

Breastfeeding and Atopic Dermatitis Risk: A Systematic Review and Meta-Analysis of Prospective Cohort Studies

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Keywords

Atopic dermatitis · Atopic eczema · Breastfeeding · Prospective cohort study · Meta-analysis

Abstract

Objectives: The effect of breastfeeding on atopic dermatitis (AD) remains controversial. To determine the association between breastfeeding and AD, we conducted an updated meta-analysis of prospective cohort studies. **Methods:** A comprehensive search of PubMed, EMBASE, MEDLINE and Cochrane Library was conducted. Studies meeting the pre-determined criteria were evaluated by 2 authors independently. The pooled relative risk (RR) adjusted for confounders with its 95% CI was calculated by a random-effects model. Heterogeneity was explored by subgroup analysis and meta-regression. **Results:** A total of 27 studies were included for meta-analysis. The pooled estimates for the effect of total and exclusive breastfeeding on AD were 1.01 (95% CI 0.93–1.10) and 0.99 (95% CI 0.88–1.11), respectively. Heterogeneity was substantial across studies (total: $p < 0.01$ or $I^2 = 65.2\%$; exclusive: $p < 0.01$ or $I^2 = 72.3\%$). There was a weak evidence for a protective effect of breastfeeding against AD in cohorts with atopic heredity (total: RR 0.85, 95% CI 0.74–0.98; exclu-

sive: RR 0.83, 95% CI 0.70–0.97). In cohorts without atopic heredity, the effect shifted to the risk side when limited to exclusive breastfeeding (RR 1.19, 95% CI 1.02–1.40) while it dropped towards null when limited to total breastfeeding (RR 1.11, 95% CI 0.94–1.31). **Conclusions:** There is no association between AD and breastfeeding, regardless of total or exclusive breastfeeding patterns. There is some evidence for a protective function of exclusive and total breastfeeding in a cohort with atopic heredity. The effect shifts to the risk side in cohorts without atopic heredity. However, these findings should be interpreted with caution because heterogeneity is evident.

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Introduction

Atopic dermatitis (AD) is one of the most common skin disorders in infants and children, which may persist in adulthood. It affects approximately 10–20% of infants and 10% of adults in developed countries, whereas its lifetime prevalence is still increasing, especially in develop-

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ing countries [1, 2]. Although AD is a nonfatal disease, it remains a profound public health problem with negative impacts on children's physical and psychosocial development. Children with AD, particularly those with severe conditions, have an increased risk for insomnia, depression, anxiety and other mental problems [3]. In the USA, it is estimated that the direct annual cost for AD is close to 5 billion USD [4].

AD has a complex pathogenesis involving a dysfunctional epidermal barrier and inappropriate immune responses [5]. Many environmental and lifestyle factors are associated with AD development, and one of the most controversial factors is breastfeeding [6, 7]. Since first reported by Grulee and Sanford [8], many studies have found a protective effect of breastfeeding on AD [9–13]. However, several studies showed no association between breastfeeding and AD [14, 15], and some studies even supported that breastfeeding might be a risk factor for AD [16, 17]. In 2001, Gdalevich et al. [18] performed a systematic review of 18 prospective studies and found a protective effect of breastfeeding on AD. In their study, the protective effect was more pronounced in children with an atopic family history. In 2009, an updated systematic review by Yang et al. [19] summarizing 21 prospective studies found no strong evidence of a protective effect of exclusive breastfeeding for at least 3 months against AD, even among children with an atopic family history. In 2015, a more recent systematic review by Lodge et al. [20] included 42 observational studies (24 cohort studies, 17 cross-sectional and 1 case-control) and showed exclusive breastfeeding for 3–4 months was associated with a reduced risk of eczema ≤ 2 years. Discrepancies between Lodge et al. [20] and previous studies may be attributed to methodological quality and design, as the protective effect found in Lodge's study was estimated principally from cross-sectional studies of low methodological quality. Also, many recently published studies assessed more deliberate adjustments for potential confounders; however, most previous systematic reviews adopted only unadjusted data for the final analysis.

Therefore, it is necessary to provide an up-to-date quantitative estimate of the breastfeeding-AD association. In addition, it remains ambiguous whether a breastfeeding-related effect is linked to different breastfeeding behaviors, such as exclusive or combined breastfeeding. To address these issues, we conducted a comprehensive systematic review and meta-analysis of prospective cohort studies to investigate the association between various breastfeeding behaviors and the risk of AD.

Materials and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000503781 for all online suppl. material) (Fig. 1) [21–32].

Results

Literature Search

The initial search retrieved 952 articles, among which 350 articles were excluded due to duplication. After reading the titles and abstracts, 447 articles were out of scope. An additional 20 articles were included after handscreening of references. Finally, 175 articles were assessed for further evaluation. In this review, 148 articles were excluded for the following reasons: 43 articles did not provide the association data, 40 articles were not prospective cohort studies, 53 articles did not meet the inclusion criteria, full texts of 9 articles were unavailable and 1 article was in process for debated results. In total, 27 articles were included in the final meta-analysis (Fig. 1).

Study Characteristics

Among these 27 articles, 21 were from Europe [10–12, 14, 16, 33–48], 4 were from Asia [17, 49–51], and another 2 were from Australia [52, 53]. There were 21 studies set in a high-income country [10–11, 14, 16, 35–37, 39–50, 52, 53], and the remaining 6 studies were from a middle-/low-income country [12, 17, 33, 34, 38, 51]. The total number of included participants was 177,445 (mean 6,572, SD 33,806), ranging from 186 to 38,757. The entire follow-up period ranged from 1 to 17 years. Regarding the assessment methods of breastfeeding, most studies used questionnaires to collect information, while some studies collected it through clinic follow-up or dietary records. Among the 27 included studies, 20 focused on exclusive breastfeeding. As for AD diagnostic criteria, only 6 studies claimed that they used standard diagnostic criteria to determine AD, while other studies diagnosed the cases without uniform criteria. In addition, 4 studies were restricted to populations with a positive family history of atopy, and 9 studies reported specific relative risks (RRs) stratified by different atopic family histories. The characteristics and extracted RRs of the included studies are presented in Tables 1 and 2, separately.

Study Quality

Using the Newcastle-Ottawa Scale (NOS) system, we found that all included studies were considered as high

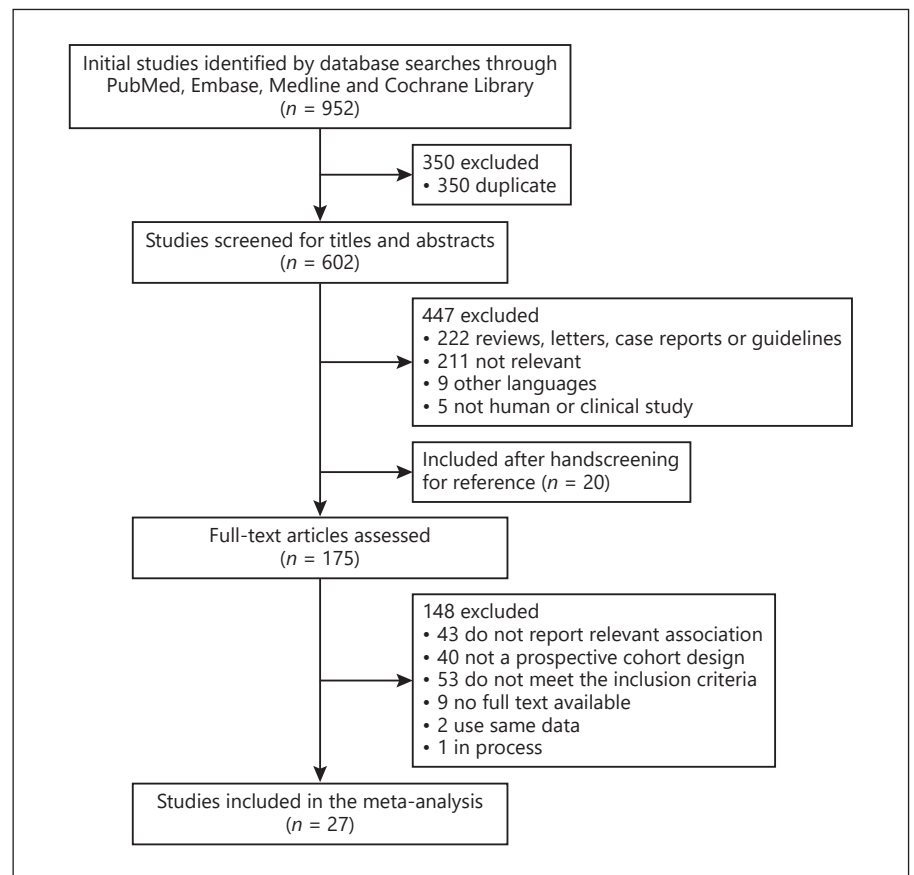


Fig. 1. Flowchart of Materials and Methods.

quality. The detailed information of NOS quality assessment is presented in online supplementary Table S1. The NOS scores compared with Lodge et al. [20] are listed in online supplementary Table S2, and no difference was indicated.

Reverse Causation

The issue of reverse causation was investigated by 7 of 27 studies [17, 35, 37, 39, 41, 50, 53] with 5 finding no evidence of reverse causality in their studies [35, 37, 39, 41, 53]. One showed, when taking account of reverse causality, no evidence of a protective effect of prolonged breastfeeding against AD among children at the age of 18 months [17]. However, another study found that breastfeeding increased the AD risk when considering reverse causation [50].

Total Breastfeeding and Risk of AD

Two of 27 publications reported RRs stratified by family history of atopy. Therefore, a total of 29 records were entered into final statistics regarding total breastfeeding

and AD risk. Using a random-effects model, we found there was no association between the risk of AD and total breastfeeding (RR 1.01, 95% CI 0.93–1.10; Fig. 2). Heterogeneity was found across studies ($p < 0.01$ or $I^2 = 65.2\%$; Fig. 2).

Subgroup Analysis and Meta-Regression

To explore potential sources of heterogeneity, we further conducted stratified analysis and meta-regression, while the heterogeneity remained high across strata (Table 3). Total breastfeeding was associated with a significantly decreased risk of AD in the subgroup with a positive family history (RR 0.85, 95% CI 0.74–0.98). However, the association changed to the reverse direction when stratified in a population without an atopic family history (RR 1.11, 95% CI 0.94–1.31), while no statistically significant difference was detected. The result of meta-regression indicated that a family history of atopy explained 15.12% of the variability between studies (p value from meta-regression < 0.05) [54].

Table 1. Characteristics of included studies

Study	Country	Sample size	Males, n	Follow-up, years	Number of cases	Feeding pattern	Reference group	BF assessment	BF duration, months	AD assessment	Criteria	Atopy FH	Adjusted variables
Flohr et al. [44], 2018	Belarus	13,557	6,981	16	/	Exclusive BF	Partial BF	Clinic follow-up	3	Clinical examination	Hanfin and Rajka	Combined	Stratum-level variables, child age at follow-up, sex, birth weight, maternal and paternal education
Wang et al. [46], 2017	UK	5,676	2,943	17	/	BF	Never BF	Questionnaire	6	Self-assessment	/	Combined	Age, sex, ethnicity, family education, Townsend deprivation index, day care attendance, number of older siblings, maternal pre- and postnatal smoking, pet ownership, parental atopy
Chiu et al. [51], 2016	Taiwan, China	186	83	4	/	BF	Partial BF	Clinical follow-up	6	Self-assessment	/	Combined	Maternal age at delivery, maternal and paternal history of atopy, passive smoke exposure from parents during pregnancy, any older siblings, household income, gestational age, gender
Taylor-Robinson et al. [47], 2016	UK	14,499	7,408	5	5,089	BF	Never BF	Questionnaire	6	Self-assessment	/	Combined	Maternal education, sex, ethnic group, maternal age, maternal atopy, BMI before pregnancy, smoking and alcohol during pregnancy, antibiotics, environmental tobacco smoke exposure in same room, exposure to grime, children in household, child care
Døgrud et al. [33], 2016	Turkey	1,377	732	1	59	Exclusive BF	Partial BF	Questionnaire	4	Physician diagnosis	Williams	Combined	Gestational age, birth weight, socioeconomic level, maternal vitamin E and folate intake during pregnancy, maternal and paternal allergic disease, infants with food allergy
Jelding-Dannemand et al. [34], 2015	Denmark	304	/	7	67	Exclusive BF	Partial BF	Clinical visits	6	Clinical examination	Hanfin and Rajka criteria	Yes, restricted to children whose mother had a history of asthma	Mother smoking during the third trimester, mother's age at childbirth, household income, older siblings, father's allergy, region, education level of parents, reverse causation
Ito and Fujiwara [49], 2014	Japan	38,757	20,105	3.5	10,189	BF, exclusive BF	Never BF	Questionnaire	6	Physician diagnosis	/	Combined	Child's sex, birth weight, gestational age, maternal age, paternal age, maternal smoking habit, paternal smoking habit, living with grandparent(s), older siblings, maternal anxiety during child rearing, maternal and paternal education, maternal work status at 6 months postpartum, average household income
Parazini et al. [35], 2014	Italy	796	377	1	222	BF, exclusive BF	Never BF	Questionnaire	5	Self-assessment and physician diagnosis	/	Combined	Gender, mother's and father's age and education, family history of atopy, cats or dogs in the house at birth, disease in pregnancy, gestational age at delivery, mode of delivery, birth weight, use of antibiotic during pregnancy, streptococcus treatment during pregnancy, antibiotic use in the newborn
Nwaru et al. [48], 2013	UK	1,924	945	10	/	Exclusive BF	Never BF	Diet record	6	Physician diagnosis	/	Combined	Maternal smoking during pregnancy, maternal atopy, birth order, child's gender, maternal age and socioeconomic status at recruitment, crown-heel length
Morales et al. [36], 2012	Spain	580	580	1.2	/	Exclusive BF	Never BF	Questionnaire	6	Self-assessment	/	Combined	Child gender, maternal atopy, maternal pre-pregnancy BMI
Chuang et al. [17], 2011	Taiwan, China	18,733	9,735	1.5	1,050	BF	Never BF	Questionnaire	12	Physician diagnosis	/	Combined	Gender, birth order, birth weight, gestational age of infants, parents' age, parents' education, parents' allergic history, place of residence, maternal smoking during pregnancy, passive smoking by pregnant women in the home, mold spores in carpet, pet in the home

Table 1 (continued)

Study	Country	Sample size	Males, <i>n</i>	Follow-up, years	Number of cases	Feeding pattern	Reference group	BF assessment	BF duration, months	AD assessment	Criteria	Atopy FH	Adjusted variables
Miyake et al. [50], 2009	Japan	763	403	1	142	Exclusive BF	Partial BF	Questionnaire	4	Self-assessment	/	Combined	Maternal age, maternal and paternal history of asthma, atopic eczema and allergic rhinitis, indoor domestic pets, family income, maternal and paternal education, maternal smoking during pregnancy, baby's sex, baby's birth weight, baby's older siblings, household smoking in same room as infant, time of delivery before third survey
Matheson et al. [52], 2007	Australia	8,280	4,242	7	813	Exclusive BF	Partial BF	Questionnaire	3	Self-assessment	/	Combined	Sex, maternal smoking, sibling atopy, paternal atopy
Mirshahi et al. [53], 2007	Australia	516	/	5	130	BF, exclusive BF	Partial BF	Questionnaire	6	Self-assessment and physician diagnosis	/	Yes, restricted to children with an FH of asthma	Intervention or control group allocation, mother's and father's history of asthma, mother smoking in pregnancy, gender of child
Sariachvili et al. [37], 2007	Belgium	976	517	1	227	BF	Never BF	Questionnaire	12	Self-assessment	/	Combined	Maternal and paternal atopy, pregnancy duration, maternal educational level and age, active and passive smoking during pregnancy, passive smoking of the child during the first year, gender, postnatal contact with pets, use of antibiotics during pregnancy, first year, parity, day care attendance
Dunlop et al. [12], 2006	Slovak Republic	1,326	660	1	207	Exclusive BF	Partial BF	Questionnaire	4	Physician diagnosis and clinical examination	SCORAD index >2	Combined	Yes, yet no details
Linneberg et al. [38], 2006	Denmark	34,793	/	1.5	3,327	Exclusive BF	Partial BF	Questionnaire	4	Self-assessment	/	Combined	Sex, parental atopy, season of birth, gestational age, head circumference, birth weight, maternal age and occupation, number of older siblings, day care at 6 months of age, pets in the home, smoking during pregnancy
Kull et al. [39], 2005	Sweden	3,670	1,828	4	588	Exclusive BF	Partial BF	Questionnaire	4	Self-assessment or physician diagnosis	/	Combined	Parental heredity
Rothenbacher et al. [10], 2005	Germany	803	420	2	165	BF	Partial BF	Telephone interview	3	Physician diagnosis	/	Yes, maternal	Atopy of father, ethnic origin of mother, duration of school education of mother
Benn et al. [14], 2004	Denmark	15,430	7,561	1.5	1,770	Exclusive BF	Partial BF	Telephone interview	4	Self-assessment	/	Combined	Sex, occupational class of the mother, maternal education, smoking in the presence of the child, household income, pet keeping, number of siblings, maternal age, day care at 6 months of age, birth weight
Laubereau et al. [41], 2004	Germany	3,903	1,979	4	/	Exclusive BF, partial BF	Partial BF, never BF	Questionnaire	4	Physician diagnosis	/	Combined	Study area, sex, maternal smoking first year, parental education, pets, number of family members with allergy, AD or asthma in core family, introduction of any solid food during the first 4 months
Kerkhof et al. [42], 2003	Netherlands	304	151	1	76	Exclusive BF	Partial BF	Questionnaire	3.25	Physician diagnosis	UK-WP	Yes, restricted to children whose mothers have respiratory allergy or asthma	Gender, birth weight, gestational age, age of mother, presence of siblings, day care attendance, cigarette smoking of parents, cat or dog in the house, region, education level of parents
Kramer et al. [45], 2003	Belarus	3,483	1,759	1	95	Exclusive BF	Partial BF	Clinic follow-up	5	Clinical examination	/	Combined	Geographic region, urban or rural location, hospital of birth, birth weight, maternal education, number of siblings in household

Table 1 (continued)

Study	Country	Sample size	Males, <i>n</i>	Follow-up, years	Number of cases	Feeding pattern	Reference group	BF assessment	BF duration, months	AD assessment	Criteria	Atopy FH	Adjusted variables
Silanen et al. [43], 2003	Finland	285	143	4	129	Exclusive BF	Partial BF	Clinic follow-up	3	Self-assessment	/	Combined	Season of birth, sex, age at starting solid foods, parental smoking, furred pets at home, number of older siblings, educational level of mother
Bergmann et al. [16], 2002	Germany	1,314	/	7	/	BF	Partial BF	Questionnaire	3	Clinical examination	Hanifin and Rajka	Combined	Age, BF duration, atopy parents, eczema parents, social status, specific sensitization, allergic rhinoconjunctivitis, asthma, number of upper respiratory tract infection (first year), gender, smoking in pregnancy, age of mother, parity, cord blood IgE > 0.9 kU/L
Kull et al. [40], 2002	Sweden	4,089	/	2	952	BF, exclusive BF	Partial BF	Questionnaire	4	Physician diagnosis	/	Combined	Gender, heredity, maternal age, smoking during pregnancy and/or during the 3 first months of life of the child, year of construction of home of the family
Schoetzau et al. [11], 2002	Germany	1,121	572	1	120	Exclusive BF	Partial BF	Dietary record	4	Physician diagnosis	/	Yes, restricted to children with a positive FH of atopy	AD in core family, atopic risk level, gender in the homogenous strata, nationality, maternal smoking, pets, parental education

BF, breastfeeding; AD, atopic dermatitis; FH, family history; BMI, body mass index; SCORAD, Scoring Atopic Dermatitis; UK-WP, UK Working Party.

The protective effect of total breastfeeding on AD was slightly stronger when using partial breastfeeding (RR 0.98, 95% CI 0.88–1.09) as a reference than when using never breastfeeding (RR 1.06, 95% CI 0.92–1.23) as a reference. However, no statistically significant differences were found in both subgroups, and the heterogeneity remained high. When stratified by country income, the effect of total breastfeeding was more protective in cohorts from middle- and low-income countries (RR 0.74, 95% CI 0.41–1.37) compared with cohorts from high-income countries (RR 1.02, 95% CI 0.94–1.10). With respect to different AD stages, total breastfeeding was associated with decreased risks in the adult AD subgroup (RR 0.62, 95% CI 0.22–1.73) as well as in the infantile AD subgroup (RR 0.92, 95% CI 0.79–1.08), while the heterogeneity of the estimates was too high to be reliable. In contrast, total breastfeeding was associated with an increased risk in children's AD (RR 1.04, 95% CI 0.94–1.16). As for different methods for AD assessment, the effect of total breastfeeding was more harmful when self-reporting the diagnosis of AD (RR 1.09, 95% CI 1.01–1.18) compared with clinical examination or physician-ascertained outcome of AD (RR 0.92, 95% CI 0.80–1.07). Different breastfeeding duration did not affect the pooled result substantially. Breastfeeding follow-up of up to 1 year was associated with a lower pooled risk for AD (RR 0.81, 95% CI 0.57–1.14), whilst increased length of breastfeeding follow-up was related with increased pooled risks (RR 1.04, 95% CI 0.96–1.14).

In our meta-regression analysis, we also included publication year and sample size as continuous covariate, differences in both did not influence pooled estimates overall. Publication year explained 7.61% of the variability between studies, and the sample size explained 18.07% of the variability between studies (Table 3).

Sensitivity Analysis

Through recalculating the pooled estimate while omitting one study each time, sensitivity analysis showed that no single study was an important source of heterogeneity. That is, the summary estimates were robust to exclude studies with different assessment criteria (online suppl. Fig. S1).

Publication Bias

Visual inspection of a funnel plot revealed asymmetry for total breastfeeding (Fig. 3), and Egger's test was significant ($p = 0.036$), while the p value for Begg's test was 0.053. The results indicated a possible small study bias

Table 2. Extracted data from included studies

Study	Exposure (months)	Reference	Adjusted RR (95% CI)	FH
Flohr et al. [44], 2018	Exclusive BF (≥ 3)	Partial BF	0.34 (0.16–0.72)	Combined
Wang et al. [46], 2017	BF (>6)	Never BF	0.98 (0.85–1.14)	Combined, to 17 years
	BF (4–6)	Never BF	0.97 (0.82–1.13)	Combined
	BF (>6)	Never BF	1.06 (0.90–1.26)	FH+
	BF (>6)	Never BF	0.89 (0.69–1.15)	FH–
	BF (>6)	Never BF	1.48 (0.99–2.21)	Combined, to 2 years
	BF (>6)	Never BF	1.24 (0.80–1.93)	Combined, to 4 years
	BF (>6)	Never BF	0.84 (0.53–1.31)	Combined, to 6 years
Chiu et al. [51], 2016	BF (>6)	Partial BF	1.31 (0.49–3.5)	Combined, to 4 years
	BF (>6)	Partial BF	0.33 (0.07–0.75)	Combined, to 1 year
	BF (>6)	Partial BF	0.36 (0.13–0.94)	Combined, to 2 years
	BF (>6)	Partial BF	0.76 (0.29–1.99)	Combined, to 3 years
Taylor-Robinson et al. [47], 2016	BF (≥ 6)	Never BF	1.17 (1.01–1.36)	Combined
	BF (0–6)	Never BF	1.03 (0.94–1.13) ¹	Combined
Doğruel et al. [33], 2016	Exclusive BF (≥ 4)	Partial BF	0.33 (0.05–1.96)	Combined
Jelding-Dannemand et al. [34], 2015	Exclusive BF (4)	Partial BF	0.99 (0.84–1.17)	FH+
Ito and Fujiwara [49], 2014	Overall BF (6)	Never BF	1.16 (1.05–1.29) ¹	Combined
	Exclusive BF (6)	Never BF	1.26 (1.12–1.41)	Combined
	BF (3–5)	Never BF	1.06 (0.95–1.19)	Combined
	BF (6+)	Never BF	1.24 (1.11–1.38)	Combined
Parazzini et al. [35], 2014	BF (5+)	Never BF	1.39 (0.91–2.12)	Combined
	Exclusive BF (5+)	Never BF	1.46 (0.95–2.25)	Combined
Nwaru et al. [48], 2013	Exclusive BF (≥ 3.75)	Never BF	1.25 (0.95–1.64)	Combined
	Exclusive BF (≥ 3.75)	Never BF	1.16 (0.83–1.61)	Yes
	Exclusive BF (≥ 3.75)	Never BF	1.46 (0.87–2.46)	No
Morales et al. [36], 2012	Exclusive BF (4+)	Never BF	0.7 (0.42–1.17) ¹	Combined
	Exclusive BF (4–6)	Never BF	0.72 (0.42–1.22)	Combined
	Exclusive BF (6+)	Never BF	0.64 (0.28–1.44)	Combined
Chuang et al. [17], 2011	BF (6+)	Never BF	1.46 (1.17–1.64) ¹	Combined
	BF (2–6)	Never BF	1.47 (1.17–1.84)	Combined
Miyake et al. [50], 2009	Exclusive BF (≥ 4)	Partial BF	1.23 (0.84–1.81)	Combined
	Exclusive BF (≥ 4)	Partial BF	1.77 (0.90–3.55)	FH+
	Exclusive BF (≥ 4)	Partial BF	0.96 (0.59–1.55)	FH–
Matheson et al. [52], 2007	Exclusive BF (≥ 3)	Partial BF	1.10 (0.92–1.33)	Combined
	Exclusive BF (≥ 3)	Partial BF	0.67 (0.49–0.92)	FH+
	Exclusive BF (≥ 3)	Partial BF	1.05 (0.83–1.32)	FH–
Mihirshahi et al. [53], 2007	BF (≥ 6)	Partial BF	1.42 (0.94–2.16)	FH+
	Exclusive BF (≥ 3)	Partial BF	1.52 (0.96–2.40)	FH+
Sariachvili et al. [37], 2007	BF (>6)	Never BF	0.87 (0.61–1.23) ¹	Combined
	BF (1–6)	Never BF	0.8 (0.4–1.3)	Combined
Dunlop et al. [12], 2006	Exclusive BF (>4)	Partial BF	0.30 (0.1–0.8)	Combined
Linneberg et al. [38], 2006	Exclusive BF (>4)	Partial BF	1.12 (1–1.25)	Combined
Kull et al. [39], 2005	Exclusive BF (≥ 4)	Partial BF	0.78 (0.63–0.96)	Combined
	Exclusive BF (≥ 4)	Partial BF	0.74 (0.55–0.99)	FH+
	Exclusive BF (≥ 4)	Partial BF	0.83 (0.62–1.13)	FH–

Table 2 (continued)

Study	Exposure (months)	Reference	Adjusted RR (95% CI)	FH
Rothenbacher et al. [10], 2005	BF (≥ 3)	Partial BF	0.73 (0.35–1.55) ¹	FH+
	BF (≥ 3)	Partial BF	0.61 (0.36–1.06) ¹	FH–
	BF (3–6)	Partial BF	0.91 (0.28–2.97)	FH+
	BF (3–6)	Partial BF	0.74 (0.35–1.56)	FH–
	BF (6+)	Partial BF	0.70 (0.32–1.50) ¹	FH+
	BF (6+)	Partial BF	0.57 (0.32–0.99) ¹	FH–
Benn et al. [14], 2004	Exclusive BF (4)	Partial BF	1.12 (0.98–1.28)	Combined
	Exclusive BF (4)	Partial BF	0.88 (0.67–1.13)	FH2+
	Exclusive BF (4)	Partial BF	1.11 (0.94–1.31)	FH1+
	Exclusive BF (4)	Partial BF	1.29 (1.06–1.55)	FH–
	Exclusive BF (3–6)	Never BF	1.59 (1.25–2.02) ¹	Combined
	Exclusive BF (6+)	Never BF	1.60 (0.94–2.72)	Combined
Laubereau et al. [41], 2004	Exclusive BF (4)	Partial BF	0.95 (0.79–1.14)	Combined
	Exclusive BF (4)	Never BF (conventional formula)	0.64 (0.45–0.90)	FH+
	Exclusive BF (4)	Never BF (conventional formula)	1.19 (0.88–1.60)	FH–
	Exclusive BF (4)	Never BF (hypoallergenic formula)	0.58 (0.41–0.81)	FH+
	Exclusive BF (4)	Never BF (hypoallergenic formula)	1.30 (0.85–1.99)	FH–
Kerkhof et al. [42], 2003	Exclusive BF (13 weeks)	Partial BF	0.6 (0.3–1.2)	FH+
Kramer et al. [45], 2003	Exclusive BF (≥ 6)	Partial BF	1.14 (0.65–2.02)	Combined
Siltanen et al. [43], 2003	Exclusive BF (>3)	Partial BF	0.68 (0.34–1.35)	FH+
	Exclusive BF (>3)	Partial BF	2.37 (1.03–5.48)	FH–
Bergmann et al. [16], 2002	BF (≥ 3)	Partial BF	1.19 (0.90–1.58)	Combined
	BF (≥ 6)	Partial BF	1.18 (0.91–1.54)	Combined
Kull et al. [40], 2002	BF (>6)	Partial BF	0.88 (0.72–1.05)	Combined
	Exclusive BF (≥ 4)	Partial BF	0.85 (0.71–1)	Combined
Schoetzau et al. [11], 2002	Exclusive BF (≥ 16 weeks)	Partial BF	0.47 (0.30–0.74)	FH+

RR, risk ratio; CI, confidence interval; FH, family history; BF, breastfeeding. ¹ The RRs are estimated according to Hamling's method [24].

with a protective effect. The pooled RR was 1.01 (95% CI 0.93–1.10) after performing the trim-and-fill method, and no study was filled up into the final analysis.

Exclusive Breastfeeding and Risk of AD

A total of 20 studies reported detailed information of exclusive breastfeeding, with one study presenting RRs stratified by different atopic family histories. Consequently, 21 records were compromised into final statistics regarding exclusive breastfeeding and AD risk. Using a random-effects model, we found that there was no association between the risk of AD and exclusive breastfeeding

(RR 0.99, 95% CI 0.88–1.11; Fig. 4). Also, heterogeneity was evident across studies ($p < 0.01$ or $I^2 = 72.3\%$; Fig. 4).

Subgroup Analysis and Meta-Regression

Details of subgroup analysis and meta-regression are presented in Table 4. Exclusive breastfeeding was associated with a decreased risk of AD in cohorts with a positive family history of atopy (RR 0.83, 95% CI 0.70–0.97). In contrast, in the population without a family history, exclusive breastfeeding showed a harmful effect (RR 1.19, 95% CI 1.02–1.40). Moreover, statistically significant differences were found across the above strata. The result of

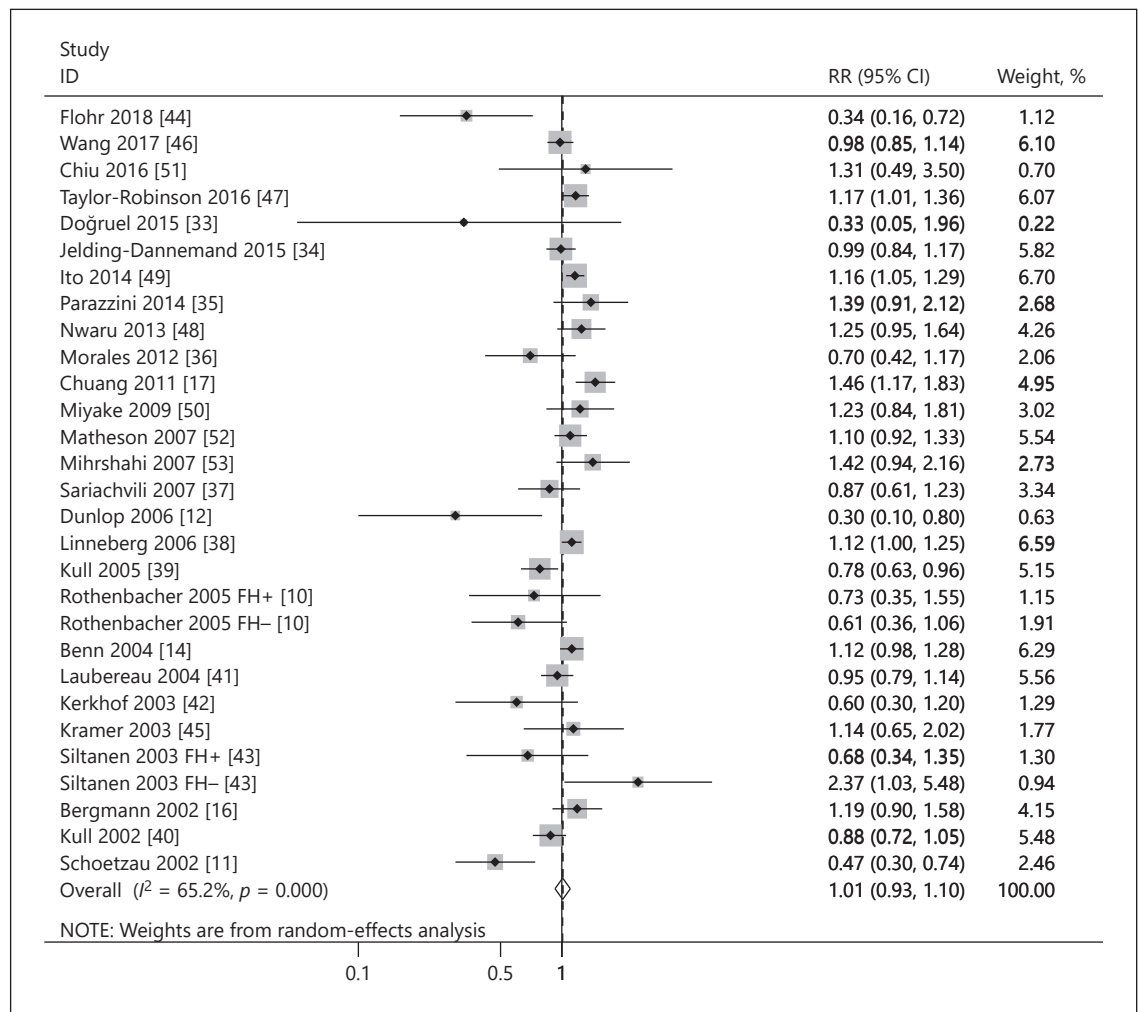


Fig. 2. Meta-analysis of AD and total breastfeeding by reference group. AD, atopic dermatitis; RR, risk ratio; CI, confidence interval; FH, family history.

meta-regression indicated that a family history of atopy explained 33.39% of variability between studies and was a potential source leading to the heterogeneity (p value from meta-regression <0.05).

The pooled estimates were similar when compared with partial breastfeeding (RR 0.98, 95% CI 0.87–1.10) or when compared with never breastfeeding (RR 0.99, 95% CI 0.71–1.37), while the heterogeneity remained high. Different levels of country income explained 11% of the variability between studies, with a lower risk found in cohorts from middle- and low-income countries (RR 0.49, 95% CI 0.22–1.10) and a higher risk found in cohorts from high-income countries (RR 1.02, 95% CI 0.92–1.14). With respect to different AD stages, exclusive breastfeeding was associated with a decreased risk in adult AD (RR

0.34, 95% CI 0.16–0.72) and infantile AD (RR 0.92, 95% CI 0.77–1.10). However, exclusive breastfeeding showed an increased risk in childhood AD (RR 1.08, 95% CI 0.93–1.25). When stratified by different methods for AD assessment, the effect of exclusive breastfeeding was more protective when clinically examined or when the physician ascertained the diagnosis of AD (RR 0.88, 95% CI 0.74–1.06) compared with self-reported ones (RR 1.21, 95% CI 1.01–1.24). Breastfeeding duration longer than 6 months (RR 1.26, 95% CI 0.92–1.74) was associated with the higher pooled risk for AD, whilst the effect was attenuated towards null when stratified in a cohort breastfed up to 6 months (RR 0.99, 95% CI 0.87–1.12). Additionally, lower pooled estimates for AD risk were seen in the length of breastfeeding follow-up up to 1 year (RR

Table 3. Total breastfeeding and the risk of AD: subgroup analysis and meta-regression

Subgroup	Number of records ^a	RR (95% CI)	Heterogeneity		Metaregression		
			I^2 , %	p value	proportion of between-study variance explained (adj. R^2), %	estimate of between-study variance (τ^2)	p value
Stratified by atopic family history					15.12	0.05	0.04
Yes	15	0.85 (0.74–0.98)*	67.4	<0.01			
No	10	1.11 (0.94–1.31)	56.2	<0.01			
Stratified by reference group					≤0	0.04	0.49
Partial BF	20	0.98 (0.88–1.09)	58.8	<0.01			
Never BF	9	1.06 (0.92–1.10)	73.7	<0.01			
Stratified by income					≤0	0.05	0.77
High-income country	23	1.02 (0.94–1.10)	61	<0.01			
Middle-/low-income country	6	0.74 (0.41–1.37)	77.8	<0.01			
Stratified by AD stage ^a					≤0	0.06	0.85
Infantile AD	18	0.92 (0.79–1.08)	70.4	<0.01			
Childhood AD	15	1.04 (0.94–1.16)	48.2	0.019			
Adult AD	2	0.62 (0.22–1.73)	86.4	<0.01			
Stratified by AD assessment method					≤0	0.04	0.23
Self-assessment	12	1.09 (1.01–1.18)*	24.8	0.2			
Clinical examination or physician diagnosis	17	0.92 (0.80–1.07)	74.9	<0.01			
Stratified by breastfeeding duration ^a					≤0	0.05	0.45
3–6 months	25	1.02 (0.92–1.12)	68.3	<0.01			
>6 months	14	1.01 (0.97–1.24)	64.6	<0.01			
Stratified by the length of follow-up					3.91	0.04	0.24
>1 year	21	1.04 (0.96–1.14)	63.3	<0.01			
≤1 year	8	0.81 (0.57–1.14)	68.2	<0.01			
Continuous variable							
Publication year	29	1.01 (0.99–1.04)	64.84	/	7.61	0.04	0.33
Sample size	29	1.00 (0.99–1.00)	61.46	/	18.07	0.03	0.20

AD, atopic dermatitis; RR, relative risk; CI, confidence interval; BF, breastfeeding. * $p < 0.05$. ^a If studies reported stratified RRs in accordance with pre-specified covariates, each RR was included into subgroup analysis and metaregression.

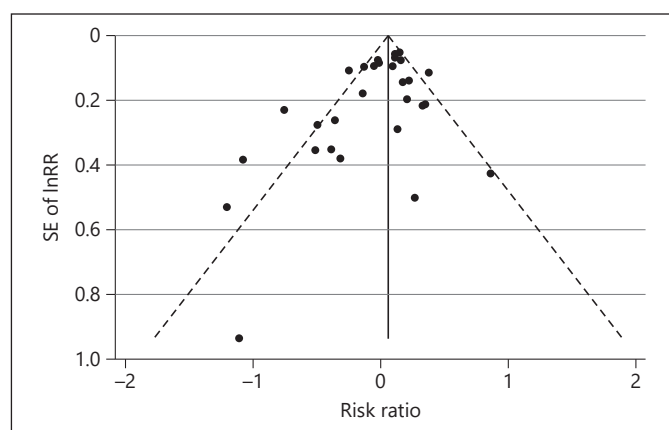


Fig. 3. The funnel plot of studies on the association between AD and total breastfeeding. AD, atopic dermatitis; SE, standard error; lnRR, the natural logarithm of risk ratio.

0.78, 95% CI 0.50–1.21), while increased lengths of breastfeeding follow-up were associated with increased pooled risks (RR 1.02, 95% CI 0.91–1.14).

Also, the continuous covariates of publication year and sample size did no influence the pooled estimates, with publication year explaining 5.17% and the sample size explaining 1.08% of the variability between studies (Table 4).

Sensitivity Analysis

Also, the result of sensitivity analysis showed that no single study affected the pooled estimate significantly with none of the studies accounting for the important source of heterogeneity. That is, the effect estimate rarely changed after studies with different assessment criteria had been excluded (online suppl. Fig. S2).

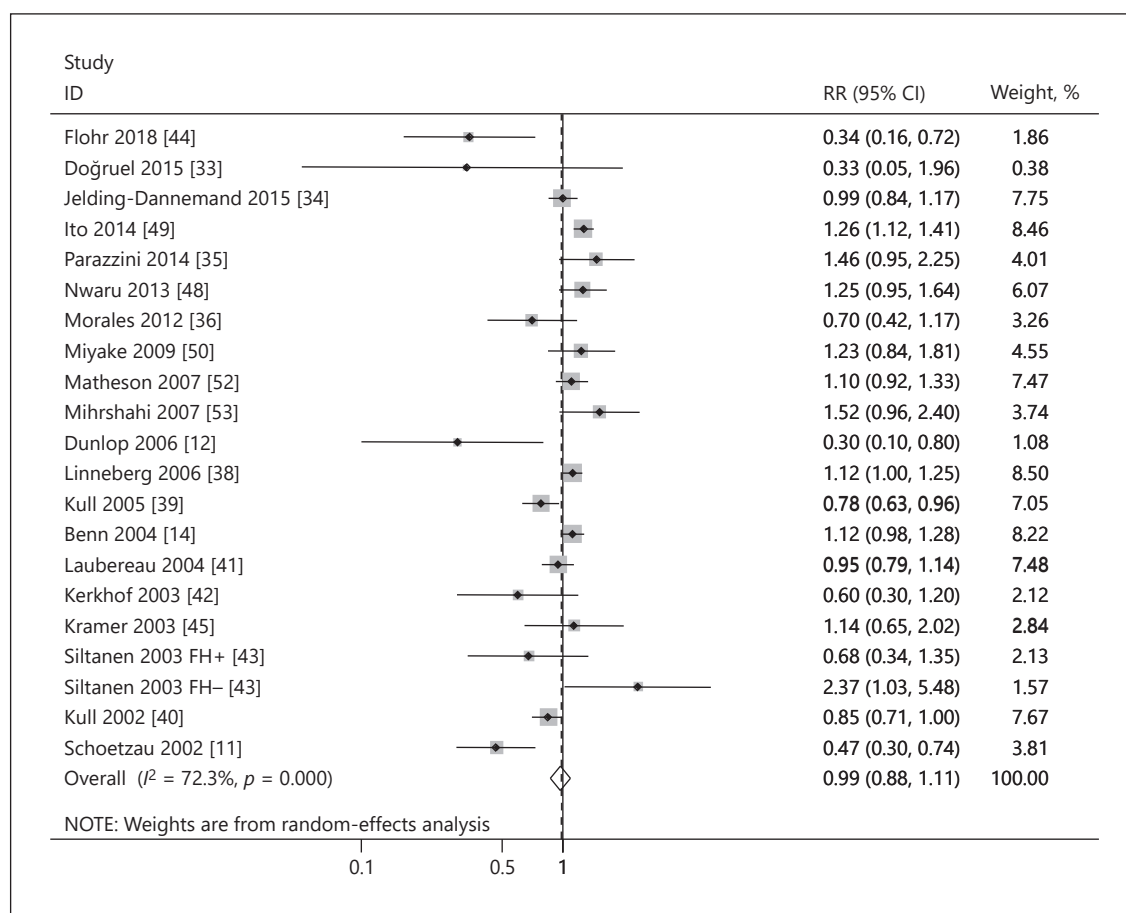


Fig. 4. Meta-analysis of AD and exclusive breastfeeding by reference group. AD, atopic dermatitis; RR, risk ratio; CI, confidence interval; FH, family history.

Publication Bias

There was some evidence of publication bias from visual inspection of the funnel plot (Fig. 5), which indicated the possibility of a small study bias. Both Egger's ($p = 0.067$) and Begg's tests ($p = 0.194$) were not significant. Therefore, no significant publication bias was observed for exclusive breastfeeding. The pooled RR was 0.99 (95% CI 0.88–1.10) after performing the trim-and-fill method, and no study was filled up into the final analysis.

Discussion

In our meta-analysis, we found there was no risk or protective association between breastfeeding (neither total nor exclusive) and AD, whereas providing a weak evidence of protective function of breastfeeding on AD from the cohort with a positive family history (total breastfeed-

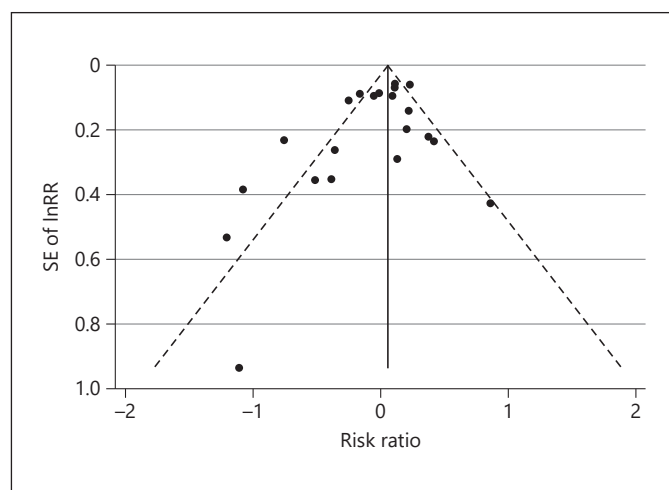
ing: RR 0.85, 95% CI 0.74–0.98; exclusive breastfeeding: RR 0.83, 95% CI 0.70–0.97). In the cohort without an atopic family history, the effect shifted towards the risk side when limited to exclusive breastfeeding (RR 1.19, 95% CI 1.02–1.40) while was attenuated towards null when limited to total breastfeeding (RR 1.11, 95% CI 0.94–1.31). However, these findings should be interpreted with caution because heterogeneity was evident in our studies.

Our results are not equally consistent with previous meta-analyses. An early meta-analysis by Gdalevich et al. [18] estimating the risk of AD and breastfeeding found a protective effect of exclusive breastfeeding with a pooled OR of 0.68. The protective effect was strengthened in the subgroup of children with a family history of atopy (OR 0.58); however, no association was found in children without a family history (OR 0.84). Yang's meta-analysis in 2009 contrasted with the previous meta-analysis, in

Table 4. Exclusive breastfeeding and the risk of AD: subgroup analysis and metaregression

Subgroup	Number of records ^a	RR (95% CI)	Heterogeneity		Metaregression		
			I^2 , %	p value	proportion of between-study variance explained (adj. R^2), %	estimate of between-study variance (τ^2)	p value
Stratified by atopic family history					33.39	0.05	0.01
Yes	13	0.83 (0.70–0.97)*	69.9	<0.01			
No	8	1.19 (1.02–1.40)*	41.4	0.102			
Stratified by reference group					≤0	0.08	0.82
Partial BF	16	0.98 (0.87–1.10)	65.1	<0.01			
Never BF	5	0.99 (0.71–1.37)	82.1	<0.01			
Stratified by income					11	0.06	0.06
High-income country	17	1.02 (0.92–1.14)	71.5	<0.01			
Middle-/low-income country	4	0.49 (0.22–1.10)	67.4	0.027			
Stratified by AD stage ^a					≤0	0.07	0.87
Infantile AD	11	0.92 (0.77–1.10)	70.9	<0.01			
Childhood AD	9	1.08 (0.93–1.25)	70.8	<0.01			
Adult AD	1	0.34 (0.16–0.72)	/	/			
Stratified by AD assessment method					0.03	0.06	0.19
Self-assessment	8	1.12 (1.01–1.24)*	27.1	0.212			
Clinical examination or physician diagnosis	13	0.88 (0.74–1.06)	79.2	<0.01			
Stratified by breastfeeding duration ^a					0.18	0.09	0.35
3–6 months	20	0.99 (0.87–1.12)	76.3	<0.01			
>6 months	4	1.26 (0.92–1.74)	24	0.267			
Stratified by the length of follow-up					≤0	0.08	0.38
>1 year	14	1.02 (0.91–1.14)	72.4	<0.01			
≤1 year	7	0.78 (0.50–1.21)	73.6	<0.01			
Continuous variable							
Publication year	21	1.01 (0.97–1.05)	70.09	/	5.17	0.06	0.55
Sample size	21	1.00 (1.00–1.00)	67.25	/	1.08	0.06	0.43

AD, atopic dermatitis; RR, relative risk; CI, confidence interval; BF, breastfeeding. * $p < 0.05$. ^a If studies reported stratified RRs in accordance with pre-specified covariates, each RR was included into subgroup analysis and meta-regression.

**Fig. 5.** The funnel plot of studies on the association between AD and exclusive breastfeeding. AD, atopic dermatitis; SE, standard error; lnRR, the natural logarithm of risk ratio.

which exclusive breastfeeding did not display a significant protective effect on AD (OR 0.89), even in children with a family history of atopy (OR 0.78). A more recent study by Lodge et al. [20], which included cross-sectional, case-control and cohort studies, showed a protective effect of exclusive breastfeeding on eczema below the age of 2 years. All previous meta-analyses intended to focus on exclusive breastfeeding and AD; nevertheless, they both included several studies that investigated the influence of breastfeeding (not exclusive breastfeeding) on AD. Some of these studies did not describe whether breastfeeding was exclusive or combined [10], and some studies calculated any breastfeeding directly [16]. In order to overcome this problem, our meta-analysis categorized studies into total breastfeeding and exclusive breastfeeding. Since multiple confounders and study designs tended to influence the effect of breastfeeding, our study only adopted adjusted RRs from prospective cohort studies into the fi-

nal meta-analysis, making the results more reasonable. To the best of our knowledge, this is the first meta-analysis for the adjusted association between breastfeeding and AD risk.

In the current meta-analysis, we found the risk of AD was different in cohorts with distinct atopic heredities although the evidence was low. Both total and exclusive breastfeeding was associated with a lower incidence rate of AD in the population with atopic heredity, and the effect shifted towards the harmful side in the population without a family history of atopy. Varying concentrations of IL-4, IL-5 and IL-13 in breast milk from allergic and nonallergic mothers may attribute to some of the controversial effects in different atopic status [55]. However, only 3 included studies reported information regarding maternal allergic condition [10, 39, 47], and we were unable to perform a detailed analysis stratified by maternal atopic status. Another possible reason is that the mother's awareness of developing AD in children with atopic heredity leads to a more delicate management support (e.g., emollient application and avoidance of trigger factors), which is beneficial for AD prevention [56]. Therefore, the decreased risk of AD observed in children with a positive family history may result from primary preventive managements rather than breastfeeding. However, we should realize that it is only our guess but is far from "on the bench" theory.

For both total and exclusive breastfeeding, the effects of breastfeeding on AD were similar when compared with partial breastfeeding or when compared with never breastfeeding. There were no associations found in all groups. Herein, we are against the opinion that "exclusivity" of breastfeeding plays an important role in the reduction of AD risk [57]. Up until now, the biological mechanisms of breast milk on AD development are not well understood, and several mechanisms may attribute to it. One of the well-recognized explanations is that mother's milk contains many immunomodulatory factors that promote the programming of the infant's immune system [58]. A prospective birth cohort study postulated the protective effect of breastfeeding was synergistic with soluble CD14 concentration in human breast milk [10]. Also, breastfeeding reduces the chance for infants to be infected that may stimulate an inappropriate immune response [57]. However, the hygiene hypothesis contrasts this opinion that early infection may be beneficial for maturation of the immune system [59], and breastfeeding is a risk factor of AD for preventing infants from being exposed to common allergens that is critical to develop a functional immune system properly [60]. Since both hy-

potheses can only explain some of the associations observed, they cannot be substantiated comprehensively, and more data are needed to elucidate the underlying mechanism.

Different income levels tend to affect estimations of the association between breastfeeding and AD. Protective effects of both total and exclusive breastfeeding were observed in studies from middle- and low-income countries, although the association did not reach statistical significance. The result was consistent with an earlier study conducted by Lodge et al. [20], and one plausible reason was different early-life exposure to infections. Environmental differences may increase the risk of early infections in children from middle- and low-income countries, and breastfeeding is known as an important factor against early life infections [61].

Generally, AD can be divided into 3 stages: infantile (birth to 2 years of age), childhood (2–12 years of age) and adult AD (older than 12 years) [62]. The characteristics and nature of different AD types are not identified [63]. In the current meta-analysis, we found a reduced risk of AD in infants while it was increased in children. Breastfeeding may protect AD development in infants but not in childhood. Since limited studies were included into the analysis of adult AD, the pooled estimates on adult AD were unreliable. We should notice that all results were not statistically significant and an excessive interpretation is untenable.

The methods used for the AD assessment may influence the result. Our study found that there was no association between breastfeeding and AD diagnosed by physicians or through clinical examination; however, we showed that breastfeeding could slightly increase the risk of self-assessed AD (total breastfeeding: RR 1.08 and exclusive breastfeeding: RR 1.12). This contrasted somewhat with the previous meta-analysis conducted by Yang et al. [19] that a protective effect of breastfeeding was observed when restricted to physician-assessed AD while no association was detected in self-reported AD. The finding may arise from misclassification since for physicians or health personnel the diagnosis of AD is rigidly specified while the diagnostic criteria for self-reported AD are relatively lax. Therefore, it is impossible for us to evaluate the influence of the above changes on the final risk estimates, which is likely to be substantial or even brings the effect to null.

Our meta-analysis also investigated whether the association varied with breastfeeding duration. Since the World Health Organization recommends exclusive breastfeeding for the first 6 months [64], we evaluated the effect of breast-

feeding duration before and beyond 6 months on AD incidence. For total breastfeeding, longer breastfeeding duration would not change the pooled estimate of AD; however, for exclusive breastfeeding, we found an increased risk in the cohort breastfed for more than 6 months. Therefore, we postulate that a longer duration of exclusive breastfeeding may be a risk factor of AD development. As for different follow-up durations, we found an increased risk in groups followed up for <1 year in both total and exclusive breastfeeding groups while the outcomes were highly heterogeneous and were not statistically significant.

Study methodology may contribute substantially to the heterogeneity; however, no randomized controlled trials are found in this study for it is not possible to randomize the breastfeeding practice of mothers. Therefore, our results were derived only from prospective cohort studies. Another possible reason is reverse causation [65], meaning that mothers are likely to extend breastfeeding once their babies present symptoms assumed to be related with sensitization. In our meta-analysis, only 6 studies assessed the influence of reverse causation, and of those that did, the effects considering reverse causation were even varying. It is not clear to us why there are different findings when taking reverse causation into account.

The 2 funnel plots of publication bias indicate a possible evidence of small study bias for there are remarkably few smaller studies that fall into the middle of the cone. It appears that smaller studies have been published if they show either a positive or negative association, but not if there was a null association. Also, this may have led to the issue of high heterogeneity observed within our meta-analyses.

Several limitations of our meta-analysis should be considered. First, heterogeneity is evident in our meta-analysis, which may result from differences in study design, study quality, analysis strategies and baseline characteristics. Although we have tried subgroup analysis and meta-regression to explore potential sources, the heterogeneity is still evidenced across most subsets. Several confounders (e.g., reverse causation) not explored in this study may be the potential sources, and more delicate mathematical models should be developed to address the issue. Second, we include only English publications and full-text publications which may result in publication bias. Moreover, the presence of a small study effect in our study may affect the reliability of outcomes founded in this meta-analysis. Third, the adjusted factors varied with studies while some unadjusted lifestyle factors, for example, maternal probiotic consumption [66] and pets in the household [67], may relate to AD development. Thus, controlling for critical factors is essential to explore the real relationship be-

tween breastfeeding and AD. Finally, because of a relatively small number of studies in subset meta-analyses, we have only conducted the analyses of publication bias over all included studies yet not among subgroups. Therefore, it is likely to have publication bias in subgroup analyses.

In conclusion, we find that breastfeeding, regardless of total or exclusive patterns, has no association with AD risk. There is a weak evidence that exclusive breastfeeding has a protective function on AD from the cohort with a positive family history of atopy; in contrast, it shows a risk effect on AD in those without atopic heredity. The protective association is also observed in the cohort with atopic heredity when total breastfeeding is considered. Therefore, we suggest that breastfeeding recommendations for AD prevention may need to take baseline characteristics into consideration. However, these findings should be interpreted with caution because heterogeneity is evident in our studies. The mechanisms underlying the breastfeed-AD association need to be further explored, which can help develop lifestyle interventions to prevent the occurrence of AD.

Key Message

There is no evidence of an increased or decreased association between atopic dermatitis and breastfeeding.

Statement of Ethics

Not applicable (all data are fully available from published articles; no humans are involved in our study).

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was supported by the Science Foundation of Zhejiang Province (2018C37101; LGD19H110001).

Author Contributions

B.L. and R.D. were involved in study conception and design. R.D., L.L., X.F. and Y.Y. were involved in acquisition of the data. B.L. and R.D. were involved in statistical analysis. B.L., R.D., L.L. and X.F. were involved in analysis and interpretation of the data. R.D. was responsible for manuscript preparation and final approval of the paper.

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