Maternal multiple micronutrient supplementation and other biomedical and socioenvironmental influences on children's cognition at age 9–12 years in Indonesia: follow-up of the SUMMIT randomised trial

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Summary

Background Brain and cognitive development during the first 1000 days from conception are affected by multiple biomedical and socioenvironmental determinants including nutrition, health, nurturing, and stimulation. An improved understanding of the long-term influence of these factors is needed to prioritise public health investments to optimise human development.

Methods We did a follow-up study of the Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT), a double-blind, cluster-randomised trial of maternal supplementation with multiple micronutrients (MMN) or iron and folic acid (IFA) in Indonesia. Of 27 356 live infants from birth to 3 months of age in 2001–04, we re-enrolled 19 274 (70%) children at age 9–12 years, and randomly selected 2879 from the 18 230 who were attending school at a known location. Of these, 574 children were oversampled from mothers who were anaemic or malnourished at SUMMIT enrolment. We assessed the effects of MMN and associations of biomedical (ie, maternal and child anthropometry and haemoglobin and preterm birth) and socioenvironmental determinants (ie, parental education, socioeconomic status, home environment, and maternal depression) on general intellectual ability, declarative memory, procedural memory, executive function, academic achievement, fine motor dexterity, and socioemotional health. The SUMMIT trial was registered, number ISRCTN34151616.

Findings Children of mothers given MMN had a mean score of 0·11 SD (95% CI 0·01–0·20, p=0·0319) higher in procedural memory than those given IFA, equivalent to the increase in scores with half a year of schooling. Children of anaemic mothers in the MMN group scored 0·18 SD (0·06–0·31, p=0·0047) higher in general intellectual ability, similar to the increase with 1 year of schooling. Overall, 18 of 21 tests showed a positive coefficient of MMN versus IFA (p=0·0431) with effect sizes from 0·00–0·18 SD. In multiple regression models, socioenvironmental determinants had coefficients of 0·00–0·43 SD and 22 of 35 tests were significant at the 95% CI level, whereas biomedical coefficients were 0·00–0·10 SD and eight of 56 tests were significant, indicating larger and more consistent impact of socioenvironmental factors (p<0·0001).

Interpretation Maternal MMN had long-term benefits for child cognitive development at 9–12 years of age, thereby supporting its role in early childhood development, and policy change toward MMN. The stronger association of socioenvironmental determinants with improved cognition suggests present reproductive, maternal, neonatal, and child health programmes focused on biomedical determinants might not sufficiently enhance child cognition, and that programmes addressing socioenvironmental determinants are essential to achieve thriving populations.

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Introduction

Determinants that influence brain and cognitive development during the first 1000 days from conception to 2 years of age can have long-term effects on brain architecture and cognitive ability.[1] Studies in high-income countries have shown the long-term cognitive consequences of early life experiences, such as intrauterine growth restriction,[2] preterm birth,[3] adverse events,[4] and early educational experiences.[5] Children in low-income and middle-income countries (LMICs) have a greater burden of risk factors for poor cognitive and behavioural development than those in high-income countries.[6] However, few studies in LMICs have assessed the association between early life experiences and later cognitive, motor, and socio-emotional ability. Identification of the biomedical and socioenvironmental determinants that most strongly predict cognitive, motor, and socioemotional function is needed for strategic design and integration of child development programmes with existing reproductive,

Research in context

Evidence before this study

The long-term effects of maternal nutrition and the interplay of early life biomedical and socioenvironmental determinants on child cognition are unclear. A better understanding is needed to prioritise public health investments to optimise human development. Of the 20 follow-up studies of randomised trials comparing maternal supplementation with three or more micronutrients to iron and folic acid (IFA), only four assessed child motor and cognitive development, and with equivocal results. These studies did not typically use a wide range of tests for multiple cognitive domains in school age children, nor detail the relative contributions of other biomedical and socioenvironmental determinants. Such evidence is important to inform policy makers of which types of interventions are likely to most effectively support children to achieve their developmental potential. We therefore examined citations in four systematic reviews of risk factors for poor child development in low-income and middle-income countries (LMICs). We identified 56 studies that enrolled pregnant women or infants younger than 2 years in LMICs and later assessed cognitive, motor, or socioemotional ability at age 5 years or older. Only five of these analysed biomedical and socioenvironmental determinants, and few included two crucial socioenvironmental determinants, maternal depression and stimulation from the home environment. Additionally, four studies assessed only general intellectual ability, while one reported on general intellectual ability, numeracy, knowledge, and achievement but did not probe specific cognitive domains. One study in Bangladesh included 2853 younger children aged 5 years, while the other four included less than 350 children with limited power to discern effects. As such, detailed analyses and quantification of long term effects of MMN and other early life socioenvironmental and biomedical determinants on multiple defined domains in older children has not been previously reported.

Added value of this study

Our study is the first, to our knowledge, to assess the long term effect of maternal MMN versus IFA on multiple cognitive, motor, and socioemotional domains in school-age children, and the first, to our knowledge, to assess procedural memory. It is the only long-term longitudinal study in a LMIC with a sample of more than 2000 children to assess the relative association of biomedical and socioenvironmental determinants, including home environment and maternal depression, with multiple domains of child abilities. We report significant effects of maternal MMN on procedural memory, on general intellectual ability in children of anaemic women, and positive shifts overall on cognitive, fine motor, and socioemotional ability.

Implications of all the available evidence

The beneficial effects of maternal MMN supplementation on birth weight, small for gestational age, and stillbirths in recent meta-analyses, and on mortality in SUMMIT, especially in anaemic women, tend to support policy change from IFA to MMN for maternal supplementation. Our findings suggest that to achieve thriving populations in multiple domains of children's abilities, current biomedical-centered programmes and interventions are not sufficient, and that additional interventions addressing socioenvironmental determinants are required.

maternal, neonatal, and child health (RMNCH) programmes.

Maternal micronutrient deficiency during pregnancy is one important and preventable risk factor for poor child development and is prevalent among women of child-bearing age in LMICs.[7] Present global policy[8] recommends iron and folic acid (IFA) supplementation during pregnancy. However, supplementation with additional micronutrients might also be needed, particularly for fetal brain development, which occurs rapidly during gestation.[9] Animal models have shown that micronutrients in addition to IFA, such as iodine, zinc, and vitamin B6, are necessary for neurodevelopment during this period.[10] In human beings, associations have been found between child development and indicators of maternal undernutrition, including anthropometric measures and micronutrient deficiencies.[11] However, few randomised controlled trials of maternal multiple micronutrient (MMN) supplementation in LMICs have assessed long-term cognitive outcomes.

The Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT)[12] was a double-blind, cluster-randomised trial of maternal supplementation with MMN or IFA in Lombok, Indonesia from 2001–04, which enrolled 31290 pregnant women who had 28426 live births. Infant mortality at 3 months was reduced by 18%, fetal loss and neonatal deaths by 11%, and an association with a reduction in the proportion of low birth weight by 14% was noted in the group receiving MMN compared with those who received IFA, with greater and significant effects in mothers who were anaemic at enrolment (38%, 29%, and 33% reductions, respectively).[13] In 487 children assessed at age 3·5 years, positive effects of MMN were recorded for cognitive ability in children of mothers who had been anaemic or undernourished at enrolment.[13] The aim of the present study was to follow-up SUMMIT children to assess the biomedical and socioenvironmental determinants of children's cognition at age 9–12 years.

Methods

Study design

The SUMMIT double-blind, cluster-randomised trial methods have been described in detail.[12] In brief, 262 government midwives throughout Lombok, Indonesia, were randomly assigned to distribute either

IFA or MMN. Pregnant women were enrolled at prenatal care clinics held by midwives. Women who provided written informed consent received a monthly supply of MMN or IFA capsules to be taken daily throughout the duration of pregnancy and until 3 months post partum. SUMMIT research assistants collected data for biomedical and socioenvironmental determinants within 72 h of enrolment. These data included mid-upper arm circumference (MUAC) and haemoglobin concentration, which were used to classify mothers as undernourished or anaemic for selection of the follow-up sample. Research assistants collected data for health outcomes and community facilitators promoted use of government health services and assessed supplement consumption. The IFA capsule contained 30 mg iron as ferrous fumarate and 400 µg folic acid. The MMN capsule, in accordance with the UN International Multiple Micronutrient Preparation (UNIMMAP),[14] contained the same amounts of IFA, plus 800·0 µg retinol (retinyl acetate), 200·0 IU vitamin D (ergocalciferol), 10·0 mg vitamin E (alpha tocopherol acetate), 70·0 mg ascorbic acid, 1·4 mg vitamin B1 (thiamine mononitrate), 1·4 mg vitamin B2 (riboflavin), 18·0 mg niacin (niacinanide), 1·9 mg vitamin B6 (pyridoxine), 1·6 µg vitamin B12 (cyanocobalamin), 15·0 mg zinc (zinc gluconate), 2·0 mg copper, 65·0 µg selenium and 150·0 µg iodine. The study was registered at http://isrctn.org, number ISRCTN34151616.

The protocol of the original study was approved by the National Institute of Health Research and Development of the Ministry of Health of Indonesia, the Provincial Planning Department of Nusa Tenggara Barat Province, and the Johns Hopkins Joint Committee on Clinical Investigation, Baltimore, USA. The protocol of the follow-up study was approved by the University of Mataram Ethical Research Committee as a certified Institutional Review Board of the National Institute of Health Research and Development of the Ministry of Health of Indonesia. Additional approvals were provided by the Provincial Planning Department of Nusa Tenggara Barat Province, and the District Health Departments of East, West, Central, and North Lombok Districts.

Participants

In this follow-up study, the participant sample was the 31 290 pregnant women enrolled in 2001–04 comprising the main cohort for the primary trial outcomes (figure 1).[12] After exclusions from 31 290 participants (287 [1%] dropped out, 397 [1%] moved, six died [<1%], 1064 [3%] were lost to follow-up, 597 [2%] had abortions, and 513 [2%] had stillbirths), 27 356 infants were confirmed from 2001–04 to be alive between birth and 12 weeks post partum, including 1128 who had been confirmed live then lost to follow-up before the 12 week visit, with 26 228 reported alive at 3 months. The proportion lost to follow-up at 3 months post partum was not different between the IFA and MMN groups. From 2012–14, we re-enrolled 19 274 (70%) of the 27 356 infants at 9–12 years of age. The follow-up sample included 688 children who had been confirmed live between birth and 12 weeks, but had been lost to follow-up before the 12 week visit.

Randomisation and masking

We selected 3068 children for cognitive assessment. First, we randomly selected a representative sample of 840 children powered to detect an effect size of

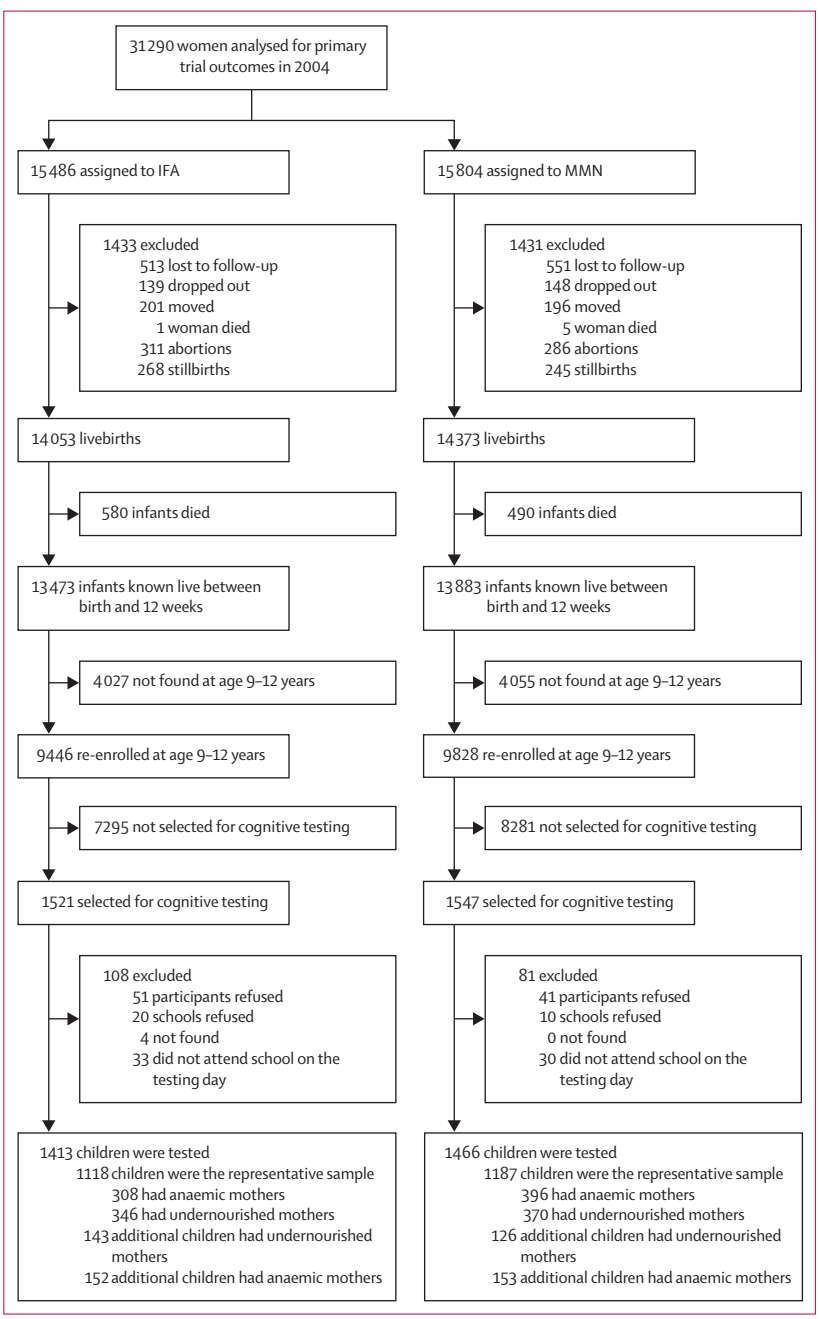

Figure 1: **Trial profile**
IFA=iron and folic acid. MMN=multiple micronutrients.

0·3 standard deviations for a normally distributed outcome (power 90%, α=0·05). Second, we over-sampled 574 children of mothers who were undernourished (MUAC <23·5 cm) and anaemic (haemoglobin <110 g/L) at enrolment, to detect the same effect size in these subgroups because MMN positively affected cognition at preschool age in these groups.[13] We then added the 487 children previously randomly selected and tested for cognitive development at preschool age,[13] and 640 children of previously randomly selected mothers whose cognitive function had been assessed.[15] Finally, we randomly selected 282 additional companion children from the re-enrolment cohort to accompany any child to the testing site when only one child was selected at a school. Selection of children was done by an automated algorithm prepared in SAS (version 9.3). In brief, the algorithm first compiled the list of all re-enrolled children at a school and selected those previously assessed as preschoolers and whose mothers had been assessed for cognitive performance. The algorithm then randomly selected children proportional to the number of re-enrollees at the school, and with proportional oversampling of children whose mothers had been either anaemic or undernourished at SUMMIT enrolment. Each list was alphabetically sorted and parsed to blocks of eight, as this comprised a testing batch, and two additional randomly selected re-enrolees were added to each block to account for potential absences on the day of testing. One list was used for each test session per school. We included in the final representative sample all children except those specifically selected for the maternal anaemia and undernutrition subgroups. We obtained cognitive data from 2879 children: 2305 in the representative sample, 305 additional children of anaemic mothers, and 269 additional children of undernourished mothers (appendix). The sample sizes provided 90% power to detect a difference of SD 0·16 in the representative sample and SD 0·22 in the children of undernourished and anaemic mothers for normally distributed outcomes. All SUMMIT scientists and personnel, government staff, and participants in the original study, and all participants and all data collectors in the follow-up study were unaware of the allocation of MMN and IFA.

See Online for appendix

Procedures

We assessed nurturing and stimulation from the environment using a locally adapted version of the Home Observation for the Measurement of the Environment (HOME) Inventory,[16] and maternal depression with the Center for Epidemiological Studies depression test.[17] The properties of these tests after adaptation are in the appendix.

Seven teams of eight people administered the cognition and motor tests at local schools where temporary facilities were set up consisting of eight stations. At two stations medical information was collected (eg, anthropometry and blood pressure). At six stations, one data collector administered 2–3 cognitive tests. Targeted children were called from their classrooms in the morning. The average duration of testing at each station was 15 min. A separate team of assessors visited the homes of participants to administer the HOME inventory and assess maternal depression and child socioemotional development. These visits were completed for 2728 (95%) of the 2879 children in the full cognitive sample.

All assessors had 3 year or 4 year post-secondary degrees. They were trained and required to be certified by passing written and practical certification exams for three positions: administration of tests at schools, implementation of home visits, and reviewing of forms and audio recordings. All verbal tests and interviews were audio recorded and reviewed for quality control as described in the appendix.

Outcomes

We selected a set of tests specifically designed to assess brain functions likely to be sensitive to nutritional influences, and important for school success and daily life. These tests were adapted to the local setting in Lombok by a panel consisting of international and local research scientists, local psychologists, and local teachers. In an iterative process, the panel's decisions were informed by formative interviews and focus groups with parents of school-age children, and a series of 12 pilot tests of 216 children aged 8–12 years (table 1; appendix). Adapted tests were evaluated for inter-rater agreement, test-retest reliability, internal reliability, and convergent validity (appendix). The inter-rater agreement ranged from 88% to 100%, test-retest reliability from r=0·30 to r=0·90, and internal reliability from Cronbach's alpha=0·65–0·87.

The first objective was to follow up school-age children (9–12 years) whose mothers had participated in SUMMIT, and assess the long-term effect of maternal MMN supplementation on child motor, cognitive, and socio-emotional development. The second was to assess, in the same context, the effect of biomedical and socioenvironmental determinants on these outcomes.

Statistical analyses

All analyses were prespecified and done with SAS (version 9.4). We examined whether children whose mothers received MMN or IFA were similar on key baseline characteristics for continuous variables by mixed effects linear regression models with a random effect of midwife on the intercept and for categorical variables by generalised linear models with midwife as a repeated measure.

All cognitive, motor, and socioemotional scores for which a lower score indicated better performance (eg picture naming speed) were reversed, thereby facilitating interpretation with positive coefficients indicating better performance in the MMN group (table 1). We log-transformed the following scores to reduce skewness from more than 1 to less than 1: speeded picture naming, visual search, visual search dual task, and Stroop test. For each continuous score, we calculated *z* scores by child sex and by 6 month age bands, because

	Test	Description
General intellectual ability		
Verbal ability: general knowledge	Information test	Children were required to verbally answer general knowledge questions, such as "How many days are in a week?" The score was the number of questions answered correctly.
Verbal ability: semantic memory and lexical retrieval	Speeded picture naming test	Children were instructed to point to and say out loud the name of each picture on a page as quickly and accurately as possible. The score was calculated as the time to complete the page divided by the number of pictures correctly named.
Non-verbal ability: spatial pattern copying	Block design test	Children were asked to copy increasingly complex patterns with coloured blocks. The score takes into account both accuracy and speed.
Declarative memory		
Declarative memory	Adapted Rey auditory verbal learning test	Children were given three learning trials in which they were asked to remember a list of 11 unrelated words presented orally. This test was followed by an interference trial requiring the immediate recall of a second 11 word list, and then a request to recall the first list (recall trial 1). After a delay of mean 7 min, participants were again asked to recall the initial list (recall trial 2), and then given a recognition test.
Procedural memory		
Procedural memory	Serial reaction time task	Children did the task with a video game pad controller and a laptop. Children were required to press the button on the game pad that corresponded to the position on the screen in which a smiley face appeared. A random block (of 60 items) was followed by four blocks that presented a standard ten-item sequence, followed by a final random block. The procedural learning score was the difference between the mean standardised reaction time on the final random block and the fourth sequence block.[18,19]
Executive function		
Visual attention	Adapted visual search task	Based on the Sky Search subtest from the Test of Everyday Attention for Children (TEACh), a local illustrator drew a series of pairs of pictures, some of which were the same and some of which were different. Children were asked to underline all pairs that were the same as fast as possible. The score was the time per correct target on the visual search task minus the time per correct target on a motor control task.
Sustained attention	Adapted visual search dual task	Based on the Sky Search Dual Task subtest from the TEACh, children were asked to complete a parallel version of the visual search task described above, which differs only in the location of the targets. As they did the visual search task, they were asked to simultaneously and silently count the number of tones presented in each item of a tone counting task. The score takes into account performance on both tasks.
Auditory attention and working memory	Digit span forward and backward	The digit span forward and backward scores were calculated as the total number of sequences of digits, correctly repeated (digit span forward) or repeated in reverse order (digit span backward), before an error was committed on two consecutive trials of the same length.
Cognitive control	Stroop numbers	Children were presented with four conditions, each consisting of 20 items. The first and last were baseline conditions, consisting of zeros (000), where children were required to name the quantity of zeros in each item (three, four, five, or six). The second was a congruent condition where the quantity corresponded to the printed number (eg, 333). The third was an incongruent condition where the quantity and the printed number did not correspond (eg, 222). Again, the task was to name the quantity, not the printed number. The total time to correctly name all of the items in each condition was recorded. The interference score was calculated as the time to complete the incongruent condition minus the time to complete the congruent condition.
Cognitive flexibility	NIH Toolbox Dimensional Change Card Sort Test	We used the ePrime version. Children were shown pictures on a tablet screen, which differed on two characteristics: shape (a truck or a ball) and colour (blue or yellow). In each trial, children were instructed to match the picture at the top of the screen to the picture on the right or the left according to the verbal computerised instructions (shape or colour). We calculated the score according to the standard National Institute of Health Toolbox method.
Educational attainment		
Literacy	Literacy test	Children were given a letter discrimination task, a word discrimination task, and a sentence discrimination task. They were instructed to mark real letters, real words, and sentences that were answered "yes" (Do birds have wings?) but not those answered "no" (Do cars have feet?) The score was the sum of the hits (correctly marked) minus false alarms (incorrectly marked) with additional points given for faster performance on the sentence task.
Arithmetic	Arithmetic test	Children were verbally asked arithmetic questions and required to answer without doing written calculations. We developed a set of items from elementary school arithmetic text books. The score was the total number correct.
Fine motor		
Motor dexterity	Purdue pegboard test	We recorded the number of pegs children were able to place in a board in 30 s, first with the right hand, then with the left hand, and then with both hands simultaneously. The pegboard average score was the average of these three trials. In the assembly trial, the child was required to assemble a peg, a washer, and a collar, and another washer in each hole on the board. The pegboard assembly score was the number of pieces correctly assembled.
Socioemotional		
Behavioural problems	Adapted Child Behavior Checklist	We developed a 50 question interview representing seven subscales of the checklist: depression, social problems, thought problems, attention problems, delinquent behaviour, aggressive behaviour, and other problems. The total score was the sum of the item scores.

For further details and references (appendix).

Table 1: **Methods and scores for assessing cognitive, motor, and socioemotional development**

both age and sex were strongly associated with most test scores. We excluded extreme outliers of more than 5 SD from the mean (0·05% of scores).

We calculated the average *z* score for each child in each of the seven domains listed in table 1: general intellectual ability (information, picture naming speed, and block design scores); declarative memory (list memory recall trial 1, recall trial 2, and recognition trial); procedural memory (serial reaction time score); executive function (visual search, visual search dual task, digit span forward and backward, Stroop numbers, and Dimensional Change Card Sort scores); academic achievement

(literacy and arithmetic scores); motor ability (pegboard average and assembly score); and socioemotional ability (adapted child behaviour checklist score). All domain scores were normally distributed.

The effect of MMN on each domain score was identified by mixed effects models with a fixed effect of supplement group and a random effect of midwife. If one assessor administered all tests in any domain, we also included a random effect of assessor. Each model was estimated first with the supplement group as the only fixed effect (model 1), second, with fixed effects of the supplement group and six baseline covariates from SUMMIT (model 2), and third, model 2 plus six covariates that were outcomes of SUMMIT (model 3). The six baseline covariates were maternal and paternal education, maternal MUAC, haemoglobin, and height, and wealth index. The outcome covariates from SUMMIT were preterm birth (<37 weeks gestation), small for gestational age calculated based on Oken and colleagues,[20] and four variables collected at the follow-up at 9–12 years of age: postnatal growth, which was calculated as the residual of small for gestational age predicting height-for-age *z* score (HAZ) at 9–12 years (with HAZ calculated based on WHO norms[21]), child haemoglobin, HOME inventory score, and maternal depression score. As described above, child age and sex were already accommodated in the calculation of *z* scores.

The appendix shows the percent of data absent for each covariate, which ranged from 0% to 17%. Baseline maternal haemoglobin during SUMMIT had been intentionally collected in a subgroup of representative women, thus 37% of selected children did not have this covariate. To avoid dropping participants from adjusted analyses due to missing covariates, we used multiple imputation as described in the appendix.[22] We also estimated model 3 using complete case analysis, for comparison.

We estimated each model first for the randomly selected representative sample of all children (n=2305), second, for children of undernourished mothers (n=1076), and third, for children of anaemic mothers (n=1009), both subgroups including those in the representative sample as well as those over-sampled for these characteristics. We used Fisher's exact test to assess whether the proportion of positive coefficients due to MMN was different from chance, and to assess whether the proportion of significant coefficients was different between the biomedical and socioenvironmental groups of determinants.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study and approved the decision to submit for publication.

Results

In the full cognitive follow-up sample (n=2879), children whose mothers had received IFA or MMN did not differ significantly in any characteristic (table 2). Likewise, in the randomly selected overall representative sample (n=2305), no significant differences were found between groups. The characteristics of the representative sample were similar to the characteristics of the 31 290 participants in the main cohort (table 2).

Of the 2631 children from whom data was obtained on the serial reaction time task, 198 (8%) did not pass the practice items, therefore the test items were not administered. An additional 374 children (14%) scored less than 80% accuracy on the test items, and were also excluded from analysis of this task in accordance with previous studies.[18,19] The proportion of children excluded did not differ between IFA (21%) and MMN (22%; p=0·49).

The estimates of the intention-to-treat effect of the intervention on each domain score adjusted for cluster randomisation and assessor (model 1) are shown in table 3. In the representative sample, children in the MMN group scored significantly higher than children in the IFA group in procedural memory (B=0·11 [95% CI 0·01–0·20], p=0·0319). In children of anaemic mothers, the MMN group scored significantly higher in general intellectual ability (B=0·18 [95% CI 0·06–0·31] where B is the unstandardised estimate of the regression coefficient, representing the change in *z* score of the outcome associated with a one-unit change in the independent variable, p=0·0047). In children of undernourished mothers, no significant effects of MMN were noted for any domain score. Overall, 18 of 21 estimates were positive, indicating the MMN group scored consistently higher than the IFA group; this was significantly greater than chance (p=0·0431).

When adjusting for baseline covariates (model 2; appendix), the same pattern was found in all three samples of children as in the model 1 intention-to-treat analysis, that is, significant effects of maternal MMN supplementation on procedural memory in the representative sample (B=0·10, 95% CI 0·00–0·20, p=0·0464) and on general intellectual ability in children of anaemic mothers (B=0·18, 95% CI 0·06–0·29, p=0·0034). When adjusting for additional covariates collected after enrolment (model 3), the same pattern was found. The estimates adjusting for all covariates (model 3) are shown in figure 2 and in the appendix.

The regression coefficients for all variables in model 3 are shown in table 4 for the representative sample of children. The socioenvironmental determinants (socioeconomic status, maternal and paternal education, HOME score, and maternal depression) showed stronger and more consistent associations with school-age cognitive, motor, and socioemotional scores, as compared with the biomedical determinants. For the socioenvironmental determinants, coefficients ranged from 0·00–0·43, and 22 (63%) of 35 coefficients were significant. For the biomedical determinants, coefficients ranged from 0·00–0·10 and eight (14%) of 56 coefficients were significant, the difference in these proportions was significant (p<0·0001).

	Full cognitive follow-up sample*			Representative sample			Main cohort
	IFA (n=1413)	MMN (n=1466)	p value IFA *vs* MMN	IFA (n=1118)	MMN (n=1187)	p value IFA *vs* MMN	Total (n=31 290)
Baseline maternal age	25·4 (6·4)	25·9 (6·1)	0·06	25·7 (6·4)	26·0 (6·0)	0·25	25·6 (6·1)
Maternal years of education	6·4 (3·4)	6·9 (3·5)	0·25	6·3 (3·5)	6·9 (3·5)	0·21	6·3 (3·7)
Paternal years of education	6·9 (3·8)	7·3 (3·9)	0·91	7·0 (3·8)	7·3 (3·9)	0·98	7·0 (4·0)
Baseline wealth quintile	..	..	0·77	..	..	0·60	..
Poorest	279/1394 (20%)	305/1453 (21%)	..	212/1100 (19%)	251/1177 (21%)	..	6245/30 014 (21%)
Second	312/1394 (22%)	327/1453 (23%)	..	245/1100 (22%)	259/1177 (22%)	..	6094/30 014 (20%)
Third	290/1394 (21%)	298/1453 (21%)	..	223/1100 (20%)	240/1177 (20%)	..	5946/30 014 (20%)
Fourth	273/1394 (20%)	281/1453 (19%)	..	226/1100 (21%)	228/1177 (19%)	..	5958/30 014 (20%)
Wealthiest	240/1394 (17%)	242/1453 (17%)	..	194/1100 (18%)	199/1177 (17%)	..	5771/30 014 (19%)
Gestational age at enrolment	..	..	0·58	..	..	0·94	..
First trimester	557/1413 (39%)	551/1466 (38%)	..	445/1118 (40%)	465/1187 (39%)	..	10371/31 238 (33%)
Second trimester	589/1413 (42%)	623/1466 (42%)	..	455/1118 (41%)	494/1187 (42%)	..	13431/31 238 (43%)
Third trimester	267/1413 (19%)	292/1466 (20%)	..	218/1118 (19%)	228/1187 (19%)	..	7436/31 238 (24%)
Parity at enrolment			0·24			0·39	
First	536/1413 (38%)	522/1466 (36%)	..	409/1118 (37%)	415/1187 (35%)	..	10 829/30 472 (36%)
2–3	585/1413 (41%)	637/1466 (43%)	..	472/1118 (42%)	519/1187 (44%)	..	13 415/30 472 (44%)
4–5	206/1413 (15%)	224/1466 (15%)	..	168/1118 (15%)	192/1187 (16%)	..	4529/30 472 (15%)
≥6	86/1413 (6%)	83/1466 (6%)	..	69/1118 (6%)	61/1187 (5%)	..	1699/30 472 (6%)
Baseline maternal MUAC <23·5 cm	530/1314 (40%)	546/1368 (40%)	0·92	346/1033 (33%)	370/1102 (34%)	0·68	9363/27 127 (35%)
Baseline maternal haemoglobin <110 g/L	460/858 (54%)	549/968 (57%)	0·21	308/663 (46%)	396/771 (51%)	0·12	8801/17 892 (50%)
Percentage of supplements consumed	82% (17)	81% (18)	0·60	82% (17)	81% (18)	0·75	79% (21)
Male child	706/1413 (50%)	728/1466 (50%)	0·90	567/1118 (51%)	580/1187 (49%)	0·33	14103/27 114 (52%)
Child age at cognitive assessment	10·8 (0·5)	10·8 (0·5)	0·17	10·7 (0·5)	10·8 (0·5)	0·09	..
Child school grade at cognitive assessment	..	..	0·65	..	..	0·47	..
Grade 2†	180/1406 (13%)	185/1461 (13%)	..	149/1111 (13%)	160/1182 (14%)	..	..
Grade 3‡	625/1406 (44%)	603/1461 (41%)	..	518/1111 (47%)	497/1182 (42%)	..	..
Grade 4§	485/1406 (35%)	579/1461 (40%)	..	364/1111 (33%)	451/1182 (38%)	..	..
Grade 5¶	116/1406 (8%)	94/1461 (6%)	..	80/1111 (7%)	74/1182 (6%)	..	..

Data are n/N (%) and mean (SD), unless otherwise stated. IFA=iron and folic acid. MMN=multiple micronutrients. MUAC=mid-upper arm circumference. *The full cognitive follow-up sample includes the representative sample plus oversampling of children of undernourished and anaemic mothers. †Mean age 10·4 years. ‡Mean age 10·6 years. §Mean age 11·0 years. ¶Mean age 11·4 years.

Table 2: **Group characteristic comparisons**

Children whose mothers received MMN supplements during pregnancy and post partum scored higher in procedural memory, maternal MUAC during pregnancy was significantly positively associated with executive function, and maternal height was positively associated with declarative memory and fine motor dexterity (table 4). Maternal haemoglobin during pregnancy, preterm birth, and small for gestational age were not significantly associated with any score. Child haemoglobin at cognitive testing was significantly associated with fine motor dexterity (table 4). Post natal growth in height (the standardised residual of small for gestation age predicting HAZ at follow-up) was significantly associated with three scores: general intellectual ability, academic achievement, and fine motor dexterity (table 4). By contrast, each of the socioenvironmental determinants was associated with three to five outcome scores (table 4). Children in low socioeconomic status households scored lower in general intellectual ability, declarative memory, executive function, academic achievement, and fine motor dexterity compared with those in high socio-economic status households (table 4). Both maternal and

	Representative sample			Children of undernourished mothers			Children of anaemic mothers		
	n	B coefficient (95% CI)	p value	n	z-score estimate (95% CI)	p value	n	z-score estimate (95% CI)	p value
General intellectual ability*	2302	0·09 (–0·03 to 0·22)	0·14	1074	0·12 (–0·02 to 0·26)	0·10	1009	0·18 (0·06 to 0·31)	0·0047
Declarative memory†	2291	0·01 (–0·09 to 0·11)	0·88	1071	0·01 (–0·11 to 0·12)	0·89	1003	0·03 (–0·09 to 0·15)	0·65
Procedural memory†	1615	0·11 (0·01 to 0·20)	0·0319	763	0·00 (–0·14 to 0·15)	0·96	743	–0·03 (–0·17 to 0·11)	0·68
Executive function*	2302	0·07 (–0·04 to 0·19)	0·19	1075	0·06 (–0·08 to 0·20)	0·41	1009	0·12 (–0·02 to 0·26)	0·10
Academic achievement*	2299	0·08 (–0·05 to 0·21)	0·21	1073	0·13 (–0·02 to 0·28)	0·09	1008	0·13 (–0·02 to 0·28)	0·10
Motor ability†	2282	–0·07 (–0·16 to 0·02)	0·14	1065	0·02 (–0·14 to 0·19)	0·78	1003	0·08 (–0·04 to 0·19)	0·21
Socioemotional†	2160	0·06 (–0·04 to 0·16)	0·23	1010	0·06 (–0·08 to 0·21)	0·40	940	0·07 (–0·07 to 0·22)	0·34

A positive coefficient indicates that the multiple micronutrients group scored higher than iron and folic acid. *Adjusted for a random effect of midwife cluster. †Adjusted for random effects of midwife cluster and data collector.

Table 3: **Intention-to-treat estimates of the effect of supplementation with maternal multiple micronutrients versus iron and folic acid on each domain score (model 1)**

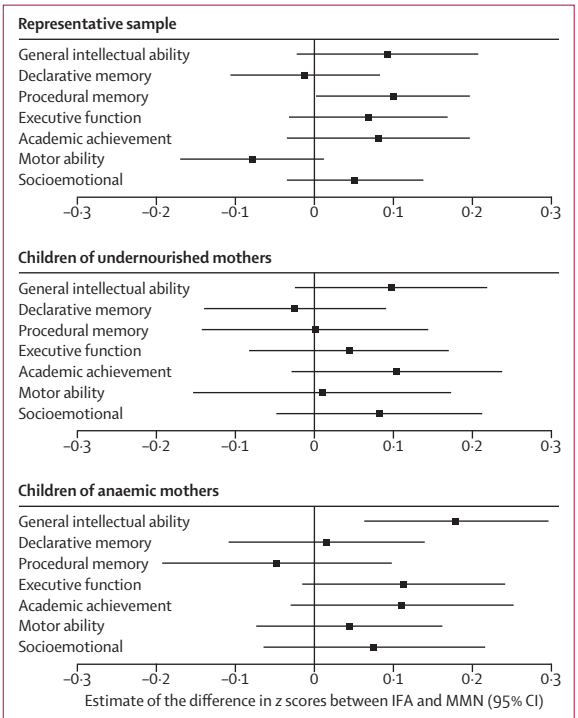

Figure 2: **Adjusted estimates of the effect of MMN versus IFA for each domain score (model 3)**
IFA=iron and folic acid. MMN=multiple micronutrients.

paternal education were significantly associated with general intellectual ability, executive function, and academic achievement, while maternal education was also associated with declarative memory and fine motor dexterity (table 4). HOME inventory score was significantly associated with general intellectual ability, declarative memory, executive function, academic achievement, and fine motor dexterity (table 4). Maternal depression was strongly associated with child socioemotional development, and was the only significant predictor of this score. Maternal depression was also associated with general intellectual ability, declarative memory, and executive function.

In the fully adjusted models (model 3) with complete case analysis, rather than multiple imputation, the coefficients for all independent variables were similar to the coefficients with multiple imputation. The median difference between each pair of coefficients in the imputed versus non-imputed models was 0·03 (IQR 0·02–0·05).

Figure 3 shows the coefficient size of each risk factor on each cognitive, motor, and socioemotional score, with all continuous variables dichotomised so that effect sizes can be compared across risk factors. The results were similar to the results of the models with continuous variables, with the socioenvironmental risk factors showing stronger and more consistent associations with the domain scores than the biomedical factors.

Discussion

We examined three groups of children: a randomly selected representative sample, and samples from undernourished and anaemic mothers. In the representative sample, children in the MMN group scored mean 0·11 SD higher than the IFA group in procedural memory. Children of anaemic mothers in the MMN group scored 0·18 SD higher in general intellectual ability. Although these were the only two significant effects of MMN, overall, 18 of 21 estimates (seven cognitive, motor, and socioemotional scores for three groups of children) were positive, indicating that the MMN group scored consistently higher than the IFA group. These non-significant positive effect sizes, ranging from 0·00 to 0·13 SD, were smaller than the study was powered to detect (0·16 SD in the representative sample and 0·22 SD in the children of undernourished and anaemic mothers). However, the proportion of positive coefficients, indicating higher scores in the MMN group, was significantly greater than chance.

	General intellectual ability (n=2302)	Declarative memory (n=2281)	Procedural memory (n=1615)	Executive function (n=2302)	Academic achievement (n=2299)	Fine motor dexterity (n=2282)	Socioemotional (n=2160)
Biomedical risk factors							
Maternal supplement (MMN *vs* IFA)	0·09 (–0·02 to 0·21)	–0·01 (–0·11 to 0·08)	0·10* (0·00 to 0·20)	0·07 (–0·03 to 0·17)	0·08 (–0·03 to 0·20)	–0·08 (–0·17 to 0·01)	0·05 (–0·03 to 0·14)
Maternal MUAC during pregnancy (*z* score)	0·03 (–0·01 to 0·07)	0·02 (–0·02 to 0·06)	0·03 (–0·02 to 0·08)	0·04* (0·00 to 0·08)	–0·01 (–0·05 to 0·04)	–0·01 (–0·05 to 0·03)	–0·02 (–0·06 to 0·02)
Maternal haemoglobin during pregnancy (*z* score)	0·01 (–0·03 to 0·05)	–0·01 (–0·05 to 0·04)	–0·01 (–0·07 to 0·04)	–0·01 (–0·06 to 0·04)	0·01 (–0·04 to 0·06)	–0·01 (–0·05 to 0·04)	–0·01 (–0·05 to 0·04)
Maternal height (*z* score)	0·04§ (0·00 to 0·08)	0·04* (0·00 to 0·09)	0·00 (–0·05 to 0·05)	0·02 (–0·02 to 0·06)	0·01 (–0·03 to 0·05)	0·06† (0·02 to 0·10)	0·02 (–0·02 to 0·06)
Preterm birth	0·00 (–0·09 to 0·10)	0·00 (–0·10 to 0·10)	–0·03 (–0·15 to 0·09)	–0·07 (–0·16 to 0·02)	–0·03 (–0·12 to 0·06)	–0·02 (–0·11 to 0·07)	0·00 (–0·09 to 0·09)
Small for gestational age	–0·09 (–0·23 to 0·05)	–0·07 (–0·20 to 0·06)	0·02 (–0·16 to 0·19)	–0·06 (–0·19 to 0·08)	–0·05 (–0·18 to 0·08)	0·01 (–0·12 to 0·14)	–0·06 (–0·16 to 0·05)
Postnatal growth in height (*z* score)	0·08† (0·03 to 0·13)	0·04 (–0·01 to 0·09)	0·01 (–0·05 to 0·06)	0·04† (–0·01 to 0·09)	0·09‡ (0·04 to 0·13)	–0·06† (–0·11 to –0·02)	–0·02 (–0·07 to 0·02)
Child haemoglobin at follow-up (*z* score)	0·02 (–0·02 to 0·07)	0·01 (–0·03 to 0·05)	–0·03 (–0·09 to 0·02)	0·03 (–0·01 to 0·07)	0·02 (–0·02 to 0·06)	0·05* (0·00 to 0·09)	0·01 (–0·04 to 0·05)
Socioenvironmental risk factors							
Low socio-economic status (wealth index below median)	–0·14† (–0·22 to –0·06)	–0·10* (–0·18 to –0·01)	–0·01 (–0·11 to 0·10)	–0·16‡ (–0·24 to –0·08)	–0·26‡ (–0·35 to –0·18)	–0·11† (–0·19 to –0·03)	0·08§ (0·00 to 0·16)
Low maternal education (<6 years)	–0·16† (–0·26 to –0·05)	–0·15† (–0·26 to –0·04)	–0·05 (–0·18 to 0·09)	–0·16† (–0·26 to –0·06)	–0·12* (–0·23 to –0·02)	–0·14† (–0·24 to –0·03)	0·03 (–0·07 to 0·13)
Low paternal education (<6 years)	–0·13* (–0·24 to –0·02)	–0·07 (–0·18 to 0·05)	–0·07 (–0·21 to 0·07)	–0·13* (–0·24 to –0·02)	–0·16† (–0·27 to –0·05)	–0·06 (–0·16 to 0·05)	0·08 (–0·03 to 0·18)
Maternal depression at follow-up (*z* score)	–0·04* (–0·08 to 0·00)	–0·04* (–0·09 to 0·00)	0·01 (–0·04 to 0·07)	–0·05† (–0·10 to –0·01)	–0·03 (–0·07 to 0·01)	0·00 (–0·04 to 0·04)	–0·43‡ (–0·46 to –0·39)
HOME inventory score at follow-up (*z* score)	0·13‡ (0·09 to 0·17)	0·06† (0·02 to 0·11)	0·02 (–0·03 to 0·07)	0·10‡ (0·05 to 0·14)	0·14‡ (0·10 to 0·18)	0·09‡ (0·05 to 0·13)	0·01 (–0·03 to 0·05)

MMN=multiple micronutrients. IFA=iron and folic acid. MUAC=mid-upper arm circumference. *p<0·05. †p<0·01. ‡p<0·001. §p<0·1.

Table 4: **Multiple regression model of each risk factor predicting each domain score in the representative sample in model 3**

In our sample, from school year grade 2 through to grade 5, cognitive scores increased on average by 0·21 SD per academic year. Thus, the effect size of 0·11 SD on procedural memory was equivalent to the increase in scores with about half a year of school, while the effect size of 0·18 SD on general intellectual ability in children of anaemic mothers was equivalent to the increase in scores with almost a full year of school. Therefore, while these effect sizes are small based on Cohen's classification,[23] they represent a substantial and meaningful developmental advance for children whose mothers received MMN, suggesting that provision of MMN during pregnancy is an effective way to pursue the UN's Sustainable Development Goal 4·2 to "ensure that all girls and boys have access to quality early childhood development so that they are ready for primary education."

In multiple regression models, socioenvironmental determinants (eg, HOME score and maternal depression) showed stronger and more consistent significant associations with school-age cognitive, motor, and socio-emotional scores, as compared with biomedical determinants (eg, maternal nutritional status and preterm birth). Socioenvironmental coefficients ranged from 0·00–0·43 SD, equivalent to the increase in scores with up to two years of school, while biomedical coefficients ranged from 0·00–0·10 SD, equivalent to up to a half a year of school. This finding suggests that present RMNCH programmes that are focused on biomedical determinants might not sufficiently enhance child cognition, and that programmes addressing socioenvironmental determinants are essential to achieve thriving populations.

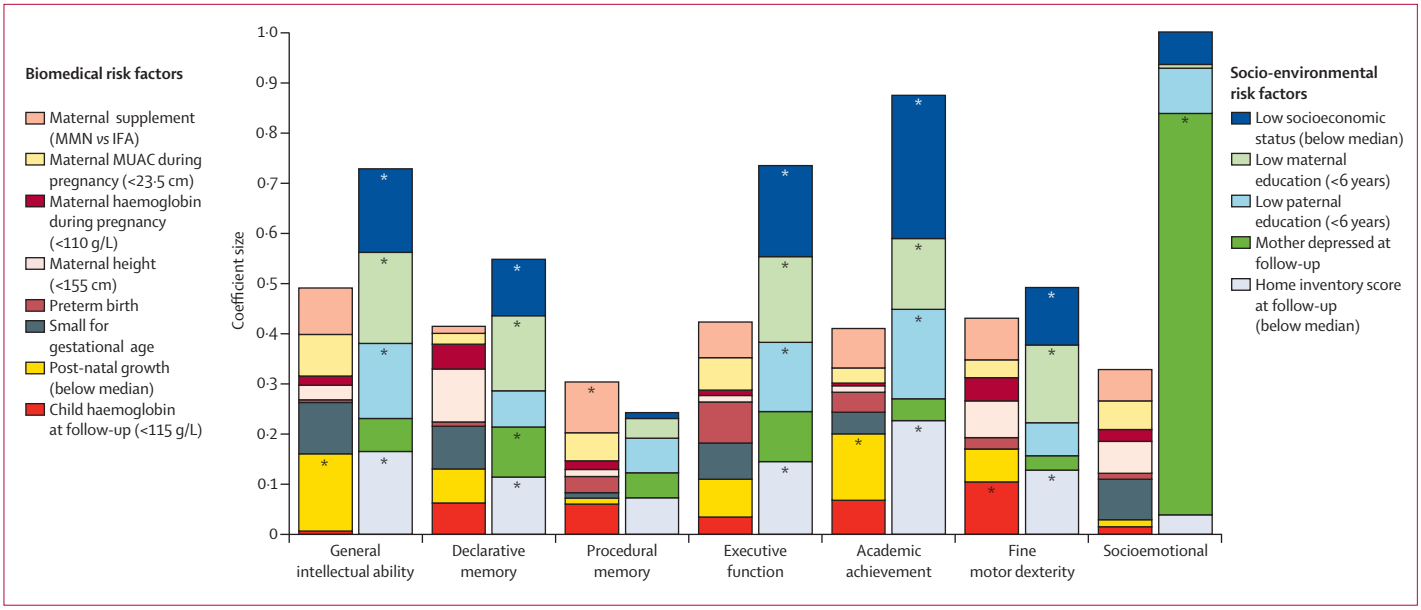

Figure 3: **Estimates of the association of each biomedical and socioenvironmental determinant with each domain score in the representative sample**
*p<0·05.

This longitudinal study is the first, to our knowledge, from pregnancy through to school age in a LMIC that assessed a large number of children on a comprehensive battery of cognitive, motor, and socioemotional tests and that examined stimulation from the home environment and maternal depression together with other socio-environmental and biomedical factors measured perinatally. Strengths of the study were the double-blind, randomised design, the large number of children followed up, the assessment of multiple specific cognitive abilities, the high quality implementation of cognitive assessments, and adaptation and evaluation of assessments in the local context. One weakness was that only children attending school were selected for cognitive assessment. However, 18 230 (95%) of the 19 274 children in the full follow-up sample were attending school at the time of re-enrolment. Another challenge was that cognitive assessments were done in schools during regular school hours instead of in specialised testing rooms, which was not an optimum testing environment. However, any noise introduced due to this factor would tend to mask differences between MMN and IFA, and yet effects were indeed detected. A third challenge was heterogeneity between assessors. Despite high inter-rater agreement, significant associations were found between the assessor who administered the test and its score, with the exception of the computerised tests (dimensional change card sort and serial reaction time). We mitigated this by controlling for assessor in the analyses of the effect of MMN.

At least 16 randomised trials have compared maternal supplementation with UNIMMAP to IFA,[14] showing positive effects of MMN on birth weight and small for gestational age,[24–26] and still births,[27] with the most recent meta-analyses including two additional large-scale trials allaying earlier concerns of adverse effects. However, effects on long-term cognitive ability remain equivocal or unknown. In our study, the specific positive effects, together with those mentioned above,[27] would support policy change from IFA to MMN. The finding that children of anaemic mothers showed positive effects of MMN on general intellectual ability is consistent with greater effects on preschool cognition[13] and infant mortality that have been found in this group.[12] This suggests that mothers who are anaemic during pregnancy have greater potential to benefit from supplementation with MMN than those who are not anaemic, perhaps because anaemia might be associated with diet and other factors causing MMN deficiency.

In four previous follow-up studies of MMN versus IFA assessing developmental outcomes, and in 56 previous longitudinal studies in LMICs assessing cognition at school age, no study examined procedural memory. Our positive findings suggest that this cognitive ability should be included in future studies. The procedural memory system underlies learning of new, and processing of established, perceptual, motor, and cognitive skills. Procedural memory might subserve a wide range of skilled activities that children and adults do automatically and are important for academic performance and daily life, such as driving, typing, arithmetic, reading, speaking, and understanding language, and learning sequences, rules, and categories.[28,29] The basal ganglia, including the caudate nucleus and the putamen (the dorsal striatum), together with connected areas of the frontal cortex are critical brain structures in procedural memory.[28,30] Dopamine has an important role in this

system, perhaps in skill consolidation.[31] The observed effect of MMN on procedural memory might be due to altered dopamine metabolism, because animal models of maternal deficiency in specific micronutrients, including iron and vitamin B6, have shown altered dopamine metabolism and impaired dopamine-related behaviours in the offspring.[32,33]

Meta-analyses of micronutrient interventions in school-age children[34] and nutrition interventions in infants younger than 2 years in LMICs,[35] have found pooled effects of about 0·1 SD. This result is consistent with the effect sizes that we reported of 0·11 SD on procedural memory in the representative sample and 0·18 SD on general intellectual ability in children of anaemic mothers. However, these effects are smaller than the effects of MMN that we noted for preschool cognition in children of undernourished and anaemic mothers, which were about 0·3–0·4 SD.[13] These findings are consistent with previous reports of diminishing effects of early childhood education programmes throughout childhood and adolescence,[36] and underscores the need for early and ongoing intervention to promote sustainable gains and mitigate loss of investments in early childhood development. In this context, the persistent and discernible effects of maternal MMN supplementation are remarkable.[10] Ongoing intervention is in line with the UN's Sustainable Development Goals 4 and 5 to ensure inclusive and equitable quality education and promote lifelong learning opportunities for all and to achieve gender equality and empower all women and girls.

The significant long-term effect of maternal MMN supplementation and the significant association with other early life biomedical risk factors, suggest that to achieve thriving populations, coverage of existing RMNCH interventions to reduce these biomedical risks needs to be improved. However, even with improved coverage, additional interventions addressing socioenvironmental risk factors are essential. The larger and more consistent effects of socioenvironmental determinants on all domain scores suggests that correction of all maternal and child biomedical conditions would not fully optimise cognitive development without additionally addressing socioenvironmental determinants. Interventions designed to enhance psychosocial nurturing and stimulation have generally resulted in larger effects on child development than those found in nutrition interventions, with meta-analyses of studies in LMICs reporting pooled effect sizes of SD 0·42 in children younger than 2 years,[35] and SD 0·31 in children aged 3–5 years.[37] Our findings indicate that investments focused on implementing interventions at scale to address socioenvironmental determinants are needed, including those to reduce maternal depression and improve educational levels of both girls and boys. This advancement would have a substantial transformational impact on the next generation.

Contributors

The SUMMIT Study Group, including SKS, MA, SS, HM, and AHS designed and implemented the original SUMMIT study. EP, SKS, MA, BH, KJA, MTU, HM, and AHS designed the follow-up study. JL designed the serial reaction time task and provided statistical advice. EP, AHS, SKS, MA, SRA, NH, AI, SS, and BH implemented the follow-up study. EP and AHS completed the data preparation, statistical analysis and drafted the manuscript with inputs from the other authors. All individual authors critiqued the manuscript and approved the final report. HM and AHS were the principal investigators of the follow-up study and AHS is the guarantor.

Declaration of interests

We declare no competing interests.

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