# Breast milk and cognitive development – resolving the nature vs. nurture conflict: A systematic review

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| Journal: | *BMJ Open* |
| Manuscript ID: | bmjopen-2013-003259 |
| Article Type: | Research |
| Date Submitted by the Author: | 20-May-2013 |
| Complete List of Authors: | Walfisch, Asnat; Hospital for Sick Children, Motherisk Program<br>Sermer, Corey; Hospital for Sick Children, Motherisk Program<br>Cressman, Alex; Hospital for Sick Children, Motherisk Program<br>Koren, Gideon; Hospital for Sick Children, Motherisk Program |
| Primary Subject Heading: | Obstetrics and gynaecology |
| Secondary Subject Heading: | Paediatrics, Reproductive medicine, Public health |
| Keywords: | Developmental neurology & neurodisability < PAEDIATRICS, PERINATOLOGY, PUBLIC HEALTH, REPRODUCTIVE MEDICINE |
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# Breast milk and cognitive development – resolving the nature vs. nurture conflict: A systematic review

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**Word count:**

Abstract: 259 words

Manuscript (excluding references): 2,221

Running title: Breast Milk and Cognitive Development – Walfisch et al

**ABSTRACT:**

**Objectives:** The association between breastfeeding and child cognitive development is conflicted by studies reporting positive and null effects. Consequently, debate remains whether such a relationship is confounded by factors associated with breastfeeding, specifically maternal socioeconomic class, IQ and education.

**Methods**: To try to resolve this debate, we conducted a systematic review of the literature investigating the association between breastfeeding and cognitive outcomes of healthy infants born at term.

**Results:** Eighty-four studies met our inclusion criteria with 34 rated as high quality, 26 as moderate and 24 as low quality. Critical assessment of accepted studies revealed the following associations: 14 (null), 25 (positive), 15 (null after adjusting for confounders), 14 (positive - diminished after adjusting for confounders), and 16 with mixed results with positive associations in sub-group analysis. Directionality of effect did not correlate with study quality, however studies showing a decreased effect after multivariate analysis were of superior quality compared to other study groupings (i.e. 12/14 high quality). Further, studies that showed null or diminished effect after multivariate analysis corrected for significantly more confounders (7.9 ± 3.4) as compared to those that found no change following adjustment (4.8 ± 4.1) ($p = 0.001$).

**Conclusion:** The results of this systematic review support a conclusion that much of the reported effect of breastfeeding on child neurodevelopment may be due to confounding. Although it is unlikely that additional work will change the current synthesis, future studies in this field 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 supports the association between breast-feeding and IQ of the offspring, debate remains whether this is a causal relationship or an association with favorable 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 eighty 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 almost twice as many confounders than studies showing no such change.
- Much of the reported effect of breastfeeding on child cognitive abilities is due to maternal cognitive and socioeconomic effects.

Strengths and limitations of this study:

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

*Funding*

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

## INTRODUCTION:

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

The potential of breast milk to enhance cognitive development has been the focus of numerous studies since Hoefer and Hardy's initial observation in 1929.[9] It is generally agreed that children who breast-feed are more intelligent, however debate remains whether this is a causal relationship or merely an association with favorable parental socioeconomic class and IQ. The beneficial effects of breastfeeding on the child's neurodevelopment are hypothesized, by some, to be mediated by long-chain polyunsaturated fatty acids (LCPUFAs)[10] which are present in human milk, but not in cow's milk or most infant formulas.[11] However, a recent systematic review of all randomized trials where mother's diet was supplemented with PUFA's during pregnancy has failed to confirm such an effect.[12]

The pendulum of opinion has swung back and forth with different investigators showing inconsistent results depending upon study design and rigor. 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 randomized controlled trials, 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 chose not to.[13] Parents who score high on a range of cognitive abilities have children with above average IQ scores.[13] In parallel, advantage in mother's IQ more than doubles the odds of

breastfeeding.[13] Thus, some of the published data demonstrates the disappearance of the breast-feeding effect on child's cognition after correction for maternal IQ.

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

Systematic reviews examining the impact of breastfeeding on cognitive abilities have reached conflicting results.[13, 17-19] The Meta-analysis by Jain et al[18] suggests that less than 25% of studies in this area have adjusted for socio-demographic 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 breast-feeding 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 (PRISMA) guidelines.[20]

*Literature search:*

Searches were conducted in the following databases (all from inception to December 2012): 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.

*Study selection:*

Both 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 [e.g. 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; and
4. The authors focused on healthy term infants and not those at increased biological risk for developmental delays (e.g. prematurity, intrauterine growth restriction).

Studies were excluded if:

1. The study group included preterm or small for gestational age babies.
2. Evaluation of the cognitive development was done 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 (A.W. and C.S.). 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 (A.W., C.S. and A.C.) 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 (A.W and C.S.) using the three category summary grading system (A, B, C) suggested by Ip et al.[19] Their system defines a generic grading system that is applicable to each type of

study design including randomized controlled trials, 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 percent 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 which 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 breast-feeding exposure and method of categorization, nature of the comparison group, cognitive development assessment tool used and

participants' age, summary of the results prior to adjustment for confounders, a list of all confounders adjusted for, differences in IQ between the groups after adjustment for possible confounders (if available), and study quality grading according to the scale described above.[19]

*Statistical analysis:*

Comparison of studies based on their results or quality was performed by Chi Square or ANOVA as appropriate.

**RESULTS:**

The flow of the literature search is displayed in Figure 1. Of the 1,696 potentially relevant citations identified, 84 studies met the *a priori* inclusion criteria for this systematic review (Table 1).[9,13,15, 21-101] 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, there were 14 studies showing no association between IQ and breastfeeding, 25 positive studies, 15 initially positive studies that became negative after accounting for confounders, and 14 studies where the initial positive effect was diminished but remained statistically significant after accounting for confounders. The remaining 16 studies showed mixed results (e.g. association only observed in the female sub-group or only in carriers of a specific allele).

In general, the directionality of the results did not correlate with the studies' quality. However, the studies showing decrease in the effect after multivariate analysis were of superior quality compared to the rest (i.e. 12 of 14 had a quality score of A).

Different studies corrected in their analyses for different potential confounders, ranging from zero to 16 total confounders (Table). Confounders commonly considered in these studies were socioeconomic status, maternal education, birth weight, gestational age, birth order and gender. Some considered 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 (7.9 ± 3.4) as compared to those that found no change following adjustment for confounders (4.8 ± 4.1) (p = 0.001). Furthermore, many of the studies

did not have a clear definition of breastfeeding or cumulative breast milk exposure. A large variety of cognitive assessment tools were used and study outcomes were measured anywhere from 8 days of age into adulthood. The significant heterogeneity in study design and rigor 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 favorable familial socioeconomic status and cognition, is not purely theoretical. From a public health perspective, if breastfeeding has biological effects on a child's IQ - this will be one of 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, these conflicts is typically resolved through randomized controlled trials (RCT), which are not ethically feasible in this case given that breastfeeding has other protective effects and the highly personal nature of the decision to breastfeed.

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

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

Our analysis reveals that there are over eighty 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 almost twice as many confounders than studies showing no such change. When compared to 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, amongst 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 and colleagues in their large study.[13] 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% confidence interval -0.19 to 1.23). In our systematic review, a similar effect was recorded by a total of 15 studies, and in addition 14 studies showed substantially diminished effect after adjustment.

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[102-103]. 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 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 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 (e.g. parental IQ). Alternatively, study designs using sibling cohorts discordant for breastfeeding may yield more robust conclusions to further clarify this dilemma.

Author's contribution:

Asnat Walfisch 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.

Corey Sermer has participated in all phases of this study including literature search, data collection and review, quality grading, and revision of the manuscript.

Alex Cressman 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.

Gideon Koren participated in all phases of this study. He initiated the study and supervised actively throughout its conduct. Specifically he was involved in the data interpretation, statistical analysis, and has written and revised a substantial part of the manuscript.

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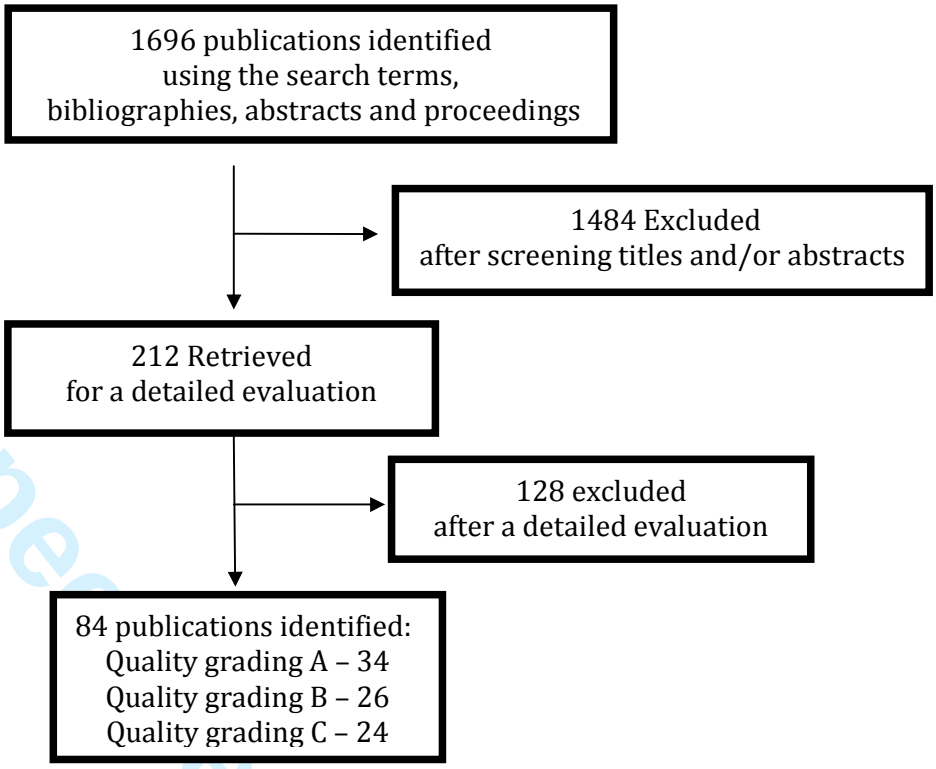
**Figure 1**
**Flow diagram:**



| 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 |
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| **Amanda et al 1992 (21)** | Prospective cohort. Feeding method collected retrospectively | 84 school aged children from two schools in India | Exclusive breast milk for more than 4 months vs. less than 4 months or formula fed | General mental ability test for children from 7-11 years (Srivastava and Saxena 1988-89) | There were significantly more breast fed (>4 m) children in the higher IQ category (IQ>109) | None. | Not provided | **C** |
| **Andres et al 2012 (22)** | Longitudinal study | 391 healthy infants enrolled in the Beginnings Study | Breast fed vs. Soy fed vs. milk-based formula fed | Assessed at ages 3, 6, 9, and 12 months using the Bayley Scales of Infant Development 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 Mental Developmental Index (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 Mental Developmental Index (MDI) score at ages 6 and 12 months ($P<0.05$) | **A** |
| **Angelsen et al 2001(23)** | Prospective cohort | 345 children | < 3 months<br>3-6 months<br>> 6 months | Bayley Scales of Infant Development (BSID) at 13 months. Wechsler Preschool and Primary Scales of Intelligence (WPPSI-R), and Peabody Developmental Motor Scales (PDMS) at age 5y | Shorter duration of breast-feeding was associated with lower scores on mental developmental tests both at 13 months and at 5 years of age. Unadjusted difference of 8 points | Maternal age, education, smoking, and Raven score (IQ) | Maternal age, education, and intelligence were significant confounder. When analyzing performance IQ and verbal IQ separately, the median IQ value, was not statistically different when adjusting for maternal Raven score | **B** |
| **Auestad et al 2001 (24)** | Prospective randomized longitudinal study comparing different formula types and non randomized breast feeding group. | 294 children from four sites in the United states | Breast feeding until age 12m, versus 3 different types of formulas (±AA, DHA) | Bayley scale for infant development at 6 and 12 months<br>Fagan test of infant intelligence at 6 and 9 months<br>MacArthur communicative development inventories at 9 and 14 months | No difference in any of the parameters checked between any study groups. | None. | No difference in any of the parameters checked between any of the study groups. | **A** |

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| **Auestad et al 2003 (25)** | Follow up study of Auestad 2001: Prospective randomized longitudinal study comparing different formula types and a non randomized breast feeding group. | 157 children from the original 294 children from four sites in the United states | Breast feeding until age 12m, versus 3 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** |
| **Bartels et al 2009 (26)** | Retrospective cohort. Breast feeding status prospectively assessed | 672 monozygotic male twin pairs<br>637 dizygotic male twin pairs<br>860 monozygotic female twin pairs<br>647 dizygotic female twin pairs<br>679 male-female twin pairs<br>598 female–male twin pairs | <Two weeks<br>>Two weeks | Dutch CITO-elementary test at age 12 years. | Breast-fed children of highly educated mothers score on average 7.6 point higher on a standardized 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 1991 (27)** | Prospective cohort | 50 children from Honolulu, Hawaii | Breastfeeding as a continuous variable over time. | The McCarthy Scales of Children's Abilities at age 3 years. | The duration of breastfeeding was significantly correlated with scores on the scales, General, cognitive, Quantitative and Memory | Socio-economic status, gender, and pesticide exposure | Remained significant, numbers not provided | **C** |
| **Birch et al 2007 (28)** | Single-center, double-blind, randomized clinical trial comparing different formula types and non randomized breast feeding group. | 52 healthy term infants enrolled for DHA and ARA supplementation and 32 breast-fed infants served as controls | Assigned diets were fed exclusively through 17 weeks of age. In the breast feeding group the average duration of breastfeeding was 43±9 weeks. | The Wechsler Preschool and Primary Scale of Intelligence, Revised (WPPSI-R) was used to assess intelligence at 4 years of age. | The control formula and DHA-supplemented groups had Verbal IQ scores poorer than the breast-fed group. There was no difference in performance or full-scale IQ between all groups. | None. | No adjustment done. | **B** |

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| **Bon 1980 (29)** | Retrospective cohort | 954 children from France | Exclusive bottle fed Vs. Breastfed for <15 days Vs. Breastfed between 15 days and 2 months; Vs. Breastfed more than two months. | The PM-47 Non-Verbal test, at 6-8.5 years of age. | Higher scores for girls who were breast-fed versus not breast-fed. No difference in boys. | Could not be assessed from the text. | Not performed. | **C** |
| **Bouwstra et al 2005(30)** | A prospective, double-blind, randomized control study comparing different formulas. Non randomized breast fed group as control. | A control formula - **n**=169, an LC-PUFA supplemented **n**=146 Breastfed group **n**=159 | Supplementation - 2 mo. All formula-fed infants received control formula between 2 and 6 mo. | The Bayley Scales of Infant Development (BSIDII) 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 2000 (31)** | Prospective cohort | 39 children born at term and from homogeneous sociocultural status in Spain. | Exclusive breast milk for at least 2 months, vs. exclusive bottle-fed. | The Bayley Scales of Infant Development 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** |
| **Caspi et al 2007 (32)** | Retrospective cohort | 858 children from the New Zealand (Dunedin) birth cohort 1848 children from the British (E-risk study) twin birth cohort | No breastfeeding Vs. breastfeeding | New Zealand cohort: IQ measured at ages 7, 9, 11, 13 years using Wechsler Intelligence Scale for Children–Revised. IQ scores combined for an overall score. British cohort: revised short form of Wechsler Preschool and Primary Scale of Intelligence–age 5 | Difference in IQ test scores between breastfed children and those not breastfed was 5.6 and 6.3 IQ points in the Dunedin and E-risk cohorts, respectively. Benefit mediated by a specific genotype. Only in children carrying the C allele. | Genetic variation in fatty acid metabolism (rs174575) Socioeconomic status, Maternal cognitive ability, Gestational age, Birth weight | Children not carrying the C allele did not benefit from breastfeeding. | **A** |

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| **Clark et al 2006 (33)** | Prospective cohort | 784 Chilean children | < 2months<br>2 > 8 months<br>> 8 months | At age 5.5 years.<br>Wechsler Preschool and Primary Scales of Intelligence – Revised (WPPSI-R)<br>Preschool Language Scale – 3rd Edition (PLS-3) the Broad Cognitive Abilities Standard Scale (BCA) of the Batería Woodcock-Muñoz-Revisada (Batería-R) | Poorer outcomes on the cognitive and language assessments were found for both the short and long extremes of breastfeeding as the sole milk source. The highest scores were observed in children who received breast milk as the sole milk source for 2–8 months. | Gender, birth weight, child's age at testing, maternal education, IQ, depression, age, father absence, paternal education, HOME score, socioeconomic status, nutritional status, iron deficiency anemia at 12 months, and iron supplementation. | Difference in IQ not significant. | **B** |
| **Daniels et al 2005 (34)** | Prospective cohort | 1984 Filipino children | Any breastfeeding during:<br>0-6m<br>6-12m<br>12-18m<br>18-24m<br>Over 24m | Philippines Nonverbal Intelligence Test of fluid abilities at ages 8.5 and 11.5 y | Poor education and suboptimal living conditions among BF mothers were strong negative confounders, causing inverse associations between BF and cognitive ability. Increased duration of any BF was of small significant benefit for cognitive development at both ages. | Parental education, paternal presence in home, maternal age, parity, alcohol during pregnancy, preterm status of child, mother reads, child's gender, baths (n/wk), dietary variety at 2 y, household income, non-income-producing assets, electricity in home, and environmental hygiene score. | 1.6 points among normal birthweight breast-fed for 12 to 18 mo vs. less than 6 mo. | **A** |
| **De Andraca et al 1998 (35)** | Prospective cohort. Sub analysis of an RCT concerning iron fortified formulas | 788 infants, 4-6 months of age. | <30 days vs. >30 days. All children in the study were breastfed for average of 75 days. | Bayley Scale of Infant Development – MDI and PDI at 12 months of age. | Breast-feeding 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,<br>Education and occupation of parents, alcohol abuse, HOME, maternal intelligence by WAIS, stressful events. | No adjustment was done for the specific association of breastfeeding and Bayley scale. | **C** |
| **De Andraca et al 1999 (36)** | Prospective cohort | 138 mother-infant dyad | Exclusive breast feeding for 6 months or more vs weaning before 45 days of age | Bayley Scale of Infant Development 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 2006 (13)** | Database analysis of a prospective study, sibling pairs analysis, and metaanalysis | 5,475 children<br>332 pairs of sibling discordant for breastfeeding status<br>545 discordant for duration of breastfeeding | 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 14y | Unadjusted effect of breastfeeding +4.7 compared to non-breastfeeding. | Maternal IQ, education, age, family poverty, HOME stimulation score, and birth order. | After adjustment the difference became non-significant. | **A** |

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| **Di girolamo et al 1993 (37)** | Prospective cohort. Breastfeeding data collected retrospectively | 80 children | Full breast-feeding for at least 4 months vs. no breast feeding since 2 weeks of age. | Bayley Scales of Infant Development at 8-30 months | Breast-feeding group had a higher average MDI (of 6 points) compared to 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 2007 (38)** | Prospective cohort | 191 Brazilian infants | 'Predominantly breast fed' 'partially breast fed' and 'non-breast fed' | Bayley Scales of Infant Development II at 12 months of age. | Full breast-feeding at 1 month was associated with a small significant benefit in mental development compared with partial or no breast-feeding. 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, hemoglobin, weight-for-age. | Full breast feeding at 1 month was associated with +3.0 points, P = 0.02 compared with partial or no breast feeding. | **C** |
| **Elwood et al 2005 (39)** | Prospective cohort. Breastfeeding data collected retrospectively | 779 men from Caerphilly, South Wales, UK | Artificially fed vs. Breastfed, duration unknown vs. Breastfed <3m vs. breastfed >3m | Men aged 60–74 years. 1. The national adult reading test (NART) 2. The AH4 13 verbal and mathematical reasoning 3. The choice reaction time (CRT) for hand-brain reaction speed. | In the normal birth weight group the mean cognitive function was similar in both groups. In the men whose birth weight had been below the median, having been artificially fed was associated with significantly lower results in 2 of the 3 tests. | Age, social class, education, birth order and family size, father's social class, father's unemployment. | In the normal birthweight group, the adjusted mean cognitive function was similar in both groups. | **B** |
| **Evenhouse et al 2005 (40)** | Database analysis of a prospective study, sibling pairs analysis. Data from the National Longitudinal Study of Adolescent Health. | 2,734 sibling pairs | No breastfeeding < 3 months 3-6 months 6-9 months 9-12 months 12-24 months >24 months | Add Health's abbreviated version of the Peabody Picture Vocabulary Test (PVT), normed for age and sex. | Persistent positive correlation between breastfeeding and cognitive ability. Unadjusted Difference in PVT 4.9 percentile points when comparing never breastfed to any breastfeeding in the full sample. | Birth weight, gender, birth order, parental investment, environmental characteristics | 1.68 percentile points higher for ever breast fed to never breastfed. | **A** |

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| **Fergusson et al 1982 (41)** | Prospective cohort | Birth cohort of children from the Dunedin Multidisciplinary Child Development Study:<br>1037 children assessed at age 3y<br>991 at age 5y<br>954 at age 7 y. | Child bottle- fed;<br>Breast-fed for up to 4 months;<br>Breast- fed for 4 months or longer. | Measures of intelligence at 3, 5 and 7 years.<br>3y-Peabody Picture Vocabulary Test 5y-Stanford Binet Intelligence Scale<br>7y-Weschler Child Intelligence Scale | Children who were breast-fed for 4 months or longer had scores which were 3.84 (average) points higher than bottle-fed infants (on scales with a standard deviation 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 1995 (42)** | Retrospective cohort | 592 first born singletons in Dundee | Breast fed on discharge from the hospital<br>Vs.<br>Bottle-fed. | Age 18 months.<br>Bayley Scales of Infant Mental and Motor Development. | Higher mental development was significantly related to breast-feeding on discharge from hospital. | Partner's social class, mother's education, height, alcohol and cigarette consumption, placental weight and the child's sex, birth weight and gestational age at birth. | After adjustment, the difference in Bayley mental development index between the groups was between 3.7 and 5.7 units. | **C** |
| **Foroushani et al 2010 (43)** | Longitudinal cohort.<br>Breastfeeding data collected retrospectively at age 2y. | 5362 singletons born in 1946 in England, Wales and Scotland | No breastfeeding<br>1-3 months<br>4+ months | Age 8 – sentence completion, reading and vocabulary.<br>Age 11 – Verbal, reading and vocabulary.<br>Age 15 – Verbal, reading and vocabulary.<br>Age 26 – reading<br>Age 43 – visual and memory. | Children who were breastfed longer scored higher on verbal tests. Tests at older age (26, 43) were not significantly different. | Birth weight, childhood illness, home conditions, parents' age and education, child's behavioral scores, parents interest in the child's development, school type. | Mean score 1.5 points higher for ages 8,11,15. Not significant at older ages. | **C** |
| **Gale et al 1996 (44)** | Prospective cohort | 994 men and women, born between 1920 and 1930 in Hertfordshire, UK | Exclusive breast feeding, exclusive bottle feeding, mixed feeding | 65-75 years old.<br>AH4 IQ test, taken on a computer. | Participants who had been exclusively breastfed had slightly higher IQ scores compared to the 2 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 2010 (45)** | Prospective cohort | 241 children born to the Southampton Women's Survey, UK. | Breast feeding<br>Fortified formula feeding<br>Unfortified formula feeding | Age 4 –<br>Wechsler Pre-School and Primary Scale of Intelligence (3rd ed.), sentence repetition and verbal fluency measured by the NEPSY | In unadjusted analysis children who were breastfed or fed with a fortified formula had significantly higher scores. | Maternal IO and education, social class, on benefits, age at birth, birthweight. | After adjustment the differences in IQ between groups became non-significant. | **A** |

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| **Ghys et al 2002 (46)** | Prospective cohort. Data on breast feeding collected retrospectively | 128 full term children | Breast-feeding was expressed as the number of months of breast-feeding regardless of possible additional formula feeding. | At 4 years:<br>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 breast-feeding showed significant correlations with cognitive development (Pearson correlation coefficient 0.26) | Plasma and RBC DHA and AA, maternal intelligence, birth weight, duration of breast-feeding and paternal educational attainment, smoking during pregnancy. | In the regression analysis the correlation disappeared. | **B** |
| **Gibson-Davis et al 2006 (47)** | Longitudinal birth cohort study. Breast-feeding information collected retrospectively at 1 year. | 1645 American-born mothers and their babies. | Breastfeeding for at least 1 month vs none. | At three 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 categorized into 1 of 3 educational-status groups. | After adjusting for demographic characteristics and maternal verbal ability, the coefficient dropped to 1.72. | **A** |
| **Gómez-Sanchiz et al 2004 (48)** | Prospective cohort, information on feeding collected retrospectively. | 238 healthy babies born at term, non-IUGR. | Formula fed, Brest-fed up to 4 months, Breast-fed for more than 4 months. | Bayley Infant Development Scale at 24 months of age | Infants breast-fed for longer than 4 months scored higher on the mental development scale than those breast-fed for less time. | Socio-demographic and neonatal variables including parental IQ score. | The results of multiple linear regression analysis showed that infants breast-fed for longer than 4 months scored 4.3 points more than those breast-fed for less time. | **A** |

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| **Greene et al 1995 (49)** | Retrospective cohort | 432 subjects. 208 males, 224 females | Breast-fed vs. non-breast fed. And Breast fed 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 6 point advantage in verbal IQ and 5.4 point advantage in reasoning IQ were observed for subjects breastfed for > I 2 weeks, compared with less. | **C** |
| **Gurka et al 2010 abstract (50)** | Prospective cohort | 1,050 children, from the National Institute of Child Health and Development Study of Early Child Care and Youth Development | Never; 0–6 months; longer than 6 months | Age: 4 years old. Standardized (mean.100; SD.15) cognitive outcomes. | Significant positive associations were observed between breastfeeding and cognitive outcomes before adjusting for other factors. | Maternal age, education, observed quality of the home environment, mother's attitude regarding modernity of parenting, and maternal verbal IQ | No difference. | **A** |
| **Hart et al 2003 (51)** | Prospective cohort | 83 healthy full term infants | Exclusively breastfed vs exclusively non-breastfed | Brazelton Neonatal Behavioral Assessment Scale (BNBAS) at mean age of 8.95 days | Breast-fed infants surpassed formula-fed infants on the items of the orientation, motor, range of state, and state refulation dimensions of the BNBAS. Breast-fed infants also exhibited fewer abnormal reflexes, signs of depression, and withdrawal. | Socioeconomic status | After adjustment for SES only, the differences remained significant. | **B** |

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| **Hoefer et al 1929 (9)** | Retrospective cohort | 383 children | Artificially fed, breast-fed for three months or less, from four to nine months, and from ten to twenty 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. | Artificially fed were inferior in all standardized measurements to those breast fed from four to nine months, and, with one exception, to those breast fed three months or less. Artificially fed equaled or excelled those breast fed from ten to twenty months. | None; similar paternal IQ | Adjustment was not done although they mention paternal IQ to be similar between the groups. | **C** |
| **Holme et al 2010 (52)** | A secondary analysis of data from follow-up study of a RCT of an intervention to reduce smoking in pregnancy | 1218 children | 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 scores. Breastfeeding was associated with a 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) | 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** |
| **Horwood et al 1998 (53)** | Longitudinal study – children studied at birth, 4 months, 1 year, at annual intervals to age 16, and 18 yrs | 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<br>Teachers rating of school performance (reading and mathematics) – age 8 and 12<br>Progressive Achievement Test of Reading Comprehension – ages 10 and 12<br>Progressive Achievement Test of Mathematics – age 11<br>Tests of scholastic abilities – age 13<br>High School Outcomes | Increasing duration of breastfeeding was associated with consistent and statistically significant increases in cognitive abilities, and children who were breastfed for >=8 months had mean test scores that were between 0.35 and 0.59 SD units higher (more than 5 points) than children who were bottle fed. | Maternal age, maternal education, family socioeconomic status, averaged standard of living, averaged family income, maternal smoking during pregnancy, gender, birth order, birth weight | Upon adjustment associations were reduced and children who were breastfed for >=8 months had scores that were 0.11-0.3 SD units (less than 3 points) higher than children who were bottle fed. | **A** |

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| **Innis et al 1996 (54)** | Retrospective cohort | 433 full term infants born in 1994 in Vancouver | Never breastfed, breastfed less than 1 month, 1-3 months, 3-6 months, 6-8 months, more than 8 months, and mixed feeding (breast and formula milk) | Visual acuity measured using acuity card procedure with Teller Acuity Cards. Cognitive development measured using the Fagan Test of Infant Intelligence, (version 4.1) at 39 +/- 1 weeks of age | There were no differences in visual acuity or novelty preference among the infants when they were stratified by incidence or duration of breastfeeding. | None. | No difference. | **B** |
| **Jacobson et al 1999 (55)** | Prospective Longitudinal study | 323 predominantly white, middle-class children born from 1980-81, at age 4, and 280 children at age 11, from 2 cohorts of similar demographic information *most exposed to PCB during pregnancy | Breastfed vs. not breastfed | McCarthy Scales of Children's Abilities and the Peabody Picture Vocabulary Test-Revised at the age of 4. Wechsler Intelligence Scale for Children-III, Wide Range Achievement Test-Revised, and the Woodcock Word, Passage, and Reading Comprehension test at the age of 11. | At both the ages of 4, and 11, breastfeeding was significantly related to higher IQ scores. | Social class, education, maternal IQ, parenting skills (Home observation for measurement of the environment (HOME)) | The relationship was reduced to non-significance after adjustment for maternal IQ and parenting skills (HOME) | **B** |
| **James et al, letter 1992 (56)** | Prospective cohort | 38 full-term children (taken as a sample from an extended Pembrokeshire farming family, UK) | Bottle-fed babies vs. breast-fed babies | IQ test At age 16 (no details) | No difference in IQ | No adjustment | No difference | **C** |
| **Jedrychowski et al 2012 (57)** | Longitudinal study | 468 term babies in Krakow, Poland. | Complementary breastfeeding (including none), Vs. exclusive breastfeeding up to 3 months, 4–6 months, or longer than 6 months. | In the first 3 years of the follow-up the Bayley Mental Scales of Infant Development-second edition (BSID-II) were used. At the age of 6 and 7, the Wechsler intelligence test for children (WISC-R) was administered. | Children on mixed breastfeeding achieved lower total IQ scores at each of 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, 2.11–5.45). | **B** |

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| **Jiang et al 2011 (58)** | Longitudinal study | 3,271 children and their mothers from the US participating in the Child Development Supplement of the Panel Study of Income Dynamics | Yes or no ever breast feeding 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 a standard deviation. Longer spells of breastfeeding are uncorrelated with increases in the measures of achievement. | **A** |
| **Johnson et al 1996 (59)** | Longitudinal study | 204 Euro-American full-term infants were followed up to the age of 3 from 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 behavior, gender, and birth order of the child | Breast feeding was associated with 4.6-point higher mean in children's Intelligence. | **A** |
| **Keim et al 2009-abstract (60)** | Prospective cohort | 347 children | Exclusively breastfed vs formula fed | Mullen Scales of Early Learning at 1 yr 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 abstract. | **C** |

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| **Kramer et al 2008 (15)** | Cluster-randomized trial. | 13,889 Belarussian children born between June 1996 and December 1997 | Experimental group vs control group: Experimental group was encouraged to breastfeed and had greater levels of breastfeeding at 3, 6, 9 and 12 months (exclusive breastfeeding also 7 fold higher at 3 months) | Wechsler Abbreviated Scales of Intelligence and teacher evaluations of academic performance in reading, writing, mathematics, and other subjects at 6.5 yrs 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 both 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 2006 (61)** | Prospective cohort | 3794 woman who delivered a singleton baby between 1981-84 in Brisbane, Australia | Never, <4 months, >= 4 months | Peabody Picture Vocabulary Test at age of 5<br>Raven's standard progressive matrices (Raven's SPM) and the Wide Range Achievements Test version 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 stage of labour, mod of delivery, apgar scores at 1 and 5 min, birthweight for sex and gestational age (z score), height for age and sex (z score), BMI for age and sex (z score) | Significance remained with mean difference in IQ of 6.8 between never and over 4 months of breast-feeding. | **A** |
| **Lucas et al 1999 (62)** | Prospective double-blind, randomized controlled study (different formulas, breastfed control group not randomized) | 447 healthy full-term children born in the UK between 1993-1995. | Breastfed for at least 6 weeks vs formula fed. | Bayley Scales of Infant Development II at 18 months. | No differences in overall developmental scores at 9 months or 18 months or in any subscale quotient at 9 months were found. | Sex, centre, maternal age, maternal education, maternal marital status, and social class | No difference with adjustment for potential confounding factors. | **A** |
| **Maimaitiming et al 2007 (63)** | Retrospective cohort | 442 infants and children inhabited by Uygur, Han, or Kazak nationality in West China | Breast fed 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** |

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| **Makrides et al 2000 (64)** | Prospective randomized double blind controlled. Different formulas. Breastfed group was used as control, but not randomized. | 68 formula fed infants and 46 breastfed infants born at term of appropriate weight | Formula fed vs breastfed | Infant VEP acuity at 16 and 34 weeks<br>Bayley's Scales of Development at 1 year and 2 years. | At 1 yr of age, MDI scores of breastfed and formula-fed infants were not different, but at 2 years of age, MDI scores of breastfed infants were higher than formula fed infants. PDI scores were similar. | Home screening questionnaire scores, occupational prestige, parental education, gender, birth weight, maternal smoking, birth order, feeding mode. | MDI score was higher at age 2 in the breastfed group. 95% CI 3-16.8. | **A** |
| **Malloy et al 1997 (65)** | Retrospective cohort | 518 children born in 1978-79 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 old | Breastfed scored significantly higher on full scale IQ; Further analyses limited to those exclusively breastfed for the first 60 days failed to demonstrate any significant relationship. | Maternal education, paternal education and annual income | Following adjustment, the difference was not significant. | **B** |
| **Martin et al 2011 (66)** | Retrospective cohort | 1431 children (twin siblings) from the greater Brisbane area | Exclusively formula fed, any breastfeeding between birth and 3 months, exclusively breastfed for 3 to 6 months, exclusively breastfed for 6 months or more | FSIQ (full scale IQ) assessed using the Multi-dimensional Aptitude Battery (MAB) at 16 years of age | Breastfeeding was significantly associated with FSIQ scores. No effect of duration of breastfeeding on FSIQ was found. | Socioeconomic status, paternal education, maternal education, gestational age, and birth weight. | The effect was no longer significant after adjustment. | **A** |
| **McCrory et al 2011 (67)** | Retrospective cross-sectional study | 8568 school children in Ireland born between 1997 and 1998. | Breastfed vs not breastfed<br>AND<br>Never breastfed, <=5 weeks, 6-15 weeks, 16-25 weeks, 26+ weeks | Age 9 years. Vocabulary component of the Drumcondra Primary Reading Test-Revised and part 1 of the Drumcondra Primary Mathematics Test-Revised. | In unadjusted analysis, children who were breastfed scored 8.67 percentage points higher on reading and 7.42 percentage points higher on math. 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, mothers 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 math respectively | **A** |

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| **Morales et al 2011 (68)** | Retrospective cohort analyzing 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 | Different types of formula fed vs breastfed | Mental development was assessed at age 14 months using the Bayley Scales of Infant Development, first Edition – MDI only, and at age 4 years old 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 synthesize these fatty acids had higher scores regardless of breastfeeding practices. | Sex, child age, psychologist, quality of neuropsychological test, maternal education, breastfeeding, and use of gas stove at home. | Not being breastfed conferred an 8- to 9-point disadvantage in cognition among children with low FADS1 activity and in a 5-8 point disadvantage in cognition among children with low ELOVL5 activity. | **A** |
| **Morris et al 1999 (69)** | Prospective cohort | 102 normal birthweight children born in Brazil at term. | Number of breastfeeds per day (recorded daily). | Bayley Scales of Infant Development 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 1988 (70)** | Prospective cohort | 229 children born in Ohio between 1981-1982 | No breastfeeding, breastfeeding =<4 months, breastfeeding >4 months | Bayley Scales of Infant Development – Mental Development Index (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 both 1 year 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 9 points higher compared to the bottle-fed infants. | **A** |

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| **Mortensen et al 2002 (71)** | Prospective longitudinal birth cohort | Mixed sample: 973 men and women<br>All-male sample: 2280 men | Divided to five groups:<br>< 1 month<br>2-3 months<br>4-6 months<br>7-9 months<br>> 9 months | Wechsler Adult Intelligence Scale (WAIS) at a mean age of 27.2 years in the mixed-sex sample.<br>Børge Priens Prøve (BPP) test at a mean age of 18.7 years in the all-male sample. | Duration of breast-feeding was associated with significantly higher scores on the Verbal, Performance, Full Scale WAIS IQs and BPP test. | Parental social status<br>Parental education<br>Single mother status<br>Mother's height, age, and weight gain during pregnancy<br>cigarette consumption during the third trimester number of pregnancies<br>Gestational age birth weight<br>Birth length<br>Indexes of pregnancy<br>Delivery complications | The results remained significant with 4.6 points higher IQ for those breast-fed over 9 months compared to less than 1 month. | **B** |
| **Mukerji et al 1993 (72)** | Cross-sectional study | 100 children aged 0-3 years. | No breast-feeding or mixed.<br>Exclusive breast-feeding for 4-9 months.<br>Exclusive breastfeeding for more than 9 months | Developmental Screening Test (DST) | In the 4-9 months exclusive breast fed group 100% had average or above average IQ.<br>In the two other groups this number was significantly lower. | None. | No adjustments were made. | **C** |
| **Nassar et al 2011 (73)** | Cross-sectional study | 42 healthy infants | Breastfed, artificially fed, mixed feeding | Bayley scale of infant development-second edition (BSID-II) between 4-6 months of age. | No difference in MDI or PDI.<br>There was significant difference only in total behavior rating scale (TBRS) and motor quality percentile 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 percentile rank. | **B** |
| **Nelson et al 1995 (74)** | Prospective cohort? | Term gestation infants | Breast fed or formula fed for 3 months | Teller Acuity Cards at 14d, 3, 4, 8, and 18 months<br>Fagan Test of Infant Intelligence at 8, 10 and 12 months<br>Bayley Scales of Infant Development at 4, 8, and 18 months | There were no significant differences between breast-fed and formula-fed infants in visual acuity at 14d, 3, 8, or 18 months, or recognition memory or the Bayley PDI or MDI at any age | | Meeting abstract only available | **C** |

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| **Niemela et al 1996 (75)** | Prospective follow-up | 726 children born between 1985-86 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 (sig difference found in relation to the general cognitive capacity and visual motor integration). No evidence of any interaction between verbal development and breastfeeding to 5 months or more. | Groups matched pairwise based on sex and maternal education. | Maternal education and parental status correlated with all cognitive scores. Sex and breastfeeding correlated with scores of the general cognitive capacity and visual motor integration tests in multiple linear regressions. | **B** |
| **Oddy et al 2003 (76)** | Prospective cohort | 1401 children at first follow up and 1283 children at second follow up from the Western Australian Pregnancy Cohort Study following 2860 children in Perth, Australia | Never breastfed, fully breastfed 0-4 months, 4-6 months, more than 6 months | Peabody Picture Vocabulary Test-Revised (PPVT-R) for receptive English vocabulary – verbal intelligence at 6 yrs Performance subtest by the Wechsler Intelligence Scale for Children – Third Edition (WISC-III) – Block Design Test at age 8yrs | On average, children breast fed for more than 6 months had mean verbal IQ scores that were 6,44 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) | breast feeding 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 difference after adjustment. | **A** |
| **Oddy et al** | Prospective | 980 children from the | Breastfed less | Western Australian Monitoring | Continuous breastfeeding was | Gender, maternal age, maternal | Results were | **A** |

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| **2011 (77)** | cohort | Western Australian Pregnancy Cohort Study following 2860 children in Perth, Australia | than 4 vs more than 4 months And Breastfed less than 6 vs more than 6 months | Standards in Education (WAMSE) scores in: math, reading, writing, and spelling at age 10yrs | significantly associated with an increase in scores with each additional month of breastfeeding for math, reading, writing, and spelling. | education, family income, marital status, parent looks at book with child at age 5, maternal country of birth | attenuated when adjusted for confounders. Significant interactions were found in math and spelling, revealing that boys were more likely to have improved academic scores if breastfed for a longer period. | |
| **Paine et al 1999 (78)** | Retrospective cohort | 96 healthy full term Caucasian children from the Adelaide area in Australia | Duration of exclusive breastfeeding | Bayley Scales of Infant Developmental at age 10-14 months | Duration of exclusive breast-feeding significantly predicted mental development scores for boys, but not for girls. Duration of breast-feeding did not predict psychomotor development scores. | Duration of breast-feeding, parents occupational prestige, parents' education level and smoking habits, number of siblings, birth order, HSQ score, gestational age, birthweight, 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, birthweight, and duration of breastfeeding. | None. | **C** |
| **Pollock et al 1994 (79)** | Prospective cohort | 3838 children from the 1970 British | Wholly breast fed for more than | Human figure drawing score, copying design score and English | Significant difference found between groups at age 5 for the | Age father left full time education, age mother left full | All results adjusted for all | **A** |

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| | | Births Survey at full term and healthy birth weight | 3 months vs. wholly bottle fed | 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, similarities, matrices, total) and Continuous outcomes: Pictorial Language test, Friendly Maths test, Edinburgh Reading test, Spelling test, and British Ability Scales (Word definitions, similarities, matrices, total) at age 10 | English Picture Vocabulary test. Significant difference found for both dichotomized outcomes and continuous outcomes for the British Ability Scales and dichotomized outcomes for the Pictorial Language test at age 10. | time education, highest educational qualifications of mother, mother's smoking behavior during pregnancy, antenatal labour preparation class attendance, infant's place of birth | other independent predictors of breast-feeding: English Picture Vocabulary test: aOR 1.50. Dichotomized outcomes: Pictorial Language test aOR 1.49 Word definitions aOR 1.55 Similarities aOR 1.64 Total aOR 1.64 Continuous outcomes: Word definitions mean diff 3.5 Matrices mean diff 2.6 Similarities mean difference 3.0 Total mean difference 3.1 | |
| **Quinn et al 2001 (80)** | Prospective cohort | 3880 healthy children from the Mater Hospital-University | Never breastfed, < 3 weeks, 3-7 weeks, 7 weeks – | Peabody Picture Vocabulary Test Revised (PPVT-R) at 5 yrs. of age. | Significantly increasing scores were found between duration of breastfeeding and the PPVT-R | Birthweight, poverty, maternal education, maternal age, time in daycare/preschool, number of | After adjusting for a wide range of biological and | **A** |

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| | | of Queensland Study of Pregnancy project | 4 months, 4-6 months, still breast feeding at 6 months | | scores. | children in household at 5 years, English speaking background for mother & father, and degree of infant stimulation | social factors, the adjusted mean for those breastfed for 6 months or more was 8.2 points higher for females and 5.8 higher for males than compared to those never breastfed (this was significant). | |
| **Rao et al 2002 (81)** | Prospective cohort | 299 children born in Norway/Sweden at appropriate size for gestational age (comparison group) | <12 weeks Vs. >12 weeks of breastfeeding AND Duration of breastfeeding as a continuum | Bayley Scales of Infant Development at 13 months of age Norwegian version of the Wechsler Preschool and Primary Scales of Intelligence – Revised at 5 yrs. of age Peabody Development Motor Scale measured at 5 yrs. of age | There were statistically significant differences in IQ between the 2-breastfeeding groups. | Site of enrolment, maternal education, maternal IQ, maternal smoking, admission to a neonatal intensive care unit, kindergarten attendance, gender and asymmetric intrauterine growth retardation | 3.7 points for total IQ and 4.1 points for performance IQ. Results remained unaltered when adjusted for confounding variables. | **B** |
| **Ribas-Fito et al 2007 (82)** | Prospective cohort | 391 children born in Spain between 1997-1999 | 0-2 weeks breastfeeding 2-20 weeks breastfeeding 20+ weeks breastfeeding | Spanish version of the McCarthy Scales of Children's Abilities (general cognitive scale, verbal scale, perceptual-performance scale, memory scale, quantitative scale, motor scale subsets) at 4 yrs. of age. | Children with longer periods of breastfeeding performed significantly better on the McCarthy cognitive scale (except motor). | Gender, academic trimester at examination, psychologist, maternal social class, maternal education, and maternal use of alcohol and tobacco during pregnancy | After adjustment for confounders, significance remained for the general cognitive scale, and a trend remained in other subsets. | **A** |
| **Richards et al 2002 (83)** | Retrospective cohort | 1741 people from the MRC National Survey of Health and | Never Up to 2 months 2-7 months | National Adult Reading Test (NART), word-list learning task (verbal memory) and timed letter | Educational Attainment: Odds of obtaining higher qualifications by the age of 26 | Early background variables: Sex, father's social class, mother's education, birth order, | Effect of BF on education was strengthened | **A** |

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| | | Development (NSHD), also known as the British 1946 birth cohort | 7+ months | search task (mental speed and concentration) at age 53. | were statistically significant, with greater odds for longer breastfeeding.<br>Cognitive Function:<br>Regression coefficients for the unadjusted effect show that breastfeeding was significantly associated with the NART and verbal memory tests. | parental interest in education and material home conditions. | after adjusting for the early background variables and remained significant. No longer significant with further adjustment for cognitive ability at age 15.<br>Cognitive function:<br>Coefficients were reduced after adjusting for the early background variables and were further reduced after adjusting for educational attainment and adult social class<br>Only NART remained sig. | |
| **Richards et al 1998 (84)** | Retrospective cohort | 511 first born offspring of the British 1946 cohort and their parent | Duration of breastfeeding. | Sentence completion test, reading test and vocabulary test at age 8 yr. | Breastfeeding was positively associated with cognitive function at age 8 in the first offspring of a national birth cohort. This | Social class, parental educational attainment, material home conditions, maternal age at birth, birth order, family size, | Non-significant; after adjusting for social class, maternal | **C** |

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| | | | | | association was not evident in the subsample of mothers of these offspring. Association in the offspring cohort became non-significant after adjusting for social class, maternal education, or maternal cognitive performance. | maternal cigarette smoking, parental interest in education, attendance at nursery school, whether offspring cohort members had been taught cognitive skills at age 4, and cognitive test scores of the mothers. | education, or maternal cognitive performance. | |
| **Rodgers et al 1978 (85)** | Longitudinal study | 1464 children at age 8 and 1398 children at age 15 from the British 1946 cohort | Never bottle-fed vs. never breastfed | Picture intelligence test and word reading test at 8 years of age Non-verbal ability, mathematics, and sentence completion tests at age 15 years of age | A preliminary analysis indicated that low scores were more likely for those who had been bottle-fed than breast-fed. The mean sentence completion scores between the two groups is statistically significant. Every test at both ages was significant except for word reading scores after correction for background factors. | Sex, social group, parental interest in education, material home conditions, sample stratification, father's education, mother's education, family size, birth rank, age at weaning | After correction for confounders, every test at both ages was significant except for word reading scores. | **B** |
| **Rogan et al 1993 (86)** | Prospective cohort | 855 newborns being followed in North Carolina were enrolled between 1978-1982 and | Bottle fed 'short breastfeeding' 'medium breastfeeding' | Bayley Mental and Psychomotor Development Index at 6, 12, 18, and 24 months of age. McCarthy General Cognitive, Verbal, Quantitative, Memory, | Bayley Mental and Psychomotor: After adjusting for co-variables, the results at all four time points were similar, differences among the groups were only statistically | Age, race, occupation, education, smoking, drinking, child's sex, birthweight, number of older siblings, prenatal PCB exposure and | Confounders integrated into model; unadjusted results not | **B** |

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| | | followed up to 5 yrs old | 'long breastfeeding' 'very long breastfeeding' | Perceptual Performace, and Motor scales at 36, 48, and 60 months of age<br>Report Card Grades from 3rd, 4th and 5th grade (averaged) | sig. at 24 months.<br>McCarthy:<br>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<br>Report Cards:<br>Showed slight increase with breastfeeding. Marginally significant after adjustment for English scores and not significant for math. | dichlorodiphenyl dichloroethene exposure , Identity of the examiner. | shown. | |
| **Santiago Burruchaga et al 2000 (87)** | Prospective cohort | 39 children born at term and from homogenous sociocultural status | Breastfed for al least 2 months vs. formula fed | Bayleys scale at 2 years of age | No statistically significant differences between groups were found in cognitive function. | Maternal age, level of education, occupation, number of children in the family,smoking. | None; confounders integrated into model. | **C** |
| **Silva et al 2006 (88)** | Longitudinal population based cohort | 9367 children from the 1970 British Cohort Study comprising individuals born during April 5-11 in | Never breastfed<br>Less than 1 month<br>1-3 months<br>More than 3 months | British Ability Scale, the Shortened Edinburgh Reading Test (word recognition), the Friendly Math Tests, and the Pictorial Language Comprehension Test at age of 10 yrs. | Breast-feeding 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 | **A** |

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| | | the UK | | | | | (standardized 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. | |
| **Silva et al 1978 (89)** | Retrospective cohort | 1037 children from the Dunedin Multidisciplinary Child Development Study | < 1 week<br>1-4 weeks<br>5-12 weeks<br>13-24 weeks<br>25-36 weeks<br>37-51 weeks<br>51+ weeks | Gross motor co-ordination, fine motor co-ordination, verbal comprehension and verbal expression, intelligence, child behavior problems at age 3 yrs. | 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.<br><br>Pairwise comparison with group matching to account for confounders. | None; pairwise matching said to account for confounders. | **B** |
| **Sloan et al 2010 (90)** | Cross-sectional observational. Breastfeeding data were obtained retrospectively. | 137 infants and mothers | Breast fed (defined as more than 1 month) vs. not breast fed (defined as less than a month a not at all) | Bayley Scales of Infant Development (second edition; Bayley, 1993), between 10 and 18 months old. | Mean cognitive scores were significantly higher in breast-fed infants (110) compared with formula-fed infants (105). Breastfeeding duration had a positive linear association with cognitive scores at one year. | Home environment (HOME score) and infant gender | The adjusted standardized beta for breastfeeding was 0.285, which remained significant after adjustment. | **C** |
| **Slykerman 2005 (91)** | Cross-sectional observational. Breastfeeding data were obtained retrospectively. | 550 infants, 50% of which were SGA at birth and 50% AGA. | Not at all,<br>less than 6 m,<br>6 to 12 m,<br>>12 m. | Stanford Binet Intelligence Scale, 4th Edition at age 3.5y-4y | 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** |

| | | | | | | | | |
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| **Steer et al 2010 (92)** | Prospective observational. Breastfeeding data were obtained prospectively. | 9656 children from the Avon Longitudinal Study of Parents and Children cohort. | Breastfeeding within the first month of life vs. never breast feeding | 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 birth weight, pre-term gestation, home environment, parenting and gender | The breastfeeding effect attenuated to a 3- point advantage after adjustment. | **B** |
| **Taylor et al 1984 (93)** | Longitudinal population based cohort. Breastfeeding data were obtained retrospectively. | 13,135 children from The Child Health and Education Study | Never breastfed<br>Less than 1 month<br>1-3 months<br>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 a standard deviation above the norm. | The age of the child at testing; the child's sex and birthweight; 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 | Breast feeding remained a significant influence on EPVT scores, but the difference between the groups was small: +0.12 in the standardized EPVT score | **A** |
| **Temboury et al 1994 (94)** | Prospective cohort | 229 infants | Breast fed – at least three months<br>Bottle-fed – none or less than 1 month | Baylay'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, birthweight, height, place of birth | The result remained significant. | **C** |
| **Thorsdottir et al 2005 (95)** | Longitudinal cohort | 85 children in Iceland | Duration of exclusive breastfeeding | The Icelandic developmental inventory at age 6 years. Information collected from the mothers. | Duration of exclusive breastfeeding, in months, was positively related to children's total developmental index. | Maternal and paternal education, and family income, birthweight, maternal BMI. | Total developmental index (B=1.07±0.5, P=0.04) | **C** |
| **Tozzi et al 2012 (96)** | Prospective cohort | 1403 children originally included in an Italian clinical trial on acellular Pertussis vaccines | Duration of exclusive breastfeeding both as a continuous variable and as a | 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 | Scores of only a few neuropsychological tests were affected by exclusive breastfeeding duration: Mean scores on vocabulary, similarities, the Boston naming test, and | Sex, birthweight, gestational age, mother's age at birth, type of delivery, family composition, parents' education, presence of chronic diseases, current | In the regression analysis, the score on one subcategory of the California verbal learning | **A** |

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| | | | categorical variable (<6mo, >6mo). | subtests. | estimated IQ improved with the duration of breastfeeding, whereas performance in one of the subtests for writing praxis decreased with breastfeeding duration. | prescription of antihistamines or antiepileptic drugs, and the amount of thimerosal to which children were exposed through vaccines. | 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 | |
| **Veena et al 2010 (97)** | Longitudinal cohort | 514 children from the Mysore Parthenon birth cohort in south India | Six categories from <3 to ≥18 months | Kaufman Assessment Battery at 9- to10-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, socio-economic status, parents' attained schooling and rural/urban residence. | No difference either unadjusted or after adjustment. | **B** |
| **Whitehouse et al 2011 (98)** | Longitudinal cohort, breast feeding data collected prospectively | 1195 live born children recruited at approximately 18 weeks gestation, Western Australian Pregnancy Cohort (Raine) Study. | (1) Never breast-fed, (2) Breast-fed predominantly for <4 months, (3) Breast-fed predominantly | 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 a SD of 15. | Strong positive association between the duration of predominant breast-feeding 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 | Children who were predominantly breast-fed for >6 months had a mean PPVT-R score that was | **A** |

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| | | | for 4–6 months (4) Breast-fed predominantly for >6 months. | | | of stressful events during pregnancy, parity, gestational age, child's sex, and proportion of optimal birthweight, a measure of the appropriateness of fetal growth, Family functioning (MMFAD), Parenting Scale, language-learning environment. | 4.04 points higher than children who were never breast-fed | |
| **Wigg et al 1998 (99)** | Longitudinal cohort, breast feeding data collected prospectively | 375 children born in Port Pirie, South Australia. | At 6 month of age: Breast fed vs. bottle-fed. Children who were breast-fed for less than 6 months would have been classified in our analysis as bottle-fed. | Bayley Scales of Infant Development 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 breast-fed children at ages 2, 4 and 7 years were 5.5 points, 4.6 points and 4.3 points in MDI, GCI and IQ scores, respectively. At age 11 to 13 years, the unadjusted advantage for the breast-fed children was 3.8 points in IQ. | Gender, maternal age at delivery, socioeconomic status, HOME score, maternal IQ, parental smoking habits, birthweight, birth rank, lifetime average blood lead concentration and whether parents were living together. | Adjusting for the covariates diminished the association of the feeding method in infancy with cognitive development. The covariates contributing most to this attenuating effect were the HOME scores, maternal IQ, socioeconomic status and parental smoking habits. | **B** |
| **Zaini et al 2005 (100)** | Retrospective cohort | 1397 children from Selangor Malaysia | <6 months >6 months | Raven's Colored Progressive Matrices at a mean age 9.6 years | Those who were breastfed less than six months performed better (31.01 vs. 30.63 out of max 36) | None. | None. | **C** |
| **Zhou et al 2007 (101)** | Prospective cohort | 302 children born between 1998 and 1999 in Adelaide, Australia | Not breast fed, Breast fed at hospital discharge, | Stanford-Binet Intelligence Scale at 4 years of age. | There was no association between duration of breast-feeding and childhood IQ in this relatively well-nourished cohort from an | Birth order and sex of the child, maternal smoking in pregnancy, parental education, parental occupation, and quality of | There was no association between breast-feeding and | **B** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Less than 6 months, More than 6 months. | | industrialized society. Before adjustment, children who were breast-fed for at least 6 m. had higher IQ than those who were breast-fed for less than 6 months | home environment | childhood IQ. | |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6-7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6-7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 8-9 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 8 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 9 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 10+flow diagram |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 10 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Table |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Table |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 13 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 12-14 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 3 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

# Breast milk and cognitive development – the role of confounders: A systematic review

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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID: | bmjopen-2013-003259.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 11-Jul-2013 |
| Complete List of Authors: | Walfisch, Asnat; Hospital for Sick Children, Motherisk Program<br>Sermer, Corey; Hospital for Sick Children, Motherisk Program<br>Cressman, Alex; Hospital for Sick Children, Motherisk Program<br>Koren, Gideon; Hospital for Sick Children, Motherisk Program |
| Primary Subject Heading: | Obstetrics and gynaecology |
| Secondary Subject Heading: | Paediatrics, Reproductive medicine, Public health |
| Keywords: | Developmental neurology & neurodisability < PAEDIATRICS, PERINATOLOGY, PUBLIC HEALTH, REPRODUCTIVE MEDICINE |
| | |

# Breast milk and cognitive development – the role of confounders: A systematic review

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**Word count:**

Abstract: 268 words

Manuscript: 2721 (excluding references)

Running title: Breast Milk and Cognitive Development – Walfisch et al

**ABSTRACT:**

**Objectives:** The association between breastfeeding and child cognitive development is conflicted by studies reporting positive and null effects. Consequently, debate remains whether such a relationship is confounded by factors associated with breastfeeding, specifically maternal socioeconomic class, IQ and education.

**Methods**: To try to resolve this debate, we conducted a systematic review of the literature investigating the association between breastfeeding and cognitive outcomes of healthy infants born at term.

**Results:** Eighty-four studies met our inclusion criteria with 34 rated as high quality, 26 as moderate and 24 as 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 to other study groupings (i.e. 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 to those that found no change following adjustment (5.6 ± 4.5) ($p = 0.04$). The majority of included studies were done during childhood (>1y, <18y, 75%) and set in high-income countries (85.5%).

**Conclusion:** The results of this systematic review support a conclusion that much of the reported effect of breastfeeding on child neurodevelopment may be due to confounding. Although it is unlikely that additional work will change the current synthesis, future studies in this field 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 supports the association between breast-feeding and IQ of the offspring, debate remains whether this is a causal relationship or an association with favorable 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 eighty 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 maternal cognitive and socioeconomic effects.

Strengths and limitations of this study:

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

*Funding*

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

## INTRODUCTION:

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

The potential of breast milk to enhance cognitive development has been the focus of numerous studies since Hoefer and Hardy's initial observation in 1929.[9] It is generally agreed that children who breast-feed are more intelligent, however debate remains whether this is a causal relationship or merely an association with favorable parental socioeconomic class and IQ. The beneficial effects of breastfeeding on the child's neurodevelopment are hypothesized, by some, to be mediated by long-chain polyunsaturated fatty acids (LCPUFAs)[10] which are present in human milk, but not in cow's milk or most infant formulas.[11] However, a recent systematic review of all randomized trials where mother's diet was supplemented with PUFA's during pregnancy has failed to confirm such an effect.[12]

The pendulum of opinion has swung back and forth with different investigators showing inconsistent results depending upon study design and rigor. 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 randomized controlled trials, 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 chose not to.[13] Parents who score high on a range of cognitive abilities have children with above average IQ scores.[13] In parallel, advantage in mother's IQ more than doubles the odds of

breastfeeding.[13] Thus, some of the published data demonstrates the disappearance of the breast-feeding effect on child's cognition after correction for maternal IQ.

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

Systematic reviews examining the impact of breastfeeding on cognitive abilities have reached conflicting results.[13, 17-19] The Meta-analysis by Jain et al[18] suggests that less than 25% of studies in this area have adjusted for socio-demographic 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 breast-feeding 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 (PRISMA) guidelines.[20]

*Literature search:*

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

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

A second, complimentary, literature search was done on April 2013 for all studies published during the period of August 2011-December 2012.

*Study selection:*

Both prospective and retrospective studies (RCTs, non-randomized 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 [e.g. 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; and
4. The authors focused on healthy term infants and not those at increased biological risk for developmental delays (e.g. prematurity, intrauterine growth restriction).

Studies were excluded if:

1. The study group included preterm or small for gestational age babies.
2. Evaluation of the cognitive development was done 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 (A.W. and C.S.). 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 (A.W., C.S. and A.C.) 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 (A.W and C.S.) using the three category summary grading system (A, B, C) suggested by Ip et

al.[19] Their system defines a generic grading system that is applicable to each type of study design including randomized controlled trials, 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 percent 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 which 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 breast-feeding exposure and method of categorization,

nature of the comparison group, cognitive development assessment tool used and participants' age, summary of the results prior to adjustment for confounders, a list of all confounders adjusted for, differences in IQ between the groups after adjustment for possible confounders (if available), and study quality grading according to the scale described above.[19]

*Statistical analysis:*

Comparison of studies based on their results or quality was performed by Chi Square or ANOVA as appropriate.

**RESULTS:**

The flow of the literature search is displayed in Figure 1. Of the 1,696 potentially relevant citations identified, 84 studies met the *a priori* inclusion criteria for this systematic review (Table 1). [9,13,15, 21-101] 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, [24-25,30-32,35-36,39,54,56,62-63,73-74,86-87,89,91,97,100-101] 28 positive studies, [9,15,21,27-29,37-38,42,48,51,57,59,61,64,68,71-72,75,79-82,85,90,94-95,98] 18 initially positive studies that became negative after accounting for confounders, [13,23,26,33,43-46,49-50,52,55,65-66,69,78,84,96] and 17 studies where the initial positive effect was diminished but remained statistically significant after accounting for confounders (Table 2). [22,34,40-41,47,53,58,60,67,70,76-77,83,88,92-93,99]

In general, the directionality of the results did not correlate with the studies' quality. However, the studies showing decrease in the effect after multivariate analysis were of superior quality compared to the rest (i.e. 14 of 17 had a quality score of A – Table 2).

Different studies corrected in their analyses for different potential confounders, ranging from zero 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 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 to those that found no change following adjustment for confounders (5.6 ± 4.5, p = 0.04). Furthermore, many of the studies did not have a clear definition of breastfeeding or cumulative breast milk exposure.

Table 3 divides the included studies according to their settings: developed vs. 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 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 rigor 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 favorable familial socioeconomic status and cognition, is not purely theoretical. From a public health perspective, if breastfeeding has biological effects on a child's IQ - this will be one of 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 randomized controlled trials (RCT), which are not ethically feasible in this case given that breastfeeding has other protective effects and the highly personal nature of the decision to breastfeed.

The closest comparison to a formal RCT in reducing selection bias would be sibling-pair analysis, when cognition of breastfed infants is compared to 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 and colleagues, [14-15] who cluster randomized women in Eastern Europe to receive or not receive formal education about the advantages of breastfeeding. This study did show favorable effects, but it has been argued that the mothers randomized for the breastfeeding promotion arm might have been influenced not only in providing higher rates of breastfeeding, but also by improving other positive health behaviors.

Our analysis reveals that there are over eighty 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 to 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, amongst 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 and colleagues in their large study.[13] 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% confidence interval -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 mid-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- and middle-income countries high rates of some degree of breastfeeding exist[102] and comparisons between breastfed and non-breastfed populations may examine more homogenous study groups (i.e. 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 breast feed 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 breast-feed.

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 number of included studies is small. Possible explanations for this finding include reduced accuracy of IQ evaluation in infancy (<1y) on one hand, and a variety of additional factors influencing IQ at an older age (>18y), on the other hand.

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 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 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 (e.g. parental IQ). Alternatively, study designs using sibling cohorts discordant for breastfeeding may yield more robust conclusions to further clarify this dilemma.

Author's contribution:

Asnat Walfisch 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.

Corey Sermer has participated in all phases of this study including literature search, data collection and review, quality grading, and revision of the manuscript.

Alex Cressman 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.

Gideon Koren participated in all phases of this study. He initiated the study and supervised actively throughout its conduct. Specifically he was involved in the data interpretation, statistical analysis, and has written and revised a substantial part of the manuscript.

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# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6-7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6-7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 8-9 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 8 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 9 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 10+flow diagram |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 10 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Table |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Table |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 13 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 12-14 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 3 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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# Breast milk and cognitive development – ~~-~~the role of confounders: ~~resolving the nature vs. nurture conflict:~~ A systematic review

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**Word count:**

Abstract: 268 ~~259~~ words

Manuscript: 2721 (excluding references): ~~2,221~~

Running title: Breast Milk and Cognitive Development – Walfisch et al

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**ABSTRACT:**

**Objectives:** The association between breastfeeding and child cognitive development is conflicted by studies reporting positive and null effects. Consequently, debate remains whether such a relationship is confounded by factors associated with breastfeeding, specifically maternal socioeconomic class, IQ and education.

**Methods**: To try to resolve this debate, we conducted a systematic review of the literature investigating the association between breastfeeding and cognitive outcomes of healthy infants born at term.

**Results:** Eighty-four studies met our inclusion criteria with 34 rated as high quality, 26 as moderate and 24 as low quality. Critical assessment of accepted studies revealed the following associations: ~~14~~ 21 (~~null~~), 28~~25~~ (~~positive~~), 18 ~~15 (~~null after adjusting for confounders~~)~~, and 17 ~~14 (~~positive - diminished after adjusting for confounders~~), and 16 with mixed results with positive associations in sub-group analysis~~. Directionality of effect did not correlate with study quality, however studies showing a decreased effect after multivariate analysis were of superior quality compared to other study groupings (i.e. ~~12/14~~ 14/17 high quality, 82%). Further, studies that showed null or diminished effect after multivariate analysis corrected for significantly more confounders (7.7~~9~~ ± 3.4) as compared to those that found no change following adjustment (5.6 ± 4.5~~4.8 ± 4.1~~) (p = 0.0401~~1~~). The majority of included studies were done during childhood (>1y, <18y, 75%) and set in high-income countries (85.5%).

**Conclusion:** The results of this systematic review support a conclusion that much of the reported effect of breastfeeding on child neurodevelopment may be due to confounding. Although it is unlikely that additional work will change the current synthesis, future studies in this field 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 supports the association between breast-feeding and IQ of the offspring, debate remains whether this is a causal relationship or an association with favorable 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 eighty 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 ~~almost twice as many~~significantly more confounders than studies showing no such change.
- Much of the reported effect of breastfeeding on child cognitive abilities is due to maternal cognitive and socioeconomic effects.

Strengths and limitations of this study:

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

*Funding*

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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**INTRODUCTION:**

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

The potential of breast milk to enhance cognitive development has been the focus of numerous studies since Hoefer and Hardy's initial observation in 1929.[9] It is generally agreed that children who breast-feed are more intelligent, however debate remains whether this is a causal relationship or merely an association with favorable parental socioeconomic class and IQ. The beneficial effects of breastfeeding on the child's neurodevelopment are hypothesized, by some, to be mediated by long-chain polyunsaturated fatty acids (LCPUFAs)[10] which are present in human milk, but not in cow's milk or most infant formulas.[11] However, a recent systematic review of all randomized trials where mother's diet was supplemented with PUFA's during pregnancy has failed to confirm such an effect.[12]

The pendulum of opinion has swung back and forth with different investigators showing inconsistent results depending upon study design and rigor. 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 randomized controlled trials, 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 chose not to.[13] Parents who score high on a range of cognitive abilities have children with above average IQ scores.[13] In parallel, advantage in mother's IQ more than doubles the odds of

breastfeeding.[13] Thus, some of the published data demonstrates the disappearance of the breast-feeding effect on child's cognition after correction for maternal IQ.

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

Systematic reviews examining the impact of breastfeeding on cognitive abilities have reached conflicting results.[13, 17-19] The Meta-analysis by Jain et al[18] suggests that less than 25% of studies in this area have adjusted for socio-demographic 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 breast-feeding 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 (PRISMA) guidelines.[20]

*Literature search:*

Searches were conducted in the following databases (all from inception to ~~December~~ July 2011~~2~~): 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 done on April 2013 for all studies published during the period of August 2011-December 2012.

*Study selection:*

Both prospective and retrospective studies (RCTs, non-~~randomised~~randomized

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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 [e.g. 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; and
4. The authors focused on healthy term infants and not those at increased biological risk for developmental delays (e.g. prematurity, intrauterine growth restriction).

Studies were excluded if:

1. The study group included preterm or small for gestational age babies.
2. Evaluation of the cognitive development was done 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 (A.W. and C.S.). 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 (A.W., C.S. and A.C.) 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 (A.W and C.S.) using the three category summary grading system (A, B, C) suggested by Ip et al.[19] Their system defines a generic grading system that is applicable to each type of study design including randomized controlled trials, 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 percent 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 which 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 breast-feeding exposure and method of categorization, nature of the comparison group, cognitive development assessment tool used and participants' age, summary of the results prior to adjustment for confounders, a list of all confounders adjusted for, differences in IQ between the groups after adjustment for possible confounders (if available), and study quality grading according to the scale described above.[19]

*Statistical analysis:*

Comparison of studies based on their results or quality was performed by Chi Square or ANOVA as appropriate.

**RESULTS:**

The flow of the literature search is displayed in Figure 1. Of the 1,696 potentially relevant citations identified, 84 studies met the *a priori* inclusion criteria for this systematic review (Table 1)~~.~~ ~~[9,13,15]~~ [9,13,15, 21-101] 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, ~~Overall,~~ there were 21~~14 studies~~ studies showing no association between IQ and breastfeeding~~,~~ [24-25,30-32,35-36,39,54,56,62-63,73-74,86-87,89,91,97,100-101] ~~29~~28~~5~~ positive studies~~,~~ [9,15,21,27-29,37-38,42,48,51,57,59,61,64,68,71-72,75,79-82,85,90,94-95,98] ~~17~~18~~5~~ initially positive studies that became negative after accounting for confounders~~,~~ [13,23,26,33,43-46,49-50,52,55,65-66,69,78,84,96] and 1~~7~~4 studies where the initial positive effect was diminished but remained statistically significant after accounting for confounders (Table 2). [22,~~The remaining 16 studies showed mixed results (e.g. association only observed in the female sub-group or only in carriers of a specific allele~~34,40-41,47,53,58,60,67,70,76-77,83,88,92-93,99~~).~~]

In general, the directionality of the results did not correlate with the studies' quality. However, the studies showing decrease in the effect after multivariate analysis were of superior quality compared to the rest (i.e. 14 ~~12~~ of ~~14~~ 17 had a quality score of A – Table 2).

Different studies corrected in their analyses for different potential confounders, ranging from zero 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 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

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diminished effect in their multivariate analysis controlled for significantly more confounders (7.79 ± 3.4) as compared to those that found no change following adjustment for confounders (5.64.8 ± 4.51) (p = 0.0401). Furthermore, many of the studies did not have a clear definition of breastfeeding or cumulative breast milk exposure. ~~A large variety of cognitive assessment tools were used and study outcomes were measured anywhere from 8 days of age into adulthood.~~

Table 3 divides the included studies according to their settings: developed vs. 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 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

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

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**DISCUSSION:**

The continuing debate of whether breastfeeding imparts direct advantage on child cognition, or whether this is merely an association with favorable familial socioeconomic status and cognition, is not purely theoretical. From a public health perspective, if breastfeeding has biological effects on a child's IQ - this will be one of 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, ~~these~~ conflicts ~~is~~ are typically resolved through randomized controlled trials (RCT), which are not ethically feasible in this case given that breastfeeding has other protective effects and the highly personal nature of the decision to breastfeed.

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

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

Our analysis reveals that there are over eighty 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 ~~almost twice as many~~significantly more confounders than studies showing no such change. When compared to 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, amongst 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 and colleagues in their large study.[13] 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% confidence interval -0.19 to 1.23).

In our systematic review, a similar effect was recorded by a total of 18~~15~~ studies, and in addition ~~14~~ 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 mid-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%

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vs. 43.5% respectively).

This may be due to the fact that in many low- and middle-income countries -high rates of some degree of breastfeeding ~~there~~ exist[s102] and ~~that~~ comparisons between breastfed and non-breastfed populations may examine more homogenous study groups (i.e. 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 ~~exists~~[13] as the choice to breast feed is associated with a family's socioeconomic status, maternal education~~, a, number of other measures of~~ maternal intelligence, and social advantage ~~(Der et al, 2006; BMJ Article; Ref 17-19 in our paper)~~.[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 -breast-feed.

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 number of included studies is small. Possible explanations for this finding include reduced accuracy of IQ evaluation in infancy (<1y) on one hand, and a variety of additional factors influencing IQ at an older age (>18y), on the other hand.

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

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detecting a significant effect in pregnancy to be submitted and published in the peer review literature is substantially lower than that of positive studies.[102-103-104] 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 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 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 (e.g. parental IQ). Alternatively, study designs using sibling cohorts discordant for breastfeeding may yield more robust conclusions to further clarify this dilemma.

Author's contribution:

Asnat Walfisch 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.

Corey Sermer has participated in all phases of this study including literature search, data collection and review, quality grading, and revision of the manuscript.

Alex Cressman 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.

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Gideon Koren participated in all phases of this study. He initiated the study and supervised actively throughout its conduct. Specifically he was involved in the data interpretation, statistical analysis, and has written and revised a substantial part of the manuscript.

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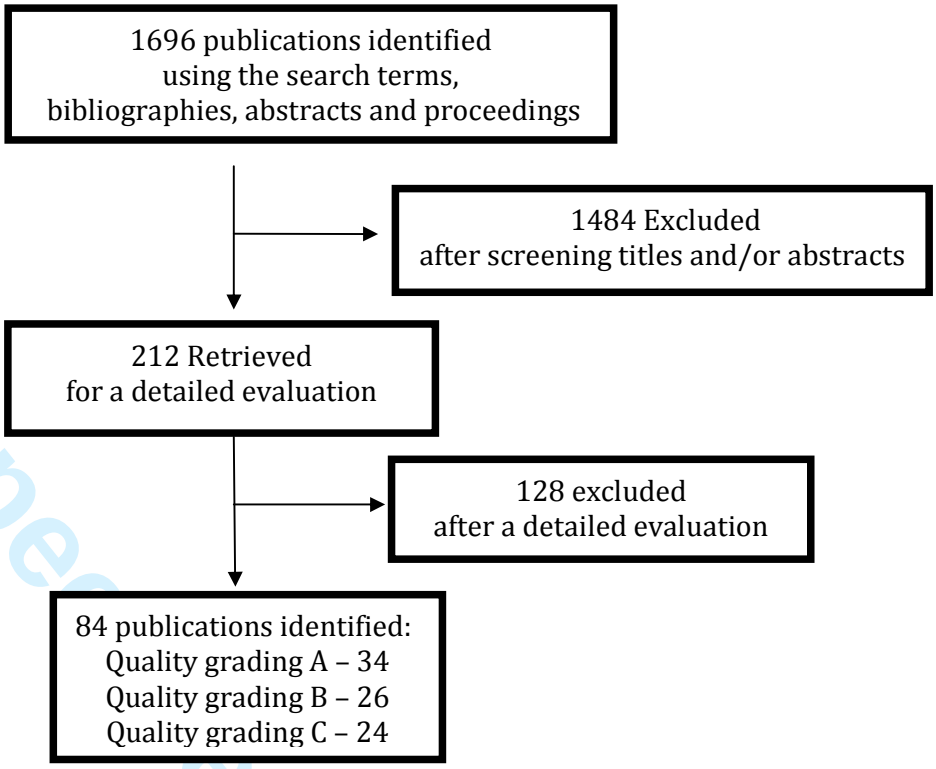
**Figure 1**
**Flow diagram:**



| 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 et al 1992 (21)** | Prospective cohort. Feeding method collected retrospectively | 84 school aged children from two schools in India | Exclusive breast milk for more than 4 months vs. less than 4 months or formula fed | General mental ability test for children from 7-11 years (Srivastava and Saxena 1988-89) | There were significantly more breast fed (>4 m) children in the higher IQ category (IQ>109) | None. | Not provided | **C** |
| **Andres et al 2012 (22)** | Longitudinal study | 391 healthy infants enrolled in the Beginnings Study in Arkansas, USA | Breast fed vs. Soy fed vs. milk-based formula fed | Assessed at ages 3, 6, 9, and 12 months using the Bayley Scales of Infant Development 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 Mental Developmental Index (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 Mental Developmental Index (MDI) score at ages 6 and 12 months ($P<0.05$) | **A** |
| **Angelsen et al 2001(23)** | Prospective cohort | 345 children in Scandinavia (Norway and Sweden) | < 3 months<br>3-6 months<br>> 6 months | Bayley Scales of Infant Development (BSID) at 13 months. Wechsler Preschool and Primary Scales of Intelligence (WPPSI-R), and Peabody Developmental Motor Scales (PDMS) at age 5y | Shorter duration of breast-feeding was associated with lower scores on mental developmental tests both at 13 months and at 5 years of age. Unadjusted difference of 8 points | Maternal age, education, smoking, and Raven score (IQ) | Maternal age, education, and intelligence were significant confounder. When analyzing performance IQ and verbal IQ separately, the median IQ value, was not statistically different when adjusting for maternal Raven score | **B** |
| **Auestad et al 2001 (24)** | Prospective randomized longitudinal study comparing different formula types and non randomized breast feeding group. | 294 children from four sites in the United states | Breast feeding until age 12m, versus 3 different types of formulas (±AA, DHA) | Bayley scale for infant development at 6 and 12 months<br>Fagan test of infant intelligence at 6 and 9 months<br>MacArthur communicative development inventories at 9 and 14 months | No difference in any of the parameters checked between any study groups. | None. | No difference in any of the parameters checked between any of the study groups. | **A** |

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| **Auestad et al 2003 (25)** | Follow up study of Auestad 2001: Prospective randomized longitudinal study comparing different formula types and a non randomized breast feeding group. | 157 children from the original 294 children from four sites in the United states | Breast feeding until age 12m, versus 3 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** |
| **Bartels et al 2009 (26)** | Retrospective cohort. Breast feeding status prospectively assessed | 672 monozygotic male twin pairs<br>637 dizygotic male twin pairs<br>860 monozygotic female twin pairs<br>647 dizygotic female twin pairs<br>679 male-female twin pairs<br>598 female–male twin pairs in the Netherlands | <Two weeks<br>>Two weeks | Dutch CITO-elementary test at age 12 years. | Breast-fed children of highly educated mothers score on average 7.6 point higher on a standardized 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 1991 (27)** | Prospective cohort | 50 children from Honolulu, Hawaii | Breastfeeding as a continuous variable over time. | The McCarthy Scales of Children's Abilities at age 3 years. | The duration of breastfeeding was significantly correlated with scores on the scales, General, cognitive, Quantitative and Memory | Socio-economic status, gender, and pesticide exposure | Remained significant, numbers not provided | **C** |
| **Birch et al 2007 (28)** | Single-center, double-blind, randomized clinical trial comparing different formula types and non randomized breast feeding group. | 52 healthy term infants enrolled for DHA and ARA supplementation and 32 breast-fed infants served as controls in Dallas, Texas | Assigned diets were fed exclusively through 17 weeks of age. In the breast feeding group the average duration of breastfeeding was 43±9 weeks. | The Wechsler Preschool and Primary Scale of Intelligence, Revised (WPPSI-R) was used to assess intelligence at 4 years of age. | The control formula and DHA-supplemented groups had Verbal IQ scores poorer than the breast-fed group. There was no difference in performance or full-scale IQ between all groups. | None. | No adjustment done. | **B** |

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| **Bon 1980 (29)** | Retrospective cohort | 954 children from France | Exclusive bottle fed Vs. Breastfed for <15 days Vs. Breastfed between 15 days and 2 months; Vs. Breastfed more than two months. | The PM-47 Non-Verbal test, at 6-8.5 years of age. | Higher scores for girls who were breast-fed versus not breast-fed. No difference in boys. | Could not be assessed from the text. | Not performed. | **C** |
| **Bouwstra et al 2005(30)** | A prospective, double-blind, randomized control study comparing different formulas. Non randomized breast fed group as control. | A control formula - **n**=169, an LC-PUFA supplemented **n**=146 Breastfed group **n**=159 in the Netherlands | Supplementation - 2 mo. All formula-fed infants received control formula between 2 and 6 mo. | The Bayley Scales of Infant Development (BSIDII) 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 2000 (31)** | Prospective cohort | 39 children born at term and from homogeneous sociocultural status in Spain. | Exclusive breast milk for at least 2 months, vs. exclusive bottle-fed. | The Bayley Scales of Infant Development 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** |
| **Caspi et al 2007 (32)** | Retrospective cohort | 858 children from the New Zealand (Dunedin) birth cohort 1848 children from the British (E-risk study) twin birth cohort | No breastfeeding Vs. breastfeeding | New Zealand cohort: IQ measured at ages 7, 9, 11, 13 years using Wechsler Intelligence Scale for Children–Revised. IQ scores combined for an overall score. British cohort: revised short form of Wechsler Preschool and Primary Scale of Intelligence–age 5 | Difference in IQ test scores between breastfed children and those not breastfed was 5.6 and 6.3 IQ points in the Dunedin and E-risk cohorts, respectively. Benefit mediated by a specific genotype. Only in children carrying the C allele. | Genetic variation in fatty acid metabolism (rs174575) Socioeconomic status, Maternal cognitive ability, Gestational age, Birth weight | Children not carrying the C allele did not benefit from breastfeeding. | **A** |

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| **Clark et al 2006 (33)** | Prospective cohort | 784 Chilean children | < 2months<br>2 > 8 months<br>> 8 months | At age 5.5 years.<br>Wechsler Preschool and Primary Scales of Intelligence – Revised (WPPSI-R)<br>Preschool Language Scale – 3rd Edition (PLS-3) the Broad Cognitive Abilities Standard Scale (BCA) of the Batería Woodcock-Muñoz-Revisada (Batería-R) | Poorer outcomes on the cognitive and language assessments were found for both the short and long extremes of breastfeeding as the sole milk source. The highest scores were observed in children who received breast milk as the sole milk source for 2–8 months. | Gender, birth weight, child's age at testing, maternal education, IQ, depression, age, father absence, paternal education, HOME score, socioeconomic status, nutritional status, iron deficiency anemia at 12 months, and iron supplementation. | Difference in IQ not significant. | **B** |
| **Daniels et al 2005 (34)** | Prospective cohort | 1984 Filipino children | Any breastfeeding during:<br>0-6m<br>6-12m<br>12-18m<br>18-24m<br>Over 24m | Philippines Nonverbal Intelligence Test of fluid abilities at ages 8.5 and 11.5 y | Poor education and suboptimal living conditions among BF mothers were strong negative confounders, causing inverse associations between BF and cognitive ability. Increased duration of any BF was of small significant benefit for cognitive development at both ages. | Parental education, paternal presence in home, maternal age, parity, alcohol during pregnancy, preterm status of child, mother reads, child's gender, baths (n/wk), dietary variety at 2 y, household income, non-income-producing assets, electricity in home, and environmental hygiene score. | 1.6 points among normal birthweight breast-fed for 12 to 18 mo vs. less than 6 mo. | **A** |
| **De Andraca et al 1998 (35)** | Prospective cohort. Sub analysis 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 average of 75 days. | Bayley Scale of Infant Development – MDI and PDI at 12 months of age. | Breast-feeding 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,<br>Education and occupation of parents, alcohol abuse, HOME, maternal intelligence by WAIS, stressful events. | No adjustment was done for the specific association of breastfeeding and Bayley scale. | **C** |
| **De Andraca et al 1999 (36)** | Prospective cohort | 138 mother-infant dyad in Chile | Exclusive breast feeding for 6 months or more vs weaning before 45 days of age | Bayley Scale of Infant Development 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 2006 (13)** | Database analysis of a prospective study, sibling pairs analysis, and metaanalysis | 5,475 children<br>332 pairs of sibling discordant for breastfeeding status<br>545 discordant for duration of breastfeeding in the | 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 14y | Unadjusted effect of breastfeeding +4.7 compared to non-breastfeeding. | Maternal IQ, education, age, family poverty, HOME stimulation score, and birth order. | After adjustment the difference became non-significant. | **A** |

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| | | USA | | | | | | |
| **Di girolamo et al 1993 (37)** | Prospective cohort. Breastfeeding data collected retrospectively | 80 children in Spain | Full breast-feeding for at least 4 months vs. no breast feeding since 2 weeks of age. | Bayley Scales of Infant Development at 8-30 months | Breast-feeding group had a higher average MDI (of 6 points) compared to 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 2007 (38)** | Prospective cohort | 191 Brazilian infants | 'Predominantly breast fed' 'partially breast fed' and 'non-breast fed' | Bayley Scales of Infant Development II at 12 months of age. | Full breast-feeding at 1 month was associated with a small significant benefit in mental development compared with partial or no breast-feeding. 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, hemoglobin, weight-for-age. | Full breast feeding at 1 month was associated with +3.0 points, P = 0.02 compared with partial or no breast feeding. | **C** |
| **Elwood et al 2005 (39)** | Prospective cohort. Breastfeeding data collected retrospectively | 779 men from Caerphilly, South Wales, UK | Artificially fed vs. Breastfed, duration unknown vs. Breastfed <3m vs. breastfed >3m | Men aged 60–74 years. 1. The national adult reading test (NART) 2. The AH4 13 verbal and mathematical reasoning 3. The choice reaction time (CRT) for hand-brain reaction speed. | In the normal birth weight group the mean cognitive function was similar in both groups. In the men whose birth weight had been below the median, having been artificially fed was associated with significantly lower results in 2 of the 3 tests. | Age, social class, education, birth order and family size, father's social class, father's unemployment. | In the normal birthweight group, the adjusted mean cognitive function was similar in both groups. | **B** |
| **Evenhouse et al 2005 (40)** | Database analysis of a prospective study, sibling pairs analysis. Data from the National Longitudinal Study of Adolescent Health. | 2,734 sibling pairs in the USA | No breastfeeding < 3 months 3-6 months 6-9 months 9-12 months 12-24 months >24 months | Add Health's abbreviated version of the Peabody Picture Vocabulary Test (PVT), normed for age and sex. | Persistent positive correlation between breastfeeding and cognitive ability. Unadjusted Difference in PVT 4.9 percentile points when comparing never breastfed to any breastfeeding in the full sample. | Birth weight, gender, birth order, parental investment, environmental characteristics | 1.68 percentile points higher for ever breast fed to never breastfed. | **A** |

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| **Fergusson et al 1982 (41)** | Prospective cohort | Birth cohort of children from the Dunedin Multidisciplinary Child Development Study:<br>1037 children assessed at age 3y<br>991 at age 5y<br>954 at age 7 y. | Child bottle- fed; Breast-fed for up to 4 months; Breast- fed for 4 months or longer. | Measures of intelligence at 3, 5 and 7 years.<br>3y-Peabody Picture Vocabulary Test 5y-Stanford Binet Intelligence Scale<br>7y-Weschler Child Intelligence Scale | Children who were breast-fed for 4 months or longer had scores which were 3.84 (average) points higher than bottle-fed infants (on scales with a standard deviation 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 1995 (42)** | Retrospective cohort | 592 first born singletons in Dundee | Breast fed on discharge from the hospital<br>Vs.<br>Bottle-fed. | Age 18 months.<br>Bayley Scales of Infant Mental and Motor Development. | Higher mental development was significantly related to breast-feeding on discharge from hospital. | Partner's social class, mother's education, height, alcohol and cigarette consumption, placental weight and the child's sex, birth weight and gestational age at birth. | After adjustment, the difference in Bayley mental development index between the groups was between 3.7 and 5.7 units. | **C** |
| **Foroushani et al 2010 (43)** | Longitudinal cohort. Breastfeeding data collected retrospectively at age 2y. | 5362 singletons born in 1946 in England, Wales and Scotland | No breastfeeding<br>1-3 months<br>4+ months | Age 8 – sentence completion, reading and vocabulary.<br>Age 11 – Verbal, reading and vocabulary.<br>Age 15 – Verbal, reading and vocabulary.<br>Age 26 – reading<br>Age 43 – visual and memory. | Children who were breastfed longer scored higher on verbal tests. Tests at older age (26, 43) were not significantly different. | Birth weight, childhood illness, home conditions, parents' age and education, child's behavioral scores, parents interest in the child's development, school type. | Mean score 1.5 points higher for ages 8,11,15. Not significant at older ages. | **C** |
| **Gale et al 1996 (44)** | Prospective cohort | 994 men and women, born between 1920 and 1930 in Hertfordshire, UK | Exclusive breast feeding, exclusive bottle feeding, mixed feeding | 65-75 years old.<br>AH4 IQ test, taken on a computer. | Participants who had been exclusively breastfed had slightly higher IQ scores compared to the 2 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 2010 (45)** | Prospective cohort | 241 children born to the Southampton Women's Survey, UK. | Breast feeding<br>Fortified formula feeding<br>Unfortified formula feeding | Age 4 –<br>Wechsler Pre-School and Primary Scale of Intelligence (3rd ed.), sentence repetition and verbal fluency measured by the NEPSY | In unadjusted analysis children who were breastfed or fed with a fortified formula had significantly higher scores. | Maternal IO and education, social class, on benefits, age at birth, birthweight. | After adjustment the differences in IQ between groups became non-significant. | **A** |

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| **Ghys et al 2002 (46)** | Prospective cohort. Data on breast feeding collected retrospectively | 128 full term children in the Netherlands | Breast-feeding was expressed as the number of months of breast-feeding regardless of possible additional formula feeding. | At 4 years:<br>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 breast-feeding showed significant correlations with cognitive development (Pearson correlation coefficient 0.26) | Plasma and RBC DHA and AA, maternal intelligence, birth weight, duration of breast-feeding and paternal educational attainment, smoking during pregnancy. | In the regression analysis the correlation disappeared. | **B** |
| **Gibson-Davis et al 2006 (47)** | Longitudinal birth cohort study. Breast-feeding information collected retrospectively at 1 year. | 1645 American-born mothers and their babies. | Breastfeeding for at least 1 month vs none. | At three 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 categorized into 1 of 3 educational-status groups. | After adjusting for demographic characteristics and maternal verbal ability, the coefficient dropped to 1.72. | **A** |
| **Gómez-Sanchiz et al 2004 (48)** | Prospective cohort, information on feeding collected retrospectively. | 238 healthy babies born at term, non-IUGR in Spain | Formula fed, Brest-fed up to 4 months, Breast-fed for more than 4 months. | Bayley Infant Development Scale at 24 months of age | Infants breast-fed for longer than 4 months scored higher on the mental development scale than those breast-fed for less time. | Socio-demographic and neonatal variables including parental IQ score. | The results of multiple linear regression analysis showed that infants breast-fed for longer than 4 months scored 4.3 points more than those breast-fed for less time. | **A** |

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| **Greene et al 1995 (49)** | Retrospective cohort | 432 subjects. 208 males, 224 females in Ireland | Breast-fed vs. non-breast fed. And Breast fed 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 6 point advantage in verbal IQ and 5.4 point advantage in reasoning IQ were observed for subjects breastfed for > I 2 weeks, compared with less. | **C** |
| **Gurka et al 2010 abstract (50)** | Prospective cohort | 1,050 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. Standardized (mean.100; SD.15) cognitive outcomes. | Significant positive associations were observed between breastfeeding and cognitive outcomes before adjusting for other factors. | Maternal age, education, observed quality of the home environment, mother's attitude regarding modernity of parenting, and maternal verbal IQ | No difference between the groups. | **A** |
| **Hart et al 2003 (51)** | Prospective cohort | 83 healthy full term infants in Texas, USA | Exclusively breastfed vs exclusively non-breastfed | Brazelton Neonatal Behavioral Assessment Scale (BNBAS) at mean age of 8.95 days | Breast-fed infants surpassed formula-fed infants on the items of the orientation, motor, range of state, and state refulation dimensions of the BNBAS. Breast-fed infants also exhibited fewer abnormal reflexes, signs of depression, and withdrawal. | Socioeconomic status | After adjustment for SES only, the differences remained significant. | **B** |

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| **Hoefer et al 1929 (9)** | Retrospective cohort | 383 children in Illinois, USA | Artificially fed, breast-fed for three months or less, from four to nine months, and from ten to twenty 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. | Artificially fed were inferior in all standardized measurements to those breast fed from four to nine months, and, with one exception, to those breast fed three months or less. Artificially fed equaled or excelled those breast fed from ten to twenty months. | None; similar paternal IQ | Adjustment was not done although they mention paternal IQ to be similar between the groups. | **C** |
| **Holme et al 2010 (52)** | A secondary analysis of data from follow-up study of a 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.<br>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 scores. Breastfeeding was associated with a 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) | 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** |
| **Horwood et al 1998 (53)** | Longitudinal study – children studied at birth, 4 months, 1 year, at annual intervals to age 16, and 18 yrs. | 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<br>Teachers rating of school performance (reading and mathematics) – age 8 and 12<br>Progressive Achievement Test of Reading Comprehension – ages 10 and 12<br>Progressive Achievement Test of Mathematics – age 11<br>Tests of scholastic abilities – age 13<br>High School Outcomes | Increasing duration of breastfeeding was associated with consistent and statistically significant increases in cognitive abilities, and children who were breastfed for >=8 months had mean test scores that were between 0.35 and 0.59 SD units higher (more than 5 points) than children who were bottle fed. | Maternal age, maternal education, family socioeconomic status, averaged standard of living, averaged family income, maternal smoking during pregnancy, gender, birth order, birth weight | Upon adjustment associations were reduced and children who were breastfed for >=8 months had scores that were 0.11-0.3 SD units (less than 3 points) higher than children who were bottle fed. | **A** |

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| **Innis et al 1996 (54)** | Retrospective cohort | 433 full term infants born in 1994 in Vancouver | Never breastfed, breastfed less than 1 month, 1-3 months, 3-6 months, 6-8 months, more than 8 months, and mixed feeding (breast and formula milk) | Visual acuity measured using acuity card procedure with Teller Acuity Cards. Cognitive development measured using the Fagan Test of Infant Intelligence, (version 4.1) at 39 +/- 1 weeks of age | There were no differences in visual acuity or novelty preference among the infants when they were stratified by incidence or duration of breastfeeding. | None. | No difference. | **B** |
| **Jacobson et al 1999 (55)** | Prospective Longitudinal study | 323 predominantly white, middle-class children born from 1980-81, at age 4, and 280 children at age 11, from 2 cohorts of similar demographic information in Michigan, USA *most exposed to PCB during pregnancy | Breastfed vs. not breastfed | McCarthy Scales of Children's Abilities and the Peabody Picture Vocabulary Test-Revised at the age of 4. Wechsler Intelligence Scale for Children-III, Wide Range Achievement Test-Revised, and the Woodcock Word, Passage, and Reading Comprehension test at the age of 11. | At both the ages of 4, and 11, breastfeeding was significantly related to higher IQ scores. | Social class, education, maternal IQ, parenting skills (Home observation for measurement of the environment (HOME)) | The relationship was reduced to non-significance after adjustment for maternal IQ and parenting skills (HOME) | **B** |
| **James et al, letter 1992 (56)** | Prospective cohort | 38 full-term children (taken as a sample from an extended Pembrokeshire farming family, UK) | Bottle-fed babies vs. breast-fed babies | IQ test At age 16 (no details) | No difference in IQ | No adjustment | No difference | **C** |
| **Jedrychowski et al 2012 (57)** | Longitudinal study | 468 term babies in Krakow, Poland. | Complementary breastfeeding (including none), Vs. exclusive breastfeeding up to 3 months, 4–6 months, or longer than 6 | 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 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, 2.11–5.45). | **B** |

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| **Jiang et al 2011 (58)** | Longitudinal study | 3,271 children and their mothers from the US participating in the Child Development Supplement of the Panel Study of Income Dynamics | Yes or no ever breast feeding 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 a standard deviation. Longer spells of breastfeeding are uncorrelated with increases in the measures of achievement. | **A** |
| **Johnson et al 1996 (59)** | Longitudinal study | 204 Euro-American full-term infants were followed up to the age of 3 from 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 behavior, gender, and birth order of the child | Breast feeding was associated with 4.6-point higher mean in children's Intelligence. | **A** |
| **Keim et al 2009-abstract (60)** | Prospective cohort | 347 children in the USA | Exclusively breastfed vs formula fed | Mullen Scales of Early Learning at 1 yr 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 abstract. | **C** |

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| **Kramer et al 2008 (15)** | Cluster-randomized trial. | 13,889 Belarussian children born between June 1996 and December 1997 | Experimental group vs control group: Experimental group was encouraged to breastfeed and had greater levels of breastfeeding at 3, 6, 9 and 12 months (exclusive breastfeeding also 7 fold higher at 3 months) | Wechsler Abbreviated Scales of Intelligence and teacher evaluations of academic performance in reading, writing, mathematics, and other subjects at 6.5 yrs 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 both 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 2006 (61)** | Prospective cohort | 3794 woman who delivered a singleton baby between 1981-84 in Brisbane, Australia | Never, <4 months, >= 4 months | Peabody Picture Vocabulary Test at age of 5<br>Raven's standard progressive matrices (Raven's SPM) and the Wide Range Achievements Test version 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 stage of labour, mod of delivery, apgar scores at 1 and 5 min, birthweight for sex and gestational age (z score), height for age and sex (z score), BMI for age and sex (z score) | Significance remained with mean difference in IQ of 6.8 between never and over 4 months of breast-feeding. | **A** |
| **Lucas et al 1999 (62)** | Prospective double-blind, randomized controlled study (different formulas, breastfed control group not randomized) | 447 healthy full-term children born in the UK between 1993-1995. | Breastfed for at least 6 weeks vs formula fed. | Bayley Scales of Infant Development II at 18 months. | No differences in overall developmental scores at 9 months or 18 months or in any subscale quotient at 9 months were found. | Sex, centre, maternal age, maternal education, maternal marital status, and social class | No difference with adjustment for potential confounding factors. | **A** |
| **Maimaitimi** | Retrospective | 442 infants and | Breast fed vs | Denver Developmental Screening | There were no differences in | none | No difference. | **C** |

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| **ng et al 2007 (63)** | cohort | children inhabited by Uygur, Han, or Kazak nationality in West China | mixed feeding | Test at age up to 3. | scores between breastfeeding vs mixed feeding groups. | | | |
| **Makrides et al 2000 (64)** | Prospective randomized double blind controlled. Different formulas. Breastfed group was used as control, but not randomized. | 68 formula fed infants and 46 breastfed infants born at term of appropriate weight in Australia | Formula fed vs breastfed | Infant VEP acuity at 16 and 34 weeks<br>Bayley's Scales of Development at 1 year and 2 years. | At 1 yr of age, MDI scores of breastfed and formula-fed infants were not different, but at 2 years of age, MDI scores of breastfed infants were higher than formula fed infants. PDI scores were similar. | Home screening questionnaire scores, occupational prestige, parental education, gender, birth weight, maternal smoking, birth order, feeding mode. | MDI score was higher at age 2 in the breastfed group. 95% CI 3-16.8. | **A** |
| **Malloy et al 1997 (65)** | Retrospective cohort | 518 children born in 1978-79 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 old | Breastfed scored significantly higher on full scale IQ; Further analyses limited to those exclusively breastfed for the first 60 days failed to demonstrate any significant relationship. | Maternal education, paternal education and annual income | Following adjustment, the difference was not significant. | **B** |
| **Martin et al 2011 (66)** | Retrospective cohort | 1431 children (twin siblings) from the greater Brisbane area | Exclusively formula fed, any breastfeeding between birth and 3 months, exclusively breastfed for 3 to 6 months, exclusively breastfed for 6 months or more | FSIQ (full scale IQ) assessed using the Multi-dimensional Aptitude Battery (MAB) at 16 years of age | Breastfeeding was significantly associated with FSIQ scores. No effect of duration of breastfeeding on FSIQ was found. | Socioeconomic status, paternal education, maternal education, gestational age, and birth weight. | The effect was no longer significant after adjustment. | **A** |
| **McCrory et al 2011 (67)** | Retrospective cross-sectional study | 8568 school children in Ireland born between 1997 and 1998. | Breastfed vs not breastfed<br>AND<br>Never breastfed, <=5 weeks, 6-15 weeks, 16-25 weeks, 26+ weeks | Age 9 years. Vocabulary component of the Drumcondra Primary Reading Test-Revised and part 1 of the Drumcondra Primary Mathematics Test-Revised. | In unadjusted analysis, children who were breastfed scored 8.67 percentage points higher on reading and 7.42 percentage points higher on math. 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, mothers 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 math respectively | **A** |

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| **Morales et al 2011 (68)** | Retrospective cohort analyzing 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 Bayley Scales of Infant Development, first Edition – MDI only, and at age 4 years old 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 synthesize these fatty acids had higher scores regardless of breastfeeding practices. | Sex, child age, psychologist, quality of neuropsychological test, maternal education, breastfeeding, and use of gas stove at home. | Not being breastfed conferred an 8- to 9-point disadvantage in cognition among children with low FADS1 activity and in a 5-8 point disadvantage in cognition among children with low ELOVL5 activity. | **A** |
| **Morris et al 1999 (69)** | Prospective cohort | 102 normal birthweight children born in Brazil at term. | Number of breastfeeds per day (recorded daily). | Bayley Scales of Infant Development 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 1988 (70)** | Prospective cohort | 229 children born in Ohio between 1981-1982 | No breastfeeding, breastfeeding =<4 months, breastfeeding >4 months | Bayley Scales of Infant Development – Mental Development Index (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 both 1 year 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 | **A** |

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| | | | | | | | average 9 points higher compared to the bottle-fed infants. | |
| **Mortensen et al 2002 (71)** | Prospective longitudinal birth cohort | Mixed sample: 973 men and women<br>All-male sample: 2280 men in Denmark | Divided to five groups:<br>< 1 month<br>2-3 months<br>4-6 months<br>7-9 months<br>> 9 months | Wechsler Adult Intelligence Scale (WAIS) at a mean age of 27.2 years in the mixed-sex sample.<br>Børge Priens Prøve (BPP) test at a mean age of 18.7 years in the all-male sample. | Duration of breast-feeding was associated with significantly higher scores on the Verbal, Performance, Full Scale WAIS IQs and BPP test. | Parental social status<br>Parental education<br>Single mother status<br>Mother's height, age, and weight gain during pregnancy<br>cigarette consumption during the third trimester number of pregnancies<br>Gestational age birth weight<br>Birth length<br>Indexes of pregnancy<br>Delivery complications | The results remained significant with 4.6 points higher IQ for those breast-fed over 9 months compared to less than 1 month. | **B** |
| **Mukerji et al 1993 (72)** | Cross-sectional study | 100 children aged 0-3 years in India | No breast-feeding or mixed.<br>Exclusive breast-feeding for 4-9 months.<br>Exclusive breastfeeding for more than 9 months | Developmental Screening Test (DST) | In the 4-9 months exclusive breast fed group 100% had average or above average IQ.<br>In the two other groups this number was significantly lower. | None. | No adjustments were made. | **C** |
| **Nassar et al 2011 (73)** | Cross-sectional study | 42 healthy infants in Cairo, Egypt | Breastfed, artificially fed, mixed feeding | Bayley scale of infant development-second edition (BSID-II) between 4-6 months of age. | No difference in MDI or PDI.<br>There was significant difference only in total behavior rating scale (TBRS) and motor quality percentile 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 percentile rank. | **B** |
| **Nelson et al 1995 (74)** | Prospective cohort | Term gestation infants in USA | Breast fed or formula fed for 3 months | Teller Acuity Cards at 14d, 3, 4, 8, and 18 months<br>Fagan Test of Infant Intelligence at 8, 10 and 12 months<br>Bayley Scales of Infant Development at 4, 8, and 18 months | There were no significant differences between breast-fed and formula-fed infants in visual acuity at 14d, 3, 8, or 18 months, or recognition memory or the Bayley PDI or MDI at any age | | Meeting abstract only available | **C** |

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| **Niemela et al 1996 (75)** | Prospective follow-up | 726 children born between 1985-86 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 (sig difference found in relation to the general cognitive capacity and visual motor integration). No evidence of any interaction between verbal development and breastfeeding to 5 months or more. | Groups matched pairwise based on sex and maternal education. | Maternal education and parental status correlated with all cognitive scores. Sex and breastfeeding correlated with scores of the general cognitive capacity and visual motor integration tests in multiple linear regressions. | **B** |
| **Oddy et al 2003 (76)** | Prospective cohort | 1401 children at first follow up and 1283 children at second follow up from the Western Australian Pregnancy Cohort Study following 2860 children in Perth, Australia | Never breastfed, fully breastfed 0-4 months, 4-6 months, more than 6 months | Peabody Picture Vocabulary Test-Revised (PPVT-R) for receptive English vocabulary – verbal intelligence at 6 yrs Performance subtest by the Wechsler Intelligence Scale for Children – Third Edition (WISC-III) – Block Design Test at age 8yrs | On average, children breast fed for more than 6 months had mean verbal IQ scores that were 6,44 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) | breast feeding 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 difference after adjustment. | **A** |

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| **Oddy et al 2011 (77)** | Prospective cohort | 980 children from the Western Australian Pregnancy Cohort Study following 2860 children in Perth, Australia | Breastfed less than 4 vs more than 4 months And Breastfed less than 6 vs more than 6 months | Western Australian Monitoring Standards in Education (WAMSE) scores in: math, reading, writing, and spelling at age 10yrs | Continuous breastfeeding was significantly associated with an increase in scores with each additional month of breastfeeding for math, 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 math and spelling, revealing that boys were more likely to have improved academic scores if breastfed for a longer period. | **A** |
| **Paine et al 1999 (78)** | Retrospective cohort | 96 healthy full term Caucasian children from the Adelaide area in Australia | Duration of exclusive breastfeeding | Bayley Scales of Infant Developmental at age 10-14 months | Duration of exclusive breast-feeding significantly predicted mental development scores for boys, but not for girls. Duration of breast-feeding did not predict psychomotor development scores. | Duration of breast-feeding, parents occupational prestige, parents' education level and smoking habits, number of siblings, birth order, HSQ score, gestational age, birthweight, 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, birthweight, and duration of breastfeeding. | None. | **C** |

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| **Pollock et al 1994 (79)** | Prospective cohort | 3838 children from the 1970 British Births Survey at full term and healthy birth weight | Wholly breast fed 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, similarities, matrices, total) and Continuous outcomes: Pictorial Language test, Friendly Maths test, Edinburgh Reading test, Spelling test, and British Ability Scales (Word definitions, similarities, matrices, total) at age 10 | Significant difference found between groups at age 5 for the English Picture Vocabulary test. Significant difference found for both dichotomized outcomes and continuous outcomes for the British Ability Scales and dichotomized outcomes for the Pictorial Language test at age 10. | Age father left full time education, age mother left full time education, highest educational qualifications of mother, mother's smoking behavior during pregnancy, antenatal labour preparation class attendance, infant's place of birth | All results adjusted for all other independent predictors of breast-feeding: English Picture Vocabulary test: aOR 1.50. Dichotomized outcomes: Pictorial Language test aOR 1.49 Word definitions aOR 1.55 Similarities aOR 1.64 Total aOR 1.64 Continuous outcomes: Word definitions mean diff 3.5 Matrices mean diff 2.6 Similarities mean difference 3.0 Total mean difference 3.1 | **A** |

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| **Quinn et al 2001 (80)** | Prospective cohort | 3880 healthy children from the Mater Hospital-University of Queensland Study of Pregnancy project | Never breastfed, < 3 weeks, 3-7 weeks, 7 weeks – 4 months, 4-6 months, still breast feeding at 6 months | Peabody Picture Vocabulary Test Revised (PPVT-R) at 5 yrs. of age. | Significantly increasing scores were found between duration of breastfeeding and the PPVT-R scores. | Birthweight, poverty, maternal education, maternal age, time in daycare/preschool, number of children in household at 5 years, English speaking background for mother & father, and degree of infant stimulation | After adjusting for a wide range of biological and social factors, the adjusted mean for those breastfed for 6 months or more was 8.2 points higher for females and 5.8 higher for males than compared to those never breastfed (this was significant). | **A** |
| **Rao et al 2002 (81)** | Prospective cohort | 299 children born in Norway/Sweden at appropriate size for gestational age (comparison group) | <12 weeks Vs. >12 weeks of breastfeeding AND Duration of breastfeeding as a continuum | Bayley Scales of Infant Development at 13 months of age Norwegian version of the Wechsler Preschool and Primary Scales of Intelligence – Revised at 5 yrs. of age Peabody Development Motor Scale measured at 5 yrs. of age | There were statistically significant differences in IQ between the 2-breastfeeding groups. | Site of enrolment, maternal education, maternal IQ, maternal smoking, admission to a neonatal intensive care unit, kindergarten attendance, gender and asymmetric intrauterine growth retardation | 3.7 points for total IQ and 4.1 points for performance IQ. Results remained unaltered when adjusted for confounding variables. | **B** |
| **Ribas-Fito et al 2007 (82)** | Prospective cohort | 391 children born in Spain between 1997-1999 | 0-2 weeks breastfeeding 2-20 weeks breastfeeding 20+ weeks breastfeeding | Spanish version of the McCarthy Scales of Children's Abilities (general cognitive scale, verbal scale, perceptual-performance scale, memory scale, quantitative scale, motor scale subsets) at 4 yrs. of age. | Children with longer periods of breastfeeding performed significantly better on the McCarthy cognitive scale (except motor). | Gender, academic trimester at examination, psychologist, maternal social class, maternal education, and maternal use of alcohol and tobacco during pregnancy | After adjustment for confounders, significance remained for the general cognitive scale, and a trend remained in other subsets. | **A** |

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| **Richards et al 2002 (83)** | Retrospective cohort | 1741 people from the MRC National Survey of Health and Development (NSHD), also known as the British 1946 birth cohort | Never<br>Up to 2 months<br>2-7 months<br>7+ months | National Adult Reading Test (NART), word-list learning task (verbal memory) and timed letter search task (mental speed and concentration) at age 53. | Educational Attainment:<br>Odds of obtaining higher qualifications by the age of 26 were statistically significant, with greater odds for longer breastfeeding.<br>Cognitive Function:<br>Regression coefficients for the unadjusted effect show that breastfeeding was significantly associated with the NART and verbal memory tests. | Early background variables: Sex, father's social class, mother's education, birth order, parental interest in education and material home conditions. | Effect of BF on education was strengthened after adjusting for the early background variables and remained significant. No longer significant with further adjustment for cognitive ability at age 15.<br>Cognitive function:<br>Coefficients were reduced after adjusting for the early background variables and were further reduced after adjusting for educational attainment and adult social class<br>Only NART remained sig. | **A** |

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| **Richards et al 1998 (84)** | Retrospective cohort | 511 first born offspring of the British 1946 cohort and their parent | Duration of breastfeeding. | Sentence completion test, reading test and vocabulary test at age 8 yr. | 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 offspring cohort became non-significant after adjusting for social class, maternal education, or maternal cognitive performance. | 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 cohort members had been taught cognitive skills at age 4, and cognitive test scores of the mothers. | Non-significant; after adjusting for social class, maternal education, or maternal cognitive performance. | **C** |
| **Rodgers et al 1978 (85)** | Longitudinal study | 1464 children at age 8 and 1398 children at age 15 from the British 1946 cohort | Never bottle-fed vs. never breastfed | Picture intelligence test and word reading test at 8 years of age Non-verbal ability, mathematics, and sentence completion tests at age 15 years of age | A preliminary analysis indicated that low scores were more likely for those who had been bottle-fed than breast-fed. The mean sentence completion scores between the two groups is statistically significant. Every test at both ages was significant except for word reading scores after correction for background factors. | Sex, social group, parental interest in education, material home conditions, sample stratification, father's education, mother's education, family size, birth rank, age at weaning | After correction for confounders, every test at both ages was significant except for word reading scores. | **B** |
| **Rogan et al** | Prospective | 855 newborns being | Bottle fed | Bayley Mental and Psychomotor | Bayley Mental and Psychomotor: | Age, race, occupation, | Confounders | **B** |

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| **1993 (86)** | cohort | followed in North Carolina were enrolled between 1978-1982 and followed up to 5 yrs old | 'short breastfeeding' 'medium breastfeeding' 'long breastfeeding' 'very long breastfeeding' | Development Index at 6, 12, 18, and 24 months of age. McCarthy General Cognitive, Verbal, Quantitative, Memory, Perceptual Performace, and Motor scales at 36, 48, and 60 months of age Report Card Grades from 3rd, 4th and 5th grade (averaged) | After adjusting for co-variables, the results at all four time points were similar, differences among the groups were only statistically sig. 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. Marginally significant after adjustment for English scores and not significant for math. | education, smoking, drinking, child's sex, birthweight, number of older siblings, prenatal PCB exposure and dichlorodiphenyl dichloroethene exposure , Identity of the examiner. | integrated into model; unadjusted results not shown. | |
| **Santiago Burruchaga et al 2000 (87)** | Prospective cohort | 39 children born at term and from homogenous sociocultural status in Spain | Breastfed for al least 2 months vs. formula fed | Bayleys scale at 2 years of age | No statistically significant differences between groups were found in cognitive function. | Maternal age, level of education, occupation, number of children in the family,smoking. | None; confounders integrated into model. | **C** |
| **Silva et al 2006 (88)** | Longitudinal population based | 9367 children from the 1970 British | Never breastfed Less than 1 | British Ability Scale, the Shortened Edinburgh Reading Test (word | Breast-feeding showed a positive association with cognition at 10 | Socioeconomic class, birth weight, parity, gestational age, | Breastfeeding was weakly | **A** |

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| | cohort | Cohort Study comprising individuals born during April 5-11 in the UK | month<br>1-3 months<br>More than 3 months | recognition), the Friendly Math Tests, and the Pictorial Language Comprehension Test at age of 10 yrs. | years before adjustment. | maternal age and maternal smoking | associated with cognitive function after adjustment (standardized 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. | |
| **Silva et al 1978 (89)** | Retrospective cohort | 1037 children from the Dunedin Multidisciplinary Child Development Study | < 1 week<br>1-4 weeks<br>5-12 weeks<br>13-24 weeks<br>25-36 weeks<br>37-51 weeks<br>51+ weeks | Gross motor co-ordination, fine motor co-ordination, verbal comprehension and verbal expression, intelligence, child behavior problems at age 3 yrs. | 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.<br><br>Pairwise comparison with group matching to account for confounders. | None; pairwise matching said to account for confounders. | **B** |
| **Sloan et al 2010 (90)** | Cross-sectional observational. Breastfeeding data were obtained retrospectively. | 137 infants and mothers in Ireland | Breast fed (defined as more than 1 month) vs. not breast fed (defined as less than a month a not at all) | Bayley Scales of Infant Development (second edition; Bayley, 1993), between 10 and 18 months old. | Mean cognitive scores were significantly higher in breast-fed infants (110) compared with formula-fed infants (105). Breastfeeding duration had a positive linear association with cognitive scores at one year. | Home environment (HOME score) and infant gender | The adjusted standardized beta for breastfeeding was 0.285, which remained significant after adjustment. | **C** |
| **Slykerman 2005 (91)** | Cross-sectional observational. | 550 infants, 50% of which were SGA at | Not at all, less than 6 m, | Stanford Binet Intelligence Scale, 4th Edition | Breastfeeding was not significantly related to | Examiner administering the intelligence test, gestation, | No difference in IQ. | **B** |

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| | Breastfeeding data were obtained retrospectively. | birth and 50% AGA in New Zealand. | 6 to 12 m, >12 m. | at age 3.5y-4y | intelligence scores in the AGA group. | gender, maternal education, marital status, parental occupation, maternal age, parity, and smoking. | | |
| **Steer et al 2010 (92)** | Prospective observational. Breastfeeding data were obtained prospectively. | 9656 children from the Avon Longitudinal Study of Parents and Children cohort, in United Kingdom | Breastfeeding within the first month of life vs. never breast feeding | 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 birth weight, pre-term gestation, home environment, parenting and gender | The breastfeeding effect attenuated to a 3- point advantage after adjustment. | **B** |
| **Taylor et al 1984 (93)** | Longitudinal population based cohort. Breastfeeding data were obtained retrospectively. | 13,135 children from The Child Health and Education Study in the United Kingdom | Never breastfed<br>Less than 1 month<br>1-3 months<br>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 a standard deviation above the norm. | The age of the child at testing; the child's sex and birthweight; 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 | Breast feeding remained a significant influence on EPVT scores, but the difference between the groups was small: +0.12 in the standardized EPVT score | **A** |
| **Temboury et al 1994 (94)** | Prospective cohort | 229 infants in Spain | Breast fed – at least three months<br>Bottle-fed – none or less than 1 month | Baylay'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, birthweight, height, place of birth | The result remained significant. | **C** |
| **Thorsdottir et al 2005 (95)** | Longitudinal cohort | 85 children in Iceland | Duration of exclusive breastfeeding | The Icelandic developmental inventory at age 6 years. Information collected from the mothers. | Duration of exclusive breastfeeding, in months, was positively related to children's total developmental index. | Maternal and paternal education, and family income, birthweight, maternal BMI. | Total developmental index (B=1.07±0.5, P=0.04) | **C** |
| **Tozzi et al 2012 (96)** | Prospective cohort | 1403 children originally included in | Duration of exclusive | An estimated IQ was obtained from scores of the vocabulary, | Scores of only a few neuropsychological tests were | Sex, birthweight, gestational age, mother's age at birth, type | In the regression analysis, the | **A** |

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| | | an Italian clinical trial on acellular Pertussis vaccines | breastfeeding both as a continuous variable and as a categorical variable (<6mo, >6mo). | 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. | 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. | of delivery, family composition, parents' education, presence of chronic diseases, current prescription of antihistamines or antiepileptic drugs, and the amount of thimerosal to which children were exposed through vaccines. | 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 | |
| **Veena et al 2010 (97)** | Longitudinal cohort | 514 children from the Mysore Parthenon birth cohort in south India | Six categories from <3 to ≥18 months | Kaufman Assessment Battery at 9-to10-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, socio-economic status, parents' attained schooling and rural/urban residence. | No difference either unadjusted or after adjustment. | **B** |
| **Whitehouse et al 2011 (98)** | Longitudinal cohort, breast feeding data | 1195 live born children recruited at approximately 18 | (1) Never breast-fed, (2) Breast-fed | Peabody Picture Vocabulary Test – Revised (PPVT-R) at age 10 years. Raw scores are transformed to | Strong positive association between the duration of predominant breast-feeding and | Maternal age at conception, maternal education, family income, and the presence of the | Children who were predominantly | **A** |

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| | collected prospectively | weeks gestation, Western Australian Pregnancy Cohort (Raine) Study. | predominantly for <4 months, (3) Breast-fed predominantly for 4–6 months (4) Breast-fed predominantly for >6 months. | standard scores, based around a mean of 100 and a SD of 15. | PPVT-R at age 10 years. | 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 birthweight, a measure of the appropriateness of fetal growth, Family functioning (MMFAD), Parenting Scale, language-learning environment. | breast-fed for >6 months had a mean PPVT-R score that was 4.04 points higher than children who were never breast-fed | |
| **Wigg et al 1998 (99)** | Longitudinal cohort, breast feeding data collected prospectively | 375 children born in Port Pirie, South Australia. | At 6 month of age: Breast fed vs. bottle-fed. Children who were breast-fed for less than 6 months would have been classified in our analysis as bottle-fed. | Bayley Scales of Infant Development 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 breast-fed children at ages 2, 4 and 7 years were 5.5 points, 4.6 points and 4.3 points in MDI, GCI and IQ scores, respectively. At age 11 to 13 years, the unadjusted advantage for the breast-fed children was 3.8 points in IQ. | Gender, maternal age at delivery, socioeconomic status, HOME score, maternal IQ, parental smoking habits, birthweight, birth rank, lifetime average blood lead concentration and whether parents were living together. | Adjusting for the covariates diminished the association of the feeding method in infancy with cognitive development. The covariates contributing most to this attenuating effect were the HOME scores, maternal IQ, socioeconomic status and parental smoking habits. | **B** |
| **Zaini et al 2005 (100)** | Retrospective cohort | 1397 children from Selangor Malaysia | <6 months >6 months | Raven's Colored Progressive Matrices at a mean age 9.6 years | Those who were breastfed less than six months performed better (31.01 vs. 30.63 out of max 36) | None. | None. | **C** |

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| **Zhou et al 2007 (101)** | Prospective cohort | 302 children born between 1998 and 1999 in Adelaide, Australia | Not breast fed, Breast fed 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 breast-feeding and childhood IQ in this relatively well-nourished cohort from an industrialized society. Before adjustment, children who were breast-fed for at least 6 m. had higher IQ than those who were breast-fed 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 breast-feeding and childhood IQ. | **B** |

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)<br>B – 9 (43)<br>C - 8 (38) |
| Positive association between IQ and BF | 28** | A – 10 (36)<br>B – 7 (25)<br>C – 11 (39) |
| Initial positive association which became negative after adjustment for confounders | 18*** | A – 6 (33.3)<br>B – 8 (44.4)<br>C – 4 (22.3) |
| Initial positive association, weakened after adjustment for confounders but remained statistically significant | 17**** | A – 14 (82)<br>B – 2 (12)<br>C – 1 (6) |

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

**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)<br>B – 2 (33.3)<br>C – 4 (66.6) |
| | Positive association between IQ and BF | 4 (30) | A – 1 (25)<br>B – 0 (0)<br>C – 3 (75) |
| | Initial positive association which became negative after adjustment for confounders | 2 (15) | A – 0 (0)<br>B – 2 (100)<br>C – 0 (0) |
| | Initial positive association, weakened after adjustment for confounders but remained statistically significant | 1 (8) | A – 1 (100)<br>B – 0 (0)<br>C – 0 (0) |
| **Developed Countries** (n = 71)** | No association between IQ and BF | 15 (21) | A – 4 (26.6)<br>B – 7 (46.6)<br>C – 4 (26.6) |
| | Positive association between IQ and BF | 24 (34) | A – 9 (37.5)<br>B – 7 (29.2)<br>C – 8 (33.3) |
| | Initial positive association which became negative after adjustment for confounders | 16 (22.5) | A – 6 (37.5)<br>B – 6 (37.5)<br>C – 4 (25) |
| | Initial positive association, weakened after adjustment for confounders but remained statistically significant | 16 (22.5) | A – 13 (81.25)<br>B – 2 (12.5)<br>C – 1 (6.25) |

IQ – Intelligence Quotient; BF – breastfeeding

**Developing:** *15, 21, 33, 34, 35, 36, 38, 63, 69, 72, 73, 97, 100
**Developed:** **9, 13, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 37, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 64, 65, 66, 67, 68, 70, 71, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 98, 99, 101

**Table 4** – Studies by age group, directionality and quality grading

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

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| | | | C – 0 (0) |
| | Initial positive association which became negative after adjustment for confounders | 1 (20) | A – 0 (0)<br>B – 1 (100)<br>C – 0 (0) |
| | Initial positive association, weakened after adjustment for confounders but remained statistically significant | 1 (20) | A – 1 (100)<br>B – 0 (0)<br>C – 0 (0) |

IQ – Intelligence Quotient; BF – breastfeeding

**Infancy*:** 22,24,35,36,37^,38,51,54,60,64^,69,70^,72^,73,74^,78^,86^,90^
**Childhood**:** 9,13,15,21,23,25,26,27,28,29,30,31,32,33,34,37^,40,41,42,43^,45,46,47,48,49,50,52,53,55,56,57, 58,59,61,62,63,64^,65,66,67,68,70^,72^,74^,75,76,77,78^,79,80,81,82,84,85,86^,87,88,89,90^,91,92,93,94,95,96, 97,98,99,100,101
**Adulthood***:** 39,43^,44,71,83

^Study examined two different age groups and therefore included in several categories.