Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies

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Summary

Background Breastfeeding is undisputedly preferable to formula feeding for infant nutrition because of its nutritional, immunological and psychological benefits. However, studies on the association between breastfeeding and development of atopic dermatitis (AD) have shown inconsistent results.

Objectives To examine the association between exclusive breastfeeding for at least 3 months after birth and the development of AD in childhood.

Methods An electronic literature search of MEDLINE (January 1966–May 2008) and EMBASE (1980–May 2008) was conducted. Prospective cohort studies that met the predetermined criteria were independently assessed by three reviewers. The pooled effect estimate was calculated by random effects model. Heterogeneity across the studies was investigated by meta-regression analysis.

Results Twenty-one studies with 27 study populations were included for meta-analysis. The summary odds ratio (OR) for the effect of exclusive breastfeeding on the risk of AD was 0·89 (95% confidence interval, CI 0·76–1·04). Heterogeneity was found across the studies (χ^2 = 83·6, d.f. = 26; P < 0·001). Breastfeeding was associated with a decreased risk of AD (OR 0·70; 95% CI 0·50–0·99) when analysis was restricted to the studies comparing breastfeeding with conventional formula feeding. The pooled OR for study populations with atopic heredity was 0·78 (95% CI 0·58–1·05).

Conclusions There is no strong evidence of a protective effect of exclusive breastfeeding for at least 3 months against AD, even among children with a positive family history.

Breastfeeding is undisputedly a preferable method for infant nutrition because of its nutritional, immunological and psychological benefits.[1] The protective effect of exclusive breastfeeding against the onset of atopic dermatitis (AD) was first reported by Grulee and Sanford[2] in 1936. Thereafter, there has been widespread support for the protective effect of breastfeeding against infantile eczema or atopic diseases.[3–10] In 2001, Gdalevich *et al.*[7] published a systematic review with a meta-analysis of prospective studies between January 1966 and May 2000 on the association between exclusive breastfeeding in the first 3 months after birth and the onset of AD in childhood. They concluded that breastfeeding is protective against incident AD in childhood. This protective effect was more pronounced in children with a family history of atopy. Since then, however, several large prospective birth cohort studies have reported conflicting results on the effect of breastfeeding. Some of them even suggested that breastfeeding might be a risk factor for AD.[11–14] Most of them have a much larger sample size and more thorough adjustments for potential confounders than earlier studies.

We conducted an updated systematic review and meta-analysis to determine the association between breastfeeding and AD after adding the information from recent prospective cohort studies.

Materials and methods

Literature search

An electronic literature search of MEDLINE (January 1966–May 2008) and EMBASE (1980–May 2008) for English

language publications was conducted using the text keywords '(breastfeeding *OR* infant formula *OR* milk, human) *AND* (atopic dermatitis *OR* eczema)', as well as medical subject headings. The search was limited to those studies carried out in humans. In addition, a manual search of references of retrieved articles was examined to ensure that all relevant English language articles up to May 2008 were identified.

Inclusion/exclusion criteria

Articles were included in the meta-analysis if they met the following criteria: (i) prospective cohort studies; (ii) reporting original data; (iii) maternal recall of the child's feeding history up to the age of 12 months; (iv) duration of breastfeeding for at least 3 months; (v) exclusive breastfeeding: no other milk products, substitutes or solid food added to the infant's diet in the first 3 months; (vi) never breastfeeding or breastfeeding < 3 months as the comparison group; (vii) specifically assessed outcome including the diagnosis of AD, atopic eczema, infantile eczema and eczema of childhood; (viii) studies in which odds ratios (ORs) of the association between breastfeeding and AD were reported or could be calculated from the data provided.

Publication selection process

This search strategy identified 1294 publications. Of these, 1204 articles were excluded after reading the titles and abstracts as being clearly not relevant to the association of breastfeeding and manifestations of AD. Ten articles were further excluded because they were non-English publications. The remaining 80 potentially relevant publications were retrieved for full-text review. Disagreements were resolved by discussion. Of the 80 publications retrieved for more detailed evaluation, three publications of clinical trials were excluded, seven publications were excluded because of nonprospective study design, 30 publications were excluded because of duration of exclusive breastfeeding < 3 months or not specified, four publications were excluded because of prolonged recall, two publications were excluded because the comparison group did not fulfil the predefined criteria and one publication was excluded because AD was not specifically assessed (Fig. 1). As

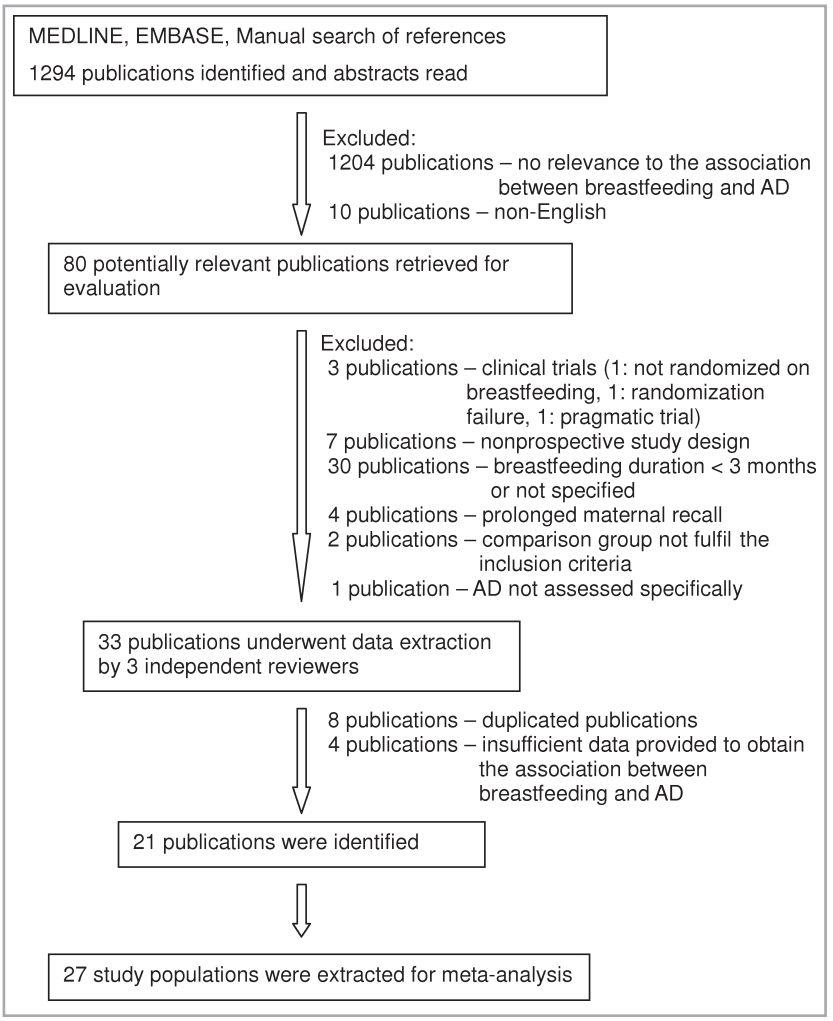

Fig 1. Flow diagram of publication selection process. AD, atopic dermatitis.

a result, 33 of the 80 publications underwent data extraction. Each publication was reviewed by three independent reviewers for data extraction.

Afterwards, eight publications were excluded because of duplicate publication. A further four articles were excluded because they did not report the data or statistical estimates allowing us to compute the association of exclusive breastfeeding and AD. Twenty-one publications were therefore identified for the final meta-analysis.

Data extraction

Twenty-one articles were evaluated by each independent investigator for complete data extraction using structured forms. Recorded data included source, publication year, location, number of participants, exposure assessment, duration of breastfeeding, type of comparison group, outcomes assessment, duration of follow-up, crude numbers of the exposed/nonexposed with regard to outcome, confounding variables being controlled, crude or adjusted ORs. The information was entered into a STATA spreadsheet for further analysis (StataCorp, College Station, TX, U.S.A.).

Statistical analysis

To achieve a normal distribution, we transformed ORs by means of a natural log scale. The standard errors of the transformed ORs were calculated from reported 95% confidence intervals (CIs). We used random effects models to calculate summary ORs to allow each of the studies in the meta-analysis to estimate a different effect size. Heterogeneity was tested using the Q statistic.[15] Method of moment analysis was used to estimate between-study variance.[15]

To examine sources of heterogeneity, we conducted meta-regression analysis with study-level covariates including type of comparison group (partial breastfeeding/conventional formula feeding), adjustment for potential confounders (yes/no), family history of atopy (yes/no) and outcome assessment (self-report/physician diagnosis).[16] The conventional formula feeding group included those fed with conventional infant formula, cow's milk or soy milk. Studies with outcome assessed by health visitors were regarded as a subgroup of physician diagnosis. To be considered as adjusted for AD risk factors, studies must have adjusted for two or more confounders. Meta-regression analysis was also performed with continuous variables encoding breastfeeding duration, the length of follow-up and publication year to examine the effect modification on the risk of AD per one unit increase. All meta-regression analyses were performed first in a univariate model then in a bivariate model. As the results did not materially change in a bivariate model, we presented the results in a univariate model to preserve maximal power.

Sensitivity analysis was performed by recalculating the risk estimate while omitting each study one at a time to determine the individual effect of each study on the pooled estimate and to identify the heavily weighted outliers. We also conducted a cumulative meta-analysis to explore the time trend of summary estimates.[17]

Finally, we used funnel plots, plots of study results against precision, to assess potential publication bias as suggested by Egger *et al.*[18] All calculations were performed using STATA version 8 software.

Results

Qualitative results

Six of 21 studies reported ORs stratified by family history of atopy. As a result, the final data set of the 21 publications included a total of 27 study populations, consisting of 34 227 participants. All the 21 publications included in the final meta-analysis were prospective cohort studies (Table 1). Ten of them were restricted to study populations with a positive family history of atopy.[19–28] The remaining 11 studies were conducted in the general population. Of these, six studies reported stratum-specific ORs stratified by the presence of family history of atopy.[4,14,29–32] Most of these studies were conducted in the developed countries. Only one of them was conducted in Belarus.[33]

Breastfeeding assessment

Methods used to assess breastfeeding varied across studies. The most commonly used method was questionnaires at delivery and the information was regularly updated by either mailed questionnaires, home visit, telephone interview or clinic follow-ups. Some studies used nutrition diary or diet record for breastfeeding assessment.[19,22,31] Duration of breastfeeding also varied, from 3 months to 6 months. As for the comparison group, exclusive breastfeeding < 3 months or breastfeeding combined with formula feeding were defined as partial breastfeeding. Fifteen studies compared with partial breastfeeding,[4,10,12,14,19–25,28,29,33,34] and six studies compared breastfeeding with infant formula, cow's milk or soy milk.[6,26,27,30–32]

Outcome assessment

The assessment of onset of AD was determined using a variety of methods across studies. In 14 studies, AD was diagnosed by physicians, including paediatricians, dermatologists or family doctors.[4,6,10,12,19–27,30] Five studies used self-reported symptoms of infantile eczema or a history of physician-diagnosed AD as outcome assessment.[14,29,32–34] Outcome was ascertained by health visitors in two studies.[28,31]

No uniform diagnostic criteria were used across studies to assess AD. Most studies used lax criteria such as pruritus, recurrent eczematous lesions and typical distributions of lesions to identify cases of AD.

The duration of follow-up to ascertain cases of AD was at least 1 year since birth. The longest was 7 years.[12] The mean duration of follow-up was 2·2 years.

Table 1 Characteristics of 21 cohort studies on the association between breastfeeding and atopic dermatitis (AD)

Source (first author and year)	Study population	Number of participants	BF assessment	BF duration (months)	Comparison group	Assessment of AD	Follow-up (years)	Adjusted OR (95% CI)	Adjustments
Matthew (1977)[4]	Birth cohort	42	Clinic follow-up	6	Partial breastfeeding	Physician diagnosis	1	FH(+): 0·75 (0·04–14·97) FH(−): 0·11 (0·02–0·67)	Parental history of eczema
Hide (1981)[30]	Birth cohort	843	Self-report by questionnaire	6	Formula	Physician diagnosis	1	FH(+): 0·73 (0·31–1·76) FH(−): 0·90 (0·46–1·77)	Parental history of allergy
Gruskay (1982)[6]	Children followed up in a private paediatric practice	895	Clinic follow-up	4	Soy milk or cow's milk	Physician diagnosis	3	0·41 (0·14–1·17)	FH (stratification)
Businco (1983)[27]	Children with a positive FH of atopy	101	Clinic follow-up	6	Soy milk or cow's milk	Physician diagnosis	3	1·2 (0·18–6·62)	Restriction on children with a positive FH of atopy
Pratt (1984)[31]	Birth cohort	198	Diet record	3	Formula	Health visitor diagnosis	4·5	FH(+): 0·72 (0·31–1·68) FH(−): 0·98 (0·40–2·44)	Atopic FH
van Asperen (1984)[22]	Children with a positive FH of atopy	79	Diet record	4	Partial breastfeeding	Physician diagnosis	1·6	1·68 (0·59–4·77)	Restriction on children with a positive FH of atopy
Chandra (1986)[26]	Children with a positive FH of atopy	109	Clinic follow-up	4	Formula	Physician diagnosis	1	0·15 (0·06–0·39)	Restriction on children with a positive FH of atopy
Poysa (1989)[21]	Children with a positive FH of atopy	91	Clinic follow-up	3	Partial breastfeeding	Physician diagnosis	1	0·81 (0·31–2·2)	Restriction on children with a positive FH of atopy
Marini (1996)[24]	Children with mothers reporting a positive FH of atopy	286	Self-report by questionnaire	5	Partial breastfeeding	Physician diagnosis	3	0·56 (0·28–1·07)	Restriction on children with a positive FH of atopy

Table 1 (*Continued*)

Source (first author and year)	Study population	Number of participants	BF assessment	BF duration (months)	Comparison group	Assessment of AD	Follow-up (years)	Adjusted OR (95% CI)	Adjustments
Herrmann (1996)[23]	Children with mothers reporting a positive FH of atopy	138	Clinic follow-up	3	Partial breastfeeding	Physician diagnosis	1	0·47 (0·18–1·31)	Restriction on children with a positive FH of atopy
Wetzig (2000)[20]	Children with both FH and increased cord blood IgE	117	Self-report by questionnaire	5	Partial breastfeeding	Physician diagnosis	1	2·68 (1·09–6·58)	Restriction on children with a positive FH of atopy
Bergmann (2002)[12]	Birth cohort	1314	Self-report by questionnaire	3	Partial breastfeeding	Physician diagnosis	7	1·29 (0·99–1·69)	Age, BF duration, atopy of parents, eczema of parents, social status, specific sensitization, allergic rhinoconjunctivitis, asthma, number of URTIs (first year), gender, smoking in pregnancy, age of mother, parity, cord blood IgE > 0·9 kU L^{-1}
Kull (2002)[10]	Birth cohort	4089	Self-report by questionnaire	4	Partial breastfeeding	Physician diagnosis	2	0·85 (0·71–1·0)	Gender, heredity, maternal age, smoking during pregnancy, year of construction of home
Schoetzau (2002)[19]	Children with FH of atopy	1121	Nutrition diary	4	Partial breastfeeding	Physician diagnosis	1	0·47 (0·30–0·74)	Restriction on children with a positive FH of atopy, atopic risk level, number of members in the core family with AD, cord blood IgE, nationality of parents, parental education, gender of the subject, pet keeping, maternal smoking
Kerkhof (2003)[25]	All children of mothers with respiratory allergy or asthma	304	Self-report by questionnaire	3	Partial breastfeeding	Physician diagnosis	1	0·6 (0·3–1·2)	Restriction on children with a positive FH of atopy, gender, birth weight, gestational age, age of mother, presence of siblings, day-care attendance, cigarette smoking of parents, cat/dog in the house

Table 1 (*Continued*)

Source (first author and year)	Study population	Number of participants	BF assessment	BF duration (months)	Comparison group	Assessment of AD	Follow-up (years)	Adjusted OR (95% CI)	Adjustments
Kramer (2003)[33]	Observational study nested in a clinical trial	3483	Clinic follow-up	6	Partial breastfeeding	Maternal interview and/or medical record	1	1·14 (0·65–2·02)	Geographic region, urban location, hospital, birth weight, maternal education, number of siblings in household
Benn (2004)[14]	Birth cohort	15 430	Self-report by telephone interview and questionnaire	4	Partial breastfeeding	Self-report by questionnaire	1·5	FH(+): 1·21 (0·98–1·28) FH(−): 1·29 (1·06–1·55)	Sex, occupation of mother, maternal education, smoking in the presence of child, income, pet keeping, number of siblings, maternal age, day care at 6 months of age, birth weight
Laubereau (2004)[32]	Birth cohort study nested in a clinical trial	3903	Self-report by questionnaire	4	Conventional cow's milk formula	Self-report by questionnaire	3	FH(+): 0·64 (0·45–0·90) FH(−): 1·19 (0·88–1·60)	Geographic area, sex, maternal smoking, parental education, pets, number of family members with allergy, AD in core family
Ludvigsson (2005)[34]	Birth cohort	8346	Self-report by questionnaire	4	Partial breastfeeding	Self-report by questionnaire	1	0·94 (0·82–1·08)	Atopic FH, parental smoking, gestational age < 37 weeks, maternal education, older sibling, pets
Rothenbacher (2005)[29]	Birth cohort	222	Self-report by telephone interview and questionnaire	3	Partial breastfeeding	Self-report by questionnaire	2	FH(+): 0·91 (0·28–2·97) FH(−): 0·74 (0·35–1·56)	Atopy of father, ethnic origin of mother, education of mother
Mihrshahi (2007)[28]	Cohort with FH of asthma nested in a clinical trial	616	Home visit by research nurses	3	Partial breastfeeding	Home visit by research nurses	5	1·52 (0·96–2·40)	Intervention or control group allocation, mother's and father's history of asthma, mother smoking in pregnancy and gender of child

BF, breastfeeding; OR, odds ratio; CI, confidence interval; FH, family history; URTI, upper respiratory tract infection.

Adjustment for confounders

Ten studies adjusted for two or more potential confounders.[10,12,14,19,25,28,29,32–34] While family history of atopy was adjusted in all of these studies, other confounders being adjusted varied across the publications, including parental education, pet-keeping in the house, parental smoking and gestational age.

Eleven studies did not adjust for any confounders or adjusted for fewer than two confounders.[4,6,20–24,26,27,30,31] Of these, seven publications were restricted to children with a positive family history of atopy.[6,20,23,24,26,27,30,31]

Quantitative results

Using a random effects model, we found that breastfeeding was associated with a slightly decreased risk of AD (OR 0·89; 95% CI 0·76–1·04) (Fig. 2). Heterogeneity was found across studies (χ^2 = 83·6, d.f. = 26; P < 0·001).

Assessment of heterogeneity

Exclusive breastfeeding was more protective against AD when compared with formula feeding than when compared with partial breastfeeding (Table 2). Restricting the analysis to the nine study populations that used conventional formula feeding as a comparison group reached a significantly protective pooled OR (OR 0·70; 95% CI 0·50–0·99). Breastfeeding was associated with a slightly decreased risk of AD in cohorts with a positive family history of atopy than in cohorts with negative family history. The pooled OR was 0·78 (95% CI 0·58–1·05) for study populations with a positive family history, and 0·93 (95% CI 0·60–1·45) for those with a negative family history.

In contrast, the protective effect of breastfeeding was attenuated toward the null when adjusting for potential confounders (OR 0·96; 95% CI 0·78–1·20). With respect to different methods of AD assessment, the effect of breastfeeding was more protective when physicians ascertained the diagnosis of AD (OR 0·78; 95% CI 0·61–0·99) compared with self-report.

In our meta-regression analysis that included breastfeeding duration as a continuous covariate, differences in breastfeeding duration did not affect pooled estimates substantially. With respect to follow-up duration, a 1-year increase of follow-up duration was associated with a 1·08-fold increased risk for AD. A 1-year increase of publication year was associated with a 1·02-fold increased risk for AD.

Sensitivity analyses

By recalculating the risk estimate while omitting each study one at a time, we found that two studies by Chandra *et al.*[26] and Schoetzau *et al.*[19] were moderately weighted outliers. Removing these two studies shifted the overall pooled OR towards the null (OR 0·98; 95% CI 0·85–1·12).

As there were some controversies[35] surrounding the study by Chandra *et al.*,[26] additional sensitivity analysis omitting only this study was performed. By omitting the study of Chandra *et al.*, the overall pooled OR was 0·94 (95% CI 0·81–1·08). The protective effect of breastfeeding against AD was no longer statistically significant (OR 0·84; 95% CI 0·64–1·09) when compared with conventional formula.

In the plots of the cumulative meta-analysis by year of publication, we observed an unstable trend in the beginning but the summary effect estimate stabilized by 2003.

Assessment of publication bias

A funnel plot showed slightly more data points from small studies below the horizontal line of summary estimate, indicating a possible publication bias favouring studies with protective effects. Egger's test indicated a marginally significant publication bias (P for bias = 0·05).

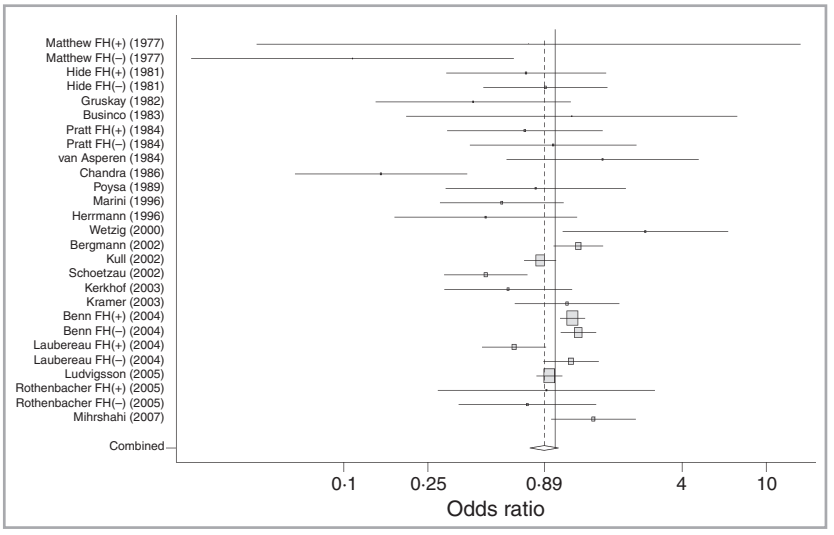

Fig 2. Forest plot for risk of atopic dermatitis associated with breastfeeding using the random effects model. FH(+) and FH(–) refer to study populations with a positive and negative family history, respectively.

Table 2 Pooled odds ratios (ORs) according to study characteristics

Group	Pooled OR (95% CI)	Number of study populations[a]	Between-group heterogeneity, P-value
Categorical variable			
Comparison group			0·15
Partial breastfeeding	0·95 (0·76–1·18)	18	
Conventional formula	0·70 (0·50–0·99)	9	
Adjusted for AD risk factors			0·10
Yes	0·96 (0·78–1·20)	13	
No	0·70 (0·51–0·96)	14	
Presence of family history[b]			0·53
Yes	0·78 (0·58–1·05)	16	
No	0·93 (0·60–1·45)	6	
Outcome assessment			0·17
Self-reported	1·01 (0·76–1·35)	8	
Physician-diagnosed	0·78 (0·61–0·99)	19	
Continuous variable			
Breastfeeding duration, per 1-month increase	0·98 (0·80–1·20)	27	0·82
Follow-up, per 1-year increase	1·08 (0·97–1·21)	27	0·16
Publication year, per 1-year increase	1·02 (1·00–1·04)	27	0·03

CI, confidence interval; AD, atopic dermatitis. [a]Twenty-seven study populations extracted from 21 studies. [b]Includes only studies with family history-specific ORs.

Discussion

This meta-analysis found no strong evidence suggesting that exclusive breastfeeding for at least 3 months was associated with a decreased risk of AD. Unlike the previous meta-analysis in 2001,[7] our meta-analysis did not find a significant protective effect of breastfeeding in children with a family history of atopy.

Heterogeneity was evident in our meta-analysis of observational studies. While confounding may still be a concern in explaining the heterogeneity, the effect modifications of study characteristics on the risk of AD were investigated and potential sources of heterogeneity were identified in Table 2. Compared with formula feeding, exclusive breastfeeding showed a protective effect against AD. This finding should be interpreted with caution because the protective effect was no longer statistically significant when the study of Chandra *et al.*[26] was excluded. There are several plausible biological mechanisms. Breast milk contains many immunomodulatory factors (IgA, cytokines and fatty acids) that promote the development of an infant's immune system.[36–42] Also, breast milk provides protection against infections that might stimulate the development of allergy.[43] Furthermore, by promoting the establishment of the intestinal flora predominantly by bifidobacteria, breastfeeding may be protecting against allergy by stimulating a Th1 response in breastfed infants.[44,45] 'Exclusivity' of breastfeeding plays an important role in protection against the onset of AD in that it can also decrease the exposure to external allergens.

This meta-analysis also found that adjustment for multiple confounders tended to attenuate the protective effect. As it has been reported that breastfeeding is more commonly observed in nonsmoking mothers and mothers with higher social status and higher education,[46–49] it is reasonable that mothers who choose breastfeeding will take other measures to prevent AD in their infants, such as using mite-proof bedding, keeping pets or taking probiotics pre-partum and during lactation. This unadjusted residual confounding might also explain that breastfeeding was associated with a much decreased risk for AD among children with atopic heredity found in the previous meta-analysis. After adjustment for these potential confounders, several recent studies showed less protective[10,34] or even harmful effects of breastfeeding on the onset of AD.[9,11,12,14,28]

Different methods for AD assessment may have significant impact on estimating the association between breastfeeding and AD. The protective effect of breastfeeding was observed only when we restricted analysis to the subgroup of studies in which outcomes were assessed by physicians or health visitors. It is possible that nondifferential misclassification of outcome may exist in studies using self-report questionnaires and bias the effect towards the null. Differential misclassification of outcome might exist in studies in which physicians diagnosed AD without blinding; unfortunately, blinding with respect to outcome assessment could not be clarified in some studies, limiting us to estimate the extent of bias.

We did not find a significant protective effect of breastfeeding in the study population with a positive family history of atopy. This contrasts somewhat with the previous meta-analysis,[7] in which breastfeeding was associated with a significantly lower incidence rate of AD in children with atopic heredity. However, the point estimate did shift towards the protective

side when we restricted the meta-analysis to the study population with atopic heredity. This suggests that the effect of breastfeeding depends on the atopic status of the parents.[7,50–52] Maternal allergic status has recently been considered an important effect modifier on the association between breastfeeding and atopic manifestations because of the differences in the fatty acid and cytokine composition of breast milk between atopic and nonatopic mothers.[40,53–56] However, due to insufficient information about the maternal atopic status from the studies included, we were not able to perform subgroup analysis by maternal allergic status.

There was a significant trend that the more recently the study was published, the less the protective effect became. This finding may be partly attributable to the fact of more deliberate adjustments for confounding in recent studies. Although the direction and magnitude of the trend remained unchanged after controlling this covariate in the meta-regression model, it became statistically insignificant. Another possible explanation is the influence of reverse causation,[57] meaning that mothers are likely to continue exclusive breastfeeding once their infants develop early signs of eczema due to the increased public awareness of the benefits of breastfeeding.

As the follow-up duration increased, the protective effect tended to decrease. Breastfeeding may have a protective effect in early childhood but not in late childhood. In a population-based cohort study from childhood to middle age, Matheson *et al.*[58] showed that in babies of atopic mothers, breastfeeding protected infants from early asthma and eczema, but did not appear to protect against the development of asthma and flexural eczema after the age of 7 years. Therefore, the duration of follow-up and age at which outcomes are assessed may have an impact on the assessed effects of breastfeeding.

The strengths of the present meta-analysis are that we adhered to the predefined standards for assessing study methodology, and restricted the recall period of the feeding history to 12 months or less to limit recall bias. Furthermore, our study included only prospective research to minimize selection bias, as randomized controlled trials on this topic are not practical on ethical grounds.

However, there were still limitations in our study. The exclusion of non-English literature may result in language bias. Of the 10 non-English publications excluded, four were original studies,[59–62] and all suggested no protective effects of breastfeeding on AD. If these four articles were included into the meta-analysis, the overall effect estimate would be further attenuated toward the null, which would not alter our conclusions. However, the possibility of bias from unpublished studies could not be totally ruled out.

Our meta-analysis disclosed significant variability between observational studies addressing the association between breastfeeding and AD. To explore the real relationship between breastfeeding and AD, further studies require a more thorough control for potential confounding, such as environmental risk factors, standardized measurements of house dust and mites, day care attendance, administration of probiotics, maternal-specific diet habits and number of siblings. More detailed information about maternal, paternal and siblings allergic status instead of combining them as 'family history of atopy' is also required for future study design.[53] Besides, standardized outcome assessments such as AD diagnosis with strict criteria by well-qualified assessors help avoid nondifferential and differential misclassifications. Future studies should also take into account the influence of reverse causation.[57,63–65] Controlling for reverse causation could be accomplished by survival analysis or risk period-specific analysis.[66] Furthermore, an extended follow-up duration is necessary to evaluate the long-term effect of breastfeeding.

In conclusion, we did not observe strong evidence of a protective effect of exclusive breastfeeding for at least 3 months against AD onset in childhood. Although the protective effect was enhanced in the subgroup of children with atopic heredity, this association was still not statistically significant.

It is widely accepted that breast milk is highly nutritious and that breastfeeding has advantages over formula feeding. It prevents early-life disorders and enhances the psychological benefits of mother–infant bonding through nursing. Although we did not observe a strong protective effect of breastfeeding against AD, it is an over-interpretation that we do not recommend breastfeeding as one would lose many benefits of breastfeeding by doing so. Another important message is that due to substantial heterogeneity across studies, our results should be interpreted with caution. More studies with standardized and deliberate methodology or a pooling project might be required for further systematic review.

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