LONG-TERM EFFECTS ON CHILD COGNITIVE DEVELOPMENT OF MULTIPLE MICRONUTRIENT SUPPLEMENTATION FROM PREGNANCY TO EARLY CHILDHOOD: EVIDENCE IS INSUFFICIENT

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Micronutrient deficiencies remain an important challenge

The World Health Organisation (WHO) recommends iron and folic acid supplementation during pregnancy, as well as the use of iron-containing micronutrient powders for young children (6-23 months) and children (2-12 years old). Implemented worldwide, such programmes have proven effective in reducing anaemia in women and children and in improving birth outcomes. Recent evidence suggests that replacing iron and folic acid supplements with multiple micronutrients during pregnancy has a positive impact on birth outcomes and poses little harm regarding mortality. However, the evidence related to small-for-gestational-age outcomes remains limited. WHO has changed the recommendation on multiple micronutrients in pregnancy from "not recommended" to "recommended in the context of rigorous research" [1].

Such strategies are rather recent and so far, little is known about the long-term effects of these multiple micronutrient supplements on child cognitive development. In an attempt to address this knowledge gap, the Nutrition Research Facility carried out a systematic literature review to assess existing evidence on the long-term cognitive effects – measured on children aged 4-14 in low- and middle-income countries – of both maternal multiple micronutrient supplementation and early childhood micronutrient powder food fortification. This work has been done in the framework of the Knowledge and Research for Nutrition project funded by the European Union.

This document is a summary of the NRF study on multiple micronutrient supplementation and its impact on child cognitive development. The full report is available here: https://www.nutrition-research-facility.eu/IMG/pdf/nrf-report-micronutrient_october2024.pdf

Knowledge about the long-term effect of multiple micronutrient supplementation on children's cognitive development is limited

The search yielded 8,815 records on October 26, 2023. Based on the defined inclusion/exclusion criteria, the records were screened in duplicate, first by title and abstract (resulting in the exclusion of 8,741 records) and then by full text (resulting in 64 additional exclusions). So finally, 10 publications were included in the review. Two publications (Sudfield et al., 2019, and Christian et al., 2010) cover two separate interventions, while two others (Zhu et al., 2018 and Zhu et al., 2023, in China) are based on the same intervention. So, in the end, the 10 publications cover 11 different interventions (Annex).

The main features of each intervention are presented in Table 1: 6 of them are randomised controlled trials; while 5 are cluster randomised controlled trials. Their quality was assessed using the Cochrane Risk of Bias assessment tool (RoB2): 7 interventions have a low risk of bias; 3 present some concerns; while 1 is classified as having a high risk of bias. 7 interventions only deal with supplementation for pregnant and lactating women, 3 only deal with infant and young children supplementation, while 1 deals with both groups. All 11 interventions report outcomes on children's cognitive development; 6 also report outcomes on motor development; and 6 report outcomes on behavioural development and mental health. Geographically, 5 interventions were conducted in Nepal (involving 281, 321, 223, 813, and 377 individuals respectively), 1 in Pakistan (1,302 individuals), 1 in Indonesia (2,879 individuals), 1 in China (1,385 individuals), 2 in Tanzania (446 and 365 individuals) and 1 in Peru (184 individuals).

The main findings of each intervention are summarised in Table 2. Overall, 36 tests or combinations of tests have been carried out to assess the effect of multiple micronutrient supplementation on some aspects of the cognitive development of children aged 4-14, compared to standard or no micronutrient supplementation. Most of them (26) showed no significant effect, 4 tests showed a statistically significant positive effect, and 6 tests reported a statistically significant negative effect (Table 2A). In addition, out of the 10 tests or combination of tests assessing motor development, none had a significant positive impact, while 6 reported a significant negative impact (Table 2B).

Finally, none of the 12 tests on behavioural development and mental health showed any significant difference between the treatment and control groups (Table 2C).

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[1] WHO, 2020 (https://iris.who.int/bitstream/handle/10665/333561/9789240007789-eng.pdf?sequence=1)

Table 1. List and characteristics of the 11 interventions included in this review

Reference	Study design/ Country / Outcome sample	Risk of bias	Intervention type
1. Caulfield et al., 2010	Randomised controlled trial Peru 184 children aged 4-5 years	Low	Micronutrient supplementation on women during pregnancy and lactation IFAZn vs. IFA Daily, from 10-16 gestational week until 1 month postpartum
2a. Christian et al., 2010 Intervention a	Randomised controlled trial Nepal 281 children aged 7-9 years	Some concerns	Micronutrient supplementation on women during pregnancy and lactation IFAZn + Vitamin A vs. IFA + Vitamin A Daily, from 11 (±5.1) gestational week until 12 weeks postpartum
2b. Christian et al., 2010 Intervention b	Randomised controlled trial Nepal 321 children aged 7-9 years	Some concerns	Micronutrient supplementation on women during pregnancy and lactation Vitamins A, B1,B2, B3, B6, B9, B12, C, D, E, K + Fe, Zn, Cu, Mg vs. IFA + Vitamin A Daily, from 11 (±5.1) gestational week until 12 weeks postpartum
3. Christian et al., 2011	Cluster Randomised controlled trial Nepal 223 children aged 7-9 years	High	Micronutrient supplementation on women during pregnancy and lactation / on children Maternal-IFAZn / child-IFAZn vs. maternal-IFA / child placebo Daily, from 11 (±5.1) gestational week to 12 weeks postpartum / daily, from 12 to 35 months-old
4. Dulal et al., 2018	Randomised controlled trial Nepal 813 children aged 12 years	Low	Micronutrient supplementation on women during pregnancy and lactation UNIMMAP vs. IFA Daily, from 12 weeks gestation until childbirth
5. Murray-Kolb et al., 2012	Cluster Randomised controlled trial Nepal 377 children aged 7-9 years	Low	Micronutrient supplementation on children IFAZn vs. placebo Daily, from 12 to 35 months of age
6. Prado et al., 2017	Cluster Randomised controlled trial Indonesia 2,879 children aged 9-12 years	Low	Micronutrient supplementation on women during pregnancy and lactation UNIMMAP vs. IFA Daily, from enrolment until three months post-partum
7a. Sudfeld et al., 2019 Intervention a	Randomised controlled trial Tanzania 446 children aged 11-14 years	Low	Micronutrient supplementation on women during pregnancy and lactation IFA + Vitamins B1,B2, B3, B6, B12, C, E vs. IFA + placebo Daily, from 12-27 gestational weeks until 6 weeks after childbirth
7b. Sudfeld et al., 2019 Intervention b	Randomised controlled trial Tanzania 365 children aged 6-8 years	Some concerns	Micronutrient supplementation on children Vitamins B1,B2, B3, B6, B9, B12, C, E (+Zn) vs. Placebo (+Zn) Daily for 18 months (1 dose 1-6 months-old - 2 doses from 7 months-old)
8. Yousafzai et al., 2016	Cluster Randomised controlled trial Pakistan 1,302 children aged 4 years	Low	Micronutrient supplementation on children IFA + Vitamins A, C vs. no supplementation Daily supplementation from 6 months of age to 24 months of age
9 & 10. Zhu et al., 2018 & 2023	Cluster Randomised controlled trial China 1,385 children aged 10-14 years	Low	Micronutrient supplementation on women during pregnancy and lactation UNIMMAP vs. IFA Daily supplementation from 13.8 (±5.8) gestational weeks until childbirth

IFA = Iron and Folic acid
IFAZn = IFA + Zn
UNIMMAP = United Nations International Multiple Micronutrient Antenatal Preparation: Vitamins A, B1,B2, B3, B6, B9, B12, C, D, E + Fe, Zn, Cu, I, Se

In any case, it is worth mentioning that: (i) only 3 interventions evaluated the long-term effects of supplementing children and only 1 evaluated continued care from pregnancy to early childhood; (ii) all the tests yielding negative outcomes are reported from 3 interventions in Nepal from the same research team (Christian et al.), and that those interventions all present concerns regarding their risk of bias (Table 1); and (iii) the study with the highest number of children (2,879) (Prado et al.) reports that, though no significant effect could be revealed in most of the tests, the proportion of positive coefficients – indicating higher scores in the multiple micronutrient group – is significantly greater than chance.

More methodological development and research are needed to assess the long-term effects of multiple micronutrient supplementation on children's cognitive capacities

Firstly, it is important to acknowledge that evidence regarding the long-term effects on children's cognitive development of multiple micronutrient supplementation whether applied to mothers or young children is limited.
From the 10 publications/11 interventions analysed in this review, no clear tendency can be identified. More data are needed to generate robust evidence.

Secondly, cognitive development is a very complex and poorly known process. There are challenges about how to measure it, especially accounting for different cultural contexts. In addition, cognitive development is influenced by a diversity of factors, beyond nutrient adequacy such as care, health, socioemotional stimulation, and education. In the interventions reviewed, such factors were not always taken into account, potentially diluting an effect of multiple micronutrient supplementation.

Thirdly, it can be hypothesised that multiple micronutrient supplementation may be more beneficial for children born to women with micronutrient deficiencies. When considering a randomly selected representative sample of mothers and/or children, this may dilute a small effect, if any, and annihilate the statistical significance of results.

In conclusion, while it is well established that multiple micronutrient supplementation is beneficial to improve birth weight and iron status for children, more methodological development and research are needed to be able to assess its long-term impact on children's cognitive capacities.

Table 2. Results of the tests on cognitive, motor, and behavioural/socio-emotional/mental development in the interventions reviewed

Reference	Aptitude tested	Effect of intervention	Test performed
A. Cognitive development tests			
1. Caulfield et al., 2010	Intelligence	no effect	Wechsler Preschool & Primary Scale of Intelligence
	Language development	no effect	Bear story
	Number concepts	no effect	Counting game
	Concept formation	no effect	Goodenough & Harris Draw-a-Person Test
	Interpersonal understanding	no effect	Friendship interview
2a. Christian et al., 2010	Intelligence	no effect	The Universal Non-Verbal Intelligence Test
	Executive function	no effect	Go/No-go test
	Executive function	negative	Stroop test 0.33 [0.09, 0.57]
	Executive function	negative	Backward digit span -0.33 [-0.57, -0.08]
2b. Christian et al., 2010	Intelligence	negative	The Universal Non-Verbal Intelligence Test -0.26 [-0.49, -0.02]
	Executive function	no effect	Go/No-go test
	Executive function	no effect	Stroop test
	Executive function	negative	Backward digit span -0.36 [-0.60, -0.13]
3. Christian et al., 2011	Intelligence	no effect	The Universal Non-Verbal Intelligence Test
	Executive function	no effect	Go/No-Go test
	Executive function	negative	Stroop test 0.40 [0.13, 0.67]
	Executive function	negative	Backward digit span -0.44 [0.17, 0.71]
4. Dulal et al., 2018	Intelligence	no effect	The Universal Non-Verbal Intelligence Test
	Executive function	no effect	Stroop test
5. Murray-Kolb et al., 2012	Intelligence	no effect	The Universal Non-Verbal Intelligence Test
	Executive function	no effect	Backward digit span
	Executive function	no effect	Go/No-Go test
	Executive function	positive	Stroop test -0.29 [-0.50, -0.09]
6. Prado et al., 2017	Intelligence	no effect	Information test / Speeded picture naming test / Block design test
	Declarative memory	no effect	Adapted Rey auditory verbal learning test
	Procedural memory	positive	Serial reaction time task 0.11 [0.01, 0.20]
	Executive function	no effect	Adapted visual search task / Adapted visual search dual task / Digit span forward and backward / Stroop numbers / NIH Toolbox Dimensional Change Card Sort Test
	Academic attainment	no effect	Literacy test / Arithmetic test
7a. Sudfeld et al., 2019	Intelligence	no effect	Atlantis, Footsteps, Hand movement, Kilifi naming test, Koh's block design test, Story completion, and verbal fluency
	Executive function	no effect	Literacy, Numeracy, NOGO, People search, ROCF copy, ROCF recall, and Shift
7b. Sudfeld et al., 2019	Intelligence	no effect	Atlantis, Footsteps, Hand movement, Kilifi naming test, Koh's block design test, Story completion, and verbal fluency
	Executive function	no effect	Literacy, Numeracy, NOGO, People search, ROCF copy, ROCF recall, and Shift
8. Yousafzai et al., 2016	Intelligence	no effect	Wechsler Preschool and Primary Scales of Intelligence
	Executive function	no effect	Stroop task, knock-tap task, big-little task, go/no go task, forward word span, Separated Dimensional Change Card Sort
	Pre-academic skills	positive	Bracken School Readiness Assessment 0.16 [0.05, 0.27]
9 & 10. Zhu et al., 2018 & 2023	Intelligence	positive	Wechsler Intelligence Scale for Children 0.13 [0.03, 0.24]
B. Motor development tests			
2a. Christian et al., 2010	Motor functions	negative	The Movement Assessment Battery for Children 0.33 [0.08, 0.57]
	Motor functions	negative	Finger-tapping test -0.41 [-0.66, -0.17]
2b. Christian et al., 2010	Motor functions	negative	The Movement Assessment Battery for Children 0.32 [0.09, 0.56]
	Motor functions	negative	Finger-tapping test -0.45 [-0.69, -0.22]
3. Christian et al., 2011	Motor functions	negative	Finger-tapping -0.46 [-0.72, -0.19]
	Motor functions	negative	The Movement Assessment Battery for Children 0.34 [0.07, 0.61]
5. Murray-Kolb et al., 2012	Motor functions	no effect	The Movement Assessment Battery for Children
	Motor functions	no effect	Finger-tapping
6. Prado et al., 2017	Motor functions	no effect	Purdue pegboard test
8. Yousafzai et al., 2016	Motor functions	no effect	Bruininks-Oseretsky Test for Motor Proficiency
C. Behavioural development, emotional and mental health tests			
1. Caulfield et al., 2010	Behavioural development	no effect	Preschool Behaviour Questionnaire: Internalizing
	Behavioural development	no effect	Preschool Behaviour Questionnaire: Externalizing
	Adaptive behaviour	no effect	Vineland Adaptive Behaviour Scales: Communication
	Adaptive behaviour	no effect	Vineland Adaptive Behaviour Scales: Daily living skills
	Adaptive behaviour	no effect	Vineland Adaptive Behaviour Scales: Socialization
	Adaptive behaviour	no effect	Vineland Adaptive Behaviour Scales: Motor skills
6. Prado et al., 2017	Socio-emotional development	no effect	Adapted Child Behavior Checklist
7a. Sudfeld et al., 2019	Mental health	no effect	Strengths and Difficulties Questionnaire and Behaviour Rating Inventory of Executive Function
7b. Sudfeld et al., 2019	Mental health	no effect	Strengths and Difficulties Questionnaire and Behaviour Rating Inventory of Executive Function
8. Yousafzai et al., 2016	Socio-emotional development	no effect	Maternal Strengths and Difficulties Questionnaire set of questions
	Socio-emotional development	no effect	Maternal Strengths and Difficulties Questionnaire set of questions
9 & 10. Zhu et al., 2018 & 2023	Socio-emotional development	no effect	Internalising, externalising, and total behaviour problem scores

The data analysis, conducted using Review Manager, calculated pooled standard mean differences (SMD) with 95% confidence intervals using a random effects model to account for variability across studies

Annex. The literature search and selection yielded only 10 publications in the scope of this review

Identification and selection process	Individual documents identified/selected
Database search: MEDLINE (Pubmed), EMBASE, CENTRAL (Cochrane Library), Web of Science, CINAHL, SCOPUS, Google scholar	**n = 8,815**
Selection based on the title and abstract along the following eligibility criteria:	**n = 74**

- ***Intervention type:*** multiple micronutrient supplementation (at least three micronutrients)
- ***Study design:*** randomised controlled trial, controlled trial, quasi-experimental, longitudinal or repeated cross-sectional
- ***Supplemented population:*** women (pregnant or lactating), infants and young children (from 6 months to 3 year-old), in low- and middle-income countries
- ***Outcomes assessed:*** at least one of the following development domains for children 4-14 years-old without developmental disability: intelligence, memory, concentration, psychomotor skills, academic achievement, social-emotional development, adaptive skills

Selection based on the title and abstract along the eligibility criteria — **n = 10**

1. Caulfield LE, Putnick DL, Zavaleta N, Lazarte F, Albornoz C, Chen P, et al. Maternal gestational zinc supplementation does not influence multiple aspects of child development at 54 mo of age in Peru. Am J Clin Nutr. 2010;92(1):130-6. doi: 10.3945/ajcn.2010.29407
2. Christian P, Murray-Kolb LE, Khatry SK, Katz J, Schaefer BA, Cole PM, et al. Prenatal micronutrient supplementation and intellectual and motor function in early school-aged children in Nepal. Jama. 2010;304(24):2716-23. doi: 10.1001/jama.2010.1861
3. Christian P, Morgan ME, Murray-Kolb L, LeClerq SC, Khatry SK, Schaefer B, et al. Preschool Iron-Folic Acid and Zinc Supplementation in Children Exposed to Iron-Folic Acid in Utero Confers No Added Cognitive Benefit in Early School-Age12. J Nutr. 2011;141(11):2042-8. doi: 10.3945/jn.111.146480
4. Dulal S, Liégeois F, Osrin D, Kuczynski A, Manandhar DS, Shrestha BP, et al. Does antenatal micronutrient supplementation improve children's cognitive function? Evidence from the follow-up of a double-blind randomised controlled trial in Nepal. BMJ Glob Health. 2018;3(1):e000527. doi: 10.1136/bmjgh-2017-000527
5. Murray-Kolb LE, Khatry SK, Katz J, Schaefer BA, Cole PM, LeClerq SC, et al. Preschool Micronutrient Supplementation Effects on Intellectual and Motor Function in School-aged Nepalese Children. Archives of Pediatrics & Adolescent Medicine. 2012;166(5):404-10. doi: 10.1001/archpediatrics.2012.37
6. Prado EL, Sebayang SK, Apriatni M, Adawiyah SR, Hidayati N, Islamiyah A, et al. Maternal multiple micronutrient supplementation and other biomedical and socio-environmental influences on children's cognition at age 9-12 years in Indonesia: follow-up of the SUMMIT randomised trial. Lancet Glob Health. 2017;5(2):e217-e28. doi: 10.1016/s2214-109x(16)30354-0
7. Sudfeld CR, Manji KP, Darling AM, Kisenge R, Kvestad I, Hysing M, et al. Effect of antenatal and infant micronutrient supplementation on middle childhood and early adolescent development outcomes in Tanzania. Eur J Clin Nutr. 2019;73(9):1283-90. doi: 10.1038/s41430-019-0403-3
8. Yousafzai AK, Obradović J, Rasheed MA, Rizvi A, Portilla XA, Tirado-Strayer N, et al. Effects of responsive stimulation and nutrition interventions on children's development and growth at age 4 years in a disadvantaged population in Pakistan: a longitudinal follow-up of a cluster-randomised factorial effectiveness trial. Lancet Glob Health. 2016;4(8):e548-58. doi: 10.1016/s2214-109x(16)30100-0
9. Zhu Z, Cheng Y, Zeng L, Elhoumed M, He G, Li W, et al. Association of Antenatal Micronutrient Supplementation With Adolescent Intellectual Development in Rural Western China: 14-Year Follow-up From a Randomized Clinical Trial. JAMA Pediatrics. 2018;172(9):832-41. doi: 10.1001/jamapediatrics.2018.1401
10. Zhu Z, Zhu Y, Wang L, Qi Q, Huang L, Andegiorgish AK, et al. Effects of antenatal micronutrient supplementation regimens on adolescent emotional and behavioral problems: A 14-year follow-up of a double-blind, cluster-randomized controlled trial. Clin Nutr. 2023;42(2):129-35. doi: 10.1016/j.clnu.2022.12.001

For more information, find the fact sheet of the study here:
https://www.nutrition-research-facility-studies.eu/Multiple-micronutrient-supplementation-during-pregnancy-lactation-and-early

https://www.nutrition-research-facility.eu/

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