

Breastfeeding and the Risk of Hospitalization for Respiratory Disease in Infancy

A Meta-analysis

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Objective: To examine breastfeeding and the risk of hospitalization for lower respiratory tract disease in healthy full-term infants with access to modern medical care.

Data Sources: MEDLINE, personal communication with researchers, the OVID databases, Dissertation Abstracts Online, and BIOSIS.

Study Selection: The titles, abstracts, and text of studies from developed countries were explored for breastfeeding exposure measures and lower respiratory tract disease hospitalization rates. For summary statistics, we required 3 inclusion criteria: (1) a feeding contrast of a minimum of 2 months of exclusive breastfeeding (no formula supplementation) vs no breastfeeding and (2) study populations that excluded sick, low birth weight or premature infants and (3) reflected affluent regions; 27% of studies met these criteria.

Data Extraction: We abstracted data from all relevant reports.

Data Synthesis: Data from all primary material (33 studies) indicated a protective association between breastfeeding and the risk of respiratory disease hospitalization. Nine studies met all inclusion criteria, and 7 cohort studies were pooled. The feeding contrasts in these 7 studies were 4 or more months of exclusive breastfeeding vs no breastfeeding. The summary relative risk (95% confidence interval) was 0.28 (0.14-0.54), using a random-effects model. This effect remained stable and statistically significant after adjusting for the effects of smoking or socioeconomic status.

Conclusion: Among generally healthy infants in developed nations, more than a tripling in severe respiratory tract illnesses resulting in hospitalizations was noted for infants who were not breastfed compared with those who were exclusively breastfed for 4 months.

Arch Pediatr Adolesc Med. 2003;157:237-243

RESPIRATORY DISEASE is the leading cause of hospitalization among young children.¹ Annually, 6% of infants younger than 1 year are hospitalized for lower respiratory tract diseases (LRTDs), according to trend data (1980-1996) in the United States.² The costs of these hospitalizations have been conservatively estimated at \$300 million, using 1985 dollars.³⁻⁵ For decades, severe infantile respiratory illness has been recognized to be an antecedent to childhood asthma.⁶⁻⁸ Recently, respiratory disease severe enough to require hospitalization in infancy has been reported to increase the risk of childhood asthma 10-fold,⁹ and annual costs for childhood asthma through age 17 years have been estimated to exceed \$1.6 billion.^{10(p790)}

Prior reviews of respiratory disease and breastfeeding from developed countries have provided equivocal results.¹¹⁻¹⁴ These studies have used illness episodes as their end point. Because both respiratory illness and infant feeding are manifest on a broad continuum, investigation

of this topic is difficult. We chose to focus on hospitalizations for LRTD in infancy as our outcome of interest because it is an important measure of illness severity and is associated with sizable direct and indirect health care costs.

Whereas breastfeeding is widely acknowledged to protect infants in the developing world from acute infectious illnesses, such as gastroenteritis or respiratory disease, the magnitude of its benefit for healthy infants with high standards of living (in terms of medical care and sanitation) is not well delineated. Recommendations from both the Surgeon General and the American Academy of Pediatrics advise women to breastfeed exclusively, that is without formula supplementation, through age 6 months^{15,16}; however, few women follow these recommendations. Whereas 67% of US women initiate breastfeeding, only 31% continue with any breastfeeding at 6 months of age.¹⁷⁻¹⁹ The impact of limited breastfeeding on the health of children has not been well studied in developed countries. Evidence-based medicine

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could fill this gap and provide further guidance to women regarding their infant feeding choices.

Our goal for this meta-analysis was to examine the risk of hospitalization for LRTD in healthy full-term infants with access to modern medical care and breastfeeding—which requires definition for both its duration and exclusivity as an infant feeding pattern. In addition, the effects of smoking and socioeconomic status (SES) as possible confounders of the relationship between breastfeeding and hospitalization for LRTD were investigated.

METHODS

DATA SOURCES

The following eligibility and exclusion criteria were prespecified. Only studies from industrialized nations that reported LRTD hospitalization rates and examined breastfeeding were sought. Studies were ineligible if they focused on geographic regions where gross malnutrition is prevalent or if they focused on children with recognized chronic illnesses (eg, cystic fibrosis), other than allergic conditions. We defined LRTD to include bronchiolitis, asthma, bronchitis, pneumonia, empyema, and infections due to specific agents (eg, respiratory syncytial virus).

A priori, we wished to focus our analysis on studies of healthy full-term infants whose living conditions reflected those of affluent developed nations. We sought studies of populations that excluded sick, premature, and/or low birth weight infants (“sick newborns”). Additionally, we looked for studies that characterized breastfeeding as exclusive (meaning little or no formula offered) and provided a duration of exclusive breastfeeding for 2, 4, or 6 months or total (any) breastfeeding for longer durations. The breastfeeding inclusion criterion was a minimum exposure of 2 months of exclusive breastfeeding or 9 months of total (any) breastfeeding compared with its absence.

We identified 34 relevant research studies through iterative searching methods.²⁰⁻⁵³ Data were provided without recompense from all but one research group, leaving 33 studies with data to examine.⁵³ We searched MEDLINE (National Library of Medicine, Bethesda, Md) for relevant articles published from 1966 to April 11, 2002, and found 2386 citations. The search strategy used was (“respiratory tract diseases”[MeSH] OR “bacterial infections and mycoses”[MeSH] OR “virus diseases”[MeSH] OR hospitalization[MeSH] OR morbidity[MeSH]) AND (breast feeding OR lactation[MeSH] OR milk, human[MeSH]); Limits: all infant: birth—23 months. Abstracts for all relevant titles were examined; bibliographies of all articles with useful data, including foreign language publications, were inspected. The OVID system’s databases for evidence-based medicine reviews (EBM Reviews, CCTR, CDSR, DARE, ACP Journal Club, CINAHL, HealthSTAR), Dissertation Abstracts Online, and BIOSIS (for books and conference publications) were searched but provided no additional relevant material. Unpublished data were actively solicited by writing to authors in the field and by contacting members of the International Society for Research in Human Milk and Lactation. Through these combined means, 10 research groups contributed further unpublished data.*

DATA EXTRACTION

The investigators independently abstracted the data without blinding using a standardized data-abstraction form. The following information was sought from each paper: authors’ names, title, year of publication, the purpose of the study, the study methods (co-

hort [prospective or retrospective] or noncohort), the age to which infants were observed, the season in which infants were enrolled, the geographic location of the study, the study size (and the number lost to follow-up), breastfeeding definitions in terms of both its duration and exclusivity, hospitalizations for LRTD, and confounding infant and household factors that studies either controlled for or matched. Data from each study were used to estimate either a relative risk or an odds ratio.

STUDY SELECTION

Hospitalization for LRTD, the outcome variable, was prespecified. We excluded reports of pulmonary complications when hospitalization was not required, as well as reports of hospitalizations for upper respiratory tract disease. Whenever possible, we restricted our analysis to first-time hospitalizations for infants within study populations. We did so to avoid any possible distortion from counting repeat hospitalizations of children with chronic conditions not yet diagnosed.

The 33 studies were examined for the inclusion criteria specified above. To make our work generalizable to populaces with high standards of living (in terms of medical care and sanitation), we eliminated 7 studies in which this might be disputed: 3 from China,^{26,27,40} 2 from South America,^{25,43} and 2 from North American Indian populations.^{23,32} To focus our work on healthy newborn infants, we dropped all studies wherein sick newborns could not be excluded from the study’s data and, applying the inclusion criteria for breastfeeding, we excluded 17 further studies,* leaving 9 studies.

STATISTICAL ANALYSIS

Hospitalization for LRTD in infancy was the primary outcome measure. Of the 9 eligible studies, 7 used cohort study designs, allowing us to report summary relative risk ratios. Additionally, the risk difference was calculated for these 7 studies to estimate the number needed to treat to prevent one LRTD hospitalization by exclusive breastfeeding.

The study designs of the 2 remaining studies, a cross-sectional analysis and an ecological design, provided odds ratios. Because of the disparate clinical characteristics of these 2 studies, their data were neither pooled into a separate summary statistic nor included with the cohort data because to do so would have required unjustifiable assumptions.

We computed the summary statistics with 95% confidence intervals using both the random-effects method of DerSimonian and Laird and the fixed-effects method of Mantel and Haenzel.⁵⁴ We present the results from the random-effects model because this model examines the inference tested in our analysis: would a random sample of studies examining some hypothetical population of studies of breastfeeding and LRTD hospitalization show a significant effect of breastfeeding? This model was preferred because it incorporates both within and between study variance into the point estimate and confidence interval calculations, which usually results in wider confidence intervals. Stata statistical software, version 7⁵⁵ was used for all summary relative risk and odds ratio computations.

RESULTS

STUDY CHARACTERISTICS

Data from 33 studies were examined, and a protective association between breastfeeding and the risk of

*References 21, 22, 25, 28, 33, 34, 36, 41, 45, 46.

*References 20, 24, 28-31, 35, 37, 41, 42, 44, 47-52.

Nine Studies That Report Hospitalizations for Lower Respiratory Tract Disease and Breastfeeding

Source	Country	Study Design	Follow-up Period, mo	Exclusion Criteria for Newborns	Risk Ratio (95% CI)
Ball and Wright, ²¹ 1999	United States	Prospective cohort	12	Sick, LBW, premature	RR, 0.32 (0.05-1.90)
Beaudry et al, ²² 1995	Canada	Retrospective cohort	6	Sick, multiple births, LBW, premature	RR, 0.13 (0.01-2.09)
Fallot et al, ³³ 1980	United States	Ecological study	3	Sick, premature	OR, 0.05 (0.01-0.38)
Fergusson et al, ³⁴ 1981	New Zealand	Prospective cohort	24	LBW, premature	RR, 0.12 (0.01-0.89)
Haby et al, ³⁶ 2001	Australia	Cross-sectional	36-60	LBW, premature	OR, 0.66 (0.26-1.70)
Hoey and Ware, ³⁸ 1997	United States	Retrospective cohort	12	Sick, multiple births, premature	RR, 0.65 (0.08-5.67)
Howie et al, ³⁹ 1990	Scotland	Prospective cohort	12	Multiple births, premature	RR, 0.15 (0.02-1.12)
Nafstad et al, ⁴⁵ 1996	Norway	Prospective cohort	12	Sick, LBW	RR, 0.15 (0.06-0.35)
Oddy et al, ⁴⁶ 1999	Australia	Prospective cohort	12	Sick, premature	RR, 0.62 (0.31-1.24)

Abbreviations: CI, confidence interval; LBW, low birth weight; OR, odds ratio; RR, relative risk.

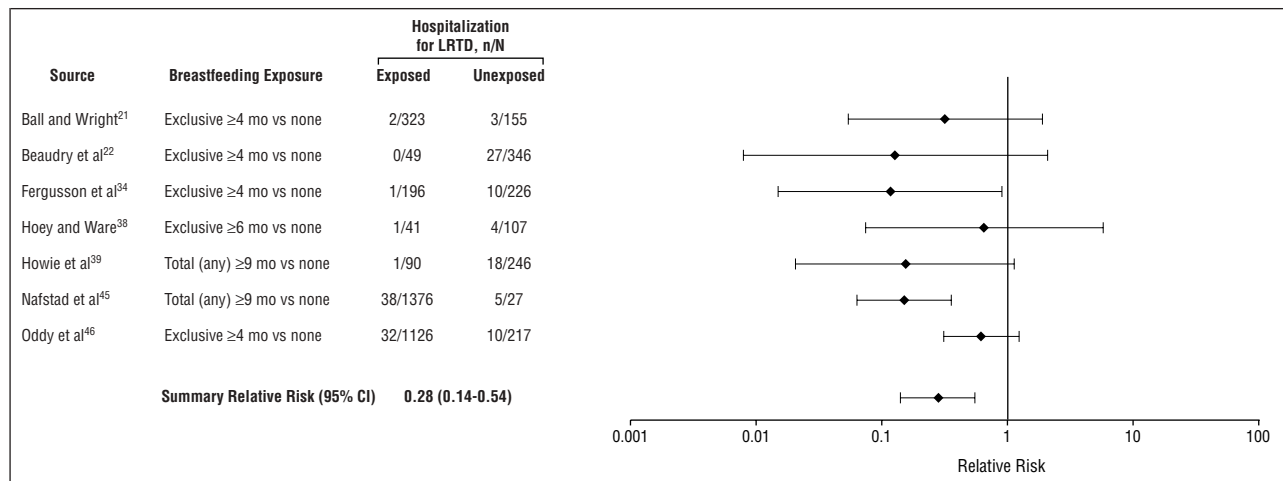


Figure 1. The risk of hospitalization for lower respiratory tract disease (LRTD) and breastfeeding exposure measures for 7 cohort studies. Breastfeeding diminishes the risk of hospitalization for respiratory disease.

LRTD hospitalization was found from each study.²⁰⁻⁵² This alone is a remarkably consistent finding for meta-analysis source material.

We present risk ratios, relative risk ratios and odds ratios, for 9 studies; the remaining 24 studies did not meet inclusion criteria, 17 because of design limitations and 7 because of demographic considerations. The **Table** presents study characteristics for these 9 studies: the exclusion criteria for sick newborns, the length of patient follow-up, and the risk ratio for each study. All 9 reports were published between 1980 and 2001. Four studies were from North America,^{21,22,33,38} 2 were from Australia,^{36,46} and 1 each was from Scotland,³⁹ New Zealand,³⁴ and Norway.⁴⁵

PRIMARY ANALYSIS

Figure 1 presents graphically the point estimates (95% confidence intervals) for each cohort study as well as that study's relative risk data. Collectively, the 7 studies observed 4525 infants. The 2 studies with odds ratios of 0.05 (0.01-0.38) and 0.66 (0.26-1.70) were not graphically presented and do not contribute to pooled risk estimates; however, these odds ratios provide additional evidence for a protective association between breastfeeding and LRTD hospitalizations.^{33,36}

Sizable differences in exposure measures and patient follow-up are noted among the 7 studies summarized. Despite this clinical heterogeneity among these 7 studies, which provide effect estimates that range from 0.12 to 0.65, no evidence of statistical heterogeneity was found when these studies were pooled ($P=.18$). Summary estimates from both the fixed- and random-effects models were similar. The summary risk ratio was 0.28 (0.14-0.54) using the random-effects model.

Additionally, we calculated the number of infants who would need to be breastfed exclusively for 4 or more months to prevent one LRTD hospitalization using the summary risk difference (0.039).⁵⁶ The number needed to treat was 26.

SENSITIVITY ANALYSIS

Because the 7 pooled studies differed clinically with respect to breastfeeding measures, length of follow-up, data collection methods, and, most likely, respiratory disease diagnoses, we performed sensitivity analyses to test the appropriateness of combining these studies. We eliminated each study, one at a time, then the 2 studies with total (any) breastfeeding^{39,45} (rather than exclusive breastfeeding, because we assumed that to establish a

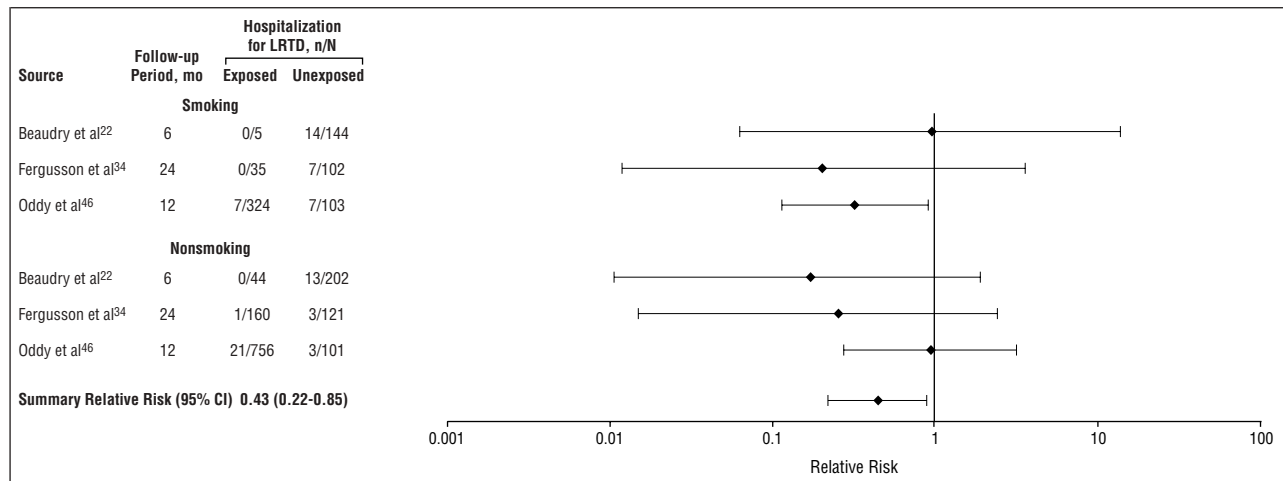


Figure 2. Data stratified on maternal smoking from 3 cohort studies that examine the risk of hospitalization for lower respiratory tract disease (LRTD) and breastfeeding. Breastfeeding exposure measures are presented in Figure 1.

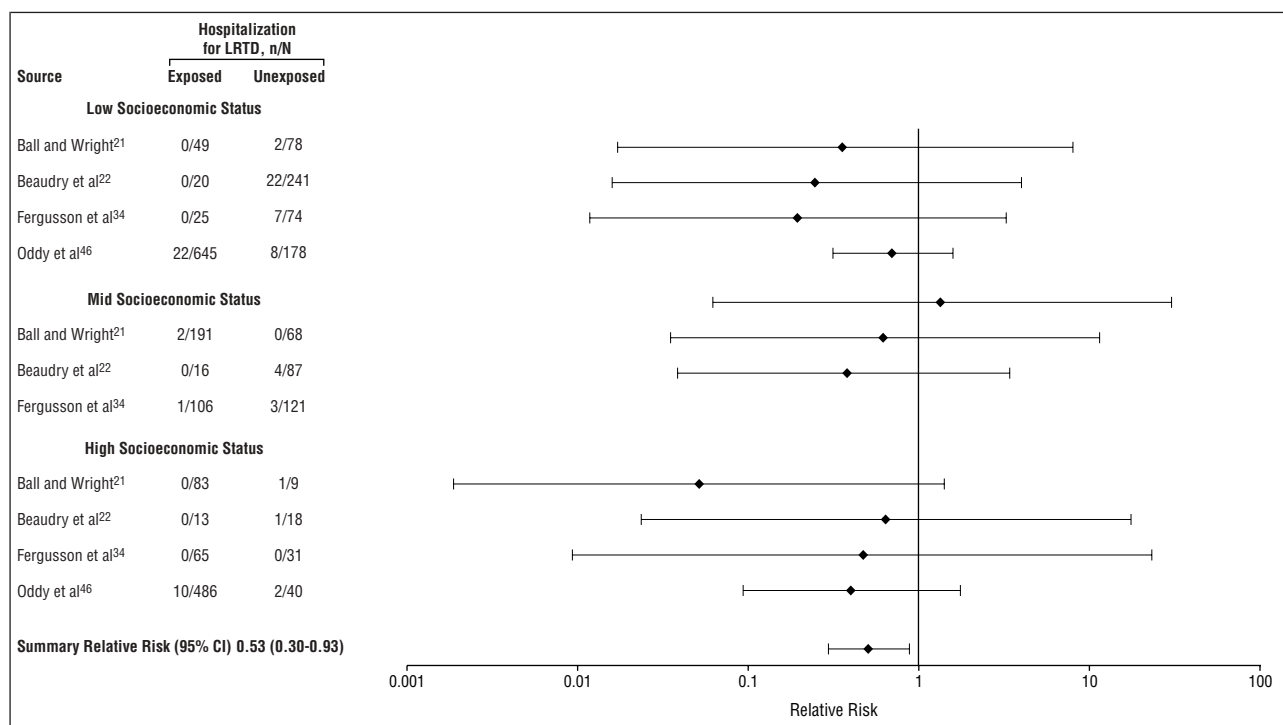


Figure 3. Data stratified on socioeconomic status from 4 cohort studies that examine the risk of hospitalization for lower respiratory tract disease (LRTD) and breastfeeding. Breastfeeding exposure measures are presented in Figure 1.

milk supply, women who breastfed long-term also breastfeed exclusively in the first months) and the 2 studies with retrospective study designs^{22,38} (rather than prospective study designs). Each time we eliminated 1 or 2 studies, we recalculated the relative risk and its confidence interval. None of these sensitivity analyses resulted in confidence intervals that included the null hypothesis or 1.0. The risk ratios for these sensitivity analyses ranged from 0.25 (0.12-0.52) to 0.47 (0.26-0.84).

To further assess the strength of the summary estimate for this meta-analysis, we examined the magnitude of the risk ratio that would be required from a new, hypothetical study that, when combined with the 7 stud-

ies identified here, would produce a summary estimate confidence interval that would include 1.0, or the null hypothesis. We chose a large sample size of 1000 subjects and assumed that half were breastfed—exclusively for 4 or more months—and half were bottle-fed. We then determined that such a hypothetical study would require a risk ratio with a magnitude of 18 or greater simply to call into question the statistical validity of the findings from this meta-analysis.

SUBGROUP ANALYSES FOR COVARIATES

Smoking and SES are 2 factors that correlate closely with both women's breastfeeding choices and infant hospital-

izations.^{16,45,50,57} To explore the effects of these covariates on our primary analysis, we present 2 subgroup analyses wherein we adjusted for SES and smoking using stratified methods.

Smoking

Three primary studies provided stratified data on maternal smoking.^{22,34,46} **Figure 2** presents the risks for LRTD hospitalization by breastfeeding exposure and stratified on maternal smoking. The crude risk ratio was 0.19 (0.10-0.38) for these 3 studies; the pooled risk ratio was 0.33 (0.13-0.83) within the smoking strata and 0.58 (0.21-1.59) within the nonsmoking strata. The summary risk ratio adjusting by stratification for smoking was 0.43 (0.22-0.85); no evidence of statistical heterogeneity was found ($P = .66$). This indicates that smoking does not account for the observed effect of breastfeeding on LRTD hospitalizations.

Socioeconomic Status

Four primary studies provided SES data; 3 provided data stratified on 3 levels of SES, and 1 provided only 2 strata. Two of these studies determined SES by paternal occupation,^{34,46} and 2 determined SES using maternal education.^{21,22} **Figure 3** presents the risk data stratified on SES. The crude risk ratio for these 4 studies with SES data was 0.37 (0.15-0.88); the pooled risk ratio was 0.62 (0.30-1.26) within the low SES strata, 0.64 (0.14-2.93) within the mid SES strata, and 0.29 (0.08-1.00) within the high SES strata for these 4 studies. The summary risk ratio after adjusting for SES was 0.53 (0.30-0.93); no evidence of statistical heterogeneity was found ($P = .82$). This indicates a measurable and independent effect of breastfeeding on the risk of LRTD hospitalization after considering SES.

COMMENT

A remarkably consistent effect was found among all the primary material amassed for this report, which is indicative of a protective role for breastfeeding against common respiratory pathogens. Exclusive breastfeeding for 4 or more months appears to diminish the risk of respiratory hospitalization in infancy to one third or less the risk observed for formula-fed infants, even in developed nations with high standards of living (in terms of medical care and sanitation). The strengths of this analysis include the magnitude of our findings, the search of published and unpublished reports, and attention to 2 important potential confounders, smoking and SES.

The absence of explicit data in the medical literature constitutes a major problem for any study of breastfeeding.^{58,59} This variable requires definition for both its duration and exclusivity; however, in the past, many authors have simplified their consideration of breastfeeding by dichotomizing its exploration. Insufficient data within primary studies made it infeasible to estimate more than one risk level for the effects associated with breastfeeding.

Case-control studies obtained for this review examined some vs no breastfeeding at a given point in time. However, several reports did not distinguish between minimal, partial, or exclusive breastfeeding; thus, feeding contrasts based on imprecisely specified breastfeed-

ing measures did not meet the inclusion criteria for this meta-analysis.

Stringent criteria were applied to the selection of all primary material used to estimate summary statistics. Our summary risk ratios derived exclusively from cohort studies. Because patient exposure data are collected without reference to illness status in cohort studies, recall bias was avoided. Additionally, we summarized only studies that offered a minimum exposure of exclusive breastfeeding for 4 or more months, or at least 9 months of total (any) breastfeeding, compared with no breastfeeding and tested the clinical assumption of combining these exposure measures. Furthermore, because a disproportionate number of sick newborns within a study population could provide a spurious association between breastfeeding and illness, we excluded all studies that included them, since sick newborns are less able to suckle and, therefore, are more likely to be bottle-fed.

Another challenge to the investigation of protective factors in infancy and respiratory disease is both seasonal and age variation. A 10-fold increase in LRTD hospitalizations occurs during the winter months, and infant respiratory hospitalization rates peak during the first 4 months of life. Therefore, studies examining spring births, when the baseline rate of respiratory disease is normally low, will have fewer outcomes and, thus, less power to detect an association with infant feeding. Publication bias may adversely affect this report but appears unlikely because of our extensive search of both published and unpublished reports (unrestricted to the examination of this study's hypothesis).

More robust findings appear to cluster with stronger breastfeeding measures (when considering all primary material), consistent with a biological phenomenon. Since maternal milk transmits both immune cells and antibodies to infants, immune modulation could explain the breastfeeding effects that are noted to extend beyond the actual period of exposure.^{60,61} In support of this view, it has been found that lymphocyte profiles differ at 6 months of age between breastfed infants and those who are not breastfed.^{62,63} Moreover, T lymphocyte profiles distinguish children who are prone to asthma in infancy from those not so predisposed.⁶⁴ Together, these observations suggest that further elucidation of immune development in relationship to infant feeding practices is warranted.

Alternative explanations for the inverse association between breastfeeding and respiratory disease require consideration. Some observers suggest that maternal smoking may account for the apparent breastfeeding effects⁶⁵ because women who smoke are less likely to breastfeed. Others indicate that observed breastfeeding effects are secondary to SES differences among women who do and do not breastfeed. We explored both hypotheses with the available data, and neither was supported. The protective association between breastfeeding and LRTD hospitalizations remained stable and statistically significant after examining the effects of either smoking or SES. Physician hesitation to separate infants from their breastfeeding mothers might account for the decreased number of hospitalizations among breastfed infants. While such a tendency is plausible, when a

What This Study Adds

Exclusive breastfeeding, that is, breastfeeding without supplementation, for 6 months is currently recommended. Its importance to the prevention of serious health conditions resulting in hospitalization for healthy full-term infants with access to modern medical care, however, has not been well quantified. How much of what type of feeding really makes a difference?

When exclusive breastfeeding is contrasted with lesser levels of breastfeeding, one can begin to measure the sizable health effects associated with this infant feeding pattern. Unless infant feeding patterns are carefully documented, their health effects will not be observed. We report a significant risk reduction in hospitalizations due to respiratory disease for infants who have been exclusively breastfed for 4 or more months.

child has serious respiratory distress, hospitalization is imperative. Furthermore, mothers may room-in or pump their milk to continue to breastfeed their hospitalized infants. Therefore, these explanations do not appear to account for the observations reported here.

Breastfeeding is a challenging area to investigate and quantify. Because it is neither feasible nor ethical to randomly assign women to breast- or bottle-feed their infants, evidence about the value of breastfeeding must derive from observational studies. Causal inference from observational work alone is difficult but may be supplemented by animal experimentation. Determining what health risks occur with varying infant feeding practices is a similar problem to that encountered with smoking; there is an inherent problem regarding who smokes or breastfeeds that plagues all such investigations (ie, personal choice may not be measured simply through demographic attributes). Even so, a meta-analysis helps to address the problem of individual differences in choice by drawing upon studies performed in societies where the behavior in question is common or rare, as in this report.

Consensus exists among the professional community about the benefits of breastfeeding, and our findings support this stance. This meta-analysis finds that formula feeding is associated with a 3.6-fold increase in an infant's risk of respiratory hospitalization when compared with a minimum of 4 months of exclusive breastfeeding. Because respiratory disease is the leading cause of hospitalization in young children—and each such hospitalization in infancy costs on average \$3500, with more than 250 000 such admissions in 1996—clearly there are large financial implications to this report.^{2,66} From this study, we estimate that for every 26 women who exclusively breastfeed for 4 months, one LRTD hospitalization might be avoided. Likewise, since early severe respiratory illness is a recognized risk factor for asthma,^{67,68} breastfeeding may be important to the prevention of asthma, with its significant health costs.^{9,46,69,70}

A 1994 *Lancet* editorial acknowledged the importance of breastfeeding by creating an analogy to immunizations as primary prevention.⁷¹ Unlike vaccines that target individual pathogens, breastfeeding provides simultaneous protection against a broad spectrum of or-

ganisms. These observations indicate a need to counteract the cultural and societal influences that minimize the importance of breastfeeding, such that less than a third of women in our society breastfeed beyond the first few months.^{18,19,72} Only with new and better studies that quantify breastfeeding appropriately will women have sufficient data with which to make well-informed infant feeding choices.

In summary, among generally healthy infants in developed nations, a tripling in severe respiratory tract illnesses resulting in hospitalizations was noted for infants who were not breastfed compared with those exclusively breastfed for 4 months. If social policies were to support all women to breastfeed beyond the newborn period, sizable health care savings would be achieved.

Accepted for publication November 7, 2002.

We thank Lincoln E. Moses, PhD, Byron W. Brown, Jr, PhD, and Phil Lavori, PhD. We also thank Sylvia Rashmi Bachrach, BS, for research assistance.

In addition, we thank the following researchers for sharing their data: P. Nafstad (Section of Epidemiology, Department of Population Health Services, National Institute of Public Health, Oslo, Norway); Herbert S. Kaufman, MD (San Francisco, Calif); John Horwood (Christchurch School of Medicine, Christchurch, New Zealand); Dr Saunders (produced an internal publication by Cullinan; Department of Computer Science and Statistics, Queen Mary College, London, England); Wendy Oddy, PhD (Department of Nutrition, Dietetics, and Food Science, Curtin University of Technology and the Institute for Child Health Research, University of Western Australia, West Perth) with Lou Landau, MD (University Department of Pediatrics, Princess Margaret Hospital for Children, Perth, Australia); Juraci A. Cesar, MD, MSc (Departamento Materno Infantil, Fundacao Universidade Federal de Rio Grande, Rio Grande, Brazil); Thomas M. Ball, MD, MPH (Department of Pediatrics, University of Arizona, Tucson) with Anne L. Wright, PhD (Department of Pediatrics and the Respiratory Sciences Center, University of Arizona, Tucson); Micheline Beaudry, PhD (Departement des Sciences des Aliments et de Nutrition, FSAA, Université Laval, Quebec City, Quebec); John L. Boyd, III, MD, MBA (Phoenix, Ariz); and Michelle Haby, PhD, MAppSc (Health Outcomes Section, Department of Human Services, Melbourne, Australia).

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