Evidence Report/Technology Assessment
Number 153

Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0022

Prepared by:
Tufts-New England Medical Center Evidence-Based Practice Center
Boston, Massachusetts

Investigators
Stanley Ip, M.D., Project Leader
Mei Chung, M.P.H.
Gowri Raman, M.D.
Priscilla Chew, M.P.H.
Nombulelo Magula, M.D.
Deirdre DeVine, M.Litt., Project Manager
Thomas Trikalinos, M.D., Ph.D.
Joseph Lau, M.D., Principal Investigator

AHRQ Publication No. 07-E007
April 2007

This report is based on research conducted by the Tufts-New England Medical Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0022). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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.

This report may be used, in whole or in part, as the basis for the development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This document is in the public domain and may be used and reprinted without permission except those copyrighted materials noted for which further reproduction is prohibited without the specific permission of copyright holders.

Suggested Citation:
Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, Trikalinos T, Lau J. Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries. Evidence Report/Technology Assessment No. 153 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center, under Contract No. 290-02-0022). AHRQ Publication No. 07-E007. Rockville, MD: Agency for Healthcare Research and Quality. April 2007.

No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, or stock options, expert testimony, grants, or patents received or pending, or royalties) that conflict with material presented in this report.

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.**

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Suzanne Haynes, Ph.D.
Office on Women's Health
Department of Health and Human Services

Beth Collins Sharp, Ph.D., R.N.
Director, EPC Program
Agency for Healthcare Research and Quality

Ernestine Murray, M.A.S., R.N.
EPC Program Task Order Officer
Agency for Healthcare Research and Quality

Acknowledgments

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.

Technical Expert Panel

David Chelmow, M.D.
Obstetrician-Gynecologist
Tufts-New England Medical Center
Tufts University School of Medicine

Kathryn G. Dewey, Ph.D.
Department of Nutrition
University of California, Davis

Gillman Grave, M.D.
Endocrinology, Nutrition & Growth
National Institute of Child Health and Human Development

Larry Grummer-Strawn, Ph.D.
National Center for Chronic Disease Prevention and Health Promotion
Centers for Disease Control and Prevention

Katherine E. Hartmann, M.D., Ph.D.
Obstetrician-Gynecologist
Vanderbilt University
Representative, American College of Obstetricians and Gynecologists

Suzanne Haynes, Ph.D.
Senior Science Advisor
Office on Women's Health
U.S. Department of Health and Human Services

Jill Janke, RNC, D.NSc.
University of Alaska
Representative, Association of Women's Health, Obstetrical and Neonatal Nurses

Ronald E. Kleinman, M.D.
Pediatric Gastroenterology and Nutrition
Department of Pediatrics
MassGeneral Hospital for Children

Michael Kramer, M.D.
McGill University Faculty of Medicine
Institute of Human Development, Child and Youth Health
The Montreal Children's Hospital

Katy Lebbing, B.S., IBCLC, RLC
Center for Breastfeeding Information
La Leche League International

Ardythe L. Morrow, Ph.D., M.Sc.
Cincinnati Children's Hospital Medical Center

David Meyers, M.D.
Center for Primary Care, Prevention, and Clinical Partnerships, (CPPO)
Agency for Healthcare Research and Quality

Barbara L. Philipp, M.D.
The Breastfeeding Center
Boston Medical Center

Lori Feldman-Winter, M.D., M.P.H., IBCLC, FAAP, FABM
Robert Wood Johnson Medical School
University of Medicine and Dentistry of New Jersey
Representative, AAP and the Section on Breastfeeding

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.

Contents

Executive Summary 1

Evidence Report 11

Chapter 1. Introduction 11

Chapter 2. Methods 13
- Overview 13
- Key Questions Addressed in This Report 13
- Definitions of Breastfeeding in This Report 14
- Literature Search Strategy 14
- Study Selection 15
- Meta-Analysis 16
- Grading of Studies Analyzed in This Report 17
- Grading of Systematic Reviews/Meta-Analyses. 17
- Grading of Individual Primary Studies in Updates and New Reviews 18
- Reporting of the Evidence 20

Chapter 3. Results 21
- Overview 21
- Literature Search Results 23
- Organization of Results 24
- Part I. Term Infant Outcomes – Relationship of Breastfeeding to Outcomes 27
  - Acute Otitis Media 27
  - Atopic Dermatitis 35
  - Gastrointestinal Infections 37
  - Lower Respiratory Tract Diseases 40
  - Asthma 42
  - Cognitive Development in Terms Infants 50
  - Obesity 62
  - Cardiovascular Diseases 68
  - Type 1 Diabetes 75
  - Type 2 Diabetes 81
  - Childhood Leukemia 84
  - Infant Mortality 90
  - Sudden Infant Death Syndrome (SIDS) 93
- Part II. Preterm Infant Outcomes – Relationship with Human milk feeding 98
  - Necrotizing Enterocolitis 98
  - Cognitive Development 103
- Part III. Maternal Outcomes – Relationship of Breastfeeding to Outcomes 111
  - Return to Pre-pregnancy Weight or Postpartum Weight Change 111
  - Type 2 Diabetes 119

Osteoporosis....124
Postpartum Depression....130
Breast Cancer....136
Ovarian Cancer....141
Other Research....155

Chapter 4. Discussion....157
Future Research....162

References and Included Studies....165

Acronyms and Abbreviations....185

Figures

Figure 1. The relationship between breastfeeding and health outcomes in term infants – meta-analysis results....21
Figure 2. The relationship between *exclusive* breastfeeding and health outcomes in term infants - meta-analysis results....22
Figure 3. The relationship between breastfeeding and maternal outcomes - meta-analysis results....23
Figure 4. Primary studies available to assess the relationship between breastfeeding and infant health outcomes....25
Figure 5. Primary studies available to assess the relationship between breastfeeding and maternal health outcomes....26
Figure 6. Meta-analysis of the association between breastfeeding and the risk of AOM compared to exclusive bottle-feeding in cohort studies....30
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)....44
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)....45
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....45
Figure 10. Random effects model of summary estimate evaluating the association of breastfeeding and SIDS....95
Figure 11. Meta-Analysis of four RCTs on the effects of breast milk feeding and NEC in preterm infants....100
Figure 12. Meta-Analysis of case-control studies on the relationship between breastfeeding and maternal ovarian cancer risk: ever breastfed versus never breastfed....143
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....144

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…….....145

Tables

Table 1. Summary of systematic review/meta-analysis on the relationship between breastfeeding and acute otitis media (AOM) 31
Table 2. Summary table for cohort studies on the relationship between breastfeeding and acute otitis media 32
Table 3. Summary of systematic review/meta-analysis on the relationship between breastfeeding and the risk of developing atopic dermatitis 36
Table 4. Summary of systematic review/meta-analysis on the relationship between breastfeeding and gastrointestinal (GI) infection.....39
Table 5. Summary of systematic review/meta-analysis on the relationship between breastfeeding and lower respiratory tract disease 41
Table 6. Summary of systematic review/meta-analysis on the relationship between breastfeeding and asthma.....47
Table 7. Summary of prospective cohort studies on the relationship between breastfeeding and asthma.....48
Table 8. Summary of systematic reviews/meta-analyses on the relationship of breastfeeding and cognitive development 54
Table 9. Summary of studies on the relationship of breast milk feeding and cognitive development.....56
Table 10. Summary of systematic reviews/meta-analyses on the relationship between breastfeeding and overweight or obesity 66
Table 11. Summary of systematic reviews/meta-analyses on the relationship between breastfeeding and total cholesterol and low-density lipoprotein cholesterol.....69
Table 12. Summary table for systematic reviews/meta-analyses on the relationship between breastfeeding in infancy and blood pressure levels later in life.....71
Table 13. Summary of systematic review/meta-analysis on the relationship between breastfeeding and long-term cardiovascular disease mortality.....74
Table 14. Summary of systematic reviews/meta-analyses on the relationship between breastfeeding and type 1 diabetes 79
Table 15. Summary of case-control studies on the relationship between breastfeeding and type 1 diabetes.....80
Table 16. Summary of systematic reviews/meta-analyses on the relationship between breastfeeding and type 2 diabetes 83
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).....87
Table 18. Summary of systematic reviews/meta-analyses on the relationship between breastfeeding and childhood leukemia.....88
Table 19. Summary of case-control study on the relationship between breastfeeding and infant mortality.....92
Table 20. Summary of systematic review/meta-analysis on the relationship between breastfeeding and Sudden Infant Death Syndrome (SIDS) 96

Table 21. Summary of case-control studies on the relationship between breastfeeding and sudden infant death syndrome (SIDS) included in the meta-analysis 97
Table 22. Meta-Analysis of four RCTs on the effects of breast milk feeding and NEC in preterm infants: Random Effects Model (D&L).....99
Table 23. Summary of systematic review/meta-analyse on the relationship between breast milk feeding and necrotizing enterocolitis (NEC) in preterm infants.....101
Table 24. Summary of studies on the relationship between breast milk feeding and necrotizing enterocolitis (NEC) in preterm infants.....102
Table 25. Summary of primary studies on the relationship of breast milk feeding and cognitive development in preterm infants.....106
Table 26. Summary of prospective cohort studies on the relationship between breastfeeding and returning to pre-pregnancy weights 114
Table 27. Summary of prospective cohort studies on the relationship between breastfeeding and postpartum weight/BMI changes 116
Table 28. Summary of systematic review/meta-analyse on the relationship between breastfeeding and maternal type 2 diabetes 122
Table 29. Summary of studies on the relationship between breastfeeding and maternal type 2 diabetes (NIDDM) 123
Table 30. Summary of case-control studies on the relationship between breastfeeding and risk of fracture in post-menopausal women.....127
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).....129
Table 32. Summary of the studies on the relationship between breastfeeding and postpartum depression 132
Table 33. Summary of systematic reviews/meta-analyses on the relationship between breastfeeding and the risk of breast cancer.....139
Table 34. Summary of case-control studies on the relationship between breastfeeding and breast cancer.....140
Table 35. Summary of case-control studies on the relationship between breastfeeding and maternal ovarian cancer 147
Table 36. Summary of case-control studies on the relationship between breastfeeding and maternal ovarian cancer by menopausal status.....151
Table 37. Summary of case-control studies on the relationship between breastfeeding and maternal ovarian cancer by histologic type 152
Table 38. Summary of pooled-analysis of case-control studies on the relationship between breastfeeding and ovarian cancer by population subgroups 154

Appendixes

Appendix A. MEDLINE® Search Strategy
Appendix B. Sample data abstraction forms
Appendix C. Evidence Tables
Appendix D. List of Excluded Studies
Appendix E. Peer Reviewers

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.