Impact of nutritional supplements on cognitive development
of children in developing countries: A meta-analysis

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Keywords for electronic database search in DFID Rigorous Literature Review

The following keywords were used for the electronic database search in the original rigorous literature review for articles published in 1992–2013, from which we extracted studies on nutritional supplementation for our meta-analysis. The keywords for searching used the intersection (AND operator) of keyword groups:

1. Union (OR operator) of these keywords for developing countries
   1.1. developing countr*
   1.2. low-income countr*
   1.3. mid-income countr*
2. Union of these keywords for children
   2.1. child*
   2.2. infant*
3. Union of these keywords for cognitive development
   3.1. academic achievement
   3.2. attention
   3.3. basic concept*
   3.4. brain develop*
   3.5. child develop*
   3.6. cognitive develop*
   3.7. communication skills
   3.8. development quotient
   3.9. DQ
   3.10. executive function*
   3.11. intelligen*
   3.12. IQ
   3.13. language develop*
   3.14. learning outcome*
   3.15. literacy
   3.16. mathematics achievement
   3.17. neural develop*
   3.18. problem solving
   3.19. school readiness
   3.20. thinking
3.21. vocabulary

4. Union of these keywords for interventions
   4.1. Intervention
   4.2. Program*
   4.3. Experiment
   4.4. Trial
   4.5. Education
   4.6. Stimulation
   4.7. Supplementation
   4.8. Food fortification
   4.9. Feeding Programme
Detailed inclusion and exclusion criteria in DFID Rigorous Literature Review

The inclusion and exclusion criteria of the original rigorous literature review, from which we extracted studies on nutritional supplementation for our meta-analysis.

1. The interventions must have begun during early childhood; that is, before the children were 8 years of age.

2. The interventions must contain at least one of the following components: (a) parent-focused education and support; (b) child-focused education and stimulation; (c) nutrition and health; and (d) income supplementation including cash transfers.

3. The interventions could be home-, centre-, and/or community-based. Centre-based approaches involved several kinds of institutions offering early years provision such as preschools, childcare centres, crèches, playgroups, day care nurseries, and nursery schools, which served as alternative physical and social environments for care, development, and education.

4. The interventions must have explicitly documented cognitive and/or schooling outcomes.

5. The evidence assessed linkages between participation in the interventions and cognitive outcomes.

6. The studies were published after 1st January 1992 and before 31st December 2012.

7. The studies provided information from a primary study which was not a literature review.

8. Research methods, statistical analyses, and findings were sufficiently detailed to provide a basis for judgment about the robustness of the conclusions; that is, the research procedures and characteristics of the sample were specified in detail, so that the validity of the results could be evaluated.

9. Comparisons (concurrent between groups or before-and-after within groups) among groups of people exposed to the intervention and those who were not exposed or less exposed to the intervention were available.

10. Studies involving special populations such as Down’s syndrome, cerebral palsy, autism or any specific form of disability (sensory, physical, intellectual, or psychological), and extreme malnutrition were not included.
Quality Assessment Coding

**Rigor of study:** Level of rigor in study design

| Code | Meaning                                                                 |
|------|-------------------------------------------------------------------------|
| 1    | Other, lowest level of rigor                                            |
| 2    | Single group before and after                                           |
| 3    | Retrospective controlled/secondary data analysis/construction of comparison groups |
| 4    | Other prospective quasi-experimental design                             |
| 5    | Quasi-experimental design with the use of an econometric model          |
| 6    | Randomized controlled trial                                             |

**Soundness of study:** Level of validity and reliability of the study

| Code | Meaning                                                                 |
|------|-------------------------------------------------------------------------|
| 1    | Low (major and or numerous deficiencies in sampling, data collection, or data analysis) |
| 2    | Medium (some deficiencies in sampling, data collection, or data analysis, but the methods and interpretations were generally valid and reliable) |
| 3    | High (demonstrates adherence to appropriate sampling and data collection methods and reliable data analysis) |

**Overall quality of study:** Code of Rigor + Code of Soundness

Studies with overall quality <6 were excluded from this study.
Table 1. Studies and interventions included

| Ref. | Country / region | Year of publication | Study quality | Test | Intervention arm | Type of intervention | N_{intervention} | N_{control} | d_{unbiased} |
|------|------------------|---------------------|---------------|------|------------------|----------------------|------------------|-------------|-------------|
| S1   | Nepal            | 2011               | 9             | EF tests, UNIT | Iron, Folic acid, Zinc | Childhood (≥18m) | 212             | 101         | -0.09       |
|      |                  |                     |               |      | Iron, Folic acid  | Childhood (≥18m) | 163             | 101         | -0.04       |
|      |                  |                     |               |      | Antenatal, Zinc: Childhood: Iron, Folic acid | Antenatal + Childhood (≥18m) | 137             | 101         | -0.02       |
|      |                  |                     |               |      | Antenatal: Zinc; Childhood: Iron, Folic acid, Zinc | Antenatal + Childhood (≥18m) | 122             | 101         | -0.09       |
| S2   | Malawi           | 2016               | 9             | EF test | Multi-nutrients (Zinc, Iron, Selenium, and Multivitamins) | Antenatal | 251             | 251         | 0.03        |
|      |                  |                     |               |      | Lipid-based nutrients (Protein, Fat, Zinc, Iron, Selenium, and Multivitamins) | Antenatal + Childhood (<18m) | 253             | 251         | 0.02        |
| S3   | Ghana            | 2016               | 8             | Vocabulary checklist, EF tests | Lipid-based nutrients | Antenatal + Childhood (<18m) | 387             | 389         | 0.02        |
|      |                  |                     |               |      | Multi-nutrients | Antenatal | 397             | 389         | 0.01        |
| S4   | Bangladesh       | 2002               | 9             | BSID II | Zinc | Antenatal | 83              | 85          | -0.31       |
| S5   | Bangladesh       | 2008               | 9             | One-step means-end problem-solving test | Food supplementation | Antenatal | 1058            | 1058       | 0.02        |
| S6   | China            | 2009               | 9             | BSID | Iron | Multi-nutrients (including Iron and Multivitamins) | Antenatal | 392             | 422         | -0.04       |
|      |                  |                     |               |      | Multi-nutrients | Antenatal | 350             | 422         | 0.11        |
| S7   | Peru             | 2010               | 9             | Self-developed tests on language and pre-arithmetic, WPPSI | Zinc | Antenatal | 85              | 78          | -0.02       |
| S8   | Nepal            | 2010               | 9             | EF tests, UNIT | Iron, Folic Acid, Zinc | Antenatal | 178             | 177         | 0.10        |
|      |                  |                     |               |      | Iron, Folic Acid | Antenatal | 103             | 177         | 0.36        |
|      |                  |                     |               |      | Multi-nutrients (Folic acid, Iron, and Multivitamins) | Antenatal | 218             | 217         | 0.15        |
| S9   | Indonesia        | 2012               | 9             | EF tests | Multi-nutrient (Zinc, Copper, Iodine, Selenium, and Multivitamins) | Antenatal | 246             | 241         | 0.00        |
| S10  | China            | 2013               | 9             | BSID II | Iron [Sample 1] | Antenatal | 165             | 280         | 0.21        |
|      |                  |                     |               |      | Multi-nutrients [Sample 1] | Antenatal | 165             | 269         | 0.19        |
|      |                  |                     |               |      | Iron [Sample 2] | Antenatal | 148             | 316         | -0.20       |
|      |                  |                     |               |      | Multi-nutrients [Sample 2] | Antenatal | 148             | 298         | -0.25       |
| S11  | Viet Nam         | 2013               | 8             | BSID III | Iron Folic Acid daily | Antenatal | 350             | 363         | -0.13       |
|      |                  |                     |               |      | Multi-nutrients twice weekly (Zinc, Iodine, Copper, Selenium, Multivitamins) | Antenatal | 335             | 363         | -0.05       |
| S12  | Mexico           | 2015               | 9             | BSID III | DHA | Antenatal | 365             | 365         | -0.09       |
| Ref. | Country / region | Year of publication | Study quality | Test | Intervention arm | Type of intervention | N intervention | N control | d unbiased |
|------|------------------|---------------------|---------------|------|------------------|----------------------|---------------|-----------|------------|
| S13  | Mexico           | 2016               | 9             | McCarthy Scales of Children’s Abilities, Conner’s Kiddie Continuous Performance Test | DHA | Antenatal | 401 | 396 | 0.05 |
| S14  | Indonesia        | 2017*              | 9             | Self-developed tests on general intelligence, EF, educational achievement | Multi-nutrients (Zinc, Copper, Iodine, Selenium, Multivitamins) | Antenatal | 1187 | 118 | 0.03 |

| Studies with childhood supplementation (started at <18 months) |
|---------------------------------------------------------------|
| Ref. | Country / region | Year of publication | Study quality | Test | Intervention arm | Type of intervention | N intervention | N control | d unbiased |
|------|------------------|---------------------|---------------|------|------------------|----------------------|---------------|-----------|------------|
| S15  | Indonesia        | 1993               | 9             | BSID | Iron | Childhood (<18m) | 24 | 23 | 0.48 |
| S16  | Guatemala        | 1993               | 6             | Achievement tests, RPM | Protein, Fat, Carbohydrate, Calcium, Phosphorous, Iron | Childhood (<18m) | 758 | 652 | 0.19 |
| S17  | Jamaica          | 1997               | 9             | EF-tests, PPVT, RPM, WRAT, SBHT | Multi-nutrient (Milk-based formula with protein) | Childhood (<18m) | 31 | 32 | 0.16 |
| S18  | Jamaica          | 2000               | 9             | EF-tests, PPVT, RPM, WISC-R | Multi-nutrient (Milk-based formula with protein) | Childhood (<18m) | 30 | 31 | 0.16 |
| S19  | Bangladesh       | 2001               | 9             | BSID | Zinc | Childhood (<18m) | 103 | 109 | 0.00 |
| S20  | Chile            | 2001               | 9             | BSID II | Zinc | Childhood (<18m) | 57 | 52 | 0.20 |
| S21  | Indonesia        | 2002               | 8             | BSID II | Milk-based micronutrient | Childhood (<18m) | 38 | 37 | 0.52 |
| S22  | Chile            | 2003               | 9             | BSID | Iron | Childhood (<18m) | 1082 | 531 | -0.04 |
| S23  | Indonesia        | 2004               | 9             | BSID | Iron, Zinc | Childhood (<18m) | 163 | 161 | 0.20 |
| S24  | Jamaica          | 2005               | 9             | EF-tests, PPVT, RPM, WRAT, WAIS | Multi-nutrient (Milk-based formula with protein) | Childhood (<18m) | 28 | 27 | 0.27 |
| S25  | India            | 2005               | 8             | BSID II | Zinc | Childhood (<18m) | 283 | 288 | 0.14 |
| S26  | Guatemala        | 2009               | 9             | Non-verbal cognitive test, Reading test | Protein, Fat, Carbohydrate, Calcium, Phosphorous, Iron | Childhood (<18m) | 736 | 735 | 0.26 |
| S27  | China            | 2010               | 7             | Development diagnostic scale, WPPSI | Multi-nutrient (Folic acid, Iron, Zinc, Multivitamins) | Childhood (<18m) | 232 | 127 | 0.08 |
| S28  | Malawi           | 2011               | 9             | GMDS | Lipid-based nutrient supplement (50g/day) | Childhood (<18m) | 56 | 56 | -0.09 |
| S29  | Thailand         | 2011               | 9             | School performance, WISC-III, RCPM | Iron, Zinc | Childhood (<18m) | 147 | 147 | -0.06 |
| S30  | Bangladesh       | 2012               | 8             | BSID II | Food supplementation | Childhood (<18m) | 77 | 59 | 0.05 |
| S31  | Chile            | 2012               | 9             | WISC, KABC, WRAT | Iron | Childhood (<18m) | 244 | 229 | -0.15 |
| S32  | Indonesia        | 2012               | 8             | GMDS | Lipid-based nutrient supplement | Childhood (<18m) | 35 | 35 | 0.30 |
| S33  | Zambia           | 2012               | 9             | BSID II | Food fortification | Childhood (<18m) | 246 | 256 | 0.19 |
| Ref | Country / region | Year of publication | Study quality | Test | Intervention arm | Type of intervention | N_{intervention} | N_{control} | Δ_{unbiased} |
|-----|------------------|---------------------|---------------|-----|-----------------|---------------------|-----------------|-------------|-------------|
| S34 | Gambia           | 2013               | 9             | Toddler attention assessment, 2-step Infant Planning Test | Fish oil (DHA and EPA/d) | Childhood (<18m) | 87              | 85          | 0.55        |
| S35 | Malawi           | 2013               | 8             | Age to achieve developmental milestone | Milk lipid-based nutrients | Childhood (<18m) | 191             | 185         | 0.00        |
| S36 | Nepal            | 2013               | 9             | Adapted Child Development Inventory | Zinc, Iron, Folic Acid | Childhood (<18m) | 282             | 276         | 0.02        |
| S37 | Bangladesh       | 2014               | 8             | BSID III | Multi-nutrient powder | Childhood (<18m) | 96              | 82          | 0.16        |
| S38 | Pakistan         | 2014               | 9             | BSID III | Multi-nutrient powder (Iron, Folic Acid, Vitamin A and C) | Childhood (<18m) | 335             | 348         | 0.30        |
| S39 | Pakistan         | 2016               | 9             | BSID III | Multi-nutrient powder (Iron, Folic Acid, Vitamin A and C) | Childhood (<18m) | 589             | 648         | 0.00        |
| S40 | Tanzania         | 2016               | 9             | BSID III | Zinc, Folic Acid, Multi-vitamin | Childhood (<18m) | 119             | 128         | 0.03        |

**Studies with childhood supplementation (started at ≥18 months)**

| Ref | Country / region | Year of publication | Study quality | Test | Intervention arm | Type of intervention | N_{intervention} | N_{control} | Δ_{unbiased} |
|-----|------------------|---------------------|---------------|-----|-----------------|---------------------|-----------------|-------------|-------------|
| S41 | Jamaica          | 2005               | 9             | GMDS | Zinc | Childhood (≥18m) | 30              | 38          | -0.17       |
| S42 | South Africa     | 2011               | 8             | KABC-II | Fortified breakfast maize-porridge | Childhood (≥18m) | 63              | 68          | 0.30        |
| S43 | Viet Nam         | 2011               | 9             | EF tests, RCM | Multi-nutrients (Iron, Zinc, Iodine, and Multivitamins) | Childhood (≥18m) | 114             | 119         | 0.17        |
| S44 | Nepal            | 2012               | 9             | EF tests | Iron, Folic acid, Zinc | Childhood (≥18m) | 169             | 166         | 0.00        |
| S45 | Malawi           | 2013               | 6             | Cambridge Neurological Test Automated Battery | School feeding programme | Childhood (≥18m) | 114             | 111         | 0.26        |
| S46 | Colombia         | 2014               | 9             | BSID III | Multi-nutrient powder (Iron, Folic Acid, Vitamin A and C) | Childhood (≥18m) | 308             | 318         | -0.07       |
| S47 | India            | 2015               | 8             | ASQ 3 | Vitamin B12, Folic Acid, Folic Acid | Childhood (≥18m) | 109             | 105         | 0.03        |

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The study was published in print in 2013 but was available online in 2012.

The study was published in print in 2017 but was available online in 2016.

Abbreviation for cognitive assessments: ASQ: Ages and Stages Questionnaire; BSID: Bayley Scales of Infant Development; EF tests: executive function tests, such as Stroop Test, Go/no-go Test; GMDS: Griffiths Mental Development Scale; KABC: Kaufman Assessment Battery for Children; PPVT: Peabody Picture Vocabulary Test; RCPM: Raven's Coloured Progressive Matrices; RPM: Raven's Progressive Matrices; SBIT: Stanford-Binet Intelligence Test; UNIT: Universal Nonverbal Intelligence Test; WAIS: Wechsler Adult Intelligence Scale; WISC: Wechsler Intelligence Scale for Children; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; WRAT: Wide Range Achievement Test
Altogether 3431 candidate studies were identified using the four search strategies. After screening the abstracts and full articles, 111 studies fulfilled the criteria and with good quality received in-depth review and 41 studies without information for effect size calculation were excluded. Among the remaining 70 studies, 43 without nutritional supplementations and two with combination of educational and nutritional interventions were further excluded. As a result, 25 studies published from 1993 to 2012 were included in the final meta-analysis (see Figure 1 for the identification procedure).
Egger’s regression test reported no significant asymmetry in the funnel plot ($z = 0.64$, $p=0.52$).
Egger’s regression test reported no significant asymmetry in the funnel plot ($z = -0.006$, $p = 1.00$).
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