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Systematic Reviews and Meta- and Pooled Analyses

Breastfeeding and Childhood Asthma: Systematic Review and Meta-Analysis

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Asthma and wheezing disorders are common chronic health problems in childhood. Breastfeeding provides health benefits, but it is not known whether or how breastfeeding decreases the risk of developing asthma. We performed a systematic review and meta-analysis of studies published between 1983 and 2012 on breastfeeding and asthma in children from the general population. We searched the PubMed and Embase databases for cohort, cross-sectional, and case-control studies. We grouped the outcomes into asthma ever, recent asthma, or recent wheezing illness (recent asthma or recent wheeze). Using random-effects meta-analyses, we estimated pooled odds ratios of the association of breastfeeding with the risk for each of these outcomes. We performed meta-regression and stratified meta-analyses. We included 117 of 1,464 titles identified by our search. The pooled odds ratios were 0.78 (95% confidence interval: 0.74, 0.84) for 75 studies analyzing "asthma ever," 0.76 (95% confidence interval: 0.67, 0.86) for 46 studies analyzing "recent asthma," and 0.81 (95% confidence interval: 0.76, 0.87) for 94 studies analyzing recent wheezing illness. After stratification by age, the strong protective association found at ages 0–2 years diminished over time. We found no evidence for differences by study design or study quality or between studies in Western and non-Western countries. A positive association of breastfeeding with reduced asthma/wheezing is supported by the combined evidence of existing studies.

asthma; breastfeeding; child; review

Abbreviations: CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio.

Editor's note: *An invited commentary on this article appears on page 1168, and the authors' response is published on page 1171.*

Asthma and other wheezing disorders are common chronic health problems in childhood, placing a great burden on children, their families, and society (1, 2). Available treatments reduce morbidity during treatment but do not alter the natural history of the disorders (3). Research related to risk and protective factors is thus a priority for public health.

Breastfeeding provides many advantages for infants, mothers, and society (4). Though breastfeeding is often recommended for primary prevention of atopic disorders in children (5), evidence of a beneficial association with asthma is inconsistent. Some studies have reported benefits of prolonged breastfeeding (6–9), but others have found no risk reduction or even an increased risk of harm in breastfed children (10–15). Except for a study that randomized maternal hospitals and polyclinics to either a breastfeeding intervention program or a control program (16), these studies have relied on observational data because it is not ethical to withdraw breastfeeding from children in a clinical trial.

One reason for the heterogeneity of results might be that some studies had methodological shortcomings. Kramer (17) proposed in 1988 that future studies meet a set of quality standards for measuring and defining exposures and outcomes, as well as for statistical analysis. Besides methodological problems, the heterogeneity of results between studies might also be caused by real differences due to measurement of outcomes at different ages, various exposures to infections in childhood, or dissimilar sociocultural environments.

The results of earlier systematic reviews on breastfeeding and childhood asthma and wheezing disorders tended to agree that breastfeeding is protective (18–23). However, those reviews have limitations; most included only studies published before 2002 (20, 22, 23), some are narrative and do not include a meta-analysis (19, 20, 23), some combined asthma with other atopic conditions (22, 23), and some did not address heterogeneity between studies (19, 22, 23) or failed to comply with standards (24, 25) for performing and reporting systematic reviews (19, 22, 23). The most recent review, published in 2011 by Brew et al. (18), found no evidence that breastfeeding protects against asthma. However, the authors identified relatively few studies, did not perform a meta-regression, and included only studies assessing asthma in children aged 5 years or older. In this study, we aimed to identify and summarize all publications on breastfeeding and the risk of asthma in children from the general population and to use stratified analyses and meta-regressions to explore potential sources of heterogeneity.

METHODS

Search and selection

We complied with the requirements for reporting meta-analyses of observational studies (24, 25) and searched the PubMed and Embase databases with the following query: [breastfeeding OR breast-feeding OR "breast feeding" OR "breast fed" OR weaning] AND [asthma OR wheeze OR wheezing OR bronchiolitis OR bronchitis]. We looked for the terms in titles and abstracts and used MeSH terms for breastfeeding. We also included titles cited in other systematic reviews on breastfeeding and asthma. This report reflects the state of the literature as of July 31, 2012.

Two authors (C.D. and D.N.) independently selected eligible studies in 2 stages: 1) scanning titles and abstracts and 2) reading full texts. We obtained full texts from electronic databases, from interlibrary loans, or by contacting the authors. At the end of each stage, the reviewers compared their decisions and resolved discrepancies.

We included fully reported original studies, both cohort (longitudinal) and noncohort studies (cross-sectional or case-control), and we excluded duplicate reports, studies in the form of conference proceedings and abstracts, and studies not published in English. We considered studies performed in the general population, excluding studies performed in special populations, such as studies including only children with a family history of atopy or asthma (children "at risk"), or those performed only in children with diagnosed asthma/wheeze that analyzed only the association between breastfeeding and asthma severity. We included studies that analyzed, as outcomes, any of the following, alone or in combination: asthma diagnosis from medical reports or physicians; parental reports of current wheezing (≥1 episodes in the past 12 months); parental reports of treatment for asthma or wheezing; parental reports of doctor diagnosis of asthma and wheezing with or without bronchial hyperresponsiveness. We excluded studies that did not differentiate between asthma/wheezing conditions and other respiratory or atopic conditions (e.g., "history of wheezing or bronchitis," "history of asthma or other allergies"), and we also excluded studies that analyzed only "wheeze ever" as an outcome.

Extraction of study characteristics

We extracted extensive information on breastfeeding, outcomes, and study estimates. In addition, we extracted author names, years of publication, dates and countries where the studies were performed, study designs, inclusion and exclusion criteria, length of follow-up periods, sample sizes, potential confounders adjusted for, types of analysis, and author conclusions. We considered "Western" the countries in Europe, North America, and South America, as well as Australia and New Zealand.

We separately extracted information on duration of any breastfeeding and duration of exclusive breastfeeding, when available. We recorded the ages at which breastfeeding was assessed and the breastfeeding categories used by each study. For outcomes, we recorded the definition used by each study, age at assessment, and the source (e.g., parents, medical records, physicians). Whenever available, we extracted reported outcome prevalence within levels of breastfeeding, as well as unadjusted and adjusted odds ratios.

Standardization of data extracted

After data extraction, we reclassified the data on breastfeeding and outcomes into categories that would facilitate a more homogenous analysis. Table 1 presents the grouping of studies after standardization and the number of studies in each group, explained in more detail below.

Outcomes. We grouped outcomes into 3 categories. The first category, "asthma ever," refers to a condition that occurred at any time in the past, including asthma diagnosis retrieved from medical records and/or parent reports of doctor diagnosis, use of asthma medication, or wheeze accompanied by bronchial hyperreactivity. The second category, "recent asthma" refers to those who met the "asthma ever" criteria within the last 12 months. The third category, "recent wheezing illness," extends the "recent asthma" group by including studies analyzing single/multiple episodes of wheezing reported in the last 12 months. We further categorized the outcomes by age of assessment, into 0–2 years, 3–6 years, or 7 or more years.

Stringent categorization of breastfeeding. For each type of breastfeeding (duration of any or exclusive breastfeeding), we considered 3 separate cut-offs, which were based on those most commonly used in the literature (i.e., ever vs. never; ≥3–4 months vs. <3–4 months; and ≥6 months vs. <6 months). For studies reporting outcome frequencies by level of breastfeeding, we recalculated the prevalence for each of the above breastfeeding cut-offs, separated by type of breastfeeding, outcome, and age at assessment. For instance, if a study reported outcome prevalence using breastfeeding categories never, 0–3 months, 4–6 months, and >6 months, we calculated 3 prevalence categories as follows: ever versus never = (0–3 months + 4–6 months + >6 months) versus never; ≥3–4 months versus <3–4 months = (4–6 months + >6 months) versus (never + 0–3 months), and ≥6 months versus <6 months = (>6 months) versus (never + 0–3 months + 4–6 months). We then calculated unadjusted odds ratios for each new cut-off,

Table 1. Number of Studies Included in the Groups Determined by Stringent Categorization of Breastfeeding, 1983–2012[a]

Age and Breastfeeding Cut-off	Asthma Ever		Recent Asthma		Recent Wheezing Illness	
	No. Reporting Total Duration of Breastfeeding	No. Reporting Exclusive Breastfeeding	No. Reporting Total Duration of Breastfeeding	No. Reporting Exclusive Breastfeeding	No. Reporting Total Duration of Breastfeeding	No. Reporting Exclusive Breastfeeding
Age 0–2 years						
Ever vs. never	5	NI	5	NI	9	NI
≥3 vs.<3 months	5	6	5	6	7	10
≥6 vs.<6 months	4	3	4	3	6	3
Age 3–6 years						
Ever vs. never	12	NI	5	NI	13	NI
≥3 vs.<3 months	5	12	3	6	6	12
≥6 vs.<6 months	2	2	1	1	4	2
Age ≥7 years						
Ever vs. never	25	NI	13	NI	24	NI
≥3 vs.<3 months	11	6	9	5	12	10
≥6 vs.<6 months	7	0	6	0	10	1

Abbreviation: NI, not included.

[a] Each cell represents a group of studies based on the stringent categorization of breastfeeding, dividing studies by outcome, age of assessment, breastfeeding type, and breastfeeding cut-off; the cells contain the number of studies on which our meta-analysis was performed. After grouping by outcome only, regardless of age and type and duration of breastfeeding, we analyzed "asthma ever" in 75 studies, "recent asthma" in 46 studies, and "recent wheezing illness" in 94 studies.

using the category of shorter duration as the reference; for the example presented above, we thus calculated 3 odds ratios. We also recorded the reported adjusted odds ratios and unadjusted odds ratios when available for studies that did not report prevalence, using the value of the most appropriate category.

The combination of 3 outcomes, 3 age groups, 2 breastfeeding types, and 3 breastfeeding categories resulted in 45 separate groups within which we could perform meta-analyses of comparable studies, after excluding the comparison group "ever versus never" for exclusive breastfeeding, which was not considered. A study could appear only once within the same group, but could belong to more than 1 group if we could recalculate more than 1 breastfeeding cut-off for that study or, if it reported results for more than 1 outcome, breastfeeding type and/or age group.

Flexible categorization of breastfeeding. To increase the number of studies that we could compare for a given outcome, we calculated odds ratios using a less stringent categorization (more vs. less breastfeeding) to compare studies regardless of how they defined and categorized breastfeeding and regardless of age of assessment. For this, we started with the stringent categorizations described above and gave priority to the highest cut-offs. Thus, in the example presented above, which reported outcome prevalence using breastfeeding categories of never, 0–3 months, 4–6 months, and more than 6 months, we recorded a "breastfeeding more versus less" category by taking the values from the "≥6 months versus <6 months" cut-off. When studies reported results for both "any breastfeeding" and "exclusive breastfeeding," we gave priority to results for exclusive breastfeeding. When studies reported results from more than 1 age group, we gave priority to results from school-aged subjects.

Quality assessment

To measure the methodological quality of studies, we defined a quality score that was based on 1) whether a study reported adjustment for at least 3 of 7 important potential confounders (17, 18), and 2) whether it satisfied at least 4 of 7 of the selected quality standards suggested by Kramer (17). If a study adjusted for 3 or more important confounders, it received a score of 1; similarly, if a study satisfied at least 4 of the 7 Kramer criteria considered, it received a score of 1. We then added these 2 scores, resulting in overall quality scores that ranged from 0–2. For reporting purposes, we labeled them low quality (0 points), medium quality (1 point), or high quality (2 points). On the basis of the literature, we considered birth weight, gestational age, ethnicity, family history of asthma or allergy, family education, socioeconomic status, and exposure to tobacco smoke pre- or postpartum to be important potential confounders. We selected the following 7 of Kramer's 12 quality standards: nonreliance on prolonged maternal recall, sufficient duration of breastfeeding (more than 2 months), sufficient exclusivity of breastfeeding, strict diagnostic criteria, control for confounding, assessment of dose-response effect, and adjustment for a family history of atopy. The other 5 criteria (blind ascertainment on infant feeding history, blind ascertainment of outcome, severity of

outcome, age of onset of outcome, and adequate statistical power) were difficult to assess in the selected studies; therefore, they were not included in the score.

Statistical analysis

We performed separate meta-analyses for each outcome, first within the 45 groups defined by breastfeeding cut-offs and then using "more versus less breastfeeding."

The odds ratios included in analyses were either provided by the studies or calculated from the reported frequencies. We used a random-effects model with the DerSimonian and Laird method to calculate weights (26). If studies reported both adjusted and unadjusted odds ratios, we used the adjusted estimates.

In the analyses using "more versus less breastfeeding," we addressed heterogeneity between studies by performing meta-analyses stratified by age, study design, Western country, recent study (conducted after 1990), and quality score. We also fitted meta-regressions, using as determinants age, study design, Western country, recent study, quality score, type of breastfeeding, and breastfeeding categorization used. The analysis for "recent wheezing illness" also included the type of recent wheezing illness (i.e., asthma vs. wheeze). Analyses were performed in Stata, version 12.0, software (StataCorp LP, College Station, Texas) using the metan and metareg commands (27).

RESULTS

Study characteristics

Search. Figure 1 presents the search and selection process. Our search yielded 1,464 titles. Eighteen articles not traced by our search were identified from other systematic reviews on the same topic. After we excluded some of the duplicate titles automatically using the reference management program, EndNote (Thomson Reuters Corp., New York, New York), we screened 1,083 titles, of which 217 were retained. We excluded 9 studies because the author was suspected of data fabrication, and the articles had been retracted by journals (28). After reading full texts, we retained 108 titles (8, 10, 12, 13, 15, 29–129). Of these, 3 were multicountry studies that reported results grouped by geographical region or affluence. We included the results of these group analyses as separate studies ($n = 12$). We thus included 117 studies in our review. Four of them used breastfeeding as a continuous variable and were excluded from meta-analyses.

Characteristics. Table 2 and Web Table 1 available at http://aje.oxfordjournals.org/ detail the characteristics of the studies we included. Most were cohort studies ($n = 57$, 49%), followed by cross-sectional ($n = 47$, 40%) and case-control studies ($n = 13$, 11%). Eighty-five studies (73%) were conducted after 1990, and 91 (77%) were performed in Western countries. Characteristics related to breastfeeding and outcomes are based on standardized categorization and

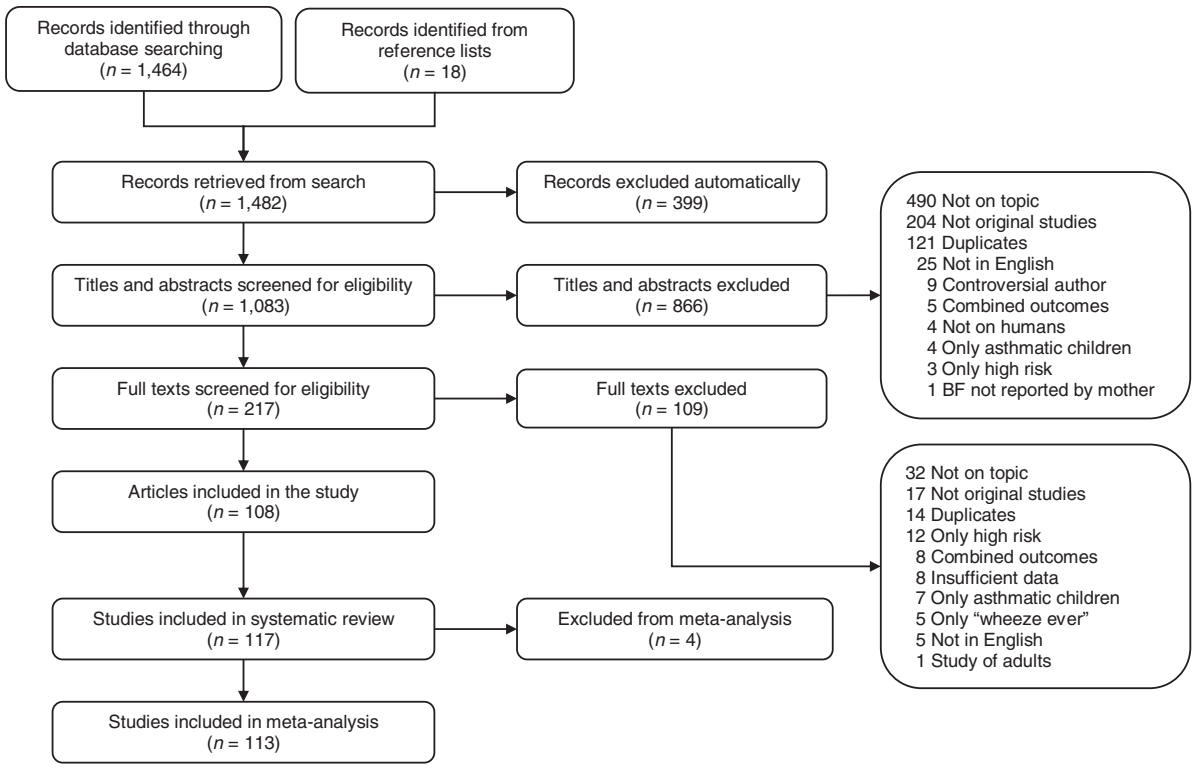

Figure 1. Flow chart showing study selection. Three articles reporting multicountry studies analyzed and reported the results separately by geographical region or affluence; we analyzed them as separate studies ($n = 12$). BF, breastfeeding.

Table 2. Characteristics of the 117 Studies Included in the Systematic Review, 1983–2012

Characteristic	No. of Studies	%
Type of study		
Cohort	57	48.7
Cross-sectional	47	40.1
Case-control	13	11.1
Age at enrollment, years		
Perinatal	51	43.6
0–6	21	18.0
≥7	39	33.3
Mixed ages	6	5.1
Decade when the study started		
Before 1970	2	1.7
1970–1979	7	6.0
1980–1989	23	19.7
1990–1999	42	35.9
After 1999	36	30.8
Not provided	7	5.98
Country income level[a]		
High	93	79.5
Upper-middle	19	16.2
Lower-middle	5	4.3
Region[b]		
Western		
Europe	48	41.0
North America	20	17.1
Australia/New Zealand	12	10.3
South America	9	7.7
Non-Western		
East Asia	11	9.4
Middle East	11	9.4
South Asia	3	2.6
Africa	1	0.8
Multiregional	2	1.7
Authors' conclusion		
Protective	62	53.0
No effect	43	36.7
Harmful	4	3.4
Depends on other factors	8	6.8
Breastfeeding		
Main exposure	55	47.0
Definition		
Duration of any breastfeeding	71	61.5
Duration of exclusive breastfeeding	43	35.0
Age at assessment		
During breastfeeding	28	23.9
During first year	21	17.9
During second year	5	4.4
After second year	63	53.8
Cut-offs analyzed[c]		
Ever vs. never	40	34.2
≥3–4 vs.<3–4 months	52	44.4
≥6 vs.<6 months	21	18.0
Outcomes		
Age at assessment, years		
0–2	21	18.0
3–6	32	27.3
≥7	62	53.0
Outcome assessed[d]		
Asthma ever	75	64.0
Recent asthma	46	40.6
Recent wheezing illness	94	80.3
Quality assessment		
Quality score[e]		
0	66	56.4
1	35	29.9
2	16	13.7
≥3 Essential confounders adjusted	23	19.7
≥4 Kramer quality criteria[f]	44	37.6
No. of confounders	5 (0–24)[g]	
No. of Kramer quality criteria[f]	3 (0–6)[g]	
No. of essential confounders[h]	2 (0–7)[g]	
Sample size	2,144 (50–168,283)[g]	

[a] Based on World Bank classification.

[b] Countries from Europe, North America, and South America, as well as Australia and New Zealand.

[c] Some studies used several breastfeeding types and categories. We gave priority to exclusive breastfeeding and higher breastfeeding cut-offs (e.g., cut-off of ≥6 vs. <6 months was given priority over a cut-off of ≥3–4 vs. <3–4 months). The table presents the cut-offs used in our meta-analysis.

[d] Asthma ever: lifelong reports of asthma diagnosis (from parent reports or medical records) and/or use of asthma/wheeze treatment and/or wheeze accompanied by bronchial hyperreactivity; from those, the ones that reported the condition in the past 12 months were analyzed separately as "recent asthma." "Recent wheezing illness" combines "recent asthma" and "recent wheezing" (single or multiple episodes in the past 12 months).

[e] One point was assigned for adjustment for 3 or more essential confounders and 1 point for meeting more than 3 Kramer quality criteria.

[f] We considered only the following 7 of the 12 Kramer criteria: nonreliance of prolonged maternal recall, sufficient duration of breastfeeding, sufficient exclusivity of breastfeeding, strict diagnostic criteria, satisfactory adjustment, assessment of dose-response effect, and assessment of effect in children at high risk.

[g] Values expressed as median (range).

[h] Essential confounders: birth weight, gestational age, ethnicity, family history of asthma or allergy, family education, socioeconomic status, and exposure to tobacco smoke pre- or postpartum.

Table continues

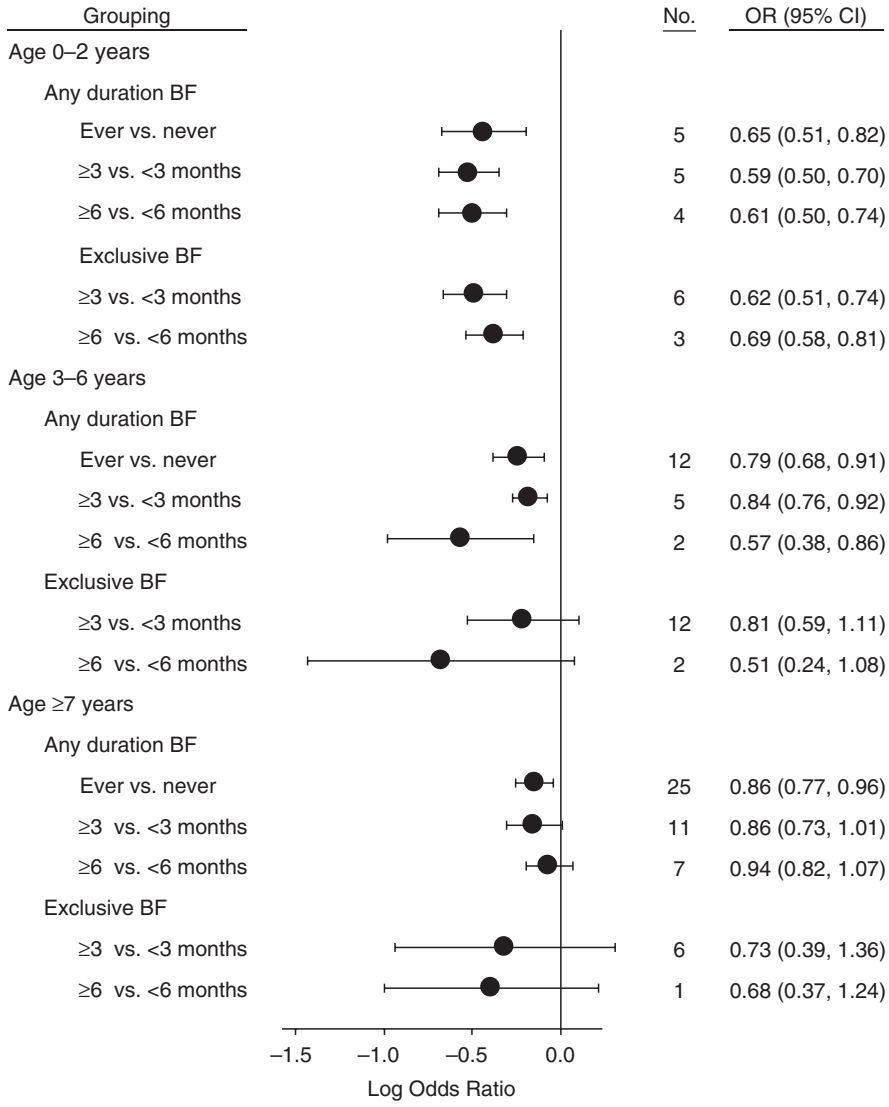

Figure 2. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of meta-analyses performed for "asthma ever" in groups determined by age, outcome, breastfeeding (BF) type, and breastfeeding cut-off (stringent categorization). The graph presents results from each of the groups determined by stringent categorization, separated by age and type of breastfeeding. For reasons of symmetry, the graph is presented on a log scale.

represent the characteristics used in meta-analysis. Breastfeeding was analyzed as the duration of any breastfeeding in 72 studies (62%) and as the duration of exclusive breastfeeding in 41 studies (35%). For 42 studies (36%), we analyzed breastfeeding categorized as "never versus ever," for 53 studies (45%) as "<3–4 versus ≥3–4 months," and for 19 studies (16%) as "<6 versus ≥6 months." We analyzed "asthma ever" in 75 studies, from which we analyzed "recent asthma" in 46 studies. "Recent wheezing illness" was analyzed in 94 studies; this included the 46 studies on "recent asthma" and an additional 48 studies analyzing only recent wheeze (single or multiple episodes). The reported samples sizes varied greatly, ranging from 50 to 168,283, with a mean of 7,111 and a median of 2,144 (Table 2; Web Table 1).

Quality assessment. Quality scores were low for 66 studies (56%), medium for 35 studies (30%), and high for 16 studies (14%). Only 44 studies (38%) met 4 or more of the 7 assessed Kramer criteria. Of the high-quality studies, 8 were cohort studies (7% of all studies). Forty studies (34%) did not adjust for confounders; the others included up to 24 confounders in their analyses. One important reason for a low quality rating was insufficient adjustment for confounders; only 23 studies (20%) adjusted for 3 or more essential confounders. Overall, 31 studies (26%) adjusted for smoking exposure during pregnancy, 10 studies (9%) adjusted for gestational age, 19 studies (16%) adjusted for birth weight, 15 studies (13%) adjusted for ethnicity, 21 studies (18%) adjusted for socioeconomic status, and 33 studies (29%)

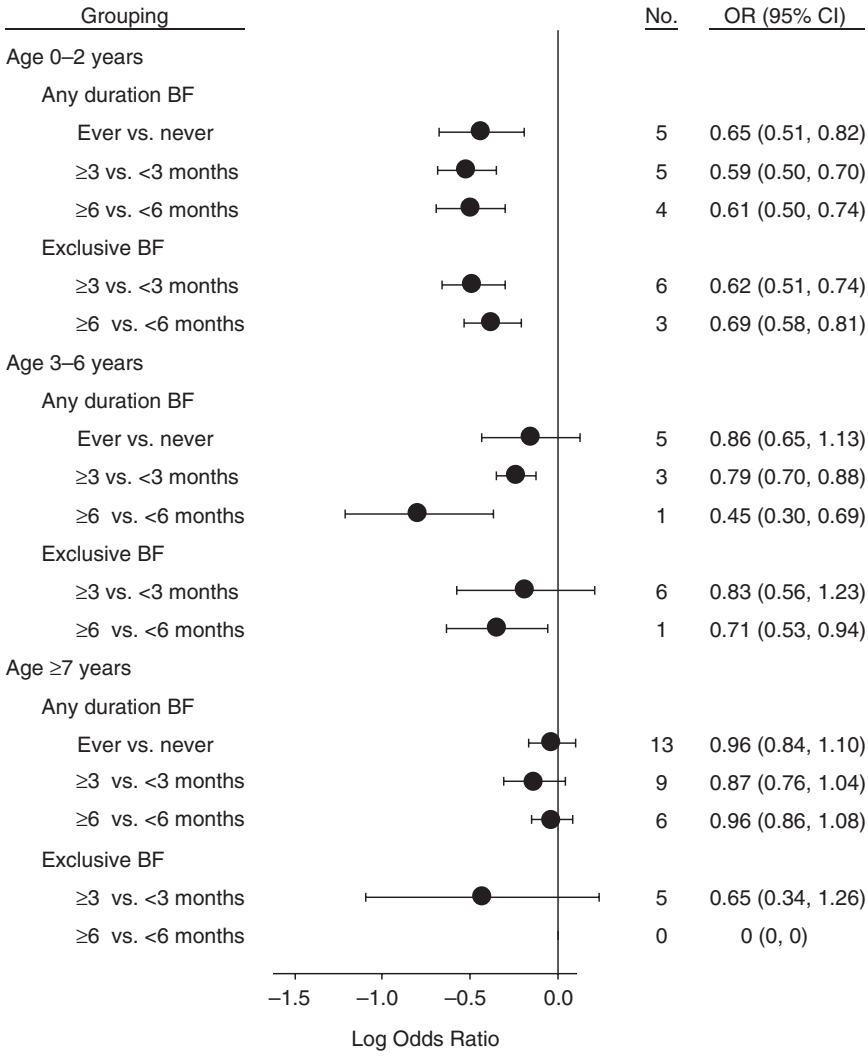

Figure 3. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of meta-analyses performed for "recent asthma" in groups determined by age, outcome, breastfeeding (BF) type, and breastfeeding cut-off (stringent categorization). The graph presents results from each of the groups determined by stringent categorization, separated by age and type of breastfeeding. For reasons of symmetry, the graph is presented on a log scale.

adjusted for family education. Half of the studies ($n = 15$) did not adjust for family history of asthma or allergy.

Meta-analysis and meta-regression

Stringent categorization of breastfeeding. Figures 2 and 3, Web Figure 1, and Web Table 2 show in detail the results of the meta-analyses performed in the 45 groups for each the 3 outcomes. Web Table 3 shows a summary of the pooled odds ratios (as medians and ranges) grouped by subjects' ages and type of breastfeeding. The medians of the pooled random-effects odds ratios in studies analyzing duration of any breastfeeding (all outcomes and all breastfeeding cut-offs) were 0.61 (range, 0.59–0.69), 0.79 (range, 0.57–0.89), and 0.94 (range, 0.86–1.02) for studies performed in children 0–2 years, 3–6 years, and 7 or more years of age, respectively. For studies analyzing the duration of exclusive breastfeeding, the corresponding medians were 0.67 (range, 0.62–0.69), 0.80 (range, 0.51–0.83), and 0.73 (range, 0.65–0.84) for studies performed in children 0–2 years, 3–6 years, and 7 or more years of age, respectively.

Flexible categorization of breastfeeding. Figures 4 and 5, Web Figure 2, and Web Table 4 present the results of the meta-analyses using the less stringent categorization "more versus less breastfeeding" in all studies and stratified by study characteristics for "asthma ever," "recent asthma," and "recent wheezing illness"; Web Figures 3–5 present the corresponding forest plots.

The meta-analyses yielded pooled odds ratios of 0.79 (95% confidence interval (CI): 0.75, 0.84) for the 75 studies reporting "asthma ever," 0.76 (95% CI: 0.67, 0.86) for

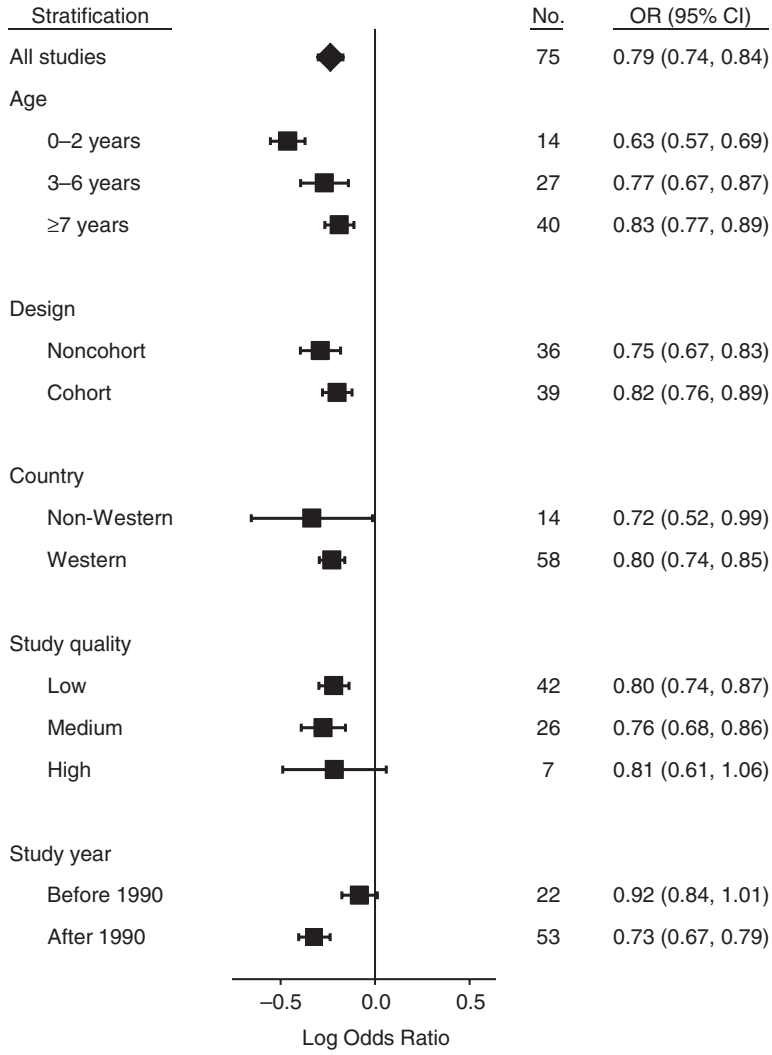

Figure 4. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of meta-analyses performed for "asthma ever" in all studies, analyzed using "more versus less breastfeeding" and stratified by age, study design, country type, and quality score. The graph presents the results from the random-effects meta-analyses performed in the entire group and stratified by age, study design, country type, and study quality. For reasons of symmetry, the graph is presented on a log scale.

the 46 studies reporting "recent asthma," and 0.81 (95% CI: 0.76, 0.87) for the 94 studies reporting "recent wheezing illness."

When we stratified by age at outcome, we found evidence of reduced risk with longer breastfeeding for all outcomes at 0–2 years, 3–6 years, and 7 or more years of age, respectively, with a consistent decreasing trend in the extent of risk reduction with older age. Meta-analyses for "asthma ever" and "recent asthma" from cohort studies, studies performed in Western countries, and studies performed before 1990 showed pooled odds ratios that tended to be closer to 1 (no association) compared with studies performed in noncohorts, in non-Western countries, and after 1990, respectively. In all analyses, we found high levels of heterogeneity, except for the analyses on "asthma ever" and "recent asthma" in studies analyzing the outcome in children 0–2 years of age and in studies classified as high quality (Web Table 4).

Meta-regressions. We present the results from the meta-regressions in Table 3. For "asthma ever," the pooled odds ratio of studies performed in children 7 or more years of age was 1.26 times higher (95% CI: 0.97, 1.6; $P = 0.08$) than that of studies assessing outcomes in children 0–2 years of age, indicating that the reduction in the risk of asthma in breastfed children is smaller in children 7 or more years of age than in children 0–2 years of age (i.e., the pooled OR is closer to 1, indicating no association). This was confirmed for "recent asthma" and "recent wheezing illness," with pooled odds ratios of studies of school-aged children of 1.32 (95% CI: 0.97, 1.57; $P = 0.08$) and 1.30 (95% CI: 1.08, 1.56; $P = 0.005$) higher, respectively, than in children 0–2 years of age. Additionally, the

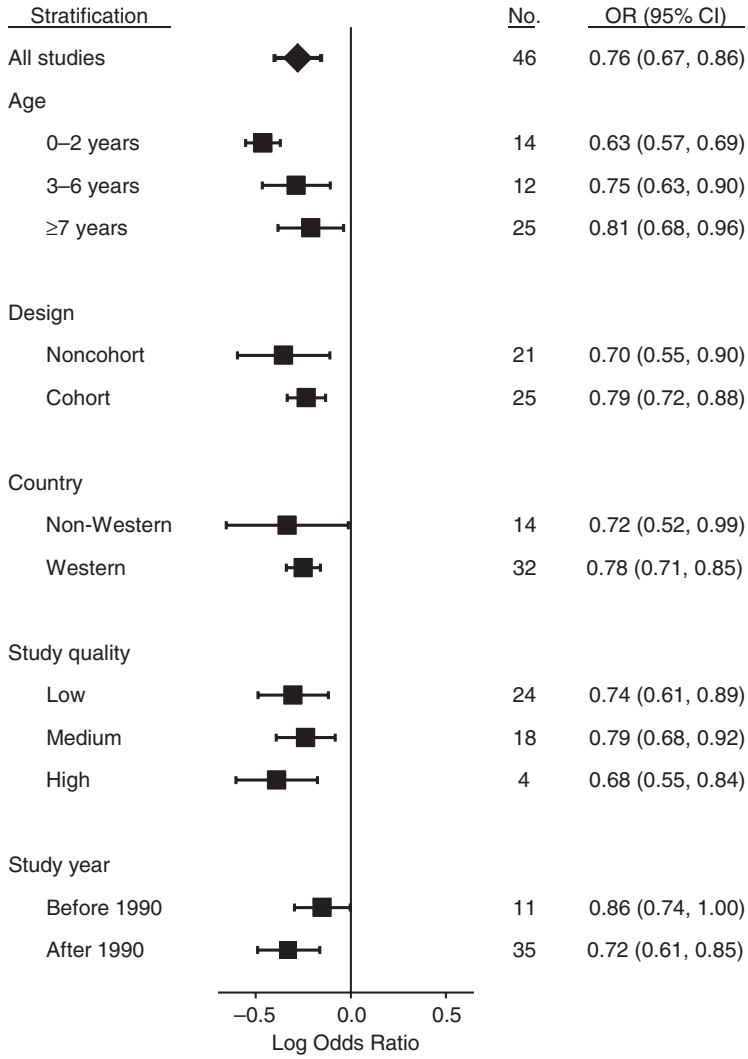

Figure 5. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of meta-analyses performed for "recent asthma" in all studies using "more versus less breastfeeding" and stratified by age, study design, country type, and quality score. The graph presents results from the random-effects meta-analyses performed in the entire group and stratified by age, study design, country type, and study quality. For reasons of symmetry, the graph is presented on a log scale.

pooled odds ratio for "asthma ever" in studies performed after 1990 was 0.76 times lower (95% CI: 0.62, 0.93; $P = 0.009$) than that of earlier studies, indicating that studies performed after 1990 report a stronger association. For neither outcome did we find evidence of systematic differences between the results of studies of cohort versus noncohort design, of higher quality versus lower quality studies, of studies performed in Western or non-Western countries, or of those studies that used different breastfeeding definitions and cut-offs.

DISCUSSION

We found evidence that children who are breastfed longer have a lower risk of developing asthma. Risk reduction is most pronounced in children 0–2 years of age and decreases with age, but is still evident at school age. Studies were highly heterogeneous, but our results were similar when we included only longitudinal cohort studies or limited the selection to studies of high methodological quality.

Compared with other reports, our review included a larger number of studies. We minimally restricted search and study selection, including studies of different methodologies, different operational definitions for breastfeeding and asthma, and different sets of confounders, which may have increased the variability of effect estimates. We tried to account for this by performing meta-analyses in standardized subgroups and by performing meta-regressions with a broad array of predictors. We included an assessment of the methodological quality of the studies using criteria based on Kramer's standards

Table 3. Results of Meta-Regression Performed Using "More versus Less Breastfeeding," 1983–2012[a]

Explanatory Variable	Asthma Ever ($n = 75$)			Recent Asthma ($n = 46$)			Recent Wheezing Illness ($n = 94$)		
	Ratio of ORs[b]	95% CI	*P* Value	Ratio of ORs[b]	95% CI	*P* Value	Ratio of ORs[b]	95% CI	*P* Value
Cohort study	1.031	0.837, 1.271	0.770	1.117	0.803, 1.553	0.500	0.917	0.776, 1.083	0.301
Western country[c]	0.924	0.731, 1.167	0.500	0.976	0.677, 1.407	0.895	1.185	0.980, 1.431	0.079
Age, years[d]									
0–2	1.00	Referent		1.00	Referent		1.00	Referent	
3–6	1.131	0.861, 1.486	0.372	1.271	0.866, 1.866	0.213	1.120	0.907, 1.383	0.288
≥7	1.257	0.972, 1.626	0.080	1.321	0.978, 1.786	0.069	1.300	1.085, 1.558	0.005
Breastfeeding definition[e]									
Any duration	1.00	Referent		1.00	Referent		1.00	Referent	
Exclusive	1.029	0.841, 1.259	0.779	1.009	0.756, 1.347	0.949	0.985	0.815, 1.190	0.874
Breastfeeding cut-off[f]									
Ever vs. never	1.00	Referent		1.00	Referent		1.00	Referent	
≥3–4 vs. <3–4 months	1.060	0.853, 1.318	0.594	0.873	0.617, 1.235	0.431	0.938	0.764, 1.151	0.534
≥6 vs. <6 months	0.985	0.767, 1.265	0.902	0.998	0.703, 1.418	0.993	0.962	0.784, 1.180	0.708
Quality score[g]	0.999	0.865, 1.154	0.988	1.082	0.846, 1.383	0.520	1.055	0.954, 1.167	0.295
Study after 1990	0.764	0.625, 0.934	0.009	0.841	0.602, 1.175	0.520	0.948	0.799, 1.125	0.538
Outcome analyzed									
Wheeze	NA			NA			1.00	Referent	
Asthma	NA			NA			0.907	0.791, 1.041	0.162
Intercept	0.798	0.546, 1.166	0.239	0.680	0.422, 1.096	0.110	0.687	0.506, 0.932	0.016

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

[a] Asthma was defined as a parent report of doctor diagnosis, use of asthma medication, wheeze accompanied by bronchial hyperreactivity, and/or data retrieved from medical records reported at any time in the past ("asthma ever"). Of those, we categorized as "recent asthma" the ones reported in the last 12 months. "Recent wheezing illness" included studies analyzing "recent asthma" and studies analyzing a single or multiple episodes of wheezing reported in the last 12 months.

[b] The meta-regression coefficients are to be interpreted as "ratios of odds ratios" (i.e., the relative change in the pooled odds ratios when the explanatory variable (study characteristic) is different by 1 unit, holding everything else constant). For example, the 1.257 coefficient for school age in the meta-regression for "asthma ever" means that the studies performed at school age yield a pooled odds ratio that is 25.7% larger than studies performed in children 0–2 years of age. In this case, it means that the protective effect of breastfeeding in children 7 or more years of age is lower than that in children 0–2 years of age (the larger OR is closer to 1, representing no effect).

[c] Countries from Europe, North America, and South America, as well as Australia or New Zealand.

[d] Age when the outcome was assessed.

[e] Whether the analysis used duration of any breastfeeding or duration of exclusive breastfeeding.

[f] The stringent categorization of breastfeeding used in analysis (ever vs. never; ≥3–4 vs. <3–4 months; or ≥6 vs. <6 months).

[g] Quality score: 1 point was assigned for adjustment for 3 or more essential confounders (birth weight, gestational age, ethnicity, family history of asthma or allergy, family education, socioeconomic status, and exposure to tobacco smoke pre- or postpartum) and 1 point for meeting more than 3 Kramer quality criteria (nonreliance on prolonged breastfeeding recall, sufficient duration of breastfeeding, sufficient exclusivity of breastfeeding, strict diagnostic criteria, adjustment for essential confounders, assessment of dose effect, and assessment of children with family history of atopy).

(17) and recent recommendations (18), and we included the quality score in the analyses that addressed the heterogeneity we found among studies.

Quality of included studies

All included studies were observational and, therefore, prone to bias. We quantified the methodological quality of each study with a quality score based on adjustment for essential confounders and the standards proposed by Kramer in 1988 (17). Based on our quality scores, the overall quality of the studies was low, especially because of insufficient adjustment for confounders; this may explain why the studies categorized by our criteria as being of low quality did not differ much from those categorized as high quality. Studies with higher quality scores were less heterogeneous, which suggests that higher quality standards increase the consistency of results, probably by reducing bias.

Interpretation of findings

Our study strongly suggests that breastfeeding is protective against the development of childhood asthma. We found the strongest association in children 0–2 years of age; the strength of the association decreased with age. This is consistent with the hypothesis that wheezing conditions in infants

are likely to be triggered by viral respiratory infections, against which breastfeeding is an established protector (130–132). As the child develops, more and more factors influence respiratory morbidity, making it difficult to discern the specific influence of breastfeeding. We do still find some evidence of risk reduction in school-aged children. There is a hypothesis that the development of later asthma is mediated by respiratory infections in early life (133–135); this would explain why the protection offered by breastfeeding in infants continues to be visible in older children.

Despite the heterogeneity among studies, results were consistent across different study designs, with similar results between cohort and noncohort designs. A potential explanation is that mothers remember the duration of breastfeeding fairly well (136, 137), even after many years, making recall bias less of a problem in cross-sectional studies, in which breastfeeding is assessed retrospectively. On the other hand, many cohort studies did not use strict diagnostic criteria for asthma, and although some assessed the duration of breastfeeding prospectively, often the analysis did not consider the timing of the onset of wheezing in the course of breastfeeding. This made cohort studies more similar to cross-sectional studies and reduced the advantages offered by a prospective study design. In addition, case-control studies, despite being retrospective, have the advantage of more objective and better constructed outcome definitions, making them less prone to biased results.

Breastfeeding practices and their impact on respiratory health may vary across countries because of differences in culture and varied economic development (106, 138, 139). Prevalence and causes of asthma may differ between countries. Therefore, the International Study of Asthma and Allergies in Childhood (ISAAC) (http://isaac.auckland.ac.nz/) stratified its analysis by dividing it into Western and non-Western countries. One ISAAC study found that breastfeeding was associated with a decreased risk of wheezing in both affluent and nonaffluent countries, but in nonaffluent countries this was true only for nonatopic wheeze (106). Our meta-analysis did not find different levels of protection offered by breastfeeding in Western versus non-Western countries. However, studies from non-Western countries were more heterogeneous, perhaps because of poorer methodological aspects of the studies, as suggested by the fact that 17% of studies performed in Western countries had a quality score of 2 (high quality), whereas only 4% of those performed in non-Western countries received this score.

Possible limitations

We excluded from our search studies reported as conference proceedings and abstracts, because we intended to extract as much information as possible, expecting the studies to be observational and therefore heterogeneous. We considered that studies published as conference proceedings or abstracts might lack the depth of information needed. We excluded non-English papers because of a lack of translators. It is possible that the exclusion of conference proceedings and abstracts introduced publication bias. Excluding studies reported in languages other than English may have introduced a bias in favor of "positive" results (140, 141). To check for the possible impact of excluding non-English studies, we analyzed the 12 eligible but excluded studies that had published abstracts in English. Unfortunately, the information contained in the abstracts was limited; therefore, we could not perform a systematic analysis. Six of the studies analyzed the outcome at more than 7 years of age, 1 study at 5 years of age, 4 studies at 0–2 years of age, and 1 at mixed ages (0–14 years). Nine studies reported "protective association," and 3 studies reported "no association." The studies reporting "no association" were performed at more than 7 years of age or at mixed ages. Although this is not a systematic analysis, we think that it shows a similar pattern to our main findings; therefore, we conclude that their exclusion did not alter the main results and interpretation.

Conclusion and recommendations

Our review brought to light the wide heterogeneity of studies that consider the role of breastfeeding in the development of asthma and some of the common methodological problems.

We make the following recommendations for future studies.

Study design. Studies should use a longitudinal design, should recruit women during pregnancy, and should assess the duration of breastfeeding and incidence of asthma symptoms prospectively. A study design based on sibling comparisons could allow for a better control for genetic and environmental factors, which are partially shared (142).

Measurement. Breastfeeding should be recorded as a continuous measurement (length in months or days) and should clearly differentiate between exclusive and total durations. Asthma should be measured objectively, differentiating between phenotypes, such as atopic and nonatopic asthma.

Analysis model. A minimum set of confounders should be considered, including exposures during pregnancy (e.g., tobacco smoke), perinatal factors (e.g., birth weight and gestational age), family's socioeconomic status, and family's history of asthma/atopy. For example, in much of the Western world, breastfeeding, particularly exclusive and of long duration, is more common among more educated women. This matters, because education and socioeconomic status are associated with the development of asthma and atopy (143, 144). The studies should analyze potential interactions when there are strong hypotheses (e.g., with maternal history of asthma or ethnicity). More advanced statistical models, such as path analysis and structural equation modeling, could be used to explore causal pathways.

Mechanisms. If, as this systematic review suggests, breastfeeding is associated with reduced risk of asthma/wheeze, future studies should analyze the mechanisms involved, including the immune protection conferred by constituents of breast milk, nonexposure to potential allergens while exclusively breastfeeding, respiratory exercise at the breast associated with improved lung volumes, and psychological factors such as emotional bonding and stress reduction for the newborn. Despite heterogeneity of the studies analyzed, this review provides strong evidence that breastfeeding is associated with reduced risk of asthma.

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