Multiple micronutrient supplementation during pregnancy, lactation, and early childhood and the long-term child development: Systematic literature review

Final study report

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Content

List of Acronyms

Acronym	Description
BMI	Body mass index
CI	Confidence interval
Fe	Iron
IFA	Iron and folic acid
IFAZn	Iron, folic acid, and zinc
IQ	Intelligence quotient
IU	International unit
LBW	Low birth weight
LMICs	Low- and middle-income countries
MABC	Movement Assessment Battery for Children
MMN	Multiple micronutrients
MNPs	Micronutrient powders
NRF	Nutrition Research Facility
RCT	Randomised controlled trial
RoB	Risk of bias
RS	Research study
SGA	Small-for-gestational age
SD	Standard deviation
SMD	Standard mean difference
UNIMMAP	United Nations International Multiple Micronutrient Antenatal Preparation
WHO	World Health Organization
Wk	Week(s)
Zn	Zinc

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Executive summary

Anaemia and micronutrient deficiencies are prevalent among pregnant women, particularly in low and middle-income countries (LMICs), contributing to adverse pregnancy outcomes. While the World Health Organization (WHO) initially recommended iron and folic acid (IFA) supplementation , evidence suggesting that multiple micronutrient (MMN) supplementation could be more effective has led the WHO to revise its guidance. Since 2020, the recommendation for MMN supplementation for pregnant women instead of IFA has shifted from "not recommended" to "recommended in the context of rigorous research". However, evidence on the effect of point-of-use fortification with micronutrient powders (MNPs) during pregnancy is limited, and WHO does not recommend it as an alternative to IFA supplementation. WHO recommends MNPs for improving iron status and reducing anaemia in young children and adolescents. The effectiveness of MMN supplementation and point-of-use MNPs during pregnancy, lactation, and early childhood on cognitive development remains inconclusive.

This systematic review examines the evidence regarding long-term effects of MMN supplementation and point-of-use MNPs during pregnancy, lactation, and early childhood on the cognitive development of children aged 4 to 14 years in LMICs.

The systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Before the screening started, the protocol was developed and registered on the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42023459846, published on September 26th, 2023). A literature search was performed following pre-defined inclusion and exclusion criteria.

On October 26th, 2023, a search was conducted across six databases, resulting in a total of 8,815 records. After removing 3,469 duplicates using COVIDENCE, 74 records underwent screening based on title and abstract in duplicate. Subsequently, 64 articles were excluded based on eligibility criteria.

The systematic review included a total of ten studies, with six assessing maternal supplementation during pregnancy, three during early childhood, and one investigating the long-term effects of continued supplementation during both pregnancy and early childhood. All studies reported on cognitive development, five on motor development, and five studies on behavioural development and mental health. Given the heterogeneity of methods and outcome measures in the studies, it was not feasible to perform a meta-analysis. Most of the studies were conducted in Asia, with the exception of one study reporting on two interventions conducted in Tanzania. Most studies did not report on the food environment. However, the target populations were primarily rural and largely characterised by food insecurity, with poor to average dietary intakes of nutrient rich-foods.

Studies included were randomised controlled trials (RCTs) or cluster-RCTs, with sample sizes ranging from 184 to 2,879 participants.

While the findings were mostly not statistically significant, maternal MMN supplementation may still have long-term effects on children's cognitive development. In some studies, the observed effects were unlikely to be due to chance alone. Potential negative outcomes of maternal MMN supplementation were reported in few studies. Despite this, there was no conclusive evidence of adverse effects. Our review highlights the limited evidence and the need for further research to establish conclusive evidence before making public health recommendations.

Additionally, evidence on the long-term effects of MMN supplementation and point-of-use MNPs for infants and young children on cognitive development remains limited, highlighting the necessity for continued research.

Given the significant health benefits of MMN for mothers in improving birth outcomes and MNPs for children in reducing anaemia and improving iron status, the WHO recommendations to replace IFA with MMN and use MNPs should remain unchanged.

Overall, there is a need for: 1) Larger, long-term RCTs to generate more robust evidence; and 2) Development and validation of tools to accurately assess developmental and cognitive performance in children, particularly in LMIC contexts. It is important to explore more sustainable alternatives, such as the use of local foods and fortified/enriched foods, to meet the nutritional requirements and improve the development of children. This is particularly relevant given the concerns about the ongoing dependence of supplementation programs on funding and technical expertise from high-income countries.

Box 1. Key messages

Maternal MMN supplementation during pregnancy and lactation did not show significant long-term effects on child development. However, few studies suggested potential associations with cognitive development.

While evidence strongly supports the benefits of maternal MMN supplementation on pregnancy outcomes, the findings suggest the need for additional research before advocating for public health recommendations about its potential long-term effects on the cognitive development of children and young adolescents.

While point-of-use fortification with MNPs in effective in improving iron status and reducing anaemia among children and young adolescents, evidence on the long-term effects of MMN supplementation and the point-of-use MNPs on cognitive development is limited, emphasizing the necessity for further research.

Given the significant health benefits of MMN for mothers in improving birth outcomes and MNPs for children in reducing anaemia and improving iron status, the WHO recommendations to replace IFA with MMN and use MNPs should remain unchanged.

Background

This Research Study (RS) has been conducted in response to the evidence needs prioritization exercise conducted by the Nutrition Research Facility (NRF) through a consultation process with decision-makers in Asia. The question being addressed was identified as a top priority for nutrition programming during a virtual regional workshop held in Asia on April 19-20, 2022. The research question was formulated as: "*What are the long-term impacts of micronutrient supplementation on the target group's cognitive development, especially in unhealthy food environments? (i.e., a food environment where diverse and nutrient-rich foods are unavailable or unaffordable*)".

The objective of this systematic review was to examine the long-term impacts of micronutrient supplementation during pregnancy and/or lactation, and during early childhood on children's cognitive development in LMICs.

Introduction

Anaemia and micronutrient deficiencies are common among pregnant women, with a higher prevalence observed in low and middle-income countries (LMICs) in Africa and Asia [1]. Approximately 30% of women of reproductive age and 37% of pregnant women suffer from iron-deficiency anaemia, contributing to adverse pregnancy outcomes such as reduced birth weight and increased risk of maternal mortality [2]. Various factors, including poor dietary diversity, low maternal education, health conditions, food insecurity, and low socio-economic status, contribute to the prevalence of anaemia. The World Health Organization (WHO) recommended daily oral iron and folic acid (IFA) supplementation with 30 mg to 60 mg of elemental iron and 400 g (0.4 mg) of folic acid during pregnancy and postpartum to address these deficiencies, and to prevent maternal anaemia, puerperal sepsis, low birth weight (LBW), and preterm birth [3]. Since 2020, the WHO has updated its antenatal care recommendations to promote a positive pregnancy experience, specifically regarding micronutrient supplementation. The updated guidance now recommends antenatal multiple micronutrient supplements (MMN), that include iron and folic acid, during pregnancy, provided that this is supported by rigorous research[1] [4]. Micronutrient supplementation during pregnancy in low- and middle-income countries: evidence of their effectiveness.

Micronutrient supplementation has been shown to be effective in improving maternal and birth outcomes [5, 6]. Supplementation of MMN to pregnant Bangladeshi women resulted in higher maternal vitamin B12 and similar ferritin and folate concentrations compared to women supplemented with IFA [7]. Evidence is strong on the effect of daily oral supplementation of MMN[2] containing IFA on reduced risk of LBW and small-for-gestational age (SGA) [6, 9]. Pregnant women supplemented with MMN containing IFA had a smaller number of LBW and SGA newborns. Replacing IFA supplements with MMN supplements could be beneficial for pregnant women in LMICs [6]. Since 2020, the WO recommends to integrate MMN supplementation with IFA into maternal nutrition and antenatal care programs in these regions, contingent upon rigorous supporting research [4]. In their recent meta-analysis, Gomes and collaborators showed that the effects of MMS on LBW, preterm

[1] Rigorous research includes implementation research using controlled clinical trials using early pregnancy ultrasound to accurately determine gestational age and assess critical maternal and perinatal outcomes, with long-term follow-up into childhood. Additionally, implementation research is necessary to evaluate the impact of switching from iron and folic acid supplements to MMN, focusing on acceptability, feasibility, sustainability, equity, and cost-effectiveness (Guideline Development Group) [4].

[2] The composition of MMN supplement differed by trial, but all contained between 13 and 15 micronutrients, including 30 mg iron and folic acid. A summary can be found in the 2019 Cochrane review conducted by Keats et al. [6]. United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) contains 800 µg vitamin A, 200 International Unit vitamin D, 10 mg vitamin E, 18 mg niacin, 400 µg folic acid, 1.4 mg vitamin B1, 1.4 mg vitamin B2, 1.9 mg vitamin B6, 2.6 µg vitamin B12, 70 mg vitamin C, 15 mg zinc, 30 mg iron, 65 µg selenium, 2 mg copper, and 150 µg iodine [8].

birth, and SGA were consistently significant across subgroups, regardless of the gestational age assessment method used, including the recommended ultrasound [10].

Point-of-use micronutrient fortification during pregnancy and childhood in low- and middle-income countries

The evidence is limited on the effect of point-of-use fortification of foods with micronutrient powders (MNPs)[3] in reducing deficiencies of micronutrients in pregnant women, and their impacts on the health of child and mother [11]. Only two studies were included in the meta-analysis by Suchdev et al. that assessed the effects of antenatal point-of-use fortification with MNPs on maternal and newborn health [11]. The first study reported only on adherence and found that women were more adherent to IFA supplements compared to point-of-use fortification with MNPs [12]. The second study found no significant difference in maternal anaemia or haemoglobin concentration near term between women who received point-of-use MNPs and those who received MMN supplements containing the same micronutrients [13]. Based on these findings, the WHO guideline states that routine use of MNPs during pregnancy is not recommended as an alternative to standard IFA supplementation or oral MMN supplementation for improving maternal and infant health outcomes [14].

Two systematic reviews conducted to assess the effects and safety of point-of-use fortification of foods with MNPs among infants and young children 6 – 23 months of age [15] [4], and in preschool- and school-age children [16][5] showed that MNPs containing iron reduce anaemia and iron deficiency. The WHO recommends point-of-use fortification with iron-containing MNPs of complementary foods in infants and young children 6-23 months of age, and of foods in children 2-12 years, to improve iron status and reduce anaemia [17].

Importance of micronutrient supplementation or fortification in the cognitive development of children

Micronutrient deficiencies in-utero and during early postnatal life can cause lasting changes in many aspects of metabolic and central functions, including impairments in cognition [18]. Brain development occurs most rapidly during gestation and the first two years of life, and it is important that nutrition provided during this period is adequate to lay the foundation for long-term development [19]. In animal models, deficiencies in specific macro- and micro-nutrients such as energy, proteins, iron, zinc, B-vitamins and essential fatty acids have been shown to impair key neurodevelopmental processes – such as myelination, synaptogenesis and neurogenesis [20]. The research evidence from observational studies suggests that micronutrients may play an important role in the cognitive development of children. However, the results of intervention trials utilizing single micronutrients are inconclusive [21]. In sub-Saharan Africa and other low-income settings, undernutrition affects millions of children and is a key risk factor for about 250 million children under 5 years not fulfilling their developmental potential.

While evidence strongly supports the effectiveness of MMN supplementation during pregnancy for improved birth outcomes, and point-of-use fortification with MNPs for reducing anaemia and improving iron status in children and young adolescents (6 months to 12 years of age), the findings are inconsistent regarding the

[3] The Cochrane review included two studies that detailed the composition of the MNPs used [11]. Hernandez et al. reported that their intervention's MNPs contained 15 mg of iron, 15 mg of zinc, 100 µg of iodine, 10 mg of vitamin E, 100 mg of vitamin C, 2.6 µg of vitamin B12, and 400 µg of folic acid [12]. The second study, by Choudhury et al., provided MNPs containing 60 mg of elemental iron, 400 µg of folic acid, 30 mg of vitamin C, and 5 mg of zinc.[13].

[4] The formulation of MNPs varied among the studies included in this Cochrane review, with MNPs containing five, six, or 15 micronutrients. Almost all of them provided 12.5 mg of elemental iron, 5 mg of zinc, 300 – 400 µg of vitamin A, and 150 – 160 µg of folic acid [15].

[5] The formulation of MNPs varied among the studies included in this Cochrane review, with MNPs containing anywhere from two to 18 vitamins and minerals. Two studies reported a formulation with six micronutrients, while three trials used a formulation with 14 micronutrients. All of the MNPs that included at least these four micronutrients contained 2.5 – 30 mg of elemental iron, 2.5 - 5 mg of zinc, 100 – 480 µg of vitamin A, and 90 – 225 µg of folic acid [16].

effectiveness of MMNs and MNPs in improving cognitive development in young children. Maternal MMN supplementation during pregnancy and lactation has been shown to have a positive impact on children's cognitive development. Prado (2012) found that MMN supplementation improved motor and visual attention/spatial abilities in children of undernourished or anaemic mothers, 3.5 years later [22]. Geletu (2019) further supported these findings in a retrospective cohort study, showing that providing low-iron MNPs every other day for three months was associated with a reduced risk of anaemia and stunting, and improved motor development in children aged 9-12 months [23]. Contrarily, Luo (2017) found that MNPs provided to infants and young children (6-11 months of age) for 18 months did not improve anaemia or cognitive outcomes of children after 18 months of age [24].

Long term effects of MMNs and MNPs on child cognitive development

An important strategy to prevent the loss of developmental potential in children exposed to malnutrition and micronutrient deficiencies in LMICs is early supplementation with specific micronutrients and essential fatty acids during both prenatal and postnatal periods [25]. Micronutrients, individually, may play an important role in the cognitive development of children [21]. However, the results from intervention trials of single nutrients are inconsistent and inconclusive [21]. A recent systematic review and meta-analysis on the role of multiple micronutrients and macronutrients supplementation included 10 prenatal and 23 postnatal nutrition interventions. The combination of micro- and macro-nutrients interventions had small effects on the mental (cognitive) development of children under-two years, compared to supplementation with single micronutrient [26].

Recently, researchers have increasingly emphasised the importance of sustainable interventions in maternal and child health, particularly in LMICs. They highlight the need for long-term studies to ensure that these interventions are effective in promoting cognitive health and breaking the cycle of poverty through improved educational and economic outcomes [20, 27-29]. For example, the WHO guideline development group highlighted the necessity for further research on the potential short- and long-term functional, developmental, and adverse outcomes associated with point-of-use MNPs [17].

This systematic review aims to summarise the existing evidence regarding the long-term effects of maternal MMN supplementation and point-of-use MNPs during pregnancy and lactation, as well as the effects of point-of-use MNPs during infancy and early childhood, on the cognitive development of children aged 4 to 14 years.

Methodology

Data sources and search strategy

The systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (S1 Checklist) [30]. Before the screening started, the protocol was developed and registered on the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42023459846, published on September 26th, 2023). A literature search was performed on October 26th, 2023.

Inclusion and exclusion criteria

We included studies if 1) the study supplemented population was - women, pregnant or lactating, or - infants and young children (from birth to 3 years of age), 2) the intervention group received MMN that was defined as at least containing three micronutrients, 3) the outcomes assessed in children 4 – 14 years of age, 4) the design was randomised controlled trial (RCT), controlled trial, quasi-experimental, longitudinal or repeated cross-sectional, 5) were conducted in LMICs, and 6) assessed at least one of the development domains in children: intelligence, memory, concentration, psychomotor skills, and academic achievement, social-emotional

development, and adaptive skills. There was no restriction regarding the duration of the intervention, language and the year of publication. Studies conducted on children under 4 years, or those with developmental disability, including cretinism, were excluded.

Search selection

Records identified using the search strategy from the respective databases were exported to EndNote X20 (www.endnote.com). All records were then exported to COVIDENCE https://app.covidence.org/. COVIDENCE was used to identify and drop duplicates. Screening based on the title and abstract, and then of full text was carried out using COVIDENCE. The first-round screening of the records conducted in November 2023 was carried out by two reviewers, who independently included relevant records following the above-mentioned eligibility criteria. Disagreements were resolved between the two reviewers by consensus-based discussions.

Outcome of the studies

The main outcome of the review is the assessment of the effect of micronutrient supplementation during pregnancy and lactation, and in infancy and early childhood on the development of children 4 years - 14 years of age. The outcome measurement includes at least one of the development domains in children: intelligence, memory, concentration, psychomotor skills, and academic achievement, social-emotional development, and adaptive skills.

Data extraction

The data extraction format was based on the Cochrane Data Collection Form for Intervention Reviews (https://dplp.cochrane.org/data extraction forms) and modified according to the study question. The data extraction form was developed and pre-tested before the data extraction and papers were assessed for eligibility from the full text to ensure inclusion criteria were met. The intervention consisted of MMN supplementation compared to a control group of pregnant and lactating women, or infants and young children (0 – 3 years) who received no micronutrient, placebo or standard of care (example of folic acid or IFA during pregnancy an lactation). The design enables the comparison of the long term, sole or additional effect of MMN supplementation intervention on cognitive development of children and young adolescents (4 – 14 years of age). The data extraction form included information on study design, inclusion and exclusion criteria, randomization, participant's age, number of participants, study dropout, setting (country), intervention details (duration, frequency, duration of follow-up), and outcome measures.

Assessment of risk of bias

The methodological quality of each included study was assessed to evaluate risk of bias (RoB) using the Cochrane risk of bias assessment tool (RoB2) (https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool). The following criteria were assessed: participant's selection, blinding of participants, personnel, and outcome assessors; incomplete data, selective assessments of reports, withdrawals, and deviation from the protocol.

Statistical analysis

Management of articles and data analysis were carried out using Review Manager (Review Manager 5.4). Qualitative appraisal was performed due to the large variation in the tests used and the limited number of studies per test/outcome. The main results were analysed by type of outcome and for each individual study. Outcomes were presented as standard mean difference (SMD) with 95% confidence intervals (95%CI). The pooled SMD was calculated using the random effects model, providing a more generalised estimation that accounts for variability among studies [31]. If the standard deviation (SD) was not provided, it was calculated using the 95%CI and sample size. Individual studies with multiple intervention arms were presented and analysed separately, ensuring that the distinct effects of each intervention were clearly delineated and accurately assessed. Control groups were selected for IFA during pregnancy and lactation (if the control group was different than that in the original manuscript) and placebo during early childhood.

Results

On October 26th, 2023, a search was conducted across six databases, resulting in a total of 8,815 records. After removing 3,469 duplicates using COVIDENCE, 8,741 records were excluded based on the title and abstract, following the exclusion and inclusion criteria, with each record reviewed in duplicate. During the full-text screening phase, 64 articles were further excluded based on eligibility criteria. Finally, ten articles were included in this systematic review (**Figure 1**).

Characteristics of the trials included in the systematic review

The studies in this systematic review explored the effects of MMN supplementation and point-of-use fortification with MNPs interventions during pregnancy, lactation, and early childhood on cognitive and developmental outcomes in children and young adolescents between the ages of 4 to 14 years. All studies reported on cognitive development, five on motor development [32-36], and five studies on behavioural development and mental health [33, 35, 37-39] (**Table 1**). Given the heterogeneity of methods and outcome measures in the studies, it was not feasible to perform a meta-analysis.

The variability in this set of eligible studies was high across nearly every aspect assessed. Most of the studies were conducted in Asia, with the exception of one study reporting on two interventions conducted in Tanzania [38]. Studies included were RCTs [32, 37, 38, 40], or cluster-RCTs [33-36, 39, 41], with sample sizes ranging from 184 to 2,879 participants. Pregnant women were the primary populations supplemented in six studies [32, 33, 37-41], with interventions focusing on supplementation with IFA and zinc (IFAZn) [32, 37], multi-vitamins [38], and MMNs [32, 33, 39-41]. The control groups received IFA [33, 37, 39-41], IFA and vitamin A [32], and IFA and placebo [38]. Of the four MMN formulas, the three which provided the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) were similar in terms of micronutrient composition and concentrations [33, 39-41] (**Table 2**). The formula used in Prado et al.'s study [33] had a slightly lower vitamin B12 content (1.6 µg compared to 2.6 µg). In contrast, the MMN used Christian et al.'s study [32] contained slightly higher amounts of vitamins A, B1, B2, B3, B6, and C, while the other micronutrient contents were comparable to the UNIMMAP formulation.

Infants and young children aged 1 to 36 months were supplemented in three studies [34, 35, 38]. Infants and young children received IFAZn in one study conducted in Nepal [34], multiple vitamins or multiple vitamins with zinc in Tanzania [38], and provided point-of-use sprinkles in Pakistan [35] (**Table 1**). The control groups received placebo [34] or no supplementation [35, 38]. Only one study evaluated children born to mothers who had received MMN supplementation and who also received supplements during preschool age [36].

Follow-up periods varied greatly among studies. Several studies had repeated follow-up time points where assessment was conducted. In this systematic review, we report on the last time point follow-up, that is within the eligible age range. For instance, evaluations of the effects of supplementation on child development in China were conducted at various ages: at age 1 year [42], at ages 7 to 10 years in a second follow-up by Li et al. [43], and at ages 10 to 14 years in a third follow-up included in this systematic review [39, 41]. Similarly, Prado et al. investigated the benefits of maternal MMN supplementation on child development at preschool age (42 months) [22], and later at ages 9 to 12 years [33]. Only the latter study was included in this systematic review.

Maternal adherence to supplements and dietary practices in the trials included in the systematic review

Maternal adherence to supplements was reported in all parent studies. Adherence, measured by the number of days in the study or by disappearance rate (the number of tablets absent from the returned bottles divided by

the total number of tablets the participant should have taken), showed a high median compliance ranging from 85% to 98% [44-49]. Importantly, supplement consumption did not differ between intervention and control groups.

Dietary intakes and micronutrient status of mothers were not consistently reported. In the follow-up study by Caulfield et al. [37], mothers had marginal zinc intake (approximately 8 mg/day) [50]. Christian et al. [32, 45] measured dietary intake by the consumption of nutrient-rich foods, such as fish/meat and yellow fruits and vegetables, with about 20% of women in three groups reporting intake at least twice during the week preceding enrolment. Iron deficiency and anaemia were prevalent in this rural area of Nepal [51, 52]. In the study population of Dulal et al. [40], Osrin et al. did not assess dietary intake, but noted that 38% of participating mothers were anaemic at enrolment (< 110 g/L) [46]. The remaining three studies did not report on maternal dietary intakes [47-49].

Similarly, the nutritional status and dietary intake of children included in the follow-up studies were not consistently reported. Caulfield et al. found no significant differences in nutritional status between the intervention and the control groups, but did not report on the children's dietary intakes [37]. In the study of Christian et al., 44% of children were stunted (height-for-age z-score < -2 SD), 16% were wasted (BMI-for-age z-score < -2 SD), and 22% were anaemic (haemoglobin concentration < 115 g/L) [32]. Between 40% and 69% of children had consumed any nutrient-rich foods in the previous week [32]. Dulal et al. did not report on children's dietary practices or the prevalence of malnutrition in the study population [40]. However, child undernutrition is common in the area, with 36.7% of children under 5 being stunted [53]. Similarly, Prado et al. [22] and Sudfeld et al. [38] did not provide information on the food environment or the nutritional characteristics of the study children and adolescents. Zhu et al. did not report on the food environment or the prevalence of malnutrition in the study children [41].

Child dietary practices and adherence to supplements in the trials included in the systematic review

Children followed up by Murray-Kolb et al. [34] took supplements on 76.8% of assigned days in the placebo group versus 72.9% in the zinc group [54]. The median compliance among children followed up by Sudfeld et al. [38] was 96% [55]. Mothers reported that 74% of children received a 30-day dose, and 17% received a 60-day dose. However, 18% of mothers did not give the MNP to their enrolled child [56]. Dietary practices during the supplementation period were not reported in any of the included studies.

At follow-up, Murray-Kolb et al. reported that 37% of children were anaemic (haemoglobin concentration < 120 g/L), with intakes of nutrient-rich foods ranging from 43% for yellow fruits to 72% for dark green vegetables and milk and dairy products [34]. Sudfeld et al. [38] did not provide information on the food environment or the nutritional characteristics of the study children. In the study by Yousafzai et al., stunting, wasting, underweight were moderate among the participating children, but anaemia prevalence was high, with more than 55% of children having haemoglobin concentrations less than 110 g/L [35].

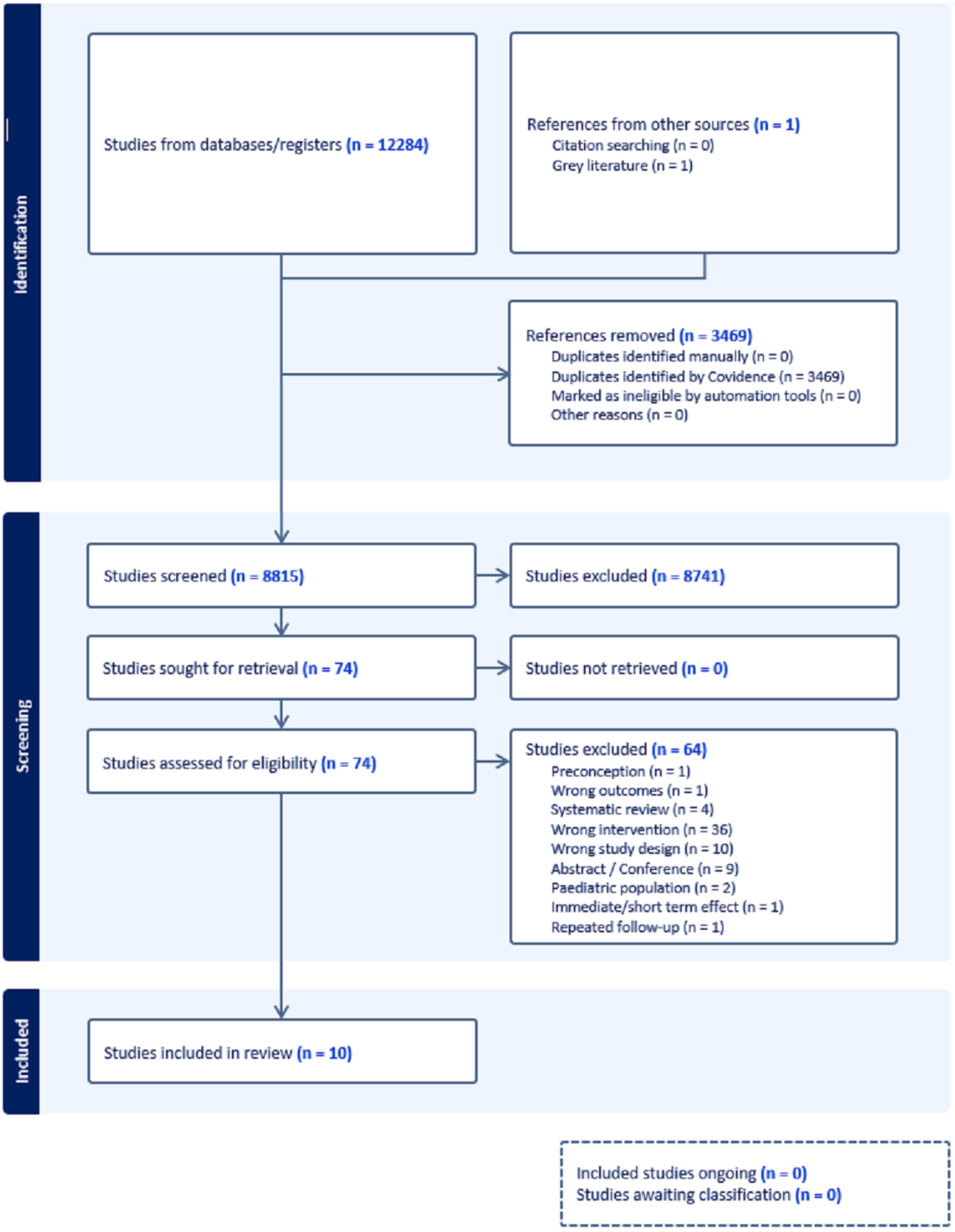

Figure 1. PRISMA study flow diagram for the systematic review.

Table 1. Summary of measures and results of articles included in systematic review

Reference	Study design and sample	Outcomes	Intervention/Duration	Measures	Results	SMD [95% Confidence Interval]
Supplementation of women during pregnancy and lactation						
Caulfield et al. [37]	RCT 184 children (Peru, 2003-2010)	(1)cognitive development, (3)behavioural development 4-5 years	Zinc + folic acid + iron vs. IFA Daily, 10-16 gestational week until 1 month postpartum	(1)Wechsler Preschool & Primary Scale of Intelligence	↔1,3	-0.04 [-0.33, 0.25]
				(1)Language development, bear story		0.02 [-0.27, 0.32]
				(1)Number concepts, counting game		0.02 [-0.28, 0.32]
				(1)Goodenough & Harris Draw-a-Person Test		-0.11 [-0.42, 0.19]
				(1)Interpersonal understanding, friendship interview		-0.16 [-0.47, 0.15]
				(3)Vineland Adaptive Behaviour Scales Communication Daily living skills Socialization Motor skills		 -0.11 [-0.40, 0.18] 0.06 [-0.23, 0.35] 0.06 [-0.23, 0.36] 0.04 [-0.25, 0.34]
				(3)Preschool Behaviour Questionnaire Internalizing Externalizing		 0.13 [-0.16, 0.42] 0.06 [-0.23, 0.35]
Christian et al. [32]	RCT 281 children (Nepal, 2007-2009)	(1)cognitive development, (2)motor development 7-9 years	Zinc + folic acid + iron + VA vs. IFA + VA Daily supplementation from 11 (±5.1) gestational week until up to 12 weeks postpartum	(1)The Universal Non-Verbal Intelligence Test (UNIT)[a]	↔1[a] ↔1[b]	-0.17 [-0.41, 0.08]
				(1)Executive function Go/No-go test[b] Stroop test(proportion who failed)[c] Backward digit span[d]	↓1[c] ↓1[d] ↓2[a] ↓2[b]	 -0.22 [-0.46, 0.03] **0.33 [0.09, 0.57]** **-0.33 [-0.57, -0.08]**
				(2)The Movement Assessment Battery for Children (MABC)[a*]		**0.33 [0.08, 0.57]**
				(2)Finger-tapping test[b]		**-0.41 [-0.66, -0.17]**
Christian et al. [32]	RCT 321 children (Nepal, 2007-2009)	(1)cognitive development, (2)motor development 7-9 years	MMNs + VA vs. IFA + VA Daily supplementation from 11 (±5.1) gestational week until up to 12 weeks postpartum	(1)The Universal Non-Verbal Intelligence Test (UNIT)[a]	↓1[a] ↔1[b]	**-0.26 [-0.49, -0.02]**
				(1)Executive function Go/No-go test[b] Stroop test(proportion who failed)[c] Backward digit span[d]	↔1[c] ↓1[d] ↓2[a] ↓2[b]	 -0.00 [-0.24, 0.23] 0.20 [-0.03, 0.44] **-0.36 [-0.60, -0.13]**
				(2)The Movement Assessment Battery for Children (MABC)[a*]		**0.32 [0.09, 0.56]**
				(2)Finger-tapping test[b]		**-0.45 [-0.69, -0.22]**

Dulal et al. [40]	RCT 813 young adolescents (Nepal, 2015-2016)	(1)cognitive development 12 years	UNIMMAP MMNs vs. IFA Daily supplementation between 12 weeks gestation until childbirth.	(1)The Universal Non-Verbal Intelligence Test (UNIT)	↔1	0.09 [-0.05, 0.23]
				(1)Executive function using a counting Stroop test		0.10 [-0.04, 0.24]
Prado et al. [33]	Cluster RCT 2879 children and young adolescents (Indonesia, 2012-2014)	(1)cognitive development, (2)motor development, (3)behavioural development 9-12 years	UNIMMAP MMN vs. IFA Daily supplementation between enrolment (34% in 1st trimester, 43% in 2nd trimester, and 23% in 3rd trimester) and three months post-partum	(1)General intellectual ability[a] (1)Declarative memory[b] (1)Procedural memory[c] (1)Executive function[d] (1)Academic achievement[e]	↔1a ↔1b ↑1c ↔1d ↔1e	0.09 [-0.03, 0.22] 0.01 [-0.09, 0.11] **0.11 [0.01, 0.20]** 0.07 {-0.04, 0.19] 0.08 [-0.05, 0.21]
				(2)Fine motor dexterity	↔2	-0.07 [-0.16, 0.02]
				(3)Socioemotional health	↔3	0.06 [-0.04, 0.16]
Sudfeld et al. [38]	RCT 446 young adolescents (Tanzania, 2015-2017)	(1)cognitive development, (3)behavioural development 11-14 years	IFA + MVs vs. IFA + Placebo Daily supplementation from 12-27 gestational weeks to 6 weeks after childbirth	(1)General Intelligence[a] (Atlantis, Footsteps, Hand movement, Kilifi naming test, Koh's block design test, Story completion, and verbal fluency)	↔1, 3	-0.02 [-0.20, 0.17]
				(1)Executive function[b] (Literacy, Numeracy, NOGO, People search, ROCF copy, ROCF recall, and Shift)		0.00 [-0.19, 0.19]
				(3)Mental health.(SDQ and the Behaviour Rating Inventory of Executive Function (BRIEF) to assess mental health)		0.05 [-0.14, 0.23]
Zhu et al. [39, 41]	Cluster RCT 1385 children and young adolescents (China, 2016)	(1)cognitive development, (3)behavioural development 10-14 years	UNIMMAP MMN vs. IFA Daily supplementation from 13.8 (±5.8) gestational weeks to childbirth.	(1)Adolescent full-scale intelligence quotient and aspects of verbal comprehension, working memory, perceptual reasoning, and processing speed indexes were assessed by the Wechsler Intelligence Scale for Children	↑1 ↔3	**0.13 [0.03, 0.24]**
				(3)Internalizing, externalizing, and total behaviour problem scores		0.05 [-0.06, 0.16]
Supplementation of infants and young children						
Murray-Kolb et al. [34]	Cluster RCT 377 children (Nepal, 2007-2009)	(1)cognitive development, (2)motor development 7-9 years	IFAZn vs. Placebo Daily supplementation from 12 to 35 months of age (length of supplementation depended on age at enrolment)	(1)The Universal Non-Verbal Intelligence Test (UNIT)[a]	↔1a,1c,1d ↑1b ↔2a,2b	0.11 [-0.10, 0.31]
				(1)Stroop test (proportion who failed)[b]		**-0.29 [-0.50, -0.09]**
				(1)Backward digit span[c]		0.18 [-0.02, 0.39]
				(1)Go/No-Go test[d]		-0.13 [-0.34, 0.07]
				(2)The Movement Assessment Battery for Children (MABC)[a*]		-0.12 [-0.32, 0.08]
				(2)Finger-tapping[b]		0.18 [-0.02, 0.39]

Sudfeld et al. [38]	RCT 365 children (Tanzania, 2015-2017)	(1)cognitive development, (3)behavioural development 6-8 years	MVs vs. No MVs Daily supplementation for 18 months. 1-6 mos old infants received one dose daily. Infants received two doses daily from 7 mos. 2x2 Factorial design provided (1) Zn+MVs (n=66); (2) Zn (n=101); (3) MVs (n=106); (4) Placebo (n=92). The analysis of MVs (group 1 and 3) vs. no MVs (group 2 and 4)	(1)General Intelligence[a] (Atlantis, Footsteps, Hand movement, Kilifi naming test, Koh's block design test, Story completion, and verbal fluency)	↔1,3	0.00 [-0.21, 0.21]
				(1)Executive function[b] (Literacy, Numeracy, NOGO, People search, ROCF copy, ROCF recall, and Shift)		0.00 [-0.21, 0.21]
				(3)Mental health.(SDQ and the Behaviour Rating Inventory of Executive Function (BRIEF) to assess mental health)		0.08 [-0.10, 0.26]
Yousafzai et al. [35]	Cluster RCT 1302 children (Pakistan, 2013)	(1)cognitive development, (2)motor development, (3)behavioural development 4 years	MNP vs. No MNP Daily supplementation from 6 months of age to 24 months of age.	(1)Cognitive capacity including Intelligent quotient[a] Executive function[b] Pre-academic skills[c]	↔1a,1b,2,3 ↑1c	 -0.10 [-0.21, 0.02] -0.03 [-0.15, 0.09] **0.16 [0.05, 0.27]**
				(2)Motor development		0.11 [-0.01, 0.24]
				(3)Social-emotional development Pro-social behaviours Behavioural problems		 -0.09 [-0.20, 0.01] -0.02 [-0.13, 0.09]
Supplementation of women during pregnancy and lactation and of infants and young children						
Christian et al. [36]	Cluster RCT 223 children (Nepal, 2007-2009)	(1)cognitive development, (2)motor development 7-9 years	M-IFAZn C-IFAZn vs. M-IFA C-Pl Daily maternal supplementation from 11 (±5.1) gestational week until up to 12 weeks postpartum, and preschool daily supplementation from 12 to 35 months of age (length of supplementation depended on age at enrolment)	(1)The Universal Non-Verbal Intelligence Test (UNIT)[a]	↔1a, 1d ↓1b ↓1c ↓2a ↓2b	-0.16 [-0.43, 0.10]
				(1)Stroop test (proportion who failed)[b]		**0.40 [0.13, 0.66]**
				(1)Backward digit span[c]		**-0.44 [-0.71, -0.18]**
				(1)Go/no-go test[d]		-0.22 [-0.48, 0.05]
				(2)The Movement Assessment Battery for Children (MABC)[a*]		**0.34 [0.07, 0.61]**
				(2)Finger-tapping[b]		**-0.46 [-0.72, -0.19]**

C-IFAZn, Child IFAZn; C-Pl, Child Placebo; IFAZn, Iron + Folic acid + Zinc; M-IFA, Maternal IFA; M-IFAZn, Maternal IFAZn; MMNs, Multiple micronutrients; MNPs, multiple micronutrient powders; MVs, Multiple vitamins; NOGO, go/no go test for sustained attention and response control; RCT, Randomised controlled trial; ROCF, Rey–Osterrieth complex figure; SDQ; Strengths and Difficulties Questionnaire; SMD, standard mean difference; Zn, Zinc ; UNIMMAP, United Nations International Multiple Micronutrient Antenatal Preparation; VA. Vitamin A.

*Higher scores are worse outcomes
1, cognitive development; 2, motor development; 3, behavioural development
↔ no effect of nutrient(s) on development; ↑ positive effect of nutrient(s) on development; ↓ negative effect of nutrient(s) on development.

Table 2. Composition of (daily) micronutrient interventions in studies included in the systematic review

	Vitamin A (µg RAE)	B1 (mg)	B2 (mg)	B3 (mg)	B6 (mg)	B12 (mcg)	Folic acid (µg)	Vit. C (mg)	Vit. D (µg)	Vit. E (mg)	Iron (mg)	Zinc (mg)	Cu (mg)	I (µg)	Se (µg)
Supplementation of women during pregnancy and lactation															
Caulfield et al. [37] IFAZn							250				60	25			
Christian et al. [32] IFAZn	1000						400				60	30			
Christian et al. [32] MMNs[1]	1000	1.6	1.8	20	2.2	2.6	400	100	10	10	60	30	2.0		
Dulal et al. [40] UNIMMAP MMNs	800	1.4	1.4	18	1.9	2.6	400	70	5.0	10	30	15	2.0	150	65
Prado et al. [33] UNIMMAP MMNs	800	1.4	1.4	18	1.9	1.6	400	70	200 (IU)	10	30	15	2.0	150	65
Sudfeld et al. [38] MVs		20	20	100	25	50	800	500		30					
Zhu et al. [39, 41] UNIMMAP MMNs	800	1.4	1.4	18	1.9	2.6	400	70	5.0	10	30	15	2.0	150	65
Supplementation of infants and young children															
Murray-Kolb et al. [34] IFAZn							50				12.5	10			
Sudfeld et al. [38] MVs (+Zn)		0.5	0.6	4	0.6	1.0	**130 mg**	60		8.0		5.0			
Yousafzai et al. [35] Sprinkle MNPs[2]	X						X	X			X				

IFAZn, Iron + Folic acid + Zinc; MMNs, Multiple micronutrients; MNPs, multiple micronutrient powders; MiVit., Vitamin; B1, Thiamine; B2, Riboflavin; B3, Niacin; B6, Pyridoxine; B12, Cobalamin; Cu, Copper; I, Iodine; Se, Selenium; MVs, Multiple vitamins; Zn, Zinc.

Additional compositions :

[1] Christian et al. [32] – vitamin K (65 µg), magnesium (100 mg).

[2] Composition not reported in the paper. MNP contained iron, folic acid, vitamin A, and vitamin C.

Risk of bias of the studies included in the systematic review

The RoB assessed using the Cochrane risk of bias assessment tool (RoB2) is presented in **Table 3**. The assessment showed that the majority of the studies ranked low for RoB, while two studies were ranked with some concerns [32, 38], and one study with a high RoB [36]. In the study of Christian et al. (2010), one group of children whose mothers were supplemented with folic acid were dropped. The authors explained their decision by the no effect of folic acid on cognitive development [32]. In the study of Sudfeld et al. (2019), children who received multi-vitamins with or without zinc were evaluated compared to children who received placebo or zinc supplementation in early childhood. The authors failed to present the results per group [38]. Finally, the study by Christian et al. (2011) included only offspring from 2 out of the 5 randomised maternal supplementation groups. The children in these groups had high dropout rates, and there were significant differences in the baseline characteristics of the study participants [36]. Consequently, we concluded that these limitations affected the quality of the evidence.

Table 3. Risk of bias of the studies included in the systematic review

	Risk of bias domain					
Reference	**D1**	**D2**	**D3**	**D4**	**D5**	**Overall risk of bias**
Caulfield et al. [37] [1]	Low	Low	Low	Low	Low	Low
Christian et al. [32] [2]	Low	Low	Some concerns	Low	Low	Some concerns
Dulal et al. [40] [3]	Low	Low	Low	Low	Low	Low
Prado et al. [33] [4]	Low	Low	Low	Low	Low	Low
Sudfeld et al. [38] [5]	Low	Low	Low	Low	Low	Low
Zhu et al. [39, 41] [6]	Low	Low	Low	Low	Low	Low
Murray-Kolb et al. [43] [7]	Low	Low	Low	Low	Low	Low
Sudfeld et al. [38] [8] **Child follow-up**	Low	Low	Low	Low	Some concerns	Some concerns
Yousafzai et al. [35] [9]	Low	Low	Low	Low	Low	Low
Christian et al. [36] [2, 7]	Some concerns	Low	Some concerns	Low	Low	High

D1: Randomization process
D2: Intervention Deviations
D3: Missing outcome data
D4: Measurement of the outcome
D5: Selection of the reported result
Additional references from the parent studies used for the evaluation of RoB:
[1] Merialdi et al. [44, 57]
[2] Christian et al. [45, 58]
[3] Osrin et al. [46]
[4] Shankar et al. [47]
[5] Fawzi et al. [48]
[6] Lingxia et al. [49]
[7] Tielch et al. [54, 59]
[8] McDonald et al. [55]
[9] Yousafzai et a. [56]

Synthesis of the outcomes

Summary of the long-term effects of maternal multiple micronutrient supplementation on cognitive outcomes.

The evaluation of the long-term effects of maternal MMN supplementation on child's and young adolescent's cognitive development was reported in six studies (**Table 1**).

General intelligence and executive function

Four analyses compared the effects of maternal MMN with IFA. Zhu et al. found a significant effect of maternal MMN supplementation on intelligence of 10-14 years old children [39, 41]. Christian et al. found that compared to IFA, maternal MMN supplementation reduced performance intelligence, and reduced or did not affect the executive function of 7-9 years old children [32]. Dulal et al. found that maternal MMN supplementation did not improve the cognitive function of 12-year old children [40]. Similarly, Prado et al. reported that maternal MMN supplementation did not significantly improve intelligence, declarative memory, executive function, or academic achievement of children and young adolescents aged 9-12 years [33]. Prado et al. found a significant improvement in procedural memory [33]. The researchers, however, reported that while non-significant, the proportion of positive coefficients indicates higher scores in the MMN group that are significantly greater than chance [33]. In one study, maternal MMN long-term effects on child cognition was compared to placebo [38]. Sudfeld et al found no effect of maternal MMN supplementation compared to placebo, on general intelligence, and executive function z-scores at 11-14 years of age [38].

Two studies compared the effects of maternal IFAZn supplementation to IFA. In Caulfield et al.'s study, IFAZn supplementation has no significant effect on the intelligence of 54-month-old children [37]. Similarly, in Christian et al.'s study, IFAZn supplementation showed no significant effect on the intelligence of 7-9-year-old children and has mixed effects on their executive function when compared to IFA alone [32].

Motor development

The results were also mixed for the motor development assessed in three studies. Prado et al. did not find significant differences in fine motor dexterity [33]. While Christian et al. found a significant decline in motor development assessed by the Movement Assessment Battery for Children (MABC), and finger-tapping test among 7-9 years old whose mothers received IFAZn or MMNs compared to those whose mothers received IFA [32]. All the groups received additional vitamin A. Our analysis comparing IFAZn or MMNs to IFA revealed a decline in motor development, that requires further investigation. The authors reported positive results of IFA with vitamin A compared to the control, which received vitamin A only [32]. The addition of zinc to iron and folic acid might have attenuated or negated the positive effect of iron on motor development. This could be due to zinc's inhibitory effect on iron absorption [60, 61].

Socioemotional development

All studies evaluating the long-term effects of maternal MMN supplementation on the socio-emotional development of children and young adolescents have consistently found no effects [33, 37-39].

Discussion

Long term effects of prenatal maternal supplementation were not observed in studies supplementing individual nutrients [21]. Helland et al. tried to explain the lack of effects on children's intelligence quotient (IQ) at 7 years of age when supplementing pregnant and lactating mothers with n-3 very-long-chain fatty acids [62]. They suggested that by age 7 years, cognitive development may be influenced by various intervening factors beyond diet. The rationale is that the beneficial effects of prenatal supplementation could have been masked by other

significant factors, such as social stimulation, diet, illness, prescribed medications, and other nutrients consumed by ages 6–7 years. For instance, evidence strongly suggests that psychosocial stimulation within the home environment has a larger impact on child development than nutrition interventions alone [33, 63, 64]. Additionally, the test battery used in the research might not have been sufficiently sensitive to detect the association between diet and cognition at this later stage [62]. In Prado et al.'s study, children of mothers with anaemia who received MMN supplementation scored significantly higher in general intellectual ability, while in the randomly selected representative sample, MMN supplementation has no significant effect on general intellectual ability of 9-12 year-old children [33]. This suggest that MMN supplementation may be more beneficial for children born to women with micronutrient deficiencies and anaemia, and that the effect, when measured across the entire study population, may be diluted and not statistically significant.

Similarly, a systematic review and meta-analysis on the role of MMN and macronutrient supplementation included 10 prenatal and 23 postnatal nutrition interventions. The combination of micro- and macro-nutrient interventions had small effects on the mental (cognitive) development of children under two years, compared to supplementation with a single micronutrient, in LMICs [26]. Leung et al. reviewed the short- and long-term effects of prenatal micronutrient supplementation on children's mental development including 18 studies supplementing single micronutrients, MMN, and essential fatty acids [65]. Although the researchers indicated that there was some evidence to support MMN's positive effect on mental development, the systematic review included only one study that supplemented MMNs and assessed the effects on a child's cognitive development at 4-5 years [37].

This systematic review summarised an additional five studies that were conducted since the 2011 systematic review by Leung et al. [65]. The evidence from these studies suggests that MMN supplementation may have long-term effects on children's cognitive development. While the findings were not consistently statistically significant, they indicate that the observed effects are unlikely to be due to chance alone. Moreover, these findings highlight the limited evidence and the need for continued research to elucidate the long-term effects of maternal MMN supplementation on cognitive and behavioural functions.

Summary of the long-term effects of multiple micronutrient supplementation and point-of-use of infants and young children on cognitive outcomes.

Three studies reported on the long-term effects of MMN supplementation and point-of-use fortification with MNPs for infants and young children on cognitive development (**Table 1**). In Nepal, Murray-Kolb et al. found that IFAZn compared to a placebo supplementation during the preschool years had no effect on aspects of intellectual, executive, and motor function at 7-9 years of age [34]. The authors reported a significantly positive effect of the supplementation on the Stroop test, a measure of the executive function. Similarly, daily supplementation of multivitamins including or not zinc, of infants for 18 months had no long-term effects on general intelligence, executive function, and mental health at 6-8 years of age [38]. One study which used point-of-use sprinkles from 6 months of age to 24 months of age in Pakistan, found no long-term effects on cognitive capacity including intelligence, executive function, motor development, and social-emotional development including pro-social behaviours and behavioural problems of children at 4 years of age [35]. Enhanced nutrition (MNPs) improved pre-academic skills compared to children who did not receive MNPs. It is noteworthy that responsive stimulation had a larger effect size on long-term child cognition.

The studies included in this review suggest no statistically significant long-term developmental benefit of MMN supplementation and point-of-use fortification with MNPs during early childhood. However, the existing evidence is limited, and does not conclusively support the absence of a long-term effect of MMN on cognitive development.

A meta-analysis of 20 randomised controlled trials conducted between 1970 and 2008 that tested the effects of supplementing at least 3 micronutrients compared to placebo found a slight increase in fluid intelligence, reflecting reasoning ability and neurological potential, but no significant impact on crystallised intelligence, which measures acquired knowledge [66]. Fluid intelligence is typically assessed through non-verbal cognitive tests, while crystallised intelligence is assessed through verbal cognitive tests [67, 68].

Summary of the long-term effects of multiple micronutrient supplementation of mothers during pregnancy and lactation and their infants and young children on cognitive outcomes.

Only one study reported on the long-term effects of maternal and child supplementation with IFAZn (both mothers and children) on child cognition at 7 – 9 years of age [36]. Children who received IFAZn and whose mothers received IFAZn had slightly lower backward digit span, reduced motor development as indicated by the higher scores in Movement Assessment Battery for Children, reduced finger tapping, and higher proportions who failed the Stroop test compared to children who received placebo supplement and whose mothers received IFA, whereas they had no difference in the Universal Nonverbal Test of Intelligence [36].

Given that there is only a single study reporting on the long-term effects of continuous maternal and offspring supplementation with MMN, no definitive conclusions can be drawn from the available evidence.

Conclusions

The systematic review assessed the long-term effects of MMN supplementation and point-of-use fortification with MNPs on child development, analysing a total of ten studies. These studies examined the effects of MMN supplementation during pregnancy and lactation (six studies), MMN supplementation and point-of-use fortification with MNPs during early childhood (three studies), and maternal and early childhood MMN supplementation (one study). Conducted between 1998 and 2012 in LMICs, most studies did not report on the food environment. However, the target populations were primarily rural and largely characteried by food insecurity, with poor to average dietary intakes of nutrient-rich foods.

Overall, maternal MMN supplementation may have long-term effects on children's cognitive development Although the findings were not statistically significant, few studies suggested potential associations with cognitive development. Despite this, the observed effects in few included studies are unlikely to be due to chance alone. However, several factors may have contributed to these findings, including the studies' limitations (not powered for these outcomes, heterogeneity in outcome measurements tools, use of an active comparator, particularly IFA during pregnancy and lactation). Additionally, the complex nature of the outcome measured, unknown baseline micronutrient status, and diets may have influenced the results. These findings highlight the limited evidence and the need for continued research to elucidate the long-term effects of maternal MMN supplementation on cognitive and behavioural functions.

The evidence regarding the long-term effects of MMN supplementation and point-of-use fortification with MNPs for infants and young children remains limited and calls for further research.

Public health impacts and recommendations

Although the results of this systematic review did not provide strong evidence to recommend or implement a program for MMN supplementation for women during pregnancy and lactation, or for point-of-use fortification with MNPs for young children, with the primary aim of promoting long-term cognitive development, there are important points to consider:

1- ***Evidence regarding other health benefits***

The evidence from existing trials strongly supports the effects of maternal MMN compared to IFA in improving birth outcomes, including reducing the risk of LBW and SGA. Similarly, the evidence is strong regarding the benefits of point-of-use MNPs for infants and children, particularly in improving iron status and reducing anaemia.

Therefore, the WHO recommendation to replace IFA with MMN and to integrate point-of-use fortification with iron-containing MNPs for complementary foods in infants and young children aged 6-23 months, as well as for foods in children 2-12 years, should remain unchanged.

2- Research gaps and needs

There is a need for: 1) Larger, long-term RCTs to generate more robust evidence; and 2) Development and validation of tools to accurately assess developmental and cognitive performance in children, particularly in LMIC contexts.

3- Cognitive development assessment challenges

Cognitive development is a relatively new domain, and its assessment in LMIC settings is still limited. This includes challenges in validating assessment tools and using them as public health outcomes, as well as accounting for cultural specificities. However, it is important to note that: 1) The evidence is strong regarding the benefits of MMN supplementation in improving maternal and birth outcomes, as well as the use of point-of-use MNPs in reducing anaemia and iron deficiency in young and pre-school children. 2) There are ongoing efforts to integrate supplementation programs into existing healthcare and other programs.

- ***Potential negative outcomes and risk-benefit analysis***

  Some studies have reported potential negative outcomes of MMN supplementation. To address this, it is important to: 1) Explore whether these findings are replicated in other studies and settings; 2) Understand the mechanisms by which MMN supplementation may have had negative effects; and 3) Carefully weigh the benefits and risks to make an informed decision about the continuation of these supplementation programs.

- ***Sustainable alternatives and program integration***

  It is important to explore more sustainable alternatives, such as the use of local foods and fortified/enriched foods, to meet the nutritional requirements and improve the development of children. This is particularly relevant given the concerns about the ongoing dependence of supplementation programs on funding and technical expertise from high-income countries.

4- Role of socioemotional stimulation and education in cognitive development

It is also important to consider the significant impact of socioemotional stimulation within the home environment and the importance of education on both short- and long-term cognitive and socioemotional development. To fully optimise cognitive development and achieve Sustainable Development Goal 4, which aims to ensure inclusive and equitable quality education, addressing socio-environmental factors in nutrition interventions is essential [33].

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Annex

Annex 1. PRISMA 2020 Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	We reviewed the checklist and applied it.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Data sources and search strategy Eligibility criteria
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Method and design Data sources and search strategy
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Annex 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Eligibility criteria Study selection
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Data extraction Data Synthesis
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Data extraction Data Synthesis
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Data extraction Data Synthesis
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Assessment of risk of bias
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Data Synthesis Analysis of subgroups
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5).	Data Synthesis

	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Data Synthesis
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesised results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Assessment of risk of bias
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Result Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	Study characteristics
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Risk of bias
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Risk of bias
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results.	Results
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	Conclusion

OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods and design
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods and design
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data Availability section, Data will be fully available under request to the corresponding author

Annex 2. Search strategy

Research question (e.g., PICO format): What are the long-term impacts of micronutrient supplementation of children and pregnant and lactating women on the children cognitive development			
NAME OF DATABASE (interface): List of terms for the search strategy			
Concept	**Line number**	**Search strategy**	
Concept 1: Cognition	1	1. Cognition 2. Cognitive development 3. Cognitive neuroscience 4. Child development 5. Language development 7. Intelligence tests 8. Intelligence quotient 9. Neuropsychological test 10. Wechsler scales[1] 11. Stanford Binet test[2] 12. Developmental psychology 13. Academic achievement 14. Academic performance	15. Learning curve 17. Aptitude test[3] 18. Multitasking behaviour 19. Executive function 20. Learning 21. Problem solving 22. Thinking 23. social-emotional development 26. Verbal skills/verbal behaviour 28. Adaptive skills
Concept 2: Infants, toddlers and children	2	1. Infant 2. Toddler 3. Preschool child 4. Child 5. School child 6. Student	7. Pupil 8. School 9. Elementary student 10. Primary school
Concept 3: Pregnancy and lactation	3	1. Prenatal/Antenatal 2. Lactation/breastfeeding 3. Pregnancy	4. Postnatal/postpartum 5. Perinatal

[1] Tests designed to measure intellectual functioning in children and adults.

[2] An individual intelligence test designed primarily for school children to predict school performance and the ability to adjust to everyday demands.

[3] aptitude tests are used to measure the potential ability to learn.

Concept 4: Micronutrient Supplementation	4	1. Micronutrient supplementation 2. Multiple micronutrient powder 3. Dietary Supplements 4. Diet supplementation 5. Mineral supplementation 6. Zinc 7. Iron	9. Iodine 10. Folic acid 11. B12 12. Vitamin A 13. Vitamin D 14. Calcium 15. Vitamin C
Concept 5: Study design	5	1. Clinical Trial 2. Randomised Controlled Trial 3. Controlled trial	4. Quasi-experimental trial 5. Prospective cohort study 6. Retrospective cohort study 7. Repeated cross-sectional
Concept 7: Low- and middle-income countries	6	1. Countries/names 2. Developing countries • Low- and middle-income countries	
Combination of concepts	7	1 AND (2 OR 3) AND 4 AND 5 AND 6	