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Review

Micronutrient Supplementation and Fortification Interventions on Health and Development Outcomes among Children Under-Five in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis

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Abstract: Micronutrient deficiencies continue to be widespread among children under-five in low- and middle-income countries (LMICs), despite the fact that several effective strategies now exist to prevent them. This kind of malnutrition can have several immediate and long-term consequences, including stunted growth, a higher risk of acquiring infections, and poor development outcomes, all of which may lead to a child not achieving his or her full potential. This review systematically synthesizes the available evidence on the strategies used to prevent micronutrient malnutrition among children under-five in LMICs, including single and multiple micronutrient (MMN) supplementation, lipid-based nutrient supplementation (LNS), targeted and large-scale fortification, and point-of-use-fortification with micronutrient powders (MNPs). We searched relevant databases and grey literature, retrieving 35,924 papers. After application of eligibility criteria, we included 197 unique studies. Of note, we examined the efficacy and effectiveness of interventions. We found that certain outcomes, such as anemia, responded to several intervention types. The risk of anemia was reduced with iron alone, iron-folic acid, MMN supplementation, MNPs, targeted fortification, and large-scale fortification. Stunting and underweight, however, were improved only among children who were provided with LNS, though MMN supplementation also slightly increased length-for-age z-scores. Vitamin A supplementation likely reduced all-cause mortality, while zinc supplementation decreased the incidence of diarrhea. Importantly, many effects of LNS and MNPs held when pooling data from effectiveness studies. Taken together, this evidence further supports the importance of these strategies for reducing the burden of micronutrient malnutrition in children. Population and context should be considered when selecting one or more appropriate interventions for programming.

Keywords: micronutrient; iron; vitamin A; zinc; lipid-based nutrient supplement; fortification; under-five; efficacy; effectiveness

1. Introduction

1.1. Background

Micronutrients (vitamins and minerals) are an essential component of the diet and are necessary for normal cellular and molecular function [1]. While micronutrients are only needed in trace amounts, their deficiency can result in wide-ranging negative health effects. Micronutrient deficiencies are especially a concern in low- and middle-income countries (LMICs), owing to inadequate consumption of food, a lack of dietary diversity, and poor absorption of nutrients due to infection, inflammation, and chronic illness [1]. Concurrent deficiencies are also relatively common. Children under-five are particularly vulnerable, as rapid growth and development necessitates a higher demand for micronutrients [1]. Worldwide, an estimated 43% of children under-five have anemia [2], 29% of children under-five in LMICs are deficient in vitamin A [3], 30% of school-aged children have insufficient iodine intake [4], and 17% of the population are deficient in zinc [5], despite a considerable degree of uncertainty in these estimates. Assessing micronutrient status in children under-five is challenging, especially in LMICs, due to a lack of resources, inconsistent definitions and tools for measuring nutritional status, and inappropriate aggregation of country level data.

Micronutrient deficiencies are associated with undesirable short- and long-term effects, including physical, developmental, and cognitive impairment, increased susceptibility to infections, higher morbidity and mortality, and decreased productivity later in life [6–9]. For example, iron-deficiency anemia in infancy and early childhood has been associated with poor motor development and irreversible cognitive defects, which impair learning and decrease educational attainment [7,10]. Iodine deficiency in childhood has also been shown to be a risk factor for developmental delay [11]. Vitamin A deficiency increases the risk of blindness in children and death from common conditions, such as diarrhea and measles [12]. Finally, zinc deficiency has been linked to impaired growth and depressed immune function, resulting in stunting, wasting, and more severe infections [13,14]. Collectively, it is estimated that undernutrition, including micronutrients deficiencies, stunting, and wasting, causes approximately 45% of deaths in all children or 3.1 million deaths annually [15].

1.2. Current Strategies and Interventions

Several strategies exist to address the problem of micronutrient malnutrition in children under-five in LMICs. These include micronutrient supplementation, lipid-based nutrient supplementation (LNS), large-scale fortification, targeted fortification, and point-of-use fortification with micronutrient powders (MNPs). Fortification is the recommended long-term strategy for increasing the dietary intake of certain micronutrients in the general population, and may be particularly successful if mandated by the government with support from the food industry [1]. However, as safety regulations limit the amount of added micronutrients to that below the tolerable upper intake level [16], individuals who consume small quantities of food, such as young children, may not achieve sufficient micronutrient intake from fortified foods. By contrast, supplementation is an effective short-term solution for preventing and addressing micronutrient deficiencies in specific at-risk groups [1]. An advantage of supplementation and MNPs is that a single dose or serving satisfies daily micronutrient needs.

Micronutrient supplementation involves the provision of a single micronutrient (iodine, iron, folic acid, vitamin A, vitamin B12, vitamin D, zinc) or multiple micronutrients in the form of capsules, tablets, drops, or syrup. Multiple micronutrient (MMN) supplements are defined as a single administration of three or more different micronutrients [17]. LNS are products containing micronutrients embedded in a food base that provides energy, essential fatty acids, and protein, and are usually given in an amount of 20–50 g/day [18]. Small-quantity LNS (SQ-LNS), such as NutriButter (20 g/day), which provides 110–150 kcal/day, are intended for use as home fortificants in LMICs to overcome nutrient deficiencies in the local diet [18]. Large-scale fortification is the process of adding micronutrients to commonly consumed foods (i.e., staple foods and condiments) during central processing to increase their nutritional value. Wheat, flour, rice, salt, sugar, oil, and milk are often selected as vehicles for

large-scale fortification because of their widespread consumption in target populations. Targeted fortification is the practice of adding micronutrients to foods designed for specific subgroups of the population, such as infant formula for infants less than 6 months of age, complementary foods for children over 6 months of age, and foods for institutional programs aimed at school- and preschool-aged children [16]. Targeted fortification does not include complementary foods fortified at the household level. Finally, MNPs are used to add micronutrients to foods at point-of-use, usually when preparing meals in the home or in schools. MNPs are packaged as single-serving sachets containing a dry mixture of micronutrients that can be directly added onto soft or semi-solid foods ready for consumption [19].

1.3. Importance of This Review

Many systematic reviews have been performed to summarize the abundant primary research on micronutrient interventions in children under-five in LMICs [12–14,20–35]. However, we identified several major gaps in the literature. The most critical among these is that the effects of individual micronutrient interventions remain inconclusive, owing to the inclusion of a limited number of trials that are typically individually underpowered. Several large-scale randomized controlled trials have been recently completed, and the inclusion of these studies in the evidence base will enable a larger sample from which to draw robust conclusions. Second, some outcomes have not been studied or remain inadequately studied. For example, the effects of vitamin A supplementation on morbidity and mortality, but not child growth, have been studied in a recent Cochrane review [12]. Third, there remains a lack of effectiveness data to inform real-life benefits of micronutrient intervention programs. The inclusion of such data, as well as understanding of an intervention's biological potential through synthesis of trial efficacy data, will better guide policy making and inform recommendations of the interventions that are likely to be successful in uncontrolled environments. Therefore, the aim of this review was to comprehensively summarize the available evidence from trials and programs on common micronutrient interventions in children under-five in LMICs. The main objectives were to examine the efficacy and effectiveness of five types of interventions on child health and nutritional status: single and MMN supplementation, LNS, targeted fortification, large-scale food fortification, and point-of-use fortification with MNPs.

2. Materials and Methods

2.1. Search Strategy

The protocol has been previously published [36] and was conducted in accordance with PRISMA guidelines. Relevant papers were identified by searching the following electronic databases: African Index Medicus, CAB Abstracts, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, International Initiative for Impact Evaluations (3ie), LILACS, MEDLINE and WHO (eLENA). We also searched clinicaltrials.gov, ProQuest Dissertations and Theses Global, and the WHO International Clinical Trials Registry Platform for relevant non-published studies. We restricted papers to those in English, French, Spanish, or Persian, based on feasibility of translation, and those that had been published on or after 1995. Additional searches for relevant program evaluations and trials were conducted in Google, Google Scholar, and websites of key international nutrition agencies including UNICEF, GAIN, Emergency Nutrition Network, IZiNCG, World Food Program, Sight and Life, Nutrition International, Hellen Keller International, and the Iodine Global Network. The reference lists of reviews and included studies were manually searched to identify any missed papers. Searches were initially completed in June 2018 and were updated on 29 October 2019. The MEDLINE search strategy can be found in Text S1.

2.2. Study Selection and Eligibility Criteria

Studies were eligible for inclusion if they (i) were a randomized or non-randomized controlled trial, controlled before-after study, or interrupted time series study in which outcomes were assessed at a

minimum of three times before and after the implementation of the intervention, (ii) were conducted in healthy children 1 month to 5 years of age living in an LMIC, (iii) compared the effect of a micronutrient supplementation intervention with that of an inactive (i.e., placebo, no intervention, or standard of care) or active control intervention (i.e., different composition of micronutrients or comparison of MMN supplementation with LNS), and (iv) examined one of the following primary or secondary outcomes. Primary outcomes include all-cause mortality, cause-specific mortality (diarrhea, lower respiratory tract infection including pneumonia, malaria, measles, meningitis, and other), and nutritional status (anemia, stunting, wasting, and underweight). Secondary outcomes include morbidity (diarrhea and lower respiratory tract infection), micronutrient concentrations/deficiencies (folate, iron, hemoglobin concentration, vitamin A, vitamin D, and zinc), growth (height, weight, length-for-age, weight-for-age, weight-for-height, head circumference, mid-upper arm circumference, and body mass index), mental and motor development, and adverse effects (bulging fontanelle, fever, gastrointestinal, headache, irritability, kidney stones, stained teeth, and other).

The micronutrient supplementation may be a single micronutrient (folic acid, iodine, iron, vitamin A, vitamin D, vitamin B12, or zinc) or MMN supplementation (≥3 micronutrients), iron-folic acid supplementation, or LNS, administered by any route and at any frequency in the form of tablets, capsules, drops, syrups, or foodlets. We also considered large-scale food fortification of staple foods or condiments, targeted fortification of formula (for infants under 6 months of age) or complementary food (for children 6 months of age and older), and point-of-use fortification with MNPs. LMICs were defined using the classification by the World Bank Group in the year of the study initiation. Studies in children outside the 1 month to 5 years age range were eligible if it was possible to isolate data for participants within the specified age range or if the age of children at baseline (mean or median) was within that range. Studies with co-interventions (e.g., anthelmintics or nutrition education) were eligible only if identical co-interventions were given to the intervention and comparison group. For trials with relevant interventions in multiple arms (e.g., varying formulations or dosages), we included only the intervention–control comparison that was most similar to other studies of that intervention type. However, for studies in which it was difficult to determine the most similar intervention arm, we combined the relevant groups into a single pairwise comparison. Apart from interrupted time-series studies, for which a comparator control group was not necessary, studies must meet all four criteria to be eligible for inclusion. We excluded single-arm trials with no control groups, studies in which the intervention was administered to the mother before or during pregnancy rather than to the infant or child, studies in disease-specific populations, and studies on the effect of supplementation for the purpose of treatment of micronutrient deficiency rather than for prevention.

Titles, abstracts, and full texts were screened for inclusion using the specified inclusion/exclusion criteria by two independent reviewers using an online systematic review platform (Covidence). After removal of duplicates, titles were screened independently, and if the title provided insufficient information, then the abstract was screened to determine eligibility for full text screening. Disagreements at the full text screening stage were resolved by consensus of the two reviewers or independently by a third reviewer.

2.3. Data Collection and Measurement

Using a piloted data collection sheet, two reviewers independently extracted information from eligible studies. Data extracted included general study characteristics (study setting, study population, study design, duration of data collection, study attrition), details on the intervention (type, duration, frequency, dosage, formulation, level of implementation, food vehicle) and control, funding sources, information on quality assessment, and quantitative outcomes (subgroups, subgroup sample sizes, outcome measures, effect estimates, and measures of uncertainty). For program evaluations, we also collected information on indicators of activity (policies, production and supply, delivery systems, quality control, and behavior change communication) and output (access and coverage, and knowledge and appropriate use). When necessary, data for each outcome were converted into a consistent format

(e.g., means and standard deviations) with the same units, such that the direction of effect always corresponded to an increase or decrease in the measure. We extracted both final (post-intervention) measurements and change from baseline scores.

To avoid double counting of participants, studies were grouped by setting, population, intervention type, and program (if applicable). Studies that included participants from the same population were combined and coded as a single study.

2.4. Risk of Bias and Quality Assessment

Two independent reviewers used the Cochrane Risk of Bias Tool and the Cochrane Effective Practice and Organization of Care (EPOC) guidelines to assess risk of bias of eligible studies as high, low, or unclear for each criterion [37,38]. Randomized controlled trials were assessed on the following: random sequence generation, concealment of allocation, blinding of participants, personnel and outcome assessors, selective reporting, and other sources of bias. We also considered the following criteria for non-randomized controlled trials and controlled before–after studies: similarity of baseline characteristics, similarity of baseline outcome characteristics, adequate prevention of knowledge of allocated interventions, and adequate protection against contamination. Interrupted time-series studies were assessed on the following: intervention independent of other changes, shape of intervention effect pre-specified, intervention unlikely to affect data collection, adequate prevention of knowledge of the allocated interventions, incomplete outcome data, selective outcome reporting, and other sources of bias. All disagreements were resolved by a third reviewer.

The GRADE tool was used to assess the quality of evidence for each primary and secondary outcome on five criteria: study limitations, consistency of effect, imprecision, indirectness, and publication bias. Quality of evidence may be upgraded if there was a large magnitude of effect, a dose response gradient, or an effect of residual confounding. Quality of evidence may be downgraded if there was a high risk of bias in individual studies, indirectness of evidence, inconsistent results across studies, imprecision of results, or publication bias.

2.5. Statistical Analyses

Statistical analyses were performed using Review Manager 5.3. We performed standard meta-analyses to generate a summary risk ratio (events per child) or rate ratio (events per child year) and 95% confidence interval (CI) for each dichotomous outcome or a mean difference (MD, if studies used the same scale to assess the outcome) or a standardized mean difference (SMD, if studies used different scales to assess the outcome) and 95% CI for each continuous outcome. Final (post-intervention) measurements and change from baseline scores were pooled in meta-analyses with MDs where applicable but not with SMDs, as differences in standard deviation in the latter case do not represent differences in the measurement scale, but rather in the reliability of the measurement. For continuous outcomes, the inverse variance random effects model was used due to expected variability in interventions, settings, and methods across studies, and to weight studies by variance of the effect estimate. Effect estimates for dichotomous outcomes were calculated using the Mantel–Haenszel random effects model. However, in some cases, the inverse variance model was used if at least one study in the analysis reported effect estimates only. We pooled the most adjusted estimates (when possible). Study characteristics of studies deemed inappropriate for meta-analysis due to substantial methodological or statistical heterogeneity were summarized in a table (Table S1). We followed an intention to treat analysis for randomized controlled trials. Author-defined control groups (e.g., placebo or no intervention) were used and pooled for each outcome. If a study had multiple eligible arms that received different interventions, they were included in the meta-analyses as separate intervention–control comparisons. Findings from non-randomized controlled trials, controlled before–after studies, and interrupted time-series designs were analyzed and reported separately. Clustered randomized effectiveness trials were pooled with both efficacy and effectiveness studies. Outcomes with data reported by fewer than 3 studies were not meta-analyzed. Studies that

incorporated a cluster randomized design were adjusted for clustering by reducing the size of the trial to its effective sample size or by inflating the standard error. Adjustments were not made if authors had adjusted for clustering. Statistical heterogeneity was assessed by visual inspection of forest plots, I^2 statistic and Chi^2 test (p value of <0.05 was considered statistically significant). For outcomes with data reported by more than 10 studies, we assessed publication bias visually by inspection of funnel plots and statistically by Egger regression [39].

Subgroup meta-analyses were conducted on the primary outcomes according to a priori defined sources of potential clinical and methodological heterogeneity: age of participants at baseline (1–5 months, 6–11 months, 12–23 months, and 24–59 months), gender (males and females), World Health Organization (WHO) regions (African, European, Eastern Mediterranean, Region of the Americas, Southeast Asia, and Western Pacific), nutritional status at baseline (anemic and non-anemic, stunted and non-stunted, and underweight and normal weight), intervention duration (<3 months, 3–5 months, and 6–12 months), and intervention frequency (daily and intermittent). A subgroup meta-analysis was conducted only if there was at least one subgroup with 3 or more studies.

3. Results

3.1. Literature Search and Study Characteristics

Of the 35,924 papers identified in the database search and 2301 identified from grey literature, 197 unique studies were eligible for inclusion (Figure 1). Of these studies, 121 studies were randomized controlled trials [40–160], 57 were cluster randomized controlled trials [161–217], 11 were non-randomized controlled trials [218–228], 2 were natural experiments [229,230], 4 were controlled before-after studies [231–234], 1 was an interrupted time-series study [235], and 1 was a propensity score matched retrospective cohort study [236]. 86 studies were conducted in Asia [43,48,49,54,55,57,59–62,69,72–76,78–80,83,86,87,92,97,98,107,110,117,119–123,129,131,134,138,139,141,143,144,146,148,149,151–153,156,157,159,161,162,164,169,176–178,180,184,187,190–194,196,197,199–201,204–208,213,215,218,223,224,228–231,234,235], 64 in Africa [40–42,45–47,50,53,56,63,65–68,70,71,82,84,85,88,94–96,99,101,104,105,108,109,111–116,118,127,130,136,137,140,142,147,150,155,158,165,172,174,175,181,183,185,186,188,203,209,211,212,214,216,226,233,236], 26 in South America [58,64,91,100,102,128,132,135,145,166–168,170,171,179,182,189,195,210,217,219–222,225,227] and 20 in North America [51,52,77,81,89,90,93,103,106,124–126,133,154,160,163,173,198,202,232]. One trial spanned three continents: Africa, Asia, and South America [44].

Sixty-one studies were on interventions that were insufficient to be pooled or reported outcomes in a format that could not be incorporated in the meta-analysis. These studies are summarized in a table format only (Table S1). The remaining 136 unique studies contributed data to the meta-analyses: 34 studies were on MNPs (32 efficacy and 9 effectiveness intervention–control comparisons), 13 studies on targeted fortification (all efficacy intervention–control comparisons), 15 studies on LNS supplementation (15 efficacy and 6 effectiveness intervention–control comparisons), 9 studies on large-scale fortification (all efficacy intervention–control comparisons), 14 studies on MMN supplementation (all efficacy intervention–control comparisons), 28 on iron supplementation (all efficacy intervention–control comparisons), 31 on zinc supplementation (all efficacy intervention-control), 4 on iron-folic acid supplementation (all efficacy intervention–control comparisons), and 16 on vitamin A supplementation (all efficacy intervention–control comparisons). Study characteristics of all included studies can be found in Table S2. All forest plots that are not presented in the results can be found in Figure S1.

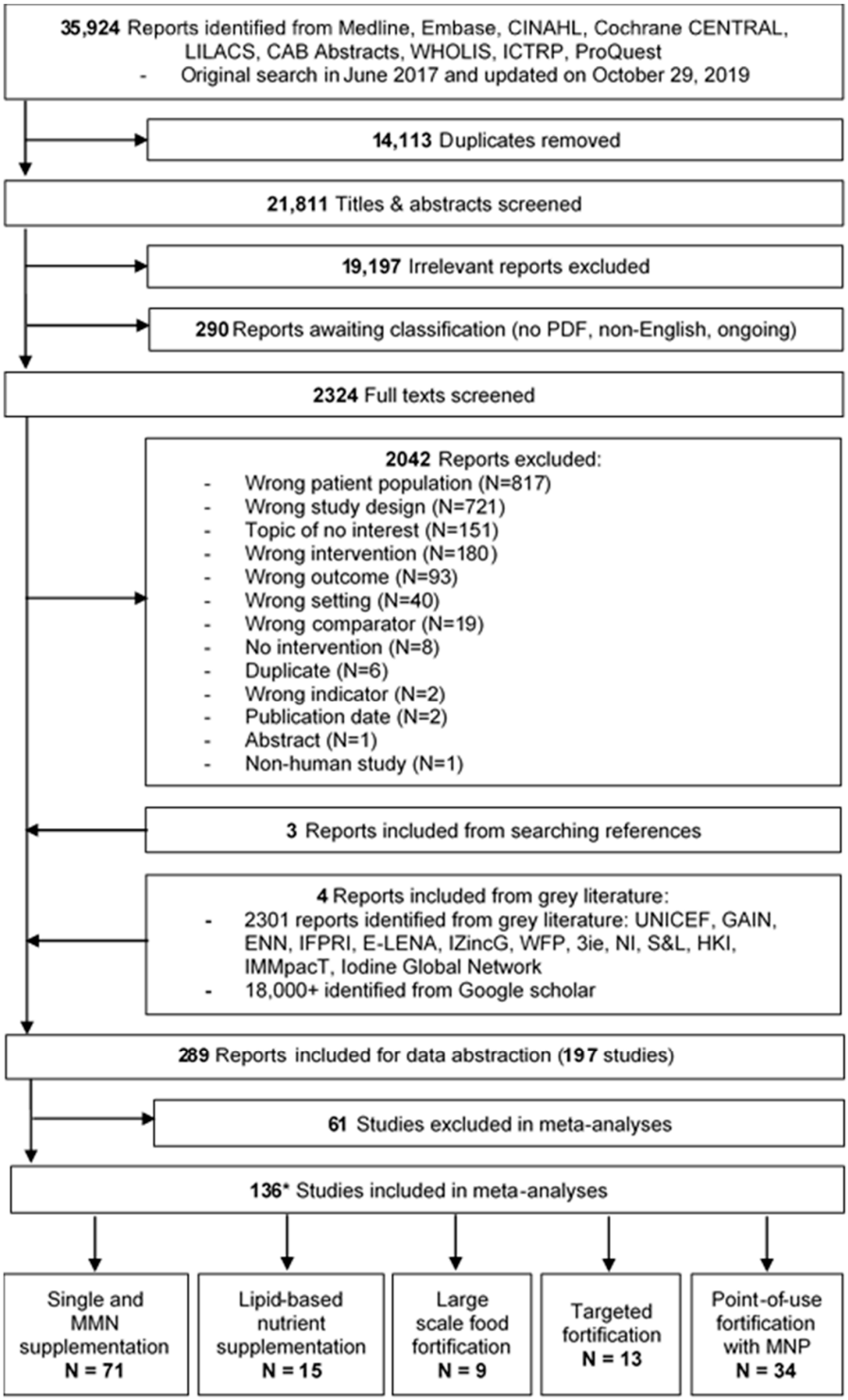

Figure 1. Screening and selection of studies included in the meta-analysis. *Some studies had multiple intervention arms that included different intervention types.

3.2. Meta-Analysis

3.2.1. Efficacy of Vitamin A Supplementation

Compared with placebo/no intervention, vitamin A supplementation was found to reduce the risk of all-cause mortality by 10% when cumulative incidence data was combined (RR 0.90, 95% CI 0.80 to 1.02; I^2 = 26%, p = 0.10), though the upper CI has just crossed the line of no effect. However, we noted

no significant effect on all-cause mortality when incidence rate data was combined. For secondary outcomes, vitamin A significantly increased plasma retinol concentration (MD 0.33 μmol/L, 95% CI 0.01 to 0.65; I^2 = 99%, p = 0.04). No significant effects were observed for the other secondary outcomes.

3.2.2. Efficacy of Zinc Supplementation

Zinc supplementation had no significant effect on the risk of anemia, stunting, wasting, and all-cause mortality. As expected, zinc supplementation decreased the risk of zinc deficiency (RR 0.37, 95% CI 0.22 to 0.62; I^2 = 93%, p = 0.0001). Zinc supplementation also decreased the incidence of diarrhea (RR 0.89, 95% CI 0.82 to 0.97; I^2 = 86%, p < 0.008). No significant effects were observed for any other secondary outcome.

3.2.3. Efficacy of Iron Supplementation

Iron supplementation was associated with a reduced risk of anemia (RR 0.55, 95% CI 0.44 to 0.70; I^2 = 82%, p < 0.00001) (Figure 2). Subgroup analyses by age at baseline showed a trend towards a greater reduction in the risk of anemia among younger (1–5-month and 6–11-month age groups), as compared to older (24–59-month), children, though the test for subgroup differences was not significant (p for subgroup differences = 0.22). A greater reduction in the risk of anemia was observed among non-anemic, versus anemic, children at baseline (p for subgroup differences = 0.07) and among those who took iron supplements for 3–6 months, versus 6–12 months, (p for subgroup differences = 0.006), though data in the latter groups is lacking. No significant effects of iron supplementation were observed for the other primary outcomes (stunting and wasting). For the secondary outcomes, iron supplementation increased hemoglobin concentration (MD 6.02 g/L, 95% CI 4.28 to 7.76; I^2 = 97%, p < 0.00001), plasma/serum ferritin concentrations (MD 20.48 μg/L, 95% CI 13.41 to 27.55; I^2 = 95%, p < 0.00001), mental development (SMD 0.14, 95% CI 0.01 to 0.28; I^2 = 3%, p = 0.04), and motor development (SMD 0.28, 95% CI 0.15 to 0.40; I^2 = 0%, p < 0.0001), and decreased risk of iron deficiency (RR 0.21, 95% CI 0.12 to 0.39; I^2 = 94%, p <0.00001) and iron deficiency anemia (RR 0.14, 95% CI 0.04 to 0.54; I^2 = 88%, p = 0.004). There were no significant effects of iron supplementation on other secondary outcomes.

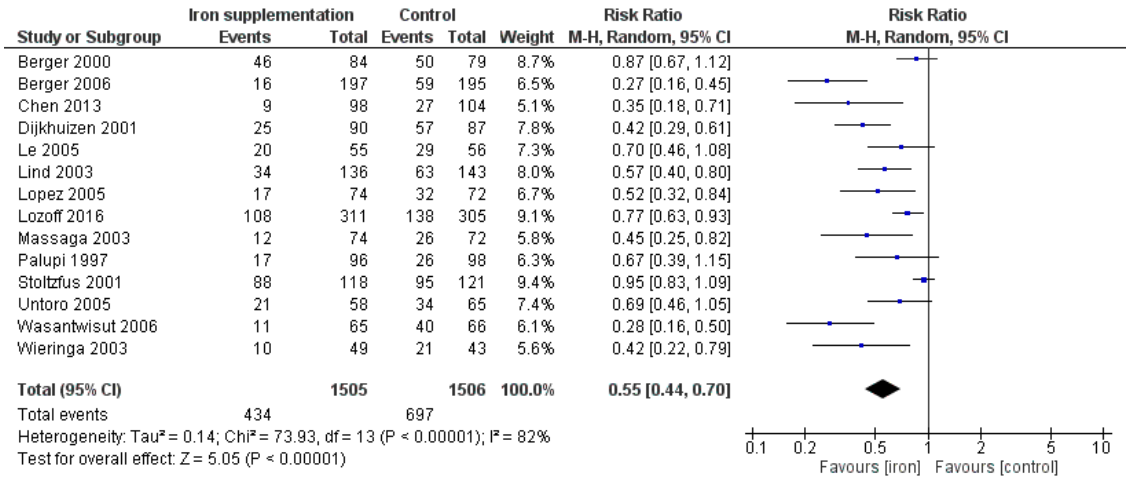

Figure 2. Iron supplementation versus placebo/no intervention (efficacy studies) on the risk of anemia (hemoglobin concentration < 110 g/L).

3.2.4. Efficacy of Iron-Folic Acid Supplementation

Iron-folic acid supplementation was found to significantly reduce the risk of anemia compared with placebo/no intervention (RR 0.80, 95% CI 0.66 to 0.97; I^2 = 65%, p = 0.02) (Figure 3). Subgroup analyses by frequency of supplementation showed a significant difference in risk of anemia by daily

versus weekly iron-folic acid supplementation, with weekly regimens showing greater benefit (p for subgroup differences = 0.01), though only 1 study contributed data to the latter group. For the secondary outcomes, supplementation with iron-folic acid increased hemoglobin concentration (MD 3.06 g/L, 95% CI 1.16 to 4.97; I^2 = 92%, p = 0.002). No significant difference between supplementation and control groups was observed for incidence of diarrhea.

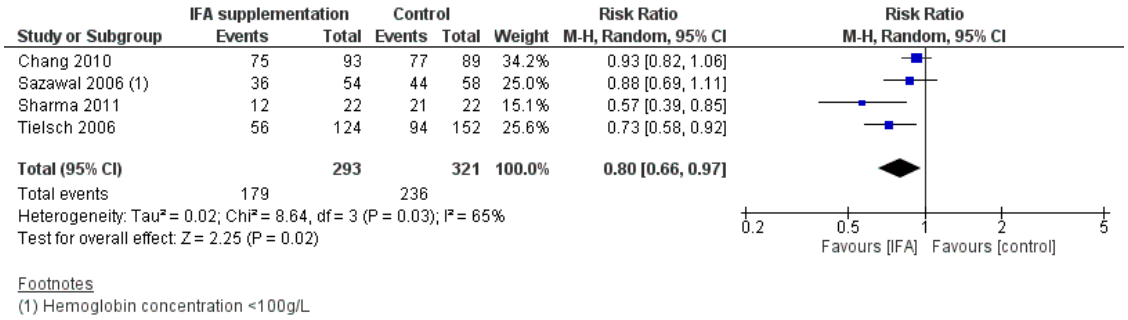

Figure 3. Iron-folic acid supplementation versus placebo/no intervention (efficacy studies) on the risk of anemia (hemoglobin concentration < 110 g/L).

3.2.5. Efficacy of MMN Supplementation

MMN supplementation was associated with a reduced risk of anemia (RR 0.69, 95% CI 0.56 to 0.85; I^2 = 79%, p = 0.0004) (Figure 4). There appeared to be a greater reduction in risk of anemia among children aged 6–11 months compared to those aged 1–5 months at baseline (p for subgroup differences = 0.03), and among children who took MMN supplementation daily as compared to intermittently (p for subgroup differences = 0.05). Significant differences were also observed by region, where greater reductions in the risk of anemia were noted among children in the Americas, Western Pacific, and African regions, as compared to Southeast Asia (p for subgroup differences = 0.001), though sample size was not evenly dispersed among regions. MMN supplementation was associated with increased height (MD 0.36 cm, 95% CI 0.01 to 0.71; I^2 = 0%, p = 0.04), length-for-age (z-score) (MD 0.09, 95% CI 0.00 to 0.17; I^2 = 43%, p = 0.04), hemoglobin concentration (MD 4.40 g/L, 95% CI 2.91 to 5.90; I^2 = 97%, p < 0.00001), plasma/serum ferritin concentration (MD 12.55 µg/L, 95% CI 3.93 to 21.27; I^2 = 62%, p = 0.004), plasma/serum retinol concentration (MD 0.11 µmol/L, 95% CI 0.07 to 0.16; I^2 = 87%, p < 0.00001), and plasma/serum zinc concentration (MD 0.95 µmol/L, 95% CI 0.23 to 1.67; I^2 = 94%, p = 0.01), and decreased soluble transferrin receptor concentration (MD −0.19 mg/L log, 95% CI −0.30 to −0.09; I^2 = 61%, p = 0.0002) and risk of iron deficiency (RR 0.41, 95% CI 0.25 to 0.66; I^2 = 72%, p = 0.0003). MMN supplementation had no significant effects on other secondary outcomes.

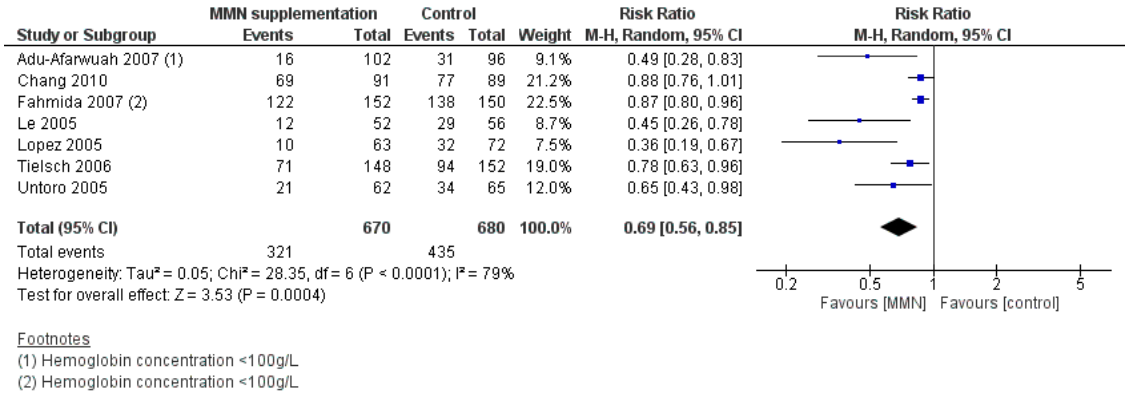

Figure 4. MMN supplementation versus placebo/no intervention (efficacy studies) on the risk of anemia (hemoglobin concentration < 110 g/L).

3.2.6. Efficacy of MNP Supplementation

MNP supplementation was associated with a lower risk of anemia compared with no intervention/placebo (RR 0.76, 95% CI 0.69 to 0.84; I^2 = 75%, p < 0.00001) (Figure 5). Subgroup analyses by age at baseline showed a trend towards a greater reduction in anemia risk among the older children (24–59-month age group) when compared to younger children (6–11 months and 12–23 months) (p for subgroup differences = 0.09). However, subgroup analyses by WHO region, intervention frequency (daily versus intermittent), intervention duration (3–5 months, 6–11 months, 12–17 months, and 18+ months), and nutritional status at baseline (anemic versus non-anemic) showed no significant differences between groups. No significant effects of MNP supplementation were observed for the other primary outcomes, including stunting, underweight, and wasting. For the secondary outcomes, MNP supplementation increased hemoglobin concentration (MD 1.85 g/L, 95% CI 1.24 to 2.47; I^2 = 85%, p < 0.00001), serum/plasma ferritin (MD 11.08 µg/L, 95% CI 10.58 to 11.58; I^2 = 95%, p < 0.00001), and risk of diarrhea (RR 1.30, 95% CI 1.11 to 1.53; I^2 = 0%, p = 0.002), and decreased soluble transferrin receptor concentration (MD −0.86 mg/L, 95% CI −1.46 to −0.26; I^2 = 84%, p = 0.005), risk of iron deficiency (RR 0.50 95% CI 0.40 to 0.63; I^2 = 77%, p < 0.00001), and risk of iron-deficiency anemia (RR 0.45 95% CI 0.34 to 0.58; I^2 = 23%, p < 0.00001). No significant effects were observed for other secondary outcomes.

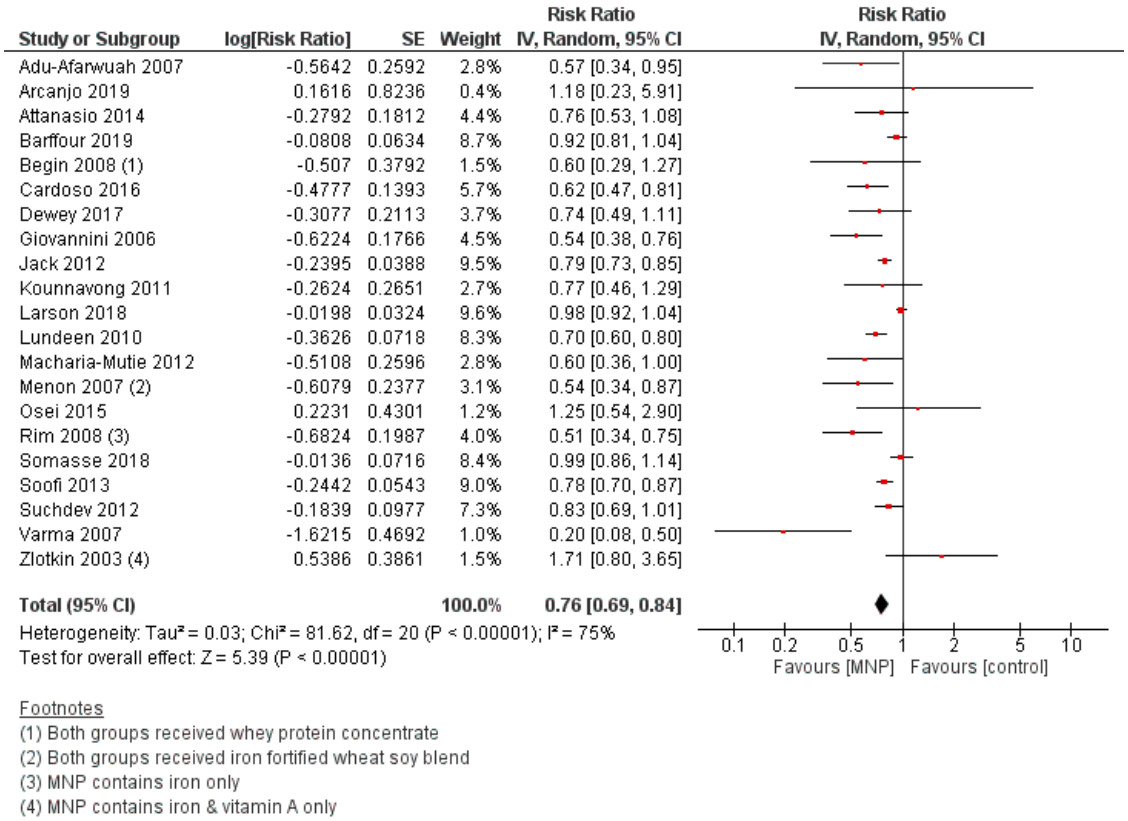

Figure 5. MNP supplementation versus placebo/no intervention (efficacy studies) on the risk of anemia (hemoglobin concentration < 110 g/L).

3.2.7. Efficacy of LNS Supplementation

LNS supplementation was associated with a reduced risk of anemia (RR 0.84, 95% CI 0.75 to 0.93; I^2 = 59%, p = 0.002) (Figure 6), stunting (RR 0.90, 95% CI 0.84 to 0.96; I^2 = 40%, p = 0.003) (Figure 7), and underweight (RR 0.90, 95% CI 0.81 to 1.01; I^2 = 88%, p = 0.06), though the upper CI just crossed the line of no effect. There was no significant impact of LNS on wasting. Subgroup analyses by WHO region showed no differences between regions for anemia, stunting, wasting, or underweight. No

other subgroup analyses were possible. For secondary outcomes, LNS supplementation led to an increase in length-for-age (z-score) (MD 0.11, 95% CI 0.05 to 0.17; I^2 = 72%, p = 0.0002), weight-for-age (z-score) (MD 0.10, 95% CI 0.04 to 0.16; I^2 = 68%, p = 0.001), and weight-for-height (z-score) (MD 0.09, 95% CI 0.04 to 0.14; I^2 = 55%, p = 0.0009). LNS also led to improvements in mental development scores for language (SMD 0.13, 95% CI 0.02 to 0.23; I^2 = 52%, p = 0.02) and personal-social/socioemotional (SMD 0.12, 95% CI -0.00 to 0.24; I^2 = 65%, p = 0.05), along with improvements in motor development generally (SMD 0.13, 95% CI 0.00 to 0.25; I^2 = 67%, p = 0.04). There were no significant effects of LNS supplementation on other secondary outcomes.

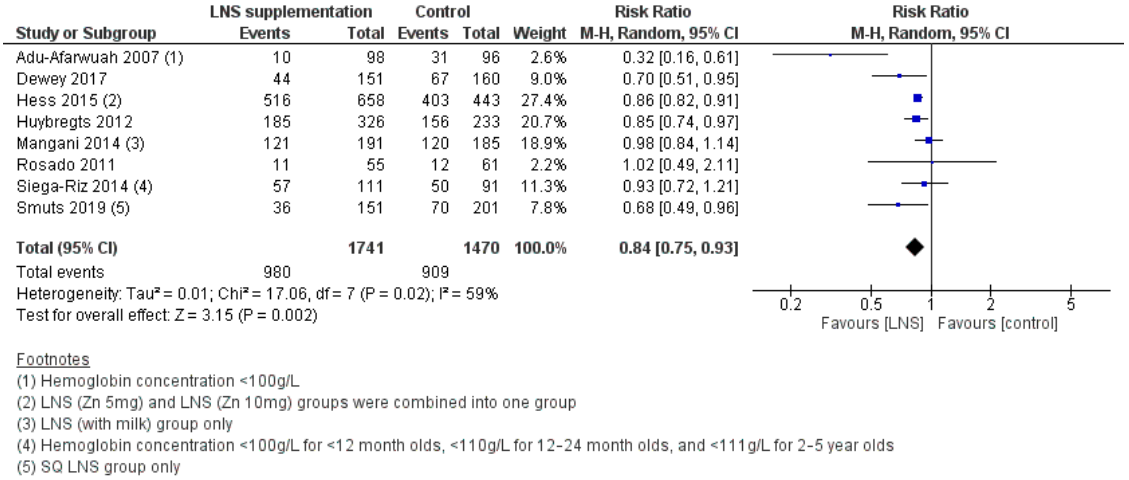

Figure 6. LNS supplementation versus placebo/no intervention (efficacy studies) on the risk of anemia (hemoglobin concentration < 110 g/L).

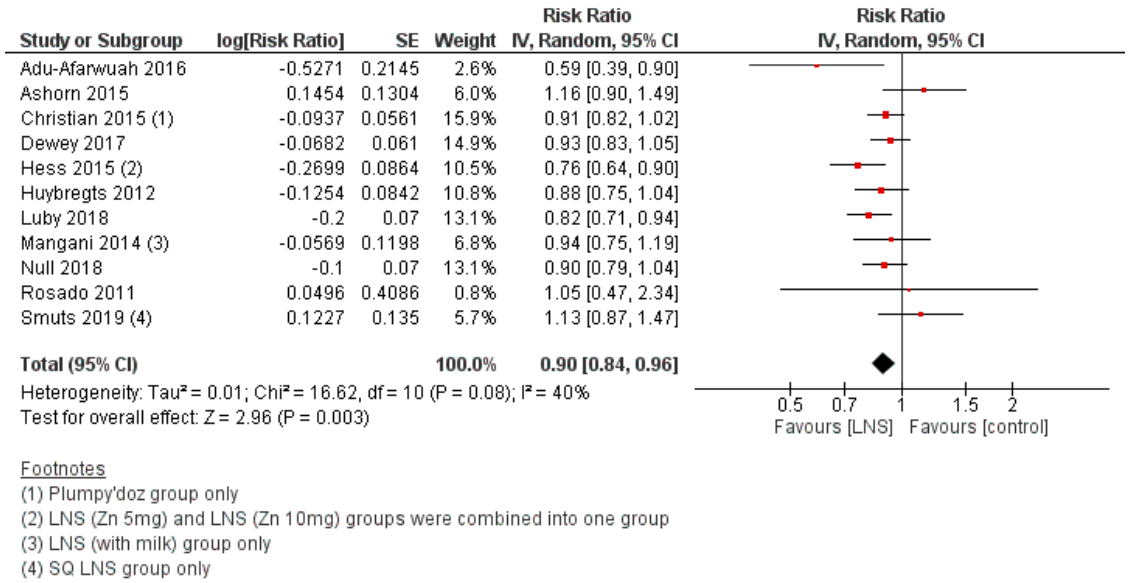

Figure 7. LNS supplementation versus placebo/no intervention (efficacy studies) on the risk of stunting (length-for-age z-score < −2).

3.2.8. Efficacy of Targeted Fortification

Targeted fortification was associated with a reduced risk of anemia compared with control (RR 0.53, 95% CI 0.32 to 0.89; I^2 = 83%, p = 0.02) (Figure 8). Subgroup analyses were not done because all subgroups had less than three studies. For the secondary outcomes, targeted fortification increased hemoglobin (MD 4.97 g/L, 95% CI 1.81 to 8.12; I^2 = 89%, p = 0.002) and serum/plasma ferritin (MD 8.19

µg/L, 95% CI 1.35 to 15.03; I^2 = 99%, p = 0.02), and likely improved serum/plasma retinol concentrations (MD 2.31 µg/dL, 95% CI -0.02 to 4.63; I^2 = 68%, p = 0.05), though the lower confidence interval just crossed the line of no effect. Targeted fortification, when compared to placebo or no intervention, also reduced the risk of iron-deficiency anemia (RR 0.28, 95% CI 0.14 to 0.59; I^2 = 61%, p = 0.0007) and iron deficiency (RR 0.36, 95% CI 0.24 to 0.56; I^2 = 69%, p < 0.00001). No significant effects were observed for other secondary outcomes.

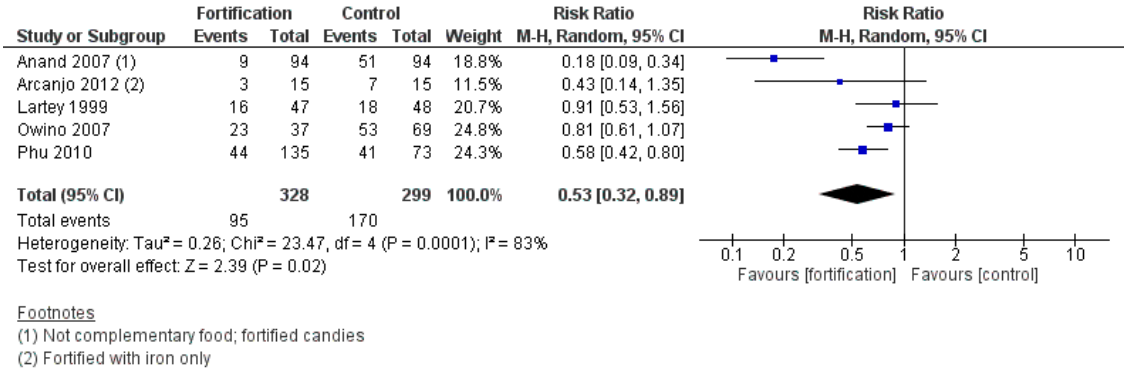

Figure 8. Targeted fortification versus placebo/no intervention (efficacy studies) on the risk of anemia (hemoglobin concentration < 110 g/L).

3.2.9. Efficacy of Large-Scale Food Fortification

Compared with placebo/no intervention, large-scale food fortification with MMN increased serum/plasma ferritin concentration (MD 2.80 µg/L, 95% CI 0.11 to 5.50; I^2 = 88%, p = 0.04) but had no significant effects on hemoglobin and serum/plasma zinc concentrations. Large-scale food fortification with iron significantly decreased the risk of anemia (RR 0.66, 95% CI 0.48 to 0.90; I^2 = 58%, p = 0.009) (Figure 9). However, there were an insufficient number of studies to do subgroup analyses for this primary outcome. Large-scale food fortification with iron had no significant effect on hemoglobin levels.

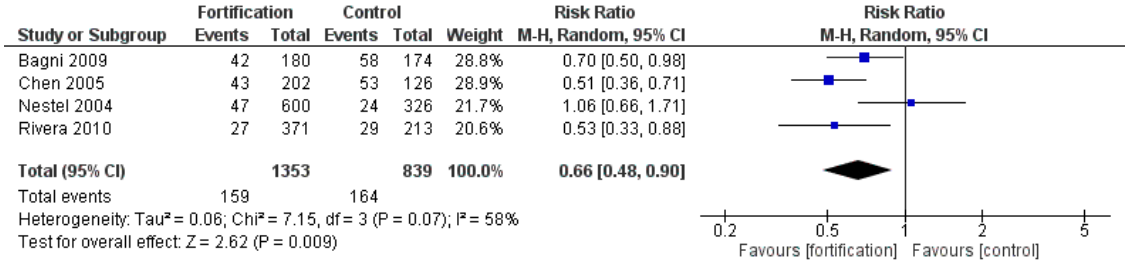

Figure 9. Large-scale food fortification with iron versus placebo/no intervention (efficacy studies) on the risk of anemia (hemoglobin concentration < 110 g/L).

3.2.10. Effectiveness of MNP Supplementation

Compared with placebo/no intervention, MNP supplementation was associated with a lower risk of anemia (RR 0.89, 95% CI 0.82 to 0.97; I^2 = 71%, p = 0.01) (Figure 10). In subgroup analyses by WHO region, a trend towards a greater reduction in anemia was observed for children in Africa and the Americas, compared to Southeast Asia and Western Pacific regions (p for subgroup differences = 0.06). Subgroup analyses by intervention duration revealed a greater reduction in anemia risk among children who had been supplemented for less time (<3 months and 3–5 months) compared to children who had been supplemented for 6+ months (p for subgroup differences = 0.03). There were no significant differences in anemia risk by nutritional status at baseline (anemic versus non-anemic). MNP supplementation had no significant effect on hemoglobin concentration.

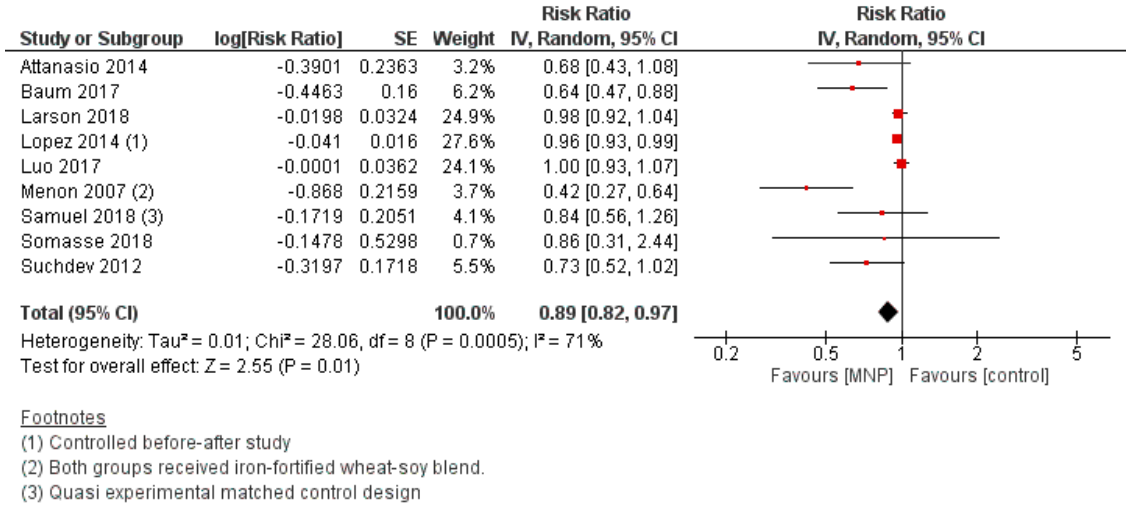

Figure 10. MNP supplementation versus placebo/no intervention (effectiveness studies) on the risk of anemia (hemoglobin concentration < 110 g/L).

3.2.11. Effectiveness of LNS Supplementation

LNS supplementation was associated with a reduced risk of anemia (RR 0.83, 95% CI 0.73 to 0.93; I^2 = 0%, p = 0.002) (Figure 11). Subgroup analyses were not conducted on this primary outcome because no subgroups had three or more studies. No significant effect was observed for the other primary outcome (stunting). For the secondary outcomes, LNS supplementation led to an increase in weight-for-height (z-score) (MD 0.09, 95% CI 0.03 to 0.15; I^2 = 62%, p = 0.006), weight-for-age (z-score) (MD 0.10, 95% CI 0.04 to 0.17; I^2 = 66%, p = 0.002), and length-for-age (z-score) (MD 0.11, 95% CI 0.02 to 0.19; I^2 = 75%, p = 0.02). There were no significant effects of LNS supplementation on other secondary outcomes.

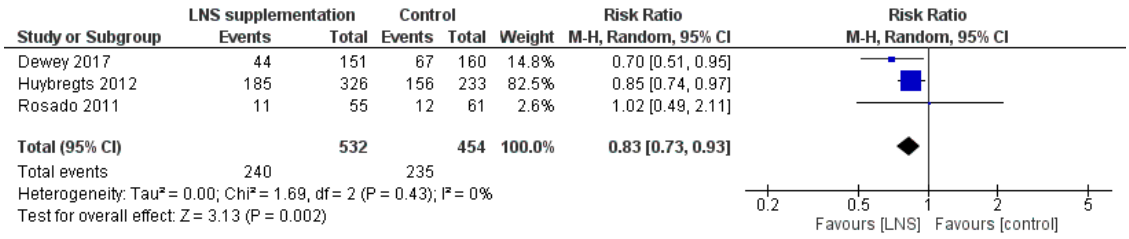

Figure 11. LNS supplementation versus placebo/no intervention (effectiveness studies) on the risk of anemia (hemoglobin concentration < 110 g/L).

4. Discussion

The purpose of this review was to summarize the available and up-to-date information on micronutrient supplementation and fortification interventions among children under-five in LMICs. To do so, we have undertaken an extensive number of analyses to examine both the efficacy and effectiveness (where data allowed) of these interventions on improving child health and development outcomes, including mortality, nutritional indicators (stunting, wasting, underweight, anemia), morbidities (lower respiratory tract infections, diarrhea), micronutrient deficiencies, and mental and motor skill development.

Though mortality data was not common, we were able to assess all-cause mortality among children taking zinc supplements and those taking vitamin A supplements, when compared to those with no intervention or placebo. With zinc, there was no significant difference between groups, and heterogenous estimates led to an uncertain pooled effect estimate with extremely wide confidence intervals. We performed two meta-analyses of vitamin A supplementation based on how the data was

reported. When combining estimates as rate ratios, there was no difference between groups. However, when combining estimates as risk ratios (cumulative incidence), then there was a 10% reduction in the risk of mortality among the group supplemented with vitamin A, although the upper confidence interval just crossed the line of no effect (RR 0.90, 95% CI: 0.80 to 1.02). Of note, there were more participants in the risk ratio analysis when compared to the rate ratio analysis, with one cluster-RCT alone reporting 122,813 deaths within a 5-year trial in north India [169]. This finding is consistent with that of a Cochrane review, whereby the risk of all-cause mortality was reduced by 12% (RR 0.88, 95% CI: 0.83 to 0.93) [12]. It should be noted that data from 19 trials were included in the analysis, many of which were excluded from ours because of date restrictions (we included data from papers published after 1995). We were able to examine all-cause mortality by sex and, while there was a trend towards a greater reduction in mortality among girls versus boys, the test for subgroup differences was not significant ($p = 0.13$). A study of vitamin A supplementation in Guinea-Bissau has noted a more pronounced effect of the intervention on mortality that advantages girls [237]. However, a review of neonatal supplementation found lower mortality among boys [238], and the Cochrane review cited above found no difference between sexes, underscoring the need for more research on this subject.

Although vitamin A supplementation is thought to improve mortality largely by decreasing childhood infections, we found no difference in the incidence of diarrhea or lower respiratory tract infections among children supplemented with vitamin A compared to those who were not. However, we did note that the rate of diarrhea was reduced by over 10% and there was a 63% reduction in the risk of zinc deficiency among children taking zinc compared to those who did not.

For iron supplementation compared to placebo or no intervention, all of the indicators of iron status were significantly improved, including hemoglobin concentration, serum/plasma ferritin, anemia, iron deficiency, and iron-deficiency anemia. In addition, there were small improvements in mental development scores (SMD 0.14, 95% CI: 0.01 to 0.28) and slightly larger improvements in motor development scores (SMD 0.28, 95% CI: 0.15 to 0.40) among children who had been supplemented with iron. Caution should be taken when interpreting these results because of the heterogeneity in time to follow-up. For example, for our mental development analysis, two studies [239,240] followed children up for 6 months, one [137] for 12 months, and one [241] for 8 years. A standardized mean difference was used as the effect measure to account for the different scales used, a method that assumes that differences in standard deviations are due to measurement differences, when there may be actual variability among the study population. There have been mixed findings of iron supplementation on development outcomes. One review among children aged 4–34 months found no differential effect on mental or psychomotor development [242], and a previous Cochrane review looking at intermittent iron supplementation among children under 12 years of age was not able to meta-analyze these types of outcomes [20]. However, other reviews have supported the claim that iron improves later cognition and intelligence of children under-five and school-aged children [243,244]. Despite this, all evidence points to the benefits of iron supplementation for improving hemoglobin and iron status, which has led to development of WHO guidelines that recommend daily iron supplementation in under-five populations where anemia prevalence is 40% or higher [245]. However, oral iron should not be given to children in malaria-endemic areas, where appropriate surveillance and preventive/management measures for malaria are not available [245].

Only four included studies examined the effects of iron-folic acid compared to placebo or no intervention and, while there was a significant reduction in anemia (20% reduction) and improvement in hemoglobin, there was no impact on diarrhea incidence with this intervention.

Among RCTs that provided MNPs containing multiple micronutrients, the risk of anemia among children under-five was substantially reduced, by 24%. Among effectiveness studies of MNPs, the risk of anemia was reduced by 11%, demonstrating the robustness of this intervention for improving anemia even in less controlled settings. MNPs did not have an effect on other nutritional indicators including stunting, wasting, and underweight, though risk of iron deficiency and iron-deficiency anemia was reduced by 50% and 55%, respectively. Of note, there was a 30% increased risk of diarrhea

with MNPs when compared to placebo or no intervention. These findings are mostly in line with the recent Cochrane review on point-of-use fortification, though the authors found no significant increase or decrease on diarrhea among participants [26]. Our results differ due to the inclusion of two additional trials in our analysis. Of these four trials, the dose of included zinc ranged from 0 mg [51] to 4.1 mg [196,203] to 10 mg [204]. Given that even 10 mg is lower than the 20 mg daily dose recommended by WHO to treat diarrhea [245], there may be room to lower this risk by increasing the dose of zinc in MNPs. However, a balance must be struck because of the notion that high zinc can lead to competition for absorption with iron. Knowing the significant contribution of diarrhea to deaths among children under-five, this is a finding that warrants further investigation. Some trials have previously reported an increase in diarrheal episodes directly following intervention initiation, with a subsequent decline in diarrhea in the following days [26], underscoring a window of time where children should be closely monitored. Interestingly, in our analysis of MMN supplementation (not in the form of powder for point-of-use fortification) versus placebo or no intervention, there was no increased risk of diarrhea incidence (RR 0.97, 95% CI: 0.87 to 1.09) and the zinc dosages ranged from 5 mg [104] to 10 mg [59,130,205] to 20 mg [49]. MMN also showed improvements in plasma/serum retinol and zinc and increases in length-for-age and weight-for-age z-scores, underscoring benefits of MMN that were not noted for MNPs.

For children under-five, we found that the LNS was effective at improving nutritional outcomes including anemia (16% reduction), stunting (10% reduction), and underweight (10% reduction). These findings are in line with the recent Cochrane review, which found a 21% reduction in anemia, a 7% and 15% reduction in moderate and severe stunting respectively, an 18% reduction in moderate wasting, and a 15% reduction in moderate underweight [29]. Five LNS studies examined the effectiveness of this intervention and found similar results in terms of anemia and length-for-age, weight-for-age, and weight-for-height z-scores, underscoring the utility of this intervention for preventative, community-based programs. Efficacy studies also noted some positive effects of LNS on mental and motor development outcomes, highlighting the link between early nutrition and development.

There were several studies that examined the efficacy of targeted fortification interventions and fewer that looked at fortification of staple foods. For both comparisons, we meta-analyzed vehicles that had been fortified with multiple, as opposed to single, micronutrients because this was more common. Similar to the effects of MNPs and MMN, we found that delivering multiple micronutrients to children through complementary foods or staple foods improved anemia and some other indicators of iron status (e.g., serum/plasma ferritin and iron deficiency), but had no impact on other nutritional indicators such as length-for-age, weight-for-age, or weight-for-height.

There are many strengths of this review, including its comprehensive nature and inclusion of efficacy and effectiveness studies. Though most program evaluations that we came across did not meet our study design criteria, as they were cross-sectional surveys before and after implementation, we were able to include several effectiveness trials of MNPs and LNS that utilized health facility- or community-based platforms to deliver interventions, which is a good representation of real-world scenarios. We have examined within this review interventions that are most relevant to children under-five in LMICs, and many of our findings extend upon or align with those of other evidence synthesis exercises. This inclusion of several different interventions and comparisons may also be a limitation of this review, as it is bulky in size, with over 130 different analyses undertaken. This has made it difficult to discuss findings completely, as interventions and populations represented by the data are so heterogenous. One must be careful not to directly compare the efficacy of one intervention to another, as this would require network meta-analysis, which we have not undertaken.

It has become clear that for micronutrient interventions to be maximally effective, it will be critical to consider context. We have outlined some strategies, such as LNS, that improve anemia, stunting, and underweight, whereas others, such as zinc supplementation, work to reduce diarrhea. We have demonstrated the reduction in all-cause mortality with vitamin A, and improvements in iron

status and anemia with iron or multiple micronutrients (delivered in several forms). Considering the high prevalence of multiple deficiencies among children in LMICs, and the frequency with which these outcomes occur, it is probable that several of these strategies should be used concurrently, and in a complementary fashion. However, in some situations, it might be necessary to consider the cost-benefit and other trade-offs of using one intervention over another to improve a specific outcome. Programs will also need to take into account the contextual factors that will ensure coverage, benefit, and sustainability of an intervention. These are factors that we were not able to examine in this review, and include cost, feasibility of implementation, strategies for monitoring and evaluation, and population-specific factors including gender-related barriers to uptake and prevalence of deficiencies at a sub-national level (which are often masked by national-level estimates). A careful diagnostic assessment should be undertaken to understand which strategies will be most beneficial for a target population. Nevertheless, the results of this review have further added to the evidence base which advocates for micronutrient supplementation and fortification strategies for improving health and development outcomes among children under-five. In particular, the positive findings emanating from the meta-analyses of effectiveness studies should support and bolster efforts in countries to reach more children with these interventions.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/12/2/289/s1, Figure S1: Additional Forest Plots, Table S1: Eligible Studies Excluded from Meta-Analyses, Table S2: Eligible Studies Included in Meta-Analyses, Text S1: MEDLINE Search Strategy.

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