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Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries

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The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Office on Women's Health, Department of Health and Human Services, requested and provided funding for this report. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.hhs.gov.**

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We acknowledge with appreciation the members of the Technical Expert Panel for their advice and consultation to the Evidence-based Practice Center (EPC) during preparation of this report. In designing the study questions and methodology at the outset of this report, the EPC consulted these technical and content experts. Broad expertise and perspectives are sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design and/or methodologic approaches do not necessarily represent the views of individual technical and content experts.

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Structured Abstract

Objectives: We reviewed the evidence on the effects of breastfeeding on short- and long-term infant and maternal health outcomes in developed countries.

Data Sources: We searched MEDLINE®, CINAHL, and the Cochrane Library in November of 2005. Supplemental searches on selected outcomes were conducted through May of 2006. We also identified additional studies in bibliographies of selected reviews and by suggestions from technical experts.

Review Methods: We included systematic reviews/meta-analyses, randomized and non-randomized comparative trials, prospective cohort, and case-control studies on the effects of breastfeeding and relevant outcomes published in the English language. Included studies must have a comparative arm of formula feeding or different durations of breastfeeding. Only studies conducted in developed countries were included in the updates of previous systematic reviews. The studies were graded for methodological quality.

Results: We screened over 9,000 abstracts. Forty-three primary studies on infant health outcomes, 43 primary studies on maternal health outcomes, and 29 systematic reviews or meta-analyses that covered approximately 400 individual studies were included in this review. We found that a history of breastfeeding was associated with a reduction in the risk of acute otitis media, non-specific gastroenteritis, severe lower respiratory tract infections, atopic dermatitis, asthma (young children), obesity, type 1 and 2 diabetes, childhood leukemia, sudden infant death syndrome (SIDS), and necrotizing enterocolitis. There was no relationship between breastfeeding in term infants and cognitive performance. The relationship between breastfeeding and cardiovascular diseases was unclear. Similarly, it was also unclear concerning the relationship between breastfeeding and infant mortality in developed countries. For maternal outcomes, a history of lactation was associated with a reduced risk of type 2 diabetes, breast, and ovarian cancer. Early cessation of breastfeeding or not breastfeeding was associated with an increased risk of maternal postpartum depression. There was no relationship between a history of lactation and the risk of osteoporosis. The effect of breastfeeding in mothers on return-to-pre-pregnancy weight was negligible, and the effect of breastfeeding on postpartum weight loss was unclear.

Conclusions: A history of breastfeeding is associated with a reduced risk of many diseases in infants and mothers from developed countries. Because almost all the data in this review were gathered from observational studies, one should not infer causality based on these findings. Also, there is a wide range of quality of the body of evidence across different health outcomes. For future studies, clear subject selection criteria and definition of “exclusive breastfeeding”, reliable collection of feeding data, controlling for important confounders including child-specific factors, and blinded assessment of the outcome measures will help. Sibling analysis provides a method to control for hereditary and household factors that are important in certain outcomes. In addition, cluster randomized controlled studies on the effectiveness of various breastfeeding promotion interventions will provide further opportunity to investigate any disparity in health outcomes as a result of the intervention.

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Appendixes and Evidence Tables are provided electronically at
http://www.ahrq.gov/downloads/pub/evidence/pdf/brfout/brfout.pdf

Executive Summary

Introduction

The purpose of this report is to summarize the literature concerning the relationship of breastfeeding and various infant and maternal health outcomes. This report was requested by the Department of Health and Human Services (DHHS) Office on Women's Health and was conducted through the Evidence-based Practice Center (EPC) program at the Agency for Healthcare Research and Quality (AHRQ).

Methods

Two key questions are addressed:

1. What are the benefits and harms for infants and children in terms of short-term outcomes, such as infectious diseases (including otitis media, diarrhea, and lower respiratory tract infections), sudden infant death syndrome (SIDS) and infant mortality, and longer-term outcomes such as cognitive development, childhood cancer (including leukemia), type I and II diabetes, asthma, atopic dermatitis, cardiovascular disease (including hypertension), hyperlipidemia, and obesity, compared among those who mostly breastfeed, mostly formula feed, and mixed feed; and how are these outcomes associated with duration of the type of feeding? Do the harms and benefits differ for any specific subpopulations based on socio-demographic factors?

2. What are the benefits and harms on maternal health short-term outcomes, such as post-partum depression and return to pre-pregnancy weight, and long-term outcomes, such as breast cancer, ovarian cancer, diabetes and osteoporosis, compared among breastfeeding, formula feeding, and mixed feeding, and how are these associated with duration of the type of feeding? Do the harms and benefits differ for any specific subpopulations based on socio-demographic factors?

Approach to Evaluating the Literature

Inclusion Criteria. As it was not feasible to review the large number of primary studies that are relevant to all the outcomes of interest, we consulted the Office on Women's Health and the technical expert panel (TEP) and developed an approach that capitalized on the existing large number of systematic reviews/meta-analyses. For outcomes of interest that have previously been reviewed systematically, we have summarized the findings from those reviews. For acute otitis media, childhood asthma, cognitive development, SIDS, infant mortality, NEC, maternal breast cancer, return to pre-pregnancy weight, and maternal type 2 diabetes, we have also updated those systematic reviews with data from primary studies published subsequent to those reviews. For outcomes that have not been previously evaluated systematically (osteoporosis, ovarian cancer, postpartum depression, infant mortality), we have reviewed those primary studies that met our inclusion criteria. Studies that examined only formula-fed infants were excluded.

Definitions of Breastfeeding. The majority of the studies did not distinguish between exclusive and partially breastfed infants, or explain the difference between "breastfeeding" and "feeding of expressed breast milk." We elected to use the term "breastfeeding" for studies in full-term infants and the term "human milk feeding" for studies in preterm infants. We elected to accept all definitions of "exclusive breastfeeding" as provided by the different study authors but qualified our conclusions with respect to those specific definitions.

Literature Search Strategy. Comprehensive literature searches of MEDLINE®, CINAHL, and the Cochrane Database of Systemic Reviews took place in November of 2005. Search terms included subject headings and text words relevant to breastfeeding and the different outcomes. Supplemental searches on selected outcomes were conducted through May of 2006. Other relevant studies were identified by technical experts or in bibliographies of selected reviews.

Specific Inclusion Criteria for Health Conditions Evaluated. We included systematic reviews, meta-analyses, observational studies, randomized controlled trials, and comparative studies that evaluated the effects or associations of breastfeeding on outcomes of interest. All studies must have either a comparator arm that evaluated formula feeding or a comparator arm that evaluated different durations of breastfeeding. Only studies conducted in developed countries were used in updates of systematic reviews/meta-analyses and de novo reviews of primary studies.

Reporting of Evidence

Methodological Quality Grade of Individual Studies. We used a three category grading system (A, B, C) to denote methodological quality of each primary study. We did not evaluate the methodological quality of the individual studies in the systematic reviews/meta-analyses.

A (good): Least bias and results are valid; a primary study that adheres mostly to the commonly held concepts of high quality

B (fair/moderate): Susceptible to some bias, but not sufficient to invalidate the results; a primary study that does not meet all the criteria in category A

C (poor): Significant biases that may invalidate the results; a primary study with serious errors in design, analysis or reporting

Methodological Quality Grade of Systematic reviews/Meta-analyses. We used a similar scheme as above for grading systematic reviews/meta-analyses. But we supplemented the scheme with the MOOSE guideline (standards for reporting for meta-analysis in observational studies in epidemiology) and an additional checklist of items that we devised to evaluate the quality of the systematic review of observational studies. Items in this checklist included questions on the following: appropriate search strategy; justification for inclusion/exclusion criteria for studies; description of well-defined population, intervention/exposure, comparator, outcomes and study designs; effort to minimize errors in data extraction; assessment of quality of individual studies; consideration on the effect of confounders; combinability of the data for meta-analysis; assessment of statistical and clinical heterogeneity; reporting accuracies; and appropriateness of the conclusions based on the reported data.

Results

We screened over 9,000 abstracts. Forty-three primary studies on infant health outcomes, 43 primary studies on maternal health outcomes, and 29 systematic reviews or meta-analyses that covered approximately 400 individual studies were included in this review.

The association studies of breastfeeding and health outcomes mostly presented results as odds ratios. To facilitate interpretation of the odds ratio, we chose to present these data as a reduction in relative risk, estimated as "(1 – odds ratio) x 100%," along with the corresponding 95% confidence interval (CI).

Full term Infant Outcomes

Acute Otitis Media. Our meta-analysis of five cohort studies of good and moderate methodological quality showed that breastfeeding was associated with a significant reduction in the risk of acute otitis media. Comparing ever breastfeeding with exclusive formula feeding, the risk reduction of acute otitis media was 23 percent (95% CI 9% to 36%). When comparing exclusive breastfeeding with exclusive formula feeding, either for more than 3 or 6 months duration, the reduction was 50 percent (95% CI 30% to 64%). These results were adjusted for potential confounders.

Atopic Dermatitis. One good quality meta-analysis of 18 prospective cohort studies on full term infants reported a reduction in the risk of atopic dermatitis by 42 percent (95% CI 8% to 59%) in children with a family history of atopy and exclusively breastfed for at least 3 months compared with those who were breastfed for less than 3 months. The meta-analysis did not distinguish between atopic dermatitis of infancy (under 2 years of age) and persistent or new atopic dermatitis at older ages. It has been postulated that the diagnosis of atopic dermatitis in patients younger than 2 years of age could be attributed to infectious etiologies, which may be prevented by breastfeeding. However, a stratified analysis by duration of followup found the risk reduction from breastfeeding was similar in subjects with less than 2 years compared with more than 2 years of followup.

Gastrointestinal Infections. For non-specific gastroenteritis, one systematic review identified three primary studies that controlled for potential confounders. These studies reported that there was a reduction in the risk of non-specific gastrointestinal infections during the first year of life in breastfed infants from developed countries. But a summary adjusted estimate taking into account potential confounders could not be determined because the studies did not provide usable quantitative data. However, a recent case-control study from England that took into account the role of potential confounders reported that infants who were breastfeeding had a 64 percent (95% CI 26% to 82%) reduction in the risk of non-specific gastroenteritis compared with infants who were not breastfeeding.

Lower Respiratory Tract Diseases. The summary estimate from a good quality meta-analysis of seven studies reported an overall 72 percent (95% CI 46% to 86%) reduction in the risk of hospitalization due to lower respiratory tract diseases in infants less than 1 year of age who were exclusively breastfed for 4 months or more. The results remained consistent after adjustment for potential confounders.

Asthma. The studies on asthma were equivocal. A previously published good quality meta-analysis reported a moderate protective effect and four recent primary studies reaching mixed conclusions, including two studies finding an increased risk of asthma associated with breastfeeding. We updated the meta-analysis with the new studies. Our analysis showed that breastfeeding for at least 3 months was associated with a 27 percent (95% CI 8% to 41%) reduction in the risk of asthma

in those subjects without a family history of asthma compared with those who were not breastfed. For those with a family history of asthma, there was a 40 percent (95% CI 18% to 57%) reduction in the risk of asthma in children less than 10 years of age who were breastfed for at least 3 months compared with those who were not breastfed. However, the relationship between breastfeeding and the risk of asthma in older children and adolescents remains unclear and will need further investigation.

Cognitive Development. One well-performed sibling analysis and three prospective cohort studies of full-term infants, all conducted in developed countries, adjusted their analyses specifically for maternal intelligence. The studies found little or no evidence for an association between breastfeeding in infancy and cognitive performance in childhood. Most of the published studies adjusted their analyses for socioeconomic status and maternal education but not specifically for maternal intelligence. For those studies that reported a significant effect after specific adjustment for maternal intelligence, residual confounding from other factors such as different home environments cannot be ruled out.

Obesity. Three meta-analyses of good and moderate methodological quality reported an association of breastfeeding and a reduction in the risk of obesity in adolescence and adult life compared with those who were not breastfed. One study reported the reduction in the risk of overweight/obesity in breastfeeders compared with non-breastfeeders was 24 percent (95% CI 14% to 33%); another study reported 7 percent (95% CI 1% to 12%). Both of these estimates took into account the role of potential confounders. Furthermore, they also showed that the magnitude of association decreased when more confounders were entered into the analyses. The third study used meta-regression and found a 4 percent reduction in the risk of being overweight in adult life for each additional month of breastfeeding in infancy. Overall, there is an association between a history of breastfeeding and a reduction in the risk of being overweight or obese in adolescence and adult life. One should be cautious in interpreting all these associations because of the possibility of residual confounding.

Risk of Cardiovascular Diseases. Results from two moderate quality meta-analyses concluded that there was a small reduction of less than 1.5 mm Hg in systolic blood pressures and no more than 0.5 mm Hg in diastolic blood pressures among adults who were breastfed in their infancy compared with those who were formula-fed. The association weakened after stratification by study size, suggesting the possibility of bias in the smaller studies.

One meta-analysis of cohort and case-control studies reported that there was a reduction in total and LDL cholesterol levels by 7.0 mg/dL and 7.7 mg/dL, respectively, in adults who were breastfed during infancy compared with those who were not. However, these findings were based on data from adults with a wide age range. The analysis did not segregate the data according to gender and potential confounders were not explicitly analyzed. Detailed information (e.g., fasting or non-fasting) on the collection of specimen for cholesterol testing was not included. Because of these deficiencies, the correct characterization of a relationship between breastfeeding and adult cholesterol levels cannot be determined at this time.

One meta-analysis found little or no difference in all-cause and cardiovascular mortality between adults who were breastfed during infancy and those who were not. There were possible biases and limitations in the studies reviewed, however. Presence of statistical heterogeneity across studies suggests that it may not have been appropriate to combine estimates from individual studies into one summary estimate. Because of these reasons, no definitive conclusion could be drawn regarding the relationship between a history of breastfeeding and cardiovascular mortality.

In summary, the relationship between breastfeeding in infancy and the risk of cardiovascular diseases cannot be confidently characterized at this time and will need further investigation.

Type 1 Diabetes. Two moderate quality meta-analyses suggest that breastfeeding for at least 3 months reduced the risk of childhood type 1 diabetes compared with breastfeeding for less than 3 months. One reported a 19 percent (95% CI 11% to 26%) reduction; the other reported a 27 percent (95% CI 18% to 35%) reduction. In addition, findings from five of six studies published since the meta-analyses reported similar results. However, these results must be interpreted with caution because of the possibility of recall biases and suboptimal adjustments for potential confounders in the studies.

Type 2 Diabetes. In one well-performed meta-analysis of seven studies of various designs, breastfeeding in infancy was associated with a 39 percent (95% CI 15% to 56%) reduced risk of type 2 diabetes in later life compared with those who were not. However, only three of seven studies adjusted for all the important confounders such as birth weight, parental diabetes, socioeconomic status, and individual or maternal body size. Though the crude and adjusted estimates did not differ in these three studies, the lack of adjustments for potential confounders such as birth weight and maternal factors by all studies could exaggerate the magnitude of an association.

Childhood Leukemia. The published studies on childhood acute lymphocytic leukemia (ALL) were equivocal; a good quality meta-analysis reported a moderate protective effect from breastfeeding and the other good quality systematic review reached the opposite conclusion. We conducted a meta-analysis including only good and fair quality case-control studies identified in the systematic review, since the meta-analysis did not provide methodological quality grading of primary studies. We found breastfeeding of at least 6 months duration was associated with a 19 percent (95% CI 9% to 29%) reduction in the risk of childhood ALL. The previous meta-analysis also reported an association between breastfeeding of at least 6 months duration and a 15 percent reduction (95% CI 2% to 27%) in the risk of acute myelogenous leukemia (AML). Overall there is an association between a history of breastfeeding for at least 6 months duration and a reduction in the risk of both leukemias (ALL and AML).

Infant Mortality. One study of moderate methodological quality evaluated the relationship between breastfeeding and infant mortality. The study reported a protective effect of breastfeeding in reducing infant mortality after controlling for some of the potential confounders. However, in subgroup analyses of the study, the only statistically significant association reported was between "never breastfed" and Sudden Infant Death Syndrome (SIDS) or the risk of injury-related deaths. Because of the limited data in this area, the relationship between breastfeeding and infant mortality in developed countries remains unclear. Further investigation is needed.

Sudden Infant Death Syndrome (SIDS). We conducted a meta-analysis by including only studies that reported clear definitions of exposure, outcomes, and results adjusted for well-known confounders or risk factors for SIDS. Our meta-analysis of seven case-control studies found that a history of breastfeeding was associated with a 36 percent (95% CI 19% to 49%) reduction in the risk of SIDS compared to those without a history of breastfeeding.

Preterm Infant Outcomes

Cognitive Development. No definitive conclusion can be made regarding the relationship between breast milk feeding and cognitive development in preterm infants. One meta-analysis reported a five points advantage in standardized mean score and one systematic review identified one primary study that reported an eight points advantage in IQ in preterm or low birth weight infants who received breast milk feeding. In three of four primary studies of moderate quality that controlled for either maternal education or maternal intelligence, the advantage from breastfeeding was reduced to a statistically non-significant level after adjustment. The roles of maternal intelligence and home

environment should be accounted for in future studies on breastfeeding and cognitive development. Keeping in mind that cognitive function measured at an early age is not necessarily predictive of later cognitive ability, one should also consider carefully the timing and the selection of appropriate testing instrument in future studies.

Necrotizing Enterocolitis (NEC). Our meta-analysis of four randomized controlled trials of breast milk versus formula in comparing the outcome of NEC demonstrated that there was a marginally statistically significant association between a history of breast milk feeding and a reduction in the risk of NEC ($P = 0.04$). The estimate of the reduction in relative risk ranged from 4 percent to 82 percent. The absolute risk difference between the two groups was 5 percent. Because of the high case-fatality rate of NEC, this difference is a meaningful clinical outcome. The wide range of the estimate reflects the relatively small number of total subjects in the studies and the small number of events. One must also be cognizant of the heterogeneity underlying these trials in interpreting the findings of the meta-analysis. Examples of which included gestational age that ranged from 23 to more than 33 weeks; birth weight ranged from less than 1,000 g to more than 1,600 g; and some trials included only "healthy" infants, while others included both "healthy" and "ill" infants.

Maternal Outcomes

Return to Pre-pregnancy Weight. Three moderate quality prospective cohort studies reported less than 1 kg weight change from pre-pregnancy or first trimester to 1 to 2 year postpartum period in mothers who breastfed. Results from four moderate quality prospective cohort studies showed that the effects of breastfeeding on postpartum weight loss were unclear. Results from all seven studies consistently showed that many factors other than breastfeeding had larger effects on weight retention or postpartum weight loss. Methodological challenges in these studies included the accurate measurement of weight change, adequate control for numerous covariables including the amount of pregnancy weight gain, and quantifying accurately the exclusivity and the duration of breastfeeding.

Maternal Type 2 Diabetes. Two large cohorts from a high quality longitudinal study of 150,000 parous women in the United States examined the relationship between breastfeeding and the risk of maternal type 2 diabetes. In parous women without a history of gestational diabetes, each additional year of breastfeeding was associated with a 4 percent (95% CI 1% to 9%) reduced risk of developing type 2 diabetes in the first cohort and a 12 percent (95% CI 6% to 18%) reduced risk in the second cohort. In women with a history of gestational diabetes, breastfeeding had no significant effect on the already increased risk of diabetes. Because only nurses were included in the cohorts, generalization of findings to the rest of the population must be done with care.

Osteoporosis. There is little or no evidence from six moderate quality case-control studies for an association between lifetime breastfeeding duration and the risk of fractures due to osteoporosis. In two of three moderate or good quality prospective cohort studies using bone mineral density as a surrogate for osteoporosis, lactation does not appear to have an effect on long-term changes in bone mineral densities. The third study found a small decrease in the bone mineral contents in the distal radius with increased duration of breastfeeding, but no significant changes in bone mineral contents in the femoral neck or the trochanter**.**

Postpartum Depression. Four prospective cohort studies of moderate methodological quality reported on the relationship between a history of breastfeeding and postpartum depression. None of the studies explicitly screened for depression at baseline before the initiation of breastfeeding and none of them provided detailed data on breastfeeding. Three of the four studies found an association between a history of short duration of breastfeeding or not breastfeeding with postpartum depression.

The results were adjusted for socio-demographic and obstetric variables. More investigation will be needed to determine the nature of this association. It is plausible that postpartum depression led to early cessation of breastfeeding, as opposed to breastfeeding altering the risk of depression. Both effects might occur concurrently.

Breast Cancer. Two meta-analyses of moderate methodological quality concluded that there was a reduction of breast cancer risk in women who breastfed their infants. The reduction in breast cancer risk was 4.3 percent for each year of breastfeeding in one meta-analysis and 28 percent for 12 or more months of breastfeeding in the other. In addition, one of the two meta-analyses and another systematic review reported decreased risk of breast cancer primarily in premenopausal women. Findings from primary studies published after the meta-analyses concurred with the findings from the earlier meta-analyses. In summary, consistent evidence from these studies suggests that there is an association between breastfeeding and a reduced risk of breast cancer.

Ovarian Cancer. We reviewed 15 case-control studies that examined the relationship between breastfeeding and the risk of ovarian cancer, and performed meta-analyses in nine studies that adjusted for potential confounders. The overall result from the nine studies showed an association between breastfeeding and a 21 percent (95% CI 9% to 32%) reduction in the risk of ovarian cancer, compared to never breastfeeding. Because not all the studies reported similar comparisons of breastfeeding durations, we had to estimate the comparable risks in five studies. Excluding these five studies from the meta-analysis results in loss of statistical significance for this association.

There was indirect evidence for a dose-response relationship between breastfeeding and a reduced risk of ovarian cancer. Breastfeeding of more than 12 months (cumulative duration) was associated with a reduced risk of ovarian cancer, compared to never breastfeeding. The 12-month cutoff was arbitrary, and the odds ratios were estimated in half of these studies.

Overall, there is evidence to suggest an association between breastfeeding and a reduction in the risk of maternal ovarian cancer. Because of the aforementioned limitations, one must be cautious in interpreting this association.

Discussion

Limitations

With the availability of many published systematic reviews on breastfeeding, we used this literature as the evidence for a large number of outcomes, supplemented by updates of these systematic reviews with new primary studies. Even though we have assessed the reporting quality of these systematic reviews (using standards of reporting of systematic reviews of observational studies (MOOSE statement), and additional parameters that we devised), we cannot reliably know the validity of the reported summary data without knowing the details of the primary studies. It should also be stressed that a well-performed systematic review does not necessarily imply that the body of evidence for a particular outcome of interest is of high quality. Any systematic review is limited by the quality of the primary studies included in the review. Unless the method used to assess the quality of the primary studies is transparent and the details made available for examination, it would be difficult to reliably determine the validity of the conclusions.

The breastfeeding literature is primarily comprised of observational studies, either cohort or case-control studies. There are a number of potential deficiencies related to the observational study designs that could limit the internal validity and the generalizability of the findings. Some of these potential deficiencies include (1) misclassification of exposure; (2) confounding from the process of self-selection; and (3) residual confounding.

We have summarized the effects of breastfeeding (or breast milk feeding) on a large number of infant and maternal outcomes. Some of the outcomes are well defined and specific (e.g., childhood acute lymphocytic leukemia, breast cancer); and some are not so well defined and non-specific (e.g., asthma, non-specific gastrointestinal infections). When the reported outcome is well defined and specific, it lends confidence that the effect reported is valid for that outcome. When the reported outcome is not well defined, one might have some reservation regarding the validity of the measured effect for that outcome. For all the above reasons, we find that there is a wide range of quality of evidence for the different outcomes examined in this review.

An important area of research that is not systematically reviewed in this report is the use of breastfeeding promotion intervention trial to measure health effects (this topic is not part of the scope of this report and it will be covered in a separate report). The best known of these types of studies is the Promotion of Breastfeeding Intervention Trial (PROBIT) conducted in the Republic of Belarus. Data from this study provided good evidence that breastfeeding is associated with a reduction in the risk of gastrointestinal infection and atopic dermatitis.

Lastly, the outcomes analyzed in this review represent only a portion of all possible health outcomes related to breastfeeding reported by investigators worldwide. To work within the constraints of resources, we relied on the advice from our panel of technical experts in finalizing the list of outcomes included in this review. Thus, some important outcomes (e.g., growth and nutrition) have, by necessity, not been included in this review.

Future Research

Observational studies will remain the major source of information in this field. Clear subject selection criteria, adopting a common definition of “exclusive breastfeeding”, reliable collection of feeding data, specific and properly quantifiable outcomes of interest, controlling for important potential confounders including child-specific factors, and blinded assessment of the outcome measures will help immeasurably to improve the quality of these studies.

Sibling analysis provides a method to control for hereditary and household factors that are important in certain outcomes, provided that those factors are similar for the siblings of interest. Although such analysis may be less susceptible to confounders and effect modifiers that are shared by siblings, one must remember that it is not immune to biases. This method should be used when the appropriate data are available.

Cluster randomized controlled studies similar to the Belarus trial will provide understanding of the effectiveness of various breastfeeding promotion interventions. Any substantial differences in the degree of breastfeeding between the two groups as a result of the intervention will provide further opportunity to investigate any disparity in health outcomes between the two groups.

Evidence Report

Chapter 1. Introduction

The Department of Health and Human Services (DHHS) Office on Women's Health has requested an evidence report from the Agency for Healthcare Research and Quality (AHRQ) through the Evidence-based Practice Center program (EPC) that would critically examine the literature concerning the relationship of breastfeeding and various infant and maternal health outcomes. EPC evidence reports summarize evidence addressing specific key questions; these reports do not make clinical practice or health policy recommendations.

Breast milk is the natural nutrition for all infants. According to the American Academy of Pediatrics (AAP), it is the preferred choice of feeding for all infants.[1] The goals of *Healthy People 2010* for breastfeeding are an initiation rate of 75 percent and continuation of breastfeeding of 50 percent at 6 months and 25 percent at 12 months postpartum.[2] National Immunization Survey of U.S. children in 2005 (NIS 2005) indicated that 73 percent had ever been breastfed. The percentage of infants who continued to breastfeed to some extent is 39 percent at 6 months and 20 percent at 12 months (www.cdc.gov/breastfeeding/data/NIS_data/data_2005.htm).

In addition to providing essential nutrients to infants, benefits of breastfeeding for both children and their mothers have been reported. Reports of the benefits for children include decreases in incidence of otitis media and gastroenteritis,[3] lower risk of obesity,[4,5] and lower risk of asthma.[6] Other benefits reported include decreased rates of sudden infant death syndrome, reduction in the incidence of type 1 and type 2 diabetes mellitus, certain types of cancer, and improved performance on certain tests of cognitive development.[7]

Reported benefits for mothers who breastfed their infants include increased postpartum uterine activity (inferentially this would lead to reduced postpartum blood loss),[8] greater weight loss postpartum compared with mothers who bottle-fed their infants,[9] decreased incidence of pre-menopausal breast cancer[10] and decreased incidence of ovarian cancer.[11]

In 2000, the DHHS Office on Women's Health, in cooperation with the Surgeon General of the United States and several governmental and non-governmental agencies, published the first departmental policy on breastfeeding, the *HHS Blueprint for Action on Breastfeeding* (www.womenshealth.gov). The DHHS Office on Women's Health endorses the recommendation from the American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), American College of Obstetricians and Gynecologists (ACOG), Association of Women's Health, Obstetrical, and Neonatal Nurses (AWHONN), Le Leche League International, National Medical Association (NMA), and many other health organizations, that mothers exclusively breastfeed for 6 months. The DHHS Office on Women's Health has commissioned a review to systematically examine the evidence for the effects of breastfeeding. The DHHS Office on Women's Health has also requested that the focus of the review be on studies from developed countries (i.e., "high income" classification by World Bank)[*] as the findings from those studies are deemed more directly applicable to population in this country.

As it is unethical to randomize subjects into breastfeeding versus non-breastfeeding groups (although there were some randomized controlled trials (RCTs) in the 1980s on preterm infants whose mothers desired not to breastfeed, their infants were randomized into those who received

[*] http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20421402~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html#High_income

donor breast milk versus those who received preterm formula[12,13]), much of the evidence on the benefits of breastfeeding came from observational studies. Observational studies are subject to confounding. One of the well-known confounders in breastfeeding research is demographic difference between mothers who breastfeed and those who chose not to breastfeed due to self-selection. Consistent with previously reported data,[14] NIS 2005 showed that mothers who breastfeed tend to be white (versus non-Hispanic black or African American), older, more educated, and in a higher socioeconomic stratum (cdc.gov/breastfeeding/data/NIS_data/data_2005.htm). While it is possible to control for some of these demographic factors, it is not possible to control for behavioral or attitudinal factors intrinsic in the desire to breastfeed. Some authors have proposed strict standards in evaluating the quality of observational studies. These standards should include the quality of the feeding data, a clear definition of the outcome, the elimination of systematic differences in outcome assessment between comparison groups (detection bias), and the control of potential and well-known confounders. The feeding data should clearly define whether it was prospectively or retrospectively collected, whether there was a precise definition of exclusive breastfeeding, and whether the duration of breastfeeding was reported.[15,16]

Large number of infant and maternal outcomes has been examined in relation to a history of breastfeeding. It was not feasible to review all possible outcomes in mothers and children for this report; we sought guidance from our panel of technical experts in the field of breastfeeding research in deciding on the specific outcomes to review. After taking into consideration the following factors: relevance and importance of outcome in a developed country, date (recent or old) of the last systematic review on the outcome, availability or non-availability of data from a developed country, consistency or inconsistency of outcomes in previously reported studies, and consideration of the possibility that breastfeeding may have potential harms as well as benefits, the following outcomes from developed countries have been designated for review: for term infants, infectious diseases (including otitis media, diarrhea, and lower respiratory tract infections), sudden infant death syndrome, infant mortality, cognitive development, childhood cancer (including leukemia), type 1 and 2 diabetes, asthma, atopic dermatitis, cardiovascular disease (including hypertension), hyperlipidemia, and obesity; for preterm infants, necrotizing enterocolitis (NEC) and cognitive development; for mothers, post-partum depression, return to pre-pregnancy weight, breast cancer, ovarian cancer, diabetes and osteoporosis.

It is also outside the scope of this report to examine the biological mechanisms underpinning the effects of breast milk and therefore, studies on individual components of breast milk will not be part of this report. Lastly, studies on the effectiveness of interventions to promote and support breastfeeding are not systematically covered in this review, as this topic will be reviewed for a subsequent report. However, there is good quality evidence to support that some of these interventions do lead to an increase in breastfeeding rates and also an improvement of certain health outcomes in the study populations. Details of one landmark study[17] and its implications for future research in the study of the effects of breastfeeding will be discussed in some details in this report.

Chapter 2. Methods

Overview

This evidence report on breastfeeding and health outcomes in infants and mothers is based on a systematic review of the literature. To identify the specific issues central to this report, the Tufts-New England Medical Center (Tufts-NEMC) Evidence-based Practice Center (EPC) held teleconferences with a panel of technical experts (TEP) and various stakeholders. A comprehensive search of the medical literature was conducted to identify studies addressing the key questions. Evidence tables of study characteristics and results were compiled, and the methodological quality of the studies was appraised. Study results were summarized with qualitative reviews of the evidence, summary tables, and quantitative summary data, when appropriate.

A number of individuals and groups supported the Tufts-NEMC EPC in preparing this report. The TEP served as our science partner. Technical experts and representatives from the Agency for Healthcare Research and Quality (AHRQ), DHHS Office on Women's Health, The National Institute of Child Health and Human Development (NICHD), Centers for Disease Control and Prevention (CDC), American Academy of Pediatrics (AAP), American College of Obstetrics and Gynecology (ACOG), Association of Women's Health, Obstetrics and Neonatal Nurses (AWHONN), and La Leche League worked with the EPC staff to refine key questions, identify important issues, and define parameters for literature review in this report.

In the early phase of exploring the literature available for this report, it was soon discovered that there was a large number of primary studies and systematic reviews/meta-analyses on the various outcomes of interest. As it was not feasible to review all the primary studies addressing the outcomes of interest, therefore, in consultation with the Office on Women's Health and the TEP, we developed an approach that capitalized on the existing systematic reviews/meta-analyses. For outcomes of interest that had previously been reviewed systematically, we assessed the quality of those reviews and summarized their findings. For selected infant (necrotizing enterocolitis, cognitive development, acute otitis media, asthma, type 1 and 2 diabetes, SIDS) and maternal (weight changes, type 2 diabetes, breast cancer) outcomes, in addition to reporting on the existing systematic reviews, we also updated them by summarizing the relevant primary studies that were published after those reviews. For outcomes of interest (osteoporosis, ovarian cancer, postpartum depression, infant mortality) that had not been reviewed systematically, we reviewed all the relevant primary studies that met our inclusion criteria.

Key Questions Addressed in This Report

Two key questions are addressed in this report. Question 1 pertains to infant outcomes and question 2 pertains to maternal outcomes. The key questions are:

1. What are the benefits and harms for infants and children in terms of short-term outcomes, such as infectious diseases (including otitis media, diarrhea, and lower respiratory tract infections), sudden infant death syndrome and infant mortality, and longer-term outcomes such as cognitive development, childhood cancer (including leukemia), type 1 and 2 diabetes, asthma, atopic dermatitis, cardiovascular disease (including hypertension), hyperlipidemia, and obesity, compared among those who mostly breastfeed, mostly

formula feed, and mixed feed; and how are these outcomes associated with duration of the type of feeding? Do the harms and benefits differ for any specific subpopulations based on socio-demographic factors?

2. What are the benefits and harms on maternal health short-term outcomes, such as post-partum depression and return to pre-pregnancy weight, and long-term outcomes, such as breast cancer, ovarian cancer, type 2 diabetes mellitus and osteoporosis, compared among breastfeeding, formula feeding, and mixed feeding, and how are these associated with duration of the type of feeding? Do the harms and benefits differ for any specific subpopulations based on socio-demographic factors?

It should be emphasized that the focus of this review is on the effects of breast milk feeding, not formula feeding. However, many studies did not distinguish between exclusive and partially breastfed infants; presumably, some of the effects reported from observational studies were from infants who received both breast milk and formula milk feedings. Studies that examined only formula fed infants were not included in this report. Lastly, studies on infant and maternal health outcomes of interventions to promote and support breastfeeding were not systematically covered in this review as that subject will be covered in a separate report. However, our panel of technical experts felt that the study of breastfeeding promotion in infants from Belarus[17] was a landmark study and offered new directions into research on effects from breast milk that it warrants discussion in this report. The details of that study are described in the section Other Research in the results chapter.

Definitions of Breastfeeding in This Report

None of the studies in this review explicitly examined the difference between "breastfeeding" an infant (infant suckling at her/his mother's nipple) and "feeding of expressed breast milk" to an infant. To distinguish between the two forms of feedings, we elected to use the term "breastfeeding" when the studies concerned primarily full-term infants (presumably they were, indeed, breastfed) and the term "breast milk feeding" when the studies concerned primarily preterm infants (as most of them received breast milk initially either by gavage- or by bottle-feeding). For term infants, "bottle-feeding" is used synonymously with "formula feeding."

Definitions of "exclusive breastfeeding" varied widely in the literature. They ranged from "no supplement of any kind including water while breastfeeding" to "occasional formula is permissible while breastfeeding." We elected to accept all definitions of "exclusive breastfeeding" as provided by the different study authors, but we qualified our findings by the details regarding those definitions.

Literature Search Strategy

We conducted a comprehensive literature search to address the two key questions. The EPC used the Ovid search engine to conduct searches on the MEDLINE® database, CINAHL database, and the Cochrane Database of Systemic Reviews. A wide variety of search terms were used to capture the many potential sources of information related to the myriad of different outcomes (see Appendix A).[*] But the different outcomes were always searched in conjunction

[*] Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/ brfouttp.htm

with the following: “breastfeeding,” “breast milk feeding,” “breast milk,” “human milk,” “nursing”, and “lactation”. Literature search of the outcomes alone without references to breast milk feeding was not conducted. The search included citations from 1966 to November of 2005. Updated searches on selected outcomes took place in April and May of 2006. We also supplemented our computer search by examining the bibliographies of the review articles. We also included articles suggested by reviewers, provided that the articles met the inclusion criteria for this review. For outcomes that were not slated for updates, additional articles suggested by reviewers were also included as an addendum if they provided useful information. We did not make efforts to identify unpublished studies.

Study Selection

Selection of Outcomes for This Review

The TEP offered advice on selection of outcomes for review. Final selection of the list of outcomes for review took into account the following factors: the importance of the outcome, whether a systematic review of the outcome has previously been reported from a developed country, whether the existing systematic review of the outcome is outdated, whether the relationship between breastfeeding and the outcome is thought to be equivocal, whether a large number of primary studies has been published recently on the outcome, and the total number of outcomes that could be adequately reviewed for this report given the time constraint.

We included the following outcomes in this report:

Term infant outcomes: acute otitis media, hospitalization for lower respiratory tract infection, gastrointestinal infection, hypertension, cardiovascular diseases, hyperlipidemia, asthma, atopic dermatitis, type 1 and 2 diabetes, obesity, sudden infant death syndrome (SIDS), infant mortality, cognitive development, and childhood cancer (including leukemia)

Preterm infant outcomes: necrotizing enterocolitis (NEC) and cognitive development

Maternal outcomes: maternal weight changes, breast cancer, ovarian cancer, post-partum depression, osteoporosis, and type 2 diabetes

Abstract Screening

All abstracts identified through the literature search were screened. At this stage, eligible studies included all English language primary experimental or observational studies that reported any health outcomes in human subjects in relation to a history of breast milk feeding. As the inclusion criteria were broad at this stage, the abstracts rejected at this stage did not undergo a second rescreening process. Abstracts that were accepted at this stage were examined a second time by different reviewers and categorized into the different outcomes of interest.

Full Article Inclusion/Exclusion Criteria

Articles that passed the abstract screening process were retrieved and the full articles were reviewed for eligibility. Full articles were examined only once unless the articles were equivocal for inclusion or exclusion. In that event, the article in question was screened again by a different reviewer and a consensus was reached after discussion with the first reviewer.

Because the outcomes selected ranged from very broad topic with common occurrence (e.g., non-specific gastrointestinal infection) to a narrowly focused topic with relatively few occurrences (e.g., SIDS), the types of studies available for each outcome varied widely in the distribution of study designs, sample sizes, and quality of breastfeeding data, it was not possible (nor desirable) to design a strict set of inclusion and exclusion criteria that would be applicable to all outcomes. Therefore, additional inclusion/exclusion criteria germane to the specific outcome were also described in the Results section under each outcome.

General inclusion criteria for the studies are as follow:

Study Design. Systematic reviews, experimental (randomized controlled trials) and observational studies (prospective cohort and case-control studies only)
Population. Healthy term infants in developed countries; preterm infants in developed countries (for NEC and cognitive development); healthy mothers in developed countries
Intervention/Exposure. Breastfeeding, breast milk feeding (maternal term and preterm milk, banked term and preterm milk, fortified or unfortified), exclusive or mixed feeding
Comparator. Formula feeding (preterm or term formula, fortified or unfortified)

Data Extraction and Analysis

For those outcomes that have been subjected to a systematic review/meta-analysis, we summarized their results into our report. In addition to the results from the systematic reviews, we have also extracted and summarized the relevant data from primary studies that were published after the latest search dates of the reports for the following infant and maternal outcomes: acute otitis media, childhood asthma, cognitive development, SIDS, infant mortality, NEC, and maternal breast cancer.

For systematic reviews/meta-analyses that reported data from both developed and developing countries, we reported only those results pertaining to developed countries, if the reported data permitted us to do so. In those instances where that were not possible, we noted that fact as a limitation of our findings.

For outcomes that have multiple systematic reviews, we noted the overlapping studies and examined whether their findings were interpreted similarly or differently across reviews and reported our analyses.

For NEC, maternal weight changes, and acute otitis media, in order to better clarify the overall findings, we also extracted relevant data from the primary studies cited in the systematic reviews and combined them with data from the primary studies that were published after the latest search dates of the reports and reanalyzed the data.

For the remaining included outcomes, we extracted and summarized the relevant data from the primary studies.

Data forms were developed separately for extraction of systematic reviews/meta-analysis and primary studies. For systematic reviews/meta-analysis, items extracted were: databases searched, study design, population characteristics, descriptions of intervention/exposure, models used for meta-analysis, results, and authors' conclusions. We reported the estimates in the meta-analyses. We also reported any attempt by the authors of the meta-analyses to explore heterogeneity using sub-group analyses or meta-regression. For primary studies, items extracted were: study design, population characteristics, eligibility criteria, descriptions of intervention/exposure, any adjustments for confounders, and results.

Meta-Analysis

We used meta-analysis to expand on the individual studies' findings, if it was appropriate and feasible to do so. Minimal criteria for meta-analysis are comparable groupings, similar study designs, and quantifiable outcome data. Secondary criteria for consideration of meta-analysis are similar study quality, similar statistical adjustment of outcomes, and other factors. Before combining the reported odds ratios or risk ratios reported in the individual studies from the previous meta-analysis with the estimates from the updated primary studies into a new summary odds ratio or risk ratio, we verified the previous reported odds ratios or risk ratios by examining the data from the original studies.

We used the DerSimonian and Laird's random effects model for all meta-analyses.[18] The random effects model assigns a weight to each study based both on the individual study variance and the between-study heterogeneity. Compared with the fixed effect model, the random effects model is more conservative in that it generally results in broader confidence intervals when between-study heterogeneity is present. We tested for heterogeneity using Cochran's Q and assessed its extent with I^2, which evaluates the proportion of between study variability that is attributed to heterogeneity rather than chance.[19,20] Intercooled Stata 8.2 was used for the calculations and graphics.

Grading of Studies Analyzed in This Evidence Report

Studies accepted in evidence reports have been designed, conducted, analyzed, and reported with various degrees of methodological rigor and completeness. Deficiencies in any of these processes may lead to biased reporting or interpretation of the results. While it is desirable to have a simple evidence grading system using a single quantity, the quality of evidence is multi-dimensional. A single metric cannot adequately capture information needed to interpret a clinical study. However, grading of information can help the reader to interpret the studies properly.

Grading of Systematic Reviews/Meta-Analyses

We assessed the methodological quality of studies based on predefined criteria. For the assessment of systematic reviews, the criteria for methodological quality was based on the QUOROM guidelines for meta-analyses and systematic reviews of RCTs (a checklist organized into 21 headings and subheadings for the preferred way to present the abstract, introduction, methods, results, and discussion sections of a report of a meta-analysis),[21] and reporting guidelines for meta-analysis in observational studies in epidemiology (MOOSE) (a checklist for the specifications for presenting background, search strategy, methods, results, discussion, conclusion, and assessment of quality of individual studies and bias (e.g., publication bias)[a]).[22] As the QUOROM and the MOOSE statements were primarily concerned with the reporting standards of the reviews, we have also supplemented those criteria with our own checklist of items designed to evaluate the quality of the systematic review of observational studies (see Appendix B[b] for details). Items in this checklist consisted of questions on appropriate search strategy;

[a] Publication bias refers to selective publication of studies according to results. When studies with non-significant or negative results are not published, the available studies may overestimate the effect.

[b] Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/ brfouttp.htm.

justification for inclusion/exclusion criteria; how well-defined were the population, intervention, comparator, outcomes and study design; effort to minimize errors in data extraction; assessment of individual study quality; consideration on the effect of confounders; combinability of the data for meta-analysis; assessment of statistical and clinical heterogeneity; reporting accuracies; and appropriateness of the conclusions based on the reported data.

We applied a three category summary grading system (A, B, C) to each systematic review/meta-analysis:

A (good)

Category A studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a rigorously conducted systematic review or meta-analysis; clear description of the population, setting, interventions and comparison groups; clear description of the content of the comparison groups; appropriate measurement of outcomes; appropriate statistical assumptions and analytic methods and reporting; appropriate consideration and adjustment for potential confounders; rigorous assessment of individual study quality; no reporting errors; and well-reasoned conclusions based on the data reported.

B (fair/moderate)

Category B studies are susceptible to some bias, but not sufficient to invalidate the results. They 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 have significant biases that may invalidate the results. The study either did not consider potential confounders or did not adjust for them appropriately. These studies have serious errors in design, analysis or reporting; have large amounts of missing information, or discrepancies in reporting.

It should be noted that while we assessed the methodological quality of the systematic reviews or meta-analyses, it was not possible to evaluate the quality of the primary studies included in those reviews/analyses, as we did not examine those studies first hand. For systematic reviews/meta-analyses that had equivocal grading between moderate and poor, the results and the reasons for the initial grade assignments were presented to the entire group of project investigators and the final grades were adjudicated.

Grading of Individual Primary Studies in Updates and New Reviews

A well-performed RCT with proper randomization, allocation concealment, clear definitions of breastfeeding exposure compared with non-breastfeeding, and blinded assessment of outcomes will yield the best evidence in supporting the causality of breast milk in affecting health outcomes. But with the recognized benefits of breast milk, this approach is ethically not feasible. Other types of studies involve following the health outcomes from randomization of intervention to promote and support breastfeeding (e.g., Belarus study[17]), this type of study will yield indirect evidence for the relationship between breastfeeding and health

outcomes provided that there is a differential effect from the intervention on breastfeeding rates between the comparison groups. Prospective observational cohort studies with proper adjustment of potential confounders provide the bulk of data in this field. However, the possibility of residual confounding that could explain the observed association between breastfeeding and the specific health outcomes can never be completely ruled out. Case-controlled design is an even less attractive option because of the concern for case selection bias and suboptimal matching to control subjects.

For the assessment of RCTs, the criteria were based on the CONSORT statement for reporting RCTs (a checklist with specifications for reporting all aspects of a trial).[23,24] We mainly considered the methods used for randomization, allocation concealment, and blinding as well as the use of intention-to-treat analysis, the report of well-described valid primary outcomes, and the dropout rate. For non-randomized trials, we used the report of eligibility criteria and assessed the adequacy of controlling for differences between comparative groups in terms of baseline characteristics and prognostic factors. We also considered the report of intention-to-treat analysis, and the crossovers when so designed, as well as important differential loss to followup between the comparative groups or overall high loss to followup. The validity and the adequate description of outcomes and results were also assessed. For the assessment of prospective cohorts and case-control studies (cross-over design and retrospective cohort studies were excluded from this review), we used a rating checklist largely based on the Newcastle-Ottawa Quality Assessment scales for cohort and case-control studies (www.ohri.ca/programs/clinical_epidemiology/oxford.htm). Items assessed included selection of cases and controls or cohorts, comparability, information concerning exposure/intervention, consideration for potential confounders, and percentage of withdrawals or dropouts. In particular, we paid close attention to the quality of the breastfeeding data, whether they were obtained prospectively or by retrospective recall, whether a distinction was made between exclusive and partial breastfeeding, and whether the duration of breastfeeding was reported. We also paid close attention to consideration of and appropriate adjustment for potential confounders.

We applied a three category summary grading system (A, B, C) to each study. This system defines a generic grading system that is applicable to each type of study design including randomized controlled trials, cohort, and case-control studies:

A (good)

Category A studies have the least bias and results are considered valid. 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 are susceptible to some bias, but not sufficient to invalidate the results. They 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 have significant biases that may invalidate the results. The study either did not consider potential confounders or did not adjust for them appropriately. These studies have serious errors in design, analysis or reporting; have large amounts of missing information, or discrepancies in reporting.

For primary studies that had equivocal grading between moderate and poor, those studies were reviewed and graded again by different reviewers and consensus was reached after discussion among the reviewers. Lastly, it should be noted that the summary quality grading system evaluates and grades the studies within their own design strata. It does not attempt to assess the comparative validity of studies across different design strata. Thus, one should be cognizant of the study design when interpreting the methodological quality grade of a study.

Reporting of the Evidence

We reported each outcome separately in its own section in the results chapter. A brief explanation of the importance of the outcome is followed by a description of inclusion/exclusion criteria of studies examined that are specific to that outcome. A description of the relevant systematic review is followed by a description of the primary studies that were published after the latest search date of the systematic review. A summary table highlighted important findings. A summary conclusion regarding breast milk and that particular outcome is made in the last section. Conclusions were drawn only from studies of high or moderate (grade A or B) methodological quality. For dichotomous outcome, either the summary risk ratio or odds ratio is reported. For continuous outcome, the comparative difference in the actual measurement for that outcome is reported (e.g., IQ points, mm Hg of blood pressure). When only studies of C quality are available, we summarize the findings from those studies and explain the reasons for the "C' rating, but we do not draw conclusions from them.

Extracted data are compiled in evidence tables. The tables offer a detailed description of the studies that addressed each of the key questions. The tables (see Appendix C)[a] provide detailed information about the study design, the sample size, the patient characteristics, the intervention and comparison group feeding methods, the followup, the major outcomes, and the methodological quality. In addition, for systematic reviews and meta-analyses, we reported the databases searched and for which time period, the number and the type of primary studies included, and the type of comparison addressed.

Summary tables succinctly report summary measures of the main outcomes evaluated. They include information regarding study design, intervention and comparison group, feeding methods, study duration or followup, sample size (subjects enrolled and analyzed in each arm), potential confounders, results of major outcomes, and methodological quality. These tables were developed by condensing information from the evidence tables. They are designed to facilitate comparisons and synthesis across studies. A methodological quality was assigned to each study as described previously.

[a] Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/ brfouttp.htm.

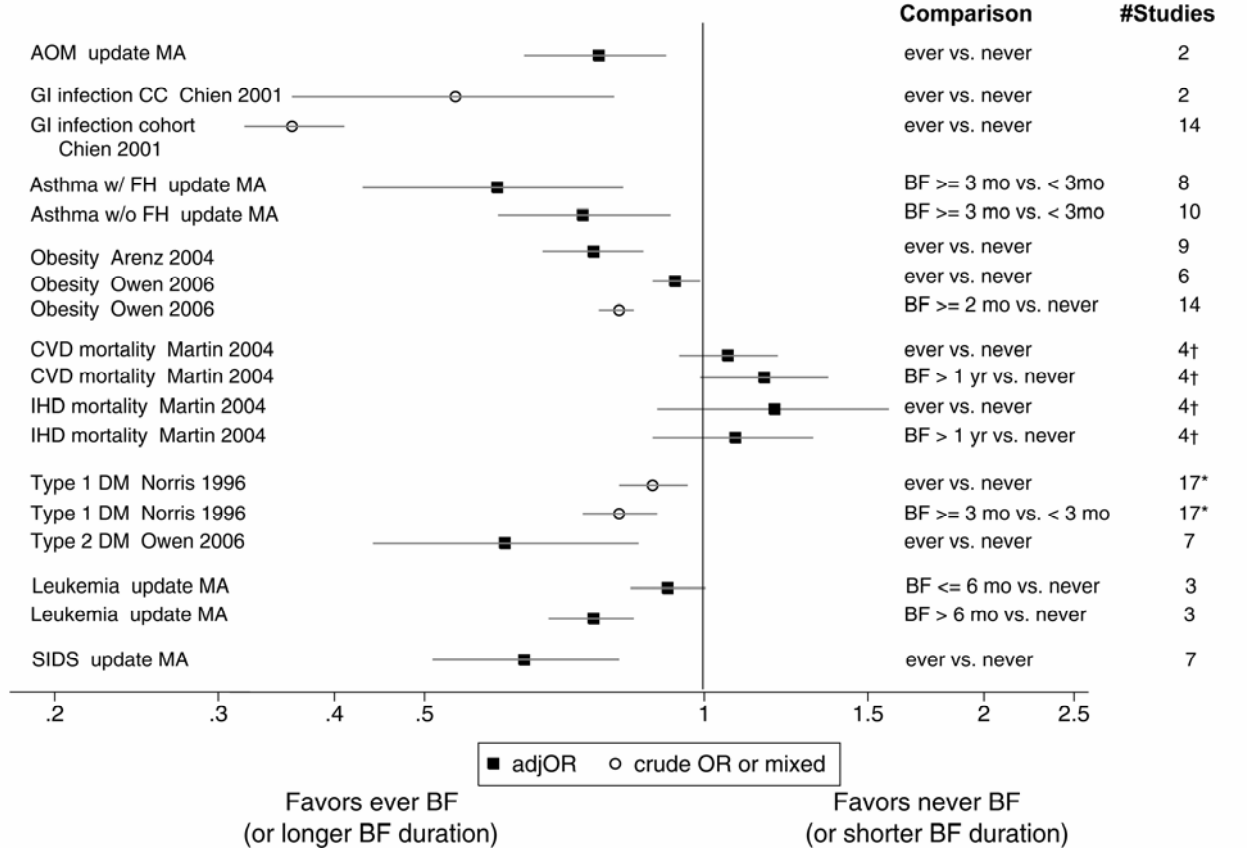
Chapter 3. Results

Overview

Twenty-three outcomes were analyzed in this report. We present three overall summary figures below to give the reader a quick overview of the results from the meta-analyses included in this report on the association of breastfeeding with health outcomes. We use the following rules to choose the results: (1) results from good or moderate quality meta-analyses, (2) the latest and/or highest quality meta-analysis is preferred if there are multiple meta-analyses addressing the same question, and (3) pooled adjusted estimate is preferred. Outcomes that did not have meta-analyses are not listed in these figures.

Three overall summary figures were created for term infant outcomes: Figure 1 for outcomes expressed as odds ratios or risk ratios comparing the different feeding groups; Figure 2 for the association between exclusive breastfeeding and infant outcomes; and Figure 3 for maternal outcomes expressed as odds ratios or risk ratios comparing the different feeding groups.

Figure 1. The relationship between breastfeeding and health outcomes in term infants - meta-analysis results

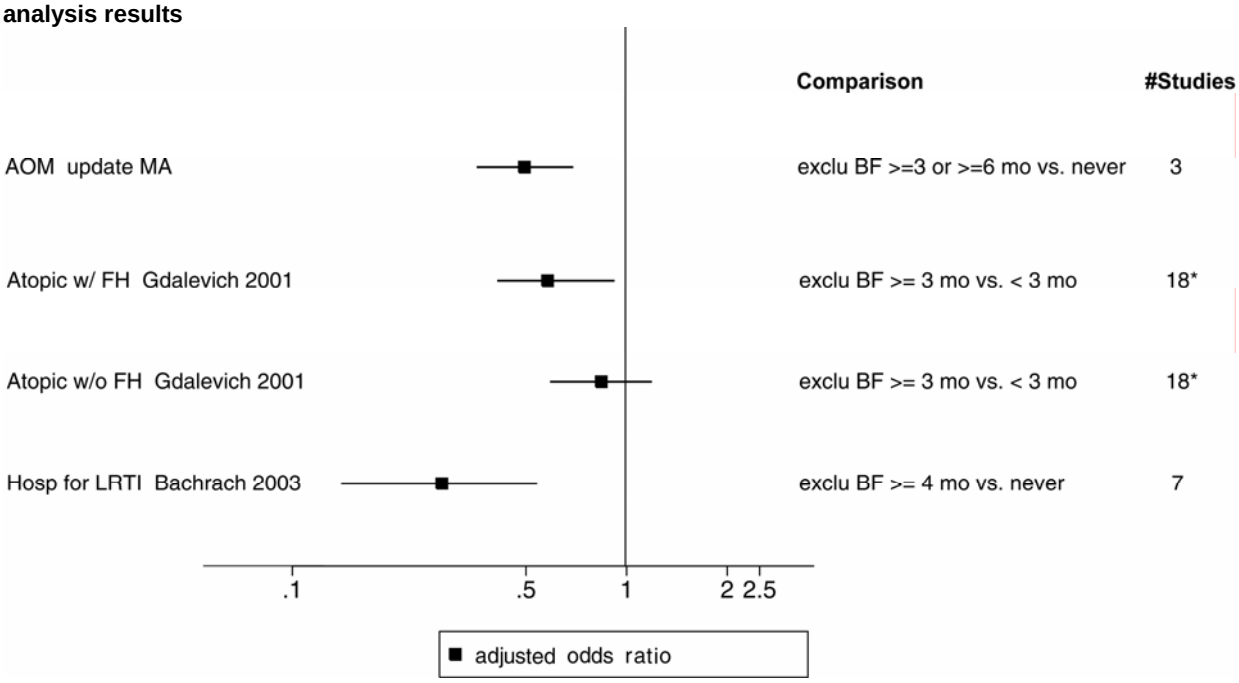


MA, meta-analysis; AOM, acute otitis media; GI, gastrointestinal; CC, case-control studies; FH, family history; CVD, cardiovascular disease; IHD, ischemic heart disease; DM, diabetes; adj, adjusted

*17 studies in total were included in Norris 1996 meta-analyses. The number of studies per comparison was not reported.

†Four historical cohort studies reported data on the relationship between breastfeeding and both CVD and IHD mortality.

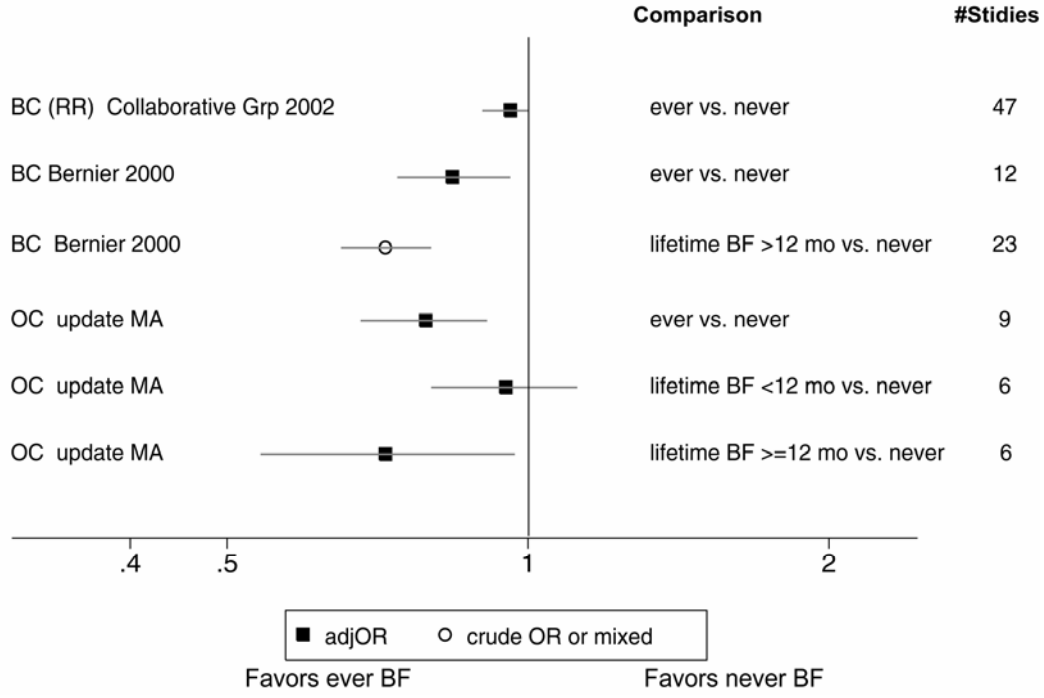
Figure 2. The relationship between exclusive breastfeeding and health outcomes in term infants - meta-analysis results



MA, meta-analysis; AOM, acute otitis media; FH, family history; Hosp, hospitalization; exclu, exclusive; LRTI, lower respiratory track infection

*18 studies in total were included in Gdalevich 2001 meta-analyses. The number of studies per comparison was not reported.

Figure 3. The relationship between breastfeeding and maternal outcomes - meta-analysis results



MA, meta-analysis; BC, breast cancer; RR, relative risk; OC, ovarian cancer; adj, adjusted

Literature Search Results

In the early phase of exploring the literature available for this report, a large number of published systematic reviews or meta-analyses were identified for various outcomes of interest. We screened over 300 abstracts for published systematic reviews and meta-analysis. We included all relevant systematic reviews and meta-analyses, although some of them included primary studies that were conducted in developing countries. A total of 29 systematic reviews or meta-analyses met our inclusion criteria. These systematic reviews or meta-analyses included a total minimum of 343 to a maximum of 494 unique primary studies (as some of the same studies were covered in multiple reviews). In this chapter, we summarized the findings and authors' conclusions from these systematic reviews and meta-analyses. If multiple systematic reviews and meta-analyses were available on the same outcome of interest, we also compared the differences and similarities between them.

We screened over 9,000 abstracts for potential relevant articles on the relationship between breastfeeding or breast milk feeding and various infant and maternal outcomes. After the initial screening, we categorized the abstracts according to the populations and outcomes of interest. For outcomes of interest that had previously been reviewed systematically, we excluded abstracts that were published before the search dates of previous systematic reviews or meta-analyses. For the remaining abstracts, we retrieved the corresponding full articles and applied additional inclusion or exclusion criteria tailored for the specific outcomes. For outcomes of interest that had not been reviewed systematically, we performed a new systematic review on all relevant primary studies that were conducted in developed countries.

Finally, a total of 43 unique primary studies on the relationship between breastfeeding and infant health outcomes, and a total of 43 unique primary studies on the relationship between breastfeeding and maternal health outcomes were included. Details of the inclusion and exclusion of abstracts and full article screenings were summarized in Figures 1 and 2. The full article inclusion or exclusion criteria were described in Chapter 2, and the additional inclusion or exclusion criteria tailored for the specific outcomes were described under each outcome section in this chapter.

Organization of Results

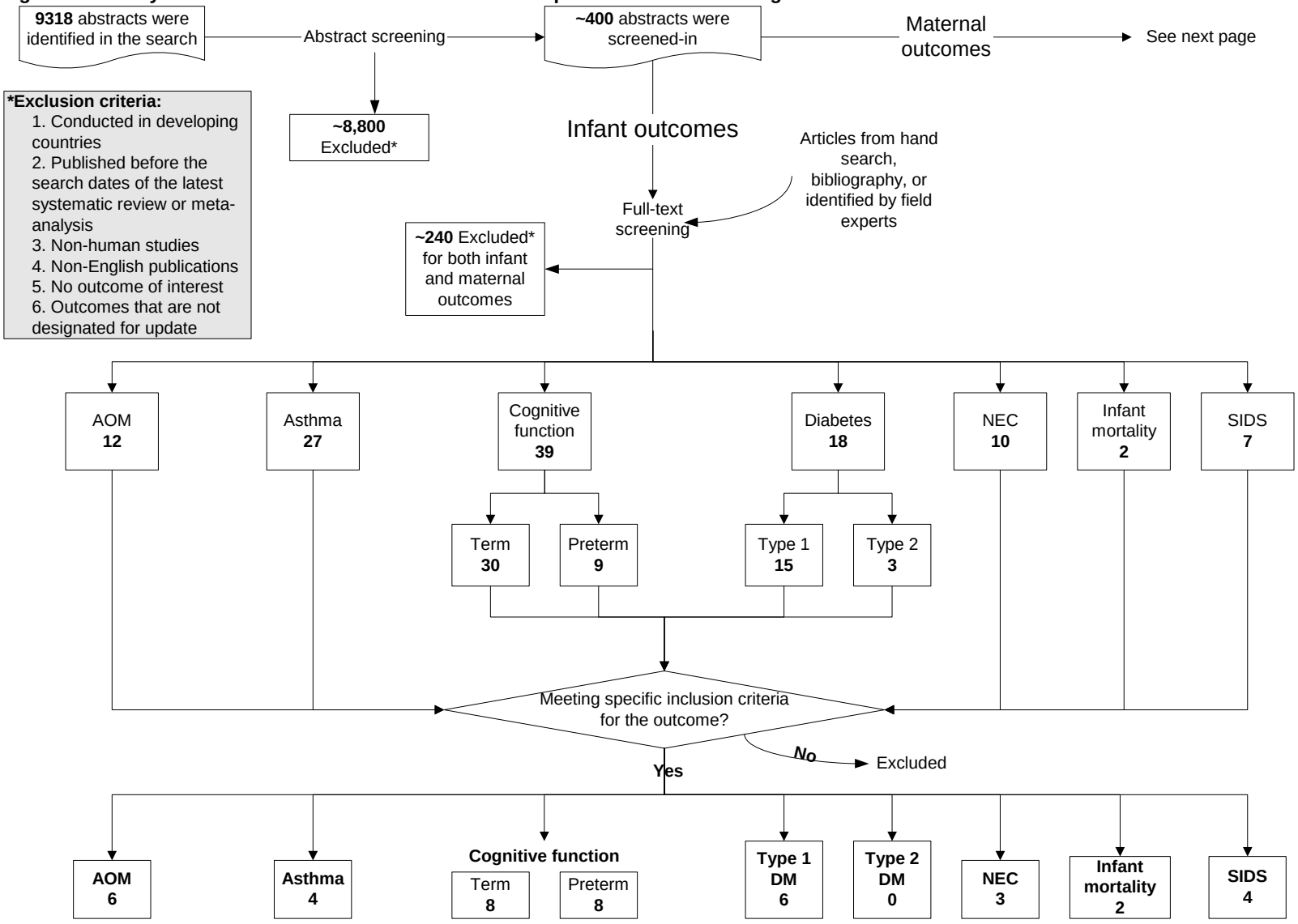
In this chapter, we grouped studies into one of the three parts of this report according to the target population – Part I: term infant outcomes, Part II: preterm infant outcomes, Part III: maternal outcomes.

In Part I, we summarized the results for health outcomes in term infants, including acute otitis media, atopic dermatitis, gastrointestinal infections, lower respiratory infection, asthma, cognitive development, obesity, cardiovascular diseases, cholesterols, blood pressure, cardiovascular mortality, type 1 and 2 diabetes, childhood leukemia, infant mortality, and sudden infant death syndrome.

In Part II, we summarized the results for necrotizing enterocolitis (NEC) and cognitive development in relationship to breast milk feeding in preterm infants, respectively.

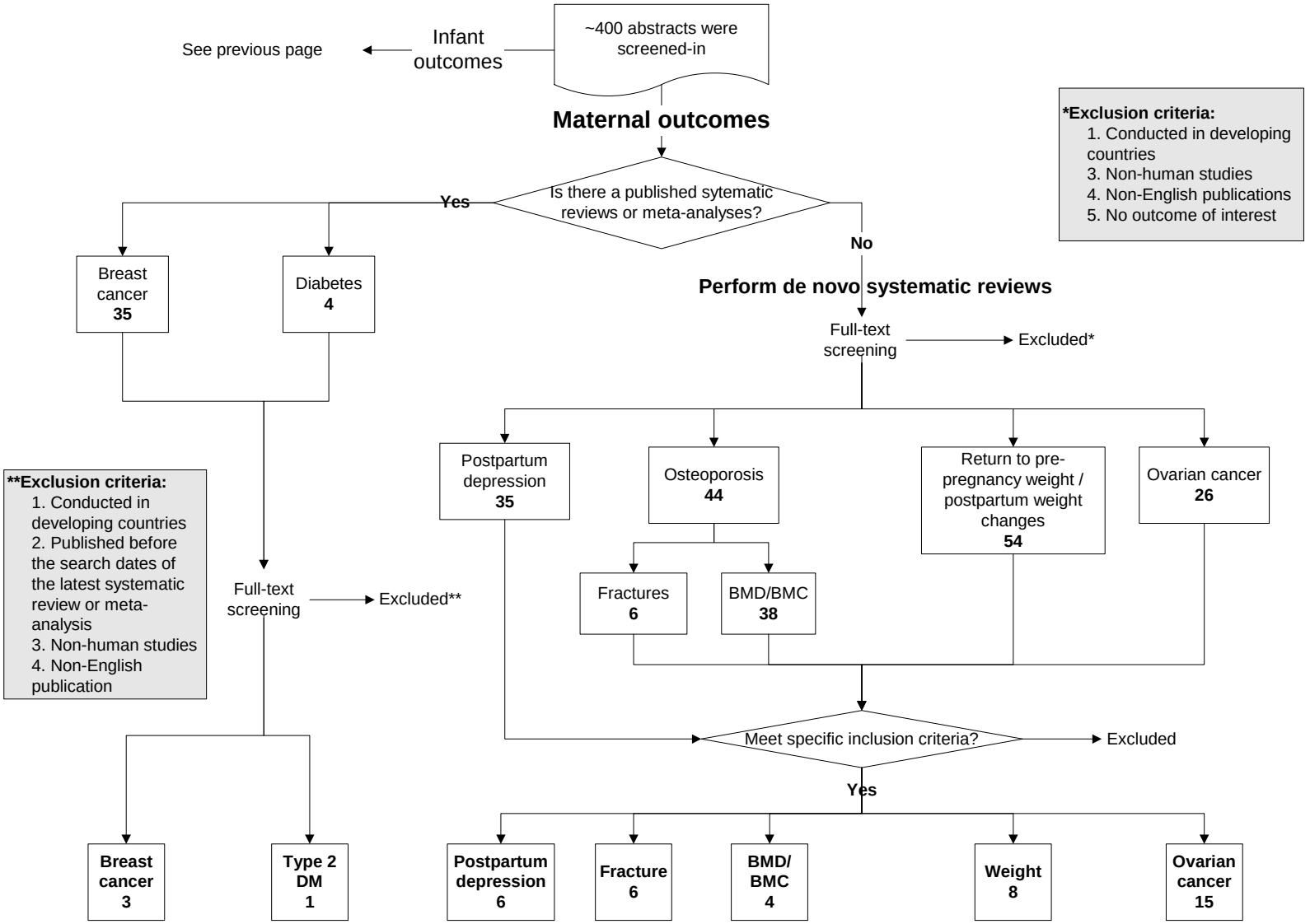
In Part III, we summarized the results for maternal health outcomes, including returning to pre-pregnancy weight, postpartum weight changes, maternal type 2 diabetes, osteoporosis, postpartum depression, breast cancer, and ovarian cancer.

Figure 4. Primary studies available to assess the relationship between breastfeeding and infant health outcomes.



A total of 43 unique studies were included for updates of infant outcomes

Figure 5. Primary studies available to assess the relationship between breastfeeding and maternal health outcomes.



A total of 43 unique studies were included for updates of maternal outcomes

Part I. Term Infant Outcomes

Relationship between Acute Otitis Media and Breastfeeding

Background

Acute otitis media (AOM) is a common childhood infection. It often begins with an upper respiratory tract infection. The viral infection predisposes the child to the development of AOM by causing eustachian tube dysfunction. The eustachian tube dysfunction enhances nasopharyngeal colonization with middle ear pathogens. The prevalence of a first attack of AOM in children under l year of age was estimated to be 44 percent.[25] Almost 70 percent of children under 6 years of age have had an episode of AOM.[25] Several risk factors have been identified for increasing the occurrence and recurrence of AOM.[26] There is a general consensus that breastfeeding protects against many infections, including AOM. Breast milk contains immunoglobulins with antibody activity against common bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae.* It also contains components that interfere with the attachment of *Haemophilus influenzae* and *Streptococcus pneumoniae* to nasopharyngeal epithelial cells. The intermittent administration of milk with anti-adhesive substances into the nasopharynx of the nursing child may reduce the extent of colonization and protect against infection.[27]

Commonly considered confounders in the studies of the relationship between breastfeeding and AOM were parental history of allergy, number of siblings, use of day care, maternal smoking, gender, ethnicity, and socioeconomic status.

We identified one meta-analysis of risk factors for AOM that aimed to further clarify possible means of preventing AOM in childhood.[28] Duration of breastfeeding was one of the factors examined. Since this meta-analysis, we identified six studies in seven publications that examined the relationship between breastfeeding and AOM.

Additional Methodological Comments

Uhari 1996 compared the risk of AOM among children who were breastfed for various durations – breastfeeding for 3 or more months versus less than 3 months, 6 or more months versus less than 6 months, and ever breastfeeding versus never breastfeeding. [28] The clinical and statistical heterogeneity of the studies included were not reported. The methodological quality of the meta-analysis was rated grade C, because there was no consideration for potential confounding and poor reporting of study characteristics (Table 1).

Since the meta-analysis was of poor quality, we decided to conduct a new meta-analysis combining adjusted odds ratios or risk ratios of AOM comparing breastfed infants with non-breastfed infants from the studies identified in Uhari 1996 and from the update search. We only included studies that reported the relationship between breastfeeding and the occurrence of AOM in infants without co-morbidities (e.g., cleft palate). Of the 10 studies included in Uhari 1996 meta-analysis, only three reported adjusted odds ratios or risk ratios of AOM comparing breastfed infants with non-breastfed infants.[29-31] Those studies are summarized in Table 2.

Studies Identified after the Systematic Review/Meta-analysis (Table 2)

A total of five cohort studies (in 6 publications)[3,32-36] and one case-control study[37] that evaluated the relationship of breastfeeding and AOM published after the search dates of Uhari's meta-analysis met our inclusion criteria. We included only studies conducted in developed countries among children without co-morbidity. In cohort studies, subjects in the studies were followed from birth to a mean of 6 to 24 months. The number of subjects evaluated ranged from 289 to 15,113 at baseline. Four of the five cohort studies were of methodological quality grade B, while the other one was of grade C. In the case-control study, the children were between the ages of 3 and 7 years at the time of examination. A total of 179 AOM cases and 305 controls were analyzed. The methodological quality of the case-control study was rated C because the analysis did not control for potential confounding.

Studies varied in the definitions of breastfeeding and comparison groups. All studies were designed to evaluate a broad range of potential risk factors in AOM, except for Scariati 1997 in which the study specifically aimed to examine the relationship between breastfeeding and infections. We focused only on the relationship between breastfeeding and AOM. The studies also varied in their definitions of the disease conditions. In most studies, definitions of AOM were based on clinical features combined with otoscopic findings. The data were collected from medical records and confirmed by a physician in all studies except for Vernacchio 2004 and Scariati 1997 where a mother was asked to report ear infection in a list of diagnoses or symptoms.

All cohort studies adjusted for potential confounders and the case-control study did not. Confounding factors considered in the studies included gender, number of siblings, family day care, nursery day care, number of children in the home, maternal age, parental race or ethnicity, parity, maternal marital status, and parental smoking.

Breastfeeding was associated with a reduced risk of AOM compared to bottle-feeding after controlling for potential confounders across the five cohort studies, although some studies did not report a statistically significant result.

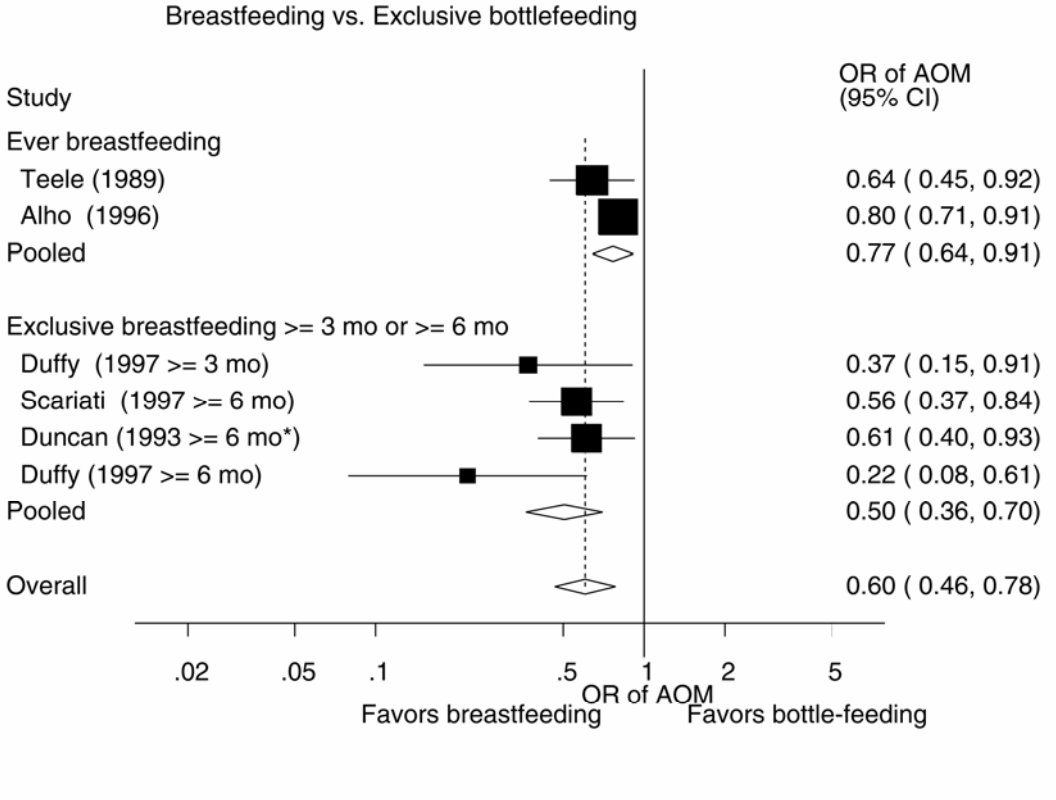
When exclusive breastfeeding for more than 3 or 6 months was compared with exclusive bottle- or formula- feeding, one study reported 28 percent[33] and another study reported 45 percent[3] relative risk reduction in AOM. The case-control study did not show a significant difference in the risk of AOM between the children who were ever breastfed and those who did not. However, the analysis did not control for any potential confounding factors.

Meta-analysis. In addition to the five cohort studies in the update search, three additional cohort studies that reported adjusted odds ratios or risk ratios of AOM from Uhari 1996 were reviewed for possible inclusion into our meta-analyses. Studies were heterogeneous in the definitions of breastfeeding and comparison groups. In order to minimize the heterogeneity, we restricted our analyses to studies that reported an adjusted odds ratio or risk ratio of AOM comparing any definition of breastfeeding duration to exclusive bottle-feeding. Five studies that reported data from a total of six comparisons met the inclusion criteria for our meta-analyses.[3,29,31,33,35] Using a random effects model, pooled data from five cohort studies of good and moderate methodological quality showed an adjusted odds ratio of AOM of 0.60 (95%CI 0.46-0.78) comparing breastfeeding to exclusive bottle-feeding. There is a significant difference in the risk reduction of AOM between the studies comparing exclusive breastfeeding with exclusive bottle-feeding and the studies comparing ever breastfeeding with exclusive bottle-feeding ($P<0.01$). Specifically, the pooled adjusted odds ratio of AOM was 0.77 (95%CI 0.64-

0.91), when comparing children who were ever breastfed with children who were exclusively bottle-fed in two studies. The pooled adjusted odds ratio was 0.50 (95%CI 0.36-0.70), when comparing children who were exclusively breastfed for at least 3 or 6 months with those who were exclusively bottle-fed for at least 3 or 6 months in three studies (providing 4 estimates).

The three studies that were excluded from our meta-analyses compared breastfeeding for more than 13 weeks, 4 months, and 6 months with breastfeeding for less than 13 weeks, 4 months, and less than 6 months, respectively.[29,30,32] There was no significant association between the risk of AOM and breastfeeding for more than 13 weeks, while a significant risk reduction in AOM was found when comparing children who were breastfed for more than 4 months or 6 months with those who were breastfed for less than 4 months or 6 months, respectively.

Figure 6. Meta-analysis of the association between breastfeeding and the risk of AOM compared to exclusive bottle-feeding in cohort studies



* Exclusive breastfeeding ≥ 6 months vs. exclusive bottle-feeding and breastfeeding < 4 mo

Conclusion

The results from our meta-analyses of cohort studies of good and moderate methodological quality showed that breastfeeding was associated with a significant reduction in the risk of AOM. Comparing ever breastfeeding with exclusive bottle-feeding, the pooled adjusted odds ratio of AOM was 0.77 (95%CI 0.64 - 0.91). When comparing exclusive breastfeeding with exclusive bottle-feeding, either for more than 3 or 6 months duration, the pooled odds ratio was 0.50 (95%CI 0.36 - 0.70).

Table 1. Summary of systematic review/meta-analysis on the relationship between breastfeeding and acute otitis media (AOM)

Author Year Population	Study description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA and limitations
Uhari 1996 AOM in children. Specific age groups not specified in the cohorts Case- control: 671 Cohort: 4,455	MA of 2 case-control and 8 cohort studies in developed countries	Any measures of breastfeeding and comparators	ND	10 studies evaluated the risk of AOM and recurrence of AOM associated with breastfeeding. The diagnosis of AOM varied, but pneumatic otoscopy was used in the diagnosis. There was no restriction on study inclusion according to the diagnostic criteria used. 22 studies evaluating an array of risk factors for development and recurrence of AOM were included in the meta-analysis. Seven of the twenty-two studies specifically evaluated the association between breastfeeding and AOM, while another 3 studies included breastfeeding among other risk factors that were evaluated. Breastfeeding for at least 3 months reduced the risk of AOM (RR=0.87; 95%CI: 0.79-0.95) Children who were breastfed for 3 or more months had a non-statistically significant reduced risk of recurrent AOM compared with those who were breastfed less than 3 months (RR 0.69, 95%CI 0.46 - 1.03). When children who were breastfed for 6 months or more were compared to those who were breastfed for less than 6 months, a statistically significant reduced risk of recurrent AOM was found (RR=0.69; 95%CI: 0.49-0.97).	C No consideration for potential confounding, no restriction on inclusion according to the diagnostic criteria used for AOM; unclear how breastfeeding data was collected

AOM, Acute Otitis Media; SR, systematic review; MA, meta-analysis

Table 2. Summary table for cohort studies on the relationship between breastfeeding and acute otitis media

Author Year Country Design	Number of subjects (Baseline /Followup)	Definition of AOM	Mean duration Followup	Breastfeeding group (n)	Comparator group (n)	OR (95% CI)		Confounders / risk factors adjusted	Quality and limitations
						Crude	Adjusted		
Studies in update search									
Vernacchio 2004 USA Prospective cohort	15,113 /11,349	Mother selects ear infection from a list of diagnoses by physician in the past month	6 mo	BF at 6 mo (2,771)	No BF at 6 mo (8,558)	0.66 (0.59-0.74)	0.69 (0.61-0.78)	Race/ethnicity, gender, daycare attendance, cigarette smoking, income, access to care	B
Scariati 1997 US Prospective cohort	1,743 / 1410	Mother reported symptoms	7 mo	Exclusive BF at 6 mo (299)	Exclusive formula at 6 mo (891)	0.45	0.56, p<0.01	Gender, maternal education, occupation, smoking, households size and income, day care use	B
					1-57% mixed feeding (81)	0.56	0.63, p=0.03		
					58-88% mixed feeding (80)	0.67	0.71, p<0.05		
					89-99% mixed feeding (59)	0.83	0.83, p=NS		
Sassen 1994 Netherlands Prospective cohort	289 /232	Clinical diagnosis by physician. Tympanometry results not used.	23.6 mo	Overall effect before stopping BF (OR per month)	Up to 4 mo after stopping BF		0.92 (0.76-1.07)	Number of siblings, SES	B

Table 2. Continued

Author Year Country Design	Number of subjects (Baseline /Followup)	Definition of AOM	Mean duration Followup	Breastfeeding group (n)	Comparator group (n)	OR (95% CI) Crude	OR (95% CI) Adjusted	Confounders / risk factors adjusted	Quality and limitations
						RR (95% CI)			
Duffy 1997 Finland[c] Prospective cohort	Exclusive breast: 178 / 53 @ 3 mo / 28 @ 6 mo	Exclusive formula: 110 @ baseline	Exclusive formula: 110 @ baseline	Exclusive 3-mo BF	Exclusive 3-mo formula	0.72 (0.52-1.00)	0.72 (0.52-1.00)	Age at colonization, day care, maternal smoking	B
	Combined BF and formula: 18 @ baseline			Exclusive 6-mo BF	Exclusive 6-mo formula	0.55 0.34-0.87)	0.55 0.34-0.87)		
	Exclusive formula: 110 @ baseline			6-mo mixed feeding	Exclusive 6-mo formula	0.71 (0.53-0.96)	0.30 (0.19-0.48)		
Alho 1996 (2 papers) Finland Retrospective cohort	2,512 / 825	>1 acute symptoms and one pneumatoscopic finding up to age 2 yrs	22 mo	Ever BF (nd)	Never BF (nd)		0.8 (0.7-0.9)[e]	Gender, number of siblings, atopy, age, season of birth, day care, parental smoking	C High dropout rate
				BF > 3 mo (735)	BF < 3 mo (90)	0.9 (0.8-1.0)			
Stenstrom, 1997 Sweden Case-control study	AOM cases: 179 Control[d]: 305	> 5 episodes of AOM (Otoscopic diagnosis) before age of 30 mo	N/A	Ever BF	Never BF	NS		None	C Unadjusted estimate only
Studies in MA that reported adjusted OR / RR									
Duncan 1993 US Prospective cohort	1220 / 1013	Diagnosed by experienced clinicians with an average of > 9 yrs in pediatric practice	12 mo	Exclusive BF ≥ 6 mo (154)	No BF and BF < 4 mo (465)		0.61 (0.40-0.92)	Parental history of allergy, number of siblings, use of day care, maternal smoking, gender, ethnicity, and maternal education	A
				BF ≥ 4 mo, suppl 4-6 mo (199)			0.72 (0.54-0.95)		
				BF ≥ 4 mo, suppl <4 mo (200)			0.85 (0.74-0.97)		

Table 2. Continued

Author Year Country Design	Number of subjects (Baseline /Followup)	Definition of AOM	Mean duration Followup	Breastfeeding group (n)	Comparator group (n)	OR (95% CI)		Confounders / risk factors adjusted	Quality and limitations
						Crude	Adjusted		
Teele 1989 US Prospective cohort	1067 / 877	Effusion in one or both middle ears accompanied by ≥ 1 signs of acute illness[b]	12 mo	Ever BF (292)	Never BF (585)	≥ 1 episode of AOM: 0.83	≥ 1 episode of AOM: 0.64 (0.44-0.91) ≥ 3 episode of AOM: 0.51 (0.30-0.89)	Site of health care, season of birth, birth weight, gender, SES, number of siblings, sibling or parental history of infection, parental smoking	B
Howie 1990 Scotland Prospective cohort	750 / 617	Mother reported that infant experienced painful or discharging ear lasting for 48 hrs or more	12 mo	Exclusive BF ≥ 13 wk (89) or partial BF ≥ 13 wk (121)	Bottle feeders (246) and BF < 13 wk(161)	0.7 (0.5–1.0)	NS in the % infants experienced ear infection	Father's social class, maternal age, and parental smoking	B

BF, breastfeeding; excl, exclusive; ROM, recurrent otitis media; SES, socioeconomic status
[a] Mean duration of exclusive BF (95% CI)
[b] Signs of acute illness including earache, otorrhea, ear tugging, fever, irritability, lethargy, anorexia, vomiting or diarrhea
[c] Proportion of infants in the individual categories of feeding method at different time cut-offs is not available
[d] Matched to the case by age and gender
[e] Values were estimated from figure. Statistically modeled to fit the whole sample.

Relationship between Atopic Dermatitis and Breastfeeding

Background

Atopic dermatitis is a common problem with an estimated lifetime prevalence in children of 10-20 percent.[38] Many studies have investigated the possible protective effect of breastfeeding on the development of atopic dermatitis. The results have been conflicting.[16,38,39] Potential confounders considered in the studies included gender, socioeconomic status, family history of atopy, parental smoking, and presence of furry animals in the home.[40]

Published Systematic Review/Meta-Analysis (Table 3)

We identified one systematic review/meta-analysis that examined the relationship between breastfeeding and the development of atopic dermatitis.[40] The methodological quality of this systematic review/meta-analysis was rated grade A.

Using the MEDLINE database from 1966 to 2000, Gdalevich 2001 identified 18 prospective studies from developed countries that qualified for inclusion in the review. Sample size of the studies ranged from 17 to 991. A total of 4,158 participants were included. Mean followup duration was 4.5 years. Study selection criteria included term infant, restriction of maternal recall of the child's feeding history limited to the first 12 months of the infants' life, the breastfeeding group in the study were exclusively breastfed for at least 3 months, blinding of the feeding history during outcome assessment, strict diagnostic criteria of atopic dermatitis provided by the authors, and control for confounding variables like socioeconomic status and family history of atopy.

Using a fixed effect model, the overall summary odds ratio for the development of atopic dermatitis was 0.68 (95% CI 0.52 - 0.88) in those subjects with at least 3 months of exclusive breastfeeding versus subjects without 3 months of exclusive breastfeeding. When the analysis was restricted to those studies with positive family history of atopy, the odds ratio was 0.58 (95%CI 0.41 - 0.92). When the analysis was restricted to those studies without a family history of atopy, the odds ratio was 0.84 (95%CI 0.59 - 1.19).

The systematic review did not make a distinction between atopic dermatitis of infancy (under 2 years of age) and persistent or new atopic dermatitis at older ages. However, in a primary analysis, the data were stratified according to different durations of followup (because the diagnosis of atopic dermatitis in patients younger than 2 years of age are sometimes attributed to symptoms of infectious origin and breastfeeding may have a protective effect against infections). The summary odds ratio in the group with less than 2 years of followup was 0.74 (95%CI 0.61 – 0.90), whereas the summary odds ratio in the group with 2 or more years of followup was 0.78 (95%CI 0.62 – 0.99).

The authors of the review concluded that there was a substantial protective effect of breastfeeding against atopic dermatitis in children with a family history of atopy.

Conclusion

Available evidence from one well-performed systematic review/meta-analysis on full term infants in developed countries suggests that exclusive breastfeeding for at least 3 months was

associated with a reduction in the risk of atopic dermatitis in those subjects with a family history of atopy.

Table 3. Summary of systematic review/meta-analysis on the relationship between breastfeeding and the risk of developing atopic dermatitis

Author Year	Studies description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA
Gdalevich 2001 Term infants 4,158 (17-991)	18 prospective cohort studies in developed countries	≥ 3 mo of exclusive breastfeeding vs. without ≥ 3 mo of exclusive breastfeeding	SES, gender, family history of atopy, parental smoking, and presence of furry animals at home; also considered disease in < 2 yr of age vs. ≥ 2 yr (to sort out the possible confounding protective effect of breastfeeding for skin rash that is infectious in etiology which might be confused with the diagnosis of atopic dermatitis)	Overall OR 0.68 (95% CI 0.52 - 0.88, fixed effect model); When restricted to those with positive family history, OR 0.58 (95%CI 0.41 - 0.92) When restricted to those without family history, OR 0.84 (95%CI 0.59 - 1.19) Authors' conclusion: "There is a substantial protective effect of breastfeeding against atopic dermatitis in children with a family history of atopy."	A

SR, systematic review; MA, meta-analysis; SES, socioeconomic status

Relationship between Gastrointestinal Infections and Breastfeeding

Background

Gastrointestinal infections are common in infants and children. Rate of diarrheal disease in US was estimated to be 1.1 episodes per person-year in children less than 5 years old.[41] Many studies have investigated the possible protective effect of breastfeeding on the development of gastrointestinal infections. A previous review of diarrhea morbidity in both developed and developing countries reported that the risk of diarrhea in infants who did not receive breast milk were 3.5 to 4.9 times higher than infants who had exclusive breastfeeding in the first 6 months of life.[42] Factors like secretory IgA, oligosaccharides, lactoferrin and others available in breast milk may protect the infant from various infections through passive immunity.[1] In vitro and in vivo binding studies have demonstrated that fucosylated glycans in breast milk inhibit binding by campylobacter jejuni, stable toxin of enterotoxigenic Escherichia coli, and major strains of calciviruses (e.g., noroviruses (also known as Norwalk-like viruses)) to their target host cell receptors.[43] One report suggests that glycoprotein lactadherin found in breast milk protects against rotavirus infection.[44] Socioeconomic status and child care variables (e.g., home versus day care, degree of crowding at home) are thought to be important confounding factors in observational studies on gastrointestinal infection and breastfeeding. As the aforementioned review also included studies before 1950, it would be instructive to review the more recent literature and assess the relationship between breastfeeding and gastrointestinal infections in infants from developed countries.

Published Systematic Review/Meta-Analysis (Table 4)

We identified one systematic review/meta-analysis that examined the relationship between breastfeeding and the development of gastrointestinal infections in children less than 1 year of age from developed countries.[45] The methodological quality of this systematic review/meta-analysis was rated grade B.

Using the MEDLINE database from 1966 to 1998, and supplementing the results with searches of the bibliographies of the primary and review articles, Chien 2001 identified 16 studies from developed countries that qualified for inclusion in the review. There were 12 prospective cohort studies totaling 5,473 subjects, 2 retrospective cohort studies totaling 504 subjects, and 2 case-control studies with 331 pairs of subjects. For the review, gastrointestinal infection was defined to be “any illness associated with vomiting, change in consistency or frequency of stools, or isolation of a known enteropathogenic bacterial or viral agent.” For the final data analysis, infant feeding practices were dichotomized into two groups: exclusive breastfeeding and partial/mixed feeding, or exclusive artificial feeding.

Results were conflicting. Nine of 16 studies (56 percent) yielded a statistically significant protective effect of breastfeeding on gastrointestinal infections. Majority of the studies suffered from methodological deficiencies. Four studies fulfilled criteria of controlling for detection bias, analyses of confounders, having a clear definition of infant feeding practices and infectious outcomes. Three of the studies reported breastfeeding was protective against non-specific gastrointestinal infection. The fourth study reported that differences in feeding practice did not

affect the attack rates of rotavirus gastroenteritis. The potential confounders examined in these studies included infant sex, race, maternal education, family living standards, marital status, paternal social class, and/or parental smoking. Even though these studies adjusted for potential confounders, the actual quantitative adjusted odds ratio or risk ratio were not reported.

The authors of the systematic review stated that "it was not possible to pool the adjusted relative measures of association" in the cohort studies reviewed. Using a fixed effect model, the summary crude odds ratio of the 14 cohort studies for the development of gastrointestinal infection was 0.36 (95% CI 0.32, 0.41; heterogeneity P<0.01); the summary odds ratio of the two case-control studies was 0.54 (95% CI 0.36 - 0.80; heterogeneity, P=0.35).

Conclusion

Available evidence from three primary studies that controlled for potential confounders suggests that breastfeeding is associated with a reduction in the risk of non-specific gastrointestinal infection during the first year of life in infants from developed countries. However, a summary adjusted effect estimate taking into account potential confounders could not be determined because not all the studies that adjusted for potential confounders provided usable quantitative data for meta-analysis.

Addendum

During the final phase for the preparation of this report, we were alerted to a recent primary study on diarrheal disease in infants in 1990s England that provided relevant quantitative data. This case-control study of 304 infants (167 cases and 137 controls) showed that the infants who were breastfeeding had a reduced risk of diarrhea compared to infants who were not breastfeeding (OR 0.36, 95% CI 0.18 to 0.74, P=0.005). The result was adjusted for age, sex, social class, contact with person in and outside household, and other factors. This study also reported that the protective effect of breastfeeding did not persist beyond 2 months after cessation of breastfeeding.[46]

Table 4. Summary of systematic review/meta-analysis on the relationship between breastfeeding and gastrointestinal (GI) infection

Author Year Population	Studies description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA
Chien 2001 Prospective cohorts: 5,473 Retrospective cohorts: 504 Case-control: 331 pairs	12 prospective cohort studies, 2 retrospective cohort studies; 2 case-control studies	Either exclusive breastfeeding and partial/mixed feeding or exclusive artificial feeding	Maternal education, single or dual parenting, family living standards, infant sex, race, maternal parity, marital status, paternal social class, maternal age, parental smoking	Conflicting results on the effect of breastfeeding on GI infection: 9/16 studies (56%) yielded a statistically significant protective effect of breastfeeding on GI infections; Majority of studies suffered from methodological deficiencies; 4 studies fulfilled criteria of controlling for detection bias, analyses of confounders, having a clear definition of infant feeding practices and infectious outcomes; 3 of these studies reported breastfeeding was protective against non-specific GI infection; Unadjusted pooled estimate of the cohort studies: OR 0.36 (95% CI 0.32, 0.41; heterogeneity P<0.01) Unadjusted pooled estimate of 2 case-control studies: OR 0.54 (95% CI 0.36, 0.80; heterogeneity P=0.35)	B

SR, systematic review; MA, meta-analysis

Relationship of Hospitalization Secondary to Lower Respiratory Tract Diseases in Infancy and Breastfeeding

Background

Respiratory infection is the most common medical problem among infants and children. Each year in the United States, three percent of all infants are hospitalized with moderate to severe respiratory infection.[47] Severe lower respiratory tract diseases may increase the risk of childhood asthma. Viral infections, especially respiratory syncytial virus (RSV) infection, are the most common cause of lower respiratory tract disease in developed countries. RSV infection occurs most frequently between 2 and 8 months of age. The risk factors associated with rates of respiratory illness include age, smoke exposure, day care, race/ethnicity, family size, education, and socioeconomic status. We identified one meta-analysis published in 2003 that compared the risk of hospitalization for respiratory diseases in healthy full term infants who were breastfed with those who were not.[48]

Published Systematic Review/Meta-Analysis (Table 5)

Bachrach 2003's meta-analysis included seven cohort (five prospective and two retrospective) studies that evaluated the relationship between breastfeeding and hospitalization risk secondary to respiratory diseases.[48] Primary studies published before April 2002 and evaluated healthy full-term infants less than 1 year of age from developed countries were included. Only data from exclusive breastfeeding of at least 2 months or any breastfeeding totaling 9 months or more were included. Exclusive breastfeeding was defined as little or no formula feeding. Studies on cystic fibrosis and allergic conditions were excluded. Unpublished data were also examined. The primary outcome variable was hospitalization for lower respiratory tract disease secondary to bronchiolitis, asthma, pneumonia, empyema, and infections due to specific agents (e.g., RSV). The meta-analysis was restricted to first hospitalization. The analysis evaluated the risk of hospitalization in 3,201 breastfed subjects and 1,324 non-breastfed subjects.

The meta-analysis used a random effects model. There was an overall 72 percent reduction in the risk of hospitalization in infants who were exclusively breastfed for 4 or more months compared with those who were formula-fed (summary relative risk 0.28, 95% CI 0.14 - 0.54). There was no change in summary relative risk in the subgroup analyses of studies that also reported relative risk adjusted for the effects of smoking or socioeconomic status. There was no statistical heterogeneity across the studies. The authors performed sensitivity analyses to assess the appropriateness of combining studies and found no changes in summary risk. In addition, the number needed to treat (NNT) was calculated to be 26. This implies that at least 26 infants will have to breastfeed exclusively for 4 or more months to prevent one infant from hospitalization secondary to respiratory diseases. The methodological quality of the meta-analysis was rated grade A.

Conclusion

The meta-analysis showed an overall 72 percent reduction in the risk of hospitalization secondary to respiratory diseases in infants who were exclusively breastfed for 4 or more months

compared with those who were formula-fed. This finding remained statistically significant after adjustment for potential confounders. There could be differences across studies with regard to duration of followup, diagnosis of respiratory disease, and other factors. However, there was no statistically significant heterogeneity detected across the studies. Taking into account the methodological quality of the meta-analysis and the consistent findings reported, we conclude that breastfeeding for 4 or more months is associated with a reduction in the risk of hospitalization secondary to lower respiratory tract diseases.

Table 5. Summary of systematic review/meta-analysis on the relationship between breastfeeding and lower respiratory tract disease

Author year Population	Study description	Intervention /Comparator	Confounders considered	Outcomes	Quality of SR/MA
Bachrach 2003 Infants <1 yr of age Exposed: 3,201 Unexposed: 1,324	MA of 7 observational studies	Breastfeeding exclusively ≥ 2 mo or ≥ 9 mo total of any (including mixed feed)	Smoking or socioeconomic status	Summary RR of 0.28, 95% CI 0.14-0.54 There was an overall 72% reduction of hospitalization among infants who were exclusively breastfed for ≥ 4 mo compared with those who were formula-fed.	A

SR, systematic review; MA, meta-analysis

Relationship between Asthma and Breastfeeding

Background

Asthma is a bronchial disorder accompanied by breathing difficulties, wheezing, coughing, and production of thick mucus. Triggering factors have been attributed to foreign substances, tobacco smoke or pollutants, exercise, infection, and emotional stress. An increase in the prevalence of asthma has been reported in some countries during the second half of the 20th century.[49] In 2002-2003, about six percent of the children in the United States had an asthma attack (www.cdc.gov/nchs/data/hus/hus05.pdf). In addition, the hygiene hypothesis (a lack of early childhood exposure to infectious agents increases susceptibility to allergic diseases[50,51]) has been proffered as a possible explanation for some of the increase in incidence and prevalence of asthma, but that hypothesis remains a matter of debate.[49] Potential confounders considered in the studies of breastfeeding and asthma include age, socioeconomic status, family history of atopy, and parental smoking.

Findings from primary studies on the relationship between breastfeeding and the development of asthma have been conflicting. One meta-analysis published in 2001 aimed to examine this relationship.[52] We identified three relevant prospective longitudinal cohort studies and one followup study (to one of the primary studies in the meta-analysis) published subsequent to the meta-analysis.[53-56] Three of the four studies met the inclusion criteria of the original meta-analysis and an updated meta-analysis stratified by family history of asthma was conducted.

Published Systematic Review/Meta-Analysis (Table 6)

Gdalevich 2001 conducted a meta-analysis that included 12 prospective observational studies with 8,183 term infants followed for a mean of 4.1 years. Study inclusion criteria included subjects from developed countries, exclusive of breastfeeding for at least 3 months, blinding of diagnosing physician to feeding status, and maternal recall of child's feeding history of not more than 12 months. Exclusive breastfeeding was defined as having no substitutes or additions. Critical appraisal of the studies was conducted based on the standards suggested by Kramer.[16] Potential confounders including age, socioeconomic status, family history of atopy, and parental smoking were controlled for by means of multivariate analysis. The outcome of asthma was diagnosis by a physician.

Meta-analysis of the 12 studies with followup of 2 or more years reported a summary odds ratio of 0.70 (95% CI 0.60 - 0.81), suggesting an association of breastfeeding and a reduction in the risk of the development of asthma. Subgroup analysis reported that children with a family history of asthma or atopy benefited more from breastfeeding (OR 0.52, 95% CI 0.35 - 0.79) in the risk reduction of the development of asthma, compared with children who did not have a family history of asthma or atopy. There was no statistical heterogeneity in the studies. Sensitivity analysis indicated the exclusion of any one study did not change the overall results. Methodological quality for the meta-analysis was rated grade A.

Studies Identified after the Published Systematic Review/Meta-Analysis (Table 7)

We identified three prospective cohort studies, including one that had both prospective and retrospective analyses, and one followup publication examining the relationship between breastfeeding and risk of the development of asthma.[53-55] Methodological quality of these four studies ranged from grade C to grade A.

Subjects selected in these studies ranged from healthy full-term infants to any live births from mainly population-based samples. Sample sizes at followup ranged from 1,037 to 4,964 with zero to 31 percent dropouts or withdrawals. Verification of asthma varied from parental confirmation through questionnaires to clinic assessment and physician diagnosis. Although all four studies adjusted for confounding, the only variable common to all studies was maternal smoking, either during pregnancy or after birth.

Two of the studies were population-based, one was hospital-based, and one study was done in a large health maintenance organization (HMO). Wright 2001 and Kull 2004 looked at exclusive breastfeeding whereas Burgess 2006 did not define breastfeeding but acknowledged that exclusive breastfeeding was in practice difficult to verify. Another issue is that there were no gold standards for the diagnosis of asthma in population studies. To confirm the diagnosis of asthma, Kull 2004 relied on clinical examinations as well as blood sampling and pulmonary function tests. Burgess 2006 used data from a questionnaire that asked about medications, symptoms, hospitalization, and family history to formulate the diagnosis. Sears 2002 based the diagnosis on pulmonary function tests with the addition of maternal description of symptoms. Wright 2001 and Kull 2004 appeared to have the most rigorous criteria for diagnosis of asthma by considering recent symptoms, results from testings, and confirmation by a physician. Two studies gathered feeding data post-delivery by recall, first study at 6 months,[53] and the second study at 2 months with another followup at 12 months.[54] Two studies relied on objective data for feeding history; Sears 2002 relied on data from nursing program records,[55] and Wright 2001 relied on breastfeeding data from clinic visits.[56] The methodological quality of the studies by Kull, Wright, and Sears were rated grade B, and Burgess was rated grade C.

Study findings. Kull 2004 followed 3,384 newborns for the first 4 years of life and reported that there was a statistically significant association of exclusive breastfeeding for 4 months or more and a reduction in the risk of the development of asthma (OR 0.72, 95%CI 0.53 - 0.97).[54] Furthermore, subgroup analysis showed that the association was stronger for children whose parents did not have a history of allergic diseases.

Sears 2002 enrolled 1,037 subjects at age 3 years and a retrospective record review found that approximately half were breastfed and half were not (533 breastfed, 504 not breastfed).[55] The subjects were followed prospectively until 21 or 26 years of age. The study found an increased risk of asthma in those subjects who were breastfed compared with those who were not for all time points assessed. Length of breastfeeding duration had no protective effect against asthma. Family history of asthma did not significantly affect these results. Even though "exclusive breastfeeding" rate was reported in the study, the authors acknowledged that it was common practice for the hospital staff to feed the newborns with formula for the first few nights post-delivery to allow the mothers to sleep.

Wright 2001 is a followup publication to one of the primary studies from the Gdalevich 2001 meta-analysis. This study reported that there was no association between duration of exclusive breastfeeding and asthma for 926 children by age 13 years followed since birth, except in those

children who were atopic and whose mothers had a history of asthma.[56] This was the only study to report that a family history of asthma is an effect modifier of breastfeeding in the increased risk of the development of asthma in children.

Burgess 2006 investigated 4,964 children at 14 years of age concerning their history of asthma ("yes" or "no") as reported by their mothers. This study found that there was no significant relationship between the duration of breastfeeding and the prevalence of asthma. The rates of asthma were the same for any given rates of breastfeeding regardless of the maternal history concerning asthma.[53] Data on feeding were collected at 6 months after birth.

Updating the Previous Meta-Analysis

We performed an update meta-analysis stratified by family history of asthma using the random effects model including three of the four recent publications.[53,54,56] The fourth study did not qualify for inclusion because it did not have a comparison group of at least 3 months duration of breastfeeding. In the subgroup analysis of those children with a positive family history of asthma, two studies (Wright[56] and Kull[54]) met the inclusion criteria set by Gdalevich. One of the studies reported a very large adjusted odds ratio (OR 8.7, 95%CI 3.4 – 22.2) in a followup of 13 year olds, compared with the other studies.[56] Sensitivity analyses were conducted to examine the source of heterogeneity by including or excluding this study. Excluding Wright, a history of exclusive breastfeeding for more than 3 months was associated with a reduction in the risk of asthma (OR_{adj} 0.60; 95%CI 0.43 - 0.82), compared with no breastfeeding. Including Wright, there was no longer a statistically significant association between a history of breastfeeding and the risk of asthma (OR_{adj} 0.81, 95%CI 0.41 – 1.60). This result suggests that the heterogeneity can be explained by a single study. Compared with the other studies in the analyses, the age of followup was 13 years in Wright 2001, while it ranged from 2 to 9 years in the other studies.

In the analysis of those children without a family history of asthma, the addition of the two subsequent studies (Kull[54] and Burgess[53]) did not alter the statistically significant association of breastfeeding and the reduction in the risk of asthma (OR 0.73, 95%CI 0.59 – 0.92) compared with the original results reported by Gdalevich. It should be noted that Burgess reported only the unadjusted odds ratio, stating that the adjusted was "minimally altered".

Figure 7. Meta-Analysis of prospective cohort studies of the association between asthma risk and breastfeeding ≥ 3 months for children with positive family history of asthma or atopy (excluding Wright 2001)

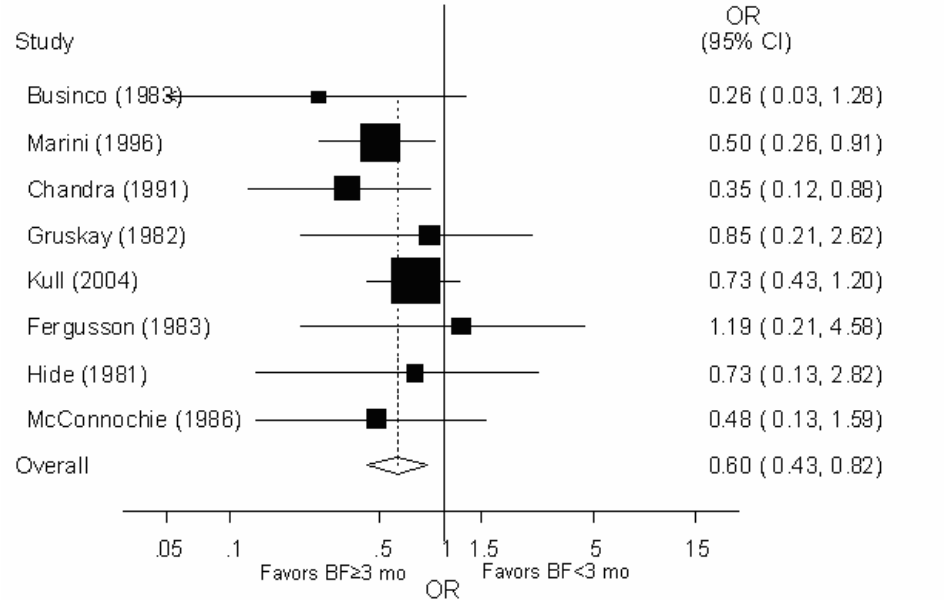


Figure 8. Meta-Analysis of prospective cohort studies of the association between asthma risk and breastfeeding ≥ 3 months for children with positive family history of asthma or atopy (including Wright 2001)

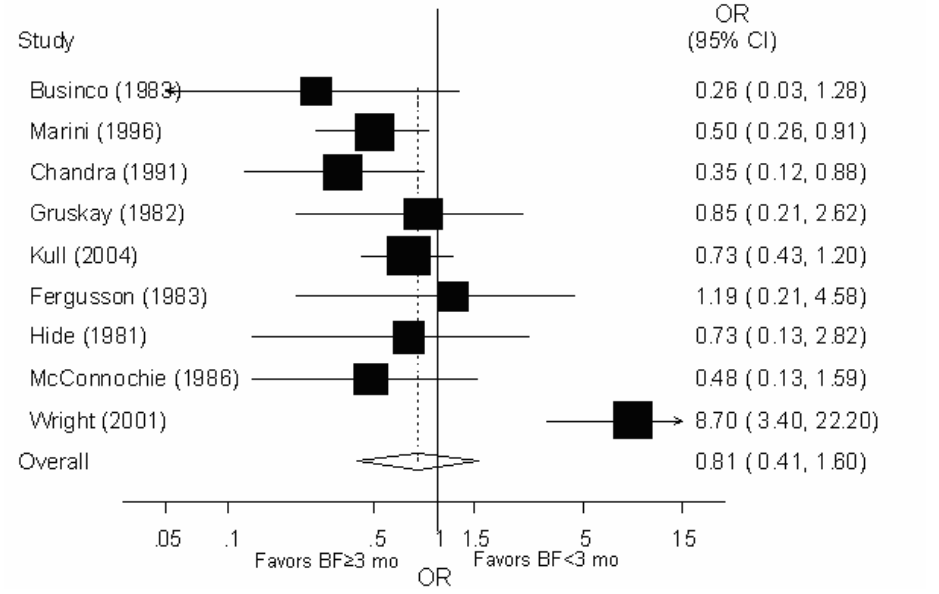
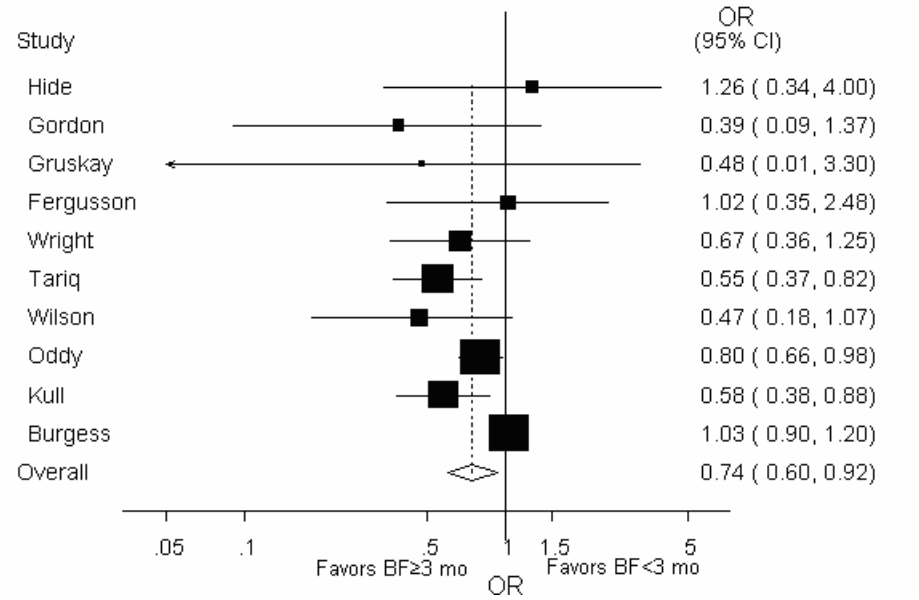


Figure 9. Meta-Analysis of prospective cohort studies of the association between asthma risk and breastfeeding ≥ 3 months for children without family history of asthma or atopy



Conclusion

A well-performed meta-analysis from 2001 concluded that breastfeeding was associated with a reduction in the risk of developing asthma. This association was stronger in those subjects with a positive family history. However, three new primary studies and one followup study reported conflicting results. With our new meta-analyses including three of these studies, it is clear that there remained an association between breastfeeding and a reduction in the risk of asthma in those subjects without a family history of asthma. This association was also found in subjects under 10 years of age with a positive family history of asthma. It is unclear whether this association changes for older children. It should also be noted that the fourth study, which did not qualify for inclusion in our new meta-analyses, reported an increase in asthma risk with increased duration of breastfeeding in those subjects with a maternal history of asthma. Further studies concerning the effect of a family history of asthma on long-term outcome of asthma is warranted.

Table 6. Summary of systematic review/meta-analysis on the relationship between breastfeeding and asthma

Author Year Population	Studies description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA and limitations
Gdalevich 2001 Term infants	MA of 12 prospective studies in developed countries	≥ 3 mo exclusive breastfeeding vs. without ≥ 3 mo of exclusive breastfeeding	SES, gender, family history of atopy, parental smoking, and presence of furry animals at home	≥ 2 years followup, breast feeding had protective effect against asthma, summary OR 0.72 (95% CI 0.62 – 0.84) Subgroup analysis of children from family with asthma or atopy showed higher protective effect of breast feeding OR 0.52 (95% CI, 0.35 - 0.79) Subgroup analysis of children from family without asthma or atopy, OR 0.73 (95% CI, 0.62 - 0.86	A

SR, systematic review; MA, meta-analysis

Table 7. Summary of prospective cohort studies on the relationship between breastfeeding and asthma

Author Year Country Population	Study Description	Breast milk feeding exposure	Assessment of asthma	Confounders adjusted for	Outcomes	Quality and limitations
Kull 2004 Sweden Enrolled: 4,089 Follow-up: 3,384 All newborns from catchments area of Stockholm	Prospective, longitudinal cohort with questionnaires at child's age of 2 months, 1, 2, and 4 years. Clinic assessment at 4 years.	Exclusive breastfeeding was dichotomized with the 25th percentile as the cutoff point (<4 months and ≥4 months) and as a 3-level categorical variable (0-2, 3-4, and ≥5 months)	At age 4 years, 4 episodes of wheezing during the last 12 months or at least 1 episode of wheezing during the same period if the child was receiving inhaled steroids	Maternal age, maternal smoking during pregnancy or at 2 months of age, and heredity of allergic diseases	• Overall exclusive breastfeeding for ≥ 4 month associated with lower risk than those who breastfed <4 months, adjOR 0.72 (0.53-0.97) • Children with no heredity of allergic diseases was associated with lower asthma risk, adjOR 0.58 (0.38-0.88) • Children with heredity of allergic diseases had adjOR 0.73 (0.43-1.20)	B No blinding
Sears 2002 New Zealand Enrolled: 1,037 Followup:1,037 Population-based cohort from single hospital center	Both prospective and retrospective cohort study design enrolled at age 3 and data collected retrospective and prospective, followed prospectively up to 21 years	Breastfeeding categorized by duration: Not breastfed Breastfed > 4 weeks	Asthma as reported by child or parent	SES, birth order, sheepskin use in infancy, maternal smoking	• Breastfeeding at least 4 weeks compared with no to less than 4 weeks associated with higher adjusted OR of asthma, 2.40 (1.36-4.26)	B
Wright 2001 USA Enrolled: 1,246 Followup: 1,043 Healthy newborns from large HMO	Prospective, longitudinal newborn cohort with questionnaires at 2, 3, 6, 9, 11, 13 years; Additional data collection by MD health surveillance	Exclusive breastfeeding categorized by duration: never breastfed breastfed <4 months breastfed >4 months	Physician diagnosed asthma, wheezing or asthma symptoms reported ≥ 2 questionnaires from ages 6 to 13 years	Maternal education, smoking status in 1st year, sex, ethnicity, 2 or more siblings at home or day care use versus neither first 6 months, paternal asthma	• Nonsignificant relationship between asthma and exclusive breastfeeding duration at 13 years • Children with maternal history of asthma: exclusive breastfeeding associated with asthma, adjusted OR 8.7 (3.4-22.2)	B No explanation for withdrawals/dropouts; discrepancies in numbers of exclusive breastfeeding; no blinding

Table 7. Continued

Author Year Country Population	Study Description	Breast milk feeding exposure	Assessment of asthma	Confounders adjusted for	Outcomes	Quality and limitations
Burgess 2006 Australia Enrolled: 7,223 Followup: 4,964 Singleton term deliveries from public clinic of University Hospital	Prospective, longitudinal cohort with questionnaires at birth, 6 months, 5 and 14 years.	Breastfeeding categorized by duration: Never breastfed < 3 weeks 3 – 6 weeks 7 weeks – 3 months ≥ 4 months	From questionnaire: episodes of asthma in past 6 months, frequency of asthma meds, asthma-related sick days from school, asthma-related hospital admissions	Maternal asthma, paternal asthma, smoking early and late pregnancy, frequency of coughs and cold first 6 months, annual family income	• Breastfeeding at least 4 months not associated with asthma compared to no breastfeeding, unadjusted OR 1.03 (0.9-1.2)	C Adjusted OR not reported, dropout/withdrawals > 30%, significant differences between completers and noncompleters, no definition or description of breastfeeding, discrepancy for % males in table.

SES, socioeconomic status

Relationship between Cognitive Development and Breastfeeding in Term Infants

Background

Many studies have examined the relationship between breastfeeding and cognitive development. Results have been conflicting. Many of them did not have a clear definition of breastfeeding or breast milk exposure. Different cognitive assessment tools were used. Outcomes were measured anywhere from less than 2 years of age to adulthoods. Confounders commonly considered in these studies were socioeconomic status, maternal education, birthweight, gestational age, birth order and gender.[57] Jain et al. considered SES and quality and quantity of stimulation of the child (including social interactions) to be crucial confounders. [58] These authors did not consider maternal or paternal intelligence, marital status, number of children, and maternal age to be crucial because to "some degree, they are markers of socioeconomic status, and are not clearly related to both feeding method and intelligence independent of socioeconomic status". Three systematic reviews from 1999 to 2002 have tried to either establish methodological standards to assess the observational studies or adjust for covariates in pooled analysis. Since the last systematic review by Jain et al. in 2002,[58] there have been eight prospective cohort studies on healthy term infants that examined the relationship of breastfeeding to some aspects of cognitive development.

Additional Methodological Comments

We searched for systematic reviews on breastfeeding and cognitive development using terms like "cognitive", "neurodevelopment", "intelligence"…etc. Using similar terms, we searched MEDLINE and CINAHL in January and April of 2006, respectively, for additional primary studies published after 2000. We also identified additional articles based on reviews of the bibliographies cited in the relevant retrieved studies from the search and from suggestions by the reviewers for this report. For primary studies, qualifying study designs included prospective cohort and case-control studies; only studies from developed countries were included. For the healthy term infants, subgroups like infants of diabetic mothers and small-for-gestational age infants were not included. For preterm infants, no subgroups were excluded. Studies concerned exclusively with individual breast milk factor supplements (e.g., long chain polyunsaturated fatty acids, nucleotides) were not included. There was no restriction on timing of and the tools used for cognitive assessment. Only data on cognitive outcomes were extracted, data from motor, psychomotor, or visual development were not extracted.

Published Meta-Analyses/Systematic Reviews (Table 8)

Jain 2002 identified 40 relevant publications (30 birth cohorts, five RCTs, five school registry cohorts, and three case-control studies) from 1929 to 2001. Most of them studied term infants. A few studies included only preterm infants in their analyses. Each study was assessed according to a set of eight clinical epidemiological standards: study design, target population, sample size, quality of feeding data (suitable definition and duration of breastfeeding, and appropriate timing and source of feeding data), whether studies controlled for socioeconomic

status and stimulation of the child, whether observers of the outcome were blind to feeding status, whether a standardized individual test of general intelligence at older than 2 years of age was used, and whether studies reported an effect size. Two studies on term infants met all the proposed methodological standards. One concluded that the effect of breastfeeding on intellect was significant (4.6 points in IQ at age 3 years in children who breastfed compared with those who bottle-fed),[59] and the other concluded that the effect on cognitive performance was statistically non-significant.[60]

Drane 2000 examined 24 studies from 1966 to 1998.[57] Twenty-one included term infants, two included low birthweight infants, and one involved small-for-gestational age infants. Each study was assessed according to a set of three methodological standards: definition of outcome, correct classification of type of infant feeding, and control of potential confounding variables (socioeconomic status, maternal education, birthweight, gestational age, birth order, gender). Five of the 24 studies met all three methodological standards. These studies indicated an advantage in IQ to breastfed infants in the range of two to five points for term infants and eight points for low birth weight infants.

Interestingly, of the two studies that were identified by Jain 2002 to have met all the proposed methodological reporting standards, the feeding data from one did not meet the feeding data reporting standard put forth in the review by Drane 2000. The study at issue was Wigg 1998, in which the following statement could be found: "Feeding methods (i.e., breast, bottle-fed or mixed) and duration of breastfeeding in infancy were recorded at age 6 months by the trained research nurse".[60] Jain 2002 interpreted that study to have met their requirement of adequate reporting of feeding data ("whether infants received breast milk exclusively or with supplemental formula or other foods"), while Drane 2000 interpreted that study not to have adequately distinguished between partial and exclusive breastfeeding. The other study that met all the methodological standards according to Jain 2002 was published in 1996,[59] but it was not included in Drane 2000's review; reason of which was not readily apparent.

Anderson 1999 examined 11 studies from 1978 to 1995 that controlled for at least five covariates (breastfeeding duration, sex, maternal smoking history, maternal age, maternal intelligence, maternal education, maternal training, paternal education, race or ethnicity, socioeconomic status, family size, birth order, birth weight, gestational age, and childhood experiences) and presented unadjusted and adjusted results.[61] Eight studies included term infants; three studies included only preterm infants. The results were combined in a meta-analysis. The adjusted (fixed effects) pooled mean difference was 3.16 points (standardized effect estimate of cognitive developmental mean score, 95% CI 2.35 - 3.98) in favor of the breastfeeding group. Low birthweight infants showed larger differences (5.18 points in cognitive developmental score; 95%CI 3.59 - 6.77) than did normal birth weight infants (2.66 points; 95%CI 2.15 - 3.17). Other methodological quality of the studies was not assessed.

Studies Identified after the Published Meta-Analysis/Systematic Review in Term Infants (Table 9)

Prospective cohort. One secondary analysis of a prospectively collected data set[62] and seven prospective cohort studies ranging from 44 to 3880 term subjects reported on the relationship between breast milk feeding and some aspects of cognitive development since 2002. [63-71]

None of the cohort studies made a clear distinction between partial and exclusive breastfeeding. Two studies stated to have a prospective design, but the breastfeeding information

was collected retrospectively. Subjects were breastfed from less than 3 weeks to 12 months. Three studies reported the proportion of subjects who breastfed for more than 6 to 7 months, they ranged from 9 percent to 62 percent.

Bayley Mental Development Index Scale (MDI) was the cognitive assessment tool for subjects under 2 years of age. Peabody Picture Vocabulary Test (PPVT-R) and Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R) were used in subjects under 7 years of age. Wechsler Adult Intelligence Scale (WAIS), Raven's standard progressive matrices, standard reading, verbal, and mathematical reasoning tests were used in adults up to 27 years of age. Time of assessment ranged from 1 to 27 years.

Der 2006 analyzed the database from the US National Longitudinal Survey of Youth 1979 (NLSY79).[62] This database has information on the participants and their offsprings. The study reported that the adjusted effect of breastfeeding on Peabody individual achievement test (standardized mean of 100 and SD of 15) at 14 years was reduced to +0.52 from +4.7 after adjustment for maternal IQ, education, age, family poverty, home stimulation, and birth order. Further analysis of 332 pairs of siblings discordant for breastfeeding status found non-significant difference between groups in both status and duration of breastfeeding. Meta-regression of nine unique studies (including the data from NLSY79) reported an advantage of breastfeeding of 0.16 cognitive points after controlling for maternal IQ and other confounders. This study was rated good methodological quality (grade A).

Der 2006 also combined its estimate with the estimate from the only other sibling analysis in the literature to date (Evenhouse 2005,[72] this study did not qualify for inclusion in this review because it was an analysis of data obtained from a cross-sectional design study). Evenhouse 2005 analyzed the database from the National Longitudinal Study of Adolescent Health (Add Health) 1994 (This database oversamples low-income, African-American, and Hispanic children and provided information on an abbreviated Peabody Picture Vocabulary Test results. There were 523 pairs of siblings with different breastfeeding history in this data set). The combined estimate from NLSY79 and Add Health was 0.025 (P=0.54) for breastfeeding status and 0.04 (P=0.271) for duration of breastfeeding.

Of the six prospective cohort studies of moderate (grade B) methodological quality, five reported an advantage in cognitive development in subjects who breastfed. Specifically, Lawlor 2006 reported that the adjusted score (for sex, parental characteristics, birthweight, and perinatal characteristics) in Raven's standard progressive matrices at age 14 years showed a mean difference of 6.79 (95%CI, 5.33-8.26) in less than 4 months of breastfeeding versus never breastfeeding (compared to an unadjusted mean of 8.20).[71] Quinn 2001 reported that the mean PPVT-R at 5 years for those breastfed for at least 6 months was 8.2 points (95%CI, 6.5-9.9) higher for females and 5.8 points (95%CI, 4.1-7.5) higher for males when compared to those never breastfed. PPVT-R was adjusted for birthweight, poverty, maternal education, maternal age, time in daycare or preschool, the number of children in the household at 5 years, English speaking background in parents, and infant stimulation.[70] Similarly, Oddy 2003 and 2004, reported that the PPVT-R score at 6 years was 3.56 point higher for children breastfed more than 6 months compared with children never breastfed (F=8.59, P=0.003).[68,69] The result was adjusted for gender, gestational age, maternal age and education, parental smoking, and the presence of older siblings. Mortensen 2002 reported that the duration of breastfeeding was associated with significantly higher scores on the verbal, performance, and full scale WAIS at 27 years.[67] With regression adjustment for parental social status and education, single mother status, mother's height, age, and weight gain during pregnancy, cigarette smoking during 3rd trimester, number of

pregnancies, estimated gestational age, birth weight, birth length, and indices of pregnancy and delivery complications, the mean full scale WAIS were 99.4, 101.7, 102.3, 106.0, and 104.0 for breastfeeding durations of < 1 month, 2 to 3 months, 4 to 6 months, 7 to 9 months, and > 9 months, respectively (P=0.003). GomezSanchiz 2004 reported that the Bayley MDI at 24 months was 4.3 points higher in those breastfed more than 4 months compared with those breastfed less than 4 months after multiple linear regression adjusting for parental IQ.[66] Angelsen 2001 reported that adjustment for differences in maternal intelligence reduced the odds ratio of having a low IQ score among children who were breastfed for <3 months compared to ≥ 6 months from 2.8 (95%CI 1.4-5.3) to 1.5 (95%CI 1.0-2.1).[64]

Conclusion

One well-performed sibling analysis and prospective studies that controlled specifically for maternal intelligence demonstrated that there is either little or no evidence for an association between breastfeeding and cognitive performance in children. It is clear that maternal intelligence is a major confounder in the studies on relationship between breastfeeding and cognitive development. For those studies that still reported a significant effect after adjustment for maternal intelligence, residual confounding from other factors like different home environments cannot be ruled out. Many studies controlled for socioeconomic status and maternal education but not specifically for maternal intelligence. It is clear that maternal intelligence should be controlled for separately from socioeconomic status and maternal education in any studies of breastfeeding and cognitive development. As cautioned by Der et al., "The generalizability of the results presented here must be considered carefully. This study and the others included in the meta-analysis are all based on samples from developed countries. Generalization of the findings beyond these and similar societies would be unwise. We have also excluded premature and low birthweight infants for whom the effect may be different."[62]

Table 8. Summary of systematic reviews/meta-analyses on the relationship of breastfeeding and cognitive development

Author Year Population	Studies description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA and limitations
Jain 2002 50 to >11,000 Term and preterm	30 birth cohorts; 2 RCTs; 5 school registry cohorts; 3 case-control studies	Breastfeeding, breast milk, or choice to breastfeed	SES (parental education, occupation, income or any combination), quality and quantity of stimulation of the child (including social interactions)	Quality of feeding data evaluated by 4 criteria (exclusive breastfeeding or not, timing of feeding data collection, source of feeding data, duration of breastfeeding): 9 articles met all 4 criteria (8 full-term cohorts). 22 studies used an appropriate measure of cognition. Only 2 studies met all the methodological standards. One study concluded that "any beneficial effect of breastfeeding on cognitive development is quite small in magnitude", another study found that children who were breastfed had mean IQ scores 4.6 points higher than those never breastfed after controlling for socioeconomic status and other factors. Among the studies that controlled for socioeconomic status and stimulation/interaction of the child, three concluded that breastfeeding promotes cognitive development, and four did not.	A
Drane 2000 N in individual studies not provided in the review Term and preterm	24 studies (1 RCT and 23 cohorts) met inclusion criteria: birth 1960-98, English language, examined cognitive development	Actual breastfeeding intervention in individual studies not described in the review	SES, maternal education, birthweight, gestational age, birth order, gender	5 studies met the 3 methodological standards (operational definition of cognitive outcome and outcome measure using standardized tests; correct classification of type of feeding: measure breastfeeding as a continuous variable or at least as a 3-level categorical variable (exclusive breast or formula-fed; partial breastfed) and control for potential confounding variables. The only RCT did not find statistical significant difference in Bayley MDI in infants fed solely on a diet of donor breast milk compared with infants fed solely on a diet of term formula. Advantages in IQ as measured by the WISC-R, Bayley and McCarthy were observed in 4 cohort studies. In term infants, effects on IQ in the range of 2-5 points (0.2-0.3 SD) were found.	B

Table 8. Continued

Author Year Population	Studies description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA and limitations
Anderson, 1999 7,081 Term and low birthweight	11 cohort studies with results adjusted for covariates	Breastfeeding vs. formula feeding (no detailed information)	breastfeeding duration, sex, maternal smoking, age, intelligence, education, training, paternal education, race or ethnicity, SES, family size, birth order, birth weight, gestational age, and childhood experiences	Adjusted (fixed effects) pooled mean difference of standardized effect estimate of cognitive developmental score was 3.16 (95% CI 2.35, 3.98) in favor of breastfeeding; An average adjusted benefit from breastfeeding of 5.18 points in cognitive developmental score was obtained for low-birth weight children across 6 available observations.	B No additional quality assessments of primary studies

MDI, Bayley Mental Development Index; SR, systematic review; MA, meta-analysis; SES, socioeconomic status

Table 9. Summary of studies on the relationship of breast milk feeding and cognitive development

Author Year Country Population	Study Description	Breast milk feeding exposure	Assessment tools for cognitive development	Confounders adjusted for	Outcomes	Quality and limitations
Database analysis of a prospective cohort study						
Der 2006 US Database from the US national longitudinal survey of youth 1979 (NLSY79) and children of the women in the survey, Full term infants	Database analysis of a prospective study; sibling pairs analysis, and meta-analysis; Cognitive test administered to children between 5 yr and 14 yr biennially from 1986 to 2002; For meta-analysis, only included studies that quantified the effect of breastfeeding on cognitive ability after controlling for parental intelligence	Breastfeeding history obtained within a year of birth in most cases	Peabody individual achievement test (PIAT) was administered to children	Adjustment for variables associated with breastfeeding in the survey, home environment (HOME-SF), child demographics, maternal characteristics	PIAT (all outcomes standardized to a mean of 100 and SD of 15) Unadjusted effect of breastfeeding +4.7 compared to non-breastfeeding (3,161 mothers, 5,475 children, 16,744 assessments); after adjustment for maternal Armed Forces Qualification Test (AFQT) score, education, age, family poverty, HOME stimulation score, and birth order, the difference became +0.52 (P=0.149) 332 pairs of sibling discordant for breastfeeding status and 545 discordant for duration of breastfeeding, difference between groups (status) = -0.63 (P=0.506); (duration) = -0.13 (P=0.866) Meta-regression of 9 unique studies (including the data from NLSY79): an advantage of breastfeeding of 0.16 after controlling for IQ and 8 additional confounders. Combined data from NLSY79 and sibling analysis study by Evenhouse 2005 (see separate extraction): estimate 0.025 (P=0.54) for breastfeeding status and 0.04 (P=0.271) for duration of breastfeeding	A No details regarding breastfeeding history

Table 9. Continued

Author Year Country Population	Study Description	Breast milk feeding exposure	Assessment tools for cognitive development	Confounders adjusted for	Outcomes	Quality and limitations
Prospective cohort						
Lawlor 2006 Australia Enrolled 7,223 Followup 3,794 (>98% term)	Enrolled subjects at birth and did Peabody Picture Vocabulary test at 5 yr and Raven's standard progressive matrices (non-verbal reasoning or general intelligence) at 14 yr, most of the data reported were from age 14 (see Quinn 2001 for 5-yr data)	Classified by never, < 4 mo, ≥ 4 mo (obtained from mothers at the 6-mo followup)	Raven's standard progressive matrices at 14 years	Sex, parental characteristics (maternal age, ethnicity, education, paternal education, family income, gravidity, maternal smoking), labor, Apgar scores, birthweight, height, BMI	At age 14 yr, Never breastfed = 694, <4 mo = 1372, ≥ 4 mo = 1,606 All parental characteristics were related to offspring IQ score. Unadjusted scores at age 14 showed a mean difference of 4.43 (95%CI 3.09 to 5.77) in <4 mos breastfeeding vs never breastfeeding; 8.20 (95%C I6.89 to 9.49) in ≥ 4 mo breastfeeding vs. never breastfeeding (P<0.001) Adjusted scores at age 14 yr (N=3,099) showed a mean difference of 4.07 (95%CI 2.61 to 5.53) in <4 mo breastfeeding vs. never breastfeeding; 6.79 (95%CI 5.33 to 8.26) in ≥ 4 mo breastfeeding vs. never breastfeeding (P<0.001) Family income, parental education and breastfeeding explained 7.5% of the variation in intelligence at age 14 yr. Loss to followup was selective, those subjects were more likely to have mothers who were from poorer social backgrounds, lower education, and younger; regression analysis repeated using Heckman's sample selection bias adjustment with maternal age, parental education, and family income as the selection variables; results of these regression models did not differ from those who had followup.	B Large drop out

Table 9. Continued

Author Year Country Population	Study Description	Breast milk feeding exposure	Assessment tools for cognitive development	Confounders adjusted for	Outcomes	Quality and limitations
Quinn 2001 Australia Enrolled 7,357 Followup 3,880 Singleton; children with major neurological abnormalities and those for whom the data were incomplete were excluded	Enrolled women attending antenatal clinic; data collected at baseline, after birth, 6 mo and 5 yr	No distinction was made between partial or complete breastfeeding; classified by never, < 3 wk, 3 to < 7 wk, 7 wk to < 4 mo, 4 mo to < 6 mo, or ≥ 6 mo	Peabody Picture Vocabulary Test (PPVT-R) was administered at 5 years.	Birth weight, poverty, maternal education, maternal age, time in daycare or preschool, number of children in the household at 5 years	Breastfeeding ≥ 6 mo 103.6 (SD 13.1) No breastfeeding 94.2 (SD 14.1) There was a significant trend towards increasing PPVT-R with increased duration of breastfeeding (P=0.0000) Before adjustment, the mean for those breastfed ≥6 mos was 10.9 points (95%,CI 9.3, 12.5) higher for females and 7.5 points (95% CI 5.9, 9.1) higher for males when compared to those never breastfed. After adjustment, the mean for those breastfed ≥6 mos was 8.2 points (95%,CI 6.5, 9.9) higher for females and 5.8 points (95%,CI 4.1, 7.5) higher for males when compared to those never breastfed.	B Large drop out

Table 9. Continued

Author Year Country Population	Study Description	Breast milk feeding exposure	Assessment tools for cognitive development	Confounders adjusted for	Outcomes	Quality and limitations
Oddy, 2003, 2004 (same data) Australia 2,393 at birth, 1,444 at 6 yr, 1,371 at 8 yr 37-39 wk gestation	Comparing no breastfeeding, <4 mo, 4-6 mo, and >6 mo of breastfeeding	90% of children were breastfed at some point, 28% were breastfed for >6 mo, solid foods were introduced at ≤6 mo in 88% of infants.	Peabody Picture Vocabulary Test (PPVT-R) was administered at 6 y/o and a Performance subtest (Perceptual organization WISC- Block Design) at 8 y/o	Gender, gestational age, maternal age and education, parental smoking, and the presence of older siblings.	Both verbal IQ and performance scores increase with increasing maternal education combined with a longer duration of breastfeeding, with the most profound effect of breastfeeding occurring in the highest education groups (P<0.005). In the lower education groups, these trends were less consistent. Before adjustments for covariates, children breastfed for >6 mo had mean verbal IQ scores 6.44 points higher and Block Design scores that were 1.13 points higher than children never breastfed. After adjustment for covariates, there was an association between duration of breastfeeding and verbal IQ with a 3.56 point advantage for children breastfed >6 mo compared with children never breastfed (P=0.003). The adjusted association of full breastfeeding with the Performance subtest was not significant (P=0.223). There was an association of low PPVT-R and non-English maternal language; children of non-English speaking parents (n=100) were excluded from further analyses.	B Large drop out

Table 9. Continued

Author Year Country Population	Study Description	Breast milk feeding exposure	Assessment tools for cognitive development	Confounders adjusted for	Outcomes	Quality and limitations
Mortensen 2002 Denmark Enrolled 9,125 (4668 males) 973 had WAIS; 2,280 had BPP & BF data	Prospective cohort; but breastfeeding information collected retrospectively at 1-year exam	Divided into 5 BF groups: ≤ 1 mo 32%; 2-3 mo 32%; 4-6 mo 24%; 7-9 mo 9%; > 9 mo 3%	2 sub-cohorts; one (50% male) took the WAIS at 27 yr; the other (100% male) took the draft board intelligence test: Borge Priens Prove (BPP) at 18.7 yr	Parental social status and education, single mother status, mother's height, age, and weight gain during pregnancy, cigarette during 3rd trimester, number of pregnancies, estimated gestational age, birthweight, birth length, and indices of pregnancy and delivery complications	Breastfeeding duration (mo) Unadjusted WAIS: <1: 98.1; 2-3: 101.3; 4-6: 103.3; 7-9: 108.2; > 9: 102.8 Adjusted WAIS: 99; 102; 102; 106; 104 P=0.003 for overall F Unadjusted BPP: 36.9; 39; 40.8; 43.1; 40.2 Adjusted BPP: 38; 39; 40; 40; 40 P=0.01 for overall F	B Large drop out
GomezSanchiz, 2003, 2004 Spain 296 at birth; 249 at 18 mo; 238 at 24 mo 37-42 wk gestation	1 rural and 1 urban sites, comparing breastfed > 4 mo, <4 mo, and formula-fed; breastfeeding information was from medical records; (reported as a prospective cohort by authors, but parents were informed of the project and gave consent for the study at 15 months check up)	≤ 4 mo 49% > 4 mo 28% (no distinction between exclusive or partial breastfeeding) Formula-fed 23%	Bayley was administered at 18 and 24 mo	Parental IQ, social class, parental education, number of siblings	Parental IQ was obtained only for 164 couples; their children had MDI 2.3 points higher than the children whose parents did not take part in IQ testing (P<0.05). Infants were breastfed for a mean of 85.7 days ± SD 76.4 days. Duration of breastfeeding had a correlation with MDI at 18 mo (r=0.42; P<0.001) and at 24 mo (r=0.37; P<0.001). At 24 mo, after multiple linear regression adjusting for parental IQ, difference between formula and breastfeeding ≤ 4 mo no longer significant; difference of 4.3 points remained significant when comparing breastfeeding > 4 mo with ≤ 4 mo.	B Bayley at young age

Table 9. Continued

Author Year Country Population	Study Description	Breast milk feeding exposure	Assessment tools for cognitive development	Confounders adjusted for	Outcomes	Quality and limitations
Angelsen, 2001 Norway and Sweden Enrolled 521 Followup 291 (5 yr) Term Excluded congenital malformations	Prospective cohort; but duration of breastfeeding retrospectively recorded at 13 mo	< 3 mo 17%; 3-6 mo 21%; ≥ 6 mo 62%	Bayley MDI at 13 mo Wechsler Preschool and Primary Scales of Intelligence (WPPSI-R) at 5 y/o	Maternal IQ, age, education, smoking	Bayley MDI at 13 mo: 117.7 (SD11.7) in ≥ 6 mo breastfeeding compared to 109.9 (SD13.1) in < 3 mo (P<0.001). There was a linear increase in MDI plotted against breastfeeding duration (P<0.001). Maternal intelligence (Raven test score) was also related to duration of breastfeeding. Adjustment for differences in maternal intelligence reduced the OR of having a low MDI among children who were breast fed for <3 mo to 1.6 (95%CI 1.1-2.3) from 3.2 (95%CI 1.7-5.9). Total IQ at 5 y/o: 111 (SD14.3) in ≥ 6 mo breastfeeding compared to 103.6 (SD14.6) in < 3 mo (P<0.001). Adjustment for differences in maternal intelligence reduced the OR of having a low IQ score among children who were breastfed for <3 mo to 1.5 (95%CI 1.0-2.1) from 2.8 (95%CI 1.4-5.3).	B Large drop out
Agostoni, 2001 Italy Enrolled 95 Followup 44 Term infants	Bayley results at 1 yr were compared in breastfeeding ≥6 mo with 3-6 mo	≥ 3 mo 46% 6 mo 31% 9 mo 18% 12 mo 11%	Bayley MDI at 1 y/o	Parity, maternal education, age, and smoking habits	Unadjusted Bayley MDI in 29 subjects breastfed > 6 mo = 94, in 15 subjects breastfed 3-6 mo = 92.1; After adjustment, Bayley MDI in 29 subjects breastfed >6 mo compared to 15 subjects breastfed 3-6 mo showed a 2.0 point advantage (95% CI –3.2, 7.3).	C Small sample size, Bayley at young age

BMI, body mass index; MDI, Mental Development Index; NLSY79, national longitudinal survey of youth 1979; PIAT, Peabody individual achievement test; PPVT-R, Peabody Picture Vocabulary Test; SR, systematic review; MA, meta-analysis; SES, socioeconomic status; WPPSI-R, Wechsler Preschool and Primary Scales of Intelligence

Relationship between Obesity and Breastfeeding

Background

The prevalence of overweight or obesity among children and adolescents has rapidly increased in the past two decades. Results from the 1999-2002 National Health and Nutrition Examination Survey (NHANES) showed that an estimated 16 percent of children and adolescents ages 6-19 years were overweight. This represents a 45 percent increase from the overweight estimate of 11 percent obtained from NHANES III (1988-94). (www.cdc.gov/nchs/products/pubs/pubd/hestats/overwght99.htm) It is increasingly recognized that nutrition in early life may have long-term physiologic effects. Relationships between the types of postnatal feeding and the subsequent development of fat and fat-free mass are quite complex and are dependent on multiple factors including differences in food composition (human milk versus formula), food delivery (breast versus bottle), food "lifestyle" (breastfeeding versus formula feeding) and food behavior (self-regulation and feeding on demand versus set schedules of feeding of predetermined amounts).[73] It is known that infants fed breast milk differ in their growth kinetics from formula-fed infants. Formula-fed infants demonstrate higher weight and length gains compared with breastfed infants. A systematic review of 19 studies in developed countries concluded that by the age of 12 months, the cumulative difference in body weight amounted to approximately 400 g less in infants breastfed for 9 months compared with formula-infants, and as much as 600-650 g less in infants breastfed for 12 months compared with formula-fed infants.[74] Differences in feeding behavior and mother-child interaction between breast- and formula-fed infants may account for some of the differences reported. For instance, breastfed infants showed a different suckling pattern, and appeared to have greater degree of control on meal sizes and feeding intervals than infants who were formula-fed.[75] Diet-related differences in the circulating levels of biochemical markers (such as leptin, ghrelin, insulin-like growth factors, and other compounds) implicated in energy metabolism during infancy might explain some of the anthropometric and behavioral differences between breastfed and formula-fed infants. These observed differences may have potential long-term consequences.[73]

Commonly considered confounders in the studies of relationship between obesity or overweight and breastfeeding were birth weight, parental overweight, parental smoking, dietary factors, physical activity, socioeconomic status (SES), age, sex, birth order, and number of siblings.

Additional Methodological Comments

We identified three systematic reviews and meta-analyses that examined the relationship between breastfeeding and childhood obesity or obesity across all ages.[76-78] Although the outcomes of interest were similar among these systematic reviews and meta-analyses, they answered slightly different research questions because of the differences in their study eligibility criteria and analyses. Thus, we have summarized and discussed these systematic reviews and meta-analyses separately.

Published Systematic Reviews/Meta-Analyses (Table 10)

Arenz 2004 was a meta-analysis of studies from 1966 to December 2003 that examined the relationship between breastfeeding and childhood obesity in children at least one year of age. Inclusion criteria for the meta-analysis were: obesity defined by a body mass index (BMI) greater than 90^{th}, 95^{th} or 97^{th} percentile; adjustment for at least three potential confounding or interacting factors; reported either odds ratio or relative risk; and last followup between 5 and 18 years of age. Nine of 28 studies reviewed met the eligibility criteria for meta-analysis. There were two prospective cohort and seven cross-sectional studies totaling more than 69,000 children from developed countries. The meta-analysis used both fixed- and random-effects models and pooled crude and adjusted odds ratios from the individual studies. Definitions of breastfeeding and comparative feedings were heterogeneous across studies. Sensitivity analyses were performed to assess for heterogeneity. The factors analyzed were cohort study or cross-sectional study, different definitions of breastfeeding, different definitions of obesity, different age groups and number of potential confounders considered for adjustment. The methodological quality of this meta-analysis was grade A.

The pooled crude odds ratio for breastfeeding and obesity defined as a BMI > 90th, 95th or 97th percentile could be calculated for six of the nine studies included. The odds ratio was 0.67 (95% CI 0.62 - 0.73). The adjusted odds ratio for the nine studies was 0.78 (95% CI 0.71 - 0.85) for both the fixed and random-effects models, suggesting that there was no heterogeneity between the studies. Sensitivity analyses showed that the protective effect of breastfeeding was more pronounced in studies with adjustment for less than seven potential confounding factors compared with adjustment for seven or more potential confounding factors (adjusted OR 0.69 vs. 0.78, respectively). Other criteria (e.g., cohort study or cross-sectional study, different definitions of breastfeeding, different definitions of obesity, different age-groups) did not affect the summary estimates significantly. For example, the pooled adjusted odds ratio of obesity was 0.76 (95%CI 0.67-0.86) in studies comparing ever breastfeeding to never breastfeeding, versus 0.74 (95%CI 0.64-0.85) in studies that used other definitions of breastfeeding and comparative feedings.

Eight studies analyzed the relationship between breastfeeding duration and the risk of overweight or obesity in later childhood. Exclusivity of breastfeeding was not reported. Four studies reported an inverse association of breastfeeding duration and the prevalence of obesity both in the crude and the adjusted estimates. One of the studies lost statistical significance after adjustment. Three studies found no significant effect of duration of breastfeeding on obesity.

Harder 2005 was a meta-analysis of 17 qualifying studies published from 1966 to December 2003. A total of 120,831 subjects (66 to 32,200 subjects per study) from developed countries were included. Eligibility criteria included any original report comparing breastfed subjects with exclusively formula-fed subjects at any age, the reports must have either reported odds ratio or contained data for the calculation of odds ratio for the risk of overweight or obesity in relationship to the feeding history, and the duration of breastfeeding must have been reported. All definitions of overweight or obesity were included. Three different meta-analytic techniques that specifically required the use of crude odds ratios and 95% confidence intervals were employed. Because of suboptimal consideration for potential confounding, we rated the methodological quality of this meta-analyses grade B.

Fourteen studies provided data for more than one category of duration of breastfeeding, leading to 52 estimates included in the meta-regression analysis. In the analysis, duration of

breastfeeding was significantly negatively related to the risk of overweight (regression coefficient: 0.94, 95%CI 0.89 - 0.98). Categorical analysis showed that from 1 month of breastfeeding onward (the reference group), the risk of subsequent overweight continued to decrease, reaching a plateau of more than 30 percent risk reduction at 9 months of breastfeeding. Using the "pool-first method" (that is to calculate a study-specific regression coefficient and corresponding 95 percent confidence interval for each study using a log-linear model and then pooled all studies with a random effects model) to quantify the dose-response relationship, the results showed that each month of breastfeeding was associated with a four percent decrease in risk of overweight per month of breastfeeding exposure (OR 0.96/month of breastfeeding, 95%CI 0.94 - 0.98). A fixed effect model reported a similar pooled odds ratio (OR 0.96/month of breastfeeding, 95%CI 0.95 - 0.98). The age at examination had little influence on the magnitude of the effect of duration of breastfeeding on the risk of overweight. The pooled odds ratio from five studies investigating subjects up to 5 years of age was 0.97 (95%CI 0.94 - 0.99); while for six studies on subjects 6 or more years of age, it was 0.96 (95%CI 0.93 - 0.99).

The effect of the duration of exclusive breastfeeding was analyzed in two studies. The pooled odds ratio for the risk of overweight per month of exclusive breastfeeding was 0.94 (95%CI 0.89 - 0.99, random effects model).

Subgroup analyses showed that the different definitions of overweight influenced the estimate of odds ratio only slightly. In eight studies that used BMI to define overweight, the pooled odds ratio was 0.96 (95%CI 0.94 - 0.98); while in three studies that used another measures (e.g., percentile of weight for length, or weight for age) to define overweight or obesity, the odds ratio was 0.93 (95%CI 0.87 - 0.99).

Lastly, Owen 2005 was a systematic review of 61 observational studies from 1966 to September 2003 that examined the effects of infant feeding on a measure of adiposity (quantitatively or narratively) in later life. Twenty-eight studies (totaling 298,900 subjects) that provided 29 unadjusted odds ratios relating the initial infant feeding method and obesity were included in a meta-analysis. A fixed effect model was used. Meta-regression and sensitivity analyses were used to examine the influence of various factors defined a priori, including the effects of adjustment for factors such as parental body size (mostly BMI), SES, and maternal smoking. Because of suboptimal consideration for potential confounding, we rated the methodological quality of this systematic review and meta-analyses grade B.

Twenty-eight of 29 estimates related breastfeeding to a lower risk of obesity in later life. Four estimates were for infants, 23 for children, and two for adults. There was evidence of marked heterogeneity among studies ($P < 0.001$). In a fixed-effect meta-analysis, breastfed subjects were less likely to be defined as obese than were formula-fed subjects (OR 0.87, 95% CI 0.85 - 0.89). In six studies, it was possible to examine the effect of adjustment for the following potential confounders: SES (based on parental education in two studies), parental BMI, and current maternal smoking or maternal smoking in early life. The pooled odds ratio in these studies changed from 0.86 (95% CI 0.81 - 0.91) before adjustment to 0.93 (95% CI 0.88 - 0.99) after combined adjustment. The effect of adjustment for birth weight (based on either actual birth weight or prevalence of low birth weight) was examined in 10 studies; this had no appreciable effect on the odds ratios.

There was no clear evidence that the protective effect of breastfeeding altered with increasing age of outcome assessment. Odds ratios of 0.50 (95% CI 0.26 - 0.94) for infants, 0.90 (95% CI 0.87 - 0.92) for young children, 0.66 (95% CI 0.60 - 0.72) for older children, and 0.80 (95% CI 0.71 - 0.91) for adults were observed (test for trend, $P = .85$, adjusted for study size; $P = .99$ with

the exclusion of infants). The protective effect of breastfeeding on obesity was stronger and more homogeneous among four studies in which initial feeding groups were exclusive (OR 0.76; 95% CI 0.70 - 0.83; test for heterogeneity between estimates, P= .143), compared with all other studies. In 14 studies that provided data on breastfeeding duration, the protective effect of breastfeeding over formula feeding was greater among subjects breastfed for at least 2 months (OR 0.81, 95% CI 0.77 - 0.84), compared with those breastfed for any duration (OR 0.89, 95% CI 0.86 - 0.91). In six studies, it was possible to examine the effect of adjustment for the following potentially important confounders: socioeconomic status, parental BMI, and current maternal smoking or maternal smoking in early life. The pooled odds ratio in these studies was reduced from 0.86 (95% CI: 0.81– 0.91) before adjustment to 0.93 (95% CI: 0.88–0.99) after adjustment.

Thirty-three studies totaling 12,505 subjects explored the relationship between breastfeeding and obesity even though they did not provide odds ratio. However, they provided 35 reports of directions of association; of these, breastfeeding was unrelated to the risk of obesity in 33, related to a reduced risk in one, and related to an increased risk in another. Studies that did not provide odds ratios were much less likely to report that breastfeeding was associated with a reduced risk of obesity, compared with studies that did provide odds ratios (1 of 35 studies and 18 of 29 studies, respectively; P < .001).

Conclusion

Findings from three systematic reviews and meta-analyses of good and moderate methodological quality suggest that a history of breastfeeding is associated with a reduction in the risk of obesity in later life. The pooled adjusted odds ratio of overweight/obesity comparing ever breastfeeders to never breastfeeders was 0.76 (95%CI 0.67-0.86) and 0.93 (95%CI: 0.88–0.99) in Arenz 2004 and Owen 2006 meta-analysis, respectively. In Harder 2005 meta-analysis, duration of breastfeeding was significantly negatively related to the unadjusted risk of overweight (regression coefficient: 0.94, 95%CI 0.89 - 0.98), and each month of breastfeeding was found to be associated with a four percent decrease in risk (unadjusted OR 0.96/month of breastfeeding, 95%CI 0.94 - 0.98). However, the results from Harder 2005 meta-analysis employed techniques that required the use of crude odds ratios from the primary studies for its summary estimates. Therefore, those estimates may not be accurate because potential confounders could not be accounted for in the analysis. As demonstrated in the sensitivity analyses in both Arenz 2004 and Owen 2005, the magnitude of effects was reduced when more confounders were adjusted for in the analyses. The observed association between breastfeeding and a reduced risk of obesity could also reflect selective reporting and/or publication bias. The exclusivity of breastfeeding was not described in the majority of the studies.

Table 10. Summary of systematic reviews/meta-analyses on the relationship between breastfeeding and overweight or obesity

Author year Population	Study description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA and limitations
Arenz 2004 Children and adolescents. One study included some adult subjects. N=69,000	MA of 7 cross-sectional and 2 prospective cohort studies in developed countries	Never BF or partly BF < 3 months vs. BF ≥ 3 month; mostly or only BF vs. mostly or only formula feeding in the first 6 months; BF never vs. ever; BF never vs. > 6 months, BF groups: <1 week, 1 week-1 months, 2-3 months, 4-6 months, 7-9 month, > 9 months (exclusivity of BF not reported)	Studies with > 3 the following relevant confounding factors birth weight, parental overweight, parental smoking, dietary factors, physical activity and SES were included. Other confounders in the included studies: age, sex, diet and weight concerns, Tanner stadium, birth order, race, introduction of solid foods, number of siblings	• The pooled adjusted OR for breastfeeding and obesity defined as BMI >90th, 95th or 97th percentile calculated for nine studies was 0.78 (95%CI 0.71-0.85) for both fixed and random-effects model. • Protective effect of breastfeeding was more pronounced in studies with adjustment for less than 7 (but more than 3) potential confounding factors compared to adjustment for seven or more potential confounding factors (OR 0.69 vs. 0.78 respectively). • Pooled adjusted OR of obesity was 0.76 (95%CI 0.67-0.86) compared ever breastfeeding to never breastfeeding, while it was 0.74 (95%CI 0.64-0.85) in studies using other definitions of breastfeeding.	A[a]
Harder 2005 Children and adolescents. Two studies included adult subjects. N=120,831 (ranged from 66 to 32,200)	MA of 16 cohort or cross-sectional studies and 1 case-control study in developed countries	Median duration of breastfeeding categories: < 1 month (reference), 1-3 month, 4-6 months, 7-9 months, > 9month. To studies that provided data for more than two categories of duration of breastfeeding, "pool-first method" was used to quantify the dose-response relation (per month of breastfeeding).	Age, sex, birth weight, SES, Tanner stage, physical activity, eating habits, concerns to gain weight, birth order, dietary intakes, maternal BMI, maternal smoking	• In the weighted meta-regression (52 estimates from 14 gave data for more than one category of duration of breastfeeding), duration of breastfeeding was significantly negatively related to risk of overweight (regression coefficient: 0.94, 95%CI 0.89-0.98). • From 1 month of breastfeeding onward, the risk of subsequent overweight continuously decreased up to a reduction of more than 30%, reaching a plateau at 9 months of breastfeeding. • Each month of breastfeeding was found to be associated with a 4% decrease in risk (OR: 0.96/month of breastfeeding, 95%CI 0.94-0.98).	B Only unadjusted ORs were combined, although some primary studies had adjustments for potential confounding

Table 10. Continued

Author year Population	Study description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA and limitations
Owen 2005 28 studies provided 29 unadjusted odds ratios relating the initial infant feeding method and obesity. Four observations were for infants, 23 for children, and 2 for adults. N=298,900 in meta-analyses N=12,505 in the studies that did not provide an estimate of relative risk	SR of 61 studies that compared a measure of obesity (quantitatively or narratively) among breastfed and formula-fed subjects; with meta-analyses of 28 studies reported sufficient data	Breastfed vs. formula-fed	Parental body size (mostly BMI), socioeconomic status, maternal smoking, physical activity, weight gain during pregnancy, introduction of solid foods, birth order, dietary intakes, maternal BMI, maternal smoking, and parental obesity/overweight	• In a fixed-effects model including all 28 studies, breastfed subjects were less likely to be defined as obese than were formula-fed subjects (OR: 0.87; 95% CI: 0.85–0.89). There was evidence of marked heterogeneity among studies (p<0.001). • Data from 6 studies, the pooled odds ratio was reduced from 0.86 (95% CI: 0.81– 0.91) before adjustment for confounders to 0.93 (95% CI: 0.88–0.99) after adjustment. • In 14 studies with information on breastfeeding duration, the protective effect of breastfeeding over formula feeding was greater among subjects breastfed for ≥2 months (odds ratio: 0.81; 95% CI: 0.77– 0.84), compared with those breastfed for any duration (odds ratio: 0.89; 95% CI: 0.86–0.91) in the same studies. • 35 studies (12,505 participants), reported only directions of association; of these, breastfeeding was unrelated to risk of obesity in 33, related to a reduced risk in 1, and related to an increased risk in 1.	B Only unadjusted ORs were combined, although some primary studies had adjustments for potential confounding

BF, Breastfed; BMI, Body Mass Index; SR, systematic review; MA, meta-analysis; MAs, meta-analyses; SES, socioeconomic status

[a] Results from overall MA was inappropriate due to heterogeneous definitions of breastfeeding and comparators across studies. However, subgroup analyses on different breastfeeding definitions were performed.

Relationship between the Risk of Cardiovascular Diseases and Breastfeeding

Background

Abnormal levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and blood pressure in adults are major risk factors for cardiovascular disease (CVD). Observational studies of large cohorts of men and women have consistently reported that serum cholesterol level >200 mg/dL was associated with an increased risk of all-cause and CVD mortality.[79,80] Each increment of 20 mm Hg of systolic blood pressure and 10 mm Hg of diastolic blood pressure doubles the risk for CVD.[81] Diet modification, weight reduction, and pharmacotherapy can reduce the risk of CVD. We identified one meta-analysis that evaluated the relationship of breastfeeding during infancy with cholesterol levels in adolescents and adults,[82] two meta-analyses that evaluated the relationship of breastfeeding with adult blood pressure,[83,84] and one systematic review and meta-analysis that examined the relationship between breastfeeding and cardiovascular disease mortality in later life.[85]

Cholesterols

Published Systematic Reviews/Meta-Analyses (Table 11)

One meta-analysis of 37 cohort and cross-sectional studies evaluated the effect of breastfeeding on total and LDL cholesterol levels among infants, adolescents, and adults.[82] All primary studies published in English language from both developed and developing countries that reported estimates of a mean difference and standard error in cholesterol levels between breastfed and formula-fed infants were included in the meta-analysis. The meta-analysis utilized a random effects model. A total of 5,829 breastfed and 4,852 formula-fed subjects were evaluated. Data from the included primary studies were categorized into three age strata: infancy (< 1 year of age), children and adolescents (1 to 16 years), and adults (17 years to 65 years). Outcomes included total and LDL cholesterol levels. No information was provided on the timing of the sample collection in relation to fasting or not fasting. Of the 37 studies, there were 26 outcomes (total or LDL cholesterol levels) in infants, 17 in children and adolescents, and nine in adults. The analysis combined data from a broad age category for the adult participants. It was unclear if there were adjustments for potential confounders such as body mass index, height, and socioeconomic status for the data on cholesterol. The methodological quality of the meta-analysis was rated grade C.

In 25 of 26 observations, infants who were breastfed reported higher mean total cholesterol levels compared with infants who were formula-fed. The overall mean difference was +24.75 mg/dL (95% CI 18.95 to 30.55). There was a statistically significant heterogeneity across the studies. The meta-analysis did not find an association between total cholesterol level and age or gender. There were only seven reported observations on LDL cholesterol levels in infants, six of which reported higher mean levels of LDL cholesterol in breastfed infants compared with formula-fed infants. The mean difference was +22 mg/dL (95% CI 15.47 to 29.0 mg/dL). There was no statistical heterogeneity.

In 16 of 17 observations, the mean total cholesterol levels in children or adolescents who were breastfed in their infancy were similar to those who were formula-fed. The overall mean difference was 0.0 mg/dL (95% CI –2.7 to 2.7 mg/dL). A statistically significant heterogeneity was observed across studies. There was no association between total cholesterol level and age or gender. There were only four observations of LDL cholesterol levels in children or adolescents. The mean levels of LDL cholesterol in children or adolescents who were breastfed in their infancy were similar to those who were formula-fed. The mean difference was +0.39 mg/dL (95% CI –2.7 to 3.09 mg/dL). There was no statistical heterogeneity between the studies.

The mean age of adults evaluated in the primary studies ranged from 17 to 64 years. Lower mean total cholesterol levels in adults who were breastfed in their infancy compared with those who were formula-fed in their infancy were reported in seven of nine observations. The overall mean difference was –6.96 mg/dL (95% CI –2.32 to –11.6 mg/dL). There was no statistically significant heterogeneity between the studies. There were only four observations of LDL cholesterol reported in adults. Adults who were breastfed in their infancy had lower mean LDL cholesterol levels compared with those who were formula-fed. The mean difference was –7.7 mg/dL (95% CI –3.09 to –12.37 mg/dL). There was no statistical heterogeneity between the studies.

Conclusion

Results from the meta-analysis of cohort and case-control studies reported that there was a reduction in total and LDL cholesterol levels in adults who were breastfed during infancy compared with those who were formula-fed. While higher serum lipid levels were observed in infancy, the meta-analysis found that breastfeeding was associated with a reduction in serum lipid level in adult life. The significance of higher serum lipid levels observed in infancy is unclear and studies have neither shown benefit nor harm from such high levels.[86] These findings were based on data from adults with a wide age range. The analysis did not segregate the data according to gender. Potential confounders were not explicitly analyzed. Detailed information (e.g., fasting or non-fasting) on the collection of specimen for cholesterol testing was not included. The methodological quality of the meta-analysis was rated grade C. Because of the poor methodological quality of the meta-analysis, we find that the conclusions drawn by the authors were suspect. We conclude that the relationship between breastfeeding and adult cholesterol levels cannot be correctly characterized at this time.

Table 11. Summary of systematic reviews/meta-analyses on the relationship between breastfeeding and total cholesterol and low-density lipoprotein cholesterol

Author year	Number of subjects	Population	Confounders considered	Study description	Intervention / Comparator	Results		Quality of SR/MA
						Combined mean difference (95%CI)		
		3 age strata:				Total cholesterol (mg/dL)	LDL cholesterol (mg/dL)	
Owen 2002	5,829 vs. 4,852	Age <1 yr	None	MA of 37 cohort and cross-sectional studies	Breastfeeding vs. formula feeding in infancy	+24.75 (18.95 to 30.55)	+22.0 (15.47 to 29.0)	C
		1 to 16 yr				0.0 (– 2.7 to 2.7)	+0.39 (–2.7 to 3.09)	
		≥17 to 65 yr				–6.96 (2.32 to 11.6)	–7.7 (3.09 to 12.37)	

LDL, low-density lipoprotein;SR, systematic review; MA, meta-analysis

Blood Pressure

Published Systematic Reviews/Meta-Analyses (Table 12)

Two meta-analyses evaluated a total of 26 studies of various designs for the effect of breastfeeding and formula feeding in infancy on systolic and diastolic blood pressure levels in adult life. The primary studies included in these meta-analyses were conducted in developed and developing countries. Outcomes assessed were differences in systolic and diastolic blood pressures in adulthood. Both meta-analyses examined potential confounders in the studies and also explored the possibility of publication bias. Potential confounders considered in the studies were age, gender, race, height, and body mass index. Among the 26 primary studies evaluated, 13 studies were common to both meta-analyses. Both meta-analyses included at least one study that included preterm infants. Duration and exclusivity of breastfeeding or formula feeding were heterogeneous in the studies. The methodological quality of both meta-analyses were rated grade B.

The meta-analysis by Martin 2005 included 15 studies with 17 observations published until 2004 that evaluated a total of 17,503 eligible subjects.[83] In these studies, blood pressure was measured in subjects whose age ranged from 1 to 60 years. The meta-analysis utilized a random effects model. Meta-regression was performed to evaluate the effect of heterogeneity in study size, age at measurement of blood pressure (<10 years, 11-45 years, >45 years), maternal recall, exclusivity of the feeds, methods of blood pressure measurement, and other variables on the summary estimates. Mean systolic blood pressures were reduced by 1.4 mm Hg (95% CI 0.6 to 2.2) in adulthood among subjects who were breastfed in infancy compared with those who were formula-fed. There was a statistically significant heterogeneity across studies for this outcome. Mean diastolic blood pressures were reduced by 0.5 mm Hg (95% CI 0.04 to 0.9) in adulthood among subjects who were breastfed in infancy compared with those who were formula-fed, with no heterogeneity for this outcome.

Owen 2003 included 24 studies published until 2003 with 26 observations for systolic blood pressure and 23 observations for diastolic blood pressure.[84] The meta-analysis evaluated 8,471 subjects who were breastfed in infancy and 11,292 who were formula-fed. In these studies, blood pressure was measured in subjects whose age ranged from 1 to 71 years. The meta-analyses

utilized a random effects model. Subgroup analyses evaluated the effect of heterogeneity in study size, age of assessment of outcomes, and year of birth. Mean systolic blood pressures were reduced by 1.10 mm Hg (95% CI 0.42 to 1.78) in adulthood among subjects who were breastfed in infancy compared with those who were formula-fed. When stratified by age groups (≤1 year, >1 to 16 years, ≥17 years), a similar association was observed among age groups that ranged from more than 1 year to 16 years. There was a statistically significant heterogeneity for this outcome. Mean diastolic blood pressures were reduced by 0.36 mm Hg (95% CI – 0.08 to 0.79) among subjects who were breastfed compared with subjects who were formula-fed. There was no statistical heterogeneity for this outcome.

Both meta-analyses observed smaller association of breastfeeding on systolic blood pressure in large studies (>300 and/or >1000 participants) compared with smaller studies. Both meta-analyses attributed this observation to publication bias. Similar effect size reduction of breastfeeding on diastolic blood pressure was not observed. In studies that adjusted for potential confounders, results remained similar before and after adjustment for potential confounders.

Conclusion

Results from both meta-analyses concluded that there was a small reduction in systolic blood pressures among adults who were breastfed in their infancy compared with those who were formula-fed. The association weakened after stratification by study size, suggesting the possibility of bias. Although both analyses had moderate methodological quality and reported similar findings, the authors had different appraisals of the public health importance of the small reduction in systolic blood pressure. In conclusion, there is an association between a history of breastfeeding during infancy and a small reduction in adult blood pressure, but the clinical or public health implication of this finding is unclear.

Table 12. Summary table for systematic reviews/meta-analyses on the relationship between breastfeeding in infancy and blood pressure levels later in life

Author year Population	Confounders considered	Study description	Intervention / Comparator	Results		Quality of SR/MA Limitations
Martin 2005 N=17,503 Age > 1to 60 yr	Considered but not pooled: age, gender, race, height, and body mass index	Meta-analysis of 15 studies (Observations within 2RCTs, 8 prospective cohorts, 1 retrospective cohort, and 4 cross-sectional studies)	Breastfeeding vs. formula feeding in infancy	Combined mean difference (95%CI) SBP mmHg –1.4 (–2.2, –0.6) p=0.001	Combined mean difference (95%CI) DBP mmHg –0.5 (–0.9, –0.04) p=0.03	B No pooled adjusted estimate
Owen 2003 N=8471 vs. 11,292 Age > 1to 71 yr		Meta-analysis of 24 studies (Observations within 1RCT, 12 cross-sectional, and 11 cohort studies)	Breastfeeding vs. formula feeding in infancy	Combined mean difference (95%CI) SBP mmHg –1.10 (–1.8, –0.4)	Combined mean difference (95%CI) DBP mmHg – 0.36 (–0.79, 0.08)	B No pooled adjusted estimate

SBP, systolic blood pressure; DBP, diastolic blood pressure; SR, systematic review; MA,meta-analysis

Cardiovascular Disease Mortality

Published Systematic Review/Meta-Analysis (Table 13)

We identified one systematic review and meta-analysis that examined the relationship between breastfeeding and cardiovascular disease (CVD) mortality in later life.[85] Articles were included in the systematic review if breastfed infants were compared with bottle-fed infants, if the outcome was cardiovascular disease or ischemic heart disease mortality, and if estimates of the association between having been breastfed and cardiovascular disease or ischemic heart disease mortality could be obtained from the paper or after correspondence with the authors. A total of four historical cohort studies from developed countries were identified, involving 25,166 subjects at baseline and 10,785 subjects at followup. The studies were not graded for their methodological quality. The meta-analysis used a random-effects model. Heterogeneity across studies was assessed. The methodological quality of this systematic review and meta-analysis was rated grade B due to incomplete consideration of the heterogeneity across studies in the meta-analyses.

The four historical cohorts included in the systematic review and meta-analysis were Wingard cohort, 1,373 birth children in California (85 percent in followup); Hertfordshire cohort, 5,908 women and 10,374 men born in Hertfordshire (43 percent in followup); Boyd Orr cohort, 4,999 men and women from a survey of diet and health in pre-war Britain (71 percent in followup); and Caerphilly cohort, 2,512 middle-aged men living in Caerphilly, South Wales (63 percent in followup). Subjects from these four cohorts were born between 1904 and 1939. Potential confounders considered in the association between the risk of CVD mortality and breastfeeding in the four studies were age, birth weight, infant health, socioeconomic status, and/or birth order.

Random-effects model showed little difference in all cause mortality between breast- and bottle-fed subjects (pooled rate ratio = 1.01; 95% CI: 0.91 - 1.13, P=0.8), and there was little evidence of heterogeneity. Five observations from three studies suggested little or no association between breastfeeding and cardiovascular disease mortality in both males and females, and one suggested a possible adverse effect (Caerphilly cohort). In random effects meta-analysis, CVD mortality was similar in breastfed versus bottle-fed subjects (pooled rate ratio = 1.06; 95% CI: 0.94 – 1.20), and there was no statistical evidence of between-study heterogeneity.

Ischemic heart disease mortality was 6 percent lower among males who had been breastfed in the Hertfordshire cohort, but 56 percent higher among breastfed females. This result was in agreement with point estimates from the Boyd Orr cohort, suggesting that ischemic heart disease mortality was 10 percent lower among males who had been breastfed, but 40 percent higher among breastfed females (although there was little statistical evidence of interaction: P = 0.2). In Caerphilly, however, ischemic heart disease mortality was 73 percent higher among breastfed males. In a random effects meta-analysis (pooled rate ratio = 1.19; 95% CI 0.89 - 1.58, P = 0.3), and there was evidence of heterogeneity.

Similar analyses were also performed to examine the association between prolonged breastfeeding (> 1 year duration) and the risk of all-cause, CVD, and ischemic heart disease mortality in later life. There was little evidence that prolonged breastfeeding was associated with all-cause mortality (pooled rate ratio: 0.94; 95% CI 0.71 – 1.24), although there was moderate statistical evidence of heterogeneity. There was some evidence that prolonged breastfeeding was associated with a 16 percent increase (95% CI 0.99 – 1.36; P = 0.06) in CVD mortality, and no

evidence of inconsistency in estimates. There was little evidence that prolonged breastfeeding was associated with ischemic heart disease mortality (rate ratio: 1.08; 95% CI 0.88 – 1.31; P = 0.5) and there was no heterogeneity.

Conclusion

The authors concluded that the data reviewed did not provide evidence that breastfeeding was related to all-cause or CVD mortality. The confidence limits around the point estimates and the observed between-study heterogeneity for associations between breastfeeding and ischemic heart disease, however, do not rule out important beneficial or adverse cardiovascular effects of breastfeeding.

There were some possible sources of bias and limitations in the studies reviewed. Two of the four studies had followup rate of less than 70 percent of the original population; therefore, selection bias cannot be ruled out. Recall bias was possible in the three studies where breastfeeding data were collect retrospectively. As confounding and biases may have distorted results from individual studies, the statistical combination of estimates into a single rate ratio needs to be interpreted with caution. All four studies in the meta-analyses were historical cohorts (born between 1904 and 1939). Given the statistical heterogeneity across studies, combining study results might not be appropriate. For the outcome of ischemic heart disease mortality, it may not be appropriate to combine results for men and women into a single analysis because of apparent effect modification by gender.

Because of the above limitations, no definitive conclusions can be drawn regarding the relationship between breastfeeding and CVD mortality. Further investigation is warranted.

Table 13. Summary of systematic review/meta-analysis on the relationship between breastfeeding and long-term cardiovascular disease mortality

Author year Population	Study description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA and limitations
Martin 2004 Wingard (1994) cohort: 1373 birth children in California (85% in follow-up) Hertfordshire cohort (update to 1999): 5908 women and 10374 men born in 11 of 12 districts in Hertfordshire (43% in followup) Boyd Orr (2003): 4999 men and women from a survey of diet and health in pre-war Britain (71% in followup) Caerphilly (2003): 2512 middle-aged men living in Caerphilly, South Wales (63% in followup) Total N=25,166 at baseline; 13,302 at followup	MA of 4 historical cohort studies in developed countries	Any or exclusively breastfed vs. bottle-fed; prolonged (>1 yr) breastfed vs. bottle-fed	Age, birth weight, infant health, socioeconomic status, number of siblings, and/or birth order	All four studies were historical cohorts born between 1904 and 1939. Five observations from three studies suggested little or no association between breastfeeding and CVD mortality in both males and females (pooled rate ratio: 1.06; 95% CI: 0.94–1.20), and one suggested a possible adverse effect (Caerphilly cohort). There was no statistical evidence of between-study heterogeneity. IHD mortality was 6% lower amongst males who had been breastfed in the Hertfordshire cohort, but 56% higher amongst breastfed females. This result is in line with point estimates from the Boyd Orr cohort suggesting that IHD mortality was 10% lower amongst males who had been breastfed, but 40% higher amongst breastfed females (although there was little statistical evidence of interaction: p=0.2). In Caerphilly, however, IHD mortality was 73% higher amongst breastfed males. In a random effects meta-analysis (pooled rate ratio: 1.19; 95% CI 0.89-1.58, p=0.3), there was evidence of heterogeneity. There was weak evidence that prolonged breastfeeding was associated with a 16% increase (95% CI: 0.99–1.36; p=0.06) in CVD mortality, and no evidence of inconsistency in estimates. There was little evidence that prolonged breastfeeding was associated with IHD mortality (rate ratio: 1.08; 95% CI: 0.88–1.31; p=0.5) and there was no heterogeneity.	B Men and women should be considered separately because of apparent effect modification by gender

IHD, Ischemic heart disease; CVD, cardiovascular disease; SR, systematic review; MA, meta-analysis

Relationship between Type 1 Diabetes and Breastfeeding

Background

Type 1 diabetes results from destruction of the insulin-producing β cells of the pancreatic islets. Various exogenous triggers, such as certain dietary factors and viruses, are thought to induce the immune-mediated process leading to extensive β cell destruction.[87] Putative mechanisms of protection against type 1 diabetes afforded by breast milk include passive immunity provided by secretory immunoglobulin A antibodies, increased β cell proliferation observed in breastfed compared with formula-fed infants, or delayed exposure to foreign food antigens in exclusively breastfed infants.[87] In addition, hypotheses have been proposed to explain the putative diabetogenicity of cow milk.[87] For example, β-lactoglobulin, a cow milk-specific protein, has been implicated as a possible trigger of the immune defect, leading to type 1 diabetes. Therefore, concerns regarding the safety and advisability of feeding cow milk-based products to infants have been raised.[88] Gersterin 1994 conducted a systematic review of the epidemiological and clinical literature that explored a possible link between cow milk and type 1 diabetes.[89] Subsequently, Norris and Scott 1996 performed meta-analyses on all published case-control studies from 1966 to 1994 that examined infant diet exposures and type 1 diabetes.[90] Since this meta-analysis, we identified six case-control studies that reported outcome of type 1 diabetes in relation to breastfeeding during infancy.

Commonly considered confounders in the relationship between type 1 diabetes and breastfeeding were maternal/parental education, maternal age at birth, birth order, household income, race/ethnicity, social class, family history of type 1 diabetes, neonatal illness, and type of delivery.

Published Systematic Reviews/Meta-Analyses (Table 14)

Gersterin 1994 conducted a systematic review on literature that explored a possible link between cow milk and type 1 diabetes. Articles were excluded if they exclusively used surrogate markers for either type 1 diabetes or cow milk exposure. A total of three ecological and time-series studies, 13 case-control studies, one cohort study, and one case series were included. Meta-analysis of all included case-control studies was performed, using a fixed effect model. Both adjusted and unadjusted odds ratios were used, but there was no further analysis or discussion on potential impacts of confounding by combining unadjusted odds ratios. The methodological quality of the systematic review and meta-analysis was rated grade B, due to insufficient consideration for the potential confounding in the primary studies.

In the included time-series and ecological studies, the results showed an inverse association (geographical and temporal) between the rate/prevalence of breastfeeding and the rate/prevalence of type 1 diabetes.

The cohort study was an analysis of two groups of children born in the UK in 1958 and 1970, who were followed for 16 and 10 years, respectively. This study did not find any association between breastfeeding for less than 1 month and the risk of development of type 1 diabetes.

In the 13 case-control studies in which the neonatal feeding history of patients with type 1 diabetes and individually matched non-diabetic control subjects were compared, the results were mixed. A total of 3,708 type 1 diabetes cases and 20,340 non-diabetic controls were included. None of these studies satisfied all six methodological criteria defined by the author. Four of the 13 case-

control studies fulfilled five of six methodological criteria (e.g., inclusion of ≥75 percent of eligible diabetic patients, unbiased selection of unrelated nondiabetic control subjects, control subjects derived from the same population as diabetic subjects, an identical means of determination of infant feeding practices in both diabetic and nondiabetic groups, blind determination of early feeding history, and identification of diabetic patients from incident cases). When these four studies were combined, the overall odds ratio (adjusted odds ratios were used) for type 1 diabetes in patients exposed to less than 3 months of breastfeeding was 1.43 (95%CI 1.15 - 1.77; P=0.3 for homogeneity). When all 13 included case-control studies were combined, the overall odds ratio (mixed crude and adjusted odds ratios were used) for type 1 diabetes in patients exposed to less than 3 months of breastfeeding was 1.37 (95%CI 1.22-1.53; P=0.11 for homogeneity).

In 1996, Norris and Scott performed a meta-analysis of infant diet and type 1 diabetes to examine further the inconsistent results reported in the literature. A total of 17 case-control studies with appropriate data for meta-analysis were included. The analysis included 4,656 type 1 diabetes cases and 16,383 non-diabetic controls. The authors abstracted case and control data for four separate exposures: breastfeeding status (ever/never), total breastfeeding duration, exposure to breast-milk substitutes, and exposure to cow milk-based substitutes. Due to the limitation of the meta-analytic technique, only unadjusted odds ratios were calculated and combined, although some primary studies had adjustments for maternal education, maternal age at birth, birth order, household income, race/ethnicity, and/or social class. Authors performed sensitivity analyses on various characteristics of study methodological quality to explore the impacts of potential biases on the summary odds ratios. The methodological quality of this meta-analysis was rated grade B, due to insufficient consideration for the potential confounding in the primary studies.

The overall odds ratio of all included case-control studies that examined the association between never breastfed and type 1 diabetes was 1.13 (95%CI 1.04 - 1.23). Among these studies, fourteen also examined type 1 diabetes risk by months of breastfeeding duration. The duration categories in the analysis were cumulative, rather than mutually exclusive (i.e., some studies provided data on both 3-month and 6 month breastfeeding data in the same subjects). The summary odds ratios showed consistently elevated risks of type 1 diabetes associated with age at first exposure to any breast milk substitutes before 6 months of age. Since the majority of the studies reported odds ratios using a cutoff of 3 months when examining continuous exposures, this cutoff was used for the meta-analysis. The summary odds ratio for type 1 diabetes in subjects who were breastfed for less than 3 months compared with those who were breastfed for at least 3 months was 1.23 (95%CI 1.12 - 1.35).

Stratified analyses of studies by methodological and study population characteristics were performed to see whether differences in these characteristics might explain the heterogeneity. The characteristics were prevalent versus incident case-control study design, adequate versus inadequate response rates of the cases and controls, the breastfeeding prevalence in the background population, the type 1 diabetes risk in the background population, and retrospective versus concurrent infant diet assessment. All of these factors had differential impacts on the summary odds ratios for the risk of type 1 diabetes associated with infant diet exposures.

Norris and Scott concluded that their meta-analysis showed that the increased risk of type 1 diabetes associated with any of the infant diet exposures was small. According to these authors, interpretation of weak associations (i.e., an odds ratio of less than 2.0) can be problematic, since weak associations can more readily be explained by biases.

Studies Identified after the Published Systematic Reviews/Meta-Analyses/Systematic Review (Table 15)

We only included all studies that examined the outcome of type 1 diabetes in relation to breastfeeding in developed countries. To be consistent with previous meta-analyses, articles were excluded if they only used surrogate markers for type 1 diabetes (e.g., the presence of islet cell antibodies). A total of six case-control studies were identified,[91-96] The studies included 1,293 patients with type 1 diabetes and 3,262 control subjects. Five studies were conducted in Europe, and one in Taiwan. Four studies were rated grade B in methodological quality; two studies were rated grade C. Commonly considered confounders in these studies were family history of type 1 diabetes, neonatal illness, maternal age at birth, birth order, maternal/parental education, and type of delivery.

In four studies, the definition of type 1 diabetes cases was children with juvenile-onset diabetes (or developing diabetes before 17 years of age). In the other two studies, the cases were registered type 1 diabetes patients who were younger than 30 years of age and children with diabetes who were identified through hospital records. Matched controls were those without type 1 diabetes selected from various sources in the same population as the cases.

Three studies reported odds ratio of type 1 diabetes comparing subjects who were ever breastfed with those who were never breastfed. Two studies found a reduced risk of type 1 diabetes in subjects who were ever breastfed (ORs 0.56[95] and 0.75[91]), while the third study reported an increased risk (OR 2.44[94]).

Three studies compared subjects who were breastfed for more than 3 months or 6 months with those who were never breastfed. Two studies reported a reduced risk of type 1 diabetes in subjects who were breastfed for more than 3 or 6 months (adjusted OR 0.57[96] and 0.25[95], respectively). The third study[94] reported an opposite finding (this was the same study that reported an increased risk with ever breastfed). A reduced risk of type 1 diabetes was found when comparing subjects who were never breastfed with those who were breastfed for more than 6 months (adjusted OR 0.36, 95%CI 0.14 - 0.94). The data also showed a slight increase in the risk of type 1 diabetes with longer duration of breastfeeding (1 month increment). The control subjects in this study were selected from children admitted to the same hospital as the cases, whether this explained the finding was unclear.

One study reported a reduced risk of type 1 diabetes comparing subjects who were initially exclusively breastfed with those who were not (adjusted OR 0.6, 95%CI 0.41 - 0.89).[93] Another study found a small, but non-significant increased risk of type 1 diabetes with not breastfeeding at discharge (RR 1.33, 95%CI 0.76 - 2.31).[92] This study was rated to have poor methodological quality because only univariate analysis was performed and potential confounders were not considered.

Conclusion

Our findings from the six additional case-control studies are similar to the findings from the two meta-analyses. However, the exclusivity of breastfeeding was not addressed in all studies, and the assessment of infant diet was based on long-term recall in five of six studies. We elected not to perform a meta-analysis, because it is unlikely to change the pooled estimates from the previous meta-analyses by adding additional three studies from the updates that compared subjects who were breastfed for more than 3 or 6 months with those who were never breastfed.

Two meta-analyses of moderate methodological quality reported statistically significant odds ratios of 1.23 and 1.43, respectively, for the risk of type 1 diabetes in subjects exposed to less than 3 months compared with more than 3 months of breastfeeding. Since case-control studies are prone to recall biases, Norris and Scott compared the odds ratios in studies relied on long-

term recall to assess infant diet with studies that did not. The results showed that studies using existing infant records to determine breastfeeding initiation and duration failed to show the associations reported in the studies relying on long-term recall for their exposure data. This suggests that subjects with type 1 diabetes were more likely to report shorter duration of breastfeeding than control subjects.

In conclusion, even though there is some evidence to suggest that breastfeeding for more than 3 months is associated with a reduced risk of type 1 diabetes, this evidence must be interpreted with caution because of the possibility of recall biases and suboptimal adjustments for potential confounders in the primary studies.

Table 14. Summary of systematic reviews/meta-analyses on the relationship between breastfeeding and type 1 diabetes

Author Year Population	Study description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA and limitations
Norris 1996 Case-control studies in which the neonatal feeding histories of patients with type 1 DM and individually matched non-DM control subjects were compared Cases: 4,656 Controls: 16,383	MA of 17 case-control studies published from 1966 to 1994.	A=breastfeeding status (ever/never) B=total breastfeeding duration C=exposure to breast-milk substitutes D=exposure to cow's milk-based substitutes	Maternal education, maternal age at birth, birth order, household income, race/ethnicity, social class	The summary OR for type 1 DM in patients who were never being breast-fed was 1.13 (95% CI 1.04-123). The summary OR for type 1 DM in subjects who were breast-fed for < 3 mo compared with those who were breast-fed for at least 3 mo was 1.23 (95%CI 1.12-1.35). Stratified analyses of studies were performed by prevalent vs. incident case-control study design, adequate vs. inadequate response rates of the cases and controls, the breastfeeding prevalence in the background population, the type 1 DM risk in the background population, and retrospective vs. concurrent infant diet assessment. All of these factors had impacts on the summary ORs for the risk of type 1 DM associated with infant diet exposures.	B Only unadjusted ORs were combined although some primary studies had adjustments for potential confounding
Gerstein 1994 Case-control studies in which the neonatal feeding histories of patients with type 1 DM and individually matched non-DM control subjects were compared Cases: 3,708 Controls: 20,340	A SR review of 3 ecological and time-series studies, 13 case-control studies, one cohort study, and one case series. MA was performed for the case-control studies.	Cow's milk exposure (and therefore non-exclusive breastfeeding) vs. Cow's milk avoidance (and therefore breastfeeding)	ND	Results from the 13 case-control studies were mixed. The combined OR for type 1 DM in patients exposed to < 3 mo of breastfeeding was 1.38 (95% CI 1.22-1.53; p=0.11 for homogeneity). An analysis of 2 cohorts of children born in the UK in 1958 and 1970 followed for 16 and 10 yr, respectively, failed to show any association between breastfeeding for < 1 mo and type 1 DM. None of the 13 case-control studies fulfilled all six methodological criteria. Four case-control studies (31%) fulfilled five out of the six criteria (considered high quality)	B Combine both crude and adj. ORs without performing sensitivity analyses on potential confounding or study quality

MA, meta-analyses; SR, systematic review

Table 15. Summary of case-control studies on the relationship between breastfeeding and type 1 diabetes

Author year *Country*	Cases (N)	Control (N)	Definition of type 1 DM	Mean Age at Dx (year)	Breastfeeding group	Comparator group	OR* (95% CI) Crude	OR* (95% CI) Adjust	Potential confounders adjusted	Quality and Limitations
EURODIAS 2002 Europe	610	1616	Onset < 15 yr in 1989-1995	ND	Ever BF	Never BF	0.75 (0.58-0.96)	0.59 (0.35-0.97)	Ht SDS, Wt SDS, maternal age, jaundice, RTI, Vit D suppl, asthma	B No demographic data; No adj. for SES
McKinney 1999 UK	196	325	Onset < 16 yr in 1993-1994	0-15	Initial exclusive BF	Initial not exclusive BF	0.68 p=0.04	0.60 (0.41-0.89)	[Sex, age][a], maternal age, maternal type 1 DM, preeclampsia, C-section, neonatal illnesses	B No adj. for SES
Tai 1998 Taiwan	177	193	Registered type 1 DM, age < 30 yr, born in 1984-1993	8.3	Ever BF	Never BF	0.56 (0.40-1.2)		[Age, sex, parental education][a], birth order, paternal age, GA, type of delivery, BW, monthly family income	B Inconsistent methods for ascertainment of BF exposure
					BF < 6 mo	Never BF	0.82 (0.47-1.42)	0.84 (0.45-1.59)		
					BF ≥ 6 mo		0.39 (0.16-0.94)	0.25 (0.09-0.69)		
Meloni 1997 Italy	100	100	Onset < 17 yr in 1983-1994	6 (1-15)	Ever BF	Never BF		2.44 (1.10-7.14)	[Age, sex][a], mother's education, number of siblings	B Hospital controls
					BF > 6 mo	BF 3-5 mo		0.85 (0.37-1.92)		
						BF 1-2 mo		2.08 (0.18-5.26)		
						BF 0 mo		2.78 (1.06-7.14)		
					BF as continuous coefficient (1 mo increment)			1.10 (0.99-1.22)		
Visalli 2003 Italy	150	750	Onset < 15 yr, born in1977-1989	ND	BF ≥ 3 mo	BF < 3 mo	0.47 (0.31-0.72)	0.57 (041-0.74)	[Age][a], family history of type 1 DM, infectious disease during pregnancy, eczema	C Inadequate response rate (>20%); No adj. For SES
Jones, 1998 UK	60	458	Dx at discharge, born in 1976-1986	ND	BF at discharge	Not BF at discharge	0.75 (0.43-1.32)		[Age, sex][a]	C Poor adj. for confounding

Dx, diagnosis; BF, breastfeeding; SR, systematic review; MA, meta-analysis; SDS, standard deviation score; Ht, height; Wt, weight; RTI, respiratory infection; Vit D suppl, Vitamin D supplementation; C-section, delivery by cesarean section; GA, gestational age; BW, birth weight; LTC, long-term recalls; adj, adjustment; SES, socioeconomic status

*Odds ratio of type 1 DM, compared the breastfeeding group to the comparator group (or the reference group), unless noted

[a] Matching factors for controls

Relationship between Type 2 Diabetes and Breastfeeding

Background

In 2002, it was estimated that a total of 18.2 million people, or 6.3 percent of the US population carried a diagnosis of diabetes (cdc.gov/diabetes/pubs/estimates.htm#prev). No data are currently available on the prevalence of type 2 diabetes in children and adolescents. The Centers for Disease Control and Prevention (CDC) estimated that among new cases of childhood diabetes, the proportion of those with type 2 diabetes ranges between eight percent and 43 percent (www.cdc.gov/diabetes/pubs/factsheets/search.htm). Type 2 diabetes begins when the body develops a resistance to insulin and no longer uses insulin properly. Adults and children who develop type 2 diabetes are typically overweight or obese and have a family history of the disease. Furthermore, offsprings of mothers who had diabetes during pregnancy had higher rates of type 2 diabetes and obesity.[97] It is increasingly recognized that nutrition in early postnatal life may have long-term physiologic effects. Studies have suggested that breastfeeding may be protective against later obesity.[77,78] Therefore, it seems biologically plausible that there may be a relationship between breastfeeding and long-term glucose and insulin metabolism.

We identified one systematic review by Taylor et al.[98] in our initial literature search and we also identified one additional systematic review by Owen et al.[99] during final phase for the preparation of this report. We did not identify any additional systematic reviews.

Commonly considered confounders in the studies of relationship between type 2 diabetes and breastfeeding were age, sex, BMI, birth weight, socioeconomic status, history of parental diabetes, maternal diabetes during pregnancy, maternal diet and smoking, and prepregnancy BMI.

Additional Methodological Comments

We have elected to describe in details only the Owen 2006 systematic review because it superseded the Taylor 2005 systematic review. Owen 2006 included two of the three primary studies that were covered in Taylor 2005. In addition, Taylor 2005 was of poor methodological quality because there was no synthesis of results and it was unclear how conclusions were drawn.

Published Systematic Reviews/Meta-Analyses (Table 16)

Owen 2006 conducted a systematic review and meta-analyses to examine the influence of breastfeeding on type 2 diabetes and blood glucose and insulin concentrations.[99] Studies that did not provide the odds ratios of type 2 diabetes comparing breastfed to formula-fed subjects were excluded. In addition to two of the three studies included in the Taylor 2005 review (the third study was excluded from Owen 2006 because it did not provide odds ratio of the disease), five additional studies were identified in the Owen 2006 review. Seven studies (six in adults and one in adolescents) totaling 76,744 subjects provided odds ratios that related initial infant feeding methods and type 2 diabetes were included in the meta-analyses. There were three historical cohort, two cross-sectional, one prospective cohort, and one case-control studies. All seven studies were conducted in developed countries. The effects of study size, year of birth, the method of ascertainment of infant feeding status (whether contemporary or recalled up to 71

years after birth), type of formula feeding, study response rate, study design, and whether infants were born pre- or full-term were examined by using meta-regression and sensitivity analyses. Sensitivity analyses were also used to examine the effect of adjustment for important confounders and of fasting status. The methodological quality of this systematic review and meta-analyses was rated grade A.

Six of seven studies related breastfeeding to a lower risk of type 2 diabetes, and there was no evidence of heterogeneity across studies. Overall, the subjects who were breastfed showed a lower risk of type 2 diabetes than those who were formula-fed (pooled adjusted OR 0.61; 95%CI 0.44-0.85, P=0.003). Three studies considered the effects of potential confounding by birth weight, parental diabetes, socioeconomic status, and individual or maternal body size, while the other four studies only considered the effects of confounding by age, sex and/or birth weight. However, the odds ratio relating breastfeeding and diabetes risk was similar before (OR 0.55; 95% CI: 0.35-0.86; P=0.009) and after adjustment for all the important confounders (OR 0.55, 95% CI 0.34-0.90; P=0.017) in the three studies. The method of ascertaining feeding exposure was unrelated to the odds ratios, although there was insufficient power to detect appreciable differences in examining the effect of potential biases (such as study size, year of birth, the method of ascertaining infant feeding status, type of formula feeding, study response rate, study design, and whether infants were born pre- or full-term) by using meta-regression and sensitivity analyses.

Studies Identified after the Published Meta-Analysis/Systematic Review

None was found.

Conclusion

Results from a high-quality systematic review and meta-analyses of seven studies suggest that breastfeeding is associated with a lower risk of type 2 diabetes in later life, compared with formula feeding. Comparing subjects who were ever breastfed to those who were formula fed, the pooled adjusted odds ratio of type 2 diabetes in later life was 0.61 (95%CI 0.44-0.85). However, only three studies appropriately adjusted for all the important confounders, including birth weight, parental diabetes, socioeconomic status, and individual or maternal body size. Even though these three studies found that adjustment did not alter the crude estimate, we cannot be completely confident that potential confounding by birth weight and maternal factors has been ruled out for the overall pooled estimate. This could lead to an overestimate of the association. Publication bias is also a possible explanation for the consistent associations observed in these studies.

Table 16. Summary of systematic reviews/meta-analyses on the relationship between breastfeeding and type 2 diabetes

Author Year Population	Study description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA and limitation
Owen 2006 N=76,744 6 studies conducted in adults and 1 study conducted in adolescents	MA of 7 studies (3 historical cohort, 2 cross-sectional, 1 prospective cohort and 1 case-control studies)	Ever breastfed vs. formula fed in all 7 studies. Feeding status was reported as being exclusive in one of these studies.	Age, sex, BMI, birth weight, socioeconomic status, parental diabetes, maternal diabetes in pregnancy, hospital duration in infancy, maternal diet and smoking, and prepregnancy BMI	• Overall, the subjects who were breastfed showed a lower risk of type 2 diabetes than did those who were formula fed (pooled OR: 0.61; 95%CI 0.44-0.85; p=0.003). • OR relating breastfeeding and diabetes risk was similar before (0.55; 95% CI: 0.35-0.86; p=0.009) and after (0.55, 95% CI 0.34-0.90; p=0.017) adjustment in 3 studies that had information on relevant confounders.	A Pooled different study designs
Taylor 2005 N=1,430 People of all ages	Systematic review of 2 cohort studies and 1 case-control study	Variable	Age, sex, birth date, parental diabetes, and birth weight	• In a retrospective cohort study of 720 people age 10-39 years old, type 2 diabetes (defined by OGTT testing) was 59% less common in exclusively breastfed people compared with those who were exclusively bottle-fed (adjusted OR: 0.41; 95%CI 0.18-0.93)	C No synthesis of results and unclear how the conclusions were reached
			GDM, use of traditional diet, smoking, and alcohol during pregnancy, mother's prepregnancy BMI, and birth weight	• In a case-control study of native Canadian, Some breastfeeding for one year or longer was a significant independent predictor of future diabetes (adjusted OR: 0.24; 95%CI 0.07-0.84) as was some breastfeeding for 6 months of longer (adjusted OR: 0.36; 95%CI 0.13-0.99).	
			None	• Type 2 diabetes (defined by OGTT testing) in the next generation was less common among children who were breastfed exclusively for > 2 months (6.9% vs. 30.1% among offspring of women without diabetes and women with diabetes, respectively) than among bottle-fed children (11.9% vs. 43.6%, respectively).	

GDM, gestational diabetes; OGTT, oral glucose tolerance test; BMI, body mass index (kg/m^2); SR, systematic review; MA, meta-analysis

Relationship between Childhood Leukemia and Breastfeeding

Background

Leukemia, the most common cancer in children, encompasses multiple diseases including three types: acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), and chronic myelogenous leukemia. In the United States, approximately 3,250 children are diagnosed with leukemia each year and 2,400 (74 percent) of them have ALL. With the exception of prenatal exposure to x-rays and specific genetic syndromes, little is known about the causes of childhood ALL (National Cancer Institute: seer.cancer.gov/publications/childhood/leukemia.pdf). Although the majority of human leukemias or lymphomas have no readily identifiable infectious etiologies, viral causes have been identified for Burkitt's lymphoma and a rare form of adult leukemia/lymphoma.[100,101] Because breast milk is noted for providing passive immunity and protection of newborns from some early infections, investigators have hypothesized that breastfeeding may reduce the risk of childhood leukemia.[102]

Some of the confounders that had been considered in the studies of the relationship between childhood leukemia and breastfeeding were age, sex, race, socioeconomic status (such as mother's education, region of residence at the time of diagnosis, parental occupation, deprivation index, and/or annual household income), parental alcohol consumption, parental smoking, birth order, birth weight, parity, and age of mother at birth of index child.

Additional Methodological Comments

We identified four systematic reviews or meta-analyses that examined the relationship between breastfeeding and childhood leukemia[103-106] We have elected to describe in details only the Guise 2005[104] systematic review and Kwan 2004[106] meta-analysis because they superseded the Beral 2001[103] meta-analysis and Davis 1998[105] systematic review. All studies included in Beral 2001 and Davis 10998 were also included in Kwan 2004 or Guise 2005, except that Guise 2005 review excluded studies published before 1990, unpublished data, and studies conducted in developing countries. Kwan 2004 also included three additional studies published after 2001. In addition, the reporting and analysis in Beral 2001 and Davis 1998 were poor due to deficiency in reporting of the meta-analysis methods, search strategy and/or study eligibility criteria, and there was a lack of consideration of potential confounding in the included studies.

Guise 2005's systematic review was the only study that reported methodological grading for individual studies. Guise 2005 did not perform a meta-analysis. Kwan 2004 combined all case-control studies regardless of their study quality into a meta-analyses. To understand further how study quality can affect the effect estimate, we decided to perform meta-analyses on the effect estimates from the four studies graded as good or fair quality in Guise 2005's systematic review.

Published Systematic Reviews/Meta-Analyses (Table 18)

Guise 2005 conducted a systematic review of case-control studies related to breastfeeding and the risk of childhood leukemia. Ten case-control studies totaling 9,653 subjects with leukemia were included. All the studies were conducted in developed countries. Study quality

was rated by the authors in a three-levels scale: good, fair, or poor. The following aspects of the study quality were assessed: reliability of the diagnoses of leukemia, comparability of the case and control groups, differences in nonrespondents in cases versus controls, and the conduct of controlling for confounding. There were two good, two fair, and six poor quality studies. All studies but one focused solely on childhood leukemia. There was no meta-analysis or statistical analysis performed. The methodological quality of this systematic review was rated grade A.

Many of the studies in Guise 2005 systematic review did not provide data on exclusivity of breastfeeding and did not consider potential confounders such as infectious exposures from household or school contacts. Six of the ten studies explicitly sought to characterize the relationship between breastfeeding and leukemia.

Guise 2005 concluded that the few high-quality studies disagreed in regards to the association between breastfeeding and the risk of ALL. Specifically, the two good-quality studies, or UKCCS and CCG study,[103,107] presented "conflicting results" (Table 17). Similarly, the two fair-quality studies disagreed on the protective effect of breastfeeding.

Kwan 2004 conducted a meta-analysis of 14 case-control studies on breastfeeding and the risk of childhood leukemia. A total of 8,051 subjects with leukemia were included in the analysis. The meta-analysis examined the relationship between short-term breastfeeding (defined as breastfeeding for 6 months or less) or long-term breastfeeding (defined as breastfeeding for more than 6 months) and the risk of childhood leukemias. Twelve studies from developed countries and two studies from developing countries, including any type of leukemia in children 15 years or younger that reported odds ratio and duration of breastfeeding, were included in the meta-analysis. Kwan 2004 did not formally assess the individual study quality. However, the potential for confounding in each study was considered in the meta-analysis. The methodological quality of this meta-analysis was rated grade A.

For each of the 14 primary studies in the meta-analysis, Kwan 2004 selected odds ratio adjusted for SES when available. The meta-analysis showed a statistically significant reduced risk of ALL with short- and long-term breastfeeding (OR 0.88, 95%CI 0.80 - 0.96; OR 0.76, 95%CI 0.68 - 0.84, respectively). The analysis reported a statistically significant reduction in AML for long-term breastfeeding (OR 0.85, 95%CI 0.73 - 0.98) but not for short-term breastfeeding (OR 0.90, 95%CI 0.80 - 1.02). The unadjusted and adjusted odds ratios for reduction of the risk of ALL in short-term breastfeeding were both statistically significant. For reduction of the risk of ALL in long-term breastfeeding, only the adjusted odds ratio was statistically significant. The same sensitivity analyses were performed for the reduction of the risk of AML in short- and long-term breastfeeding, and similar results were found.

Studies included in the additional analysis. Guise 2005 identified two good and two fair methodological quality studies. We have analyzed these studies further as detailed below.

The two good studies were the UKCCS and the CCG studies. The UKCCS included 1,401 (87 percent) ALL and 214 (13 percent) AML case patients recruited from health programs that enrolled 98 percent of the total childhood cancers throughout England, Scotland and Wales over the period 1991-1998; control subjects were selected from population-based health rosters. In contrast, the CCG study included 1,744 (79 percent) ALL and 456 (21 percent) AML case patients enrolled from specific CCG centers, and control subjects were selected via random-digit-dialing. Both studies excluded leukemia diagnoses less than 1 year of age because most leukemias occurring during infancy are thought to have different etiologies from childhood leukemias. Both studies found that long-term breastfeeding (> 6 months duration) was protective for ALL, but the confidence interval for the risk estimate from the UKCCS did not exclude unity

(1.00), whereas the confidence interval for the risk estimate reported by the CCG study clearly excluded unity (1.00), indicating statistical significance. The UKCCS, however, found no association between short- or long-term breastfeeding and the risk of AML, while the CCG study found a significant protective effect of long-term breastfeeding for AML.

The two fair quality studies were Dockerty 1999 and Rosenbaum 2000. They were graded fair quality due to potential selection biases.[108,109] Dockerty 1999 included 121 newly diagnosed leukemia cases (ages 0-14 years) and 121 age- and sex-matched control subjects selected randomly from the New Zealand national birth records. The primary purpose of the study was to examine the relationship between infections, vaccinations, and the risk of childhood leukemia. Breastfeeding was one of the secondary factors examined in the study. Compared with children who never breastfed, those who breastfed for more than 6 months to 1 year had about a 20 percent reduced risk of ALL; those who were breastfed for more than 1 year had the lowest risk (OR 0.47; 95%CI 0.15 – 1.43). Even though these estimates were not statistically significant (Table 22), a trend analysis indicated a statistically significant effect in reducing the risk of ALL with increasing duration of breastfeeding (P = 0.04). Rosenbaum 2000 included 255 ALL cases from hospital registries and 760 matched control randomly selected from birth certificates in US. This study aimed to examine the relationship between early child-care (including breastfeeding) and the risk of childhood ALL. Like Dockerty 1999, children under 1 year of age were included in Rosenbaum 2000. The analysis of the relationship between breastfeeding and the risk of childhood ALL did not adjust for any other potential confounders, except for the factors used to identify matched controls (gender, race, and birth year). They found that 47 percent of cases of ALL and 51 percent of control were breastfed at birth (OR 1.20, 95%CI was not reported). This association was not statistically significant.

Meta-analysis. We used a random-effects model to combine SES-adjusted odds ratios of ALL in relation to short-term (≤ 6 months) and long-term (> 6 months) breastfeeding from UKCCS[103], CCG[107]study, and Dockerty 1999 (Table 17). Rosenbaum 2000 was excluded from the analysis because the duration of breastfeeding was not reported. The results from our meta-analysis suggest that long-term breastfeeding is associated with a reduction in the risk of ALL (OR 0.80; 95%CI 0.71 - 0.91).

Table 17. Combined SES-adjusted ORs of ALL for the three case-control studies rated as good and fair methodological quality in the systematic review by Guise et al. (2005)

Study	OR (≤ 6 mo vs. never BF)	Lower CI	Upper CI
UKCCS 2001			
<1 mo	0.90	0.77	1.04
1-6 mo	0.98	0.82	1.17
CCG study 1999	0.86	0.73	1.01
Dockerty 1999	1.24	0.47	3.23
Pooled	0.91	0.83	1.00
Kwan 2004 meta-analysis results	0.88	0.80	0.96

Study	OR (> 6 mo vs. never BF)	Lower CI	Upper CI
UKCCS 2001	0.89	0.75	1.05
CCG study 1999	0.72	0.60	0.87
Dockerty 1999			
>6 mo to 1 yr	0.82	0.29	2.27
>1 yr	0.47	0.15	1.43
Pooled	0.80	0.71	0.91
Kwan 2004meta-analysis results	0.76	0.68	0.84

Conclusion

Our meta-analyses of the three case-control studies concerning breastfeeding and the risk of ALL were consistent with the results from Kwan 2004's meta-analysis, but with smaller effect size and smaller statistical significance (Table 17). Kwan 2004 also found an association between a history of breastfeeding and a reduced risk of AML. We conclude that there is association between a history of breastfeeding of at least 6 months duration and a reduction in the risk of both ALL and AML.

Further evaluation of the biological mechanisms underlying this relationship while taking into consideration potential biases can be achieved with more large-scale case-control studies utilizing population-based and socioeconomic status-matched controls.

Table 18. Summary of systematic reviews/meta-analyses on the relationship between breastfeeding and childhood leukemia

Author Year Population	Study description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA and limitations
Guise 2005 Childhood ALL or all childhood leukemias: 9,653	SR of 10 case-control studies in developed countries	Any measures of breastfeeding and comparators	Gender, year of birth, race, SES (region of residence, maternal education, family income), gestational age, birthweight, maternal age, and smoking	• Six studies were conducted in European countries. Six of the studies explicitly sought to characterize the relationship between breastfeeding and leukemia as the primary objective, whereas the others included breastfeeding measures from the perspective measuring broader characteristics of the immune system and early infections in the etiology. Of the 10 studies, 2 were of good quality, 2 were of fair quality, and 6 were of poor quality. • The 2 good-quality studies (UKCCS and CCG studies) present "conflicting results" regarding the association between breastfeeding and leukemia. • Similarly, the 2 fair-quality studies disagreed on the protective effect of breastfeeding.	A Interpretation of "conflicting results" for the 2 good-quality studies was based on statistical significance only
Kwan 2004 Children with ALL, AML or ANLL: 6,835 (Note: 8 of the 14 studies excluded cases of leukemia in infants)	MA of 14 case-control studies in both developed and developing countries	Compared short-term breastfeeding (≤6 months) or long-term breastfeeding (>6 months) to no breastfeeding or never been breastfed	Age, sex, race, SES (mother's education, region of residence at the time of diagnosis, parental occupation, deprivation index, and/or annual household income), parental alcohol consumption, parental smoking, birth order, birthweight, parity, age of mother at birth of index child.	• A significant negative association was observed between short-term breastfeeding and ALL (OR=0.88, 95% CI 0.80-0.96), but the AML results (OR=0.90, 95% CI 0.80-1.02) were not significant. • A significant negative association was observed between long-term breastfeeding and ALL (OR=0.76, 95% CI 0.68-0.84), and AML (OR=0.85, 95% CI 0.73-0.98).	A 2 studies from developing countries
Beral 2001 Children with all leukemia, including ALL: 7,401	MA of 15 case-control studies in both developed and developing countries	Compared ever breastfeeding, breastfeeding duration ≤ 6 months, or breastfeeding duration > 6 months to never been breastfed	ND	• There is evidence of a statistically significant reduction in the OR associated with ever having been breastfed (OR=0.86, 95%CI 0.81-0.92) and having been breastfed for more than 6 months (OR=0.78, 95% CI 0.71-0.85).	C No methods of meta-analysis; no description of search strategy and study eligibility; no consideration of potential confounding

Table 18. Continued

Author Year Population	Study description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA and limitations
Davis 1998 Children with all leukemia, ALL or ANLL: 1,656	SR of 5 case-control studies in developed countries	Compared any breastfeeding, or long-term breastfeeding (6-8 months) to artificial infant feeding (or never been breastfed)	None	• None of the included studies reported a significant association between all leukemia, ALL or ANLL and infant feeding.	C Poor reporting of search strategy and study eligibility; no consideration of potential confounding

ALL, acute lymphocytic leukemia; ANLL, Acute non-lymphocytic leukemia; AML, acute myeloid leukemia; SES, socioeconomic status; SR, systematic review; MA, meta-analysis

Relationship between Infant Mortality and Breastfeeding

Background

Infant mortality (both neonatal and post-neonatal mortality) is on the decline in both developing and developed countries during the past four decades. In the United States, the national average of infant mortality was 7.0 deaths per 1000 live births in 2002.[110] Leading causes of infant death in a developed country include congenital abnormalities, pre-term births, low birth weight, Sudden Infant Death Syndrome (SIDS), problems related to complications of pregnancy, and respiratory distress syndrome.[110] The common risk factors that are associated with infant mortality include infant and maternal age, gender, race, socioeconomic status, birth order, birth weight, congenital malformation at birth, and maternal smoking during pregnancy. Breastfeeding protects against infectious diarrhea and respiratory diseases, which are the leading causes of infant mortality in developing countries.[111] However, the role of breastfeeding in preventing infant deaths in developed countries is less clear. We elect to review the relationship between breastfeeding and post-neonatal mortality.

Additional Methodological Comments

For this section, infant mortality is defined as any death that occurred more than 1 month but less than 12 months after birth. Neonatal mortality (death < 1 month of age) is not considered in this review. No published meta-analysis was identified that evaluated the relationship between breastfeeding and infant mortality. We included only studies conducted in developed countries that evaluated the relationship between breastfeeding and infant mortality (excluding SIDS).

Results (Table 19)

We identified two studies conducted in the United States that evaluated the role of breastfeeding in infant deaths other than SIDS.[112,113]; one study did not qualify for inclusion in this review because it was an analysis based on data collected from cross-sectional surveys.[113] The study that qualified for inclusion was a case-control study that selected subjects from nationally representative samples.[112] The study excluded infants who died at less than one month of age. The methodological quality of the study was rated grade B.

Chen 2004 analyzed the 1988 US National Maternal and Infant Health Survey (NMIHS) data using a case-control study design. Their sample included 1,204 infants who died between 28 days and 1 year of age. The authors excluded infants who died from congenital anomalies or malignant tumors. In an attempt to address the issue of reverse causality, only infants who survived beyond the neonatal period were included and feeding status was categorized based on the assessments undertaken some time before death occurred. The controls included 7,740 live births who were alive and older than 1 year of age at the time of survey. Mothers were surveyed using a mailed questionnaire. Breastfeeding was assessed as “ever breastfed” or “never breastfed.” The study did not report the mean or the range of duration of maternal recall for breastfeeding. Overall and cause-specific odds ratios were calculated to evaluate “ever” versus “never” breastfeeding. Since there was an oversampling of black and low birth weight infants in the original sample, in order for the study population to be more representative of the US

population, additional analyses were performed with SUDAAN software adjusted samples. This adjusted sample included a total of 9,145 cases and 3,186,497 controls. The analyses were adjusted for sampling strategy and potential confounders such as maternal age, education, smoking, infant gender, race, birth weight, congenital malformation, live birth order, plurality, and status of enrollment in the Special Supplemental Nutrition Program for Women, Infant, and Children program (WIC). The study reported that the odds of death in the postneonatal period were 21 percent lower for "ever breastfed" compared with "never breastfed" infants. However, in subgroup analyses of cause-specific death, the only statistically significant association was reported between SIDS (in the original sample) or injury-related death (in the SUDAAN-adjusted sample) and "never breastfed" status.

Conclusion

One study of moderate methodological quality using a large sample of infants reported a protective effect of breastfeeding in reducing infant mortality after controlling for some of the potential confounders. However, in subgroup analyses of the study, the only statistically significant association reported was between "never breastfeeding" and SIDS or the risk of injury-related deaths. Because of the limited data in this area, the relationship between breastfeeding and post-neonatal infant mortality remains unclear. Further research is warranted.

Table 19. Summary of case-control study on the relationship between breastfeeding and infant mortality

Author year *Country*	Cases (N)	Control (N)	Definition of infant mortality	Mean Age at Dx (year)	Breastfeeding group	Comparator group	OR* (95% CI)		Potential confounders adjusted	Quality and limitations
							Crude	Adjust		
Chen 2004 USA National Maternal and Infant Health Survey 1998 (NMIHS)	Postneonatal death [a] (9145)	Live birth [a] (3 186 497)	Death	> 28d of age	% Ever	% Never	nd	0.79 (0.67-0.93)	Maternal: age, education, smoking Infant: gender, race, birth weight, congenital malformation, live birth order, plurality, and WIC status	B (in subgroup analyses statistically significant association was reported between injury-related death or SIDS and "never breastfed" status)
	Postneonatal death [b] (1204)	Live birth [b] (7740)					nd	0.76 (0.65-0.88)		

[a] SUDAAN software adjusted sample
[b] Original sample

Relationship between Sudden Infant Death Syndrome (SIDS) and Breastfeeding

Background

Sudden infant death syndrome (SIDS) is the leading cause of mortality among infants aged 1 to 12 months in the United States.[114] SIDS accounted for a death rate of 0.55 per 1000 live births for the year 2004 according to the National Center for Health Statistics (NCHS) at CDC (www.cdc.gov/nchs/deaths.htm.). Several modifiable risk factors for SIDS are sleeping positions, maternal smoking, and bed sharing. Other potential risk factors include birth weight, gender, and socioeconomic status. The relationship of breastfeeding and SIDS has been evaluated among a broad range of potential risk factors. However, the role of breastfeeding as a protective factor in SIDS is unclear. One meta-analysis published in 2000 assessed the relationship of breastfeeding and SIDS.

Additional Methodological Comments

We identified four eligible studies conducted in developed countries that evaluated the role of breastfeeding in SIDS, and published since 1997, the cutoff date for the literature search of the published meta-analysis. .

Published Systematic Review/Meta-Analysis (Table 20)

One meta-analysis[115] of 23 studies (18 case-control; four nested case-control; and one observational cohort) evaluated the relationship of breastfeeding and SIDS. All studies were conducted in developed countries from 1965 to 1997. Studies that reported a minimal definition of SIDS – sudden unexplained death of an infant or young child – met the eligibility criteria. The meta-analysis analyzed a total of 4,251 cases of SIDS and 58,055 controls. Seventeen studies included subjects from birth to 2 years old when SIDS occurred; eight studies did not provide age data. The studies differed in their definition of breastfeeding exposure. Also, the studies varied in their description of SIDS. Of these, only 14 studies reported autopsy-confirmed diagnoses of SIDS. Three studies were specifically designed to examine the relationship of breastfeeding and SIDS. The rest of the studies examined multiple risk factors and their association with SIDS, of which feeding history would be one.

The meta-analysis utilized a random effects model. It reported an overall risk of SIDS twice as great for formula-fed infants compared with breastfed infants (crude odds ratio (OR) of 2.11; 95% CI 1.66 to 2.68). The methodological quality of individual studies was appraised. The authors conducted a separate meta-analysis for those studies published since 1988 when more advanced epidemiological and autopsy procedures were available. A separate analysis was also performed for those studies with “high” quality scores. The results from these meta-analyses concurred with the overall result. Heterogeneity was not explored, i.e., no subgroup analyses were performed to account for the different definitions of interventions or outcomes. The authors reported “no publication bias”. Differences in case matching precluded them from combining adjusted odds ratios in the meta-analysis. Four of the 16 studies showed a dose response trend

with the risk of SIDS increasing with increasing formula feeding. The overall methodological quality of the meta-analysis was rated grade C.

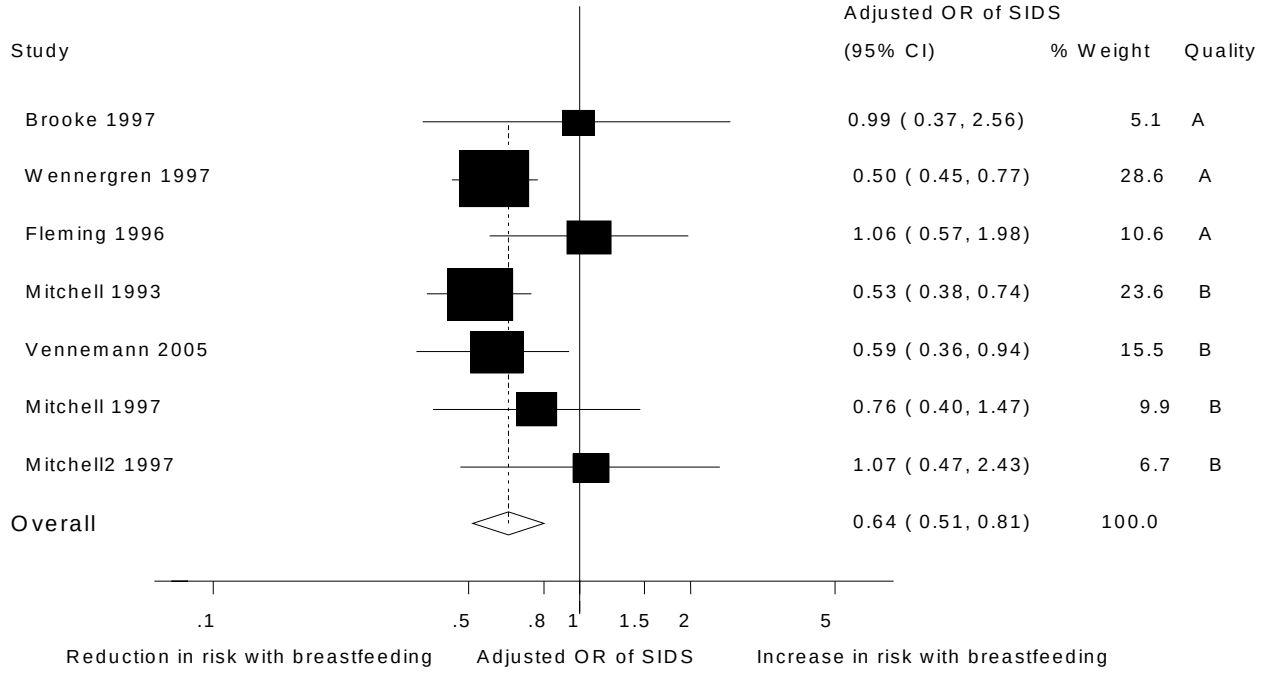
Studies Identified after the Published Meta-Analysis (Table 21)

We identified four eligible studies from five publications conducted in developed countries and published since 1997 that evaluated the relationship of breastfeeding and SIDS.[116-120] Three were case-control studies and the fourth, a case-cohort study (a cohort study analyzed as a case-control study). The methodological quality ranged from grades B to C. There were a total of 769 cases of SIDS and 2,681 controls.

All studies were designed to evaluate a broad range of potential risk factors for SIDS. The studies differed in their description of the duration of breastfeeding. Similarly, the studies varied in their definition of the time interval when SIDS occurs in infants, but all studies reported autopsy-confirmed diagnoses. The mean age of the infants with SIDS ranged from 2 to 19 weeks. All studies provided adjusted odds ratios for the association of breastfeeding and SIDS. Three of the four studies identified statistically significant increased risk of SIDS in bottle-fed infants.[117,119,120] Two studies reported that the risk of SIDS was twice or more for non-breastfed infants compared with some or ever breastfed infants.[117,119] One study reported an approximately two times increased risk of SIDS among those breastfed less than 2 weeks compared with those breastfed more than 2 weeks.[120] One case-cohort study (a cohort study analyzed as case-control study) did not find a statistically significant increased risk of SIDS in bottle fed infants.[118]

Meta-analysis results. Because of the limitations of the previous meta-analysis, we elected to conduct our own meta-analysis using only studies that provided an objective definition of SIDS (autopsy confirmed SIDS among infants 1 week to 1 year of age), clear reporting of breastfeeding data, and outcomes adjusted for important confounders or risk factors (e.g., sleeping positions, maternal smoking, and socioeconomic status). Four studies included in the previously published meta-analysis[121-124] and two studies published since 1997 met the eligibility criteria.[118,120] The majority of the studies provided data on ever versus never breastfeeding and this was combined using a random effects model. The results from our meta-analysis found that ever breastfeeding was associated with a reduction in both crude and adjusted risk of SIDS (crude OR 0.41; 95%CI (0.28, 0.58), and adjusted OR 0.64; 95%CI (0.51, 0.81), respectively); both estimates were statistically significant with a reduction in SIDS for the ever breastfed infants.

Figure 10. Random effects model of summary estimate evaluating the association of breastfeeding and SIDS



Conclusion

Results from the previously published meta-analysis of case-control studies concluded that an overall crude risk of SIDS was twice as great for formula-fed infants compared with breastfed infants. The conclusion may be biased because the reported association was not adjusted for potential confounders. Misclassification biases may occur because of differences among studies with regard to definitions of breastfeeding exposure, definitions of SIDS, and the wide age range of population included in the studies.

Findings from the four studies published subsequent to the meta-analysis in developed countries concurred with the findings from the meta-analysis. All studies reported autopsy-confirmed diagnoses of SIDS and adjusted for potential confounders. However, the definitions of breastfeeding exposure and the time intervals accepted for defining SIDS varied across studies. Three of four studies reported statistically significant increased risk of SIDS associated with non-breastfeeding or reduced duration of breastfeeding and the fourth study reported a statistically non-significant increased risk.

Our meta-analysis included only studies that reported clear definitions of exposure, outcomes, and results adjusted for well-known confounders or risk factors for SIDS. The summary estimate found a statistically significant adjusted odds ratio for an association between breastfeeding and a reduced risk of SIDS (adjusted OR 0.64, 95%CI 0.51 - 0.81). We conclude that there is a relationship between breastfeeding and a reduced risk of SIDS.

Table 20. Summary of systematic review/meta-analysis on the relationship between breastfeeding and Sudden Infant Death Syndrome (SIDS)

Author year	Study description	Number of subjects	Population	Intervention /Comparator	Results	Quality of SR/MA
McVea 2000	MA of 23 observational studies	Cases 4,251 Controls 58,055	Children who were diagnosed of SIDS	Breastfeeding (any)	The pooled OR for the 23 studies using random effects model resulted in an OR = 2.11 (95% CI 1.66-2.68) i.e., the overall risk of SIDS was twice as great for bottle-fed infants compared to breastfed infants. The pooled OR from the higher quality studies also demonstrated a two fold increase in risk among bottle fed infants OR = 2.24 The pooled OR from studies after 1988 OR = 2.32 Confounders: Individual studies adjusted for potential confounders; 6 studies reported adjusted OR; 4 studies reported no protective effect of breastfeeding, while 2 reported adjusted OR that remained significant. Dose-response relationship: 4 out of 9 studies showed a dose response trend with the risk of SIDS increasing with increasing formula feeding. None of the studies had sufficient power to demonstrate a statistically significant difference between partial vs. no breastfeeding.	C

SR, systematic review; MA, meta-analysis

Table 21. Summary of case-control studies on the relationship between breastfeeding and sudden infant death syndrome (SIDS) included in the meta-analysis

Author year *Country*	Cases (N)	Control (N)	Definition of SIDS	Mean Age at Dx (week)	Breastfeeding group	Comparator group	OR* (95% CI) Crude	OR* (95% CI) Adjust	Potential confounders adjusted	Quality and limitations
Wennegran, 1997 Alm 2002 Scandinavia	244	869	Validated definition	16	Ever (At the time of death)	Never	0.59 (0.4, 0.83)	0.5 (0.45, 0.77)	Sleep position, maternal smoking, bottle feeding at the time of death and age at the time of death	A
Fleming, 1996 UK	195	780	7d-1y	nd	Ever	Never	0.5 (0.35, 0.71)	1.06 (0.57, 1.98)	Maternal age, gestation, birth weight, exposure to tobacco, sleeping environment	A
Brooke, 1992 UK (Scotland)	147	275	7d-1y	15-18	Ever (At the time of death)	Never	0.22 (0.11, 0.47)	0.99 (0.37, 2.56)	Exposure to Parental smoking, sleep position, old mattress use, maternal age <27, deprivation score of 7, drug treatment in previous wk, marital status of the mother, SE status, gender of the infant, birth weight etc	A
Mitchell, 1993 New Zealand Population 1987-1990	460	1757	>28d-1yr	nd	Ever (At the time of discharge from obstetric dept)	Never	0.42(0.33, 0.53)	0.53(0.38, 0.74)	Region, time of day, baby's age, antenatal class, school leaving age of mother, marital status of mother, sex of baby, admission to neonatal unit, number of previous pregnancies, socioeconomic status, birthweight, gestational age, race of baby, season, mothers age at first pregnancy, mothers age at birth, sleeping position, bed sharing with another person, maternal smoking and breastfeeding	B
Vennemann 2005 Germany	333	998	8d-1 yr	19	>2 wk	<2 wk	0.19 (0.14, 0.25)	0.59 (0.36, 0.94)	Maternal age, family status, smoking in pregnancy. Previous live births and socioeconomic status	B
Mitchell 1997[a] New Zealand	79	679	29d-1 yr	2.6-9	Any at initial contact	None at initial contact	0.60 (0.35, 1.03)	0.76 (0.40,1.47)	Maternal age, marital status, age mother left school, previous number of pregnancies, infant's sex, ethnicity of infant, birthweight, sleep position, and bed sharing/maternal smoking combinations	B
	38	588			Any at 2 mo	None at 2 mo	0.76 (0.41, 1.39)	1.07 (0.47, 2.43)		

[a] A case-cohort study

Part II. Preterm Infant Outcomes

Relationship between Necrotizing Enterocolitis and Breast Milk Feeding in Preterm Infants

Background

Necrotizing enterocolitis (NEC) is a serious gastrointestinal disease in the preterm infants. No definitive causes have been identified. A population-based epidemiological study published in 2002 reported that the highest incidence occurred in infants with birth weights 750 to 1000 g and decreased with increasing birth weights.[125] Observational studies have suggested that breast milk might be protective. There have been very few randomized controlled trials (RCTs) that examined this issue. McGuire 2001 performed a meta-analysis of RCTs of breast milk comparing with formula milk in preterm infants to reduce the risk of NEC.[126] Since that meta-analysis, we identified one RCT[127] and two prospective cohort studies[128,129] that reported outcome of NEC in preterm infants in relation to a history of breast milk feeding. Some of the potential confounders that may affect the results of neonatal morbidity and mortality include birth weight, ethnicity, and sex.[128]

Published Systematic Review/Meta-Analysis (Table 23)

McGuire 2001's meta-analysis compared formula feeding with term breast milk feeding in low birth weight or preterm infants. Three RCTs published in 1983 and 1984 totaling 308 preterm infants were included: Gross 1983 compared formula with unfortified term donor breast milk;[12] Tyson 1983 compared preterm formula with pooled banked term breast milk;[13] and Lucas 1984[130] (results for NEC reported in 1990[131]) compared preterm formula with banked term breast milk as the sole diet. In the meta-analysis comparing formula with breast milk, the risk ratio for developing NEC was 2.5 (95% CI 0.9 - 7.3); risk difference was 0.05 (95% CI 0.00 - 0.1). The authors concluded that there was no statistically significant difference in the risk of NEC with either form of milk feeding.

Studies Identified after the Published Systematic Review/Meta-Analysis (Table 24)

Randomized controlled trial. Schanler 2005 enrolled 243 infants ≤ 29-week gestation whose mothers were expected to breastfeed.[127] If these infants' own mothers' milk were unavailable, the infants were then randomly assigned to receive either pasteurized donor milk or preterm formula. However, both groups continued to receive mother's milk partially if they were available during the study. The infants who were fed mother's milk exclusively were not randomized and served as a reference group. The incidence of NEC in Donor milk versus Preterm formula was 5/78 versus 10/88 (P = 0.27). The non-randomized group "mother's milk" had fewer repeated episodes of late-onset sepsis and/or NEC (OR 0.18, 95% CI 0.04 - 0.79) compared with combined groups "donor milk" and "preterm formula". The methodological quality of this study was rated B.

Prospective cohort. Furman 2003 was a prospective cohort study on 119 infants with gestational age < 33 weeks and birth weight 600-1499 g.[128] Enteral feeding was begun by day 2 or 3 of life, parenteral nutrition was continued until a daily enteral intake of 120 mL/kg of body weight was reached. Infants received their mother's milk in the sequence it was expressed, except that fresh rather than frozen milk was given if available. Maternal milk was fortified, and preterm infant formula was offered when the infant reached a daily oral intake of at least 110 mL/kg. Limited availability of maternal milk was the sole reason infants were fed preterm formula in addition to maternal milk. Four subgroups were analyzed: no maternal milk, daily maternal milk of 1-24 mL/kg, 25-49 mL/kg, and ≥ 50 mL/kg. Rates of NEC did not differ according to the amounts of maternal milk received. The results of the regression analysis were adjusted for birth weight, ethnicity, and sex. The methodological quality of this study was rated B.

Ronnestad 2005 was a prospective cohort study of late-onset sepsis on 462 infants with gestational age <28 weeks or birth weight < 1000 g in Norway.[129] NEC was not the primary outcome of interest; it was studied as a potential confounder in the analysis of late-onset sepsis. Four hundred five survived until day 7. Participating centers had a common policy of achieving full enteral feeding with the mother's milk or banked donor milk as early as possible, although there was no uniformity in a detailed protocol for feeding strategies. Enteral feeding with breast milk was commenced within 1, 2, or 3 days for 61 percent, 92 percent, and 96 percent of the infants, respectively. Nine of 405 (2.2 percent) patients had confirmed NEC. There was no concurrent comparison reported in this study. The methodological quality of this study was rate C with respect to the outcome of NEC.

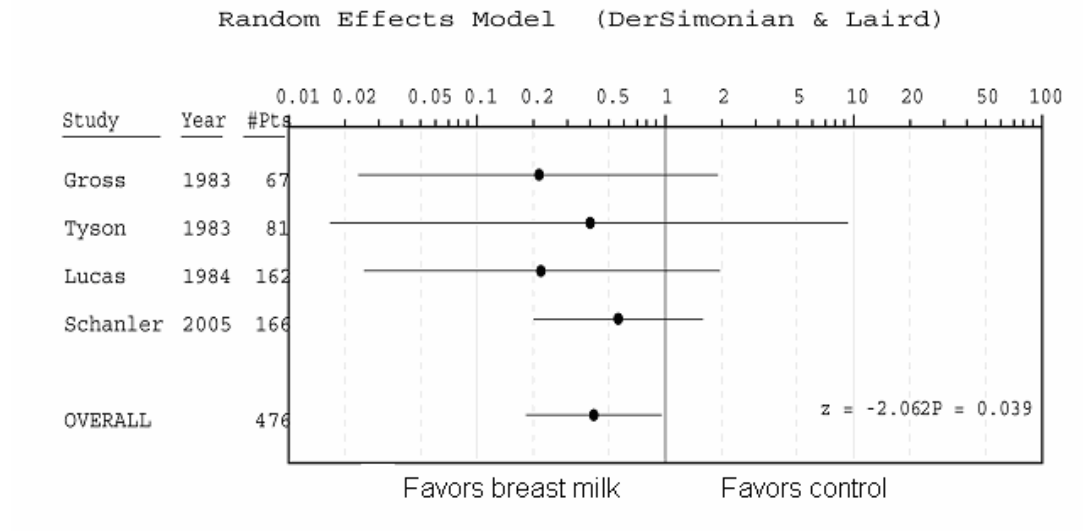
Updating the previous meta-analysis. We performed a new meta-analysis using a random effects model by combining the data from the Schanler 2005 RCT with the three RCTs in McGuire 2001. We combined all breast milk into one group because the proportion of the preterm versus term banked breast milk in the four studies cannot be determined. For outcome, we only counted confirmed cases of NEC as provided by the authors (either pneumatosis intestinalis or confirmed at surgery). We reported the results as risk ratios of developing NEC. The meta-analysis of four RCTs with a total of 476 infants provided a risk ratio of 0.42 (95% CI 0.18, 0.96) for the development of NEC, in favor of breast milk (Table 22; Figure 11).

Table 22. Meta-Analysis of four RCTs on the effects of breast milk feeding and NEC in preterm infants: Random Effects Model (D&L)

Study, year	Breast milk feeding		Control		Risk Ratio	95% CI	
	Event	Total	Event	Total		Low	High
Gross, 1983	1	41	3	26	0.21	0.02	1.93
Tyson, 1983	0	37	1	44	0.39	0.02	9.41
Lucas. 1984	1	86	4	76	0.22	0.03	1.93
Schanler, 2005	5	78	10	88	0.56	0.20	1.58
Total patients = 476	7	242	18	234	0.42	0.18	0.96

z = -2.0629 2P = 0.039
Overall Heterogeneity: Q = 1.02 Tau^2 = 0.0000

Figure 11. Meta-Analysis of four RCTs on the effects of breast milk feeding and NEC in preterm infants



Conclusion

Even though the observational study by Furman et al. did not find a difference in the rates of NEC according to the amount of maternal milk received by the infants, our meta-analysis of four RCTs demonstrated that there was a marginally statistically significant association between breast milk feeding and the reduction in the risk of NEC. The confidence interval for the estimate in the relative risk reduction ranged from four percent to 82 percent. The absolute risk difference was five percent. The wide confidence of the estimate reflects the relatively small number of total subjects in the studies and the small number of events. One must be cognizant of the clinical heterogeneity underlying these RCTs in interpreting the findings of the meta-analysis. Some of them were: different time periods when the studies were conducted; different preterm formulas as comparators; wide range of gestational ages and birth weights in the subjects; different degree of illnesses in the subjects; and others. How the heterogeneity in the studies affected the findings is unclear. Lastly, one may question the importance of an absolute risk difference of five percent between groups. Taking into account the high case-fatality rate of NEC, we consider this estimate is of meaningful clinical difference. In conclusion, there is evidence to support an association between breast milk feeding and a reduction in the risk of NEC in preterm infants.

Table 23. Summary of systematic review/meta-analysis on the relationship between breast milk feeding and necrotizing enterocolitis (NEC) in preterm infants

Author year	Study description	N	Population	Intervention/Comparator	Results	Quality for SR or MA
McGuire 2001	MA of 3 RCTs	310	Gross 1983 27-33 wk, < 1600 g N=67 US	Unfortified term donor breast milk, fed until 1800 g or until withdrawal secondary to feed intolerance or NEC; compared to standard calorie, protein enriched formula	formula vs. breast milk, RR: 2.5 (95% CI 0.9, 7.3); RD: 0.05 (95% CI 0.0, 0.1)	B
			Tyson 1983 "very low birth weight infants" N=81 US	Pooled banked term breast milk, allocation at 10th day of life, fed until 2000 g or until withdrawal secondary to illness requiring parenteral fat or protein; compared to enriched calorie and protein formula		
			Lucas 1984 preterm infants < 1850 g N=162 UK	Banked term breast milk 200 mL/kg/d, fed until 2000 g or until d/c; compared to enriched calorie and protein formula		

SR, systematic review; MA, meta-analysis

Table 24. Summary of studies on the relationship between breast milk feeding and necrotizing enterocolitis (NEC) in preterm infants

Author year	N	Population	Intervention/Comparator	Outcomes	Quality
Randomized Controlled Trial					
Schanler 2005	243	<29 wk infants, mothers expected to breastfeed US	Donor milk (DM) (+ mother's milk partially) Small quantities of mother's milk (~20 mL/kg/day) was initiated in the first week and continued for ~3 to 5 days before the volume was advanced. Milk intake was increased by ~20 mL/kg daily to 100 mL/kg, at which time milk fortifier was added, this was advanced by ~20 mL/kg daily until 160 mL/kg per day was achieved. Comparator: Preterm formula (PF) (+ mother's milk partially) Reference group: non-randomized, exclusive mother's milk (MM)	Incidence of NEC: DM vs. PF: 5/78 vs. 10/88 (P=0.27) Non-randomized group MM had fewer repeated episodes of late-onset-sepsis and/or NEC (OR 0.18; 95% CI 0.04–0.79) compared with combined groups DM and PF	B
Prospective Cohort Studies					
Furman 2003	119	<33 wk, birth weight 600-1499 g US	The study compared the effect of varying dosages of maternal milk on neonatal outcomes. Intravenous dextrose during the first 24 hrs; enteral intake was begun by day 2 or 3 of life, parenteral nutrition was continued until a daily enteral intake of 120 mL/kg of body weight was reached. Infants received their mother's milk in the sequence it was expressed, except that fresh rather than frozen milk was given if available. Maternal milk was fortified, and preterm infant formula was offered when the infant reached a daily oral intake of at least 110 mL/kg. Limited availability of maternal milk was the sole reason infants were fed preterm formula in addition to maternal milk.	0 maternal milk 3/40 1-24 mL/kg 2/29 (OR 1.15 95% CI 0.8-12.13) 25-49 mL/kg 2/18 (OR 1.99 95% CI 0.14-21.03) ≥ 50 mL/kg 0/32 (OR 0 95% CI 0 – 3.56) Results were adjusted for birth weight, ethnicity, and sex	B
Ronnestad 2005	462	<28 wk or birth weight < 1000g Norway	Tube feeding with breast milk was usually started within a few hours after delivery, with 1 to 2 mL of milk every 2 or 3 hrs, increasing by 0.5 to 1 mL every 6 to 8 hrs as tolerated. Enteral nutrition was supplemented with parenteral glucose from day 1, amino acids and lipids from day 2 and day 3, respectively.	Enteral feeding with breast milk was commenced within 1, 2, or 3 days for 61%, 92%, and 96% of the infants. 9/405 (2.2%) patients had confirmed NEC.	C No adjustment for potential confounders specific for NEC

DM, donor milk; MM, exclusive mother's milk; NEC, necrotizing enterocolitis; PF, preterm formula

Relationship between Cognitive Development and Breast Milk Feeding in Preterm Infants

Background

Many studies have examined the relationship between breastfeeding and cognitive development. Results have been conflicting. Most of the studies were observational in design. Many of them did not have a clear definition of breastfeeding or breast milk exposure. Different cognitive assessment tools were used. Outcomes were measured anywhere from less than 2 years of age to adulthood.

Three systematic reviews from 1999 to 2002 have tried to either establish methodological standards to assess the observational studies or adjust for covariates in pooled analysis (see discussion of confounders in section on cognitive outcomes in term infants). Since the last systematic review by Jain et al. in 2002,[58] there have been eight cohort studies on preterm infants that examined the relationship of breast milk feeding to some aspects of cognitive development.

A note of caution is in order here. The Mental Developmental Index of the Bayley Scales of Infant Development is widely used to assess the cognitive ability of young children in the studies reviewed in this report. One must keep in mind that the primary purpose of the Bayley Scales is to identify children who may be at risk from developmental delay; it was not the primary purpose to use the results of the Bayley Scales to predict IQ at a later age. Even though some recent studies on preterm infants have shown some predictive ability of the Bayley Scales, the ability to do so is imperfect.[132,133] Comorbidities (e.g., neurological impairment, extremely low birth weight, other neonatal illnesses), early intervention, environmental, and socioeconomic factors are some of the additional important variables that could affect the prediction of future cognitive function.

Published Systematic Review/Meta-Analysis (Please Refer To Table 8 In Part I)

Studies Identified after the Published Systematic Review/Meta-Analysis (Table 25)

Since 2002, five prospective cohort studies,[134-139] two nested case control studies,[140,141] and one secondary data analysis of a previous randomized controlled trial on supplemental arachidonic and docosahexaenoic acid[142] reported on the relationship between breast milk feeding and some aspects of cognitive development in preterm infants. Sample size of the studies ranged from 39 to 1,035. Five of the studies were of moderate methodological quality,[135,137,140-142] and three studies were of poor methodological quality.[134,136,138,139] Each study was graded within its own study design stratum and only with respect to the data on the relationship of breast milk feeding and cognitive development.

Gestational age of the infants ranged from 26 to 33 weeks. Except for one study that specifically enrolled children who had cerebral ultrasound abnormalities, including echodensity, echolucency, and/or ventriculomegaly,[140] the rest of the studies excluded infants with severe congenital abnormalities. Some also excluded infants with perinatal asphyxia and sensorineural abnormalities.

One study reported that half of the subjects had received breast milk exclusively.[137] Most studies provided information on the amount of breast milk intake and whether the milk had added cow-milk based fortifiers or not while the subjects were in the neonatal wards, but the information on breast milk intake was less informative after discharge to home. Three studies reported the proportion of subjects who breastfed for more than 6 to 7 months; they were 20 percent,[140] 27 percent,[137] and 29 percent,[141] respectively.

Bayley Mental Development Index Scale (MDI) was the cognitive assessment tool for subjects up to 2 years of age. Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R) was used in subjects under 7 years of age. Weschler Intelligence Scale for Children (WISC-R) was used in 7 years and 11 years old. Kaufman Assessment Battery for children (test for overall intellectual function) and Peabody Picture Vocabulary Test (PPVT-R) were administered to 6 to 8 year old children in one study.[140]

Prospective cohort. Elgen 2003 prospectively studied 130 low birth weight children at 5 years and 11 years of age using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R) and the Weschler Intelligence Scale for Children (WISC-R), respectively.[135] Twenty-seven percent of them received less than 30 percent breast milk in the neonatal ward. After adjustment for parental confounding (paternal and maternal education), breast milk was no longer a statistically significant predictor of IQ.

Pinelli 2003 prospectively studied 128 infants with birth weight <1,500 g at 6 months and 12 months corrected age using Bayley Mental Development Index Scale (MDI).[137] Fifty percent of them received breast milk exclusively in the neonatal ward. Twenty-seven percent of infants were breastfeeding at 6 months. After adjustment for sex, SES, birth weight and maternal age, no statistically significant difference in MDI at 12 months was found between the predominantly breastfed group and the predominantly formula-fed group.

The other three lesser quality studies suffered from selection biases (e.g., convenience sample), lack of adjustment for potential confounders (e.g., lack of adjustment for maternal intelligence), small sample sizes, or had issues with incomplete reporting.

One prospective study (in two publications) with post hoc comparisons reported significant differences ($P < 0.05$) in Bayley MDI at 6 months between substantial breast milk feeding group (> 75 percent of nutrition as breast milk) and intermediate (25-75 percent) or minimal feeding groups (< 25 percent) (94.2±8.8 vs. 91.7±7.2 vs. 90.5±8.5, respectively).[134,136] Maternal education or SES were not adjusted for in these results.

In a cohort study of subjects from a convenience sample (29 in breast milk group; 10 in formula group), a regression analysis showed an association between the amount of milk infants received in the special care nursery and the Bayley MDI at 7 months ($r=0.4$, $R^2=0.1$, $P < 0.05$) and 12 months ($r= 0.4$, $R^2=0.2$, $P < 0.025$).[139]

In a prospective study of 775 preterm infants who were fed breast milk and 260 preterm infants who were not fed breast milk, the adjusted Bayley MDI at 18 to 22 months of age was 79.9 ± 18 (SD) in the breast milk group versus 75.8 ± 16 (SD) in the no breast milk group ($P = 0.07$).[138] The result was adjusted for maternal (education, age, marital status) and perinatal (sex, gestational age, oxygen need, birth weight, and illnesses) factors. Mothers in the breast milk group were more likely to have private health insurance, be white and married, and have a college degree. Mothers who had low household income, higher parity, or were black were less likely to provide breast milk feeds. It was unclear if the results were actually adjusted for household income or not. Further analysis of breast milk intake by quintile relative to the no

breast milk group showed that there was a 13.1 point difference in MDI between ≤ 20th quintile and >80th quintile (P<0.0044).

Re-analysis of a previous RCT on supplemental arachidonic and docosahexaenoic acid. O'Connor 2003 re-analyzed data on 463 subjects from a randomized controlled trial on supplemental formulas in infants less than 33 weeks gestation.[142] Bayley MDI was evaluated at 12 months corrected age. There were no differences in the Bayley MDI among feeding groups. After controlling for home environment and maternal intelligence, there was a significant positive association between duration of breastfeeding and the Bayley MDI at 12 months corrected age in a "full" statistical model (P = 0.03, adjusted for large number of preplanned covariates for developmental outcomes), but not in a "reduced" statistical model (P = 0.07, adjusted only for those preplanned covariates with a P value of < 0.15)**.**[142]

Nested case-control. Smith 2003 studied 119 preterm subjects with cerebral ultrasound abnormalities and 320 subjects (presumably without ultrasound abnormalities) matched for gestational age in a nested case-control design.[140] The Kaufman Assessment Battery for children were administered to these 6 to 8 years old subjects. In the regression model that included adjustment for maternal verbal ability, home environment, and composite socioeconomic status, the advantage in overall intellectual function associated with direct breastfeeding was 3.6 points (95% CI -0.3 to 7.5; outcome measure was standardized with a mean of 100 points and a standard deviation of 15 points).

Horwood 2001 studied 280 subjects with very low birth weight at 7 years using WISC-R.[141] After adjustment for perinatal (sex, gestation, birth weight, multiple birth, Apgar score), socio-demographic (family income, single/two parent family, child ethnicity), and maternal factors (age, education, smoking), there remained a significant association between duration of receipt of breast milk and verbal IQ, with a 6 point advantage for infants who received breast milk for ≥ 8 months compared with no breastfeeding (P<0.001).

Conclusion

No definitive conclusion can be made regarding the relationship between breast milk feeding and cognitive development in preterm infants. One meta-analysis reported a five points advantage in standardized mean score and one systematic review identified one primary study that reported an eight points advantage in IQ in preterm or low birth weight infants who received breast milk feeding. In three of four primary studies of moderate quality that controlled for either maternal education or maternal intelligence, the advantage from breastfeeding was reduced to a statistically non-significant level after adjustment; the fourth study reported a positive association between duration of breastfeeding and the Bayley MDI at 12 months after controlling for maternal intelligence and home environment.

The roles of maternal intelligence and home environment should be accounted for in future studies on breastfeeding and cognitive development. Keeping in mind that cognitive function measured at an early age is not necessarily predictive of later cognitive ability, one should also consider carefully the timing and the selection of appropriate testing instrument in future studies. In addition, clear subject selection criteria, controlling for differences in early complications of prematurity and its relation to receiving breast milk, accounting for subjects lost to follow up, clear distinction between direct breastfeeding and bottle/gavage feeding of breast milk, collect data on breast milk fortifiers or supplemental preterm formulas, and better data collection on breast milk feeding after discharge from the neonatal units will improve the quality of these studies.

Table 25. Summary of primary studies on the relationship of breast milk feeding and cognitive development in preterm infants

Author Year Country Population	Study Description	Breast milk feeding exposure	Assessment tools	Confounders adjusted for	Outcomes	Quality and limitations
Prospective cohort						
Elgen 2003 Norway 130 Low birth weight (<2000 g)	Cohort assessed at 5 yr and 11 yr; excluded cerebral palsy, blindness, deafness, multiple malformations, chromosomal abnormalities	27% received <30% breast milk in neonatal ward	Weschler Preschool and Primary Scale of Intelligence- R at 5 yr; Weschler Intelligence Scale for Children-R (WISC-R) at 11 yr	Breast milk, birth weight, paternal and maternal education, chorioamnionitis, gestational age, length of oxygen treatment, sex, 5 minute Apgar, smoking during pregnancy, intrapartum stress, cerebral hemorrhage in subjects with birth weight <1500 g	Unadjusted regression: lack of breast milk was associated with a mean reduction in IQ of 5.8 points (95% CI –11 to –1). After adjustment for parental confounding, breast milk was no longer a statistically significant predictor of IQ.	B Lack of detailed information on breast milk exposure
Pinelli 2003 Canada 148 <1500 g 128 breastfeeding; 20 formula-fed infants were recruited as controls	Cohort from an RCT on conventional breastfeeding support versus supplementary structured breastfeeding counseling; excluded multiple births, severe congenital abnormalities, infants of non-English speaking parents	50% exclusively; some received fortification per explicit criteria; 27% still breastfeeding at 6 mo	Bayley MDI at 6 mo and 12 mo	Sex, SES, birth weight, maternal age	64/128 infants received breast milk exclusively; Adjusted MDI at 6 mo (corrected age) for >80% breastmilk group: 93 (SD 16); for <80% breastmilk group: 94 (SD 15); Adjusted MDI at 12 mo (corrected age) for >80% breastmilk group: 92 (SD 15); for <80% breastmilk group: 91 (SD 12); P>0.05 for all comparisons	B Cognitive testing at a young age

Table 25. Continued

Author Year Country Population	Study Description	Breast milk feeding exposure	Assessment tools	Confounders adjusted for	Outcomes	Quality and limitations
Vohr 2006 US 1,035 Preterm with mean gestation of 26.5 wk and birth weight of ~790 g	Enrolled prospectively in the Glutamine Trial at 15 sites of Neonatal Research Network; survivors who received some breast milk and had cognitive testing	Breast milk group– received some breast milk during hospitalization; total volume received calculated per day, values were interpolated for days of the week in which the data were not collected	Bayley Mental Development Index (MDI) at 18 to 22 mos corrected age	marital status, maternal education, age, race/ethnicity, infant's gestational age, gender, culture positive sepsis, grade 3 to 4 intraventricular hemorrhage, oxygen at 36 wks gestational age, necrotizing enterocolitis, and weight <10th %tile	There were 775 infants in the breast milk group and 260 in the no breast milk group. 95 subjects' Bayley could not be administered successfully; these data were not included. Mothers of infants who were seen at followup were more likely to have received prenatal care than mothers of infants who were not seen. There were no differences in infant characteristics. Information on breast milk feeding was not collected after discharge from hospital. 30.6% of infants in the breast milk group were still receiving breast milk. Mothers in the breast milk group were more likely to be white, married, have a college degree and have private health insurance. Mothers who had low household income, higher parity or were black were less likely to provide breast milk feeds. Adjusted Bayley MDI 79.9 $\pm$ 18 in BM 75.8 $\pm$ 16 in noBM P=0.0709 MDI <85* 421 (58.1%) in BM 168 (70.9%) in noBM P=0.0355 Multiple regression with adjusted factors=0.53 for MDI, P=0.0002 Breast milk intake was analyzed by quintile relative to the no breast milk group; for MDI, there was a 13.1 point difference between $\leq$ 20th quintile and >80th quintile (P<0.0044).	C Unclear if family income was adjusted for or not; cognitive test at young age; *proportion of subjects with MDI <85 could not have been adjusted

Table 25. Continued

Author Year Country Population	Study Description	Breast milk feeding exposure	Assessment tools	Confounders adjusted for	Outcomes	Quality and limitations
Eidelman, 2004 Feldman, 2003 Israel 86 gestational age 30.5 wk (26-33 wk)	3 groups stratified by amount of breast milk feeding; cognitive assessment at 6 mo corrected age; excluded infants with IVH grade 3 or 4, perinatal asphyxia, metabolic, genetic disease	3 groups: >75% of nutrition as breast milk; 25-75%; and <25%; duration of breast milk feeding: no data	Bayley MDI at 6 mo	Number of breastfeeding episodes was used as a covariate; MANCOVA performed with human milk and infant gender as the between subject factors	Univariate analyses showed group differences on the MDI. Post hoc comparisons reported significant differences between the substantial milk group and the other two groups: 94.2±8.8 vs. 91.7±7.2 vs. 90.5±8.5 (P<0.05)	C Not adjusted for SES, maternal education or intelligence; small sample size; cognitive testing at a young age
Bier 2002 US 39 28.6 wk gestation (range 23-34 wk); 29 in breast milk group; 10 in formula group	convenience sample; excluded infants with mothers who used illicit drugs, had mental illness, HIV infection, and others;	17% of mean volume intake in breast milk group was from premature formula, 9/29 (31%) continued breastfeeding between 3 and 7 mo corrected age	Bayley MDI assessed at 7 mo and 12 mo	maternal result of Peabody Picture Vocabulary Test (PPVT) and days of oxygen	Adjusted for maternal Peabody Picture Vocabulary Test (PPVT) result; mean Bayley MDI at 7 mo, breast milk group = 94 ± 7, in formula group = 90 ± 9 (Difference NS); at 12 mo, breast milk group = 101 ± 11, formula group = 90 ± 9 (P<0.05); regression analysis showed an association between the amount of milk infants received in the special care nursery by gavage and/or bottle and the Bayley MDI at 7 mo (P<0.05) and 12 mo (P<0.025).	C Convenience sample; small sample size, cognitive testing at a young age

Table 25. Continued

Author Year Country Population	Study Description	Breast milk feeding exposure	Assessment tools	Confounders adjusted for	Outcomes	Quality and limitations
Nested case-control						
Smith, 2003 US 119 with ultrasound abnormalities; 320 frequency matched (1:4) were included; gestational age 27.4 wk	Birth subjects from Developmental Epidemiology Network (n=1442); 439 subjects who had undergone neuropsychological testing and for whom parental questionnaires were completed by 9/2002 were included in this study	153 did not receive breast milk; 142 received expressed milk without progressing to direct breastfeeding; 125 received direct breastfeeding (the majority of them first received expressed breast milk); 20% of infants received breast milk > 6 mo.	Kaufman; Peabody Picture Vocabulary Test and Clinical Evaluation of Language Fundamentals; California Children's Verbal Learning Test; at age 6-8 yr	Maternal verbal ability, Home Observation for Measurement of the Environment Inventory, SES, duration of hospitalization	Outcome measures were standardized with a mean of 100 points and standard deviation of 15 points. Breast milk feedings were associated with higher unadjusted test scores for each domain of cognitive function except memory. In the regression model that included social advantage and neonatal morbidity, the adjusted score in overall intellectual function associated with direct breastfeeding was reduced to 3.6 points (95% CI, -0.3 to 7.5).	B 27% of subjects with ultrasound abnormalities; the timing of collection of breastfeeding data was not reported
Horwood, 2001 New Zealand 280 Very low birth weight survivors of a national birth cohort	retrospective recall of breast milk feeding and duration of feeding; assessed at 7 yr; excluded sensorineural disability and incomplete breastfeeding data	Breastfed < 4 mo (n=99) (49%) 4-7 mo (n=46) (22%) ≥ 8 mo (n=59) (29%) Not breastfed (n=76)	WISC-R at 7 yr	Perinatal, socio-demographic (family income, single/two parent family, child ethnicity), and maternal factors (age, education, smoking);	Children who were breastfed ≥ 8 mo had mean verbal IQ 10.2 (SD 0.56) higher and mean performance IQ 6.2 (SD 0.35) higher than children who did not receive breast milk. After adjustment for covariates, there remained a significant association between duration of receipt of breast milk and verbal IQ, with a 6 point advantage for infants who received breast milk for ≥ 8 mo compared with no breastfeeding (P<0.001).	B

Table 25. Continued

Author Year Country	Study Description	Breast milk feeding exposure	Assessment tools	Confounders adjusted for	Outcomes	Quality and limitations
Secondary data analysis of a previous RCT on supplemental arachidonic and docosahexaenoic acid						
O'Connor, 2003 Chile, US, UK 463 <33 wk gestation	Cohort, secondary analysis of a previous RCT on supplemental arachidonic and docosahexaenoic acid; excluded congenital abnormalities that could affect growth and development, major surgery, and others	divided into 4 mutually exclusive groups: predominantly breast milk or formula groups; ≥ or < 50% of total energy as breast milk; 43 infants (9%) on predominantly breast milk until term corrected age; 119 (26%) on predominantly formula until term corrected age	Bayley at 12 mo	Maternal intelligence and home environment	No differences in the Bayley MDI were found among feeding groups. There was a positive association between duration of breastfeeding and the Bayley MDI at 12 mo corrected age (P=0.032 in full, and P=0.073 in reduced statistical models) after controlling for home environment and maternal intelligence.	B Cognitive testing at a young age

Bayley MDI, Bayley Mental Development Index; MANCOVA , Multivariate analysis of variance; NS, Non-significant; PPVT, Peabody Picture Vocabulary Test; SES, socioeconomic status; WISC-R, Weschler Intelligence Scale for Children-R;

Part III. Maternal Outcomes

Relationship between Return to Pre-Pregnancy Weight or Postpartum Weight Change and Breastfeeding

Background

Return to pre-pregnancy weight is desirable since postpartum weight retention is a possible risk factor for obesity and its ensuing medical complications.[143] The change in weight results from changes in energy metabolism during pregnancy and lactation. This is mediated through the complex neuroendocrine and biochemical stimuli that follow from conception.

Despite the fact that the average weight retention associated with child bearing is modest, estimated at approximately 1.51 kg (s.d.=5.95 kg)[144-146] for some, there is some risk of major weight gain with pregnancy. Ohlin and Rossner 1990 reported changes in body weight that ranged from –12.3 to +26.5 kg from preconception to 1 year postpartum.[144] In various studies, the proportion of women retaining 5 kg or more after 6 months postpartum ranged from 14 to 20%.[146-148] Studies of the impact of physiological and behavioral influences, such as dietary intake, physical activity, and lactation on postpartum weight change reported mixed results. Studies of postpartum weight changes in lactating and non-lactating women also were equivocal within and across populations, with some showing that the length and intensity of breastfeeding were associated with less weight retention after pregnancy, while other studies reported that women who fed their infants formula lost more weight than women who nursed their infants.

Commonly considered confounders in the relationship between return to pre-pregnancy weight or post-partum weight change and breastfeeding were pre-pregnancy weight or BMI, age, educational level, physical activity, parity, smoking status, dieting practice, and ethnicity.

Additional Methodological Comments

To assess the relationship between breastfeeding and return to pre-pregnancy weight and postpartum weight/BMI changes, we relied on Fraser 2003,[149] the only published systematic review of the effect of lactation on maternal body weight. Since Fraser 2003 did not provide any descriptive or summary tables for further analysis, we contacted the authors to obtain copies of their evidence tables. However, the tables made available lacked the appropriate data for additional clarification of the authors' conclusions. Therefore, we decided to perform a primary analysis of all the studies cited in Fraser 2003. We also screened the references in the primary studies to identify additional studies for inclusion in our systematic review. In addition, we also evaluated primary studies that were published after Fraser 2003 and from suggestions by the reviewers of this report. These primary studies had been identified by our general literature search on the intervention of breastfeeding (see Methods chapter). We did not perform a search on maternal weight change by itself without any reference to breastfeeding.

Because of the known methodological problems in the studies of the relationship between breastfeeding and maternal weight,[15,150,151] we adopted the following inclusion criteria for our review: prospective cohort studies conducted in developed countries which directly compared

weight changes of nonlactating women with that of lactating women and for whom the exclusivity or the amount of breastfeeding was clear. The sample size criterion was at least 50 women per feeding group in the final analyses (e.g., lactating versus nonlactating).

For studies of the relationship between postpartum weight change and breastfeeding, studies need to control for subjects' gestational weight gain or pre-pregnancy weight and have at least 3-months postpartum followup to be included.

Results (Tables 26-27)

A total of 54 potentially relevant articles were retrieved for full-text screening. Forty-five articles were excluded because they were cross-sectional design, non-comparative studies, review articles, sample size less than 50 subjects per group, or had unclear breastfeeding data (exclusivity or amount of breastfeeding not clearly reported).

We included a total of three prospective cohort studies that examined the relationship between exclusive or full breastfeeding and return to pre-pregnancy weight[145,152,153] and five prospective cohort studies (in six publications) that examined postpartum weight changes in relation to exclusive breastfeeding.[144,154-157] One study, Linne 2003, was a 15-year followup of the two earlier Ohlin and Rossner studies of 1990 and 1996.

The reporting of breastfeeding data varied across studies. Some studies reported explicit and quantifiable amount of breastfeeding (e.g., providing at least two-thirds of the needed energy intake per kilogram of the infant's weight in breast milk, or infants received 120 mL/day or less of other milk until at least 1 year of age), while others did not quantify the amount of breastfeeding the infants received.

Relationship between breastfeeding and return to pre-pregnancy weight (Table 26)

A total of three prospective cohort studies were identified, involving 4,318, 540, and 95 women, with follow up durations of 3 years, 1 year and 1.5 years postpartum, respectively. All studies were conducted in the United States. All studies enrolled nulliparous and primiparous women between 24 and 40 years of age with normal and above normal pre-pregnancy weights, and all three studies were rated methodological quality grade B.

Overall effect of breastfeeding on return to pre-pregnancy weight or weight retention was negligible. The average weight retention was only within 1 kg range at 1 to 2 years postpartum. The large study of 4,318 nulliparous and primiparous women reported that, compared with women who did not breastfeed, exclusive breastfeeding was associated with a weight gain of approximately 1 kg from pre-pregnancy to 1 to 2 years postpartum, adjusting for age, physical activity and pre-pregnancy BMI.[152] This finding is only statistically significant for nulliparous women who had normal pre-pregnancy weight (BMI < 25) and for those primiparous women who were overweight at baseline (BMI ≥ 25). However, the duration of exclusive breastfeeding was not related to the magnitude of weight change from pre-pregnancy to 1 to 2 year postpartum. The study of 540 parous women reported that breastfeeding at 1 year was significantly associated with less weight retention from first trimester to 1 year postpartum ($P = 0.04$). The study of 95 nulliparous and primiparous women found that less weight was retained by lactating women than by non-lactating women, and this was statistically significant.[153] Exclusive breastfeeding was associated with approximately 1 kg weight loss from pre-pregnancy to 1 year postpartum. Bottle-feeding was associated with a weight retention of 2 kg during the same time period. Once lactation was discontinued, slower rates of weight loss were observed. Exclusively breastfeeding

women achieved their pre-pregnancy weights about 6 months earlier than women who exclusively bottle-fed their infants.

Relationship between breastfeeding and postpartum weight changes (Table 27)

Five prospective cohort studies involving a total of 2,097 parous women were identified. Followup durations ranged from 6 months to 15 years. Two studies were conducted in Sweden, two in the United States, and one in Canada. This group of studies measured the post-delivery weight changes in women. Half of the studies did not report women's pre-pregnancy weights. All studies attempted to control for various confounding factors that could influence the relationship between breastfeeding and postpartum weight changes. Five studies were of moderate methodological quality (Grade B), and one of poor methodological quality (Grade C).

The results from the five studies were inconsistent. Among the studies utilized a lactation score to express duration and intensity or exclusivity of breastfeeding, amount of breastfeeding was negatively associated with the postpartum weight change.[144,157] Among the three studies that examined postpartum weight changes and compared women who exclusively breastfed with women who partially breastfed or exclusively bottle-fed, none of them found a significant relationship between weight loss and breastfeeding among the comparison groups.[155,156,158]

Conclusion

Based on the results from three prospective cohort studies, we concluded that the overall effect of breastfeeding on return-to-pre-pregnancy weight (weight change from pre-pregnancy or first trimester to 1 to 2 year postpartum) was negligible (less than 1 kg). Results from four prospective cohort studies showed that the effects of breastfeeding on postpartum weight loss were unclear. All seven studies consistently suggested that many other factors have larger effects on weight retention or postpartum weight loss than breastfeeding. Examples of which included annual household income, baseline BMI, ethnicity, gestational weight gain, and energy intake. Undoubtedly, all these factors need to be carefully considered in any future investigation of the relationship between breastfeeding and postpartum weight changes.

Table 26. Summary of prospective cohort studies on the relationship between breastfeeding and returning to pre-pregnancy weights

Author Year Country (N baseline /followup)	Study followup period(s)	Breastfeeding exposure	Comparative feeding groups	Pre-pregnancy weight (kg) / BMI (kg/m^2)	Confounders adjusted for	Results	Quality and limitations
Sichieri 2003 US Nulliparous: 1,538/1,538; Primiparous: 2,810/2,810	3 yr	Exclusive breastfeeding: introduction of daily formula/milk was assumed to represent the end of exclusive breastfeeding period[a]	Never breastfeeding	62 / 82% <25; 18% ≥25	Age, physical activity, BMI, gestational weight gain	After adjusting for confounders, lactation was associated with a weight gain from prepregnancy to 1-2 yr postpartum of approximately 1 kg (statistically significant only for women nulliparous with a baseline BMI <25 (P=0.02) and for those women primiparous with a baseline BMI ≥25 (P=0.04), comparing women who breastfed with women who did not. Duration of exclusive lactation was unrelated to the magnitude of weight change from prepregnancy to 1-2 yr postpartum (P>0.40). Effect of breastfeeding on maternal weight is negligible.	B
Olson, 2003 US 597/540	1 yr postpartum	Breastfeeding after 6 mo was considered to be non-exclusive; a breastfeeding score similar to Ohlin and Rossner's was constructed[b]		ND / 59% ≤26; 41% >26	Age, educational level, smoking status at 1 yr post-partum, annual household income level, pre-pregnancy BMI category, and parity, gestational weight gain	Women who were breastfeeding at 1 yr retained[c] less weight compared with the women who weren't (P = 0.04). Breastfeeding at all other time points and the breastfeeding score were not significantly related to postpartum weight retention. Women at < 185% federal poverty index ratio (PIR) who gained more in pregnancy than Institute of Medicine (IOM) recommendations were 3.73 kg heavier that low income women who gained below or within the IOM guidelines for gestational weight gain (P<0.001).	B

Table 26. continued

Author Year Country (N baseline /followup)	Study followup period(s)	Breastfeeding exposure	Comparative feeding groups	Pre-pregnancy weight (kg) / BMI (kg/m2)	Confounders adjusted for	Results	Quality and limitations
Janney 1997 US 110/95	0.5, 2, 4, 6, 12, and 18 mo postpartum	Fully breastfeeding was defined as providing at least 2/3 of the needed energy intake per kilogram of the infant's weight in breast milk	Partial breastfeeding; full bottle feeding	59.7 / 22.2	Weight gained during pregnancy, amount of education, parity, type of delivery, season of delivery, marital status, age, smoking status before and during pregnancy, physical activity	Duration of lactation practice was a significant predictor of postpartum weight retention over time (P<0.001). Breastfeeding women achieved their pre-pregnancy weights ~ 6 months earlier than women who bottle-fed their infants. Time returned to prepregnancy weights (mo postpartum):[d] Bottle-feeding only: ~18 Partly breast-feeding at 2 mo, and bottle-feeding thereafter: ~12 Fully breast-feeding for 6 month and bottle-feeding thereafter: ~11 Fully breastfeeding for 6 mo, partly breast-feeding at 12 mo, and bottle-feeding at 18 mo: ~ 10 Martial status is predictor of weight retention over time (0.5-18 mo after parturition) P<0.001. Study showed greater weight retention in unmarried than married women.	B

BMI, Body Mass Index; IOM, Institute of Medicine; ND, not documented; PIR, poverty index ratio

[a] Individual breastfeeding data were collected retrospectively in the followup. Women asked to recall their lifetime breastfeeding history.
[b] 1 point for each week of coverage of exclusive breastfeeding and 0.5 point for each week of mixed feeding.
[c] Weight measured in the first trimester of pregnancy was used to calculate weight retention.
[d] Estimated values from figure

Table 27. Summary of prospective cohort studies on the relationship between breastfeeding and postpartum weight/BMI changes

Author Year Country (N baseline /followup)	Study followup period(s)	Breastfeeding exposure	Comparative feeding groups	Pre-pregnancy weight (kg) / BMI (kg/m^2)	Confounders adjusted for	Results	Quality and limitations
Ohlin 1990; Ohlin 1996 Sweden 2295/1423 Stockholm Pregnancy and Women's Nutrition Study (SPAWN)	1 yr postpartum	Lactation score (scale 0-48): Every month with full lactation was given 4 points, and every month with mixed feeding was given 2 points.		59.6 / 21.5	Weight gain during pregnancy, lactation score, age, pre-pregnancy BMI, parity, weight retention after previous pregnancy, dieting, profession, smoking habits, contraceptive practices, physical activity.	Overall, relationship between the Δ weight and lactation score is statistically significant though weak (r=-0.09, p<0.01). The weight loss between 2.5 and 6 months postpartum was significantly higher in groups with lactation scores >20 than < 20. However, the total weight loss between 2.5 and 12 months postpartum did not differ significantly between groups. 30% lost weight, 56% gain 0-5 kg, 13% gained 5-10 kg and 1.5% gained >=10 kg 1 year after delivery. Frequency of overweight women (BMI>=23.9) increased from 13% before pregnancy to 21% 1 year post-partum (p<0.001) The coefficients between the Δ weight and lactation score, age, pre-pregnancy weight and parity were very low (multiple r=0.38, p<0.001). Lactation and age increased the total proportion of explained variance by about 1% each.	B
Linne 2003 Stockholm 1423/563[e] (SPAWN)	15 yr	Ohlin's lactation score (scale 0-48)		59.8 / 21.5	As above	Those women who became overweight had lower lactation scores than women who remained normal weight at 15 years follow up (21.7 vs. 24.0, P < 0.05).	C High drop out rate

Table 27. continued

Author Year Country (N baseline /followup)	Study followup period(s)	Breastfeeding exposure	Comparative feeding groups	Pre-pregnancy weight (kg) / BMI (kg/m^2)	Confounders adjusted for	Outcomes	Quality and limitations
Walker 2004 US ND/382	6 wk, and 3, 6, and 12 mo postpartum	Full (exclusive) breastfeeding	Partial breastfeeding; full bottle feeding	ND	Ethnicity, maternal education, parity, smoking, physical activity, time of weight measurement, interaction of ethnicity and time, pre-pregnant BMI, gestational weight gain, energy intakes, fat intake, contraception, emotional eating, depressive symptoms	Infant feeding method was not associated with postpartum BMI (p=0.140)[a] Ethnicity is associated with BMI (P=0.001). In addition, BMI for the ethnic groups is parallel until 3 months postpartum when the African American and Hispanic groups begin increasing in BMI while the White group begins decreasing. At 6 months, the White group continues to decrease, the African American group continues to increase and the Hispanic groups begins to decrease.	B
Haiek 2001 Canada 242/236	6 wk, 3-5, 6-8 mo, and 9 mo postpartum	Predominantly breastfeeding (i.e., exclusive breastfeeding or average daily intake of formula of 4 oz or less)	Mixed-feeding (i.e., average daily intake of formula and breast milk of > 4 oz); predominantly bottle-feeding (i.e., exclusive bottle-feeding or average daily intake of breast milk of 4 oz or less)	22.5	Gestational weight gain, postpartum smoking, infant's solid intake, maternal place of birth	The unadjusted monthly rate of weight change was similar among the three feeding groups for all time periods. For none of the time periods was the rate of weight loss greater in the predominantly breastfeeding group. In the multivariate regression model, neither mixed-feeding nor predominant bottle-feeding was significantly associated with postpartum weight change (breast-feeding group was the reference).	B

Table 27. continued

Author Year Country (N baseline /followup)	Study followup period(s)	Breastfeeding exposure	Comparative feeding groups	Pre-pregnancy weight (kg) / BMI (kg/m^2)	Confounders adjusted for	Outcomes	Quality and limitations
Brewer 1989 US 70/56	3 and 6 mo postpartum	Exclusive breastfeeding	Exclusive formula feeding; mixed breast and formula feeding	ND	Age, parity, pre-pregnancy weight, socioeconomic data, energy intake, energy expenditure exclusive of lactation (physical activity)	Weight loss averaged 1.6, 2.1, and 1.5 kg/mo for exclusive breastfeed, exclusive formula feed, and mixed feed, respectively during the first 3 mo corrected for an initial fluid loss of 2 kg. Exclusive breastfeed resulted in an additional 0.43 kg/mo loss over the second 3 mo (P<0.005) with mixed feed averaging a 0.27 kg loss and nonlactating women experiencing essentially no change. All groups significantly declined in mean maternal weight over the 6-mo postpartum period (p<0.001). No significant differences in total weight loss were observed between the lactating and non-lactating groups.	B

BMI, body mass index.

[a] This study is the 15-yr followup of Ohlin 1990;1996. Responders were slightly older, had higher educational attainment, and higher income than non-responders. Nonresponse was more common in non-Nordic citizens.

[b] Other variables also included the multivariate model: ethnicity, time, pre-pregnant BMI and other variables (such as parity, gestational weight gain, Cesarean section etc.)

Relationship between Maternal Type 2 Diabetes and Breastfeeding

Background

Studies have shown that lactation has a beneficial effect on glucose and lipid metabolism; and improved pancreatic beta-cell function in women with gestational diabetes.[159,160] Thus, it is plausible that lactation could reduce the risk of the development of type 2 diabetes.

Commonly considered confounders in the studies of relationship between maternal type 2 diabetes and breastfeeding were parity, body mass index (BMI), diet, physical activity, family history of diabetes, and smoking status.

Published Systematic Review/Meta-Analysis (Table 28)

One systematic review examined the effect of breastfeeding on maternal risk of subsequent diabetes.[98] The authors identified three studies that evaluated the effects of breastfeeding on glucose tolerance and insulin levels; one study that evaluated the risk factors for recurrent gestational diabetes (GDM); and one study that examined the relationship between lactation and the risk of developing type 2 diabetes in women who had GDM. For this report, we focused only on the one study that examined the relationship between breastfeeding and the risk of developing type 2 diabetes in women with GDM.

Kjos 1998 conducted a retrospective cohort study of 904 Hispanic American women with GDM.[161] Kjos 1998 found that the use of progestin-only oral contraceptives was associated with an almost three-fold risk of developing type 2 diabetes compared with the use of combination estrogen-progestin oral contraceptives for breastfeeding Latina women with recent GDM. Since progestin-only oral contraceptive use was invariably associated with breastfeeding in this cohort, the authors then looked for an independent effect of breastfeeding on the risk of developing diabetes among women who initially elected nonhormonal forms of contraception and who were breastfeeding at the time of their initial postpartum examination. The results showed that the risk of developing diabetes in these women was not significantly different from the risk in women who elected nonhormonal contraception but did not breastfeed (unadjusted RR 0.90, 95%CI 0.56 - 1.46; adjusted RR 1.16, 95%CI 0.70 - 1.92). The authors of the systematic review did not assess the quality of this study.

The authors of the systematic review concluded that although no study has ever reported an increased risk of developing diabetes from breastfeeding, a single study did show a potential harm from the use of progestin-only oral contraceptive among breastfeeding Latino women with recent GDM.

Studies Identified after the Published Systematic Review/Meta-Analysis (Table 29)

One prospective, longitudinal cohort study on the association between the duration of lactation and the incidence of type 2 diabetes was identified.[162] The study consisted of two large cohorts in the United States, including participants from the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II). The Nurses' Health Study (NHS) was initiated in 1976 and

enrolled 121,700 women from 11 states. Participants were between 30 and 55 years of age at baseline, and each woman completed a detailed baseline questionnaire regarding diseases and health related topics. The Nurses' Health Study II (NHS II), begun in 1989, enrolled 116,671 women from 14 states. Participants were between 25 and 42 years of age and completed a similar baseline questionnaire as well as biennial followup questionnaires. This study was graded as high methodological quality (grade A).

The assessments of lactation history and type 2 diabetes were performed longitudinally. Women in the NHS II were also asked to report the diagnosis of GDM on each biennial questionnaire. Cox proportional hazards model was used to calculate the hazard ratio (HR) for type 2 diabetes by lactation history. All models were age-adjusted. Potential confounders including parity, BMI at age 18 years, diet, physical activity, family history of diabetes, and smoking status were included in the multivariate model a priori. Lifetime lactation history among parous women was stratified into six groups: none (reference group), 0 to 3 months, more than 3 to 6 months, more than 6 to 11 months, more than 11 to 23 months, and more than 23 months. Lifetime duration was updated every 2 years. Linear trend was assessed using midpoints of lactation categories. In the analysis of HR per year of lactation, the midpoints of reporting categories to calculate total lifetime lactation were used because this was the closest approximation of the original reported duration.

In the NHS, women who had ever breastfed had a covariate-adjusted HR for type 2 diabetes of 0.97 (95%CI 0.91 - 1.02) compared with women who never breastfed. There was a modest but statistically significant inverse association between duration of lactation and the risk of type 2 diabetes. In the multivariate-adjusted model including current BMI, each additional year of lactation was associated with an HR of 0.96 (95%CI 0.92 - 0.99) for type 2 diabetes.

Among women who had ever breastfed in the NHS II, the covariate-adjusted HR for type 2 diabetes was 0.90 (95%CI 0.77 - 1.04). Each year of lactation was associated with a covariate-adjusted HR of 0.84 (95%CI 0.78 - 0.89). When BMI was added to this model, the HR was 0.88 (95%CI 0.82 - 0.94) for each additional year of lactation.

Women with a history of GDM had a markedly increased risk of type 2 diabetes in the NHS II cohort, with 624 cases per 100,000 person years compared with 118 cases per 100,000 person-years among those without such a history. Lactation had no effect on diabetes risk in the GDM group, with a covariate-adjusted HR of 0.96 (95% CI 0.84 - 1.09) per additional year of lactation.

The effects of exclusive versus total breastfeeding could be compared in the NHS II cohort data. In models controlling for age and parity, each year of lifetime exclusive breastfeeding was associated with an HR for type 2 diabetes of 0.63 (95%CI 0.54 - 0.73), while each year of total breastfeeding was associated with an HR of 0.76 (95%CI 0.71 - 0.81).

Conclusion

Based on the longitudinal study of two large cohorts in the United States with over 150,000 parous women, we conclude that a longer duration of lifetime breastfeeding is associated with a reduced risk of developing type 2 diabetes among parous women who did not have a history of GDM. There was a difference in the risk of developing type 2 diabetes between women with and without GDM in relation to lactation. Compared with women who did not have a history of GDM, women with a history of GDM had a markedly increased risk of type 2 diabetes; and lactation showed no significant relationship with diabetes risk among this group of women. One

must be cautious in interpreting these findings, as they are only generalizable to population with characteristics similar to that of the Nurses' Health cohort.

Table 28. Summary of systematic review/meta-analysis on the relationship between breastfeeding and maternal type 2 diabetes

Author year Population	Study description	Intervention /Comparator	Confounders considered	Results	Quality of SR/MA and limitations
Taylor 2005 Kjos et al. (1998): A retrospective cohort study of 904 Latinas living in US with GDM (based on National Diabetes Data Group Criteria) who gave birth between January 1987 and March 1994, in whom postpartum diabetes was excluded at 4 to 16 weeks post partum.	SR of 1 retrospective cohort study on the association between breast milk feeding (or lactation) and maternal type 2 diabetes	At their baseline postpartum visits, 461 of the study subjects chose to use an oral contraceptive (OC) and 443 chose a nonhormonal method of contraception. Of those electing to use an OC, 78 were given the progestin-only OC since they were breast-feeding at their baseline postpartum visits and planned to continue breast-feeding. Since progestin-only OC use was invariably associated with breast-feeding in this cohort, the author then looked for an independent effect of breast-feeding on the risk of developing type 2 diabetes among women who initially elected nonhormonal forms of contraception (n=443).	Gestational age at diagnosis of GDM, highest fasting glucose level during the index pregnancy, and glucose area under the curve from the diagnostic OGTT	The risk of developing type 2 diabetes was not significantly different between breastfeeding women and bottle feeding women who chose non-hormonal forms of contraception (adjusted RR: 1.16; 95%CI 0.70-1.92)	C[a] No synthesis of results and unclear how the conclusions were reached

GDM, gestational diabetes; RR, relative risk

[a] We did not grade the methodological quality for Kjos 1998 in the systematic review. Taylor 2005 review is also summarized in infant outcome - type 2 DM section.

Table 29. Summary of studies on the relationship between breastfeeding and maternal type 2 diabetes (NIDDM)

Author year Country	Study design	Number of subjects	Mean age at follow-up (year)	Definitions of type 2 diabetes	Breast milk feeding duration (months), parous women only	Adjusted[a] Hazard Ratio (95%CI)	P value for trend	Quality
Stuebe 2005 US	Prospective longitudinal cohorts (NHS and NHS II studies) NHS: prospective analysis using cases from 1986 to 2002 NHS II, retrospective analysis using lactation data from 1997 and 2003, cases from 1989 to 2001, parous women only	Nurses' Health Study (NHS): 121,700 (83,585 parous women) NHS II: 116,671 (73,418 parous women)	NHS: ~52 NHS II: ~35	(1) 1 or more classic symptoms (i.e., excessive thirst, polyuria, weight loss, or hunger) plus either a fasting glucose level of 140 mg/dL (7.8 mmol/L) or more or random plasma glucose level of 200 mg/dL (11.1 mmol/L) or more; (2) at least 2 instances of elevated plasma glucose concentration (fasting glucose ≥140 mg/dL, random plasma glucose ≥200 mg/dL, or oral glucose tolerance test ≥200 mg/dL after 2 hours) on different occasions in the absence of symptoms; or (3) treatment with insulin or an oral hypoglycemic medication. The criteria for diagnosis of diabetes changed in 1997, when a fasting glucose level of 126 mg/dL (7.0 mmol/L) or higher was made the diagnostic threshold.	NHS –			A
					None	Reference		
					>0 to 3	0.98 (0.91-1.05)	.02	
					>3 to 6	1.03 (0.94-1.13)		
					>6 to 11	0.96 (0.87-1.06)		
					>11 to 23	0.92 (0.84-1.02)		
					>23	0.88 (0.78-1.00)		
					Per year of lactation	0.96 (0.92-0.99)		
					NHS II –			
					None	Reference		
					>0 to 3	1.04 (0.86-1.26)	<.001	
					>3 to 6	0.91 (0.73-1.14)		
					>6 to 11	0.87 (0.72-1.06)		
					>11 to 23	0.88 (0.74-1.06)		
					>23	0.67 (0.54-0.84)		
					Per year of lactation	0.88 (0.82-0.94)		
					NHS II, never had GDM –			
					None	Reference		
					>0 to 3	1.00 (0.81-1.24)	<.001	
					>3 to 6	0.80 (0.62-1.04)		
					>6 to 11	0.86 (0.70-1.07)		
					>11 to 23	0.77 (0.62-0.95)		
					>23	0.58 (0.45-0.75)		
					Per year of lactation	0.84 (0.78-0.91)		
					NHS II, ever had GDM –			
					None	Reference		
					>0 to 3	1.18 (0.72-1.93)	NS	
					>3 to 6	1.30 (0.75-2.25)		
					>6 to 11	0.89 (0.53-1.49)		
					>11 to 23	1.19 (0.76-1.87)		
					>23	0.97 (0.58-1.61)		
					Per year of lactation	0.96 (0.84-1.09)		

GDM, gestational diabetes

[a] Confounders adjusted in the model include parity, BMI, diet, physical activity, family history of diabetes, and smoking status.

Relationship between Osteoporosis and Breastfeeding

Background

Osteoporosis is a condition of decreased bone mass. This leads to fragile bones that are at an increased risk for fractures. The World Health Organization (WHO) has established criteria for making the diagnosis of osteoporosis, and for determining levels that predict higher chances of fractures. These criteria are based on comparing bone mineral density (BMD) in a particular patient with those of a healthy 25-year-old female (T-scores). BMD values (T-scores) which fall well below the average for the 25-year-old female (stated statistically as 2.5 standard deviations below the average) are diagnosed as osteoporosis. Although BMD T-scores were based originally on assessment of BMD at the hip by dual-energy X-ray absorptiometry (DXA), they have been applied to define diagnostic thresholds at other skeletal sites and for other techniques. Experts have expressed concern that this approach may not produce comparable data between sites and techniques. Of the various sampling sites, measurements of BMD made at the hip predict hip fracture better than measurements made at other sites, while BMD measurement at the spine predicts spine fracture better than measurements at other sites (consensus.nih.gov/2000/2000Osteoporosis111html.htm).

Calcium and bone metabolism is substantially altered during pregnancy and lactation. The typical daily loss of calcium in breast milk has been estimated to range from 280 to 400 mg, although daily losses as great as 1000 mg calcium have been reported.[163] Physiologically, during nursing, the body could theoretically meet this demand by increasing the intestinal absorption of calcium, decreasing renal calcium losses, and increasing the resorption of calcium from the maternal skeleton. Bone densities can decrease and increase 3 to 10 percent in the span of a few months in healthy mothers.[164] Prospective cohort studies have reported that lactation is associated with bone mineral loss in the first 6 months to 1 year postpartum, but such loss rebounds overtime.[165-169]

Confounders commonly considered in the studies of relationship between fracture risk and breastfeeding were age, hormone replacement therapy, parity and BMI.

Inclusion and Exclusion Criteria

To evaluate the relationship between breastfeeding and the development of osteoporosis, we included all studies that examined the link between breastfeeding and fracture. We also included long-term prospective cohort studies (greater than 1 year of followup duration) that examined the relationship between the duration of breastfeeding and changes in bone mineral densities or bone mineral contents. Articles were excluded if they only used surrogate measures of fracture (e.g., fracture risk score or index) or bone turnover markers.

Results (Tables 30-31)

A total of 44 potential relevant articles were retrieved for full-text screening. Thirty-four articles were excluded due to various reasons (e.g., cross-sectional design, relatively short duration of follow up (< 2 years), studies done in developing countries). We included a total of six case-control studies that examined the risk of fractures in relation to a history of

breastfeeding,[170-175] and four long-term prospective cohort studies that examined the changes of bone mineral densities or bone mineral contents in relation to the duration of breastfeeding.[176-179]

Risk of fractures in relation to a history of breastfeeding (Table 30). A total of six case-control studies were identified. There were a total of 1,594 subjects with hip, forearm, or vertebral fractures and 3,523 controls. All subjects were post-menopausal women with an age that ranged from 45 to 103 years old. Three studies were conducted in the United States; one study each was conducted in Australia, Hong Kong, and Sweden. Four studies were rated methodological quality grade B; two was rated grade C.

Incident cases of hip and forearm fractures were identified from hospital or clinical records (with or without radiography confirmations) in five studies. Matched or unmatched general population controls living in the same area were used in three studies, while hospital controls were used in the other two studies. In the remaining one study, all women who were living in three housing blocks were enrolled. Cases of definite vertebral fractures were classified according to the radiological diagnoses and the remaining enrolled subjects without fractures were classified as control subjects. Assessments of breastfeeding history were based on subjects' long-term recalls in all studies. Only one study reported blinded interviewers.

Overall, there was no significant association between a history of breastfeeding and the risk of hip, forearm, or vertebral fractures after adjustment for potential confounders. In four of six studies, parity was considered a potential effect modifier or confounder. Other confounders examined included age, body mass index or weight, hormone replacement therapies, and bilateral oophorectomy. None of the studies provided data on the exclusivity of breastfeeding.

Long-term changes in bone mineral densities or bone mineral contents in relation to the duration of lactation (Table 31). A total of four prospective cohort studies were identified. Followup durations ranged from 2.5 to 12 years. Studies were done in different countries: one studied 113 pre-menopausal parous women in Japan, one studied 169 pre- and peri-menopausal parous women with European heritage living in the United States, one studied 92 pre-menopausal women in Finland, and one studied 121 post-menopausal women in Denmark. One study was of methodological quality grade A, two were of grade B, and one was of grade C, respectively.

Matsushita 2002 examined the effects of multiple pregnancies on BMD of lumbar spine (L2-L4) in 110 parous Japanese women. The outcome was the percent change in BMD, calculated by subtracting the value at the time of the initial pregnancy from the value at the time of the second pregnancy. The results showed that the BMD after the subsequent delivery was significantly higher than the BMD after the initial delivery ($P = 0.001$), with a percent change in BMD of 1.4 percent. Independent determinants of the percent change in BMD were explored by multiple regression analysis. The length of lactation between the deliveries showed no correlation with the percent change in BMD (correlation coefficient = -0.06, $P = 0.702$). Age was the most significant predictor for the percent change in BMD in the model.

Sowers 1992 examined various risk factors for 5-year radial BMD changes in 169 pre- and post-menopausal parous women with European heritage living in the United States. The authors reported that "a recalled history of breastfeeding in parous women did not predict significant differences in BMD level or amount of BMD change".

Uusi-Rasi 2002 examined the relationship between physical activity, calcium intake, and the maintenance of bone mass in 92 non-smoking premenopausal women living in Finland. The effects of total breastfeeding duration on changes in bone mineral contents (BMC) were also

analyzed. According to the multiple stepwise regression analyses, the statistically significant independent predictors for site-specific bone loss were low calcium intake at the baseline and change in body weight both at the proximal femur and at the distal radius sites. In addition, breastfeeding was associated with radial bone loss; the longer the duration of breastfeeding the greater the bone loss (correlation coefficient = -0.34, P = 0.015).

Hansen 1991 examined the risk factors for the development of postmenopausal osteoporosis over a 12-year period in 121 postmenopausal women living in Denmark. One hundred eleven of them (92 percent) had one or more pregnancies (mean 2.6) and breastfed their infants for a mean total breastfeeding duration of 13 months. Comparing postmenopausal women who never breastfed their infants with those who did, there was no significant difference in lumbar spine BMD between groups. In addition, there was no significant difference in the annual rate of postmenopausal bone loss between these two groups.

Conclusion

There is no evidence of an association between lifetime breastfeeding duration and osteoporosis. In six case-control studies, there was no significant relationship between a history of lactation and the risk of fractures in postmenopausal women. In two of three moderate or good quality prospective cohort studies using bone mineral density as a surrogate for osteoporosis, lactation does not appear to have an effect on long-term changes in bone mineral densities. The third study found a small decrease in the bone mineral contents in the distal radius with increased duration of breastfeeding, but no significant changes in bone mineral contents in the femoral neck or the trochanter. However, these findings should be interpreted with caution because the feeding history was obtained by maternal recall and data on exclusivity of breastfeeding were not provided. Further investigation with accurate breastfeeding data is warranted.

Table 30. Summary of case-control studies on the relationship between breastfeeding and risk of fracture in post-menopausal women

Author year Country	Cases (N)	Controls (N)	Definition of fracture	Mean Age at Dx of fracture (year)	Lactation group	Comparator group	OR (95% CI) Age-adjusted	OR (95% CI) Full adjusted*	Potential confounders adjusted	Quality and limitations
All post-menopausal women										
Alderman 1986 USA	164	318	Hip fractures based on clinical records	50-74	BF 1-12 mo	Never BF		1.60 (0.91-2.96)	Age, natural logarithm of the duration of estrogen use, and relative weight	B
					BF 13-24 mo			0.40 (0.17-1.10)		
					BF > 24 mo			0.50 (0.21-1.44)		
	180		Forearm fractures based on clinical records		BF 1-12 mo	Never BF		0.80 (0.45-1.58)		
					BF 13-24 mo			0.80 (0.40-1.79)		
					BF > 24 mo			0.80 (0.38-1.87)		
Cumming 1993 Australia	174	137	Hip fractures presenting to the hospitals	65-100	Ever BF	Never BF	0.72 (0.43-1.20)	0.64 (0.30-1.38)	Age, BMI, history of HRT, current use of psychotropic medications, current smoking status, current dairy product consumption, score on mental state, current PA and health status	B
Hoffman 1993 USA	170	173	First hip fracture confirmed by radiography identified from hospital records	50-103	Ever BF	Never BF	0.66 (0.41-1.05)		Age	B
					BF ≤ 12 mo	Never BF	0.67 (0.39-1.13)			
					BF > 12 mo		0.64 (0.32-1.29)			
Chan 1996 Hong Kong	144	163	Definite vertebral fractures by radiography	75	BF < 24 mo	Never BF	0.70 (0.40-1.30)		Age	C Parous women were not separated
					BF ≥ 24 mo		0.60 (0.30-1.00)			

Table 30. Continued

Author year Country	Cases (N)	Controls (N)	Definition of fracture	Mean Age at Dx of fracture (year)	Lactation group	Comparator group	OR (95% CI) Age-adjusted	OR (95% CI) Full adjusted*	Potential confounders adjusted	Quality and limitations
Kreiger 1982 USA	98	83[b] 801[c]	First hip fracture confirmed by radiography identified from hospital records	45-74	BF (12-month increase)			0.50 (0.20-0.90)[b] 0.60 (0.30, 1.0)[c]	Age and BMI, bilateral ovariectomy, and HRT	C Sample size in BF analysis was not described; hospital controls
Parous post-menopausal women										
Michaelsson 2001 Sweden	664	1,848	Hip fractures based on clinical or register records	71	BF 6-10 mo BF 11-16 mo BF > 16 mo	BF 1-5 mo	0.83 (0.66-1.05) 0.84 (0.65-1.08) 0.76 (0.60-0.98)	0.87 (0.68-1.11) 0.86 (0.66-1.12) 0.86 (0.67-1.12)	Age, HRT, oral contraceptive use, and BMI	B
					BF (3-month increase)		0.96 (0.94-0.99)	0.98 (0.95-1.01)		
Alderman 1986 USA	268	211	Hip or forearm fractures based on clinical records	50-74	BF 1-12 mo BF 13-24 mo BF > 24 mo	Never BF		1.20 (0.73-1.95) 0.70 (0.34-1.29) 0.80 (0.38-1.51)	Same as above	B
Cumming 1993 Australia	131	107	Hip fractures presenting to the hospitals	65-100	Ever BF	Never BF	0.47 (0.22-0.99)	0.55 (0.10-2.90)	Same as above	B
					BF 0.5-3 mo[a]		0.56 (0.19-1.68)	0.64 (0.13-3.06)		
					BF 3-6 mo[a]	Never BF	0.41 (0.15-1.13)	0.79 (0.18-3.51)		
					BF 6-9 mo[a]		0.47 (0.19-1.19)	0.41 (0.09-1.82)		
					BF >9 mo [a]		0.28 (0.07-1.18)	0.24 (0.04-1.53)		
Hoffman 1993 USA	103	125	First hip fracture confirmed by radiography identified from hospital records	50-103	Ever BF	Never BF		0.87 (0.47-1.61)	Age, and number of live births	B
					BF ≤ 12 mo	Never BF		0.80 (0.42-1.55)		
					BF > 12 mo			1.08 (0.45-2.60)		

Dx, diagnosis; BF, breastfeeding; HRT, hormone replacement therapy; PA, physical activity
* Adjusted for potential confounders, including age
[a] Average breastfeeding duration per child; [b] trauma controls ; [c] non-trauma controls

Table 31. Summary of prospective cohort studies on the relationship between duration of breastfeeding and the long-term changes of bone mineral density (BMD) or bone mineral content (BMC)

Author, Year Country	Population	Mean baseline age (yr)	Mean duration of followup (yr)	N	Duration of lactation	ΔBMD (g/cm^2) or ΔBMC	*p*	Quality and limitations
Matsushita, 2001 Japan	Pre-menopausal, parous women	30	2.5	113	Length of lactation between 1st and 2nd delivery (mo)	ΔBMD_{spine}: -0.06% [a]	NS	A
Sowers, 1992 USA	Mixed pre- & peri-menopausal, parous women	22-54	5	169	Lactation vs. no lactation	"No significant differences in BMD level or change"	NS	B
Uusi-Rasi, 2002 Finland	Pre-menopausal women	28 (25-30)	4.2 (3.2-5.4)	92	Total duration of breastfeeding [b]	$\%\Delta BMC_{femoral\ neck}$ [c]	NS	B
						$\%\Delta BMC_{trochanter}$ [c]	NS	
						$\%\Delta BMC_{distal\ radius}$: β=-0.34 [c]	0.01	
Hansen, 1991 Denmark	Post-menopausal women	51	12	121	Lactation (87%): mean 13 mo vs. no lactation [b]	ΔBMD_{spine}: 0.04	NS	C No confounders adjusted; unclear if nonporous women were included
						ΔBMC_{arm}: 0.1% per year	NS	

NS, not statistically significant; BMD_{spine}, lumbar spine bone mineral density; BMC_{arm}, forearm bone mineral content

[a] Variables in the multiple regression model: interval between the scans (yr), lumbar spine BMD after the initial delivery (g/cm^2), bone area (BA) after the initial delivery (cm^2), body weight after the initial delivery (kg), age at initial delivery (yr), ΔBA (cm^2), body weight changes between the scans (kg) length of lactation between the scans (mo), interval between the time at which breast-feeding was stopped and the next conception (mo); age at next delivery (yr). Dependent variable, ΔBMD%, r^2=0.174, p=0.037. The percent change in BMD (ΔBMD%) was calculated by subtracting the value at the time of the first pregnancy from the value at the time of the second pregnancy

[b] Not clear whether nulliparous women were included in the analyses

[c] Multivariate stepwise regression for percent bone loss included the following variables: age, body weight, muscle strength, estimated maximal oxygen uptake and calcium intake, the absolute changes in body weight, muscle strength, estimated maximal oxygen uptake, calcium intake, physical, activity, duration of breastfeeding and time from weaning. Only statistical significant variables were kept in the final model.

Relation between Postpartum Depression and Breastfeeding

Background

Postpartum depression is a serious health problem. The prevalence has been estimated at around 13%.[180] It not only affects mother's health, it also affects her ability to care for her infant. Breastfeeding plays a role in affecting an infant's health and in maternal-infant bonding. It is important to understand the nature of the relationship between postpartum depression and the decision to initiate and continue breastfeeding.

Many studies have examined the relationship between breastfeeding and the development of postpartum depression. The results have been quite variable. This may be explained by the lack of a uniform standard in arriving at a diagnosis of postpartum depression. Some studies used questionnaires and some used clinical interviews and different criteria of depression. Many of the studies had relatively small number of subjects. Furthermore, the items commonly used to assess clinical depression like fatigue and sleep problems are to be expected in caring for a newborn. Some of the potential confounders thought to be important in studies of depressive symptoms and feeding practices were marital status, employment status, and whether or not the pregnancy was planned.[181]

Additional Methodological Comments

We screened the abstracts identified from the MEDLINE general search on breastfeeding in November 2005. Abstracts qualifying for full text retrieval included studies on the relationship between breastfeeding and postpartum depression, psychological disorders, psychiatric illnesses, or mental health issues. We also identified additional articles based on reviews of the bibliographies cited in the relevant retrieved studies from the search. We only included studies that had at least 100 nursing mothers. Qualifying study designs included prospective cohort studies and case-control studies. All methods of assessment of depression were included. Only data pertaining to the relationship of breastfeeding and postpartum depression were extracted from the studies.

Results (Table 32)

Prospective cohort. A total of six prospective cohort studies qualified for inclusion.[181-186] There were no case-control studies. The number of women in each study ranged from 113 to 2,375. Three of six studies were rated methodological quality grade B within their respective study design hierarchy and with respect to only the data on the relationship of breastfeeding and postpartum depression. Studies of methodological quality grade C suffered from a combination of incomplete reporting of relevant data, inadequate blinding, lack of or suboptimal adjustment for confounding factors.

Four of six studies did not have specific inclusion criteria based on baseline mental health status. Four studies screened for depression using the Edinburgh Postnatal Depression Scale (EPDS), but the cut off point ranged from 9 to 13 (lowest severity score was zero, highest severity score was 30). Four studies established the diagnosis of depression after clinical interviews. None of the studies provided a clear definition of breastfeeding.

Four prospective cohort studies of moderate methodological quality totaling 4,941 subjects reported postpartum depression rates of 6% to 18%.[181-183,185] In addition to a history of breastfeeding, all of the studies also considered socio-demographic and obstetric variables as independent predictors of postpartum depression. Assessment of depression by self-reported questionnaires or interviews took place from 1 to 12 months after birth. Except for one study,[182] all of them reported that not breastfeeding or early cessation of breastfeeding was associated with postpartum depression. One study reported that onset of postpartum depression occurred before cessation of breastfeeding in most cases.[185] One study reported that depressed mothers were less likely to continue breastfeeding beyond 2 to 4 months compared with mothers who were not depressed.[183] In the one study that reported no significant difference in the development of depression in mothers who breastfed versus those who did not breastfeed, women who were breastfeeding at 1 month and were worried about breastfeeding were significantly more likely to become depressed than those who did not worry (RR 3.0, 95%CI 1.041 - 9.216).[182]

Despite the poor methodological quality of the remaining studies, their findings were also consistent with those from studies of moderate quality. One study reported that high EPDS scorers experienced breastfeeding more negatively than the low EPDS scorers (51% versus 16%, $P < 0.0001$).[186] One study reported that mothers who were depressed were less likely to initiate breastfeeding.[184]

Conclusion

Studies of moderate quality reported an association between not breastfeeding or short duration of breastfeeding and postpartum depression. More investigation will be needed to determine the nature of this association. It is plausible that postpartum depression led to early cessation of breastfeeding, as opposed to breastfeeding altering the risk of depression. Both effects might occur concurrently. Additional factors that may have a bearing on both postpartum depression and the decision to initiate or terminate breastfeeding should also be sought. Moreover, documentation of baseline mental health status before the initiation of breastfeeding and detailed recording of breastfeeding data will improve the quality of the studies and help understand the nature of the association.

Table 32.Summary of the studies on the relationship between breastfeeding and postpartum depression

Author Year Country Population	Study description	Definition of depression	Confounders adjusted for	Comparators	Results	Quality and limitations
Prospective Cohort						
Warner 1996 UK 2,375 Subjects recruited from postnatal wards prior to discharge	Home interview 6-8 wk after delivery; Edinburgh Postnatal Depression Scale (EPDS) was completed at the interview	Screening: high and low scores using an EPDS threshold of 12/13	Socio-demographic and obstetric variables	Examined "not breastfeeding" as one of the factors in logistic analysis	280/2,375 scored >12 on EPDS; not breastfeeding at 6 wk (OR 1.52, 95%CI 1.12-2.06), unplanned pregnancy (OR 1.44), unemployment in mother (OR 1.56) or in head of household (OR 1.50) were associated with an EPDS >12 in a stepwise logistic analysis.	B No detailed information on breastfeeding
Henderson 2003 Australia 1,745 Subjects recruited from postnatal wards; not under psychological care at the time of recruitment	Self-reported questionnaires were completed at 2, 6, and 12 mo after birth; subjects with high EPDS score were offered a diagnostic interview	Screening: EPDS >12. Diagnosis: DSM IV	Demographic, perinatal, and postnatal factors	Examined "early cessation of breastfeeding" in adjusted hazard ratio	18% developed depression in the 12 mo after birth. Early cessation of breastfeeding was found to be associated with postpartum depression (adjusted hazard ratio 1.25, 95% CI 1.03 to 1.52). Onset of postpartum depression occurred before cessation of breastfeeding in most cases.	B No detailed information on breastfeeding

Table 32. Continued

Author Year Country Population	Study description	Definition of depression	Confounders adjusted for	Comparators	Results	Quality and limitations
Chaudron 2001 US 465 Subjects not depressed at 1 month postpartum	Subjects participated in an interview during the 2nd trimester, and at 1 and 4 mo after delivery; both the Diagnostic Interview Schedule (DIS) and Center for Epidemiologic Studies Depression Scale (CES-D) were administered at each interview	DSM-III-R criteria; ≥16 on the CES-D; and/or receiving antidepressants	Age, depression during pregnancy, postpartum thoughts of death and dying, difficulty falling asleep	Breastfeeding vs. not breastfeeding	6% became depressed between 1 and 4 mo; Women who breastfed their infants were not significantly different in their development of depression from women who did not breastfeed. Of those women who were breastfeeding at 1 mo, women who worried about breastfeeding were significantly more likely to become depressed than those who did not worry (P=0.04)	B No detailed information on breastfeeding

Table 32. Continued

Author Year Country	Study description	Definition of depression	Confounders adjusted for	Comparators	Results	Quality and limitations
Cooper 1993 UK 243 at Oxford; 113 at Cambridge No restriction on mental health status prior to enrollment noted	2 separate cohort studies (Oxford and Cambridge) At Cambridge, prospective subjects were screened at 6 wk postpartum using the EPDS. All high scorers (≥13) and other selected participants received full psychiatric assessment between 2 and 3 mo postpartum.	Research Diagnostic Criteria (RDC)	Social class, age, and education	Reported only on "ceased breastfeeding"	At Oxford, 56% of subjects with psychiatric symptoms versus 23% of subjects without psychiatric symptoms had ceased breastfeeding by 8 wk postpartum (P<0.01). In eight, depression preceded cessation of breastfeeding; in two, depression was the subsequent event; and in four, the two events arose contemporaneously. At Cambridge, 56% of subjects with an episode of depression versus 21% of subjects without depression postpartum had ceased breastfeeding by 8 wk (P<0.001). In all cases, the onset of depression preceded the cessation of breastfeeding.	B No detailed information on breastfeeding
Seimyr 2004 Sweden 352 All Swedish speaking pregnant women from six antenatal clinics, with their partners or alone	Administered EPDS at 2 mo before childbirth (I), 2 mo (II) and 12 mo (III) after child birth	Cut-off point of 9/10 on EPDS is used to set the threshold for vulnerability to depression	Did not report actual adjustment, but reported that there was no difference with regards to age, education, parity, and length of marital relationship between low and high-scoring women	Breastfed vs. not breastfed	Fewer high EPDS (I) scorers breastfed compared to the low scorers (82% vs. 94%, P<0.02) Fewer high EPDS (II) scorers breastfed compared to the low scorers (85% vs. 93%, P<0.08) High EPDS scorers experienced breastfeeding more negatively than the women scoring low on EPDS. High EPDS (II) scorers breastfed for a shorter time compared to the low-scoring women (4.6 mo vs. 5.3 mo, P<0.04)	C No adjustment for confounders with respect to breastfeeding

Table 32. Continued

Author Year Country	Study description	Definition of depression	Confounders adjusted for	Comparators	Results	Quality and limitations
Hannah 1992 UK 231 Women who had delivered a live baby	Questionnaires (general questionnaire and EPDS) on 5th day postpartum and repeat EPDS at 6 weeks postpartum	Postpartum depression defined by EPDS ≥ 13 at 6 weeks	Did not report adjustment for breastfeeding, but did report that low mood after a previous delivery was a predictor of post-natal depression	Ever breastfed vs. never breastfed	At 6 wk, 18/26 (69%) women with EPDS ≥ 13 vs. 175/200 (88%) women with EPDS < 13 had ever breastfed.	C No adjustment for confounders with respect to breastfeeding

CES-D, Center for Epidemiological Studies Depression Scale; DIS, Diagnostic Interview Schedule; DSM IV, Diagnostic Statistical Manual; EPDS, Edinburgh Postnatal Depression Scale; RDC, Research Diagnostic Criteria

Relationship between Maternal Breast Cancer and Ovarian Cancer and Breastfeeding

Background

Breast cancer is the second most frequently diagnosed and second most deadly cancer among women.[187] Risk factors associated with increased risk of breast cancer include: family history, nulliparity, early menarche, hormone replacement therapy, obesity, and advanced age. Ovarian cancer ranks seventh in the most frequently diagnosed and fourth in the most deadly cancer among women.[187] Risk factors for ovarian cancers are similar to those of breast cancer. While breast and ovarian cancers are closely associated with parity, women with increased parity also have increased lifetime duration of breastfeeding. Therefore, it would be instructive to examine the relationship of breastfeeding and the risk of developing breast or ovarian cancer.

Breast Cancer

Methods

We identified two meta-analyses and one systematic review that evaluated the relationship between breastfeeding and maternal breast cancer.[188-190] We also identified 23 primary studies published since 2001, the cut-off date for literature search used in the latest meta-analysis. Primary studies were screened based on the same inclusion criteria described in the latest meta-analysis. In addition, we elected to include only primary studies conducted in developed countries. Twenty of the 23 primary studies were excluded for the following reasons: studies published in developing countries (5); studies that did not meet the eligibility criteria (e.g., studies that did not provide data on the following: incident invasive breast cancers, reproductive factors, and use of hormonal preparation) (13); duplicate study (1); and review that was not systematically conducted (1). A total of three studies from developed countries published subsequent to the latest meta-analysis were included in the update.[191-193]

Published Systematic Reviews and/or Meta-Analyses (Table 33)

The most recent meta-analysis published by the Collaborative Group on Hormonal Factors in breast cancer combined 45 studies published through 2001 and two unpublished studies.[189] The meta-analysis evaluated a total of 50,302 parous women with incident invasive breast cancer and 96,973 controls. Included in the meta-analysis were primary studies that analyzed at least 100 cases of incident invasive breast cancers per study regardless of the menopausal status with additional information on reproductive factors and use of hormonal preparations. Both cohort and case-control studies from developed and developing countries were included. Individual subject data from the primary studies were analyzed for homogeneity across study definitions. The majority of the primary studies did not differentiate between exclusive and partial breastfeeding, and some studies varied in the definition of “ever breastfeeding”. The average age at diagnosis of breast cancer in the studies was 50 years. There was a higher proportion of women with either nulliparity or low parity in the breast cancer group compared with the control group. In addition, lower number of the parous women in the breast cancer group had ever

breastfed their infants compared with the control group. There was a statistically significant reduction in risk of breast cancer by 4.3% (95% CI 2.9-5.8) for each year of breastfeeding. The reduction in the risk of breast cancer with breastfeeding remained unaltered even after stratification for potential confounders such as parity, number of children breastfed, menopausal status, and lifetime duration of breastfeeding. The results were also adjusted for ethnic origin, education, family history of breast cancer, age at menarche, height, weight, body mass index, and use of hormonal contraceptives, alcohol, and tobacco. Decrease in the relative risk of breast cancer associated with each year of breastfeeding remained homogeneous across the studies with regards to developed versus developing countries, age at diagnosis, menopausal status, family history of breast cancer, and study designs. In addition, the decrease in relative risk of breast cancer in parous women, according to breastfeeding history (ever versus never) and number of births, was more pronounced after four or more births. The methodological quality of the meta-analysis was rated grade A.

In the meta-analysis by Bernier 2000 evaluated the relationship of breastfeeding with histologically diagnosed breast cancer in parous women.[188] The meta-analysis combined 25,871 cases and 44,910 controls from 23 primary case-control studies. Criteria for inclusion are studies from developed and developing countries published in English or French languages between 1980 and 1998 that provided usable data for the calculation of odds ratio of breastfeeding and breast cancer risk. The meta-analysis used both fixed and random effects model. There was a small, but statistically significant decreased risk of breast cancer in women who had breastfed their infants compared with women who had not. The decreased risk was further explored by examining the menopausal status at the time of diagnosis of breast cancer and the duration of breastfeeding. Women who were pre-menopausal at the time of diagnosis of breast cancer had a small but statistically significant decreased risk of breast cancer compared with menopausal women. The duration of breastfeeding was divided into categories of 1 to 6 months, 7 to 12 months, and more than 12 months. When these categories of breastfeeding were compared with non-breastfeeding, only those whose lifetime duration of breastfeeding was longer than 12 months (compared to never) had a small but statistically significant reduction in the risk of breast cancer in subgroup analysis. The authors reported that there was no “publication bias”. The methodological quality of the meta-analysis was rated grade B.

Another systematic review included all English language studies published through 1998 and enrolled at least 200 women with breast cancer.[190] In addition, only studies that explicitly adjusted for the number of full-term pregnancies and age at first birth were included. The data included 19,482 cases and 37,627 controls from 24 case-control studies, and 3,857 cases identified from three longitudinal followup studies that comprised of 229,574 subjects. The case-control studies were conducted in hospital- or population-based settings. Studies conducted in developed and developing countries were included. Based on qualitative appraisal, the authors concluded that either there was no relationship between breastfeeding and the risk of development of breast cancer or there was a weak protective effect of ever breastfeeding against the development of breast cancer. The authors did report some reduction in the risk of development of breast cancer in premenopausal women who had breastfed their infants for long duration. The methodological quality of the systematic review was rated grade B.

Studies Published after the Systematic Reviews/Meta-Analyses (Table 34)

We identified three eligible studies from developed countries that were published subsequent to the latest meta-analysis.[191-193] One study was multi-center;[192] the remainders were single center.[191,193] One study was a prospective cohort of Korean women and evaluated only premenopausal women.[193] The other two were case-control studies; one evaluated the relationship between breast cancer and breastfeeding among carriers of deleterious BRCA1 and BRCA2 mutations,[192] the other evaluated incident invasive breast cancer patients.[191] Two studies included only women whose mean age at diagnosis of breast cancer was in the premenopausal range.[192,193] All studies reported a statistically significant reduced risk or odds of breast cancer with increased duration of breastfeeding, which varied across the studies. The duration of breastfeeding ranged from 12 to 24 or more months. The methodological quality of the studies ranged from grade B to C.

Conclusion

Results from both meta-analyses concluded that there was a reduction in the risk of breast cancer in women who breastfed their infants. No studies evaluated exclusive breastfeeding. Studies also reported decreased risk or odds of breast cancer in women with a lifetime breastfeeding of more than 12 months. Neither one of the meta-analyses detected any publication bias. In addition, one of the meta-analyses and the systematic review reported decreased odds of breast cancer primarily in premenopausal women. Findings from primary studies published subsequent to the meta-analyses concurred with the findings from the meta-analyses. In conclusion, there is evidence to support the observation that breastfeeding is associated with a reduction in the risk of breast cancer.

Table 33. Summary of systematic reviews/meta-analyses on the relationship between breastfeeding and the risk of breast cancer

Author Year	Number of subjects	Study description	Population	Confounders considered	Intervention /Comparator	Results	Quality for SR/MA
Collaborative Group on Hormonal Factors in Breast Cancer 2002	50,302 cases 96,973 controls	MA of cohort and case-control studies	Incident invasive breast cancer	Ethnic origin, education, family history of breast cancer, age at menarche, height, weight, body mass index, and use of hormonal contraceptives, alcohol, and tobacco	Per 12 mo of breastfeeding	RR reduction of breast cancer 4.3% (99% SE 0.8)	A
					Breastfeeding ever / never	Adjusted RR 0.96 (99% SE 0.2, p=.04)	
					Increasing duration of breastfeeding	Adjusted RR 0.38 (99% SE 0.01, p<.0001)	
Bernier 2000	25,871 cases 44,910 controls	MA of case-control studies	Parous women with histologically diagnosed breast cancer	Age at diagnosis or at full term pregnancy, parity, ethnicity, age at menarche, family history of breast cancer, parity	Breastfeeding ever / never	Summary OR 0.84 (0.78-0.91	B
					Breastfeeding ever versus never and menopausal at the time of breast cancer diagnosis	Summary OR 0.84 (0.69-1.03)	
					Breastfeeding ever versus never and non menopausal at the time of breast cancer diagnosis	Summary OR 0.81 (0.72-0.91)	
					Breast feeding 0+ to 6 mo versus never	Summary OR 1.00 (0.86-1.16)	
					6+ to 12 mo v never	Summary OR 0.97 (0.86-1.09)	
					12+ mo v never	Summary OR 0.72 (0.65-0.80)	
Lipworth 2000	19,482 cases 37,627 controls	SR of case-control studies	Premenopausal women with breast cancer	Yes, descriptive summary	Breastfeeding ever / never	*Qualitative review* Author's conclusion "Evidence supporting protective factor of breastfeeding for breast cancer is limited and should be interpreted with caution."	B

MA, meta-analyses; SR, systematic review; RR, relative risk; OR, odds ratio; SE, standard error; NA, not applicable

Table 34. Summary of case-control studies on the relationship between breastfeeding and breast cancer

Author, year Country	Cases (N)	Controls (N)	Definition of disease	Age at diagnosis of disease (year)	Breastfeeding group	Comparator group	Confounders adjusted	Adjusted odds ratio (95% CI)	Quality
Lee 2003[a] Korea	149		Incident	33-44	1-12 mo	Never (N=161)	Age, oral contraceptives, parity, smoking, exercise and obesity	0.8 (0.7, 1.0) NS	A
	32				13-24 mo			0.7 (0.5, 1.1) NS	
	18				>24 mo			0.6 (0.3, 1.0) P=.04	
Jernstrom 2004 Multi-center	685	685	Invasive BRCA1	39	≤1 yr	Never	Oral contraceptive use and parity	0.89 (0.68, 1.17) NS	B
					>1 yr			0.55 (0.38, 0.80) P=.001	
	280	280	Invasive BRCA2	39	≤1 yr	Never		1.12 (0.73, 1.71) NS	
					>1 yr			0.95 (0.56, 1.59) NS	
Gammon 002 USA	1,508	1,556	Incident; invasive and in-situ	<35 to 85+	<2 mo	Never	Age	0.95 (0.72, 1.24)	C
					2-5 mo			0.82 (0.62, 1.09)	
					6-13 mo			1.06 (0.82, 1.36)	
					14+ mo			0.70 (0.54, 0.92)	

[a] Prospective cohort study; Relative risk

Ovarian Cancer

Methods

No meta-analysis was identified on this topic. Eligible designs included prospective cohorts, case-cohort studies or nested case-control studies. Cross-sectional studies were excluded, as described in the Methods section. Eligible studies were conducted in developed countries. We quantified the association between breastfeeding and any type of histopathologically defined maternal ovarian cancer. No specific exclusion criteria were used for the participants in the primary studies.

We recorded or estimated odds ratios for the association between breastfeeding and ovarian cancer for the following comparisons: women who ever breastfed versus never breastfed; women who breastfed less than 12 months (cumulative duration) versus those who never breastfed; and women who breastfed at least 12 months (cumulative duration) versus never. The 12-months cutoff was arbitrary, and was chosen for symmetry with analyses on maternal breast cancer outcomes. At a minimum, studies that were included in the meta-analyses must have been adjusted for parity (or used matching for parity). Adjustment for the use of oral contraceptives (or appropriate matching) was desirable but not mandatory. Studies that reported unadjusted effects only were not included in the meta-analyses, but are reported in the tables and text.

For each study, we estimated the odds ratios for the comparisons of interest when they were not directly reported. This was done for studies that analyzed breastfeeding as an ordinal categorical predictor using cutoffs other than 12 months, provided that mothers who never breastfed were the reference category. In such studies, the odds ratios for the comparisons of interest were estimated by combining odds ratios for different durations of breastfeeding using a random effects model. For example, Riman 2002[194] did not report the odds ratio of ever versus never breastfeeding, but reported odds ratios for specific durations of breastfeeding versus never breastfeeding. Compared with women who never breastfed, the adjusted odds ratio in the Riman study for 1 to 5 months of cumulative breastfeeding was 0.99 (95%CI 0.64 -1.52); for 6 to 11 months, it was 0.77 (95%CI 0.50 - 1.19) and for at least 12 months of cumulative breastfeeding, it was 0.87 (95%CI 0.56 - 1.35). We can estimate the odds ratio of ever versus never breastfeeding in the Riman 2002 study with a random effects meta-analysis of the aforementioned duration-specific odds ratios (estimated adjusted odds ratio was 0.87, 95%CI 0.68 - 1.12).

Results (Tables 35-38)

We did not identify any prospective studies. We found 15 eligible case-control studies that examined the relationship between breastfeeding and maternal ovarian cancer.[194-210] In addition, we identified three studies that conducted secondary analyses on population subgroups including white, black, and Jewish women by pooling data from case-control studies.[211-213] Population-based controls were used in nine of the 15 studies and hospital-based controls were used in the remaining six. A total of 6,006 subjects with ovarian cancer were studied. The smallest sample included 76 subjects with ovarian cancer matched with 76 hospital-based controls,[208] and the largest included 1,028 subjects matched with 2,390 hospital-based controls.[195]

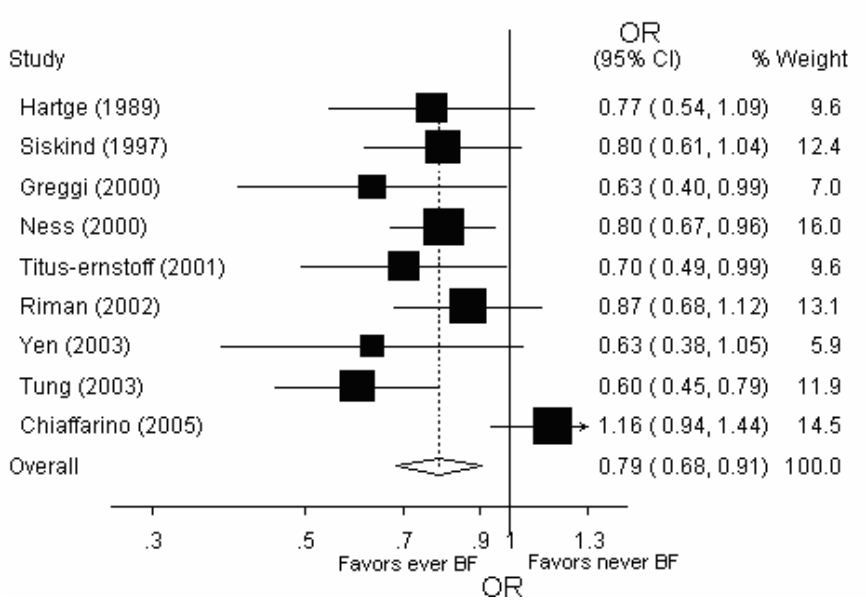
Data were gathered from interviewers using structured questionnaires, and therefore outcome assessment was not blinded. Participant's age ranged from 17 to 79 years. The reporting of information on breastfeeding duration generally did not distinguish between exclusive or partial breastfeeding. Terms commonly used were breastfeeding, lactation, and in one instance, nursing. In 13 out of 15 case-control studies the outcome was histologically confirmed epithelial ovarian cancer. All protocols included women regardless of menopausal status, except for one study that examined peri- and postmenopausal women, and another restricted to women under age 55 years.[194,198] One primary study included white women only.[202] None of the studies verified details of the breastfeeding history by objective data such as hospital or clinic records. Finally, there was wide variability in how breastfeeding duration was categorized in the various studies (Table 35). Because of potential recall bias of breastfeeding history, lack of data verification, and lack of blinding, the majority of the case control studies (n=11) was rated methodological grade B. The remaining four case-control studies were rated grade C. All studies adjusted for parity, and all but one study also adjusted for oral contraceptive use.

Meta-analyses

Ever breastfed versus never breastfed. Nine studies with a total of 4,387 cases and 10,574 controls were included in the comparison of ever versus never breastfeeding **(**Figure 12**).** The random effects meta-analysis found an association between breastfeeding and reduced ovarian cancer risk (OR_{adj} 0.79, 95%CI 0.68 – 0.91).[194,195,197,199-201,204-206,210] There was a statistically significant between-study heterogeneity (P=0.02), which was mainly due to the outlying study of Chiaffarino 2005. Excluding the study yielded very similar estimates without a statistically significant heterogeneity.

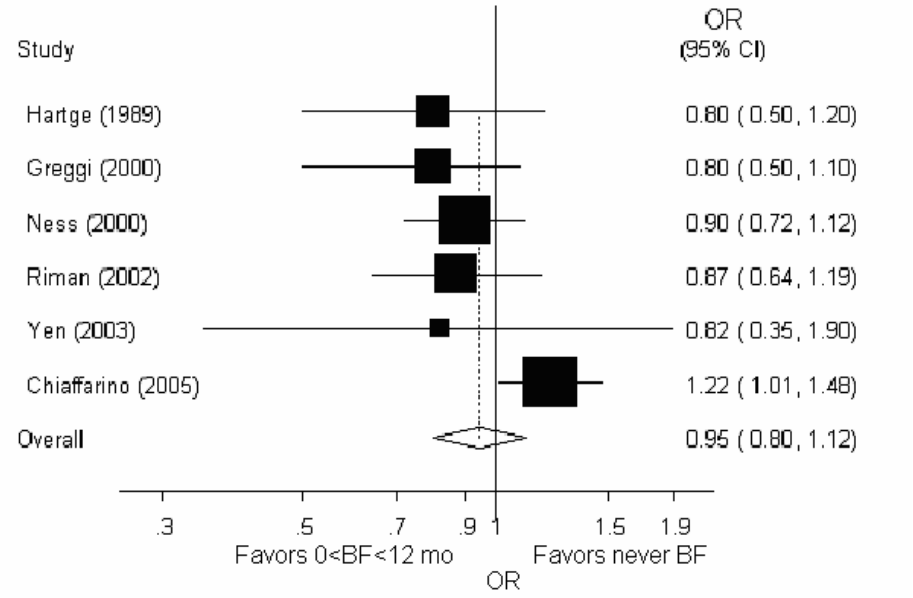
For five of the nine studies we, estimated the odds ratio of ever versus never breastfeeding.[194,197,199-201,210] If we exclude these five studies from the meta-analysis, a total of 2,582 cases and 4,138 controls remained; and the association between breastfeeding and reduced ovarian cancer risk was no longer statistically significant (OR_{adj} 0.80, 95%CI 0.59 – 1.09)[195,204-206] Again, there was a statistically significant heterogeneity among the four remaining studies ($p<0.01$), but the heterogeneity was not readily explained by the characteristics of the primary studies. Excluding the study by Chiaffarino 2005,[195], which was an obvious outlier, the summary odds ratio suggested a slightly stronger (and formally statistically significant) association (0.70 [95%CI, 0.59-0.83]).

Figure 12. Meta-Analysis of case-control studies on the relationship between breastfeeding and maternal ovarian cancer risk: ever breastfed versus never breastfed.



Less than 12 months of cumulative breastfeeding versus never breastfed. Cumulative breastfeeding for less than 12 months was not statistically significantly associated with a decreased risk of ovarian cancer in a meta-analysis of six studies, including 1,911 cases and 5,007 controls in total (OR_{adj} 0.95; 95%CI: 0.80 – 1.12). (Figure 13) The odds ratios for this comparison were estimated for three of the six studies.[194,195,200,201] There was no statistically significant heterogeneity between the six studies. Two studies (Chiaffarino 2005[195] and Hartge 1989[199]) were included in this meta-analysis despite the fact that they used as cutoffs shorter cumulative duration of breastfeeding (10 and 9 months, respectively). Excluding them, the summary of the adjusted odds ratio remained statistically non-significant (0.87, 95%CI 0.74 - 1.02).

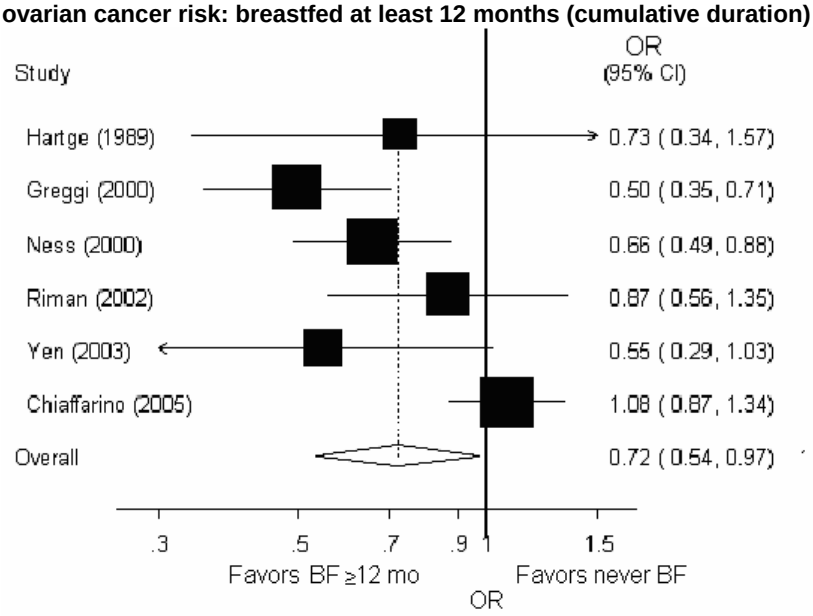
Figure 13. Meta-Analysis of case-control studies on the relationship between breastfeeding and maternal ovarian cancer risk: breastfed less than 12 months (cumulative duration) versus never breastfed



Two studies (Chiaffarino 2005[195] and Hartge 1989[199]) were included in this meta-analysis despite the fact that they used as cutoffs shorter cumulative different than 12 months (10 and 9 months, respectively). A sensitivity analysis that excluded them yielded similar inferences (summary of adjusted odds ratios 0.87 [95%CI 0.74, 1.02]).

At least 12 months of cumulative breastfeeding versus never breastfed. Six studies including 1,650 cases and 4,575 controls provided adjusted odds ratios for this comparison,[194,197,210] or allowed an approximation.[195,199-201] (Figure 14) Breastfeeding of at least 12 months cumulative duration was associated with 28% lower odds for ovarian cancer (OR_{adj} 0.72, 95%CI 0.54 – 0.97). There was a statistically significant heterogeneity across the six studies. Two studies (Chiaffarino 2005[195] and Hartge 1989[199]) were included in this meta-analysis despite the fact that they used as cutoffs shorter cumulative duration of breastfeeding (10 and 9 months, respectively). Excluding them, the summary adjusted odds ratio was even more suggestive of a protective association (0.63 [95%CI 0.50, 0.79]).

Figure 14. Meta-Analysis of case-control studies on the relationship between breastfeeding and maternal ovarian cancer risk: breastfed at least 12 months (cumulative duration) versus never breastfed.



Two studies (Chiaffarino 2005[195] and Hartge 1989[199]) were included in this meta-analysis despite the fact that they used as cutoffs shorter cumulative different than 12 months (10 and 9 months, respectively). A sensitivity analysis that excluded them yielded similar inferences (summary of adjusted odds ratios 0.63 [95%CI 0.50, 0.79]).

Subgroup analyses and additional results

Pre- versus post-menopausal women (Table 36). Three studies reported on the risk of ovarian cancer stratified by menopausal status. There were sporadic statistically significant associations between specific categories of breastfeeding duration and reduced risk for ovarian cancer in Sikind 1997[204] and Tung 2005.[207] Tung 2005 reported a significant dose-response trend between increasing breastfeeding duration and reduction in maternal ovarian cancer risk for post-menopausal women (P value for trend = 0.003). No statistically significant dose-response trends were found in the postmenopausal stratum of Tung 2005 and in both strata in the other two studies. Wynder 1969 reported that in premenopausal women, 10 percent of the cases versus seven percent of the controls breastfed for 12 months or more;[209] for postmenopausal women, 24 percent of the cases versus 21 percent of the controls breastfed for 12 months or more. No statistical comparison was reported.

Risk by histologic type (Table 37). Five studies reported the relationship between breastfeeding and the risk of ovarian cancer subgrouped by tumor histology.[194,195,201,205-207] Comparisons between tumor types included mucinous versus nonmucinous, and invasive versus borderline tumors. Data were limited to allow robust conclusions per histologic type. Moreover, these analyses were subgroup analyses, and therefore, should be viewed as hypothesis forming observations and be interpreted conservatively.

Sporadic associations between specific durations or breastfeeding and reduced risk for histological subtypes were reported in all studies except for Chiaffarino 2005. Breastfeeding was not protective for mucinous or serous cancers consistently across the five studies. Increased duration of breastfeeding was associated with reduced risk for non-mucinous cancers in Tung 2003 (P for trend < 0.001). Titus-Ernstoff 2001 reported an association of breastfeeding with reduced risk for combined endometrioid and clear cell carcinomas, and Riman 2002 reported an

association with reduced risk for clear cell ovarian cancer for a specific duration of cumulative breastfeeding (5 months).

Pooled analysis of subgroups (Table 38). Secondary subgroup analyses were conducted on different racial groups in three studies. John 1993 studied 53 cases of ovarian cancer in black women using data from seven case-control studies,[211] whereas Whittemore 1992 examined data of white women from the same studies and added the cases from five additional studies for a combined population of 1,071 cases. Ever having breastfed was not associated with the risk of development of ovarian cancer in black women but was reported to reduce the risk for white women. Whittemore 1992 divided the sample into hospital and population subjects, the odds ratio for those who breastfed their infants compared with those who did not in the development of ovarian cancer were 0.73 (95%CI 0.51-1.0) and 0.81 (95%CI 0.68-0.95), respectively.[212] Modugno 2003 analyzed 242 Jewish women from five studies conducted in Israel and the United States.[213] This was a cohort study comparing carriers and noncarriers of BRCA1 or BRCA2. The study did not find a difference between carriers and noncarriers of BRCA1 or BRCA2 mutation in the breastfeeding status or breastfeeding duration and the risk of ovarian cancer.

Conclusion

We reviewed 15 case-control studies that examined the relationship between breastfeeding and the risk of ovarian cancer, and performed quantitative syntheses using data from nine studies that adjusted for potential confounders. The overall result from the nine studies suggests an association between breastfeeding and a reduction in the risk of ovarian cancer. Because the reporting in these studies was inconsistent, we needed to estimate the odds ratios in five of nine studies for the meta-analysis. Excluding these five studies results in loss of statistical significance for this association.

There was indirect evidence for a dose-response relationship between breastfeeding and a reduction in the risk of ovarian cancer. Breastfeeding of less than 12 months (cumulative duration) was not statistically significantly associated with a reduction in the risk of ovarian cancer in a meta-analysis of six studies. However, breastfeeding of more than 12 months (cumulative duration) was associated with a reduction in the risk of ovarian cancer, compared with never breastfeeding. We caution that the cutoff of 12 months was arbitrary, and the odds ratios were estimated in half of these studies. Therefore, the interpretation of the postulated dose-response relationship should be done with caution.

Finally, several studies assessed subgroups of pre- and post-menopausal women and ovarian cancer histology. Overall, few sporadic statistically significant associations were identified in some subgroups and for some specific durations of breastfeeding. These findings do not constitute robust evidence.

We conclude that there is some evidence to suggest an association between breastfeeding and a reduction in the risk of maternal ovarian cancer. However, one must be cautious in interpreting this association because it was largely based on estimations of the odds ratios from retrospective studies.

Table 35. Summary of case-control studies on the relationship between breastfeeding and maternal ovarian cancer

Author Year Country	Cases (N)	Controls (N)	Definition of disease	Mean / median age at dx of disease (year)	Breastfeeding group	Comparator group	Confounders adjusted	Adjusted odds ratio (95% CI)	Quality
Chiaffarino 2005 Italy	1,028	2,390	Epithelial ovarian cancer based on histology	56[a]	Ever BF	Never BF	Age, center, education, parity, oral contraceptive use, family history of ovarian/breast cancer in first degree relatives	1.16 (0.93-1.43)	B
					BF 1-4 mo	Never BF		1.20 (0.91-1.59)	
					BF 5-8 mo			1.24 (0.95-1.62)	
					BF 9-16 mo			1.01 (0.77-1.33)	
					BF ≥17 mo			1.21 (0.85-1.71)	
Riman 2002 Sweden	655	3899	Epithelial ovarian cancer based on histology	Cases 62 Controls 63	BF 1-5 mo	BF <1 mo	Age, BMI, parity, age at menopause, duration of oral contraceptive use, HRT use	0.99 (0.64-1.52)	B
					BF 6-11 mo			0.77 (0.50-1.19)	
					BF ≥12 mo			0.87 (0.56-1.35)	
Siskind 1997 Australia	618	724	Epithelial ovarian cancer based on histology	Cases 57 Controls 56	Ever BF	Never BF	Age, parity, age at 1st birth, education, oral contraceptive use, smoking history, menopausal status	0.80 (0.61-1.04)	B
					BF 1-6 mo			0.89 (0.65-1.2)	
					BF 7-12 mo			0.68 (0.49-0.94)	
					BF 13-24 mo			0.84 (0.59-1.2)	
					BF 25-36 mo			0.69 (0.38-1.3)	
					> 36 mo			0.77 (0.34-1.8)	
					Reduction risk per month BF			0.99 (0.97-1.0)	

Table 35. Continued

Author Year Country	Cases (N)	Controls (N)	Definition of disease	Mean / median age at dx of disease (year)	Breastfeeding group	Comparator group	Confounders adjusted	Adjusted odds ratio (95% CI)	Quality
Tung 2003; 2005 USA	558	607	Epithelial ovarian cancer based on histology	Cases Mucinous 50 Nonmucinous 55 Controls 56	Ever BF	Never BF	Age, ethnicity, study site, education, oral contraceptive use, tubal ligation	0.6 (0.4-0.7)	B
					BF ≤5 mo			0.6 (0.4-0.9)	
					BF 6-16 mo			0.6 (0.4-0.9)	
					BF >16 mo			0.6 (0.4-0.8)	
Ness 2000 Modugno 2001 USA	531	1190	Epithelial ovarian cancer based on histology	Cases Invasive 53 Borderline 45 Controls 49	BF 1-5 mo	Never BF	Age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy, breastfeeding	0.9 (0.7-1.2)	B
					BF 6-11 mo			0.9 (0.6-1.3)	
					BF 12-23 mo			0.7 (0.5-1.1)	
					BF ≥24 mo			0.6 (0.4-1.0)	
Risch 1994 Canada	450	564	Epithelial ovarian cancer based on histology	Cases 57 Controls 58	Total duration BF of cases (0.51 yr)	Total duration of controls (0.65 yr)	Regression adjusted for 3 age groups, continuous variables age, total duration of oral contraceptive use	0.89 (0.75-1.05)	B
					BF duration/ pregnancy of cases (2.24 mo)	BF duration/ pregnancy of controls (2.72 mo)		0.87 (0.76-0.99	

Table 35. Continued

Author Year Country	Cases (N)	Controls (N)	Definition of disease	Mean or median age at dx of disease (year)	Breastfeeding group	Comparator group	Confounders adjusted	Adjusted odds ratio (95% CI)	Quality
Gwinn 1990 USA	436	3833	Epithelial ovarian cancer based on histology	20-54		Never BF	Pregnancy, oral contraceptive use, age, and age-pregnancy interaction	Relative risk	B
					Ever BF			0.6 (0.5-0.8)	
					BF 1-2 mo			0.6 (0.5-0.9)	
					BF 3-5 mo			0.8	
					BF 6-11 mo			0.8	
					BF 12-23 mo			0.7	
					BF ≥24 mo			0.3	
Titus-Ernstoff 2001 USA	378	417	Epithelial ovarian cancer based on pathology or slides	Cases 20-74 Controls matched within 4 years	Ever BF	Never BF	Age, state, parity	0.7 (0.5-1.0)	B
					BF <3 mo			0.9 (0.6-1.4)	
					BF 3-6 mo			0.7 0.5-1.1)	
					BF >6 mo			0.7 (0.4-1.0)	
					2.4% Reduction risk per month BF				
Greggi 2000 Italy	330	721	Ovarian cancer based on histology	54	BF ≤12 mo	Never BF	Age, education, parity, oral contraceptive use, family history of ovarian cancer	0.8 (1.0-1.1)	B
					BF >12 mo			0.5 (0.4-0.8)	
Hartge 1989 USA	203	257	Epithelial ovarian cancer based on histology	Cases 54 Controls 55		Never BF	Age, race, parity, difficulty conceiving, oral contraceptives, surgical menopause, HRT, or family history of ovarian cancer as needed	Rate ratio	B
					BF 1-9 mo			0.8 (0.5-1.2)	
					BF 10-18 mo			0.5 (0.2-0.9)	
					BF 19-110 mo			1.1 (0.5-2.6)	

Table 35. Continued

Author Year Country	Cases (N)	Controls (N)	Definition of disease	Mean or median age at dx of disease (year)	Breastfeeding group	Comparator group	Confounders adjusted	Adjusted odds ratio (95% CI)	Quality
Yen 2003 Taiwan	86	369H	Epithelial ovarian cancer based on histology	Cases 47 Controls 44	BF ≤1 yr BF >1 yr	Never BF	Parity	0.82 (0.35-1.9) 0.55 (0.29-1.01)	B
Risch 1983 USA	284	705P	Malignant & borderline malignant epithelial ovarian cancer	Cases 20-74 Controls 21-75	BF ≥3 mo	BF <3 mo[b]	Age at diagnosis 20-44, nulliparous, no miscarriages, < 1 year total exposure to combined oral contraceptives, non-obese	Relative risk 0.69 (0.50-0.96)	C
Cramer 1983 USA	215	215P	Epithelial ovarian cancer	53	Ever BF	Never BF	None	Crude relative risk 1.11 (0.70-1.76)	C
Wynder 1969 USA	158	300H	Epithelial ovarian cancer based on histology	Cases 52 Control ND	No difference between groups for never BF	---	ND	---	C
West 1966 USA	76	76H	Malignant ovarian cancer based on pathology	Cases 53 Controls 50	Cases (6.6 mo) Controls (5.8 mo) p > 0.3	---	None	---	C

Dx, diagnosis; BF, breastfeeding; Mo, month(s); Yr, year(s)

[a] Chiaffarino -dx within past year, Risch –dx within past 18 months
[b] Nulliparous and parous women

Table 36. Summary of case-control studies on the relationship between breastfeeding and maternal ovarian cancer by menopausal status

Author Year Country	Cases (N)	Controls (N)	Definition of disease	Mean or median age at dx of disease (year)	Breastfeeding group	Comparator group	Confounders adjusted	OR_{adj} (95% CI)	p for trend	Quality
Tung 2003; 2005 USA	Pre-menopausal 217	Pre-menopausal 256	Epithelial ovarian cancer based on histology	Cases 55 Controls 55	BF ≤6 mo	Never BF	Age, ethnicity, study site, education, tubal ligation, HRT, ovulation	0.96 (0.49-1.85)	0.003	B
					BF 6-12 mo			0.81 (0.43-1.54)		
					BF >12 mo			0.46 (0.22-0.97)		
	Post-menopausal 341	Post-menopausal 351			BF ≤6 mo	Never BF		0.64 (0.41-1.02)	0.08	
					BF 6-12 mo			0.60 (0.36-1.00)		
					BF >12 mo			0.69 (0.43-1.12)		
Siskind 1997 Australia	Pre-menopausal 215	Pre-menopausal 264	Epithelial ovarian cancer based on histology	Cases 58 Controls 57	BF 1-6 mo	Never BF	Age, parity, age at 1st birth, education, oral contraceptive use, smoking history, menopausal status	0.75 (0.46-1.21)	ND	B
					BF 7-12 mo			0.53 (0.31-0.94)		
					BF 13-24 mo			1.03 (0.54-1.95)		
					BF >24 mo			0.29 (0.08-1.04)		
	Post-menopausal 403	Post-menopausal 460			BF 1-6 mo	Never BF		0.98 (0.65-1.47)	ND	
					BF 7-12 mo			0.83 (0.54-1.26)		
					BF 13-24 mo			0.88 (0.56-1.38)		
					BF 25-36 mo			0.93 (0.46-1.88)		
					BF >36 mo			1.27 (0.50-3.2)		
Wynder 1969 USA	Pre-menopausal 55	Pre-menopausal 95	Epithelial ovarian cancer based on histology	Cases 52 Control ND	BF >12 mo 9% Cases 7% Controls	---	ND	---	---	C
	Post-menopausal 95	Post-menopausal 205			BF >12 mo 24% Cases 21% Controls					

Dx, diagnosis; BF, breastfeeding; Mo, month(s); Yr, year(s)

Table 37. Summary of case-control studies on the relationship between breastfeeding and maternal ovarian cancer by histologic type

Author Year Country	Cases (N)	Controls (N)	Mean age at dx of disease (year)	Histologic type (n)	Breastfeeding group	Comparator group	Confounders adjusted	Adjusted odds ratio (95% CI)	p for trend	Quality
Chiaffarino 2005 Italy	1028	2390	Cases 56 Controls 57	Serous (492)	Ever BF	Never BF	Age, center, education, parity, oral contraceptive use, family hx of ovarian/ breast cancer in 1° relatives	1.1 (0.85-1.48)	0.71	B
				Mucinous (81)				1.59 (0.82-3.07)	ND	
Titus-Ernstoff 2001 USA	528	523	Cases 20-74 Controls matched within 4 years	Serous borderline (86)	Ever BF	Never BF	Age, state, parity	0.8 (0.4-1.6)	0.61	B
				Serous invasive (229)				1.0 (0.6-1.4)	0.34	
				Mucinous (83)				0.6 (0.3-1.2)	0.88	
				Endometrioid/clear cell (130)				0.4 (0.2-0.7)	0.04	
Tung 2003 USA	558	607	Cases Mucinous 50 Nonmucinous 55 Controls 56	Mucinous (109)	Ever BF BF ≤5 mo BF 6-16 mo BF >16 mo	Never BF	Age, ethnicity, study site, education, oral contraceptive use, tubal ligation	0.8 (0.5-1.4) 0.6 (0.4-1.4) 0.7 (0.3-1.3) 0.9 (0.8-1.8)	0.99	B
				Nonmucinous (449)	Ever BF BF ≤5 mo BF 6-16 mo BF >16 mo	Never BF		0.8 (0.5-1.4) 0.7 (0.4-0.9) 0.5 (0.3-0.7) 0.4 (0.3-0.7)	0.0005	
Ness 2000 Modugno 2001 USA	531	1,190	Cases Invasive 53 Borderline 45 Controls 49	Borderline Serous (79) Mucinous (60)	Months BF		Age, number of live births, years of oral contraceptive use, years of non-contraceptive estrogen use and months breastfed, tubal ligation, hysterectomy, family history of ovarian and breast cancer, ethnicity	0.95* (0.92-1.00) 0.99 (0.96-1.02)	ND	B
				Invasive Serous (278) Mucinous (52) Endometrioid (136) Other (150)	Months BF			1.00 (0.99-1.01) 1.01 (0.98-1.03) 0.98 (0.95-1.00) 0.97* (0.94-1.00)	ND	

Table 37. Continued

Author Year Country	Cases (N)	Controls (N)	Mean age at dx of disease (year)	Histologic type (n)	Breastfeeding group	Comparator group	Confounders adjusted	Adjusted odds ratio (95% CI)	p for trend	Quality
Riman 2002 Sweden	655	3,899	Cases 62 Controls 63	Invasive Serous (240)	BF 1-5 mo BF 6-11 mo BF ≥12 mo	BF <1 mo	Age, BMI, parity, age at menopause, duration of oral contraceptive use, HRT use	0.87 (0.50-1.53) 0.61 (0.35-1.09) 0.87 (0.49-1.54)	ND	B
				Mucinous (44)	BF 1-5 mo BF 6-11 mo BF ≥12 mo	BF <1 mo		2.19 (0.49-9.87) 1.75 (0.39-7.87) 0.83 (0.17-4.14)	ND	
				Endometrioid (126)	BF 1-5 mo BF 6-11 mo BF ≥12 mo	BF <1 mo		1.05 (0.47-2.34) 1.10 (0.50-2.46) 1.02 (0.44-2.37)	ND	
				Clear cell (25)	BF 1-5 mo BF 6-11 mo BF ≥12 mo	BF <1 mo		0.54 (0.16-1.87) 0.23 (0.06-0.88) 0.24 (0.06-0.97)	ND	

* $p<0.05$

Table 38. Summary of pooled-analysis of case-control studies on the relationship between breastfeeding and ovarian cancer by population subgroups

Author Year Country	Population characteristic	Cases (N)	Controls (N)	Definition of disease	Mean age at dx of disease (year)	Breastfeeding group	Comparator group	Confounders adjusted	Adjusted odds ratio (95% CI)	Quality
Whittemore[a] 1992 USA	White	201	1,081	Epithelial ovarian cancer	ND	Ever BF	Never BF	Age, study, parity, oral contraceptive use	0.73 (0.51-1.0)	B
						BF 1-5 mo			0.95 (0.62-1.5)	
						BF 6-11 mo			0.40 (0.20-0.78)	
						BF 12-23 mo			0.70 (0.36-1.4)	
						BF ≥24 mo			0.59 (0.22-1.6)	
		870	4,624			Ever BF	Never BF		0.81 (0.68-0.95)	
						BF 1-5 mo			0.87 (0.72-1.1)	
						BF 6-11 mo			0.74 (0.57-0.96)	
						BF 12-23 mo			0.69 (0.51-0.94)	
						BF ≥24 mo			0.74 (0.49-1.1)	
John[b] 1993 USA	Black	53	259	Epithelial ovarian cancer	Cases Invasive 53 Borderline 37 Controls ND	Ever BF	Never BF	Study, birth year, reference age, parity	0.90 (0.42-1.9)	B
						BF 1-5 mo			1.0 (0.39-2.6)	
						≥6 mo			0.85 (0.36-2.0)	
Modugno[c] 2003 USA, Israel	Jewish	95	147	Epithelial ovarian cancer	Cases BRCA1 51 BRCA2 61 Controls BRCA- 58	BRCA1 Ever BF	BRCA-	Age at diagnosis, year of birth, number of live births, oral contraceptive use, history of tubal ligation	1.36 (0.68-2.73)	B
						Duration BF			1.01 (0.98-1.04)	
						BRCA2 Ever BF	BRCA-		0.70 (0.28-1.72)	
						Duration BF			1.02 (0.99-1.05)	
						BRCA1/2 Ever BF	BRCA-		1.09 (0.61-1.97)	
						Duration BF			1.02 (0.99-1.04)	

H-hospital or clinic controls; P, population controls

[a] Sample also included Cramer 1983 and Hartge 1989; [b] Sample also included Ness 2000.

[c] Cases defined as Jewish women with ovarian cancer and BRCA1 or BRCA2 mutation, controls defined as ovarian cancer cases only.

Other Research

An important area of research that is not systematically reviewed in this report is the use of breastfeeding promotion intervention trial to measure health effects (this topic will be covered in a separate report). The best known of these types of studies is the Promotion of Breastfeeding Intervention Trial (PROBIT) conducted in the Republic of Belarus.[17] This was a cluster randomized controlled trial of 34 maternal hospitals and associated polyclinics with a total of 17,046 mother-infant pairs consisting of full term infants and their healthy mothers who intended to breastfeed. The experimental intervention was modeled on the Baby-Friendly Initiative of the World Health Organization and United Nations Children's Fund, which emphasizes assistance with initiating and maintaining breastfeeding and lactation and postnatal breastfeeding support. The control intervention was continuation of the usual infant feeding practices. Results from the study showed that infants in the intervention arm were more likely to be exclusively breastfed at 3 months (43.3% vs. 6.4%; P<0.001) and at 6 months (7.9% vs. 0.6%; P=0.01), and had a significant reduction in the risk of one or more gastrointestinal infections (9.1% vs. 13.2%; adjusted OR 0.60; 95%CI 0.40-0.91) and of atopic dermatitis (3.3% vs. 6.3%; adjusted OR 0.54; 95%CI 0.31-0.95), but no significant reduction in respiratory tract infection. Secondary observational analysis showed that the group of infants who were exclusively breastfed at least 6 months compared to the group of infants who were breastfed 3 to 6 months had a statistically significant reduced risk of one or more episodes of gastrointestinal infection in the first 12 months of life (RR 0.67; 95%CI 0.46-0.97), which was maintained in a multivariate mixed model controlling for geographic origin, urban versus rural location, maternal education, and number of siblings in the household (adjusted OR = 0.61; 95%CI 0.41-0.93).[214] The same analysis also reported that there was a very low absolute risk of atopic dermatitis in both feeding groups but no risk reduction in the group that was exclusively breastfed for at least 6 months compared with the group that was exclusively breastfed for 3 to 6 months.

Chapter 4. Discussion

Twenty-three outcomes were analyzed in this report. Approximately 400 articles would needed to be reviewed if only articles with primary data were included; this is a much larger volume of literature than can be feasibly reviewed within the time period of this report. With the availability of many published systematic reviews on breastfeeding, we used this literature as the evidence for a large number of outcomes, supplemented by updates of these systematic reviews with new primary studies. We performed several new systematic reviews on outcomes not previously reported. The existing systematic reviews were conducted over a wide span of time and by diverse groups of investigators; there were large variations in the approach and quality of these reviews.

Even though we have assessed the reporting quality of these systematic reviews (using standards of reporting of systematic reviews of observational studies – MOOSE statement[22] and additional parameters that we devised), we cannot reliably know the validity of the reported summary data without knowing the details of the primary studies. A number of systematic reviews reported that inclusion and exclusion of some primary studies were reached by consensus between at least two investigators. Without knowing the details of how those consensuses were reached, it would be difficult to replicate the findings in those reviews as it is quite plausible that someone who is not familiar with the details of the consensus might have come up with a different set of studies for inclusion in the review. It should also be stressed that a well-performed systematic review does not necessarily imply that the body of evidence for a particular outcome of interest is of high quality. While some systematic reviews assessed the quality of the individual studies, the methods used varied. Any systematic review is limited by the quality of the primary studies included in the review. Unless the method used to assess the quality of the primary studies is transparent and the details made available for examination, it would be difficult to reliably determine the validity of the conclusions.

In most circumstances, it would be unethical to randomize mother-infant pair into breastfeeding (or breast milk feeding) or not breastfeeding arm in a trial. Therefore, the breastfeeding literature is primarily comprised of observational studies, either cohort or case-control studies. There are a number of potential deficiencies related to the study designs that could limit the internal validity and the generalizability of the findings. Some of these potential deficiencies include (1) misclassification of exposure; (2) confounding from the process of self-selection; (3) residual confounding; and (4) insufficient statistical power.

Misclassification of exposure (breastfeeding status/duration) is likely in the studies reviewed in this report. Most studies relied on mothers' recall for the data on breastfeeding. Recall is prone to error. One study from South Africa reported that at 6 to 9 months post-delivery, 13 percent of mothers could not remember the specific timing when they gave something other than breast milk to their infant. In those mothers who could remember, 57 percent of them overestimated the duration of exclusive breastfeeding by about 8 weeks, and 15 percent underestimated the duration by about 3 weeks.[215] Misclassification, may bias the effect estimate; particularly if the recall error is nonrandom, such as in studies where cases are more likely to underestimate the amount of breastfeeding than controls (for an example, see Norris and Scott 1996[90]).

In studies where subjects were self-selected, there could be confounding from the process of self-selection (e.g., if subjects who perceive their diseases are due to a lack of breastfeeding were more likely to participate in the study).

Residual confounding is a possibility for all observational studies, because it is difficult (if not impossible) to control for all potential confounding variables in these studies. Although it is possible to control for differences in demographic factors, it may not be possible to control for behavioral factors intrinsic in the desire to breastfeed.

Large sample size is often needed to examine the relationship between breastfeeding and various diseases and health conditions because of the need to adjust for numerous confounders to minimize all the potential biases described earlier. It is impossible to predict how these different limitations may interact to increase or decrease the effect estimate.

Compounding the issue of less-than-ideal study design are the heterogeneity of the breast milk itself and differences in how the feedings of breast milk were defined across different studies. The composition of breast milk varies both within and between individuals.[216,217] The composition could vary depending on preterm versus term delivery, the maternal diet, maternal body weight, time of day, beginning versus near the end of feed, first few months of lactation versus later lactation, milk volume, and numerous other factors. On the other hand, the composition of formulas has also changed significantly over the last twenty years. For example, contemporary formulas have added ingredients like nucleotides and long-chain polyunsaturated fatty acids that were absent from older formulations. How the heterogeneity both within and between comparators would affect the effect estimate is unclear. Also, studies defined breastfeeding differently. Many studies did not have a category of “exclusive breastfeeding”. In the ones that did have this category, “exclusive” could mean no supplement of any kind including water or it could mean occasional formula supplement is permissible. This mixing in of formula in the “exclusive” breastfeeding group may potentially dilute the true effect of breast milk and bias the results toward the null finding. In addition, no study in this review examined the differences between actually breastfeeding an infant and bottle or gavage feeding an infant with breast milk. How the act of breastfeeding itself plays a role in the different effects measured is unknown.

We have summarized the effects of breastfeeding (or breast milk feeding) on a large number of infant and maternal outcomes. Some of the outcomes are well defined and specific (e.g., childhood acute lymphocytic leukemia, breast cancer); and some are not so well defined and non-specific (e.g., asthma, gastrointestinal infections). When the reported outcome is well defined and specific, it lends confidence that the effect reported is valid for that outcome. When the reported outcome is not well defined, one might have some reservation regarding the validity of the measured effect for that outcome.

For all the above reasons, we find that there is a wide range of quality of evidence for the different outcomes examined in this review.

For severe lower respiratory tract diseases, good quality studies did find a relationship between breastfeeding and a reduction in the risk of hospitalization secondary to lower respiratory tract diseases.

For acute otitis media, the results from our meta-analyses of cohort studies of good and moderate methodological quality showed that breastfeeding was associated with a significant reduction in the risk of acute otitis media. Comparing ever breastfeeding with exclusive bottle-feeding, the pooled adjusted odds ratio of acute otitis media was 0.77 (95%CI 0.64 - 0.91). When comparing exclusive breastfeeding with exclusive bottle-feeding, either for more than 3 or 6 months duration, the pooled odds ratio was 0.50 (95%CI 0.36 - 0.70).

For non-specific gastroenteritis, one systematic review identified three primary studies that controlled for potential confounders. These studies reported that there was a reduction in the risk

of non-specific gastrointestinal infections during the first year of life in breastfed infants from developed countries, although the observed range of risk reduction was wide. However, one recent case-control study of 304 infants (167 cases and 137 controls) from England showed that the infants who were breastfeeding had a reduced risk of diarrhea compared to infants who were not breastfeeding (adjusted OR 0.36, 95% CI 0.18 to 0.74, P=0.005). The result was adjusted for age, sex, social class, contact with person in and outside household, and other factors. Also, analysis of nested observational cohorts from the Belarus trial showed that the group of infants who were exclusively breastfed for at least 6 months compared to the group of infants who were breastfed for 3 to 6 months had a statistically significant reduced risk of one or more episodes of gastrointestinal infection in the first 12 months of life (adjusted OR = 0.61; 95%CI 0.41-0.93).[214] The result was adjusted for geographic origin, urban versus rural location, maternal education, and number of siblings in the household.

For necrotizing enterocolitis (NEC) in preterm infants, our meta-analysis of four RCTs found a marginally statistically significant reduction (5% risk difference) of the NEC risk with breast milk feeding. Taking into account the high case-fatality rate of NEC, we consider this estimate is of meaningful clinical difference. However, One must be cognizant of the clinical heterogeneity underlying these RCTs in interpreting the findings of the meta-analysis. Three of the four RCTs were published in the 1980's. Whether infants born in the early 1980's should be combined with infants born in the late 1990's into a meta-analysis is debatable. Neonatal care has made tremendous strides in the last 20 years. Present day preterm formula milk is vastly different from preterm formula milk 20 years ago. All the studies had patient populations that were quite heterogeneous, gestational age ranged from 23 weeks to more than 33 weeks and birth weight ranged from less than 1000 g to more than 1,600 g. One study included only "healthy" infants, another included both "healthy" and "ill" infants. In addition, the types of breast milk, the methods of feedings, and the times of enrollments into the trials were all different. How the heterogeneity in the studies affected the findings is not clear. In addition, studies examining the issue of NEC were frequently also examining the issue of neonatal sepsis, as it is not possible to have NEC without concomitant sepsis. In future studies, it would be worthwhile to examine the relationship of breast milk exposure and sepsis in preterm infants.

For asthma, our subgroup analysis showed that breastfeeding was associated with a reduced risk in children under 10 years of age with a positive family history. However, this association does not hold true for older children as one publication reported a very large adjusted odds ratio (OR 8.7, 95%CI 3.4 – 22.2) for developing asthma in children 6 to 13 years of age who were exclusively breastfed for at least 4 months and had a positive history of maternal asthma.[56] The relationship of breastfeeding, maternal history, and long-term outcome of asthma bears further investigation.

For atopic dermatitis, available evidence from one well-performed systematic review on full term infants in developed countries suggest that exclusive breastfeeding for at least 3 months confer a protective advantage in the development of atopic dermatitis in those subjects with a family history of atopy. The systematic review did not make a distinction between atopic dermatitis of infancy (under 2 years of age) and persistent or new atopic dermatitis at older ages. This is important because the diagnosis of atopic dermatitis in patients younger than 2 years of age are sometimes attributed to symptoms of infectious origin and breastfeeding may have a protective effect against infections. But a stratified analysis by different durations of followup showed that the risk reduction was similar in those with less than 2 years compared with more than 2 years of followup.

For cognitive outcome in term infants from developed countries, sibling analysis and prospective studies that controlled specifically for maternal intelligence found little or no evidence to support an association between breastfeeding and cognitive performance in children. Most of the published studies adjusted their analyses for socioeconomic status and maternal education but not specifically for maternal intelligence. For those studies that still reported a significant effect after specific adjustment for maternal intelligence, residual confounding from other factors like different home environments cannot be ruled out.

No definitive conclusion regarding the relationship of breast milk exposure and cognitive development in preterm infants can be drawn at this time. Studies that controlled for maternal intelligence reported conflicting results. In addition to maternal intelligence, comorbidities (e.g., neurological impairment, extremely low birth weight, other neonatal illnesses), early intervention, environmental, and socioeconomic factors should also be controlled for in future investigation of this relationship.

For adult blood pressure, evidence suggests that there is an association between a history of breastfeeding during pregnancy and a small reduction in adult blood pressure, but the clinical or public health implication of this finding is unclear. Furthermore, The association weakened after stratification by study size, suggesting the possibility of bias.

For adult cholesterol, a lack of explicit analysis of potential confounders in the meta-analysis hampered the conclusion drawn from the study. Therefore, the relationship between breastfeeding and adult cholesterol levels cannot be adequately addressed at this time.

For cardiovascular mortality in adults, the meta-analysis was limited by the statistical heterogeneity across studies, apparent outcome modification by differences in gender (and therefore, calls into question the appropriateness of combining outcomes from men and women into a single analysis), and more than 30% of the subjects dropped out in the studies. Because of these reasons, no definitive conclusions can be drawn regarding the relationship between breastfeeding and cardiovascular mortality. Further investigation is warranted.

For Sudden Infant Death Syndrome (SIDS), our meta-analysis included only studies that reported clear definitions of exposure, outcomes, and results adjusted for well-known confounders or risk factors for SIDS. The summary estimate found a statistically significant adjusted odds ratio for an association between breastfeeding and a reduced risk of SIDS (adjusted OR 0.64, 95%CI 0.51 - 0.81). We conclude that there is a relationship between breastfeeding and a reduced risk of SIDS. One must be cautious in interpreting this relationship, however. As this finding stems from analysis of observational studies, this finding cannot prove causality. It is plausible that infants who breastfed and breastfed well are less prone to SIDS because of some yet unclarified neurophysiological reasons, and not because breastfeeding itself directly confers a protective effect. Further investigation is warranted.

For post-neonatal mortality (excluding SIDS), there are insufficient data to characterize the relationship between breastfeeding and post-neonatal infant mortality adequately. Further investigation is warranted.

For childhood leukemia, available evidence suggests that there is an association between breastfeeding and a reduced risk of acute lymphocytic leukemia and acute myelogenous leukemia. Our findings from the meta-analyses of the three case-controlled studies that were graded good or fair quality by one systematic review were consistent with the results from the other meta-analysis, but with smaller effect size and smaller statistical significance. Further evaluation of the biological mechanisms underpinning this relationship while taking into

consideration potential biases can be achieved with more large-scale case-controlled studies utilizing population-based and socioeconomic status-matched controls.

For obesity, evidence from three systematic reviews and meta-analyses suggests that a history of breastfeeding is associated with a reduction in the risk of obesity in later life. However, one must be aware of the possibility of residual confounding in interpreting this association. The pooled adjusted odds ratio of obesity comparing ever breastfed to never breastfed was 0.76 (95%CI 0.67-0.86) in one meta-analysis and 0.93 (95%CI: 0.88–0.99) in the other. The magnitude of effects was reduced when more confounders were adjusted in these analyses.

For type 2 diabetes, based on findings from a high-quality systematic review and meta-analyses of seven studies, early breastfeeding was associated with a lower risk of type 2 diabetes in later life compared with those initially formula-fed. However, only three studies appropriately adjusted for all the important confounders, including birth weight, parental diabetes, socioeconomic status, and individual or maternal body size. Even though these three studies found that adjustment did not alter the crude estimate, we cannot be completely confident that potential confounding by birth weight and maternal factors has been ruled out for the overall pooled estimate. This potentially could exaggerate the magnitude of the association.

For type 1 diabetes, even though there are some data to support that breastfeeding for more than 3 months is associated with a reduced risk of type 1 diabetes, this finding must be interpreted with caution because of the likelihood of recall biases and suboptimal adjustments for potential confounders in the primary studies.

For postpartum depression, studies of moderate quality reported an association between not breastfeeding or short duration of breastfeeding and postpartum depression. It is plausible that postpartum depression led to early cessation of breastfeeding, as opposed to breastfeeding altering the risk of depression. Both effects might occur concurrently. Additional factors that may have a bearing on both postpartum depression and the decision to initiate or terminate breastfeeding should be sought. Documentation of baseline mental health status before the initiation of breastfeeding and detailed recording of breastfeeding data will improve the quality of the studies and help understand the nature of the association.

There is no evidence of an association between lifetime breastfeeding duration and maternal osteoporosis. Lactation does not appear to have an effect on long-term changes in bone mineral densities. However, this conclusion is limited by the fact that the feeding history in the studies was obtained by maternal recall and no data on exclusivity of breastfeeding were available. Further investigation with accurate breastfeeding data is warranted.

For breast cancer, there is good evidence to support the observation that breastfeeding is associated with a reduction in the risk of breast cancer. This association is more likely in those women with increased lifetime months of breastfeeding their infants.

For ovarian cancer, there is some evidence to suggest an association between breastfeeding and a reduction in the risk of maternal ovarian cancer. However, one must be cautious in interpreting this association because it was largely based on estimations of the odds ratios from retrospective studies.

For postpartum weight change, we found that the overall effect of breastfeeding on return-to-pre-pregnancy weight (weight change from pre-pregnancy or first trimester to 1 to 2 year postpartum) was negligible (less than 1 kg), and the effect of breastfeeding on postpartum weight change was unclear. Results from the studies also suggest that many other factors have larger effects on weight retention or postpartum weight loss than breastfeeding. Methodological

challenges in these studies include the accurate measurement of energy balance, adequate control for numerous covariables, and quantifying accurately the exclusivity and the duration of breastfeeding. None of the included studies tackled all of these challenges.

Concerning the risk of maternal type 2 diabetes, a longer duration of lifetime breastfeeding is associated with a reduced risk of developing type 2 diabetes among parous women who did not have a history of gestational diabetes (GDM). There was a difference in the risk of developing type 2 diabetes between women with and without GDM in relation to lactation. Compared with women who did not have a history of GDM, women with a history of GDM had a markedly increased risk of type 2 diabetes; and lactation showed no significant relationship with diabetes risk among this group of women. One must be cautious in interpreting these findings, as they are only generalizable to population with characteristics similar to that of the Nurses' Health cohort.

An important area of research that is not systematically reviewed in this report is the use of breastfeeding promotion intervention trial to measure health effects (this topic is not part of the scope of this report and it will be covered in a separate report). The best known of these types of studies is the previously described Promotion of Breastfeeding Intervention Trial (PROBIT) conducted in the Republic of Belarus.[17] Data from this study provided good evidence that breastfeeding is associated with a reduction in the risk of gastrointestinal infection and atopic dermatitis. Whether results from studies conducted in other countries are applicable to the United States is unclear. In Belarus, mothers often stay in the hospital close to one week post delivery, infant formulas can cost as much as 20% of an average salary, and there is an obligatory prolonged maternity leave (approximately 3 years in most cases). In contrast, in the United States, mothers are often discharged within 48 hours post delivery and formula manufacturers provide rebates to the Special Supplemental Nutrition Program for Women, Infants, and Children (www.wicprogram.org). The factors in Belarus could work in conjunction with the intervention to help promote the increase in the rate of exclusive breastfeeding. On the other hand, one may argue that the results reported in the Belarus study could serve as a best-case scenario in terms of the potential benefits of breastfeeding when optimal promotion and support of breastfeeding are in place. More research in this country along the line of the Belarus study should be considered.

Of note, there were a few individual primary studies on asthma, cardiovascular mortality, and type 1 diabetes that reported increase in risk of those diseases in subjects who had been breastfed. Even though those studies were few in numbers, those findings should not be ignored and further investigation should be done.

Lastly, the outcomes analyzed in this review represent only a portion of all possible health outcomes related to breastfeeding reported by investigators worldwide. To work within the constraints of resources, we relied on the advice from our panel of technical experts in finalizing the list of outcomes included in this review. Thus, some important outcomes (e.g., growth and nutrition) have, by necessity, not been included in this review. Additional systematic reviews germane to those important outcomes would be of value.

Future Research

Assessment of the association between breastfeeding and health outcomes

Observational studies will remain the major source of information in this field. Clear subject selection criteria, adopting a common definition of "exclusive breastfeeding", reliable collection of feeding data, specific and properly quantifiable outcomes of interest, controlling for important potential confounders including child-specific factors, and blinded assessment of the outcome measures will help immeasurably to improve the quality of these studies. Traditional

retrospective case-control studies, usually used when the disease is rare, are less desirable because of the many caveats noted earlier. Prospective nested case-control studies with blinded assessment of the outcome measures would provide more reliable results.

As have been mentioned previously, it is not possible to eliminate self-selection bias in observational studies because of behavioral or attitudinal factors intrinsic in the desire to breastfeed. Thus, it is worthwhile to study these factors to further understand the reasons for the decision to breastfeed.

Sibling analysis provides a method to control for hereditary and household factors that are important in certain outcomes, provided that those factors are similar for the siblings of interest. Although such analysis may be less susceptible to confounders and effect modifiers that are shared by siblings, one must remember that it is not immune to biases. This method should be used when the appropriate data are available.

There is a large degree of heterogeneity across studies among many of the outcomes. The heterogeneity persisted after adjusting for potential confounders. It might be helpful to study breast milk composition (e.g., oligosaccharides, nucleotides, and others) with respect to the residual heterogeneity. In addition, maternal genetic variations in the production of those factors of interest from breast milk can be studied (for an example, see the discussion by Newburg 2005[218] concerning the variability of antidiarrheal effect of breastfeeding according to the prevalence of the secretor gene (*fucosyltransferase 2*) and the Lewis gene (*fucosyltransferase 3*) in the study population).

Assessment of the efficacy/effectiveness of breastfeeding promotion interventions

Cluster randomized controlled studies similar to the Belarus trial will provide understanding of the effectiveness of various breastfeeding promotion interventions. Any substantial differences in the degree of breastfeeding between the two groups as a result of the intervention will provide further opportunity to investigate any disparity in health outcomes between the two groups.

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List of Acronyms and Abbreviations

Abbreviation	Description
Adj	Adjusted
AHRQ	Agency for Healthcare Research and Quality
ALL	Acute Lymphocytic Leukemia
AML	Acute myeloid leukemia
AOM	Acute Otitis Media
Bayley MDI	Bayley Mental Development Index
BF	Breastfeeding
BMC_{arm}	Forearm bone mineral content
BMD_{spine}	Lumbar spine bone mineral density
BMI	Body mass index
BW	Birth weight
CDC	Centers for Disease Control and Prevention
CES-D	Center for Epidemiological Studies Depression Scale
CI	Confidence interval
C-section	Delivery by cesarean section
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DIS	Diagnostic Interview Schedule
DM	Donor milk
DSM IV	Diagnostic Statistical Manual
Dx	Diagnosis
EPDS	Edinburgh Postnatal Depression Scale
Exclu	Exclusive
FH	Family history
GA	Gestational age
GDM	Gestational diabetes
H	Hospital or clinic controls
Hosp	Hospitalization
HRT	Hormone replacement therapy
Ht	Height
IHD	Ischemic heart disease
IOM	Institute of Medicine
IQ	Intelligence quotient
LDL	Low-density lipoprotein
LRTI	Lower respiratory track infection
LTC	Long-term recalls

Abbreviation	Description
MA	Meta-analysis
MANCOVA	Multivariate analysis of variance
MDI	Bayley Mental Development Index
MM	Exclusive mother's milk
Mo	Months
NA	Not applicable
ND	No data/not documented
NEC	Necrotizing Entercolitis
NLSY79	National longitudinal survey of youth 1979
NS	Non-significant
OC	Ovarian cancer
OGTT	Oral glucose tolerance test
OR	Odds Ratio
P	Population controls
PA	Physical activity
PIAT	Peabody individual achievement test
PIAR	Poverty index ratio
PPVT-R	Peabody Picture Vocabulary Test
ROM	Recurrent Otitis Media
PF	Preterm formula
RDC	Research Diagnostic Criteria
RR	Relative risk
RTI	Respiratory infection
SBP	Systolic blood pressure
SDS	Standard deviation score
SE	Standard error
SES	Socioeconomic status
SR	Systematic review
SUDAAN	Software adjusted sample
TEP	Technical Expert Panel
Vit D suppl	Vitamin D supplementation
WISC-R	Weschler Intelligence Scale for Children
wk	Week
WPPSI-R	Wechsler Preschool and Primary Scales of Intelligence
Wt	Weight
Yr	Year

Appendix A. MEDLINE® Search Strategy

MEDLINE 1966-April 2006

#	Search History	Results
1	exp infant nutrition/	28620
2	exp Milk, Human/	10900
3	human milk.mp.	5231
4	(human adj2 milk).tw.	6040
5	breast milk.mp.	4994
6	breastmilk.mp.	315
7	breast feeding.mp.	18905
8	breastfeed$.mp.	5099
9	breast fed.mp.	3434
10	breastfed.mp.	1339
11	(breast adj2 fed).tw.	3705
12	exp lactation/	24059
13	(lactating or lactation).mp.	33361
14	or/1-13	68554
15	exp HIV Infections/	150356
16	HIV.mp.	151368
17	*fatty acids/	21008
18	*amino acids/	32481
19	or/15-18	243664
20	14 not 19	66018
21	limit 20 to animals	32196
22	20 not 21	33822
23	limit 22 to english language	27054
24	follow-up studies/	308818
25	(follow-up or followup).tw.	340039
26	exp Case-Control Studies/	297283
27	(case adj20 control).tw.	44954
28	exp Longitudinal Studies/	508275
29	longitudinal.tw.	62652
30	exp Cohort Studies/	548011
31	cohort.tw.	73505
32	(random$ or rct).tw.	324163
33	exp Randomized Controlled Trials/	39966
34	exp random allocation/	54141

35	exp Double-Blind Method/	84061
36	exp Single-Blind Method/	9446
37	randomized controlled trial.pt.	208988
38	clinical trial.pt.	420410
39	controlled clinical trials/	3005
40	(clin$ adj trial$).tw.	90860
41	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.	80586
42	exp PLACEBOS/	24212
43	placebo$.tw.	91878
44	exp Research Design/	197961
45	exp Evaluation Studies/	539139
46	exp Prospective Studies/	195111
47	exp Comparative Study/	1233790
48	or/24-47	2803651
49	23 and 48	8238
50	limit 49 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index)	360
51	49 not 50	7878

Appendix B. Sample Data Abstraction Forms

Evidence table for Systematic Reviews

Author, Year[UI]	**Topic**
Systematic reviews/Meta-analyses/Both	
Databases searched (Dates of literature search)	
Countries where primary studies conducted (Developed countries only or mixed)	
Study design [No. of studies]	
No. of subjects	
Study population and sampling	
Intervention/Exposure	
Comparator	
Outcomes	
Methods used for meta-analyses	
Heterogeneity assessments	
Results	
Authors' conclusions	
Quality of the systematic review	
Comments	

Author, yr:
Topic of the systematic review*/MA:

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	
2	Types of exposure or intervention used	
3	Types of study designs used	
4	Study population	
	Reporting of Search strategy	
5	Search strategy, including time period and key words	
6	Effort to include all available studies (contact with authors)	
7	Databases and registries searched	
8	Method of addressing published articles other than English	
9	Method of handling abstracts and unpublished studies	
	Reporting of Methods	
10	Rationale for selection and/or coding of data	
11	Assessment of confounding	
12	Assessment of quality	
13	Assessment of heterogeneity	
14	Description of statistical methods sufficient to replicate	
15	Provision of appropriate tables and graphs	
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	
17	Tables giving descriptive information of each study included	
18	Results of sensitivity testing (subgroup analysis)	
19	Indication of statistical uncertainty of findings	
20	Quantitative assessment of bias (eg. publication bias)	
	Overall quality	

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	
8	Were results reported accurately (eg, no discrepancies between text and tables)?	
9	Were conclusions justified by the reported/collected data and analysis?	

Author, Year, UI #

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Pre-pregnancy BW (range): Pre-pregnancy BMI (range): Race: Enrolled/Evaluate: Location: Sites: Funding:					

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/confounders/limitations Comments

A: strong, B: moderate, C: weak	A	B	C
Selection		x	
Study design		x	
Confounder		x	
Blinding			
Data collection		x	
Withdraw and dropout			x
Analyses		x	
Intervention integrity			

Overall:

Domain/question	***Place an "X" in one***				
Selection Bias					
Are individuals selected to participate likely to be representative of target population?	Very likely	Somewhat likely	Not likely		
What % of selected individuals agreed to participate?	80-100	60-79	<60	ND	NA
Allocation Bias (RCTs only, for quasi-experimental, case-control/before/after, no control group or other skip to "Confouncders")					
Is the method of random allocation stated	Yes	No			
If the method of random allocation is stated, is it appropriate	Yes	No			
Was the method of random allocation reported as concealed?	Yes	No			
Confounders					
Prior to the intervention, were there between group differences for important confounders reported in the paper?	Yes	No	Can't tell		
If there were differences between groups for important confounders, were they adequately managed in the analysis?	Yes	No	NA		
Were there important confounders NOT reported in the paper (describe above under quality score)?	Yes	No			
Blinding					
Was (were) the outcome assessor(s) blinded to the intervention or exposure status of the participants?	Yes	No	ND	NA	
Data Collection methods					
Were data collection tools shown or are they known to be valid?	Yes	No			
Were data collection tools shown or are they known to be reliable?	Yes	No			
Withdrawals and Dropouts					
Indicate the % of participants completing the study. (If the % differs by groups, record the lowest).	80-100	60-79	<60	ND	NA
Analysis					
Is there a sample size calculation or power calculation	Yes	Partially	No		
Is there a statistically significant difference between groups?	Yes	No	ND		
Are the statistical methods appropriate?	Yes	No	ND		
Indicate the unit of allocation	Community	Organization/group	Provider	Client	Institution
Indicate the unit of analysis	Community	Organization/group	Provider	Client	Institution
If the unit of allocation and analysis differed, was the cluster analysis done?	Yes	No	NA		
Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?	Yes	No	Can't tell		
Intervention Integrity					
What % of participants received the allocated intervention or exposure of interest?	80-100	60-79	<60	ND	NA
Was the consistency of the intervention measured (i.e. intervention was provided to all participants in the same way)?	Yes	No	ND	NA	
Is it likely that subjects received an unintended intervention (contamination or cointervention) that may influence the results?	Yes	No	Can't tell		

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

Acute Otitis Media

Alho 1996
Duffy 1997
Sassen 1994
Stenstrom 1997
Uhari 1994 SRMA*
Vernacchio 2004

* Systematic Review/Meta-Analysis

Alho, 1996[8633605]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): ND Mean BW (range): ND % Male: ND Race: ND Enrolled/Evaluate: 2512/ 825 Location: Northern Finland Sites: Single Funding:	Retrospective Mean follow-up = 22 mo	All pregnant women in the two northernmost provinces of Finland with estimated dates of delivery between July1, 1985 and June30, 1986 were enrolled. The research program investigated the fetal period and the later development and illnesses of the children.	Breastfeeding among children older than 3 mo of age	Bottle feeding among children older than 3 mo of age

Alho, 1996[8633605]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Diagnostic criteria for AOM: At least one acute Symptom- Earache, fever, irritability, respiratory symptoms, Restless sleep, etc. and one pneumo-otoscopic finding- distinct redness and outward bulging or reduced mobility of the eardrum	Adjusted OR Confounders: Day care Parental smoking	OR=0.9 CI: 0.8 - 1.0	A: strong, B: moderate, C: weak — A: ; B: x ; C: Selection — A: ; B: x ; C: Study design — A: ; B: x ; C: Confounder — A: ; B: x ; C: Blinding — A: ; B: ; C: Data collection — A: ; B: ; C: x Withdraw and dropout — A: ; B: ; C: x Analyses — A: ; B: x ; C: Intervention integrity — A: ; B: x ; C: Overall: C High dropout rate

Duffy, 1997 [9310540]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): Mean BW (range): % Male: 52 Race: 99% Caucasian Enrolled/Evaluate: 306/238 Location: USA Sites: Multi Funding: National Institute Of Child Health and Human Development Grant 19679	Prospective Follow-up duration: 24 mo	Consecutive infants at well baby visits shortly after birth. Infants with craniofacial abnormalities, genetic disorders, immune deficiencies were excluded	Changes in feeding modes were assessed at scheduled office visits • Exclusive milk breastfeeding • Combined breast- and formula-feeding Maternal guardians completed a questionnaire at 24months to determine the reliability of various postnatal parameters. *K* statistics: r>0.9 for classification and duration of feeding modes (birth, 3, 6, and 12 mo of age)	Changes in feeding modes were assessed at scheduled office visits • Formula feeding

Duffy, 1997 [9310540]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
AOM defined by presence of one or more of Fever, irritability, ear pain, pulling at the ears, And Tympanic membrane changes including Increased thickness, bulging, loss of landmarks, Decreased mobility	RR Confounder: age of colonization	Exclusive BF at 3 mo was associated with RR= 0.62; 95%CI: 0.43-.89; At 6 mo, RR=0.46; 95%CI: 0.29-0.74	A: strong, B: moderate, C: weak / A / B / C Selection / / x / Study design / x / / Confounder / / x / Blinding / / / Data collection / x / / Withdraw and dropout / / x / Analyses / / x / Intervention integrity / x / / Overall: B

Sassen, 1994 [7978038]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): ND Mean BW (range): ND % Male: 53 Race: 96.6% Dutch Enrolled/Evaluate: 289/232 Location: Netherlands Sites: Multi; 1 urban and 2 rural Funding: ND	Prospective Mean follow-up = 23.6 mo	Children born between July 1987 and October 1988	Before breastfeeding was stopped (or per month)	Up to 4 mo after stopping

Sassen, 1994 [7978038]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
AOM diagnosis by physician; If purulent otorrhea; or if treatment for AOM given Criteria for AOM consisted of: Acute symptoms- ear ache, fever, irritability, restless sleep, etc. Otoscopic signs- distinct redness and/or Outward bulging of the tympanic membrane Tympanometry results not used	Adjusted for 1. Number of siblings 2. Socio-economic status 3. Duration of breastfeeding	OR= 0.92 95% CI: 0.76-1.07	A: strong, B: moderate, C: weak — A / B / C Selection — / — / x Study design — x / — / — Confounder — / x / — Blinding — / — / — Data collection — / x / — Withdraw and dropout — / — / x Analyses — x / — / — Intervention integrity — x / — / — Overall: B Parents who are not Dutch could not Enroll their infants because the Questionnaire was not translated

Stenstrom, 1997 [9039487]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): Mean BW (range): % Male: 61 Race: Enrolled/Evaluate: Location: Sweden Sites: Single/Multi Funding:	Case-control At examination children were between 3 and 7 years old Controls were between 4 and 6 years	All children born in the period 1978-81 registered to have had five or more episodes of AOM before age 30mo were selected and classified as cases (otitis-prone) From the official computerized population register in Malmo, 412 children with less than 5 episodes of AOM Were selected at random as a control group, and matched with otitis-prone children for age and sex so that each otitis-prone child had two matched controls	Ever breastfeeding	Never breastfeeding

Stenstrom, 1997 [9039487]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
AOM diagnosed otoscopically by an ENT physician, Pediatrician or general practitioner	Estimates not reported No adjustment for confounders	No differences between the groups found	A: strong, B: moderate, C: weak — A: x; B: ; C: Selection — A: x; B: ; C: Study design — A: ; B: x; C: Confounder — A: ; B: ; C: x Blinding — A: ; B: ; C: Data collection — A: ; B: x; C: Withdraw and dropout — A: ; B: x; C: Analyses — A: ; B: x; C: Intervention integrity — A: ; B: x; C: Overall: C No confounders adjusted

Evidence table for Systematic Reviews of Breastfeeding and Acute otitis media

Author, Year[UI] Topic	Uhari, 1996 Acute otitis media
Literature search (Dates)	Medline (1966-1994); Other databases searched? (yes); unpublished data used? (no)
Countries where primary studies conducted	Finland, USA, Scotland
Study eligibility / inclusion criteria	Search was limited to the English language and to human subjects. Only original studies of risk factors with adequate control groups and that reported actual numbers of patients were included
Study design [No. Of studies]	2Case-control [12,17] 8Observational [[13,15,16,20,22,23,25,27]
No. of subjects	Case control: 671 Observational: 4455 Breastfeeding > 3 months 2,548 Breastfeeding > 6 months 3,384 Breastfeeding (yes/no) 2, 193
Study population (definition in included studies)	Studies of association between breastfeeding and acute otitis media and recurrence of AOM • Specific age groups of children in the cohorts are not specified
Intervention/Exposure (definition in included studies)	The studies reviewed reported breastfeeding as yes/no or breastfeeding ≥ 3months vs < 3 months or breastfeeding ≥ 6 months vs < 6 months
Comparator (definition in included studies)	Duration of breastfeeding
Outcomes (definition in included studies)	10 studies evaluated the risk of Acute otitis media and recurrence of Acute otitis associated with breast milk feeding. The diagnosis of AOM varied, but pneumatic otoscopy was used in the diagnosis. There was no restriction on study inclusion according to the diagnostic criteria used. Twenty-two studies evaluating an array of risk factors for development and recurrence of AOM were included in the Meta-analysis. Seven of the twenty-two studies explicitly evaluated the association between breast milk feeding and AOM, while another 3/22 studies included breast milk feeding among other risk factors that were evaluated. All the studies agreed on the protective effect of breast milk feeding against AOM.
Heterogeneity assessments	Pooled estimate of the relative risk and the 95% CI were calculated from data from studies that were sufficiently homogeneous. Pooled estimates of risks were derived with the random effects model. Details of clinical and statistical heterogeneity assessment is published elsewhere
Quality assessments	Not done
Publication bias assessments	Not done
Statistical Analysis or meta-analytic methods	Random effects model used for the pooled estimates of risks
Results	• breastfeeding for at least 3 months and AOM ;RR=0.87; 95% CI: 0.79 – 0.95; p = 0.003 • breastfeeding yes/no and recurrent AOM: RR=0.48; 95% CI: 0.32-0.72; p=0.0004 • breastfeeding ≥ 3 mo vs < 3 mo and recurrent AOM: RR= 0.69; 95% CI: 0.46-1.03; p=0.07 • breastfeeding ≥ 6 mo vs < 6 mo and recurrent AOM: RR= 0.69; 95% CI: 0.49-0.97; p=0.03
Quality of the systematic review	Not done
Author's interpretations of the results	• In the meta-analysis, breastfeeding was beneficial and breastfeeding even for only 3 months decreased the risk of AOM

Author, Year[UI]	Topic	Uhari, 1996	Acute otitis media
		• Breastfeeding for 6 months or more decreased the recurrence of AOM • Breastfeeding should be promoted to protect against acute otitis media.	
Comments / Limitations		There was no restriction on inclusion according to the diagnostic criteria used for AOM. There are no details on how breastfeeding data was collected or duration of follow-up. Meta-analyses combined both case-control and cohort studies and did not address the potential biases in the individual studies.	

Author, yr: Uhari, 1994
Topic of the systematic review*/MA: Acute otitis media

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Yes
2	Types of exposure or intervention used	Yes
3	Types of study designs used	Yes
4	Study population	Yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Yes
6	Effort to include all available studies (contact with authors)	No (Medline only)
7	Databases and registries searched	Yes
8	Method of addressing published articles other than English	No
9	Method of handling abstracts and unpublished studies	No
	Reporting of Methods	
10	Rationale for selection and/or coding of data	No
11	Assessment of confounding	No
12	Assessment of quality	No
13	Assessment of heterogeneity	Yes
14	Description of statistical methods sufficient to replicate	Yes
15	Provision of appropriate tables and graphs	Yes
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Yes
17	Tables giving descriptive information of each study included	Partially
18	Results of sensitivity testing (subgroup analysis)	No
19	Indication of statistical uncertainty of findings	Yes
20	Quantitative assessment of bias (eg. publication bias)	No
	Overall quality	C

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Partially
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	Yes
5	Was individual study quality (such as sample size, study design, blinding, various	No

	Evaluation of quality of a systematic review or meta-analysis	Yes /No /Partially
	biases and confounders, study subject attrition rate…etc.) assessed?	
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	No
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Yes
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Yes
8	Were results reported accurately (eg, no discrepancies between text and tables)?	N/A
9	Were conclusions justified by the reported/collected data and analysis?	Yes

Vernacchio, 2004 [15126021]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): Mean BW (range): 3,400,median % Male: 50.8 Race: 68.4% both parents white Enrolled/Evaluate: 15,113/11,349 Location: USA Sites: Multi Funding: Contract no. 1-HD-4-3221 National Institute of Child and Human Development and the National Institute on Deafness and other Communication Disorders	Prospective Followup- 6 mo	6 mo old infants who participated in the infant care practices study	Breastfeeding A child was considered to be breastfed at 6 mo if he or she was breastfeeding at the time of the 6 mo questionnaire, whether or not supplemental formula or solid foods were used	No breastfeeding A child was considered not to be breastfed at 6 mo if he or she was not breastfeeding at the time of the 6 mo questionnaire

Vernacchio,2004 [15126021]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
As part of the 6 mo questionnaire, each mother was asked health care provider in the month prior to date of completing the questionnaire. I so, they were asked to select a diagnosis from a menu of options that included "ear infection"	OR Confounders Gender Daycare attendance Mother's marital status Mother's age Mother's parity Number of children in the home	Unadjusted OR=0.66 95%CI: 0.59-0.74 Adjusted OR=0.69 95%CI: 0.61-0.78	A: strong, B: moderate, C: weak Selection: B Study design: B Confounder: B Blinding: Data collection: A Withdraw and dropout: A Analyses: A Intervention integrity: B Overall: B

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

Asthma

Burgess 2006
Gdalevich 2001 SRMA*
Kull 2004
Sears 2002
Wright 2001

* Systematic Review/Meta-Analysis

Burgess, 2006 [16585289]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 185 Mean BW (range): 3402 % Male: 52 Race: ND Enrolled/Evaluate: 7223/4964 Location: Australia Sites: Single Funding: ND	Prospective cohort with questionnaires at birth, 6 months, 5 and 14 years. Breastfeeding data collected at 6 months	Mothers and term singletons	Categories: Never breastfed < 3 weeks 3 – 6 weeks 7 weeks – 3 months ≥ 4 months	NA

Burgess, 2006 [16585289]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
At 14 years, mother reported asthma, qualitative answers to episodes of asthma past in 6 months. Supplemental questionnaire at 14 year follow-up requesting data on frequency of asthma meds, asthma-related sick days from school, asthma-related hospital admissions, parental history of asthma	Chi-square for categorical variables Logistic regression adjusting for breastfeeding, maternal asthma, paternal asthma, smoking early and late pregnancy, frequency of coughs and cold first 6 months, annual family income	Outcome: Asthma Breastfeeding duration: No BF; 3 wk-3 mo; ≥4 mo OR_{unadj} (95% CI): 1.0; 1.03 (0.9-1.2); 1.03 (0.9-1.2) Of 4,964 subjects with breastfeeding and asthma data, 1408 (28%) mother-reported cases of adolescent asthma 3,720 returned 14 year follow-up questionnaire Nonsignificant relationship between duration of breastfeeding and asthma. Stratification for parental asthma or child's sex had no effect. No association for breastfeeding duration and asthma meds, asthma-related sick days from school or hospitalization	A: strong, B: moderate, C: weak: A; B; C Selection: x Study design: x Confounder: x Blinding: x Data collection: x Withdraw and dropout: x Analyses: x Intervention integrity: NA No reporting of adjusted OR, discrepancy for % males in table, dropout/withdraw > 30%, significant differences between completers and noncompleters, no definition or description of breastfeeding. Overall C

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI] Topic	Gdalevich, 2001 Asthma
Literature search (Dates)	Medline (1966 to 1999); Other databases searched? (no); unpublished data used? (no)
Countries where primary studies conducted	Developed only: USA, Canada, UK, Italy, Australia and New Zealand
Study eligibility / inclusion criteria	Prospective studies; maternal recall of the child's feeding history of not more than 12 months; duration of BF for 3 months or more.
Study design [No. Of studies]	Prospective study design [12]
No. of subjects	8,183
Study population (definition in included studies)	Children (with and without family h/o atopy and asthma and combined population)
Intervention/Exposure (definition in included studies)	Exclusive breastfeeding (3 mo or more with no substitutes or supplements to mother's milk or solids)
Comparator (definition in included studies)	without $\geq$ 3 mo of exclusive breastfeeding
Outcomes (definition in included studies)	Asthma (Diagnosed by physician, consecutive reporting of wheezing beyond the age of 1 year, and treatment for lower respiratory tract allergy were defined as study outcomes)
Heterogeneity assessments	Yes by graphical presentation and application of heterogeneity test
Quality assessments	Unclear; studies critically appraised on 8 items (maternal recall; blinded to exposure; duration of bf; exclusivity of bf; diagnostic criteria; blinded ascertainment of outcome; age; control for confounding)
Publication bias assessments	Yes; calculation of the fail-safe N
Statistical Analysis or meta-analytic methods	Fixed effect model ; was also compared to random effects model Metric used odds ratio
Results	The summary OR was 0.47 (95% CI, 0.34-0.66) in the 5 studies (1788 subjects) with less than 2 years of follow-up, and 0.72 (95% CI, 0.62-0.84) in the 12 studies with 2 or more years of follow-up. The protective effect estimate of BF was more pronounced in the children with a family history of atopy in the subset of studies that assessed this population separately, OR= 0.52 (95% CI, 0.35-0.79), than in the studies in which both unstratified population data and children without atopic first-degree relatives were included, OR = 0.73 (95% CI, 0.62-0.86). When we further restricted the analysis to studies involving only children without a family history of atopy, the OR was 0.99 (95% CI, 0.48-2.03). Exclusion from the analysis of the studies with borderline blinding of diagnosing physicians10,15,19 or those lacking a statement of BF exclusivity20 yielded respective ORs of 0.71 (95% CI, 0.61-0.84) and 0.72 (95% CI, 0.61-0.85).
Quality of the systematic review	A
Author's interpretations of the results	The summary analysis of the 12 prospective studies supports the role of exclusive BF in the prevention of childhood asthma. The protective effect was higher in the subgroup of children with a positive family history of asthma or atopy.
Comments / Limitations	Children age range not mentioned; included studies that did not adjust for confounding;

Author, yr: Gdalevich, 2001
Topic of the systematic review*/MA: Asthma

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Y
2	Types of exposure or intervention used	Y
3	Types of study designs used	Y
4	Study population	Y
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Y
6	Effort to include all available studies (contact with authors)	Y
7	Databases and registries searched	Y
8	Method of addressing published articles other than English	N
9	Method of handling abstracts and unpublished studies	Y
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Y
11	Assessment of confounding	Y
12	Assessment of quality	Y
13	Assessment of heterogeneity	Y
14	Description of statistical methods sufficient to replicate	Y
15	Provision of appropriate tables and graphs	Y
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Y
17	Tables giving descriptive information of each study included	Y
18	Results of sensitivity testing (subgroup analysis)	Y
19	Indication of statistical uncertainty of findings	Y
20	Quantitative assessment of bias (eg. publication bias)	N
	Overall quality	**A**

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Y
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Y
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Y
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	Y
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Y
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Y
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Y
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Y
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Y
9	Were conclusions justified by the reported/collected data and analysis?	Y

Kull, 2004; Kull, 2002
Wickman 2003

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): ND Mean BW (range): ND % Male: 50.5 Race: ND Enrolled/Evaluate: 4089/3601 Location: Sweden Sites: Multiple Funding: Nonprofit; government	Prospective, longitudinal cohort with final data collection at 4 year follow-up	All newborns from February 1994 through November 1996 in a predefined area of Stockholm, Sweden were invited to the study. 4089 (75%) of all infants were included. Data from all 4 questionnaires (at 2 months, 1, 2, and 4 years of age) were available for 3619 (88%) children. Complete answers on the subjects of breast-feeding, potential confounders, and outcome were required to be included in the analyses, leaving 3601 children (88% of the original study base) for analyses.	The independent variable of breast-feeding was categorized as follows: exclusive breast-feeding was dichotomized with the 25th percentile as the cutoff point (<4 months and ≥4 months) and as a 3-level categorical variable (0-2, 3-4, and ≥5 months). The variable for exclusive breast-feeding was used in combination with a dichotomized variable of partial breast-feeding (0-2 and ≥3 months) to disentangle the effects of exclusive breast-feeding and an additional period of partial breast-feeding. The period of additional partial breast-feeding was calculated from the point when exclusive breastfeeding was finished.	Exclusive breastfeeding 0-2 months Exclusive breastfeeding <4 months

Kull, 2004; Kull, 2002

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Asthma: At 4 years of age, asthma was defined as at least 4 episodes of wheezing during the last 12 months or at least 1 episode of wheezing during the same period if the child was receiving inhaled steroids. Early-onset persistent asthma implies that the child fulfilled the asthma criteria not only at 4 years but also during the first 2 years of life. Early-onset transient asthma denotes that the child was fulfilling asthma criteria during the first 2 years of life but not at 4 years of age. Late onset of asthma implies that the child was not classified as having asthma during the first 2 years of life but fulfilled the asthma criteria at 4 years.	The relationship between breast-feeding and health outcomes was analyzed with logistic regression, adjusted for maternal age, maternal smoking during pregnancy or at 2 months of age, and heredity. Heredity: Heredity for allergic diseases was defined as physician diagnosed asthma, hay fever, or both in combination with allergy to a furred pet, pollen, or both in 1 (single heredity) or 2 (double heredity) parents.	See table below	See table below

Outcome		Exclusive BF		
		0-2 mo	3-4 mo	≥5 mo
Asthma	n/N	48/541	41/701	111/2142
OR_{adj} (95% CI)		1.0	0.67 (0.43-1.03)	0.61 (0.42-0.86)
Asthma & No heredity	n/N	30/383	24/502	55/1500
OR_{adj} (95% CI)		1.0	0.61 (0.36-1.06)	0.48 (0.30-0.77)
Asthma & Heredity	n/N	18/158	17/199	56/642
OR_{adj} (95% CI)		1.0	0.76 (0.37-1.54)	0.81 (0.46-1.44)
Early-onset & persistent asthma	n/N	25/532	19/687	36/2118
OR_{adj} (95% CI)		1.0	0.56 (0.30-1.04)	0.35 (0.21-0.60)
Early-onset transient asthma	n/N	36/532	19/687	73/2118
OR_{adj} (95% CI)		1.0	0.39 (0.22-0.69)	0.51 (0.30-0.77)
Late onset of asthma	n/N	22/532	21/687	73/2118
OR_{adj} (95% CI)		1.0	0.71 (0.38-1.31)	0.82 (0.50-1.35)

Note: The interaction between asthma and heredity was not statistically significant.

The prevalence of asthma among children exclusively breastfed for less than 4 months was 9.1% compared with 6.4% among children breast-fed for 4 months or more (OR_{adj}, 0.72; 95% CI, 0.53-0.97). The OR_{adj} for asthma related to breast-feeding for 4 months or more was 0.58 (95% CI, 0.38-0.88) in children without heredity for allergic diseases and 0.73 (95% CI, 0.43-1.20) in children with heredity.

A: strong, B: moderate, C: weak	A	B	C
Selection	x		
Study design	x		
Confounder	x		
Blinding		x	
Data collection	x		
Withdraw and dropout	x		
Analyses	x		
Intervention integrity	N/A		

Overall: A

Sears, 2002 [16585289]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): ND Mean BW (range):ND % Male: ND Race: ND Enrolled/Evaluate: 1037/1037 Location: New Zealand Sites: Single Funding: Government	Ambidirectional cohort study - enrolled at age 3 and followed prospectively up to 21 years. Accompanied and unaccompanied assessments at 3, 5, 7, 9, 11, 13, 15, 18, 21, and 26 years.	Population study of live-born children	Categories: Not breastfed Breastfed > 4 weeks Breastfed definition includes some formula feeding during birthing stay at hospital. Feeding history including duration of breastfeeding from regular, initially weekly, home & clinic visits during first 2-3 years	NA

Sears, 2002 [16585289]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>At age 9 years, ever having asthma from comprehensive questionnaires by interviewers with data on frequency of wheezing, asthma diagnosis, drugs, clinical characteristics, admissions; current asthma defined as positive response as reported by child or parent with accompanied symptoms of last 12 months; some verification by airway hyper-responsiveness</td>
<td>Chi-square for categorical variables
Multivariate regression controlling for SES, birth order, sheepskin use in infancy, maternal smoking</td>
<td>
<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">BF status</th><th rowspan="2">P value</th></tr>
<tr><th>No BF (n=504)</th><th>>4 weeks n=(533)</th></tr>
<tr><td>Asthma ever at 9 years n/N
OR_{adj} (95% CI)</td><td>27/417 (6%)
1.0</td><td>47/398 (12%)
1.93 (1.18-3.17)</td><td>0.0081</td></tr>
<tr><td>Current asthma at 26 years n/N
OR_{adj} (95% CI)</td><td>74/496 (15%)
1.0</td><td>113/484 (23%)
1.74 (1.26-2.40)</td><td>0.0008</td></tr>
<tr><td>Current asthma with AHR at 9 years n/N
OR_{adj} (95% CI)</td><td>11/409 (3%)
1.0</td><td>28/385 (7%)
2.83 (1.39-5.78)</td><td>0.0028</td></tr>
<tr><td>Asthma ever at 9 years Family history negative n/N
OR_{adj} (95% CI)</td><td>10/229 (4%)</td><td>23/216 (11%)
2.61 (1.21-5.62)</td><td></td></tr>
<tr><td>Asthma ever at 9 years Family history positive n/N
OR_{adj} (95% CI)</td><td>16/174 (9%)</td><td>23/174 (13%)
1.50 (0.77-2.96)</td><td>0.291</td></tr>
</table>
AHR, airway hyper-responsiveness to methacholine or salbutamol
Multivariate analysis of current asthma at 9 years with breastfeeding > 4 weeks with adjusted OR 2.40 (1.36-4.26), p = 0.0027
Analysis for different duration of BF showed similar results of greater risk of asthma at 9 years for more
</td>
<td>
<table>
<tr><th>A: strong, B: moderate, C: weak</th><th>A</th><th>B</th><th>C</th></tr>
<tr><td>Selection</td><td>x</td><td></td><td></td></tr>
<tr><td>Study design</td><td>x</td><td></td><td></td></tr>
<tr><td>Confounder</td><td>x</td><td></td><td></td></tr>
<tr><td>Blinding</td><td>x</td><td></td><td></td></tr>
<tr><td>Data collection</td><td>x</td><td></td><td></td></tr>
<tr><td>Withdraw and dropout</td><td>x</td><td></td><td></td></tr>
<tr><td>Analyses</td><td>x</td><td></td><td></td></tr>
<tr><td>Intervention integrity</td><td>N/A</td><td></td><td></td></tr>
</table>
Overall: A
</td>
</tr>
</table>

Wright, 2000 [11065066]
Wright, 2001 [11182011]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): ND Mean BW (range): ND % Male: ND Race: ND Enrolled/Evaluate: 1,246/926 Location: USA Sites: Multiple Funding: Government	Prospective, longitudinal newborn cohort with questionnaires ascertaining respiratory health at 2, 3, 6, 9, 11, 13 years Additional data collection by health surveillance visit to MD	Healthy newborn infants	Children classified by duration of exclusive breast feeding: never breast fed, breast fed exclusively <4 months, breast fed exclusively >4 months	NA

Wright, 2000 [11065066]
Wright, 2001 [11182011]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Physician diagnosed asthma, wheezing or asthma symptoms reported ≥ 2 questionnaires from ages 6 to 13 years	Bivariate analyses between feeding history and asthma, and stratified by maternal asthma status Logistic regression to assess odds of asthma, recurrent wheeze were related to breast feeding and maternal asthma adjusting for confounders: maternal education, smoking status in 1st year, sex, ethnicity, 2 or more siblings at home or day care use versus neither first 6 months, paternal asthma	Age 6-13: Nonsignificant for breastfeeding duration and asthma Nonsignificant for breastfeeding duration and asthma for children with non-asthmatic mothers OR_{adj} 2.1 (0.9-5.1) Significant for maternal asthmatics OR_{adj} 8.7 (3.4-22.2)	A: strong, B: moderate, C: weak

Maternal asthma status		BF status: Never BF	<4 mo	≥4 mo
Maternal asthma	%	9.1	23.5	46
	n/N	1/11	12/51	17/37
p<0.05				
No maternal asthma		11.4	12.3	13
		15/132	48/390	38/294

A: strong, B: moderate, C: weak	A	B	C
Selection	x		
Study design	x		
Confounder	x		
Blinding		x	
Data collection		x	
Withdraw and dropout		x	
Analyses		x	
Intervention integrity	NA		

Overall B
No explanation for WD/dropouts, discrepancies in numbers for exclusive BF

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

Atopic Dermatitis

Gdalevich 2001 SRMA*

* Systematic Review/Meta-Analysis

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI] Topic	Gdalevich 2001 (UI 11568741) Atopic dermatitis
Literature search (Dates)	Medline (1966 to 5/2000); Other databases searched? No; unpublished data used? No
Countries where primary studies conducted	Not reported; but all studies were performed in developed countries
Study eligibility / inclusion criteria	Prospective studies of full-term infants in whom the ORs of atopic dermatitis associated with breastfeeding were reported or could be calculated. Exclusion: breastfeeding duration of <3 months; see paper for additional inclusion/exclusion criteria
Study design [No. Of studies]	18 prospective studies were included
No. of subjects	4158 subjects
Study population (definition in included studies)	Full-term infants
Intervention/Exposure (definition in included studies)	Exclusive breastfeeding for ≥ 3 months
Comparator (definition in included studies)	
Outcomes (definition in included studies)	Strict diagnostic criteria for atopic dermatitis provided by the authors of the primary studies
Heterogeneity assessments	Nonsignificant heterogeneity (P=0.27)
Quality assessments	
Publication bias assessments	
Statistical Analysis or meta-analytic methods	
Results	Fixed effect, overall OR 0.68 (95% CI 0.52, 0.88); After exclusion of unblinded studies, OR 0.77 (95% CI 0.60, 0.98) Analyses restricted to those with positive family history, OR 0.58 (95%CI 0.41, 0.92) Analyses restricted to those without family history, OR 0.84 (95%CI 0.59, 1.19)
Quality of the systematic review	A
Author's interpretations of the results	There is a substantial protective effect of breastfeeding against atopic dermatitis in children with a family history of atopy.
Comments / Limitations	

Author, yr: Gdalevich 2001
Topic of the systematic review*/MA: Atopic dermatitis

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Y
2	Types of exposure or intervention used	Y
3	Types of study designs used	Y
4	Study population	Y
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Y
6	Effort to include all available studies (contact with authors)	Y
7	Databases and registries searched	Y
8	Method of addressing published articles other than English	N
9	Method of handling abstracts and unpublished studies	N
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Y
11	Assessment of confounding	Y
12	Assessment of quality	Y
13	Assessment of heterogeneity	Y
14	Description of statistical methods sufficient to replicate	Y
15	Provision of appropriate tables and graphs	Y
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Y
17	Tables giving descriptive information of each study included	N
18	Results of sensitivity testing (subgroup analysis)	Y
19	Indication of statistical uncertainty of findings	Y
20	Quantitative assessment of bias (eg. publication bias)	N
	Overall quality	

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Y
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Y
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Y
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	Y
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Y
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Y
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Y
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Y/N
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Y
9	Were conclusions justified by the reported/collected data and analysis?	Y

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

CVD Mortality

Martin 2004 SRMA*

* Systematic Review/Meta-Analysis

Evidence table for Systematic Reviews of Breastfeeding

Author,Year[UI] Topic	Martin, 2004 Cardiovascular Mortality
Literature search (Dates)	Medline (up to April 2003); Other databases searched? (yes); unpublished data used? (yes)
Countries where primary studies conducted	Developed countries: US and UK
Study eligibility / inclusion criteria	Articles were considered eligible for inclusion in the current review if infants who had been breastfed were compared with those who had been bottle (artificially) fed, if the outcome was cardiovascular disease or ischemic heart disease mortality, and if estimates of the association between having been breastfed in infancy and cardiovascular disease or ischemic heart disease mortality could be obtained from the paper or after correspondence with the authors.
Study design [No. Of studies]	Historical cohort studies [4]
No. of subjects	25,166 at baseline; 10,785 at follow-up
Study population (definition in included studies)	Wingard, 1994: 1373 birth children in California Hertfordshire cohort: 5908 women and 10374 men born in 11 of 12 districts in Hertfordshire Boyd Orr: 4999 men and women from a survey of diet and health in pre-war Britain Caerphilly, 2003: 2512 meddle-aged men living in Caerphilly, South Wales
Intervention/Exposure (definition in included studies)	• Any or exclusive breastfeeding. If results for both any or exclusive breastfeeding were presented in the paper, the exclusive breastfeeding association was used in the meta-analysis. • Prolonged breastfeeding: any or exclusive breastfeeding >1 year.
Comparator (definition in included studies)	Exclusive bottle-feeding
Outcomes (definition in included studies)	Cardiovascular disease or ischemic heart disease mortality
Heterogeneity assessments	Cochran's Q statistic I^2 test
Quality assessments	No quality score was used, although specific aspects of the quality of each study, including control of confounding, loss to follow-up, recall bias, definition of breastfeeding, and sample size, were discussed
Publication bias assessments	Not done, although there was a discussion on publication bias as one of the potential limitations of the meta-analyses.
Statistical Analysis or meta-analytic methods	Random effect model
Results	• All four studies were historical cohorts born between 1904 and 1939. • Random-effect models showed little difference in all cause mortality between breast and bottle-fed subjects (pooled rate ratio: 1.01; 95% CI: 0.91-1.13, p=0.8), and there was little evidence of heterogeneity. • Five observations from three studies suggested little or no association between breastfeeding and cardiovascular disease mortality in both males and females, and one suggested a possible adverse effect (Caerphilly cohort). In random effects meta-analysis, cardiovascular disease mortality was similar in breastfed versus bottlefed subjects (pooled rate ratio: 1.06; 95% CI: 0.94–1.20). There was no statistical evidence of between-study heterogeneity. • Ischemic heart disease mortality was 6% lower amongst males who had been breastfed in the Hertfordshire cohort, but 56% higher amongst breastfed females. This result is in line with point estimates from the Boyd Orr cohort suggesting that ischemic heart disease mortality was 10% lower amongst males who had been breastfed, but 40% higher amongst breastfed females (although there was little statistical evidence of interaction: p=0.2). In Caerphilly, however, ischemic heart disease mortality was 73% higher amongst breastfed males. In a random effects meta-analysis, there was evidence of heterogeneity.

Author,Year[UI] Topic	Martin, 2004 Cardiovascular Mortality
	• There was little evidence that prolonged breastfeeding was associated with all-cause mortality (pooled rate ratio: 0.94; 95% CI: 0.71–1.24), although there was moderate statistical evidence of heterogeneity. • There was weak evidence that prolonged breastfeeding was associated with a 16% increase (95% CI: 0.99–1.36; p=0.06) in cardiovascular disease mortality, and no evidence of inconsistency in estimates. • There was little evidence that prolonged breastfeeding was associated with ischemic heart disease mortality (rate ratio: 1.08; 95% CI: 0.88–1.31; p=0.5) and there was no heterogeneity.
Quality of the systematic review	B
Author's interpretations of the results	• There are at least three possible sources of bias in the studies reviewed: selection bias, information bias or recall bias (except for one study) and publication bias. Only 2 of the 4 studies had at least 70% of the target population in the follow-up. Recall bias is unlikely in only Hertfordshire cohort as breastfeeding was prospectively ascertained. Publication bias is possible but the studies were relatively large and unpublished estimates were obtained. • As confounding and bias may have distorted results from individual studies, the statistical combination of estimates into a combined rate ratio needs to be interpreted with caution. Our new analysis, together with evidence from published and unpublished literature, does not provide strong evidence that breastfeeding is related to all-cause or cardiovascular disease mortality. The confidence limits around our point estimates and the observed between-study heterogeneity for associations between breastfeeding and ischemic heart disease, however, do not rule out important beneficial or adverse cardiovascular effects of breastfeeding. • Although we found little evidence to support a cardioprotective effect of breastfeeding extending into old age, its beneficial influence on infant and child health and cognitive development supports the idea that it should be promoted as the infant feeding method of choice.
Comments / Limitations	We agree with authors' conclusion and discussion on the limitations of the meta-analyses. However, given large heterogeneity across studies (especially for IHD mortality), meta-analyses might not be appropriate. At least for the outcome of IHD mortality, men and women should be combined separately because of apparent effect modification by gender. Results from Hertford cohort were only adjusted for age.

Author, yr: Martin, 2004
Topic of the systematic review*/MA: CVD mortality

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Yes
2	Types of exposure or intervention used	Yes
3	Types of study designs used	Yes
4	Study population	Yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Yes
6	Effort to include all available studies (contact with authors)	Yes
7	Databases and registries searched	Yes
8	Method of addressing published articles other than English	No
9	Method of handling abstracts and unpublished studies	Yes
	Reporting of Methods	
10	Rationale for selection and/or coding of data	No
11	Assessment of confounding	Yes
12	Assessment of quality	Yes
13	Assessment of heterogeneity	Partially
14	Description of statistical methods sufficient to replicate	Yes
15	Provision of appropriate tables and graphs	Yes
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Yes
17	Tables giving descriptive information of each study included	Yes
18	Results of sensitivity testing (subgroup analysis)	No
19	Indication of statistical uncertainty of findings	Yes
20	Quantitative assessment of bias (eg. publication bias)	No
	Overall quality	**B**

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Yes
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	No
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Yes
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Partially
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	No
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Partially
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Yes
9	Were conclusions justified by the reported/collected data and analysis?	Yes

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

Leukemia

Beral 2001 SRMA*
Davis 1998 SRMA*
Guise 2005 SRMA*
Kwan 2004 SRMA*

* Systematic Review/Meta-Analysis

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI] Topic	Beral (or USCCS Investigators), 2000; 2001 Leukemia
Literature search (Dates)	ND
Countries where primary studies conducted	Mixed developed and developing countries
Study eligibility / inclusion criteria	Not described. Meta-analyses were performed for the associations between breastfeeding and leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, other childhood cancers and all childhood cancers combined. For the purpose of our review, we focus on childhood leukemia only.
Study design [No. Of studies]	Case-control studies [15]
No. of subjects	Cases: 7,401 Controls: 14,587
Study population (definition in included studies)	Cases: Children with all leukemia, including ALL Controls: ND
Intervention/Exposure (definition in included studies)	Ever breastfeeding Breastfeeding duration ≤ 6 months Breastfeeding duration > 6 months
Comparator (definition in included studies)	never breast fed
Outcomes (definition in included studies)	All leukemia, including ALL
Heterogeneity assessments	ND
Quality assessments	ND
Publication bias assessments	ND
Statistical Analysis or meta-analytic methods	This is a primary study (UKCCS study) plus meta-analyses. No methods of meta-analyses were described.
Results	The UKCCS results did not differ significantly from those of previous studies. Results from previous studies were combined with UKCCS results. For childhood leukemia, there is evidence of a statistically significant reduction in the OR associated with ever having been breastfed (OR=0.86, 95%CI 0.81-0.92) and having been breastfed for more than 6 months (OR=0.78, 95% CI 0.71-0.85).
Quality of the systematic review	C
Author's interpretations of the results	It is unclear whether the apparent small reduction in the risk of each type of childhood cancer reported here is a non-specific effect of breastfeeding on childhood cancer or whether it reflects some systematic bias shared by the majority of the case-control studies that have investigated etiological factors in childhood cancer. We are unable to decide which of these possibilities is the more likely.
Comments / Limitations	This is a primary study (UKCCS study) plus meta-analyses. Authors focused on their results regarding the association between breastfeeding and childhood cancer in UKCCS study. No methods for the meta-analyses were described. They did not report the standard steps required for a systematic review, including explicit search criteria, inclusion and exclusion criteria, and quality assessment. However, we agree with the author's interpretations of the results.

Author, yr: Beral 2000; 2001
Topic of the systematic review*/MA: Leukemia

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Yes
2	Types of exposure or intervention used	Yes
3	Types of study designs used	Yes
4	Study population	No
	Reporting of Search strategy	
5	Search strategy, including time period and key words	No
6	Effort to include all available studies (contact with authors)	No
7	Databases and registries searched	No
8	Method of addressing published articles other than English	No
9	Method of handling abstracts and unpublished studies	No
	Reporting of Methods	
10	Rationale for selection and/or coding of data	No
11	Assessment of confounding	No
12	Assessment of quality	No
13	Assessment of heterogeneity	Yes
14	Description of statistical methods sufficient to replicate	Yes
15	Provision of appropriate tables and graphs	Yes
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Yes
17	Tables giving descriptive information of each study included	No
18	Results of sensitivity testing (subgroup analysis)	No
19	Indication of statistical uncertainty of findings	Yes
20	Quantitative assessment of bias (eg. publication bias)	No
	Overall quality	C

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Unclear
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	No
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	No
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	No
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	No
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	No
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	No
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Yes
9	Were conclusions justified by the reported/collected data and analysis?	Yes

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI] Topic	Davis, 1998 Leukemia
Literature search (Dates)	Medline ("over the past 10 to 15 years"); Other databases searched? (no); unpublished data used? (no)
Countries where primary studies conducted	Primarily developed countries: UK, USA, Italy Included one developing country: China For the purpose of our review, we excluded the study from China
Study eligibility / inclusion criteria	Not described, except the author stated that hypothesis of the study was that artificial infant feeding (or never breast fed) increases the risk for cancer in childhood. For the purpose of our review, we focus on childhood leukemia only.
Study design [No. Of studies]	Case-control studies [5]
No. of subjects	All leukemia [reported in 1 study]- Cases: 171 Controls: 342 Acute lymphoblastic leukemia (ALL) [reported in all 5 studies]- Cases:1,356 Controls: 1,336 Acute non-lymphoblastic leukemia (ANLL) [reported in 2 studies]- Cases: 129 Controls: 379
Study population (definition in included studies)	Cases: Children with all leukemia, ALL or ANLL Controls: Children with no cancers, except for one study used children with rhabdomyosarcoma as controls
Intervention/Exposure (definition in included studies)	Any breastfeeding Long-term breastfeeding: more than 6 to 8 months
Comparator (definition in included studies)	Artificial infant feeding (or never breast fed)
Outcomes (definition in included studies)	"All leukemia, ALL, and ANLL"
Heterogeneity assessments	ND
Quality assessments	ND
Publication bias assessments	ND
Statistical Analysis or meta-analytic methods	No meta-analysis was performed. The odds ratio and 95% CI or p values for the relationship between infant feeding and cancer in childhood were provided in the papers; in other cases where the number of exposed and unexposed cases and controls were provided, additional effect estimates were calculated in order to compare studies.
Results	None of the included studies reported a significant association between all leukemia, ALL or ANLL and infant feeding.
Quality of the systematic review	C
Author's interpretations of the results	No evidence of an association between infant feeding and any childhood cancer except for Hodgkin's disease.
Comments / Limitations	The main purpose of this review was to examine the association between infant feeding and childhood cancer. Due to non-significant findings for leukemia, the author did not focus on the results on leukemia. Inclusion or exclusion criteria were not described, no assessments of study heterogeneity or methodology quality.

Author, yr: Davis, 1998
Topic of the systematic review*/MA: Leukemia

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Yes
2	Types of exposure or intervention used	Yes
3	Types of study designs used	Yes
4	Study population	Yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	No
6	Effort to include all available studies (contact with authors)	No
7	Databases and registries searched	Yes
8	Method of addressing published articles other than English	No
9	Method of handling abstracts and unpublished studies	No
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Yes
11	Assessment of confounding	No
12	Assessment of quality	No
13	Assessment of heterogeneity	No
14	Description of statistical methods sufficient to replicate	N/A
15	Provision of appropriate tables and graphs	Yes
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	No
17	Tables giving descriptive information of each study included	Yes
18	Results of sensitivity testing (subgroup analysis)	N/A
19	Indication of statistical uncertainty of findings	N/A
20	Quantitative assessment of bias (eg. publication bias)	N/A
	Overall quality	C

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	No
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	No
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	No
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	No
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	N/A
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	No
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Yes
9	Were conclusions justified by the reported/collected data and analysis?	Partially

Evidence table for Systematic Reviews of Breastfeeding

Author,Year[UI] Topic	Guise, 2005 Leukemia
Literature search (Dates)	Medline (1990-March 2004); Other databases searched? (no); unpublished data used? (no)
Countries where primary studies conducted	Developed countries only: Netherlands, Italy, US, Germany, Australia, New Zealand, Canada, England, Wales, Scotland, Sweden, France
Study eligibility / inclusion criteria	Studies providing data regarding the association of breastfeeding and occurrence of childhood leukemia. A study must have been in full text, been published after 1990, contained more than 100 participants, had concurrent comparison groups, been conducted in a developed country, and been published in the English language.
Study design [No. Of studies]	Case-control studies [10]
No. of subjects	9,653 leukemia cases
Study population (definition in included studies)	Cases: Childhood ALL or all childhood leukemias Controls: Matched or unmatched population (majority) and hospital controls
Intervention/Exposure (definition in included studies)	Any measures of breastfeeding
Comparator (definition in included studies)	Any
Outcomes (definition in included studies)	Childhood ALL or all childhood leukemias defined in the original studies
Heterogeneity assessments	ND
Quality assessments	2 independent investigators rated study quality by using criteria from the US Preventive Services Task Force and the National Health Service Center for Reviews and Dissemination. Three levels of grade: good, fair and poor quality. Studies received a poor rating if the cases were not assessed reliably, if the groups assembled were not comparable, if there was considerable attrition or differences in nonrespondents between cases and controls, or if there was not adequate consideration given to confounding.
Publication bias assessments	ND
Statistical Analysis or meta-analytic methods	No meta-analysis or statistical analysis was performed.
Results	Ten studies met all inclusion criteria and were reviewed for study quality to identify 2 good-quality case-control studies, 2 fair-quality studies, and 6 poor-quality studies. Of the 10 studies, 6 were conducted in European countries. All studies but 1 focused solely on childhood leukemia. The majority included <1000 cases. Notably, 6 of the studies explicitly sought to characterize the relationship between breastfeeding and leukemia as the primary objective, whereas the others included breastfeeding measures from the perspective measuring broader characteristics of the immune system and early infections in the etiology. The presented results focus on details and findings of the 2 good-quality studies, comparisons to the 2 fair quality studies, factors that distinguish them from studies rated as "poor" in quality, and implications for future research. The 2 good-quality studies (UKCCS and CCG studies) present conflicting results regarding the association between breastfeeding and leukemia. Similarly, the 2 fair-quality studies disagreed on the protective effect of breastfeeding.
Quality of the systematic review	A
Author's interpretations of the results	Of the 10 studies reviewed, only 4 were sufficient to provide at least fair-quality evidence regarding the association between maternal breastfeeding and childhood leukemia. Half of these 4 studies associated breastfeeding with a lower risk of ALL. Our review differs in methodology from previous meta-analyses performed by Beral et al and Kwan et al. Either of these groups examined studies for quality or used quality ratings as a determinate for

Author,Year[UI] Topic	Guise, 2005 Leukemia
	inclusion in analysis. The primary findings of our review indicate that there are few high-quality studies. The studies frequently failed to measure important factors such as breastfeeding exclusivity (reporting ever breastfed rather than quantifying breastfeeding by exclusivity combined with duration) and consideration of other important confounders such as SES and other infectious exposures (such as household or school contacts). None of the studies included in this systematic review ere without flaw. An optimal study might be conducted within the framework of a large population-based registry or cohort with full access to medical records, pathology, and demographic data that would be able to accurately identify all cases of ALL diagnosed (with pathologic confirmation) at >1 year of age within a defined time period.
Comments / Limitations	A meta-analysis by Beral, 2001 (or UKCCS investigators) seemed to have performed a comprehensive search, but they did not report the standard steps required for a systematic review, including explicit search criteria, inclusion and exclusion criteria, and quality assessment. This meta-analysis included 15 studies. Of these 15 studies, 8 were also included in Guise, 2005. Four were excluded because they were published before 1990, and 3 were conducted in developing countries. Guise, 2005 (10 studies included) and Kwan, 2004 (14 studies included) had same set of studies, except that Guise excluded studies published before1990, and in developing countries. Guise, 2005 did not include non-peer-reviewed studies. Guise et al. discussed the differences between their review and previous meta-analyses by UKCCS investigators and Guise, 2005 in details. We thought their comments were fair. It would have been preferable if meta-analyses by taking into account study quality grading were also performed.

Author, yr: Guise, 2005
Topic of the systematic review*/MA: Leukemia

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Yes
2	Types of exposure or intervention used	Yes
3	Types of study designs used	Yes
4	Study population	Yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Yes
6	Effort to include all available studies (contact with authors)	No
7	Databases and registries searched	Yes
8	Method of addressing published articles other than English	No
9	Method of handling abstracts and unpublished studies	No
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Yes
11	Assessment of confounding	Yes
12	Assessment of quality	Yes
13	Assessment of heterogeneity	N/A
14	Description of statistical methods sufficient to replicate	N/A
15	Provision of appropriate tables and graphs	Yes
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	No
17	Tables giving descriptive information of each study included	Yes
18	Results of sensitivity testing (subgroup analysis)	N/A
19	Indication of statistical uncertainty of findings	N/A
20	Quantitative assessment of bias (eg. publication bias)	N/A
	Overall quality	**A**

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Yes
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	Yes
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Yes
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Yes
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	No
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Yes
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Yes
9	Were conclusions justified by the reported/collected data and analysis?	Partially

Evidence table for Systematic Reviews of Breastfeeding

Author, Topic Year[UI]	Kwan, 2004 Leukemia
Literature search (Dates)	Medline (up to 2003); Other databases searched? (yes); unpublished data used? (yes)
Countries where primary studies conducted	Mostly developed countries: Netherlands, Italy, US, Germany, Australia, New Zealand, Canada, England, Wales, Scotland, Sweden, France 2 developing countries: China, Russia,
Study eligibility / inclusion criteria	Studies that presented data on any type of leukemia on children 15 years or younger in terms of an odds ratio and confidence interval and analyzed duration of breastfeeding in months were selected for the analysis.
Study design [No. Of studies]	Case-control studies [n=14] *Note 12 studies in developed countries. Since this is a meta-analysis article, we could not separate these 12 studies. Three of the 14 studies were not peer-reviewed.
No. of subjects	6,835 ALL cases and 1,216 acute myeloid leukemia (AML), which included ANLL
Study population (definition in included studies)	Eight of the 14 studies excluded cases of leukemia in infants (usually children younger than 1 year of age) to avoid possible biases associated with premature cessation of breastfeeding in children with cancer and also because most leukemias occurring during infancy are know to have different etiologies from childhood leukemias.
Intervention/Exposure (definition in included studies)	Short-term breastfeeding, defined as breastfeeding for six months or less Long-term breastfeeding, defined as breastfeeding for more than six months
Comparator (definition in included studies)	No breastfeeding or never been breast-fed
Outcomes (definition in included studies)	The ALL classification was generally straightforward, with only one study specifying “leukemia” instead of “ALL”. Four studies used the classifications “other leukemias” or ANLL instead of AML. Nevertheless, they were included in the AML group since the majority of such cases are AML cases.
Heterogeneity assessments	Chi-square statistic
Quality assessments	ND, although there are comments on the potential biases for each included study in the summary tables
Publication bias assessments	Funnel plot
Statistical Analysis or meta-analytic methods	Fixed- and random-effect models. For each of the 14 articles reviewed, and R and its 95% CI were extracted. When available, ORs adjusted for SES were selected since SES was the most widely used potential confounder in these studies.
Results	• No evidence of publication bias was apparent for studies reporting results on the association between long-term breastfeeding and risk of ALL (p=0.58) or AML (p=0.46). • A significant negative association was observed between short-term breastfeeding and ALL (OR=0.88, 95%CI 0.80-0.96), but the AML results (OR=0.90, 95%CI 0.80-1.02) were not significant. • A significant negative association was observed between long-term breastfeeding and ALL (OR=0.76, 95%CI 0.68-0.84), and AML (OR=0.85, 95%CI 0.73-0.98). • Heterogeneity statistics for leukemia types and duration of breastfeeding were not significant except for the ALL analysis addressing short-term breastfeeding (p=0.03). However, the results from fixed- and random-effect models were almost exactly the same. • The following table (modified from table 4 in the original table) shows the ORs for SES-adjusted data from the meta-analysis , as well as separately from the United Kingdom Childhood Cancer study (UKCCS) and the Children’s Cancer Group (CCG) study. Overall, SES as a potential confounder appeared to play no substantial role in the findings of either the short-term or long-term breastfeeding studies.

Author, Year[UI]	Topic	Kwan, 2004	Leukemia

Duration of breastfeeding	*OR (95% CI)*	
	ALL	AML
Meta-analysis	N=6470 (85%)	N=1179 (15%)
≤6 months	0.90 (0.82, 0.99)	0.91 (0.80, 1.04)
>6 months	0.75 (0.67, 0.85)	0.85 (0.73, 0.98)
UKCCS 2001	N=1401 (87%)	N=214 (13%)
≤6 months	0.90 (0.77, 1.04)	0.85 (0.60, 1.20)
>6 months	0.89 (0.75, 1.05)	0.65 (0.43, 1.00)
CCG study 1999	N=1744 (79%)	N=456 (21%)
≤6 months	0.86 (0.73, 1.01)	0.95 (0.68, 1.33)
>6 months	0.72 (0.60, 0.87)	0.57 (0.39, 0.84)

Quality of the systematic review	A
Author's interpretations of the results	This meta-analysis demonstrated protective association between breastfeeding and risk of childhood ALL and possibly AML. However, three alternative explanations must be considered First, a systematic bias may be present in case-control studies of childhood leukemia arising from differential participation rates for case and control samples that differed in SES. In the current meta-analysis, participation rates could be calculated for only six of the 14 included studies. For five of these six studies, the participation rates for cases were higher than those for controls, and in most of these studies, the controls were higher SES than the cases. Therefore the association of breastfeeding with SES in combination with differential participation rates by SES could have biased the OR toward a protective effect. Second, the effect on ALL risk may be spurious, as suggested by the results of the two cohort studies (Ref#22 and 23), unfortunately, these studies provided no information regarding AML. Third, the protective effect of breastfeeding may not be limited to ALL. Further evaluation of the biological mechanisms while taking into consideration potential biases can be feasibly achieved with more large-scale case-control studies utilizing population-based, SES-matched controls. In conclusion, the potential protective effect of breastfeeding on risk of childhood ALL may be more complicated than the current literature suggests. Nevertheless, the available evidence suggests that such a protective effect exists for both ALL and AML, with the caveats noted.
Comments / Limitations	We agree with authors' concerns regarding potential biases in the included studies. Their conclusion was appropriately cautious. However, the review still combined all studies regardless of these potential biases, and over-emphasized the importance of the results from the meta-analysis. We could not determine whether specific study should be included in the analyses. Perhaps combining results from only high-quality studies would be preferable, but unfortunately the review did not appraise the methodological quality of the primary studies.

Author, yr: Kwan, 2004
Topic of the systematic review*/MA: Leukemia

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Yes
2	Types of exposure or intervention used	Yes
3	Types of study designs used	Yes
4	Study population	Yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Yes
6	Effort to include all available studies (contact with authors)	Yes
7	Databases and registries searched	Yes
8	Method of addressing published articles other than English	No
9	Method of handling abstracts and unpublished studies	Yes
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Yes
11	Assessment of confounding	Yes
12	Assessment of quality	Yes
13	Assessment of heterogeneity	Yes
14	Description of statistical methods sufficient to replicate	Yes
15	Provision of appropriate tables and graphs	Yes
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Yes
17	Tables giving descriptive information of each study included	Yes
18	Results of sensitivity testing (subgroup analysis)	Yes
19	Indication of statistical uncertainty of findings	Yes
20	Quantitative assessment of bias (eg. publication bias)	Yes
	Overall quality	**A**

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Yes
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	No
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Yes
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Yes
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Yes
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Yes
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Yes
9	Were conclusions justified by the reported/collected data and analysis?	Yes

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

Cognitive

Agostoni 2001
Anderson 1999 SRMA*
Angelsen 2001
Der 2006
Drane 2000 SRMA*
GomezSanchiz 2003 2004
Jain 2002 SRMA*
Lawlor 2006
Mortensen 2002
Oddy 2003 2004
Quinn 2001

* Systematic Review/Meta-Analysis

Agostoni, 2001 [11787675]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): term Mean BW (range): % Male: 55% Race: Enrolled/Evaluate: 44/44 Location: Italy Sites: Single/Multi Funding:	Prospective cohort; Bayley results at 1 y/o were compared in breastfeeding ≥6 mo with 3-6 mo	Term infants; exclusively breastfed ≥3 mo		

Agostoni, 2001 [11787675]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Cognitive outcome of interest: Bayley Mental Development Index (MDI)	Adjustment for parity, maternal education, age, and smoking habits	After adjustment, Bayley MDI in 29 subjects breastfed >6 mo compared to 15 subjects breastfed 3-6 mo showed a 2.0 point advantage (95% CI –3.2, 7.3).	A: strong, B: moderate, C: weak / A / B / C Selection / / / x Study design / / / x Confounder / / x / Blinding / / x / Data collection / / / Withdrawal and dropout / / / x Analyses / / / x Intervention integrity / / / Overall: C Small sample size, Bayley at young age

Evidence table for Systematic Reviews

Author, Year[UI] Topic	Anderson, 1999 [UI] Cognitive Development
Systematic reviews/Meta-analyses/Both	Meta-analysis
Databases searched (Dates of literature search)	Medline (1966-1996); references identified in bibliographies.
Countries where primary studies conducted (Developed countries only or mixed)	Developed countries only: UK, US, Australia, Germany, New Zealand, and Spain
Study design [No. of studies]	Observational (n=11)
No. of subjects	7,081
Study population and sampling	• Studies of association between breastfeeding and cognitive development in full-term and low-birth weight infants (?premature)
Intervention/Exposure Comparator	Many of the studies that were reviewed only reported breastfeeding versus bottle feeding, without more detailed information on exclusivity, frequency, or duration. Information on timing and duration of breastfeeding were included where available.
Outcomes	•
Methods used for meta-analyses	Both fixed effects and random effects were calculated
Heterogeneity assessments	See below
Results	• Unadjusted (fixed effects) pooled mean difference for the 11 observations was 5.32 (95% CI, 4.51, 6.14); heterogeneous across studies • Adjusted (fixed effects) pooled mean difference was 3.16 (95% CI, 2.35, 3.98); homogeneous across studies • An average adjusted benefit of 5.18 points was obtained for low-birth weight children across 6 available observations
Authors' conclusions	After adjustment for key cofactors, breast-feeding was associated with significantly higher scores for cognitive development than was formula feeding
Quality of the systematic review	B
Comments	No appraisals of study quality (other than confounding); effect score is a standardized mean difference score of different cognitive measurements

Author, yr: Anderson, 1999
Topic of the systematic review*/MA: Cognitive SR

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Y
2	Types of exposure or intervention used	Y
3	Types of study designs used	Y
4	Study population	Y
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Y/N
6	Effort to include all available studies (contact with authors)	N
7	Databases and registries searched	Y
8	Method of addressing published articles other than English	N
9	Method of handling abstracts and unpublished studies	N
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Y
11	Assessment of confounding	Y
12	Assessment of quality (in addition to confounding)	N
13	Assessment of heterogeneity	Y
14	Description of statistical methods sufficient to replicate	Y
15	Provision of appropriate tables and graphs	Y
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Y
17	Tables giving descriptive information of each study included	Y
18	Results of sensitivity testing (subgroup analysis)	Y
19	Indication of statistical uncertainty of findings	Y
20	Quantitative assessment of bias (eg. publication bias)	N
	Overall quality	

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Y
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Y
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Y/N
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	N
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	N
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Y/N
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Y
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Y
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Y
9	Were conclusions justified by the reported/collected data and analysis?	Y

Angelsen, 2001 [11517096]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 39.6 wk Mean BW (range): 3656 g % Male: Race: white Enrolled/Evaluate: 521/345/291 (5 yr) Location: Norway & Sweden Sites: Multi Funding:	Prospective cohort; 10% randomly selected from eligible population; Duration of breastfeeding: retrospectively recorded	White, parity 1 or 2, singleton, registered prior to 20th wk gestation Excluded: <37 wk gestation, congenital malformation	<3 mo, 3-6 mo, ≥ 6 mo	

Angelsen, 2001 [11517096]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Cognitive outcomes of interest: Bayley mental scores at 13 mo Wechsler Preschool and Primary Scales of Intelligence (WPPSI-R) at 5 y/o	Maternal IQ, age, education, smoking	Bayley mental score at 13 mo: 117.7 (SD11.7) in ≥ 6 mo breastfeeding compared to 109.9 (SD13.1) in < 3 mo (P<0.001). There was a linear increase in mental development index plotted against breastfeeding duration (P<0.001). Maternal intelligence (Raven test score) was also related to duration of breastfeeding. Adjustment for differences in maternal intelligence reduced the OR of having a low mental developmental index among children who were breast fed for <3 mo to 1.6 (95%CI 1.1-2.3) from 3.2 (95%CI 1.7-5.9). Total IQ at 5 y/o: 111 (SD14.3) in ≥ 6 mo breastfeeding compared to 103.6 (SD14.6) in < 3 mo (P<0.001, Sheffe's test). Adjustment for differences in maternal intelligence reduced the OR of having a low IQ score among children who were breastfed for <3 mo to 1.5 (95%CI 1.0-2.1) from 2.8 (95%CI 1.4-5.3).	A: strong, B: moderate, C: weak — A: ; B: ; C: Selection — B: x Study design — C: x Confounder/bias — B: x Blinding — B: x Data collection — B: x Withdrawal and dropout — C: x Analyses — B: x Intervention integrity Overall: B Results from multivariate analyses not reported.

Der, 2006 UI 17020911

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): term Mean BW (range): % Male: Race: Enrolled/Evaluate: 3161 mothers and 5475 children Location: US Sites: Multi Funding:	Database analysis of a prospective study; sibling pairs analysis, and meta-analysis; Database from the US national longitudinal survey of youth 1979 (NLSY79) and children of the women in the survey, Peabody individual achievement test (PIAT) was administered to children between the ages of 5 and 14 biennially from 1986 to 2002, all outcomes standardized to a mean of 100 and SD of 15; maternal cognitive ability was measured with the Armed Forces Qualification Test (AFQT); For meta-analysis, only included studies that quantified the effect of breastfeeding status on cognitive ability after controlling for parental intelligence among full term infants (Medline 1966 to 1/2006 and other sources)	Excluded <35 wk gestation, <2500 g, born before 1979	Breastfeeding history obtained within a year of birth in most cases	

Der, 2006

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Cognitive outcome of interest: Peabody individual achievement test	Adjustment for variables associated with breastfeeding in the survey, home environment (HOME-SF), child demographics, maternal characteristics	Unadjusted effect of breastfeeding +4.7 compared to non-breastfeeding (3161 mothers, 5475 children, 16,744 assessments); after adjustment for maternal AFQT score, education, age, family poverty, HOME stimulation score, and birth order, the difference became +0.52 (P=0.149) 332 pairs of sibling discordant for breastfeeding status and 545 discordant for duration of breastfeeding, difference between groups (status) = -0.63 (P=0.506); (duration) = -0.13 (P=0.866) Meta-regression of 9 unique studies (including the data from NLSY79): an advantage of breastfeeding of 0.16 after controlling for IQ and 8 additional confounders. Combined data from NLSY79 and sibling analysis study by Evenhouse (see separate extraction): estimate 0.025 (P=0.54) for breastfeeding status and 0.04 (P=0.271) for duration of breastfeeding	A: strong, B: moderate, C: weak: A / B / C Selection: / x / Study design: x / / Confounder: x / / Blinding: / / Data collection: / / Withdraw and dropout: x / / Analyses: x / / Intervention integrity: / / Overall: A No details regarding breastfeeding history

Domain/question	***Place an "X" in one***				
Selection Bias					
Are individuals selected to participate likely to be representative of target population?	Very likely	Somewhat likely	Not likely		
What % of selected individuals agreed to participate?	80-100	60-79	<60	ND	NA
Allocation Bias (RCTs only, for quasi-experimental, case-control/before/after, no control group or other skip to "Confounders")					
Is the method of random allocation stated	Yes	No			
If the method of random allocation is stated, is it appropriate	Yes	No			
Was the method of random allocation reported as concealed?	Yes	No			
Confounders					
Prior to the intervention, were there between group differences for important confounders reported in the paper?	Yes	No	Can't tell		
If there were differences between groups for important confounders, were they adequately managed in the analysis?	Yes	No	NA		
Were there important confounders NOT reported in the paper (describe above under quality score)?	Yes	No			
Blinding					
Was (were) the outcome assessor(s) blinded to the intervention or exposure status of the participants?	Yes	No	ND	NA	
Data Collection methods					
Were data collection tools shown or are they known to be valid?	Yes	No			
Were data collection tools shown or are they known to be reliable?	Yes	No			
Withdrawals and Dropouts					
Indicate the % of participants completing the study. (If the % differs by groups, record the lowest).	80-100	60-79	<60	ND	NA
Analysis					
Is there a sample size calculation or power calculation	Yes	Partially	No		
Is there a statistically significant difference between groups?	Yes	No	ND		
Are the statistical methods appropriate?	Yes	No	ND		
Indicate the unit of allocation	Community	Organization/group	Provider	Client	Institution
Indicate the unit of analysis	Community	Organization/group	Provider	Client	Institution
If the unit of allocation and analysis differed, was the cluster analysis done?	Yes	No	NA		
Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?	Yes	No	Can't tell		
Intervention Integrity					
What % of participants received the allocated intervention or exposure of interest?	80-100	60-79	<60	ND	NA
Was the consistency of the intervention measured (i.e. intervention was provided to all participants in the same way)?	Yes	No	ND	NA	
Is it likely that subjects received an unintended intervention (contamination or cointervention) that may influence the results?	Yes	No	Can't tell		

Evidence table for Systematic Reviews of Breastfeeding

Author,Year[UI] Topic	Drane 2000 Cognitive Development
Literature search (Dates)	Database not specified; literature search from 1966-98
Countries where primary studies conducted	
Study eligibility / inclusion criteria	Subjects born between 1960 and 1998, English language, studies examined some aspect of cognitive development
Study design [No. Of studies]	Studies were assessed to determine if they met 3 methodological standards: definition of outcome: operational definition of cognitive outcome and outcome measure using standardized tests; correct classification of type of feeding: measure breast feeding as a continuous variable (duration of exclusive breast feeding or proportion of diet as breast milk) or at least as a 3-level categorical variable (exclusive breast or formula fed; partial breast fed); and control for potential confounding variables: socio-economic status, maternal education, birth weight, gestational age, birth order, gender in studies measuring verbal ability
No. of subjects	
Study population (definition in included studies)	Term and preterm infants
Intervention/Exposure (definition in included studies)	
Comparator (definition in included studies)	
Outcomes (definition in included studies)	
Heterogeneity assessments	
Quality assessments	
Publication bias assessments	
Statistical Analysis or meta-analytic methods	
Results	24/30 studies met entry criteria. 5 studies met the 3 methodological standards. Lucas 1992, Lucas 1994, Horwood 1998, Malloy 1998; Rogan 1993 (considered to have met 2.5 standards because the duration that a baby was mostly breast fed was measured) Lucas 1994 was a RCT, the remaining 5 studies were cohorts. Advantages in IQ as measured by the WISC-R, Bayley and McCarthy Scales were observed in Lucas 1992, Rogan 1993, Pollock 1994, and Horwood 1998. In term infants, effects on IQ in the range of 2-5 points (0.2-0.3 SD) were found. In low birth weight infants who received breast milk, Lucas 1992 reported an 8 IQ point advantage. Lucas 1994 did not find statistical significant difference in Bayley Mental Development Scale scores in infants fed solely on a diet of donor breast milk compared with infants fed solely on a diet of term formula. Malloy 1998 did not find an effect of infant feeding on WISC-R scores at 9-10 years of age in term infants.
Quality of the systematic review	B
Author's interpretations of the results	"The question of whether breast feeding and formula feeding have differential effects on cognitive development has not been comprehensively answered. A minority of the studies reviewed met acceptable standards for validity and, thus, are likely to provide inaccurate estimates of the association between infant feeding and cognitive development."
Comments / Limitations	The methodological standards proposed may not be universally accepted. Study designs were not taken into consideration. Conclusions are also limited by the fact that almost all the studies were cohorts.

Author, yr: Drane, 2000
Topic of the systematic review*/MA: cognitive

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Y
2	Types of exposure or intervention used	Y
3	Types of study designs used	Y
4	Study population	Y
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Y
6	Effort to include all available studies (contact with authors)	N
7	Databases and registries searched	N
8	Method of addressing published articles other than English	N
9	Method of handling abstracts and unpublished studies	N
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Y
11	Assessment of confounding	Y
12	Assessment of quality	Y
13	Assessment of heterogeneity	Y/N
14	Description of statistical methods sufficient to replicate	N/A
15	Provision of appropriate tables and graphs	Y
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Y
17	Tables giving descriptive information of each study included	Y/N
18	Results of sensitivity testing (subgroup analysis)	N/A
19	Indication of statistical uncertainty of findings	N/A
20	Quantitative assessment of bias (eg. publication bias)	N/A
	Overall quality	

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Y/N
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Y
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Y
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	N
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Y/N
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Y
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Y
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Y/N
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Y
9	Were conclusions justified by the reported/collected data and analysis?	Y

GomezSanchiz, 2003 [12635980]
GomezSanchiz, 2004 [15494884]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 39.6 wk Mean BW (range): 3344 g % Male: Race: Enrolled/Evaluate: 296/249 at 18 mo; 238 at 24 mo Location: Spain Sites: 1 rural, 1 urban Funding:	Prospective cohort from 1 rural (born 10/1995-9/1997) and 1 urban (born 3/1996-2/1998) sites, comparing breastfed > 4 mo, <4 mo, and formula fed; parents were informed of the project at 15 mo, Bayley was administered at 18 mo and 24 mo	37-42 wk gestation, Apgar at 5 minutes ≥7, birthweight 2500-4500 g; Exclusion: multiple births, adopted babies, mechanical ventilation, hospitalization during the neonatal period, major physical malformation, chromosome disorder, psychosocial risks or any circumstances likely to result in "retarded development", height or weight <3%tile at 18 mo	Information about type and duration of feeding was taken from medical records	

GomezSanchiz, 2003 [12635980]
GomezSanchiz, 2004 [15494884]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Cognitive outcome of interest: Bayley Mental Development index	Adjusted for parental IQ	249/296 completed the study at 18 mo; 238 completed the study at 24 mo; the only difference between children taking part in the study and those not taking part was that the latter were less frequently first in birth order. Parental IQ was obtained only for 164 couples; their children had Mental Development Index 2.3 points higher than the children whose parents did not take part in IQ testing (P<0.05). Infants were breastfed for a mean of 85.7 days ± SD 76.4 days. Duration of breastfeeding had a correlation with Mental Development Index at 18 mo (r=0.42; P<0.001) and at 24 mo (r=0.37; P<0.001). Mental Development Index at 18 mo Formula 106.0±9.2 Breastfeeding ≤ 4 mo 111.5±9.6 Breastfeeding > 4 mo 118.2±8.9 P<0.05 by Bonferroni in all post hoc pair comparisons At both 18 mo and 24 mo, after multiple linear regression adjusting for parental IQ, difference between formula and breastfeeding ≤ 4 mo no longer significant; difference of 4.3 points remained significant when comparing breastfeeding > 4 mo with ≤ 4 mo.	A: strong, B: moderate, C: weak — A / B / C Selection — x Study design — x Confounder — B: x Blinding — B: x Data collection — B: x Withdrawal and dropout — B: x Analyses — B: x Intervention integrity Overall: B

Domain/question	***Place an "X" in one***				
Selection Bias					
Are individuals selected to participate likely to be representative of target population?	Very likely	Somewhat likely	Not likely		
What % of selected individuals agreed to participate?	80-100	60-79	<60	ND	NA
Allocation Bias (RCTs only, for quasi-experimental, case-control/before/after, no control group or other skip to "Confounders")					
Is the method of random allocation stated	Yes	No			
If the method of random allocation is stated, is it appropriate	Yes	No			
Was the method of random allocation reported as concealed?	Yes	No			
Confounders					
Prior to the intervention, were there between group differences for important confounders reported in the paper?	Yes	No	Can't tell		
If there were differences between groups for important confounders, were they adequately managed in the analysis?	Yes	No	NA		
Were there important confounders NOT reported in the paper (describe above under quality score)?	Yes	No			
Blinding					
Was (were) the outcome assessor(s) blinded to the intervention or exposure status of the participants?	Yes	No	ND	NA	
Data Collection methods					
Were data collection tools shown or are they known to be valid?	Yes	No			
Were data collection tools shown or are they known to be reliable?	Yes	No			
Withdrawals and Dropouts					
Indicate the % of participants completing the study. (If the % differs by groups, record the lowest).	80-100	60-79	<60	ND	NA
Analysis					
Is there a sample size calculation or power calculation	Yes	Partially	No		
Is there a statistically significant difference between groups?	Yes	No	ND		
Are the statistical methods appropriate?	Yes	No	ND		
Indicate the unit of allocation	Community	Organization/group	Provider	Client	Institution
Indicate the unit of analysis	Community	Organization/group	Provider	Client	Institution
If the unit of allocation and analysis differed, was the cluster analysis done?	Yes	No	NA		
Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?	Yes	No	Can't tell		
Intervention Integrity					
What % of participants received the allocated intervention or exposure of interest?	80-100	60-79	<60	ND	NA
Was the consistency of the intervention measured (i.e. intervention was provided to all participants in the same way)?	Yes	No	ND	NA	
Is it likely that subjects received an unintended intervention (contamination or cointervention) that may influence the results?	Yes	No	Can't tell		

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI]	Topic	Jain, 2002	Cognitive Development
Literature search (Dates)	Medline (1996-2/2001); Other databases searched? (no); unpublished data used? (no)		
Countries where primary studies conducted			
Study eligibility / inclusion criteria	English language studies; independently assessed the relationship between breastfeeding and a cognitive outcome; tests of motor ability alone were not included		
Study design [No. Of studies]	30 birth cohorts; 2 RCTs; 5 school registry cohorts; 3 case-control studies		
No. of subjects	Ranged from 50 to >11,000		
Study population (definition in included studies)	Term and pre-term children		
Intervention/Exposure (definition in included studies)	Breastfeeding, breast milk, or choice to breast feed		
Comparator (definition in included studies)			
Outcomes (definition in included studies)	Appropriate outcome: standardized individual measure of general intelligence and that the assessment be done when the child was at least 2 years of age		
Heterogeneity assessments			
Quality assessments	Following were examined for each article: overall design of the study, sample size, target population, quality of feeding data, control of susceptibility bias, blinding, outcome measures, and format of results		
Publication bias assessments			
Statistical Analysis or meta-analytic methods			
Results	40 studies from 1929 to 2/2001 were included in this review 1. 40 separate papers were published. Because some of these papers investigated the same sample, there were only studies of 33 different groups of children. 2. 30 cohorts (27 with full-term children), 2 RCTs in preterm children, 5 school registry cohorts, and 3 case-control studies. 3. 35 articles either studied mixed full-term and preterm infants, only full-term infants, or did not specify the gestational age or birth weight. 5 articles studied exclusively low birth weight infants. 4. Sample size ranged from 50 to >11,000 5. Quality of feeding data (exclusive breastfeeding or not, timing of feeding data collection, source of feeding data, duration of breastfeeding): 9 articles met all 4 criteria (8 full-term cohorts); 15 articles did not adequately define breastfeeding by failing to report whether infants only received breast milk or were supplemented with formula or food. 2 preterm observational birth cohorts did not meet standard for appropriate definition of breastfeeding, it was defined as the "intent to breastfeed." 21 studies did not meet the standard for timing of data collection because the information was obtained either too late or too early. 27 included a feeding group for whom breastfeeding duration was at least 1 month. 6. 9 studies controlled adequately for both socioeconomic status and level of stimulation of the child; 31 studies controlled for socioeconomic status. 7. 15 studies stated that observers of the outcome were blind to feeding status. 8. 22 studies used an appropriate measure of cognition. Of the remaining studies, 8 measured outcomes in children <2 years of age, 3 used screening measures to		

Author, Year[UI]	Topic	Jain, 2002	Cognitive Development
		assess cognition, 1 case control study used the presence of a learning disorder as its outcome measure, the other 2 case control studies used the diagnoses of pervasive developmental disorder and infantile autism, respectively, as outcome measures. 9. 33 studies reported some way to interpret the clinical significance of results, and 21 allowed calculation of an effect size. 10. 7 studies that found that the effects of breastfeeding statistically significant in the unadjusted analysis, became insignificant when controlling for socioeconomic status, stimulation, or other factors. 11. Only 2 studies met all the methodological standards. One study concluded that "any beneficial effect of breastfeeding on cognitive development is quite small in magnitude", another study found that children who were breastfed had mean IQ scores 4.6 points higher than those never breastfed after controlling for socioeconomic status and other factors. Among the studies that controlled for socioeconomic status and stimulation/interaction of the child (not including the previous 2), 3 concluded that breastfeeding promotes cognitive development, and 4 did not.	
Quality of the systematic review		A	
Author's interpretations of the results		"No convincing evidence exists regarding he comparative effects of breastfeeding and artificial feeding on intelligence."	
Comments / Limitations		Selection of methodological standards may not be acceptable to all investigators.	

Author, yr: Jain, 2002
Topic of the systematic review*/MA: cognitive

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Y
2	Types of exposure or intervention used	Y
3	Types of study designs used	Y
4	Study population	Y
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Y
6	Effort to include all available studies (contact with authors)	N
7	Databases and registries searched	Y
8	Method of addressing published articles other than English	Y
9	Method of handling abstracts and unpublished studies	N
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Y
11	Assessment of confounding	Y
12	Assessment of quality	Y
13	Assessment of heterogeneity	Y/N
14	Description of statistical methods sufficient to replicate	Y
15	Provision of appropriate tables and graphs	Y
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	N/A
17	Tables giving descriptive information of each study included	Y
18	Results of sensitivity testing (subgroup analysis)	N
19	Indication of statistical uncertainty of findings	Y/N

		Reporting yes/no
20	Quantitative assessment of bias (eg. publication bias)	N
	Overall quality	

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Y
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Y
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Y
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	Y
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Y
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Y
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Y
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Y/N
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Y
9	Were conclusions justified by the reported/collected data and analysis?	Y

Lawlor 2006 [16466433]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): term and preterm (>98% term in followup N=3794) Mean BW (range): 3794 (% Male: 52% Race: Enrolled/Evaluate: 7223/3999 (5 yrs)/3794 (14 yrs) Location: Australia Sites: Single Funding:	Prospective cohort; Peabody Picture Vocabulary test at 5 years and Raven's standard progressive matrices at 14 years	Live birth who did not die before discharge from hospital	Duration of breastfeeding (never, <4 mos, ≥ 4 mos) was obtained from mothers at the 6-month followup assessment	

Lawlor 2006 [16466433]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>Cognitive outcome of interest: Raven's standard progressive matrices at 14 years</td>
<td>Adjustment for sex, parental characteristics (maternal age, ethnicity, education, paternal education, family income, gravidity, maternal smoking), labor, Apgar scores, birthweight, height, BMI</td>
<td>At age 14 years, Never breastfed = 694, <4 months = 1372, ≥ 4 months = 1606
All parental characteristics were related to offspring IQ score. Unadjusted scores at age 14 showed a mean difference of 4.43 (95%CI 3.09 to 5.77) in <4 mos breastfeeding vs never breastfeeding; 8.20 (95%CI6.89 to9.49) in ≥ 4 mos breastfeeding vs never breastfeeding (P<0.001)

Adjusted scores at age 14 (N=3099) for sex, parental characteristics (maternal age, ethnicity, education, paternal education, family income, gravidity, maternal smoking), labor, Apgar scores, birthweight, height, BMI showed a mean difference of 4.07 (95%CI 2.61 to 5.53) in <4 mos breastfeeding vs never breastfeeding; 6.79 (95%CI 5.33 to 8.26) in ≥ 4 mos breastfeeding vs never breastfeeding (P<0.001)

Family income, parental education and breastfeeding explained 7.5% of the variation in intelligence at age 14.

Loss to followup was selective, those subjects were more likely to have mothers who were from poorer social backgrounds, lower education, and younger; regression analysis repeated using Heckman's sample selection bias adjustment with maternal age, parental education, and family income as the selection variables; results of these regression models did not differ from those who had followup.</td>
<td>
<table>
<tr><td>A: strong, B: moderate, C: weak</td><td>A</td><td>B</td><td>C</td></tr>
<tr><td>Selection</td><td>x</td><td></td><td></td></tr>
<tr><td>Study design</td><td></td><td>x</td><td></td></tr>
<tr><td>Confounder</td><td>x</td><td></td><td></td></tr>
<tr><td>Blinding</td><td></td><td></td><td>x</td></tr>
<tr><td>Data collection</td><td></td><td></td><td></td></tr>
<tr><td>Withdrawal and dropout</td><td></td><td></td><td>x</td></tr>
<tr><td>Analyses</td><td>x</td><td></td><td></td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td></td></tr>
</table>
Overall: B
No information on exclusivity of breastfeeding, unclear if cognitive evaluation is blinded, large drop out
</td>
</tr>
</table>

Domain/question	***Place an "X" in one***				
Selection Bias					
Are individuals selected to participate likely to be representative of target population?	Very likely	Somewhat likely	Not likely		
What % of selected individuals agreed to participate?	80-100	60-79	<60	ND	NA
Allocation Bias (RCTs only, for quasi-experimental, case-control/before/after, no control group or other skip to "Confounders")					
Is the method of random allocation stated	Yes	No			
If the method of random allocation is stated, is it appropriate	Yes	No			
Was the method of random allocation reported as concealed?	Yes	No			
Confounders					
Prior to the intervention, were there between group differences for important confounders reported in the paper?	Yes	No	Can't tell		
If there were differences between groups for important confounders, were they adequately managed in the analysis?	Yes	No	NA		
Were there important confounders NOT reported in the paper (describe above under quality score)?	Yes	No			
Blinding					
Was (were) the outcome assessor(s) blinded to the intervention or exposure status of the participants?	Yes	No	ND	NA	
Data Collection methods					
Were data collection tools shown or are they known to be valid?	Yes	No			
Were data collection tools shown or are they known to be reliable?	Yes	No			
Withdrawals and Dropouts					
Indicate the % of participants completing the study. (If the % differs by groups, record the lowest).	80-100	60-79	<60	ND	NA
Analysis					
Is there a sample size calculation or power calculation	Yes	Partially	No		
Is there a statistically significant difference between groups?	Yes	No	ND		
Are the statistical methods appropriate?	Yes	No	ND		
Indicate the unit of allocation	Community	Organization/group	Provider	Client	Institution
Indicate the unit of analysis	Community	Organization/group	Provider	Client	Institution
If the unit of allocation and analysis differed, was the cluster analysis done?	Yes	No	NA		
Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?	Yes	No	Can't tell		
Intervention Integrity					
What % of participants received the allocated intervention or exposure of interest?	80-100	60-79	<60	ND	NA
Was the consistency of the intervention measured (i.e. intervention was provided to all participants in the same way)?	Yes	No	ND	NA	
Is it likely that subjects received an unintended intervention (contamination or cointervention) that may influence the results?	Yes	No	Can't tell		

Mortensen 2002 [11988057]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): Mean BW (range): % Male: 490/973 (50% in cohort 1); 2280 (100% in cohort 2) Race: Enrolled/Evaluate: 973 had WAIS, 2280 had BPP test Location: Denmark Sites: Single/Multi Funding:	Prospective cohort but the breastfeeding information was collected retrospectively at the 1-year examination. There were 2 sub-cohorts; one participated in an ongoing developmental research program between 1982-1994 and took the WAIS at 27.2 years old; the other one took the draft board intelligence test: Borge Priens Prove (BPP) at 18.7 years; the BPP has a correlation of 0.82 with the full scale WAIS IQ.	Excluded twins		

Mortensen 2002 [11988057]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Relationship of WAIS score and BPP score to duration of breastfeeding	Adjusted for parental social status and education, single mother status, mother's height, age, and weight gain during pregnancy, cigarette during 3rd trimester, number of pregnancies, estimated gestational age, birthweight, birth length, and indices of pregnancy and delivery complications	Breastfeeding duration WAIS: <1mo 99.4; 2-3 mo 101.7; 4-6 mo 102.3; 7-9 mo 106.0; >9 mo 104.0 Adjusted: P=0.003 for overall F test BPP: 38.0; 39.2; 39.9; 40.1; 40.1 Adjusted: P=0.01 for overall F test	A: strong, B: moderate, C: weak Selection: B Study design: B Confounder: C Blinding: C Data collection: B Withdrawal and dropout: B Analyses: B Intervention integrity: Overall: B

Domain/question	***Place an "X" in one***				
Selection Bias					
Are individuals selected to participate likely to be representative of target population?	Very likely	Somewhat likely	Not likely		
What % of selected individuals agreed to participate?	80-100	60-79	<60	ND	NA
Allocation Bias (RCTs only, for quasi-experimental, case-control/before/after, no control group or other skip to "Confounders")					
Is the method of random allocation stated	Yes	No			
If the method of random allocation is stated, is it appropriate	Yes	No			
Was the method of random allocation reported as concealed?	Yes	No			
Confounders					
Prior to the intervention, were there between group differences for important confounders reported in the paper?	Yes	No	Can't tell		
If there were differences between groups for important confounders, were they adequately managed in the analysis?	Yes	No	NA		
Were there important confounders NOT reported in the paper (describe above under quality score)?	Yes	No			
Blinding					
Was (were) the outcome assessor(s) blinded to the intervention or exposure status of the participants?	Yes	No	ND	NA	
Data Collection methods					
Were data collection tools shown or are they known to be valid?	Yes	No			
Were data collection tools shown or are they known to be reliable?	Yes	No			
Withdrawals and Dropouts					
Indicate the % of participants completing the study. (If the % differs by groups, record the lowest).	80-100	60-79	<60	ND	NA
Analysis					
Is there a sample size calculation or power calculation	Yes	Partially	No		
Is there a statistically significant difference between groups?	Yes	No	ND		
Are the statistical methods appropriate?	Yes	No	ND		
Indicate the unit of allocation	Community	Organization/group	Provider	Client	Institution
Indicate the unit of analysis	Community	Organization/group	Provider	Client	Institution
If the unit of allocation and analysis differed, was the cluster analysis done?	Yes	No	NA		
Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?	Yes	No	Can't tell		
Intervention Integrity					
What % of participants received the allocated intervention or exposure of interest?	80-100	60-79	<60	ND	NA
Was the consistency of the intervention measured (i.e. intervention was provided to all participants in the same way)?	Yes	No	ND	NA	
Is it likely that subjects received an unintended intervention (contamination or cointervention) that may influence the results?	Yes	No	Can't tell		

Oddy, 2003 [12562475] contains the same data as in Oddy, 2004 [15384602]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 37-39 wk Mean BW (range): % Male: Race: Enrolled/Evaluate: 2393 term at birth, 1444 at 6 years, 1371 at 8 years Location: Australia Sites: Single/Multi Funding:	Prospective cohort comparing no breastfeeding, <4 mo, 4-6 mo, and >4 mo of breastfeeding; Peabody Picture Vocabulary Test (PPVT-R) was administered at 6 y/o and a Performance subtest (Perceptual organization WISC- Block Design) at 8 y/o	Children with non-English speaking parents were excluded; preterm infants were also excluded		

Oddy, 2003 [12562475] contains the same data as in Oddy, 2004 [15384602]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Score of PPV-R at 6 y/o and Block Design score at 8 y/o	Association between breastfeeding duration and PPVT-R at 6 years and Block Design at 8 years were adjusted for gender, gestational age, maternal age and education, parental smoking, and the presence of older siblings.	90% of children were breastfed at some point, 28% were breastfed for >6 mo, solid foods were introduced at ≤6 mo in 88% of infants Both verbal IQ and performance scores increase with increasing maternal education combined with a longer duration of breastfeeding, with the most profound effect of breastfeeding occurring in the highest education groups (P<0.005). In the lower education groups, these trends were less consistent. After adjustment for covariates, there was an association between duration of breastfeeding and verbal IQ with a 3.56 point advantage for children breastfed >6 mo compared with children never breastfed (F=8.59, P=0.003). The adjusted association of full breastfeeding with the Performance subtest was not significant (F=1.49, P=0.223).	A: strong, B: moderate, C: weak — A / B / C Selection — / x / — Study design — / x / — Confounder — / — / x Blinding — / — / x Data collection — / x / — Withdrawal and dropout — / — / x Analyses — / x / — Intervention integrity — / — / — Overall: B

Domain/question	***Place an "X" in one***				
Selection Bias					
Are individuals selected to participate likely to be representative of target population?	Very likely	Somewhat likely	Not likely		
What % of selected individuals agreed to participate?	80-100	60-79	<60	ND	NA
Allocation Bias (RCTs only, for quasi-experimental, case-control/before/after, no control group or other skip to "Confounders")					
Is the method of random allocation stated	Yes	No			
If the method of random allocation is stated, is it appropriate	Yes	No			
Was the method of random allocation reported as concealed?	Yes	No			
Confounders					
Prior to the intervention, were there between group differences for important confounders reported in the paper?	Yes	No	Can't tell		
If there were differences between groups for important confounders, were they adequately managed in the analysis?	Yes	No	NA		
Were there important confounders NOT reported in the paper (describe above under quality score)?	Yes	No			
Blinding					
Was (were) the outcome assessor(s) blinded to the intervention or exposure status of the participants?	Yes	No	ND	NA	
Data Collection methods					
Were data collection tools shown or are they known to be valid?	Yes	No			
Were data collection tools shown or are they known to be reliable?	Yes	No			
Withdrawals and Dropouts					
Indicate the % of participants completing the study. (If the % differs by groups, record the lowest).	80-100	60-79	<60	ND	NA
Analysis					
Is there a sample size calculation or power calculation	Yes	Partially	No		
Is there a statistically significant difference between groups?	Yes	No	ND		
Are the statistical methods appropriate?	Yes	No	ND		
Indicate the unit of allocation	Community	Organization/group	Provider	Client	Institution
Indicate the unit of analysis	Community	Organization/group	Provider	Client	Institution
If the unit of allocation and analysis differed, was the cluster analysis done?	Yes	No	NA		
Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?	Yes	No	Can't tell		
Intervention Integrity					
What % of participants received the allocated intervention or exposure of interest?	80-100	60-79	<60	ND	NA
Was the consistency of the intervention measured (i.e. intervention was provided to all participants in the same way)?	Yes	No	ND	NA	
Is it likely that subjects received an unintended intervention (contamination or cointervention) that may influence the results?	Yes	No	Can't tell		

Quinn 2001 [11885710]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): Mean BW (range): % Male: 53% Race: Enrolled/Evaluate: 4049/3880 Location: Australia Sites: Single Funding:	Prospective cohort; data were collected at enrollment, shortly after birth, at 6 months and at 5 years. Peabody Picture Vocabulary Test (PPVT-R) was administered at 5 years. Results were analyzed in relation to breastfeeding duration.	Singleton; At 5 years, children with major neurological abnormalities and those for whom the data were incomplete were excluded		

Quinn 2001 [11885710]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Score on PPVT-R	Adjusted for birthweight, poverty, maternal education, maternal age, time in daycare or preschool, number of children in the household at 5 years	Breastfeeding ≥6 mo 103.6 (SD 13.1) No breastfeeding 94.2 (SD 14.1) There was a significant trend towards increasing PPVT-R with increased duration of breastfeeding (P=0.0000) After adjustment, the mean for those breastfed ≥6 mo was 8.2 points (95%CI 6.5, 9.9) higher for females and 5.8 points (95%CI 4.1, 7.5) higher for males when compared to those never breastfed.	A: strong, B: moderate, C: weak / A / B / C Selection / / x / Study design / / / x Confounder / / x / Blinding / / / x Data collection / / x / Withdrawal and dropout / / x / Analyses / / x / Intervention integrity / / / Overall: B

Domain/question	***Place an "X" in one***				
Selection Bias					
Are individuals selected to participate likely to be representative of target population?	Very likely	Somewhat likely	Not likely		
What % of selected individuals agreed to participate?	80-100	60-79	<60	ND	NA
Allocation Bias (RCTs only, for quasi-experimental, case-control/before/after, no control group or other skip to "Confounders")					
Is the method of random allocation stated	Yes	No			
If the method of random allocation is stated, is it appropriate	Yes	No			
Was the method of random allocation reported as concealed?	Yes	No			
Confounders					
Prior to the intervention, were there between group differences for important confounders reported in the paper?	Yes	No	Can't tell		
If there were differences between groups for important confounders, were they adequately managed in the analysis?	Yes	No	NA		
Were there important confounders NOT reported in the paper (describe above under quality score)?	Yes	No			
Blinding					
Was (were) the outcome assessor(s) blinded to the intervention or exposure status of the participants?	Yes	No	ND	NA	
Data Collection methods					
Were data collection tools shown or are they known to be valid?	Yes	No			
Were data collection tools shown or are they known to be reliable?	Yes	No			
Withdrawals and Dropouts					
Indicate the % of participants completing the study. (If the % differs by groups, record the lowest).	80-100	60-79	<60	ND	NA
Analysis					
Is there a sample size calculation or power calculation	Yes	Partially	No		
Is there a statistically significant difference between groups?	Yes	No	ND		
Are the statistical methods appropriate?	Yes	No	ND		
Indicate the unit of allocation	Community	Organization/group	Provider	Client	Institution
Indicate the unit of analysis	Community	Organization/group	Provider	Client	Institution
If the unit of allocation and analysis differed, was the cluster analysis done?	Yes	No	NA		
Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?	Yes	No	Can't tell		
Intervention Integrity					
What % of participants received the allocated intervention or exposure of interest?	80-100	60-79	<60	ND	NA
Was the consistency of the intervention measured (i.e. intervention was provided to all participants in the same way)?	Yes	No	ND	NA	
Is it likely that subjects received an unintended intervention (contamination or cointervention) that may influence the results?	Yes	No	Can't tell		

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

Gastrointestinal Infections

Chien 2001 SRMA*
Quigley 2006

* Systematic Review/Meta-Analysis

Evidence table for Systematic Reviews of Breastfeeding

Author, Topic Year[UI]	Chien, 2001 UI 11795054 Gastrointestinal (GI) Infection
Literature search (Dates)	Medline (1996 to 1/1998); Other databases searched? (Yes) Science Citation Index was used to identify frequently cited articles in the reference lists of studies from MEDLINE; unpublished data used? No
Countries where primary studies conducted	Industrialized countries (UK, New Zealand, US, Australia, Scotland)
Study eligibility / inclusion criteria	GI infection was defined to be any illness associated with vomiting, change in consistency or frequency of stools, or isolation of a known enteropathogenic bacterial or viral agent; GI outcome restricted to first year of life; excluded studies in which mortality was employed as a combined outcome event; excluded studies in which all the various types of infections were combined as an outcome measure
Study design [No. Of studies]	Prospective (12 studies, 5473 subjects) and retrospective (2 studies, 504 subjects) cohort studies; case-control studies (2 studies, 331 pairs);
No. of subjects	See above
Study population (definition in included studies)	
Intervention/Exposure (definition in included studies)	
Comparator (definition in included studies)	Infant feeding practices grouped into either exclusive breastfeeding and partial/mixed feeding or exclusive artificial feeding
Outcomes (definition in included studies)	
Heterogeneity assessments	Yes
Quality assessments	
Publication bias assessments	
Statistical Analysis or meta-analytic methods	Fixed effect model; pooled results weighted according to sample size
Results	Conflicting results on the effect of breastfeeding on GI infection: 9/16 studies (56%) yielded a statistically significant protective effect of breastfeeding on GI infections; Majority of studies suffered from methodological deficiencies; 4 studies fulfilled criteria of controlling for detection bias, analyses of confounders, having a clear definition of infant feeding practices and infectious outcomes; 3 of these studies reported breastfeeding was protective against GI infection; Pooled estimate of the cohort studies: OR 0.36 (95% CI 0.32, 0.41; heterogeneity P<0.01) Pooled estimate of 2 case-control studies: OR 0.54 (95% CI 0.36, 0.80; heterogeneity P=0.35)
Quality of the systematic review	B
Author's interpretations of the results	"No firm conclusion can be drawn about the magnitude of a protective effect of breastfeeding against infections in industrialized countries, there is no doubt that it is protective in the case of many infants. This trend is most obvious in the studies of the highest quality."
Comments / Limitations	Random effect model would be more appropriate; weighted according to sample size; not analyzed for potential confounding

Author, yr: Chien, 2001
Topic of the systematic review*/MA:

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Y
2	Types of exposure or intervention used	Y
3	Types of study designs used	Y
4	Study population	Y
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Y/N
6	Effort to include all available studies (contact with authors)	N
7	Databases and registries searched	Y
8	Method of addressing published articles other than English	N
9	Method of handling abstracts and unpublished studies	N
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Y
11	Assessment of confounding	Y/N
12	Assessment of quality	Y
13	Assessment of heterogeneity	Y
14	Description of statistical methods sufficient to replicate	Y
15	Provision of appropriate tables and graphs	Y
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Y
17	Tables giving descriptive information of each study included	Y
18	Results of sensitivity testing (subgroup analysis)	N
19	Indication of statistical uncertainty of findings	Y
20	Quantitative assessment of bias (eg. publication bias)	N
	Overall quality	

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Y/N
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Y
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Y
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	N
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Y/N
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Y
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Y/N
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Y/N
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Y
9	Were conclusions justified by the reported/collected data and analysis?	Y

Quigley, 2006 [16308409]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): Mean BW (range): % Male: 58 Race: Enrolled/Evaluate: 167 cases/ 137 controls Location: UK Sites: Multi Funding:	Case-control study; stratified by age group (0-3 mo, 3-5.9 mo, 6-8.9 mo, ≥ 9 mo), social deprivation score, location of practice (London, not London); questionnaire on current milk feeding	< 1 yr old and had data on infant feeding	Current exclusive breast milk (only milk received was breast milk, but many had been weaned on to solids), mixed feeding	Current formula

Quigley, 2006 [16308409]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
A diarrheal case was defined as "someone who presented to the General Practitioner with loose stools or significant vomiting < 2 weeks, in the absence of a known non-infectious cause and preceded by a symptom-free period of 3 weeks."	age, sex, weaning, social class, travel, no access to food mixer, contact with person with diarrhea/vomiting in and outside household Multivariate analysis	Completed questionnaire: 190 cases (60%); 161 controls (90%); excluded 23 cases and 24 controls (no feeding data, no match, "other" feeding) Analyzed: 167 cases/ 137 controls Adjusted OR of diarrhea Current BF 0.36 (95% CI 0.18, 0.74) Current not BF 1 P=0.005 "Little evidence of the protection of breastfeeding persisting beyond 2 months following breastfeeding cessation."	A: strong, B: moderate, C: weak — A / B / C Selection — B Study design — B Confounder — A Blinding Data collection — B Withdraw and dropout — B Analyses — B Intervention integrity Cannot rule out recall or response biases

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

Infant Mortality

Chen 2004

Chen 2004 [15121986]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): ND Mean BW (range):<2500g 26% live birth (controls) and 24% postneonatal death (cases) % Male: 50.3 live birth 59.8% postneonatal death Race: White 44.4 (controls) 50.0 (cases) Black 52.2 (controls) 46.6 (cases) Others 3.4 (controls) 3.4 (cases) Enrolled/Evaluate: NA Location: national level data Sites: Multi (population based) Funding: ND	Case control study design Follow-up NA	Subjects included in the 1988 US National Maternal and Infant Health Survey data to analyze the association between breastfeeding and postneonatal death.	Ever vs Never	Ever vs Never

Chen 2004 [15121986]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Post neonatal death: death after 28 days	Because of the oversampling of black and low birth weight infants SUDAAN adjusted analysis was performed to re-weight the sample for the overall estimates and to calculate the ORs and 95% confidence intervals in the final models. Logistic regression models Adjusted for mother's age, education, and smoking during pregnancy and infant's gender, race (except for race subgroup analyses), birth weight (except for birth weight subgroup analyses), congenital malformation reported at birth, live birth order, plurality, and WIC status.	Showed an OR of 0.79 (95% CI: 0.67–0.93) for ever breastfed. Race-specific analyses gave similar estimates for the OR, although the proportion ever breastfed was much lower in black infants. For duration of breastfeeding, comparing cases who survived 3 months (n = 691 in original sample and n = 5363 after adjustment with SUDAAN) and all controls, 3 months or more of breastfeeding showed an OR of 0.62 (95% CI: 0.46–0.82), less (ie, more protective) than the OR for ever/never breastfed (0.79; 95% CI:0.67–0.93). The OR for overall postneonatal death was 0.74 (95% CI: 0.63–0.87). Among cases only, a proportional hazard model showed that the risk of death at any specific time was marginally lower in the ever breastfed infants (hazard ratio: 0.91; 95% CI: 0.79–1.06).	A: strong B: moderate C: weak A B C Selection x Study design x Confounder x Blinding x Data collection x Withdraw and dropout x Analyses x Intervention integrity x Overall B

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

Respiratory Tract Diseases

Bachrach 2003 SRMA*

* Systematic Review/Meta-Analysis

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI] Topic	Bachrach, 2003 [12622672] Respiratory Illness
Literature search (Dates)	Medline (1966-2002); Other databases searched? (yes); unpublished data used? (yes)
Countries where primary studies conducted	Developed countries (US, Canada, New Zealand, Australia, Scotland, Norway)
Study eligibility / inclusion criteria	Included studies from developed countries; healthy full-term infants; and provided data on exclusive breast feeding Excluded studies on cystic fibrosis and allergic conditions; sick, premature, and/or low birth weight infants
Study design [No. Of studies]	Prospective cohort [5]; retrospective cohort [2]; ecological study [1]; cross-sectional [1]. Only cohort studies were combined.
No. of subjects	3201 exposed / 1324 unexposed
Study population (definition in included studies)	Healthy full term infants
Intervention/Exposure (definition in included studies)	Exclusive breastfeeding at least of 2 months or 9 months of total (any) breastfeeding
Comparator (definition in included studies)	None breastfeeding
Outcomes (definition in included studies)	Hospitalization due to lower respiratory tract disease (LRTD) in infancy: bronchiolitis, asthma, pneumonia, empyema, and infections due to specific agents (eg, RSV)
Heterogeneity assessments	Yes; No statistical heterogeneity. Used sensitivity analysis to test appropriateness of combining studies.
Quality assessments	None
Publication bias assessments	None (but the authors examined unpublished data)
Statistical Analysis or meta-analytic methods	Random effects model; subgroup analyses for two covariates – smoking and SES
Results	Summary relative risk from 7 cohort studies: 0.28 (0.14 - 0.54)
Quality of the systematic review	A
Author's interpretations of the results	Consistent effect was found among all primary studies that indicated a protective role of breastfeeding in LRTD
Comments / Limitations	Included studies that had precise definition of breastfeeding

Author, yr: Bachrach, 2003
Topic of the systematic review*/MA: Breastfeeding and LRTI

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Y
2	Types of exposure or intervention used	Y
3	Types of study designs used	Y
4	Study population	Y
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Y
6	Effort to include all available studies (contact with authors)	Y
7	Databases and registries searched	Y
8	Method of addressing published articles other than English	Y
9	Method of handling abstracts and unpublished studies	Y
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Y
11	Assessment of confounding	Y
12	Assessment of quality	N
13	Assessment of heterogeneity	Y
14	Description of statistical methods sufficient to replicate	Y
15	Provision of appropriate tables and graphs	Y
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Y
17	Tables giving descriptive information of each study included	Y
18	Results of sensitivity testing (subgroup analysis)	Y
19	Indication of statistical uncertainty of findings	N
20	Quantitative assessment of bias (eg. publication bias)	N
	Overall quality	**A**

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	partially
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	no
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	yes
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	yes
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	yes
8	Were results reported accurately (eg, no discrepancies between text and tables)?	yes
9	Were conclusions justified by the reported/collected data and analysis?	yes

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

Obesity

Arenz 2004 SRMA*
Harder 2005 SRMA*
Owen 2005 SRMA*

* Systematic Review/Meta-Analysis

Evidence table for Systematic Reviews of Breastfeeding

Author,Year[UI] Topic	Arenz, 2004 [15314625] Obesity
Literature search (Dates)	Medline (1966-Dec 2003); Other databases searched? (yes); unpublished data used? (no)
Countries where primary studies conducted	Developed countries: Germany, USA, Britain, Australia, New Zealand, Czech Republic
Study eligibility / inclusion criteria	• Population-based cohort, cross-sectional or case–control studies with children older than 1 y at the last follow-up stage, published in English, French, Italian, Spanish or German. • Only studies with adjustment for at least three of the following relevant confounding or interacting factors birth weight, parental overweight, parental smoking, dietary factors, physical activity and socioeconomic status were included in this meta-analysis. • Odds ratio or relative risk had to be reported and age at the last follow-up had to be between 5 and 18 y; feeding-mode had to be assessed and reported and obesity as outcome had to be defined by body mass index (BMI) percentiles >90, 95 or 97 kg/m2. If risk estimates were calculated for different percentile values in a particular study, the estimate for the highest percentile-value was included in the meta-analysis.
Study design [No. Of studies]	Studies did not meet inclusion criteria for meta-analyses: prospective cohort study [11]; retrospective cohort [1]; cross-sectional study [4]; case-control study [2] Studies met inclusion criteria for meta-analyses: prospective cohort study [2]; cross-sectional study [7]
No. of subjects	For studies met inclusion criteria for meta-analyses only: 69,000
Study population (definition in included studies)	Children and adolescents. One study included some adult subjects but the various odds ratios were reported depending on age and not clear which odds ratio was used in the meta-analyses.
Intervention/Exposure (definition in included studies) Comparator (definition in included studies)	Definition of feeding mode varied across studies: Never BF or partly BF < 3 months vs. BF ≥ 3 month; mostly or only BF vs. mostly or only formula feeding in the first 6 months; BF never vs. ever; BF never vs. > 6 months, BF groups: <1 week, 1 week-1 months, 2-3 months, 4-6 months, 7-9 month, > 9 months (exclusivity of BF not reported)
Outcomes (definition in included studies)	Definition of childhood obesity varied across studies: BMI ≥97th percentile, >95th percentile, definition according to Cole et al.
Heterogeneity assessments	Sensitivity analyses by testing the stability of the findings across different approaches in study design, exposure ascertainment and selection of study participants.
Quality assessments	ND
Publication bias assessments	Funnel plot
Statistical Analysis or meta-analytic methods	Fixed-effect and random-effect model: both crude and adjusted odds ratios (AOR) of the studies were used.
Results	• In total, 28 studies met the inclusion criteria for the systematic review, 19 of them were not eligible for the meta-analysis. • The pooled crude OR for breast-feeding and obesity defined as BMI >90th, 95th or 97th percentile could be calculated for six studies. In the fixed-effects model, the OR was 0.67, 95% CI (0.62, 0.73). In the random effects model an almost identical OR was found (data not shown). • The AOR calculated for nine studies was 0.78, 95% CI (0.71, 0.85) for both fixed and random-effects model. • Sensitivity analyses were performed, comparing the studies according to the following criteria: cohort study or cross-sectional study, different definitions of breast-feeding, different definitions of obesity, different age-groups and number of potential confounders considered for adjustment. The protective effect of breast-feeding was more pronounced in studies with adjustment for less than seven potential confounding factors compared to adjustment for seven or more potential confounding factors. • The funnel plot showed an asymmetric pattern, which was due to a particular study. The funnel plot regression analysis did not reject the null hypothesis of symmetry (df=8,

Author,Year[UI] Topic	Arenz, 2004 [15314625] Obesity
	P=0.71), suggesting that there was no publication bias.
Quality of the systematic review	A
Author's interpretations of the results	"The results from meta-analysis indicate that breast-feeding is associated with a small but consistent protective effect against obesity risk in later childhood."
Comments / Limitations	Highly heterogeneous definitions of breastfeeding across studies overall meta-analysis was inappropriate, but sensitivity analyses were performed to reduce heterogeneity. Sensitivity analyses are very important but very few studies in each stratum due to small number of studies met the criteria for meta-analyses.

Author, yr: Arenz, 2004
Topic of the systematic review*/MA:

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Yes
2	Types of exposure or intervention used	Yes
3	Types of study designs used	Yes
4	Study population	Yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Yes
6	Effort to include all available studies (contact with authors)	Yes
7	Databases and registries searched	Yes
8	Method of addressing published articles other than English	No
9	Method of handling abstracts and unpublished studies	No
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Yes
11	Assessment of confounding	Yes
12	Assessment of quality	Yes
13	Assessment of heterogeneity	Yes
14	Description of statistical methods sufficient to replicate	Yes
15	Provision of appropriate tables and graphs	Yes
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Yes
17	Tables giving descriptive information of each study included	Yes
18	Results of sensitivity testing (subgroup analysis)	Yes
19	Indication of statistical uncertainty of findings	Yes
20	Quantitative assessment of bias (eg. publication bias)	Yes
	Overall quality	A

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Yes
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	ND
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Yes
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Yes
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Yes
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Yes
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Partially
9	Were conclusions justified by the reported/collected data and analysis?	Yes

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI] Topic	Harder, 2005 [16076830] Obesity
Literature search (Dates)	Medline (1966-December 2003); Other databases searched? (yes); unpublished data used? (no)
Countries where primary studies conducted	Developed countries: UK, US, Canada, Germany, Australia, New Zealand, Czechoslovakia
Study eligibility / inclusion criteria	1) an original report comparing breastfed subjects with exclusively formula-fed subjects (referent group) of any given age, 2) report the odds ratio and 95% CI (or data to calculate them) of overweight or obesity associated with breastfeeding, and 3) report the duration of breastfeeding for at least one exposure group.
Study design [No. Of studies]	Cohort (including cross-sectional design) [16]; case-control study [1]
No. of subjects	Ranged 66 to 32,200 total 120,831
Study population (definition in included studies)	Primarily children. Two studies included adults.
Intervention/Exposure (definition in included studies)	Median duration of breastfeeding categories: < 1 month (reference), 1-3 month, 4-6 months, 7-9 months, > 9month Each month increase in the duration of breastfeeding: We calculated a study specific regression coefficient and corresponding 95% CI for each study by use of a log-linear model. The resulting odds ratio and 95% CI for change in risk for each month of breastfeeding were pooled with a random-effect model
Comparator (definition in included studies)	
Outcomes (definition in included studies)	Any definition of overweight or obesity, varied across studies
Heterogeneity assessments	ND
Quality assessments	ND
Publication bias assessments	Funnel plot with Begg test and Egger test
Statistical Analysis or meta-analytic methods	Unadjusted odds ratios and 95% CI were calculated directly from the data given in the articles, where possible. Otherwise, the published odds ratio and 95% CI were used. Three approaches were taken: First, duration of breastfeeding as the independent variable and the weighted odds ratio for overweight in breastfed probands, compared with formula-fed subjects, as the dependent variable (for meta-regression). Second, the random-effect model pooled odds ratio for overweight in breastfed subjects was calculated separately for five predefined categories of duration of breastfeeding. Third, the pool-first method was used to combine the regression coefficients obtained from the studies (for trend estimation). For meta-regression analysis, all duration-specific odds ratios had to be related to the respective duration of breastfeeding. The median of the upper and lower limits of each category of duration of breastfeeding was assigned to the particular estimate in each study. Estimates were plotted against the respective duration of breastfeeding as independent variable. A weighted meta-regression with duration of breastfeeding as the covariate was perform (random-effects model). For studies that provided data for more than two categories of duration of breastfeeding, we applied the “pool-first method” to quantify the dose-response relation. This was possible for 11 studies. We calculated a study specific regression coefficient and corresponding 95% CI for each study by use of a log-linear model. The resulting odds ratio and 95% CI for change in risk for each month of breastfeeding were pooled with a random-effect model.
Results	• From the 17 studies that reported duration of breastfeeding, 14 gave data for more than one category of duration of breastfeeding, leading to 52 estimates included in the meta-regression analysis. In the weighted meta-regression, duration of breastfeeding was significantly negatively related to risk of overweight (regression coefficient: 0.94, 95%CI 0.89-0.98).

<table>
<tr><td>Author, Year[UI]</td><td>Topic</td><td>Harder, 2005 [16076830]</td><td>Obesity</td></tr>
<tr><td></td><td colspan="3">
• From 1 month of breastfeeding onward, the risk of subsequent overweight continuously decreased up to a reduction of more than 30%, reaching a plateau at 9 months of breastfeeding.
<table>
<tr><th></th><th colspan="5">Duration of breastfeeding</th></tr>
<tr><td></td><td><1 mo</td><td>1-3 mo</td><td>4-6 mo</td><td>7-9 mo</td><td>>9 mo</td></tr>
<tr><td>No. of duration-specific study estimates</td><td>5</td><td>14</td><td>15</td><td>11</td><td>7</td></tr>
<tr><td>OR for overweight</td><td>1.0</td><td>0.81</td><td>0.76</td><td>0.67</td><td>0.68</td></tr>
<tr><td>95% CI</td><td>0.65, 1.55</td><td>0.74, 0.88</td><td>0.67, 0.86</td><td>0.55, 0.82</td><td>0.50, 0.91</td></tr>
</table>
• Each month of breastfeeding was found to be associated with a 4% decrease in risk (OR: 0.96/month of breastfeeding, 95%CI 0.94-0.98). A fixed-effects model revealed a similar pooled OR and a nearly identical 95% CI (OR: 0.96/month of breastfeeding, 95%CI 0.95-0.98)
• In only two of these studies was the influence of the duration of exclusive breastfeeding analyzed. The pooled OR for risk of overweight per month of exclusive breastfeeding was 0.94 (95%CI 0.89-0.99, random-effect model)
• Subgroup analyses revealed that the definition of overweight influenced the estimate only slightly. In studies that used BMI to define overweight, the pooled OR was 0.96 (95%CI 0.94-0.98) for 8 studies, while the OR was 0.93 (95%CI 0.87-0.99) for the 3 studies that used another measure to define overweight or obesity.
• The age at examination had only a marginal influence on the magnitude of the effect of duration of breastfeeding on risk of overweight. The pooled OR from all 5 studies investigating probands up to or including 5 years of age was 0.97 (95%CI 0.94-0.99), while in older subjects aged 6 or more years, it was 0.96 (95%CI 0.93-0.99) for 6 studies.
• No evidence of publication bias was observed, as indicated by a symmetric funnel plot and a nonsignificant Begg test and Egger test.
</td></tr>
<tr><td>Quality of the systematic review</td><td colspan="3">B</td></tr>
<tr><td>Author's interpretations of the results</td><td colspan="3">"Using three different techniques, we show that a longer duration of breastfeeding is associated with a larger decrease in risk of overweight. Each of the three methods used in our study has its own advantages and limitations."
"In summary, we found that the duration of breastfeeding is inversely and linearly associated with the risk of overweight. The risk of overweight was reduced by 4% for each month of breastfeeding. This effect lasted up to a duration of breastfeeding of 9 months and was independent of the definition of overweight and age at follow-up. Even if interpreted as being of relatively small size, this association, if causal, might be of importance for the general population. Since the majority of studies analyzed here used partially breastfed subjects, it might be concluded that, beyond exclusive breastfeeding, also longer partial breastfeeding up to 9 months leads to a greater decrease in risk of overweight in later life, which might be considered in future clinical recommendation."</td></tr>
<tr><td>Comments / Limitations</td><td colspan="3">The meta-analyses addressing the relationship between duration of breastfeeding and the risk of overweight was well-performed. However, the authors' conclusion implied a causal relationship, which is not appropriate because most of the "cohort" studies included in the analyses were in fact cross-sectional studies because the breastfeeding exposure was ascertained retrospectively at the time of the assessment of obesity. Causality cannot be ascertained in cross-sectional design. Most importantly, crude OR was used in the meta-analyses, which is the major limitation.</td></tr>
</table>

Author, yr: Harder, 2005
Topic of the systematic review*/MA: Obesity

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Yes
2	Types of exposure or intervention used	Yes
3	Types of study designs used	Yes
4	Study population	Yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Yes
6	Effort to include all available studies (contact with authors)	Yes
7	Databases and registries searched	Yes
8	Method of addressing published articles other than English	No
9	Method of handling abstracts and unpublished studies	No
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Yes
11	Assessment of confounding	Partially
12	Assessment of quality	Partially
13	Assessment of heterogeneity	No
14	Description of statistical methods sufficient to replicate	Yes
15	Provision of appropriate tables and graphs	Yes
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Yes
17	Tables giving descriptive information of each study included	Yes
18	Results of sensitivity testing (subgroup analysis)	Yes
19	Indication of statistical uncertainty of findings	Yes
20	Quantitative assessment of bias (eg. publication bias)	Yes
	Overall quality	**B**

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Yes
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	ND
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Partially
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Yes
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Yes
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Partially
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Yes
9	Were conclusions justified by the reported/collected data and analysis?	Yes

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI] Topic	Owen, 2005 Obesity
Literature search (Dates)	Medline (completed in September 2003); Other databases searched? (yes); unpublished data used? (no)
Countries where primary studies conducted	Developed and developing countries: UK, Germany, USA, Canada, Italy, Turkey, Australia, New Zealand, Slovak Republic, China, Czech Republic, Sweden
Study eligibility / inclusion criteria	61 studies that compared a measure of obesity (quantitatively or narratively) among breastfed and formula-fed subjects were considered. Studies that defined the odds of obesity or being overweight for breastfed and formula-fed subjects were reported more often and were included in a meta-analysis; 28 studies with 29 estimates (1 study reported results for 2 populations) met this inclusion criterion.
Study design [No. Of studies]	Historical cohort, prospective cohort, cross-sectional studies: total 61 studies, and 28 studies included in the meta-analyses
No. of subjects	N=298,900 in the overall meta-analysis
Study population (definition in included studies)	28 studies (298,900 subjects) provided 29 unadjusted odds ratios relating the initial infant feeding method and obesity. Four observations were for infants, 23 for children, and 2 for adults.
Intervention/Exposure (definition in included studies) Comparator (definition in included studies)	Breastfed vs. formula-fed. The exclusiveness of infant feeding was based on the classification given in each article. The feeding groups were defined as being mutually exclusive in 4 studies, the breastfed group included mixed feeders in 7 studies and the formula-fed group included mixed feeders in 7 studies. In 2 studies in which infants were breastfed exclusively, the exclusivity of formula feeding could not be determined.
Outcomes (definition in included studies)	Any measures of obesity or adiposity. Most studies used a percentile cutoff based on BMI, describing subjects at the tail of the distribution. The 95th or 97th percentile was used most often, although some studies used cutoff values as low as the 85th percentile. A smaller number of studies used absolute BMI values or cutoff values based on standardized weight or weight for height. Studies involving infants used definitions based on percentiles of weight for length or percentiles of weight only.
Heterogeneity assessments	Q test with chi-square statistics
Quality assessments	ND
Publication bias assessments	Begg funnel plot. Reporting bias was also assessed.
Statistical Analysis or meta-analytic methods	Results from fixed-effects models are reported throughout, because these reflect only the random error within each study, are more conservative because they are less affected by results of smaller studies that show stronger associations, and make no assumptions about the representativeness of the available studies. Meta-regression was used to examine the influence of the following factors (defined a priori) with a test for trend: study size (<500, 500–2500, or >2500 subjects), age group at outcome measurement (infants <=1 year of age, young children >1 to 9 years of age, older children 10 to <16 years of age, or adults >=16 years of age), year of birth, and response rates (analyzed as a continuous variable). The effects of adjustment for factors such as parental body size (mostly BMI), socioeconomic status, and maternal smoking were examined in 6 studies that provided data before and after adjustment for all 3 of these factors. The effects of study methods, particularly the method of ascertainment of infant feeding status (whether contemporary or recalled over a period of >=3 years), study response rate, and definition of obesity (equivalent to <95th percentile, 95th to <97th percentile, or >=97th percentile of BMI), were examined with meta-regression and sensitivity analyses.
Results	• Among 61 observational studies that reported on the effects of infant feeding on a measure of adiposity in later life, 28 studies (298 900 subjects) provided 29 unadjusted odds ratios relating the initial infant feeding method and obesity. Four observations were for infants, 23 for children, and 2 for adults.

Author, Year[UI] Topic	Owen, 2005 Obesity
	• In a fixed-effects model including all studies, breastfed subjects were less likely to be defined as obese than were formula-fed subjects (OR: 0.87; 95% CI: 0.85–0.89). There was evidence of marked heterogeneity among studies (p<0.001). • Odds ratios of 0.50 (95% CI: 0.26– 0.94) for infants, 0.90 (95% CI: 0.87– 0.92) for young children, 0.66 (95% CI: 0.60–0.72) for older children, and 0.80 (95% CI: 0.71– 0.91) for adults were observed (test for trend, P= .85, adjusted for study size; P=.99 with the exclusion of infants). • In 6 studies, it was possible to examine the effect of adjustment for the following potentially important confounders: socioeconomic status, parental BMI, and current maternal smoking or maternal smoking in early life. The pooled odds ratio in these studies was reduced from 0.86 (95% CI: 0.81– 0.91) before adjustment to 0.93 (95% CI: 0.88–0.99) after combined adjustment. • In 14 studies with information on breastfeeding duration, the effect of breastfeeding over formula feeding was greater among subjects breastfed for >=2 months (OR: 0.81; 95% CI: 0.77– 0.84), compared with those breastfed for any duration (OR: 0.89; 95% CI: 0.86–0.91) in the same studies. • Studies that did not provide odds ratios were much less likely to report that breastfeeding was associated with a reduced risk of obesity, compared with studies that did provide odds ratios (1 of 35 studies and 18 of 29 studies, respectively; P<.001).
Quality of the systematic review	B
Author's interpretations of the results	"The association between breastfeeding and obesity could reflect selective reporting and/or publication. Our results indicated selective reporting of odds ratios by studies that showed a relationship between breastfeeding and reduced risk of obesity. However, because the studies that did not present odds ratios were on average much smaller than those that presented data, their inclusion had a minimal impact on effect estimates."
Comments / Limitations	Why not use random-effect model?

Author, yr: Owen, 2005
Topic of the systematic review*/MA:

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Yes
2	Types of exposure or intervention used	Yes
3	Types of study designs used	Yes
4	Study population	Yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Yes
6	Effort to include all available studies (contact with authors)	Yes
7	Databases and registries searched	Yes
8	Method of addressing published articles other than English	No
9	Method of handling abstracts and unpublished studies	No
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Yes
11	Assessment of confounding	Partially
12	Assessment of quality	Yes
13	Assessment of heterogeneity	Yes
14	Description of statistical methods sufficient to replicate	Yes
15	Provision of appropriate tables and graphs	Yes
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Yes
17	Tables giving descriptive information of each study included	Yes
18	Results of sensitivity testing (subgroup analysis)	Yes
19	Indication of statistical uncertainty of findings	Yes
20	Quantitative assessment of bias (eg. publication bias)	Yes
	Overall quality	**B**

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Yes
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	Yes
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Yes
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Partially
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Yes
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Yes
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Yes
9	Were conclusions justified by the reported/collected data and analysis?	Yes

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

Sudden Infant Death Syndrome

Hauck 2003
McVea 2000 SRMA*
Mitchell 1997
Schellscheidt 1997
Venneman 2005

* Systematic Review/Meta-Analysis

Hauck, 2003 [UI# 12728140]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 89 days for cases and 85 days for controls Mean BW (range): 2813 g cases and 2915g for controls % Male: nd Race: 75% black; 13.1% Hispanic white; 11.9% non-Hispanic white Enrolled/Evaluate: 260 SIDS and 260 matched controls Location: community Sites: Single/Multi Population based Funding: Gov	Case-control study Follow-up NA	Cases: Included Chicago resident infants whose death between Nov 1993 and April 1996 was determined by the office of medical examiner of Cook County, Illinois to be caused by SIDS Two weeks after caregivers were asked 235 questions Controls: One living control infant was matched to each case infant on maternal race/ethnicity, age at death/interview; and birth weight. They were randomly selected in groups of 20 for white infants and in groups of 40 for Hispanic and black infants	Breastfeeding current yes and ever yes	Breastfeeding current no and ever no

Hauck, 2003 [UI# 12728140]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
SIDS: The sudden death of an infant under 1 yr of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history.	Univariate and multivariate models Adjusted for maternal age, marital status, education, and index of prenatal care	Breast feeding No was reference Breast feeding ever No (cases v controls)/Yes (cases v controls) N=205 v 130 / 55 v 130 OR=0.2 (0.1-0.3) Adj OR=0.4 (0.2-0.7) Breastfeeding current No (cases v controls)/Yes (cases v controls) N=243 v 199 / 17 v 61 OR=0.2 (0.1-0.4) Adj OR=0.3 (0.2-0.7)	A: strong, B: moderate, C: weak Selection: x Study design: x Confounder: x Blinding: Data collection: Withdraw and dropout: Analyses: Intervention integrity: x

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI]	McVea 2000 [11138219] SIDS
Topic	The role of breastfeeding in sudden infant death syndrome (SIDS)
Key questions addressed	Question 1 – Infant mortality
Dates of literature search –	1966-1997
Databases searched	MEDLINE-all English language literature search Dissertation Abstracts Online Bibliography of all relevant articles
Countries where primary studies conducted (Developed v developing)	Developed (Regions - North America, Europe, and Australia)
Study eligibility / inclusion criteria	Minimal definition of SIDS was met (sudden unexplained death of an infant or young child) Original data presented that allowed calculation of an odds ratio for bottle feeding
Study design [No. Of studies]	Total = 23 Case control [18] Nested case control [4] Cohort [1]
No. of subjects	Cases (n=99) Controls (n=47 413)
Study population (definition in included studies)	Children (Age range birth to 2 years when outcome occurred – 17 studies; 8 studies nd on age range)
Intervention (definition in included studies)	Breast feeding (No standard method of measuring breast feeding was used in the studies - breastfed at birth, breastfed at the time of death, "breast fed", "partially breast fed")
Comparator (definition in included studies)	Bottle fed (nd)
Outcomes (definition in included studies)	SIDS (autopsy proven in majority – 14 studies, death certificates or coroner's reports – 4 studies, unclear – 6 studies)
Heterogeneity	Not explored although studies were heterogeneous with respect to a variety of factors
Quality of Individual studies	Yes. Quality scores of studies ranged from 11 to 36 points (on a 42 point max score) Better quality studies reported slightly higher risks of bottle feeding
Publication bias	Yes. "The shape of the funnel graph endorsed the absence of publication bias of only positive studies"
Statistical Analysis	Random Effects model Used unadjusted odds ratio for the meta-analysis Separate meta-analysis was performed using only those studies with "good" quality scores and after 1988 Dose-response relationship explored
Results	The pooled OR for the 23 studies using random effects model resulted in an OR = 2.11 (95% CI 1.66-2.68) i.e. the overall risk of SIDS was twice as great for bottle-fed infants compared to breastfed infants. The pooled OR from the higher quality studies also demonstrated a two fold increase in risk among bottle fed infants OR = 2.24 The pooled OR from studies after 1988 OR = 2.32 Confounders: Individual studies adjusted for potential confounders; 6 studies reported adjusted OR; 4 studies reported no protective effect of breastfeeding, while 2 reported adj OR that remained significant. Dose Response relationship: 4 out of 9 studies showed a dose response trend with the risk of SIDS increasing with increasing formula feeding. None of the studies had sufficient power to demonstrate a statistically significant difference between partial v no breastfeeding.
Quality of the systematic review	C (see limitations)

Author, Year[UI]	McVea 2000 [11138219]	SIDS
Comments / Limitations	Misclassification of SIDS and breastfeeding Unadjusted odds ratio for pooled analysis Heterogeneity not explored Unable to combine studies with adjusted OR in the pooled analysis because of differences in case matching	

Author, yr: McVea, 2000
Topic of the systematic review*/MA: The role of breastfeeding in SIDS

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Y
2	Types of exposure or intervention used	Y
3	Types of study designs used	Y
4	Study population	Y
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Y
6	Effort to include all available studies (contact with authors)	N
7	Databases and registries searched	Y
8	Method of addressing published articles other than English	N
9	Method of handling abstracts and unpublished studies	Y
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Y
11	Assessment of confounding	N
12	Assessment of quality	Y
13	Assessment of heterogeneity	N
14	Description of statistical methods sufficient to replicate	Y
15	Provision of appropriate tables and graphs	Y
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Y
17	Tables giving descriptive information of each study included	Y
18	Results of sensitivity testing (subgroup analysis)	N
19	Indication of statistical uncertainty of findings	Y
20	Quantitative assessment of bias (eg. publication bias)	N
	Overall Quality	C

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	partially
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	partially
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	no
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	yes
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	yes
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	yes
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	no
8	Were results reported accurately (eg, no discrepancies between text and tables)?	yes
9	Were conclusions justified by the reported/collected data and analysis?	partially

Mitchell 1997 [UI# 9346984]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 2.6-9.1 wk for cases; 2.4-9.2 wk for controls Mean BW (range): <2500 to 3500+ % Male: 60% cases; 52% controls Race: Maori 56% cases and 22% controls Non Maori 44% cases and 78% controls Enrolled/Evaluate: 232 cases and 922 controls Location: community Sites: Single/Multi Population based Funding: Gov	Case-cohort study design 2 yr cohort; follow-up duration NA	Cases: All deaths registered by the New Zealand Health Information Service as attributable to SIDS in the postneonatal age group (dying after 28 completed days and within the first year of life) form the cases of this study. 98% of deaths classified as SIDS have had a autopsy. Controls: Randomly selected sample from a prospectively collected cohort on all births in the 2 yr period. The method of sampling was 1) a date of birth was randomly selected from all the days in the study period; 2) an obstetric hospital was randomly chosen in proportion to the number of births; 3) in the obstetric hospital with multiple births on nominated date of birth random numbers were used to select a particular infant from among those born on that day; 4) a direction variable which indicates to either go forward or back in looking for a birth in the situation where the hospital did not have one on the nominated day was also randomly chosen	Three measures of breastfeeding reference yes Exclusive breastfeeding at discharge from the obstetric hospital; any breastfeeding at initial contact; and any breast feeding at 2 months	No for the three measures of the breastfeeding

Mitchell 1997 [UI# 9346984]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
SIDS: dying after 28 completed days and within the first year of life	Univariate and multivariate analysis Controlled for: maternal age, marital status, age mother left school, previous number of pregnancies, infant's sex, ethnicity of infant, birthweight, sleep position, breastfeeding and bed sharing/maternal smoking combinations.	The three measures of breastfeeding were not statistically associated with a statistically significant reduction in the risk of SIDS	A: strong, B: moderate, C: weak: A / B / C Selection: / / x Study design: x / / Confounder: x / / Blinding: / / Data collection: / / Withdraw and dropout: / / Analyses: / / Intervention integrity: / / x
Comments	The controls were randomly selected from a prospective cohort; however the analysis was conducted as a case-control study. Overall quality = B		

Schellscheidt J 1997 [UI# 9266202]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 8 days to one yr Mean BW (range): nd % Male: nd Race: nd Enrolled/Evaluate: 59 Location: community Sites: Single/Multi Population based study Funding: nd	Case-control study Follow-up Not applicable Incidence of SIDS during the 2 yrs	For cases: No positive autopsy findings; minimal findings without any relationship to death; findings possibly related to death (but not explaining it) and autopsy findings explaining death. For controls: Two controls were selected for each case of the same age ±4 weeks and sex randomly by the pediatrician or a general practitioner	Breastfeeding in weeks >12 wks (ref)	Breastfeeding in weeks 1-6 wks 7-12 wks None

Schellscheidt J 1997 [UI# 9266202]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Same as eligibility criteria	Variables were entered as dichotomous indicators Analyses were univariate. No confounders were adjusted	Breast feeding cases versus controls None (N=29 vs 27) OR=7.7 (2.7, 22.3) 1-6 wk (N=12 vs 40) OR=2.1 (0.7, 6.7) 7-12 wk (N=10 vs 39) OR=1.8 (0.6, 6.0) >12 wk (N=7 vs 50) REF	

A: strong, B: moderate, C: weak	A	B	C
Selection	x		
Study design	x		
Confounder			x
Blinding		x	
Data collection		x	
Withdraw and dropout			
Analyses			x
Intervention integrity			

Vennemann, 2005 [UI# 16188764]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): nd Mean BW (range): nd % Male: cases 60.4% Controls 60.3% Race: nd Enrolled/Evaluate: SIDS cases 404/333 Location: population based Sites: Single/Multi 18 centers involved Funding: nd	Case-control study design Duration SIDS during 3 yr period Follow-up duration NA	Cases: All reported cases of sudden and unexpected deaths in the first year of life after the first 7 d and all cases were autopsied. Controls: Three controls with the best age matching were chosen	Breastfeeding >2 wk yes	Breastfeeding >2wk No

Vennemann, 2005 [UI# 16188764]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Sudden and unexpected deaths in the first year of life after the first 7 d and all cases were autopsied.	Univariate and multivariate analysis were done using conditional logistic regression. The multivariate model includes all variables which were found significant at the 5% level in the univariate analysis except gestational age, as this was closely related to birthweight	Breastfeeding >2wk Yes N=165/827 (cases/controls) No N=168/171 Univariate OR=5.36 (3.97-7.23) Multivariate OR=1.71 (1.06-2.77)	A: strong, B: moderate, C: weak Selection: A x Study design: A x Confounder: B x Blinding: B x Data collection: B x Withdraw and dropout: B x Analyses: B x Intervention integrity: B x Overall = B

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

Type 1 DM

EURODIAS 2002
Gerstein 1994 SRMA*
Jones 1998
McKinney 1999
Meloni 1997
Norris 1996 SRMA*
Tai 1998
Visalli 2003

* Systematic Review/Meta-Analysis

EURODIAS, 2002 [12351473]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Age at Dx of IDDM: ND Mean GA (range): ND Mean BW (range): ND % Male: ND Race: ND Enrolled/Evaluate: 683/610 for cases; 2167/1616 for controls Location: Europe Sites: Multi Funding: Government	Case-control study	Cases: cases were identified from a population-based register of childhood-onset diabetes operating in a sub-study of EURODIAB (5 participating centers) Controls: a population-based sample of control children, matched to the patients in age distribution, was obtained in each center using sources that depended on local circumstances as previously described (including schools, population register, polyclinics, and general practitioner register)	Parents were interviewed or filled in the questionnaire regarding information about infant feeding (duration of breast-feeding, age at introduction of formula feeding, dairy milk, food containing fruit, vegetable, fish, meat, and egg). Breast-feeding of any duration (or ever breast-feeding)	Never breast-feeding

EURODIAS, 2002 [12351473]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Pooled ORs of IDDM for exposures obtained from each center	Mantel Haenszel approach was used to pool odds ratio (ORs) for exposures (e.g. breastfeeding, early introduction of solid food) obtained from each center, to test the significance of the combined OR, and to test for heterogeneity in the ORs between centers. To adjust for potential confounders, logistic regression analysis was used with terms included in the model to represent centers. Adjustments included height SDS, weight SDS, maternal age at delivery, neonatal jaundice, neonatal respiratory infection, vitamin D supplementation, and asthma.	Breast-feeding of any duration was associated with a reduction in risk, with a pooled OR of 0.75 (95% CI 0.58-0.96) and no evidence of heterogeneity between centers. The introduction of cow's milk before 3 months of age (OR 1.15, 95%CI 0.74-1.81), cow's milk or formula (OR 1.01, 95%CI 0.81-1.25), or solid foods (OR 0.74, 95%CI 0.57-0.95) was not associated with any significant elevation in risk. Indeed the finding for solid foods suggested a reduced risk, although there was significant heterogeneity between centers ($p<0.001$). The OR associated with breastfeeding in multivariate analysis remained significant (OR=0.59, 95%CI 0.35-0.97)	A: strong, B: moderate, C: weak: A x, B, C Selection: B x Study design: B x Confounder: A x Blinding: C x Data collection: B x Withdraw and dropout: B x Analyses: A x Intervention integrity: N/A Overall: B Long-term recalls

Q1: Insulin-Dependent Diabetes Mellitus

Author, Year[UI]	Gerstein, 1994 [8112184]	Type 1 Diabetes Mellitus
Literature search (Dates)	Medline (no data); Other databases searched? (no); unpublished data used? (yes)	
Countries where primary studies conducted	Developed countries only: Norway, Denmark, Italy, US, Australia, Canada, Sweden, Finland, UK	
Study eligibility / inclusion criteria	Articles or letters to the editor were eligible for inclusion if they reported original research dealing with both type I diabetes and cow's milk exposure or avoidance and were published in peer-reviewed journals. Articles were excluded if they exclusively used surrogate markers for either type I diabetes or cow's milk exposure.	
Study design [No. Of studies]	Ecological and time-series studies [3]; Case-control studies [13]; Cohort study [1]; case series [1]	
No. of subjects	Data available for case-control studies only: Cases: 3,708 Controls: 20,340	
Study population (definition in included studies)	• Ecological and time-series studies in which the prevalence of type I DM was compared with the rate of breast-feeding or cow's milk consumption in different populations or over a specified period of time. • Case-control studies in which the neonatal feeding histories of patients with type I DM and individually matched non-DM control subjects were compared. Studies that used population breast-feeding registries as control data also were included, because the low prevalence of type I DM in the general population ensures that population data is representative of the breast-feeding habits of non-DM individuals. • There was a letter to the editor reporting an analysis of two cohort studies and an article that described the neonatal feeding history of a series of patients with DM. • There were no controlled trials of exposure to cow's milk.	
Intervention/Exposure (definition in included studies)	Cow's milk exposure (and therefore non-exclusive breastfeeding)	
Comparator (definition in included studies)	Cow's milk avoidance (and therefore breastfeeding)	
Outcomes (definition in included studies)	Type I DM. Surrogate markers of type I DM (such as the presence of islet cell antibodies) were excluded.	
Heterogeneity assessments	Q statistics and chi-square distribution	
Quality assessments	Six methodological criteria were assessed for case-control studies only. Each criterion was marked individually and listed in a summary table of all studies. There was no summary grading.	
Publication bias assessments	Not done	
Statistical Analysis or meta-analytic methods	Meta-analyses of ORs were done for case-control studies. Both adjusted (preferred) and unadjusted ORs were used. Fixed-effect model.	

Author, Year[UI]	Gerstein, 1994 [8112184]	Type 1 Diabetes Mellitus
Results	• Time-series and ecological studies showed an association (geographically and temporally) between rate/prevalence of breastfeeding and the incidence of type I DM. • Results from the 13 case-control studies were mixed. Some of these studies demonstrated that patients with type I DM were more likely to have a history of neonatal cow's milk exposure or a short/negative history of breast-feeding than non-DM control subjects; other studies failed to demonstrate such a relationship. When these results were meta-analyzed, the OR for type I DM in patients exposed to <3 months of breast-feeding was 1.38 (95% CI 1.22-1.53; p=0.11 for homogeneity). Similarly, the overall OR for cow's milk exposure before 3-4 months of age in patients with type I DM was 1.57 (95% CI 1.19-2.07; p=0.10 for homogeneity). • An analysis of two cohorts of children born in the UK in 1958 and 1970 followed for 16 and 10 years, respectively, failed to show any association between breastfeeding for <1 month and type I DM.	
Quality of the systematic review	B	
Author's interpretations of the results	The results of this review are consistent with the hypothesis that avoidance of cow's milk products during the first few months of life may reduce the risk of type I DM. A feeding intervention trial in which susceptible newborns would be randomized to receive formula with or without cow's milk and followed for the development of DM would most clearly resolve the issue.	
Comments / Limitations	This systematic review primarily aimed to examine the relationship between early cow's milk exposure and type I DM. However, exclusive breastfeeding is a way of avoidance of cow's milk exposure; then therefore this review also examined the association between breastfeeding and type I DM. The exclusivity of breastfeeding was not addressed in the meta-analyses. Combining both adjusted and crude OR.	

Author, yr: Gerstein, 1994
Topic of the systematic review*/MA: Type 1 DM

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Yes
2	Types of exposure or intervention used	Yes
3	Types of study designs used	Yes
4	Study population	Yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	No
6	Effort to include all available studies (contact with authors)	No
7	Databases and registries searched	Yes
8	Method of addressing published articles other than English	No
9	Method of handling abstracts and unpublished studies	No
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Yes
11	Assessment of confounding	No
12	Assessment of quality	Yes
13	Assessment of heterogeneity	Yes
14	Description of statistical methods sufficient to replicate	Yes
15	Provision of appropriate tables and graphs	Yes
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Yes
17	Tables giving descriptive information of each study included	Yes
18	Results of sensitivity testing (subgroup analysis)	Yes
19	Indication of statistical uncertainty of findings	Yes

		Reporting yes/no
20	Quantitative assessment of bias (eg. publication bias)	Yes
	Overall quality	**B**

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Partially
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	No
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Yes
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Partially
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Partially
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Yes
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Yes
9	Were conclusions justified by the reported/collected data and analysis?	Yes

Jones, 1998 [9698133]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Age at Dx of IDDM: ND Mean GA (range): ND Mean BW (range): ND % Male: 53 Race: ND Enrolled/Evaluate: <76/60 for cases Location: UK Sites: Multi Funding: Government	Case-control study	Cases: Oxford Record Linkage Study (ORLS) records of hospital admissions for discharge diagnoses coded to diabetes mellitus were searched. Cases were identified as children who were diagnosed with diabetes 1965-1987, and who had been born during 1965-1986 (N=315). 98% of cases born 1970-1986 were matched with 5 or more controls each. Controls: for cases born 1970-1986, 8 controls from all livebirths in the ORLS areas were randomly selected. Controls were individually matched to cases on sex, year and hospital of delivery, or if domiciliary to another domiciliary delivery. Exclusion: children with cystic fibrosis or major congenital anomalies, or who were part of twin or higher order deliveries. Breastfeeding data were routinely collected only from 1976 so this result is based upon 60 cases and 458 controls born 1976-1986, of which 7 controls had missing data.	Breastfeeding at discharge	Not breastfeeding at discharge

Jones, 1998 [9698133]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Relative risk of IDDM	Relative risks were calculated by estimating rate ratios using conditional logistic regression for matched case-control studies.	There was a small, but not significant, raised risk of diabetes with not breastfeeding at discharge (RR=1.33, 95% CI: 0.76-2.31).	A: strong, B: moderate, C: weak — A: ; B: ; C: x Selection: ; ; x Study design: ; x; Confounder: ; ; x Blinding: ; x; Data collection: ; ; x Withdraw and dropout: ; ; x Analyses: ; ; x Intervention integrity: N/A Overall: C Poor adjustments for confounding; Poor definition of BF exposure

McKinney, 1999 [10372244]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Age at Dx of IDDM: 0-15 Mean GA (range): 11% ≤37 wks Mean BW (range): 7% <2500g, 58% 2500-3500g; 35% ≥3500g % Male: 55 Race: 95% White, 3.5% India or Pakistan Enrolled/Evaluate: 202/196 for cases354/325 for controls Location: UK Sites: Single Funding: Private	Case-control study	Cases: Incident cases included those diagnosed with type 1 DM over a 2-year period (1993-1994) and taken from the population-based Yorkshire Childhood Diabetes Register (YCDR). The register ascertained children from 3 independent sources and was estimated to be 97% complete. Controls: 2 control subjects per case, matched by sex and age, were randomly selected from the primary care registrations of the Family Health Service Authority (FHSA) of the matched case. Exclusion: 6 cases and 29 control subjects had no matching control subjects or cases and were lost to the matched analysis	Mothers were interviewed. Participation rates for the interview study were 93.6% and 81.9% for case and control mothers, respectively. Initial exclusive breast feeding (yes): mothers were asked how the infant was first fed	Initial exclusive breast feeding (no)

McKinney, 1999 [10372244]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
OR of IDDM	ORs with95% CI and p values were calculated using conditional logistic regression with a single term in the model for univariate estimates. Variables significantly associated with disease obtained from the analysis of individual variables were modeled together in a multivariable analysis. Variables significant at the 5% level in a univariate analysis in our study were mother's age (<25, 25-35, >35), type 1 diabetes mothers, preeclampsia, delivery by cesarean section, neonatal illnesses, and breast feeding. These potential explanatory variables were modeled together in a multivariable analysis.	Factors in the model / Cases / Controls / OR (95% CI) n: 196 / 325 Mother's age 25-35 years: 123 / 182 / 1.69 (1.11-2.60) >35 years: 2.07 (0.97-4.43) Mother with IDDM: 4 / 0 / -- Preeclampsia: 44 / 49 / 1.60 1.01-2.54) Cesarean delivery: 34 / 35 / 1.45 (0.82-2.55 Neonatal illnesses ≥1: 61 / 35 / 1.55 (1.00-2.42) Initial exclusive breast feeding: 73 / 151 / 0.60 (0.41-0.89) Results show all variables retained their significance in the multivariate model. The addition of neonatal illnesses and breast feeding significantly improved the model fit (likelihood ratio test, chi squared 9.96, P = 0.007). Note: Crude OR = (73*174)/(151*123)=0.68, p=0.04	A: strong, B: moderate, C: weak / A / B / C Selection: x Study design: x Confounder: x Blinding: x Data collection: x Withdraw and dropout: x Analyses: x Intervention integrity: N/A Overall: B No adj. for SES

Meloni, 1997 [9051384]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Age at Dx of IDDM: 6 (1-15) yr Mean GA (range): ND Mean BW (range): ND % Male: 53 Race: ND Enrolled/Evaluate: 115/100 for cases Location: Italy Sites: Single Funding: ND	Case-control study	Cases: All diabetic subjects followed up at the university hospital who met the inclusion criteria: 1: age < 17 years at diagnosis of IDDM, 2) diagnosis of IDDM was achieved between 1983 and1994, and 3) patient's mother was currently living, which was considered necessary to obtain accurate infant diet information. According to these criteria, 100 IDDM patients (of the 115 eligible) were included. Controls: children admitted at the same university hospital, matched each diabetic case for sex and age. None of the control subjects had a family history of IDDM.	Long-term maternal recall of the duration of complete or partial breast-feeding during infant's 1st year of life.	Long-term maternal recall of the age at which dietary products containing cow's milk were introduced into the diet during infant's 1st year of life

Meloni, 1997 [9051384]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Risk of IDDM, compared children who had been breast-fed to those who had not been breast fed Risk of IDDM, compared children who had been breast-fed for 1-2 months, 3-5 months, or >6 months to those who had not been breast-fed.	The OR of diabetes according to breast-feeding, the duration of breast-feeding, the age at introduction of dietary products containing cow's milk, and the age at introduction of solid food were estimated by means of conditional logistic regression, where the strata were defined by single year of age at interview and sex. Also included in the models were terms for mother's education and number of siblings.	See table below	See table below

	IDDM cases	Controls	OR (95% CI)
BF			
Yes	84	70	1*
No	16	30	0.41 (0.19-0.91)
Duration of BF (mo)			
>6	25	19	1*
3-5	41	25	1.18 (0.52-2.68)
1-2	18	26	0.48 (0.19-1.24)
0	16	30	0.36 (0.14-0.94)
Continuous coefficient**			1.10 (0.99-1.22)

*reference category
**continuous per 1 month increase

A: strong, B: moderate, C: weak	A	B	C
Selection		x	
Study design		x	
Confounder		x	
Blinding			x
Data collection		x	
Withdraw and dropout		x	
Analyses	x		
Intervention integrity	N/A		

Overall: B
Limitations: Long-term maternal recalls. Hospital controls

Q1: Insulin-Dependent Diabetes Mellitus

Author, Year[UI]	Norris, 1996 [8664407]	Type 1 Diabetes Mellitus
Literature search (Dates)	Medline (1966-1994); Other databases searched? (no); unpublished data used? (yes)	
Countries where primary studies conducted	Developed countries only: Norway, Denmark, Italy, US, Australia, Canada, Sweden, Finland, British Isles, Ireland, UK	
Study eligibility / inclusion criteria	Inclusion: all epidemiologic studies examining infant diet and IDDM risk Exclusion: studies with insufficient data for meta-analyses	
Study design [No. Of studies]	Case-control studies [17]	
No. of subjects	Cases: 4,656 Controls: 16,383	
Study population (definition in included studies)	Cases: IDDM patients identified from diabetes clinics, school surveys, registries, physician surveys, or pediatric departments. Controls: non-IDDM controls selected from siblings, national population data, friends, classmates, physician referred samples, national population registry, random sample of household, child health system, or schools and day care	
Intervention/Exposure (definition in included studies)	A=breastfeeding status (ever/never) B=total breastfeeding duration	
Comparator (definition in included studies)	C=exposure to breast-milk substitutes D=exposure to cow's milk-based substitutes	
Outcomes (definition in included studies)	Odds ratios for the risk of IDDM	
Heterogeneity assessments	"The addition to the model of a variable for each study in the analyses resulted in an improvement in the overall fit of the model (as determined by the log-likelihood statistic) compared with the model containing only the exposure variable, indicating heterogeneity of effect across studies. We also evaluated study heterogeneity by adding to the model product terms obtained by multiplying the exposure variable by each study variable."	
Quality assessments	Sensitivity analyses on various study characteristics	
Publication bias assessments	Including unpublished data	
Statistical Analysis or meta-analytic methods	Stratified unconditional logistic regression was used to estimate OR and 95%CI. This method weights each study by its sample size. Variables for the individual studies and for the exposure of interest were included in the model. Both matched and unmatched ORs were used.	
Results	• The summary odds ratio (OR) of the 18 studies that examined the association between never being breast-fed and IDDM was 1.13 (95% CI = 1.04-123). • Meta-analyses of summary ORs were done in the 14 studies that examined IDDM risk by months of breastfeeding duration. The duration categories in the analyses were cumulative, rather than mutually exclusive. The summary OR for IDDM in subjects who were breast-fed for less than 3 months compared with those who were breast-fed for at least 3 months was 1.23 (95%CI = 1.12-1.35). • When comparing the ORs by whether or not the studies relied on long-term recall to assess infant diet, studies using existing infant records to determine breastfeeding initiation and duration failed to show the associations reported in the studies relying on long-term recall for their exposure data.	
Quality of the systematic review	B	
Author's interpretations of the results	Our meta-analysis showed that the increased risk of IDDM associated with any of the infant diet exposures is small Interpretation of weak associations (that is, generally an OR<2) can be problematic, since weak associations can more readily be explained by bias.	

Author, Year[UI]	Norris, 1996 [8664407]	Type 1 Diabetes Mellitus
Comments / Limitations	Very thoughtful analyses but the analysis cannot be replicated due to lack of individual study data. Only crude ORs were used in the meta-analyses due to limitation of meta-analytic technique. Conclusions were well justified.	

Author, yr: Norris, 1996
Topic of the systematic review*/MA: Type 1 DM

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	yes
2	Types of exposure or intervention used	yes
3	Types of study designs used	yes
4	Study population	yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	no
6	Effort to include all available studies (contact with authors)	yes
7	Databases and registries searched	yes
8	Method of addressing published articles other than English	no
9	Method of handling abstracts and unpublished studies	yes
	Reporting of Methods	
10	Rationale for selection and/or coding of data	yes
11	Assessment of confounding	yes/no
12	Assessment of quality	yes
13	Assessment of heterogeneity	yes
14	Description of statistical methods sufficient to replicate	yes
15	Provision of appropriate tables and graphs	yes
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	no
17	Tables giving descriptive information of each study included	yes
18	Results of sensitivity testing (subgroup analysis)	yes
19	Indication of statistical uncertainty of findings	yes
20	Quantitative assessment of bias (eg. publication bias)	yes
	Overall quality	**B**

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Partially
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	Yes
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Yes
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Partially
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Yes
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Yes
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Yes
9	Were conclusions justified by the reported/collected data and analysis?	Yes

Tai, 1998 [9925351]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Age at Dx of IDDM: 8.3±3.3 SD Mean GA (range): 1% ≤36 wk; 99% >36 wk Mean BW (range): 21% <3 kg, 69% 3-3.9 kg; 10% ≥4 kg % Male: 37 Race: Asian Enrolled/Evaluate: 117/117 for cases; 193/193 for controls Location: Taipei, R.O.C. Sites: Single Funding: Government	Case-control study	Cases: From 1984 to 1993, there were a total of 161 registered type 1 diabetes patients who were under the age of 30, born in Taipei City and continuously living in the same city. Among these, 119 (73%) subjects agreed to participate in the study. Their overnight fasting serum C-peptide concentration was < 0. 12 nmol/l and/or an increment in C-peptide from basal value after 1mg glucagons intravenous injection. Controls: The control group was selected from normal classmates or colleagues of the type 1 diabetes subjects. They were frequency-mated for age, sex, and parental and individual educational levels. All controls had a plasma glucose concentration, 2 h after 1.75 g/kg glucose loading, <140 mg/dl, fasting C-peptide value >0.16 nmol/l and were negative for islet cell antibody.	In the majority of the study subjects (79% cases and 75% controls), their mothers were interviewed by 2 trained nurses. In the remaining study subjects, the questionnaire interviews were answered by the subjects themselves or by their fathers with the help of their mothers. Feeding style during infancy: breast-feeding Duration of breast-feeding: <6, ≥6 months	Never breast-fed (totally on cow's milk)

Tai, 1998 [9925351]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>OR of developing IDDM</td>
<td>Age and sex were adjusted using logistic regression analysis. The age-sex-adjusted ORs were estimated from the regression coefficient and its S.E. for the risk factor.
Multiple logistic regression analysis was then carried out by including risk factors which were statistically significant in univariate analyses as well as those reported in other studies in the model.</td>
<td>I. Age-sex-adjusted ORs of developing IDDM (univariate):
<table>
<tr><th>Risk factors</th><th>Cases N</th><th>Controls N</th><th>OR (95% CI)</th></tr>
<tr><td>Feeding style during infancy</td><td></td><td></td><td></td></tr>
<tr><td>Breast-feeding</td><td>46</td><td>82</td><td>1.00</td></tr>
<tr><td>Cow's milk</td><td>70</td><td>109</td><td>1.43 (0.83-2.47)</td></tr>
<tr><td>Duration of BF (months)</td><td></td><td></td><td></td></tr>
<tr><td>Never</td><td>70</td><td>109</td><td>1.00</td></tr>
<tr><td><6</td><td>32</td><td>52</td><td>0.82 (0.47-1.42)</td></tr>
<tr><td>≥6</td><td>10</td><td>25</td><td>0.39 (0.16-0.94)</td></tr>
</table>
II. Multiple logistic regression in which the order of pregnancy, paternal age at the conception of the study subjects, gestational age, type of delivery, birth weight, duration of breast-feeding and monthly family income were included in the model.
<table>
<tr><th>Duration of BF (months)</th><th>OR (95% CI)</th></tr>
<tr><td>Never</td><td>1.00</td></tr>
<tr><td><6</td><td>0.84 (0.45-1.59)</td></tr>
<tr><td>≥6</td><td>0.25 (0.09-0.69)</td></tr>
</table>
The dose-response relationship with type 1 DM for pregnancy order and the reverse pattern for duration of breast-feeding remained statistically significant after adjustment for multiple risk factors.</td>
<td>
<table>
<tr><th>A: strong, B: moderate, C: weak</th><th>A</th><th>B</th><th>C</th></tr>
<tr><td>Selection</td><td></td><td>x</td><td></td></tr>
<tr><td>Study design</td><td></td><td>x</td><td></td></tr>
<tr><td>Confounder</td><td>x</td><td></td><td></td></tr>
<tr><td>Blinding</td><td></td><td></td><td>x</td></tr>
<tr><td>Data collection</td><td></td><td></td><td>x</td></tr>
<tr><td>Withdraw and dropout</td><td></td><td>x</td><td></td></tr>
<tr><td>Analyses</td><td></td><td>x</td><td></td></tr>
<tr><td>Intervention integrity</td><td colspan="3">N/A</td></tr>
</table>
Overall: B

Inconsistent methods for BF exposure ascertainments</td>
</tr>
</table>

Visalli, 2003 [12876166]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Age at Dx of IDDM: ND Mean GA (range): ND Mean BW (range): ND % Male: 50 Race: ND Enrolled/Evaluate: 330/150 for cases; 1200/750 for controls Location: Italy Sites: Multi Funding:	Case-control study	Cases: type 1 DM patients selected (330 cases) for this study were diagnosed within the EURODIAS ACE study, and were born between 1977 and 1989. Controls: population based control subjects born in the same period were chosen from primary and secondary school enrolment records in the region, and the selection process was designed in collaboration with EURODIAS Substudy 2 group. Out of 1,100 controls replied to the questionnaires, 750 were randomly selected, matching 1 case with 5 controls by age.	Questionnaires were distributed to all parents of cases and controls. Duration of breast feeding ≥ 3 months End of breast feeding ≥ 3 months	Duration of breast feeding < 3 months End of breast feeding < 3 months

Visalli, 2003 [12876166]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
OR of IDDM	Conditional logistic regression analysis was performed to adjust the possible confounders (those significant in univariate analyses).	I. Univariate analysis: Risk factors — OR — 95% CI Full term birth — 1.44 — 0.81-2.56 Duration of BF < 3 mo — 2.12 — 1.38-3.26 Beginning of weaning < 3 mo — 1.81 — 1.06-3.07 End of breast feeding < 3 mo — 2.03 — 1.24-3.33 Cow's milk before 23 mo — 1.49 — 0.72-3.11 II. Multivariate logistic regression analysis for risk factors which have been found to be significant Risk factors — OR — 95% CI Duration of BF < 3 mo — 1.74 — 1.40-2.45 Family history of type 1 DM — 1.17 — 1.05-1.76 Presence of infectious disease during mother's pregnancy — 1.60 — 1.32-2.20 Occurrence of eczema — 1.61 — 1.25-2.66	A: strong, B: moderate, C: weak — A — B — C Selection — — — x Study design — — x — Confounder — — x — Blinding — — — x Data collection — — x — Withdraw and dropout — — — x Analyses — x — — — Intervention integrity — N/A Overall: C Only 45% of the eligible cases were able to be contacted.

Appendix C. Evidence Tables

Part I. Term Infant Outcomes

Infant Type 2 DM

Owen 2006 SRMA*
Taylor 2005 SRMA*

* Systematic Review/Meta-Analysis

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI] Topic	Owen, 2006 Type 2 diabetes
Literature search (Dates)	Medline (1966-November 2004); Other databases searched? (yes); unpublished data used? (no)
Countries where primary studies conducted	Developed countries: UK, US, Canada, Dutch
Study eligibility / inclusion criteria	Exclusion criteria: infant feeding status or measures of diabetes were not recorded. Studies did not compare diabetic outcomes among those formula and breastfed. Studies did not provide the odds of type 2 diabetes, mean differences in blood glucose, or differences in plasma insulin between those breastfed and formula fed. Note: For the purpose of this review, we only focus on those studies reported OR of type 2 diabetes as an outcomes.
Study design [No. Of studies]	Historical cohort study [3]; Cross-sectional study [2]; Prospective cohort [1]; Case-control study [1]
No. of subjects	Total of 76,744 subjects
Study population (definition in included studies)	6 studies conducted in adults and 1 conducted in adolescents
Intervention/Exposure (definition in included studies)	Ever breastfed vs. formula fed in all 7 studies. Feeding status was reported as being exclusive in one of these studies.
Comparator (definition in included studies)	
Outcomes (definition in included studies)	OR (95% CI) of type 2 diabetes
Heterogeneity assessments	Chi-squared test. Meta-regression and sensitivity analysis were used to examine potential heterogeneity across studies (see Quality assessment)
Quality assessments	The effect of study size, year of birth, the method of ascertainment of infant feeding status (whether contemporary or recalled up to 71 y after birth), type of formula fed, study response rate (analyzed as a continuous variable), study design (randomized controlled trial, case-control, or cohort), and whether infants were born pre- or full-term was examined by using meta-regression and sensitivity analysis. Sensitivity analyses were used to examine the effect of adjustment for important confounders and of fasting status.
Publication bias assessments	Funnel plots with Begg and Egger tests
Statistical Analysis or meta-analytic methods	Fixed-effect model.
Results	• Six of the 7 studies related breastfeeding to a lower risk of type 2 diabetes, and there was no evidence of heterogeneity across studies. • Overall, the subjects who were breastfed showed a lower risk of type 2 diabetes than did those who were formula fed (pooled OR: 0.61; 0.44-0.85; p=0.003). • Three studies had information on relevant confounders (birthweight, parental diabetes, socioeconomic status, and individual or maternal body size). However the OR relating breastfeeding and diabetes risk was similar before (0.55; 95% CI: 0.35-0.86; p=0.009) and after (0.55, 95% CI 0.34-0.90; p=0.017) adjustment. • The method for ascertaining feeding exposure was unrelated to the ORs.
Quality of the systematic review	A
Author's interpretations of the results	In the present overview of published studies relating infant feeding and risk of diabetes, the pooled estimate from 6 studies conducted in adults and 1 study conducted in adolescents showed that early breastfeeding was consistently associated with a lower risk of type 2 diabetes in later life compared with those initially formula fed.

Author, Year[UI] Topic	Owen, 2006 Type 2 diabetes
	Publication bias is an important potential explanation for the consistent associations observed in these published studies. The results provide no evidence of marked publication bias, although the statistical power of formal tests was limited by the small number of studies available for analysis. It is possible that confounding by birthweight and maternal factors could lead to overestimation of the association between breastfeeding and diabetes in later life.
Comments / Limitations	Pooled different study designs

Author, yr: Owen, 2006
Topic of the systematic review*/MA: Type 2 DM

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	yes
2	Types of exposure or intervention used	yes
3	Types of study designs used	yes
4	Study population	yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	yes
6	Effort to include all available studies (contact with authors)	no
7	Databases and registries searched	yes
8	Method of addressing published articles other than English	no
9	Method of handling abstracts and unpublished studies	no
	Reporting of Methods	
10	Rationale for selection and/or coding of data	yes
11	Assessment of confounding	yes
12	Assessment of quality	yes
13	Assessment of heterogeneity	yes
14	Description of statistical methods sufficient to replicate	yes
15	Provision of appropriate tables and graphs	yes
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Yes
17	Tables giving descriptive information of each study included	yes
18	Results of sensitivity testing (subgroup analysis)	yes
19	Indication of statistical uncertainty of findings	yes
20	Quantitative assessment of bias (eg. publication bias)	yes
	Overall quality	**A**

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Yes
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	Partially
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Yes
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Yes
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Yes
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Yes
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Yes
9	Were conclusions justified by the reported/collected data and analysis?	Yes

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI] Topic	Taylor, 2005 [UI] Type 2 diabetes
Literature search (Dates)	Medline (1966-2003); Other databases searched? (yes); unpublished data used? (no)
Countries where primary studies conducted	Developed countries only: US, Canada, Germany
Study eligibility / inclusion criteria	Search was limited to the English language and to human subjects. All studies involved term singleton infants unless otherwise noted.
Study design [No. Of studies]	Cohort studies [2]; case-control study [1]
No. of subjects	1,514
Study population (definition in included studies)	• Studies of association between breastfeeding and type 2 diabetes • Children of mothers with diabetes
Intervention/Exposure (definition in included studies)	Many of the studies that were reviewed only reported breastfeeding versus bottle feeding, without more detailed information on exclusivity, frequency, or duration. Information on timing and duration of breastfeeding were included where available.
Comparator (definition in included studies)	
Outcomes (definition in included studies)	• Impaired glucose tolerance (IGT): fasting glucose < 140 mg/dL and 2-hour glucose > 140 mg/dL (after 1.75 g/kg OGTT) • Type 2 diabetes (NIDDM): 2-hour glucose ≥ 200 mg/dL (after 75 g OGTT) or fasting glucose ≥ 126 mg/dL
Heterogeneity assessments	N/A
Quality assessments	N/A
Publication bias assessments	N/A
Statistical Analysis or meta-analytic methods	N/A
Results	Association between breastfeeding and type 2 DM: • Consistently in 2 studies (1 retrospective cohort; 1 case-control study), exclusive breastfeeding is associated with lower risk of diabetes. Children of Mothers with DM: • One retrospective cohort study found that DM in the next generation was less common among breastfed children than among bottle-fed children, of both mothers with DM and without DM.
Quality of the systematic review	C
Author's interpretations of the results	Based on the literature reviewed, breastfeeding should be strongly encouraged for all women, with or without diabetes.
Comments / Limitations	No synthesis of results or appraisals of study quality. Unclear how the conclusions were reached.

Author, yr: Taylor, 2005
Topic of the systematic review*/MA: Type 2 DM

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	yes
2	Types of exposure or intervention used	yes
3	Types of study designs used	yes
4	Study population	yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	yes
6	Effort to include all available studies (contact with authors)	no
7	Databases and registries searched	yes
8	Method of addressing published articles other than English	no
9	Method of handling abstracts and unpublished studies	no
	Reporting of Methods	
10	Rationale for selection and/or coding of data	yes
11	Assessment of confounding	partially
12	Assessment of quality	no
13	Assessment of heterogeneity	N/A
14	Description of statistical methods sufficient to replicate	N/A
15	Provision of appropriate tables and graphs	no
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	no
17	Tables giving descriptive information of each study included	no
18	Results of sensitivity testing (subgroup analysis)	N/A
19	Indication of statistical uncertainty of findings	yes
20	Quantitative assessment of bias (eg. publication bias)	no
	Overall quality	C

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Partially
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	No
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	No
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Partially
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	No
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Partially
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Unclear (no tables)
9	Were conclusions justified by the reported/collected data and analysis?	No

Appendix C. Evidence Tables

Part II. Preterm Infant Outcomes

Cognitive Premature Infants

Bier 2002
Eidelman 2004
Elgen 2002
Feldman 2003
Horwood 2001
O'Connor 2003
Pinelli 2003
Smith 2003
Vohr 2006

Bier 2002 [2003020034]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range) breast milk group: 28.6 wk (23-34) Mean BW (range): 1174 g (600-1965) % Male: 45% Race: Enrolled/Evaluate: 29 in human milk group; 10 in formula group Location: US Sites: Multi Funding:	Non-randomized comparison of breast milk versus formula fed preterm infants (convenience sample)	Excluded infants with mothers who used illicit drugs, had mental illness, HIV infection, and others.		

Bier 2002 [2003020034]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Bayley MDI at 7-month and at 12-month	Adjusted for maternal result of Peabody Picture Vocabulary Test (PPVT) and days of oxygen	Mean Bayley MDI at 7 month, human milk group = 94 ± 7, in formula group = 90 ± 9 (Difference NS) At 12 months, human milk group = 101 ± 11, formula group = 90 ± 9 (P<0.05) ANOVA, adjusted for days of oxygen and maternal PPVT, Bayley MDI in human milk vs formula, 100 ± 12 vs 91 ± 10 (R^2, P<0.025) Regression analysis showed an association between the amount of milk infants received in the special care nursery (mL/wk) by gavage and/or bottle and the Bayley MDI at 7 mo (P<0.05) and 12 mo (P<0.025).	A: strong, B: moderate, C: weak / A / B / C Selection / / / x Study design / / / x Confounder/bias / / x / Blinding / / x / Data collection / / / x Withdraw and dropout / / / x Analyses / / / x Intervention integrity / / / Actual number of mothers approached for participation was not accounted for, small sample size, cognitive test at young age, principal investigator was available to all mothers at all times to answer feeding related questions

Eidelman 2004 [15384601]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 30.5 wk (26-33 wk) Mean BW (range): 1298 g (640-1720 g) % Male: 53% Race: Evaluated: 86 Location: Israel Sites: Single Funding:	Prospective cohort separated into 3 groups based on amount of human milk feeding; Bayley scales assessed at 6 months corrected age	<33 wk gestation; birth weight < 1750 g; exclusion criteria: intraventricular hemorrhage grade 3 or 4, perinatal asphyxia, metabolic or genetic disease	Exact amount of human milk and formula an infant received was recorded after each meal. Divided into >75% of nutrition as human milk; 25-75%; and <25%	

Eidelman 2004 [15384601]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
MDI at 6 months corrected age	Number of breastfeeding episodes was used as a covariate; MANCOVA performed with human milk and infant gender as the between subject factors	The number of breastfeeding episodes was <5%. Univariate analyses showed group differences on the MDI. Post hoc comparisons reported significant differences between the substantial milk group and the other two groups: 94.2±8.8 vs 91.7±7.2 vs 90.5±8.5 (P<0.05)	A: strong, B: moderate, C: weak — A / B / C Selection — x Study design — x Confounder — x Blinding — B: x Data collection — x Withdraw and dropout — x Analyses — x Intervention integrity Not adjusted for SES, maternal education or intelligence; small sample size;, cognitive testing at young age

Elgen, 2003 [14580653]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): BW (range): <2000 g % Male: Race: Evaluate: 130 Location: Norway Sites: Single/Multi Funding:	Prospective cohort, followed 'til 11 yr	Born in the county of Hordaland, Norway, between 4/1986 and 8/1988; survived to 11 yr; low birth weight; no cerebral palsy, blindness, deafness, multiple malformations, or chromosomal abnormalities	27% received <30% human milk in neonatal ward	

Elgen, 2003 [14580653]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Weschler Preschool and Primary Scale of Intelligence- Revised at 5 yr; Weschler Intelligence Scale for Children-Revised at 11 yr	Breast milk, birth weight, paternal and maternal education, chorioamnionitis, gestational age, length of oxygen treatment, sex, Apgar at 5 minutes, smoking during pregnancy, intrapartum stress, cerebral hemorrhage in subjects with birth weight <1500 g	Unadjusted regression: lack of breast milk was associated with a mean reduction in IQ of 5.8 points (95% CI –11 to –1). After adjustment for parental confounding, breast milk was no longer a statistically significant predictor of IQ (paternal education was a significant confounder with breast milk).	A: strong, B: moderate, C: weak / A / B / C Selection / / x / Study design / / / x Confounder/bias / / x / Blinding / / x / Data collection / / / x Withdraw and dropout / / / x Analyses / / x / Intervention integrity / / / Lack of detailed information on breast milk exposure

Feldman, 2003 [12918090]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 30 wk (26-33) Mean BW (range): 1298 (640-1720) % Male: Race: Enrolled/Evaluate: 86 Location: Israel Sites: Single/Multi Funding:	Prospective cohort; consecutive enrollment (6 declined)	<33 wk gestation; <1750 g Excluded infants with congenital malformation, severe hemorrhage; also excluded poverty, single parenting, teenage mothering, and maternal drug use	>75%, 25-75%, and <25% nutrition from breast milk; exact amount of breast milk and formula the infant received was recorded after each meal by nursing staff	

Feldman, 2003 [12918090]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Bayley MDI at 6 months corrected age	Multivariate ANOCOVA with breast milk and infant gender as the between-subject factors and the number of breast-feeding episodes as the covariate was computed for the cognitive indices at 6 months	An overall main effect for breast milk group was found (F=3.14, P<0.05) Univariate analysis: A (n=34) >75% group MDI 94.16 ± 8.75 B (n=21) 25-75% 91.66 ± 7.20 C (n=31) <25% 90.53 ± 8.54 (F=3.34, P<0.05, A>B, C)	A: strong, B: moderate, C: weak — A / B / C Selection — x / / Study design — / / x Confounder/bias — / / x Blinding — / / x Data collection — / x / Withdraw and dropout — / x / Analyses — / / x Intervention integrity — / / Not adjusted for SES, maternal education or intelligence; small sample size; cognitive testing at young age

Horwood, 2001 [11124919]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): Mean BW (range): % Male: Race: Evaluated: 298/280 analyzed Location: New Zealand Sites: Single/Multi Funding:	Cross-sectional; all 413 very low birth birthweight infants who were live born in 1986 who were admitted to one neonatal unit; retrospective recall of breast milk feeding and duration of feeding; children were assessed by WISC-R (excluded 17 children who could not reliably be assessed because of sensorineural disability; 1 child was excluded because the data on breastfeeding were missing) at 7 yr	Live born very low birthweight infants	Not breastfed (n=76) Breastfed < 4 months (n=99) 4-7 months (n=46) ≥ 8 months (n=59)	

Horwood, 2001 [11124919]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
WISC-R	Controlled for perinatal, socio-demographic (family income, single/two parent family, child ethnicity), and maternal factors (age, education, smoking); the data were analyzed using multiple linear regression techniques in which the measures of verbal and performance IQ were regressed on the four level measure of breastfeeding treated as a continuous variable and significant covariate factors.	Children who were breastfed ≥ 8 months had mean verbal IQ 10.2 (SD 0.56) higher and mean performance IQ 6.2 (SD 0.35) higher than children who did not receive breast milk. After adjustment for covariates, there remained a significant association between duration of receipt of breast milk and verbal IQ, with a 6 point advantage for infants who received breast milk for ≥ 8 months compared with no breastfeeding (P<0.001).	

A: strong, B: moderate, C: weak	A	B	C
Selection		x	
Study design			x
Confounder/bias		x	
Blinding			x
Data collection			x
Withdraw and dropout		x	
Analyses		x	
Intervention integrity			

O'Connor, 2003 [14508214]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
GA): <33 wk BW (range): 750-1805 g % Male: Race: Enrolled/Evaluate: 463 Location: US, UK and Chile Sites: Multi Funding:	Cohort, re-analysis of a previous RCT on supplemented formulas	Could be enrolled within 72 hours of first enteral feeding initiated by the 28th day of life; excluded congenital abnormalities that could affect growth and development, major surgery, and others	4 mutually exclusive groups: 1. predominantly human milk (see details in paper) 2. predominantly formula 3. ≥ 50% of total energy as human milk 4. < 50% of total energy as human milk	

O'Connor, 2003 [14508214]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Bayley at 12 mo; MacArthur Communicative Development Inventories at 9 mo, 14 mo	Maternal intelligence and home environment	No differences in the Bayley MDI were found among feeding groups. There was a positive association between duration of breastfeeding and the Bayley MDI at 12 months corrected age (P=0.032 in full, and P=0.073 in reduced statistical models) after controlling for home environment and maternal intelligence.	A: strong, B: moderate, C: weak / A / B / C Selection / / / x Study design / / x / Confounder/bias / x / / Blinding / / / x Data collection / / / x Withdraw and dropout / / / x Analyses / / x / Intervention integrity / / / Cognitive testing at a young age

Pinelli, 2003 [2003083348]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): <1500 g Mean BW (range): % Male: Race: Enrolled/Evaluate: 148/137 Location: Canada Sites: Single Funding:	Prospective cohort (consecutive enrollment); sample from a RCT on conventional breastfeeding support versus supplementary structured breastfeeding counseling; 20 totally formula fed infants were recruited as controls	Excluded: multiple births, severe congenital abnormalities; infants of non-English speaking parents	>80% breast milk vs <80% breast milk or no breast milk	

Pinelli, 2003 [2003083348]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Bayley MDI at 12 mo	Sex, SES, birth weight, maternal age	64/128 infants received breastmilk exclusively; Adjusted MDI at 6 mo (corrected age) for >80% breastmilk group: 93 (SD 16); for <80% breastmilk group: 94 (SD 15); Adjusted MDI at 12 mo (corrected age) for >80% breastmilk group: 92 (SD 15); for <80% breastmilk group: 91 (SD 12); P>0.05 for all comparisons	A: strong, B: moderate, C: weak — A: ; B: x; C: Selection — A: ; B: x; C: Study design — A: ; B: ; C: x Confounder/bias — A: ; B: x; C: Blinding — A: ; B: ; C: x Data collection — A: ; B: ; C: x Withdraw and dropout — A: ; B: x; C: Analyses — A: ; B: ; C: x Intervention integrity — A: ; B: ; C: Cognitive test at a young age

Smith, 2003 [14630603]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Median GA (range): 27.4 wk Median BW (range): 1014 g % Male: Race: Enrolled/Evaluate: 439/420 Location: US Sites: Multi Funding:	Cohort; subjects were from Developmental Epidemiology Network cohort (n=1442), 439 enrolled in follow up studies at 6 to 8 yr	Surviving children with selected ultrasound abnormalities were included (n=119), and a random sample (1:4 ratio) of infants frequency matched for gestation were included; had undergone neuropsychological assessment and for whom parental questionnaires were complete by 9/2002	Received expressed milk without progressing to direct breastfeeding, received direct breastfeeding	No human milk

Smith, 2003 [14630603]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Kaufman Assessment Battery for Children (an estimate for overall intellectual function); Peabody Picture Vocabulary Test and Clinical Evaluation of Language Fundamentals (verbal); California Children's Verbal Learning Test (memory); Wide Range Assessment of Visual Motor Abilities (visual-spatial skill) These measures were standardized with a mean of 100 points and standard deviation of 15 points.	Maternal verbal ability, Home Observation for Measurement of the Environment Inventory, SES, duration of hospitalization	Compared with nonparticipating mothers, those who participated were older, more educated, more likely to be married, be non-smokers, and have private medical insurance. 153 subjects did not receive human milk; 142 received expressed milk without progressing to direct breastfeeding; 125 received direct breastfeeding (the majority of them first received expressed breast milk); 20% of infants received breast milk >6 mo. Breast milk feedings were associated with higher unadjusted test scores for each domain of cognitive function except memory. In the regression model that included social advantage and neonatal morbidity, the adjusted score in overall intellectual function associated with direct breastfeeding was reduced to 3.6 points (95% CI, -0.3, 7.5) from 10.7 (95%CI, 7.0, 14.4). Breastfed children had an advantage in visual-motor integration measure (adjusted IQ 5.1, 95% CI, 1.0, 9.2)	A: strong, B: moderate, C: weak: A, B, C Selection: C Study design: C Confounder/bias: A Blinding: C Data collection: B Withdraw and dropout: B Analyses: B Intervention integrity: 27% of subjects with ultrasound abnormalities; the timing of collection of breastfeeding data was not reported

Vohr, 2006 [16818526]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 26.5 wk Mean BW (range): 785 g (BM), 794 (no) % Male: 45% Race: Enrolled/Evaluate: 1159/1035 Location: US Sites: Multi Funding:	Prospective cohort; Bayley results at 18 to 22 mos corrected age; examiner blinded to feeding history, primary caretaker stayed with the child during the Bayley examination	Enrolled prospectively in the Glutamine Trial at 15 sites of Neonatal Research Network; survivors	Breast milk – received some breast milk during hospitalization; total volume received calculated per day, values were interpolated for days of the week in which the data were not collected	

Vohr, 2006 [16818526]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations
Comments</th></tr>
<tr>
<td>Cognitive outcome of interest: Bayley Mental Development Index (MDI)</td>
<td>Adjustment for marital status, maternal education, age, race/ethnicity, infant's gestational age, gender, culture positive sepsis, grade 3 to 4 intraventricular hemorrhage, oxygen at 36 wks gestational age, necrotizing enterocolitis, and weight <10th %tile</td>
<td>There were 775 infants in the breast milk group and 260 in the no breast milk group. 95 subjects' Bayley could not be administered successfully; these data were not included. Mothers of infants who were seen at followup were more likely to have received prenatal care than mothers of infants who were not seen. There were no differences in infant characteristics. Information on breast milk feeding was not collected after discharge from hospital. 30.6% of infants in the breast milk group were still receiving breast milk. Mothers in the breast milk group were more likely to be white, married, have a college degree and have private health insurance. Mothers who had low household income, higher parity or were black were less likely to provide breast milk feeds.

Adjusted Bayley MDI 79.9 ± 18 in BM 75.8 ± 16 in noBM P=0.0709

MDI <85 421 (58.1%) in BM 168 (70.9%) in noBM P=0.0355

Multiple regression with adjusted factors=0.53 for MDI, P=0.0002

Breast milk intake was analyzed by quintile relative to the no breast milk group; for MDI, there was a 13.1 point difference between ≤ 20th quintile and >80th quintile (P<0.0044)</td>
<td>
<table>
<tr><td>A: strong, B: moderate, C: weak</td><td>A</td><td>B</td><td>C</td></tr>
<tr><td>Selection</td><td></td><td>x</td><td></td></tr>
<tr><td>Study design</td><td></td><td></td><td>x</td></tr>
<tr><td>Confounder/bias</td><td></td><td></td><td>x</td></tr>
<tr><td>Blinding</td><td></td><td>x</td><td></td></tr>
<tr><td>Data collection</td><td></td><td></td><td>x</td></tr>
<tr><td>Withdraw and dropout</td><td></td><td>x</td><td></td></tr>
<tr><td>Analyses</td><td></td><td></td><td>x</td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td></td></tr>
</table>
Residual confounding from home environment cannot be ruled out; Bayley at young age; proportion of subjects with MDI <85 could not have been adjusted; unclear if income was adjusted or not (Results did not indicate that it was, but the discussion said it was); unclear if Bayley was done blinded to feeding history (not stated in Methods, but the discussion said it was)
</td>
</tr>
</table>

Appendix C. Evidence Tables

Part II. Preterm Infant Outcomes

Necrotizing Enterocolitis

Furman 2003
Gross 1983
Lucas 1984 1990
McGuire 2001 SRMA*
Ronnestad 2005
Schanler 2005
Tyson 1983

* Systematic Review/Meta-Analysis

Furman, 2003 [UI# 12517197]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 28 wk Mean BW (range): 1056 g % Male: 57% Race: Enrolled/Evaluate: 119 Location: Cleveland Sites: Single Funding:	Prospective cohort; The study compared the effect of varying dosages of maternal milk on neonatal outcomes	Singleton, birth weight 600-1499 g, gestational age < 33 wk, no positive drug screen, major congenital anomaly, intrauterine infection, or insurmountable maternal social factors	Intravenous dextrose during the first 24 hrs; enteral intake was begun by day 2 or 3 of life, parenteral nutrition was continued until a daily enteral intake of 120 mL/kg of body weight was reached. Infants received their mother's milk in the sequence it was expressed, except that fresh rather than frozen milk was given if available. Maternal milk was fortified, and preterm infant formula was offered when the infant reached a daily oral intake of at least 110 mL/kg. Limited availability of maternal milk was the sole reason infants were fed preterm formula in addition to maternal milk.	

Furman, 2003 [UI# 12517197]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
NEC in the 4 subgroups: No maternal milk Daily 1-24 mL/kg of maternal milk Daily 25-49 mL/kg of maternal milk Daily ≥ 50 mL/kg of maternal milk	Logistic regression; adjusted for birth weight, ethnicity, and sex	0 maternal milk 3/40 1-24 mL/kg 2/29 (OR 1.15 95% CI 0.8-12.13) 25-49 mL/kg 2/18 (OR 1.99 95% CI 0.14-21.03) ≥ 50 mL/kg 0/32 (OR 0 95% CI 0 – 3.56)	

A: strong, B: moderate, C: weak	A	B	C
Selection			
Study design			x
Confounder		x	
Blinding			x
Data collection		x	
Withdraw and dropout		x	
Analyses		x	
Intervention integrity			x

Gross, 1983 [UI# :6848932]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 31 wk Mean BW (range): 1322 g % Male: Race: Enrolled/Evaluate: Location: US Sites: Single Funding:	Random number assignment into 3 groups: mature human milk, preterm human milk, whey-based formula; any infant withdrawn from the study was replaced by the next infant enrolled, until there were 20 infants in each group; remained in the study until they reached 1800 g	27 – 33 wk gestation; ≤ 1600 g; no congenital abnormalities or major diseases; ability to begin enteral feed by 6th day of life; absence of breast milk from own mother	Feedings began between the first and sixth days of life.	

Gross, 1983 [UI#:6848932]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
NEC (abdominal distention, gastric aspirates, guaiac-positive stools, and pneumatosis intestinalis)	NEC was analyzed as infants who withdrew from the study	67 infants recruited for the study; 1/41 (BM) vs. 3/26 (FM) with NEC	

A: strong, B: moderate, C: weak	A	B	C
Selection	x		
Study design	x		
Confounder			x
Blinding		x	
Data collection		x	
Withdraw and dropout		x	
Analyses			x
Intervention integrity			

Lucas, 1984 [UI# 6476868]; 1990 [UI# 1979363]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 31 wk Mean BW (SD): 1370 g (320 g) % Male: Race: Enrolled/Evaluate: Location: UK Sites: /Multi Funding:	Randomization within 48 h of birth for infants whose mothers decided not to breastfeed, randomized into banked donor human milk vs. preterm formula; only infants fed exclusively on donor milk or formula were compared	<1850 g, excluded severe congenital abnormalities		

Lucas, 1984, [UI# 6476868]; 1990 [UI# 1979363]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Confirmed NEC – required surgery or who died	Logistic regression was used to adjust for factors that have been associated with NEC.	1/86 (BM) vs. 4/76 (FM) OR 4.7 (0.5 – 43)	

A: strong, B: moderate, C: weak	A	B	C
Selection	x		
Study design	x		
Confounder	x		
Blinding		x	
Data collection	x		
Withdraw and dropout	x		
Analyses	x		
Intervention integrity			

Evidence table for Systematic Reviews of Breastfeeding and NEC

Author,Year[UI] Topic	McGuire, 2001 [11687169] NEC
Literature search (Dates)1966-10/2003	Medline; Other databases searched? (yes, CENTRAL, EMBASE, CINAHL); unpublished data used? (no)
Countries where primary studies conducted	ND
Study eligibility / inclusion criteria	RCT comparing feeding with formula milk versus term human milk in low birth weight or preterm infants
Study design [No. Of studies]	RCT: 3 studies with outcomes re: NEC
No. of subjects	287
Study population (definition in included studies)	Gross 1983 27-33 wk, bw < 1600 g Tyson 1983 very low birth weight infants Lucas 1984 preterm infants < 1850 g
Intervention/Exposure (definition in included studies)	Gross 1983 unfortified term donor breast milk, fed until 1800 g or until withdrawal secondary to feed intolerance or NEC Tyson 1983 pooled banked term human milk, allocation at 10th day of life, fed until 2000 g or until withdrawal secondary to illness requiring parenteral fat or protein Lucas 1984 banked term human milk 200 mL/kg/d, fed until 2000 g or until d/c
Comparator (definition in included studies)	Gross 1983 standard calorie (0.67 kcal/mL, protein enriched (1.9 g/100 mL) formula Tyson 1983 enriched calorie (0.87 kcal/mL), protein enriched (2.2 g/100 mL) formula Lucas 1984 enriched calorie (0.80 kcal/mL), protein enriched (2.0 g/100 mL) formula at 180 mL/kg/d
Outcomes (definition in included studies)	Necrotizing enterocolitis
Heterogeneity assessments	
Quality assessments	Gross 1983 & Tyson 1983 The studies did not attempt blinding of parents, carers, or assessors. Adverse events were not reported as primary end points but rather as withdrawal criteria. Lucas 1984 The study did not attempt blinding of parents, carers, or assessors. Data on NEC on all 159 recruited infants were reported
Publication bias assessments	
Statistical Analysis or meta-analytic methods	3 trials were combined in a meta-analysis: formula vs human milk, RR: 2.5 (95% CI 0.9, 7.3); RD: 0.05 (95% CI 0.00, 0.1)
Results	Gross 1983 incidence of NEC in formula vs human milk: RR 2.4 (95% CI 0.3, 21.6); RD: 0.07 (95% CI 0.09, 0.22) Tyson 1983 incidence of NEC in formula vs human milk: RR 4.2 (95% CI 0.2, 85.3); RD: 0.05 (95% CI –0.03, 0.12) Lucas 1984 incidence of NEC in formula vs human milk: RR 2.2 (95% CI 0.6, 8.4); RD: 0.04 (95% CI –0.03, 0.12)
Quality of the systematic review	
Author's interpretations of the results	We did not find any statistically significant difference in the risk of NEC with formula milk versus term human milk feeding.
Comments / Limitations	Donor milk, not mother specific milk

Author, yr: McGuire, 2001
Topic of the systematic review*/MA:

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Y
2	Types of exposure or intervention used	Y
3	Types of study designs used	Y
4	Study population	Y
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Y
6	Effort to include all available studies (contact with authors)	Y
7	Databases and registries searched	Y
8	Method of addressing published articles other than English	Y/N
9	Method of handling abstracts and unpublished studies	N
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Y
11	Assessment of confounding	Y/N
12	Assessment of quality	Y
13	Assessment of heterogeneity	Y
14	Description of statistical methods sufficient to replicate	Y
15	Provision of appropriate tables and graphs	Y
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Y
17	Tables giving descriptive information of each study included	N
18	Results of sensitivity testing (subgroup analysis)	Y
19	Indication of statistical uncertainty of findings	Y
20	Quantitative assessment of bias (eg. publication bias)	N
	Overall quality	

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Y
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	Y
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Y
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	Y/N
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Y/N
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Y/N
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Y
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Y
8	Were results reported accurately (eg, no discrepancies between text and tables)?	Y/N
9	Were conclusions justified by the reported/collected data and analysis?	Y

Ronnestad, 2005 [UI# 15687416]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 22-27 wk Mean BW (range): 845 g (est.) % Male: 56% Race: Enrolled/Evaluate: 462 enrolled; 405 survived until day 7 Location: Norway Sites: Multi-center Funding:	Prospective cohort	Participating centers had a common policy of achieving full enteral feeding with the mother's milk or banked donor milk as early as possible, although there was no consensus in terms of a detailed protocol for feeding strategies. All infants born in Norway in 1999 and 2000 with gestational age of <28 wk or birth weight < 1000 g.	Tube feeding with human milk was usually started within a few hours after delivery, with 1 to 2 mL of milk every 2 or 3 hrs, increasing by 0.5 to 1 mL every 6 to 8 hours as tolerated. Enteral nutrition was supplemented with parenteral glucose from day, amino acids and lipids from day 2 and day 3, respectively.	

Ronnestad, 2005 [UI# 15687416]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
This was a study primarily examining late-onset septicemia (after day 6 of life) that also reported outcome on NEC after day 6 of life.	No analysis/adjustment specific to NEC was reported.	Enteral feeding with human milk was commenced within 1, 2, or 3 days for 61%, 92%, and 96% of the infants. 9/405 (2.2%) patients had confirmed NEC.	

A: strong, B: moderate, C: weak	A	B	C
Selection			
Study design			x
Confounder			x
Blinding			x
Data collection			
Withdraw and dropout		x	
Analyses			x
Intervention integrity			x

Schanler, 2005 [UI# 16061595]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 23-26wk & 27-29 wk Mean BW (range): 952 g % Male: 53% Race: ND Enrolled/Evaluate: 243 Location: Texas Children's Hospital Sites: Multi Funding: government	RCT 4 days to 90 days of age or discharge from the hospital	Infants with mother expected to breastfeed; if mother's own milk was unavailable; then infants were randomized to Donor Milk versus Preterm formula	Donor milk (DM) (+ mother's milk partially) Reference group: non-randomized, exclusive mother's milk (MM) Small quantities of mother's milk (~20 mL/kg/day) was initiated in the first week and continued for ~3 to 5 days before the volume was advanced. Milk intake was increased by ~20 mL/kg daily to 100 mL/kg, at which time milk fortifier was added, this was advanced by ~20 mL/kg daily until 160 mL/kg per day was achieved.	Preterm formula (PF) (+ mother's milk partially)

Schanler, 2005 [UI# 16061595]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
NEC Only cases of NEC that occurred after the infant attained a milk intake of ≥50 mL/kg were analyzed for the primary outcome.	17 infants (21%) in DM were switched to PF because of poor weight gain. All infants remained in the original assigned group for analysis.	Incidence of NEC: DM vs PF: 5/78 vs 10/88 (*P*=0.27) Non-randomized group MM had fewer repeated episodes of late-onset-sepsis and/or NEC (OR 0.18; 95% CI 0.04–0.79) compared with combined groups DM and PF	

A: strong, B: moderate, C: weak	A	B	C
Selection		x	
Study design	x		
Confounder	x		
Blinding		x	
Data collection			
Withdraw and dropout		x	
Analyses		x	
Intervention integrity		x	

Tyson, 1983 [UI# - 6864403]

Study characteristics	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean GA (range): 31.5 wk Mean BW (range): 1232 g % Male: Race: Enrolled/Evaluate: Location: US Sites: Single Funding:	RCT; infants were not enrolled until the 10th day; enrolled into donor human milk or formula milk groups	Infants whose mothers continued to provide milk at 10 days were excluded, as infants with any significant illnesses		

Tyson, 1983 [UI# - 6864403]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
NEC confirmed at surgery; suspected NEC	NEC was analyzed as subjects who dropped out of the study.	0/37 (BM) vs. 1/44 (FM) for confirmed NEC	

A: strong, B: moderate, C: weak	A	B	C
Selection			x
Study design		x	
Confounder			x
Blinding		x	
Data collection		x	
Withdraw and dropout		x	
Analyses			x
Intervention integrity			

Appendix C. Evidence Tables

Part III. Maternal Outcomes

Breast Cancer

Bernier 2000 SRMA*
CGHFBC 2002 SRMA*
Gammon 2002
Jernstrom 2004
Lee 2003
Lipworth 2000 SRMA*

* Systematic Review/Meta-Analysis

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI] Topic	Bernier, 2000 Breast cancer
Literature search (Dates)	Medline (1980-1998); Other databases searched? (yes-Embase); unpublished data used? (no)
Countries where primary studies conducted	Developed and developing countries (Estonia, Canada, USA, Sicilia, Costa Rica, Australia, India, China, Greece, Italy, Mexico, New Zealand)
Study eligibility / inclusion criteria	A study was included in the analysis: 1) it was published between 1980 and 1998 2) it presented primary original data; 3) it was published either in English or French; 4) the type of study was either a case-control, or a prospective cohort study; 5) data on breastfeeding exposure were reported and used in the analysis 6) breast cancer was the event of interest 7) specific odds ratio measuring the breastfeeding and breast cancer association were given or could be derived. Excluded were studies in which data from parous women who had not breastfed could not be separated from nulliparous women
Study design [No. Of studies]	23 [Case-control studies]
No. of subjects	25871 cases/44910 controls
Study population (definition in included studies)	Parous women with breast cancer
Intervention/Exposure (definition in included studies)	Breastfeeding (Ever)
Comparator (definition in included studies)	Breastfeeding (never)
Outcomes (definition in included studies)	Breast cancer (histologically diagnosed)
Heterogeneity assessments	Yes; homogeneity graph and by subgroup analysis (menopausal status; duration of breastfeeding)
Quality assessments	Unclear (MA discussed methodologic quality with subheading of origin of the women; breast cancer diagnosis; and data collection)
Publication bias assessments	Yes (funnel plot)
Statistical Analysis or meta-analytic methods	Both random and fixed effects model
Results	Breast cancer risk ever vs never breastfeeding Pooled OR using the fixed effects model 0.90 (0.86-0.94) Pooled OR using random effects model 0.84 (0.78-0.91 These results were not modified using adjusted ORs Breast cancer risk according to the menopausal status at the time of the diagnosis in ever vs never breastfeeding mothers Menopausal at the time of breast cancer diagnosis Pooled OR using the fixed effects model 1.01 (0.94-1.09) Pooled OR using random effects model 0.84 (0.69-1.03) Non-menopausal at the time of breast cancer diagnosis Pooled OR using the fixed effects model 0.83 (0.76-0.91) Pooled OR using random effects model 0.81 (0.72-0.91) Breast cancer risk according to duration of breast feeding 0+ to 6 mo v never Pooled OR using the fixed effects model 1.02 (0.94-1.10) Pooled OR using random effects model 1.00 (0.86-1.16) 6+ to 12 mo v never Pooled OR using the fixed effects model 0.97 (0.88-1.06) Pooled OR using random effects model 0.97 (0.86-1.09) 12+ mo vs. never Pooled OR using the fixed effects model 0.75 (0.70-0.80)

Author, Year[UI] Topic	Bernier, 2000 Breast cancer
	Pooled OR using random effects model 0.72 (0.65-0.80)
Quality of the systematic review	B
Author's interpretations of the results	Breastfeeding appeared to be a protective factor but was of small magnitude compared with other known risk factors of breast cancer
Comments / Limitations	Quality score for individual studies not assessed

Author, yr: Bernier 2000
Topic of the systematic review*/MA: Breast cancer and breastfeeding

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Y
2	Types of exposure or intervention used	Y
3	Types of study designs used	Y
4	Study population	Y
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Y
6	Effort to include all available studies (contact with authors)	N
7	Databases and registries searched	Y
8	Method of addressing published articles other than English	N
9	Method of handling abstracts and unpublished studies	N
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Y
11	Assessment of confounding	Y
12	Assessment of quality	Unclear
13	Assessment of heterogeneity	Y
14	Description of statistical methods sufficient to replicate	Y
15	Provision of appropriate tables and graphs	Y
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Y
17	Tables giving descriptive information of each study included	Partially yes
18	Results of sensitivity testing (subgroup analysis)	Y
19	Indication of statistical uncertainty of findings	N
20	Quantitative assessment of bias (eg. publication bias)	Y
	Authors' Conclusions	
21	Consistent with the presented results	Y
22	Commenting on the validity of the conclusions	Y
23	Presenting alternative explanations	Y
	Overall quality	**B**

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	Yes
2	Did authors give justifications for inclusion/exclusion criteria pertaining to studies of interest?	Partially
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	Yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	Partially
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	No
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	Yes
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	Yes
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	Yes
8	Were results reported accurately (eg, no discrepancies between text and tables)?	No
9	Were conclusions justified by the reported/collected data and analysis?	Yes

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI] Topic	Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) 2002 [12133652] Breast Cancer
Literature search (Dates)	ND Available in prior publications Medline (nd); Other databases searched? (nd); unpublished data used? (yes)
Countries where primary studies conducted	International studies including developed and developing nations
Study eligibility / inclusion criteria	Studies that had data on at least 100 women with incident invasive breast cancer and had recorded information on each women with respect to reproductive factors and use of hormonal preparations. For the cohort studies, a nested case-control study design was used, in which four randomly selected controls per case were matched for age at diagnosis and where appropriate, broad geographical region
Study design [No. Of studies]	case-control and cohort studies [47]
No. of subjects	50,302/96,973
Study population (definition in included studies)	Women with breast cancer and controls
Intervention/Exposure (definition in included studies)	Breastfeeding (Ever and lifetime months of breastfeeding (median))
Comparator (definition in included studies)	Breastfeeding Never
Outcomes (definition in included studies)	Breast cancer (ND)
Heterogeneity assessments	Subgroup analyses including women from developed and developing countries, women of different ages, ethnic origins, familial patterns of disease, and 11 other possible relevant factors
Quality assessments	None
Publication bias assessments	ND
Statistical Analysis or meta-analytic methods	Analyses were routinely stratified by study, by center within study, by fine divisions of age, by age at first birth and by menopausal status. Where appropriate, parous women are further stratified by fine divisions of parity. Data combined by means of the Mantel-Haenszel stratification technique, the stratum specific quantities calculated being the standard observed minus expected numbers of women with breast cancer, together with their variances and covariates.
Results	% reduction in relative risk of breast cancer per 12 months of breastfeeding and 99% (SE)= 4.3 (0.8) Data also available for floating absolute risk and floated SE for subgroups Parous women who never breastfed v ever breastfed Life time months of breastfeeding
Quality of the systematic review	A
Author's interpretations of the results	The longer women breastfeed the more they are protected against breast cancer. The lack of or short lifetime duration of breastfeeding typical of women in developed countries makes a major contribution to the high incidence of breast cancer in these countries.
Comments / Limitations	Individual patient level data

Author, yr: Collaborative group on Hormonal factors in breast cancer, 2002
Topic of the systematic review*/MA: Breast cancer and breastfeeding

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Y
2	Types of exposure or intervention used	Y
3	Types of study designs used	Y
4	Study population	Y
	Reporting of Search strategy	
5	Search strategy, including time period and key words	N
6	Effort to include all available studies (contact with authors)	N
7	Databases and registries searched	N
8	Method of addressing published articles other than English	N
9	Method of handling abstracts and unpublished studies	N
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Y
11	Assessment of confounding	Y
12	Assessment of quality	N
13	Assessment of heterogeneity	Y
14	Description of statistical methods sufficient to replicate	Y
15	Provision of appropriate tables and graphs	Y
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Y
17	Tables giving descriptive information of each study included	Y
18	Results of sensitivity testing (subgroup analysis)	Y
19	Indication of statistical uncertainty of findings	N
20	Quantitative assessment of bias (eg. publication bias)	N
	Authors' Conclusions	
21	Consistent with the presented results	Y
22	Commenting on the validity of the conclusions	Y
23	Presenting alternative explanations	Y
	Overall quality	A

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	No
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	yes
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	partially
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Individual patient level data
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	yes
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	yes

	Evaluation of quality of a systematic review or meta-analysis	Yes /No /Partially
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	yes
8	Were results reported accurately (eg, no discrepancies between text and tables)?	yes
9	Were conclusions justified by the reported/collected data and analysis?	yes

Gammon 2002 [12206514]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): <35 to 85+ yrs Menopause: mix Race: white 92-93%; Black 5%; and other 2-3% Enrolled/Evaluate: 1508 cases/1556 controls Location: population based Sites: Multi Funding: Gov	Women with newly diagnosed breast cancer (invasive and in-situ)	Case control study design Follow-up duration nd	Cases were women newly diagnosed with a first primary *in situ* or invasive breast cancer between August 1, 1996, and July 31, 1997, confirmed by the physician and the medical record, who were residents of either Nassau or Suffolk counties in New York at the time of their diagnosis, and who spoke English. (Over 97% of all residents in these two counties are English-speaking.) Controls: Control women were a sample of current residents of Nassau and Suffolk counties who spoke English, who did not have a personal history of breast cancer, and who were frequency matched to the expected distribution of case women by 5-year age group.	By duration: <2 months 2-5 months 6-13 months 14+ months	Never lactated

Gammon 2002 [12206514]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Risk for breast cancer among those who donated a blood sample	Unconditional and multiple logistic regression model identified using backward selection model	Among parous women lactation for 14 or more months decreased the odds of breast cancer (n=102) 0.70 (0.54, 0.92) compared to those who never lactated (ref group) or less than lactated <14 mo Lactation <2 mo, 2-5 mo, and 6-13 mo when compared to never lactated group had non significant results for the odds of breast cancer development.	A: strong, B: moderate, C: weak / A / B / C Selection / / / x Study design / / x / Confounder / / / x Blinding / / / x Data collection / x / / Withdraw and dropout / / / Analyses / / / x Intervention integrity / / / x Overall: C

Jernstrom 2004 [15265971]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 39 Menopause: ND Race: Jewish 30% cases French Canadian 10% Other white 59% Black1% Other 0.5% Enrolled/Evaluate: 1927/1830 Location: hospital based Sites: Multi Funding: ND	Women with carriers of gene mutation BRCA1 and BRCA2	Case-control study design Follow-up 8.2 (time between breast cancer diagnosis and the completion of study questionnaire.	Selected Eligible subjects who carried a mutation in either the BRCA1 or the BRCA2 gene were drawn from a database	For women who gave an approximate length of breastfeeding (e.g., 3–5 months), the midpoint of duration was used. The year of breast cancer diagnosis and years of all pregnancies were recorded. If both occurred during the same calendar year, it was not possible to establish the sequence of breast cancer and pregnancy. Only live births that occurred at least one calendar year before a diagnosis of breast cancer were captured. Twin births were considered to be one birth with respect to breast-feeding.	Exposure information on control subjects (e.g., breast-feeding, parity) was restricted to the period before the date of a diagnosis of breast cancer in the matched case subject.

Jernstrom 2004 [15265971]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Breast cancer among BRCA1 and BRCA 2	Conditional logistic regression for odds ratios (ORs) in the univariate and multivariate analyses. In the first analysis, parity and oral contraceptive use were used as covariate variables. Because of the strong association between parity and breast-feeding, secondary analysis was performed a that excluded all nulliparous women. All analyses were adjusted for oral contraceptive use.	In univariate analyses subjects who had breastfed their kids >1y and had BRCA1 gene polymorphism (OR 0.56; 95% CI 0.41 to 0.76) had statistically significant reduced odds of breast cancer compared to none breastfeeding. Breastfeeding ≤1 yr + BRCA1 (OR 0.89; 95% CI 0.70, 1.15; p<.001) and breastfeeding + BRCA2 were not associated with reduced odds. In multivariate subjects who had breastfed their kids >1y and had BRCA1 gene polymorphism (OR 0.55; 95% CI 0.38 to 0.80) had statistically significant reduced odds of breast cancer compared to none breastfeeding. The trend per month of breast feeding also decreased the odds of breast cancer	A: strong, B: moderate, C: weak — A / B / C Selection: x Study design: B Confounder: x Blinding: Data collection: B Withdraw and dropout: B Analyses: B Intervention integrity: B Overall grade: B

Lee SY, 2003 [12704674]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 33-44 Menopause: Pre Race: Asian 100% Enrolled/Evaluate: 110604 Location: population based Sites: Multi Funding: Gov	Earlier menarche Oral contraceptive use Ever smoke Alcohol use Exercise (yes) [data available by duration of lactation]	Prospective observational cohort Follow-up 6 yrs	Premenopausal women who were enrolled in the Korean Medical Insurance Corporation (KMIC) and participated in the Korean Women's cohort	Ever vs Never Periods of lactation 1-12 months 13-24 months	Ever vs Never Periods of lactation 1-12 months 13-24 months

Lee SY, 2003 [12704674]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Incident breast cancers	In bivariate analyses, the authors examined the relation between lactation and traditional breast cancer risk factors, adjusting for age. In these bivariate analyses, the authors tested for trends across categories of duration of lactation, using parous women who never breastfed as the reference. In Cox proportional hazard models, age, age at menarche, number of children, age at first pregnancy, oral contraceptives, smoking, exercise and obesity were controlled to delineate the independent effects of lifetime lactation. In all analyses, a 2-sided alpha level of 0.05 was considered statistically significant.	Compared to parous women who had no history of lactation, periods of lactation of 1–12 months or 13–24 months were associated with decreased risk of breast cancer (RR, 0.8; 95% CI, 0.7–1.0 or RR, 0.7; 95% CI, 0.5–1.1, respectively), and this risk decreased even further for those with who breastfed for more than 24 months (RR, 0.6; 95% CI, 0.3–1.0)	A: strong, B: moderate C: weak: A / B / C Selection: / x / Study design: x / / Confounder: x / / Blinding: / / x Data collection: / / x Withdraw and dropout: / x / Analyses: / x / Intervention integrity: / x / Overall: B

	Person-years	Breast cancer	Multivariate model RR (95%CI)
Never	263,472	161	Ref
1-12	256,199	149	0.8 (0.7-1.0) NS
13-24	39,125	32	0.7 (0.5-1.1) NS
>24	23,556	18	0.6 (0.3-1.0) p = 0.0438
p for trend			<0.001

Evidence table for Systematic Reviews of Breastfeeding

Author, Year[UI] Topic	Lipworth, 2000 [10675379] Breast Cancer
Literature search (Dates)	Medline (1966-1998); Other databases searched? (no); unpublished data used? (no)
Countries where primary studies conducted	International studies including developed and developing nations
Study eligibility / inclusion criteria	Studies that included more than 200 cases overall and explicitly controlled for number of full-term pregnancies and age at first birth
Study design [No. Of studies]	Case-control studies
No. of subjects	23461/52948
Study population (definition in included studies)	Premenopausal women with breast cancer and controls (nd)
Intervention/Exposure (definition in included studies)	Breastfeeding (ever)
Comparator (definition in included studies)	Breastfeeding (never)
Outcomes (definition in included studies)	Breast cancer (nd)
Heterogeneity assessments	None
Quality assessments	ND
Publication bias assessments	ND
Statistical Analysis or meta-analytic methods	No meta-analysis; only qualitative review
Results	"Ever" breastfeeding effect remains inconclusive with results indicating either no association or a weak protective effect against breast cancer. Few studies also reported an inverse association between increasing life-time breastfeeding and breast cancer risk in parous women.
Quality of the systematic review	B
Author's interpretations of the results	"Evidence supporting protective factor of breastfeeding for breast cancer is limited and should be interpreted with caution."
Comments / Limitations	

Author, yr: Lipworth, 2000 [10675379]
Topic of the systematic review*/MA: Breast Cancer

		Reporting yes/no
	Reporting of Background	
1	Description of study outcomes	Yes
2	Types of exposure or intervention used	Yes
3	Types of study designs used	Yes
4	Study population	Yes
	Reporting of Search strategy	
5	Search strategy, including time period and key words	Yes
6	Effort to include all available studies (contact with authors)	Partially
7	Databases and registries searched	Partially
8	Method of addressing published articles other than English	No
9	Method of handling abstracts and unpublished studies	No
	Reporting of Methods	
10	Rationale for selection and/or coding of data	Yes
11	Assessment of confounding	Yes
12	Assessment of quality	No
13	Assessment of heterogeneity	Yes
14	Description of statistical methods sufficient to replicate	Not applicable
15	Provision of appropriate tables and graphs	Partially
	Reporting of Results	
16	Graphic summarizing of individual study estimates and overall	Not applicable
17	Tables giving descriptive information of each study included	Yes
18	Results of sensitivity testing (subgroup analysis)	Not applicable
19	Indication of statistical uncertainty of findings	Not applicable
20	Quantitative assessment of bias (eg. publication bias)	Not applicable
	Overall quality	B

*When grading a systematic review, please skip item #14, 18-20
Please fill the white areas only

	Evaluation of quality of a systematic review or meta-analysis	**Yes /No /Partially**
1	Is search strategy appropriate/relevant to the key question(s)?	yes
2	Did authors give justifications for inclusion/exclusion criteria pertaining to the studies of interest?	no
3	Were Population, Intervention/Exposure, Comparator/Control, Outcomes, and Study Designs well-defined?	yes
4	Did authors attempt to minimize errors in data extraction (such as collecting the relevant data, double data extraction, verification of data extraction…etc.)?	nd
5	Was individual study quality (such as sample size, study design, blinding, various biases and confounders, study subject attrition rate…etc.) assessed?	Partially
6	Did authors consider appropriate confounders and justification for adjusting or not adjusting for those confounders?	yes
7	Was the justification for combining or not-combining data for meta-analysis, or the use of a particular analytic method or model appropriate?	no
8	Was heterogeneity explored (this is in addition to any statistical test of heterogeneity, did the authors look at the actual differences in PICOS, for example?)?	no
8	Were results reported accurately (eg, no discrepancies between text and tables)?	no
9	Were conclusions justified by the reported/collected data and analysis?	yes

Appendix C. Evidence Tables

Part III. Maternal Outcomes

Osteoporosis-BMD

Hansen 1991
Matsushita 2002
Sowers 1992
Uusi-Rasi 2002

Osteoporosis-Fracture

Alderman 1986
Chan 1996
Cumming 1993
Hoffman 1993
Kreiger 1982
Michaelsson 2001

Hansen, 1991 [UI#1790399]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 51 Menopause: post Race: ND Enrolled/Evaluate: 178/121 Location: Denmark Sites: Single Funding:	healthy	Prospective cohort (12 years)	In 1979, 178 women completed a 2-year, prospective study receiving placebo. They had been selected by questionnaire and a medical screening examination. All had passed a natural menopause 6 months to 3 years earlier and were free of disease or medications known to influence the calcium metabolism. In 1989, 12 years after the start of the original study, all 178 women were re-contacted for a follow-up examination. Of these, 24 (13%) were unable to participate: 6 women had died, 9 suffered from diseases which made participation impossible, 6 unwilling to participate for personal reasons, 2 had emigrated, and 1 could not be located. Among the 154 women underwent the follow-up examination, 24 women were excluded due to owing to post-trial treatment with sex hormones for more than 1 year and another 9 women presenting with disease known to influence calcium metabolism were excluded as well.	111 women (92%) had experienced 1 or more pregnancies (mean: 2.6); 87% breast fed for a mean total lactation period of 13 months	No lactation

Hansen, 1991 [UI#1790399]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Lumbar spine BMD, measured by DEXA. BMD is calculated as BMC divided by the area of interest from L2 to L4 including the intervertebral discs. BMD only measured in the follow-up. Forearm BMC was measured by single photon absorptiometry (^{125}I). The rate of postmenopausal bone loss (% per year) was determined as the difference in % between the measurement in 1979 and the measurement obtained in 1989 divided by 10 years.	Student's t test for unpaired data	ΔBMC_{arm}% per year; ΔBMD_{spine} Lactation (-): -1.8±0.8; 0.84±0.18 Lactation (+): -1.7±0.8; 0.88±0.14 p-value: NS; NS	A: strong, B: moderate, C: weak Selection: C Study design: B Confounder: C Blinding: B Data collection: B Withdraw and dropout: C Analyses: C Intervention integrity: Overall: C Univariate analyses for BMD/BMC outcomes and lactation. Unclear whether no lactation group including non-parous women

Matsushita, 2001 [UI#12200655]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 30.1 Menopause: pre Race: Asian (assumed) Enrolled/Evaluate: 113/113 Location: Japan Sites: Single Funding: ND	Healthy, well-nourished	Longitudinal cohort study Mean interval between each delivery = 2.5 years	Postpartum Japanese women, aged 20-40 years, who delivered a singleton infant at the university hospital between 1994 and 1999. Women who had 2nd pregnancy were included. Exclusion criteria included complications and medications before or during pregnancy, that would affect bone metabolism, delivery before 36 weeks' gestation, or bed rest in excess of 7 days.	Lactation information including length and source of lactation (breast-fed or formula-fed) was collected by questionnaire immediately after the subsequent delivery. Only 1 woman had formula-fed, and the other breast fed with (n=46) or without (n=66) formula fed. Whether breast-feeding had been exclusive, predominant, or on-demand, and when alternative food had been introduced, was not available because of ambiguous memory.	

Matsushita, 2001 [UI#12200655]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
BMD of the lumbar spine (L2-L4) was measured by DEXA within 7 days of delivery. 113 of women became pregnant again and they had 2nd BMD measurement within 7 days of the next delivery. The percent change in BMD (ΔBMD%) was calculated by subtracting the value at the time of the first pregnancy from the value at the time of the second pregnancy.	BMD and backgrounds of consecutive pregnancies were compared using a paired t-test. Multiple regression analysis was performed to look for independent predictors of ΔBMD%. BMD after the initial delivery was included as an independent variable to adjust for regression toward the mean.	Lumbar BMD of 110 women after the initial and the subsequent delivery was 1.006±0.117 and 1.019±0.115 g/cm^2, respectively. BMD after the subsequent delivery was significantly higher than that after the initial delivery (p=0.001), with a ΔBMD% of 1.4±4.2%. Independent determinants of ΔBMD% were explored by multiple regression analysis: the length of lactation between the scans showed no correlation with ΔBMD% (coefficient=-0.06±0.157 SEM, p=0.702). Age was the most significant predictor for ΔBMD% in the model.	A: strong, B: moderate, C: weak / A / B / C Selection / x / / Study design / x / / Confounder / x / / Blinding / / x / Data collection / x / / Withdraw and dropout / x / / Analyses / / x / Intervention integrity / / / Overall: A

Sowers, 1992 [UI#4543]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Menopause: mix Race: European Enrolled/Evaluate: 217/181 Location: US Sites: Single Funding: Government	ND	Prospective cohort (5 year)	In 1984, BMD of women In aged 22-54 years living in a single rural community were measured by single-photon densitometry. The community was selected for study because of the mineral characteristics of the community water supply. Women were eligible to participate in the baseline study if they had lived in the community the previous 5 years, were able to complete face-to-face interview, were ambulatory and reported themselves to be of northern European heritage. In 1989, a follow-up survey reexamined 181 of the 217 women who participated in the baseline survey. Nonrespondents to the follow-up survey were less likely to be married, were younger, had a greater Quetelet index, and had a slightly greater BMD than participants at baseline	Subjects were interviewed at baseline and follow-up for various factors, including lactation.	

Sowers, 1992 [UI#4543]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
BMD was expressed as the bone mineral to bone width ratio. Percent change was calculated as 100% - follow-up value/baseline value	Multiple-variable regression analyses were used to assess relationships between BMD change or baseline BMD values and the explanatory variables adjusting for age and estrogen status. Stepwise regression was used to generate models considering all other important variables, including age, estrogen status, parity, age at first pregnancy, and weight.	Nulliparous women (n=12) had significantly lower BMD at baseline and follow-up than parous women (n=169) before and after adjusting for age and estrogen status. A recalled history of breast-feeding in parous women did not predict significant differences in BMD level or amount of BMD change. We had insufficient sample size to test whether duration of breast-feeding in excess of 6 months for a single infant or 6 months cumulative time from breast-feeding multiple infants was associated with significant differences in BMD.	A: strong, B: moderate, C: weak / A / B / C Selection / / X / Study design / / X / Confounder / / X / Blinding / / X / Data collection / / X / Withdraw and dropout / / / X Analyses / / X / Intervention integrity / / / Overall: B

Uusi-Rasi, 2002 [UI#11991440]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 28.4 Menopause: pre Race: ND Enrolled/Evaluate: 132/92 Location: Finland Sites: Single/Multi Funding: private	healthy	Prospective cohort 4.2 (range 3.2-5.4) years	Healthy, non-smoking women willing to participate in original cross-sectional study. Inclusion criteria were a daily dietary calcium intake of over 1200 mg (Ca+) or under 800 mg (Ca-) and vigorous physical activity more than twice a week, or light to moderate activity no more than once a week. Women who had intermediate levels of physical activity or calcium intake or used calcium supplements were excluded. Altogether 92 women out of the 132 original 25- to 30-year-old subjects participated in the follow-up measurements.	Total duration of breastfeeding (one long period or sum of many periods of breastfeeding	

Uusi-Rasi, 2002 [UI#11991440]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
BMC at the proximal femoral neck and total trochanter region and the distal radius of the dominant side was measured with dual energy X-ray absorptiometry.	Repeated-measures analyses of variance were used to analyze the between group differences in changes in site-specific BMC. Regression models for % bone loss using a multivariate stepwise regression analysis that included baseline variables: age, body weight, muscle strength, estimated maximal oxygen uptake and calcium intake, the absolute changes in body weight, muscle strength, estimated maximal oxygen uptake, calcium intake, physical activity, duration of breastfeeding and time from weaning.	The mean decrease in BMC (95% CI) was 1.5% (0.7% to 2.4%) for the femoral neck, 0.6% (-0.8% to 1.9%) for the trochanter and 6.0% (4.5% to 7.4%) for the distal radius during the follow-up According to the multiple stepwise regression analyses, the statistically significant independent predictors for site-specific bone loss were low calcium intake at the baseline and change in body weight both at the proximal femur and at the distal radius. High calcium intake, as well as an increase in body weight, were associated with less bone loss at all the measured bone site. In addition, breastfeeding was associated with radial bone loss; the longer the duration of breastfeeding the greater the bone loss (Multiple regression coefficient= -0.34 +- 0.14 SE, p=0.015). Breastfeeding was not associated with femoral neck or trochanter BMC loss	A: strong, B: moderate, C: weak — A: ; B: x; C: Selection — A: ; B: x; C: Study design — A: ; B: x; C: Confounder — A: ; B: ; C: x Blinding — A: ; B: x; C: Data collection — A: ; B: x; C: Withdraw and dropout — A: ; B: ; C: x Analyses — A: ; B: x; C: Intervention integrity — A: ; B: ; C: Overall: B

Alderman, 1986 [UI#3728442]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 50-74 Menopause: post (assumed) Race: White Enrolled/Evaluate: 355/344 for cases; 562/318 for controls Location: US Sites: Multi Funding: Government	ND	Case-control study	Cases: Between 1976 and 1980, all women with hip fracture who sought care from a 62% sample of orthopedic surgeons were eligible. Women with forearm fracture who sought care from these orthopedists were eligible if the physician's practice had records that allowed tracing of all outpatients. Women who sought care for vertebral fractures were not eligible because we believed that they represented a small and probably unrepresentative group of women with vertebral fracture. Exclusion: nonwhite, younger than 50 or older than 74 years of age, nonresidents of King County, residents of institutions at the time of fracture, or if they had multiple or pathologic fractures. Controls: unmatched control women were identified through 3 door-to-door area-based surveys of the general population of King Country conducted in 1976, 1977, and 1979. Comparable exclusion criteria were used.	The duration of lactation was calculated by summing the number of months of lactation associated with each birth, and was treated in separate analyses as a categorical variable (taking values 0, 1 to 12, 13 to 24 and more than 24 months) and as continuous variable (taking values from 0 to 109 months) 11/355 cases missing data on lactation	253/562 control women missing data on lactation

Alderman, 1986 [UI#3728442]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>Risk of hip or forearm fractures</td>
<td>Logistic regression was used. The logistic model was evaluated for confounding by forward selection method. Only parity and variables with independent confounding effects were included in the final model. The same procedure was repeated to examine the association between fracture and duration of lactation.</td>
<td>Logistic regression analysis did not reveal a substantial change in risk of fracture with increasing duration of lactation when lactation was treated as a categorical variable. Adjustment for confounding effects of age, relative weight, and duration of estrogen use did not alter these results.
Similar results were obtained when lactation was treated as a continuous variable. Separate analysis of women with hip fracture suggested that an increase in months of breastfeeding was associated with an irregular decreased in risk of fracture.</td>
<td>
<table>
<tr><td>A: strong, B: moderate, C: weak</td><td>A</td><td>B</td><td>C</td></tr>
<tr><td>Selection</td><td></td><td>x</td><td></td></tr>
<tr><td>Study design</td><td></td><td>x</td><td></td></tr>
<tr><td>Confounder</td><td></td><td>x</td><td></td></tr>
<tr><td>Blinding</td><td></td><td></td><td>x</td></tr>
<tr><td>Data collection</td><td></td><td></td><td>x</td></tr>
<tr><td>Withdraw and dropout</td><td></td><td>x</td><td></td></tr>
<tr><td>Analyses</td><td></td><td>x</td><td></td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td></td></tr>
</table>
Overall: B
</td>
</tr>
</table>

Chan, 1996 [UI#8783297]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 75 (70-79) Menopause: post Race: Chinese Enrolled/Evaluate: 481/481 Location: Hong Kong Sites: Single Funding: Government	ND	Case-control study	Chinese women aged 70-79 years who were living in Geriatric Housing Scheme in Hong Kong. Subjects with a known history of metabolic bone disorder, cancer, or who were on long-term steroid treatment, were excluded. No subjects with such histories but 3 subjects on steroid therapy were excluded from the study. Cases: definite or doubtful vertebral fracture Control: the remaining enrolled subjects (women with no fractures)	Home-visit interviews by a standardized, structured questionnaire was administered by 2 trained research nurses who was blinded to the fracture status. Period of lactation: less than 24 months, or 24 months or more	Period of lactation: never

Chan, 1996 [UI#8783297]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Diagnosis of vertebral fracture according to Black et al.: definite vertebral fracture: when any of the 3 vertebral ratios was 3 SD or more away from the mean; doubtful fracture: any of the 3 vertebral ratios was 2-2.99 SD away from the mean. A woman with 1 or more definite fractures was classified as a definite case, a woman with no definite fractures but one or more doubtful fractures as a doubtful case, and the rest as controls.	Logistic regression: OR for vertebra fracture among definite case and control; doubtful cases and controls. Analysis adjusted for age.	There were no significant differences in the age of menarche and menopause between definite cases, doubtful cases, and controls. The risk of definite fracture decreased with the number of children given birth to and the duration of breast-feeding.	A: strong, B: moderate, C: weak — A / B / C Selection — / X / — Study design — / X / — Confounder — / — / X Blinding X / — / — Data collection — / X / — Withdraw and dropout — / X / — Analyses — / X / — Intervention integrity N/A Overall: C Did not separate parous women.

Period of lactation	% in definite cases (n=144)	% in doubtful cases (n=174)	% in controls (n=163)	Age-adj OR (95% CI)	
				Definite cases & control	Doubtful cases & control
Never	63	45	53	1.0	1.0
<24 mo	18	22	20	0.7 (0.4-1.3)	1.3 (0.7-2.2)
≥24 mo	19	33	27	0.6 (0.3-1.0	1.5 (0.9-2.4

Cumming, 1993 [UI#8225744]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 65-100 Menopause: post Race: D Enrolled/Evaluate: Location: Australia Sites: Multi Funding: ND	Self-reported heath (for directly interviewed subjects only: 104 cases and 114 controls) Cases: 23% excellent, 50% good, 20% fair; 6% poor Controls: 26% excellent, 51% good, 21% fair; 5% poor	Population-based case-control study	All people aged ≥65 living in a postcode-defined area in Sydney between 3/1990 and 8/1991. Total of 11 hospitals were included in the study. Cases: People with hip fractures presenting to the hospitals. The case ascertainment varied across hospitals. Controls: People living in private homes in the community and from people living in nursing homes and hostels. The controls comprised a probability sample of people aged ≥65 years living in the 11 postcodes of the study base during the same time period as the cases. Proxy respondents were used for elderly people with cognitive impairment and those with various other health problems. A shortened questionnaire was used to interview proxy respondents.	For all women: Ever breastfeeding For parous women only: Average duration of breastfeeding per child (months)	For all women: Never breastfeeding

Cumming, 1993 [UI#8225744]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>Risk of hip fracture</td>
<td>Data analysis: crude, stratified and multivariate methods to produce OR for associations between hip fracture and exposure variables. Age is the strongest predictor of hip fracture and so all results were adjusted for age.
Multiple logistic regressions were controlling for several confounding variables. Selection of confounders for inclusion in these models was based a priori knowledge of risk factors for hip fracture and the strength of univariate associations between exposure variables and hip fracture. Confounders (other than age) were entered into models as categorical variables.</td>
<td>There were 311 women in this study: 174 cases and 137 controls. The response rate was 96% for cases and 82% for controls. Proxy interviews were required for 93 subjects. Most cases (78%) were recruited from 1 teaching hospital. A history of use of HRT was more common among controls than among cases (age-adj OR: 0.55, 95%CI 0.24-1.27).
<table>
<tr><th></th><th colspan="3">Age- and proxy-adjusted</th><th colspan="2">Multivariate-adjusted</th></tr>
<tr><th></th><th>Cases</th><th>Ctrl</th><th>OR (95%CI)</th><th>No. subjects in the model</th><th>OR (95%CI)</th></tr>
<tr><td colspan="6">All women</td></tr>
<tr><td>BF-</td><td></td><td></td><td></td><td>N=176</td><td></td></tr>
<tr><td>Never</td><td>60</td><td>42</td><td>1.00</td><td></td><td>1.00</td></tr>
<tr><td>Ever</td><td>106</td><td>95</td><td>0.72 (0.43-1.20)</td><td></td><td>0.64 (0.30-1.38)</td></tr>
<tr><td colspan="6">Parous women</td></tr>
<tr><td>BF-</td><td></td><td></td><td></td><td>N=140</td><td></td></tr>
<tr><td>Never</td><td>25</td><td>12</td><td>1.00</td><td></td><td>1.00</td></tr>
<tr><td>Ever</td><td>106</td><td>95</td><td>0.47 (0.22-0.99)</td><td></td><td>0.55 (0.10-2.90)</td></tr>
<tr><td>Average duration of BF per child (mo)</td><td></td><td></td><td></td><td>N=136</td><td></td></tr>
<tr><td>0</td><td>19</td><td>11</td><td>1.00</td><td></td><td>1.00</td></tr>
<tr><td>0.5-3</td><td>17</td><td>16</td><td>0.56 (0.19-1.68)</td><td></td><td>0.64 (0.13-3.06)</td></tr>
<tr><td>3-6</td><td>17</td><td>24</td><td>0.41 (0.15-1.13)</td><td></td><td>0.79 (0.18-3.51)</td></tr>
<tr><td>6-9</td><td>18</td><td>23</td><td>0.47 (0.19-1.19)</td><td></td><td>0.41 (0.09-1.82)</td></tr>
<tr><td>>9</td><td>7</td><td>10</td><td>0.28 (0.07-1.18)</td><td></td><td>0.24 (0.04-1.53)</td></tr>
</table>
For women who had one or two children, breastfeeding markedly reduce the risk of hip fracture in later life. After adjusting for age and number of children, the OR in parous women for breastfeeding all children versus breastfeeding none was 0.26 (95%CI 0.10-0.69)</td>
<td>
<table>
<tr><td>A: strong, B: moderate, C: weak</td><td>A</td><td>B</td><td>C</td></tr>
<tr><td>Selection</td><td></td><td>X</td><td></td></tr>
<tr><td>Study design</td><td></td><td>X</td><td></td></tr>
<tr><td>Confounder</td><td></td><td>X</td><td></td></tr>
<tr><td>Blinding</td><td></td><td></td><td>X</td></tr>
<tr><td>Data collection</td><td></td><td>X</td><td></td></tr>
<tr><td>Withdraw and dropout</td><td></td><td></td><td>X</td></tr>
<tr><td>Analyses</td><td></td><td>X</td><td></td></tr>
<tr><td>Intervention integrity</td><td colspan="3">N/A</td></tr>
</table>
Overall: B

Missing data for covariates in the multivariate model, so the number of subjects in the model is limited.</td>
</tr>
</table>

Hoffman, 1993 [UI#8338971]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 50-103 Menopause: post Race: White Enrolled/Evaluate: 286/174 cases; 311/174 controls Location: USA Sites: Multi Funding: ND	Hospital cases and controls	Case-control study	Cases: a sample of radiologically confirmed cases of first hip fracture among white women aged 45 years and older was drawn from among admissions to one of 30 hospitals between 9/1987 and 7/1989 Controls: white hospital controls, frequency-matched to cases by 10-year age group and by hospital of admission during the same time period. Exclude subjects with a prior hip fracture, pathological fracture secondary to cancer, evidence of bony metastases, severe cognitive, language, or hearing impairment, died in the hospital shortly after surgery, or medically unstable	Ever lactated Lactated ≤ 12 mo Lactated > 12 mo	Never lactated

Hoffman, 1993 [UI#8338971]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Risk of hip fracture	Conditional logistic regression models were used to remove the effect of matching cases and controls. Because the age intervals were wide, age was controlled for as continuous variable. Variables that changed crude estimates by 10% or greater were retained as confounding variables. For lactation, only the number of live births was retained.	Lactation was associated with reduced odds of hip fracture among all women (OR=0.66 [0.41-1.05]) Restricting the analysis to parous women and controlling for number of live births, there was no association between ever having lactated or duration of lactation and hip fracture (OR for lactation of 12 months or less=0.80 [0.42-1.55]); OR for lactation of more than 12 months=1.08 [0.45-2.60]) Duration of lactation did not confound the negative association between parity and hip fracture.	A: strong, B: moderate, C: weak: A / B / C Selection: / / X Study design: / X / Confounder: / X / Blinding: / / X Data collection: / X / Withdraw and dropout: / / X Analyses: / X / Intervention integrity: / / Overall: B

Kreiger, 1982 [UI#7102649]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 45-74 Menopause: post Race: ND Enrolled/Evaluate: 149/98 for cases; 1345/884 Location: US Sites: Multi Funding: ND	Hospital cases and controls	Case-control study	Women aged 45-74 years admitted to surgical services of 4 Connecticut hospitals between 9/1977 and 5/1979. Cases: women admitted to 1 of the 4 study hospitals with a first diagnosis of hip fracture, either intra- or extra- capsular, confirmed by x-ray. Controls: systematic sample of women admitted to the inpatient surgical services of the 3 largest hospitals. Controls included had a wide variety of diagnoses, and no more than 5% of the controls were in any single diagnostic category. Exclusion: women with reproductive cancers, who did not speak English, who lived outside of Connecticut, or last menstrual period was within 1 year of hospital admission or if the admitting diagnosis of a disease related to estrogen use.	98 of 149 cases (66%) of hip fracture and 884 of 1345 controls (66%) were interviewed. Variable: Breastfeeding 12-month increase	Before the data analysis began, the controls were divided into 2 groups: trauma control group and nontrauma control.

Kreiger, 1982 [UI#7102649]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Odds ratio of hip fracture, compared cases to trauma or nontrauma controls.	Linear logistic regression, adjusted for age and for Quetelet index (similar to BMI), bilateral ovariectomy, and estrogen replacement therapy.	Linear logistic regression, adjusted for age and for Quetelet index (0.01 increase), bilateral ovariectomy (yes/no), and estrogen replacement therapy (60-month increase): Variable: Breastfeeding; Unit: 12-month increase Cases and trauma control: Adj OR (95% CI): 0.5 (0.2, 0.9) Cases and non-trauma control: Adj OR (95% CI): 0.6 (0.3, 1.0)	A: strong, B: moderate, C: weak Selection: B Study design: B Confounder: B Blinding: C Data collection: C Withdraw and dropout: C Analyses: C Intervention integrity: Overall: C Sample size in breastfeeding analysis was not described. Did not separate out parous women.

Michaelsson, 2001 [UI#2001082617]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Cases=72.5; Controls=70.5 Menopause: post Race: ND Enrolled/Evaluate: 715/664 for cases evaluated Location: Sweden Sites: Multi Funding: ND	ND	Case-control study; a comprehensive questionnaire at a mean interval of 95 days after the fracture; associations between lactation and hip fracture were only analyzed for parous women	Cases: All fractures of the proximal femur that occurred between 10/ 1993 and 2/1995 among women resident in 6 counties in Sweden who were born after 1913. Using clinical records or operation registers in all 24 hospitals in the study area, a total of 1,597 possible incident cases were identified. Those with a fracture due to malignancy (n=26); high-energy trauma (n-4); incorrect diagnosis (n=41); old fracture (n-10); blindness (n=5); birth outside Sweden (n=202); excluded: severe alcoholic abuse, psychosis, or senile dementia (n=576); or death within 3 months of the fracture (n=123). After exclusions, 1,610 eligible cases remained and were approached with. The Swedish inpatient register identified 34 additional cases. Controls: Native-born women were randomly selected from the national population register in the month before the start of the study. Potential controls aged 70-80 years were frequency matched (2 controls per 1 case) to the expected hip fracture age distribution within county of residence. Controls aged 50-69 years were randomly selected from the population register as part of a breast cancer study being conducted at the same time with the same questionnaire. For these women, frequency matching to the expected number of breast cancer cases provided 2-4 times as many controls as hip fracture cases in each 5-year age group and country of residence. Of the 4,870 candidate controls in the hip fracture analysis, 4,059 were eligible for the study, 610 were born outside of Sweden, 257 died before being approached, 44 were senile or psychotic, and 2 were blind.	Duration of breastfeeding was considered in 4 classes defined by the quartiles of either total duration or mean duration per child of breastfeeding among controls	

Michaelsson, 2001 [UI#2001082617]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>OR of hip fracture</td>
<td>Unconditional logistic regression were used as measure of association. The multivariate analyses included the covariates age, BMI, oral contraceptive use, HRT use, and smoking status. Interactions were considered.
Associations between lactation and hip fracture were only analyzed for parous women</td>
<td>Long total duration of breastfeeding was associated with a reduction in risk (table 3 in paper), but this association disappeared after adjustment for parity, body mass index, and use of exogenous estrogens. There were no substantial risk differences in analyses that considered mean duration of breastfeeding per child (quartiles 0–2, 3–4, 5–6, and 7 months per child or more) (data not shown). Long duration of breastfeeding also had no substantial association with hip fracture risk among those with their first pregnancy as a teenager or among those with their first pregnancy after age 30 years. The relative risk estimates for lactation and parity were similar for cervical and trochanteric hip fracture (data not shown).</td>
<td>
<table>
<tr><td>A: strong, B: moderate, C: weak</td><td>A</td><td>B</td><td>C</td></tr>
<tr><td>Selection</td><td>x</td><td></td><td></td></tr>
<tr><td>Study design</td><td></td><td>x</td><td></td></tr>
<tr><td>Confounder</td><td></td><td>x</td><td></td></tr>
<tr><td>Blinding</td><td></td><td></td><td>x</td></tr>
<tr><td>Data collection</td><td></td><td>x</td><td></td></tr>
<tr><td>Withdraw and dropout</td><td></td><td>x</td><td></td></tr>
<tr><td>Analyses</td><td></td><td>x</td><td></td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td></td></tr>
</table>
Overall: B
</td>
</tr>
</table>

Appendix C. Evidence Tables

Part III. Maternal Outcomes

Ovarian Cancer

Chiaffarino 2005
Cramer 1983
Greggi 2000
Gwinn 1990
Hartge 1989
John 1993
Modugno 2003
Ness 2000
Riman 2002
Risch 1983
Risch 1994
Siskind 1997
Titus-ernstoff 2001
Tung 2003, 2005
West 1966
Whittemore 1992
Wynder 1969
Yen 2003

Chiaffarino, 2005 [UI# 15975644]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Median age (range): Cases: 56 (18-79) Controls: 57 median (17-79) Menopause: ND Race: ND Enrolled/Evaluate: Cases: 1031/1028 Controls: 2411/2390 Location: Italy Sites: Multi-center Funding: Private, government	Cases: ND Controls: traumatic conditions 26%, nontraumatic orthopedic disorders 28%, acute surgical conditions mostly abdominal diseases 15%, miscellaneous illnesses (ear, nose throat, teeth) 31%	Case-control Data collection by interviews using structured questionnaire	Case: Histologicaly confirmed epithelial ovarian cancer diagnosed in past year, admitted to major or teaching hospital Control: residents of same geographic area, admitted to same network of hospitals for acute, non-neoplastic, unrelated to known or likely risk factors for ovarian cancer, exclusion include hormonal and gynecological diseases, or ovariectomized	Breast feeding status determined by questionnaire	Breast feeding status determined by questionnaire

Chiaffarino, 2005 [UI# 15975644]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>Ovarian cancer confirmed by histology</td>
<td>Unconditioned multiple logistic regression adjusting for age, center, education, parity, oral contraceptive use, family history of ovarian/breast cancer in first degree relatives</td>
<td>
<table>
<tr><th>Exposure status</th><th>Cases n (%)</th><th>Controls n (%)</th><th>OR_{adj} (95% CI)</th></tr>
<tr><td>Never breastfed</td><td>368(36)</td><td>878 (37)</td><td>1.0</td></tr>
<tr><td>Ever breastfed</td><td>660 (64)</td><td>1512 (63)</td><td>1.16 (0.93-1.43)</td></tr>
<tr><td>Breastfed 1-4 months</td><td>157 (15)</td><td>358 (15)</td><td>1.20 (0.91-1.59)</td></tr>
<tr><td>Breastfed 5-8 months</td><td>180 (18)</td><td>366 (15)</td><td>1.24 (0.95-1.62)</td></tr>
<tr><td>Breastfed 9-16 months</td><td>195 (19)</td><td>451 (19)</td><td>1.01 (0.77-1.33)</td></tr>
<tr><td>Breastfed ≥17 months</td><td>128 (12)</td><td>337 (14)</td><td>1.21 (0.85-1.71)</td></tr>
<tr><td>x^2 for trend</td><td></td><td></td><td>0.03 (p=0.87)</td></tr>
</table>
<table>
<tr><th rowspan="2">Exposure status</th><th colspan="3">Odds $ratio_{adj}$ (95% CI)</th></tr>
<tr><th>Serous</th><th>Mucinous</th><th>Other subtypes</th></tr>
<tr><td>Never breastfed</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Ever breastfed</td><td>1.1 (0.85-1.48)</td><td>1.59 (0.82-3.07)</td><td>1.08 (0.71-1.62)</td></tr>
<tr><td>Breastfed 1-4 mo</td><td>1.3 (0.90-1.85)</td><td></td><td></td></tr>
<tr><td>Breastfed 5-8 mo</td><td>1.16 (0.81-1.65)</td><td></td><td></td></tr>
<tr><td>Breastfed 9-16 mo</td><td>1.06 (0.74-1.51)</td><td></td><td></td></tr>
<tr><td>Breastfed ≥17 mo</td><td>0.87 (0.55-1.39)</td><td></td><td></td></tr>
<tr><td>x^2 for trend</td><td>0.14 p=0.71</td><td></td><td></td></tr>
</table>
</td>
<td>
<table>
<tr><th>A: strong, B: moderate, C: weak</th><th>A</th><th>B</th><th>C</th></tr>
<tr><td>Selection</td><td></td><td>X</td><td></td></tr>
<tr><td>Study design</td><td></td><td>X</td><td></td></tr>
<tr><td>Confounder</td><td></td><td></td><td>X</td></tr>
<tr><td>Blinding</td><td></td><td>X</td><td></td></tr>
<tr><td>Data collection</td><td></td><td></td><td>X</td></tr>
<tr><td>Withdraw and dropout</td><td></td><td>X</td><td></td></tr>
<tr><td>Analyses</td><td>X</td><td></td><td></td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td></td></tr>
</table>
Potential recall bias
</td>
</tr>
</table>

Cramer, 1983 [UI# 6578366]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age: 53 Menopause: ND Race: White Enrolled/Evaluate: Cases: 215 Controls: 215 Location: USA Sites: Multi-center Funding: Government	ND	Case-control Data collection by questionnaires	Cases: white females with epithelial ovarian cancer residing in greater Boston area Controls: matched residents of same precinct, age within 2 years, race. Only bilateral oophorectomy excluded.	Breastfeeding status determined by questionnaire	Breastfeeding status determined by questionnaire

Cramer, 1983 [UI# 6578366]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
All types of epithelial ovarian cancer	Chi-square	Crude relative risks 1.11 (0.70-1.76) never breastfed parous cases (86/137) vs controls (106/176) Non-significant trend in risk for ovarian cancer with number of children breastfed.	A: strong, B: moderate, C: weak — A: ; B: X; C: Selection — A: ; B: X; C: Study design — A: ; B: X; C: Confounder — A: ; B: ; C: X Blinding — A: ; B: X; C: Data collection — A: ; B: ; C: X Withdraw and dropout — A: ; B: X; C: Analyses — A: ; B: ; C: X Intervention integrity — A: ; B: ; C: Minimal reporting of data Potential recall bias

Greggi, 2000 [UI# 11006030]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Median age (range): Cases: 54 (13-80) Controls: 55 (19-80) Menopause: mix Race: ND Enrolled/Evaluate*: Cases: 440/330 Controls 868/721 Location: Italy Sites: Single Funding: Private *Parous	Cases: ND Controls: traumatic conditions 29%, nontraumatic orthopedic disorders 21%, acute abdominal diseases generally requiring surgery 17%, miscellaneous illnesses (ear, nose throat, teeth) 33%	Case-control Data collection by hospital interviews	Cases: admitted histologically confirmed diagnosis of epithelial ovarian cancer Controls: admitted to same hospital, similar age strata, acute nongynecological, nonhormonal, or nonneoplastic condition	Breast feeding status determined by interview	Breast feeding status determined by interview

Greggi, 2000 [UI# 11006030]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Epithelial ovarian cancer confirmed by histology	Mantel-Haenzel adjusted for age; unconditional multiple logistic regression estimates including terms for age, education, parity, oral contraceptive use, family history of ovarian cancer	See table below	See table below

Exposure status*	Cases 330 (%)	Controls 721 (%)	OR_{adj} (95% CI) Mantel-Haenzel	OR_{adj} (95% CI) Multivariate regression
Never breastfed	84 (25)	120 (17)	1.0	1.0
Breastfed ≤12 months	136 (41)	294 (41)	0.6 (0.5-0.9)	0.8 (1.0-1.1)
Breastfed >12 months	110 (33)	307 (43)	0.5 (0.3-0.7)	0.5 (0.4-0.8)

*Parous

A: strong, B: moderate, C: weak	A	B	C
Selection		X	
Study design		X	
Confounder		X	
Blinding		X	
Data collection			X
Withdraw and dropout			X
Analyses		X	
Intervention integrity			

Potential recall bias

Gwinn, 1990 [UI# 2348208]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): ND Menopause: mix Race: ND Enrolled/Evaluate: Cases: 494/436 Controls: 4236/3833 Location: USA Sites: Multi center Funding:	ND	Case-control Controls contacted by random telephone Data collection by interview of standard questionnaire	Cases: 20-54 year, resides in 1 of 8 study areas, ovarian cancer by histology Controls: matched for age, resides in same 8 areas, no ovaries or unknown number of ovaries are exclusion	Breast feeding status determined by interview, duration in months regardless of pattern	Breast feeding status determined by interview

Gwinn, 1990 [UI# 2348208]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Epithelial ovarian cancer confirmed by histology	Logistic regression adjusted for pregnancy, oral contraceptive use, age, and age-pregnancy interaction	See table below * Parous women only β –0.024 Each month of breastfeeding reduced risk by 2.4% Most protection due to first exposure rather than number of pregnancies	See table below Ovarian cancer confirmed by histology in majority of cases

Breastfeeding duration (month)*	Cases n (%)	Controls n (%)	RR_{adj} (95% CI)
0	184 (57)	1517 (46)	1.0
1-2	40 (12)	552 (17)	0.6 (0.5-0.9)
3-5	32 (10)	330 (10)	0.8
6-11	33 (10)	379 (11)	0.8
12-23	25 (8)	321 (10)	0.7
≥ 24	7 (2.2)	213 (6.4)	0.3

A: strong, B: moderate, C: weak	A	B	C
Selection		X	
Study design		X	
Confounder		X	
Blinding		X	
Data collection		X	
Withdraw and dropout		X	
Analyses	X		
Intervention integrity			

Hartge, 1989 [UI# 2750791]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Cases: 54 (20-79) Controls: 55 Menopause: mix Race: Cases: 12% black Controls: 14% black Enrolled/Evaluate: Cases: 296/203* Controls: 343/257* Location: USA Sites: Multi Funding: Government *Parous women (evaluated)	Serous 28% Serous, low malignant potential 12% Mucinous 6% Mucinous, low malignant potential 3% Endometrioid, low malignant potential 26% Clear cell 4% Mixed epithelial 8% Undifferentiated 10% Controls: Infectious 2% Neoplasm 5% Endocrine-metabolic 5% Blood disease or blood-forming organs 1% Nervous system 8% Eye, ear, mastoid 8% Varicose veins, hemorrhoids 1% Respiratory 8% Digestive system 16% Urinary 5% Skin 2% Musculoskeletal 22% Congenital 1% Ill-defined 5% Fractures/injuries 11%	Case-control Data collection with interviewer of standard questionnaire and medical records review	Cases: primary epithelial ovarian cancer confirmed by microscopic slides and medical records, included low malignant potential tumors as well as malignant tumors Controls: hospitalized for other conditions, matched for age, hospital, race, at least one ovary. Excluded if psychiatric diagnosis or related to major exposures of interest	Breastfeeding status determined by interview	Breastfeeding status determined by interview

Hartge, 1989 [UI# 2750791]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>Primary epithelial ovarian cancer confirmed by microscopic slides and medical records</td>
<td>Rate ratio of ovarian cancer incidence in exposed group to corresponding unexposed group, adjusted for confounding variables by stratified contingency table analysis and by logistic regression models, adjustments for age and race, and parity, difficulty conceiving, oral contraceptives, surgical menopause, HRT, or family history of ovarian cancer as needed</td>
<td>
<table>
<tr><th>Breastfeeding duration (month)*</th><th>Cases n (%)</th><th>Controls n (%)</th><th>Rate ratio$_{adj}$ (95% CI)</th></tr>
<tr><td>0</td><td>112 (55)</td><td>121 (47)</td><td>1.0</td></tr>
<tr><td>1-9</td><td>62 (31)</td><td>84 (33)</td><td>0.8 (0.5-1.2)</td></tr>
<tr><td>10-18</td><td>16 (7.9)</td><td>37 (18)</td><td>0.5 (0.2-0.9)</td></tr>
<tr><td>19-110</td><td>13 (6.4)</td><td>15 (7.4)</td><td>1.1 (0.5-2.6)</td></tr>
</table>
* Parous women only
Adjusted for age and race
Trend test p = 0.14

Number of months breastfeeding not related to risk
</td>
<td>
<table>
<tr><th>A: strong, B: moderate, C: weak</th><th>A</th><th>B</th><th>C</th></tr>
<tr><td>Selection</td><td></td><td>X</td><td></td></tr>
<tr><td>Study design</td><td></td><td>X</td><td></td></tr>
<tr><td>Confounder</td><td></td><td>X</td><td></td></tr>
<tr><td>Blinding</td><td></td><td>X</td><td></td></tr>
<tr><td>Data collection</td><td></td><td>X</td><td></td></tr>
<tr><td>Withdraw and dropout</td><td></td><td>X</td><td></td></tr>
<tr><td>Analyses</td><td></td><td>X</td><td></td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td></td></tr>
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John, 1993 [UI# 8418303]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Cases: Invasive 53 Borderline 37 Controls: ND Menopause: mix Race: Black Enrolled/Evaluate: Cases: 110/53 Controls: 365/259 69% population 31% hospital Location: USA Sites: 7 of 12 studies Funding: Government	Invasive cancer 65% Low malignant 32% Unknown 3%	Case-control Data from 7 studies of cases diagnosed between 1971 and 1986. Individual patient data collected by interview from 7 case-control studies conducted in US	Epithelial ovarian cancer Controls: population and hospital subjects, bilateral oophorectomy excluded	Breastfeeding status determined by interview	Breastfeeding status determined by interview

John, 1993 [UI# 8418303]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Epithelial ovarian cancer	Conditional logistic regression adjusted for study, birth year, reference age, parity		

Breastfeeding duration (month)*	Cases n (%)	Controls n (%)	RR_{adj} (95% CI)
Never breastfed	24 (45)	102 (39)	1.0
Ever breastfed	29 (55)	157 (61)	0.90 (0.42-1.9)
1-5	11 (21)	52 (20)	1.0 (0.39-2.6)
≥6	18 (34)	103 (40)	0.85 (0.36-2.0)
Trend per month			0.99 p=0.57

* Parous

A: strong, B: moderate, C: weak	A	B	C
Selection		X	
Study design		X	
Confounder			X
Blinding		X	
Data collection			X
Withdraw and dropout		X	
Analyses		X	
Intervention integrity			

Data unavailable for use of oral contraceptives and years of ovulation

Overlap with Hartge 1989 and Cramer 1983

Modugno, 2003 [UI# 12946038]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): BRCA1 51 BRCA2 61 BRCA- 58 Menopause: mix Race: 100% Jewish Enrolled/Evaluate: Cases: 95 Controls: 147 Location: USA, Israel Sites: Multi Funding: Government	ND	Case-control Cases screened for Ashkenazi founder mutations BRCA1 (185delAG or 5382insC) or BRCA2 (6174delT) Controls were ovarian cases without BRCA1/2 genotype Individual patient data collected by interview from 4 case-control studies. Two US population studies (100 cases), one hospital-based study from 11 US and Israel centers (208 cases), and one US genetic counseling center (14 cases)	Jewish women with epithelial ovarian cancer, no breast cancer history, BRCA1/2 confirmed by data sequencing	ND	ND

Modugno, 2003 [UI# 12946038]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Invasive epithelial ovarian cancer confirmed by histology	Unconditioned logistic regression adjusted for age at diagnosis, year of birth, number of live births, oral contraceptive use, history of tubal ligation. Mantel-Haenszel test for heterogeneity		

	OR_{adj} (95% CI)			
	BRCA- (n=147)	BRCA1/2 (n=95)	BRCA1 (n=64)	BRCA2 (n=31)
Breastfeeding	1.0	1.09 (0.61-1.97)	1.36 (0.68-2.73)	0.70 (0.28-1.72)
Breastfeeding duration*	1.0	1.02 (0.99-1.04)	1.01 (0.98-1.04)	1.02 (0.99-1.05)

* Parous women

A: strong, B: moderate, C: weak	A	B	C
Selection			X
Study design		X	
Confounder			X
Blinding		X	
Data collection			X
Withdraw and dropout		X	
Analyses		X	
Intervention integrity			

10% overlap in samples between the US genetic center & hospital-based study
Classification of Jewish varied between studies

One population study, Ness 2000, has been reported

Ness, 2000 [UI# 11021606]
Modugno, 2001 [UI# 11308435]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Cases: Invasive 53 Borderline 45 Controls: 49 Menopause: mix Race: ND Enrolled/Evaluate: Cases: 767/531* Controls: 1215/1190* Location: USA Sites: Multi Funding: Government *Parous women (evaluated)	Invasive epithelial 616 Serous 45% Mucinous 8% Endometrioid 22% Other 24% Borderline epithelial 151 Serous 52% Mucinous 40% Endometrioid 2% Other 6% Other includes clear cell, mixed cell, undifferentiated or poorly differentiated	Case-control Data collection by interview Controls identified by random-digit dialing from HFCA lists	Histologically confirmed epithelial ovarian cancer diagnosed past 6 months, 20-69 years Controls: ≤ 65 years, matched by 5 years and 3 digit exchange Exclusion: outside counties of referral hospital, prior diagnosis of ovarian cancer, non-English speaking, mentally incompetent, critically ill, prior bilateral oophorectomy	Breastfeeding status determined by interview, length recorded on life calendar	Breastfeeding status determined by interview, length recorded on life calendar

Ness, 2000 [UI# 11021606]
Modugno, 2001 [UI# 11308435]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>Epithelial ovarian cancer confirmed by histology</td>
<td>Multivariate unconditional logistic regression adjusted for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy, breastfeeding

For analyses by histology: multivariate unconditional logistic regression adjusted for age, number of live births, years of oral contraceptive use, years of noncontraceptive estrogen use and months breastfed, tubal ligation, hysterectomy, family history of ovarian and breast cancer, ethnicity</td>
<td>
<table>
<tr><th>Breastfeeding duration (month)*</th><th>Cases n (%)</th><th>Controls n (%)</th><th>Odds ratio$_{adj}$ (95% CI)</th></tr>
<tr><td>0</td><td>299 (56)</td><td>577 (48)</td><td>1.0</td></tr>
<tr><td>1-5</td><td>117 (22)</td><td>259 (22)</td><td>0.9 (0.7-1.2)</td></tr>
<tr><td>6-11</td><td>46 (8.7)</td><td>119 (10)</td><td>0.9 (0.6-1.3)</td></tr>
<tr><td>12-23</td><td>40 (7.5)</td><td>124 (10)</td><td>0.7 (0.5-1.1)</td></tr>
<tr><td>≥24</td><td>29 (5.5)</td><td>111 (9.3)</td><td>0.6 (0.4-1.0)</td></tr>
</table>
* Parous women only
<table>
<tr><th>Histologic subgroup (N)</th><th>Months breastfed Odds ratio$_{adj}$ (95% CI)</th></tr>
<tr><td>Serous (357)</td><td>1.00 (0.98-1.01)</td></tr>
<tr><td>Mucinous (112)</td><td>1.00 (0.98-1.02)</td></tr>
<tr><td>Endometrioid (139)</td><td>0.97 (0.94-1.00)</td></tr>
<tr><td>Other (159)</td><td>0.97 (0.94-1.00)</td></tr>
<tr><td>All (767)</td><td>0.99 (0.98-1.00)</td></tr>
</table>
</td>
<td>
<table>
<tr><th>A: strong, B: moderate, C: weak</th><th>A</th><th>B</th><th>C</th></tr>
<tr><td>Selection</td><td></td><td>X</td><td></td></tr>
<tr><td>Study design</td><td></td><td>X</td><td></td></tr>
<tr><td>Confounder</td><td></td><td>X</td><td></td></tr>
<tr><td>Blinding</td><td></td><td></td><td>X</td></tr>
<tr><td>Data collection</td><td></td><td>X</td><td></td></tr>
<tr><td>Withdraw and dropout</td><td></td><td></td><td>X</td></tr>
<tr><td>Analyses</td><td></td><td>X</td><td></td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td></td></tr>
</table>
</td>
</tr>
</table>

Riman, 2002 [UI# 12181107]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Cases: 62 Controls: 63 Menopause: mix Race: ND Enrolled/Evaluate: Cases: 914/655 Controls: 4148/3899 Location: Sweden Sites:NA Funding: Private, government	All invasive (655) Serous (337) Mucinous (60) Endometrioid (180) Clear cell (43) Other/undifferentiated (35)	Case-control Data collected by self-administered questionnaires followed up by phone for missing or inconsistent details	Swedish born women 50-74 years old with epithelial ovarian cancer confirmed by histology identified by national registry Controls: randomly selected population national registry Exclusion: previous ovarian malignancy or bilateral oophorectomy	Breastfeeding status determined by questionnaires	Breastfeeding status determined by questionnaires

Riman, 2002 [UI# 12181107]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Epithelial ovarian cancer confirmed by histology	Unconditional logistic regression adjusted for age, bmi, parity, age at menopause, duration of oral contraceptive use, HRT use	See tables below	See tables below

Breastfeeding duration (months)	Cases n (%)	Controls n (%)	OR_{adj} (95% CI)
<1	33 (7.2)	161 (15)	1.0
1-5	134 (29)	612 (15)	0.99 (0.64-1.52)
6-11	134 (29)	840 (19)	0.77 (0.50-1.19)
≥12	158 (34)	1,024 (14)	0.87 (0.56-1.35)

Parous women

Breastfeeding duration (months)	Odds $Ratio_{adj}$ (95% CI)			
	Serous	Mucinous	Endometrioid	Clear cell
<1	1.0	1.0	1.0	1.0
1-5	0.87 (0.50-1.53)	2.19 (0.49-9.87)	1.05 (0.47-2.34)	0.54 (0.16-1.87)
6-11	0.61 (0.35-1.09)	1.75 (0.39-7.87)	1.10 (0.50-2.46)	0.23 (0.06-0.88)
≥12	0.87 (0.49.-1.54)	0.83 (0.49-1.54)	1.02 (0.44-2.37)	0.24 (0.06-0.97)

A: strong, B: moderate, C: weak	A	B	C
Selection	X		
Study design		X	
Confounder		X	
Blinding	X		
Data collection		X	
Withdraw and dropout		X	
Analyses		X	
Intervention integrity			

50% of cases and controls were contacted by phone for missing or inconsistent data; unknown if breastfeeding status category <1 month includes no breastfeeding or data was unavailable

Risch, 1983 [UI# 6681935]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Cases: 20-74 Controls: 21-75 Menopause: mix Race: white Enrolled/Evaluate: Cases: 284 Controls: 705 Location: USA Sites: Multi Funding: Government	ND	Case-control Data collection by interview Cases	Epithelial ovarian cancer diagnosed in past 18 months, reside in 6 specified counties of Washington and Utah and identified by population-based cancer reporting systems, age 34-74 for Washington cases, age 20-74 for Utah cases Controls: household survey conducted in same counties by standard geographic sampling methods or telephone selected from directories. Utah samples matched for age and Washington samples matched for age range. Exclusion included bilateral oophorectomy ≤ 1 year Additional case-control exclusion: nonwhite, incomplete reproductive histories	Breastfeeding status determined by interview	Breastfeeding status determined by interview

Risch, 1983 [UI# 6681935]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Epithelial ovarian cancer	Linear logistic regression adjusted for age at diagnosis 20-44, nulliparous, no miscarriages, < 1 year total exposure to combined oral contraceptives, nonobese	RR 0.79 per year of lactation p=0.034, is associated with decreased ovarian cancer risk Cases reported less time breastfeeding than controls 3+ total months lactation – RR 0.69 (0.50-0.96) p=0.026	

A: strong, B: moderate, C: weak	A	B	C
Selection			X
Study design		X	
Confounder		X	
Blinding		X	
Data collection			X
Withdraw and dropout		X	
Analyses		X	
Intervention integrity			

Risch, 1994 [UI# 7942759]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Cases: 57 Controls: 58 Menopause: mix Race: 96% white Enrolled/Evaluate: Cases: 450 Controls: 564 Location: Canada Sites: Multi Funding: Government	ND	Case-control Data collection by interview using questionnaire incorporating life events calendar – conducted at subject's home	Primary malignant or borderline malignant epithelial ovarian cancer confirmed by histology, age 35-79, residents of Ontario located through Ontario Cancer Registry, living subjects Controls: obtained from Enumeration Composite Record listing compiled by Ontario Ministry of Revenue, matched for area of residence and age range, exclusion included bilateral oophorectomy < 1 year, living subjects	Breastfeeding status determined by interview	Breastfeeding status determined by interview

Risch, 1994 [UI# 7942759]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Primary malignant or borderline malignant epithelial ovarian cancer confirmed by pathology reports	Multivariate unconditional continuous logistic regression adjusted for 3 age groups, continuous variables age, total duration of oral contraceptive use	See table below *Adjusted for number of full-term pregnancies Inverse association with total duration of lactation Inverse association with average duration per pregnancy, p=0.030 Pregnancies with lactation slightly more protective than pregnancies without	See table below Slightly greater number for controls born in Canada or US, smaller percentage of cases were parous or ever used OC and among those cases had fewer full-term pregnancies and used OC for shorter periods of time

No of full-term pregnancies	Mean		Odds $ratio_{adj}$ (95% CI)
	Cases	Controls	
Total duration* (year)	0.51	0.65	0.89 (0.75-1.05)
Average duration of lactation/pregnancy* (months)	2.24	2.72	0.87 (0.76-0.99)

A: strong, B: moderate, C: weak	A	B	C
Selection		X	
Study design		X	
Confounder			X
Blinding		X	
Data collection		X	
Withdraw and dropout		X	
Analyses			X
Intervention integrity			

Siskind, 1997 [UI# 9229212]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age* (range): Cases: 57 Controls: 56 Menopause: mix Premenopausal Cases: 35% Controls: 36% Race: ND Enrolled/Evaluate*: Cases: 824/618 Controls: 855/724 Location: Australia Sites: Multi Funding: Government, private *Parous	ND	Case-control Data collection by interviewer with questionnaire at discharge or clinic follow-up, in homes for all controls and homes or clinics for cases Controls randomly selected through electoral roll	Cases: Histologically confirmed primary epithelial ovarian cancer, 18-79 years, ≥ 1 live birth Controls: similar age and region Exclusion: history of ovarian cancer or bilateral oophorectomy, incapable of completing questionnaire	Breastfeeding status determined by questionnaire	Breastfeeding status determined by questionnaire

Siskind, 1997 [UI# 9229212]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Primary epithelial ovarian cancer confirmed by histology	Multiple logistic regression with covariates: age, parity, age at 1st birth, education, oral contraceptive use, smoking history, menopausal status		

Breastfeeding duration (month)	Cases n (%)	Controls n (%)	Odds ratio$_{adj}$ (95% CI)
0	168 (27)	155 (21)	1.0
1-6	180 (29)	190 (26)	0.89 (0.65-1.2)
7-12	125 (20)	187 (26)	0.68 (0.49-0.94)
13-24	107 (17)	141 (19)	0.84 (0.59-1.2)
25-36	25 (4)	39 (5)	0.69 (0.38-1.3)
>36	13 (2)	12 (2)	0.77 (0.34-1.8)
Any	450 (73)	569 (79)	0.80 (0.61-1.04)
Per month			0.99 (0.98-1.0)

* Parous women only

A: strong, B: moderate, C: weak	A	B	C
Selection		X	
Study design		X	
Confounder		X	
Blinding			X
Data collection		X	
Withdraw and dropout		X	
Analyses	X		
Intervention integrity			

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Primary epithelial ovarian cancer confirmed by histology	Multiple logistic regression with covariates: age, parity, age at 1st birth, education, oral contraceptive use, smoking history, menopausal status	See table below	See table below

Breastfeeding duration (month)	Premenopausal		Postmenopausal	
	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)
	Odds ratio$_{adj}$ (95% CI)		Odds ratio$_{adj}$ (95% CI)	
0	75 (35)	66 (25)	93 (23)	89 (19)
	1.00		1.00	
1-6	69 (32)	78 (29)	111 (27)	112 (24)
	0.75 (0.46-1.21)		0.98 (0.65-1.47)	
7-12	34 (16)	72 (27)	91 (23)	115 (25)
	0.53 (0.31-0.94)		0.83 (0.54-1.26)	
13-24	33 (15)	36 (14)	74 (18)	105 (23)
	1.03 (0.54-1.95)		0.88 (0.56-1.38)	
>24	4 (4)	12 (5)	---	
	0.29 (0.08-1.04)			
25-36	---		21 (5)	27 (6)
			0.93 (0.46-1.88)	
>36	---		13 (3)	12 (3)
			1.27 (0.50-3.2)	

* Parous women only

A: strong, B: moderate, C: weak	A	B	C
Selection		X	
Study design		X	
Confounder		X	
Blinding			X
Data collection		X	
Withdraw and dropout		X	
Analyses	X		
Intervention integrity			

Titus-Ernstoff, 2001 [UI# 11237375]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (%): Cases Controls <30 29(5.2) 37(7.1) 30-39 78(14) 89(17) 40-49 159(28) 136(26) 50-59 126(22) 118(23) 60-69 118(21) 117(22) ≥70 53(9.4) 26(5.0) Menopause: mix Race: ND Enrolled/Evaluate: Cases: 563/378* Controls: 523/417* Location: USA Sites: Multi Funding: Government * Parous women only	Serous borderline 86 Serous invasive 229 Mucinous 83 Endometrioid/clear cell 130 * Parous women only	Case-control Data collection by interviewer with questionnaire in homes for all controls and case Controls selected by random digit dialing, >60 years by Town Books	Cancer registry and hospital board cases of epithelial ovarian cancer including lesions of borderline malignancy, 20-74 years, Controls: matched by age within 4 years and telephone sampling unit, >60 years were matched by age and precinct, exclusion included bilateral oophorectomy	Breastfeeding status determined by interview	Breastfeeding status determined by interview

Titus-Ernstoff 2001 [UI# 11237375]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>Epithelial ovarian cancer by pathology report or microscopy slides</td>
<td>Unconditional logistic regression adjusted for age, state, parity</td>
<td>
<table>
<tr><th>Breastfeeding duration (month)*</th><th>Cases n (%)</th><th>Controls n (%)</th><th>Odds ratio$_{adj}$ (95% CI)</th></tr>
<tr><td>0</td><td>239 (63)</td><td>223 (53)</td><td>1.0</td></tr>
<tr><td><3</td><td>43 (11)</td><td>48 (12)</td><td>0.9 (0.6-1.4)</td></tr>
<tr><td>3-6</td><td>54 (14)</td><td>76 (18)</td><td>0.7 0.5-1.1)</td></tr>
<tr><td>>6</td><td>42 (11)</td><td>70 (17)</td><td>0.7 (0.4-1.0)</td></tr>
<tr><td>Ever</td><td>139 (37)</td><td>194 (47)</td><td>0.7 (0.5-1.0)</td></tr>
<tr><td>P for trend</td><td></td><td></td><td>0.21</td></tr>
</table>
* Parous women only
<table>
<tr><th rowspan="2">Breastfeeding Status</th><th colspan="4">Odds Ratio$_{adj}$ (95% CI)</th></tr>
<tr><th>Serous borderline (n=86)</th><th>Serous invasive (n=229)</th><th>Mucinous (n=83)</th><th>Endometrioid /Clear cell (n=130)</th></tr>
<tr><td>Never breastfed</td><td>1.0</td><td>1.0</td><td>1.0</td><td>1.0</td></tr>
<tr><td>Ever breastfed</td><td>0.8 (0.4-1.6)</td><td>1.0 (0.6-1.4)</td><td>0.6 (0.3-1.2)</td><td>0.4 (0.2-0.7)</td></tr>
<tr><td>P for trend[1]</td><td>0.61</td><td>0.34</td><td>0.88</td><td>0.04</td></tr>
</table>
[1]Average duration (months) per breastfed child
</td>
<td>
<table>
<tr><th>A: strong, B: moderate, C: weak</th><th>A</th><th>B</th><th>C</th></tr>
<tr><td>Selection</td><td></td><td>X</td><td></td></tr>
<tr><td>Study design</td><td></td><td>X</td><td></td></tr>
<tr><td>Confounder</td><td></td><td>X</td><td></td></tr>
<tr><td>Blinding</td><td></td><td></td><td>X</td></tr>
<tr><td>Data collection</td><td></td><td>X</td><td></td></tr>
<tr><td>Withdraw and dropout</td><td></td><td>X</td><td></td></tr>
<tr><td>Analyses</td><td></td><td>X</td><td></td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td></td></tr>
</table>
</td>
</tr>
</table>

Tung, 2003 [UI# 14507598], Tung 2005 [UI# 15692075]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Cases: 50 Mucinous 55 Nonmucinous Controls: 56 Menopause: premenopausal 39% Race %: Cases Mucinous / Cases Nonmucinous / Controls Asian 51 / 34 / 42 White 30 / 50 / 44 Other 19 / 16 / 14 Enrolled/Evaluate: Cases: 558 Controls: 607 Location: USA Sites: Multi Funding: Government	Invasive n=431 Mucinous 11% Serous 51% Endometrioid 17% Clear cell 11% Other(undifferentiated, squamous, transitional) 10% Borderline n=127 Mucinous 48% Serous 52%	Case-control Data collection by interviewer with questionnaire including life calendar in homes for 95% of all interviewed	Cases: ≥18 years, epithelial ovarian cancer confirmed by histology, identified by population-based cancer registry, reside in Los Angeles, California or Hawaii for 1 year prior to diagnosis Controls: ≥18 years, reside in Los Angeles, California or Hawaii for 1 year prior to Interview, no prior history of ovarian cancer, ≥1 intact ovary, matched for age (±5 years), ethnicity, study site, randomly selected from neighborhood walk procedure in LA and Hawaii Department of Health state-wide annual survey list	Breastfeeding status determined by interview	Breastfeeding status determined by interview

Epithelial ovarian cancer confirmed by histology

Polytomous logistic model adjusted for age, ethnicity, study site, education, oral contraceptive use, tubal ligation

Unconditional logistic regression adjusted for age, ethnicity, study site, education, tubal ligation, HRT, ovulation variables

Breastfeeding	Odds ratio$_{adj}$ (95% CI)		
	All cases	Mucinous	Nonmucinous
Never	1	1	1
Ever	0.6 (0.4-0.7)	0.8 (0.5-1.4)	0.5 (0.4-0.7)
Breastfeeding duration (month)*			
0	1	1	1
≤5	0.6 (0.4-0.9)	0.6 (0.4-1.4)	0.7 (0.4-0.9)
6-16	0.6 (0.4-0.9)	0.7 (0.3-1.3)	0.5 (0.3-0.7)
>16	0.6 (0.4-0.8)	0.9 (0.8-1.8)	0.4 (0.3-0.7)
P for trend*	0.011	0.99	0.0005

*Based on likelihood ratio test comparing models with and without a trend variable that was assigned median values for the categories

Total breastfeeding duration (year)*	Odds ratio$_{adj}$ (95% CI)	
	Premenopausal	Postmenopausal
0	1	
<0.5	0.96 (0.49-1.85)	0.64 (0.41-1.02)
0.5-1.0	0.81 (0.43-1.54)	0.60 (0.36-1.00)
>1.0	0.46 (0.22-0.97)	0.69 (0.43-1.12)
P for trend	0.003	0.08

Odds ratio$_{adj}$ (95% CI	Breastfeeding		Breastfeeding duration (month)*			
Invasive cases	Never	Ever	≤5	6-16	>16	P for trend*
All cases	1	0.5 (0.4-0.7)	0.6 (0.4-0.9)	0.5 (0.4-0.8)	0.5 (0.3-0.7)	0.002
Mucinous		1.2 (0.6-2.7)	0.7 (0.3-1.8)	1.1 (0.5-2.6)	1.2 (0.5-3.0)	0.30
Serous		0.5 (0.3-0.7)	0.6 (0.4-0.9)	0.5 (0.3-0.8)	0.4 (0.2-0.7)	0.96
Endometrioid		0.5 (0.3-0.9)	0.6 (0.3-1.2)	0.6 (0.3-1.3)	0.3 (0.1-1.0)	0.10
Clear cell		0.5 (0.2-1.0)	0.6 (0.3-1.5)	0.5 (0.3-1.4)	0.3 (0.1-1.1)	0.40

A: strong, B: moderate, C: weak	A	B	C
Selection		X	
Study design		X	
Confounder		X	
Blinding			X
Data collection		X	
Withdraw and dropout		X	
Analyses	X		
Intervention integrity			

Controls were better educated had greater number of full-term pregnancies, use oral contraceptive more, higher frequency of tubal ligation

West, 1966 [UI# 5939299]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Cases: 53 Controls: 50 Menopause: mix Race: ND Enrolled/Evaluate: Cases: 97/76 Controls: 91/76 Location: USA Sites: Multi Funding: ND	Cases: Pseudo-mucinous cystadenocarcinoma 23 Serous cystadenocarcinoma 16 Cystadenocarcinoma and adenocarcinoma 43 Carcinoma 6 Granulosa cell 5 Teratoma 1 Dysgerminoma 1 Meso-meta-nephroma 1 Unclassified 1 Controls: (25 diagnoses) Endometriosis 19 Simple cyst 10 Pseudo-mucinous cystadenoma 9 Dermoid cyst 8	Case-control Data collection by interview	Cases: malignancy of ovary, 50 mile radius of Boston, exclusion includes >75 years and co-existent malignancy of another organ that was not metastatic from ovary and recurrent cases Controls: female hospital patients matched for age ± 5 years, residence and date of surgery, next operated case of benign ovarian neoplasms from same hospital as malignant case	Breast feeding status determined by interview	Breast feeding status determined by interview

West, 1966 [UI# 5939299]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations
Comments</th></tr>
<tr>
<td>Malignant ovarian cancer confirmed by pathology</td>
<td>T test with p level of 0.01 for significance</td>
<td>76 matched pairs
Lactation (months)
Cases Controls
6.6 5.8

p > 0.3</td>
<td>
<table>
<tr><td>A: strong, B: moderate, C: weak</td><td>A</td><td>B</td><td>C</td></tr>
<tr><td>Selection</td><td></td><td></td><td>X</td></tr>
<tr><td>Study design</td><td></td><td>X</td><td></td></tr>
<tr><td>Confounder</td><td></td><td></td><td>X</td></tr>
<tr><td>Blinding</td><td></td><td></td><td>X</td></tr>
<tr><td>Data collection</td><td></td><td>X</td><td></td></tr>
<tr><td>Withdraw and dropout</td><td></td><td>X</td><td></td></tr>
<tr><td>Analyses</td><td></td><td></td><td>X</td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td></td></tr>
</table>
Cases and controls classified as private and service with more control taken from service care implying differ SES. Only descriptive statistics given for education. Not adjusting for potential confounders
</td>
</tr>
</table>

Whittemore, 1992 [UI# 1476141]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Cases: ND Controls: ND Menopause: mix Race: White Enrolled/Evaluate: Cases: 2197/1071 Controls: 8893/5705 Location: USA Sites: 12 studies, of which 7 with breastfeeding data Funding: Government	ND	Case-control Data from 12 studies conducted from 1956-1986. 6 hospital and 6 population (random-digit dialing) controls. Breastfeeding data from 7 studies; 2 hospital- and 5 population-based studies	Studies with individual patient data collected from personal interviews through structured questionnaires, data coded and stored electronically, variable definitions documented Cases: newly diagnosed invasive epithelial tumors at US hospital Controls: reside in US, during time of case ascertainment, no gynecological condition if hospital controls	Breastfeeding status determined by interview	Breastfeeding status determined by interview

Whittemore, 1992 [UI# 1476141]

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Invasive epithelial tumors</td>
<td>Conditional logistic regression with odds ratio adjusted for age, study, parity, oral contraceptive use</td>
<td>
<table>
<tr><th>Breastfeeding duration (month)*</th><th>Cases n (%)</th><th>Controls n (%)</th><th>RR_{adj} (95% CI)</th></tr>
<tr><td colspan="4">Hospital studies</td></tr>
<tr><td>0</td><td>117 (58)</td><td>612 (57)</td><td>1.0</td></tr>
<tr><td>1-5</td><td>49 (24)</td><td>237 (22)</td><td>0.95 (0.62-1.5)</td></tr>
<tr><td>6-11</td><td>13 (6)</td><td>110 (10)</td><td>0.40† (0.20-0.78)</td></tr>
<tr><td>12-23</td><td>16 (8)</td><td>78 (7)</td><td>0.70 (0.36-1.4)</td></tr>
<tr><td>≥24</td><td>6 (3)</td><td>44 (4)</td><td>0.59 (0.22-1.6)</td></tr>
<tr><td>Any breastfeeding</td><td>84 (42)</td><td>469 (43)</td><td>0.73 (0.51-1.0)</td></tr>
<tr><td>Trend per month</td><td></td><td></td><td>0.99 p=0.18</td></tr>
<tr><td colspan="4">Population studies</td></tr>
<tr><td>0</td><td>478 (55)</td><td>2152 (47)</td><td>1.0</td></tr>
<tr><td>1-5</td><td>208 (24)</td><td>1188 (26)</td><td>0.87 (0.72-1.1)</td></tr>
<tr><td>6-11</td><td>88 (10)</td><td>567 (12)</td><td>0.74 (0.57-0.96)</td></tr>
<tr><td>12-23</td><td>61 (7)</td><td>449 (10)</td><td>0.69 (0.51-0.94)</td></tr>
<tr><td>≥24</td><td>35 (4)</td><td>268 (6)</td><td>0.74 (0.49-1.1)</td></tr>
<tr><td>Any breastfeeding</td><td>392 (45)</td><td>2472 (53)</td><td>0.81† (0.68-0.95)</td></tr>
<tr><td>Trend per month</td><td></td><td></td><td>0.99†</td></tr>
</table>
* Parous
† p<0.01
Risk reduction per month of breastfeeding within 6 months delivery exceeds that for subsequent breastfeeding
Hospital 2.5% vs 1.4% Population 1.2% vs 0.9%
</td>
<td>
<table>
<tr><th>A: strong, B: moderate, C: weak</th><th>A</th><th>B</th><th>C</th></tr>
<tr><td>Selection</td><td></td><td>X</td><td></td></tr>
<tr><td>Study design</td><td></td><td>X</td><td></td></tr>
<tr><td>Confounder</td><td></td><td></td><td>X</td></tr>
<tr><td>Blinding</td><td></td><td>X</td><td></td></tr>
<tr><td>Data collection</td><td></td><td></td><td>X</td></tr>
<tr><td>Withdraw and dropout</td><td></td><td>X</td><td></td></tr>
<tr><td>Analyses</td><td></td><td>X</td><td></td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td></td></tr>
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Hospital-based studies overlap with Hartge 1989
Population-based studies overlap with Cramer 1983

Wynder, 1969 [UI# 5764976]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Cases: 52 Controls: ND Menopause: mix Race: Cases: 91% White 9% Black Controls: 94% White 6% Black Enrolled/Evaluate: Cases: 158 Controls: 300 Location: USA Sites: Multi Funding: Government	Serous cystadenocarcinoma 28 Pseudo-mucinous cystadenocarcinoma 10 Endometrioid carcinoma 11 Solid adenocarcinoma 91 Miscellaneous Granulose cell tumor 4 Teratoma 1 Carcinoid 1 Others 2 Unspecified 10	Case-control Hospital-based population Data collection by interview	Epithelial ovarian cancer confirmed by histology, functionary or dysontogenetic tumors excluded Eight additional cases of diagnosis other than adenocarcinoma and endometrioid cancers Controls matched for age	Breastfeeding status determined by interview	Breastfeeding status determined by interview

Wynder, 1969 [UI# 5764976]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Epithelial ovarian cancer confirmed by histology	ND	No difference between groups for age of first nursing or never nursing	

	158 Cases		300 Controls	
	Premenopausal (55)	Postmenopausal (95)	Premenopausal (95)	Postmenopausal (205)
BF ≥12 months	10%	24%	7%	21%

A: strong, B: moderate, C: weak	A	B	C
Selection			X
Study design			X
Confounder			X
Blinding		X	
Data collection			X
Withdraw and dropout		X	
Analyses			x
Intervention integrity			

Yen, 2003 [UI# 12713998]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Median age (range): Cases: 47 (20-75) Controls: 44 (20-75) Menopause: mix Race: ND Enrolled/Evaluate: Cases: 86 Controls: 369 Location: Taiwan Sites: Multi Funding: Government	Cases: Serous (27%0 Mucinous (27%) Endometrioid (21%) Clear cell (15%) Unspecified adenocarcinoma (2%) Controls: Trauma (28%) Nontraumatic orthopedic conditions (30%) Surgery (19%) Miscellaneous (23%) medical, eye, nose, throat, dental	Case-control Data collection by in-hospital interview	Newly diagnosed primary invasive epithelial ovarian cancer confirmed by histology, Taiwan resident for > 20 years Controls: matched for age, same hospital admission at same time for nonmalignant, nongynecologic condition, nonhormonal or nondigestive tract diseases, no long term modification of diet Exclusion: major gynecologic operation including hysterectomy with or without oophorectomy or oophorectomy only, severe illness	Breast feeding status determined by interview	Breast feeding status determined by interview

Yen, 2003 [UI# 12713998]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Primary invasive epithelial ovarian cancer confirmed by histology	Conditional multivariate logistic regression model adjusted for number of live birth		

Breastfeeding duration (years)	Cases n (%)	Controls n (%)	OR_{adj} (95% CI)
0	41 (48)	176 (48)	1.0
≤1	8 (9)	42 (11)	0.82 (0.35-1.9)
>1	37 (43)	151 (41)	0.55 (0.29-1.01)

Breastfeeding for more than one year is trend for protection

A: strong, B: moderate, C: weak	A	B	C
Selection		X	
Study design		X	
Confounder		X	
Blinding			X
Data collection		X	
Withdraw and dropout		X	
Analyses		X	
Intervention integrity			

Appendix C. Evidence Tables

Part III. Maternal Outcomes

Postpartum Depression

Chaudron 2001
Cooper 1993
Hannah 1992
Henderson 2003
Murray 2003
Seimyr 2004
Warner 1996

Chaudron 2001, [UI# 1446151]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 29 yr (SD 4.4) Race: 69% white Enrolled/Evaluate: 465 Location: US Sites: Multi Funding:		Prospective cohort; the study examined predictors of new-onset postpartum depression during postpartum months 1-4; data from the Wisconsin Maternity Leave and Health Project (WMLHP); subjects participated in a 90-minute home interviews during the second trimester, and at 1 and 4 months after delivery; both the DIS and CES-D were administered at each interview; DIS questions about fatigue and sleep were modified to account for disturbances caused by night-time infant care	Between weeks 12 and 25 of a non-high-risk pregnancy; >18 yr; non-handicapped; living within Milwaukee or Dane counties; living with the baby's father; one of the couple was employed; had a telephone; spoke English well enough to understand interviewer; able to complete questionnaire; not depressed at 1 month postpartum; Excluded subjects who did not complete follow up at 4 months		

Chaudron 2001, [UI# 1446151]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Postpartum depression defined by: 1. Diagnosis of major depression on NIMH Diagnostic Interview Schedule (DIS) per DSM-III-R criteria 2. ≥16 on the Center for Epidemiologic Studies Depression Scale (CES-D); and /or 3. receiving antidepressants	Age, depression during pregnancy, postpartum thoughts of death and dying, difficulty falling asleep (see full discussion in paper)	327/465 breastfed; 27/465 became depressed between 1 and 4 months; Women who breastfed their infants were not significantly different in their development of depression from women who bottlefed their infants. Of those women who were breastfeeding at 1 month postpartum (n=327), women who worried about breastfeeding were significantly more likely to become depressed than those who did not worry (relative risk 3.0, CI 1.041-9.216, P=0.04)	

A: strong, B: moderate, C: weak	A	B	C
Selection		x	
Study design		x	
Confounder		x	
Blinding			x
Data collection		x	
Withdraw and dropout			
Analyses		x	
Intervention integrity			

Cooper, 1993 [UI# 8463993]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Enrolled/Evaluate: 243 women at Oxford; 113 at Cambridge Location: UK Sites: Multi Funding:		2 separate prospective cohort studies (Oxford and Cambridge)	See ref 12 in paper for criteria for Oxford; For Cambridge: primiparous, 20-40 yr, had a partner, 37-42 wk gestation, infant ≥ 2.5 Kg, and no gross congenital abnormality	Of those who attempted to initiate breastfeeding, those who terminated before 8 wk were compared with those who did not	

Cooper, 1993 [UI# 8463993]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
At Oxford, Present State Examination (PSE) was used to determine psychiatric symptoms. At Cambridge, prospective subjects were screened at 6 wk postpartum using the Edinburgh Postnatal Depression Scale (EPDS). All high scorers (≥13), 78% of the intermediate scorers (10-12), and a random sample of low scorers (≤ 9) received full psychiatric assessment between 2 and 3 months postpartum. 58 who met Research Diagnostic Criteria (RDC) criteria for major and minor depression, and 55 who were psychiatrically well were interviewed in full. At Cambridge, Standardized Psychiatric Interview (SPI) was used.	Social class, age, and education	At Oxford, 14/25 subjects (56%) with psychiatric symptoms versus 40/175 subjects (23%) without psychiatric symptoms had given up breastfeeding by 8 wk postpartum (P<0.01). In eight, depression preceded cessation of breastfeeding, in two depression was the subsequent event, and in four, the two events arose contemporaneously. Low social class and younger age were also determinants of early cessation of breastfeeding. Antenatal psychiatric status did not predict breastfeeding outcome. At Cambridge, 30/54 subjects (56%) with an episode of depression versus 10/48 subjects (21%) without depression postpartum had given up breastfeeding by 8 wk (P<0.001). Lower educational attainment was also associated with early cessation of breastfeeding. In all cases, the onset of depression preceded the cessation of breastfeeding.	A: strong, B: moderate, C: weak: A / B / C Selection: / x / Study design: / / x Confounder: / x / Blinding: / / x Data collection: / / x Withdraw and dropout: / / x Analyses: / x / Intervention integrity: / /

Hannah 1992, [UI# 1617360]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Evaluated: 231 Location: UK Sites: Multi Funding:	ND	Prospective cohort, questionnaires (general questionnaire and Edinburgh Postnatal Depression Scale (EPDS)) on 5th day postpartum and repeat EPDS at 6 weeks postpartum	Women who had delivered a live baby	ND	

Hannah 1992, [UI# 1617360]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Postpartum depression defined by EPDS score ≥ 13 at 6 weeks.	Chi-square	At 6 weeks, 8/26 (31%) women with EPDS score ≥ 13 vs 25/200 (12%) women with EPDS < 13 only did bottle feeding (P<0.04). [Or 18/26 (69%) women with EPDS score ≥ 13 vs 175/200 (88%) women with EPDS < 13 had ever breastfed.]	A: strong, B: moderate, C: weak / A / B / C Selection / / / x Study design / / / x Confounder / / / x Blinding / / / x Data collection / / / x Withdraw and dropout / / / x Analyses / / / x Intervention integrity / / /

Henderson 2003, [UI# 12911800]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Race: Enrolled/Evaluate: 1745 enrolled Location: Australia Sites: Multi Funding:		Prospective cohort, population from a RCT on the effectiveness of maternal debriefing on the incidence of postnatal psychological morbidity; self-reported questionnaires were completed at 2, 6, and 12 months after birth; the questionnaire included a measure of current breastfeeding status; The Edinburgh Postnatal Depression Scale (EPDS) was used to screen for symptoms of depression at each of the follow-up intervals. All subjects who scored > 12 on the scale, subjects being treated for a psychological disorder, subjects taking antidepressants, and a stratified sample of women with low EPDS scores were offered a diagnostic interview. The interview enabled a diagnosis of depression to be made based on DSM IV.	Before 72 hr postpartum, given birth to health infants >35 wk gestation, English speaking, >18 yrs, not under psychological care at the time of recruitment; cases were excluded if no information about breastfeeding status was given at any interval (n=56)	Primary endpoint was duration of breastfeeding	

Henderson 2003, [UI# 12911800]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Diagnosis of depression based on DSM IV (data obtained from diagnostic interview)	Adjusted for demographic, perinatal, and postnatal factors	Breastfeeding was initiated by 1670/1745 women (96%); 57% still breastfeeding at 6 months (30% fully); 22% still breastfeeding to some extent at 12 months. 314/1745 (18%) developed depression in the 12 months after birth, 63% showing the first symptom by 2 months. After adjustment for confounding factors, early cessation of breastfeeding was found to be associated with postnatal depression (adjusted hazard ratio 1.25, 95% CI 1.03 to 1.52). Onset of postnatal depression occurred before cessation of breastfeeding in most cases.	A: strong, B: moderate, C: weak Selection: B Study design: B Confounder: B Blinding: C Data collection: B Withdraw and dropout: B Analyses: B Intervention integrity

Murray, 2003 [UI# 12848402]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 25 yr in self-exclusion group; 28 yr in take-up group Menopause: pre/post/mix Race: 75 in self-exclusion group; 81 in take-up group Location: UK Sites: Single/Multi Funding:	History of depression was common, as were health problems, and depressed or anxious mood in pregnancy	Cohort study; 403 women from a RCT of a preventive intervention for postpartum depression were identified as being high risk for depression from antenatal screening; 2 groups were formed; one group from the control arm (routine care) of the RCT was willing to receive additional home-based Health Visiting in the last 5 weeks of pregnancy and the first 8 weeks postpartum; the other group refused the intervention	Vulnerable to postpartum depression per screening results		

Murray, 2003 [UI# 12848402]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Predictive Index for Postpartum Depression		Comparing the self-exclusion group (n=75) with the take-up group (n=81), the infants in the self-exclusion group were less likely to be breastfed, both immediately after birth (63% vs 83%, P=0.007) and at 10 days (31% vs 54%, P=0.01)	

A: strong, B: moderate, C: weak	A	B	C
Selection		x	
Study design			x
Confounder			x
Blinding			x
Data collection			x
Withdraw and dropout		x	
Analyses		x	
Intervention integrity			

Seimyr 2004, [UI# 15376402]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 29 yr (18-43) Race: Enrolled/Evaluate: 352 women Location: Sweden Sites: Multi Funding:		Prospective cohort, Edinburgh Postnatal Depression Scale (EPDS) result at 2 months before childbirth (I), 2 months (II)and 12 months (III) after childbirth	All Swedish speaking pregnant women at six antenatal clinics were invited to participate, with their partners or alone		

Seimyr 2004, [UI# 15376402]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Cut-off point of 9/10 on EPDS scale is used to set the threshold for vulnerability to depression	Did not report actual adjustment, but reported that there was no difference with regards to age, education, parity, and length of marital relationship between low and high-scoring women	63 women (21%) scored high on EPDS at the end of pregnancy; 54 (17%) at 2 months; 28 (12%) at 12 months. ~50% of the high EPDS (I) scorers also scored high on EPDS (II), and 39% of those who were high EPDS (II) scorers continued to score high on EPDS (III). Fewer high EPDS (I) scorers breastfed compared to the low scorers (82% vs 94%, P<0.02) Fewer high EPDS (II) scorers breastfed compared to the low scorers (85% vs 93%, P<0.08) High EPDS scorers experienced breastfeeding more negatively than the women scoring low on EPDS (I) (40% vs 20%, P<0.03) and on EPDS (II) (51% vs 16%, P<0.0001). High EPDS (II) scorers breastfed for a shorter time compared to the low-scoring women (4.6 months, SD 2.4 vs 5.3 months, SD 1.9, P<0.04)	A: strong, B: moderate, C: weak / A / B / C Selection / / x / Study design / / / x Confounder / / / x Blinding / / / x Data collection / / x / Withdraw and dropout / / x / Analyses / / x / Intervention integrity / / /

Warner, 1996 [UI# 8733800]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 28 yr (15-46 yr) Race: Eligible/Enrolled: 2978/2375 Location: UK Sites: Multi Funding:	Prospective cohort	Recruited subjects over a 20-month period from two postnatal wards prior to discharge, subjects agreed to a home visit 6-8 wk after delivery; Edinburgh Postnatal Depression Scale (EPDS) was completed at the interview	Living outside the district and insufficient English to understand the questionnaire		

Warner, 1996 [UI# 8733800]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
EPDS score > 12	13 socio-demographic and obstetric variables were entered individually into a logistic regression analysis with high and low EPDS as the outcome variable using a threshold of 12/13; those variables showing a significant association with high EPDS scores were entered into a stepwise logistic regression analysis	280/2375 scored >12 on EPDS; Unplanned pregnancy, not breastfeeding at 6 wk (OR 1.52, 95%CI 1.12-2.06), unemployment in mother or head of household were associated with an EPDS score >12 in a stepwise logistic analysis	A: strong, B: moderate, C: weak / A / B / C Selection / / x / Study design / / / x Confounder / x / / Blinding / / / x Data collection / / x / Withdraw and dropout / / x / Analyses / / / x Intervention integrity / / /

Appendix C. Evidence Tables

Part III. Maternal Outcomes

Maternal Weight

Brewer 1989
Janney 1997
Linne 2003
Ohlin 1990
Olson 2003
Sichieri 2003
Walker 2004

Brewer 1989 [2916446]

Study characteristics	Population	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Pre-pregnancy BW (range): ND Pre-pregnancy BMI (range): ND Race: white Enrolled/Evaluate: 70/56 Location: US Sites: Single Funding:	Well-educated, middle to upper middle income range	Prospective cohort; to study postpartum changes in body weight in lactating vs. nonlactating women up to 6 mo postpartum; mothers were visited in the hospital within 1 to 2 d of delivery and at home at 3 and 6 mo postpartum, weights were objectively measured; detailed information on infant diet was collected by monthly questionnaires completed by the mothers. Mother's calorie intake measured. Three-day maternal food records were also completed at 3 and 6 months postpartum. Energy intake (kcal) was calculated by computer from food records with the Nutritional Analysis System (Louisiana State University, Baton Rouge, LA).	Good health, ≥ 18 yr, mothers of full term infants		

Brewer 1989 [2916446]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Exclusive breastfeeding; exclusive formula feeding; mixed breast and formula feeding	ANCOVA; covariables included maternal age, parity, prepregnancy weight, initial postpartum measurement for each variable, and others	"If weight change during the first 3 mo is corrected for an initial fluid loss of 2 kg, weight loss averaged 1.6, 2.1, and 1.5 kg/mo for exclusive breastfeed, exclusive formula feed, and mixed feed, respectively. Exclusive breastfeed resulted in an additional 0.43 kg/mo loss over the second 3 mo with mixed feed averaging a 0.27 kg loss and nonlactating women experiencing essentially no change." No significant differences in total weight loss were observed between the lactating and non-lactating groups. Exclusive breastfeeding resulted in a significant decrease in weight between 3 and 6 months ($P < 0.05$).	A: strong, B: moderate, C: weak: A / B / C Selection: B Study design: B Confounder: B Blinding: C Data collection: B Withdraw and dropout: C Analyses: B Intervention integrity: Overall: B

Janney, 1997 [9356528]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 29.3 (20-40) Pre-pregnancy BW (range): 59.7 (43.1-93.0) kg Pre-pregnancy BMI (range): 22.2 (16.9-33.7) kg/m^2 Race: 96% White Enrolled/Evaluate: 110/71 Location: US Sites: Single Funding: ND		Prospective, longitudinal study (0.5, 2, 4, 6, 12, and 18 mo post-partum)	Pregnant nulliparous and primiparous women aged 20-40 y in their 3rd trimester were recruited from birthing education classes and obstetric practices. To be eligible for participation, the women must have declared either that they had no intention of breastfeeding or that they intended to breast-feed for >= 6 months. Exclusion criteria were a history of endocrine, renal, liver, or chronic respiratory illness; complications of pregnancy, including HTN and GDM; fetal complications or complications at delivery; delivery of an infant small for gestational age; and delivery of twins.	Fully breast-feeding was defined as providing at least 2/3 of the needed energy intake per kilogram of the infant's weight in breast milk. See article for how this estimation was made.	Partly breast-feeding or bottle-fed

Janney, 1997 [9356528]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Postpartum weight retention over time	Longitudinal regression analysis: proc mixed and glm procedures	Most women (66.7%) fully breastfed for 6 mo. Duration of lactation practice was a significant predictor of postpartum weight retention over time - (P<0.001) - not only in the longitudinal regression model containing only lactation practice and months since parturition but also in the multiple-variable longitudinal regression model. Regardless of lactation practice, women consistently lost weight from 0.5 to 18 mo after parturition. The weight-retention curve appeared to be curvilinear, with slower rates of weight loss occurring after 12 mo postpartum. Overall, less weight was retained by lactating women than by nonlactating women. Even women who breast-fed for < 4 mo retained less weight than women who bottle-fed their infants. Additionally, women who switched to partly breast-feeding had weight retention rates intermediate between those of women fully breast-feeding and those bottle-feeding. Once lactation was discontinued, slower rates of weight loss were observed. Breast-feeding women achieved their prepregnancy weights about 6 month earlier than women who only bottle-fed their infants (see Figure 5 in original paper).	

Janney, 1997 [9356528]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
		The following data were estimated from Figure 5 in the original paper: 1) Time returned to prepregnancy weights: Bottle-feeding only: ~18 months postpartum Partly breast-feeding at 2 mo, and bottle-feeding or infant weaned at 4, 6, 12, and 18 months: ~12 months postpartum Fully breast-feeding for 6 month and bottle-feeding or infant weaned at 12 and 18 month: ~11 months postpartum Fully breastfeeding for 6 month, partly breast-feeding for 12 month, and bottle-feeding or infant weaned at 18 month: ~ 10 months postpartum 2) Weight retention at 6 months postpartum: Fully breastfeeding for 6 months (n=57): ~ +3 kg Partly breastfeeding at 2 month and bottle-feeding at 4 and 6 months (n=10): ~ +3.5 kg Fully bottle-feeding for 6 months (n=12): ~ +5 kg	A: strong, B: moderate, C: weak / A / B / C Selection / / x / Study design / x / / Confounder / / / x Blinding / / / Data collection / x / / Withdraw and dropout / / / x Analyses / / x / Intervention integrity / / / Overall: B

Linne, 2003 [14634683]

Study characteristics	Population	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 45 yr (at 15 yr follow up) Pre-pregnancy BW (range): 59.8 kg Pre-pregnancy BMI (range): 21.5 kg/m^2 Race: Enrolled/Evaluate: 1423/563 (at 15 yr) Location: Stockholm Sites: Multi Funding:	Cross section of the metropolitan population from both inner city of Stockholm and its suburbs; a range of socioeconomic groups	Prospective cohort; longitudinal study of women's weight gain during pregnancy, at 1 yr postpartum and at 15 yr follow up; feeding data were collected retrospectively by questionnaires at 2.5, 6, 12 mo and at 15 yr; for women who still lived in the Stockholm area, weights were measured in the University hospital (n=363); for women who lived far away, weights were self-reported (n=200)	2 outliers were excluded: BMI of 47; first child at 49 yr	Measured by lactation score: every month of full lactation was given 4 points, every month of mixed lactation was given 2 points; total sum (0-48) indicated the individual lactation amount	

Linne, 2003 [14634683]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Overweight (BMI > 25), normal weight (BMI 20-25);	ANOVA was used to analyze weight change at four time points; women who were overweight at prepregnancy and at follow up and those who lost weight and regained a BMI in the normal range at 15 yr were excluded from the analysis	Those women who became overweight had lower lactation scores than women who remained normal weight at 15 years follow up (21.7 ± 11.0 vs. 24.0 ± 9.4, t=2.25, df = 488, $P < 0.05$). Responders were slightly older, had higher educational attainment, and higher income than non-responders. Nonresponse was more common in non-Nordic citizens.	A: strong, B: moderate, C: weak Selection: C Study design: B Confounder: C Blinding: C Data collection: B Withdraw and dropout: C Analyses: B Intervention integrity: Overall: C

Ohlin, 1990 [2341224]; Ohlin, 1996 [8732961]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 29.5 (17-49) Pre-pregnancy BW (range): 59.6 (39-129) kg Pre-pregnancy BMI (range): 21.5 (15.4-43.0) kg/m^2 Race: ND Enrolled/Evaluate: 2295 (at 2 mo) /1423 (at 1 yr) Location: Sweden Sites: Multi Funding: Government		Women were studied retrospectively during pregnancy at maternity clinics, and monitored prospectively up to 1 year after delivery.	All mothers who, during one year, came to the maternity clinic for the last routine control, i.e. 6-15 weeks after the delivery, were invited by their midwives to take part in the study. Women who were going to move within a short time and those with obvious language and communication problems were not invited. Exclusion: twin births, use of insulin during pregnancy, GI problems with severe energy losses (heavy vomiting or diarrhea) and pre-pregnant body weights were not available.	Lactation score: a scoring system was constructed in order to express duration and intensity of breast feeding. Every month with full lactation was given 4 points, and every month with mixed feeding was given 2 points. The total sum (0-48) indicated the individual lactation amount.	

Ohlin, 1990 [2341224]; Ohlin, 1996 [8732961]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
The body weight 1 year after delivery (Δ weight)	Ranged influence of different factors on the Δ weight was analyzed by a multiple stepwise regression analysis	30% lost weight, 56% gain 0-5 kg, 13% gained 5-10 kg and 1.5% gained >=10 kg 1 year after delivery. Frequency of overweight women (BMI>=23.9) increased from 13% before pregnancy to 21% 1 year post-partum (p<0.001) Ranged influence of different factors on the Δ weight: The coefficients between the Δ weight and lactation score, age, pre-pregnancy weight and parity were very low (multiple r=0.38, p<0.001) and significant correlations do not necessarily indicate causality. Weight gain during pregnancy had the strongest influence, and explained 12.7% of the variation of the Δ weight (p<0.001). Lactation and age increased the total proportion of explained variance by about 1% each. Simple correlation coefficient between the Δ weight and lactation score was –0.09 (p<0.01)	A: strong, B: moderate, C: weak — A / B / C Selection — / x / — Study design — / x / — Confounder — / x / — Blinding — / — / — Data collection — / — / x Withdraw and dropout — / — / x Analyses — / x / — Intervention integrity — / — / —

Olson, 2003 [12532163]

Study characteristics	Population	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): Pre-pregnancy BW (range): kg Pre-pregnancy BMI (range): kg/m^2 Race: white (96%) Enrolled/Sample/Evaluate: 622/597/540 Location: US Sites: Single Funding:	Rural, socio-economically diverse	Prospective cohort; to study the relative importance of gestational weight gain, postpartum exercise, food intake and breastfeeding to weight change from early pregnancy to 1 yr postpartum; weight was measured at antenatal and 1 yr postpartum visit (varied between 9 and 19 mo); 32/540 self-reported weight at 1 yr; breastfeeding data collected at 6 wk obstetric visit; 6 mo and 1 yr questionnaires. Food frequency questionnaires were completed at 1st or 2nd trimester of pregnancy, 6 months postpartum, and 1 yr postpartum.	≥ 18 yr; healthy, gave birth to full-term singletons	Breastfeeding after 6 mo was considered to be non-exclusive; a breastfeeding score similar to Ohlin and Rossner's was constructed: 1 point for each wk of exclusive breastfeeding and 0.5 point for each wk of mixed feeding	

Olson, 2003 [12532163]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Weight change from early pregnancy to 1 yr postpartum; major weight gain was defined as ≥ 4.55 kg at 1 yr postpartum	Univariate and multiple linear regression; weights taken between 9 and 19 mo were eligible for inclusion, actual number of mo postpartum at the measurement of the "1 yr postpartum body weight" was entered into all of the regression models; variables in the initial model included age, education, smoking status, income, marital status, prepregnancy BMI category and parity; 3 subjects with poor fit were removed from the analysis; a model reduction method was applied at the 10% significance level to produce an inclusive, reduced model Using food frequency data, the difference in the daily energy intake from 6 months to 1 yr postpartum was calculated for each woman. The Wilcoxon rank sum test was used to assess change in total daily energy intake across the five categories of self-reported behavior change in amount of food intake.	Only the 597 women who delivered full term infants were included in the sample; 540 had 1 yr weight recorded; Women who were breastfeeding at 1 yr retained less weight compared with the women who weren't (P = 0.04). Breastfeeding at all other time points and the breastfeeding score were not significantly related to postpartum weight retention.	A: strong, B: moderate, C: weak — A / B / C Selection — x Study design — x Confounder — x Blinding — C: x Data collection — x Withdraw and dropout — x Analyses — x Intervention integrity Overall: B

Sichieri, 2003 [12821967]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 24-40 yr Pre-pregnancy BW (range): Stratified by BMI at baseline Pre-pregnancy BMI (range): % BMI < 25kg/m^2 in 1989: 81.5% BW mean, ALL: 58.0 kgs % BMI > 25kg/m^2 in 1989: 18.5% BW mean, ALL: 80.4 kgs Race: ND Enrolled/Evaluate: 1,538/1,538 nulliparous at baseline; 2,810/2,810 primiparous at baseline Location: USA Sites: Single/Multi: mailed questionnaire Funding: Supported by FundaCBo CAPESCoordenaq20 de Aperfeicoamento de Pessoal de Nivel Superior and Boston Obesity Nutrition Research Center (DK 46200)	None documented	The cohort of the Nurse's Health Study II, with analysis restricted to women who were aged 24 to 40 y at baseline (1989), who had a history of no more than one past full-term pregnancy at baseline, gave birth to one child between 1990 and 1991, but had no other pregnancies during the follow-up. SUBJECTS: 1,538 of the 33,082 nulliparous women and 2,810 of the 20,261 primiparous, in 1989. The NHS II Cohort has been followed up every 2 yr to ascertain incident diseases and exposures including parity and body weight. Individual breastfeeding data were collected retrospectively in the 1997 follow-up. Women were asked to recall their lifetime breastfeeding history.	Excluded from analysis: those who reported use of insulin, hypoglycemic drugs, or thyroid disease at baseline or followup were excluded from analysis	For each birth, women were asked if they had breastfed for at least a month and if so they were asked to report the month in which they introduced the formula. Introduction of daily formula/milk was assumed to represent the end of exclusive breastfeeding period. Duration of exclusive breastfeeding was categorized into 0, 1-3, 4-7, 8-11, and 12 months or more. Exclusive breastfeeding: Women were asked to recall their lifetime breastfeeding history. They were asked to answer 2 questions: 1) "Did you breastfeed at least one month?" 2) "Which month did you introduce formula?" If the answer to the 1st questions was "no, not at all", the duration was considered to be zero. Data from these 2 questions were combined with parity data from 1991 and 1993 questionnaires.	

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations
Comments</th></tr>
<tr>
<td>To assess whether women who breastfed were different in terms of their weight changes than women who did not, weight change from prepregnancy (in 1989) to postpregnancy (in 1993) was estimated according to exclusive breastfeeding duration using linear regression models.</td>
<td>The longitudinal models were based on mixed effects analysis. These models permitted the authors to test differences in prepregnancy weight at baseline (group effect), weight gain with pregnancy (time-dependent effect of period I), and weight change after pregnancy (time-dependent effect of period II) by breastfeeding status. If breastfeeding groups differed at baseline but had the same change in weight during follow-up, a group effect but not a time-dependent effect would be seen.</td>
<td>After adjusting for age, physical activity, and BMI, lactation was associated with a weight gain from 1989 to 1993 of approximately 1 kg (statistically significant only for women nulliparous in 1989 with a BMI <25 kg/m2 (P=0.02) and for those women primiparous in 1989, with a BMI ≥25 kg/m2 (P=0.04)) comparing women who breastfed with women who did not. Duration of lactation was unrelated to the magnitude of weight change (P>0.40 for all comparisons).
Maternal weight change associated with breastfeeding is minimal among normal weight women, and for overweight women the weight gained in pregnancy Is not reduced by breastfeeding.</td>
<td>
<table>
<tr><td>A: strong, B: moderate, C: weak</td><td>A</td><td>B</td><td>C</td></tr>
<tr><td>Selection</td><td>x</td><td></td><td></td></tr>
<tr><td>Study design</td><td></td><td>x</td><td></td></tr>
<tr><td>Confounder</td><td>x</td><td></td><td></td></tr>
<tr><td>Blinding</td><td></td><td></td><td>x</td></tr>
<tr><td>Data collection</td><td></td><td>x</td><td></td></tr>
<tr><td>Withdraw and dropout</td><td></td><td>x</td><td></td></tr>
<tr><td>Analyses</td><td>x</td><td></td><td></td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td></td></tr>
</table>
Overall: B
</td>
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</table>

Walker, 2004 [15778139]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): ND (>18 yr) Pre-pregnancy BW (range): ND Pre-pregnancy BMI (range): ND Race: 26% African American, 44% Hispanic, 30% White Enrolled/Evaluate: ND/382 Location: US Sites: Single Funding: Government	healthy	Prospective, longitudinal cohort (post-delivery, and 6 wk, and 3, 6, and 12 months postpartum). Energy intakes were measured at above times by average of one 24-hour recall and two food records at each observation. Fat intakes measured by Food Habits Questionnaire (Kristal, 1990).	Healthy women, singleton pregnancies with prenatal care funded through Medicaid; had a parity not exceeding III; were conversant in English; and were age 18 or higher.	Full (exclusive) or partial breastfeeding, or bottle feeding, measured at post-delivery, 6 wk, and 3, 6, and 12 months postpartum	

Walker, 2004 [15778139]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Postpartum BMI	General linear mixed models, also known as hierarchical linear models, were used. Forward additive method (or forward selection) was used to select variables for inclusion in the model.	Infant feeding method was not associated with postpartum BMI (p=0.140) when ethnicity, time, pre-pregnant BMI and a bunch of other variables (such as parity, gestational weight gain, Cesarean section, etc) were included in the model.	A: strong, B: moderate, C: weak — A: ; B: x; C: Selection — A: ; B: x; C: Study design — A: ; B: x; C: Confounder — A: ; B: x; C: Blinding — A: ; B: ; C: Data collection — A: ; B: x; C: Withdraw and dropout — A: ; B: ; C: x Analyses — A: ; B: x; C: Intervention integrity — A: ; B: ; C: Overall: B

Appendix C. Evidence Tables

Part III. Maternal Outcomes

Type 2 DM

Stuebe 2005

Stuebe, 2005 [16304074]

Study characteristics	Subjects' health conditions	Study design and follow-up duration	Eligibility criteria	Breastfeeding Exposures or Interventions	Control Exposures or Interventions
Mean age (range): 52 at follow-up Menopause: mix Race: ND Enrolled/Evaluate: see results Location: US Sites: Multi Funding: Government	ND	Prospective, longitudinal study	The Nurses' Health Studies consist of 2 large cohorts enrolled in prospective, longitudinal studies of women's health The Nurses' Health Study (NHS) was initiated in1976 and enrolled 121,700 women from 11 states. Participants were between 30 and 55 years of age at baseline, and each woman completed a detailed baseline questionnaire regarding diseases and health related topics. The second cohort, the Nurses' Health Study II (NHS II), began in 1989, enrolling 116,671 women from 14 states. Participants were between 25 and 42 years of age and completed a similar baseline questionnaire as well as biennial follow-up questionnaires.	Women in the Nurses' Health Studies (NHS) reported parity at baseline in 1976. Lactation history was assessed once, in 1986, when women were asked to report total lifetime duration lactation. In NHS II, women reported the number of pregnancies lasting more than 5 months at baseline and on each biennial questionnaire. Lactation history was assessed 3 times. In 1993, 1997, and 2003. Information on parity was used to derive retrospectively each participant's total cumulative lactation at each 2-year interval. Total duration of lactation was calculated based on the number of months after birth that the participant reported stopping breastfeeding altogether. Using the 1997 and 2003 NHS II data, duration of exclusive lactation could be calculated based on the reported timing of introduction of formula or solid food.	

Stuebe, 2005 [16304074]

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Ascertainment of Type 2 Diabetes Mellitus A case of diabetes was confirmed if a woman reported 1 of the following: (1) 1 or more classic symptoms plus either a fasting glucose of ≥140 mg/dL or random plasma glucose ≥ 200 mg/dL ; (2) at least 2 instances of elevated plasma glucose concentration (fasting glucose ≥140 mg/dL, random plasma glucose ≥200 mg/dL, or oral glucose tolerance test ≥200 mg/dL after 2 hours) on different occasions in the absence of symptoms; or (3) treatment with insulin or an oral hypoglycemic agent. The criteria for diagnosis of diabetes changed in 1997, when a fasting glucose level of ≥126 mg/dL was made the diagnostic threshold. **Ascertainment of Gestational Diabetes** Women in the NHS II were asked to report the diagnosis of gestational diabetes on each biennial questionnaire. To validate the study's diagnostic criteria, 20,422 participants completed a detailed questionnaire, and 92% corroborated their diagnosis. A review of medical records for 120 of these women	Lifetime lactation history among parous women was stratified into 6 groups: None (referent), > 0 to 3 mo, > 3 to 6 mo, > 6 to 11 mo,> 11 to 23 mo, and > 23 mo. In the NHS, lactation information was used from the 1986 questionnaire. In the NHS II analysis, lactation history was derived from self-reported pregnancies assessed every 2 years and lactation reports in 1997 and 2003. Lifetime duration was updated every 2 years. Linear trend was assessed using midpoints of lactation categories. All models were age-adjusted. Potential confounders, including parity, body mass index at age 18 years, diet, physical activity, family history of diabetes, and smoking status, were included in the multivariate model.	In the NHS cohort, 83,585 parous women reported lifetime duration of lactation; of these, 64% had ever breastfed. In the NHS II cohort, 73,418 parous women reported duration of lactation, and 85% had ever breastfed. In the NHS, women who had ever breastfed had a covariate-adjusted HR for type 2 diabetes of 0.97 (95%CI 0.91 - 1.02) compared with women who never breastfed. There was a modest but statistically significant inverse association between duration of lactation and the risk of type 2 diabetes. In the multivariate-adjusted model including current BMI, each additional year of lactation was associated with an HR of 0.96 (95%CI 0.92 - 0.99) for type 2 diabetes. Among women who had ever breastfed in the NHS II, the covariate-adjusted HR for type 2 diabetes was 0.90 (95%CI 0.77 - 1.04). Each year of lactation was associated with a covariate-adjusted HR of 0.84 (95%CI 0.78 - 0.89). When BMI was added to this model, the HR was 0.88 (95%CI 0.82 - 0.94)	A: strong, B: moderate, C: weak / A / B / C Selection / x / / Study design / x / / Confounder / x / / Blinding / / x / Data collection / x / / Withdraw and dropout / x / / Analyses / x / / Intervention integrity / / / Overall: A

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
confirmed definite or probable gestational diabetes in 94%. To assess screening for gestational diabetes, a random sample of 100 study participants was surveyed, of whom 83% reported undergoing a 50-g, 1-hour glucose challenge test. Gestational diabetes history was not assessed in the NHS cohort.		for each additional year of lactation. Women with a history of GDM had an increased risk of type 2 diabetes in the NHS II cohort, with 624 cases per 100,000 person years compared with 118 cases per 100,000 person-years among those without such a history. Lactation had no effect on diabetes risk in the GDM group, with a covariate-adjusted HR of 0.96 (95% CI 0.84 - 1.09) per additional year of lactation. The effects of exclusive versus total breastfeeding could be compared in the NHS II cohort data. In models controlling for age and parity, each year of lifetime exclusive breastfeeding was associated with an HR for type 2 diabetes of 0.63 (95%CI 0.54 - 0.73), while each year of total breastfeeding was associated with an HR of 0.76 (95%CI 0.71 - 0.81).	

Appendix D. List of Excluded Studies

AbouSaleh MT, Ghubash R, Karim L, et al. Hormonal aspects of postpartum depression. Psychoneuroendocrinology 1998 Jul;23(5):465-75. **Developing country**

AbuSabha R, Greene G. Body weight, body composition, and energy intake changes in breastfeeding mothers. J Hum Lact 1998 Jun;14(2):119-24. **Non-comparative study**

Adair LS, Pollitt E, Mueller WH. Maternal anthropometric changes during pregnancy and lactation in a rural Taiwanese population. Hum Biol 1983 Dec;55(4):771-87. **Non-comparative study**

Affinito P, Tommaselli GA, di Carlo C, et al. Changes in bone mineral density and calcium metabolism in breastfeeding women: a one year follow-up study. J Clin Endocrinol Metab 1996 Jun;81(6):2314-8. **Less than 1 year follow-up**

Alder E, Bancroft J. The relationship between breast feeding persistence, sexuality and mood in postpartum women. Psychol Med 1988 May;18(2):389-96. **N<100**

Alder EM, Cox JL. Breast feeding and post-natal depression. J Psychosom Res 1983;27(2):139-44. **N<100**

Alm B, Wennergren G, Norvenius SG, et al. Breast feeding and the sudden infant death syndrome in Scandinavia. Arch Dis Child 2002 June; 86(6): 400-2. **Included in MA**

Andreev A, Arjas E. Acute middle ear infection in small children: a Bayesian analysis using multiple time scales. Lifetime Data Anal 1998;4(2):121-37. **Not relevant**

Aniansson G, Svensson H, Becker M, et al. Otitis media and feeding with breast milk of children with cleft palate. Scand J Plast Reconstr Surg Hand Surg 2002;36(1):9-15. **Otitis media in children with cleft palate**

Atalah E, Lagos I, Grez M, et al. [Effect of lactation on the weight and body composition of wet nurses]. [Spanish]. Archivos Latinoamericanos de Nutricion 1983 Sep;33(3):649-63. **Non-English language publication**

Auestad N, Scott DT, Janowsky JS, et al. Visual, cognitive, and language assessments at 39 months: a follow-up study of children fed formulas containing long-chain polyunsaturated fatty acids to 1 year of age. Pediatrics 2003 Sep;112(3 Pt 1):e177-e183. **Not relevant**

Barbosa L, Butte NF, Villalpando S, et al. Maternal energy balance and lactation performance of Mesoamerindians as a function of body mass index. Am J Clin Nutr 1997 Sep;66(3):575-83. **Not relevant**

Bastian LA, West NA, Corcoran C, et al. Number of children and the risk of obesity in older women. Prev Med 2005 Jan;40(1):99-104. **Case control study**

Batstra L, Neeleman J, Hadders-Algra M. Can breast feeding modify the adverse effects of smoking during pregnancy on the child's cognitive development? J Epidemiol Community Health 2003 Jun;57(6):403-4. **Not relevant**

Bauer DC, Browner WS, Cauley JA, et al. Factors associated with appendicular bone mass in older women. The Study of Osteoporotic Fractures Research Group.[see comment]. Ann Intern Med 1993 May 1;118(9):657-65. **Cross-sectional study**

Becher H, Schmidt S, ChangClaude J. Reproductive factors and familial predisposition for breast cancer by age 50 years. A case-control-family study for assessing main effects and possible gene-environment interaction.[see comment]. Int J Epidemiol 2003 Feb;32(1):38-48. **Included in MA**

Bjorkelund C, Lissner L, Andersson S, et al. Reproductive history in relation to relative weight and fat distribution. Int J Obes Relat Metab Disord 1996 Mar;20(3):213-9. **Cross-sectional study**

Boonyaratavej N, Suriyawongpaisal P, Takkinsatien A, et al. Physical activity and risk factors for hip fractures in Thai women. Osteoporos Int 2001;12(3):244-8. **Developing country**

Bouwstra H, Dijck-Brouwer DA, Boehm G, et al. Long-chain polyunsaturated fatty acids and neurological developmental outcome at 18 months in healthy term infants. Acta Paediatr 2005 Jan;94(1):26-32. **Not relevant**

Bouwstra H, DijckBrouwer DA, Wildeman JA, et al. Long-chain polyunsaturated fatty acids have a positive effect on the quality of general movements of healthy term infants. Am J Clin Nutr 2003 Aug;78(2):313-8. **Not relevant**

Bradshaw MK, Pfeiffer S. Feeding mode and anthropometric changes in primiparas. Hum Biol 1988 Apr;60(2):251-61. **Insufficient sample size**

Butte NF, Garza C, Stuff JE, et al. Effect of maternal diet and body composition on lactational performance. Am J Clin Nutr 1984 Feb;39(2):296-306. **Non-comparative study**

Butte NF, Hopkinson JM. Body composition changes during lactation are highly variable among women. [Review] [45 refs]. J Nutr 1998 Feb;128(2:Suppl):Suppl-385S. **Review**

Carranza-Lira S, Mera JP. Influence of number of pregnancies and total breast-feeding time on bone mineral density. Int J Fertil Womens Med 2002 Jul;47(4):169-71. **Developing country**

Chan GM, Ronald N, Slater P, et al. Decreased bone mineral status in lactating adolescent mothers. J Pediatr 1982 Nov;101(5):767-70. **Less than 1 year follow-up**

Chan SM, Nelson EA, Leung SS, et al. Bone mineral density and calcium metabolism of Hong Kong Chinese postpartum women--a 1-y longitudinal study. Eur J Clin Nutr 2005 Jul;59(7):868-76. **Less than 1 year follow-up**

Chang-Claude J, Eby N, Kiechle M, et al. Breastfeeding and breast cancer risk by age 50 among women in Germany. Cancer Causes Control 2000 Sep;11(8):687-95. **Pre 2001**

Coitinho DC, Sichieri R, quino Benicio MH. Obesity and weight change related to parity and breast-feeding among parous women in Brazil. Public Health Nutr 2001 Aug;4(4):865-70. **Developing country**

Cox JL, Chapman G, Murray D, et al. Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. J Affect Disord 1996 Jul 29;39(3):185-9. **Reference, not relevant**

Cox JL, Connor Y, Kendell RE. Prospective study of the psychiatric disorders of childbirth. Br J Psychiatry 1982 Feb;140:111-7. **N<100**

Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale.[see comment]. Br J Psychiatry 1987 Jun;150:782-6. **N<100**

Cox ML, Khan SA, Gau DW, et al. Determinants of forearm bone density in premenopausal women: a study in one general practice. Br J Gen Pract 1991 May;41(346):194-6. **No BF exposure**

Cramer DW, Welch WR, Scully RE, et al. Ovarian cancer and talc: a case-control study. Cancer 1982 Jul 15;50(2):372-6. **Not relevant**

Dalton K. Prospective study into puerperal depression. Br J Psychiatry 1971 Jun;118(547):689-92. **N<100**

Dennis KJ, Bytheway WR. Changes in body weight after delivery. J Obstet Gynaecol Br Commonw 1965;(72):94-102. **Breastfeeding exclusivity unclear**

Dequeker J, Tobing L, Rutten V, et al. Relative risk factors for osteoporotic fracture: a pilot study of the MEDOS questionnaire. Clin Rheumatol 1991 Mar;10(1):49-53. **No exposure; study 2: cross-sectional study**

Dewey KG, Cohen RJ, Brown KH, et al. Effects of exclusive breastfeeding for four versus six months on maternal nutritional status and infant motor development: results of two randomized trials in Honduras. J Nutr 2001 Feb;131(2):262-7. **Not relevant**

Duffy SW, Jakes RW, Ng FC, et al. Interaction of dense breast patterns with other breast cancer risk factors in a case-control study. Br J Cancer 2004 Jul 19;91(2):233-6. **Population not well-defined**

Dufour DL, Reina JC, Spurr GB. Energy intake and expenditure of free-living, lactating Colombian women in an urban setting. Eur J Clin Nutr 2002 Mar;56(3):205-13. **Developing country**

Dugdale AE, Eaton-Evans J. The effect of lactation and other factors on post-partum changes in body-weight and triceps skinfold thickness. Br J Nutr 1989 Mar;61(2):149-53. **Unclear exclusive breastfeeding**

Egan KM, Stampfer MJ, Rosner BA, et al. Risk factors for breast cancer in women with a breast cancer family history. Cancer Epidemiol Biomarkers Prev 1998 May;7(5):359-64. **Pre 2001**

Engel J, Anteunis L, Volovics A, et al. Risk factors of otitis media with effusion during infancy. Int J Pediatr Otorhinolaryngol 1999 May 25;48(3):239-49. **High risk patients included, with 9 ventilated patients**

Enger SM, Ross RK, Paganini-Hill A, et al. Breastfeeding experience and breast cancer risk among postmenopausal women. Cancer Epidemiol Biomarkers Prev 1998 May;7(5):365-9. **Pre 2001**

Erkkola M, Pigg HM, Virta-Autio P, et al. Infant feeding patterns in the Finnish type I diabetes prediction and prevention nutrition study cohort. Eur J Clinl Nutr 2005 Jan;59(1):107-13. **No outcomes of interest**

Findeisen M, Vennemann M, Brinkmann B, et al. German study on sudden infant death (GeSID): design, epidemiological and pathological profile. Int J of Legal Med 2004 Jun;118(3):163-9. **Duplicate data of Venneman 2005**

Fituch CC, Palkowetz KH, Goldman AS, et al. Concentrations of IL-10 in preterm human milk and in milk from mothers of infants with necrotizing enterocolitis. Acta Paediatr 2004 Nov;93(11):496-500. **Not relevant**

Florey CD, Leech AM, Blackhall A. Infant feeding and mental and motor development at 18 months of age in first born singletons.[see comment]. Int J Epidemiol 1995;24 Suppl 1:S21-S26. **Included in systematic review**

Fox KM, Magaziner J, Sherwin R, et al. Reproductive correlates of bone mass in elderly women. Study of Osteoporotic Fractures Research Group. J Bone Miner Res 1993 Aug;8(8):901-8. **Cross-sectional study**

Fregene A, Newman LA. Breast cancer in sub-Saharan Africa: how does it relate to breast cancer in African-American women? Cancer 2005 Apr 15;103(8):1540-50. **Developing country**

Furberg H, Newman B, Moorman P, et al. Lactation and breast cancer risk. Int J Epidemiol 1999 Jun;28(3):396-402. **Pre 2001**

Gale CR, Martyn CN. Breastfeeding, dummy use, and adult intelligence.[see comment]. Lancet 1996 Apr 20;347(9008):1072-5. **Included in systematic review**

Galler JR, Ramsey FC, Harrison RH, et al. Postpartum maternal moods and infant size predict performance on a national high school entrance examination. J Child Psychol Psychiatry 2004 Sep;45(6):1064-75. **No outcomes of interest**

Gao YT, Shu XO, Dai Q, et al. Association of menstrual and reproductive factors with breast cancer risk: results from the Shanghai Breast Cancer Study. Int J Cancer 2000 Jul 15;87(2):295-300. **Developing country**

Geervani P, Jayashree G. A study on nutritional status of adolescent and adult pregnant and lactating women and growth of their infants. J Trop Pediatr 1988 Oct;34(5):234-7. **Developing country**

Ghannam NN, Hammami MM, Bakheet SM, et al. Bone mineral density of the spine and femur in healthy Saudi females: relation to vitamin D status, pregnancy, and lactation. Calcif Tissue Int 1999 Jul;65(1):23-8. **Cross-sectional study, developing country**

Gilliland FD, Hunt WC, Baumgartner KB, et al. Reproductive risk factors for breast cancer in Hispanic and non-Hispanic white women: the New Mexico Women's Health Study. Am J Epidemiol 1998 Oct 1;148(7):683-92. **Pre 2001**

Greene GW, Smiciklas-Wright H, Scholl TO, et al. Postpartum weight change: how much of the weight gained in pregnancy will be lost after delivery? Obstet Gynecol 1988 May;71(5):701-7. **Not relevant**

Hadji P, Ziller V, Kalder M, et al. Influence of pregnancy and breast-feeding on quantitative ultrasonometry of bone in postmenopausal women. Climacteric 2002 Sep;5(3):277-85. **Cross-sectional study**

Harlow BL, Weiss NS, Roth GJ, et al. Case-control study of borderline ovarian tumors: reproductive history and exposure to exogenous female hormones. Cancer Res 1988 Oct 15;48(20):5849-52. **Borderline tumor**

Harrison GA, Boyce AJ, Platt CM, et al. Body composition changes during lactation in a New Guinea population. Ann Hum Biology 1975 Oct;2(4):395-8. **Cross-sectional study**

Hart S, Boylan LM, Carroll S, et al. Brief report: breast-fed one-week-olds demonstrate superior neurobehavioral organization. J Pediatr Psychology 2003 Dec;28(8):529-34. **Not relevant**

Hartge P, Hoover R, McGowan L, et al. Menopause and ovarian cancer. Am J Epidemiol 1988 May;127(5):990-8. **Duplicate study to Harge '89; no additional data**

Hawker GA, Forsmo S, Cadarette SM, et al. Correlates of forearm bone mineral density in young Norwegian women: the Nord-Trondelag Health Study. Am J Epidemiol 2002 Sep 1;156(5):418-27. **Cross-sectional study**

Hejar AR, Chong FB, Rosnan H, et al. Breast cancer and lifestyle risks among Chinese women in the Klang Valley in 2001. Med J Malaysia 2004 Jun;59(2):226-32. **Developing country**

Hildreth NG, Kelsey JL, Li Volsi VA, et al. An epidemiologic study of epithelial carcinoma of the ovary. Am J Epidemiol 1981 Sep;114(3):398-405. **No quantitative data**

Hilson JA, Rasmussen KM, Kjolhede CL. High prepregnant body mass index is associated with poor lactation outcomes among white, rural women independent of psychosocial and demographic correlates. J Hum Lact 2004 Feb;20(1):18-29. **No outcomes of interest**

Holt GM, Wolkind SN. Early abandonment of breast feeding: causes and effects. Child Care Health Dev 1983 Nov;9(6):349-55. **N<100**

Honda A, Kurabayashi T, Yahata T, et al. Lumbar bone mineral density changes during pregnancy and lactation. Int J Gynaecol Obstet 1998 Dec;63(3):253-8. **Cross-sectional study**

Horwood LJ, Fergusson DM. Breastfeeding and later cognitive and academic outcomes. Pediatrics 1998 Jan;101(1):E9. **Included in systematic review**

Hu JF, Zhao XH, Chen JS, et al. Bone density and lifestyle characteristics in premenopausal and postmenopausal Chinese women. Osteoporos Int 1994 Nov;4(6):288-97. **Cross-sectional study**

Hummel M, Fuchtenbusch M, Schenker M, et al. No major association of breast-feeding, vaccinations, and childhood viral diseases with early islet autoimmunity in the German BABYDIAB Study.[see comment]. Diabetes Care 2000 Jul;23(7):969-74. **No outcomes of interest**

Huo D, Lauderdale DS, Li L. Influence of reproductive factors on hip fracture risk in Chinese women. Osteoporos Int 2003 Aug;14(8):694-700. **Developing country**

Jacobson SW, Chiodo LM, Jacobson JL. Breastfeeding effects on intelligence quotient in 4- and 11-year-old children. Pediatrics 1999 May;103(5):e71. **Pre 2001**

Jacobson SW, Jacobson JL, Frye KF. Incidence and correlates of breast-feeding in socioeconomically disadvantaged women. Pediatrics 1991 Oct;88(4):728-36. **N<100**

Johnell O, Nilsson BE. Life-style and bone mineral mass in perimenopausal women. Calcif Tissue Int 1984 Jul;36(4):354-6. **Cross-sectional study**

Jones G, Scott FS. A cross-sectional study of smoking and bone mineral density in premenopausal parous women: effect of body mass index, breastfeeding, and sports participation. J Bone Miner Res 1999 Sep;14(9):1628-33. **No BF exposure, cross-sectional study**

Kac G, Benicio MH, Velasquez-Melendez G, et al. Breastfeeding and postpartum weight retention in a cohort of Brazilian women. Am J Clin Nutr 2004 Mar;79(3):487-93. **Developing country**

Kalkwarf HJ, Specker BL. Bone mineral loss during lactation and recovery after weaning. Obstet Gynecol 1995 Jul;86(1):26-32. **Less than 1 year follow-up**

Kamitsuka MD, Horton MK, Williams MA. The incidence of necrotizing enterocolitis after introducing standardized feeding schedules for infants between 1250 and 2500 grams and less than 35 weeks of gestation. Pediatrics 2000 Feb;105(2):379-84. **Not relevant**

Keeping JD, Najman JM, Morrison J, et al. A prospective longitudinal study of social, psychological and obstetric factors in pregnancy: response rates and demographic characteristics of the 8556 respondents. Br J Obstet Gynaecol 1989 Mar;96(3):289-97. **Not relevant**

Kendell RE, McGuire RJ, Connor Y, et al. Mood changes in the first three weeks after childbirth. J Affect Disord 1981 Dec;3(4):317-26. **N<100**

Khedr EM, Farghaly WM, Amry S, et al. Neural maturation of breastfed and formula-fed infants. Acta Paediatr 2004 Jun;93(6):734-8. **Not relevant**

Koetting CA, Wardlaw GM. Wrist, spine, and hip bone density in women with variable histories of lactation. Am J Clin Nutr 1988 Dec;48(6):1479-81. **Cross-sectional study**

Kramer FM, Stunkard AJ, Marshall KA, et al. Breast-feeding reduces maternal lower-body fat. J Am Diet Assoc 1993 Apr;93(4):429-33. **Insufficient sample size**

Laizner AM, Jeans ME. Identification of predictor variables of a postpartum emotional reaction. Health Care Women Int 1990;11(2):191-207. **Not relevant**

Lederman SA, Alfasi G, Deckelbaum RJ. Pregnancy-associated obesity in black women in New York City. Matern Child Health J 2002 Mar;6(1):37-42. **Not relevant**

Lee CY, Ko IS, Kim HS, et al. Development and validation study of the breast cancer risk appraisal for Korean women. Nurs Health Sci 2004 Sep;6(3):201-7. **No hormonal data given**

Lee EO, Ahn SH, You C, et al. Determining the main risk factors and high-risk groups of breast cancer using a predictive model for breast cancer risk assessment in South Korea. Cancer Nurs 2004 Sep;27(5):400-6. **Not relevant**

Li R, Jewell S, Grummer-Strawn L. Maternal obesity and breast-feeding practices. Am J Clin Nutr 2003 Apr;77(4):931-6. **Not relevant**

Lim S, Joung H, Shin CS, et al. Body composition changes with age have gender-specific impacts on bone mineral density. Bone 2004 Sep;35(3):792-8. **No BF exposure, cross-sectional study**

Lovelady CA, Garner KE, Moreno KL, et al. The effect of weight loss in overweight, lactating women on the growth of their infants.[see comment]. N Engl J Med 2000 Feb 17;342(7):449-53. **Not relevant**

Lumachi F, Ermani M, Brandes AA, et al. Breast cancer risk in healthy and symptomatic women: results of a multivariate analysis. A case-control study. Biomed Pharmacother 2002 Oct;56(8):416-20. **Population not well-defined**

Malloy MH, Berendes H. Does breast-feeding influence intelligence quotients at 9 and 10 years of age? Early Hum Dev 1998 Jan 9;50(2):209-17. **Included in systematic review**

Marcus PM, Baird DD, Millikan RC, et al. Adolescent reproductive events and subsequent breast cancer risk. Am J Public Health 1999 Aug;89(8):1244-7. **Pre 2001**

Marini A, Vegni C, Gangi S, et al. Influence of different types of post-discharge feeding on somatic growth, cognitive development and their correlation in very low birthweight preterm infants. Acta Paediatr Suppl 2003 Sep;91(441):18-33. **Not relevant**

Matsumoto I, Kosha S, Noguchi S, et al. Changes of bone mineral density in pregnant and postpartum women. J Obstet Gynaecol 1995 Oct;21(5):419-25. **Less than 1 year follow-up**

McCredie M, Paul C, Skegg DC, et al. Reproductive factors and breast cancer in New Zealand. Int J Cancer 1998 Apr 13;76(2):182-8. **Pre 2001**

McCredie M, Paul C, Skegg DC, et al. Breast cancer in Maori and non-Maori women. Int J Epidemiol 1999 Apr;28(2):189-95. **Pre 2001**

McKeown T, Aaby P. The influence of reproduction on body weight in women. J Endocrinol 1957;15:393-409. **Cross-sectional study**

McLennan JD, Kotelchuck M, Cho H. Prevalence, persistence, and correlates of depressive symptoms in a national sample of mothers of toddlers. J Am Acad Child Adolesc Psychiatry 2001 Nov;40(11):1316-23. **Not relevant**

Meeske K, Press M, Patel A, et al. Impact of reproductive factors and lactation on breast carcinoma in situ risk. Int J Cancer 2004 May 20;110(1):102-9. **No hormonal data given**

Melton LJ, III, Bryant SC, Wahner HW, et al. Influence of breastfeeding and other reproductive factors on bone mass later in life. Osteoporos Int 1993 Mar;3(2):76-83. **Cross-sectional study**

Mezzacappa ES, Katlin ES. Breast-feeding is associated with reduced perceived stress and negative mood in mothers. Health Psychol 2002 Mar;21(2):187-93. **N<100**

Mihatsch WA, von Schoenaich P, Fahnenstich H, et al. Randomized, multicenter trial of two different formulas for very early enteral feeding advancement in extremely-low-birth-weight infants.[erratum appears in J Pediatr Gastroenterol Nutr 2002 Nov;35(5):739]. J Pediatr Gastroenterol Nutr 2001 Aug;33(2):155-9. **Not relevant**

Milner JD, Stein DM, McCarter R, et al. Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma. Pediatrics 2004 Jul;114(1):27-32. **Not relevant, 25% premature infants**

Minami Y, Ohuchi N, Taeda Y, et al. Risk factors for benign breast disease according to histopathological type: comparisons with risk factors for breast cancer. Jpn J Cancer Res 1998 Feb;89(2):116-23. **Pre 2001**

Minami Y, Tsubono Y, Nishino Y, et al. The increase of female breast cancer incidence in Japan: emergence of birth cohort effect. Int J Cancer 2004 Mar 1;108(6):901-6. **Review**

Misri S, Sinclair DA, Kuan AJ. Breast-feeding and postpartum depression: is there a relationship? Can J Psychiatry 1997 Dec;42(10):1061-5. **N<100**

Modugno F, Ness RB, Allen GO, et al. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. Am J Obstet Gynecol 2004 Sep;191(3):733-40. **No breastfeeding data**

Monobe H, Ishibashi T, Fujishiro Y, et al. Factors associated with poor outcome in children with acute otitis media. Acta Otolaryngol (Stockh) 2003 Jun;123(5):564-8. **Not relevant**

Montella M, De Marco MR, Romeo F, et al. Survival in ovarian cancers treated at National Cancer Institute in Naples Italy 1985-1990. Eur J Gynaecol Oncol 1993;14(3):249-54. **No BF exposure**

More C, Bettembuk P, Bhattoa HP, et al. The effects of pregnancy and lactation on bone mineral density.[see comment]. Osteoporos Int 2001;12(9):732-7. **Less than 1 year follow-up**

Morley R. Breast feeding and cognitive outcome in children born prematurely. Adv Exp Med Biol 2002;503:77-82. **Review**

Morley R, Fewtrell MS, Abbott RA, et al. Neurodevelopment in children born small for

gestational age: a randomized trial of nutrient-enriched versus standard formula and comparison with a reference breastfed group. Pediatrics 2004 Mar;113(3 Pt 1):515-21. **Not relevant**

Morrison J, Najman JM, Williams GM, et al. Socio-economic status and pregnancy outcome. An Australian study. Br J Obstet Gynaecol 1989 Mar;96(3):298-307. **Not relevant**

Motil KJ, Sheng H, Kertz BL, et al. Lean body mass of well-nourished women is preserved during lactation. Am J Clin Nutr 1998 Feb;67(2):292-300. **Exclusive and mixed feeding data combined**

Murphy S, Khaw KT, May H, et al. Parity and bone mineral density in middle-aged women. Osteoporos Int 1994 May;4(3):162-16. **Cross-sectional study**

Murray L, Woolgar M, Murray J, et al. Self-exclusion from health care in women at high risk for postpartum depression. J Public Health Med 2003 Jun;25(2):131-7. **Not relevant**

Naismith DJ, Ritchie CD. The effect of breast-feeding and artificial feeding on body-weights, skinfold measurements and food intakes of forty-two primiparous women. Proc Nutr Soc 1975 Dec;34(3):116A-117A, 1975 Dec. **Abstract**

Najman JM, Morrison J, Williams GM, et al. The employment of mothers and the outcomes of their pregnancies: an Australian study. Public Health 1989 Maya;103(3):189-98. **Not relevant to any outcomes**

Najman JM, Morrison J, Williams GM, et al. Unemployment and reproductive outcome. An Australian study. Br J Obstet Gynaecol 1989 Marb;96(3):308-13. **Not relevant to any outcomes**

Nasca PC, Greenwald P, Chorost S, et al. An epidemiologic case-control study of ovarian cancer and reproductive factors. Am J Epidemiol 1984 May;119(5):705-13. **No BF exposure**

Newcomb PA, Egan KM, TitusErnstoff L, et al. Lactation in relation to postmenopausal breast cancer. Am J Epidemiol 1999 Jul 15;150(2):174-82. **Pre 2001**

Niemela M, Uhari M, Mottonen M. A pacifier increases the risk of recurrent acute otitis media in children in day care centers. Pediatrics 1995 Nov;95(5 Pt 1):884-8. **Not relevant**

O'Neill T, Murphy P, Greene VT. Postnatal depression--aetiological factors. Irish Med J 1990 Mar;83(1):17-8. **N<100**

Oddy WH. Breastfeeding and asthma in children. A prospective cohort study. Adv Exp Med Bio 2000;478:393-4. **Duplicate with Oddy 1999, included in meta-analysis**

Oddy WH, de Klerk NH, Sly PD, et al. The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. Eur Respir J 2002 May;19(5):899-905. **Duplicate with Oddy 1999, included in meta-analysis**

Oddy WH, Peat JK, de Klerk NH. Maternal asthma, infant feeding, and the risk of asthma in childhood. J Allergy Clin Immunol 2002 Jul;110(1):65-7. **Duplicate with Oddy 1999, included in meta-analysis**

Oddy WH, Sherriff JL, de Klerk NH, et al. The relation of breastfeeding and body mass index to asthma and atopy in children: a prospective cohort study to age 6 years. Am J Public Health 2004 Sep;94(9):1531-7. **Duplicate with Oddy 1999, included in meta-analysis**

Olsen LC, Mundt MH. Postpartum weight loss in a nurse-midwifery practice. J Nurse Midwifery 1986 Jul;31(4):177-81. **Breastfeeding exclusivity unclear**

Orwoll ES, Bauer DC, Vogt TM, et al. Axial bone mass in older women. Study of Osteoporotic Fractures Research Group. Ann Intern Med 1996 Jan 15;124(2):187-96. **Cross-sectional study**

Otto SJ, de Groot RH, Hornstra G. Increased risk of postpartum depressive symptoms is associated with slower normalization after pregnancy of the functional docosahexaenoic acid status. Prostaglandins Leukotr Essent Fatty Acids 2003 Oct;69(4):237-43. **Not relevant**

Paine BJ, Makrides M, Gibson RA. Duration of breast-feeding and Bayley's Mental Developmental Index at 1 year of age. J Paediatr Child Health 1999 Feb;35(1):82-5. **Pre 2001**

Parker JD. Postpartum weight change. [Review] [21 refs]. Clin Obstet Gynecol 1994 Sep;37(3):528-37. **Review**

Paton LM, Alexander JL, Nowson CA, et al. Pregnancy and lactation have no long-term deleterious effect on measures of bone mineral in healthy women: a twin study. Am J Clin Nutr 2003 Mar;77(3):707-14. **Not all had 2 year follow-up**

Pearson D, Kaur M, San P, et al. Recovery of pregnancy mediated bone loss during lactation. Bone 2004 Mar;34(3):570-8. **Less than 1 year follow-up**

Peters RK, Kjos SL, Xiang A, et al. Long-term diabetogenic effect of single pregnancy in women with previous gestational diabetes mellitus.[see

comment]. Lancet 1996 Jan 27;347(8996):227-30. **No breastfeeding exposure**

Pettitt DJ, Knowler WC. Long-term effects of the intrauterine environment, birth weight, and breast-feeding in Pima Indians. Diabetes Care 1998 Aug;21(Suppl 2):B138-B141. **Included in systematic review**

Piers LS, Diggavi SN, Thangam S, et al. Changes in energy expenditure, anthropometry, and energy intake during the course of pregnancy and lactation in well-nourished Indian women. Am J Clin Nutr 1995 Mar;61(3):501-13. **Developing country**

Pitt B. "Atypical" depression following childbirth. Br J Psychiatry 1968 Nov;114(516):1325-35. **N<100**

Plagemann A, Harder T, Franke K, et al. Long-term impact of neonatal breast-feeding on body weight and glucose tolerance in children of diabetic mothers. Diabetes Care 2002 Jan;25(1):16-22. **Included in systematic review**

Plagemann A, Harder T, Kohlhoff R, et al. Impact of early neonatal breast-feeding on psychomotor and neuropsychological development in children of diabetic mothers. Diabetes Care 2005 Mar;28(3):573-8. **Not relevant**

Potter S, Hannum S, McFarlin B, et al. Does infant feeding method influence maternal postpartum weight loss? J Am Diet Assoc 1991 Apr;91(4):441-6. **Retrospective study**

Prentice AM, Whitehead RG, Roberts SB, et al. Long-term energy balance in child-bearing Gambian women. Am J Clin Nutr 1981 Dec;34(12):2790-9. **Developing country**

Purdie D, Green A, Bain C, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. Int J Cancer 1995 Sep 15;62(6):678-84. **Duplicate study to Siskind 1997, no additional data**

Purwanto H, Sadjimin T, Dwiprahasto I. Lactation and the risk of breast cancer. Gan to Kagaku Ryoho [Jpn J Cancer Chemotherapy] 2000 May;27(Suppl 2):474-81. **Pre 2001**

Rami B, Schneider U, Imhof A, et al. Risk factors for type I diabetes mellitus in children in Austria. Eur J Pediatr 1999 May;158(5):362-6. **Duplicate data – included in EURODIAB**

Richards M, Wadsworth M, Rahimi-Foroushani A, et al. Infant nutrition and cognitive development in the first offspring of a national UK birth cohort. Dev Med Child Neurol 1998 Mar;40(3):163-7. **Included in systematic review**

Rojahn A, Lindgren CG. Enteral feeding in infants <1250 g starting within 24 h post-partum. Eur J of Pediatr 2001 Oct;160(10):629-32. **Not relevant**

Rookus MA, Rokebrand P, Burema J, et al. The effect of pregnancy on the body mass index 9 months postpartum in 49 women. Int J Obes 1987;11(6):609-18. **Breastfeeding exclusivity unclear**

Rooney BL, Schauberger CW. Excess pregnancy weight gain and long-term obesity: one decade later. Obstet Gynecol 2002 Aug;100(2):245-52. **Breastfeeding exclusivity unclear**

Rosenblatt KA, Thomas DB. Lactation and the risk of epithelial ovarian cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Epidemiol 1993 Apr;22(2):192-7. **Included developing countries**

Rossner S. Weight gain in pregnancy. [Review] [17 refs]. Human Reproduct 1997 Oct;12:Suppl-5. **Review, duplicate with Ohlin study**

Rush D, Lumey LH, Ravelli AC, et al. The indirect association of lactation with subsequent perimenopausal body weight. Eur J of Clin Nutr 1996 Jan;50(1):12-6. **Cross-sectional study**

Sadurskis A, Kabir N, Wager J, et al. Energy metabolism, body composition, and milk production in healthy Swedish women during lactation. Am J Clin Nutr 1988 Jul;48(1):44-9. **Non-comparative study**

Samuelsson U, Ludvigsson J. Seasonal variation of birth month and breastfeeding in children with diabetes mellitus. J Pediatr Endocrinol 2001 Jan;14(1):43-6. **Same subjects as Samuelsson, 1993 in the MA but include results from new analyses**

Schauberger CW, Rooney BL, Brimer LM. Factors that influence weight loss in the puerperium. Obstet Gynecol 1992 Mar;79(3):424-9. **No data**

Schneider AP. Risk factor for ovarian cancer. N Engl J Med 1987 Aug 20;317(8):508-9. **Abstract**

Schwartz SM, Weiss NS, Daling JR, et al. Incidence of histologic types of uterine sarcoma in relation to menstrual and reproductive history. Int J Cancer 1991 Sep 30;49(3):362-7. **No outcomes of interest**

Sheikh GN. Observations of maternal weight behavior during the puerperium. Am J Obstet Gynecol 1971 Sep 15;111(2):244-50. **Unclear exclusive breastfeeding**

Singh Y, Sayami P, Sayami G, et al. Nepalese breast cancer in relation to reproductive factors: comparison between Nepalese and Japanese cases. Anticancer Res 2002 Jan;22(1A):319-23. **Developing country**

Sinigaglia L, Varenna M, Binelli L, et al. Effect of lactation on postmenopausal bone mineral density of the lumbar spine. J Reprod Med 1996 Jun;41(6):439-43. **Cross-sectional study**

Soltesz G, Jeges S, Dahlquist G. Non-genetic risk determinants for type 1 (insulin-dependent) diabetes mellitus in childhood. Hungarian Childhood Diabetes Epidemiology Study Group. Acta Paediatr 1994 Jul;83(7):730-5. **Developing country**

Sowers M, Corton G, Shapiro B, et al. Changes in bone density with lactation.[see comment]. JAMA 1993 Jun 23;269(24):3130-5. **Less than 1 year follow-up**

Sowers M, Wallace RB, Lemke JH. Correlates of forearm bone mass among women during maximal bone mineralization. Prev Med 1985 Sep;14(5):585-96. **Cross-sectional study**

Sowers M, Zhang D, Janney CA. Interpregnancy weight retention patterning in women who breastfed. J Matern Fetal Med 1998 Mar;7(2):89-94. **No data**

Stene LC, Joner G, Norwegian Childhood Diabetes Study Group. Atopic disorders and risk of childhood-onset type 1 diabetes in individuals. Clin Exp Allergy 2004 Feb;34(2):201-6. **No BF exposure**

Steyn NP, Mann J, Bennett PH, et al. Diet, nutrition and the prevention of type 2 diabetes. [Review] [248 refs]. Public Health Nutr 2004 Feb;7(1A):147-65. **Review**

Susman VL, Katz JL. Weaning and depression: another postpartum complication. Am J Psychiatry 1988 Apr;145(4):498-501. **Case report**

Tamminen T. The impact of mother's depression on her nursing experiences and attitudes during breastfeeding. Acta Paediatr Scand Suppl No 344 1988;77:87-94. **N<100**

Tappin D, Ecob R, Brooke H. Bedsharing, roomsharing, and sudden infant death syndrome in Scotland: a case-control study.[see comment]. J Pediatr 2005 Jul;147(1):32-7. **No BF data**

Tarkka MT, Paunonen M, Laippala P. Factors related to successful breast feeding by first-time mothers when the child is 3 months old. J Adv Nurs 1999 Jan;29(1):113-8. **Not relevant**

Thomson AM, Billewicz WZ, Thompson B, et al. Body weight changes during pregnancy and lactation in rural African (Gambian) women. J Obstet Gynaecol Br Commonw 1966 Oct;73(5):724-33. **Developing country**

Titus-Ernstoff L, Egan KM, Newcomb PA, et al. Exposure to breast milk in infancy and adult breast cancer risk. J Natl Cancer Inst 1998 Jun 17;90(12):921-4. **Breast fed infant related cancer**

Tryggvadottir L, Olafsdottir EJ, Gudlaugsdottir S, et al. BRCA2 mutation carriers, reproductive factors and breast cancer risk. Breast Cancer Res 2003;5(5):R121-R128. **Included in MA**

Tryggvadottir L, Tulinius H, Eyfjord JE, et al. Breast cancer risk factors and age at diagnosis: an Icelandic cohort study. Int J Cancer 2002 Apr 1;98(4):604-8. **Pre 2001**

Tuppurainen M, Kroger H, Honkanen R, et al. Risks of perimenopausal fractures--a prospective population-based study. Acta Obstet Gynecol Scand 1995 Sep;74(8):624-8. **No BF exposure**

Tuppurainen M, Kroger H, Saarikoski S, et al. The effect of gynecological risk factors on lumbar and femoral bone mineral density in peri- and postmenopausal women. Maturitas 1995 Feb;21(2):137-45. **Cross-sectional study**

Unay B, Sarici SU, Ulas UH, et al. Nutritional effects on auditory brainstem maturation in healthy term infants. Arch Dis in Child Fetal Neonatal Ed 2004 Mar;Edition 89(2):F177-F179. **Not relevant**

Ursin G, Bernstein L, Lord SJ, et al. Reproductive factors and subtypes of breast cancer defined by hormone receptor and histology. Br J Cancer 2005 Aug 8;93(3):364-71. **No hormonal data given**

Ursin G, Bernstein L, Wang Y, et al. Reproductive factors and risk of breast carcinoma in a study of white and African-American women. Cancer 2004 Jul 15;101(2):353-62. **No hormonal data given**

van Hemert AM, Vandenbroucke JP, Birkenhager JC, et al. Prediction of osteoporotic fractures in the general population by a fracture risk score. A 9-year follow-up among middle-aged women. Am J Epidemiol 1990 Jul;132(1):123-35. **No outcomes of interest**

Van Raaij JM, Schonk CM, Vermaat-Miedema SH, et al. Energy cost of lactation, and energy balances of well-nourished Dutch lactating women: reappraisal of the extra energy requirements of lactation. Am J Clin Nutr 1991 Mar;53(3):612-9. **Non-comparative study**

Vennemann MM, Bajanowski T, Butterfass-Bahloul T, et al. Do risk factors differ between explained sudden unexpected death in infancy (SUDI) and SIDS? Arch Dis Child Epub ahead of print doi:10 1136/adc 2006 101337 2006 Aug 25. **Duplicate of Vennemann 2005**

Verge CF, Howard NJ, Irwig L, et al. Environmental factors in childhood IDDM. A population-based, case-control study. Diabetes Care 1994 Dec;17(12):1381-9. **Included in MA**

Virtanen SM, Rasanen L, Ylonen K, et al. Early introduction of dairy products associated with increased risk of IDDM in Finnish children. The Childhood in Diabetes in Finland Study Group. Diabetes 1993 Dec;42(12):1786-90. **Studies in the MA**

Walker LO, FreelandGraves J. Lifestyle factors related to postpartum weight gain and body image in bottle- and breastfeeding women. J Obstet Gynecol Neonatal Nurs 1998 Mar;27(2):151-60. **Cross-sectional study**

Webster J, Moore K, McMullan A. Breastfeeding outcomes for women with insulin dependent diabetes. J Hum Lact 1995 Sep;11(3):195-200. **Not relevant**

Weiss NS, Lyon JL, Liff JM, et al. Incidence of ovarian cancer in relation to the use of oral contraceptives. Int J Cancer 1981 Dec;28(6):669-71. **No BF exposure**

Whiteman MK, Hillis SD, Curtis KM, et al. Reproductive history and mortality after breast cancer diagnosis. Obstet Gynecol 2004 Jul;104(1):146-54. **No outcomes of interest**

Winkvist A, Rasmussen KM. Impact of lactation on maternal body weight and body composition. [Review] [71 refs]. J Mammary Gland Biol Neoplasm 1999 Jul;4(3):309-18. **Review**

Wosje KS, Kalkwarf HJ. Lactation, weaning, and calcium supplementation: effects on body composition in postpartum women. Am J Clin Nutr 2004 Aug;80(2):423-9. **Breastfeeding exclusivity unclear**

Yasumizu T, Nakamura Y, Hoshi K, et al. Bone metabolism after human parturition and the effect of lactation: longitudinal analysis of serum bone-related proteins and bone mineral content of the lumbar spine. Endocr J 1998 Oct;45(5):679-86. **Less than 1 year follow-up**

Yen ML, Yen BL, Bai CH, et al. Risk factors for ovarian cancer in Taiwan: a case-control study in a low-incidence population. Gynecol Oncol 2003 May;89(2):318-24. **Developing country**

Young TK, Martens PJ, Taback SP, et al. Type 2 diabetes mellitus in children: prenatal and early infancy risk factors among native Canadians. Arch Pediatr Adolesc Med 2002 Jul;156(7):651-5. **Included in systematic review**

Zhang J, Liu G, Wu J, et al. Pregnancy-associated breast cancer: a case control and long-term follow-up study in China. J Exp Clin Cancer Res 2003 Mar;22(1):23-7. **Developing country**

Zhang M, Lee AH, Binns CW. Reproductive and dietary risk factors for epithelial ovarian cancer in China. Gynecol Oncol 2004 Jan;92(1):320-6. **Developing country**

Zhang M, Xie X, Lee AH, et al. Prolonged lactation reduces ovarian cancer risk in Chinese women. Eur J Cancer Prev 2004 Dec;13(6):499-502. **Developing country**

Zheng T, Duan L, Liu Y, et al. Lactation reduces breast cancer risk in Shandong Province, China. Am J Epidemiol 2000 Dec 15;152(12):1129-35. **No hormonal data given**

Zheng T, Holford TR, Mayne ST, et al. Lactation and breast cancer risk: a case-control study in Connecticut. Br J Cancer 2001 Jun 1;84(11):1472-6. **Pre 2001**

Ziegler AG, Schmid S, Huber D, et al. Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies.[see comment]. JAMA 2003 Oct 1;290(13):1721-8. **No outcomes of interest**

Appendix E. Peer Reviewers

The peer reviewer comments on a preliminary draft of this report were considered by the EPC in preparation of this final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers. The authors gratefully acknowledge the peer reviewers.

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