Global perceptions of food allergy thresholds in 16 countries

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Breastfeeding and asthma and allergies: a systematic review and meta-analysis

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ABSTRACT

Aim: To systematically review the association between breastfeeding and childhood allergic disease.

Methods: Pre-determined inclusion/exclusion criteria identified 89 articles from PUBMED, CINAHL and EMBASE databases. Meta-analyses performed for categories of breastfeeding and allergic outcomes. Meta-regression explored heterogeneity.

Results: More versus less breastfeeding (duration) was associated with reduced risk of asthma for children (5-18yrs), particularly in medium/low income countries, and with reduced risk of allergic rhinitis ≤5 years, but this estimate had high heterogeneity and low quality. Exclusive breastfeeding for 3-4 months was associated with reduced risk of eczema ≤2 years (estimate principally from cross-sectional studies of low methodological quality). No association found between breastfeeding and food allergy (estimate had high heterogeneity and low quality). Meta-regression found differences between study outcomes may be attributable to length of breastfeeding recall, study design, country income and date of study inception. Some of the protective effect of breastfeeding for asthma may be related to recall bias in studies of lesser methodological quality.

Conclusion*:* There is some evidence that breastfeeding is protective for asthma (5-18yrs). There is weaker evidence for a protective effect for eczema ≤2 years and allergic rhinitis ≤5 years of age, with greater protection for asthma and eczema in low income countries.

Keywords: Allergic disease, Asthma, Meta-analysis, Systematic Review

Key Notes

- There is low Grade quality evidence that longer duration of breastfeeding is associated with a reduced risk of asthma in children aged 5-18 years.

- There is low to very low Grade quality evidence that breastfeeding is associated with a reduced risk of: allergic rhinitis in children up to 5 years of age, and eczema in children up to 2 years of age
- No association was found between breastfeeding and food allergy
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Abbreviations:

GRADE/Grade - the Grading of Recommendations Assessment, Development, and Evaluation system

CINAHL: Cumulative Index of Nursing and Allied Health Literature;

EMBASE: Excerpta Medica database

ISAAC International study of Asthma and Allergies in Childhood

NOS Newcastle-Ottawa Scale

PRISMA stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses .

PUBMED search engine for published medical literature

INTRODUCTION

Allergic diseases are common in childhood and a significant cause of morbidity (1). During recent decades there has been a dramatic rise in prevalence of these conditions (2, 3), which include asthma, eczema, and allergic rhinitis, and a similar, delayed increasehas been observed for food allergy in the last 10-15 years (4). Over 300 million people worldwide suffer from asthma. Allergic rhinitis is estimated to affect between 10 to 30% of the global population (3). Eczema and food allergy also represent major public health problems (5) and are both associated with profound negative impacts on health-related quality of life (6, 7). The complexity and severity of allergic disease continues to increase, particularly in children and young adults, who bear most of the burden of disease (8).

Breast milk is an immunologically complex solution, containing multiple compounds that support infant growth and facilitate development of host defence mechanisms (9). In addition to passive immunity (from bioactive components such as secretory IgA and IgG), breast milk also contains factors that actively stimulate the infant immune system (10). Consequently, breast milk provides both protective and stimulatory signals, which may confer contrasting effects on immune function development and subsequent susceptibility to allergic disease (9). However, detailed interactions between breastfeeding, the infant immune system function and subsequent allergic disease are complex and not fully understood.

Many studies have attempted to assess the role of breastfeeding in the development of allergic disease with inconsistent findings. While most have found a protective effect of breastfeeding on allergic diseases (11-13), several others have found no association (14, 15) or even an increased risk of childhood asthma for subsets of individuals (16, 17). Differences in methodological quality and design may account for some of these discrepancies, but it is also likely that the true association is dependent on a combination of factors which have been inconsistently assessed between studies. These include duration of breastfeeding, timing of the introduction of solids, characteristics and cultural practices of the population of interest and exact definitions including ages for the various allergic outcomes. The inconsistency of findings from original studies may also be due to changes in breastfeeding behaviour over time, especially among specific sub-groups. Temporal changes in infant feeding recommendations have influenced breastfeeding behavioural changes, with at-risk groups being particularly vulnerable. The effects of breastfeeding guidelines, and study designs and quality will also vary by country, cultural beliefs, and income levels. Furthermore, the real possibility of reverse causation, whereby early allergic symptoms in the infant determine a longer course of breastfeeding (18) is rarely taken into account. This may be especially pertinent for more recent studies from higher income countries.

Previous systematic reviews have, in general, found a protective effect of breastfeeding on these various allergic outcomes (10, 19-21). However, as described by Dogaru and colleagues, many have had methodological limitations, such as not addressing heterogeneity between studies or failing to comply with standards for performing systematic reviews (19). Also, few have attempted to assess this association over the spectrum of allergic conditions: asthma, eczema, allergic rhinitis and food allergy. This is important because of the substantial overlap in allergic diseases with shared phenotypes.

This systematic review aims to provide a comprehensive analysis of the current evidence through employing sound search methods, investigating the heterogeneity and quality of included studies, and contextualising the results with respect to these findings. Overall, we aim to provide a resource to better inform public health recommendations in the area of breastfeeding and allergic outcomes.

METHODS

On 2 October 2014 PUBMED, CINAHL and EMBASE electronic databases were systematically searched from inception. The search strategy included terms for breast feeding and allergic disease (available from Supporting Information File (SI_Table1)). We included observational (cohort, cross-sectional, case-control) and experimental (randomised and quasi-randomised controlled trials) original studies published in full text and in English. There were no limits to the age of reported outcomes, except for asthma where we included articles reporting outcomes at 5 years or older, to avoid misclassification with viral associated early transient wheeze (22). Studies on premature births (<37 weeks gestation) were excluded. There were no restrictions on population type (population based, high-risk). We also manually searched reference lists of primary studies and related review articles for additional studies meeting our inclusion criteria.

Outcomes of interest were current symptoms or diagnosis (within the past 12 months) of the following allergy-related conditions: asthma, eczema, allergic rhinitis and food allergy. Recent disease was defined as either recent symptoms or health-care utilisation for the respective allergy-related conditions. The acceptable criteria for outcome definitions were:

1) Asthma defined as: physician diagnosed asthma, parent or self-reported asthma or wheeze, spirometrically diagnosed asthma, or asthma recorded on health related databases.
2) Allergic rhinitis defined as: physician diagnosed allergic rhinitis/hay fever, parent or self-reported hay fever, or hay fever recorded on health related databases.
3) Eczema/Atopic dermatitis defined as: physician diagnosed eczema, parent or self-reported eczema, by validated eczema diagnostic criteria (e.g. UK working party, International Study of Asthma and Allergies in Childhood (ISAAC) survey), or eczema recorded on health related databases.
4) Food allergy defined as: physician diagnosed food allergy, parent or self-reported food allergy, by objective measures (serum IgE, skin prick testing, oral food challenge), or food allergy recorded on health related databases

Two authors (DT and ML or XD) independently screened titles and abstracts of all identified records. Duplicates and multiple reports from the same study with the same outcomes were excluded. Studies assessed as eligible, potentially eligible or unclear were retrieved in full-text where available, to assess for inclusion. Any disagreements either at this stage or further on in the process were settled by consultation with a third author (CL).

Data extraction

Study characteristics and outcomes were extracted from each included study by two authors working independently (DT and ML or XD) using a standard data collection form created for this purpose. Information extracted included: First author, date of publication; study design, number of study centres and location, study setting, date of study; number of participants, mean age, age range, gender, inclusion criteria, exclusion criteria; breastfeeding classifications; length of breastfeeding recall; outcome definitions; confounders and interactions; effect estimates and 95% CI.

Quality assessment / Risk of bias in included studies

Study quality was assessed independently by two authors (DT and ML or XD) using both the Newcastle-Ottawa scale (NOS) (23) for individual studies, (a design specific scale -cross-sectional versus case-control versus cohort study) and the GRADE guidelines (24) to assess quality by outcome over a range of studies. Sources of bias were rated as high, low or unclear. NOS study quality was graded according to total score. Cohort and case-control studies: very good = 9-10; good = 7-8; satisfactory = 5-6; unsatisfactory = 0-4. Cross-sectional: very good = 6-7; good = 5; satisfactory = 4; unsatisfactory = 0-3.

Data categorization

Studies were grouped according to type of breastfeeding exposure and then further grouped by age of outcome, nature of effect measure (e.g. Odds Ratio, Hazard Ratio, etc.) and study type. Final groups with three or more studies were suitable for meta-analysis. Breastfeeding categories included:

- Ever versus Never: children receiving breast milk at any time compared with those never breast fed.

- More or Less than 3-4 months: children fed with breast milk up to 3-4 months compared to other feeding modes.
- More or Less. This category was created to include all studies which compared groups with relatively more and relatively less breast milk exposure. In order to choose between multiple available odds ratios for a single study we preferentially selected estimates for exclusive breast feeding, then longest duration versus shortest. If multiple ages of outcome were available we chose the oldest up to 18 years.

Prior to pooling, we stratified by age of outcome based on clinical knowledge of likely phenotypes. For asthma this was outcomes during childhood (5-18) and those in adulthood >18. For eczema, early childhood eczema/infantile eczema (<=2 years) and eczema > 2years. Both allergic rhinitis and food allergy were stratified into outcomes before and after 5 years of age.

Analysis

Studies were considered suitable for meta-analysis if they provided an adjusted measure of the effect of breastfeeding on allergic outcomes with 95 % confidence intervals. Heterogeneity of the pooled estimate was assessed using the I^2 statistic. If I^2 was below 25%, fixed effects were presented, if between 25 % and 75%, random effects (re) presented. If the I^2 was above 75%, we provided the pooled estimate, but considered it unreliable. Funnel plots were used to assess publication bias. Egger's tests were used to quantify small study effects when there were at least 10 studies in a pooled analysis. Substantial heterogeneity was explored through subgroup analysis using meta-regression if there were 10 estimates likely in each subgroup strata. The subgroups defined prior to the analysis included age of outcome assessment, category of breastfeeding exposure, year of study, birth year of participants, length of recall for breastfeeding exposure, type of study and income level. Income was

categorized as high if it was included in the top 50 countries on the World Bank list by Gross National Income per capita (2013) (25).

RESULTS

Search process and results

Our search performed on 2 October 2014 identified 4784 records. Following removal of duplicates, 3420 titles and abstracts were screened, yielding 388 full-text articles for assessment. Exclusion of 299 articles according to eligibility criteria left 89 articles for inclusion. Some articles reported on multiple outcomes. Overall we included 42 articles with asthma/wheeze outcomes, 42 articles with eczema outcomes, 16 articles with allergic rhinitis outcomes and 13 with food allergy outcomes (Fig1).

Asthma/Wheeze

The 42 records for asthma/wheeze comprised 23 records from cohort studies(12, 14, 17, 26-45), 17 records from cross-sectional studies (46-61) and 2 records from case-control studies (62, 63). Due to multiple records from the same study, the total number of studies these records represented was: 17 cohorts, 12 cross-sectional studies and 2 case-control studies. All studies were population based except one cohort study from a high allergy risk population (37). All but two (28, 31) of the 17 cohort studies were from the 50 most affluent countries (25). In contrast, 8 of 12 cross-sectional studies were based in less affluent countries. The number of participants varied between 223 and 13,889 for cohort studies; 474 and 206,453 for cross-sectional studies and 463 and723 for case-control studies (SI Table 2).

Study quality

By design, the evidence from prospective cohort studies is of better quality than evidence from case-control or cross-sectional studies. Cohort and case-control studies were generally of good quality as determined by the NOS (range satisfactory to very good) whilst cross-sectional studies generally rated lower at satisfactory (range unsatisfactory to good) (SI Tables 3, 4 & 5). A major issue influencing study quality was failure to adjust for key confounders, most commonly socioeconomic status and family history of allergic disease. Additionally, the definition of the outcome measure varied. Many studies reported wheeze in the past 12 months, whilst more rigorous definitions involved doctors' diagnosis of asthma along with current wheeze, current medication, or current classic spirometry changes.

Synthesis of study findings

We pooled studies of different types together for analysis, however, forest plots are presented for the main exposures stratified by study type

Ever versus Never breastfeeding and asthma 5-18yrs (SI Fig 1)

There was a protective effect of ever breastfeeding on asthma from 5-18 years when the effect estimates from 3 cohort studies and 10 cross-sectional studies were pooled; random effects (re) OR 0.88 (95%CI; 0.82,0.95); Overall I^2 was 44%. (Grade assessment of evidence quality (Grade) +) (Table 2). To explore the possible role of affluence, this group was stratified by country income (GDP). There was a reduced risk of asthma for ever breastfed children in high income countries; re OR 0.90 (0.83, 0.97) I^2 18% and a slightly greater beneficial effect in medium/low income countries; re OR 0.78 (0.70, 0.88) I^2 0%. Notably, the heterogeneity was substantially lower (Overall $I^{2=}$20%). (SI Fig 2). Further exploration with meta-regression suggested that affluence explained all the variability between studies,

however there were too few studies in each sub-group for this to be reliable (Table 2). There was some evidence of publication bias from the funnel plot and Egger's test (p=0.018), with a propensity for publishing small studies showing protective effects. (SI Fig 3)

Exclusive breastfeeding≥3-4 months versus Less and asthma 5-18yrs (SI Fig 4)

Although the pooled point estimates were below 1, there was no significant association found between exclusive breastfeeding for longer than 3-4 months and asthma at 5-18 years and substantial heterogeneity in the estimates. This was true for both cohort studies (n=5) and for all types of observational study combined (n=8). The pooled estimates were re OR 0.94; 0.69, 1.29, I^2 =81% and re OR 0.89; 0.71, 1.11, I^2 =72% respectively. (Grade ++)

More versus Less breastfeeding and asthma 5-18yrs (Fig2)

Including 29 records (13 cohort, 14 cross-sectional and 2 case-control), we found a reduced risk of asthma with more versus less breastfeeding; re OR 0.90; 0.84, 0.97, $I^{2=}$ 63% (Grade ++). Subgroup analysis according to affluence again found some evidence for a reduced risk in high income countries (re OR 0.93; 0.83, 1.04, $I^{2=}$ 70%), and a greater beneficial effect in middle/low income countries (re OR 0.86; 0.79, 0.94, I^2 9%).(Fig 3) Meta-regression suggested that affluence did not help explain the between study variance (Table 2).

More versus Less breastfeeding and asthma 5-18yrs, with parental or family history of asthma/atopy (SI Fig 5)

Five studies investigated the association between breastfeeding and allergic disease stratified by familial atopy (17, 34, 40, 42, 57). Pooling of these estimates found no association between breastfeeding and asthma either in children with or without a family history of allergic disease. (re ORs: 1.08 (0.74, 1.58) I^2 78% and 1.2 (0.91, 1.59) I^2 64% respectively).

Both of the studies that investigated the relationship between breastfeeding and asthma into adulthood found an increased risk (17, 43). In the Tasmanian Longitudinal Health Study (TAHS), Matheson et al found an increased risk of asthma from the age of 14 to 44 years but only in children of atopic mothers who exclusively breastfed for at least 3 months. In the Dunedin cohort, Sears et al found an increased risk of asthma from the age of 9 to 26. This relationship was not modified by the allergic history of either parent.

The issue of reverse causation was addressed by four of the 42 studies. Two found no evidence (26, 29), a third found a non-significant tendency to breastfeed longer for infants with early signs of eczema (37), and the fourth found some degree of reverse causation after exclusion of those with wheeze or eczema during the breastfeeding period (64).

Three studies addressed the association between breastfeeding and atopic asthma phenotypes. Breastfeeding was found to reduce the risk of asthma in non-atopic children in one study (27) and conversely to reduce the risk of asthma in atopic children in two studies (44, 64).

Subgroup analysis by meta-regression (SI Table 3)

Investigation of potentially influential subgroups within these data found two factors of interest: length of recall of breastfeeding (which explained 29% of the between study variability) and year of the child's birth (which explained around 16%). In terms of the subgroup pooled estimates, there is evidence that some of the protective effect of breastfeeding on asthma may be related to recall bias in studies of lesser methodological quality. The cross-sectional and case-control studies were associated with a greater protective effect than cohort studies. Those studies with less adjustment for pertinent confounders and fewer participants also reported a stronger protective effect than those with good control and more participants.

Eczema

The 42 records for eczema comprised 24 records from cohort studies (32, 37, 65-86), 17 from cross-sectional studies (48, 52-55, 59, 60, 87-96) and one case-control (97). There were 26 studies from high income countries and 14 from middle/low income countries. Two studies presented multi-country data. The number of participants varied between 80 and 20,579 for the cohort studies and 470 and 206,453 for the cross-sectional studies (SI Table 6).

Study quality

Cohort studies were generally of good quality as determined by the NOS (range satisfactory – very good) whilst cross-sectional studies were generally of satisfactory quality (range unsatisfactory to good) (SI Tables 3, 4 & 5). A common issue was failure to adjust for essential confounders including family history of allergic disease. Breastfeeding exposure measurement was also an area of weakness, relying on parental report and, especially in the cross-sectional studies, a period of recall which ranged from 1-20 years.

Synthesis of study findings

Studies were grouped into those reporting eczema up to or after the age of 2 years. There was a reduced risk of eczema below the age of 2 years from pooling the 6 cohort studies' estimates comparing exclusive breastfeeding greater than 3-4 months with other feeding types (re OR 0.74; 0.57,0.97, I^2 62%, Grade +) (Fig 4). There was some visual evidence of publication bias on the funnel plot, with more small studies showing a protective effect. (SI Fig 6) However, there was no association found between the risk of eczema up to 2 years for the exposure of more versus less breastfeeding (15 cohorts, 1 cross-sectional study)(re OR 0.95; 0.85, 1.07, I^2 =70 %, Grade ++) (Fig 5).

After 2 years neither the ever breastfeeding, nor the more versus less exposures were associated with eczema. Ever versus never: 9 cross-sectional studies and one cohort study, re OR 1.07; 0.98, 1.16, I^2 =43%, Grade ++).(SI Fig 7) More versus less: 14 cross-sectional studies and 6 cohorts, re OR 1.09; 0.99, 1.20, I^2 86%, Grade +.(SI Fig 8) Although the more versus less category suggested weak evidence for an increased risk, the heterogeneity of the estimate was too high for the estimate to be reliable.

Pooled estimates from studies which investigated the association between breastfeeding and eczema by familial history of allergic disease did not find a different risk in the strata. (SI Fig 9)

Reverse causation was explored by 5 out of 42 studies (37, 75, 77, 79, 84) with only one finding evidence of a non-significant tendency to breastfeed longer for children with early eczema symptoms (37).

Subgroup analysis by meta-regression (Table 3)

Age of eczema outcome explained 16 % of the variability between studies, with a lower risk found for children up to 2 years. Both the study design and length of breastfeeding recall were related to the pooled estimates, explaining 16% and 57% of the between study variability. Cohort studies and breastfeeding recall of up to 1 year were associated with lower pooled risk for eczema from breastfeeding, whilst increased length of breastfeeding recall and cross-sectional study design were associated with increased pooled risks. Additionally, lower pooled estimates for eczema risk were seen in middle/low income countries when compared to high income countries. The exclusive breastfeeding category was also associated with a lower eczema risk compared with both ever versus never and more versus less.

Allergic Rhinitis

The association between breastfeeding and allergic rhinitis was investigated by 5 cohort studies (31, 66, 98-100) and 11 cross sectional studies (48, 52-55, 59, 60, 96, 101-103). The number of participants varied between 361 and 13,889 for the cohorts, and 1,402 to 206,453 for the cross-sectional studies. All except one study (98) were population based. (SI Table 7)

Synthesis of study findings

Pooling of 12 estimates for more versus less breastfeeding without consideration of study type or age of outcome found a non-significant protective effect for allergic rhinitis: re OR 0.92; 0.84, 1.01, I^2 74%. (Fig 6) After stratification by age of outcome however, a reduced risk of allergic rhinitis associated with breastfeeding was found only below the age of 5 years from pooling 6 estimates (4 cross-sectional, 2 cohort): re OR 0.79 (0.63, 0.98), I^2 84%, Grade 0 (SI Fig 10). Limiting to the 4 cross-sectional studies found a reduced heterogeneity and re OR 0.64, (0.64, 0.82), I^2 69%.(SI Fig 11) In contrast, there was no association or a non-significant increase in the risk of allergic rhinitis after 5 years from pooling 9 studies (5 cross-sectional, 4 cohort): re OR 1.05 (0.99, 1.12), I^2 43%, Grade +. (SI figure 12) Analysis by study type, regardless of outcome age, found a reduced risk for 9 cross-sectional studies (re OR 0.88; 0.77, 1.00, I^2 77%) and no association for 3 estimates from cohort studies (re OR 0.99; 0.85, 1.15, I^2 78%).(Fig 6) One cross-sectional study found no interaction by parental atopy (101).

Food Allergy

There were 9 cohort (11, 17, 70, 79, 85, 104-107) and 4 cross-sectional studies (101, 108-110) investigating the association between breastfeeding and food allergy. The numbers of participants in the cohorts ranged from 163 to 21,766, and from 1,278 to 13,110 in the cross-

sectional studies. Pooling of 12 estimates (6 cohort, 6 cross-sectional) for more versus less breastfeeding found no association with food allergy, although heterogeneity was very high (RE OR 1.02; 0.88, 1.18, I^2 86%). (Fig 7) After stratification for age of outcome, there was no association from pooling 12 estimates below the age of 5 years where heterogeneity was still too high for the estimate to be reliable (6 cohort, 6 cross-sectional) (re OR 1.07; 0.92, 1.24, I^2 85%, Grade+). (SI Fig 13) There was no association when the estimates from three cohort and one cross-sectional study were pooled for food allergy after the age of 5 years (re OR 1.08; 0.73, 1.58, I^2 65%, Grade+). (SI Fig 14)

The only study that investigated the interaction of family allergic history on the association between breastfeeding and food allergy found the risk was increased only in those with a family history (OR 5.3; 1.2-24.1) (79). This estimate should be interpreted with caution considering the very wide confidence intervals which reflect a small sample size (n=163). Furthermore, in their analysis, Kusunoki et al (110) demonstrated that the initial elevated risk of food allergy (defined by parent report of food reaction) in their data, associated with breastfeeding, was caused by reverse causation. There was no association when analyses were controlled for early disease symptoms and family history.

The main issue concerning the quality of studies on food allergy was the accuracy of outcome assessment. Most of the studies relied on parental report of symptoms or parental report of physician diagnosis. Only two studies used oral food challenge (107, 109), the recognized gold standard for food allergy diagnosis.

DISCUSSION

We found evidence that breastfeeding reduced the risk of asthma in childhood and weak evidence for reductions in the risk of eczema up to 2 years and allergic rhinitis up to 5 years of age. There was no risk or protective association for food allergy. The Grade quality assessment for all these conclusions indicated an evidence confidence level of very low to low. As it is not possible to randomize breastfeeding exposure, our evidence comes only from observational studies (cohort, cross-sectional and case-control). The Grade ratings reflect this, as meta-analyses of observational studies are assigned an initially low rating, prior to further assessment of possible biases. The consistency of our results across three of the four allergic outcomes however may lend further credence to the findings. A lack of association with food allergy may be due to the delay in the food allergy epidemic, especially in studies from earlier times.

Asthma

Virally mediated early transient wheeze in younger children is a potential source of imprecision in asthma classification. Restricting this systematic review to asthma/wheeze outcomes from the age of 5 years, we found a reduced risk of asthma in childhood (5-18 years) associated with all categories of breastfeeding exposure. Exploring the moderate-high heterogeneity suggested that this risk reduction may be overstated, with more protective estimates contributed by studies of lower methodological quality in terms of study design and control of confounding. Further subgroup analysis in the Ever versus Never breastfeeding classification found that all the between study variability could be explained according to the income category of the countries, with breastfeeding in studies from middle/low income countries conferring more protection from asthma risk. This could not be confirmed when using the estimates for all breastfeeding categories.

One mechanism which may explain a greater reduction of asthma associated with breastfeeding in middle/low income countries is through respiratory infections in childhood. Not only are early life respiratory infections associated with early transient wheeze in young children, but they are also one of the strongest known risk factors for asthma in older children (111, 112). Breastfeeding in early life is a known source of protection against early life infections (113). Greater protection conferred by breastfeeding may be seen in middle/low income countries where children are at greater risk of more (and more severe) respiratory infections. The income specific factors which change this risk may include: prevention of pathogen transmission through hygiene measures or prevention of overcrowding, vaccination programmes for young children, for example influenza vaccination, or a better standard of care for children with respiratory infections (even if this care is only supportive). A second possible mechanism concerns the microbiome hypothesis of allergic disease. More hygiene measures and changed behaviours in high income countries may reduce the exposure of children to the microbial diversity required for normal immune functioning. The beneficial effects of breastfeeding on asthma may, therefore, not be as apparent in high income communities.

Due to the small number of studies reporting breastfeeding in early life and asthma in adulthood, we were unable to perform a meta-analysis. Although both studies investigating this association (17, 43) found an increased risk of asthma, their results were inconsistent concerning the role of family allergic history. Also, at least one of the studies was prone to breastfeeding recall bias (17). These cohorts were both based in high risk, high income populations, and their findings are unlikely to be generalisable to populations with lower asthma risk and /or lower incomes.

In earlier systematic reviews and meta-analyses, Gdalevich et al (114) found a reduction in asthma risk in children exclusively breastfed for 3 months, especially in children

with a family history of atopy. Most of their included studies were in younger children where viral wheeze may cause misclassification. To address this issue, Brew et al (115) reviewed the literature in 2011, including 31 publications between 2000 and 2010 for children aged over 5 years, finding no association. Finally Dogaru et al (19) published a systematic review in 2014, including 117 publications and finding a reduced risk of ever asthma in all age groups but particularly up to the age of 2 years. The protective effect appeared to diminish with age and was only modest after the age of 7 years. In agreement with the subgroup analysis in Dogaru et al, we noted that there were greater protective effects for more recent studies, which may be attributed to improved methodology or increased publication bias. Furthermore, on meta-regression we both found a more protective effect in studies of weaker methodology, suggesting that we should be cautious concerning the quality of the evidence and accuracy of the pooled estimates. The conclusions of Brew et al differ from the others. One reason may be restriction of the outcome to breastfeeding for at least 3 months. In our review, as in the review by Dogaru et al (19), subgroup analyses showed that breastfeeding classification appeared to have little influence on the pooled risk estimate for asthma. It is possible that including further studies in the Brew et al review may have given greater power.

Eczema and Allergic Rhinitis

For both eczema and allergic rhinitis, we found some low quality evidence of a reduced risk in early life (eczema ≤2years, allergic rhinitis ≤ 5years) associated with breastfeeding. For eczema, this was limited to exclusive breastfeeding for 3-4 months in cohort studies. After this age the protective effect of breastfeeding disappeared and there was weak evidence for an increased risk. Subgroup analysis found breastfeeding was associated with a greater eczema risk in studies of lower methodological design and longer recall of breastfeeding. These studies predominated in the pooled estimates for eczema over the age of 2 years. Although

the allergic rhinitis studies were too few for subgroup analysis, we postulate that the changing risk associated with older age groups may also be attributable to methodological issues. Breastfeeding seemed to confer greater protection against eczema in middle/low income countries, although this was not a significant source of between study difference. This observation may also be explained by protection from early life infections, if viral associated rash in infants is misdiagnosed as eczema. Alternatively, environmental differences may increase the risk of eczema in high income communities. Additionally, breastfeeding protection from allergic rhinitis in early life may also be explained by the difficulty of differentiating between allergic rhinitis and viral rhinovirus infections in very young children. The reduced risk associated with breastfeeding in younger age groups could be attributed to the viral protection from breast milk rather than protection from allergic rhinitis.

With regard to systematic reviews on breastfeeding and eczema, an early study (20) found a reduced risk of eczema synthesizing 18 prospective studies in 2001. There was evidence of more protective effect in children at high-risk. A more recent systematic review and meta-analysis of 27 populations (116) however, also restricted to prospective cohort studies, found no strong evidence of a protective effect of exclusive breastfeeding for at least 3 months, even in children with a family history of allergy. Our finding of a protective effect for eczema below the age of 2 years in the exclusive breastfeeding group is novel, and suggests that breastfeeding may only be protective for the infantile eczema phenotype.

In a 2002 systematic review (21), including 6 studies published between 1966 and 2000, exclusive breastfeeding was found to protect against allergic rhinitis in children with and without a family history of atopy. All of these studies assessed allergic rhinitis below the age of 5 years. Our findings are similar but extend this analysis to include 16 studies and to the over 5 age group where the diagnosis of allergic rhinitis may be less contaminated by viral rhinovirus infection.

Food Allergy

Breastfeeding was found to be neither a protective factor nor a risk factor for food allergy, however the number of records included was lower than those for other outcomes, limiting our ability to find associations and explore subgroups. The very high heterogeneity associated with the pooled estimates makes these values unreliable. Variability may be due to methodological differences including outcome definitions which in most cases did not include oral food challenge. It is difficult to explain why breastfeeding, in our review, appears to be protective for the 3 other common childhood allergic diseases but not for food allergy. Apart from the smaller number of studies and the inaccuracy of the outcome measurement, this may be explained by the relative delay in the food allergy epidemic and concurrent changes in breastfeeding guidelines that may have masked any association between breastfeeding and food allergy in the current studies. Alternatively, the current rise in food allergy in westernized countries may be attributable to different factors than other allergic diseases.

A systematic review on breastfeeding and food allergy (117) found a protective effect for cow's milk allergy in children at high risk with 4 months exclusive breastfeeding. However, we must be cautious in drawing conclusions in highly select subgroups, especially when no main effects are observed.

Limitations

One of the challenges to finding solid evidence in this area is that all the available evidence is derived from observational studies (cohort, cross-sectional, case control), which have an inherent set of biases and inability to control for unknown confounders. Although studies exist involving randomization of groups to educational interventions for infant feeding (31), these studies advocate breastfeeding advice as one of a suite of measures making it difficult

to attribute risk or protection to individual components.

Investigation of subgroups within the asthma and eczema outcomes found one of the important sources of between study heterogeneity was length of recall of breastfeeding. In both analyses, recall up to one year was associated with a greater reduction of allergic disease than breastfeeding recall of longer duration. Mothers with allergic children who made decisions to breastfeed longer may recall a longer breastfeeding history than mothers whose children are not allergic. This is an important source of potential recall bias which requires consideration when interpreting the evidence.

Reverse causation, namely the initiation or continuation of breastfeeding for reasons of familial allergy or early signs of allergic disease in the child, was explored in a minority of studies. It is possible that parents stop breastfeeding their children if there are early signs of allergic disease. This would be unlikely however considering the breastfeeding guidelines with regard to allergic disease (118). Failure to account for reverse causation will underestimate the protective effect of breastfeeding on allergic disease. This may be part of the reason for the weak evidence of an increase in the risk of eczema and allergic rhinitis associated with breastfeeding in older compared with younger children. Very few of the included studies assessed reverse causation, and of those that did, only three found evidence that it may influence the relationship between breastfeeding and allergic disease (37, 64, 110). Nevertheless, this is something which should be considered in all studies. It is not clear why there are different findings concerning reverse causation, however recall bias may be an issue, and prospective collection of early allergic disease status with respect to breastfeeding practices is needed to assess this more accurately.

We found no evidence to support a greater positive or negative effect from breastfeeding if the infant had a family history of allergic disease. Meta-analysis of 6 asthma studies and separately 7 eczema studies that considered this issue, found no modification by

family history.

In our review, by assessing all disease outcomes separately, we have discerned a pattern of reduction in early disease and no association or possible increase in adult disease. Subgroup analysis raised the possibility that the increased risk in older age groups may be due to methodological issues related to length of breastfeeding recall, study type or date of study inception. Alternatively, risk reduction in younger age groups may reflect breastfeeding protection from early viral infections which can be either misdiagnosed as allergic disease (allergic rhinitis, eczema) or a potential mediator of allergic disease (asthma). Another possibility is that breastfeeding may only be protective for early allergic disease phenotypes.

We were unable to comment on whether specific lengths of breastfeeding and/or exclusive breastfeeding would confer a greater reduction in allergic disease risk because of a lack of studies specifically addressing these issues.

CONCLUSION

There is weak evidence that breastfeeding, regardless of length or exclusivity, is protective for allergic disease. There is evidence of greater protection in middle/low income countries and no evidence that these associations were modified by an allergic family history. The protective effect for asthma, eczema, and allergic rhinitis appears to be greater in early life raising the possibility of mediation through protection from viral disease, misdiagnosis of viral disease, or effects only on specific phenotypes. There is weak evidence for waning protection or increasing risk in older children. Exploration of subgroups suggests that this effect may be partially mediated through bias induced by length of breastfeeding recall, or poorer methodology in earlier studies.

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Author Statement

All authors contributed to multiple parts of this systematic review. SD, KA, AL, CL, DT, ML, *RT* & GB contributed to framing the research question. DT led data collection assisted by ML, XD, RT, GB and CL who all contributed to searching, collection and abstraction of data. All authors contributed to data analysis and appraisal. CL led manuscript preparation, assisted by all authors.

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Table 1 GRADE assessment of quality of evidence for each outcome in the systematic review+

Asthma 5-18 years									
	No of studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Sample size	OR (95% CI)	Quality
Ever vs Never	13	Serious limitations	No serious Inconsistency	No serious indirectness	No serious imprecision	Likely	341,684	0.88 (0.82,0.95)	+
Exclusive More vs less than 3-4months	8	Serious limitations	No serious Inconsistency	No serious indirectness	No serious imprecision	Unlikely	16,773	0.89 (0.71, 1.11)	++
More vs less BF	29	Serious limitations	No serious Inconsistency	No serious indirectness	No serious imprecision	Unlikely	391,238	0.90 (0.84, 0.97)	++
Eczema									
Eczema <=2yrs									
Exclusive More vs less than 3-4months	6	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Likely	12,865	0.74 (0.57,0.97)	+
More vs less BF	17	Serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Unlikely	62,166	0.95 (0.85, 1.07)	++
Eczema > 2 years									
Ever vs Never	10	Serious limitations	No serious Inconsistency	No serious indirectness	No serious imprecision	Unlikely	310,808	1.07 (0.98, 1.16)	++
More vs less BF	20	Serious limitations	Serious Inconsistency	No serious indirectness	No serious imprecision	Unlikely	374,215	1.09 (0.99, 1.20)	+
Allergic Rhinitis									
<=5yrs									
More vs less BF	6	Serious limitations	Serious inconsistency	No serious indirectness	No serious imprecision	Likely	5,954	0.79 (0.63, 0.98)	-
>5yrs									
More vs less BF	10	Serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Unlikely	317,696	1.05 (0.99, 1.12)	+
Food Allergy									
<=5yrs									
More vs less BF	12	Serious limitations	Serious inconsistency	No serious indirectness	No serious imprecision	Unlikely	41,084	1.07 (0.92, 1.24)	+
>5yrs									
More vs less BF	4	Serious limitations	Serious inconsistency	No serious indirectness	No serious imprecision	Unlikely	19,794	1.08 (0.73, 1.58)	+

Grade Quality: High = 4+; Moderate = 3+; Low = 2+; Very Low = 1+

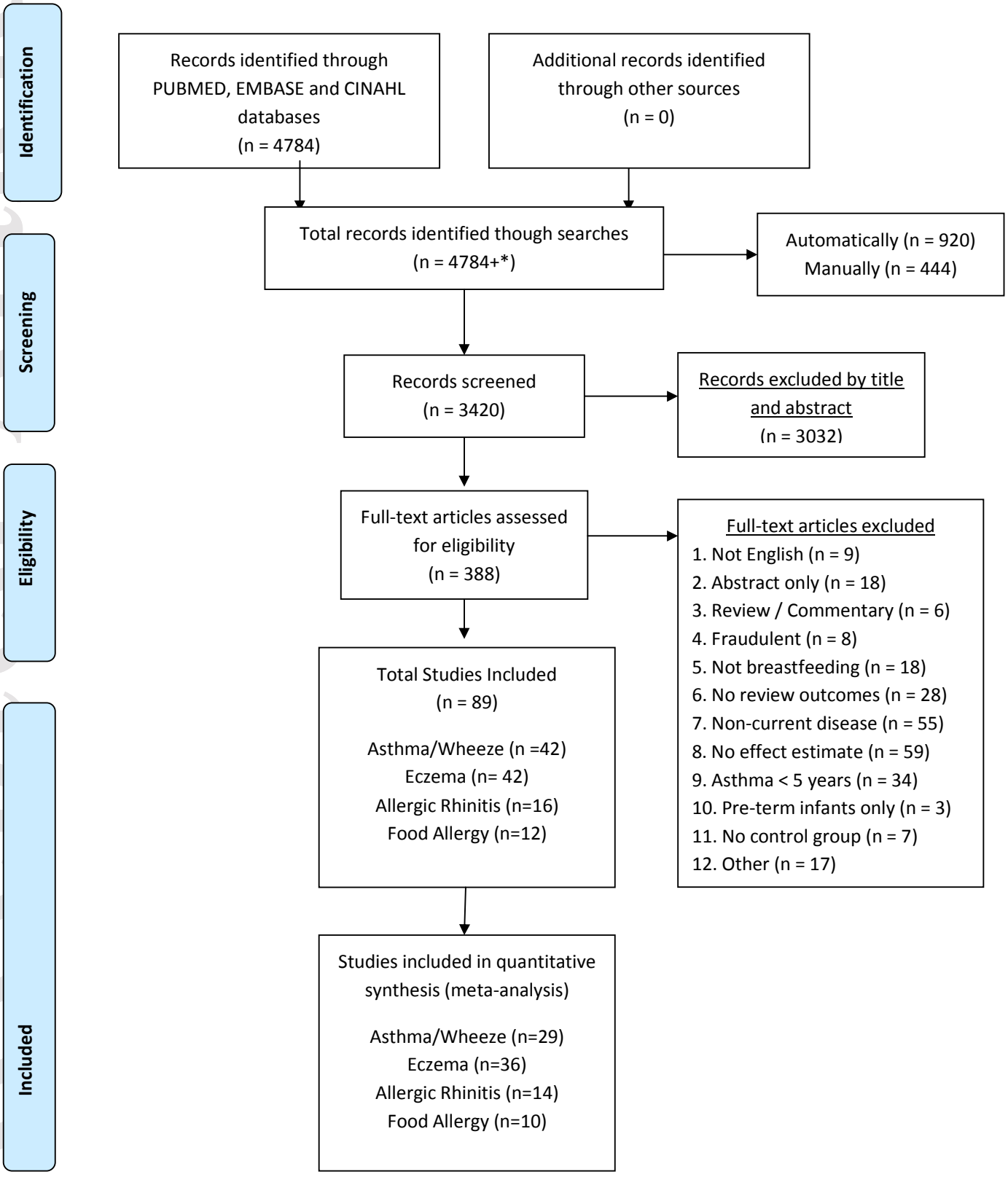
Table 2 Breastfeeding and the risk of asthma: Random-effects meta-analyses of risk by subgroup.

Subgroup	Number of records	Pooled odds ratio and 95% confidence interval	Proportion between study variability explained (adj R^2 %)	Estimate of remaining between study variance (tau^2)
Age of asthma outcome				
5-10 years	13	0.88 (0.77; 1.01)	0	0.0359
> 10 years	16	0.93 (0.85; 1.01)		
Study size				
< 1000 participants	6	0.83 (0.54; 1.27)	0	0.0418
1000 – 10000 participants	18	0.92 (0.83; 1.03)		
≥ 10000 participants	6	0.91 (0.84; 0.97)		
Year at birth				
1961-1989	14	0.98 (0.88; 1.09)	15.9	0.0292
1990-1997	13	0.82 (0.73; 0.93)		
Study design				
Cohort	13	0.94 (0.80; 1.11)	0	0.0361
Cross-sectional	14	0.68 (0.48; 0.94)		
Case-control	2	0.67 (0.61; 0.74)		
Length of recall of breastfeeding				
0 <=1yrs	9	0.80 (0.69;0.94)		
>1- <=7yrs	6	1.24 (1.00; 1.55)	28.5	0.0242
>7 – 18 yrs	14	0.88 (0.81;0.95)		
Control for confounding				
Low	2	0.68 (0.45; 1.03)	0	0.0388
Medium	12	0.89 (0.82; 0.98)		
High	16	0.95 (0.85; 1.06)		
Setting				
High income country	19	0.93 (0.83; 1.04)	0	0.0389
Middle/low income country	9	0.86 (0.79; 0.94)		
Setting- Ever vs Never only				
High income country	6	0.52 (0.27, 0.99)	100	0
Middle/low income country	6	0.86(0.80, 0.92)		
Categorization of breastfeeding				
Ever vs never	8	0.92 (0.85;1.00)	0	0.0419
Exclusive vs other	13	0.90 (0.81; 1.00)		
More vs less(not in categories above)	8	0.92 (0.68; 1.25)		
Total	**29**	**0.90 (0.84; 0.97)**		

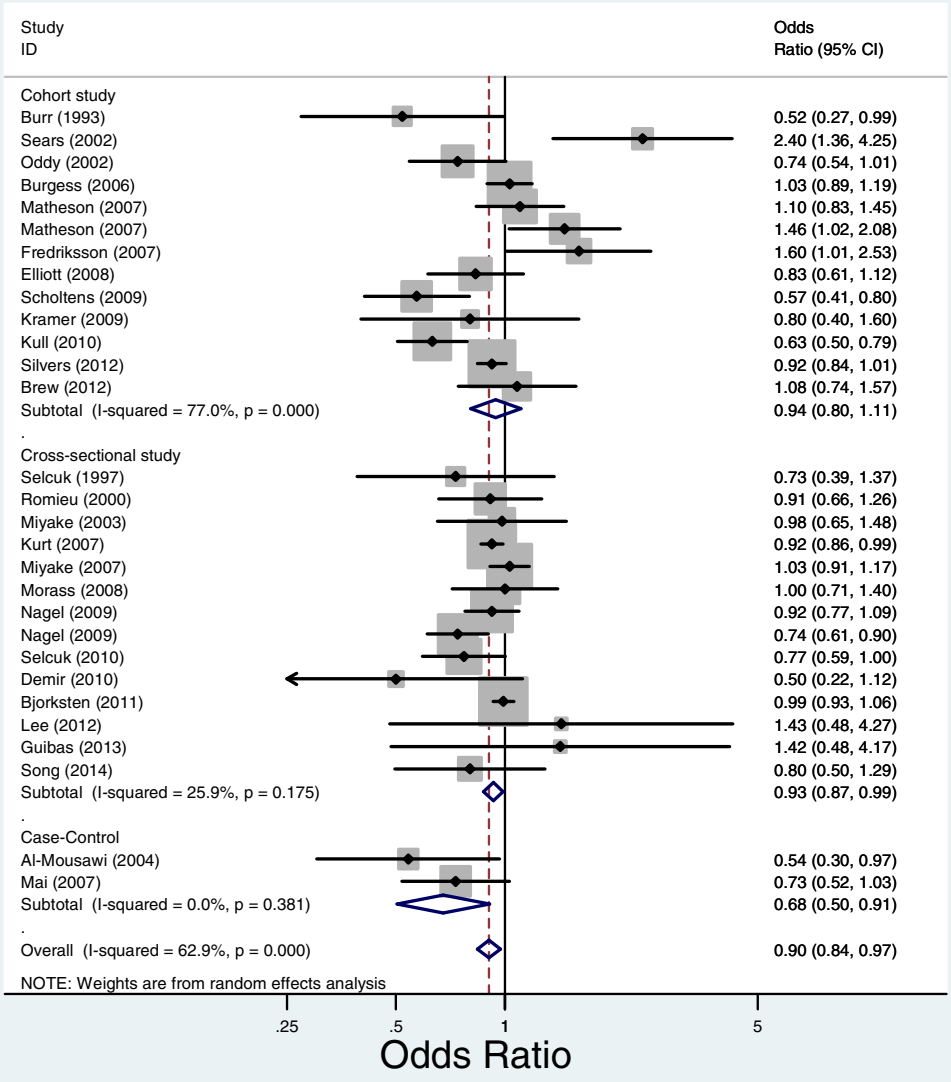
Table 3 Breastfeeding and the risk of eczema: Random-effects meta-analyses of risk by subgroup.

Subgroup	Number of records	Pooled odds ratio and 95% confidence interval	Proportion between study variability explained (adj R^2 %)	Estimate of remaining between study variance (tau^2)
Age of eczema outcome				
6months - 2 years	11	0.92 (0.83; 1.03)	16.2	0.0159
3-20 years	14	1.04 (0.96; 1.14)		
Study size				
< 1000 participants	6	0.96 (0.89; 1.02)	0	0.0261
1000 – 10000 participants	11	0.87 (0.72; 1.05)		
≥ 10000 participants	5	1.07 (1.00; 1.16)		
Year at birth				
1958-1994	12	1.01 (0.89; 1.13)	0	0.0338
1995-2008	10	1.00 (0.91; 1.11)		
Study design				
Cohort	14	0.96 (0.86; 1.07)	16.2	0.0159
Cross-sectional	11	1.04 (0.95; 1.13)		
Length of recall of breastfeeding				
<=1 yrs	14	0.94 (0.85;1.03)	56.5	0.0040
7-20 yrs	10	1.11 (1.01; 1.22)		
Control for confounding				
Low	5	0.95 (0.74; 1.24)	0	0.0286
Medium	11	1.01 (0.90; 1.13)		
High	9	1.02 (0.92; 1.13)		
Setting				
High income country	15	1.02 (0.91; 1.14)	0	0.0358
Middle/low income country	8	0.94 (0.85; 1.03)		
Categorization of breastfeeding				
Ever vs never	9	1.11 (0.98;1.25)	0	0.0190
Exclusive vs other	9	0.88 (0.79; 0.98)		
More vs less(not in categories above)	7	1.04 (0.93; 1.16)		
Total	**25**	**1.00 (0.94; 1.06)**		

Figure 1. PRISMA flow diagram. Breastfeeding on asthma and allergic outcomes



More vs Less breastfeeding and the risk of wheeze/asthma 5-18 years of age



More vs Less breastfeeding and the risk of wheeze/asthma 5-18 years by country income