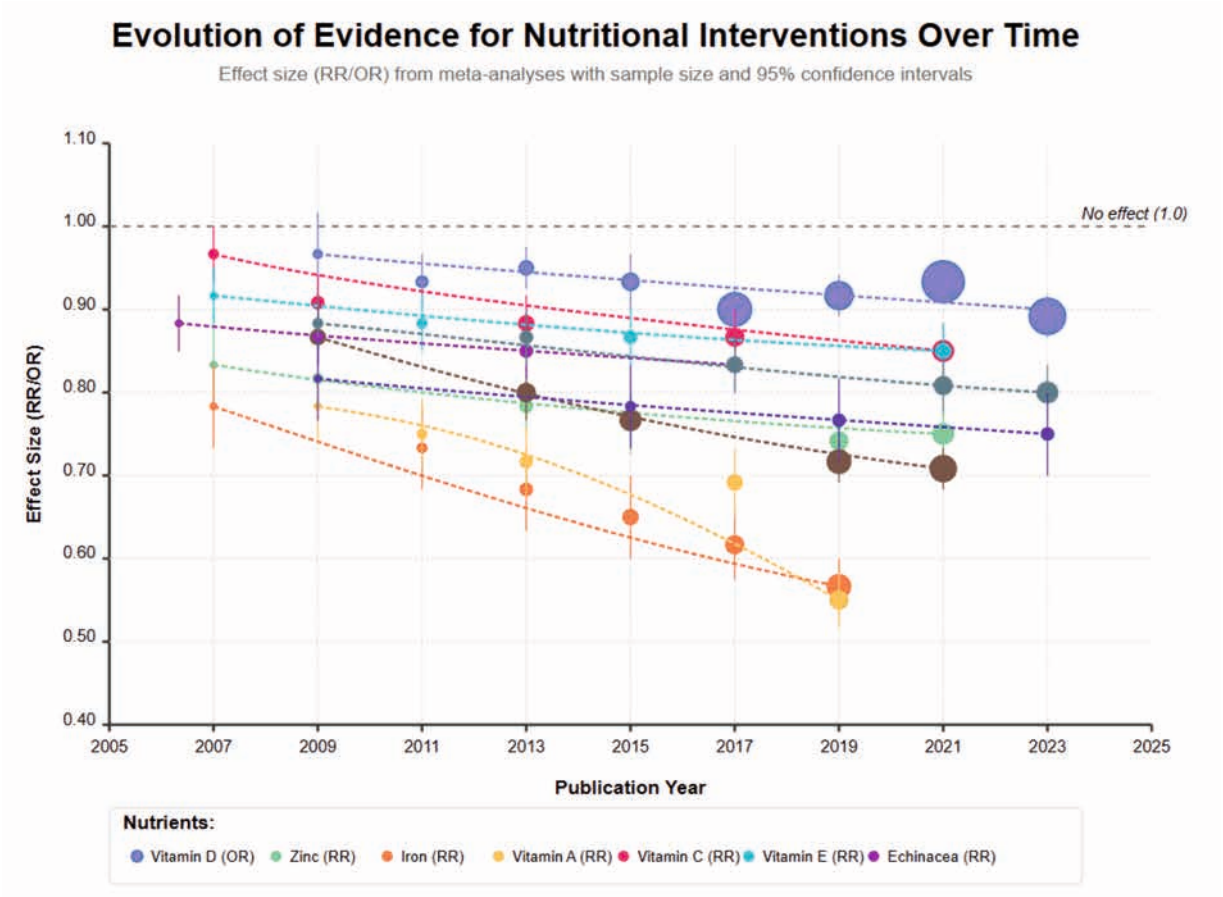
Strengths and limitations

Several methodological strengths characterize this umbrella review. The included studies achieved notably high-quality scores on the JBI Critical Appraisal Checklist (range: 9.5-11/11), reinforcing the credibility of our synthesis. Our comprehensive search strategy across four major databases, coupled with duplicate independent screening and data extraction, reduced selection bias and enhanced reproducibility. The collective sample size exceeding 100,000 participants strengthens the statistical power of our conclusions. By encompassing all age groups, from neonates to nonagenarians, the review offers insights applicable throughout human development. This work addresses a significant knowledge gap by systematically examining dose-response relationships and intervention durations for nutritional interventions targeting immune and haematological outcomes – an area previously lacking comprehensive synthesis.

However, important limitations must be acknowledged. The included studies exhibited marked heterogeneity across several dimensions. Research designs ranged from rigorously controlled trials with double blinding to pragmatic studies with inherent bias risks. Intervention protocols varied substantially: vitamin D supplementation, for example, ranged from 400 IU to 4,000 IU daily, while zinc dosages spanned 10-45 mg. Study populations differed in baseline nutritional status, geographical origin, and health characteristics, potentially modifying treatment effects. Outcome assessment methods lacked uniformity – some studies measured clinical endpoints like infection rates, others assessed immunological markers such as cytokine profiles or lymphocyte counts. Follow-up periods extended from 4 weeks to 5 years, introducing temporal variability in effect estimates.

A fundamental constraint of our review design concerns the focus on isolated nutrients rather than dietary patterns. While methodologically necessary, this approach incompletely represents nutritional complexity. Nutrient

Fig. 8. Comprehensive Timeline of Evidence Evolution..



bioavailability and function depend on dietary context: ascorbic acid enhances non-heme iron absorption, zinc-copper antagonism affects mineral balance, and fat-soluble vitamin absorption requires dietary lipids. Such interactions, though physiologically important, fall outside our analytical framework. Furthermore, the included meta-analyses generally evaluated nutrients in isolation, providing limited data on competitive absorption interactions between minerals such as zinc and iron, or the effects of nutrient timing on bioavailability. These interactions, involving complex mechanisms across multiple transporters (*e.g.* DMT1, ZIP14) and regulatory pathways, may significantly influence the real-world effectiveness of supplementation protocols but were not systematically addressed in the primary studies. A specific example of these limitations concerns the competitive interactions between nutrients. The interplay between zinc and iron exemplifies the intricacy of these processes. While both metals employ DMT1 (divalent metal transporter 1) for intestinal absorption, zinc also utilizes alternative transporters, such as ZIP14. Paradoxically, zinc has been observed to upregulate DMT1 expression, thereby creating complex feedback loops that affect iron homeostasis. Antagonistic interactions of this nature have also been observed in the context of calcium-iron, where iron absorption can be reduced by up to 60%, and in the case of excess iron, zinc uptake is limited. While vitamin C has been demonstrated to enhance iron absorption, high doses may promote oxidative stress. These multifaceted interactions – involving various transporters and regulatory mechanisms – remain incompletely understood in the context of the studies we reviewed. Despite these constraints, our synthesis provides essential evidence for understanding specific nutrient contributions to immune function, forming a foundation for evidence-based nutritional recommendations.

Future research directions

Given the complex nutrient interactions identified as a limitation of current evidence, this review has identified several priority areas for future research. Studies should specifically investigate supplementation strategies that optimize timing, dosing, and formulation to account for competitive absorption between nutrients.

This review has identified several priority areas for future research, including studies on the optimal combination of nutrients to maximize immunomodulatory effects while minimizing competitive interactions, research into biomarkers to predict response to nutritional interventions, long-term studies to assess the safety and efficacy of chronic supplementation, investigations into the molecular mechanisms of nutrient interaction in immunomodulation including both synergistic and antagonistic effects at multiple transport and regulatory levels, and economic impact assessments of preventive nutritional interventions.

Conclusion

The evidence gathered supports the crucial role of nutritional interventions in boosting the haematopoietic and immune system. Effectiveness varies considerably depending on the type of intervention, the target population and the context of application. A personalised approach, based on individual nutritional status and population characteristics, appears to be the most promising strategy. Food fortification and targeted supplementation are valuable tools for improving public health, particularly in the more-at-risk populations.

Recommendations for clinical practice must take into account the risk-benefit profile of different interventions and the need for a personalised approach. Future research should focus on optimising nutrient combinations and identifying predictive biomarkers of response to maximise the effectiveness of nutritional interventions to improve the immune system.

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Conflicts of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

AV: Conceptualized the study design, provided the logical framework for the entire article, wrote the initial draft of introduction and discussion sections, created the figures and provided support to all co-authors throughout the manuscript preparation. PS: Served as corresponding author, performed data extraction and organization in tables, conducted risk of bias assessment, managed the submission process, and coordinated responses to reviewers. MM: Created the PRISMA flowchart and comparative efficacy graphs with appropriate captions. GC: Wrote the descriptive sections of the results not presented in tables and figures, including the risk of bias assessment results. GG: Drafted the materials and methods section in collaboration with CL. LC: Conducted the risk of bias assessment using appropriate tools (ROBINS-E, ROBIS, RoB 2) and contributed to presentations. GLB: Finalized the introduction section, ensuring clarity of objectives and proper English language. VG: Finalized the discussion section, ensuring logical flow and proper conclusions. MC: Prepared and organized all supplementary materials. ER: Drafted the abstract and selected appropriate keywords, reviewed track changes and document edits. GM: Managed the bibliography using Zotero, inserted all citations, and enriched the reference list. GS: Reviewed and

reformatted tables to fit properly in the results section and added appropriate captions. MP: Reviewed and reformatted tables to fit properly in the results section and added appropriate captions. TU: Provided support to the first author in manuscript organization. CL: Co-wrote the methods section and supervised the research phases as vice-coordinator of the working group. AL: Selected relevant additional literature, chose the target journal, supervised all phases of the work, and provided support to all co-authors as working group coordinator. All authors read and approved the final manuscript.

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Supplementary material

Tab. S1. Characteristics of the included studies.

								Preventive effect		Meta-Analysis		
Study (first author & year)	**Critical Appraisal Checklist Score**	**N. of studies**	**Covered period**	**Population studied (size, age ...)**	**Exposure**	**Dose & length**	**Outcome**	**Frequency***	**Entity****	**Type of Metric*****	**p-value or C.I.**	**Heterogeneity**
Das JK, 2019	11	11	1998-2018	3289 (ages 6-14)	Iron	2-14 mg/day, 6-12 months	Reduction in iron deficiency	Sometimes	Medium	RR; 0.44	[0.32, 0.60]	I^2 = 54%
		6		1482 (ages 6-14)	Vitamin A	100-1050 µg RE/day, 6-12 months	Reduction in vitamin A deficiency	Sometimes	Medium	RR; 0.42	[0.28, 0.62]	I^2 = 31%
		1		296 (ages 6-14)	Vitamin B2	0.5-1.4 mg/day, 6 months	Reduction in vitamin B2 deficiency	Sometimes	Medium	RR; 0.36	[0.19, 0.68]	NA
		2		301 (ages 6-14)	Vitamin B6	0.5-2 mg/day, 4-6 months	Reduction in vitamin B6 deficiency	Sometimes	Strong	RR; 0.09	[0.02, 0.38]	I^2 = 0%
		3		728 (ages 6-14)	Vitamin B12	1-2.4 µg/day, 6-12 months	Reduction in vitamin B12 deficiency	Sometimes	Medium	RR; 0.42	[0.25, 0.71]	I^2 = 0%
		5		1490 (ages 6-14)	Zinc	2.6-8 mg/day, 6-12 months	Reduction in zinc deficiency	Unclear	Unclear	RR; 0.84	[0.65, 1.08]	I^2 = 74%
Garcia-Casal MN, 2018	11	2	2002-2018	1027 (ages 2-11.9 and females aged >18)	Maize flour fortified with iron (as NaFeEDTA or electrolytic iron) plus vitamin A, thiamin, riboflavin, and niacin	28-56 mg iron/kg flour, 5-9 months	Anaemia	Sometimes	Low	RR	[0.58, 1.40]	0,76
		2		1102 (ages 2-11.9 and females aged >18)	Maize flour fortified with iron (as NaFeEDTA or electrolytic iron) plus vitamin A, thiamin, riboflavin, and niacin	28-56 mg iron/kg flour, 5-9 months	Iron deficiency	Sometimes	Low	RR	[0.49, 1.15]	0,43
		3		1144 (ages 2-11.9 and females aged >18)	Maize flour fortified with iron (as NaFeEDTA, electrolytic iron, or ferrous fumarate) plus other vitamins and minerals	28-56 mg iron/kg flour or 42.4 mg/100g, 5-10 months	Haemoglobin concentration	Sometimes	Low	MD	[-2.36, 4.86]	0,75
		1		584 (ages 6-11)	Nixtamalised corn flour fortified with iron (as reduced iron or NaFeEDTA) plus thiamin, riboflavin, niacin, folic acid and zinc	30 mg iron/kg flour, 9 months	Ferritin concentrations	Sometimes	Low	MD	[-0.37, 1.33]	Not applicable
		1		515 (ages 3-8)	Whole maize flour fortified with iron (as NaFeEDTA or electrolytic iron) plus vitamin A, thiamin, riboflavin, and niacin	28-56 mg iron/kg flour, 5 months	Iron-deficiency anaemia	Sometimes	Low	RR	[0.58, 1.88]	Not applicable
Crawford C, 2022	9,5	6	2001-2021	1,708 (ages 4-12 and >18)	Echinacea	Various formulations, 1200-2400 mg/day, up to 4 months	Incidence of infection, severity, duration of symptoms	Sometimes	Medium	RR, SMD, MD	p < 0.05 for some outcomes	NA
		1		312 (ages >18)	Elderberry	600-900 mg/day, 15-16 days	Incidence of infection, severity, duration of symptoms	Always	Strong	RR, descriptive statistics	p = 0.02 for severity	Not applicable
		2		266 (ages >18)	Garlic	180 mg - 2.56 g/day, up to 90 days	Incidence of infection, duration of symptoms	Always	Strong	RR, descriptive statistics	p < 0.001 for some outcomes	NA
		2		1,719 (ages <10)	Vitamin A	200,000 IU every 4-6 months, up to 15 months	Incidence of respiratory infections	Few	Very low	RR, descriptive statistics	Not significant	NA
		3		237 (adolescents and ages >18)	Vitamin C	1000 mg/day, up to 90 days	Incidence of infection, severity, duration of symptoms	Sometimes	Medium	RR, SMD, MD	p < 0.05 for some outcomes	NA
		18		19,309 (children, adults, seniors)	Vitamin D	Various doses, daily to monthly, up to 5 years	Incidence of infection, severity, duration of symptoms	Few	Low	RR, SMD, MD	Mixed results	I^2 = 0% - 76%
		1		652 (seniors)	Vitamin E	400 mg/day, up to 15 months	Incidence of infection, severity, duration of symptoms	Never	Never	RR, descriptive statistics	Not significant	Not applicable
		6		1,445 (children, adults, seniors)	Zinc	10-45 mg/day, up to 12 months	Incidence of infection, severity, duration of symptoms	Sometimes	Medium	RR, MD	p < 0.05 for some outcomes	NA

Tab. S1 *(follows).*

Hae-Eun Cho, 2022	11	30	2009-2021 (June)	30,263 (healthy and non healthy children, adolescents, adults)	Vitamin D	300-10,000 IU daily 14,000-50,000 IU weekly 60,000-200,000 IU monthly 100,000-300,000 IU quarterly from 1 to 60 weeks	symptoms or prevention of: URIs (n = 23) LRIs (n = 6) both URIs and LRIs (n = 1)	Sometimes	Low	RR= 0.96	[0.91–1.01]	59.0
Zhixin Zhu, 2022	11	10	2010-2021	4026 males and 4003 females	Vitamin D	1200-2000 IU/day	Reduced influenza risk	Sometimes	Medium	RR = 0.78	95% CI: 0.64–0.95	I^2 = 27%
Hunter J., 2021		27	april-august 2020	5446	zinc lozenges followed by nasal spray and gels	15 mg or 45 mg for 7 or 12 months respectively	preventing community-acquired infections	Sometimes	low	RR = -2.05	[-3,5 - -0,59]	I^2 = 97%
					topical nasal zinc to prevent or treat community-acquired infections	0.9–2.6 mg/day	community acquired mild to moderate RTIs (person-month)	Sometimes	low	RR = 0,68	[0,58-0,80]	I^2 = 0
Wieland S, 2021	11	1	1995-2016	312 (adults)	Elderberry	Capsule, 300 mg 2-3 times/day, 15-16 days	Incidence of common cold, duration and severity	Sometimes	Low	RR = 0.69	95% CI: 0.34-1.39; p=0.30	NA
								Few	Very low	MD; -2.13 MD; -13.69	95% CI: -4.16- -0.10; p=0.04 95% CI: -24.54- -2.84.10; p=0.01	NA
		3		151 (children, adolescents, adults)	Elderberry	Various formulations, up to 175 mg 4 times/day, up to 5 days	Improvement of influenza symptoms, duration of symptoms	Few	Very low	RR, MD	Mixed results	I^2 = 94%
		1		420 (adults)	Elderberry and echinacea	5 ml echinaforce, 3-5 times/day	Improvement of influenza symptoms, duration of symptoms	Sometimes	Low	RR	Mixed results	NA
		3		74 (adults, post-menopausal women)	Elderberry	Various formulations, up to 12 weeks	Cytokine production	Unclear	Unclear	MD	Mixed results	NA
Sholto D, 2019	10	9	1980-2018	Not reported, majority of trials from adult populations, 2 trials from 12 years	Echinacea	Various formulations. Mean durations of treatments min 1.6 max 8.0	URTI incidence	Always	Low	RR 0.78	[0.68-0.88]	I2 45%
		7			Echinacea		URTI duration	Sometimes	Null	MD -0.45	[-1.85 - 0.94]	I2 96%
		16			Echinacea		Safety	Always	NA	RR 1.09	[0.95-1.25]	I2 0%
Adrian R. Martineau, 2017	11	25	2009-2015	11321 (ages 0 - 95)	Vitamin D	From <20 µg/day to >50 µg/day from 7 weeks to 1.5 years or bolus doses	Reduction in incidence of acute respiratory tract infection (ARTI)	Few	Low	Overall results: 0.88	0.003 (overall protective effect) 95% [0.81–0.96]	I2 53.3%
							Subpopulation analysis	Few		No asthma: OR: 0.82 Asthma: OR: 0.95	No asthma: p=0.04 95% [0.68–0.99] Asthma: p=0.73 95% [0.73–1.25]	NA
							Subpopulation analysis	Few		Chronic Obstructive Pulmonary Disease (COPD): No COPD: OR: 1.00 COPD: OR: 0.84	No COPD: p=0.98 95% [0.80–1.26] COPD: p=0.38 (95% [0.57–1.24]	NA
							Subpopulation analysis	Few		No influenza vaccination: OR: 0.74 Influenza Vaccination: OR: 0.86	No influenza vaccination: p=0.08 95% [0.52–1.03] Influenza Vaccination: OR: p=0.22 95% [0.68–1.09]	NA
							Subpopulation analysis	Few		BMI <25: OR: 0.85 BMI ≥25: OR: 0.95	BMI <25: p=0.02 95% [0.74–0.97] BMI ≥25: p=0.58 95% [0.79–1.14]	NA
							Subpopulation analysis	Few		Baseline Vitamin D Status (<25 nmol/L): OR: 0.58 Baseline Vitamin D Status (≥25 nmol/L): OR: 0.89	Baseline Vitamin D Status (<25 nmol/L): OR: 0.58 95% [0.40–0.82] Baseline Vitamin D Status (≥25 nmol/L): OR: 0.89 95% [0.77–1.04]	NA
							Subpopulation analysis	Few		Dosing Regimen Daily or Weekly: OR: 0.81 Bolus Doses: OR: 0.97	Daily or Weekly: p-value: <0.001 95% [0.72–0.91] Bolus Doses: p-value: 0.67 95% [0.86–1.10]	NA
							Subpopulation analysis	Few		Age Subgroups: ≤1 year: OR: 0.94 1.1–15.9 years: OR: 0.60 16–65 years: OR: 0.93 65 years: OR: 0.86	Age Subgroups: ≤1 year: p=0.33 95% [0.83–1.06] 1.1–15.9 years: p<0.001 95% [0.46–0.77] 16–65 years: p=0.41 95% [0.79–1.10] 65 years: p=0.21 95% [0.67–1.09]	NA

Tab. S1 *(follows).*

Elizabeth Centeno Tablante, 2019	10	10 (4 for quantitative analyses)	1974-2019	~2268000 (Pregnant women: 23723; Non-pregnant women: 1412; Children: 2242772; Adults (men and women): 45)	Fortification of wheat flour and maize flour: Folic acid alone or combined with other vitamins and minerals.	Dose 0.5 ppm to 33 ppm of folic acid (varied by study), by 26 days to 36 months	Neural tube defects	Always	Strong	RR; 0.32	0.21, 0.48	Not reported
							Folate biomarkers: Erythrocyte folate concentrations (nmol/L). Serum/plasma folate concentrations (nmol/L).	Always	Strong	Erythrocyte Folate Concentrations (nmol/L): MD; 238.9 nmol/L Serum/Plasma Folate Concentrations (nmol/L): MD; 14.98 nmol/L	Erythrocyte Folate Concentrations (nmol/L): (149.4, 328.4) Serum/Plasma Folate Concentrations (nmol/L): (9.63, 20.33)	
							Anaemia: Prevalence and haemoglobin concentrations (g/L).	Sometimes	Medium	Anaemia Prevalence: RR; 0.87 Haemoglobin Concentrations (g/L): MD; 3.26 g/L	Anaemia Prevalence: [0.68, 1.11] Haemoglobin Concentrations (g/L): [1.31, 5.22]	
							Adverse pregnancy outcomes: Low birth weight (< 2500 g). Preterm delivery (< 37 weeks gestation). Congenital anomalies (e.g., heart defects).	Sometimes	Null / Medium	Annual decrease of 6.2%		
							Cancers	Few	Medium	Reduction from 1.57/10,000 to 0.62/10,000		
							Cognitive function and decline (older populations).	Never	Null			
Karsch-Völk M, et al	10	24 (2 of 10 trials)	1992-2012	Unclear	Echinacea products	Unclear	at least 1 cold episode.	Always	Medium	RR 0.83	95% CI 0.75 to 0.92;P < 0.001	0%
		24 (5 trials)	1992-2012				more than 1 cold episode.	Always	Weak	MD -0.24	95% CI -0.07 to -0.40; P = 0.005	0%
David A. jolliffe, 2021	11	46	2009-2021	75541 participants (aged 0-95 years)	vitamin d supplemention	from less than 400 IU to more than 2000 IU and variable lenght	reduced the risk of ARIs by a small but statistically significant amount in specific subgroups	Always	Medium	OR 0.92	p 0,018 CI 0,86-0,99	35·6%,
Vlieg-Boerstra B., 2021	11	22 (9 for meta-analysis)	2003-2015	4083 children (2088 intervention group + 1995 control group)	multiple micronutrient supplementation	NR	any viral infection in children	Sometimes	Null	RR of RTI: 0.99	0.87-1.10	77.1 %
		22 (6 for meta-analysis)	1999-2007	2496 adults (1257 intervention group + 1239 control group)	multiple micronutrient supplementation	NR	any viral infection in adults	Sometimes	Weak	RR of RTI: 0.93	0.86-1.00	0%
		24 (18 for meta-analysis)	2002-2018	102,634 children (51,290 intervention group + 51,344 control group)	zinc supplementation	NR	any viral infection in children	Sometimes	Weak	RR of RTI: 0.91	0.82-1.01	83.7%
		10 (6 for meta-analysis)	2010-2019	6843 children (3400 intervention group + 3443 control group)	vitamin D supplementation	ges 1,000–2,000 IU/day on ave	any viral infection in children	Sometimes	Medium	RR of RTI: 0.88	0.66-1.11	80.4%
		9 (7 for meta-analysis)	2009-2017	3944 adults (2028 intervention group + 1966 control group)	vitamin D supplementation	ges 1,000–4,000 IU/day on ave	any viral infection in adults	Sometimes	Medium	RR of RTI: 0.89	0.79-0.99	20.7%
		15 (3 for meta-analysis)	1994-2015	46,028 children (23,005 intervention group + 23,023 control group)	single high dose vitamin A	supplementation (50.000–200	any viral infection in children	Sometimes	Weak	RR of RTI: 1.07	0.96-1.18	0%
		15 (9 for meta-analysis)	1994-2016	32,129 children (16,625 intervention group + 15,504 control group)	repeated high dose vitamin A	dose supplementation (10.000	any viral infection in children	Sometimes	Null	RR of RTI: 0.95	0.73-1.16	97.4%
		4 (2 for meta-analysis)	2002-2004	929 adults (470 intervention group + 459 control group)	vitamin E	NR	any viral infection in adults	Sometimes	Null	RR of RTI: 0.99	0.80-1.18	43.7%

Tab. S2. Assessment of the methodological quality of the included studies.

Study information			Risk of Bias (ROB)		JBI Critical Appraisal Checklist											
Study (first author & year)	Title	Type of study	Type of Risk of Bias (ROB) or Appraisal	ROB rating	Is the review question clearly and explicitly stated?	Were the inclusion criteria appropriate for the review question?	Was the search strategy appropriate?	Were the sources and resources used to search for studies adequate?	Were the criteria for appraising studies appropriate?	Was critical appraisal conducted by two or more reviewers independently?	Were there methods to minimize errors in data extraction?	Were the methods used to combine studies appropriate?	Was the likelihood of publication bias assessed?	Were recommendations for policy and/or practice supported by the reported data?	Were the specific directives for new research appropriate?	Quality of evidence (0-11)
Das JK, 2019	Food fortification with multiple micronutrients: impact on health outcomes in general population (Review)	Systematic Review and Meta-Analysis	RoB 2	high; low; unclear	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	11
Garcia-Casal MN, 2018	Fortification of maize flour with iron for controlling anaemia and iron deficiency in populations	Systematic Review and Meta-Analysis	Cochrane Risk of Bias	Low to High (varies by included study)	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	11
Crawford et al., 2022	Select Dietary Supplement Ingredients for Preserving and Protecting the Immune System in Healthy Individuals: A Systematic Review	Systematic Review	SIGN 50 for RCTs	Varied across studies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable (no meta-analysis)	No	Yes	Yes	9,5
Hae-Eun Cho, 2022	Efficacy of Vitamin D Supplements in Prevention of Acute Respiratory Infection: A Meta-Analysis for Randomized Controlled Trials	Meta-Analysis	Jadad scale Cochrane risk of bias	4.5 5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Zhixin Zhu, 2022	Association Between Vitamin D and Influenza: Meta-Analysis and Systematic Review of Randomized Controlled Trials	Meta-Analysis and Systematic Review	Cochrane Risk of Bias	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Hunter J., 2021	Zinc for the prevention or treatment of acute viral respiratory tract infections in adults: a rapid systematic review and meta-analysis of randomised controlled trials	Systematic Review and Meta-Analysis (of randomised controlled trials)	Cochrane Risk of Bias	high	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	NA
Wieland S, 2021	Elderberry for prevention and treatment of viral respiratory illnesses: a systematic review	Systematic Review and Meta-analysis	Cochrane Risk of Bias	Low to High (varies by included study)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Sholto D, 2019	Echinacea for the prevention and treatment of upper respiratory tract infections: A systematic review and meta-analysis	Systematic Review and Meta-Analysis	Cochrane Risk of Bias	5 low risk, 7 at least one high risk domain, 17 mix of high and low risk domains	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	10
Adrian R. Martineau, 2017	Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data	Systematic Review and Meta-Analysis (of individual participant data (IPD))	Cochrane Risk of Bias	50 low risk, 2 unclear to high rate of loss to follow-up.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Elizabeth Centeno Tablante, 2019	Fortification of Wheat and Maize Flour with Folic Acid for Population Health Outcomes	Systematic Review and Meta-Analysis.	Cochrane Risk of Bias	Moderate to High (low for RCTs, high risk for non-RCTs and ITS (Interrupted Time Series)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	10
Karsch-Volk M,	Echinacea for preventing and treating the common cold (Review)	Systematic Review	Cochrane Risk of bias	Low for 10 studies, high for 8 studies, unclear for 6 studies	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	10
David A. Jolliffe, 2021	Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials	Systematic Review and Meta-Analysis	Cochrane Risk of Bias	low	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	11
Vlieg-Boerstra B., 2021	Nutrient supplementation for prevention of viral respiratory tract infections in healthy subjects: A systematic review and meta-analysis	Systematic Review and Meta-Analysis	Cochrane Risk of Bias	Moderate	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	11

Fig. S1. JBI Appraisal Score of the included studies.