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	$N_{intervention}$	$N_{control}$	$d_{unbiased}$
Studies with at least one combined antenatal and childhood supplementation									
S1	Nepal	2011	9	EF tests, UNIT	Iron, Folic acid, Zinc	Childhood (≥18m)	212	101	-0.09
					Iron, Folic acid	Childhood (≥18m)	163		-0.04
					Antenatal: Zinc; Childhood: Iron, Folic acid	Antenatal + Childhood (≥18m)	137		-0.02
					Antenatal: Zinc; Childhood: Iron, Folic acid, Zinc	Antenatal + Childhood (≥18m)	122		-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		0.02
S3	Ghana	2016	8	Vocabulary checklist, EF tests	Lipid-based nutrients	Antenatal + Childhood (<18m)	387	389	0.02
					Multi-nutrients	Antenatal	397		0.01
Studies with antenatal supplementation									
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	Antenatal	392	422	-0.04
					Multi-nutrients (including Iron and Multivitamins)	Antenatal	350		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		0.36
					Multi-nutrients (Folic acid, Iron, and Multivitamins)	Antenatal	218		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 (Zinc, Iron, Copper, Iodine, Selenium, Multivitamins) [Sample 1]	Antenatal	165	269	0.19
					Iron [Sample 2]	Antenatal	148	316	-0.20
					Multi-nutrients (Zinc, Iron, Copper, Iodine, Selenium, Multivitamins) [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		-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[b]	9	Self-developed tests on general intelligence, EF, educational achievement	Multi-nutrients (Zinc, Copper, Iodine, Selenium, Multivitamins)	Antenatal	1187	1118	0.03
					Studies with childhood supplementation (started at <18 months)				
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, SBIT	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	Childhood (<18m)	163	164	0.20
					Iron, Zinc	Childhood (<18m)	161		0.21
					Zinc	Childhood (<18m)	162		0.21
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
				Development diagnostic scale, WPPSI	Protein	Childhood (<18m)	116		-0.12
S28	Malawi	2011	9	GMDS	Lipid-based nutrient supplement (50g/day)	Childhood (<18m)	56	56	-0.09
					Lipid-based nutrient supplement (25g/day)	Childhood (<18m)	51		-0.09
S29	Thailand	2011	9	School performance, WISC-III, RCPM	Iron	Childhood (<18m)	147	139	-0.06
					Iron, Zinc	Childhood (<18m)	135		-0.03
					Zinc	Childhood (<18m)	139		-0.07
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	$N_{intervention}$	$N_{control}$	$d_{unbiased}$
S34	Gambia	2013 [a]	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
					Soy milk lipid-based nutrients	Childhood (<18m)	188		-0.04
					Corn-soy blend	Childhood (<18m)	183		-0.02
S36	Nepal	2013	9	Adapted Child Development Inventory	Zinc	Childhood (<18m)	276	268	-0.02
					Iron, Folic Acid	Childhood (<18m)	268	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	Childhood (<18m)	121	126	0.05
					Folic Acid, Multi-vitamin	Childhood (<18m)	119	128	0.03

Studies with childhood supplementation (started at ≥18 months)

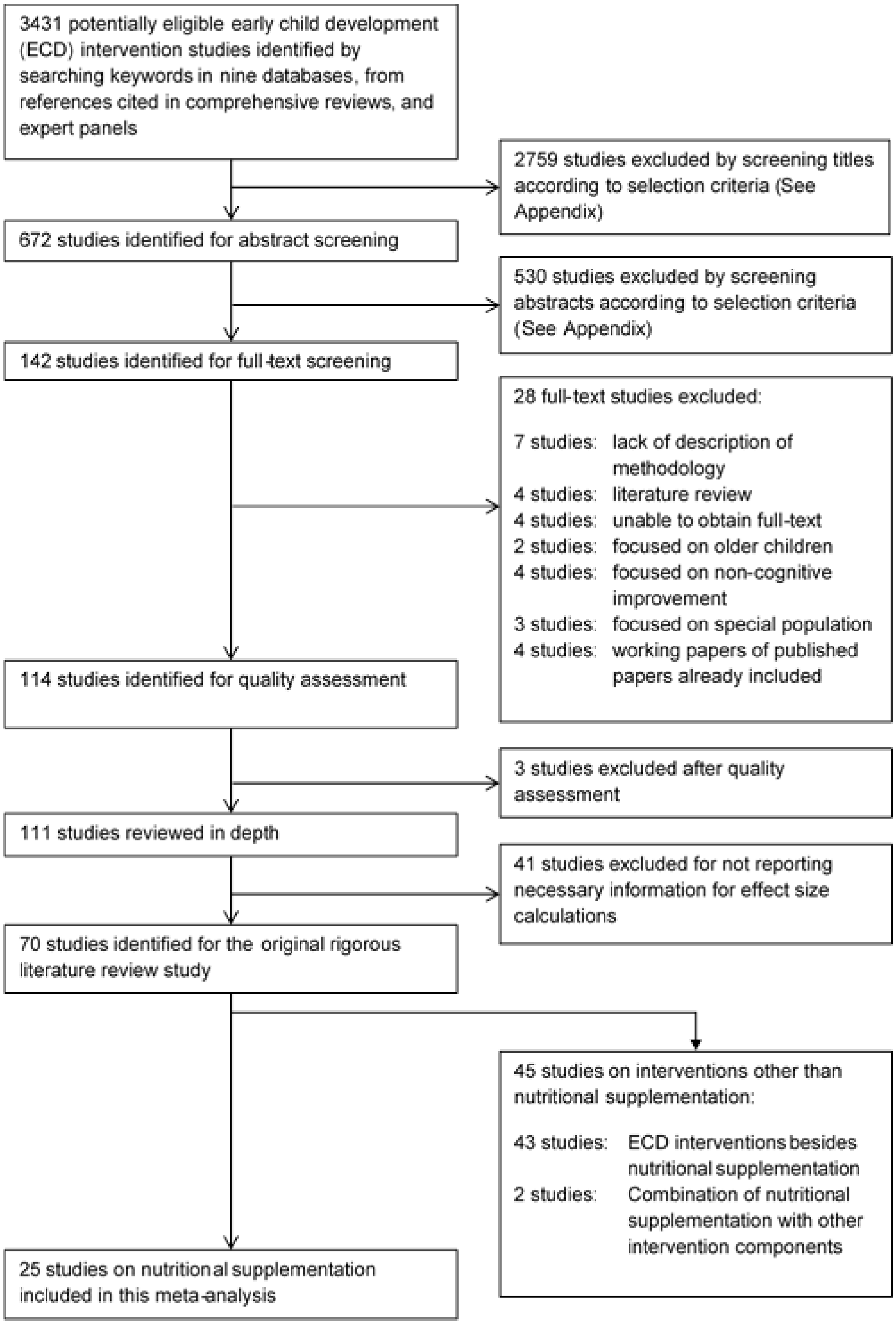
Ref.	Country / region	Year of publication	Study quality	Test	Intervention arm	Type of intervention	$N_{intervention}$	$N_{control}$	$d_{unbiased}$
S41	Jamaica	2005	9	GMDS	Zinc	Childhood (≥18m)	30	38	-0.17
S42	South Africa	2011	8	KABC-II	Fortified breakfast maize-porridge	Childhood (≥18m)	63	68	0.30
S43	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	Childhood (≥18m)	169	176	0.00
					Iron, Folic acid, Zinc	Childhood (≥18m)	199		-0.01
					Zinc	Childhood (≥18m)	144		0.06
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	Childhood (≥18m)	109	105	-0.03
					Folic Acid	Childhood (≥18m)	107		0.01
					Vitamin B12, Folic Acid	Childhood (≥18m)	101		0.11

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

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

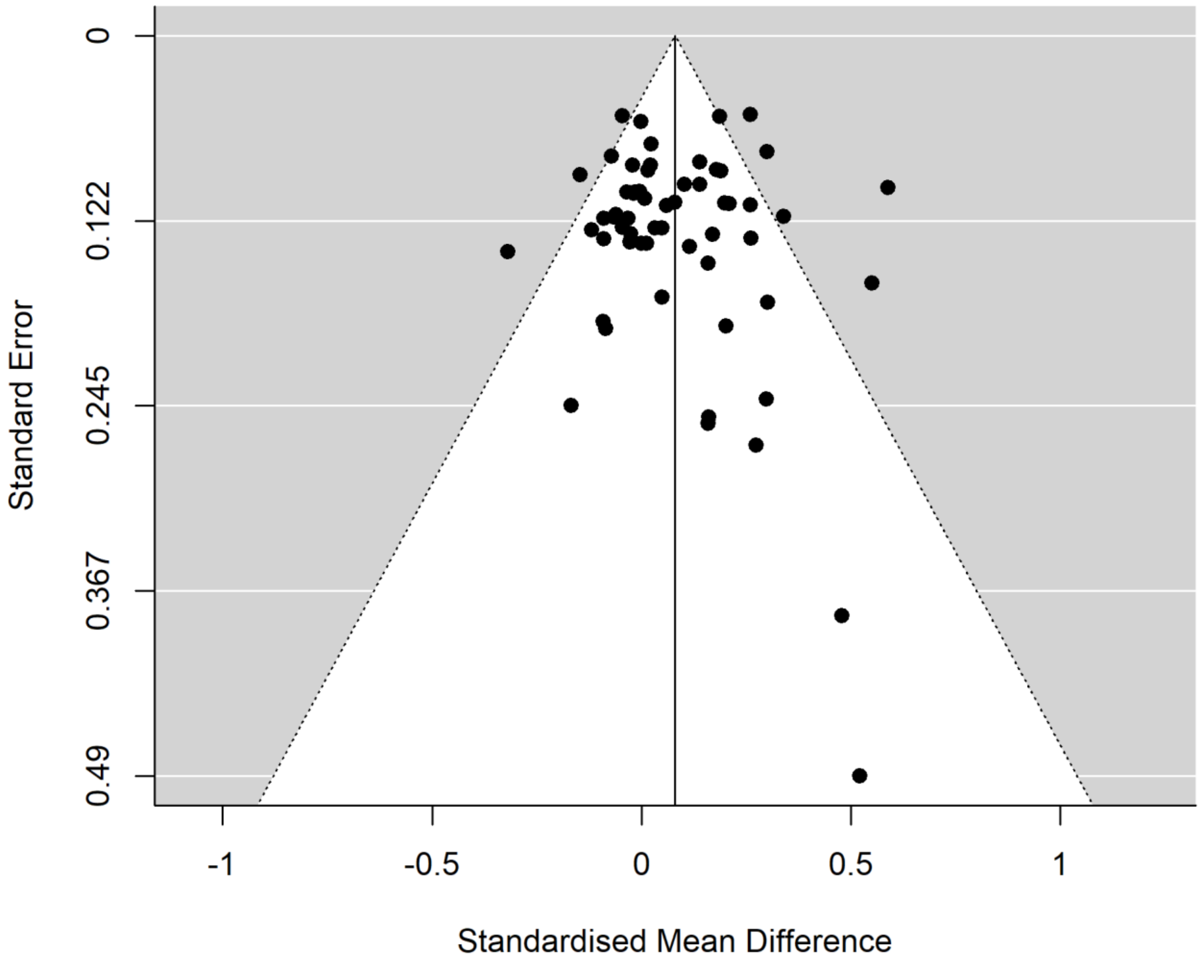
Abbreviation for cognitive assessments: ASQ: Ages and Stages Questionnaire; BSID: Bayley Scales of Infant Development; EF tests: executive function tests, such as Stroop Test, Go/no-go Test; GMDS: Griffiths Mental Development Scale; KABC: Kaufman Assessment Battery for Children; PPVT: Peabody Picture 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

Figure 1. Literature search in original DFID review for papers published 1992–2012



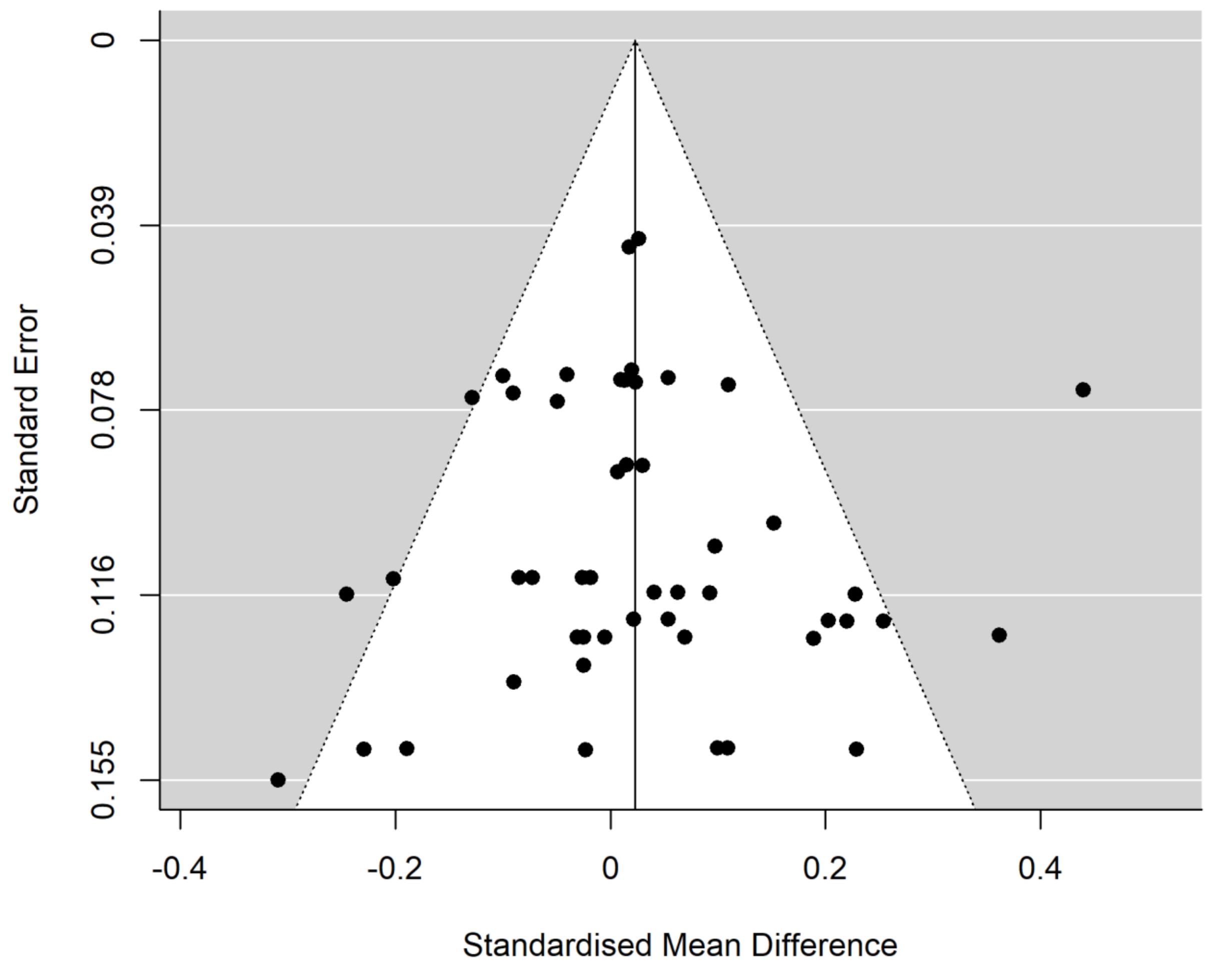
Altogether 3431 candidate studies were identified using the four search strategies. After screening the abstracts and full articles, 111 studies fulfilled the criteria and with good quality received in-depth review and 41 studies without information for effect size calculation were excluded. Among the 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).

Figure 2. Funnel plot for childhood supplementations



Egger's regression test reported no significant asymmetry in the funnel plot (z 0.64, $p=0.52$).

Figure 3. Funnel plot for antenatal supplementations



Egger's regression test reported no significant asymmetry in the funnel plot (z -0.006, p=1.00).

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