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 studies 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’s9 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)\textsuperscript{10} which are present in human milk, but not in cow’s milk or most infant formulas.\textsuperscript{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.\textsuperscript{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.\textsuperscript{13} Parents who score high on a range of cognitive abilities have children with above average IQ scores.\textsuperscript{13} In parallel, advantage in mother’s IQ more than doubles the odds of breastfeeding.\textsuperscript{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\textsuperscript{14} \textsuperscript{15} or in preterm infants.\textsuperscript{16} In the breastfeeding promotion intervention trial (PROBITE Trial) by Kramer \textit{et al}\textsuperscript{9} 3, IQ scores and academic performance tests were more favourable in the intervention group; however, statistically significant differences were only shown for some of the sub-scores.

Systematic reviews examining the impact of breastfeeding on cognitive abilities have reached conflicting results.\textsuperscript{13} 17–19 The meta-analysis by Jain \textit{et al}\textsuperscript{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.\textsuperscript{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 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. 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.

Statistical analysis
Comparison of studies based on their results or quality was performed by $\chi^2$ 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). The overall agreement between reviewers on the inclusion of studies was 100%.

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 studies showing a decrease in the effect after multivariate analysis controlled for significant confounders (table 2). 18 initially positive studies that became negative after accounting for confounders, and 17 studies where the initial positive effect was diminished but remained statistically significant after accounting for confounders (table 2).

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.
| 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 Singh21 | 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 200123 | 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 (WPSSI-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 al24 | 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 study groups | A |
| Auestad et al25 | 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
| 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<sup>26</sup> | 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<sup>27</sup> | 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 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 | Socioeconomic status, gender and pesticide exposure | Remained significant, numbers not provided | C |
| Birch et al<sup>28</sup> | 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 | None | No adjustment carried out | B |
| Bon<sup>29</sup> | 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<sup>30</sup> | 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<sup>31</sup> | 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 |
| 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<sup>2</sup> | 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. | 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) | Children not carrying the C allele did not benefit from breastfeeding | A |
| Clark et al<sup>3</sup> | Prospective cohort | 784 Chilean children | <2 months | 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. | 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) | Children not carrying the C allele did not benefit from breastfeeding | B |
| Daniels and Adair<sup>38</sup> | 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 | 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 | 1.6 points among normal birth weight breastfed for 12–18 months vs less than 6 months | A |
| De Andraca et al<sup>35</sup> | 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 |
| 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[6]  | 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[7]          | 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 |
| Girolamo et al[77]   | 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[68]   | 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[29]     | 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 | 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 Persistent positive correlation between breastfeeding and cognitive ability | Adjusted for family income, maternal 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 9–12 months | Add Health’s abbreviated version of the Peabody Picture Vocabulary Test | 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 |
|----------------------|--------------|-------------------|----------------------|----------------------------------------------------------|---------|-------------------------|-----------------------------------|-------------------|
| **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 Birth weight, childhood illness, home conditions, parents’ age and education, child’s behavioural scores, parents interest in the child’s development, school type | After adjustment, the difference in the Bayley mental development index between the groups was between 3.7 and 5.7 units Mean score 1.5 points higher for ages 8, 11, 15. Not significant at older ages | 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 | Partner’s IQ and education, maternal IQ and education, social class, on benefits, age at birth, birth weight | After adjustment, no association was found between adult intelligence and method of infant feeding After adjustment, the differences in IQ between groups became non-significant | B |
| **Gale and Martin**[^44] | Prospective cohort | 994 men and women, born between 1920 and 1930 in Hertfordshire, UK | Exclusive breastfeeding, exclusive bottle feeding, mixed feeding | Age 8—WPPSI (3rd edn.), sentence repetition and verbal fluency measured by NEPSY | 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 |
| 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\(^a^6\)   | 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 \(^a^7\) | 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\(^a^8\) | 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\(^a^9\) | 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 >1 | C                   |

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| 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 |
|----------------------|--------------|-------------------|----------------------|----------------------------------------------------------|---------|------------------------|---------------------------------|------------------------|
| Gurka et al abstract\(^{20}\) | 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 | 2 weeks, compared with less No difference between the groups | A |
| Hart et al\(^{1}\) | Prospective cohort | 83 healthy full-term infants in Texas, USA | Exclusively breastfed v 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\(^{22}\) | 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 |
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 |
|----------------------|--------------|--------------------|----------------------|----------------------------------------------------------|---------|--------------------------|----------------------------------|----------------------|
| Horwood and Fergusson53 | 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 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 | 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) 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 | | C |
| Innis et al64 | 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) | 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 | There were no differences in visual acuity or novelty preference among the infants when they were stratified by incidence or duration of breastfeeding At the ages of 4 and 11, breastfeeding was significantly related to higher IQ scores | None | No difference | B |
| Jacobson et al55 | 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 | Breastfed vs not breastfed | Wechsler Intelligence Scale for Children—age 8 and 9 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 | 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 | Social class, education, maternal IQ, parenting skills (Home observation for measurement of the environment (HOME)) | | B |
| James56 | 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
| 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 |
|----------------------|--------------|-------------------|----------------------|----------------------------------------------------------|------------------|--------------------------|----------------------------------|------------------------|
| Jedrychowski et al.  | Longitudinal study | Pembrokeshire farming family, UK) 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. | 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. | 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 | Breasftfeeding was associated with a 4.6-point higher mean in the children's Intelligence | A |
| Keim et al. abstract | 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<sup>15</sup> | Cluster-randomised trial. | 13,889 Belarusian 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<sup>11</sup> | 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<sup>2</sup> | 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, marital status, and social class | No difference with adjustment for potential confounding factors | A |
| Maimaitiming and Wang<sup>22</sup> | 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<sup>24</sup> | 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 higher at age 2 in the breastfed | Home screening questionnaire scores, occupational prestige, MDI score was higher at age 2 in the breastfed | A |

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| 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 |
|----------------------|--------------|------------------|----------------------|----------------------------------------------------------|---------|--------------------------|----------------------------------|----------------------|
| Malloy and Berendes<sup>66</sup> | 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 | Following adjustment, the difference was not significant | | B |
| Martin et al<sup>67</sup> | 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, or exclusivity 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, gestational age and birth weight | The effect was no longer significant after adjustment | A |
| McCrory and Layte<sup>67</sup> | 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 higher in reading and 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<sup>68</sup> | 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 | 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 |

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<sup>69</sup> | 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<sup>70</sup> | 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<sup>71</sup> | 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 Friens 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 pregnanacies 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<sup>72</sup> | 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 |

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Table 1 Continued

| Author and reference | Study design | Target population | Breast milk exposure | Breast milk assessment tool and participant age | Results | Confounders adjusted for | Difference in IQ after adjustment | Study quality grading |
|----------------------|--------------|-------------------|----------------------|---------------------------------------------|----------|--------------------------|-----------------------------------|----------------------|
| Nassar et al<sup>23</sup> | 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 | In the two other groups this number was significantly lower | 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<sup>24</sup> | 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<sup>25</sup> | Prospective follow-up | 726 children born between 1985 and 1996 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 | | B |
| Oddy et al<sup>26</sup> | 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 Weschler 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 effect | A |

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| 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 |
|----------------------|--------------|--------------------|----------------------|----------------------------------------------------------|---------|-------------------------|----------------------------------|----------------------|
| Oddy et al⁷⁷          | 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 al³⁸        | 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 |
| Pollock⁷⁹            | 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 |
| 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 |
|----------------------|--------------|-------------------|----------------------|----------------------------------------------------------|---------|-------------------------|--------------------------------|------------------------|
| Quinn *et al* | 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 | | A |
| Rao *et al* | 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 Gender, academic trimester at examination, | 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* | 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 better | After adjustment for confounders, significance | | A |

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| 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 |
|----------------------|--------------|-------------------|----------------------|---------------------------------------------------------|---------|-------------------------|-----------------------------------|---------------------|
| Richards et al\textsuperscript{a}\textsuperscript{b} | Retrospective cohort | 1741 people from the MRC National Survey of Health and Development (NSHD), also known as the British 1946 birth cohort | Never | 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 | A |
| Richards et al\textsuperscript{a}\textsuperscript{c} | 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 |

\textsuperscript{a}Richards et al. BMJ Open 2013;3:e003259. doi:10.1136/bmjopen-2013-003259

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| 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 |
|----------------------|--------------|--------------------|----------------------|----------------------------------------------------------|---------|------------------------|-------------------------------|---------------------|
| Rodgers**65**        | 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 | Offspring cohort became non-significant after adjusting for social class, maternal education or maternal cognitive performance. 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. Cohort members had been taught cognitive skills at age 4, and cognitive test scores of the mothers. | 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. |
| Rogan and Gladen**66** | 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 significant 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 |

**Note:** The table continues with additional studies and data.
| 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 |
|----------------------|--------------|--------------------|----------------------|----------------------------------------------------------|---------------------------------|--------------------------------|---------------------------------|---------------------|
| Santiago Burruchaga et al<sup>87</sup> | 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 | Marginally significant after adjustment for English scores and not significant for maths scores | Maternal age, level of education, occupation, number of children in the family, smoking | None; confounders integrated into model | C |
| Silva et al<sup>88</sup> | Longitudinal population-based cohort | 9367 children from the 1970 British Cohort Study comprising individuals born during April 5–11 in the UK | Never breastfed | 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<sup>89</sup> | Retrospective cohort | 1037 children from the Dunedin Multidisciplinary Child Development Study | 0–1 week | 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, socioeconomic class, general mental ability (IQ), level of education | None; pairwise matching said to account for confounders | B |
| Sloan et al<sup>90</sup> | 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 | 

<sup>87</sup> Santiago Burruchaga et al. 87. *BMJ Open* 2013;3:e003259. doi:10.1136/bmjopen-2013-003259

<sup>88</sup> Silva et al. *BMJ Open* 2013;3:e003259. doi:10.1136/bmjopen-2013-003259

<sup>89</sup> Silva et al. *BMJ Open* 2013;3:e003259. doi:10.1136/bmjopen-2013-003259

<sup>90</sup> Sloan et al. *BMJ Open* 2013;3:e003259. doi:10.1136/bmjopen-2013-003259
| 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 |
|----------------------|--------------|-------------------|----------------------|----------------------------------------------------------|---------|------------------------|-----------------------------------|---------------------|
| Slykerman et al<sup>31</sup> | 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<sup>62</sup> | 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<sup>33</sup> | 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<sup>44</sup> | 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<sup>95</sup> | 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 | Continued | C |
| 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 |
|----------------------|--------------|-------------------|----------------------|----------------------------------------------------------|---------|--------------------------|-------------------------------|----------------------|
| Tozzi et al<sup>96</sup> | 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) | Information collected from the mothers | 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<sup>97</sup> | 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<sup>98</sup> | 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 |

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| 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 |
|----------------------|-------------|-------------------|----------------------|---------------------------------------------------------|---------|-------------------------|-----------------------------------|---------------------|
| Wigg et al.          | 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 | Appropriateness of fetal growth, family functioning (MMFAD), Parenting Scale, language-learning environment | 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.         | 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.          | 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 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 studies by directionality and quality grading.

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 34 39 54 56 62 63 70 73 74 77 84 86 87 89 91 97 100 101 103
†References: 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 33–46 49 50 52 55 66 69 78 84 96
§References: 22 24 40 41 47 53 58 60 67 70 76 77 83 88 92 93 99

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 27–36 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.

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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 socio-economic 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

| 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)          |
|                            | Positive association between IQ and BF                                                 | 5 (28)                | B—3 (33.3)          |
|                            | Initial positive association which became negative after adjustment for confounders.  | 2 (11)                | C—3 (33.3)          |
|                            | Initial positive association weakened after adjustment for confounders but remained statistically significant | 2 (11)                |                     |
| Childhood 1–18 years of age n=70 | No association between IQ and BF                                                      | 14 (20)               | A—10 (38.5)         |
|                            | Positive association between IQ and BF                                                | 26 (37)               | B—6 (23)            |
|                            | Initial positive association which became negative after adjustment for confounders. | 16 (23)               | C—10 (38.5)         |
|                            | Initial positive association weakened after adjustment for confounders but remained statistically significant | 14 (20)               |                     |
| Adulthood ≥18 years of age n=5  | No association between IQ and BF                                                       | 2 (40)                | A—0 (0)             |
|                            | Positive association between IQ and BF                                                | 1 (20)                | B—1 (50)            |
|                            | Initial positive association which became negative after adjustment for confounders. | 1 (20)                | C—1 (50)            |
|                            | Initial positive association weakened after adjustment for confounders but remained statistically significant | 1 (20)                |                     |

*Study examined two different age groups and therefore included in several categories. BF, breastfeeding.
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\(^{19}\) 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 literature search, data collection and review, quality grading, and revision of the manuscript.
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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None.

**Provenance and peer review**

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**Data sharing statement**

The study protocol is available with the authors upon request.

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