Short-term effects of breastfeeding

A SYSTEMATIC REVIEW ON THE BENEFITS OF BREASTFEEDING ON DIARRHOEA AND PNEUMONIA MORTALITY

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Summary

Background

Several studies suggest that breastfeeding has clear short-term benefits, particularly reducing morbidity and mortality due to infectious diseases in childhood. These benefits have been reported in low and middle income and in high-income countries.

Objective

This systematic review and meta-analysis was aimed at assessing the effect of breastfeeding on respiratory infections and diarrheal disease in childhood.

Search strategy

Two independent literature searches were carried out, comprising the MEDLINE (1966 to December 2011) and Scientific Citation Index databases.

Selection criteria

We selected observational and randomized studies, published in English, French, Spanish or Portuguese that evaluated the associations between breastfeeding and diarrhea or respiratory infections outcomes in children younger than 5 years of age. Studies that did not use an internal comparison group were excluded from the meta-analyses. The type of categorization of breastfeeding varied by study, but in all of them it was possible to compare a group with more intense breastfeeding practices with another with less intense breastfeeding. (e.g., ever versus never breastfed; breastfed for x months versus breastfed for less than x months, exclusively versus partially or not breastfed, etc.).

Data extraction and analysis

Two reviewers using a standardized protocol independently evaluated the manuscripts; any disagreements were solved by consensus. Heterogeneity among studies was assessed with the Q-test and I-square. Because heterogeneity was evident for all outcomes, random-effects models were used throughout.

Effect on diarrhea

We identified 15 studies that provided 18 estimates on the effect of breastfeeding on diarrhea morbidity among children < 5 years. More intense breastfeeding practices were associated with a pooled relative risk of diarrhea incidence of 0.69 (95% confidence interval: 0.58; 0.82) compared to less intense breastfeeding. Among infants aged ≤ 6 months, we obtained 49 estimates from 23 studies, with a corresponding pooled relative risk 0.37 (95% confidence interval: 0.27; 0.50). We also identified

11 studies that evaluated children aged > 6 months, among whom the pooled relative risk was 0.46 (95% confidence interval: 0.28; 0.78). Breastfeeding also decreased the risk of hospitalization from diarrhea [pooled relative risk: 0.28 (95% confidence interval: 0.16; 0.50) and diarrhea mortality [pooled relative risk: 0.23 (95% confidence interval: 0.13; 0.42)]. Furthermore, we identified three randomized trials of breastfeeding promotion; diarrhea morbidity was lower in the group receiving the intervention [pooled relative risk: 0.69 (95% confidence interval: 0.49; 0.96)].

Effect on respiratory infection

We identified 18 studies that provided 22 estimates on the effect of breastfeeding on any respiratory infection outcome for any subgroup of under-five children, and 16 studies that restricted the analysis to infants aged ≤ 6 months. Breastfeeding reduced the risk of hospitalization for respiratory infection by 57% [pooled relative risk: 0.43 (95% confidence interval: 0.33; 0.55)], and this protective effect did not change with age. Studies that compared breastfed with non-breastfed children reported the highest protective effect [pooled relative risk: 0.33 (95% confidence interval: 0.24; 0.46)] against hospitalization for respiratory infection. Mortality from lower respiratory tract infections was also reduced among breastfed children [pooled relative risk: 0.30 (95% confidence interval: 0.16; 0.56)]. Furthermore, breastfeeding also reduced the prevalence or incidence of lower respiratory tract infection [pooled relative risk: 0.68 (95% confidence interval: 0.60; 0.77)].

Limitations

Because nearly all studies included in the analyses are observational, we were not able to completely rule out the possibility that the beneficial effect of breastfeeding was due to self-selection of breastfeeding mothers or residual confounding. Nevertheless, we identified three randomized trials in which breastfeeding promotion reduced the risk of diarrhea.

Reviewer's conclusion

The available evidence suggests that breastfeeding reduces the risk of diarrhea and respiratory infection. All effects were statistically significant, and for most outcomes the magnitude of the effects were large. Protection was observed both in low income and high income countries.

CHAPTER 1

Introduction

Breastfeeding has well-established short-term benefits, particularly the reduction of morbidity and mortality due to infectious diseases in childhood. A pooled analysis of studies carried out in middle/low income countries showed that breastfeeding substantially lowers the risk of death from infectious diseases in the first two years of life (*1*). These benefits have also been reported in high-income countries. Based on data from the United Kingdom Millennium Cohort, Quigley et al (*2*) estimated that optimal breastfeeding practices could prevent a substantial proportion of hospital admissions due to diarrhea and lower respiratory tract infection.

A systematic review by Kramer et al (*3*) confirmed that exclusive breastfeeding in the first 6 months of life decreases morbidity from gastrointestinal and allergic diseases, without any negative effects on growth. Given such evidence, it has been recommended that in the first six months of life, every child should be exclusively breastfed, with partial breastfeeding continued until two years of age (*4*).

This systematic review and meta-analysis was aimed at assessing the effect of breastfeeding on respiratory infection and diarrhea disease in childhood.

... CHAPTER 2 ...

Methodological issues

Randomized controlled trials often provide the best evidence on the association between an exposure – such as breastfeeding – and a health outcome. Randomization results in a high likelihood that the study will not be affected by confounding or self-selection (*5*). Furthermore, existing guidelines propose standards for conducting, analyzing and reporting clinical trials, which help increase the validity of the evidence (*6*).

On the other hand, the short-term benefits of breastfeeding evaluated in the present meta-analyses are an ethical challenge to the design of randomized trials on the consequences of breastfeeding. It is currently unethical to randomly allocate subjects to receive breastmilk. But, it is ethically sound to allocate mothers to receive – or not to receive – breastfeeding counseling. In Belarus, the Promotion of Breastfeeding Trial (*7*) randomly assigned maternity hospitals and their affiliated polyclinics to the Baby-Friendly Hospital Initiative. The proportion of infants exclusively breastfed at 3 and 6 months was substantially higher among infants from the intervention group. This trial is ethically sound because mothers were randomly assigned to receive intense breastfeeding promotion, compared to usual care in the hospitals. On the other hand, compliance to the intervention was far from universal, only 43.3% of the infants in the intervention group were exclusively breastfed at 3 months compared to 6.4% in the comparison arm. In Mexico, Morrow et al (*8*) randomly allocated mothers to one of the intervention group (six or three breastfeeding-counseling home visits) or to the control group. The proportion of exclusively breastfed infants at 3 months was higher among those whose mother received six visits. In another trial in India, mothers were assigned to receive or not visit on promotion of exclusive breastfeeding, at 3 months the proportion of exclusively breastfed infants was higher among infants in the intervention group (*9*). In these trials, intervention and control groups represented a mixture of breastfeeding practices. Therefore, the effect of breastfeeding is underestimated, and statistical power is reduced.

The assessment of the evidence on the health consequences of breastfeeding is mostly based on observational studies because of the small number of randomized controlled trials. Prospective birth cohort studies are the next-best design in terms of strength of evidence.

Below, we discuss the strengths and weaknesses of observational studies, as well as approaches that may help overcome their main shortcomings.

Factors affecting internal validity

Losses to follow-up

If losses to follow-up are high, selection bias may be introduced. This may affect both randomized and observational studies. In order to assess the study susceptibility to selection bias, baseline data, such as breastfeeding duration, should be compared between those subjects who were followed up and those who were not. If attrition rates are not related to breastfeeding duration or other baseline characteristics, selection bias is unlikely (*10*). Unfortunately, this information was not available for some studies.

Misclassification

Inaccurate measurement of exposure or outcome leads to misclassification. And misclassification may be differential or non-differential.

Retrospective studies are more susceptible to recall bias and direction of bias may be modified. For example, Huttly et al (*11*) observed that Brazilian mothers of high socioeconomic status tended to overestimate the breastfeeding duration, whereas among poor mothers this was not the case. This differential recall of breastfeeding duration would overestimate the protective effect of breastfeeding because high socioeconomic status is associated with a lower risk of infectious diseases in childhood.

On the other hand, if the measurement error is not related to exposure or outcome, non-differential misclassification occurs. Such bias underestimates the measure of association, and, therefore, reduces the likelihood of observing a significant association. Indeed, in a meta-analysis on the relationship between maternal smoking in pregnancy and breastfeeding duration, the odds ratio for weaning at 3 months was inversely related to the length of recall for exposure and outcome (*12*).

Confounding

Confounding is one of the challenges in interpreting the evidence of observational studies. Even large studies that managed to measure the possible confounders may still be affected by residual confounding, if the confounder variables were not properly measured or adjusted for. Some methods have been suggested to improve causal inference. These include comparison of siblings in within-family analyses, which allow controlling for unmeasured maternal and family variables (socioeconomic status, maternal variables) as well as for self-selection bias, because these characteristics are shared among siblings. Usually, sibling studies assess the effect of discordance on breastfeeding duration or complementary feeding on the outcome. A limitation of these studies is that heterogeneity in breastfeeding duration is smaller among siblings than that observed among unrelated individuals and the sample size for the sibling analysis are smaller, decreasing statistical power. In the present systematic reviews and meta-analyses, we did not observe any study on the short-term effects of breastfeeding that have used this approach.

Another strategy involves the comparison across studies with a different confounding structure. In this approach, if an association is causal, the association should be observed in every setting, in spite of differing confounding structures.

Reverse causality

Reverse causality occurs when breastfeeding is stopped as a consequence of hospitalization or an episode of diarrhea or respiratory disease (*13*). Cross-sectional and retrospective studies are more susceptible to this bias that tends to overestimate the protective effect of breastfeeding against infections because the prevalence of breastfeeding is underestimated among those who developed diarrhea or respiratory infection.

This bias can be avoided by the following strategies:

- exclusion of deaths or episodes occurring within the first 7 days of life;
- assessment of infant feeding practices before the onset of the episode.

Main sources of heterogeneity among studies

Heterogeneity among observational studies is unavoidable, and well-conducted meta-analyses must incorporate a detailed evaluation of main sources of heterogeneity (*14*). The following possible sources of heterogeneity were considered for all reviews in the present meta-analyses.

Year of birth

Studies that assessed the effect of breastfeeding on infectious diseases have been carried out at different times in the past. During this period, the diets of non-breastfed infants and the environmental condition have changed markedly in some areas around the world. Therefore, the year of birth of the studied population may affect the long-term effects of breastfeeding, representing a source of heterogeneity among studies. This possibility was investigated in the present review.

Length of recall of breastfeeding

Misclassification of breastfeeding duration has been discussed in the section on factors affecting internal validity. Feeding history is usually assessed retrospectively, with different length of recall. As previously mentioned, length of recall is related to misclassification of breastfeeding duration. This bias tends to increase with the time elapsed since weaning, with mothers who breastfed for a short period being more likely to exaggerate breastfeeding duration, while the opposite is observed for women who breastfed for long periods (*11,15*). Therefore, length of recall is a potential source of heterogeneity among studies.

Categories of breastfeeding duration

Studies on the short-term consequences of infant feeding have compared different groups according to breastfeeding duration. Some studies compared ever-breastfed subjects to those never breastfed, whereas other studies compared subjects breastfed for less than a given number of months to those breastfed for longer periods. For the assessment of the long-term consequences of breastfeeding, the comparison of ever versus never breastfed makes sense if the first hours of life are considered as a critical window for the programming effect of breastfeeding, for example if an epigenetic mechanism is being postulated (*16*). Concerning the evaluation of the short-term effects of breastfeeding, usually there is no critical-window effect, but rather a cumulative effect of breastfeeding. Therefore, studies that compared ever vs. never breastfed subjects would tend to underestimate any association. The classification of breastfeeding duration is another factor to be considered in heterogeneity analyses.

Study setting

The majority of the studies on the effect of breastfeeding on diarrhea and respiratory infections have been carried out in low-income countries. The findings from these studies may not hold for populations exposed to different environmental and nutritional factors because of differences in the type of milk fed to non-breastfed infants. Furthermore, infants who are not exclusively breastfed are exposed to a variety of foodstuffs, such as industrialized formula, animal milk or traditional weaning. This heterogeneity in the group that is not exposed to exclusive breastfeeding must be taken into account. This issue is related to the age of the cohort, discussed above, and to the setting of the study, e.g. high or low-income country. Finally, we should bear in mind that in low-income countries, non-breastfed infants are more exposed to weaning foods that are contaminated with pathogens that may cause gastrointestinal infections (*17,18*). These differences in environmental condition may modify the effect of infant feeding.

••• **CHAPTER 3** •••

Search methods

Selection criteria for studies

In the present meta-analyses, we searched for observational and randomized studies, published in English, French, Spanish or Portuguese that evaluated the associations between breastfeeding and diarrhea and respiratory infections outcomes.

Studies that did not use an internal comparison group were excluded. We did not apply any restrictions on the type of categorization of breastfeeding (never versus breastfed, breastfed for more or less than a given number of months, exclusively breastfed for more or less than a given number of months). Instead, as discussed in the previous section, the type of categorization of breastfeeding was considered as possible source of heterogeneity among the studies.

Type of outcome measures

In the present systematic reviews and meta-analyses, we searched for manuscripts that have assessed the following diarrhea and respiratory infection outcomes:

- Mortality
- Hospitalization
- Incidence
- Prevalence

For the review on respiratory infection, we excluded those studies that evaluated the relationship between breastfeeding and upper respiratory infection.

In the review on diarrhea outcomes, studies that evaluated the effect of breastfeeding on pathogen-specific diarrhea, such as Shigella or rotavirus, were excluded from the review.

Search strategy

We tried to identify as many relevant studies as possible, minimizing the likelihood of selection bias. Two independent literature searches were carried out, using the terms described below. Initially, we searched Medline (1966 to December 2011) using the following terms for breastfeeding: breastfeeding; breast feeding; breastfed; breastfeed; bottle feeding; bottle fed; bottle feed; infant feeding; human milk; formula milk; formula feed; formula fed; weaning.

Every breastfeeding term was combined with each of the following terms for the outcomes:

- **Mortality:** Infant mortality; pneumonia AND mortality; pneumonia and death; respiratory infection AND mortality; respiratory infection and death; lower respiratory tract infection and mortality; lower respiratory tract infection and death; diarrhea AND mortality; diarrhea AND death.

- **Hospitalization:** hospitalization; AND infant OR childhood; AND pneumonia OR respiratory infection OR lower respiratory tract infection OR diarrhea
- **Incidence/prevalence:** infant OR childhood; AND pneumonia OR respiratory infection OR lower respiratory tract infection OR diarrhea

Initially, we scanned through the titles of studies identified in the electronic search to exclude those that were clearly irrelevant. Thereafter, abstracts were perused to further exclude studies. Finally, the full text of the remaining studies was retrieved and relevant articles were identified. In addition to the electronic search, reference lists of the articles identified was searched, and we perused the Web of Science Citation Index for manuscripts citing the identified articles. Attempts were made to contact the authors of all studies that did not provide sufficient data to estimate the pooled effect. We also contacted the authors to clarify any queries on the study methodology or result.

CHAPTER 4

Review methods

Assessment of study characteristics

In the present systematic review and meta-analyses, study quality was not evaluated using summary scores. On the other hand, study characteristics considered as being relevant methodological aspects were assessed and the contribution of each one to the heterogeneity among studies was evaluated (*19*). The following study characteristics were abstracted.

TABLE 4.1

Characteristics abstracted from each study.

Characteristic	Categorization
Sample size	Continuous
Follow-up rates (if applicable)	Continuous
Type of study	Randomized trial Birth cohort Other
Categorization of breastfeeding	Never versus ever < or >= than X months (any breastfeeding) < or >= than X months (exclusive breastfeeding)
Outcome	Incidence Prevalence Mortality Hospitalization
Control for confounding	None Age Socioeconomic and demographic variables Socioeconomic, demographic and birthweight Socioeconomic, demographic, birthweight and maternal smoking
Type of study population	Low income Middle income High income
Year of birth of subjects	Continuous
Age at outcome assessment	Continuous
Susceptibility to reverse causality	Yes No

Data abstraction

Two independent reviewers extracted data on the above characteristics from each study using a standardized protocol, and disagreements were resolved by consensus rating.

Data analysis

Pooled effect estimates

In the meta-analyses, effect measures were presented as pooled relative risks. Definition of exposure to breastfeeding followed the classification used in each study, and a relative risk < 1 indicated that breastfed subjects presented a lower risk of the outcome.

Fixed or random-effects model

To pool the studies estimates, we used a fixed and a random-effects model. Under the fixed-effect model, we assume that there is one true effect size and the difference among studies results is due to random variation. In the fixed-effect model, studies are weighted by their precision (inverse of the standard error) (*20*). On the other hand, under the random-effects model we assume that the true effects also vary, and the pooled effect needs to take into consideration the additional source of variation. In the random-effect model, studies are weighted by their precision plus the estimate of the between studies variance (heterogeneity) (*21*). By incorporating a second source of variability (variance between studies) in the estimate of the variance, the confidence interval in the random-effect model is wider than that for the fixed-effect model. Because the between studies variance is the same for every study, the random-effect model gives greater weight to smaller studies.

In the present meta-analyses, heterogeneity among studies was assessed with the Q-test and I-square; if either method suggested that between-studies variability was higher than that expected by chance, a random-effects model was used (*21*). Otherwise, a fixed-effect model is recommended. In this series of meta-analyses, heterogeneity was evident for all outcomes, and thus random-effects models were used throughout.

Publication bias

Studies reporting statistically significant associations are more likely to be published and to be cited by others articles, whereas small studies with negative findings are less often published. Therefore, studies reporting an association are more likely to be included in a systematic-review. Publication bias is more likely to affect small studies because the great amount of resources (time and money) spent in larger studies makes them more likely to be published, regardless of their results (*20*). In meta-analysis, publication bias is a type of selection bias.

Funnel plots and Egger's test are usually employed to assess the presence of publication bias (*22*), but in the present meta-analyses we did not estimate the likelihood of selection bias with the funnel plot or the Egger's test because several comparisons were done. On the other hand, the analyses were stratified according to study size, in order to assess the impact of publication bias on the pooled estimate.

Reverse causality

Cross-sectional and retrospective studies on the short-term consequences of breastfeeding are susceptible to reverse causality. Because breastfeeding may be stopped due to an illness or hospital admission, the assessment of feeding status at the moment of the interview may increase the proportion of non-breastfed infants among those who developed the outcome. This bias tends to overestimate the short-term protective effect of breastfeeding. In order to avoid such bias, the study should evaluate the feeding practices prior to the onset of the episode. In the present meta-analyses, we evaluate whether the studies were susceptible to reverse causality.

Assessing heterogeneity

The last phase of the analyses relied on meta-regression to assess the contribution of study characteristics to between-study variability (*23*). In this approach, if the data are homogenous or if the heterogeneity is fully explained by the covariates, the random-effects model is reduced to a fixed effect model. This analysis was performed using the METAREG command within STATA. Each of the items listed in table 4.1 were included as covariates in the meta-regression, one at a time, rather than using an overall score. This approach allows the identification of aspects of study design that were responsible for heterogeneity between studies (*24*).

... CHAPTER 5 ...

Diarrhea

In spite of recent progress, diarrhea remains as one of the leading causes of death among children < 5 years. In 2010, diarrhea was estimated to have caused about 800,000 child deaths globally (*25*). In 1984, a comprehensive review indicated that promotion of breastfeeding was one of the most important interventions for controlling diarrhea among children (*26*). In the 2003 Lancet Child Survival series, breastfeeding promotion was again identified as one of the most cost-effective interventions against under-five deaths in general, and against diarrhea in particular (*27*).

Biological plausibility

Several mechanisms for a possible protective effect of breastfeeding against gastrointestinal infections have been proposed, including the presence in breastmilk of substances with antimicrobial or immunological properties, avoidance of contamination (as in non-human milk or baby bottles), and the general nutritional status of breastfed infants.

Breastmilk contains several antimicrobial and anti-inflammatory factors, hormones, digestive enzymes and growth modulators that protect against infections. Below, we briefly discuss the evidence on the protective effect of some of the components of breastmilk.

Oligosaccharides are the third largest solid component of human milk. It has been suggested that oligosaccharides homology to cell surface carbohydrates would block the attachment of pathogens to the infant's mucosa, preventing the development of gastrointestinal infections (*28*).

Breastmilk also confers immunity against gastrointestinal infections by carrying antibodies (secretory IgA) produced by mothers who have been exposed to such pathogens, protecting the infant from developing an infection (*29,30*).

Lactoferrin, one of the main proteins in human milk can destroy pathogens and reduce inflammatory responses. Furthermore, lactoferrin increases the activity of the immune system because it is a growth factor for lymphocytes (*31*).

A second mechanism is that non-breastfed infants are more exposed to pathogens that may cause diarrhea than breastfed subjects. Many studies attest to the presence of pathogens in foods offered to infants. For example, in The Gambia, Rowland et al (*17*) observed that weaning foods traditionally given to children were contaminated with microorganisms that could cause gastrointestinal infections. Another study from Chile showed that most feeding bottles harbored large numbers of pathogens that could cause gastrointestinal infection (*18*).

Last, it has been proposed that in low-income settings optimal breastfeeding practices can prevent undernutrition associated with repeated infections and with the use of over-diluted breastmilk substitutes (*32*). Good nutrition is essential for non-specific immunity that contributes to fighting infections in general.

When reviewing the mechanisms through which breastfeeding may protect against diarrhea, it is important to consider the different settings where studies are carried out. Whereas the biological characteristics of breastmilk do not seem to vary markedly in high- and low-income societies, the other two mechanisms (contamination and nutritional status of non-breastfed infants) are likely to play a much larger role in poor societies without proper sanitation and with inadequate weaning foods.

Overview of the evidence

The protective effect of breastfeeding against mortality and morbidity from diarrhea has been widely studied. In the electronic search, we identified five systematic reviews and/or meta-analyses on this subject.

In 1984, Feachem & Koblinsky (*26*) systematically reviewed the evidence on the association between diarrhea morbidity and infant feeding. In relation to exclusively or partially breastfed infants, the median risk of morbidity from diarrhea among infants who were not breastfed was 3.0 for those younger than 2 months of age, 2.4 for infants aged 3 to 5 months and about 1.4 for those aged 6 to 11 months. Among children older than 1 year of age, no association between breastfeeding and diarrhea was observed. Furthermore, the relative risk of diarrhea in infants under 6 months of age who were not breastfed ranged from 3.5 to 4.9, in comparison to those who were exclusively breastfed. In this age group, it was estimated that promotion of breastfeeding would reduce diarrhea morbidity by 8% to 20%, depending on different assumptions, and mortality would decrease by 24 to 27%.

Huttly et al (*33*) updated in 1997 the Feachem & Koblinsky (*26*) review of potential interventions for the prevention of morbidity from diarrhea in childhood. Breastfeeding was again pointed as one of the key preventive strategies for prevention of childhood diarrhea.

Also in 1997, Golding et al (*34*) systematically reviewed the evidence on the relationship between breastfeeding and cause-specific diarrhea or gastroenteritis. Both in developed or in developing countries, exclusive breastfeeding protected infants under six months from diarrhea and gastroenteritis. The protective effect was not consistent for rotavirus infection but was clearly observed for non-viral pathogens. The authors concluded that breastfeeding protected the infant against non-viral diarrhea.

In 2004, Kramer et al (*3*) reviewed the evidence on the effect on child health and growth of exclusive breastfeeding for 6 months. Morbidity from gastrointestinal diseases was lower among infants who were exclusively breastfed for 6 months, in comparison to infants exclusively breastfed for 3–4 months.

Recently, Lamberti et al (*35*) evaluated the effect of breastfeeding duration on morbidity and mortality from diarrhea. Among infants younger than 6 months, the risk of dying from diarrhea was 10.5 (95% confidence interval: 2.79; 39.6) times higher among those infants who were not breastfed in relation to those who were exclusively breastfed. Among children in the age range 6 to 23 months, the protective effect of breastfeeding was smaller, but still statistically significant [relative risk 2.18 (95% confidence interval: 1.44; 4.16)]. Therefore, the evidence from this recent review also indicated that breastfeeding protects against diarrhea.

In the present systematic review and meta-analysis, the electronic search identified 41 studies that provided 81 estimates on the relative risk of morbidity, mortality or hospitalization from diarrhea according to infant feeding.

Studies published since 2007 that were not included in any of the previous cited systematic reviews and meta-analyses reported on research carried out in Denmark (*36*), Bangladesh (*37*), Philippines (*38*), Zimbabwe (*39*) and Guinea (*40*), and two from the United Kingdom (*2, 41*), all of which confirmed the presence of strong protection by breastfeeding. Further details on these studies are provided in Tables 5.1 to 5.3.

Update of the existing meta-analyses

A new meta-analysis was carried out including (a) studies included in the existing meta-analyses; (b) the recently published studies described above, and (c) a small number of older studies that had not been identified by the earlier reviews but were detected in our computerized search starting in 1966.

Studies reporting on subgroups of infants – for example, preterm or low birthweight – were not included in the review. Neither were studies reporting on diarrhea due to specific agents.

Due to the large number of available studies, we calculated pooled effects separately for morbidity, hospitalizations and mortality. For each outcome we present initially analyses that included all children under five years, followed by studies restricted to children under six months of age, and to those including children aged 6-59 months.

For children < 5 years of age, we identified 15 studies that provided 18 estimates on the effect of breastfeeding on morbidity (Table 5.1). Figure 5.1 shows that among children < 5 years of age, breastfed children were less likely to present diarrhea. When studies reporting on incidence and prevalence were combined, the pooled relative risk was 0.69 (95% confidence interval: 0.58; 0.82)].

The effect of breastfeeding among infants aged ≤ 6 months was also assessed. We identified 23 studies (Table 5.2) that provided 49 estimates on the effect of breastfeeding on diarrhea morbidity or mortality. Figure 5.2 shows that morbidity due to diarrhea was lower among breastfed infants. [pooled relative risk 0.37 (95% confidence interval: 0.27; 0.50)]. Because there was clear heterogeneity among studies, the estimates were pooled using a random-effect model. With respect to age at assessment of morbidity, we observed that the protective effect of breastfeeding seemed to be largest among infants younger than 4 months. On the other hand, because the confidence interval of the estimates from younger children overlapped with those for children aged 5 and 6 months, the difference was not statistically significant. (Figure 5.3). In Figure 5.4, the association between morbidity (incidence or prevalence) from diarrhea and infant feeding was stratified according to the categories of feeding used for comparison. Those studies that compared exclusive breastfed infants with non-exclusive breastfeeding and those that compared partial breastfed infants with those not breastfed were those reporting the smallest mean effect of breastfeeding on morbidity. On the other hand, the effect of breastfeeding was highest in studies that compared exclusively breastfed with non-breastfed infants.

In the literature search, we identified 11 studies that provided 14 estimates on the association between breastfeeding and morbidity or mortality from diarrhea among children aged > 6 months. (Table 5.3) The risk of morbidity from diarrhea was lower among those infants who were breastfed [pooled relative risk 0.46 (95% confidence interval: 0.28; 0.78)]. (Figure 5.5) With respect to the categorization of breastfeeding, most studies on children > 6 months of age compared children who were breastfed with those who were not breastfed. Independent of the categorization, there were consistent inverse associations between breastfeeding intensity and diarrhea outcomes. (Figure 5.6)

Figure 5.7 shows that breastfeeding decreased the risk of hospitalization from diarrhea [pooled relative risk: 0.28 (95% confidence interval: 0.16; 0.50)]. There was marked heterogeneity among studies, and the protective effect of breastfeeding was higher among young infants.

With respect to mortality, breastfeeding markedly decreased the risk of diarrhea mortality [pooled relative risk: 0.23 (95% confidence interval: 0.13; 0.42)]. Similarly to the observed for hospitalization, the effect of breastfeeding was higher among infants younger than 6 months. (Figure 5.8)

Table 5.4 shows that infants who were exclusively breastfed presented lower risk of morbidity from diarrhea even in relation to predominantly breastfed infants. Furthermore, infants who were not breastfed had the greatest risk of morbidity or hospitalization.

We identified three randomized trials in which breastfeeding promotion was related to diarrhea outcomes, whose results are summarized below. Because such analyses do not entail a comparison of breastfeeding categories, they could not be incorporated in our main meta-analyses. In Mexico, Morrow et al (*8*) showed that breastfeeding promotion increased the duration of breastfeeding; diarrhea episodes in the intervention group were reported for 12% of all infants, compared to 26% in the comparison group, a protection of 52%. In a randomized trial of exclusive breastfeeding promotion in India, the 7-day diarrhea prevalence was lower in the intervention than in the control communities at 3 months [0.64 (95% confidence interval: 0.44; 0.95)] and 6 months [0.85 (95% confidence interval: 0.72; 0.99)] (*9*). In the Belarus PROBIT trial (*7*), maternity hospitals were randomized to receive or not to receive promotion of exclusive breastfeeding. Children in the intervention group were less likely to present one or more episodes of gastrointestinal infections [odds ratio 0.60 (95% confidence interval: 0.40; 0.91)]. Hospital admissions were similar in both groups [odds ratio 0.92 (95% confidence interval: 0.62; 1.37)].

Data from the Belarus trials were also analyzed to compare risks of diarrhea according to breastfeeding categories, and these are incorporated in the present meta-analyses (Table 5.1). Taken together, the results of these trials support the presence of a causal effect of breastfeeding promotion against diarrhea morbidity. The pooled results on diarrhea morbidity from these three trials are presented in Figure 5.9, with a pooled relative risk of 0.69 (95% confidence interval: 0.49; 0.96). Such a significant effect was detected even though analyses were based on intent to treat, that is, both intervention and comparison groups included compliers and non-compliers.

Conclusion

In the assessment of the evidence on the short-term consequence of breastfeeding, confounding is an important methodological issue that should be taken into consideration, as discussed in a previous section. In low-income countries confounding is expected to underestimate the benefit of breastfeeding on diarrhea outcomes because breastfeeding tends to be more frequent among the poor. In high-income countries, where the rich tend to breastfeed for longer than the poor, confounding may be expected to operate in the opposite direction. In the meta-analysis on morbidity from diarrhea among infants ≤ 6 months of age, most studies were from low and middle-income countries. We observed that the pooled estimates were similar between studies that only reported unadjusted results [pooled relative risk: 0.39 (95% confidence interval: 0.30; 0.49) and those that adjusted their estimates for socioeconomic and other variables [pooled relative risk 0.35 (95% confidence interval: 0.23; 0.54)]. This suggests that the present meta-analysis was not affected by confounding. Furthermore, in low-income settings we expected negative confounding, that is, underestimation of the true effect, and results from most studies showed strong protection.

A second type of bias is reverse causality, that is, breastfeeding may have been interrupted or modified because of the diarrhea episode, thus leading to an association in the opposite direction than the one being postulated (*13*). Only one study explicitly accounted for this possibility, by ensuring that information on feeding practices was obtained for a date previous to the onset of the episode. This study showed substantial protection associated with breastfeeding (*42*).

Publication bias is another methodological issue that should be taken into consideration in the assessment of evidence from meta-analyses. The selective publication of small positive studies may overestimate the benefit of an intervention. Funnel plot is one of the strategies used to assess the susceptibility of the meta-analysis to publication bias. In the present meta-analysis, given the large number of different comparisons being made, we opted for not generating funnel plots. Instead, we stratified the analyses by sample size and observed that among infants ≤ 6 months of age, the mean effect of breastfeeding on morbidity from diarrhea was similar among studies with a sample size < 1000 subjects (pooled relative risk 0.39) and those with ≥ 1000 subjects (pooled relative risk 0.36). This finding suggests that publication bias is not distorting the results of the review.

In light of different comparisons of breastfeeding categories in the available studies (e.g. breastfed versus non-breastfed; predominantly breastfed versus partially breastfed; exclusively breastfed versus non-breastfed; and many other combinations), the overall pooled results must be interpreted with due caution. In these pooled results we compared children with greater exposure to breastfeeding against those in a lower exposure category – which in some cases included infants who were not receiving any breastmilk, but in other comparisons included children who were partially, or non-exclusively breastfed. Because many studies were available on diarrhea morbidity, it was possible to carry out separate meta-analyses for different types of comparisons (Figures 5.4 and 5.6) but for hospital admissions and mortality this was not possible. Nevertheless, it is reassuring that results from the different types of comparisons all point out to protective effects of breastfeeding.

Of the 81 comparisons included in this review, only four (*43–46*) showed higher risks associated with more intense breastfeeding, and these four had confidence intervals that included the unity.

The findings from our review suggest that breastfeeding substantially protects against morbidity/mortality from diarrhea and that such protection is higher among infants who are exclusively breastfed in the first 6 months of life. The protection afforded by more intense breastfeeding is in the orders of 80–90% for mortality and hospital admissions, and of 50% for morbidity. These results are robust, being observed in high and low-income settings, and across a number of different diarrhea related outcomes. Our updated and expanded results are consistent with the conclusions of previous reviews of the literature. The protection afforded by breastfeeding against diarrhea is certainly one of the most consistent findings in the epidemiological literature on any type of outcome, in the same category as for example the association between smoking and lung cancer.

TABLE 5.1

Breastfeeding and diarrhea outcomes among children < 5 years of age: studies included in the meta-analysis in ascending order of year of publication and subjects age at which outcome was measured

Author, Year	Year of birth of subjects	Study design	Age at assessment of the outcome	Outcome	Comparison	Relative risk (95% confidence interval)
Ellestad-Sayed (*47*), 1979	1971–1975	Cohort	0–12 months	Hospitalization	Breastfed vs. not breastfed	0.10 (0.01; 0.70)
Cunningham (*48*), 1979	1974–1976	Cohort	0–12 months	Incidence	Breastfed vs. not breastfed	0.52 (0.31; 0.81)
Cushing (*44*), 1982	1979	Cohort	0–12 months	Incidence	Breastfed vs. not breastfed	1.26 (0.76; 2.06)
Victora (*42*), 1987	1984–1985	Case-control	0–12 months	Mortality	Predominant breastfed vs. partial breastfed	0.27 (0.07; 1.00)
					Predominant breastfed vs. not breastfed	0.05 (0.02; 0.15)
Garrido (*49*), 1990	1987–1989	Case-control	0–12 months	Mortality	Predominant breastfed vs. partial breastfed	0.26 (0.07; 1.00)
					Predominant breastfed vs. not breastfed	0.13 (0.03; 0.56)
Chen (*50*), 1994	1981–1983	Cohort	0–18 months	Hospitalization	Breastfed vs. never breastfed	0.67(0.47; 0.94)
Mondal (*51*), 1996	Not available	Cohort	0–12 months	Incidence	Exclusive breastfed at 4 months vs. not exclusive breastfed at 4 months	0.33 (0.11; 0.96)
Molbak (*52*), 1997	1984–1986	Cohort	0–4 years	Prevalence	Exclusive breastfed vs. not breastfed	0.75 (0.56; 1.00)
Arifeen (*53*), 2001	1993–1995	Cohort	0–12 months	Mortality	Exclusive breastfed at 4 months vs. partial or not breastfed at 4 months	0.25 (0.09; 0.67)
Kramer (*54*), 2003	1996–1997	Randomized trial (observational analyses)	0–12 months	Prevalence	Exclusive breastfed for 6 months vs. exclusive breastfed for 3 months	0.67 (0.46; 0.97)
Kramer (*54*), 2003	1996–1997	Randomized trial (observational analyses)	0–12 months	Hospitalization	Exclusive breastfed for 6 months vs. exclusive breastfed for 3 months	0.79 (0.42; 1.49)
Vieira (*55*), 2003	2000–2001	Cross-sectional	0–12 months	Prevalence	Breastfed vs. not breastfed	0.83 (0.65; 1.05)
Quigley (*2*), 2007	2000 –2001	Cohort	0–8 months	Hospitalization	Exclusive breastfed vs. not breastfed	0.37 (0.18; 0.78)
Diallo (*40*), 2009	2005	Cross-sectional	0–9 months	Prevalence	Exclusive breastfed vs. non-exclusive breastfed	0.44 (0.21; 0.89)
Ethelberg (*36*), 2006	1999–2001	Case-control	0–12 months	Prevalence	Breastfed vs. not breastfed	0.44 (0.26; 0.75)
Benner, 2011	Not available	Cross-sectional	0–3 years	Prevalence	Breastfed vs. not breastfed	0.70 (0.58; 0.84)

TABLE 5.2

Breastfeeding and diarrhea outcomes among children < 6 months of age: studies included in the meta-analysis in ascending order of year of publication and subjects age at which outcome was measured

Author, Year	Year of birth of subjects	Study design	Age at assessment of the outcome	Outcome	Comparison groups	Relative risk (95% confidence interval)
Grantham-McGregor (*56*), 1970	1967–1968	Cohort	0–4 months	Incidence	Predominant breastfed vs. not predominant breastfed	0.29 (0.03; 1.15)
Wray (*43*), 1978	Not available	Cross-sectional	0–5 months	Prevalence	Predominant breastfed vs. not breastfed	0.34 (0.18; 0.67)
					Predominant breastfed vs. partial breastfed	0.46 (0.21; 0.91)
					Partial breastfed vs. not breastfed	0.75 (0.44; 1.27)
Brown (*57*), 1989	Not available	Cohort	0–5 months	Incidence	Exclusive breastfed vs. predominant breastfed	0.79 (0.51; 1.23)
					Exclusive breastfed vs. partial breastfed	0.69 (0.45; 1.04)
					Exclusive breastfed vs. not breastfed	0.39 (0.24; 0.63)
Mahmood (*58*), 1989	1983–1984	Case-control	2–3 months	Hospitalization	Exclusive breastfed vs. partial breastfed	0.16 (0.07; 0.36)
					Exclusive breastfed vs. not breastfed	0.03 (0.01; 0.07)
Mahmood (*58*), 1989	1983–1984	Case-control	4–5 months	Hospitalization	Exclusive breastfed vs. partial breastfed	0.34 (0.10; 1.11)
					Exclusive breastfed vs. not breastfed	0.04 (0.01; 0.14)
Popkin (*59*), 1990 (Rural area)	1983–1984	Cohort	0–2 months	Prevalence	Exclusive breastfed vs. predominant breastfed	0.32 (0.26; 0.4)
					Exclusive breastfed vs. not breastfed	0.06 (0.04 0.15)
Popkin (*59*), 1990 (Urban area)	1983–1984	Cohort	0–2 months	Prevalence	Exclusive breastfed vs. predominant breastfed	0.45 (0.37; 0.50)
					Exclusive breastfed vs. not breastfed	0.18 (0.14; 0.23)
Popkin (*59*), 1990 (Rural area)	1983–1984	Cohort	2–4 months	Prevalence	Exclusive breastfed vs. predominant breastfed	0.47 (0.41; 0.56)
					Exclusive breastfed vs. not breastfed	0.07 (0.05; 0.16)
Popkin (*59*), 1990 (Urban area)	1983–1984	Cohort	2–4 months	Prevalence	Exclusive breastfed vs. predominant breastfed	0.51 (0.47; 0.56)
					Exclusive breastfed vs. not breastfed	0.18 (0.15; 0.22)
Popkin (*59*), 1990 (Rural area)	1983–1984	Cohort	4–6 months	Prevalence	Exclusive breastfed vs. predominant breastfed	0.31 (0.26; 0.40)
					Exclusive breastfed vs. not breastfed	0.07 (0.05; 0.19)
Popkin (*59*), 1990 (Urban area)	1983–1984	Cohort	4–6 months	Prevalence	Exclusive breastfed vs. predominant breastfed	0.45 (0.43; 0.48)
					Exclusive breastfed vs. not breastfed	0.21 (0.18; 0.25)
Ketsela (*60*), 1990	Not available	Cross-sectional	0–6 months	Prevalence	Exclusive breastfed vs. predominant breastfed	0.29 (0.19; 0.44)
Brito Hernandez (*61*), 1995	1992–1993	Cross-sectional	< 5 months	Prevalence	Breastfed vs. not breastfed	0.45 (0.21; 0.96)

Author, Year	Year of birth of subjects	Study design	Age at assessment of the outcome	Outcome	Comparison groups	Relative risk (95% confidence interval)
Al-Ali (*62*), 1997	1994	Cross-sectional	0–5 months	Prevalence	Predominantly breastfed vs. not breastfed	0.31 (0.16; 0.59)
					Predominant breastfed vs. partial breastfed	0.88 (0.40; 1.92)
Lopez-Alarcon (*63*), 1997	Not available	Cohort	0–6 months	Incidence	Predominant breastfed vs. not breastfed	0.46 (0.27; 0.79)
					Breastfed vs. Not breastfed	0.65 (0.28; 1.49)
Clemens (*64*), 1999	1995–1997	Cohort	0–6 months	Incidence	Exclusive breastfed vs. not breastfed	0.67 (0.47; 0.97)
					Partial breastfed vs. not breastfed	0.72 (0.52; 1.01)
Raisler (*65*), 1999	1988	Cohort	0–6 months	Prevalence	Predominant breastfed vs. not breastfed	0.54 (0.43; 0.66)
WHO (*1*), 2000	1984–1991	Pooled analysis	0–6 months	Mortality	Breastfed vs. not breastfed	0.16 (0.11; 0.24)
Vieira (*55*), 2003	2001	Cross-sectional	0–6 months	Prevalence	Exclusive breastfed vs. not breastfed	0.52 (0.29; 0.93)
					Exclusive breastfed vs. predominant breastfed	0.77 (0.39; 1.55)
					Breastfed vs. not breastfed	0.58 (0.35; 0.96)
Khadivzadeh (*66*), 2004	Not available	Cross-sectional	6 months	Prevalence	Exclusive breastfed vs. partial breastfed	0.41 (0.21; 0.78)
Macias-Carrillo (*67*), 2005	1994	Cohort	0–3 months	Prevalence	Predominant breastfed vs. partial breastfed	0.39 (0.24; 0.62)
					Predominant breastfed vs. not breastfed	0.30 (0.16; 0.51)
Bahl (*45*), 2005	1995–1997	Cohort	6–26 weeks	Hospitalization	Exclusive breastfed vs. predominant breastfed	0.67 (0.23; 2.01)
					Predominant breastfed vs. not breastfed	0.18 (0.07; 0.46)
Bahl (*45*), 2005	1995–1997	Cohort	6–26 weeks	Mortality	Exclusive breastfed vs. predominant breastfed	1.36 (0.37; 5.03)
					Predominant breastfed vs. not breastfed	0.11 (0.03; 0.39)
Mihrshahi (*37*), 2007	2002–2003	Cross-sectional	0–3 months	Prevalence	Exclusive breastfed vs. not exclusive breastfed	0.73 (0.54; 0.98)
Mihrshahi (*46*), 2008	1999–2001	Cohort	0–5 months	Prevalence	Exclusive breastfed vs. predominant breastfed	1.79 (0.24; 12.5)
					Exclusive breastfed vs. partial breastfed	0.34 (0.17; 0.71)
Koyanagi (*39*), 2009	1997–2000	Cohort	3–6 months	Prevalence	Exclusive breastfed vs. partial breastfed	0.49 (0.27; 0.90)
Hengstermann (*387*), 2010	2007	Case control	0–6 months	Hospitalization	Exclusive breastfed vs. not breastfed	0.10 (0.02; 0.38)
Tarrant (*68*), 2010	1997	Cohort	0–6 months	Hospitalization	Exclusive breastfed vs. not breastfed	0.51 (0.25; 1.05)

TABLE 5.3

Breastfeeding and diarrhea outcomes among children > 6 months of age: studies included in the meta-analysis in ascending order of year of publication and subjects age at which outcome was measured

Author, Year	Year of birth of subjects	Study design	Age at assessment of the outcome	Outcome	Comparison groups	Relative risk (95% confidence interval)
Wray (*43*), 1978	Not stated	Cross-sectional	6–11 months	Prevalence	Breastfed vs. not breastfed	1.18 (0.74; 1.89)
Briend (*69*), 1988	1985–1986	Cohort	12–36 months	Prevalence	Breastfed vs. not breastfed	0.76 (0.72; 0.81)
Briend (*69*), 1988	1985–1986	Cohort	12–36 months	Mortality	Breastfed vs. not breastfed	0.47 (0.31; 0.68)
Mahmood (*58*), 1989	1983–1984	Case-control	6–7 months	Hospitalization	Partial breastfed vs. not breastfed	0.20 (0.07; 0.63)
Mahmood (*58*), 1989	1983–1984	Case-control	8–11 months	Hospitalization	Partial breastfed vs. not breastfed	0.11 (0.02; 0.53)
Brown (*57*), 1989	Not stated	Cohort	6–11 months	Incidence	Breastfed vs. not breastfed	0.77 (0.61; 0.96)
Knight (*70*), 1992	1987–1989	Case control	4–23 months	Prevalence	Predominant breastfed vs. not breastfed	0.20 (0.02; 2.27)
					Partial breastfed vs. not breastfed	0.12 (0.01; 1.08)
Molbak (*71*), 1994	1984–1986	Cohort	12–35 months	Mortality	Breastfed vs. not breastfed	0.29 (0.12; 0.71)
Al-Ali (*62*), 1997	1993–1994	Cross-sectional	6–14 months	Number of episodes	Predominant breastfed vs. not breastfed	0.32 (0.18; 0.59)
Mulder-Sibanda (*72*), 1999	1990–1991	Cross-sectional	6–11 months	Prevalence	Breastfed vs. not breastfed	0.12 (0.09; 0.18)
Mulder-Sibanda (*72*), 1999	1990–1991	Cross-sectional	12–23 months	Prevalence	Breastfed vs. not breastfed	0.54 (0.30; 0.95)
WHO (*1*), 2000	1984–1991	Pooled analysis	6–11 months	Mortality	Breastfed vs. not breastfed	0.53 (0.32; 0.83)
Fisk (*41*), 2011	1999–2007	Birth cohort	6–12 months	Prevalence	Breastfed vs. not breastfed	0.43 (0.30; 0.61)

TABLE 5.4

Effect of infant feeding on diarrhea outcomes in infants younger than 6 months

Outcome	Exposure category	Reference category		
		Exclusive breastfed	Predominant breastfed	Partial breastfed
Diarrhea incidence or prevalence	Predominant breastfed	0.44 (0.38; 0.50)		
	Partial breastfed	0.51 (0.37; 0.70)	0.50 (0.32; 0.79)	
	Not breastfed	0.20 (0.13; 0.29)	0.42 (0.33; 0.54)	0.73 (0.55; 0.97)
Hospitalization from diarrhea	Predominant breastfed	0.67 (0.23; 1.98)		
	Partial breastfed	0.20 (0.10; 0.41)		
	Not breastfed	0.09 (0.02; 0.44)	0.18 (0.07; 0.46)	

FIGURE 5.1

Relative risk and its 95% confidence interval of diarrhea morbidity (prevalence or incidence) in children < 5 years of life comparing breastfeeding categories in different studies

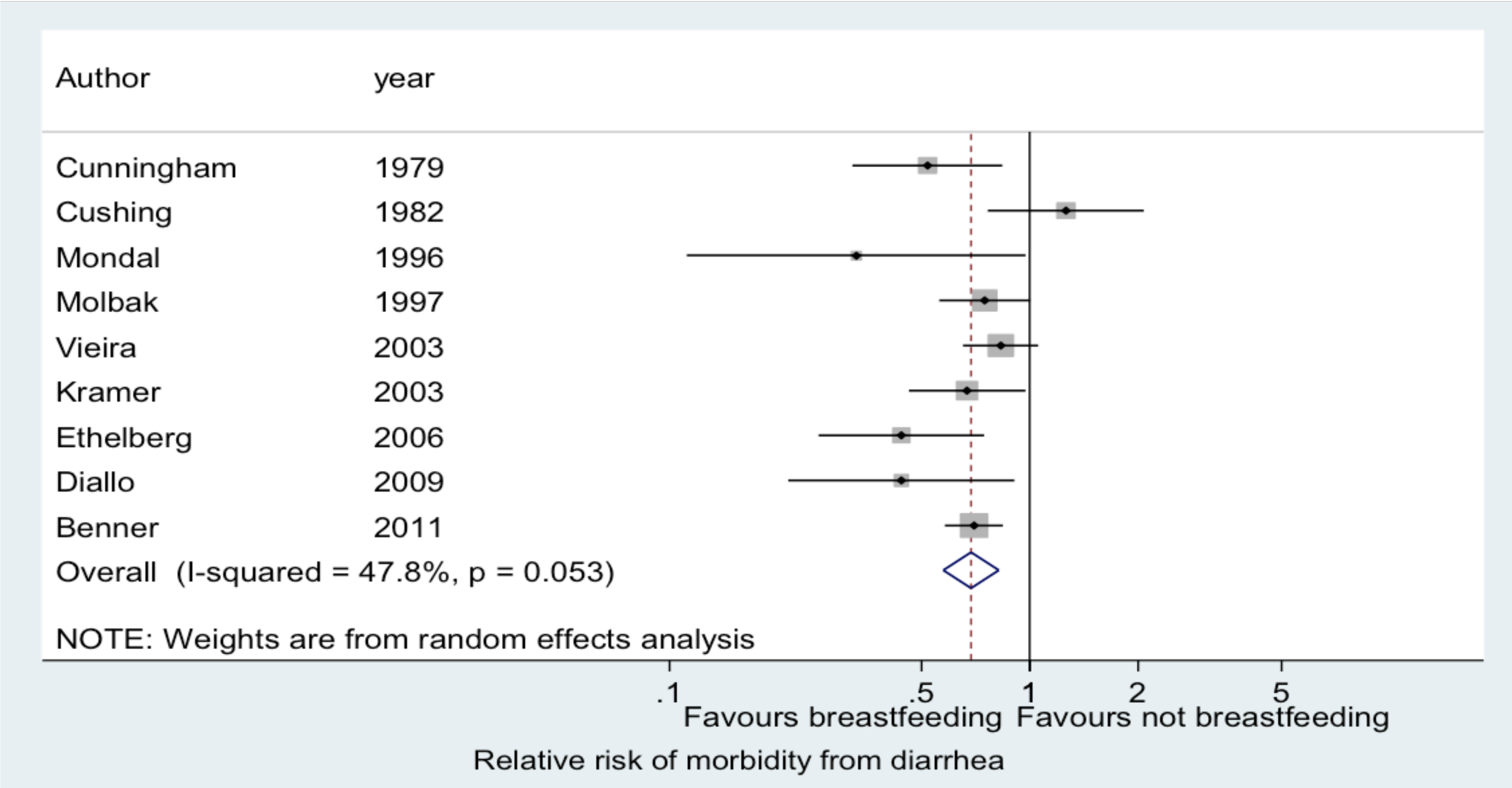


FIGURE 5.2

Relative risk and its 95% confidence interval of diarrhea morbidity (prevalence or incidence) in children ≤ 6 months of life comparing breastfeeding categories in different studies

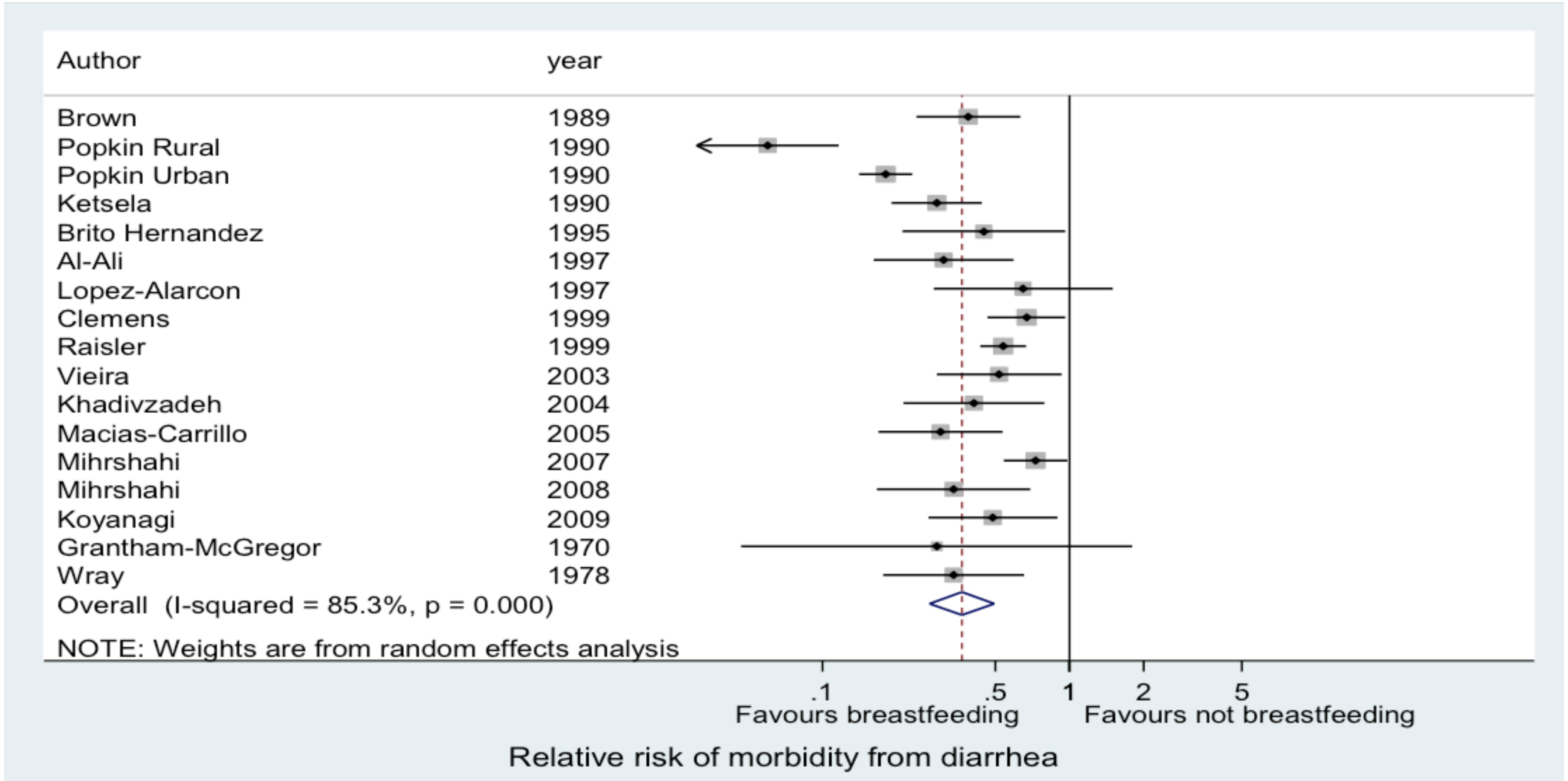


FIGURE 5.3

Relative risk and its 95% confidence interval of diarrhea morbidity (prevalence or incidence) in children ≤ 6 months of age according to age at assessment of morbidity from diarrhea

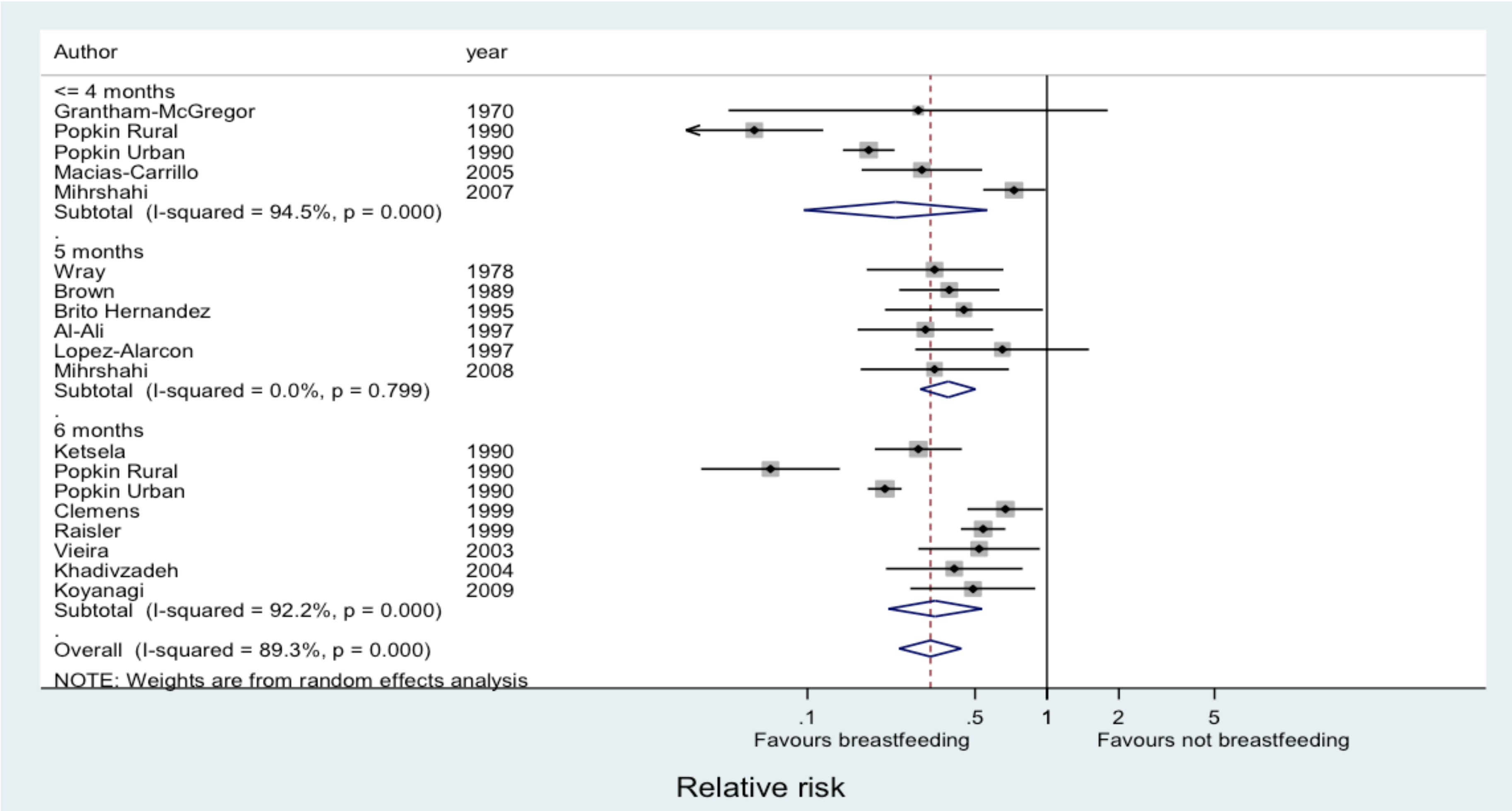


FIGURE 5.4

Relative risk and its 95% confidence interval of diarrhea morbidity (prevalence or incidence) in children ≤ 6 months of age according to the type of comparison between categories of infant feeding

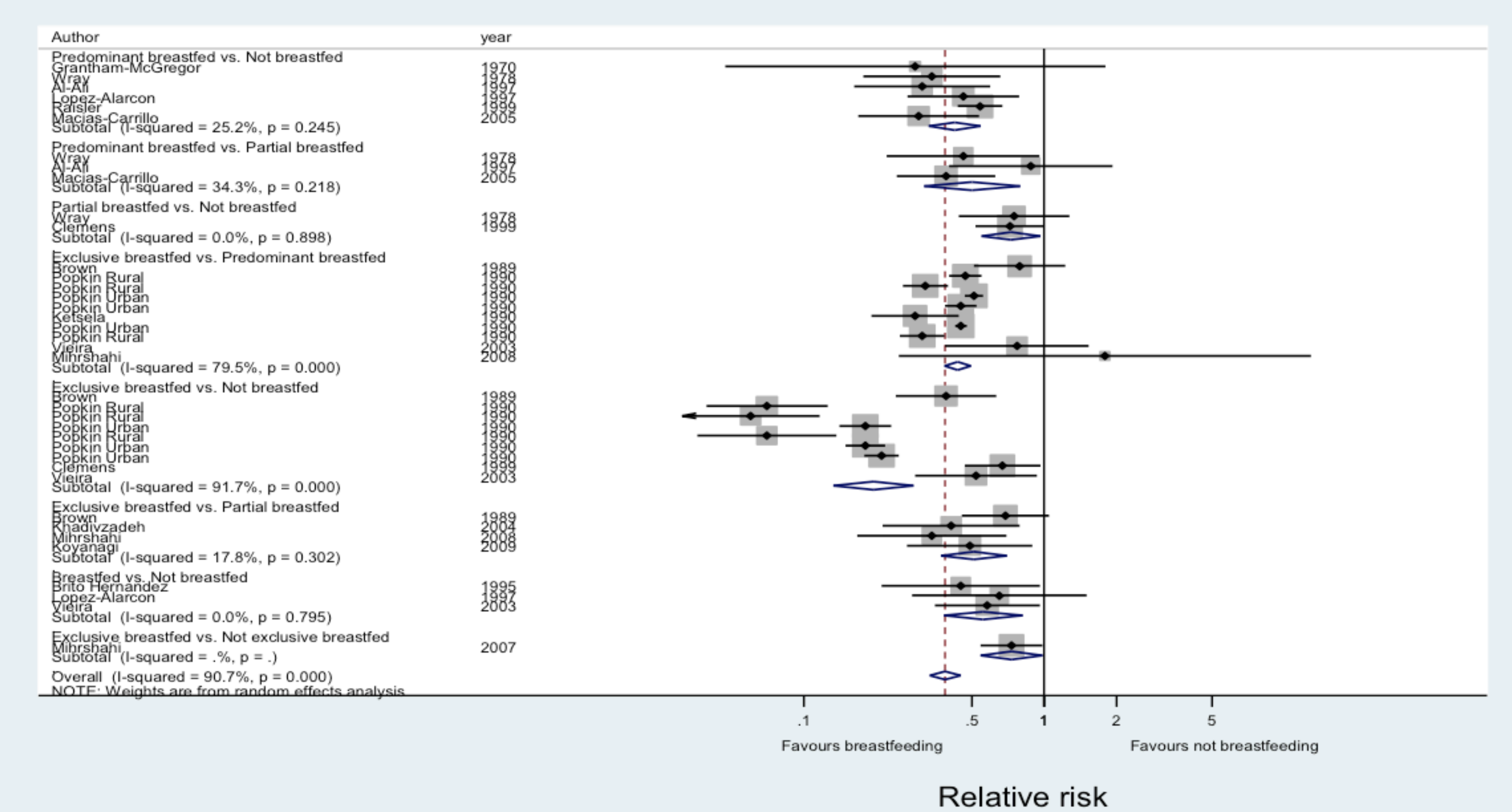


FIGURE 5.5

Relative risk and its 95% confidence interval of diarrhea morbidity (prevalence or incidence) in children > 6 months of life comparing breastfeeding categories in different studies

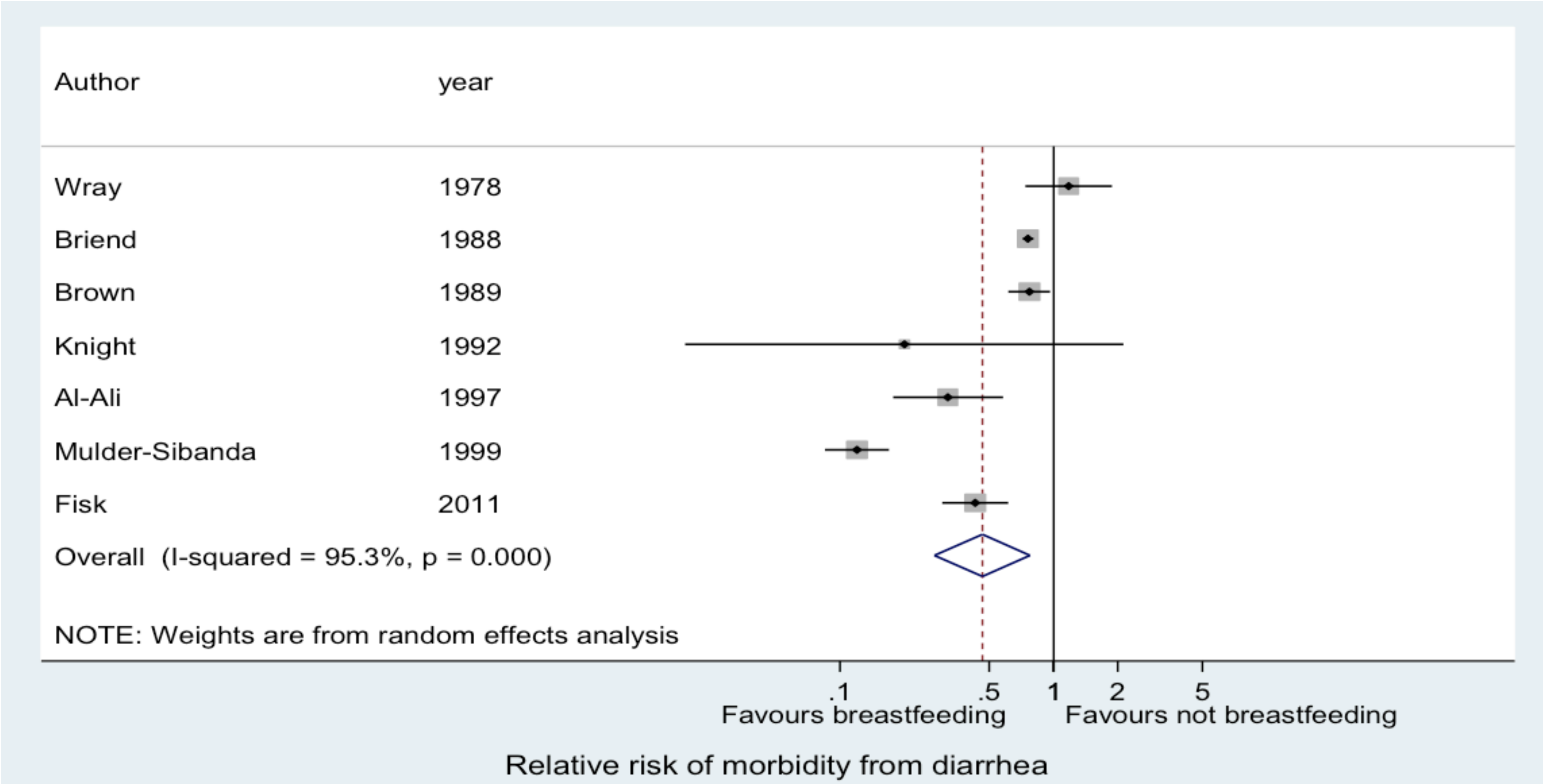


FIGURE 5.6

Relative risk and its 95% confidence interval of diarrhea morbidity (prevalence or incidence) in children > 6 months of age according to the different comparisons between categories of infant feeding

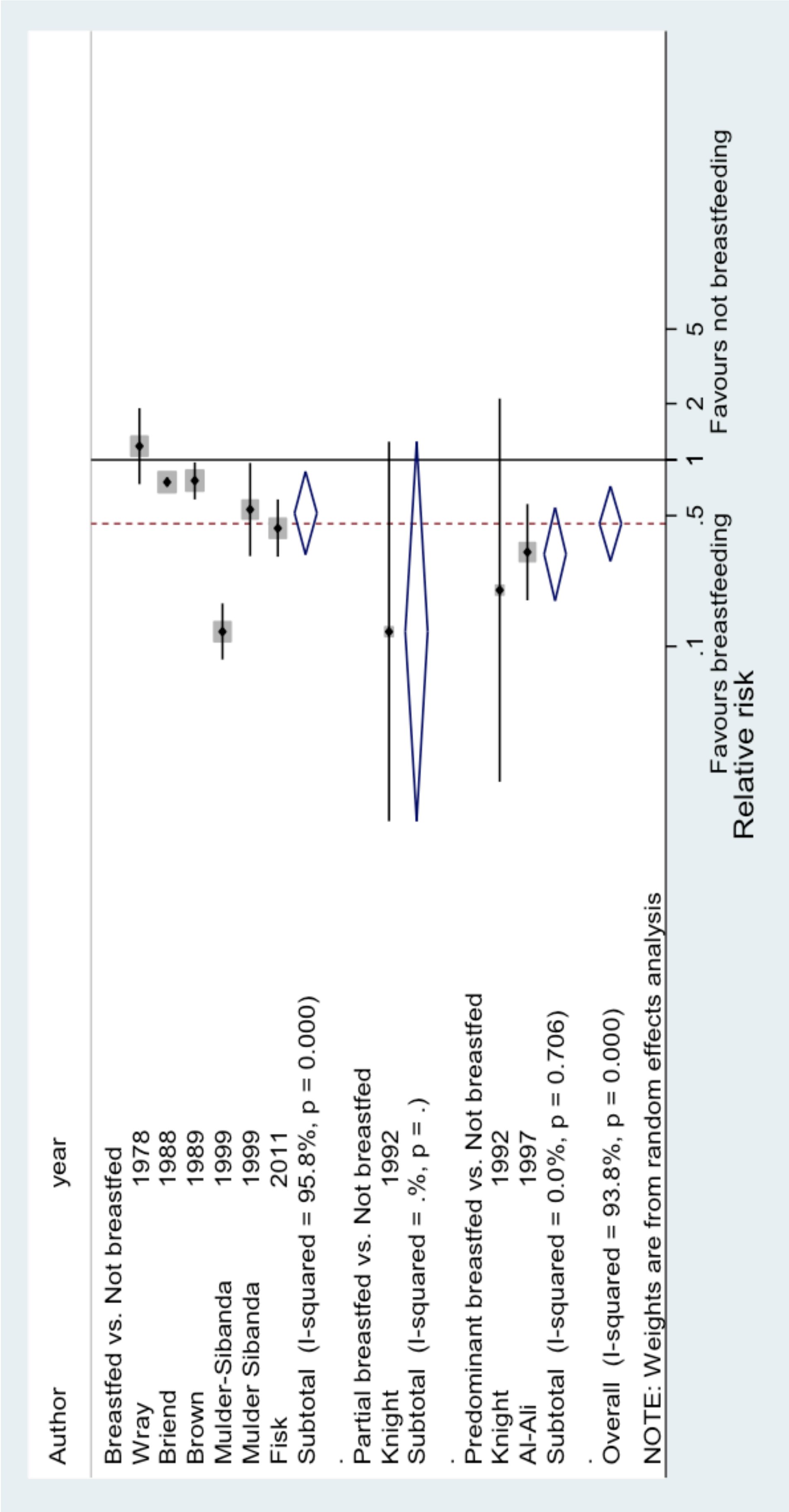


FIGURE 5.7

Relative risk and its 95% confidence interval of hospitalization from diarrhea comparing breastfeeding categories in different studies

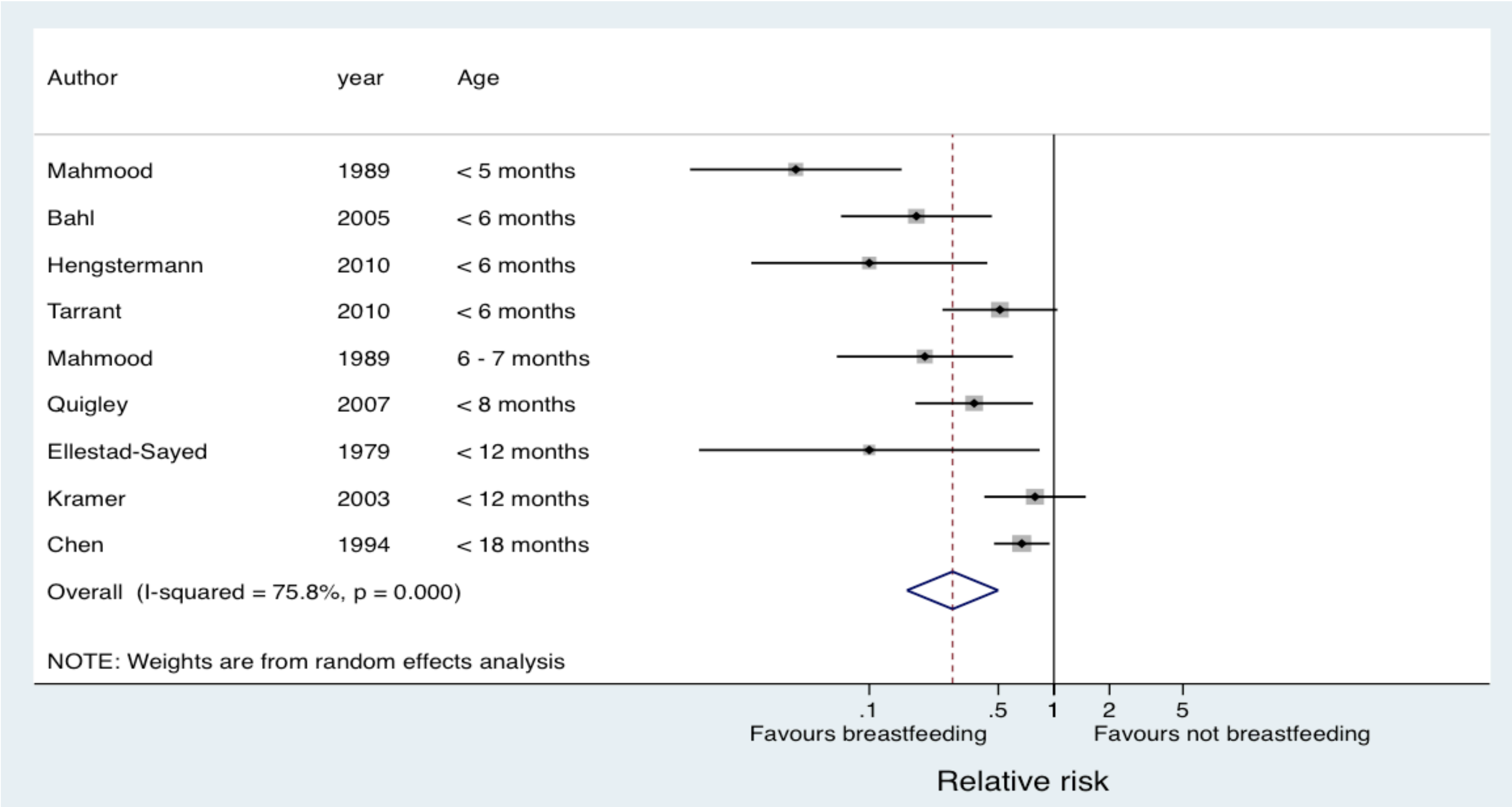


FIGURE 5.8
Relative risk and its 95% confidence interval of mortality from diarrhea comparing breastfeeding categories in different studies

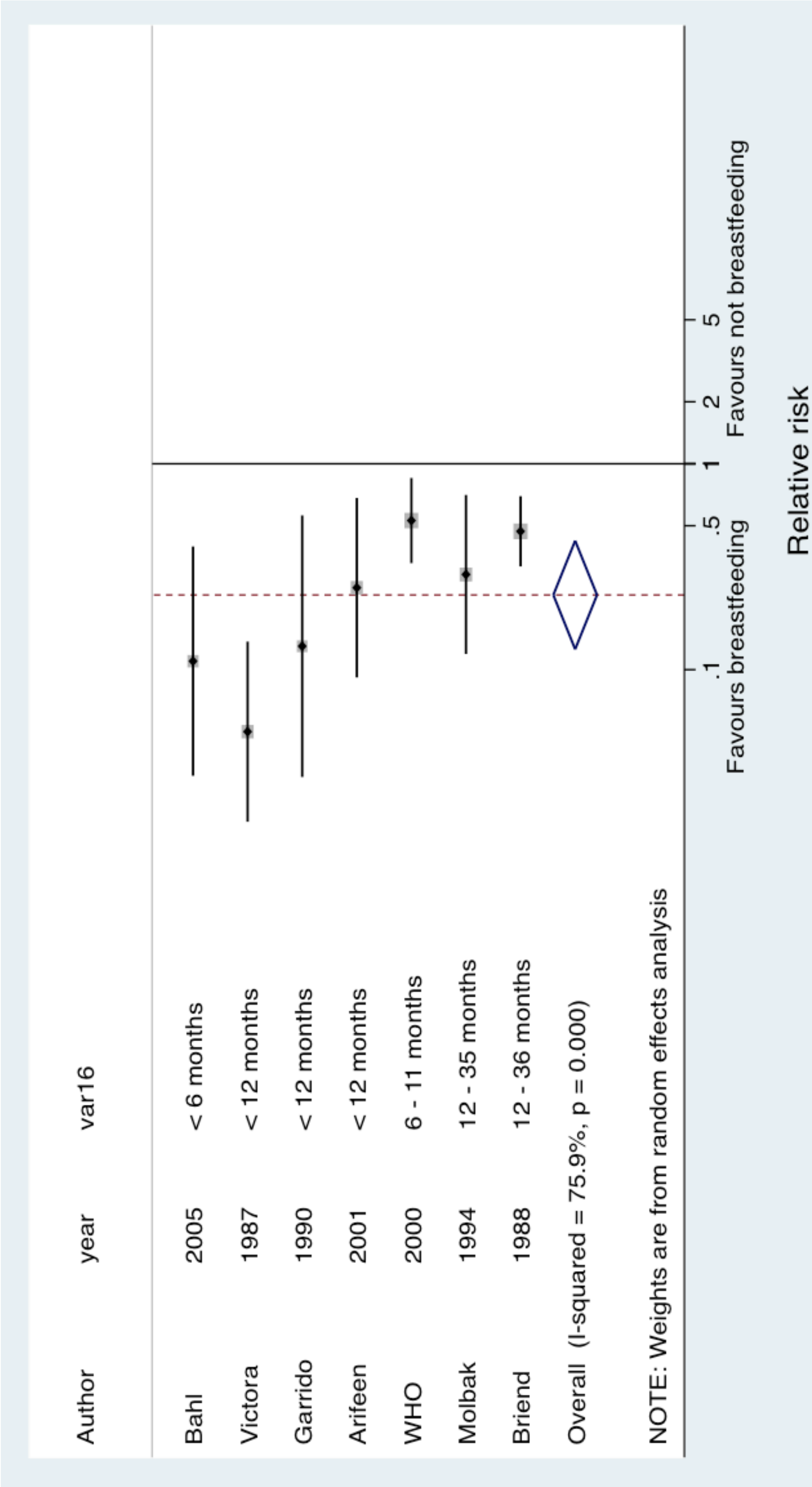
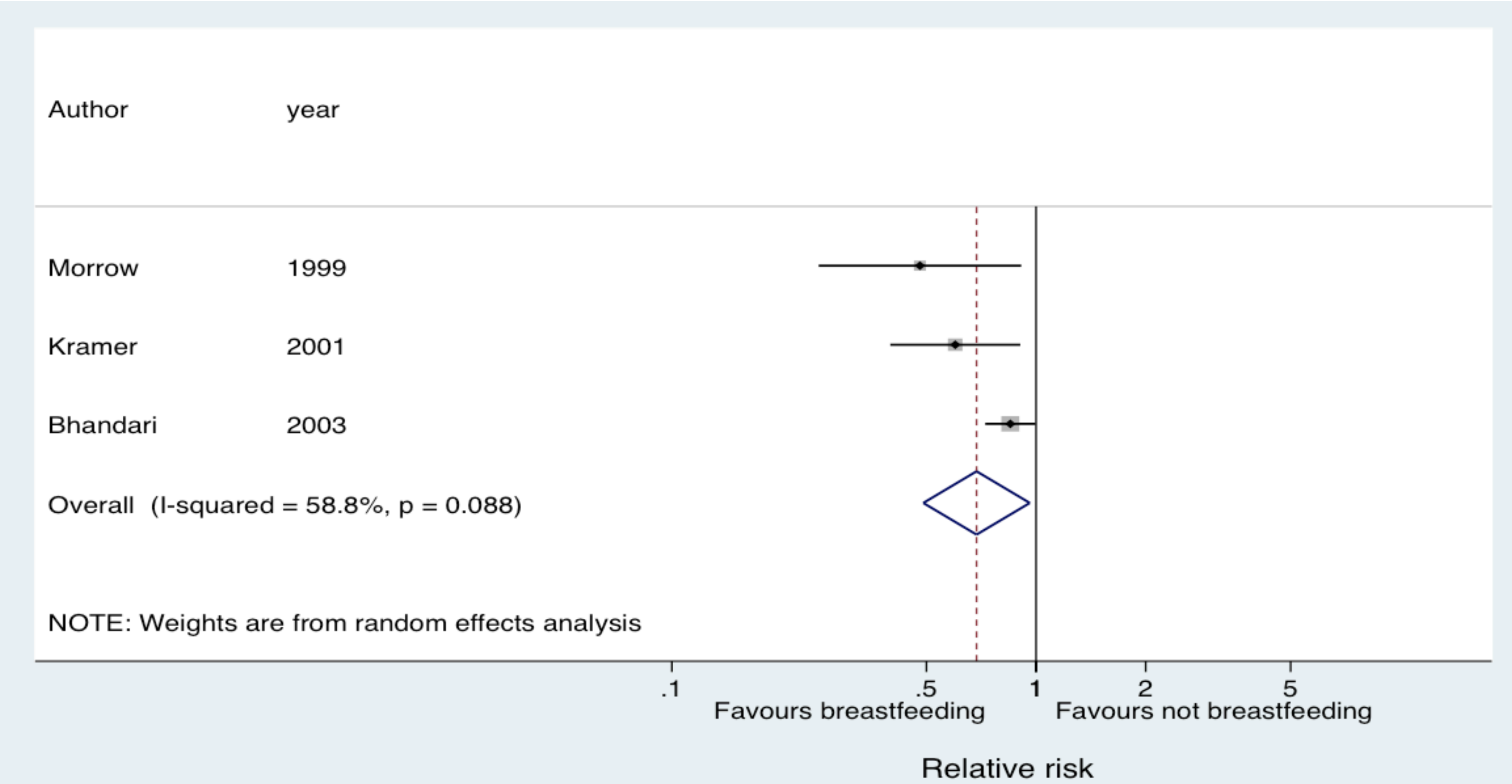


FIGURE 5.9

Relative risk and its 95% confidence interval of morbidity from diarrhea comparing children in the breastfeeding intervention group in relation to those in the control group



CHAPTER 6

Respiratory infection

In spite of recent progress, respiratory infections continue to be the leading cause of death among children < 5 years, worldwide. In 2010, it was estimated that 1.384 million deaths among children under 5 years were caused by pneumonia (*25*). Promotion of breastfeeding has been considered as one of the most cost-effective interventions against such deaths (*27*). A systematic review concluded in 2009 that breastfeeding also protect infants against respiratory infections in industrialized countries (*73*).

Biological plausibility

Several mechanisms explaining a possible protective effect of breastfeeding against respiratory infections have been proposed, including the presence in breastmilk of substances with antimicrobial or immunological properties and the improved general nutritional status of breastfed infants.

Breast milk contains immune cells, antibodies, immune modulators and growth modulators that protect the child against respiratory infection. For example, secretory IgA antibodies may transfer immunity from previously exposed mothers to their children (*74*). Furthermore, cytokines and growth factors may be transferred via human milk and stimulate the infant's immune system (*75*).

It has also been suggested that oligosaccharides may inhibit the attachment of pathogens to the infant's mucosa, preventing respiratory infections (*75*).

Furthermore, in low-income settings breastfeeding can reduce the risk of undernutrition due to repeated infections and use of improper weaning foods (*32*). Because adequate nutritional status is essential for non-specific immunity that contributes to fighting infections in general, improved nutrition is a possible mechanism explaining the protective effect of breastfeeding.

Overview of the evidence

The protective effect of breastfeeding against mortality and morbidity from respiratory infections has been widely studied. In the electronic search, we identified five reviews and/or meta-analyses on this subject.

In 1984, Kovar et al (*77*) reviewed the evidence on the association between infant feeding and infant health, reporting that many of the studies identified had observed a protective effect of breastfeeding against respiratory infections. The authors did not reach a firm conclusion on the effect of breastfeeding for the following reasons: a) most studies did not adjust their estimates for possible confounding variables; and b) several of the studies that did not detect statistically significant associations failed to compare extreme categories of breastfeeding, i.e., exclusively vs. non-breastfed infants. In 1997, Golding et al (*78*) reviewed the evidence on the protective effect of breastfeeding against respiratory and other infections. Six studies on lower respiratory tract infections were identified. In three studies, the adjusted odds ratio was not statistically significant, whereas among the other three studies the crude results were statistically significant, but no adjusted estimates were provided. For this reason, the authors concluded that there was no evidence for an association between breastfeeding and lower respiratory tract infection. It should be noted that these early reviews were severely limited by the poor quality of most studies available at the time.

With the advent of meta-analytic techniques, the quality of available reviews improved. A first meta-analysis by Bachrach et al (*79*) in 2003 assessed the relationship between breastfeeding and the risk of hospitalization for lower respiratory disease among term infants living in high-income settings. Data from seven cohort studies were pooled, leading to the conclusion that breastfeeding reduced the risk of hospitalization by 72% [pooled relative risk: 0.28 (95% confidence interval: 0.14; 0.54)].

In 2009, Duijts et al (*73*) produced an updated systematic review of the effect of breastfeeding on infections during infancy in industrialized countries. The studies included in the review had to fulfill at least three of the following internal validity criteria: (a) avoidance of detection bias; (b) adjustment for possible confounding variables, such as socioeconomic status, size of the family, maternal smoking and maternal schooling; (c) use of clear definition of infant feeding; and (d) having well-defined outcomes. With respect to respiratory infections, 13 of the 16 included studies reported a protective effect of breastfeeding. There was no attempt to pool the results of these studies through meta-analysis.

In 2010, McNeil et al (*80*) also reviewed the evidence on the effect of exclusive breastfeeding on the risk of hospitalization for lower respiratory tract infection, and six studies were identified. All of these reported lower risks of hospitalization among exclusively breastfed infant, but in only two studies the confidence interval did not include the unity. The authors concluded that any formula use was associated with an increased risk of hospitalization. Pooled results were not presented.

In the present systematic review and meta-analysis, we were able to include a substantially larger number of studies than in any of the above-described reviews and apply modern meta-analytic tools for obtaining pooled estimates The electronic search identified 36 studies that provided 50 estimates on the relative risk of morbidity, mortality or hospitalization from respiratory infections according to infant feeding.

New studies, that appeared since 2007, included research carried out in the United Kingdom (*2*), Brazil (*81*), Bangladesh (*37, 46*), Philippines (*82*), Zimbabwe (*39*), Guinea (*40*), Canada (*83*), Hong Kong (*84*), and Netherlands (*85*), Seven of these ten studies reported statistically significant protective effects of breastfeeding.

The meta-analysis was carried out including the recently published studies cited above, those included in the previous systematic reviews and meta-analyses, and a few other older studies. We identified 18 studies that provided 22 estimates on the effect of breastfeeding on any respiratory infection outcome for any subgroup of under-five children (Table 6.1), but not restricted to children under 6 months. Table 6.2 shows that 16 studies provided 24 additional estimates on the effect of infant feeding on morbidity or mortality from respiratory diseases among children aged ≤ 6 months. Three studies (*42, 86, 87*) had already been included in a pooled analyses, and we used the results from the latter instead of the individual study results (*1*). Table 6.3 shows that we also identified four studies that evaluated the effect of breastfeeding on respiratory infections among children older than 6 months.

Results of the meta-analyses were separated by outcome, and are presented in Figures 6.1–6.5. Concerning hospitalization for respiratory infection (respiratory, lower respiratory tract infection or pneumonia), breastfeeding reduced the risk by 57% [pooled relative risk: 0.43 (95% confidence interval:

0.33; 0.55)]. Figure 6.1 shows that in contrast to what has been observed for diarrhea outcomes, the protective effect of breastfeeding was not modified by the age at which children were evaluated. For example, among the four studies (*45, 82, 84, 88*) that assessed infants aged < 6 months the pooled relative risk of hospitalization among breastfed infants was 0.41 (95% confidence interval: 0.25; 0.69), whereas among the seven studies (*47, 54, 81, 89–92*) that evaluated children younger than 12 months the pooled effect was 0.42 (95% confidence interval: 0.25; 0.69).

Figure 6.2 shows that those studies that compared breastfed with non-breastfed children reported the highest protective effect of breastfeeding [pooled relative risk: 0.33 (95% confidence interval: 0.24; 0.46) against hospitalization for respiratory infection. For four other comparisons between categories of breastfeeding (breastfed vs. not breastfed; exclusive breastfed vs. not breastfed, predominant breastfed vs. not breastfed, and partial breastfed vs. not breastfed) we identified two or more studies. Figure 6.2 shows that the confidence interval of the pooled effect of each one of these comparisons did not include the unity. Therefore, in spite of the different categories being compared, breastfed infants were less likely to be hospitalized.

With respect to mortality from lower respiratory tract infections, we identified four studies that provided six estimates on the effect of breastfeeding. Figure 6.3 shows that three of the four estimates were homogeneous, with relative risks ranging from 0.34 to 0.42. On the other hand, Bahl et al (*45*) reported a much stronger protective effect of breastfeeding and its confidence interval did not include the estimate from the remaining studies. Breastfeeding reduced the risk of death for respiratory infection by 70% [pooled relative risk: 0.30 (95% confidence interval: 0.16; 0.56)]. Given the small number of studies that assessed the effect of breastfeeding on mortality and the heterogeneity of categories of breastfeeding that were compared, we did not stratify the analysis according to categories of breastfeeding.

Figure 6.4 shows the studies that assessed the effect of breastfeeding on morbidity (prevalence or incidence) from lower respiratory infection. Breastfeeding also reduced the prevalence or incidence of lower respiratory tract infection [pooled relative risk: 0.68 (95% confidence interval: 0.60; 0.77)]. Similarly to the observed for hospitalization and mortality from lower respiratory tract infections, the effect of breastfeeding on morbidity was not modified by the age at assessment of morbidity.

Figure 6.5 shows that the effect of breastfeeding on incidence or prevalence of lower respiratory tract infection does not seems to vary according the types of categories of breastfeeding that were compared, but these results must be interpreted with caution because several types of comparisons were adopted only by one or two studies, providing therefore imprecise estimates.

In the literature search, we identified the Belarus PROBIT trial (*8*), in which maternity hospitals were randomized to receive or not to receive promotion of exclusive breastfeeding. The proportion of children who were hospitalized for respiratory infection was similar among the groups [odds ratio: 0.85 (95% confidence interval: 0.57; 1.27)]. As mentioned in the previous section, this analysis did not compare breastfeeding categories and therefore it could not be incorporated in the meta-analysis. On the other hand, the Belarus trial also compared the risk of hospitalization for respiratory infection according to breastfeeding categories, and this result is incorporated in the present meta-analyses (Table 6.1) (*54*).

Conclusion

Methodological pitfalls of analyses of breastfeeding and disease were laid out many years ago, yet few recent studies have taken these into consideration (*13*). In particular, self-selection of mothers who breastfeed for longer periods of time can bias results of existing studies. This is particularly problematic in high-income settings, where mothers who breastfeed tend to be more educated and health-conscious (*93*). Adjustment for socioeconomic position and maternal education is essential, but even so residual confounding remains as a possibility.

Another problem is reverse causality, that is, breastfeeding being stopped due to an illness or hospital admission. This poses a special problem in cross-sectional or retrospective studies, which can be avoided by asking about feeding practices prior to the onset of the episode. Nevertheless, few of the existing studies seem to have taken this into consideration, and reverse causality bias tends to overestimate the protective effect of breastfeeding against infections. Indeed, for hospitalization from respiratory infection, the protective effect of breastfeeding was higher among those four studies (*82, 89, 94, 95*) that avoided the reverse causality bias [pooled relative risk 0.33 (95% confidence interval: 0.23; 0.49)], than among the 13 that did not avoid this bias [pooled relative risk: 0.46 (95% confidence interval: 0.34; 0.61)].

As discussed in the previous section, confounding is one of the methodological issues that should be taken into consideration when assessing the short-term consequences of breastfeeding. Similarly to diarrhea, in low-income countries the benefit of breastfeeding on respiratory outcomes are likely underestimated by confounding because breastfeeding tends to be more frequent among the poor, among whom mortality is also higher. In high-income countries, where the rich tend to breastfeed for longer than the poor, confounding may be expected to operate in the opposite direction. In the meta-analysis on respiratory infection outcomes among infants ≤ 6 months of age, studies from developing countries reported that the protective effect of breastfeeding was similar in studies that only reported unadjusted results [pooled relative risk: 0.60 (95% confidence interval: 0.36; 1.01) and studies that adjusted their estimates for socioeconomic and other variables [pooled relative risk 0.50 (95% confidence interval: 0.33; 0.75)], suggesting that confounding is not a likely explanation for the findings.

Publication bias is another methodological issue that should be taken into consideration in the assessment of evidence from meta-analyses. Funnel plot is one of the strategies used to assess the susceptibility of the meta-analysis to publication bias. As in the previous meta-analysis for diarrhea outcomes, we did not generate funnel plots because several different comparisons were done. On the other hand, we stratified the analyses by sample size and observed that among infants ≤ 6 months of age, the mean effect of breastfeeding on respiratory infection outcomes was similar among studies with a sample size < 1000 subjects (pooled relative risk 0.59) and those with ≥ 1000 subjects (pooled relative risk 0.56). This finding suggests that publication bias is not distorting the results of the review.

The only randomized trial on hospital admissions due to respiratory infections compared a group of children born in hospitals with breastfeeding promotion programs, to children born in similar hospitals without such a program. It showed a non-significant reduction of 15% 7. Given that compliance with breastfeeding promotion in this trial was only partial, these results are not inconsistent with the levels of protection documented in the present meta-analysis.

Our review suggests that breastfeeding protects against respiratory infection outcomes. Levels of protection were around 30% for morbidity, about 50% for hospital admissions and about 60% for mortality, suggesting that breastfeeding affects not only the incidence but also the severity of these infections. These results are robust, being observed in high and low-income settings, across different respiratory infections related outcomes, and evident in studies using different definitions of breastfeeding categories.

TABLE 6.1

Breastfeeding and respiratory infections among children < 5 years of age: studies included in the meta-analysis in ascending order of year of publication and subjects age at which outcome was measured. Studies restricted to children under 6 months of age are not included

Author, Year	Year of birth of subjects	Study design	Age	Outcome	Comparison	Relative risk (95% confidence interval)
Ellestad-Sayed (*47*), 1979	1971–1975	Cohort	0–12 months	Hospitalization for lower respiratory tract infection	Breastfed vs. not breastfed	0.32 (0.17; 0.59)
Cunningham (*48*), 1979	1974–1976	Cohort	0–12 months	Incidence of lower respiratory tract infection	Breastfed vs. not breastfed	0.20 (0.08; 0.43)
Fergusson (*96*), 1981	Not available	Cohort	0–24 months	Hospitalization for lower respiratory tract infection	Exclusive breastfed vs. not breastfed	0.12 (0.01; 0.89)
Forman (*97*), 1984	1960–1977	Cohort	0–12 months	Incidence of pneumonia	Predominant breastfed vs. not breastfed	0,71 (0,41; 1,15)
Victora (*42*), 1987	1984–1985	Case-control	0–12 months	Mortality for respiratory infection	Predominant breastfed vs. partial breastfed	3.33 (0.71; 10.0)
					Predominant breastfed vs. not breastfed	0.34 (0.15; 0.77)
Chen (*98*), 1988	1981	Cohort	0–18 months	Hospitalization for respiratory infection	Breastfed vs. never breastfed	0.47 (0.30; 0.75)
Wright (*99*), 1989	1980–1984	Cohort	0–12 months	Incidence of non-wheezing lower respiratory tract infection	Breastfed ≥ 4 months vs. Breastfed < 1 month	0.68 (0.38; 1.21)
Howie (*91*), 1990	1983–1986	Cohort	0–12 months	Hospitalization for respiratory infection	Breastfed vs. not breastfed	0.44 (0.22; 0.90)
Victora (*95*), 1994	1988–1990	Case-control	0–24 months	Hospitalization for pneumonia	Predominant breastfed vs. partial breastfed	0.65 (0.36; 1.18)
					Predominant breastfed vs. not breastfed	0.38 (0.23; 0.65)
Nafstaad (*92*), 1996	1992–1993	Cohort	0–12 months	Hospitalization for lower respiratory tract infection	Breastfed ≥ 9 months vs. never breastfed	0.15 (0.06; 0.35)
Cesar (*89*), 1999	1993	Case-control	0–12 months	Hospitalization for pneumonia	Predominant breastfed vs. not breastfed	0.26 (0.11; 0.59)
					Partially breastfed vs. Not breastfed	0.06 (0.03; 0.13)
Oddy (*90*), 1999	1989–92	Cohort	0–12 months	Hospitalization for lower respiratory tract infection	Exclusive breastfed ≥ 4 months vs. not breastfed	0.62 (0.31; 1.24)
Arifeen (*53*), 2001	1993–1995	Cohort	0–12 months	Mortality for respiratory infection	Exclusive breastfed at 4 months vs. Partial or not breastfed at 4 months	0.36 (0.17; 0.79)
Kramer (*54*), 2003	1996–1997	Randomized trial (Observational analysis)	0–12 months	Hospitalization for respiratory infection	Exclusive breastfed for 6 months vs. partial breastfed 3-7 months	0.96 (0.73; 1.26)

Author, Year	Year of birth of subjects	Study design	Age	Outcome	Comparison	Relative risk (95% confidence interval)
Quigley (*2*), 2007	2000–2001	Cohort	0–8 months	Hospitalization for lower respiratory tract infection	Exclusive breastfed vs. not breastfed	0.67 (0.48; 0.92)
					Partial breastfed vs. not breastfed	0.70 (0.48; 1.00)
Macedo (*81*), 2007	1996–1998	Case–control	0–12 months	Hospitalization for respiratory infection	Breastfed ≥ 6 months vs. Breastfed ≤ 1 month	0.43 (0.27; 0.71)
Diallo (*40*), 2009	2005	Cross-sectional	0–9 months	Prevalence of respiratory infection	Exclusive breastfed vs. not exclusive breastfed	0.38 (0.21; 0.62)
Banerji (*83*), 2009	2000–2002	Case-control	0–24 months	Hospitalization for lower respiratory tract infection	Breastfed vs. not breastfed	0.28 (0.09; 0.83)

TABLE 6.2

Breastfeeding and respiratory infections among children < 6 months of age: studies included in the meta-analysis in ascending order of year of publication and subjects age at which outcome was measured. Studies with an upper limit of age above 6 months are not included

Author, Year	Year of birth of subjects	Study design	Age	Outcome	Comparison group	Relative risk (95% confidence interval)
French (*100*), 1967	1958–1960	Cross-sectional	0–3 months	Prevalence of pneumonia	Breastfed vs, not breastfed	0.56 (0.13; 2.39)
Leventhal (*94*), 1986	1979–1982	Case–control	0–3 months	Hospitalization for pneumonia	Breastfed vs. not breastfed	0.20 (0.02; 1.72)
Pisacane (*88*), 1994	Not available	Case-control	0–6 months	Hospitalization for lower respiratory tract infection	Breastfed vs. not breastfed	0.22 (0.09; 0.55)
Brito Hernandez (*61*), 1995	1992–1993	Cross-sectional	0–5 months	Prevalence of respiratory infection	Breastfed vs. not breastfed	0.54 (0.30; 0.96)
Beaudry (*101*), 1995	1982–1983	Cohort	0–6 months	Incidence of respiratory infection	Breastfed vs. not breastfed	0.73 (0.58; 0.92)
Cushing (*102*), 1998	1988–1990	Cohort	0–6 months	Incidence of lower respiratory tract infection	Predominant breastfed vs. not breastfed	0.79 (0.67; 0.94)
					Partial breastfed vs. not breastfed	0.95 (0.78; 1.16)
Raisler (*65*), 1999	1988	Cohort	0–6 months	Incidence of pneumonia	Predominant vs. not breastfed	0.77 (0.44; 1.33)
WHO (*1*), 2000	1984–1991	Pooled analysis	0–6 months	Mortality for respiratory infection	Breastfed vs. not breastfed	0.42 (0.29; 0.63)
Koch (*103*), 2003	1994–1996	Cohort	0–5 months	Incidence of lower respiratory tract infection	Exclusive breastfed vs. partial breastfed	0.39 (0.14; 1.06)
					Exclusive breastfed vs. not breastfed	0.27 (0.09; 0.81)
Bahl (*45*), 2005	1995–1997	Cohort	6–26 weeks	Hospitalization for lower respiratory tract infection	Exclusive breastfed vs. Predominantly breastfed	0.86 (0.45; 1.64)
					Predominant breastfed vs. not breastfed	0.40 (0.15; 1.08)
Bahl (*45*), 2005	1995–1997	Cohort	6–26 weeks	Mortality from lower respiratory tract infection	Predominant breastfed vs. not breastfed	0.03 (0.006; 0.15)
Mihrshahi (*37*), 2007	2002–2003	Cross-sectional	0–3 months	Prevalence of respiratory infection	Exclusive breastfed vs. not exclusive breastfed	0.76 (0.63; 0.91)
Mihrshahi (*46*), 2008	1999–2001	Cohort	0–5 months	Prevalence of respiratory infection	Exclusive breastfed vs. predominant breastfed	0.75 (0.41; 1.10)
					Exclusive breastfed vs. partial breastfed	0.64 (0.42; 0.89)
Koyanagi (*39*), 2009	1997–2000	Cohort	3–6 months	Incidence of lower respiratory tract infection	Exclusive breastfed vs. partial breastfed	0.96 (0.61; 1.54)

Author, Year	Year of birth of subjects	Study design	Age	Outcome	Comparison group	Relative risk (95% confidence interval)
Duijts (*85*), 2010	2002–2006	Cohort	≤ 6 months	Prevalence of lower respiratory tract infection	Exclusive breastfed vs. never breastfed	0.35 (0.09; 1.36)
Hengstermann (*82*), 2010	2007	Case control	0–6 months	Hospitalization for pneumonia	Exclusive breastfed vs. not breastfed	0.33 (0.14; 0.83)
					Breastfed vs. not breastfed	0.36 (0.19; 0.67)
Tarrant (*84*), 2010	1997	Cohort	0–6 months	Hospitalization for respiratory infection	Predominant breastfed vs. not breastfed	0.64 (0.42; 0.97)
					Partial breastfed vs. not breastfed	0.79 (0.64; 0.97)

TABLE 6.3

Breastfeeding and respiratory infections among children > 6 months of age: studies included in the meta-analysis in ascending order of subjects age at which outcome was measured

Author, Year	Year of birth of subjects	Study design	Age	Outcome	Comparison	Relative risk (95% confidence interval)
Chantry (*104*), 2006	1986–1994	Cross-sectional	6–24 months	Prevalence of pneumonia	Predominant breastfed ≥ 4 months vs. never breastfed	0.50 (0.16; 1.56)
WHO (*1*), 1 2000	1984–1991	Pooled analysis	6–11 months	Mortality for respiratory infection	Breastfed vs. not breastfed	0.40 (0.22; 0.71)
Duijts (*85*), 2010	2002–2006	Cohort	7–12 months	Prevalence of lower respiratory tract infection	Exclusive breastfed vs. never breastfed	0.57 (0.20; 1.49)
Fisk (*105*), 2011	1999–2007	Cohort	6–12 months	Prevalence of respiratory infection	Breastfed vs. not breastfed	0.72 (0.58; 0.89)

FIGURE 6.1

Relative risk and its 95% confidence interval of hospitalization due to respiratory infection, lower respiratory tract infection or pneumonia in children < 5 years of age

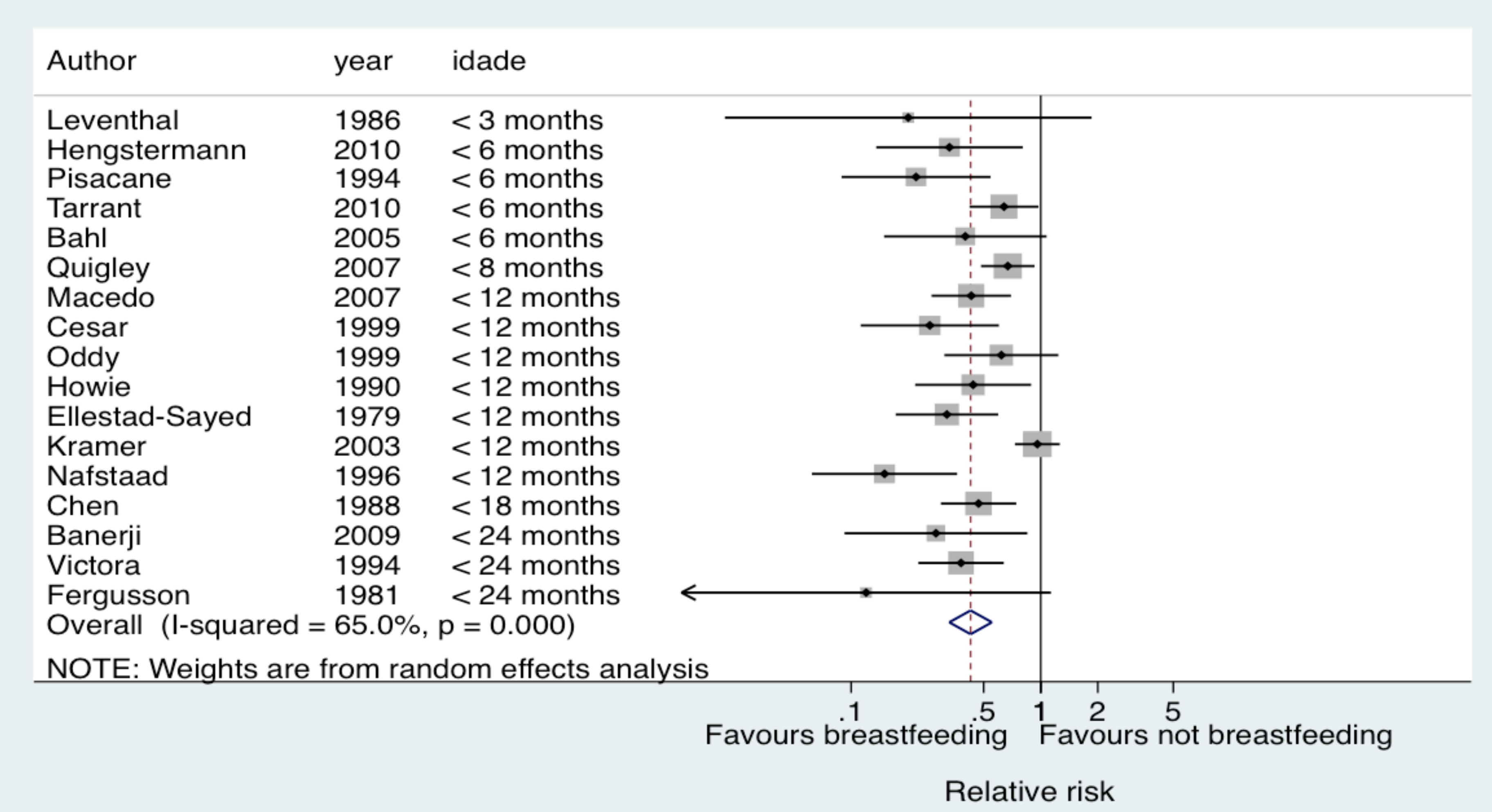


FIGURE 6.2

Relative risk and its 95% confidence interval of hospitalization for respiratory infection, lower respiratory tract infection or pneumonia in children < 5 years of age, according to breastfeeding categories

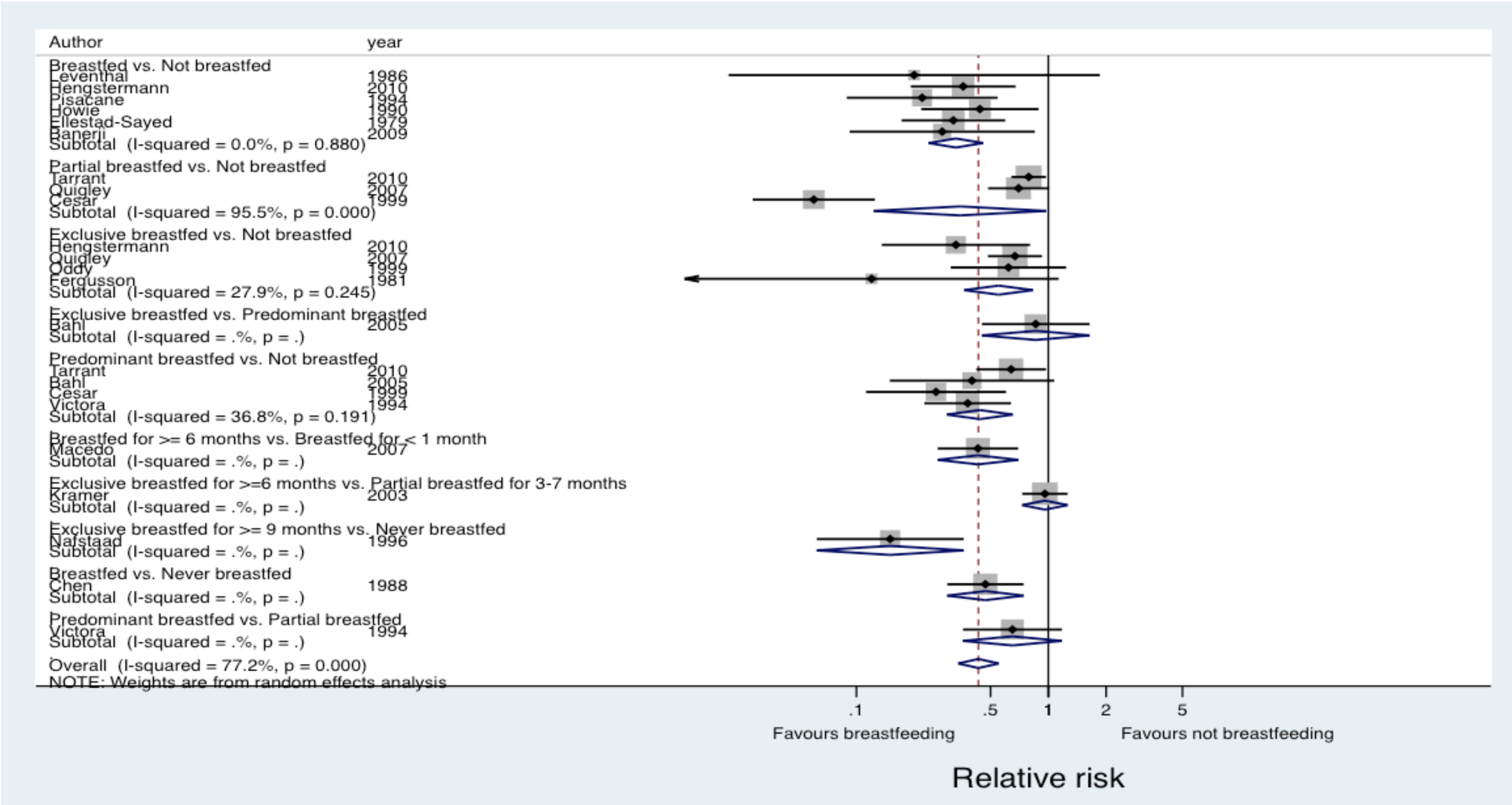


FIGURE 6.3

Relative risk and its 95% confidence interval for mortality for respiratory infection or lower respiratory tract infection in children < 5 years of age

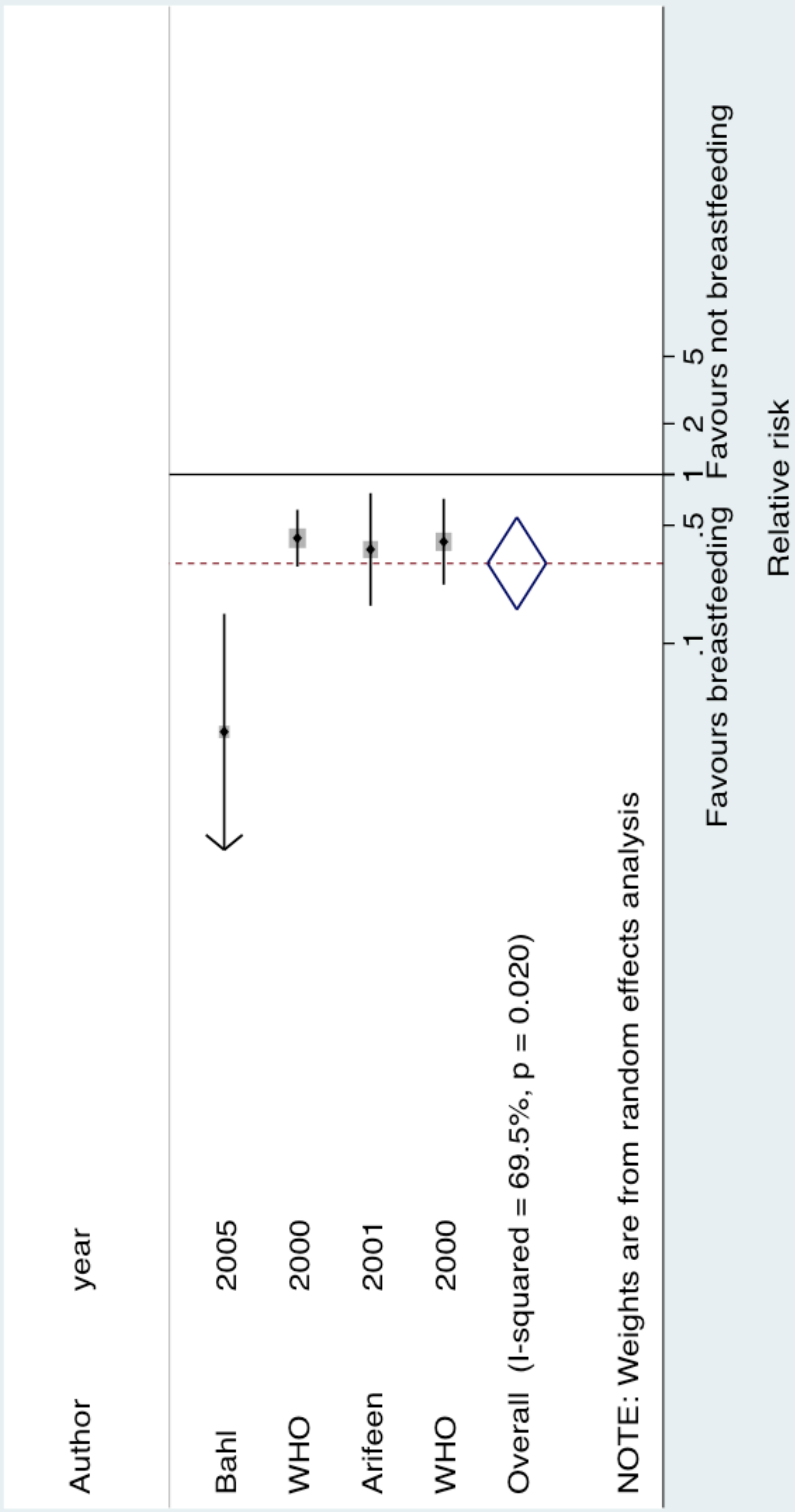


FIGURE 6.4

Relative risk and its 95% confidence interval of lower respiratory tract infection (prevalence or incidence) comparing breastfeeding categories in different studies

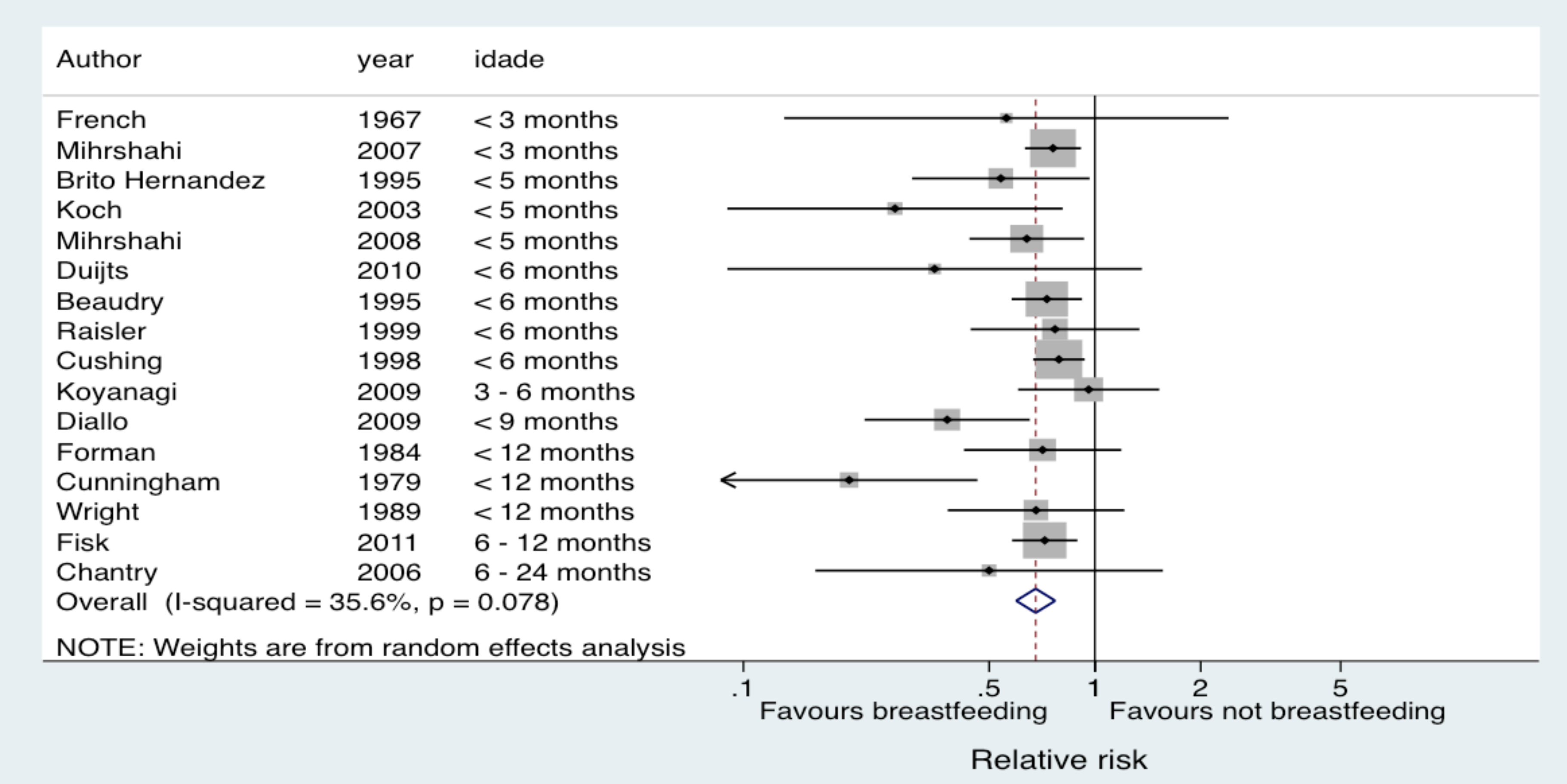
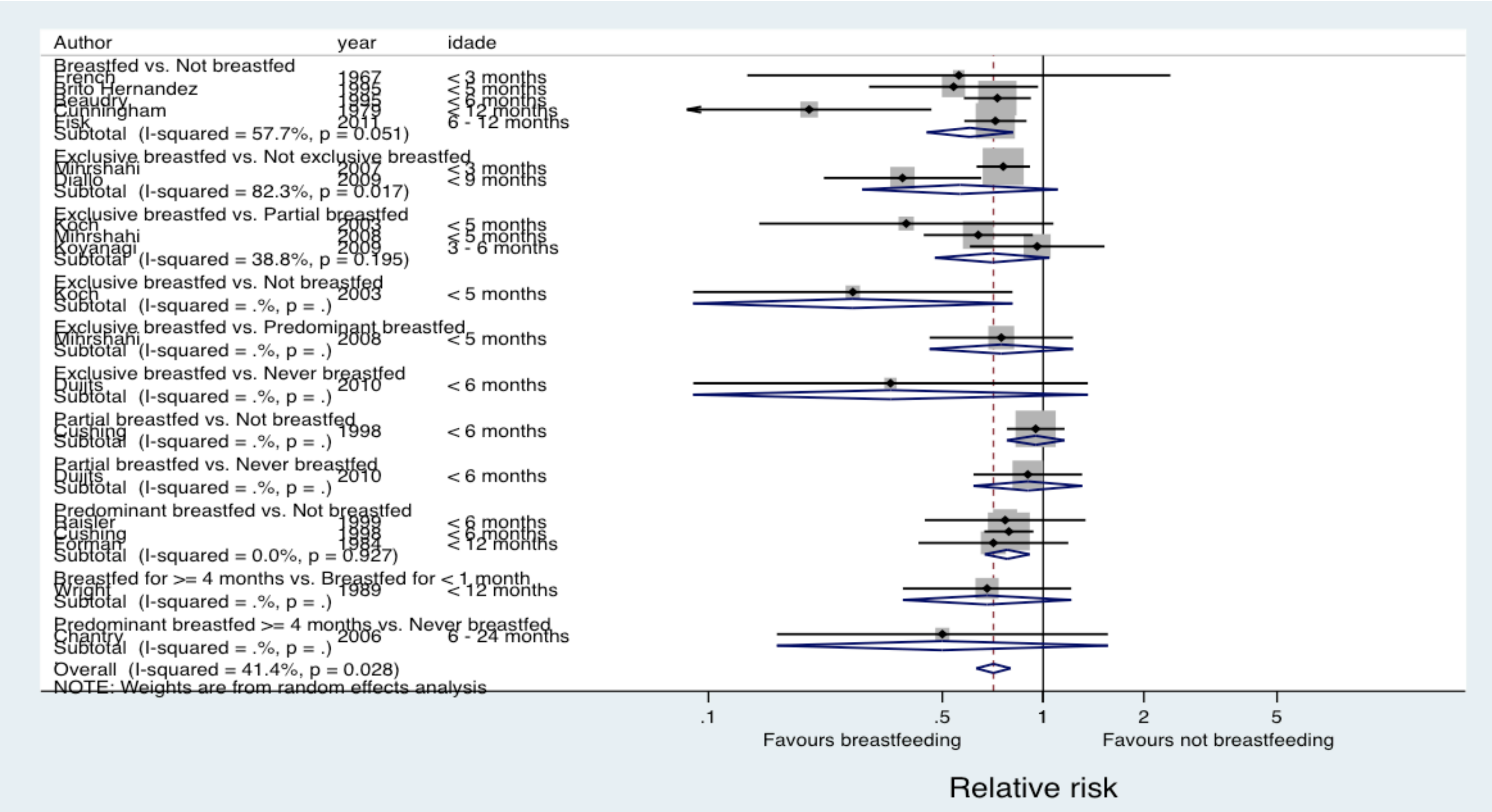


FIGURE 6.5

Relative risk and its 95% confidence interval of lower respiratory tract infection (prevalence or incidence), according to breastfeeding categories



••• **CHAPTER 7** •••

Conclusions

The available evidence suggests that breastfeeding protects against diarrhea and respiratory infection in childhood. Because the meta-analyses are almost exclusively based on observational studies the possibility of self-selection and residual confounding must be taken into consideration.

With respect to confounding, in the present review, we believe that the findings were not susceptible to residual confounding because a strong protective effect of breastfeeding was observed in low-income countries. In these countries duration of breastfeeding is higher among the poor. Therefore, confounding by socioeconomic status should underestimate the protection afforded by breastfeeding.

Reverse causality should also be taken into consideration in the assessment of the evidence on the short-term effects of breastfeeding. As previously discussed, breastfeeding may have been interrupted or modified by an episode of infectious diseases, thus leading to an association in the opposite direction than the one being postulated (*13*). For the review on breastfeeding and diarrhea, only one study explicitly accounted for this bias, by ensuring that information on feeding practices was obtained for a date previous to the onset of the episode. This study showed substantial protection associated with breastfeeding (*42*). For hospitalization from respiratory infection, we identified four studies that avoided the reverse causality bias and the protective effect of breastfeeding was higher among these studies (*38,89,94,95*).

Publication bias is another methodological issue that should be taken into consideration; the selective publication of small positive studies may overestimate the benefit of breastfeeding. In the present review, we stratified the analyses by sample size and observed that the protective effect of breastfeeding was not modified by sample size. Suggesting, therefore, that publication bias is not distorting the results.

Interpretation of results from observational studies may be aided by also taking into consideration the findings of randomized studies. We identified three randomized trials in which breastfeeding promotion was related to diarrhea outcomes (*7–9*). Diarrhea morbidity was lower in the group receiving the intervention [pooled relative risk: 0.69 (95% confidence interval: 0.49; 0.96)]. This protection was observed even though the analyses were based on intent to treat, that is, both intervention and comparison groups included compliers and non-compliers. For respiratory infection, we identified one randomized trial that compared hospital admissions due to respiratory infections between a group of children born in hospitals with breastfeeding promotion programs and those who were born in similar hospitals without such a program. It showed a non-significant reduction of 15% (*7*). Given that compliance with breastfeeding promotion in this trial was only partial, these results are not inconsistent with the levels of protection documented in the present meta-analysis.

Our conclusions are outlined below.

Diarrhea

The protective effect of breastfeeding against diarrhea incidence was higher among infants aged ≤ 6 months. But, a protective effect was observed among older children. Breastfeeding also decreased severity of diarrhea; hospitalization and mortality were 72% and 77% lower among breastfed infants, respectively. Furthermore, as described above, in three randomized trials of breastfeeding promotion, morbidity was lower in the group receiving the intervention [pooled relative risk: 0.69 (95% confidence interval: 0.49; 0.96)]. We concluded that breastfeeding protects against diarrhea.

Respiratory infection

For respiratory infection, the protective effect of breastfeeding was not modified by age. Breastfeeding also reduced the risk of hospitalization [pooled relative risk: 0.43 (95% confidence interval: 0.33; 0.55)] and mortality [pooled relative risk: 0.30 (95% confidence interval: 0.16; 0.56)]. We concluded that breastfeeding protects against respiratory infection.

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