ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original research article

Breastfeeding and risk of childhood asthma: a systematic review and meta-analysis

Mike Xue, Emily Dehaas, Nagendra Chaudhary, Paul O'Byrne, Imran Satia, Om P. Kurmi

Please cite this article as: Xue M, Dehaas E, Chaudhary N, *et al*. Breastfeeding and risk of childhood asthma: a systematic review and meta-analysis. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00504-2021).

Breastfeeding and risk of childhood asthma: a systematic review and meta-analysis

Mike Xue[1], Emily Dehaas[2], Nagendra Chaudhary[3], Paul O'Byrne[4,5], Imran Satia[4,5], Om P Kurmi[4,5,6]

Affiliations:
[1]Department of Family Medicine, Queen's University, Kingston, K7L 3G2, Canada
[2]Department of Medicine, University of Toronto, Toronto, M5S 1A8, Canada
[3]Department of Pediatrics, Universal College of Medical Sciences, Bhairahawa, Nepal
[4]Department of Medicine, Division of Respirology, McMaster University, Hamilton, Canada
[5]Firestone Institute for Respiratory Health, St Joseph's Healthcare, Hamilton, Canada
[6]Faculty Centre for Intelligent Healthcare, Faculty of Health and Life Sciences, Coventry University, Coventry, CV1 5FB

Correspondence to:

Dr Om P. Kurmi
Faculty Centre For Intelligent Healthcare, Faculty of Health and Life Sciences
Coventry University, Richard Crossman Building, Priory Street, COVENTRY, CV1 5FB
Email : om.kurmi@coventry.ac.uk
Mobile : +44 (0) 7392 096445

ABSTRACT

Objective

To investigate the relationship between breastfeeding and the development of pediatric asthma.

Methods:

A systematic review and meta-analysis was conducted with MEDLINE, EMBASE, CINAHL and ProQuest Nursing and Allied Health source databases. Retrospective/prospective cohorts in children <18 years old with breastfeeding exposure reported were included. The primary outcome was a diagnosis of asthma by a physician or using a guideline-based criterion. A secondary outcome was asthma severity.

Results

Forty-two studies met inclusion criteria. Thirty-seven studies reported the primary outcome of physician/guideline-diagnosed asthma, and five studies reported effects on asthma severity. Children with longer duration/more breastfeeding compared to less have a lower risk of asthma (OR=0.84; 95% CI: 0.75-0.93, I^2=62.4%). Similarly, a lower risk of asthma was found in children who had more exclusive breastfeeding versus less exclusive breastfeeding (0.81; 0.72-0.91, I^2=44%). Further stratified analysis of different age groups demonstrated a lower risk of asthma in the 0-2 age group (0.73; 0.63-0.83) and the 3-6 age group (0.69; 0.55-0.87), there was no statistically significant effect on the 7+ age group.

Conclusion

The finding suggests that the duration and exclusivity of breastfeeding are associated with a lower risk of asthma in children less than seven years of age.

REVIEW REGISTRATION

PROSPERO CRD42018099831

INTRODUCTION

The 2018 Global Asthma Report estimates that 339 million people worldwide are affected by asthma (1). This number continues to rise, particularly in children (2, 3). Multiple factors contribute to the development of asthma, including genetic predisposition and environmental factors such as early respiratory infection, antibiotic use, and smoking exposure (4–6). Despite a multitude of studies on the subject, the relationship between breastfeeding and asthma continues to be difficult to elucidate. This is due to a variety of challenges, such as recall bias of breastfeeding exposure, inconsistent statistical management of confounders, variable definitions of diagnosis and a general scarcity of randomized control trials (RCT) and high quality cohort studies (7, 8).

Three previous systematic reviews with meta-analyses related to asthma and breastfeeding have been published in the last 10 years (Table E-1) (8–10). Two indicated that any breastfeeding or increased breastfeeding was protective against asthma. The third review showed no statistically significant association between breastfeeding and asthma (10). These previous reviews included many case-control/cross-sectional studies of low quality, used less specific outcomes such as wheezing and self-reported asthma (8–10), and one of them only looked at children over the age of 5 (9, 10). All meta-analyses had substantial heterogeneity. The most recent review was completed by Lodge *et al.* (9) and included articles up until 2014.

We aimed to provide an updated meta-analysis exploring the relationship between breastfeeding and asthma in childhood. To increase the quality of the included studies and reduce heterogeneity relative to prior meta-analyses , the current analysis was restricted to cohort studies and/or RCTs. Strict definitions of asthma were used to develop a more specific assessment for how the duration and exclusivity of breastfeeding impact the development of childhood asthma at different ages.

METHODS

Search strategy

In brief, a comprehensive search of cohort studies published until January 2020 in MEDLINE, EMBASE, CINAHL and ProQuest Nursing and Allied Health databases were used. A manual search through references of included studies and review articles for additional resources was also carried out. Full details of the search can be found in Table E-2. Further details on the study protocol can be accessed on PROSPERO (ID: CRD42018099831).

Study selection, inclusion, and exclusion criteria

Studies were eligible for inclusion if 1) they captured breastfeeding data (i.e. presence, duration, and/or exclusivity), 2) had an outcome of a diagnosis of asthma fitting below criteria, 3) included data for children <18, and 4) was a cohort study/RCT.

Definitions of breastfeeding

- Exclusive breastfeeding was based on WHO criteria, where infants received only breast milk with no other liquids or solids. All other types of breastfeeding that did not meet these criteria were categorised as partial breastfeeding, ie. breastfeeding with solids/formula.
- Breastfeeding Interventions:
    - More exclusive versus less exclusive breastfeeding encompasses comparisons where exclusive breastfeeding was done relatively longer than the comparator. For example, exclusive breastfeeding >3 months compared to exclusive breastfeeding <3 months or partial breastfeeding 1 month or no breastfeeding.
    - More versus less breastfeeding encompasses all comparisons where the intervention was relatively longer in duration than the comparator. For example, exclusive breastfeeding >3 months versus exclusive feeding <3 months or partial breastfeeding >1 month versus no breastfeeding
    - Ever versus never encompasses any breastfeeding duration that was compared to no breastfeeding at all.

Definition of asthma

Only studies with either physician-diagnosed asthma or appropriate strict guidelines for asthma definition were included. These guidelines included BTS/SIGN, GINA and Canadian Pediatric Society (11–13). Alternatively, included studies could use secondary outcomes of asthma severity such as hospitalisation, medication use, and spirometry.

Data extraction

Two evaluators (M.X. and E.D.) independently assessed all articles through abstract and title screening. Articles that met the inclusion criteria during the initial screening underwent full-text screening to determine eligibility for data extraction. Any disagreements at the level of abstract/title or full-text screening were resolved through consensus. Where consensus between the two evaluators was not possible, a third reviewer was consulted (O.K.). Figure 1 shows a flowchart with the article identification process.

Data were extracted using a standardised form and included author name, study design, study period, age of assessment, country, sex, risk factors, asthma definition, reported breastfeeding and method of assessment, study outcomes, and adjustment for confounders.

The primary outcome of interest was asthma risk. The secondary measures of interest were asthma severity. The effect sizes reported on the risk of asthma and/severity outcomes included information on hazard ratios, risk ratios, odds ratios, and prevalence.

Risk of bias assessment

The risk of bias of individual articles was evaluated using a modified Newcastle-Ottawa Scale (NOS) for cohort studies (Table 1). When assessing the comparability of cohorts, the confounders of interest were gestational age, family history of asthma/atopy and pre/post-natal exposure to smoking. This was based on previously identified significant asthma risk factors (14). In addition, article quality was then translated to ‘good,’ ‘fair,’ or ‘low’ based on the number of stars and additional preset criteria (Table 1). This step was important as certain study features are more relevant to the overall quality than others but may receive the same weighting in the standard NOS system. The method for converting the NOS stars was adapted from a previous study published by the AHRQ and outlined in Table 1 (15).

Table 1. Study quality based on Modified* Newcastle Ottawa Score for cohort studies.

Article	(1) Representativeness of the exposed cohort	(2) Selection of the non-exposed cohort	(3) Ascertainment of exposure	(4) Appropriate temporality for breastfeeding assessment*	(5) Comparability of cohorts based on the design or analysis controlled for confounders (/2)	(6) Assessment of outcome	(7) Appropriate number of follow-ups conducted for detection of outcome*	(8) Adequacy of follow-up of cohorts	Total(/9)	Quality**
Ajetunmobi et al. 2015[35]	*	*	-	*	*	*	*	-	6	fair
Alm et al. 2008[36]	*	*	-	*	**	-	*	-	6	fair
Bacopoulou et al. 2009[51]	*	*	-	*	*	-	-	-	4	low
Bion et al. 2016[21]	*	*	*	*	**	*	*	*	9	good
Burr et al. 1993[52]	-	*	-	*	-	*	*	*	5	low
Celind et al. 2018[41]	*	*	-	*	**	-	*	-	6	fair
Chiu et al. 2016[22]	*	*	*	*	**	*	*	-	8	good
Davidson et al. 2010[57]	*	*	*	-	-	*	-	-	4	low
den Dekker et al. 2016[42]	*	*	-	*	*	-	*	-	5	fair
Elliot et al. 2008[58]	*	*	-	*	-	-	*	-	4	low
Fredriksson et al. 2007[43]	*	*	-	-	*	-	*	*	5	fair
Karmaus et al. 2008[31]	*	*	-	*	*	*	*	*	7	good
Kiechl-Kohlendorfer et al. 2007[44]	*	*	-	*	*	*	*	-	6	fair
Klingberg et al. 2019[32]	*	*	-	*	**	*	*	-	7	good
Klopp et al. 2017[33]	*	*	-	*	**	-	*	*	7	good
Kull et al. 2002[45]	*	*	-	*	*	-	*	*	6	fair
Lee et al. 2017[34]	*	*	*	*	**	-	*	*	8	good
Leung et al. 2016[23]	*	*	-	*	**	*	*	*	8	good
Mandhane et al. 2007[59]	*	*	*	-	-	*	*	-	5	low
Mcconnochie et al. 1986[60]	-	*	*	*	-	-	-	*	4	low
Midodzi et al. 2010[24]	*	*	-	*	**	-	*	*	7	good
Midwinter et al. 1987[61]	-	*	-	*	-	-	*	*	4	low

Mihrshahi et al. 2007[46]	-	*	*	*	**	*	*	*	8	fair
Milner et al. 2004[62]	-	*	-	-	-	-	*	*	3	low
Miyake et al. 2008[47]	*	*	-	*	*	-	*	-	5	fair
Nwaru et al. 2013 (1)[25]	*	*	*	*	**	-	*	*	8	good
Nwaru et al. 2013 (2)[53]	-	*	-	*	**	-	*	-	5	low
Oddy et al. 2002[27]	*	*	-	*	**	-	*	*	7	good
Oddy et al. 2004[28]	*	*	-	*	**	-	*	*	7	good
Sbihi et al. 2016[54]	*	*	*	-	*	*	*	*	7	low
Silvers et al. 2009[29]	*	*	-	*	**	-	*	*	7	good
Silvers et al. 2012[26]	*	*	-	*	**	-	*	*	7	good
Standl et al. 2012[55]	*	*	*	*	-	-	*	-	5	low
Sunyer et al. 2006[48]	*	*	*	*	*	-	-	*	6	fair
Turner et al. 2008[49]	-	*	-	*	**	-	*	-	7	fair
van Meel et al. 2017[30]	*	*	-	*	**	-	*	*	7	good
Von Kobyletzki et al. 2012[50]	*	*	-	*	*	-	*	-	5	fair
Wickman et al. 2003[37]	*	*	-	*	*	-	*	*	6	fair
Wilson et al. 1998[38]	*	*	*	*	*	-	-	*	6	fair
Wright et al. 2000[39]	*	*	*	*	*	-	*	-	6	fair
Wright et al. 2001[56]	*	*	*	*	-	-	*	-	5	low
Yamakawa et al. 2015[40]	*	*	-	*	*	-	*	*	6	fair

*NOS Modifications

1. Selection:
    a. Demonstration that outcome of interest was not present at the start of the study - since this is essentially an assessment of temporality of the exposure but is not particularly applicable to the types of articles we are screening, we will change it to:
    b. Does the article assess for breastfeeding at an appropriate time to avoid recall bias (i.e. <2 years of age)
2. Comparability: Our 3 adjusted confounders will be: A study will receive 1 star for adjusting for all 3 and an additional 1 star for adjusting for other confounders
    a. Family history of asthma or atopy
    b. Gestational age
    c. Cigarette exposure pre or post-natal
3. Outcome: Follow up length
    a. Follow up length is not relevant for the detection of outcome we are looking for
    b. Instead we will look at the frequency of follow up as this is more sensitive for transient asthma diagnoses that may not be chronic
    c. This will be rater dependent; however, points that will be considered include the total number of follow-ups as well as the timing of the follow-ups(i.e. Asthma at 10 years, 4 well-spaced follow-ups vs 3 in the first year and 1 at 10 years)

**Newcastle-Ottawa Score conversion to AHRQ - low, fair and good quality scale:

- Low:
    - <4 NOS stars OR no adjustment for confounders (5) OR non-representative population (1) OR major flaw in methodology as determined by assessors

- Fair:
    - 4-6 NOS stars with adjustment of confounders (5) AND representative sample (1) AND an appropriate number of follow-ups conducted for detection of outcome (7)
- Good:
    - >6 NOS stars AND adjustment of confounders with the inclusion of key confounders (5) AND representative sample (1) AND an appropriate number of follow-ups conducted for detection of outcome (7) AND assessment of breastfeeding at a temporally appropriate time to reduce recall bias (4)

Data synthesis and statistical analysis

Data are grouped based on type of breastfeeding, duration of breastfeeding, and asthma outcome variables. The analysis was further stratified by different age groups (0-2, 3-6 and 7+ years), and study quality. The duration of breastfeeding was analysed as more versus less breastfeeding, ever versus never breastfeeding, breastfeeding for >3 months versus <3 months and >6 months versus <6 months. For studies that collected data at multiple ages in the same participants, only the oldest was used in the analysis. If a study had a group comparing the duration of feeding 4 months versus one month, it would be included in the >3 versus <3-month analysis. Studies that compared multiple different feeding durations to the same reference group could have multiple groups in the same analysis but no two included groups could have overlapping intervention groups. Studies could have groups included in multiple different analyses (i.e.. exclusive more versus less, ever vs never, age stratified analysis, etc.). Studies that did not have duration-specific comparisons but instead used per month of additional breastfeeding as outcomes could not be included within the meta-analyses.

Where available, adjusted hazard ratios, odds ratios or relative risks were preferentially extracted in the data extraction sheet. A very limited number of studies reported hazard ratios and relative risks; only studies that reported odds ratio were used to estimate pooled effect size during meta-analysis using a random-effects inverse variance method (16). We also assessed the publication bias using a funnel plot and Begg's test for small-study effect (17, 18). Heterogeneity was assessed by I^2 statistics and potential sources of heterogeneity for a number of variables (age, study design, country of study, birth cohort, and ethnicity) using meta-regression (19). The meta-analyses were conducted using Stata (version 16) software.

RESULTS

Search findings

The database search resulted in 3069 articles (Figure 1). Following initial title/abstract screening, 193 full-text articles were reviewed for eligibility based on the criteria described above. A total of 42 articles met the inclusion criteria, from which data were extracted; however, data from only 23 articles were suitable for meta-analysis. Thirty-seven articles analysed breastfeeding's impact on asthma development, and 5 analysed its impact on asthma severity (Figure 1). Of these 42 studies, 38 were prospective cohorts, and 4 were retrospective cohorts. No RCTs met inclusion criteria. Thirty-seven articles from western countries and 5 articles from eastern countries were identified; however, there was no representation of low income countries as defined by the World Bank (20). See Table E-3 for individual study information.

Study quality: Risk of bias assessment

Of the 42 articles, 14 (33%) were of good quality (21–34), 16 (38%) were of fair quality (35–50), and 12 (29%) were of low quality (51–62) based on our modified NOS scoring system (Table 1). Low-quality articles typically were single-centre studies, tertiary care settings, or populations selected for specific illnesses. Additionally, they may not have had an appropriate assessment of breastfeeding to minimise recall bias, lacked adjustments for major confounders and/or did not assess for asthma within optimal time frames. Of the 42 included articles, 32 (76%) adjusted for multiple confounders and 18 articles (43%) adjusted for three key confounders (gestational age, family history and smoking exposure) (31). Overall, a large majority of studies (71%) fell within fair and good quality for cohort studies.

Diagnosis of asthma

Children who had more exclusive breastfeeding compared to those with less exclusive breastfeeding had a 19% lower risk of asthma (OR=0.81; 95% CI: 0.72-0.91, I^2=44.0%) (Figure 2). Similarly, children with more breastfeeding compared to those with less breastfeeding had a 16% lower risk of asthma (OR= 0.84; 95% CI: 0.75-0.93 I^2= 62.4%). For children that were ever breastfed compared to never breastfed the lowered risk was not statistically significant (OR= 0.87; 95% CI: 0.72-1.04, I^2= 72.6%) (Figure 2).

For children with more exclusive breastfeeding versus less, when either low quality studies or both low and fair quality studies were excluded, the protective effect against asthma remained similar at 18% and 19% respectively (Figure 3). However, for the more versus less breastfeeding analysis, the 16% protective effect against asthma was greater when excluding low quality articles (19%) or both low and fair quality articles (18%). In the case of ever versus never breastfeeding, exclusion of low quality (OR = 0.77; 0.63, 0.95, I^2=44.8%) or low and fair quality studies (OR = 0.81; 0.66, 0.998, I^2=47.1%) demonstrated a greater magnitude and developed a statistically significant difference (Figure 3).

Duration of breastfeeding

Children with exclusive breastfeeding for >6 months compared to <6 months had a 30% lower risk of asthma (0.70; 0.53-0.92) (Figure 3); however, this data was pooled from only two articles (37, 49). The article published by Wickman and colleagues in 2003 assessed 4089 children for doctor-diagnosed asthma at two years of age. They found a statistically significant benefit with >6 months versus <3 months of exclusive breastfeeding (0.67; 0.5-0.91). The second study, published in 2008 by Turner and colleagues, included 154 infants recruited from a single antenatal clinic. They found no statistically significant benefit for doctor-diagnosed asthma diagnosis at 3, 6, and 11

years, although values trended toward a beneficial effect, particularly in the 3-year-old analysis (0.44; 0.19-1.00). Both studies were assessed as fair-quality. Exclusive breastfeeding for >3 months versus <3 months had 25% lower risk of asthma (0.75; 0.65-0.87).

Children with any type of breastfeeding for >6 months compared to <6 months had a 24% lower risk (0.76; 0.68-0.85). Any breastfeeding for >3 months versus <3 months had a 21% lower risk of asthma (0.79; 0.71-0.87).

Age of children

Breastfeeding in the age group 0-2 and 3-6 years old had 27% and 31% lower risk of asthma respectively, but no statistically significant effect in the 7+ age group (Figure 3). Articles in the meta-analyses for ages <7 were predominantly good/fair quality, while age 7+ articles were predominantly of low quality and mainly came from different age groups from a single study (59).

Asthma severity

Five articles assessed the duration of breastfeeding on the impact of asthma severity (23, 35, 40, 44, 57). There were no articles that quantified the number of exacerbations, medication use, frequency, or spirometry. The surrogate marker of severity commonly seen within these studies was hospitalisation due to asthma. There was little consistency in the potential trends/effects of breastfeeding. Two articles demonstrated trends towards protective odds ratios (40, 44), and two articles had trends towards harmful hazard ratios (23, 35) and the fifth contained only prevalence data (57). We did not perform a meta-analysis due to inconsistent outcome measures, few articles, and lower quality studies.

Publication bias and small study effects

Publication bias was assessed by graphical representation of funnel plots, and the Begg's test assessed small study effects. We found no publication bias and no small study effects for exclusive breastfeeding versus less exclusive breastfeeding, more breastfeeding versus less breastfeeding, and for ever breastfeeding versus never (Figure 4).

Heterogeneity

The heterogeneity was measured using the I^2 statistics. There was wide variation in heterogeneity ranging from 44% in the exclusive breastfeeding group to 62% in the more versus less breastfeeding group and the highest (73%) in the ever versus never breastfeeding group. We explored the potential sources of heterogeneity (study design, birth cohort, ethnicity, country, and age) in ever versus never breastfeeding using a

meta-regression command. Only the ethnicity ($p<0.03$) was found to contribute to heterogeneity significantly whereas, no statistically significant heterogeneity was contributed by study design ($p=0.729$), country of study ($p=0.680$), and age ($p=0.815$). Birth cohort was dropped from the model due to collinearity.

DISCUSSION

This systematic review and meta-analysis demonstrated that both longer duration of any breastfeeding and exclusive breastfeeding is associated with a decreased likelihood of developing asthma, particularly in children <7 years old. The results of longer duration of any breastfeeding demonstrated similar protective effects compared to prior reviews; however, this review is the first to clearly demonstrate a pooled protective effect of longer duration of exclusive breastfeeding.

Current WHO guidelines recommend exclusive breastfeeding for six months (63). Although the findings of our study support this recommendation, only two articles were included in the meta-analysis for exclusive breastfeeding >6 months versus <6 months (37, 49). This likely reflects the challenge that many parents experience with meeting this recommendation. In addition, national breastfeeding guidelines vary in their recommendations for timing of solid food introduction, with many citing 4 to 6 months (64). We found a reduced risk for asthma development in children with >3 months of exclusive breastfeeding when compared with those <3 months. Additionally, any breastfeeding for more than three months and six months showed a significant benefit for asthma prevention. Thus, babies who do not meet the six months of exclusive breastfeeding guidelines may still receive some protection against asthma development with partial or intermittent breastfeeding.

When stratifying by age, the benefit of breastfeeding was evident for ages 0-2 and 3-6, but no benefit was seen in those 7+ years of age. This lack of effect may be driven by a broad representation of low-quality articles within that analysis. It may also be that breastfeeding protects against earlier-onset asthma rather than late-onset asthma as has previously been suggested (8). This phenomenon was described in an article by Sbihi and colleagues (65), which examined a nationally representative Canadian birth cohort of 11,652 children. They identified three different childhood asthma trajectories: late-onset non-remitting, early-onset chronic, and transient asthma. A lack of breastfeeding only led to increased risk of transient and early onset of chronic asthma. There was no significant impact of breastfeeding in the late-onset cohort, suggesting that factors other than breastfeeding may be equally or more important to asthma development in older children.

Strengths and Limitations

With our updated search, 11 new cohort studies were identified since 2014 (21, 22, 26, 28–31, 35, 48–50), when the most recent systematic review search was conducted (8). Our search was broad and incorporated more databases than other recent systematic reviews (8–10). Of the recently completed systematic reviews, only Lodge and colleagues included any allied health databases. Inclusion/exclusion criteria were more stringent than previous studies, as we included only cohort studies. This improves the overall quality of the meta-analyses and mitigates recall bias. Similar breastfeeding cutoffs were used with prior systematic reviews with the addition of a more exclusive vs less exclusive comparison in our study.

Additionally, we selected studies with clear reporting of physician diagnosis of asthma or strict guideline-based diagnosis of asthma (8, 66). Prior systematic reviews included studies with wheeze as an outcome (8–10). This could have confounding effects as breastfeeding may also reduce viral-induced wheeze. Our approach does not completely reduce the potential for misdiagnosis of asthma as objective physiological evidence was not assessed in these studies. However, performing spirometry, bronchodilator reversibility, or bronchial provocation challenges is often not feasible in young children. On the flip side, by limiting the diagnosis of asthma, some of the nuances of a highly heterogeneous disease may be lost. As well, we were unable to stratify for current asthma and ever asthma which was done by Dogaru *et. al*.

To assess quality, we adapted the Newcastle Ottawa Scale (NOS) to place more weight on a study's ability to prevent recall bias, adjust for confounders and assess asthma within reasonable time frames. These are important factors that would not be directly accounted for in the standard NOS for cohort studies. Despite a strict scoring system, 37% of studies were considered fair, and 35% of studies were of good quality. It is difficult to directly compare the quality of analyses within our study to previous systematic reviews as each used different quality criteria; however, they all report the majority of studies being of low or very low quality within their analyses (see Table 1).

Heterogeneity in the data depended on the analysis, but the majority were within the moderate range (Figure 3). For major analyses, our heterogeneity was similar or lower compared to analyses in previous systematic reviews. This may be explained by our use of more stringent inclusion criteria, including limitation to cohort studies and physician/criterion diagnosed asthma, thus reducing methodological heterogeneity. Despite this, some analyses still showed considerable heterogeneity, with the country being the major contributor. This could be related to prognostic factors within different countries.

Although we aimed to improve the quality of our meta-analyses by restricting observational data to cohort studies, this limited the total number of studies available. For example, we did not identify any robust cohort studies assessing the relationship between asthma and breastfeeding in low-income countries, thus leading to less generalizability in those regions.

There was limited data addressing maternal atopy and its influence on breastfeeding effects. Similarly, we were unable to stratify by sex, which has been highlighted as a risk factor in recent literature with evidence that childhood asthma severity and frequency are differentially affected by the pubertal stage between males and females (67). It would be interesting to learn if breastfeeding similarly has differential benefits impacted by sex. The additional restriction of articles to the English language may have also introduced bias into our results, reducing the generalizability.

Conclusions

This review highlights that breastfeeding has an important role in reducing the risk of developing asthma in early childhood. Compared to previous systematic reviews, the relationship is better established due to the higher quality of articles used in the meta-analyses. This result, along with many other health benefits attributed to breastfeeding, reinforces breastfeeding recommendations by national and international bodies.

Future studies designed to explore the relationship between breastfeeding and asthma should utilise prospective cohort design to minimise recall bias in breastfeeding duration and regularly assess for the diagnosis and current symptoms of asthma. Stringent criteria for diagnosis should be used to minimise misdiagnosis of wheeze due to other causes. Studies need to ensure confounders are accounted for and aim to adjust for key confounders such as gestational age, exposure to cigarette smoking, and atopic history.

Contributors: MX and ED share joint first authorship. MX, ED and OK designed the review. Database search, article identification, data extraction and risk of bias assessment were conducted by MX and ED. MX and OK analysed the data. MX, ED and OK drafted the manuscript. OK provided advice at multiple different stages. All authors critically reviewed the manuscript and approved the final manuscript submission. The corresponding author attests that all listed authors meet authorship criteria and that no others have been omitted.

Funding: This study did not receive any specific funding.

Competing interests: All authors have completed the ICMJE uniform disclosure form and declare no conflict of interest related to this manuscript.

Ethical Approval: Not required

Data sharing: Full datasets can be obtained from the corresponding author at om.kurmi@coventry.ac.uk

Dissemination to patient/participant groups not applicable.

Provenance and peer review: Not commissioned; externally peer reviewed.

References

1. Global Asthma Report 2018. 2018;at <http://www.globalasthmareport.org/>.
2. Beasley R, Semprini A, Mitchell EA. Risk factors for asthma: is prevention possible? *Lancet* 2015;386 North:1075–1085.
3. WHO. Asthma. 2017;at <https://www.who.int/news-room/fact-sheets/detail/asthma>.
4. Castro-Rodríguez JA, Stern DA, Halonen M, Wright AL, Holberg CJ, Taussig LM, Martinez FD, J.A. C-R, D.A. S, M. H, A.L. W, C.J. H, L.M. T, F.D. M. Relation between infantile colic and asthma/atopy: A prospective study in an unselected population. *Pediatrics* 2001;108:878–882.
5. Gelfand EW. Pediatric asthma: A different disease. *Proc Am Thorac Soc* 2009;6:278–282.
6. L. D, Duijts L. Fetal and infant origins of asthma. *Eur J Epidemiol* 2012;27:1–10.
7. Kramer MS. Does breast feeding help protect against atopic disease? Biology, methodology, and a golden jubilee of controversy. *J Pediatr* 1988;112:181–190.
8. Dogaru CM, Nyffenegger D, Pescatore AM, Spycher BD, Kuehni CE. Breastfeeding and Childhood Asthma: Systematic Review and Meta-Analysis. *Am J Epidemiol* 2014;179:1153–1167.
9. Lodge CJ, Tan DJ, Lau MXZ, Dai X, Tham R, Lowe AJ, Bowatte G, Allen KJ, Dharmage SC. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. *Acta Paediatr (Oslo, Norw 1992)* 2015;104:38–53.
10. Brew BK, Allen CW, Toelle BG, Marks GB. Systematic review and meta-analysis investigating breast feeding and childhood wheezing illness. *Paediatr Perinat Epidemiol* 2011;25:507–518.
11. BTS/SIGN British Guideline on the Management of Asthma. BTS/SIGN British Guideline on the Management of Asthma. 2019;at <https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/>.
12. Global Strategy for Asthma Prevention. 2020 GINA Main Report. 2020;at <https://ginasthma.org/gina-reports/>.
13. Ducharme FM, Dell SD, Radhakrishnan D, Grad RM, Watson WTAT, Yang CL, Zelman M. Diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Paediatric Society position paper. *Paediatr Child Heal* 2015;20:.
14. Castro-Rodriguez JA, Forno E, Rodriguez-Martinez CE, Celedón JC. Risk and Protective Factors for Childhood Asthma: What Is the Evidence? *J Allergy Clin Immunol Pract* 2016;4:1111–1122.
15. John M. Eisenberg Center for Clinical Decisions and Communications Science. *Evaluation and Treatment of Cryptorchidism*. *Comp Eff Rev Summ Guid Clin* Agency for Healthcare Research and Quality (US); 2007. at <http://www.ncbi.nlm.nih.gov/pubmed/24156114>.
16. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:964–967.
17. Begg CB, Macaskill P, Irwig L, Walter SD. A comparison of methods to detect publication bias in meta-analysis (multiple letters). *Stat Med* 2002;
18. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J* 1997;315:629–634.

19. Thompson SG, Higgins JPT. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002;21:1559–1573.
20. Low income. *World Bank* 2021;at <https://data.worldbank.org/income-level/low-income>.
21. Bion V, Lockett GA, Soto-Ramírez N, Zhang H, Venter C, Karmaus W, Holloway JW, Arshad SH. Evaluating the efficacy of breastfeeding guidelines on long-term outcomes for allergic disease. *Allergy* 2016;71:661–670.
22. Chiu CY, Liao SL, Su KW, Tsai MH, Hua MC, Lai SH, Chen LC, Yao TC, Yeh KW, Huang JL. Exclusive or Partial Breastfeeding for 6 Months Is Associated With Reduced Milk Sensitization and Risk of Eczema in Early Childhood: The PATCH Birth Cohort Study. *Medicine (Baltimore)* 2016;95:e3391–e3391.
23. Leung JYYY, Kwok MK, Leung GM, Schooling CM. Breastfeeding and childhood hospitalizations for asthma and other wheezing disorders. *Ann Epidemiol* 2016;26:21–27.e3.
24. Midodzi WK, Rowe BH, Majaesic CM, Saunders LD, Senthilselvan A. Early life factors associated with incidence of physician-diagnosed asthma in preschool children: results from the Canadian Early Childhood Development cohort study. *J Asthma Off J Assoc Care Asthma* 2010;47:7–13.
25. Nwaru BI, Craig LCA, Allan K, Prabhu N, Turner SW, McNeill G, Erkkola M, Seaton A, Devereux G. Breastfeeding and introduction of complementary foods during infancy in relation to the risk of asthma and atopic diseases up to 10 years. *Clin Exp Allergy J Br Soc Allergy Clin Immunol* 2013;43:1263–1273.
26. Silvers KM, Frampton CM, Wickens K, Pattemore PK, Ingham T, Fishwick D, Crane J, Town GI, Epton MJ, Group NZA and ACS. Breastfeeding protects against current asthma up to 6 years of age. *J Pediatr* 2012;160:991–996.e1.
27. Oddy WH, Peat JK, de Klerk NH. Maternal asthma, infant feeding, and the risk of asthma in childhood. *J Allergy Clin Immunol* 2002;110:65–67.
28. Oddy WH, Sherriff JL, de Klerk NH, Kendall GE, W.H. O, J.L. S, N.H. DK, G.E. K. Breastfeeding, body mass index, and asthma and atopy in children. *Adv Exp Med Biol* 2004;554:387–390.
29. Silvers KM, Frampton CM, Wickens K, Epton MJ, Pattemore PK, Ingham T, Fishwick D, Crane J, Town GI, Crane J, Duignan M, Epton MJ, Fishwick D, Fitzharris P, Ingham T, Irvine V, Kelly R, Lampshire P, Lane J, Leadbitter P, McCartin F, MacDonald C, McLeod S, Nicholson A, Pattermore P, Roff K, Sawyer G, Siebers R, Town GI, *et al.* Breastfeeding protects against adverse respiratory outcomes at 15 months of age. *Matern Child Nutr* 2009;5:243–250.
30. van Meel ER, de Jong M, Elbert NJ, den Dekker HT, Reiss IK, de Jongste JC, Jaddoe VWV V, Duijts L. Duration and exclusiveness of breastfeeding and school-age lung function and asthma. *Ann Allergy, Asthma Immunol Off Publ Am Coll Allergy, Asthma, Immunol* 2017;119:21–26.e2.
31. Karmaus W, Dobai AL, Ogbuanu I, Arshard SH, Matthews S, Ewart S. Long-term effects of breastfeeding, maternal smoking during pregnancy, and recurrent lower respiratory tract infections on asthma in children. *J Asthma Off J Assoc Care Asthma* 2008;45:688–695.

32. Klingberg S, Brekke HK, Ludvigsson J. Introduction of fish and other foods during infancy and risk of asthma in the All Babies In Southeast Sweden cohort study. *Eur J Pediatr* 2019;178:395–402.
33. Klopp A, Vehling L, Becker A, Subbarao P, Mandhane P, Turvey S, Sears M, Azad M. Do infants fed expressed breast milk have an increased risk of developing childhood asthma compared to directly breastfed infants? *Allergy, Asthma Clin Immunol* 2017;13:.
34. Lee M-T, Wu C-C, Ou C-Y, Chang J-C, Liu C-A, Wang C-L, Chuang H, Kuo H-C, Hsu T-Y, Chen C-P, Yang KD. A prospective birth cohort study of different risk factors for development of allergic diseases in offspring of non-atopic parents. *Oncotarget* 2017;8:10858–10870.
35. Ajetunmobi OM, Whyte B, Chalmers J, Tappin DM, Wolfson L, Fleming M, MacDonald A, Wood R, Stockton DL, Group GC for PHBPS. Breastfeeding is associated with reduced childhood hospitalization: evidence from a Scottish Birth Cohort (1997-2009). *J Pediatr* 2015;166:620–625.e4.
36. Alm B, Erdes L, Möllborg P, Pettersson R, Norvenius SG, Aberg N, Wennergren G, SG N, Aberg N, Wennergren G, Åberg N, Wennergren G. Neonatal antibiotic treatment is a risk factor for early wheezing. *Pediatrics* 2008;121:697–702.
37. Wickman M, Melén E, Berglind N, Lennart Nordvall S, Almqvist C, Kull I, Svartengren M, Pershagen G. Strategies for preventing wheezing and asthma in small children. *Allergy Eur J Allergy Clin Immunol* 2003;58:742–747.
38. Wilson AC, Forsyth JS, Greene SA, Irvine L, Hau C, Howie PW. Relation of infant diet to childhood health: seven year follow up of cohort of children in Dundee infant feeding study. *Br Med J* 1998;316:21–25.
39. Wright AL, Holberg CJ, Taussig LM, Martinez F. Maternal asthma status alters relation of infant feeding to asthma in childhood. *Adv Exp Med Biol* 2000;478:131–137.
40. Yamakawa M, Yorifuji T, Kato T, Yamauchi Y, Doi H. Breast-feeding and hospitalization for asthma in early childhood: A nationwide longitudinal survey in Japan. *Public Health Nutr* 2015;18:1756–1761.
41. Strömberg Celind F, Wennergren G, Vasileiadou S, Alm B, Goksör E. Antibiotics in the first week of life were associated with atopic asthma at 12 years of age. *Acta Paediatr Int J Paediatr* 2018;107:1798–1804.
42. den Dekker HT, Sonnenschein-van der Voort AMM, de Jongste JC, Anessi-Maesano I, Arshad SH, Barros H, Beardsmore CS, Bisgaard H, Phar SC, Craig L, Devereux G, van der Ent CK, Esplugues A, Fantini MP, Flexeder C, Frey U, Forastiere F, Gehring U, Gori D, van der Gugten AC, Henderson AJ, Heude B, Ibarluzea J, Inskip HM, Keil T, Kogevinas M, Kreiner-Møller E, Kuehni CE, Lau S, *et al.* Early growth characteristics and the risk of reduced lung function and asthma: A meta-analysis of 25,000 children. *J Allergy Clin Immunol* 2016;137:1026–1035.
43. Fredriksson P, Jaakkola N, Jaakkola JJ. Breastfeeding and childhood asthma: a six-year population-based cohort study. *BMC Pediatr* 2007;7:39.

44. Kiechl-Kohlendorfer U, Horak E, Mueller W, Strobl R, Haberland C, Fink F-MM, Schwaiger M, Gutenberger K-HH, Reich H, Meraner D, Kiechl S. Neonatal characteristics and risk of atopic asthma in schoolchildren: results from a large prospective birth-cohort study. *Acta Paediatr (Oslo, Norw 1992)* 2007;96:1606–1610.
45. Kull I, Wickman M, Lilja G, Nordvall SL, Pershagen G. Breast feeding and allergic diseases in infants - A prospective birth cohort study. *Arch Dis Child* 2002;87:478–481.
46. Mihrshahi S, Ampon R, Webb K, Almqvist C, Kemp AS, Hector D, Marks GB, Team C. The association between infant feeding practices and subsequent atopy among children with a family history of asthma. *Clin Exp Allergy J Br Soc Allergy Clin Immunol* 2007;37:671–679.
47. Miyake Y, Tanaka K, Sasaki S, Kiyohara C, Ohya Y, Fukushima W, Yokoyama T, Hirota Y, Group OM and CHS. Breastfeeding and the risk of wheeze and asthma in Japanese infants: the Osaka Maternal and Child Health Study. *Pediatr Allergy Immunol Off Publ Eur Soc Pediatr Allergy Immunol* 2008;19:490–496.
48. Sunyer J, Torrent M, Garcia-Esteban R, Ribas-Fitó N, Carrizo D, Romieu I, Antó JM, Grimalt JO. Early exposure to dichlorodiphenyldichloroethylene, breastfeeding and asthma at age six. *Clin Exp Allergy J Br Soc Allergy Clin Immunol* 2006;36:1236–1241.
49. Turner S, Zhang G, Young S, Cox M, Goldblatt J, Landau L, Le Souëf P. Associations between postnatal weight gain, change in postnatal pulmonary function, formula feeding and early asthma. *Thorax* 2008;63:234–239.
50. von Kobyletzki LB, Bornehag C-GG, Hasselgren M, Larsson M, Lindström CB, Svensson Å. Eczema in early childhood is strongly associated with the development of asthma and rhinitis in a prospective cohort. *BMC Dermatol* 2012;12:11.
51. Bacopoulou F, Veltsistan we be optimistic about asthma in childhood? A Greek cohort studya A, Vassi I, Gika A, Lekea V, Priftis K, Bakoula C, Veltsista A, Vassi I, Gika A, Lekea V, Priftis K, Bakoula C. Can we be optimistic about asthma in childhood? A Greek cohort study. *J Asthma Off J Assoc Care Asthma* 2009;46:171–174.
52. Burr ML, Limb ES, Maguire MJ, Amarah L, Eldridge BA, Layzell JC, Merrett TG. Infant feeding, wheezing, and allergy: a prospective study. *Arch Dis Child* 1993;68:724–728.
53. Nwaru BI, Takkinen H-M, Niemelä O, Kaila M, Erkkola M, Ahonen S, Haapala A-M, Kenward MG, Pekkanen J, Lahesmaa R, Kere J, Simell O, Veijola R, Ilonen J, Hyöty H, Knip M, Virtanen SM. Timing of infant feeding in relation to childhood asthma and allergic diseases. *J Allergy Clin Immunol* 2013;131:78–86.
54. Sbihi H, Tamburic L, Koehoorn M, Brauer M. Perinatal air pollution exposure and development of asthma from birth to age 10 years. *Eur Respir J* 2016;47:1062–1071.

55. Standl M, Sausenthaler S, Lattka E, Koletzko S, Bauer C-P, Wichmann H-E, von Berg A, Berdel D, Krämer U, Schaaf B, Lehmann I, Herbarth O, Klopp N, Koletzko B, Heinrich J, Group Gini and LisaS. FADS gene cluster modulates the effect of breastfeeding on asthma. Results from the GINIplus and LISAplus studies. *Allergy* 2012;67:83–90.
56. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax* 2001;56:192–197.
57. Davidson R, Roberts SE, Wotton CJ, Goldacre MJ. Influence of maternal and perinatal factors on subsequent hospitalisation for asthma in children: evidence from the Oxford record linkage study. *BMC Pulm Med* 2010;10:14.
58. Elliott L, Henderson J, Northstone K, Chiu GY, Dunson D, London SJ. Prospective study of breast-feeding in relation to wheeze, atopy, and bronchial hyperresponsiveness in the Avon Longitudinal Study of Parents and Children (ALSPAC). *J Allergy Clin Immunol* 2008;122:49–54, 54.e1–3.
59. Mandhane PJ, Greene JM, Sears MR. Interactions between breast-feeding, specific parental atopy, and sex on development of asthma and atopy. *J Allergy Clin Immunol* 2007;119:1359–1366.
60. McConnochie KM, Roghmann KJ. Parental smoking, presence of older siblings, and family history of asthma increase risk of bronchiolitis. *Am J Dis Child* 1986;140:806–812.
61. Midwinter RE, Morris AF, Colley JRT. Infant feeding and atopy. *Arch Dis Child* 1987;62:965–967.
62. Milner JD, Stein DM, McCarter R, Moon RY, JD M, DM S, McCarter R, RY M. Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma. *Pediatrics* 2004;114:27–32.
63. Kramer MS, Kakuma R, MS K, Kakuma R. Optimal duration of exclusive breastfeeding. *Cochrane Database Syst Rev* 2012;CD003517-CD003517.doi:10.1002/14651858.CD003517.pub2.
64. Koletzko B, Hirsch NL, Jewell JM, Dos Santos Q, Breda J, Fewtrell M, Weber MW. National Recommendations for Infant and Young Child Feeding in the World Health Organization European Region. *J Pediatr Gastroenterol Nutr* 2020;71:672–678.
65. Sbihi H, Koehoorn M, Tamburic L, Brauer M. Asthma trajectories in a population-based birth cohort impacts of air pollution and greenness. *Am J Respir Crit Care Med* 2017;195:607–613.
66. Michel G, Silverman M, Strippoli MPF, Zwahlen M, Brooke AM, Grigg J, Kuehni CE. Parental understanding of wheeze and its impact on asthma prevalence estimates. *Eur Respir J* 2006;28:1124–1130.
67. Zein JG, Erzurum SC. Asthma is Different in Women. *Curr Allergy Asthma Rep* 2015;15:28.

Figure 1. PRISMA Flow Chart highlighting article identification process

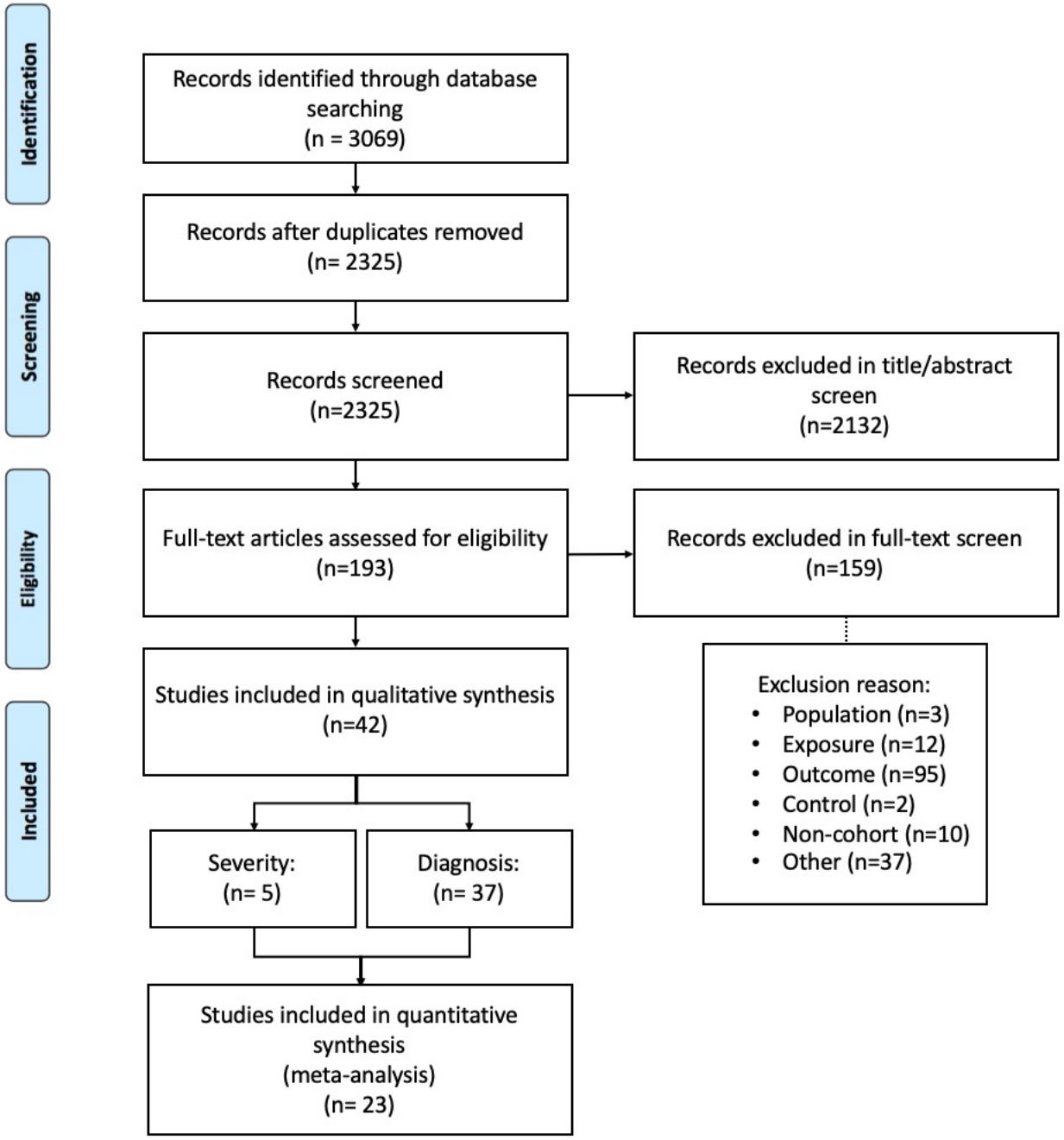
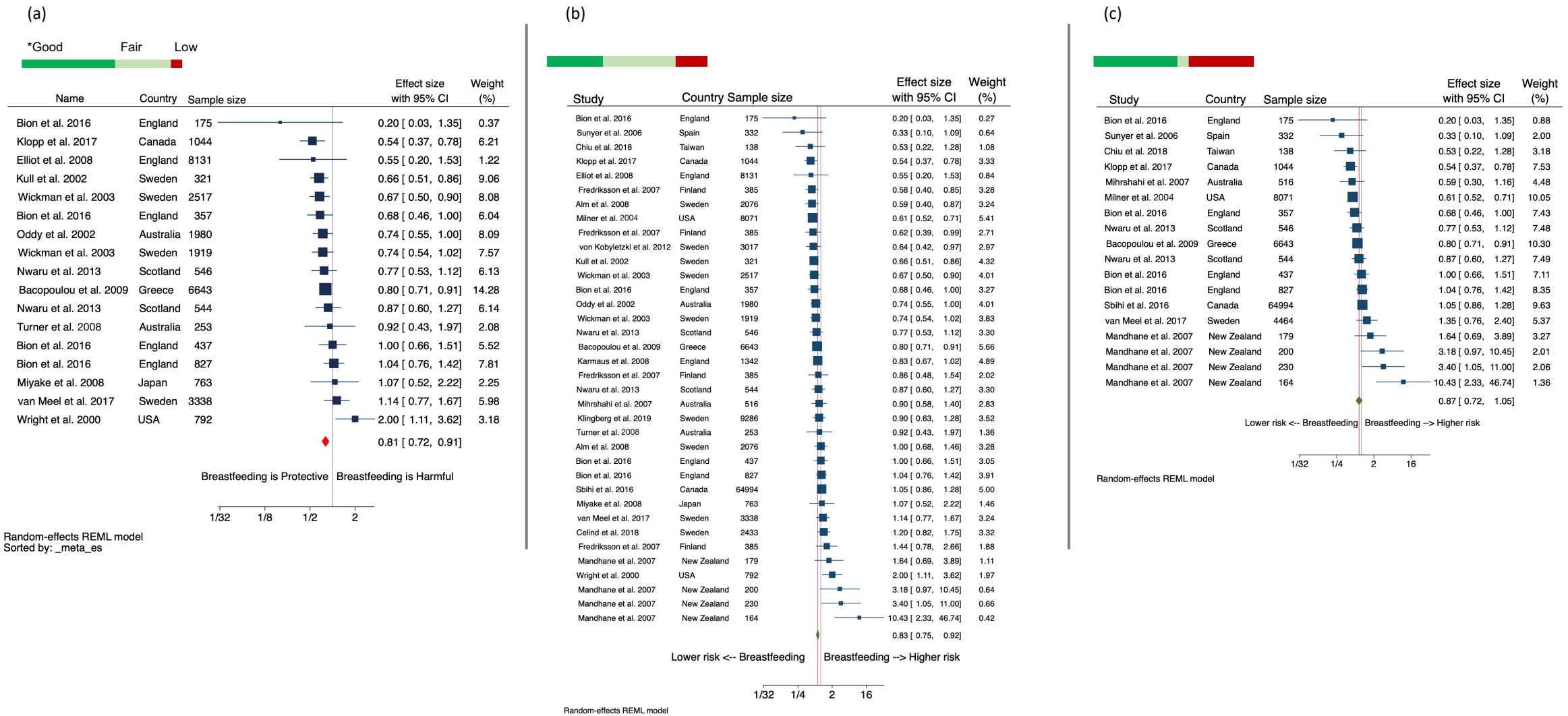


Figure 2. Pooled effect sizes and quality* of main analyses (a) more exclusive** breastfeeding vs less exclusive breastfeeding, (b) more breastfeeding vs less breastfeeding, and (c) ever versus never breastfed



*colored bar representing proportion of groups of good/fair/poor quality

** 'more' implying longer duration and 'exclusive' indicating breast milk only with no other solids/liquids

Figure 3. Pooled effect sizes of all meta-analyses including breastfeeding type, duration, age, and study quality

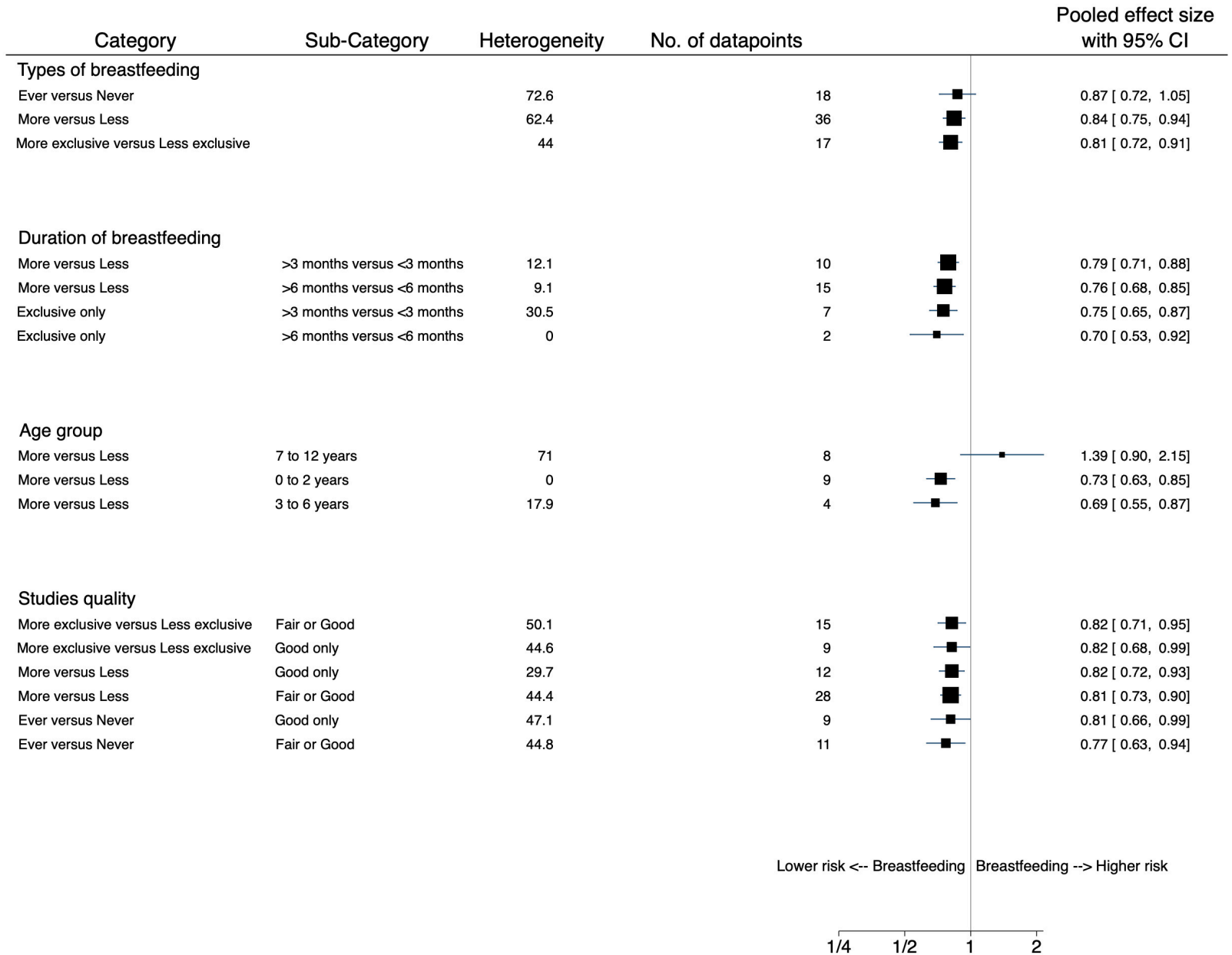
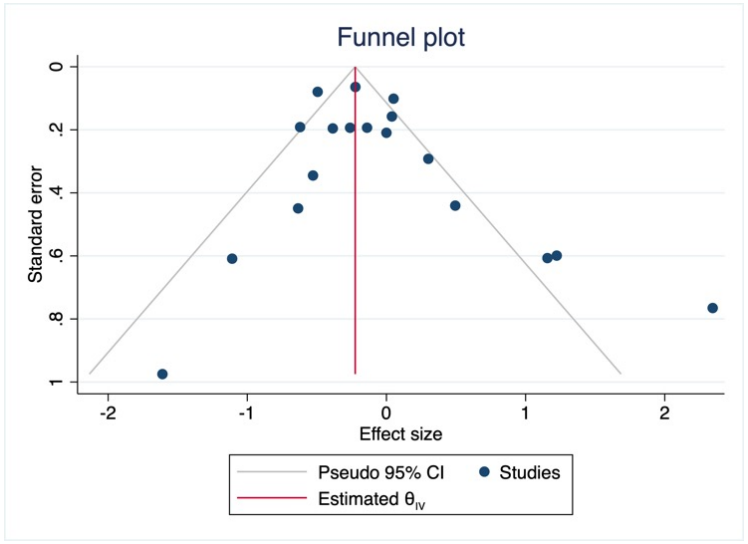
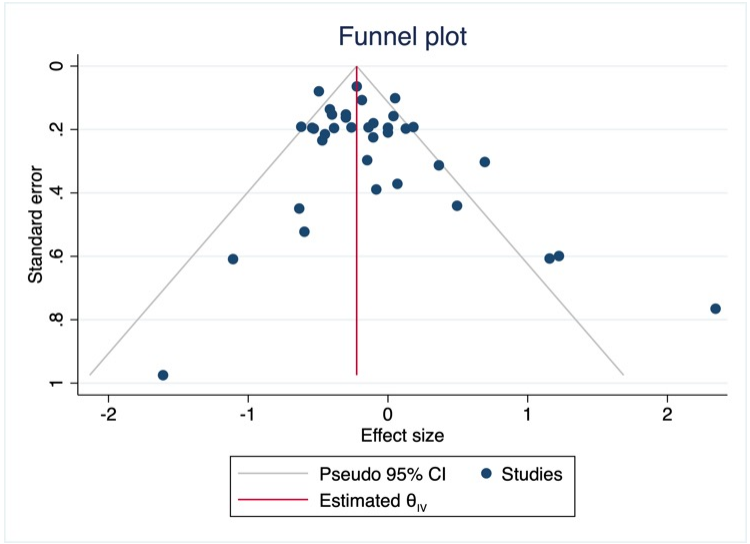


Figure 4. Funnel plots evaluating for publication bias in the main analyses (a) More exclusive* breastfeeding versus less exclusive breastfeeding, (b) more breastfeeding versus less breastfeeding, and (c) ever breastfed versus never breastfed

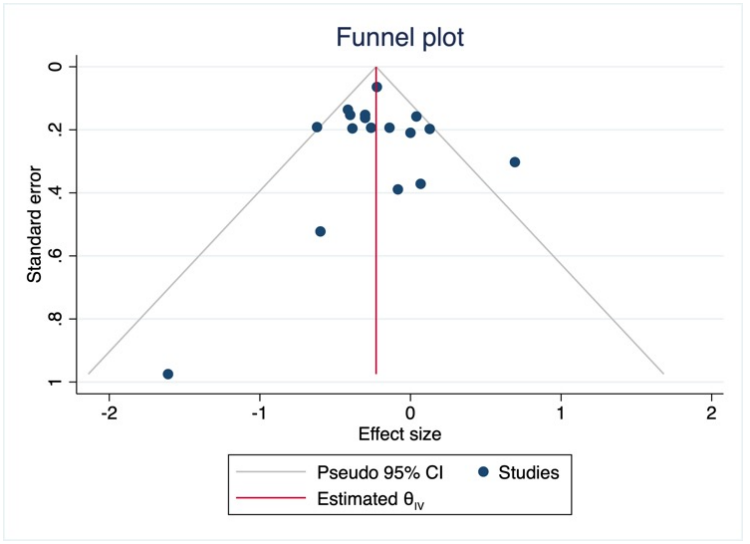
(a)



(b)



(c)



* 'more' implying longer duration and 'exclusive' indicating breast milk only with no other solids/liquids

SUPPLEMENTARY DOCUMENT

Table E-1. Summary of recent systematic reviews and meta-analyses

Article	Databases	Date of search	Inclusion Criteria	Major Outcomes Analysed	Number of Studies	Major Results (Odds [CI95%, Heterogeneity])*	Subgroups Analyzed	Study Quality
Lodge 2015, Acta Paediatrica	PubMed, CINAHL and EMBASE	July 2015	Observational (cohort and non-cohort) and experimental studies published in full length in English with wheeze at any age and/or asthma >= 5 years of age. Excluded studies on premature births. Included outcomes were spirometric or physician diagnosed asthma including parental report or from database and reported asthma or wheeze.	Asthma or wheeze	29	Ever vs. Never 0.88 (0.82, 0.95) I^2 = 44% Exclusive >3-4 vs. <3-4 months 0.89 (0.71, 1.11) I^2 = 72% More vs. Less 0.90 (0.84, 0.97) I^2 = 63%	age (5-10, >10), study size, year at birth, study design, length of breastfeeding, control for confounding, country affluence	NOS/Grade Score very low to low
Dogaru 2014, American Journal of Epidemiology	PubMed and EMBASE	December 2013	Fully reported original observational studies (cohort and non-cohort) published in English, excluding studies in special populations (e.g. atopic history) and those exploring only asthma severity. Included outcomes are physician-diagnosed asthma including parental report, treatment for asthma/wheezing, and parental reports of wheezing in the last 12mo.	Asthma ever, current asthma	113	More vs. Less (ever diagnosed with asthma) 0.79 (0.74, 0.84) I^2 = 71.4% More vs. Less (asthma symptoms within 12mo) 0.76 (0.67, 0.86) I^2 = 91.6%	Age (0-2, 3-6, >=7), design, country affluence, study quality, study year	Kramer Criteria low: 56%, medium: 35%, high: 14%
Brew 2011, Paediatric and Perinatal Epidemiology	MEDLINE and EMBASE	August 2011	Observational (birth cohort and non-cohort) of children 5-18 years age at follow-up with breastfeeding data of 'any', 'none', or exclusive for at least 3-4 months. Included outcomes were current wheezing illness (within the last 12mo).	Current wheezing illness	31	Ever vs. Never 0.97 (0.90, 1.04) I^2 = 63% Exclusive >3-4 vs. <3-4 months 0.96 (0.86, 1.06) I^2 = 54%	Age (5-8, 8-18), Study type, adjustment for confounding, feeding recall, retention rate, country affluence, definition of wheezing illness	Study-specific criteria Ever vs. Never - very low or low: 61% Exclusive - very low or low: 54%

*Definitions of Ever vs. Never and More vs. Less breastfeeding were equivalent between studies and consistent with definitions used in the current review

Table E-2. Search terms and results of database searches

	PubMed	CINAHL	EMBASE	ProQuest Nursing/Allied Health	Summary
Search Details	Search terms: (breastfe* OR breast fe* OR "infant nutrition" OR "breast milk" OR "human milk" OR wean* OR bottle fe*) AND (asthma OR wheez* OR bronchospasm OR "bronchial hyperreactivity" OR "bronchus hyperreactivity" OR "bronchial hypersensitivity") filters: human children 0-18 english result: 985 articles	Search terms: (breastfe* OR breast fe* OR "infant nutrition" OR "breast milk" OR "human milk" OR wean* OR bottle fe*) AND (asthma OR wheez* OR bronchospasm OR "bronchial hyperreactivity" OR "bronchus hyperreactivity" OR "bronchial hypersensitivity") filters: english result: 333	Search terms: (breastfe* OR breast fe* OR "infant nutrition" OR "breast milk" OR "human milk" OR wean* OR bottle fe*) AND (asthma OR wheez* OR bronchospasm OR "bronchial hyperreactivity" OR "bronchus hyperreactivity" OR "bronchial hypersensitivity") filters: human English Child of unspecified age result: 973	Search terms: (breastfe* OR breast fe* OR "infant nutrition" OR "breast milk" OR "human milk" OR wean* OR bottle fe*) AND (asthma OR wheez* OR bronchospasm OR "bronchial hyperreactivity" OR "bronchus hyperreactivity" OR "bronchial hypersensitivity") filters: Adolescent (13-18 years), Child (6-12 years), Infant (1-23 months), Newborn (birth to 1 month), Preschool child (2-5 years) English result: 305	Search Results June 2018: Total: 2596 (from 4 databases) After removal of Duplicates: 2096 Renewal Search (June 2018-Jan 2020) Pubmed, CINAHL, EMBASE and ProQuest Nursing/Allied Health were re-searched for the above timeframe a total of 473 articles (50, 24 and 169 + 230) – 429 after duplicate removal

Table E-3. Summary of study characteristics

Article	Cohort	Design	Country	Study Period	Cohort Size	Age (years)	Breastfeeding Type (cut off)+	Groups included in analyses (months)	Effect Size Measure*	Outcome**	Quality
Ajetunmobi et al. 2015[35]	National Health Service, National Services Scotland	Retrospective	Scotland	1997-2009	502948	0-15	exclusive (1-2 months)	None	HR	Hospitalization discharge diagnosis	Fair
Alm et al. 2008[36]	Infants of Western Sweden	Prospective	Sweden	2003-2004	4921	1	partial (9 months)	>9 vs 5-8 >9 vs 0-4	OR	Criteria: wheezing disorder and inhaled corticosteroids (ICS) use	Fair
Bacopoulou et al. 2009[51]	Greek National Perinatal Survey	Prospective	Greece	1983-2001	6643	0-7	exclusive (3 months)	>3 vs 0	OR	Physician diagnosis and treatment	Low
Bion et al. 2016[21]	Isle of Wight Cohort The Food Allergy and Intolerance Research Cohort	Prospective	England	1989-2008 2001-2011	1087 460	10, 18 10	exclusive, partial (4,6 months)	>6 vs 0 <6 vs 0 4 vs 0 <4 vs 0	RR	Physician diagnosis and wheeze or treatment in past 12 months	Good
Burr et al. 1993[52]	*No name*	Prospective	Wales	1982-1989	452	0-7	ever	None	Pr	Study pediatrician diagnosis	Low
Celind et al. 2018[41]	*No name*	Prospective	Sweden	2003-2015	2433	12	partial (4 months)	>4 vs <4	OR	Physician diagnosis and wheeze or treatment in past 12 months	Fair
Chiu et al. 2016[22]	Prediction of Allergies in Taiwanese Children	Prospective	Taiwan	2007-2010	138	2, 3 , 4	partial (6 months)	>6 vs <6	OR	GINA guideline and either recurrent wheeze or current treatment with confirmation by study pediatric pulmonologist	Good
Davidson et al. 2010[57]	Oxford Record Linkage Study	Retrospective	England	1970-1989	4017	2-11+	ever	None	Pr	Hospitalization with ICD codes	Low
den Dekker et al. 2016[42]	Generation R Study	Prospective	Netherlands	2002-ongoing	4093	0-6	exclusive, partial (4,6 months), ever, per month	None	OR	Physician diagnosis and wheeze in past 12 months	Fair
Elliot et al. 2008[58]	Avon Longitudinal Study of Parents and Children	Prospective	England	1991-ongoing	8131	7.5	exclusive (4 months)	>4 vs <4	OR	Physician diagnosis and either wheeze or treatment in past 12 months	Low
Fredriksson et al. 2007[43]	*No name*	Prospective	Finland	1984-1997	385	7-14	partial (multiple 3-12 months)	4-6 vs 0-3 7-9 vs 4-6 10-12 vs 4-6 >12 vs 4-6	OR, Pr	Physician diagnosis	Fair
Karmaus et al. 2008[31]	Isle of Wight Cohort	Prospective	England	1989-2008	1342	1-10	partial (3 months)	>3 vs <3	RR	Physician diagnosis and wheeze in past 12 months	Good

Kiechl-Kohlendorfer et al. 2007[44]	Survey of Tyrol, Austria	Prospective	Austria	1994-2005	33808	5-11	exclusive, partial (1-2 months)	None	OR, Pr	Hospitalization with ICD codes and 2 study pediatric pulmonologist confirmation	Fair
Klingberg et al. 2019[32]	All Babies In Southeast Sweden Cohort	Prospective	Sweden	1997-2014	9286	0-17	partial (9-10 months)	>9.75 vs <7.5	OR	ICD codes for atopic/non-atopic asthma	Good
Klopp et al. 2017[33]	Canadian Healthy Infant Longitudinal Development Study	Prospective	Canada	2009-2015	2534	3	exclusive (3 months), ever	>3 vs 0	OR, Pr	Possible/probably asthma diagnosis by medical professional	Good
Kull et al. 2002[45]	Children, Allergy, Milieu, Stockholm Epidemiological Cohort	Prospective	Sweden	1994-1996	321	0-2	exclusive (4 months), partial (6 months)	>6 vs <6 >4 vs <4	OR, Pr	Criteria: either 3 wheeze episodes and ICS, or hyperreactivity without signs of respiratory infection	Fair
Lee et al. 2017[34]	*No name*	Prospective	Taiwan	1998-2009	737	3-6	partial (1 month)	>1 vs <1	OR	Physician diagnosis with exercise induced cough and/or night cough >2 weeks in past 6 months	Good
Leung et al. 2016[23]	Children of 1997, Hong Kong Chinese Birth Cohort	Prospective	Hong Kong	1997-2012	8301	0.25-12	exclusive, partial (3 months)	None	HR	Hospitalization based on ICD codes	Good
Mandhane et al. 2007[59]	Dunedin multidisciplinary health and development research study	Prospective	New Zealand	1972-1998	418	9	partial (1 month), ever	>1 vs 0	OR, Pr	Current wheeze and methacholine challenge	Low
Mcconnochie et al. 1986[60]	*No name*	Retrospective	USA	1971-1981	224	0-10	ever	>0 vs <0	RR, Pr	Physician diagnosis and treatment	Low
Midodzi et al. 2010[24]	Canadian Early Childhood Development cohort	Prospective	Canada	1996-2003	8499	2-5	partial (3 months)	>3 vs 0 <3 vs 0	HR, Pr	Physician diagnosis	Good
Midwinter et al. 1987[61]	*No name*	Prospective	England	1979-1984	367	0-5	exclusive (1 month), Ever	None	Pr	Physician diagnosis	Low
Mihrshahi et al. 2007[46]	*No name*	Prospective	Australia	1997-1999	516	5	partial (3,6 months), ever	>6 vs <6 >3 vs <3 >0 vs <0	OR, Pr	Wheeze in past 12 months with previous diagnosis, hospitalization or positive bronchodilator test	Fair
Milner et al. 2004[62]	National Maternal and Infant Health Survey	Retrospective	USA	1988-1991	8071	0-3	ever	>0 vs <0	OR, Pr	Diagnosis by medical professional	Low
Miyake et al. 2008[47]	Osaka Maternal and Child Health Study	Prospective	Japan	2001-2005	763	0-2	Exclusive (4 months) Partial (6 months)	>4 vs <4 >6 vs <6	OR, Pr	Physician diagnosis	Fair
Nwaru et al. 2013 (1)[25]	Study of Eczema and Asthma to Observe the influence of Nutrition	Prospective	Scotland	1997-2008	879	0-10	exclusive, partial (2-3, 3-4 months), ever	>3.75 vs 0 <3.75 vs 0	OR	Physician diagnosis	Good

Nwaru et al. 2013 (2)[53]	Finnish Type 1 Diabetes Prediction and Prevention	Prospective	Finland	1994-1999	2617	5	partial (9-10 months)	9.5 vs <5 9.5 vs 5.0-9.5	HR	Physician diagnosis and either wheeze or asthma treatment in past 12 months	Low
Oddy et al. 2002[27]	Western Australian Pregnancy Cohort	Prospective	Australia	1989-1996	1980	6	exclusive (4 months)	>4 vs <4	OR, Pr	Physician diagnosis and wheeze in past 12 months	Good
Oddy et al. 2004[28]	Western Australian Pregnancy Cohort	Prospective	Australia	1989-1996	1485	6	per month	None	OR	Physician diagnosis and wheeze in past 12 months	Good
Sbihi et al. 2016[54]	The Border Air Quality Study	Retrospective	Canada	1999-2009	65448	0-10	ever	>0 vs 0	OR	Physician billing/discharge ICD codes	Low
Silvers et al. 2009[29]	New Zealand Asthma and Allergy Cohort Study	Prospective	New Zealand	1997-2002	1011	0-1.25	per month	None	OR	Physician diagnosis and wheeze in past 12 months and inhaler	Good
Silvers et al. 2012[26]	New Zealand Asthma and Allergy Cohort Study	Prospective	New Zealand	1997-2007	999	2	per month	None	OR	Physician diagnosis and wheeze in 12 months and inhaler	Good
Standl et al. 2012[55]	GINIplus & LISAplus	Prospective	Germany	1995-2008 1997-2009	1691	0.5-10	exclusive (multiple 1-6 months)	None	Pr	Physician diagnosis with IgE for atopic asthma	Low
Sunyer et al. 2006[48]	Menorca, Spain Cohort Study	Prospective	Spain	1997-2004	332	0-6.5	ever	>0 vs 0	OR	Physician diagnosis	Fair
Turner et al. 2008[49]	*No name*	Prospective	Australia	N/A	253	2-11	exclusive (6 months)	>6 vs <6	OR	Physician diagnosis	Fair
van Meel et al. 2017[30]	Generation R Study	Prospective	Sweden	2002-2016	4464	10	exclusive, partial (6 months), ever, per month	>6 vs 0 >6 vs <2-4 >6 vs 4-6	OR	Physician diagnosis and either wheeze or treatment in past 12 months	Good
Von Kobyletzki et al. 2012[50]	Dampness in Building and Health (DBH)	Prospective	Sweden	2000-2005	3017	1-5	partial	>6 vs <6	Pr	Physician diagnosis	Fair
Wickman et al. 2003[37]	Children, Allergy, Milieu, Stockholm Epidemiological Cohort	Prospective	Sweden	1994-1998	3692	0.25-2	exclusive	>6 vs <3 4-5 vs <3	OR, Pr	Criteria: 3 wheeze episodes and either ICS or hyperreactivity without signs of respiratory infection	Fair
Wilson et al. 1998[38]	Dundee Infant Feeding Study	Prospective	Scotland	1983-1993	545	0-10	exclusive, partial (3-4 months), ever	None	Pr	Physician diagnosis or current asthma treatment	Fair
Wright et al. 2000[39]	Tucson Children's Respiratory Study	Prospective	USA	1980-1995	792	0-11	exclusive (4 months)	>4 vs <4	OR	Physician diagnosis and wheeze in the past 12 months	Fair
Wright et al. 2001[56]	Tucson Children's Respiratory Study	Prospective	USA	1980-ongoing	926	6-13	exclusive (4 months), ever	None	Pr	Physician dx + either wheeze or asthma symptoms	Low

										reported on 2+ questionnaires	
Yamakawa et al. 2015[40]	Longitudinal Survey of Babies in the 21st Century	Prospective	Japan	2001-2008	13853	0.5-3.5	exclusive, partial (multiple 1-7 months), ever, per month	None	OR	Hospitalization in past 12 months for asthma	Fair

*HR = hazard ratio, OR = odds ratio, Pr = Prevalence

** Outcome definitions have been paraphrased for simplicity