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Breast milk and cognitive development—the role of confounders: a systematic review

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ABSTRACT

Objectives: The association between breastfeeding and child cognitive development is conflicted by studies reporting positive and null effects. This relationship may be confounded by factors associated with breastfeeding, specifically maternal socioeconomic class and IQ.

Design: Systematic review of the literature.

Setting and participants: Any prospective or retrospective study, in any language, evaluating the association between breastfeeding and cognitive development using a validated method in healthy term infants, children or adults, was included.

Primary and secondary outcome measures: Extracted data included the study design, target population and sample size, breastfeeding exposure, cognitive development assessment tool used and participants' age, summary of the results prior to, and following, adjustment for confounders, and all confounders adjusted for. Study quality was assessed as well.

Results: 84 studies met our inclusion criteria (34 rated as high quality, 26 moderate and 24 low quality). Critical assessment of accepted studies revealed the following associations: 21 null, 28 positive, 18 null after adjusting for confounders and 17 positive—diminished after adjusting for confounders. Directionality of effect did not correlate with study quality; however, studies showing a decreased effect after multivariate analysis were of superior quality compared with other study groupings (14/17 high quality, 82%). Further, studies that showed null or diminished effect after multivariate analysis corrected for significantly more confounders (7.7±3.4) as compared with those that found no change following adjustment (5.6±4.5, p=0.04). The majority of included studies were carried out during childhood (75%) and set in high-income countries (85.5%).

Conclusions: Much of the reported effect of breastfeeding on child neurodevelopment is due to confounding. It is unlikely that additional work will change the current synthesis. Future studies should attempt to rigorously control for all important confounders. Alternatively, study designs using sibling cohorts discordant for breastfeeding may yield more robust conclusions.

ARTICLE SUMMARY

Article focus

- Although most published data support the association between breastfeeding and IQ of the offspring, debate remains whether this is a causal relationship or an association with favourable parental characteristics.
- We conducted a systematic review of the literature investigating the association between breastfeeding and cognitive outcomes of healthy term infants.

Key messages

- Over 80 studies addressing this issue were published with conflicting results.
- Studies where the initial positive effect of breastfeeding on IQ disappeared or diminished after multivariate analysis controlled for significantly more confounders than studies showing no such change.
- Much of the reported effect of breastfeeding on child cognitive abilities is due to the maternal cognitive and socioeconomic effects.

Strengths and limitations of this study

- The significant heterogeneity in study design and rigour precluded the conduct of a formal meta-analysis.

INTRODUCTION

Breastfeeding confers a range of nutritional and immunological advantages upon infants including reduction in childhood illness,[1–5] diabetes[6 7] and obesity.[8]

The potential of breast milk to enhance cognitive development has been the focus of numerous studies since Hoefer and Hardy's[9] initial observation in 1929. It is generally agreed that children who breastfeed are more intelligent; however, debate remains whether this is a causal relationship or merely an association with favourable parental socioeconomic class and IQ. The beneficial effects of breastfeeding on the child's neurodevelopment are hypothesised by some

to be mediated by long-chain polyunsaturated fatty acids (PUFA)[10] which are present in human milk, but not in cow's milk or most infant formulas.[11] However, a recent systematic review of all randomised trials where mother's diet was supplemented with PUFAs during pregnancy has failed to confirm such an effect.[12]

The pendulum of opinion has swung back and forth with different investigators showing inconsistent results depending upon study design and rigour. The Achilles heel of most of these studies, and the probable explanation for the conflicting results, is the difficulty in controlling for confounders that may affect child development. Furthermore, the ability to clarify this relationship is hindered by ethical considerations, which preclude randomised controlled trials (RCT), given that breastfeeding has other protective effects and the highly personal nature of the decision to breastfeed.

Well-established confounders in breastfeeding research include demographic and IQ differences between mothers who breastfeed and those who choose not to.[13] Parents who score high on a range of cognitive abilities have children with above average IQ scores.[13] In parallel, advantage in mother's IQ more than doubles the odds of breastfeeding.[13] Thus, some of the published data demonstrates the disappearance of the breastfeeding effect on child's cognition after correction for maternal IQ.

In an attempt to partially overcome these sources of bias, a few randomised trials have been published, with randomisation to breastfeeding promotion[14 15] or in preterm infants.[16] In the breastfeeding promotion intervention trial (PROBIT Trial) by Kramer *et al*[15], IQ scores and academic performance tests were more favourable in the intervention group; however, statistically significant differences were only shown for some of the subscores.

Systematic reviews examining the impact of breastfeeding on cognitive abilities have reached conflicting results.[13 17–19] The meta-analysis by Jain *et al*[18] suggests that less than 25% of studies in this area have adjusted for sociodemographic confounders.

There is a paucity of literature critically assessing the current published evidence within this field. In trying to address these challenges, the objective of the present work was to conduct a systematic review of published studies investigating the association between breastfeeding and neurodevelopmental outcome of healthy infants born at term.

METHODS

The study was conducted based on a prospectively prepared protocol, using the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.[20]

Literature search

Searches were conducted in the following databases (all from inception to July 2011): MEDLINE(R) with Daily Update, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment, NHS Economic Evaluation Database, EMBASE and PsycINFO using the OvidSP interface and on Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index-Science (CPCI-S), and Conference Proceedings Citation Index—Social Science & Humanities (CPCI-SSH) using the Web of Knowledge interface.

A search strategy was developed based on the MEDLINE, EMBASE and PsycINFO database subject headings and the 'Used for' synonyms listed in the scope notes for the terms 'breast feeding', 'human milk', 'breast milk', 'infant formula', 'artificial milk', 'cognition', 'intelligence' and 'intelligent quotient'. Reference lists of identified studies, textbooks, previously published systematic reviews and review articles were also searched. No language restrictions were applied and studies in languages other than English were translated for incorporation into the study.

A second complimentary literature search was carried out on April 2013 for all studies published during the period August 2011–December 2012.

Study selection

Prospective and retrospective studies (RCTs, non-randomised controlled clinical trials, cohort studies, longitudinal studies and case-control studies) were included if

1. One of the study aims was to address the question of breastfeeding and cognitive development;
2. The authors used reliable validated methods to evaluate cognitive development (eg, Bayley scales of infant development, Wechsler Intelligence Scale for Children Revised (WISC-R));
3. Prospective or retrospective documentation of use and duration of breastfeeding was used;
4. The authors focused on healthy term infants and not those at increased biological risk for developmental delays (eg, prematurity, intrauterine growth restriction).

Studies were excluded if

1. The study group included preterm or small for gestational age babies.
2. Evaluation of cognitive development was carried out using only a non-reliable or subjective tool (such as school grades, or maternal report).
3. Dietary patterns and breastfeeding were not evaluated since birth.

Titles and abstracts were reviewed for possible exclusion by two reviewers (AW and CS). If both reviewers excluded a citation, it was eliminated from further review. If at least one reviewer included the citation or if there was insufficient information to make a determination from the title and abstract, the full article was obtained for review. Full text articles were reviewed by three authors (AW, CS and AC) for suitability for

inclusion. Disagreements regarding study eligibility were resolved by consensus.

Study quality grading

Quality assessment of individual studies was performed by two authors (AW and CS) using the three category summary grading system (A, B, C) suggested by Ip *et al*.[19] Their system defines a generic grading system that is applicable to each type of study design including RCTs and cohort and case-control studies as follows:

A (good): A study that adheres mostly to the commonly held concepts of high quality including the following: clear description of the population, setting, interventions and comparison groups; clear description of the comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20% dropout; clear reporting of dropouts and appropriate consideration and adjustment for potential confounders.

B (fair/moderate): Category B studies do not meet all the criteria in category A because they have some deficiencies, but none of them are likely to cause major biases. The study may have suboptimal adjustment for potential confounders. The study may also be missing information, making it difficult to assess limitations and potential problems.

C (poor): Category C studies either did not consider potential confounders or did not adjust for them appropriately. These studies may have serious shortcomings in design, analysis or reporting; have large amounts of missing information, or discrepancies in reporting.

Data extraction

Extracted data were compiled in an evidence table. The table includes a description of the studies that addressed the key question according to the inclusion/exclusion criteria. The table provides information about study design, target population and sample size, description of breastfeeding exposure and method of categorisation, nature of the comparison group, cognitive development assessment tool used and participants' age, summary of the results prior to adjustment for confounders, a list of all confounders adjusted for, differences in IQ between the groups after adjustment for possible confounders (if available), and study quality grading according to the scale described above.[19]

Statistical analysis

Comparison of studies based on their results or quality was performed by χ^2 or analysis of variance as appropriate.

RESULTS

The flow of the literature search is displayed in figure 1. Of the 1696 potentially relevant citations identified, 84 studies met the a priori inclusion criteria for this systematic review (table 1).[9 13 15 21–101] The overall agreement between reviewers on the inclusion of studies was 100%.

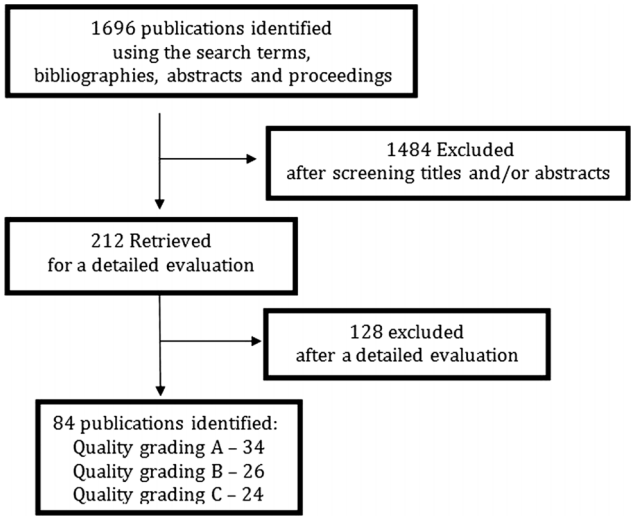

Figure 1 Search flow.

Out of these 84 publications, 34 were rated as high quality (grade A), 26 as moderate (grade B) and 24 as low quality (grade C). Overall, based on the primary endpoint of cognitive function, there were 21 studies showing no association between IQ and breastfeeding,[24 25 30–32 35 36 39 54 56 62 63 73 74 86 87 89 91 97 100 101] 28 positive studies,[9 15 21 27–29 37 38 42 48 51 57 59 61 64 68 71 72 75 79–82 85 90 94 95 98] 18 initially positive studies that became negative after accounting for confounders,[13 23 26 33 43–46 49 50 52 55 65 66 69 78 84 96] and 17 studies where the initial positive effect was diminished but remained statistically significant after accounting for confounders (table 2).[22 34 40 41 47 53 58 60 67 70 76 77 83 88 92 93 99]

In general, the directionality of the results did not correlate with the quality of the studies. However, the studies showing a decrease in the effect after multivariate analysis were of superior quality compared with the rest of the studies (ie, 14 of 17 had a quality score of A—table 2).

Different studies corrected in their analyses for different potential confounders, ranging from 0 to 16 total confounders (table 1). Confounders commonly considered in these studies were socioeconomic status, maternal education, birth weight, gestational age, birth order and gender. Some considered the quality and quantity of stimulation of the child to be crucial confounders but did not consider maternal or paternal intelligence and other important factors. Studies that showed null or diminished effect in their multivariate analysis controlled for significantly more confounders (7.7±3.4) as compared with those that found no change following adjustment for confounders (5.6±4.5, p=0.04). Furthermore, many of the studies did not have a clear definition of breastfeeding or cumulative breast milk exposure.

Table 1 Accepted studies

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
Amanda and Singh[21]	Prospective cohort. Feeding method collected retrospectively	84 school-aged children from two schools in India	Exclusive breast milk for more than 4 months vs less than 4 months or formula fed	General mental ability test for children from 7–11 years (Srivastava and Saxena 1988–1989)	There were significantly more breastfed (>4 m) children in the higher IQ category (IQ>109)	None	Not provided	C
Andres *et al*	Longitudinal study	391 healthy infants enrolled in the Beginnings Study in Arkansas, USA	Breastfed vs soy fed vs milk-based formula fed	Assessed at ages 3, 6, 9 and 12 months using the Bayley Scales of Infant Development (BSID) second edition, from which the Mental Developmental Index (MDI) and Psychomotor Development Index (PDI) were derived	BF infants scored slightly higher than formula-fed infants on the MDI score at ages 6 and 12 months ($p<0.05$). Confounders included in the model	Socioeconomic status, mother's age and IQ, gestational age, gender, birth weight, head circumference, race, age and diet history	BF infants scored 1–2 points higher than formula-fed infants on the MDI score at ages 6 and 12 months ($p<0.05$)	A
Angelsen *et al* 2001[23]	Prospective cohort	345 children in Scandinavia (Norway and Sweden)	<3 months 3–6 months >6 months	BSID at 13 months. Wechsler Preschool and Primary Scales of Intelligence (WPPSI-R), and Peabody Developmental Motor Scales (PDMS) at age 5 years	Shorter duration of breastfeeding was associated with lower scores on mental developmental tests both at 13 months and at 5 years of age. Unadjusted difference of eight points	Maternal age, education, smoking and Raven score (IQ)	Maternal age, education and intelligence were significant confounders. When analysing performance IQ and verbal IQ separately, the median IQ value was not statistically different when adjusting for maternal Raven score	B
Auestad *et al*[24]	Prospective randomised longitudinal study comparing different formula types and non-randomised breastfeeding group	294 children from four sites in the USA	Breastfeeding until age 12 m, vs three different types of formulas (±AA, DHA)	Bayley scale for infant development at 6 and 12 months Fagan test of infant intelligence at 6 and 9 months MacArthur communicative development inventories at 9 and 14 months	No difference in any of the parameters checked between any study groups	None	No difference in any of the parameters checked between any of the study groups	A
Auestad *et al*[25]	Follow-up study of Auestad 2001: prospective randomised longitudinal study comparing different formula types and a non-randomised breastfeeding group	157 children from the original 294 children from four sites in the USA	Breastfeeding until age 12 months, vs three different types of formulas (±AA, DHA)	At 39 months, standard tests of IQ (Stanford Binet IQ), receptive vocabulary (Peabody Picture Vocabulary Test-Revised), and expressive vocabulary (mean length of utterance)	No difference in any of the parameters checked between any study groups	None	No difference in any of the parameters checked between any study groups	A

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
Bartels *et al*[26]	Retrospective cohort. Breastfeeding status prospectively assessed	672 monozygotic male twin pairs 637 dizygotic male twin pairs 860 monozygotic female twin pairs 647 dizygotic female twin pairs 679 male–female twin pairs 598 female–male twin pairs in the Netherlands	<2 weeks >2 weeks	Dutch CITO-elementary test at age 12 years	Breastfed children of highly educated mothers score on average 7.6 points higher on a standardised test of cognitive abilities than formula-fed children of mothers with a low education	Maternal education, income	A significant positive effect of breastfeeding on cognitive abilities above the expected positive effect of maternal education. Exact numbers not provided	B
Bauer *et al*[27]	Prospective cohort	50 children from Honolulu, Hawaii	Breastfeeding as a continuous variable over time	The McCarthy Scales of Children's Abilities at age 3 years	The duration of breastfeeding was significantly correlated with scores on the scales, General, cognitive, Quantitative and Memory	Socioeconomic status, gender and pesticide exposure	Remained significant, numbers not provided	C
Birch *et al*[28]	Single-center, double-blind, randomised clinical trial comparing different formula types and non-randomised breastfeeding group	52 healthy term infants enrolled for DHA and ARA supplementation and 32 breastfed infants served as controls in Dallas, Texas, USA	Assigned diets were fed exclusively through 17 weeks of age. In the breastfeeding group, the average duration of breastfeeding was 43±9 weeks	WPPSI-R was used to assess intelligence at 4 years of age	The control formula and DHA-supplemented groups had Verbal IQ scores poorer than the breastfed group. There was no difference in performance or full-scale IQ between all groups	None	No adjustment carried out	B
Bon[29]	Retrospective cohort	954 children from France	Exclusive bottle-fed vs breastfed for <15 days vs breastfed between 15 days and 2 months; vs breastfed for more than 2 months	The PM-47 Non-Verbal test, at 6–8.5 years of age	Higher scores for girls who were breastfed vs not breastfed. No difference in boys	Could not be assessed from the text	Not performed	C
Bouwstra *et al*[30]	A prospective, double-blind, randomised control study comparing different formulas. Non-randomised breastfed group as control	A control formula—n=169, an LC-PUFA supplemented n=146 Breastfed group n=159 in the Netherlands	Supplementation—2 months All formula-fed infants received control formula between 2 and 6 months	BSID-II at 18 months	Bayley's MDI and PDI result values did not differ significantly between the three groups	Parity, HOME score, parental Education	No difference between the groups	B
Burruchaga *et al*[31]	Prospective cohort	39 children born at term and from homogeneous sociocultural status in Spain	Exclusive breast milk for at least 2 months, vs exclusive bottle-fed	BSID at 22 months	Bayley's MDI and PDI result values did not differ significantly between the groups	Maternal education, head circumference, maternal occupation, birth order, smoking status	No difference between the groups	C

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
Caspi *et al*[32]	Retrospective cohort	858 children from the New Zealand (Dunedin) birth cohort. 1848 children from the British (E-risk study) twin birth cohort	No breastfeeding vs breastfeeding	New Zealand cohort: IQ measured at ages 7, 9, 11 and 13 years using Wechsler Intelligence Scale for Children–Revised. IQ scores combined for an overall score British cohort: revised short form of WPPSI–age 5	Difference in IQ test scores between breastfed children and those not breastfed was 5.6 and 6.3 IQ points in the Dunedin and E-risk cohorts, respectively Benefit mediated by a specific genotype. Only in children carrying the C allele	Genetic variation in fatty acid metabolism (rs174575) Socioeconomic status, Maternal cognitive ability, Gestational age, birth weight	Children not carrying the C allele did not benefit from breastfeeding	A
Clark *et al*[33]	Prospective cohort	784 Chilean children	<2 months 2>8 months >8 months	At age 5.5 years WPPSI-R. Preschool Language Scale—3rd Edition (PLS-3) the Broad Cognitive Abilities Standard Scale (BCA) of the Batería Woodcock-Muñoz-Revisada (Batería-R)	Poorer outcomes on the cognitive and language assessments were found for both the short and long extremes of breastfeeding as the sole milk source. The highest scores were observed in children who received breast milk as the sole milk source for 2–8 months	Gender, birth weight, child's age at testing, maternal education, IQ, depression, age, father's absence, paternal education, HOME score, socioeconomic status, nutritional status, iron deficiency anaemia at 12 months, and iron supplementation	Difference in IQ not significant	B
Daniels and Adair[34]	Prospective cohort	1984 Filipino children	Any breastfeeding during: 0–6 months 6–12 months 12–18 months 18–24 months Over 24 months	Philippines Non-verbal Intelligence Test of fluid abilities at ages 8.5 and 11.5 years	Poor education and suboptimal living conditions among BF mothers were strong negative confounders, causing inverse associations between BF and cognitive ability. Increased duration of any BF was of small significant benefit for cognitive development at both ages	Parental education, paternal presence in home, maternal age, parity, alcohol during pregnancy, preterm status of child, mother reads, child's gender, baths (n/week), dietary variety at 2 years, household income, non-income-producing assets, electricity in home, and environmental hygiene score	1.6 points among normal birth weight breastfed for 12–18 months vs less than 6 months	A
De Andraca *et al*[35]	Prospective cohort. Subanalysis of an RCT concerning iron fortified formulas	788 infants, 4–6 months of age in Chile	<30 days vs >30 days. All children in the study were breastfed for an average of 75 days	BSID—MDI and PDI at 12 months of age	Breastfeeding for more than 30 days was associated with significantly lower scores (2.5 points less in MDI and 2.3 in PDI). Probably due to low SES	SES, education and occupation of parents, alcohol abuse, HOME, maternal intelligence by WAIS, stressful events	No adjustment was carried out for the specific association of breastfeeding and Bayley scale	C

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
De Andraca *et al*[36]	Prospective cohort	138 mother-infant dyad in Chile	Exclusive breastfeeding for 6 months or more vs weaning before 45 days of age	BSID at 12 months of age	No difference between the groups in MDI and PDI	None; study reports similar family characteristics in each group	No difference	C
Der *et al*[13]	Database analysis of a prospective study, sibling pairs analysis and metaanalysis	5475 children 332 pairs of sibling discordant for breastfeeding status 545 discordant for duration of breastfeeding in the USA	Breastfeeding vs no breastfeeding. Breastfeeding history obtained mostly within a year of birth	Peabody individual achievement test (PIAT) was administered to children between 5 and 14 years	Unadjusted effect of breastfeeding +4.7 compared with non-breastfeeding	Maternal IQ, education, age, family poverty, HOME stimulation score and birth order	After adjustment, the difference became non-significant	A
Di girolamo *et al*[37]	Prospective cohort. Breastfeeding data collected retrospectively	80 children in Spain	Full breastfeeding for at least 4 months vs no breastfeeding since 2 weeks of age	BSID at 8–30 months	Breastfeeding group had a higher average MDI (of six points) compared with the bottle-fed group, but no difference in PDI	Parental education and age, gender, birth order	Remained significant. Data not provided	C
Eickmann *et al*[38]	Prospective cohort	191 Brazilian infants	'Predominantly breastfed' 'partially breast fed' and 'non- breast fed'	BSID-II at 12 months of age	Full breastfeeding at 1 month was associated with a small significant benefit in mental development compared with partial or no breastfeeding. No additional advantage in mental development was found with longer durations of full breastfeeding	Adjusted for family income, possession of TV and fridge, flush toilet, maternal work and years of schooling, number of children under 5 years, home stimulation index, smoking during pregnancy, birth weight, infant's sex, haemoglobin, weight-for-age	Full breastfeeding at 1 month was associated with +3.0 points, p=0.02 compared with partial or no breastfeeding	C
Elwood *et al*[39]	Prospective cohort. Breastfeeding data collected retrospectively	779 men from Caerphilly, South Wales, UK	Artificially fed vs breastfed, duration unknown vs breastfed <3 months vs breastfed >3 months	Men aged 60–74 years The national adult reading test (NART) The AH4 13 verbal and mathematical reasoning 3. The choice reaction time (CRT) for hand-brain reaction speed	In the normal birth weight group, the mean cognitive function was similar in both groups. In the men whose birth weight had been below the median, having been artificially fed was associated with significantly lower results in two of the three tests	Age, social class, education, birth order and family size, father's social class, father's unemployment	In the normal birth weight group, the adjusted mean cognitive function was similar in both groups	B
Evenhouse and Reilly[40]	Database analysis of a prospective study, sibling pairs analysis. Data from	2734 sibling pairs in the USA	No breastfeeding <3 months 3–6 months 6–9 months 9–	Add Health's abbreviated version of the Peabody Picture Vocabulary Test	Persistent positive correlation between breastfeeding and cognitive ability	Birth weight, gender, birth order, parental investment,	1.68 centile points higher for ever breastfed to never breastfed	A

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
	the National Longitudinal Study of Adolescent Health		12 months 12–24 months >24 months	(PVT), normed for age and sex	Unadjusted Difference in PVT 4.9 centile points when comparing never breastfed to any breastfeeding in the full sample	environmental characteristics		
Fergusson *et al*[41]	Prospective cohort	Birth cohort of children from the Dunedin Multidisciplinary Child Development Study: 1037 children assessed at age 3 years 991 at age 5 years 954 at age 7 years	Child bottle-fed; Breast-fed for up to 4 months; Breastfed for 4 months or longer.	Measures of intelligence at 3, 5 and 7 years. 3 years-Peabody Picture Vocabulary Test 5 years-Stanford Binet Intelligence Scale 7 years-Weschler Child Intelligence Scale	Children who were breastfed for 4 months or longer had scores which were 3.84 (average) points higher than bottle-fed infants (on scales with an SD of 10)	Maternal intelligence (SRA verbal scale), maternal education, childhood experiences. Maternal training in child-rearing, family socioeconomic status. Birth weight and gestational age	A small but statistically significant benefit in the test scores of breastfed vs Bottle-fed infants (mean=1.89)	A
Florey *et al*[42]	Retrospective cohort	592 firstborn singletons in Dundee	Breastfed on discharge from the hospital vs Bottle-fed	Age 18 months. Bayley Scales of Infant Mental and Motor Development	Higher mental development was significantly related to breastfeeding on discharge from hospital	Partner's social class, mother's education, height, alcohol and cigarette consumption, placental weight and the child's sex, birth weight and gestational age at birth	After adjustment, the difference in the Bayley mental development index between the groups was between 3.7 and 5.7 units	C
Foroushani *et al*[43]	Longitudinal cohort. Breastfeeding data collected retrospectively at age 2 years	5362 singletons born in 1946 in England, Wales and Scotland	No breastfeeding 1–3 months 4+ months	Age 8—sentence completion, reading and vocabulary Age 11—Verbal, reading and vocabulary. Age 15—Verbal, reading and vocabulary. Age 26—reading Age 43—visual and memory	Children who were breastfed longer scored higher on verbal tests. Tests at older age (26, 43) were not significantly different	Birth weight, childhood illness, home conditions, parents' age and education, child's behavioural scores, parents interest in the child's development, school type	Mean score 1.5 points higher for ages 8, 11, 15. Not significant at older ages	C
Gale and Martyn[44]	Prospective cohort	994 men and women, born between 1920 and 1930 in Hertfordshire, UK	Exclusive breastfeeding, exclusive bottle feeding, mixed feeding	65–75 years old. AH4 IQ test, taken on a computer	Participants who had been exclusively breastfed had slightly higher IQ scores compared with the two other groups	The use of a dummy in infancy, number of older siblings, father's occupational class, and mother's age at the participant's birth	After adjustment, no association was found between adult intelligence and method of infant feeding	B
Gale *et al*[45]	Prospective cohort	241 children born to the Southampton Women's Survey, UK	Breastfeeding Fortified formula feeding Unfortified formula feeding	Age 4—WPPSI (3rd edn.), sentence repetition and verbal fluency measured by NEPSY	In unadjusted analysis, children who were breastfed or fed with a fortified formula had significantly higher scores	Maternal IQ and education, social class, on benefits, age at birth, birth weight	After adjustment, the differences in IQ between groups became non-significant	A

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
Ghys *et al*[46]	Prospective cohort. Data on breastfeeding collected retrospectively	128 full-term children in the Netherlands	Breastfeeding was expressed as the number of months of breastfeeding regardless of possible additional formula feeding	At 4 years: Dutch adaptation of the Kaufman Assessment Battery for Children (K-ABC), the Groningen Developmental Scale (GOS). And items of the motor scale of the McCarthy Scales of Children's Mental Abilities	Duration of breastfeeding showed significant correlations with cognitive development (Pearson correlation coefficient 0.26)	Plasma and RBC DHA and AA, maternal intelligence, birth weight, duration of breastfeeding and paternal educational attainment, smoking during pregnancy	In the regression analysis, the correlation disappeared	B
Gibson-Davis and Brooks-Gunn [47]	Longitudinal birth cohort study. Breastfeeding information collected retrospectively at 1 year	1645 American-born mothers and their babies	Breastfeeding for at least 1 month vs none	At 3 years of age: Peabody Picture Vocabulary Test-Third Edition	In unadjusted mean comparisons, breastfed children had Peabody Picture Vocabulary Test scores that were 6.6 points higher than children who were not breastfed	An extensive set of demographic characteristics, including mother's Peabody Picture Vocabulary Test and the Home Observation for Measurement of the Environment score. Mothers were categorised into one of three educational-status groups	After adjusting for demographic characteristics and maternal verbal ability, the coefficient dropped to 1.72	A
Gomez-Sanchiz *et al*[48]	Prospective cohort, information on feeding collected retrospectively	238 healthy babies born at term, non-IUGR in Spain	Formula fed, Breastfed up to 4 months, Breastfed for more than 4 months	Bayley Infant Development Scale at 24 months of age	Infants breastfed for longer than 4 months scored higher on the mental development scale than those breastfed for less time	Sociodemographic and neonatal variables including parental IQ score	The results of multiple linear regression analysis showed that infants breastfed for longer than 4 months scored 4.3 points more than those breastfed for less time	A
Greene *et al*[49]	Retrospective cohort	432 participants. 208 males, 224 females in Ireland	Breastfed vs non-breastfed And Breastfed for up to 12 weeks vs more than 12 weeks	Age: 11–16 years Raven's Standard progressive matrices test and subsets of the Primary Mental Ability Test namely verbal meaning, reasoning and number facility	The breastfed children showed a highly significant advantage over the non-breastfed children for all measures of IQ assessed, ranging from a 4.3 point advantage in Raven's IQ to a 6.0 point advantage in Primary mental abilities IQ	Birth weight, gestational age, birth rank, child's sex, social class, mother's age and mother's educational level	Following adjustment, the beneficial effect of breastfeeding (yes vs no) was statistically non-significant. A six point advantage in verbal IQ and 5.4 point advantage in reasoning IQ were observed for participants breastfed for >I	C

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
							2 weeks, compared with less	
Gurka *et al* abstract[50]	Prospective cohort	1050 children, from the National Institute of Child Health and Development Study of Early Child Care and Youth Development in the USA	Never; 0–6 months; longer than 6 months	Age: 4 years old Standardised (mean.100; SD.15) cognitive outcomes	Significant positive associations were observed between breastfeeding and cognitive outcomes before adjusting for other factors	Maternal age, education, observed quality of the home environment, mother's attitude regarding modernity of parenting, and maternal verbal IQ	No difference between the groups	A
Hart *et al*[51]	Prospective cohort	83 healthy full-term infants in Texas, USA	Exclusively breastfed vs exclusively non-breastfed	Brazelton Neonatal Behavioral Assessment Scale (BNBAS) at a mean age of 8.95 days	Breastfed infants surpassed formula-fed infants on items of orientation, motor, range of state, and state regulation dimensions of the BNBAS. Breastfed infants also exhibited fewer abnormal reflexes, signs of depression and withdrawal	Socioeconomic status	After adjustment for SES only, the differences remained significant	B
Hoefer and Hardy[9]	Retrospective cohort	383 children in Illinois, USA	Artificially fed, breastfed for 3 months or less, from 4 to 9 months and from 10 to 20 months	Age—7–13 years. Stanford Revision of the Binet-Simon intelligence test and the Pintner-Patterson performance scale (a nonverbal intelligence test), and by a group educational test, the Stanford achievements test	Infants artificially fed were inferior in all standardised measurements to those breastfed from 4 to 9 months, and, with one exception, to those breastfed 3 months or less. Those artificially fed equalled or excelled those breastfed from 10 to 20 months	none; similar paternal IQ	Adjustment was not carried out, although they mention that paternal IQ was similar between the groups	C
Holme *et al*[52]	A secondary analysis of data from a follow-up study of an RCT of an intervention to reduce smoking in pregnancy	1218 children in Birmingham, UK	Not breastfed, Breastfed up to 2 months, 2–4 months, over 4 months. Also, any breastfeeding vs none	British Ability Scales (Total IQ, Visual IQ, and verbal IQ), and Quick Neurological Screening Test (QNST) at age 9 years	Before adjustment, breastfeeding was significantly associated with higher total, verbal and visual IQ scores, and increasing duration was significantly correlated with IQ scoresBreastfeeding was associated with a	Maternal demographics (including education, race and age), smoking history, work patterns, depression, social support, neonatal details and ill-health in the child	Total IQ became non-significant after adjustment	A

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
					crude total IQ increase of 5.49 points, which was reduced to 1.78 points on analysis with breastfeeding as a binary variable (yes/no—still significant)			
Horwood and Fergusson[53]	Longitudinal study—children studied at birth, 4 months, 1 year, at annual intervals to age 16, and 18 years	1064 children born in New Zealand in 1977	Not breastfed, breastfed for <4 months, breastfed for 4–7 months, breastfed for ≥8 months	Revised Wechsler Intelligence Scale for Children (total IQ)—age 8 and 9 Teachers' rating of school performance (reading and mathematics)—age 8 and 12 Progressive Achievement Test of Reading Comprehension—ages 10 and 12 Progressive Achievement Test of Mathematics—age 11 Tests of scholastic abilities—age 13 High School Outcomes	Increasing duration of breastfeeding was associated with consistent and statistically significant increases in cognitive abilities, and children who were breastfed for ≥8 months had mean test scores that were between 0.35 and 0.59 SD units higher (more than 5 points) than children who were bottle-fed	Maternal age, maternal education, family socioeconomic status, averaged standard of living, averaged family income, maternal smoking during pregnancy, gender, birth order, birth weight	Upon adjustment, associations were reduced and children who were breastfed for ≥8 months had scores that were 0.11–0.3 SD units (less than three points) higher than children who were bottle-fed	A
Innis *et al*[54]	Retrospective cohort	433 full-term infants born in 1994 in Vancouver	Never breastfed, breastfed less than 1 month, 1–3 months, 3–6 months, 6–8 months, more than 8 months, and mixed feeding (breast and formula milk)	Visual acuity measured using acuity card procedure with Teller Acuity Cards. Cognitive development measured using the Fagan Test of Infant Intelligence, (V.4.1) at 39 ±1 weeks of age	There were no differences in visual acuity or novelty preference among the infants when they were stratified by incidence or duration of breastfeeding	None	No difference	B
Jacobson *et al*[55]	Prospective Longitudinal study	323 predominantly white, middle-class children born from 1980 to 1981, at age 4, and 280 children at age 11, from two cohorts of similar demographic information in Michigan, USA *Most exposed to PCB during pregnancy	Breastfed vs not breastfed	McCarthy Scales of Children's Abilities and the Peabody Picture Vocabulary Test-Revised at the age of 4 Wechsler Intelligence Scale for Children-III, Wide Range Achievement Test-Revised, and the Woodcock Word, Passage, and Reading Comprehension test at the age of 11	At the ages of 4 and 11, breastfeeding was significantly related to higher IQ scores	Social class, education, maternal IQ, parenting skills (Home observation for measurement of the environment (HOME))	The relationship was reduced to non-significance after adjustment for maternal IQ and parenting skills (HOME)	B
James[56]	Prospective cohort	38 full-term children (taken as a sample from an extended	Bottle-fed babies vs breastfed babies	IQ test At age 16 (no details)	No difference in IQ	No adjustment	No difference	C

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
		Pembrokeshire farming family, UK)						
Jedrychowski *et al*[57]	Longitudinal study	468 term babies in Krakow, Poland	Complementary breastfeeding (including none), vs exclusive breastfeeding up to 3 months, 4–6 months, or longer than 6 months	In the first 3 years of the follow-up, the Bayley Mental Scales of Infant Development-second edition (BSID-II) were used. At the age of 6 and 7, the Wechsler intelligence test for children (WISC-R) was administered	Children on mixed breastfeeding achieved lower total IQ scores at each of the IQ check-ups compared with those who were exclusively breastfed	Maternal education, baby's gender, parity, and weight gain in pregnancy	Children breastfed exclusively for >6 months increased by 3.8 points (95% CI 2.11 to 5.45)	B
Jiang *et al*[58]	Longitudinal study	3271 children and their mothers from the USA participating in the Child Development Supplement of the Panel Study of Income Dynamics	Yes or no ever breastfeeding and, never breastfed; less than 6 months, 7–12 months, and more than 12 months	Woodcock Johnson Psycho-Educational Battery-Revised (WJ-R) test score and Wechsler Intelligence Scale for Children-Revised (WISC-R) test score at 3 and 6 years of age	Breastfed children had higher scores on WJ-R and WISC-R tests	Child's age, race and ethnicity, sex, number of siblings, whether the child was first born to the mother, whether the child was born preterm, whether the child was born SGA, HOME scale, maternal IQ, age, education, health status, insurance, marital status, working, income	Three out of the five effects remain significant; the effect sizes are smaller, with only one effect size being larger than one-fifth of the SD. Longer spells of breastfeeding are uncorrelated with increases in the measures of achievement	A
Johnson *et al*[59]	Longitudinal study	204 Euro-American full-term infants were followed up to the age of three from the Galveston (Texas) area	Breastfed vs not breastfed AND Duration of breastfeeding	At age 3 years; Stanford-Binet Fourth Edition and Peabody Picture Vocabulary Test-Revised	Breastfeeding added significantly to the prediction of the Composite IQ Comprehension factor, Vocabulary, Absurdities, Memory for Sentences, and Peabody Picture Vocabulary Test-Revised. Duration of breastfeeding only added to the prediction of Vocabulary scores	Socioeconomic status, HOME scores (parenting skills), mother's intelligence, mother's smoking behaviour, gender and birth order of the child	Breastfeeding was associated with a 4.6-point higher mean in the children's Intelligence	A
Keim *et al*-abstract[60]	Prospective cohort	347 children in the USA	Exclusively breastfed vs formula fed	Mullen Scales of Early Learning at 1 year of age	Infants exclusively breastfed demonstrated better visual reception, fine motor and overall cognitive development at 12 months than formula fed infants (4–6 points)	Preterm birth, smoking, race/ethnicity, education	Differences were weakened after adjustment. No numbers provided in the abstract	C

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
Kramer *et al*[15]	Cluster-randomised trial.	13 889 Belarussian children born between June 1996 and December 1997	Experimental group vs control group: Experimental group was encouraged to breastfeed and had greater levels of breastfeeding at 3, 6, 9 and 12 months (exclusive breastfeeding also sevenfold higher at 3 months)	Wechsler Abbreviated Scales of Intelligence and teacher evaluations of academic performance in reading, writing, mathematics and other participants at 6.5 years of age	The experimental group had higher means on all of the Wechsler Abbreviated Scales of Intelligence measures, with cluster-adjusted mean differences of 7.5 points for verbal IQ, 2.9 points for performance IQ, and 5.9 points for full-scale IQ. Teachers' academic ratings were significantly higher in the experimental group for reading and writing	Maternal (and paternal) IQ, as well as all other demographic and confounding variables, should be distributed randomly between the treatment groups and should not confound the treatment effect	Cluster-adjusted mean differences of 7.5 points for verbal IQ, 2.9 points for performance IQ, and 5.9 points for full-scale IQ	A
Lawlor *et al*[61]	Prospective cohort	3794 woman who delivered a singleton baby between 1981 and 1984 in Brisbane, Australia	Never, <4 months, ≥4 months	Peabody Picture Vocabulary Test at the age of 5 Raven's standard progressive matrices (Raven's SPM) and the Wide Range Achievements Test V.3 (WRAT3) at 14 years	Univariate analysis of breastfeeding vs IQ showed a significant difference between the breastfeeding groups (higher scores associated with longer breastfeeding up to 8.6 points difference)	Gender, maternal age, maternal ethnicity, maternal education, paternal education, family income, gravidity, maternal smoking, fetal distress, duration of the first and second stages of labour, mode of delivery, apgar scores at 1 and 5 min, birth weight for sex and gestational age (z score), height for age and sex (z score), BMI for age and sex (z score)	Significance remained with a mean difference in IQ of 6.8 between never and over 4 months of breastfeeding	A
Lucas *et al*[62]	A prospective, double-blind RCT (different formulas, breastfed control group not randomised)	447 healthy full-term children born in the UK between 1993 and 1995	Breastfed for at least 6 weeks vs formula fed	BSID-II at 18 months	No differences in overall developmental scores at 9 months or 18 months or in any subscale quotient at 9 months were found	Sex, centre, maternal age, maternal education, maternal marital status, and social class	No difference with adjustment for potential confounding factors	A
Maimaitiming and Wang[63]	Retrospective cohort	442 infants and children inhabited by Uygur, Han or Kazak nationality in West China	Breastfed vs mixed feeding	Denver Developmental Screening Test at age up to 3	There were no differences in scores between breastfeeding vs mixed feeding groups	None	No difference	C
Makrides *et al*[64]	A prospective, randomised, double-blind	68 formula-fed infants and 46 breastfed infants	Formula fed vs breastfed	Infant VEP acuity at 16 and 34 weeks Bayley's Scales of	At 1 year of age, MDI scores of breastfed and formula-fed infants were	Home screening questionnaire scores, occupational prestige,	MDI score was higher at age 2 in the breastfed	A

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
	controlled. Different formulas. Breastfed group was used as control, but not randomised	born at term of appropriate weight in Australia		Development at 1 and 2 years	not different, but at 2 years of age, MDI scores of breastfed infants were higher than those of formula fed infants. PDI scores were similar	parental education, gender, birth weight, maternal smoking, birth order, feeding mode	group. 95% CI 3 to 16.8	
Malloy and Berendes[65]	Retrospective cohort	518 children born in 1978–1979 in Washington DC who were exposed to chloride-deficient formulas	No breastfeeding (176) vs any time length of breastfeeding (342)	Weschler Intelligence Scale-Revised at 9 or 10 years of age	Breastfed scored significantly higher on full-scale IQ; Further analyses limited to those exclusively breastfed for the first 60 days failed to demonstrate any significant relationship	Maternal education, paternal education and annual income	Following adjustment, the difference was not significant	B
Martin *et al*[66]	Retrospective cohort	1431 children (twin siblings) from the greater Brisbane area	Exclusively formula fed, any breastfeeding between birth and 3 months, exclusively breastfed for 3–6 months, exclusively breastfed for 6 months or more	FSIQ (full-scale IQ) assessed using the Multidimensional Aptitude Battery (MAB) at 16 years of age	Breastfeeding was significantly associated with FSIQ scores. No effect of duration of breastfeeding on FSIQ was found	Socioeconomic status, paternal education, maternal education, gestational age and birth weight	The effect was no longer significant after adjustment	A
McCrory and Layte[67]	Retrospective cross-sectional study	8568 school children in Ireland born between 1997 and 1998	Breastfed vs not breastfed AND Never breastfed, ≤5 weeks, 6–15 weeks, 16–25 weeks, 26+ weeks	Age 9 years. Vocabulary component of the Drumcondra Primary Reading Test-Revised and part 1 of the Drumcondra Primary Mathematics Test-Revised	In unadjusted analysis, children who were breastfed scored 8.67 percentage points higher on reading and 7.42 percentage points higher on maths. Evidence of dose–response relationship was weak	Gender, birth weight, gestation period, NICU, primary and secondary carer's social class, primary carer's education level, household income, mother's age at birth, Irish/Non-Irish, number of children's books in the home	After adjustment, remained significant but weakened: 3.24 and 2.23 percentage points in reading and maths, respectively	A
Morales *et al*[68]	Retrospective cohort analysing polymorphisms in genes encoding enzymes involved in LC-PUFA synthesis	Two population-based birth cohorts n=400 mother-child pairs from INMA-Sabadell; and n=340 children from INMA-Menorca in Spain	Different types of formula fed vs breastfed	Mental development was assessed at age 14 months using the BSID, first Edition —MDI only, and at age 4 years by the Spanish version of the McCarthy Scales of Children's Abilities (MCSA)	Children with variants associated with lower synthesis of LC-PUFA had higher scores when breastfed, while those with greater capacity to synthesise these fatty acids had higher scores regardless of breastfeeding practices	Sex, child age, psychologist, quality of neuropsychological test, maternal education, breastfeeding, and use of gas stove at home	Not being breastfed conferred an 8-point to 9-point disadvantage in cognition among children with low FADS1 activity and a 5–8-point disadvantage in cognition among children with low ELOVL5 activity	A

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Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
Morris *et al*[69]	Prospective cohort	102 normal birth weight children born in Brazil at term	Number of breastfeeds per day (recorded daily)	BSID at 6 months and 12 months (MDI and PDI)	Breastfeeding frequency over the first 4 weeks of life, but not later, was significantly associated with mental development (MDI) at 6 months of age	Socioeconomic data: family income, a household resources index, a housing quality index, a water and sanitation index, and maternal and paternal literacy	An average of one extra breastfeed per day resulted in an increase of approximately one-quarter of a point. The effect was no longer apparent at 12 months of age	B
Morrow-Tlucak *et al*[70]	Prospective cohort	229 children born in Ohio between 1981 and 1982	No breastfeeding, breastfeeding=<4 months, breastfeeding >4 months	BSID—MDI at 6 months, 1 year and 2 years of age	Significant differences in MDI scores between the three groups (longer breastfeeding=higher scores) at 1 and 2 years of age (no significant difference at 6 months)	Parent education (mean of both parents), maternal attitude (Authoritarian Family Ideology), maternal intelligence (PPVT-R), cigarette use, maternal age, rage, marital status, Home Observation for Measurement of the Environment (HOME) at age 1, HOME at age 2, exact age at time of testing	With covariate control, a small but significant relationship between duration of breastfeeding and Bayley MDI at 1 and 2 years was detected. Infants breastfed for 4 months or more scored on average nine points higher compared with the bottle-fed infants	A
Mortensen *et al*[71]	Prospective longitudinal birth cohort	Mixed sample: 973 men and women All-male sample: 2280 men in Denmark	Divided into five groups: <1 month 2–3 months 4–6 months 7–9 months >9 months	Wechsler Adult Intelligence Scale (WAIS) at a mean age of 27.2 years in the mixed-sex sample. Børge Priens Prøve (BPP) test at a mean age of 18.7 years in the all-male sample	Duration of breastfeeding was associated with significantly higher scores on the Verbal, Performance, Full Scale WAIS IQs and BPP test	Parental social status Parental education Single mother status Mother's height, age and weight gain during pregnancy cigarette consumption during the third trimester number of pregnancies Gestational age birth weight Birth length Indexes of pregnancy Delivery complications	The results remained significant with 4.6 points higher IQ for those breast-fed over 9 months compared with those breastfed for less than 1 month	B
Mukerji *et al*[72]	Cross-sectional study	100 children aged 0–3 years in India	No breastfeeding or mixed. Exclusive breastfeeding for 4–9 months. Exclusive breastfeeding for more than 9 months	Developmental Screening Test (DST)	In the 4–9 months exclusive breastfed group, 100% had average or above average IQ.	None	No adjustments were made	C

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
					In the two other groups this number was significantly lower			
Nassar *et al*[73]	Cross-sectional study	42 healthy infants in Cairo, Egypt	Breastfed, artificially fed, mixed feeding	Bayley scale of infant development-second edition (BSID-II) between 4 and 6 months of age	No difference in MDI or PDI. There was significant difference only in the total behaviour rating scale (TBRS) and motor quality centile rank	No significant difference between groups in terms of age, sex, and socioeconomic standard (indirectly adjusted for with multiple regression)	Significant increase in mean adjusted TBRS and motor quality centile rank	B
Nelson *et al*[74]	Prospective cohort	Term gestation infants in USA	Breastfed or formula fed for 3 months	Teller Acuity Cards at 14 days, 3, 4, 8, and 18 months Fagan Test of Infant Intelligence at 8, 10 and 12 months BSID at 4, 8 and 18 months	There were no significant differences between breastfed and formula-fed infants in visual acuity at 14 days, 3, 8 or 18 months, or recognition memory or the Bayley PDI or MDI at any age		Meeting abstract only available	C
Niemela and Jarvenpaa [75]	Prospective follow-up	726 children born between 1985 and 1986 in Finland	Breastfed <5 months, breastfed >5 months (matched pairwise based on maternal education and sex)	Non-verbal Columbian Mental Maturity Scale (CMM), visual integration using the Beery test and active vocabulary by naming of pictures at 56 months	Children breastfed for 5 months or more attained higher scores in developmental tests (significance difference found in relation to the general cognitive capacity and visual motor integration). No evidence of any interaction between verbal development and breastfeeding to 5 months or more	Groups matched pairwise based on sex and maternal education	Maternal education and parental status correlated with all cognitive scores. Sex and breastfeeding correlated with scores of the general cognitive capacity and visual motor integration tests in multiple linear regressions	B
Oddy *et al*[76]	Prospective cohort	1401 children at first follow-up and 1283 children at second follow-up from the Western Australian Pregnancy Cohort Study following 2860 children in Perth, Australia	Never breastfed, fully breastfed 0–4 months, 4–6 months, more than 6 months	Peabody Picture Vocabulary Test-Revised (PPVT-R) for receptive English vocabulary —verbal intelligence at 6 years Performance subtest by the Wechsler Intelligence Scale for Children—Third Edition (WISC-III)—Block Design Test at age 8 years	On average, children breastfed for more than 6 months had mean verbal IQ scores that were 644 points higher and Block Design scores that were 1.13 points higher than children never breastfed (small but significant differences)	Gestational age, maternal age, maternal education, parental smoking and older siblings (all covariates that were significantly correlated with verbal IQ and the performance subtest or breastfeeding)	Breastfeeding for >6 months was associated with an increase in verbal IQ of 3.56 points. The Performance subtest was weakened and was no longer a significant	A

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Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
							difference after adjustment	
Oddy *et al*[77]	Prospective cohort	980 children from the Western Australian Pregnancy Cohort Study following 2860 children in Perth, Australia	Breastfed less than 4 vs more than 4 months and breastfed less than 6 vs more than 6 months	Western Australian Monitoring Standards in Education (WAMSE) scores in: maths, reading, writing and spelling at age 10 years	Continuous breastfeeding was significantly associated with an increase in scores with each additional month of breastfeeding for maths, reading, writing and spelling	Gender, maternal age, maternal education, family income, marital status, parent looks at book with child at age 5, maternal country of birth	Results were attenuated when adjusted for confounders. Significant interactions were found in maths and spelling, revealing that boys were more likely to have improved academic scores if breastfed for a longer period	A
Paine *et al*[78]	Retrospective cohort	96 healthy full-term Caucasian children from the Adelaide area in Australia	Duration of exclusive breastfeeding	Bayley Scales of Infant Development at age 10–14 months	Duration of exclusive breastfeeding significantly predicted mental development scores for boys, but not for girls. Duration of breast-feeding did not predict psychomotor development scores	Duration of breastfeeding, parents' occupational prestige, parents' education level and smoking habits, number of siblings, birth order, HSQ score, gestational age, birth weight, age of testing, maternal age and gender were considered as possible independent variables —independent variables with $p<0.02$ included in the model— gender, maternal age, birth weight and duration of breastfeeding	None	C
Pollock[79]	Prospective cohort	3838 children from the 1970 British Births Survey at full term and healthy birth weight	Wholly breastfed for more than 3 months vs wholly bottle-fed	Human figure drawing score, copying design score and English Picture Vocabulary Test score at age 5. Dichotomised outcomes: Pictorial Language Test, Friendly Maths test, Edinburgh Reading test, Spelling Test, British Ability Scales (Word definitions,	Significant difference found between groups at age 5 for the English Picture Vocabulary test. Significant difference found for dichotomised outcomes and continuous outcomes for the British Ability Scales and	Age father left full time education, age mother left full time education, highest educational qualifications of mother, mother's smoking behaviour during pregnancy, antenatal labour preparation	All results adjusted for all other independent predictors of breastfeeding: English Picture Vocabulary test: aOR 1.50. Dichotomised	A

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Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
				similarities, matrices, total) and Continuous outcomes: Pictorial Language test, Friendly Maths test, Edinburgh Reading test, Spelling test, and British Ability Scales (Word definitions, similarities, matrices, total) at age 10	dichotomised outcomes for the Pictorial Language test at age 10	class attendance, infant's place of birth	outcomes: Pictorial Language test aOR 1.49 Word definitions aOR 1.55 Similarities aOR 1.64 Total aOR 1.64 Continuous outcomes: Word definitions mean diff 3.5 Matrices mean diff 2.6 Similarities mean difference 3.0 Total mean difference 3.1	
Quinn *et al*[80]	Prospective cohort	3880 healthy children from the Mater Hospital-University of Queensland Study of Pregnancy project	Never breastfed, <3 weeks, 3–7 weeks, 7 weeks—4 months, 4–6 months, still breast feeding at 6 months	Peabody Picture Vocabulary Test Revised (PPVT-R) at 5 years of age	Significantly increasing scores were found between duration of breastfeeding and the PPVT-R scores	Birth weight, poverty, maternal education, maternal age, time in daycare/preschool, number of children in household at 5 years, English speaking background for mother and father, and degree of infant stimulation	After adjusting for a wide range of biological and social factors, the adjusted mean for those breastfed for 6 months or more was 8.2 points higher for females and 5.8 higher for males when compared with those never breastfed (this was significant)	A
Rao *et al*[81]	Prospective cohort	299 children born in Norway/Sweden at appropriate size for gestational age (comparison group)	<12 weeks vs >12 weeks of breastfeeding AND Duration of breastfeeding as a continuum	BSID at 13 months of age Norwegian version of the WPPSI-R at 5 years. of age Peabody Development Motor Scale measured at 5 years of age	There were statistically significant differences in IQ between the 2-breastfeeding groups	Site of enrolment, maternal education, maternal IQ, maternal smoking, admission to a neonatal intensive care unit, kindergarten attendance, gender and asymmetric intrauterine growth retardation	3.7 points for total IQ and 4.1 points for performance IQ. Results remained unaltered when adjusted for confounding variables	B
Ribas-Fito *et al*[82]	Prospective cohort	391 children born in Spain between 1997 and 1999	0–2 weeks breastfeeding 2–20 weeks breastfeeding 20 + weeks breastfeeding	Spanish version of the McCarthy Scales of Children's Abilities (general	Children with longer periods of breastfeeding performed significantly	Gender, academic trimester at examination,	After adjustment for confounders, significance	A

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Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
				cognitive scale, verbal scale, perceptual-performance scale, memory scale, quantitative scale, motor scale subsets) at 4 years of age	better on the McCarthy cognitive scale (except motor)	psychologist, maternal social class, maternal education, and maternal use of alcohol and tobacco during pregnancy	remained for the general cognitive scale, and a trend remained in other subsets	
Richards *et al*[83]	Retrospective cohort	1741 people from the MRC National Survey of Health and Development (NSHD), also known as the British 1946 birth cohort	Never Up to 2 months 2–7 months 7+ months	National Adult Reading Test (NART), word-list learning task (verbal memory) and timed letter search task (mental speed and concentration) at age 53	Educational Attainment: odds of obtaining higher qualifications by the age of 26 were statistically significant, with greater odds for longer breastfeeding Cognitive Function: regression coefficients for the unadjusted effect show that breastfeeding was significantly associated with the NART and verbal memory tests	Early background variables: Sex, father's social class, mother's education, birth order, parental interest in education and material home conditions	Effect of BF on education was strengthened after adjusting for the early background variables and remained significant. No longer significant with further adjustment for cognitive ability at age 15 Cognitive function: Coefficients were reduced after adjusting for the early background variables and were further reduced after adjusting for educational attainment and adult social class Only NART remained significance	A
Richards *et al*[84]	Retrospective cohort	511 first-born offspring of the British 1946 cohort and their parent	Duration of breastfeeding	Sentence completion test, reading test and vocabulary test at age 8 years	Breastfeeding was positively associated with cognitive function at age 8 in the first offspring of a national birth cohort. This association was not evident in the subsample of mothers of these offspring. Association in the	Social class, parental educational attainment, material home conditions, maternal age at birth, birth order, family size, maternal cigarette smoking, parental interest in education, attendance at nursery school, whether offspring	Non-significant; after adjusting for social class, maternal education or maternal cognitive performance	C

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Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
					offspring cohort became non-significant after adjusting for social class, maternal education or maternal cognitive performance	cohort members had been taught cognitive skills at age 4, and cognitive test scores of the mothers		
Rodgers[85]	Longitudinal study	1464 children at age 8 and 1398 children at age 15 from the British 1946 cohort	Never bottle-fed vs never breastfed	Picture intelligence test and word reading test at 8 years of age Non-verbal ability, mathematics and sentence completion tests at age 15 years of age	A preliminary analysis indicated that low scores were more likely for those who had been bottle-fed than breastfed. The mean sentence completion scores between the two groups are statistically significant. Every test at both ages was significant except for word reading scores after correction for background factors	Sex, social group, parental interest in education, material home conditions, sample stratification, father's education, mother's education, family size, birth rank, age at weaning	After correction for confounders, every test at both ages was significant except for word reading scores	B
Rogan and Gladen[86]	Prospective cohort	855 newborns being followed in North Carolina were enrolled between 1978 and 1982 and followed up to 5 years old	Bottle-fed 'short breastfeeding' 'medium breastfeeding' 'long breastfeeding' 'very long breastfeeding'	Bayley Mental and PDI at 6, 12, 18 and 24 months of age. McCarthy General Cognitive, Verbal, Quantitative, Memory, Perceptual Performance and Motor scales at 36, 48, and 60 months of age Report Card Grades from 3rd, 4th and 5th grade (averaged)	Bayley Mental and Psychomotor: After adjusting for covariables, the results at all four time points were similar and differences among the groups were only statistically significance at 24 months McCarthy: All scales showed trends towards higher scores with increasing length of breastfeeding, but the relationship was weakest for the motor scale. Differences after adjustment were only significant at 3 and 4 years (marginally at 5 years) between length of breastfeeding groups Report Cards: Showed slight increase with breastfeeding.	Age, race, occupation, education, smoking, drinking, child's sex, birth weight, number of older siblings, prenatal PCB exposure and dichlorodiphenyl dichloroethene exposure, identity of the examiner	Confounders integrated into model; unadjusted results not shown	B

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Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
					Marginally significant after adjustment for English scores and not significant for maths			
Santiago Burruchaga *et al*[87]	Prospective cohort	39 children born at term and from homogeneous sociocultural status in Spain	Breastfed for at least 2 months vs formula fed	Bayley's scale at 2 years of age	No statistically significant differences between groups were found in cognitive function	Maternal age, level of education, occupation, number of children in the family, smoking	None; confounders integrated into model	C
Silva *et al*[88]	Longitudinal population-based cohort	9367 children from the 1970 British Cohort Study comprising individuals born during April 5–11 in the UK	Never breastfed Less than 1 month 1–3 months More than 3 months	British Ability Scale, the Shortened Edinburgh Reading Test (word recognition), the Friendly Math Tests, and the Pictorial Language Comprehension Test at the age of 10 years	Breastfeeding showed a positive association with cognition at 10 years before adjustment	Socioeconomic class, birth weight, parity, gestational age, maternal age and maternal smoking	Breastfeeding was weakly associated with cognitive function after adjustment (standardised coefficient 0.07). However, this effect was much smaller in the structural equation model adjusting for the same variables and did not reach significance level, suggesting that it is of little clinical importance	A
Silva *et al*[89]	Retrospective cohort	1037 children from the Dunedin Multidisciplinary Child Development Study	<1 week 1–4 weeks 5–12 weeks 13–24 weeks 25–36 weeks 37–51 weeks 51+ weeks	Gross motor co-ordination, fine motor co-ordination, verbal comprehension and verbal expression, intelligence, child behaviour problems at age 3 years	Comparison of the groups resulted in only one significant difference among 96 comparisons made. No significant differences in age of attainment of milestones, gross or fine motor ability scores, verbal comprehension or expression, ability, intelligence, the incidence of separation problems, hyperactivity, height, weight and head circumference	Socioeconomic class, general mental ability (IQ), level of education Pairwise comparison with group matching to account for confounders	None; pairwise matching said to account for confounders	B
Sloan *et al*[90]	Cross-sectional observational.	137 infants and mothers in Ireland	Breastfed (defined as more than 1 month) vs not		Mean cognitive scores were significantly higher		The adjusted standardised β for	C

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
	Breastfeeding data were obtained retrospectively		breastfed (defined as less than a month or not at all)	BSID (second edition; Bayley, 1993), between 10 and 18 months of age	in breast-fed infants (110) compared with formula-fed infants (105). Breastfeeding duration had a positive linear association with cognitive scores at 1 year	Home environment (HOME score) and infant gender	breastfeeding was 0.285, which remained significant after adjustment	
Slykerman *et al*[91]	Cross-sectional observational. Breastfeeding data were obtained retrospectively	550 infants, 50% of which were SGA at birth and 50% AGA in New Zealand	Not at all, less than 6 months, 6–12 months, >12 months	Stanford Binet Intelligence Scale, 4th Edition at age 3.5–4 years	Breastfeeding was not significantly related to intelligence scores in the AGA group	Examiner administering the intelligence test, gestation, gender, maternal education, marital status, parental occupation, maternal age, parity and smoking	No difference in IQ	B
Steer *et al*[92]	Prospective observational. Breastfeeding data were obtained prospectively	9656 children from the Avon Longitudinal Study of Parents and Children cohort, in the UK	Breastfeeding within the first month of life vs never breastfeeding	Wechsler Intelligence Scale for Children, 8 years old	Breastfeeding showed a strong association with full-scale IQ with breastfed children scoring 8 points higher IQ on average in unadjusted analyses	Maternal education, paternal social class, low birthweight, preterm gestation, home environment, parenting and gender	The breastfeeding effect attenuated to a 3-point advantage after adjustment	B
Taylor and Wadsworth[93]	Longitudinal population-based cohort. Breastfeeding data were obtained retrospectively	13 135 children from The Child Health and Education Study in the UK	Never breastfed Less than 1 month 1–3 months More than 3 months	English picture vocabulary test (EPVT) adapted from the American Peabody Picture Vocabulary Test, at 5 years of age	Children breast-fed for three or more months scoring over one-quarter of the SD above the norm	The age of the child at testing; the child's sex and birth weight; whether there were older or younger siblings in the home when the study child was five years old; home furnishings and equipment; maternal age at the child's birth; maternal smoking and the social index	Breastfeeding remained a significant influence on EPVT scores, but the difference between the groups was small: +0.12 in the standardised EPVT score	A
Temboury *et al*[94]	Prospective cohort	229 infants in Spain	Breastfed—at least 3 months Bottle-fed—none or less than 1 month	Bayley's scale at age 18–29 months	Bottle-fed infants had lower IMD scores (index of mental development)	Maternal age, education and social class, job, psychosocial risk, number of children, infants' shyness, tantrum, hyperactivity, gender, birth weight, height, place of birth	The result remained significant	C
Thorsdottir *et al*[95]	Longitudinal cohort	85 children in Iceland	Duration of exclusive breastfeeding	The Icelandic developmental inventory at age 6 years.	Duration of exclusive breastfeeding, in	Maternal and paternal education and family	Total developmental	C

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
				Information collected from the mothers	months, was positively related to children's total developmental index	income, birth weight, maternal BMI	index (B=1.07 ±0.5, p=0.04)	
Tozzi *et al*[96]	Prospective cohort	1403 children originally included in an Italian clinical trial on acellular Pertussis vaccines	Duration of exclusive breastfeeding both as a continuous variable and as a categorical variable (<6 months, >6 months)	An estimated IQ was obtained from scores of the vocabulary, similarities, block design and coding tests at 10–12 years of age An estimation of IQ was obtained from the scores of the four WISC-R subtests	Scores of only a few neuropsychological tests were affected by exclusive breastfeeding duration: Mean scores on vocabulary, similarities, the Boston naming test and estimated IQ improved with the duration of breastfeeding, whereas performance in one of the subtests for writing praxis decreased with breastfeeding duration	Sex, birth weight, gestational age, mother's age at birth, type of delivery, family composition, parents' education, presence of chronic diseases, current prescription of antihistamines or antiepileptic drugs, and the amount of thimerosal to which the children were exposed through vaccines	In the regression analysis, the score on one subcategory of the California verbal learning test was negatively associated with breastfeeding for longer than 6 months No difference was detected in any of the other test scores included in the analysis	A
Veena *et al*[97]	Longitudinal cohort	514 children from the Mysore Parthenon birth cohort in south India	Six categories from <3 to ≥18 months	Kaufman Assessment Battery at 9-year-old to 10-year-old children	Within this cohort, in which prolonged breastfeeding was the norm (90% breastfed ≥6 months), there were no associations between longer duration of breastfeeding and cognitive function	Age, sex, gestation, birth size, maternal age, parity, socioeconomic status, parents' attained schooling and rural/urban residence	No difference either unadjusted or after adjustment	B
Whitehouse *et al*[98]	Longitudinal cohort, breastfeeding data collected prospectively	1195 live born children recruited at approximately 18 weeks' gestation, Western Australian Pregnancy Cohort (Raine) Study	(1) Never breastfed, (2) Breastfed predominantly for <4 months, (3) Breastfed predominantly for 4–6 months (4) Breastfed predominantly for >6 months	Peabody Picture Vocabulary Test—Revised (PPVT-R) at age 10 years. Raw scores are transformed to standard scores, based around a mean of 100 and an SD of 15	Strong positive association between the duration of predominant breastfeeding and PPVT-R at age 10 years	Maternal age at conception, maternal education, family income and the presence of the biological father in the family home, maternal smoking and alcohol consumption during pregnancy, maternal experience of stressful events during pregnancy, parity, gestational age, child's sex and proportion of optimal birth weight, a measure of the	Children who were predominantly breastfed for >6 months had a mean PPVT-R score that was 4.04 points higher than that of children who were never breastfed	A

Continued

Table 1 Continued

Author and reference	Study design	Target population	Breast milk exposure	Cognitive development assessment tool and participant age	Results	Confounders adjusted for	Difference in IQ after adjustment	Study quality grading
						appropriateness of fetal growth, family functioning (MMFAD), Parenting Scale, language-learning environment		
Wigg *et al*[99]	Longitudinal cohort, breastfeeding data collected prospectively	375 children born in Port Pirie, South Australia	At 6 month of age: breastfed vs bottle-fed Children who were breastfed for less than 6 months would have been classified in our analysis as bottle-fed	BSID at age 2, the McCarthy Scales of Children's Abilities age 4 and Wechsler Intelligence Scale for Children at age 7, 11, 13	Estimated unadjusted advantages for the breastfed children at ages 2, 4 and 7 years were 5.5 points, 4.6 points and 4.3 points in the MDI, GCI and IQ scores, respectively At age 11–13 years, the unadjusted advantage for the breastfed children was 3.8 points in IQ	Gender, maternal age at delivery, socioeconomic status, HOME score, maternal IQ, parental smoking habits, birth weight, birth rank, lifetime average blood lead concentration and whether parents were living together	Adjusting for the covariates diminished the association of the feeding method in infancy with cognitive development. The covariates contributing most to this attenuating effect were the HOME scores, maternal IQ, socioeconomic status and parental smoking habits	B
Zaini *et al*[100]	Retrospective cohort	1397 children from Selangor Malaysia	<6 months >6 months	Raven's Colored Progressive Matrices at a mean age 9.6 years	Those who were breastfed less than 6 months performed better (31.01 vs 30.63 of max 36)	None	None	C
Zhou *et al*[101]	Prospective cohort	302 children born between 1998 and 1999 in Adelaide, Australia	Not breastfed, breastfed at hospital discharge, less than 6 months, more than 6 months	Stanford-Binet Intelligence Scale at 4 years of age	There was no association between duration of breastfeeding and childhood IQ in this relatively well-nourished cohort from an industrialised society. Before adjustment, children who were breastfed for at least 6 months had a higher IQ than those who were breastfed for less than 6 months	Birth order and sex of the child, maternal smoking in pregnancy, parental education, parental occupation and quality of home environment	There was no association between breastfeeding and childhood IQ	B

BF, breastfeeding; BMI, body mass index; LC-PUFA, long-chain polyunsaturated fatty acids; RCT, randomised controlled trial.

Table 2 Studies by directionality and quality

Direction of findings	Number of studies	Quality grading (%)
No association between IQ and BF	21*	A—4 (19) B—9 (43) C—8 (38)
Positive association between IQ and BF	28†	A—10 (36) B—7 (25) C—11 (39)
Initial positive association which became negative after adjustment for confounders	18‡	A—6 (33.3) B—8 (44.4) C—4 (22.3)
Initial positive association weakened after adjustment for confounders but remained statistically significant	17§	A—14 (82) B—2 (12) C—1 (6)

*References: 24 25 30–32 35 36 39 54 56 62 63 73 74 86 87 89 91 97 100 101
†References: 9 15 21 27–29 37 38 42 48 51 57 59 61 64 68 71 72 75 79 82 85 90 94 95 98
‡References: 13 23 26 33 43–46 49 50 52 55 65 66 69 78 84 96
§References: 22 34 40 41 47 53 58 60 67 70 76 77 83 88 92 93 99
BF, breastfeeding.

Table 3 divides the included studies according to their settings: developed versus developing world. The majority of included studies were set in the developed world (71/84, 85.5% vs 13/84, 15.5% in the developing world). The quality of the studies set in developing countries were generally poorer, given our criteria: 46% graded A+B (6/13) in studies set in developing countries, compared with 76% (54/71) in studies set in developed countries. Developing country studies were also more likely to reach a null association or null association after adjustment for confounding compared with developed country studies (8/13, 61% vs 31/84, 37%, respectively).

A large variety of cognitive assessment tools were used and study outcomes were measured anywhere from 8 days of age into adulthood. Table 4 divides the included

Table 3 Studies by setting, directionality and quality grading

Setting	Direction of findings	Number of studies (%)	Quality grading (%)
Developing countries (n=13)	No association between IQ and BF	6 (46)	A—0 (0) B—2 (33.3) C—4 (66.6)
	Positive association between IQ and BF	4 (30)	A—1 (25) B—0 (0) C—3 (75)
	Initial positive association which became negative after adjustment for confounders.	2 (15)	A—0 (0) B—2 (100) C—0 (0)
	Initial positive association weakened after adjustment for confounders but remained statistically significant	1 (8)	A—1 (100) B—0 (0) C—0 (0)
Developed countries (n=71)	No association between IQ and BF	15 (21)	A—4 (26.6) B—7 (46.6) C—4 (26.6)
	Positive association between IQ and BF	24 (34)	A—9 (37.5) B—7 (29.2) C—8 (33.3)
	Initial positive association which became negative after adjustment for confounders.	16 (22.5)	A—6 (37.5) B—6 (37.5) C—4 (25)
	Initial positive association weakened after adjustment for confounders but remained statistically significant	16 (22.5)	A—13 (81.25) B—2 (12.5) C—1 (6.25)

Developing: Refs. 15 21 33–36 38 63 69 72 73 97 100
Developed: Refs. 9 13 22–32 37 39–62 64–71 74–96 98 99 101
BF, breastfeeding.

Table 4 Studies by age group, directionality and quality grading

Age group	Direction of findings	Number of studies (%)	Quality grading (%)
Infancy ≤1 year of age n=18	No association between IQ and BF	9 (50)	A—3 (33.3) B—3 (33.3) C—3 (33.3)
	Positive association between IQ and BF	5 (28)	A—0 (0) B—1 (20) C—4 (80)
	Initial positive association which became negative after adjustment for confounders.	2 (11)	A—0 (0) B—1 (50) C—1 (50)
	Initial positive association weakened after adjustment for confounders but remained statistically significant	2 (11)	A—1 (50) B—0 (0) C—1 (50)
Childhood 1–18 years of age n=70	No association between IQ and BF	14 (20)	A—3 (21) B—5 (36) C—6 (43)
	Positive association between IQ and BF	26 (37)	A—10 (38.5) B—6 (23) C—10 (38.5)
	Initial positive association which became negative after adjustment for confounders.	16 (23)	A—6 (37.5) B—6 (37.5) C—4 (25)
	Initial positive association weakened after adjustment for confounders but remained statistically significant	14 (20)	A—12 (86) B—2 (14) C—0 (0)
Adulthood ≥18 years of age n=5	No association between IQ and BF	2 (40)	A—0 (0) B—1 (50) C—1 (50)
	Positive association between IQ and BF	1 (20)	A—0 (0) B—1 (100) C—0 (0)
	Initial positive association which became negative after adjustment for confounders.	1 (20)	A—0 (0) B—1 (100) C—0 (0)
	Initial positive association weakened after adjustment for confounders but remained statistically significant	1 (20)	A—1 (100) B—0 (0) C—0 (0)

Infancy: Refs. [22 24 35–37* 38 51 54 60 64* 69 70* 72* 73 74* 78* 86* 90*]
Childhood: Refs. [9 13 15 21 23 25–34 37* 40–43* 45–50 52 53 55–59 61–64* 65–68 70* 72* 74* 75–78* 79–82 84–86* 87–90* 91–101]
Adulthood: Refs. [39 43* 44 71 83]
*Study examined two different age groups and therefore included in several categories.
BF, breastfeeding.

studies according to age groups of participants: infancy, childhood and adulthood, with the corresponding direction of results and study quality. The majority of included studies measured intelligence during the childhood period (age 1–18 years: 70/93 studies, 75%). Studies performed during childhood and reaching an initial positive association, weakened after adjustment, were generally of higher quality than other studies (12/14 quality grade A, 86%, table 4). Studies performed during infancy or adulthood were more likely to find a null association (before or after adjustment) compared with studies performed during childhood (Infancy group—61%, adulthood—60%, childhood 43%, table 4).

The significant heterogeneity in study design and rigour precluded the conduct of a formal meta-analysis.

DISCUSSION

The continuing debate of whether breastfeeding imparts direct advantage on child cognition, or whether this is merely an association with favourable familial socioeconomic status and cognition, is not purely theoretical. From a public health perspective, if breastfeeding has biological effects on a child's IQ, this will be one of the very few cost-effective means to significantly improve a child's neurodevelopment. If, on the other hand, there is no such effect, in the case where breastfeeding is either impossible or not sought by the mother, this will allow these women to rest assured that their choice will not have long-term developmental consequences.

In the case of other comparable therapeutic dilemmas, conflicts are typically resolved through RCTs, which

are not ethically feasible in this case, given that breastfeeding has other protective effects and the highly personal nature of the decision to breastfeed.

The closest comparison to a formal RCT in reducing selection bias would be sibling-pair analysis, when cognition of breastfed infants is compared with that of their siblings who were formula fed. This design ensures similar socioeconomic and maternal characteristics. Unfortunately, the few studies that have followed this design reached conflicting results.[13 40]

The second closest design to RCT was employed in the PROBIT study by Kramer *et al*,[14 15] who cluster randomised women in Eastern Europe to receive or not receive formal education about the advantages of breastfeeding. This study did show favourable effects, but it has been argued that the mothers randomised for the breastfeeding promotion arm might have been influenced not only in providing higher rates of breastfeeding, but also by improving other positive health behaviours.

Our analysis reveals that there are over 80 studies addressing this issue and that their results divide almost evenly between positive and negative associations. The quality of 'positive' or 'negative' studies did not differ, except for higher quality on average in studies that showed an apparent decrease in effect after multivariate analysis.

We have shown that studies where the initial positive effect of breastfeeding on IQ disappeared or substantially diminished after multivariate analysis controlled for significantly more confounders than studies showing no such change. When compared with a meta-analysis conducted 14 years ago,[17] it appears that many more new studies did attempt to control for confounding measures of socioeconomic status and parental education, among others.

Given that more tight control of confounders resulted in greater likelihood of disappearance of breastfeeding effect, it can be argued that the remaining positive effect reflects residual uncontrolled bias, as shown by Der *et al*[13] in their large study. In that study, before adjustment, breastfeeding was associated with an increase of around 4 points in mental ability. Post hoc analysis revealed that adjustment for maternal intelligence accounted for most of this effect—where full adjustment for a range of relevant confounders yielded a small (0.52) and non-significant effect size (95% CI −0.19 to 1.23).

In our systematic review, a similar effect was recorded by a total of 18 studies, and in addition 17 studies showed substantially diminished effect after adjustment.

When we examined studies based on setting (table 3), we found that the majority of the 84 included studies were set in the developed world (85%). Studies completed in middle-income and low-income countries were nearly twice as likely to find a null association (before or after adjustment) compared with studies set in developed countries (61% vs 43.5%, respectively).

This may be due to the fact that in many low-income and middle-income countries high rates of some degree of breastfeeding exist[102] and comparisons between breastfed and non-breastfed populations may examine more homogeneous study groups (ie, parental socioeconomic status, income and parental IQ).[34] In contrast, studies originating in the developed world exhibit a greater heterogeneity between breastfed and non-breastfed populations[13] as the choice to breastfeed is associated with a family's socioeconomic status, maternal education, maternal intelligence and social advantage.[13 17–19] If a biological effect truly exists between breastfeeding and infant IQ, one would expect this relationship to exist in multiple settings, including the developing world. The fact that this relationship is less apparent in developing countries suggests that much of the observed relationship may be due to parental social advantage, confounding the choice to breastfeed.

This systematic review includes studies using a large variety of cognitive assessment tools and age span. The majority of included studies measured intelligence during the childhood period (age 1–18 years, 75%). Studies performed during infancy or adulthood were more likely to find a null association (before or after adjustment), although the number of included studies is small. Possible explanations for this finding include reduced accuracy of IQ evaluation in infancy (<1 year) on the one hand, and a variety of additional factors influencing IQ at an older age (>18 years), on the other.

Another factor that needs to be seriously considered in our review is the existence of bias against the null hypothesis. The likelihood of studies not detecting a significant effect in pregnancy to be submitted and published in the peer review literature is substantially lower than that of positive studies.[103 104] This can create a distorted balance that may seriously affect the conclusions on effects of interventions.

In conclusion, this systematic review suggests that much of the reported effect of breastfeeding on child cognitive abilities is due to the maternal cognitive and socioeconomic effects. When considered together with the fact that a recent systematic review failed to corroborate a biological effect of milk PUFA on brain development, it is quite likely that breastfeeding does not, by itself, directly affect child IQ.

Although it is unlikely that additional studies will change substantially the current synthesis, future studies in this field should attempt to rigorously control for all important confounders even if they are difficult to obtain (eg, parental IQ). Alternatively, study designs using sibling cohorts discordant for breastfeeding may yield more robust conclusions to further clarify this dilemma.

Contributors AW has participated in all phases of this study including literature search, data collection and review, quality grading, interpretation of the results, and has written a part of the manuscript and the revised manuscript. CS has participated in all phases of this study including literature search, data collection and review, quality grading, and revision of the

manuscript. AC has participated in the literature search, data collection and review, translation of foreign language manuscripts, and has taken a significant part in the manuscript preparation and revision. GK participated in all phases of this study. He initiated the study and supervised actively throughout its conduct. Specifically, he was involved in data interpretation and statistical analysis, and has written and revised a substantial part of the manuscript.

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