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REVIEW

Zinc intake, status and indices of cognitive function in adults and children: a systematic review and meta-analysis

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In developing countries, deficiencies of micronutrients are thought to have a major impact on child development; however, a consensus on the specific relationship between dietary zinc intake and cognitive function remains elusive. The aim of this systematic review was to examine the relationship between zinc intake, status and indices of cognitive function in children and adults. A systematic literature search was conducted using EMBASE, MEDLINE and Cochrane Library databases from inception to March 2014. Included studies were those that supplied zinc as supplements or measured dietary zinc intake. A meta-analysis of the extracted data was performed where sufficient data were available. Of all of the potentially relevant papers, 18 studies met the inclusion criteria, 12 of which were randomised controlled trials (RCTs; 11 in children and 1 in adults) and 6 were observational studies (2 in children and 4 in adults). Nine of the 18 studies reported a positive association between zinc intake or status with one or more measure of cognitive function. Meta-analysis of data from the adult's studies was not possible because of limited number of studies. A meta-analysis of data from the six RCTs conducted in children revealed that there was no significant overall effect of zinc intake on any indices of cognitive function: intelligence, standard mean difference of < 0.001 (95% confidence interval (CI) –0.12, 0.13) $P = 0.95$; executive function, standard mean difference of 0.08 (95% CI, –0.06, 022) $P = 0.26$; and motor skills standard mean difference of 0.11 (95% CI –0.17, 0.39) $P = 0.43$. Heterogeneity in the study designs was a major limitation, hence only a small number ($n = 6$) of studies could be included in the meta-analyses. Meta-analysis failed to show a significant effect of zinc supplementation on cognitive functioning in children though, taken as a whole, there were some small indicators of improvement on aspects of executive function and motor development following supplementation but high-quality RCTs are necessary to investigate this further.

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INTRODUCTION

Brain growth and development are critically dependent on several micronutrients.[1–3] Zinc is a key modulator of intracellular and intercellular neuronal signalling[4] that is found in high levels in the brain particularly the hippocampus, considered as the area involved in learning and memory,[5–7] and in the amygdala, striatum and neocortex.[7–9] Zinc is essential for the activity of a large number of metalloenzymes, cellular functions including RNA and DNA synthesis,[10] cellular growth, differentiation and metabolism. During early development, cellular activity may be particularly sensitive to zinc deficiency, which has been shown to compromise cognitive development.[11,12] Experimental studies in animals have shown that, during the early stages of brain development, deficiency of zinc caused brain defects,[13] reducing the cerebellum size[14] and altering zinc homeostasis,[15] whereas zinc deficiency during the latter stages of brain development impaired function.[16] Zinc-deficient rats experienced diminished learning and some working memory deficit[17–20] and pups whose dams have suffered prenatal zinc deficiency tend to be more aggressive than pups whose dams suffered prenatal undernutrition.[21] Evidence in humans, however, is less clear and the exact role of zinc on brain function and cognitive development remain poorly understood.[11,22–25]

It has been estimated that 20% of the world population are zinc deficient[26] and countries with a prevalence of poor dietary zinc intake of $>25\%$ are considered at high risk of zinc deficiency.[27] Zinc deficiency occurs in individuals and populations whose diets are low in sources of readily bioavailable zinc (such as red meat and seafood) and high in unrefined cereals (rich in phytate and dietary fibre).[28–30] These dietary patterns are characteristics that are common in many developing countries where zinc deficiency has a major impact on child development.[12,31,32] The precise role of zinc in cognitive function is still unclear, however, zinc is present in relatively high concentrations in the hippocampal and neocortical regions of the brain. Much of the evidence for the role of zinc in the function of the central nervous system has come from animal studies, which have shown that zinc deficiency results in reduced activity, poor memory and attention,[33] also in offspring rats, zinc deficiency during the last trimester of pregnancy and during lactation impaired spatial learning and memory and had a negative effect on motor activity.[18] Although studies in humans, the observational studies have suggested a relationship between zinc deficiency and poor cognition, but the evidence from randomised controlled trials (RCTs) during infancy, pregnancy and lactation has shown little effect.[34] The essential role of zinc in the central nervous systems is marked during brain growth,

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particularly between 24 and 40 weeks after conception,[3] which is the period where the brain goes through extraordinary structural changes, and it is during this critical time that the brain is most sensitive of zinc deficiency and its deficiency will affect the involvement of zinc in various enzymes and neurochemical processes such as synaptic transmission and the release of neurotransmitters.[35]

The specific question we sought to address in this systematic review was 'what is the evidence for an association between zinc intake, through diet or supplement, zinc status (plasma zinc concentration), and indices of cognitive function in adults and children?'. A narrative review is presented in this article, along with a meta-analysis of the data was undertaken where studies were sufficiently homogenous in terms of their design and the outcomes measured. This review was part of a wider systematic review process to identify studies assessing the relationships between zinc intake, status and various health outcomes in health populations within the EURRECA (European Micronutrient Recommendations Aligned) framework.[36]

MATERIALS AND METHODS

Search strategy

The databases Ovid MEDLINE, Ovid Embase and the Cochrane Library were used to search for relevant papers from inception, initially to February 2010, and then updated to March 2014. Both indexing and text terms were used and languages included were restricted to those spoken in the EURRECA network (English, Dutch, French, German, Hungarian, Italian, Norwegian, Polish, Spanish, Greek or Serbian).

The search and paper selection procedures were conducted according to EURRECA protocols.[37,38] The full Ovid MEDLINE search strategy can be found in Table 1. Reference lists of retrieved articles and published literature reviews were also checked for relevant studies. Authors were contacted to request missing data or clarify methods or results, some replied to our request and data values were used in the analysis, if no reply from the author, the study was excluded or additional conversion of data was performed, for example, transforming interquartile ranges (IQRs) to s.d. The search process is illustrated in Figure 1. It should be noted that these search strategies were part of the wider zinc systematic review that investigated a range of intake–status–health relationships, which refers to the study of the relationship between zinc intake and status, zinc intake and health, and zinc status and health outcomes that were considered within EURRECA.[39] The search was therefore intentionally broad in order to capture a range of health outcomes, which is the reason for the high number of identified studies and the relatively low proportion of relevant cognitive studies. The updated search followed the same search strategy. Details of the search, selection, data extraction and statistical methods developed and used by the EURRECA consortium can be access at www.eurreca.org.

Inclusion/exclusion criteria. The titles and abstracts were screened and sorted on the basis of predefined inclusion criteria: relevant to the research question, human study, zinc intake–

Table 1. Search strategy: EMBASE, MEDLINE March 2014

Search no	*Search term*	*Results*	*Search type*
1	randomized controlled trial.pt	366 322	Advanced
2	controlled clinical trial.pt	87 769	Advanced
3	randomized.ab	656 647	Advanced
4	placebo.ab	343 941	Advanced
5	clinical trials as topic.sh	168 553	Advanced
6	randomly.ab	457 059	Advanced
7	trial.ab	677 661	Advanced
8	randomised.ab	131 650	Advanced
9	6 or 3 or 7 or 2 or 8 or 1 or 4 or 5	1 903 586	Advanced
10	(animals not (human and animals)).sh	5 241 748	Advanced
11	9 not 10	1 777 274	Advanced
12	(cohort* or "case control*" or cross-sectional* or "cross sectional" or case-control* or prospective or "systematic* review*").mp	2 423 333	Advanced
13	exp meta-analysis/ or exp multicenter study/ or follow-up studies/ or prospective studies/ or intervention studies/ or epidemiologic studies/ or case-control studies/ or exp cohort studies/ or longitudinal studies/ or cross-sectional studies/	3 389 546	Advanced
14	13 or 12	4 207 248	Advanced
15	14 not 10	4 131 683	Advanced
16	11 or 15	5 304 597	Advanced
17	((zinc or zn or "zinc sulphate" or "zinc gluconate" or "zinc acetate" or methionine or "zinc isotope*") adj3 (intake* or diet* or supplement* or deplet* or status or serum or plasma or leukocyte or concentration* or expos* or fortif* or urine or hair)).ti,ab.	45 693	Advanced
18	Nutritional Support/ or Dietary Supplements/ or nutritional requirements/	140158	Advanced
19	exp Nutritional Status/ or exp Deficiency Diseases/ or supplementation/ or diet supplementation/ or dietary intake/ or exp diet restriction/ or exp mineral intake/ or Diet/ or Food, Fortified/ or nutrition assessment/ or Nutritive Value/ or Breast feeding/ or exp infant food/ or bottle feeding/ or infant formula/	786125	Advanced
20	(intake* or diet* or supplement* or deplet* or status or serum or plasma or leukocyte or concentration* or expos* or fortif* or urine or hair).ti,ab.	8 833 552	Advanced
21	18 or 19 or 20	9 146 891	Advanced
22	zinc/	132 400	Advanced
23	22 and 21	72 546	Advanced
24	23 or 17	88 668	Advanced
25	16 and 24	9230	Advanced
26	limit 25 to humans	7899	Advanced
27	limit 26 to yr = "2013 -Current"	672	Advanced

Embase 1974 to 2014 week 09, Ovid MEDLINE(R) 1946 to February 2014 week 04.

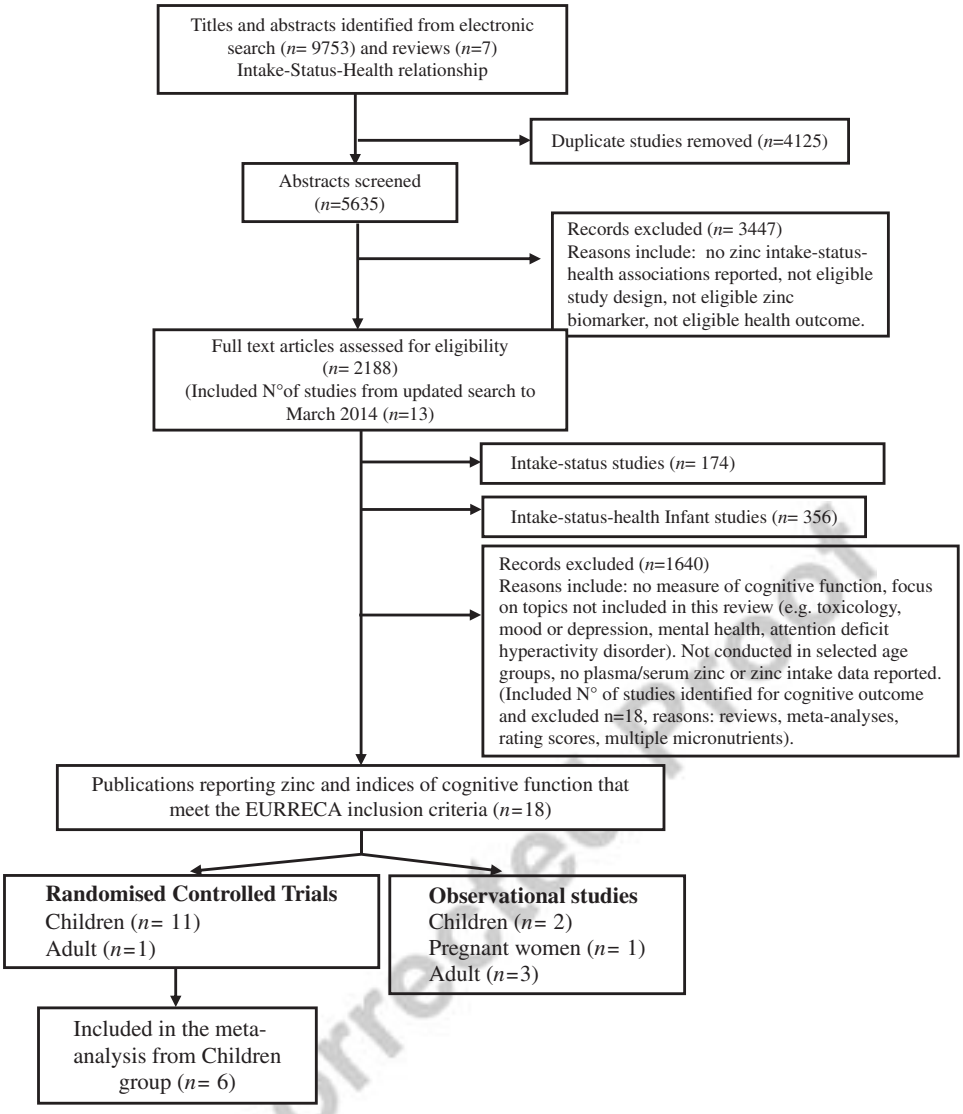


Figure 1. Study selection process for the systematic review.

plasma/serum zinc status–cognition relationship, reviews, RCTs, cohort studies, cohort nested case–control studies and cross-sectional studies. Included studies were those conducted in apparently healthy human populations that supplied zinc supplementation either as zinc gluconate, zinc sulphate, zinc acetate, zinc picolinate or zinc oxide or measured dietary zinc intake with either a validated food frequency questionnaire, a dietary history method, a 24-h recall method for at least 3 days or a food record/diary for at least 3 days (observational studies), which are established best practise methods.[36,40] For studies to be included in this review, both zinc intake/status measurement had to occur either in adults or children. Thus, intervention and observational studies reporting zinc intake/status and cognitive domains in adults and children were included. Studies were excluded if they were non-RCT, a group RCT (community trial), case–control studies, or uncontrolled trials (an intervention without a control group) or were commentaries, reviews or duplicate publications from the same study. Of all studies included in the strategic review, only those RCTs in children reporting sufficient data on zinc intake/status and cognitive domains were included in the subsequent meta-analysis.

This review focused on studies conducted in children (aged 1 to <18 years), and adults ($\geq$ 18 years). Studies relating to infants (aged 0–12 months) were excluded from this review because the systematic review and meta-analyses in infants were conducted by the research team at ULPGC and reported elsewhere.[41]

Data extraction

For each of the studies, data were extracted independently by two reviewers and input into a standardised database. Extracted data included population characteristics, dose of zinc in intervention studies, duration of the study, dietary intake of zinc, mean concentration of zinc in plasma or serum for observational studies and measures of cognitive function. Unit conversions to μmol/l were performed for the observational studies, which reported μg/dl for serum/plasma zinc concentrations. Variances that were provided as IQRs were converted to s.d., using the following formula: s.d. = IQR/1.35 where IQR = 75th percentile–25th percentile. The characteristics of these studies are presented in Tables 2a and 2b. A database of the references found in the systematic search can be found on the EURRECA website.[42]

Assessment of risk of bias in included studies

The criteria for assessing risk of bias of the included RCTs were adapted from the Cochrane Handbook for Systematic Reviews.[43]

Table 2a. Characteristics of identified studies assessing zinc intake/status and cognitive function. Randomised controlled trials ($n = 12$) reporting the effect of dietary zinc intake/serum or plasma zinc status on cognitive function in adults and children

Study, year, country	*Sex, age*	*Treatment groups*	*Micronutrient type*	*Duration*	*Outcome measure*	*Main results*
Adults						
Maylor *et al.*[56] UK France Italy	188 Males and females aged 55–70 years 199 Males and females aged 71–87 years	Placebo ($n = 63$) 15 mg Zn/day ($n = 60$) 30 mg Zn/day ($n = 65$) Placebo ($n = 67$) 15 mg Zn/day ($n = 66$) 30 mg Zn/day ($n = 66$)	Zinc gluconate	6 Months	CANTAB consisting of: -Visual memory by PRM -Working memory by SSP and SWM -Attention by reaction time and MTS	Significant improvement for SWM errors with 15 and 30 mg/day at 3 months ($P = 0.030$), Significant detrimental effect of 15 mg/day for MTS latency ($P = 0.015$).
Children						
Gibson *et al.*[64] Canada	60 Males aged 5–7 years	Placebo (hair zinc concentration > 1.68 μmol/l) ($n = 42$) Zinc group (hair zinc concentration < 1.68 μmol/l) 10 mg Zn/day ($n = 14$)	Zinc sulphate	12 Months	Attention span assessed using four subtests from the DTLA: -Sentence imitation -Word sequences -Oral directions -Design reproduction	No significant effect of zinc supplementation on attention span scores.
Cavan *et al.*[66] Guatemala	162 Males and females aged 81.5 s.d. (7.0) m.	Placebo ($n = 79$) 10 mg Zn/day ($n = 75$)	Zinc as amino acid chelate	25 Weeks	Total cognition score assessed using three subtests from the DTLA: -Letter sequences -Oral directions -Design reproduction	No significant effect of zinc supplementation on cognition measures.
Penland *et al.*[62] China	372 Males and females aged 6–9 years Number of children in each treatment group not stated	20 mg zinc (Z) 20 mg zinc with micronutrient (ZM) Micronutrients alone (M)	Zinc alone (Z) Zinc with micronutrients (ZM) Micronutrients alone (M)	10 Weeks	CPAS-R consisting of six subtests: -Continuous performance -Design matching -Delayed design matching -Concept formation -Finger tapping -Visual motor tracking	Z and/or ZM significantly improved performance on all subtests compared with M ($P < 0.05$).
Sandstead *et al.*[63] China	740 Males and females aged 6–9 years 'subjects divided equally between treatments'	20 mg zinc alone (Z) 20 mg zinc with Micronutrients (ZM) Micronutrients alone	Zinc alone (Z) Zinc with micronutrients (ZM) Micronutrients alone (M).	10 Weeks	CPAS-R consisting of six subtests: -Continuous performance -Design matching -Delayed design matching -Concept formation -Finger tapping -Visual motor tracking	Significant effect of ZM on continuous performance, visual motor tracking and concept formation compared with M or Z ($P < 0.01$).
Tamura *et al.*[65] UK	355 Males and females aged 5.3 s.d. (0.3) years	Placebo ($n = 182$) Zinc group ($n = 173$)	Zinc sulphate	21 Weeks given prenatally at ~19 weeks gestation	-Differential ability scales (non-verbal, verbal, general conceptual ability: IQ) -Visual sequential memory -Auditory sequential memory -Knox cube -Gross motor scale -Grooved pegboard	No significant effect of zinc supplementation on any cognition measure.
Gewa *et al.*[59] Kenya	554 Males and females aged 7.6 s.d. (1.3) years	Control ($n = 130$) Vegetarian supplement ($n = 147$) Milk supplement ($n = 144$) Meat supplement ($n = 133$)	No additional Zn 1.35–1.68 mg Zn 1.46–1.66 mg Zn 2.38–2.89 mg Zn	24 Months	-RCPM -Verbal meaning test -Arithmetic test -Digit span (DS)-forward test -Digit span (DS)-backward test	Available Zn intake was associated with significantly higher gains in digit span test scores over time ($P < 0.05$). A child with a daily high intake of available zinc gained 0.73 more points in the DS-total test. No significant differences were found for RCPM, verbal meaning score and arithmetic score.

Table. 2a. (Continued)

Study, year, country	*Sex, age*	*Treatment groups*	*Micronutrient type*	*Duration*	*Outcome measure*	*Main results*
Tupe *et al.*[51] India	180 Females aged 10–16 years	Control ($n=60$) Diet supplementation ($n=60$) 20 Zn mg/day ($n=60$)	No additional Zn 1.6-2.6 mg Zn 20 mg ayurvedic zinc	10 Weeks	-SRT -RRT -Memory -RPM	SRT ($P<0.05$) and RRT ($P<0.05$) decreased significantly in the Zn and diet supplemented groups compared with baseline. Memory ($P<0.05$) and RPM ($P<0.05$) scores significantly increased in Zn and diet supplemented groups compared with baseline and control.
Caulfield *et al.*[61] Peru	205 Males and females aged 4–5 years	Control (iron and folic acid only) ($n=96$) Iron, folic acid+25 mg Zn ($n=85$)	Zinc sulphate	26–30 Weeks given prenatally starting 10–14 weeks gestation	-WPPSI -Language development -Number concepts -Concept formation	No significant effect of zinc supplementation for any outcome measure.
Christian *et al.*[60] Nepal	676 Males and females aged 7–9 years	Control (vitamin A only) ($n=177$) Iron+folic acid ($n=103$) Iron, folic acid+30 mg zinc ($n=178$) Multiple micronutrients ($n=218$)	Zinc sulphate	From early pregnancy to 3 months postpartum	-UNIT (six subtests: symbolic memory, cube design, spatial memory, analogic reasoning, object memory, mazes) -Go/no-go task -Stroop test -Backward digit span -MABC -Finger-tapping test	No significant effect of zinc supplementation for any outcome measure.
Murray-Kolb *et al.*[57] Nepal	688 Males and females aged 7–9 years	Placebo ($n=176$) Iron and folic acid ($n=169$) 10 mg Zn ($n=144$) Iron, folic acid+10 mg Zn ($n=199$)	Zinc	12–35 Months	-UNIT -Go/no-go task -Stroop test -Backward digit span test -MABC -Finger-tapping test	Unadjusted analyses revealed a significant overall difference across tests for Zn supplementation compared with no zinc ($P=0.04$). No significant effect of Zn supplementation was found for individual tests.
Pongcharoen *et al.*[58] Thailand	560 Males and females, aged 9.3 s.d. (0.3) years	Placebo ($n=139$) 10 mg Zn ($n=139$) Iron ($n=147$) Iron and 10 mg Zn ($n=135$)	Zinc sulphate	6 Months Infants supplemented aged 4–6 months	-WISC-III (six verbal subtests: information, similarities, arithmetic, vocabulary, comprehension, digit span; six performance subtests: picture completion, coding, picture arrangement, block design, object assembly, symbol search) -RCPM	No significant effect of Zn supplementation was found for any test.

Q6 **Table 2b.** Characteristics of identified studies assessing zinc intake/status and cognitive function. Observational studies ($n = 6$) reporting the effect of dietary zinc intake/serum or plasma zinc status on cognitive function

Study, year, country	*Sex, age*	*Study design*	*Duration*	*Zinc intake/status marker reported and dietary/analytical method*	*Outcome measure*	*Main results*
Adults						
Ortega *et al.*[53] Spain	260 Males and females aged 65–90 years	Cross-sectional	NA	7-Day weighed food record and FFQ	-MMSE -PMSQ	MMSE results improved with increasing intakes of zinc ($r = 0.135$, $P < 0.05$) in men and women.
Gao *et al.*[54] China	188 Males and females, aged $\geqslant 65$ years	Cross-sectional	NA	Plasma zinc (ICP-MS)	Composite cognition score based on six tests: -CSID -IU story recall test -Animal fluency test -CERAD word list learning -CERAD word list recall and -The IU token test	Plasma zinc was not significantly associated with the composite cognitive score.
Lam *et al.*[52] USA	1451 Males and females aged 60–94 years	Cross-sectional	NA	Plasma zinc (ICP-AES)	Cognitive function scores of a battery of 12 tests: -Buschke total recall -Buschke long-term recall -Buschke short-term recall -Heaton immediate recall -Heaton delayed recall, -Heaton copying -MMSE -Serial 7's -'World' backward -Blessed items -Trails, part B -Category fluency	-In men, plasma Zn concentrations were not significantly associated with cognitive function scores. -In women, lower plasma zinc concentrations were related to poorer performance on tests of concentration ($P = 0.008$).
Pregnant women						
Stoecker *et al.*[55] Ethiopia	99 Females >24 weeks gestation aged 27.7 s.d. (4.7) years	Cross-sectional	NA	Plasma zinc (AAS)	RAVEN CPM	RAVEN CPM (A) score was correlated with plasma zinc ($r = 0.27$, $P < 0.008$).
Children						
Hubbs-Tait *et al.*[67] USA	42 Males and females aged 3–5 years	Cross-sectional	NA	Plasma zinc (AAS)	McCarthy scales of children's abilities, which included verbal and perceptual score -5 subtests of the verbal scale -6–7 subtests of the perceptual performance scale	Hierarchical regression analyses revealed that zinc explained significant unique variance in McCarthy scales of children's abilities verbal score ($P = 0.01$).
Umamaheswari *et al.*[50] India	100 Males and females aged 6-11 years	Interventional 5 mg Zn/day (in the form of syrup)	3 Months	Serum zinc (AAS)	-Binet–Kamath scale -Digit forward -Sentence repetition -Story recall -Picture recall -Benton visual retention test -Cattell's retentivity test	Verbal ($P = 0.05$), non-verbal memory ($P < 0.01$) and IQ ($P = 0.05$) were significantly improved after supplementation in 9- to 11-year-old children. In 6- to 8-year-old children, only verbal memory was significantly improved after zinc supplementation ($P < 0.01$).

Abbreviations: AAS, atomic absorption spectroscopy; CANTAB, Cambridge automated neuropsychological test battery; CERAD, consortium to establish a registry for Alzheimer's disease; CPAS, cognitive psychometric assessment; CPAS-R, cognition-psychomotor assessment system-revised; CSID, community screening instrument for dementia; DTLA, Detroit tests of learning aptitude; DS, digit span; FFQ, food frequency questionnaire; ICP-MS, inductively coupled plasma-mass spectrometry; ICP-AES, inductively coupled plasma atomic emission spectrometer; IQ, intelligent quotient; IU, the Indiana University story recall; MABC, movement assessment battery for children; MTS, matching to sample visual search; MMSE, mini-mental state examination; NA, not applicable; PMSQ, Pfeiffer's mental status questionnaire; PRM, pattern recognition memory; RAVEN CPM, Raven's coloured progressive matrices test; RPM, Raven's progressive matrices; RRT, recognition reaction time; SRT, simple reaction time; SSP, spatial span; SWM, spatial working memory; UNIT, universal non-verbal intelligence test; WISC-III, Wechsler intelligence scale for children-third edition; WPPSI, Wechsler preschool and primary scale of intelligence.

Studies were not included or excluded on the basis of their quality assessment. Rather the assessment of study quality provides a context for interpreting the reported effect sizes. The criteria for the RCTs and observational studies are presented in Tables 4a and 4b, respectively. Based on these indicators, two reviewers decided on the overall risk of bias. Disagreements were resolved by discussion.

Meta-analysis

Meta-analysis of data extracted from six RCTs conducted in children was undertaken using Review Manager (v5.2). RCT studies that were included for meta-analysis were those which measured one of the following cognitive domains: intelligence, executive function and motor development. These outcomes are described in Table 3 with corresponding studies, the test used and the function assessed. All data input for meta-analysis were cross-checked (NML and VHM). All RCTs were grouped per population. Of the RCTs in children, those that measured the same cognitive outcome were subgrouped, and those which provided sufficient outcome data (mean and s.d.) were included in the meta-analysis. Owing to the different scales used by the cognitive tests, the standardised mean difference was used in the random effects meta-analysis. For the quantification of heterogeneity between studies the $(I)^2$ value was used.[44] Studies were also sorted by effect size, defined as the measurement of the magnitude of the phenomenon.[45] The limited data available from observational studies meant that it was not possible to combine these studies in a meta-analysis.

RESULTS

Selection of articles

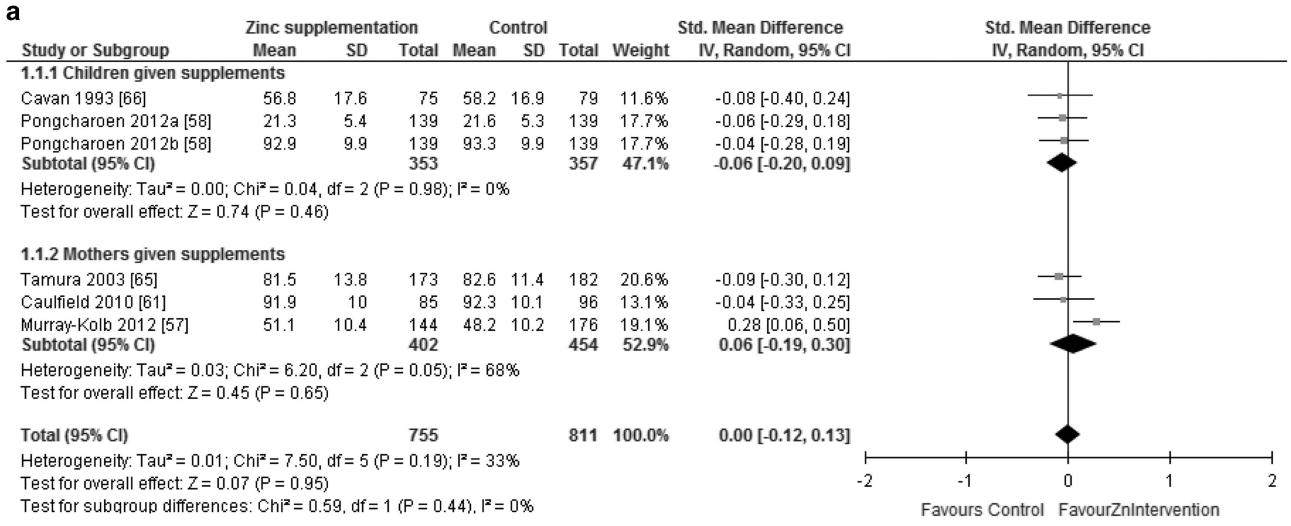
A diagram illustrating results of the systematic search and selection process is presented in Figure 1. A total of 5635 articles

Table 3. Categorisation of cognitive function tests

Aspects of cognitive function	*Cognitive test*	*Specific functions assessed by test*	*Study reference*
Motor skills	CPAS-R	Assesses cognitive abilities, interests and dispositions by questionnaires	62,63
	Gross motor scale	Development of gross motor function	65
	McCarthy scales of children's abilities	Measures mental and motor abilities	67
	MABC, finger tapping	Assessment of motor coordination, motor speed and dexterity	57,60
	Grooved pegboard, dominant, non-dominant hands	Manipulative dexterity	65
	Concept formation	Draw a person	61
	Trails, part B,	Visuomotor tracking and attention	52
Executive function: memory	CANTAB: PRM	Visual memory	56,62
	Spatial span, SWM, DS	Working memory	56,59
	Visual and auditory sequential memory	Visual or auditory memory span	65
	Short-term memory	Storage of information for a limited period	50
	Visual memory		51
	Buschke recall	Short and long-term storage, retention of the total recall	52
	Heaton recall	Memory for geometric forms	52
	Blessed items,	Concentration and memory	52
	Category fluency	The subject names as many animals as possible in 1 min	52
	Stroop test	Inhibitory control	57,60
	Animal fluency test	measure of executive function	54
	The IU story recall test	Memory	54
Attention	SRT, RRT, reaction time, MTS	Measures attention, cognitive speed for reaction tasks	51,56
	Attention span scores	Length of time to concentrate	64
	MMSE	Screen dementia, measures orientation, registration, attention, calculation, memory, language skill	52,53
Global cognitive function	CSID, CERAD word list recall.	CSID, screening tool for dementia	54
	PMSQ	Cognitive capacity	53
Language	Bear story, number concepts, CERAD	Language and narrative development	61
	The IU token test	Measure of language comprehension and working memory	54
Intelligence	Verbal, non-verbal ability, general conceptual ability IQ	Differential ability scales, IQ is the ratio of tested mental age to chronological age and is expressed as a quotient multiplied by 100	65
	Binet–Kamath scale	Determine the level of intellectual and cognitive functioning	50
	UNIT	The UNIT provides a comprehensive assessment of non-verbal intelligence	57
	WISC-III	Measures intellectual functioning	58
	RAVEN CPM	Test of non-verbal intelligence	51,58,59,67
	WPPSI	Assess cognitive and intellectual abilities	61
	DTLA	Measures general and specific mental abilities	66

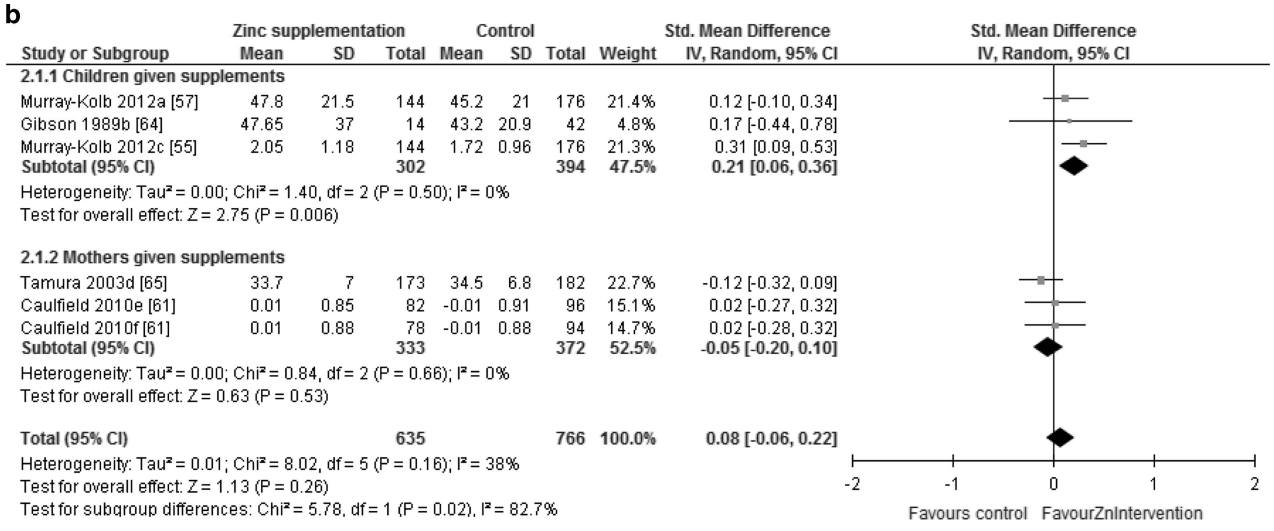
Abbreviations: CANTAB, Cambridge automated neuropsychological test battery; CERAD, consortium to establish a registry for Alzheimer's disease; word list learning test; the CERAD word list recall test; CPAS, cognitive psychometric assessment; CPAS-R, cognition-psychomotor assessment system-revised; CSID, community screening instrument for dementia; DTLA, Detroit tests of learning aptitude; DS, digit span; IU, the Indiana University; the IU story recall, the IU token test; IQ, intelligent quotient; MABC, movement assessment battery for children; MMSE, mini-mental state examination; MTS, matching to sample visual search; PMSQ, Pfeiffer's mental status questionnaire; PRM, pattern recognition memory; RAVEN CPM/RCPM, Raven's coloured progressive matrices test; RPM, Raven's progressive matrices; RRT, recognition reaction time; SRT, simple reaction time; SWM, spatial working memory; UNIT, universal non-verbal intelligence test; WISC-III, Wechsler intelligence scale for children-third edition; WPPSI, Wechsler preschool and primary scale of intelligence.

were identified as potentially relevant for inclusion in the wider search on zinc intake, status and health outcomes in all populations. Of these, 3447 were excluded based upon screening abstracts. Two independent reviewers screened 10% of the abstracts in duplicate and any discrepancies were discussed before screening the remaining references. A further update to the search in March 2014 found 13 further relevant articles. The full texts of the remaining 2188 manuscripts were assessed to determine inclusion and exclusion by two independent reviewers and disagreements rectified through discussion. A total of 1640 studies were excluded because they did not meet the inclusion criteria. In all, 174 studies relating to zinc intake–status



Abbreviations:
[a]Pongcharoen, 2012 [58] Raven's Colour Progressive Matrices (RCPM)
[b]Pongcharoen, 2012 [58] Wechsler Intelligence Scale for Children (WISC) test, full scale
Cavan 1993 [66] Total cognitive score
Tamura 2003 [65] General conceptual ability Intelligence Quotient (IQ)
Caulfield 2010 [61] Intelligence full IQ
Murray-Kolb 2012 [57] Universal Non Verbal Intelligence Test (UNIT) score

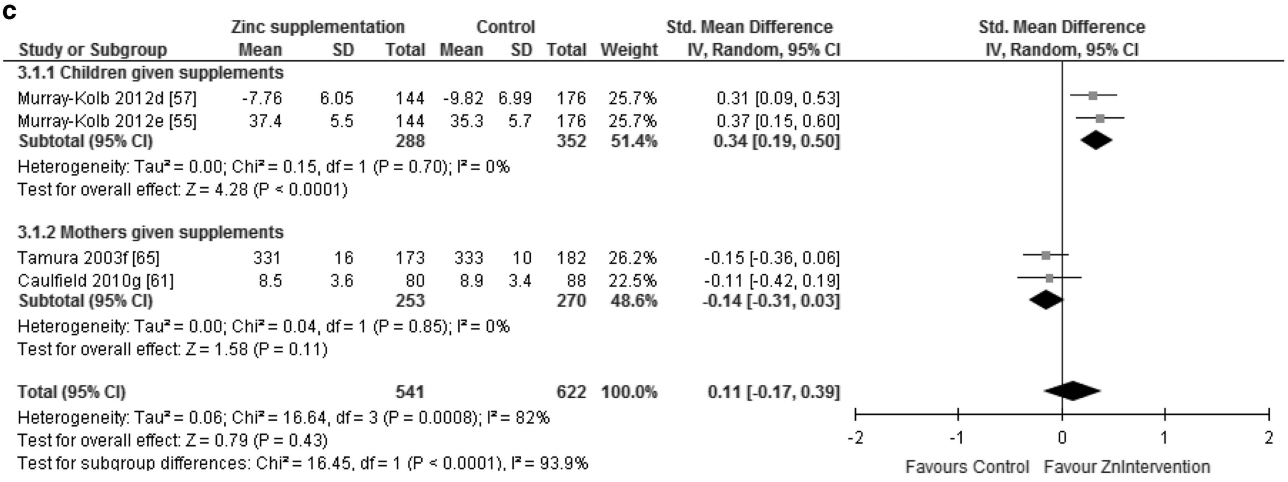
Standard mean difference (SMD) analysis and sorting by effect size is shown in the 3 Forest plots



Abbreviations:
[a]Murray-Kolb, 2012 [57] Go no go test %
[b]Gibson, 1989 [64] Cognitive score median converted to mean value
[c]Murray-Kolb, 2012 [57] Backward digit span
[d]Tamura, 2003[65] Visual sequential memory score
[e]Caulfield, 2010 [61] Language development
[f]Caulfield, 2010 [61] Counting game

Figure 2. Forest plots of RCTs of intelligence, executive function and motor outcome in children. (**a**) The effect of zinc supplementation on intelligence in children. (**b**) The effect of zinc supplementation on executive function in children. (**c**) The effect of zinc supplementation on motor outcome in children.

c



Abbreviations:
[d]Murray-Kolb, 2012 [57] MABC test where lower score indicates a higher motor skill, therefore means have been converted to a negative score for meta-analysis.
[e]Murray-Kolb, 2012 [57] Tapping
[f]Tamura, 2003[65] Gross motor scale score
[g]Caulfield, 2010 [61] Concept formation

Figure 2. Continued.

relationships have been reported elsewhere,[46–48] and 356 infants studies were also passed to another team within the EURRECA network for a separate review.[49] The final selection included 12 RCTs (11 in children) and 6 observational studies, all of which were published between 1985 and 2009.

Reasons for exclusion

A total of 3447 abstracts were excluded, for the following reasons: no zinc data, no baseline data, no measurement of the relationship of zinc intake/status with cognition, ineligible study design, ineligible dietary zinc measurement (that is, neither validated food frequency questionnaire, dietary history method nor a 24-h recall for at least 3 days), or ineligible biomarker of zinc (that is, neither plasma/serum, urine nor hair zinc concentrations). For the purpose of this review, studies with infant were not included ($n = 356$) as this has been reported elsewhere.[41] A further 1814 studies were excluded because they did not assess cognitive function outcomes or they provided insufficient data to be considered for a comparative analysis, were not conducted on healthy participants, provided zinc as a multi-micronutrient supplement or were published in a language outside the scope of this study.

Studies included. A total of 18 studies that reported zinc intake or plasma/serum zinc and its association with cognitive function met the inclusion criteria. Twelve were RCTs and six were observational studies. A summary of the key characteristics of these studies are given in Tables 2a and 2b. Studies were conducted in Europe ($n = 3$), North America ($n = 3$), Asia ($n = 8$), Africa ($n = 2$), Central America ($n = 1$) and South America ($n = 1$) and age of participants ranged from 23 to 94 years for adults (including pregnant women), and 3–16 years for children. In the majority of studies included in this article, children were under 10 years old; only two studies included older children.[50,51]

Adults and pregnant women. A small number of studies included in this review (5 of 18) addressed the relationship between zinc intake and/or status on cognitive function in adults, four of which were observational cross-sectional studies[52–55] and one was an RCT.[56] The search identified only one observational study conducted in pregnant women.[55] Meta-analyses of adults or pregnant women could not be performed because of the variability in the presentation of the data and the lack of comparable studies.

Children. Eleven RCTs[51,57–66] and two observational studies[50,67] were conducted with children. In five studies, supplements were given before cognitive testing; either prenatally to pregnant women between 10 and 19 weeks of gestation with children assessed for cognitive skills at age 4–9 years[60,61,65] or postnatal supplementation for up to 2 years (4–35 months old), with cognitive skills assessed in a follow-up at age 7- to 9-year old[57] or mean age of 9.3-year old.[58] For these studies, supplements were given in the form of a caplet,[60] tablet[57,61,65] or in a form of syrup.[58] The remaining six RCT studies assessed cognitive function immediately after supplementation[51,59,62–64,66] in children aged on average 81.5 months[66] and 7.6-year old[59] and age ranging from 5- to 7-year old,[64] 6- to 9-year old[62,63] and 10- to 16-year old.[51] Participants were given zinc supplements, either in the form of a zinc sulphate solution[64] as a tablet[51,62,63,66] or as a meat supplement.[59] The two observational studies compared plasma zinc concentrations with cognitive function in children aged 3- to 5-year[67] and 6- to 11-year old.[50]

Indices of cognitive function. The indices of cognitive development and function used in the studies included in this review are summarised in Table 3. They included measures of motor skills, executive function (memory, attention, language and global cognitive function) and intelligence. Of the 18 studies described in Tables 2a and 2b, nine reported a positive association between zinc intake or status with one or more measure of cognitive function.[50,51,53,55,56,59,62,63,67] Negative associations or no significant effect were reported for the remaining nine studies.[52,54,57,58,60,61,64–66]

Meta-analysis of data from studies with children

A random effects model was used to investigate the impact of zinc intake on indices of cognitive function including intelligence (six data sets from five publications),[57,58,61,65,66] executive function (six

data sets from four publications)[57,61,64,65] and motor development (four data sets from three publications).[57,61,65]

The analysis yielded a pooled standard mean difference for the impact of zinc supplementation on intelligence of < 0.001 (95% confidence interval (CI) −0.12, 0.13) $P = 0.95$; executive function, 0.08 (95% CI, −0.06, 022) $P = 0.26$ and motor skills, 0.11 (95% CI −0.17, 0.39) $P = 0.43$. These results revealed no significant overall effect of zinc supplementation on these cognitive function domains (Figures 2a–c, respectively). Stratifying the data by subgroups based on whether the child was given the supplements or given prenatally to the mother, revealed that maternal supplementation during pregnancy did not have a significant impact on these cognitive domains in children assessed during childhood. For trials in which the supplements were given directly to the child, there was a significant effect of supplementation on executive function (mean difference = 0.21, 95% CI 0.06, 0.36, $P = 0.006$) and motor skills (mean difference = 0.34, 95% CI 0.19, 0.50, $P < 0.0001$; Figures 2b and c). However, this must be interpreted with caution because of the limited number of data sets contributing to these analyses, two of which come from the same study.[57]

Risk of bias

The risk of bias for each study identified was assessed. Twelve RCTs studies were assessed and a high risk of bias was found for most of the studies, except for three,[57,58,60] which had moderate-to-low risk of bias (Table 4a). Six observational studies were assessed, and a moderate risk of bias was found for most of the studies, except for two,[50,67] which had high risk of bias and one,[55] which had low risk of bias (Table 4b). The sources of bias included inadequate information about sources of funding, unclear adequacy of sequence generation (randomisation procedure) and inadequate blinding.

DISCUSSION

The purpose of this review was to present the evidence for the relationship between zinc intake and/or zinc status (plasma/serum zinc concentration), and indices of cognitive function in adults (⩾18 years) and children (aged 1 to < 18 years). This review differs from other reviews in that it includes both intervention and observational studies that investigated the association between zinc intake, through diet or supplement, zinc status (plasma/serum zinc concentration), and indices of cognitive function in adults and children and a short meta-analyses of studies in the child group.

Narrative overview

Adult and pregnant women. Of the five studies identified,[52–56] three suggested a positive association between zinc intake and measures of cognitive function.[53,55,56] Ortega *et al.*[53] indicated a small but significant correlation ($r = 0.135$, $P < 0.05$), between increased zinc intake and mini-mental state examination test. Stoecker *et al.*[55] reported a positive correlation between plasma zinc concentration and Raven's coloured progressive matrices test scores, a test of non-verbal intelligence, in women in their third trimester of pregnancy ($r = 0.27$, $P < 0.008$). Results revealed a weak, positive association between the test score and plasma zinc concentration. The study by Maylor *et al.*[56] indicated both a positive significant effect of zinc supplementation on memory ($P = 0.030$) and a negative significant effect on indices of attention (matching to sample visual search; $P = -0.015$). Two studies examined the association between plasma zinc concentration and cognitive score.[52,54] One of these revealed that lower plasma zinc was significantly correlated with poor cognitive performance in women ($P = 0.008$) but not in men,[52] whereas the other study[54] failed to find any association in men or women.

Children—executive function. The studies included in this review reported contrasting outcomes of the relationship between zinc intake/status on indices of executive function, including attention, inhibitory control, memory and language. Gibson *et al.*[64] reported that zinc supplementation had no significant effect on attention span in boys aged 5 – 7 years, which was consistent to the findings reported by Tamura *et al.*[65] in a group of girls and boys of a similar age. In contrast, a positive association was reported between zinc intake and the digit span scores test, which measures verbal working memory ability, in children[59] and adolescent girls.[51] In the studies where the supplements were given prenatally, no effect was reported on working memory or inhibitory control[57,60] or language development.[61]

Children—intelligence. Intelligence was measured using a variety of tests detailed in Table 3. Cavan *et al.*[66] reported that zinc supplementation in children had no significant effect on the total cognitive score of the Detroit tests of learning aptitude, which tests general mental abilities,[68] although children did responded to zinc supplementation with significant changes in cognitive scores.[66] This concurs with the results of the study by Gewa *et al.*[59] conducted in children in Kenya in which children's diets were supplemented with meat in order to increase their overall zinc intake. After 2 years, there were no significant differences in Raven test scores between the children consuming additional meat, compared with those consuming the control diets. Furthermore, prenatal zinc supplementation did not have a significant effect on

Table 4a. Assessment of risk of bias of included randomised controlled trials reporting zinc intake and serum/plasma zinc in children and adults (adapted from the Cochrane handbook)

Study	*Adequate sequence generation*	*Allocation concealment adequate*	*Adequate blinding*	*Dropouts adequate and outcome data complete*	*Funding adequate*	*Lack of other potential threats to validity*	*Overall risk of bias*
Maylor *et al.*[56]	Unclear	Unclear	Yes	Yes	Yes	Unclear	High
Tamura *et al.*[65]	Yes	Unclear	Yes	Unclear	Yes	Unclear	High
Penland *et al.*[62]	Unclear	Unclear	Yes	Unclear	Yes	Unclear	High
Tupe and Chiplonkar[51]	Unclear	Unclear	Yes	Unclear	Yes	Unclear	High
Murray-Kolb *et al.*[57]	Unclear	Yes	Yes	Yes	Yes	Yes	Moderate
Pongcharoen *et al.*[58]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Gewa *et al.*[59]	Unclear	Unclear	No	Yes	Yes	Unclear	High
Christian *et al.*[60]	Unclear	Yes	Yes	Yes	Yes	Yes	Moderate
Caulfield *et al.*[61]	Yes	Yes	Yes	Yes	No	Yes	High
Sandstead *et al.*[63]	Unclear	Unclear	Yes	Unclear	Yes	No	High
Gibson *et al.*[64]	Unclear	Yes	Yes	Yes	No	Yes	High
Cavan *et al.*[66]	Unclear	Unclear	Yes	Unclear	Yes	No	High

Table 4b. Assessment of risk of bias of included observational studies reporting zinc intake and serum/plasma zinc in children and adults (adapted from the Cochrane handbook)

Study	*List confounders in review list*	*Study dealt with confounding factors adequately*	*Assessment of exposure (zinc intake or status) adequate*	*Information on funder adequate*	*Lack of other potential threats to validity*	*Overall risk of bias*
Ortega *et al.*[53]	Yes	Yes	Yes	No	Unclear	Moderate
Gao *et al.*[54]	Yes	Unclear	Yes	Yes	Yes	Moderate
Lam *et al.*[52]	Yes	Yes	Yes	Yes	Yes	Moderate
Stoecker *et al.*[55]	Yes	Unclear	Yes	Yes	Yes	Low
Hubbs-Tait *et al.*[67]	Unclear	No	Yes	Yes	Yes	High
Umamaheswari *et al.*[50]	Unclear	Unclear	Yes	Yes	Yes	High

any indices of intelligence measured in children aged 4–9 years.[60,61,65]

A follow-up study in which zinc supplements were given to children from 12 to 35 months, indicated that there were significant improvements in intellectual function scores in the zinc supplemented group compared with the placebo control group when children were followed up at 7–9 years of age. However, when adjustments were made for co-variants, the difference was not significant.[57] A study of similar design also reported no long-term effects of zinc supplementation given from 4 to 6 months, on indices of intelligence at age 9.3 s.d. (0.3) years.[58]

Children—motor skills. Penland *et al.*[62] undertook a study in Chinese children of the impact of 10 weeks supplementation with zinc alone or zinc plus miconutrients or micronutrients alone, on indices of motor function. The test used was the cognition-psychomotor assessment-revised (CPAS-R) battery, which revealed that zinc, and zinc with micronutrients, significantly improved performance in all subtests of the CPAS-R battery. In addition, Sandstead *et al.*[63] showed that zinc plus micronutrients significantly improved neuropsychologic performance including the tasks of tapping, circular tracking (motor) and oddity (concept formation) compared with micronutrients or zinc alone. Hubbs-Tait *et al.*[67] reported a negative association between plasma zinc concentration and motor scores from the motor subset within the McCarthy scales of children's ability test. Prenatal zinc supplementation did not have a significant effect on motor score in a follow-up study of children aged 5.3 (s.d. 0.3) year.[65]

Meta-analysis. One of the challenges researchers encounter when comparing studies in this field is the broad variety of study designs and outcome measures used. For the meta-analysis part of this review, only RCTs conducted in children were included, with outcome measures clustered into three main cognitive domains: intelligence, executive function and motor outcome. Reasons for excluding studies from meta-analyses included: only percentage change in measurements reported,[51] lack of control group,[62,63] test scores reported as differences rather than the mean and s.d. data for both intervention and placebo group to enable analytical comparison.[59]

Results from the meta-analyses of the impact of zinc supplementation on cognitive domains in children indicated that supplements given prenatally did not have a long-term impact on offspring during childhood but supplements given directly to children may have a positive impact on executive function and motor skills. Despite the small number of studies that were eligible for the meta-analysis, it could be argued that the usefulness of this meta-analysis lies in the analyses per cognitive domain and in the categorisation of prenatal supplementation and supplements given to children that add an insight into the effect of zinc supplementation in both situations. Irrespective of the instrument used (UNIT, WISC), it was considered a logical process to combine studies that measured intelligence and similarly this was done for executive function and motor outcome. Well-designed RCT studies,[69] which follow standardised measurement techniques to facilitate direct comparison of outcome data with other studies, are required to measure zinc intake and/or status and cognitive function relationships

Comparisons with findings from other studies

The narrative review in this article highlights the limited number of studies looking at the association between zinc intake/status and cognitive function, particularly in the adult and children populations. The main findings of this review are the evaluation of the range of cognitive aspects that were assessed in the included studies in the narrative review (memory, attention, cognitive score, performance, motor skills, intelligence, language and inhibitory response) and its association with zinc intake and/or plasma zinc status, where 9 studies out of 18 reported a positive association. In addition, evidence from the six RCTs conducted in children that examined the effect of zinc supplementation either pre or post-nataly, revealed that the overall pooled standard mean difference of the impact of zinc supplementation on intelligence, executive function and motor outcome was not significant. The strength of this systematic review is in the unique methodology of the defined criteria of identifying zinc intake, biomarker of zinc status and the health outcome cognitive function identified, following a thorough systematic review process following EURRECA best practises and guidelines.

Recent reviews of children and zinc supplementation for mental and motor development have found no convincing evidence that zinc supplementation has a beneficial effect on motor or mental development. A recent Cochrane review[70] used a different meta-analytical approach to the one used in the present review, including both infants and children together, and reported no effect of zinc on intelligence, executive function or motor development in children from birth up to 5 years of age. This review, however, focussed on neonates, infants and toddlers up to 5 years of age, rather than older children.[70] Similarly, Brown *et al.*[71] conducted a review on zinc supplementation of children up to 30 months of age and reported no significant overall impact on mental and motor development.

Other reviews have examined the effect of multi-micronutrient supplementation on cognition rather than zinc alone.[72,73] Best *et al.*[72] concluded that four of six included studies reported a significant ($P < 0.05$) beneficial effect of multi-micronutrient food fortification on memory and Eilander *et al.*[73] reported a significant overall effect of micronutrient supplementation on academic performance ($P = 0.044$), but not for crystallised intelligence (the acquiring of knowledge and learning that considers short-term memory, visual perception, retrieval ability, cognitive processing speed and sustained attention).[73] A recent review by Nyaradi *et al.*[74] examined the role of nutrition on children's neurocognitive development from pregnancy through childhood and reported that evidence from observational studies suggests that multiple micronutrients may have an important role in children's cognitive

development, with the results of intervention trials using single micronutrients remaining inconclusive. It is difficult to determine a specific effect of zinc intake or status on indices of cognition, partly because of the methodological challenges of assessing long-term cognition effects, but also because the identification of 'at risk populations' (identified vulnerable population exposed to zinc deficiency) seems to be a key factor in disentangling the impact of supplementation on cognitive outcomes.[75]

The major limitation in the interpretation of the meta-analysis is the paucity of data that could be included because of the difference of the study design and the type of cognitive test administered per cognitive domain. In addition, many of the studies included in our meta-analysis were assessed as having moderate-to-high risk of bias, which may have impacted on the reported pooled effect sizes. Limits on the number of studies eligible for meta-analysis, however, meant that we were unable to restrict meta-analyses to studies at low (or lower) risk of bias, or to stratify studies according to risk of bias. Furthermore, a reliable and specific biomarker of zinc status has not yet been identified.[76] However, our previously published systematic review of biomarkers of zinc status have confirmed that, in healthy individuals, plasma zinc concentration does respond to changes in dietary intake.[77] All the studies included in this review were conducted in healthy individuals, therefore we are confident that plasma zinc concentration (although not perfect) is a reasonable biomarker for zinc status, and is widely used as such in the studies reported in this review despite poor sensitivity and specificity.[78,79]

CONCLUSIONS

Although some studies report a positive effect of zinc intake/status on cognitive function,[50,51,53,55,56,59,62,63,67] others reported mixed results.[52,54,57,58,60,61,64–66] Therefore, to date, the evidence regarding the effect of zinc intake or status on cognitive function is lacking and inconsistent. Therefore, although the meta-analysis of a subset of the studies conducted in children showed no significant overall effect of zinc supplementation on any of the identified cognitive domains, a positive effect of zinc supplementation on cognitive function cannot be ruled out. However, there remains a paucity of well-designed carefully controlled long-term trials investigating the relationship between zinc intake, status and cognitive function in humans. Studies should be reported in a consistent and standardised manner or in comparable units of measurement to facilitate future comparisons and more readily contribute to the body of scientific evidence.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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