Breastfeeding and Childhood Asthma Systematic Review and Meta-Analysis

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ABBREVIATIONS

$CI_{95\%}$=95% confidence interval; ORs=odds-ratios

RUNNING HEAD

Breastfeeding and asthma: systematic review

ABSTRACT

Asthma and wheezing disorders are common chronic health problems in childhood. Breastfeeding provides health benefits, but is not known whether or how breastfeeding decreases the risk of developing asthma. We performed a systematic review with meta-analysis of studies on breastfeeding and asthma in unselected children, published between 1983 and 2012. We searched PubMed and Embase for cohort, cross-sectional and case-control studies. We grouped the outcomes into asthma ever, recent asthma and recent wheezing illness (recent asthma combined with 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 1464 titles identified by search. The pooled odds ratios (95% confidence intervals) were 0.78 (0.74,0.84) for 75 studies analysing a*sthma ever*, 0.76 (0.67,0.86) for 46 studies analysing *recent asthma* and 0.81 (0.76,0.87) for studies analysing recent wheezing illness. When stratified by age, the strong protective association found at age 0-2years diminished over time. We found no evidence for differences by study design, 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.

KEYWORDS

Breast Feeding

Asthma

Review

Child

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 (3). Research related to risk and protective factors are thus a priority for public health.

Breastfeeding provides many advantages for infants, mothers and society (4). Though 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 found no risk reduction or even an increased risk of harm in breast fed children (10-15). Excepting a study that randomized maternal hospitals and polyclinics to either a breastfeeding intervention program or to a control program (16), these studies rely on observational data since it is not ethical to withdraw breastfeeding from one study arm 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, and for statistical analysis. Besides methodological problems, the heterogeneity of results between studies might also be caused by real differences due to outcomes measured at different ages, various exposure to infections in childhood or dissimilar socio-cultural environments.

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 include 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 and colleagues (18), found no evidence that breastfeeding protects against asthma. However, the authors included only

studies assessing asthma in children aged 5 or older, did not perform a meta-regression, and identified relatively few studies.

In this study, we aimed to identify and summarize all publications on breastfeeding and risk of asthma in unselected children, and use stratified analyses and meta-regressions to explore potential sources of heterogeneity.

MATERIAL AND METHODS

We complied with the requirements for reporting meta-analyses of observational studies (24, 25).

Search and selection

We searched PubMed and Embase 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 title and abstract and used MeSH terms for breastfeeding. We also included titles listed by other systematic reviews on breastfeeding and asthma. This report reflects the state of the literature as of July 31st 2012.

Two authors (CD and DN) independently selected eligible studies in two stages: 1) scanning titles and abstracts; and (2) reading full-text. We obtained full texts from electronic databases, inter-library loans, or by contacting the authors. At the end of each stage, the reviewers compared their decisions and discussed discrepancies.

We included fully reported original studies, both cohort (longitudinal) and non-cohort studies (cross-sectional or case-control), and 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 only children with diagnosed asthma/wheeze that analysed only the association between breastfeeding and asthma severity. We included studies that analysed, as outcomes, any of the following, alone or in combination: asthma diagnosis from medical reports; parental reports of *current wheezing* (≥1 episode in the past 12 months), *treatment for asthma or wheezing*; *doctor diagnosis of asthma* and *wheezing with bronchial hyper-responsiveness*. 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 also excluded studies that analysed only "wheeze ever" as an outcome.

Extraction of study characteristics

We extracted extensive information on breastfeeding, outcomes and study estimates (see below). In addition, we extracted author names and year of publication, date and country where the study was performed, study design, inclusion and exclusion criteria, length of follow-up, sample size, potential confounders adjusted for, type of analysis and author conclusion. We considered "Western" the countries from Europe, Australia/New Zealand or North and South America.

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

Standardization of data extracted

After 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. Outcomes were grouped into (a) *asthma ever:* a condition that occurred at any time in the past, including asthma diagnostic retrieved from medical records and/or parent report of doctor diagnosis, use of asthma medication, wheeze accompanied by bronchial hyper-reactivity; of those, we categorized as (b) *recent asthma* the ones reported in the last 12

months. We then created the (c) *recent wheezing illness* category, extending the *recent asthma* group by including studies analysing 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* and *≥7 years*.

Breastfeeding stringent categorization. For each type of breastfeeding (duration of any or exclusive breastfeeding) we created three separate categorizations, based on the categories 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 prevalences for each of the above breastfeeding categorizations, separated by type of breastfeeding, outcome and age of assessment. For instance, if a study reported outcome prevalence using breastfeeding categories *never, 0 to 3 months, 4 to 6 months* and *>6 months,* we calculated 3 prevalences as follows: *ever vs. never* = (0 to 3 months + 4 to 6 months + >6 months) *vs.* (never); *≥3-4 months vs. <3-4 months* = (4 to 6 months + >6 months) *vs.* (never + 0 to 3 months) and *≥6 months vs.<6 months* = (>6 months) vs. (never + 0 to 3 months + 4 to 6 months). We then calculated unadjusted odds-ratios for each new categorization, using the category of shorter duration as reference; for the example presented above we thus calculated 3 odds-ratios. Whenever available, we also recorded the reported adjusted odds-ratios and unadjusted odds-ratios 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 categories “ever vs. never” for exclusive breastfeeding, which were not considered. A study could appear only once within the same group, but could belong to more than one group if we could recalculate more than one breastfeeding categorization, if it reported results for more than one outcome, breastfeeding type and/or age group.

Breastfeeding flexible categorization. To increase the number of studies that we could compare for a given outcome, we calculated ORs using a less stringent categorization (*more vs. less breastfeeding*) to compare studies regardless 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-off. Thus, in the example presented above, which reported outcome prevalence using breastfeeding categories *never, 0 to 3 months, 4 to 6 months* and *>6 months,* we recorded a *breastfeeding more vs. less* category taking the values from the *≥ 6 months vs.< 6 months* categorization. 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 one age group, we gave priority to results from school-age.

Quality assessment

To measure the methodological quality of studies, we defined a quality score based on (a) whether a study reported adjustment for at least three of seven important potential confounders (17, 18) and (b) whether it satisfied at least four of seven of the selected quality standards suggested by Kramer (17). We assigned one point for each of these criteria, resulting in a score that ranged from 0 to 2. For reporting purposes, we labelled them 0=low, 1=medium, and 2= high quality. Based on literature, we considered *birth weight, gestational age, ethnicity, family history of asthma or allergy, family education, socio-economic status* and *exposure to tobacco smoke pre- or post-partum* to be important potential confounders. We selected the following seven of Kramer's twelve quality standards: *non-reliance 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 five criteria (blind ascertainment on infant feeding history, blind ascertainment of outcome,

severity of outcome, age of onset of outcome, adequate statistical power) were difficult to assess in the selected studies and therefore 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 the *more vs. less breastfeeding* categorization.

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-ratio, we used the adjusted estimates.

In the analyses using *more vs. less breastfeeding* we addressed heterogeneity between studies by performing meta-analyses stratified by age, study design, Western country, recent study (conducted before/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 type of recent wheezing illness (asthma vs. wheeze). Analyses were done in Stata 12.0 (Stata Corporation, Austin, Texas) and used the *metan* and *metareg* commands (27).

RESULTS

Study characteristics

Search. Figure I presents the search and selection process. Our search yielded 1464 titles. Eighteen articles, not traced by our search, were identified from other systematic reviews on the same topic. After some of the duplicate titles were automatically excluded by the managing program (EndNote), we screened 1083 titles, of which 217 were retained. We dropped nine 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 (12, 29-135). Of these, 3 were multi-country 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. Tables 2 and Web Table 1 (online repository) 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 represent the characteristics used in meta-analysis. Breastfeeding was analysed as duration of any breastfeeding in 72 studies (62%), and as duration of exclusive breastfeeding in 41 studies (35%). For 42 (36%) studies we analysed breastfeeding categorized as *never vs. ever*, for 53 studies (45%) as *<3-4 months vs. ≥3-4 months*, and for 19 studies (16%) as *<6 months vs. ≥6 months*. We analysed *asthma ever* in 75 studies, from which we analysed *recent asthma* in 46 studies. *Recent wheezing illness* was analysed in 94 studies; this includes the 46 studies on *recent asthma* and additional 48 studies analysing 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. The quality score was low for 66 studies (56%), medium for 35 (30%) and high for 16 (14%) of the studies. Only 44 studies (38%) met ≥4 of the 7 assessed Kramer criteria. Of the high quality, 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 low quality rating was insufficient adjustment for confounders: only 23 studies (20%) adjusted for ≥3 essential confounders. Thus 31 (26%) studies adjusted for smoking exposure during pregnancy, 10 (9%) and 19 (16%) studies adjusted for gestational age and birth weight, respectively; 15 (13%) adjusted for ethnicity; 21 (18%) adjusted for socio-economic status and 33 (29%) for family education; half of the studies (59) did not adjust for family history of asthma or allergy.

Meta-analysis and meta-regression

Breastfeeding stringent categorization. Figures 2, 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 three outcomes, and Web Table 3 a summary of the pooled ORs (medians and ranges), grouping them by age and type of breastfeeding. The medians (range) of the pooled random-effects ORs in studies analysing duration of any breastfeeding (all outcomes and all breastfeeding cut-offs) were 0.61 (0.59-0.69), 0.79 (0.57-0.89) and 0.94 (0.86-1.02) for studies performed in children 0-2 years, 3-6 years and ≥7 years of age, respectively. For studies analysing duration of exclusive breastfeeding, the corresponding medians (range) were 0.67 (0.62-0.69), 0.80 (0.51-0.83) and 0.73 (0.65-0.84) for studies performed in children 0-2 years, 3-6 years and ≥7 years of age, respectively.

Breastfeeding flexible categorization. Figures 4,5; Web Figure 2 and Web Table 4 present the results of the meta-analyses using the less stringent categorization *more vs. 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 ORs ($CI_{95\%}$) of 0.79 (0.75,0.84) for the 75 studies reporting *asthma ever;* 0.76 (0.67,0.86) for the 46 studies reporting *recent asthma;* and 0.81 (0.76,0.87) for the 94 studies reporting *recent wheezing illness*.

When we stratified by age at outcome, we found evidence of a reduced risk with longer breastfeeding for all outcomes at 0-2 years, 3-6 years and ≥*7* 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 ORs that tended to be closer to 1 (no association) compared with studies performed in non-cohorts, 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 analysing the outcome in children 0-2 years 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 OR of studies performed in children ≥7 years of age was 1.26 times higher ($CI_{95\%}$=0.97,1.6; *P*=0.08) than the pooled OR of studies assessing outcomes in children 0-2 years old, indicating that the reduction in risk of asthma in breastfed children is smaller in children ≥7 years of age than in children 0-2 years old (the pooled OR is closer to 1, no-association). This was confirmed for *recent asthma* and *recent wheezing illness*, with pooled OR of studies performed at school age 1.32 ($CI_{95\%}$=0.97,1.57; *P*=0.08) and 1.30 ($CI_{95\%}$ =1.08,1.56; *P*=0.005) higher, respectively, than in children 0-2 years old. Additionally, the pooled OR for *asthma ever* of studies performed after 1990 was 0.76 times lower ($CI_{95\%}$=0.62,0.93; *P*=0.009) than earlier studies, indicating that studies performed after 1990 report a stronger association. For neither outcome did we find evidence of systematic differences between results of studies of cohort versus non-cohort design, of higher versus

lower quality, performed in Western or non-Western countries, or between those that used different breastfeeding definitions and categorizations.

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 old 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 operationalizations 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 (17) and recent recommendations (18) and 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 score, the overall quality of the studies was low, especially due to insufficient adjustment for confounders; this may explain why the studies categorized by our criteria as of low and high quality did not differ much. Studies with a higher quality score were less heterogeneous, which suggests that higher quality standards increase 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 old; the strength of association decreases 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 (136-138). 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 at school age. There is a hypothesis that development of later asthma is mediated by respiratory infections in early life; (139-141) this would explain why the protection offered by breastfeeding in infants continues to be visible in older children.

Despite the heterogeneity between studies, results are consistent across different study designs, with similar results between cohort and non-cohort. A potential explanation is that mothers remember the duration of breastfeeding fairly well (142, 143), even after many years, making a recall bias be less of a problem in cross-sectional studies, where breastfeeding is assessed retrospectively. On the other hand, many cohort studies did not use strict diagnostic criteria for asthma, and while some assessed duration of breastfeeding prospectively, often the analysis did not consider the timing of 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 a more objective and better constructed outcome definition, 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 (144-146). 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 non-affluent countries, but in non-affluent countries this was true only for non-atopic wheeze (145). Our meta-analysis did not find different levels of protection offered by breastfeeding in Western vs. non-Western countries. However, studies from non-Western countries were more heterogeneous, perhaps due to 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), while only 4% of 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, due to lack of translators. It is possible that exclusion of conference proceedings/abstracts has introduced publication bias. Excluding studies reported in other languages than English may have introduced a bias in favour of "positive results" (147, 148). To check a possible impact of excluding non-English studies, we analysed the 12 eligible studies, which had their abstracts in English. Unfortunately the information contained in the abstracts was limited; therefore we could not perform a systematic analysis. Half of them (6) analysed the outcome at >7 years, 1 study at 5 years, 4 studies at age 0 to 2 years, and 1 at mixed ages (0 to 14 years). Nine studies reported "protective association" and 3 studies reported "no association." The studies reporting "no association" were performed at > 7 years or mixed ages. While this is not a systematic analysis, we think that it shows a similar pattern with our main findings and therefore their exclusion did not alter the main results and their 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, recruit women during pregnancy and assess 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 [149].

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

Analysis model. A minimum set of confounders should be considered, including exposures during pregnancy (tobacco smoke), perinatal factors (birth weight and gestational age), family's socio-economic 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 socio-economic status are associated with development of asthma and atopy [150; 151]. The studies should analyse 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 modelling 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 analyse the mechanisms involved, including immune protection conferred by constituents of the breast milk; non-exposure to potential allergens while exclusively breastfeeding, as well as respiratory exercise at breast associated

with improved lung volumes or psychological factors such as emotional binding and stress reduction for the newborn.

Despite this heterogeneity, this study provides strong evidence that breastfeeding is associated with reduced risk of asthma.

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

	Asthma ever		***Recent asthma***		***Recent wheezing illness***	
age	*total*	*exclusive*	*total*	*exclusive*	*total*	*exclusive*
0-2 years						
ever vs. never	5	*N/A*	5	*N/A*	9	*N/A*
≥3mo vs. <3mo	5	6	5	6	7	10
≥6mo vs. <6mo	4	3	4	3	6	3
3-6 years						
ever vs. never	12	*N/A*	5	*N/A*	13	*N/A*
≥3mo vs. <3mo	5	12	3	6	6	12
≥6mo vs. <6mo	2	2	1	1	4	2
≥7 years						
ever vs. never	25	*N/A*	13	*N/A*	24	*N/A*
≥3mo vs. <3mo	11	6	9	5	12	10
≥6mo vs. <6mo	7	0	6	0	10	1

Abbreviations: BF=breastfeeding; mo=months; N/A=not applicable

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

Table 2. Study Characteristics of the 117 Selected Studies (1983-2012)

General characteristics	No	%
Type of study		
cohort	57	48.7
cross-sectional	47	40.1
case-control	13	11.1
Age at enrolment		
perinatal	51	43.6
0 to 6 years	21	18.0
≥7 years	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 income	93	79.5
upper-middle income	19	16.2
lower-middle income	5	4.3
Region[b]		
Western		
Europe	48	41.0
North-America	20	17.1
Australia	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
Multi-Regional	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 BF	71	61.5
duration of exclusive BF	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
Categorizations analysed[c]		
ever vs. never	40	34.2
≥3-4 months vs. <3-4 months	52	44.4
≥6 months vs. <6 months	21	18.0
Outcomes		
Age at assessment		
0-2 years	21	18.0
3-6 years	32	27.3
≥7 years	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
Nr. of confounders[g]	5 (0–24)	
Nr. of Kramer quality criteria[f, g]	3 (0–6)	
Nr. of essential confounders[g,h]	2 (0–7)	
Sample size[g]	2,144 (50–168,283)	

[a]Based on World Bank classification

[b]Countries from Europe, North- and South-America and Australia/New Zealand

[c]Some studies used several breastfeeding types and categories. We gave priority to exclusive breastfeeding and higher breastfeeding categories. The table presents the categorizations 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 hyper-reactivity; from those, the ones that reported the condition in the past 12 months were analysed 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 adjusting for ≥3 essential confounders and one point for meeting >3 Kramer quality criteria

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

[g]Median [range]

[h]Essential confounders: birth weight, gestational age, ethnicity, family history of asthma or allergy, family education, socio-economic status and exposure to tobacco smoke pre- and post-partum

Table 3. Results of Meta-Regression Performed Using "More vs. Less Breastfeeding" Categorization[a] (1983-2012)

	Asthma ever, (N=75)			Recent asthma, (N=46)			Recent wheezing illness, (N=94)		
	ratio of ORs[b]	**CI**	***P***	**ratio of ORs[b]**	**CI**	***P***	**ratio of ORs[b]**	**CI**	***P***
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[d]									
0-2 years	*ref.*			*ref.*			*ref.*		
3-6 years	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 years	1.257	0.972,1.626	0.080	1.321	0.978,1.786	0.069	1.300	1.085,1.558	0.005
BF definition[e]									
any duration	*ref.*			*ref.*			*ref.*		
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
BF categorization[f]									
ever vs. never	*ref.*			*ref.*			*ref.*		
≥ 3-4 mo vs. <3-4 mo	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 mo vs. <6 mo	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	N/A			N/A			*ref.*		
asthma	N/A			N/A			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: BF=breastfeeding; mo=months; OR=odds ratio; CI=95% confidence interval; N/A=not applicable; ref.=reference

[a]Asthma was defined as: parent report of doctor diagnosis, use of asthma medication, wheeze accompanied by bronchial hyper-reactivity 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 analysing *recent asthma* and studies analysing single/multiple episodes of wheezing reported in the last 12 months)

[b]The meta-regression coefficients are to be interpreted as "ratio of odds ratios", i.e., the relative change in the pooled ORs when the explanatory variable (study characteristic) is different by one 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 OR 25.7% larger than studies performed in children 0-2 years old. In this case it means that the protective effect of breastfeeding in children *≥7 years of age* is lower than the one in children 0-2 years old (the larger OR is closer to 1, the non-effect).

[c]Country from Europe, North- and South-America or Australia/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 breastfeeding stringent categorization used in analysis (ever vs. never; ≥ 3-4 months vs. <3-4 months; or ≥6 months vs. <6 months)

[g]Quality score: one point is assigned for adjusting for ≥3 essential confounders (birth weight, gestational age, ethnicity, family history of asthma or allergy, family education, socio-economic status and exposure to tobacco smoke pre and postpartum) and one point for meeting >3 Kramer quality criteria (non-reliance on prolonged breastfeeding recall; sufficient duration of breastfeeding; sufficient exclusivity of breastfeeding; strict diagnostic criteria; adjustment for essential confounders; assessment of dose-effect; assessment of children with family history of atopy)

FIGURES LEGENDS

Figure 1. Study selection

Three articles reporting multi-country studies analysed and reported the results separately by geographical region or affluence; we analysed then as separate studies (n=12).

Abbreviations: BF=breastfeeding

Figure 2. ASTHMA EVER: pooled odds-ratios of meta-analyses performed in groups determined by age, outcome, breastfeeding type and breastfeeding cut-off (stringent categorization)

Note. The graph presents pooled odds ratios with confidence intervals for the meta-analyses performed in each of the stringent breastfeeding categorization groups, separated by age and type of breastfeeding. For reasons of symmetry, the graph is presented on a log-scale.

Abbreviations: No. = number of studies meta-analysed in each group; OR=odds ratio; CI=confidence intervals (95%)

Figure 3. RECENT ASTHMA: pooled odds-ratios of meta-analyses performed in groups determined by age, outcome, breastfeeding type and breastfeeding cut-off (stringent categorization)

The graph presents pooled odds ratios with confidence intervals for the meta-analyses performed in each of the stringent breastfeeding categorization groups, separated by age and type of breastfeeding. For reasons of symmetry, the graph is presented on a log-scale.

Abbreviations: No. = number of studies meta-analysed in each group; OR=odds ratio; CI=confidence intervals (95%)

Figure 4. ASTHMA EVER: pooled odds-ratios of meta-analyses performed by "more vs. less breastfeeding" in all studies and stratified by age, design, country and quality score

The graph presents pooled odds-ratios and 95% confidence intervals 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.

Abbreviations: No. = number of studies meta-analysed in each group; OR=odds ratio; CI=confidence intervals (95%)

Figure 5. RECENT ASTHMA: pooled odds-ratios of meta-analyses performed by "more vs. less breastfeeding" in all studies and stratified by age, design, country and quality score

The graph presents pooled odds-ratios and 95% confidence intervals 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.

Abbreviations: No. = number of studies meta-analysed in each group; OR=odds ratio; CI=confidence intervals (95%)