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### Permalink

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### Journal

The American Journal of Clinical Nutrition, 109(Suppl\_7)

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### Publication Date

2019-03-01

### DOI

10.1093/ajcn/nqy283

Peer reviewed

# Infant milk-feeding practices and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span: a systematic review

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## ABSTRACT

**Background:** During the Pregnancy and Birth to 24 Months Project, the USDA and Department of Health and Human Services initiated a review of evidence on diet and health in these populations.

**Objectives:** The aim of these systematic reviews was to examine the relation of 1) never versus ever feeding human milk, 2) shorter versus longer durations of any human milk feeding, 3) shorter versus longer durations of exclusive human milk feeding prior to infant formula introduction, 4) feeding a lower versus higher intensity of human milk to mixed-fed infants, and 5) feeding a higher intensity of human milk by bottle versus breast with food allergies, allergic rhinitis, atopic dermatitis, and asthma.

**Methods:** The Nutrition Evidence Systematic Review team conducted systematic reviews with external experts. We searched CINAHL, Cochrane, Embase, and PubMed for articles published between January 1980 and March 2016, dual-screened the results according to predetermined criteria, extracted data from and assessed the risk of bias for each included study, qualitatively synthesized the evidence, developed conclusion statements, and graded the strength of the evidence.

**Results:** The systematic reviews numbered 1–5 above included 44, 35, 1, 0, and 0 articles, respectively. Moderate, mostly observational, evidence suggests that 1) never versus ever being fed human milk is associated with higher risk of childhood asthma, and 2) among children and adolescents who were fed human milk as infants, shorter versus longer durations of any human milk feeding are associated with higher risk of asthma. Limited evidence does not suggest associations between 1) never versus ever being fed human milk and atopic dermatitis in childhood or 2) the duration of any human milk feeding and allergic rhinitis and atopic dermatitis in childhood.

**Conclusions:** Moderate evidence suggests that feeding human milk for short durations or not at all is associated with higher childhood asthma risk. Evidence on food allergies, allergic rhinitis, and atopic dermatitis is limited. *Am J Clin Nutr* 2019;109(Suppl):772S–799S.

**Keywords:** breastfeeding, human milk, food allergy, atopic dermatitis, allergic rhinitis, asthma, infant, toddler, child, systematic review

## Introduction

Pregnancy and the period from birth to 24 mo (B-24) are sensitive windows during which diet has a particularly strong influence on the life course health trajectory (1). The USDA and Department of Health and Human Services planned the Pregnancy and Birth to 24 Months (P/B-24) Project to begin examining evidence relating diet during pregnancy and the first 2 y of life with growth and health outcomes throughout the life span (2–4).

The systematic reviews (SRs) in this article examine the relationships between infant milk-feeding practices and food

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Published in a supplement to *The American Journal of Clinical Nutrition*. This article is one in a series of systematic reviews completed with support from the USDA's Nutrition Evidence Systematic Review team as part of the Pregnancy and Birth to 24 Months Project. The supplement is sponsored by the USDA Food and Nutrition Service. The Supplement Coordinator for the supplement publication was Joanne M Spahn, USDA Center for Nutrition Policy and Promotion, Alexandria, VA. Supplement Coordinator disclosure: No conflicts of interest or financial ties to disclose. The Guest Editor for this supplement was Pieter J Sauer. Guest Editor disclosure: No conflicts of interest to disclose.

SAA, LB, TJ, KMJ, LAN-R, KOO'B, EO, RP-E, and EEZ contributed equally to this work.

Publication costs for this supplement were defrayed in part by the payment of page charges. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, Editor, or Editorial Board of *The American Journal of Clinical Nutrition*.

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Abbreviations used: B-24, birth to 24 months; DBH, Dampness in Buildings and Health; IgE, immunoglobulin E; ISAAC, International Study of Asthma and Allergy in Childhood; MAS, Multicentre Allergy Study; NESR, Nutrition Evidence Systematic Review; PROBIT, Promotion of Breastfeeding Intervention Trial; SCORAD, Scoring Atopic Dermatitis; SR, systematic review; TEC, Technical Expert Collaborative.

First published online March 28, 2019; doi: <https://doi.org/10.1093/ajcn/nqy283>.

allergies, allergic rhinitis, atopic dermatitis, and asthma. According to the National Institute of Allergy and Infectious Diseases, food allergy affects ~5% of children and ~4% of adults in the United States; however, its prevalence is increasing (5). The Institute reports that atopic dermatitis affects ~30% of the population (6), and the CDC reports that ~8% of the population suffers from asthma (7) and from hay fever (8). Although all atopic diseases can affect quality of life, the prevention of food allergy and asthma is particularly important because these can be life-threatening diseases.

The purpose of this article is to summarize the results of 5 SRs conducted to answer the following questions:

- What is the relationship between never versus ever feeding human milk and food allergies, allergic rhinitis, atopic dermatitis, and asthma?
- What is the relationship between shorter versus longer durations of any human milk feeding and food allergies, allergic rhinitis, atopic dermatitis, and asthma?
- What is the relationship between shorter versus longer durations of exclusive human milk feeding prior to the introduction of infant formula and food allergies, allergic rhinitis, atopic dermatitis, and asthma?
- What is the relationship between feeding a lower versus higher intensity, proportion, or amount of human milk to mixed-fed infants and food allergies, allergic rhinitis, atopic dermatitis, and asthma?
- What is the relationship between feeding a higher intensity, proportion, or amount of human milk by bottle versus by breast and food allergies, allergic rhinitis, atopic dermatitis, and asthma?

## Methods

The Nutrition Evidence Systematic Review (NESR) team (previously the Nutrition Evidence Library, or NEL), which consisted of analysts and librarians who were trained in SR methodology and had advanced degrees in fields such as nutrition and library science, collaborated with a group of subject matter experts, called a Technical Expert Collaborative (TEC), to complete SRs using methods that are described in detail in this supplement (9). TEC members provided individual input on SR materials developed by the NESR staff but did not provide formal group advice or recommendations to the government.

### Scope of the systematic review

TEC members specified the target population, exposures and comparators, outcomes, critical confounding variables, and key definitions for the SRs according to the analytic framework shown in **Figure 1**. In the SRs, “infant milk-feeding practices” referred to the feeding of human milk or infant formula (or a combination). TEC members chose to use the term “human milk feeding” instead of “breastfeeding” for precision. “Breastfeeding” may be understood to mean feeding human milk at the breast when, in fact, feeding method was rarely distinguished by the authors of studies included in the SRs. TEC members intended to examine the feeding of human milk whether or not it was fed at the breast.

For the comparison of never with ever feeding human milk, TEC members did not define any minimum amount for “ever feeding human milk.” Likewise, for the comparisons of shorter with longer durations of any and exclusive human milk feeding, TEC members did not define thresholds for “shorter duration” or “longer duration.” They examined all comparisons of never with ever feeding human milk (or vice versa) and of shorter with longer durations (or vice versa) as defined by the authors of the studies included in the SRs.

The SR question pertaining to the duration of exclusive human milk feeding only examined exclusive human milk feeding preceding the introduction of infant formula. It did not examine the duration of exclusive human milk feeding preceding the time of introduction of complementary foods and beverages (e.g., 4 compared with 6 mo). This was done to avoid overlap with another SR in the P/B-24 Project that examined the timing of the introduction of complementary foods and beverages and its relationship with food allergies, allergic rhinitis, atopic dermatitis, and asthma (10).

### Literature search, screening, and selection

The librarians developed a literature search strategy that used exposure terminology but not outcome terminology (available at <https://nesr.usda.gov>) so that one search could be used to identify literature in support of SRs examining infant milk-feeding practices with several different outcomes (4). The librarians conducted a broad search in CINAHL, Cochrane, Embase, and PubMed using the search date range of January 1980–March 2016. The search excluded articles published before 1980 because the US Congress passed the Infant Formula Act in 1980, which established nutrient requirements for commercial infant formulas in the United States and thus health effects associated with formula consumption before 1980 might be different (11).

TEC members defined inclusion and exclusion criteria a priori (**Table 1**), which NESR analysts used to dual-screen the search results and the results of a manual search of the references of included articles and existing SRs. TEC members reviewed the search terms and list of included articles to ensure completeness of the body of evidence.

### Data extraction and risk-of-bias assessment

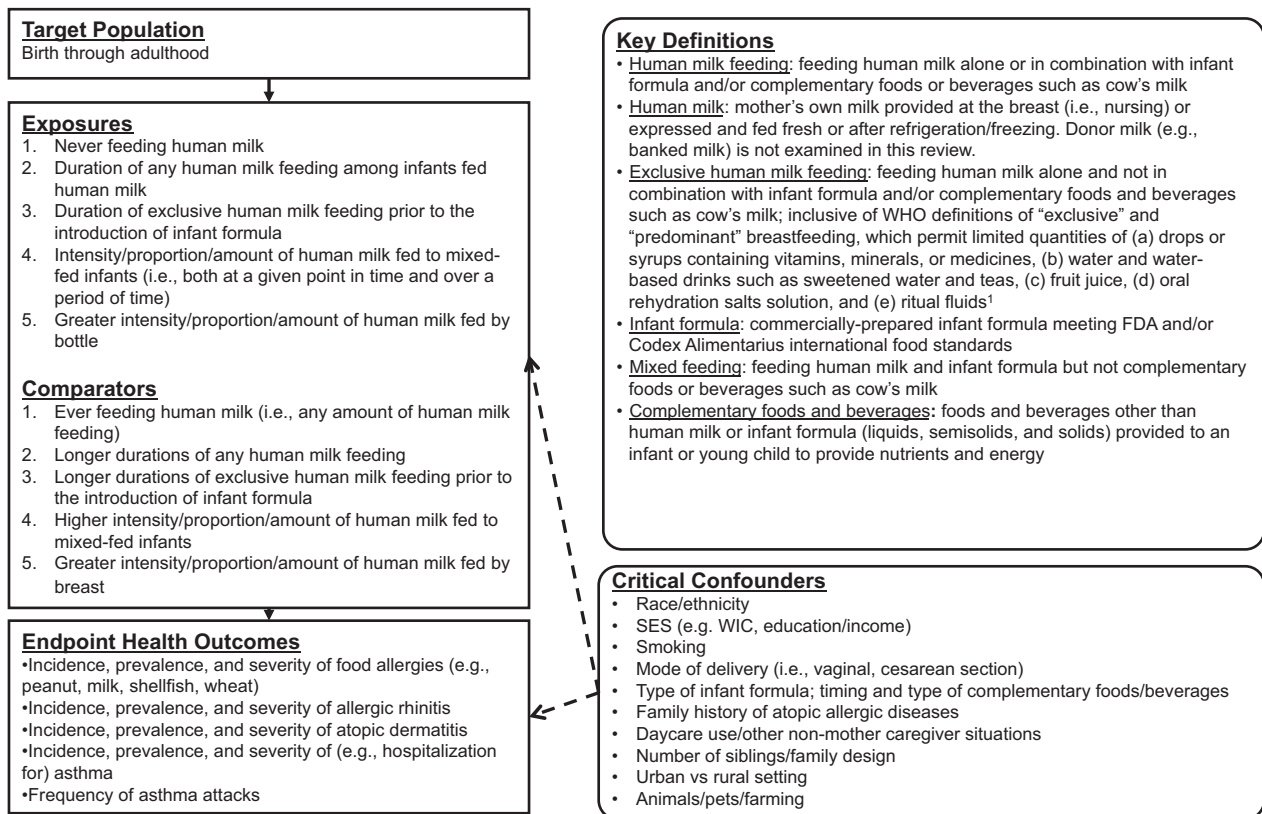
NESR analysts assembled a table of systematically extracted data from each article included in the SRs (i.e., study characteristics, sample characteristics, exposures and outcomes, risks of bias, and funding sources). Two NESR analysts independently completed the NEL Bias Assessment Tool for each article to identify the risks of bias (9) (<https://nesr.usda.gov>).

### Evidence synthesis, conclusion statement development, and grading the strength of the evidence

NESR analysts and TEC members engaged in a series of conference calls to review, discuss, and synthesize the evidence by age group. TEC members examined both significant and nonsignificant associations (e.g., ORs and CIs) for a thorough synthesis of the evidence. To answer the SR questions, conclusion statements were carefully constructed to accurately reflect the synthesis of evidence. Conclusion statements do not draw

### Systematic review questions:

1. What is the relationship between never vs. ever feeding human milk and food allergies, allergic rhinitis, atopic dermatitis, and asthma?
2. What is the relationship between shorter vs. longer durations of any human milk feeding and food allergies, allergic rhinitis, atopic dermatitis, and asthma?
3. What is the relationship between shorter vs. longer durations of exclusive human milk feeding prior to the introduction of infant formula and food allergies, allergic rhinitis, atopic dermatitis, and asthma?
4. What is the relationship between feeding a lower vs. higher intensity/proportion/amount of human milk to mixed-fed infants and food allergies, allergic rhinitis, atopic dermatitis, and asthma?
5. What is the relationship between feeding a higher intensity/proportion/amount of human milk by bottle vs. by breast vs. and food allergies, allergic rhinitis, atopic dermatitis, and asthma?



**FIGURE 1** Analytic framework for the systematic reviews on infant milk-feeding practices and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span. This framework illustrates the overall scope of the project, including the population, exposures, and comparators and outcomes of interest. It also includes definitions for key terms and identifies key confounders considered in the systematic review. <sup>1</sup>WHO. Indicators for assessing infant and young child feeding practices: conclusions of a consensus meeting held 6–8 November 2007 in Washington D.C. Geneva (Switzerland): WHO; 2008. FDA, Food and Drug Administration; SES, socioeconomic status; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

implications, nor should they be interpreted to be dietary guidance. The strength of the evidence underlying each conclusion statement was graded strong, moderate, limited, or grade not assignable according to the NESR grading rubric (9) (<https://nesr.usda.gov>), which takes into consideration the internal validity, consistency, adequacy, impact, and generalizability of the evidence. Finally, TEC members identified research recommendations.

## Results

The literature search yielded 31,335 articles, and the bodies of evidence for the 5 SRs on infant milk-feeding practices and food allergies, allergic rhinitis, atopic dermatitis, and asthma comprise 73 articles. A table of articles excluded during full-text screening, with the rationale for exclusion, is available at <https://nesr.usda.gov>.

None of the included articles examined the intensity, proportion, or amount of human milk fed to mixed-fed infants or fed by bottle versus by breast, and only 1 article (12) examined the duration of exclusive human milk feeding prior to the introduction of infant formula. Additional information about these 3 SRs is available at <https://nesr.usda.gov>. Herein, we present evidence for the remaining 2 SRs:

- What is the relationship between never versus ever feeding human milk and food allergies, allergic rhinitis, atopic dermatitis, and asthma?
- What is the relationship between shorter versus longer durations of any human milk feeding and food allergies, allergic rhinitis, atopic dermatitis, and asthma?

**TABLE 1** Inclusion and exclusion criteria established for the selection of studies to include in the systematic reviews on infant milk-feeding practices and food allergies, allergic rhinitis, atopic dermatitis, and asthma<sup>1</sup>

Category	Inclusion criteria	Exclusion criteria
Study design	Randomized controlled trials; nonrandomized controlled trials; prospective cohort studies; retrospective cohort studies; case-control studies	Cross-sectional studies; before-and-after studies; uncontrolled studies; narrative reviews; systematic reviews; meta-analyses
Publication status	Published in peer-reviewed journals	Gray literature, including unpublished data, manuscripts, reports, abstracts, and conference proceedings
Language	Published in English	Published in languages other than English
Date range	Published 1980–December 2015 <sup>2</sup>	Published prior to 1980
Source of foods, beverages, or nutrients	Human milk: mother's own milk (MOM), i.e., human milk fed at the breast or expressed and fed fresh or after refrigeration/freezing; infant formula: commercially prepared infant formula meeting FDA (87) or Codex Alimentarius (88) food standards	Human milk from third parties (e.g., banked/donor milk); infant formulas that are not commercially prepared or that do not meet FDA (87) or Codex Alimentarius (88) food standards
Study setting	Countries listed as Very High or High on the 2014 Human Development Index <sup>3</sup> (86)	Countries listed as Medium or Low on the 2014 Human Development Index (86)
Study participants	Human participants; males, females	Nonhuman participants (e.g., animal studies, in vitro studies); hospitalized patients, not including birth and immediate postpartum hospitalization of healthy infants
Age of study participants	Exposure age: infants (0–12 mo), toddlers (12–24 mo); outcome age: infants (0–12 mo) and toddlers (12–24 mo) for food allergies, allergic rhinitis, and atopic dermatitis, and children (2–12 y), adolescents (13–18 y), and adults (≥19 y) for all outcomes	Outcome age: infants (0–12 mo) and toddlers (12–24 mo) for asthma outcomes, only, as outcomes in this age group may represent transient recurrent wheeze (89)
Size of study groups	Studies with ≥ 30 participants per study group or a power analysis indicating that the study is appropriately powered for the outcome(s) of interest	Studies with <30 participants per study group with no power analysis indicating that the study is appropriately powered for the outcome(s) of interest
Health status of study participants	Studies done in generally healthy populations; studies done in populations where infants were full term (≥37 and 0/7 wk gestational age); studies done in populations with elevated chronic disease risk, or that enroll some participants with a disease or with the health outcome of interest	Studies that exclusively enroll participants with a disease or the health outcome of interest; studies done in hospitalized participants (except for birth and immediate postpartum hospitalization of healthy infants) or malnourished participants; studies in exclusively preterm infants (gestational age <37 wk), exclusively infants who have low birth weight (<2500 g) or exclusively infants who are small for gestational age

<sup>1</sup>FDA, Food and Drug Administration.

<sup>2</sup>In 1980 the Infant Formula Act was passed (11) and December 2015 was when the literature search was performed.

<sup>3</sup>When a country was not included in the Human Development Index ranking, country classification from the World Bank was used instead.

### Never versus ever feeding human milk and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span

Forty-four articles met the inclusion criteria for this SR question (12–55). None examined food allergies or atopic dermatitis in adolescence or adulthood, allergic rhinitis in age groups other than childhood, or asthma in adulthood, and TEC members concluded that the scant evidence with methodologic limitations was insufficient to determine whether never versus ever being fed human milk is associated with food allergies from birth through childhood (13–17), allergic rhinitis in childhood (18, 19), or asthma in adolescence (20). Additional information about these topics is available at <https://nesr.usda.gov>. Evidence about asthma in childhood and atopic dermatitis from birth through childhood is presented below.

#### Asthma in childhood.

Twenty-one articles presented evidence about never versus ever being fed human milk and asthma in childhood (17–19, 21–38) (Table 2). The evidence differed between the studies that

included children only and the studies that included children as well as adolescents.

*Evidence in children only.* Nineteen articles examined asthma in children only (17–19, 21–36). These articles presented evidence from 14 prospective cohort studies (18, 19, 21, 22, 25, 26, 28, 29, 31–36), 1 additional cohort study with prospective and retrospective analyses in separate articles (17, 30), 1 nested case-control study (27), and 1 case-control study with unique evidence across 2 articles (23, 24) (i.e., there were 17 independent studies in total). Data about infant milk-feeding practices were collected from parent report by questionnaire, interview, or diary, and studies compared infants who never consumed human milk with infants ever fed human milk (17, 19, 21–25, 29–31, 34, 36), fed human milk for heterogeneous ranges of duration (18, 26–28, 31–33, 35), and fed human milk exclusively for ≥3 mo (25) or until weaning (36). Asthma outcomes were based on medical record (23–25, 27, 30), clinical assessment (19, 26, 29), parent report of a diagnosis or symptoms (17–19, 22, 28–30, 32–36), and parent report via the validated instrument (56) from the International Study of Asthma and Allergy in Childhood (ISAAC) (18, 31).



**TABLE 2** Evidence examining the relationship between never versus ever feeding human milk and asthma in childhood<sup>1</sup>

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Never vs. ever feeding human milk exposure <sup>2</sup>	Significant associations with asthma	Nonsignificant associations with asthma
Arshad, 2005 (21)	Prospective cohort (IOW)	UK	<i>n</i> = 1373 Baseline: birth Sex: NR Race/ethnicity: NR	Exclusive FF vs. not	None	Current diagnosis of asthma at 10 y: NS (data NR)
Burr, 1993 (19)	Prospective cohort <sup>3</sup>	UK	<i>n</i> = 453 Baseline: birth Race/ethnicity: NR Risk: 100% family history (parent or sibling)	Ever BF vs. never BF	None	Proportion of infants ever BF vs. never BF with asthma by 7 y (parents' report): 23% vs. 20%, NS
Colen, 2014 (37)	Prospective cohort (National Longitudinal Study of Youth 1979 Cohort)	USA	<i>n</i> = 8237 in the full sample, 7319 in the sibling subsample, 1773 in the discordant sibling subsample (i.e., siblings fed differently in infancy) Baseline: birth Race/ethnicity: 74.49% non-Hispanic white, 17.28% non-Hispanic black, 8.23% Hispanic	BF vs. not BF	Asthma at 4–14 y (full sample between-family estimate): $\beta$ = 0.261 (SE = 0.106), <i>P</i> < 0.05 Asthma at 4–14 y (sibling subsample between-family estimate): $\beta$ = 0.237 (SE = 0.117), <i>P</i> < 0.05	Proportion of infants ever BF vs. never BF with asthma by 7 y (diagnosis): 27% vs. 34%, NS Proportion of infants BF vs. not BF with asthma at 4–14 y (discordant sibling subsample): 7.95% vs. 8.89%, NS Asthma at 4–14 y (sibling subsample within-family estimate): $\beta$ = 0.023 (SE = 0.222), NS
Hillemeier, 2015 (22)	Prospective cohort (ECLS-B)	USA	<i>n</i> = 6900 Baseline: birth Race/ethnicity: ~53% non-Hispanic white, ~11.5% Mexican with $\geq$ 1 foreign-born parent, ~7% Mexican with 2 US-born parents, ~7% other Hispanic, ~14% African American, ~2.5% Asian American, ~4.5% other race	BF vs. FF	None	Asthma diagnosis by age 60 mo: OR: 0.87 (95% CI: 0.70, 1.07) Number of asthma attacks from 24 to 60 mo among children with asthma: $\beta$ = -0.20, NS Taking prescription medicine for asthma at 48 or 60 mo among children with asthma: OR: 0.90, NS Asthma hospitalization or emergency room visit from 24 to 60 mo among children with asthma: OR: 0.62, <i>P</i> < 0.1
Infante-Rivard 1993 (23)	Case-control	Canada	<i>n</i> = 457 cases, 457 controls Baseline: 3–4 y Race/ethnicity: NR	No BF vs. BF	Asthma at age 3–4 y: OR: 1.47 (95% CI: 1.02, 2.13)	None
Infante-Rivard, 2001 (24)	Case-control	Canada	<i>n</i> = 404 cases from the 1993 study (294 with persistent asthma, 110 with transient asthma), 457 controls Baseline: 3–4 y Race/ethnicity: NR	No BF vs. any duration of BF	None	Persistent asthma from age 3–4 to 9–11 y: OR: 1.30 (95% CI: 0.85, 2.01) Transient asthma from age 3–4 to 9–11 y: OR: 1.17 (95% CI: 0.60, 2.28)
Larsson, 2008 (18)	Prospective cohort (DBH)	Sweden	<i>n</i> = 4779 in the full sample without asthma at baseline, 3320 in the subsample without wheezing at baseline, 935 in the subsample with wheezing at baseline Baseline: 1–4 y Race/ethnicity: NR	No BF vs. BF > 6 mo	5-y cumulative incidence of asthma by age 6–9 y in the full sample with no asthma at baseline: OR: 2.64 (95% CI: 1.28, 5.46) 5-y cumulative incidence of asthma by age 6–9 y in the subsample with no asthma and no wheezing ever at baseline: OR: 2.64 (95% CI: 1.18, 5.93)	None

(Continued)

TABLE 2 (Continued)

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Never vs. ever feeding human milk exposure <sup>2</sup>	Significant associations with asthma	Nonsignificant associations with asthma
Leung, 2016 (25)	Prospective cohort (Children of 1997 Birth Cohort)	Hong Kong	n = 8301 Baseline: first postnatal visit Race/ethnicity: NR	Partially BF for any length of time or EBF <3 mo vs. never BF	5-y cumulative incidence of asthma by age 6-9 y in the subsample with no asthma, but with wheezing at baseline: OR: 4.08 (95% CI: 1.21, 13.72) None	Public hospital admissions for asthma from >3 mo to 12 y: HR: 1.12 (95% CI: 0.87, 1.43) Public hospital admissions for asthma from >3 mo to 2 y: HR: 0.63 (95% CI: 0.32, 1.25) Public hospital admissions for asthma from >2 to 6 y: HR: 1.14 (95% CI: 0.85, 1.53) Public hospital admissions for asthma from >3 mo to 6 y: HR: 1.03 (95% CI: 0.79, 1.35) Public hospital admissions for asthma from >6 to 12 y: HR: 0.87 (95% CI: 0.41, 1.83) Public hospital admissions for asthma from >3 mo to 12 y: HR: 1.27 (95% CI: 0.82, 1.98) Public hospital admissions for asthma from >3 mo to 2 y: HR: 1.69 (95% CI: 0.64, 4.50) Public hospital admissions for asthma from >2 to 6 y: HR: 1.11 (95% CI: 0.64, 1.90) Public hospital admissions for asthma from >3 mo to 6 y: HR: 1.19 (95% CI: 0.74, 1.92) Public hospital admissions for asthma from >6 to 12 y: HR: 1.05 (95% CI: 0.35, 3.19) Allergic asthma at 6 y: OR: 0.385 (95% CI: 0.145, 1.003)
Maas, 2011 (26)	Prospective cohort <sup>3</sup> (PREVASC)	Netherlands	n = 387 Baseline: Birth Race/ethnicity: NR	BF 1-11 wk vs. BF 0 wk BF 12-25 wk vs. BF 0 wk BF ≥26 wk vs. BF 0 wk	None Allergic asthma at 6 y: OR: 0.247 (95% CI: 0.093, 0.655) None	None Allergic asthma at 6 y: OR: 0.523 (95% CI: 0.187, 1.458) None
Martel, 2009 (27)	Nested case-control	Canada	n = 745 cases, 833 controls Baseline: birth Sex: NR Race/ethnicity: NR Risk: 85% family history (mothers)	BF <6 mo vs. no BF BF ≥6 mo vs. no BF	Asthma in childhood (maximum age 10 y): OR: 0.70 (95% CI: 0.53, 0.92) None	Asthma in childhood (maximum age 10 y): OR: 0.77 (95% CI: 0.57, 1.03)
Młodzi, 2010 (28)	Prospective cohort (NLSYC ECD)	Canada	n = 8499 Baseline: <2 y Race/ethnicity: NR	BF 0-3 mo vs. never BF BF >3 mo vs. never BF	None Asthma at 2-5 y: HR: 0.82 (95% CI: 0.69, 0.97)	Asthma at 2-5 y: HR: 0.85 (95% CI: 0.70, 1.00) None

(Continued)

TABLE 2 (Continued)

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Never vs. ever feeding human milk exposure <sup>2</sup>	Significant associations with asthma	Nonsignificant associations with asthma
Mirshahri, 2007 (29)	Prospective cohort <sup>3</sup> (CAPS)	Australia	<i>n</i> = 516 Baseline: birth Sex: NR Race/ethnicity: NR	Ever BF vs. never BF	None	Probable current asthma at 5 y: OR: 0.59 (95% CI: 0.30, 1.16)
Miller, 2001 (30)	Prospective or retrospective cohort depending on the analysis (NMIHS/LF)	USA	<i>n</i> = 3883 Baseline: birth Race/ethnicity: 55.0% non-Hispanic white, 45.0% non-Hispanic black	BF vs. no BF	Asthma by 3 y (maternal report): OR: 0.68 (95% CI: 0.49, 0.97)	Asthma by 3 y (physician report from retrospective medical chart review): OR: 0.94 (95% CI: 0.70, 1.26)
Miner, 2004 (17)	Prospective cohort (NMIHS/LF)	USA	<i>n</i> = 8073 Baseline: birth Race/ethnicity: 51% black, 46% white, 3% other	Ever BF vs. never BF	Asthma at 3 y (maternal report): OR: 0.61 (95% CI: 0.52, 0.71)	None
Nwaru, 2013 (31)	Prospective cohort (SEATON)	UK	<i>n</i> = 934, subsamples with and without family history of atopy NR Baseline: birth Race/ethnicity: NR	Ever BF vs. no BF	None	Asthma by 10 y: OR: 0.81 (95% CI: 0.59, 1.13) Asthma up to age 10 y in subsample with no family history of atopy: OR: 0.80 (95% CI: 0.42, 1.55) Asthma up to age 10 y in subsample with family history of atopy: OR: 0.78 (95% CI: 0.53, 1.14) Asthma by 10 y: OR: 0.90 (95% CI: 0.61, 1.35) Asthma up to age 10 y in subsample with no family history of atopy: OR: 1.25 (95% CI: 0.59, 2.66)
Orivuori, 2014 (32)	Prospective cohort (PASTURE)	Finland, France, Germany, Switzerland	<i>n</i> = 853 Baseline: birth Race/ethnicity: NR	BF $\geq$ 2.25 mo vs. no BF	None	Asthma up to age 10 y in subsample with family history of atopy: OR: 0.77 (95% CI: 0.49, 1.23) Asthma by 10 y: OR: 0.76 (95% CI: 0.53, 1.09) Asthma up to age 10 y in subsample with no family history of atopy: OR: 0.58 (95% CI: 0.27, 1.23)
Rosas-Salazar, 2015 (38)	Case-control	USA	<i>n</i> = 509 cases, 618 controls Baseline: mean: 10 y (range: 6–14 y) Race/ethnicity: 100% Puerto Rican	BF $\geq$ 2.25 mo vs. no BF	None	Asthma up to age 10 y in subsample with family history of atopy: OR: 0.77 (95% CI: 0.51, 1.17) Asthma at 4 y: OR: 1.22 (95% CI: 0.32, 4.63) Asthma between 4 and 6 y: OR: 0.69 (95% CI: 0.22, 2.21)
				Never BF vs. BF > 6 mo	None	None
				BF 0–6 mo vs. no BF	Asthma at 6–14 y: OR: 0.7 (95% CI: 0.5, 1.0), <i>P</i> = 0.04	None
				BF > 6 mo vs. no BF	None	Asthma at 6–14 y: OR: 1.5 (95% CI: 1.0, 2.4), <i>P</i> = 0.06
				BF 0–2 mo vs. no BF	Asthma at 6–14 y: OR: 0.6 (95% CI: 0.5, 0.9)	None

(Continued)



TABLE 2 (Continued)

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Never vs. ever feeding human milk exposure <sup>2</sup>	Significant associations with asthma	Nonsignificant associations with asthma
Scholten, 2009 (33)	Prospective cohort (PIAMA)	Netherlands	n = 3 115 in the full sample, 2238 in the subsample with nonallergic mothers, 877 in the subsample with allergic mothers Baseline: birth Race/ethnicity: NR	BF 2-4 mo vs. no BF BF 4-6 mo vs. no BF BF 6-8 mo vs. no BF BF 8-10 mo vs. no BF BF 10-12 mo vs. no BF BF > 12 mo vs. no BF BF 1-16 wk vs. no BF  BF > 16 wk vs. no BF	None None None None None None None  Asthma at 3 y: OR: ~0.65 (95% CI: ~0.50, ~0.85) Asthma at 3 y in subsample with nonallergic mothers: OR: ~0.70 (95% CI: ~0.50, ~1.00) Asthma at 3 y in subsample with allergic mothers: OR: ~0.55 (95% CI: ~0.35, ~0.90) Asthma at 5 y: OR: ~0.50 (95% CI: ~0.35, ~0.90) Asthma at 5 y in subsample with nonallergic mothers: OR ~0.70 (95% CI: ~0.50, ~1.00) Asthma at 6 y: OR: ~0.60 (95% CI: ~0.45, ~0.80) Asthma at 6 y in subsample with nonallergic mothers: OR: ~0.50 (95% CI: ~0.35, ~0.75) Asthma at 7 y: OR: ~0.65 (95% CI: ~0.50, ~0.90) Asthma at 7 y in subsample with non-allergic mothers: OR: ~0.65 (95% CI: ~0.45, ~0.95) Asthma at 8 y: OR: 0.57 (95% CI: 0.41, 0.80); chronic asthma by 8 y: OR: 0.65 (95% CI: 0.44, 0.96) Asthma at 8 y in subsample with nonallergic mothers: OR: ~0.50 (95% CI: ~0.35, ~0.75)	Asthma at 6-14 y: OR: 0.9 (95% CI: 0.6, 1.3) Asthma at 6-14 y: OR: 0.6 (95% CI: 0.2, 1.8) Asthma at 6-14 y: OR: 1.6 (95% CI: 0.9, 3.0) Asthma at 6-14 y: OR: 2.9 (95% CI: 0.3, 25.2) Asthma at 6-14 y: OR: 1.5 (95% CI: 0.6, 3.4) Asthma at 6-14 y: OR: 1.4 (95% CI: 0.6, 3.1) Asthma at 8 y: OR: 0.82 (95% CI: 0.61, 1.09) Chronic asthma by 8 y: OR: 0.87 (95% CI: 0.62, 1.24) Asthma at 4 y: OR: ~0.80 (95% CI: ~0.60, ~1.05) Asthma at 4 y in subsample with nonallergic mothers: OR: ~0.75 (95% CI: ~0.55, ~1.10) Asthma at 4 y in subsample with allergic mothers: OR: ~0.85 (95% CI: ~0.50, ~1.35) Asthma at 5 y in subsample with allergic mothers: OR: ~0.60 (95% CI: ~0.40, ~1.05) Asthma at 6 y in subsample with allergic mothers: OR: ~0.75 (95% CI: ~0.45, ~1.30) Asthma at 7 y in subsample with allergic mothers: OR: ~0.65 (95% CI: ~0.40, ~1.10) Asthma at 8 y in subsample with allergic mothers: OR: ~0.80 (95% CI: ~0.50, ~1.35)

(Continued)

TABLE 2 (Continued)

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Never vs. ever feeding human milk exposure <sup>2</sup>	Significant associations with asthma	Nonsignificant associations with asthma
Sunyer, 2006 (34)	Prospective cohort	Spain	n = 462 Baseline: birth Sex: NR	BF vs. no BF	Asthma at 6.5 y: OR: 0.33 (95% CI: 0.08, 0.87)	None
van Beijsterveldt, 2008 (35)	Prospective cohort	Netherlands	n = 23,444 Baseline: birth Sex: NR	BF 0.5–3 mo vs. no BF BF > 3 mo vs. no BF	None None	Asthma by 5 y: OR: 0.96 (95% CI: 0.83, 1.09) Asthma by 5 y: OR: 0.92 (95% CI: 0.79, 1.08)
Wilson, 1998 (36)	Prospective cohort (Dundee Infant Feeding Study)	UK	n = 545 Baseline: birth Race/ethnicity: NR	Bottle feeding vs. partial BF Bottle feeding vs. EBF	None Percentage probability of asthma by 7 y: 18.6% (95% CI: 17.2%, 20.0%) vs. 21.7% (95% CI: 17.3%, 26.1%) None	Percentage probability of asthma by 7 y: 18.6% (95% CI: 17.2%, 20.0%) vs. 21.7% (95% CI: 17.3%, 26.1%) None

<sup>1</sup>  $\beta$ , regression coefficient; BF, breastfed/breastfeeding; CAPS, Childhood Asthma Prevention Study; DBH, Dampness in Buildings and Health; EBF, exclusively breastfed/exclusive breastfeeding; ECLS-B, Early Childhood Longitudinal Study Birth Cohort; FF, formula fed/formula feeding; IOW, Isle of Wight; NLSY ECD, Canadian National Longitudinal Study of Children and Youth Early Childhood Development Cohort; NMIHS/LF, 1988 National Maternal and Infant Health Survey and 1991 Longitudinal Follow-up; NR, not reported; PASTURE, Protection Against Allergy Study in Rural Environments; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; PREVASC, Prevention of Asthma in Children; ref, reference; SEATON, Study of Eczema and Asthma to Observe the Influence of Nutrition; SR, systematic review.

<sup>2</sup>Exposures, as defined by the authors of the studies included in the body of evidence, which address never versus ever feeding human milk or vice versa.

<sup>3</sup>The cohort was sampled from a randomized controlled trial; however, the data of interest for this SR are unrelated to randomization.

<sup>4</sup>Study authors stated that there were no differences between feeding groups but the CIs do not overlap.

**TABLE 3** Evidence examining the relationship between never versus ever feeding human milk and atopic dermatitis from birth to 24 mo<sup>1</sup>

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Never vs. ever feeding human milk exposure <sup>2</sup>	Significant associations with atopic dermatitis	Nonsignificant associations with atopic dermatitis
Burr, 1989 (39)	Prospective cohort <sup>3</sup>	UK	n = 483 Baseline: birth Race/ethnicity: NR Risk: 100% family history (parent or sibling)	BF at some time vs. never BF	None	Proportion of infants BF at some time vs. never BF with eczema symptoms by 12 mo: 35% vs. 40%, NS
Chuang, 2011 (40)	Prospective cohort (TBCS)	Taiwan	n = 20,172 Baseline: birth Race/ethnicity: NR Risk: 0% with atopic dermatitis by 6 mo (exclusion criterion)	BF ≤1 mo vs. no BF BF ≤2 mo vs. no BF BF ≤6 mo vs. no BF BF ≤12 mo vs. no BF BF > 12 mo vs. no BF	Atopic dermatitis between 6 and 18 mo: OR: 1.25 (95% CI: 1.00, 1.56), P = 0.049 Atopic dermatitis between 6 and 18 mo: OR: 1.37 (95% CI: 1.08, 1.74), P = 0.009 Atopic dermatitis between 6 and 18 mo: OR: 1.47 (95% CI: 1.17, 1.84), P = 0.001 Atopic dermatitis between 6 and 18 mo: OR: 1.44 (95% CI: 1.11, 1.87), P = 0.006 Atopic dermatitis between 6 and 18 mo: OR: 1.49 (95% CI: 1.15, 1.93), P = 0.003	None
Harris, 2001 (41)	Prospective cohort	UK	n = 624 Baseline: birth Race/ethnicity: NR	Ever BF vs. never BF	None	Doctor-diagnosed eczema by 2 y: OR: 0.97 (95% CI: 0.64, 1.47), P = 0.89 Visible dermatitis by 2 y: OR: 1.25 (95% CI: 0.67, 2.35), P = 0.47 Maternally reported eczema by 2 y: OR: 0.93 (95% CI: 0.63, 1.36), P = 0.71 Eczema from birth to 13 wk: $\chi^2$ : 2.36 (95% CI: NR), NS Eczema from 14 to 26 wk: $\chi^2$ : 1.52 (95% CI: NR), NS Eczema from 27 to 39 wk: $\chi^2$ : 0.02 (95% CI: NR), NS Eczema from 40 to 52 wk: $\chi^2$ : 0.15 (95% CI: NR), NS Eczema from birth to 13 wk: $\chi^2$ : 0.77 (95% CI: -3.2, 2.4) Eczema from 14 to 26 wk: $\chi^2$ : 0.89 (95% CI: -1.3, 6.6) Eczema from 27–39 wk: $\chi^2$ : 0.58 (95% CI: -3.6, 3.6) Eczema from 40 to 52 wk: $\chi^2$ : 0.12 (95% CI: -3.5, 4.6)
Howie, 1990 (42)	Prospective cohort	UK	n = 617 Baseline: birth Sex: NR Race/ethnicity: NR	Bottle feeders (FF) vs. early weaners (BF < 13 wk)	None	
Ivakhnenko, 2013 (13)	Nonrandomized controlled trial <sup>4</sup>	Ukraine	n = 104 Baseline: birth Sex: NR Race/ethnicity: NR	Bottle feeders (FF) vs. breast feeders (BF ≥ 13 wk)	None	
Mallet, 1992 (43)	Prospective cohort <sup>3</sup>	France	n = 139 Baseline: birth Sex: NR Race/ethnicity: NR Risk: 100% family history (≥ 1 parent or sibling)	BF vs. standard FF FF alone vs. FF with BF	Proportion of infants BF vs. standard FF with atopic dermatitis during the first 18 mo: 3.92% vs. 16.98%, P < 0.05	Eczema at 2 y: NS (data NR)
Miskelly, 1988 (44)	Prospective cohort <sup>3</sup>	UK	n = 487 Baseline: birth Race/ethnicity: NR Risk: 100% family history (≥ 1 parent or sibling)	Ever BF vs. never BF	None	Eczema in the first year of life: 35% vs. 40%, NS

(Continued)

TABLE 3 (Continued)

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Never vs. ever feeding human milk exposure <sup>2</sup>	Significant associations with atopic dermatitis	Nonsignificant associations with atopic dermatitis
Morales, 2012 (45)	Prospective cohort (INMA Project)	Spain	n = 580 Baseline: birth Race/ethnicity: NR	Predominant BF <2 mo vs. never BF	None	Atopic eczema from birth to 6 mo: OR: ~0.7 (95% CI: ~0.3, ~1.5) Atopic eczema from 7 to 14 mo: OR: ~0.6 (95% CI: ~0.3, ~1.3) Recurrent atopic eczema from birth-6 mo to 7-14 mo: OR: ~0.4 (95% CI: ~0.0, ~1.3) Atopic eczema from 0 to 14 mo: OR: 0.67 (95% CI: 0.33, 1.36) Atopic eczema from 7 to 14 mo in subsample of infants with onset ≥7 mo: OR: 0.75 (95% CI: 0.27, 2.08) Atopic eczema from birth to 6 mo: OR: ~0.9 (95% CI: ~0.4, ~1.9) Atopic eczema from 7 to 14 mo: OR: ~0.8 (95% CI: ~0.4, ~1.5) Recurrent atopic eczema from birth-6 mo to 7-14 mo: OR: ~0.6 (95% CI: ~0.2, ~1.7) Atopic eczema from 0 to 14 mo: OR: 0.90 (95% CI: 0.48, 1.69) Atopic eczema from 7 to 14 mo in subsample of infants with onset ≥7 mo: OR: 0.95 (95% CI: 0.37, 2.44) Atopic eczema from birth to 6 mo: OR: ~0.7 (95% CI: ~0.4, ~1.3) Atopic eczema from 7 to 14 mo: OR: ~0.6 (95% CI: ~0.3, ~1.1) Recurrent atopic eczema from birth-6 mo to 7-14 mo: OR: ~0.5 (95% CI: ~0.2, ~1.1) Atopic eczema from 0 to 14 mo: OR: 0.72 (95% CI: 0.42, 1.22) Atopic eczema from 7 to 14 mo in subsample of infants with onset ≥7 mo: OR: 0.74 (95% CI: 0.34, 1.63) Atopic eczema from 7 to 14 mo: OR: ~0.6 (95% CI: ~0.2, ~1.4) Recurrent atopic eczema from birth-6 mo to 7-14 mo: OR: ~0.7 (95% CI: ~0.2, ~2.0) Atopic eczema from 0 to 14 mo: OR: 0.64 (95% CI: 0.28, 1.44) Atopic eczema from 7 to 14 mo in subsample of infants with onset ≥7 mo: OR: 0.42 (95% CI: 0.11, 1.57) Atopic dermatitis up to 2 y: OR: 0.84 (95% CI: 0.40, 1.76)
Orivuori, 2014 (32)	Prospective cohort (PASTURE)	Finland, France, Germany, Switzerland	n = 853 Baseline: birth Race/ethnicity: NR	Never BF vs. BF >6 mo	None	
Parazzini, 2014 (46)	Prospective cohort	Italy	n = 796 Baseline: birth Race/ethnicity: NR	BF only vs. no BF BF/other milks vs. no BF	None None	12-mo incidence of atopic dermatitis at 12 mo: RR: 1.34 (95% CI: 0.90, 2.02) 12-mo incidence of atopic dermatitis at 12 mo: RR: 1.13 (95% CI: 0.71, 1.80)

(Continued)

TABLE 3 (Continued)

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Never vs. ever feeding human milk exposure <sup>a</sup>	Significant associations with atopic dermatitis	Nonsignificant associations with atopic dermatitis
Rothenbacher, 2005 (47)	Prospective cohort	Germany	n = 803 Baseline: birth Race/ethnicity: NR (nationality: 90.0% German, 2.4% Turkish, 7.6% other)	BF only 1–4 mo vs. BF 0 mo BF only ≥5 mo vs. BF 0 mo BF/other milks 1–4 mo vs. BF 0 mo BF/other milks ≥5 mo vs. BF 0 mo BF <3 mo vs. never BF	None None None None None	12-mo incidence of atopic dermatitis at 12 mo: RR: 1.28 (95% CI: 0.70, 2.35) 12-mo incidence of atopic dermatitis at 12 mo: RR: 1.46 (95% CI: 0.95, 2.25) 12-mo incidence of atopic dermatitis at 12 mo: RR: 1.15 (95% CI: 0.72, 1.84) 12-mo incidence of atopic dermatitis at 12 mo: RR: 1.39 (95% CI: 0.91, 2.12) Cumulative incidence of atopic dermatitis at 2 y: 27.5% vs. 13.2%, NS Cumulative incidence of atopic dermatitis at 2 y: 22.1% vs. 13.2%, NS Cumulative incidence of atopic dermatitis at 2 y: 17.9% vs. 13.2%, NS Cumulative incidence of atopic dermatitis at 2 y: 21.3% vs. 13.2%, NS Eczema during the first year: OR: 1.3 (95% CI: 0.9, 1.8) Eczema during the first year: OR: 0.8 (95% CI: 0.4, 1.3) Eczema during the first year: OR: 0.8 (95% CI: 0.5, 1.3) Eczema during the first year: OR: 1.0 (95% CI: 0.6, 1.5)
Sariachvili, 2007 (48)	Prospective cohort (PIPO Project)	Belgium	n = 976 Baseline: birth Race/ethnicity: NR	Ever BF vs. never BF BF 1–6 mo vs. never BF BF 7–12 mo vs. never BF BF ≥13 mo vs. never BF	None None None None	Eczema in the first 2 y in subsample with mothers with allergy, no asthma: OR: 0.90 (95% CI: 0.61, 1.31) Eczema in the first 2 y in subsample with mothers with allergy, no asthma: OR: 0.90 (95% CI: 0.52, 1.57) Eczema in the first 2 y in subsample with mothers with asthma: OR: 1.39 (95% CI: 0.51, 3.78) Eczema in the first 2 y in subsample with mothers with no allergy, no asthma: OR: 0.71 (95% CI: 0.42, 1.20)
Snijders, 2007 (49)	Prospective cohort (KOALA Birth Cohort)	Netherlands	n = 2516, 1538 in the subsample with mothers with no allergy/no asthma, 652 in the subsample with mothers with allergy/no asthma, 217 in the subsample with mothers with asthma Baseline: birth Race/ethnicity: NR	BF 0–3 mo vs. never BF BF 4–6 mo vs. never BF BF 7–9 mo vs. never BF	None None None	Eczema in the first 2 y in subsample with mothers with allergy, no asthma: OR: 0.86 (95% CI: 0.43, 1.71) Eczema in the first 2 y in subsample with mothers with asthma: OR: 1.40 (95% CI: 0.44, 4.42) Eczema in the first 2 y in subsample with mothers with no allergy, no asthma: OR: 0.69 (95% CI: 0.40, 1.19) Eczema in the first 2 y in subsample with mothers with allergy, no asthma: OR: 0.68 (95% CI: 0.34, 1.38) Eczema in the first 2 y in subsample with mothers with asthma: OR: 0.70 (95% CI: 0.22, 2.27)

(Continued)

TABLE 3 (Continued)

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Never vs. ever feeding human milk exposure <sup>2</sup>	Significant associations with atopic dermatitis	Nonsignificant associations with atopic dermatitis
Snijders, 2007 (50)	Prospective cohort (KOALA Birth Cohort)	Netherlands	n = 2405 Baseline: birth Race/ethnicity: NR	BF > 9 mo vs. never BF	Eczema in the first 2 y in subsample with mothers with no allergy, no asthma: OR: 0.51 (95% CI: 0.29, 0.89)	Eczema in the first 2 y in subsample with mothers with allergy, no asthma: OR: 0.63 (95% CI: 0.31, 1.29)
				Ever BF vs. never BF	None	Eczema in the first 2 y in subsample with mothers with asthma: OR: 1.67 (95% CI: 0.53, 5.21)
				BF 0–3 mo vs. never BF	None	Early development of eczema (0–3 mo): OR: 1.30 (95% CI: 0.96, 1.77)
				BF 4–6 mo vs. never BF	None	Eczema during first year of life: OR: 0.98 (95% CI: 0.71, 1.34)
Snijders, 2008 (51)	Prospective cohort (KOALA Birth Cohort)	Netherlands	n = 2434 Baseline: birth Race/ethnicity: NR	BF 4–6 mo vs. never BF	None	Eczema between 4 and 12 mo: OR: 0.98 (95% CI: 0.66, 1.46)
				BF ≥ 7 mo vs. never BF	None	Eczema during first year of life: OR: 0.94 (95% CI: 0.66, 1.34)
				BF ≥ 4 mo vs. never BF	None	Eczema during first year of life: OR: 0.80 (95% CI: 0.57, 1.12)
				BF 0–3 mo vs. never BF	None	Eczema between 4 and 12 mo: OR: 0.77 (95% CI: 0.52, 1.15)
Turati, 2016 (12)	Case-control	Italy	n = 451 cases, 451 controls Baseline: median, 5 mo (range: 3–24 mo) Sex: 67% male Race/ethnicity: NR	BF 4–6 mo vs. never BF	None	Eczema (parent report) by 2 y: OR: 1.00 (95% CI: 0.75, 1.33)
				BF 7–9 mo vs. never BF	None	Atopic dermatitis (assessed) at 2 y: OR: 1.11 (95% CI: 0.51, 2.41)
				BF > 9 mo vs. never BF	None	Eczema (parent report) by 2 y: OR: 0.87 (95% CI: 0.55, 1.35)
				Never BF vs. ever BF	None	Atopic dermatitis (assessed) at 2 y: OR: 2.58 (95% CI: 0.77, 8.67)

<sup>1</sup>BF, breastfed/breastfeeding; FF, formula-fed/formula feeding; INMA, Infancia y Medio Ambiente; KOALA Birth Cohort, Child, Parent and Health: Lifestyle and Genetic Constitution; NR, not reported; PASTURE, Protection Against Allergy Study in Rural Environments; PIPO Project, Prospective Study on the Influence of Perinatal factors on the Occurrence of Asthma and Allergies; ref, reference; SR, systematic review; TBACS, Taiwan Birth Cohort Study.

<sup>2</sup>Exposures, as defined by the authors of the studies included in the body of evidence, which address never versus ever feeding human milk or vice versa.

<sup>3</sup>The cohort was sampled from a randomized controlled trial; however, the data of interest for this SR are unrelated to randomization.

<sup>4</sup>Study was a randomized controlled trial; however, the data of interest for this SR used a nonrandomized comparison group.



**TABLE 4** Evidence examining the relationship between never versus ever feeding human milk and atopic dermatitis in childhood<sup>1</sup>

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Never vs. ever feeding human milk exposure <sup>2</sup>	Significant associations with atopic dermatitis	Nonsignificant associations with atopic dermatitis
Bergmann, 2002 (52)	Prospective cohort (MAS)	Germany	<i>n</i> = 939 Baseline: birth Sex NR Race/ethnicity: NR Risk: "risk enriched" 38% family history ( $\geq 2$ first-degree relatives or IgE concentrations)	Ever BF vs. never BF	None	Atopic eczema through 7 y: OR: 1.615 (95% CI: 0.933, 2.795)
Burr, 1993 (19)	Prospective cohort <sup>3</sup>	UK	<i>n</i> = 453 Baseline: birth Race/ethnicity: NR Risk: 100% family history (parent or sibling)	Ever BF vs. never BF	None	Proportion of infants ever BF vs. never BF with eczema at age 7 y: 37% vs. 35%, NS
Larsson, 2008 (18)	Prospective cohort (DBH)	Sweden	<i>n</i> = 4779 Baseline: 1–4 y Race/ethnicity: NR	No BF vs. BF >6 mo	None	5-y cumulative incidence of eczema by age 6–9 y: OR: 0.64 (95% CI: 0.33, 1.24)
Mihrshahi, 2007 (29)	Prospective cohort <sup>3</sup> (CAPS)	Australia	<i>n</i> = 516 Baseline: birth Sex: NR Race/ethnicity: NR Risk: 100% family history of asthma (parent or sibling)	Ever BF vs. never BF	None	Eczema at 5 y: OR: 1.38 (95% CI: 0.61, 3.12)
Nwaru, 2013 (31)	Prospective cohort (SEATON)	UK	<i>n</i> = 934, 770 in subsample with no eczema by 6 mo, 131 in subsample with eczema by 6 mo Baseline: birth Race/ethnicity: NR	Ever BF vs. never BF	None	Eczema up to age 10 y: OR: 1.06 (95% CI: 0.83, 1.35) Eczema up to age 10 y in subsample with no eczema by 6 mo: OR: 1.22 (95% CI: 0.91, 1.63) Eczema up to age 10 y in subsample with eczema by 6 mo: OR: 0.87 (95% CI: 0.51, 1.49)
				BF <2.25 mo vs. never BF	None	Eczema up to age 10 y: OR: 1.12 (95% CI: 0.84, 1.51) Eczema up to age 10 y in subsample with no eczema by 6 mo: OR: 1.25 (95% CI: 0.87, 1.79) Eczema up to age 10 y in subsample with eczema by 6 mo: OR: 0.95 (95% CI: 0.50, 1.81)
				BF $\geq 2.25$ mo vs. never BF	None	Eczema up to age 10 y: OR: 1.04 (95% CI: 0.81, 1.35) Eczema up to age 10 y in subsample with no eczema by 6 mo: OR: 1.23 (95% CI: 0.90, 1.68) Eczema up to age 10 y in subsample with eczema by 6 mo: OR: 0.83 (95% CI: 0.46, 1.50)
						Atopic dermatitis up to 4 y: OR: 0.83 (95% CI: 0.40, 1.69)
Orivuori, 2014 (32)	Prospective cohort (PASTURE)	Finland, France, Germany, Switzerland	<i>n</i> = 853 Baseline: birth Race/ethnicity: NR	Never BF vs. BF >6 mo	None	
Purvis, 2005 (53)	Prospective cohort <sup>4</sup> (ABC Study)	New Zealand	<i>n</i> = 550 Baseline: birth Race/ethnicity: NR; 100% New Zealanders of European descent Risk: ~50% born SGA	BF <6 mo vs. never BF	Atopic dermatitis at 3.5 y: OR: 6.12 (95% CI: 1.22, 30.7)	None
				BF $\geq 6$ mo vs. never BF	Atopic dermatitis at 3.5 y: OR: 12.0 (95% CI: 2.62, 54.8)	None
Sariachvili, 2010 (54)	Nested case-control (PIPO Project)	Belgium	<i>n</i> = 252 cases, 305 controls Baseline: birth Race/ethnicity: NR	Ever BF vs. never BF	None	Eczema up to age 4 y: OR: 0.77 (95% CI: 0.50, 1.18)
Zutavern, 2004 (55)	Prospective cohort	UK	<i>n</i> = 604 Baseline: birth Race/ethnicity: NR	Ever BF vs. never BF	None	Eczema by age 5.5 y: OR: 0.71 (95% CI: 0.47, 1.1)

<sup>1</sup>ABC, Auckland Birthweight Collaborative; BF, breastfed/breastfeeding; CAPS, Childhood Asthma Prevention Study; DBH, Dampness in Buildings and Health; IgE, immunoglobulin E; MAS, Multicentre Allergy Study; NR, not reported; PASTURE, Protection Against Allergy Study in Rural Environments; PIPO Project, Prospective Study on the Influence of Perinatal Factors on the Occurrence of Asthma and Allergies; ref, reference; SEATON, Study of Eczema and Asthma to Observe the Influence of Nutrition; SGA, small for gestational age; SR, systematic review.

<sup>2</sup>Exposures, as defined by the authors of the studies included in the body of evidence, which address never versus ever feeding human milk or vice versa.

<sup>3</sup>The cohort was sampled from a randomized controlled trial; however, the data of interest for this SR are unrelated to randomization.

<sup>4</sup>The cohort was sampled from a case-control study; however, the data of interest for this SR are unrelated to case/control status.

**TABLE 5** Evidence examining the relationship between shorter versus longer durations of any human milk feeding and allergic rhinitis in childhood<sup>1</sup>

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Shorter vs. longer duration of any human milk feeding exposure <sup>2</sup>	Significant associations with allergic rhinitis	Nonsignificant associations with allergic rhinitis
Codispoti, 2010 (61)	Prospective cohort (CCAAPS)	USA	<i>n</i> = 80 African Americans, 218 non-African Americans Baseline: birth Race/ethnicity: 22.2% African American, 77.8% non-African American Risk: 100% family history ( $\geq 1$ parent)	BF duration (mo)	Allergic rhinitis at age 3 y in African-American subsample: OR: 0.8 (95% CI: 0.6, 0.9)	Allergic rhinitis at age 3 y in the non-African-American subsample: OR: 1.0 (95% CI: 0.96, 1.1)
Kramer, 2007 (60)	Cluster RCT <sup>3</sup> (PROBIT)	Belarus	<i>n</i> = 13,889 Baseline: birth Race/ethnicity: NR	Experimental group (higher rates of any BF measured at 3, 6, 9, and 12 mo) vs. control group	None	Ever had hay fever symptoms by 6.5 y: OR: 1.1 (95% CI: 0.6, 1.9) Hay fever symptoms in the past 12 mo at 6.5 y: OR: 1.0 (95% CI: 0.6, 1.8)
Larsson, 2008 (18)	Prospective cohort (DBH)	Sweden	<i>n</i> = 4779 Baseline: 1–4 y Race/ethnicity: NR	BF duration <3 mo vs. >6 mo	None	5-y cumulative incidence of rhinitis by age 6–9 y: OR: 0.96 (95% CI: 0.63, 1.46) 5-y cumulative incidence of any rhinitis symptoms by age 6–9 y: OR: 0.80 (95% CI: 0.59, 1.07)
				BF duration 3–6 mo vs. >6 mo	None	5-y cumulative incidence of rhinitis during by age 6–9 y: OR: 0.94 (95% CI: 0.69, 1.29) 5-y cumulative incidence of any rhinitis symptoms during by age 6–9 y: OR: 1.03 (95% CI: 0.84, 1.25)
Nwaru, 2013 (63)	Prospective cohort (DIPP)	Finland	<i>n</i> = 3112 Baseline: birth Race/ethnicity: NR Risk: 100% high-risk genotype for T1D	Total BF <5 mo vs. >9.5 mo	None	Allergic rhinitis at 5 y: OR: ~1.3 (95% CI: ~1.0, ~1.8)
				Total BF 5–9.5 mo vs. >9.5 mo	None	Allergic rhinitis at 5 y: OR: ~1.2 (95% CI: ~0.9, ~1.5)
Sandini, 2011 (64)	Prospective cohort <sup>4</sup>	Finland	<i>n</i> = 891 Baseline: birth Race/ethnicity: NR Risk: 100% family history ( $\geq 1$ parent)	BF duration $\geq 2$ mo vs. <2 mo	None	Allergic rhinitis at 5 y: OR: 1.87 (95% CI: 0.55, 6.36)
von Kobyletzki, 2012 (62)	Prospective cohort (DBH)	Sweden	<i>n</i> = 3124 Baseline: 1–2 y Race/ethnicity: NR	BF $\leq 6$ mo vs. > 6 mo	None	5-y cumulative incidence of rhinitis by age 6–7 y: OR: 1.02 (95% CI: 0.73, 1.43)

<sup>1</sup>BF, breastfeeding/breastfed; CCAAPS, Cincinnati Childhood Allergy and Air Pollution Study; DBH, Dampness in Buildings and Health; DIPP, Type 1 Diabetes Prediction and Prevention; NR, not reported; PROBIT, Promotion of Breastfeeding Intervention Trial; RCT, randomized controlled trial; ref, reference; SR, systematic review; T1D, type 1 diabetes.

<sup>2</sup>Exposures, as defined by the authors of the studies included in the body of evidence, which address shorter versus longer durations of any human milk feeding or vice versa.

<sup>3</sup>Cluster RCT of an intervention to promote prolonged duration and exclusivity of breastfeeding rather than an RCT of breastfeeding per se.

<sup>4</sup>The cohort was sampled from an RCT; however, the data of interest for this SR are unrelated to randomization.

Statistically significant associations were reported by 9 studies across 11 articles (17, 18, 23, 24, 26–28, 30, 33, 34, 36). The studies provided consistent evidence of an association between never versus ever being fed human milk and higher asthma risk and suggested that the predominant difference between the statistically significant and nonsignificant associations was statistical power.

Seven of the studies that found significant associations were prospective cohort studies. Specifically, Larsson et al. (18) compared children never fed human milk with children fed human milk for >6 mo and found higher odds of asthma during the 5-y observation period in the full sample of children with no asthma at baseline (1–4 y of age; OR: 2.64; 95% CI: 1.28, 5.46) and in subsamples of children who did and did not have wheezing at baseline [OR (95% CI): 4.08 (1.21, 13.72) and 2.64 (1.18, 5.93), respectively]. Maas et al. (26) found lower odds of allergic asthma at 6 y of age when being fed human milk for 12–25 wk was compared with not being fed human milk (OR: 0.247; 95% CI: 0.093, 0.655); and when the exposure was being fed human milk for 1–11 wk, the upper limit of the CI was 1.003. A comparison of being fed human milk for  $\geq 26$  wk with not being fed human milk had a nonsignificant association in the same direction with a wide CI indicative of suboptimal statistical power. Midodzi et al. (28) reported a lower HR for asthma at 2–5 y of age when children who were fed human milk for >3 mo were compared with those who were never fed human milk (HR: 0.82; 95% CI: 0.69, 0.97). Further, when the exposure was being fed human milk for 0–3 mo, the upper limit of the CI around the nonsignificant association was 1.00. Miller et al. (30) and Milner et al. (17) examined the same cohort. In prospective analyses, ever being fed human milk was associated with lower odds of asthma by maternal report at (17) and by (30) 3 y of age [OR (95% CI): 0.61 (0.52, 0.71) and 0.68 (0.49, 0.97), respectively]. When Miller et al. (30) used physician reports from a retrospective medical chart review to determine whether children had been diagnosed with asthma by 3 y of age, the association was in the same direction but was not statistically significant (OR: 0.94; 95% CI: 0.70, 1.26). The authors described several plausible reasons for the discrepancy between maternal report and medical records, including response rate (i.e., the presence of maternal report when medical providers did not respond), health care utilization (i.e., the presence of maternal report when a medical record did not exist due to socioeconomic factors), and medical coding (e.g., for ease, providers may have coded reactive airway disease as asthma in medical charts); however, an additional explanation is that the analyses in both articles were unadjusted and may have been prone to confounding. Scholtens et al. (33) examined asthma in the full sample and subsamples of children with allergic and nonallergic mothers. The full-sample analyses found lower odds of asthma in 3-, 5-, 6-, 7-, and 8-y-old children (ORs between 0.50 and 0.65) and lower odds of chronic asthma by 8 y of age (OR: 0.65; 95% CI: 0.44, 0.96) in children fed human milk for >16 wk than in those not fed human milk, and the association at 4 y of age was in the same direction but not statistically significant. The subsample analyses of children with nonallergic mothers were very similar, although chronic asthma by 8 y of age was not assessed. In the subsample analyses of children with allergic mothers, the associations were in the same direction but not statistically significant, with the exception of a lower odds of asthma at 3 y of age. Sunyer et al. (34) found

that children fed human milk had lower odds of asthma at 6.5 y of age than children never fed human milk (OR: 0.33; 95% CI: 0.08, 0.87). Wilson et al. (36) reported that the percentage probability of asthma by 7 y of age was higher in children never fed human milk (18.6%; 95% CI: 17.2%, 20.0%) than in children who were exclusively fed human milk (12.1%; 95% CI: 10.9%, 13.4%). However, a comparison of never with partial feeding of human milk was not statistically significant.

In a nested case-control study, Martel et al. (27) examined a sample in which ~85% of both cases and controls had mothers with a history of asthma and found lower odds of childhood asthma up to 10 y of age when being fed human milk for <6 mo was compared with never being fed human milk (OR: 0.70; 95% CI: 0.53, 0.92). When being fed human milk for  $\geq 6$  mo was compared with never being fed human milk, the upper limit of the CI was 1.03.

Finally, in a case-control study, Infante-Rivard et al. (23) compared never with ever being fed human milk and reported higher odds of asthma at 3–4 y of age (OR: 1.47; 95% CI: 1.02, 2.13). When the study examined asthma that persisted from 3–4 y of age to 9–11 y of age, and transient asthma that was present at 3–4 y of age but not at 9–11 y of age (24), the associations were in the same direction but had wider CIs indicative of suboptimal statistical power [OR (95% CI): 1.30 (0.85, 2.01) and 1.17 (0.60, 2.28), respectively].

The majority of nonsignificant associations were consistent in direction with the significant associations (22, 24, 26–31, 33, 35), suggesting that never being fed human milk was associated with higher risk of asthma, and some of the nonsignificance was due to inadequate power. The minority of nonsignificant associations were discrepant (19, 25, 32) or did not report point estimates so direction could not be assessed (21). Some of the nonsignificant associations were from unadjusted analyses (19, 21, 35) and may have been prone to confounding.

*Evidence from studies including both children and adolescents together.* A prospective cohort study (37) and a case-control study (38) examined asthma in children and adolescents together. Both studies reported statistically significant associations, but the evidence was inconclusive. Colen et al. (37) found a significant association between ever compared with never being fed human milk and higher risk of asthma at 4–14 y in the full sample ( $\beta$ : 0.261; SE: 0.106;  $P < 0.05$ ) and also among the subsample of children who were siblings ( $\beta$ : 0.237; SE: 0.117;  $P < 0.05$ ). Of note, they also conducted a within-family analysis of siblings with discordant exposures (i.e., 1 sibling was fed human milk and the other was not), and this analysis found no difference in the proportion of siblings fed human milk compared with not being fed human milk who had asthma at 4–14 y, suggesting that residual confounding explained the significant difference observed in the between-family analyses. The case-control study by Rosas-Salazar et al. (38) reported conflicting results. When compared with children and adolescents never fed human milk, the children and adolescents fed human milk for <6 mo had lower odds of asthma (OR: 0.7; 95% CI: 0.5, 1.0;  $P = 0.04$ ). On the other hand, there was a nonsignificant association between being fed human milk for  $\geq 6$  mo and higher odds of asthma that had a wide CI with a lower limit of 1.0.

To summarize, all 9 studies with statistically significant associations in childhood suggested that never versus ever being

fed human milk was associated with higher risk of asthma (17, 18, 23, 24, 26–28, 30, 33, 34, 36). The nonsignificant associations provided further evidence of a relationship between never being fed human milk and asthma in childhood because they were mostly consistent in direction with the significant associations (22, 24, 26–31, 33, 35), and some of the analyses appeared to be underpowered. The evidence from studies examining children and adolescents together was mixed (37, 38), and it was difficult to determine whether or not the heterogeneous associations were due to the inclusion of adolescents in the samples because evidence in adolescents alone was scant.

#### *Atopic dermatitis from birth to 24 mo.*

Sixteen articles presented inconclusive evidence on never versus ever being fed human milk and atopic dermatitis during the B-24 period (12, 13, 32, 39–51) (Table 3). The small number of significant associations was inconsistent in direction. Ivakhnenko et al. (13) found that a larger proportion of infants fed infant formula than fed human milk had atopic dermatitis by 18 mo of age (16.98% compared with 3.92%,  $P < 0.05$ ), whereas Chuang et al. (40) found that being fed human milk for durations of  $\leq 1$ ,  $\leq 2$ ,  $\leq 6$ ,  $\leq 12$ , and  $> 12$  mo (compared with not being fed human milk) was associated with higher odds of atopic dermatitis between 6 and 18 mo of age (ORs between 1.25 and 1.49). In a third study, Snijders et al. (49) found that being fed human milk for  $> 9$  mo (compared with never being fed human milk) was associated with lower odds of eczema by 2 y of age in a subsample of children whose mothers had no allergies or asthma (OR: 0.51; 95% CI: 0.29, 0.89). However, the significant association was limited to 1 (49) of the 3 articles by Snijders et al. (49–51) about the study, and to 1 of the 12 relevant analyses in the article. The nonsignificant associations were also inconsistent in direction, with no discernible trend in the direction of the point estimates (12, 32, 39, 41–48). In addition to the mixed evidence, TEC members had concerns about the specificity of the diagnosis of atopic dermatitis during the B-24 period.

#### *Atopic dermatitis in childhood.*

Eight prospective cohort studies (18, 19, 29, 31, 32, 52, 53, 55) and 1 nested case-control study (54) examined the relationship between never versus ever being fed human milk and atopic dermatitis in childhood (Table 4). Data about infant milk-feeding practices were collected by diary, questionnaire, and interview. Infants never fed human milk were compared with infants categorized as ever fed human milk (19, 29, 31, 48, 52, 55) or fed human milk for heterogeneous ranges of duration (18, 31, 32, 53). Atopic dermatitis was defined based on parent responses to items from the ISAAC questionnaire (18, 31, 54), parent report of a physician's diagnosis (29, 32, 55), a positive Scoring Atopic Dermatitis (SCORAD) score (32), or physical examination plus parent-reported case history (19, 29, 52, 53). Bergman et al. (52), Burr et al. (19), and Mirshahi et al. (29) examined atopic dermatitis in at-risk or "risk-enriched" samples based on family history or immunoglobulin E (IgE) concentrations. The comparisons of interest by Sariachvili et al. (54), Larsson et al. (18), and Burr et al. (19) were

unadjusted, whereas the remaining studies considered a range of confounders.

Most of the associations between never versus ever feeding human milk and atopic dermatitis in childhood were nonsignificant. The samples in the studies by Bergman et al. (52), Mirshahi et al. (29), and Orivuori et al. (32) may have been too small for sufficient statistical power to examine the comparisons of interest for this SR, as they had wide CIs around their nonsignificant associations. The only study with statistically significant associations was by Purvis et al. (53). However, the associations from this study may not be generalizable because the study was originally intended to examine differences between infants born small and appropriate for gestational age and recruited a sample in which about half of the participants were born small for gestational age (although the study authors noted that this was accounted for in the statistical analysis). In the remaining studies, the nonsignificant associations were inconsistent in direction.

#### **Shorter versus longer durations of any human milk feeding and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span**

Thirty-five articles met the inclusion criteria for this SR question (14, 18, 32, 37, 52, 54, 57–85). None of the articles examined food allergies, allergic rhinitis, or atopic dermatitis in adolescence or adulthood; and TEC members concluded that the scant evidence with methodologic limitations was insufficient to determine whether or not the duration of any human milk feeding was associated with food allergies from birth through childhood (14, 57, 58), allergic rhinitis during the B-24 period (59), or asthma in adulthood (79, 80). Additional information about these topics is available at <https://nesr.usda.gov>. Evidence on allergic rhinitis in childhood, asthma in childhood and adolescence, and atopic dermatitis from birth through childhood is presented below.

#### *Allergic rhinitis in childhood.*

One cluster randomized controlled trial examined the relationship between shorter versus longer durations of any human milk feeding and allergic rhinitis in childhood (Table 5). Kramer et al. (60) presented evidence from the Promotion of Breastfeeding Intervention Trial (PROBIT), a cluster randomized controlled trial of an intervention to promote prolonged duration and exclusivity of human milk feeding among mothers who chose to feed human milk. Study pediatricians collected human milk-feeding data at well-baby medical appointments. The intervention group had higher rates of human milk feeding than the control group measured at 3, 6, 9, and 12 mo. There was no association between group status and ever having hay fever symptoms or having hay fever symptoms in the previous 12 mo, which were assessed by study pediatricians through the use of the ISAAC questionnaire (56).

There were also 4 prospective cohort studies that presented evidence across 5 articles (18, 61–64) (Table 5) [unique evidence from the Dampness in Buildings and Health (DBH) study was presented by Larsson et al. (18) and von Kobyletzki et al. (62)]. Two of the studies examined high-risk cohorts (based on family



history of allergic disease) (61, 64), and a third study examined children who were at risk for type 1 diabetes (63). Data about the duration of human milk feeding were collected by parent questionnaire and assessed as a continuous variable by Codispoti et al. (61) and as heterogeneous categorical variables by the other studies (18, 62–64). Allergic rhinitis was defined based on parent responses to items from the ISAAC questionnaire (18, 61–63), parent report of physician diagnosis (18), or positive skin-prick test or allergen-specific IgE concentration  $\geq 0.7$  kU/L plus a history of symptoms (64). The comparisons of interest in 2 studies were unadjusted (18, 62, 63), and the remaining studies considered a range of confounders (61, 64).

Nearly all of the associations across the 4 prospective cohort studies were nonsignificant, with no discernible trend in the direction of the point estimates. The only statistically significant association was that reported by Codispoti et al. (61), who found that a longer duration of human milk feeding was associated with lower risk of allergic rhinitis in 3-y-old African Americans (OR: 0.8; 95% CI: 0.6, 0.9). There were no comparable analyses in other studies in this body of evidence that would allow TEC members to examine whether this association is typical among African American children.

### *Asthma in childhood and adolescence.*

One cluster randomized controlled trial examined the relationship between shorter versus longer durations of any human milk feeding and asthma in childhood (Table 6). In the PROBIT (described previously), Kramer et al. (60) found no significant association between group status and ever having asthma by 6.5 y, which was assessed by study pediatricians through the use of the ISAAC instrument.

There were also 17 prospective cohort studies that presented evidence across 18 articles (18, 32, 37, 62–67, 69–75, 77, 78) (Table 6) [unique evidence from the DBH study was presented by Larsson et al. (18) and von Kobyletzki et al. (62)] and 2 case-control studies (68, 76). Data on human milk feeding were collected by interviews, diaries, or questionnaires given to parents and assessed as a continuous variable (37, 66, 69, 73, 74, 77) and heterogeneous categorical variables (18, 32, 62–65, 67, 68, 70–72, 75–78). The outcome was usually based on parent report of morbidity or physician diagnosis, or a combination of the 2 (18, 32, 37, 62, 63, 69, 72, 74, 75, 77, 78), although a few studies used physician diagnosis (66, 67, 73) or accessed medical records (64, 69).

Statistically significant associations were reported by 6 prospective cohort studies (18, 37, 63, 70, 74, 78). With 1 exception (37), these studies provided consistent evidence of an inverse association between the duration of any human milk feeding and asthma risk in children and adolescents and suggested that the predominant difference between the statistically significant and nonsignificant associations was statistical power.

Specifically, in the study by Hovland et al. (78) a larger proportion of the participants who never had asthma ( $n = 322$ ) were fed human milk for  $>4$  mo than participants who had asthma; however, the difference was only significant with the subsample of participants with asthma in remission during puberty (10–16 y of age; OR: 0.22; 95% CI: 0.08, 0.65) and not in the subsamples with asthma during puberty. Kull et al. (70) examined shorter compared with longer durations of exclusive

plus additional partial human milk feeding. Being fed human milk for  $\geq 3$  mo after 3–4 mo of exclusive human milk feeding and being fed human milk for  $\geq 5$  mo after  $\geq 3$  mo of exclusive human milk feeding (i.e., longer durations) compared with being fed human milk for 0–2 mo after 0–2 mo of exclusive human milk feeding (i.e., a shorter duration) were associated with lower odds of asthma at 4 y of age [OR (95% CI): 0.44 (0.21, 0.87) and 0.43 (0.25, 0.74), respectively]. The nonsignificant associations were in the same direction but had wider CIs, indicative of suboptimal statistical power. In the DBH study, Larsson et al. (18) and von Kobyletzki et al. (62) examined the 5-y cumulative incidence of asthma by age 6–7 y (62) and by age 6–9 y (18) in a sample of children who did not have asthma at baseline and in subsamples of children who did (18) and did not (18, 62) have wheezing at baseline. In the subsample of children with wheezing at baseline, Larsson et al. (18) found higher odds of asthma in children fed human milk for  $<3$  mo and for 3–6 mo compared with  $>6$  mo [OR (95% CI): 2.11 (1.12, 3.00) and 1.84 (1.09, 3.11), respectively]. In analyses of the full sample and the subsample with no wheezing at baseline, the nonsignificant associations were in the same direction and had wide CIs, indicative of a lack of statistical power (18, 62). In a sample with high risk for type 1 diabetes, Nwaru et al. (63) found higher HRs among children fed human milk for  $<5$  mo and 5–9.5 mo compared with  $>9.5$  mo [HR (95% CI): 1.91 (1.21, 3.02) and 1.97 (1.28, 3.02), respectively]. Silvers et al. (74) examined the duration of any human milk feeding as a continuous variable and found lower odds of asthma at 3 and 4 y of age as the number of months of human milk feeding increased [OR (95% CI): 0.94 (0.91, 0.97) and 0.96 (0.92, 0.99), respectively]. At 5 y of age, the upper limit of the CI was 1.00, and at 6 y of age the CI included the null. Colen et al. (37) conducted the only prospective cohort study with a statistically significant association that showed that a longer compared with a shorter duration of any human milk feeding was associated with higher risk of asthma. It examined asthma from 4 to 14 y using a between-family estimate from the full sample as well as a within-family estimate from a subsample of sibling participants. In the full sample, each additional week of feeding human milk tended to increase asthma; however, the effect size was small ( $\beta$ : 0.004; SE: 0.002;  $P < 0.05$ ) and a nonsignificant, and similarly small, effect size was found in the sibling subsample analysis.

Statistically significant associations were also reported by both case-control studies (68, 76), which provided additional evidence of an inverse association between the duration of any human milk feeding and asthma risk in children and adolescents. Karunasekera et al. (68) reported that being fed human milk for  $\leq 6$  mo compared with  $>6$  mo was associated with higher odds of asthma at age 1–10 y (OR: 2.0; 95% CI: 1.2, 3.2), and Al-Mousawi et al. (76) reported that being fed human milk for  $>2$  mo compared with  $<2$  mo was associated with lower odds of asthma at age 8–15 y (OR: 0.54; 95% CI: 0.30, 0.96).

To summarize, 7 of 8 studies with statistically significant associations had findings that suggested that shorter versus longer durations of any human milk feeding are associated with higher relative risk of asthma in childhood and adolescence (18, 63, 68, 70, 74, 76, 78), and the remaining study found a small positive association between duration and asthma (37). In these studies, and across most of the observational studies in the body of evidence, the nonsignificant associations provided further

**TABLE 6** Evidence examining the relationship between shorter versus longer durations of any human milk feeding and asthma in childhood and adolescence<sup>1</sup>

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Shorter vs longer duration of any human milk feeding exposure <sup>2</sup>	Significant associations with asthma	Nonsignificant associations with asthma
Al-Mousawi, 2004 (76)	Case-control	Kuwait	<i>n</i> = 160 cases, 303 controls Baseline: 8–15 y Sex: 73% male Race/ethnicity: NR	BF >2 mo vs. <2 mo	Asthma diagnosis at age 8–15 y (in model that includes sensitization defined by SPT): OR: 0.54 (95% CI: 0.30, 0.96) Asthma diagnosis at age 8–15 y (in model that includes sensitization defined by IgE concentration): OR: 0.45 (95% CI: 0.26, 0.80)	None  Asthma at 3–6 y: OR: 0.890 (95% CI: 0.580, 1.368)
Bergmann, 2000 (65)	Prospective cohort (MAS)	Germany	<i>n</i> = 880 Baseline: birth Sex: NR Race/ethnicity: NR Risk: "risk enriched" 38% family history (≥2 first-degree relatives or IgE concentrations) <i>n</i> = 8237 in the full sample, 7319 in the sibling subsample Baseline: birth Race/ethnicity: 74.49% non-Hispanic white, 17.28% non-Hispanic black, 8.23% Hispanic	BF >6 mo vs. ≤6 mo	None	
Colen, 2014 (37)	Prospective cohort (National Longitudinal Study of Youth 1979 Cohort)	USA	<i>n</i> = 1933 Baseline: 1–7 y Race/ethnicity: NR	BF duration (wk)	Asthma at 4–14 y in the full sample (between-family estimate): $\beta$ = 0.004 (SE = 0.002), <i>P</i> < 0.05	Asthma at 4–14 y in the sibling subsample (within-family estimate): $\beta$ = 0.006 (SE = 0.008)
Fredriksson, 2007 (77)	Prospective cohort	Finland		BF 0–3 mo vs. 4–6 mo BF 7–9 mo vs. 4–6 mo BF 10–12 mo vs. 4–6 mo BF > 12 mo vs. 4–6 mo	None None None None	Current asthma in participants ages 7–14 y: OR: 1.44 (95% CI: 0.78, 2.66) Current asthma in participants ages 7–14 y: OR: 1.16 (95% CI: 0.65, 2.08) Current asthma in participants ages 7–14 y: OR: 1.72 (95% CI: 0.97, 2.08) Current asthma in participants ages 7–14 y: OR: 1.60 (95% CI: 0.83, 2.08)
Grandjean, 2010 (66)	Prospective cohort	Denmark	<i>n</i> = 464 Baseline: birth Race/ethnicity: NR	Per 1-mo decrease in BF duration from 7 mo Per 1-mo increase in BF duration from 7 mo BF duration (mo) in participants with asthma vs. no allergy	None None None	Current asthma in participants ages 7–14 y: OR: 1.10 (95% CI: 0.92, 1.32) Current asthma in participants ages 7–14 y: OR: 1.03 (95% CI: 1.00, 1.05) Current or past history of asthma by 5 or 7 y: 9.3 (IQR: 7, 12) vs. 9.9 (IQR: 6, 12), <i>P</i> = 0.58
Hovland, 2015 (78)	Prospective cohort (Environment and Childhood Asthma Study)	Norway	<i>n</i> = 322 with asthma never, 107 with pubertal asthma, 121 with asthma in remission in puberty, and 33 with pubertal onset of asthma Baseline: birth Race/ethnicity: NR	BF >4 mo vs. ≤4 mo	Proportion of participants with asthma (0–10 y) in remission during puberty (10–16 y) vs. never had asthma who BF >4 mo: 80.2% vs. 91.2%, <i>P</i> < 0.01	Proportion of participants with pubertal asthma at 10–16 y vs. never had asthma who BF >4 mo: 86.3% vs. 91.2% Proportion of participants with pubertal onset of asthma at 10–16 y vs. never had asthma who BF >4 mo: 86.7% vs. 91.2%
				BF >4 mo vs. ≤4 mo	Asthma (0–10 y) in remission during puberty (10–16 y): OR: 0.22 (95% CI: 0.08, 0.65)	None

(Continued)



TABLE 6 (Continued)

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Shorter vs longer duration of any human milk feeding exposure <sup>2</sup>	Significant associations with asthma	Nonsignificant associations with asthma
Karmanus, 2008 (67)	Prospective cohort (HOW)	UK	n = 1224 Baseline: birth Sex: NR Race/ethnicity: NR	BF ≥3 mo vs. <3 mo	None	Repeated measurement of asthma at ages 1, 2, 4, 10 y: RR: 0.83 (95% CI: 0.67, 1.02) Repeated measurement of asthma at ages 4 or 10 y: RR: 0.82 (95% CI: 0.64, 1.06) None
Karunasekera, 2001 (68)	Case-control	Sri Lanka	n = 300 cases, 300 controls Baseline: 1-10 y Sex: NR Race/ethnicity: NR	BF ≤6 mo vs. >6 mo	Asthma at 1-10 y: OR: 2.0 (95% CI: 1.2, 3.2)	None
Klennert, 2001 (69)	Prospective cohort	USA	n = 145 Baseline: birth Sex: NR Race/ethnicity: "primarily Caucasians" Risk: 100% family history (mothers)	BF duration	None	Asthma at 6-8 y: NS (data NR)
Kramer, 2007 (60)	Cluster RCT <sup>3</sup> (PROBIT)	Belarus	n = 13,889 Baseline: birth Race/ethnicity: NR	Experimental group (higher rates of any BF measured at 3, 6, 9, and 12 mo) vs. control group	None	Ever had asthma by 6.5 y: OR: 1.2 (95% CI: 0.7, 1.9)
Kull, 2004 (70)	Prospective cohort (BAMSE)	Sweden	n = 3670 Baseline: birth Race/ethnicity: NR	EBF 0-2 mo + additional partial BF ≥3 mo vs. EBF 0-2 mo + additional partial BF 0-2 mo EBF 3-4 mo + additional partial BF 0-2 mo vs. EBF 0-2 mo + additional partial BF 0-2 mo EBF ≥3 mo + additional partial BF 0-2 mo vs. EBF 0-2 mo + additional partial BF 0-2 mo EBF ≥5 mo + additional partial BF 0-2 mo vs. EBF 0-2 mo + additional partial BF 0-2 mo	Asthma at 4 y: OR: 0.44 (95% CI: 0.21, 0.87) None None None	Asthma at 4 y: OR: 0.90 (95% CI: 0.47, 1.73) None Asthma at 4 y: OR: 0.67 (95% CI 0.34, 1.32)
Larsson, 2008 (18)	Prospective cohort (DBH)	Sweden	n = 4483 in the full sample without asthma at baseline, 3320 in the subsample without wheezing at baseline, 935 in the subsample with wheezing at baseline Baseline: 1-4 y Race/ethnicity: NR	BF duration <3 mo vs. >6 mo BF duration 3-6 mo vs. >6 mo	5-y cumulative incidence of asthma by age 6-9 y in the subsample with no asthma, but with wheezing at baseline: OR: 2.11 (95% CI: 1.12, 3.00) None Asthma at 4 y: OR: 0.43 (95% CI: 0.25, 0.74)	5-y cumulative incidence of asthma by age 6-9 y in the full sample with no asthma at baseline: OR: 1.54 (95% CI: 0.98, 2.43) 5-y cumulative incidence of asthma by age 6-9 y in the subsample with no asthma and no wheezing ever at baseline: OR: 1.31 (95% CI: 0.70, 2.45) 5-y cumulative incidence of asthma by age 6-9 y in the full sample with no asthma at baseline: OR: 1.40 (95% CI: 0.98, 2.00) 5-y cumulative incidence of asthma by age 6-9 y in the subsample no asthma and no wheezing ever at baseline: OR: 1.18 (95% CI: 0.73, 1.91)

(Continued)

TABLE 6 (Continued)

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Shorter vs longer duration of any human milk feeding exposure <sup>2</sup>	Significant associations with asthma	Nonsignificant associations with asthma
Nwaru, 2013 (63)	Prospective cohort (DIPP)	Finland	n = 3142 Baseline: birth Race/ethnicity: NR Risk: 100% high-risk genotype for T1D	Total BF <5 mo vs. >9.5 mo Total BF 5–9.5 mo vs. >9.5 mo	Asthma at 5 y: HR: 1.91 (95% CI: 1.21, 3.02) Asthma at 5 y: HR: 1.97 (95% CI: 1.28, 3.02)	None None
Oddy, 1999 (71)	Prospective cohort (Western Australia Pregnancy Cohort Study) <sup>4</sup>	Australia	n = 2187 Baseline: birth Race/ethnicity: 2.5% Aboriginal descent	BF stopped by 3 mo vs. not BF stopped by 4 mo vs. not BF stopped by 5 mo vs. not BF stopped by 6 mo vs. not BF ≤3 mo vs. >6 mo	None None None None None	Asthma diagnosed by a doctor by age 6 y: OR: 1.12 (95% CI: 0.91, 1.34) Asthma diagnosed by a doctor by age 6 y: OR: 1.14 (95% CI: 0.94, 1.40) Asthma diagnosed by a doctor by age 6 y: OR: 1.20 (95% CI: 0.98, 1.47) Asthma diagnosed by a doctor by age 6 y: OR: 1.18 (95% CI: 0.97, 1.45) Asthma at 4 y: OR: 1.32 (95% CI: 0.57, 3.05) Asthma between 4 and 6 y: OR: 0.76 (95% CI: 0.36, 1.62) Asthma at 4 y: OR: 0.79 (95% CI: 0.30, 2.06)
Orivuori, 2014 (32)	Prospective cohort (PASTURE)	Finland, France, Germany, Switzerland	n = 853 Baseline: birth Race/ethnicity: NR	BF 3–6 mo vs. 6 mo	None	Asthma between 4 and 6 y: OR: 0.76 (95% CI: 0.36, 1.62) Asthma at 4 y: OR: 0.79 (95% CI: 0.30, 2.06)
Ronmark, 2002 (72)	Prospective cohort	Sweden	n = 3247 Baseline: 7–8 y Race/ethnicity: NR	BF ≤3 mo vs. unspecified longer duration	None	Asthma between 4 and 6 y: OR: 0.56 (95% CI: 0.25, 1.23) Ever asthma by 9–10 y: RR: 0.46 (95% CI: 0.20, 1.04)
Sandini, 2011 (64)	Prospective cohort <sup>4</sup>	Finland	n = 891 Baseline: birth Race/ethnicity: NR Risk: 100% family history (≥1 parent)	BF duration ≥2 mo vs. <2 mo	None	Asthma with IgE sensitization at 5 y: OR: 0.99 (95% CI: 0.22, 4.39)
Sigurs, 1995 (73)	Prospective cohort <sup>5</sup>	Sweden	n = 140 Baseline: <1 y Race/ethnicity: NR Risk: 33% infancy respiratory syncytial virus bronchiolitis	Total BF duration (mo)	None	Asthma at 3 y: RR: 0.8 (95% CI: 0.65, 1.02)
Silvers, 2012 (74)	Prospective cohort (New Zealand Asthma and Allergy Cohort)	New Zealand	n = 892 Baseline: birth Race/ethnicity: 14.6% Maori	Duration of any BF (mo)	Current asthma at 3 y: OR: 0.94 (95% CI: 0.91, 0.97) Current asthma at 4 y: OR: 0.96 (95% CI: 0.92, 0.99)	Current asthma at 5 y: OR: 0.98 (95% CI: 0.94, 1.00) Current asthma at 6 y: OR: 0.99 (95% CI: 0.96, 1.03) Asthma by 3–4 y: OR: 1.55 (95% CI: 0.61, 3.92)
Strassburger, 2010 (75)	Prospective cohort <sup>4</sup>	Brazil	n = 347 Baseline: birth Race/ethnicity: NR	BF <6 mo vs. BF ≥6 mo	None	Asthma by 3–4 y: OR: 1.55 (95% CI: 0.61, 3.92)
von Kobyletzki, 2012 (62)	Prospective cohort (DBH)	Sweden	n = 3124 in the subsample without asthma or wheezing at baseline Baseline: 1–2 y Race/ethnicity: NR	BF ≤6 mo vs. BF >6 mo	None	5-y cumulative incidence of asthma by age 6–7 y in the subsample with no asthma and no wheezing ever at baseline: OR: 1.14 (95% CI: 0.68, 1.90)

<sup>1</sup>  $\beta$ , regression coefficient; BAMSE, Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology; BF, breastfed/breastfeeding; DBH, Dampness in Buildings and Health; DIPP, Type 1 Diabetes Prediction and Prevention; HLA, human leukocyte antigen; IgE, immunoglobulin E; IOW, Isle of Wight; MAS, Multicentre Allergy Study; NR, not reported; PASTURE, Protection Against Allergy Study in Rural Environments; PROBIT, Promotion of Breastfeeding Intervention Trial; RCT, randomized controlled trial; ref, reference; SPT, skin-prick test; SR, systematic review; T1D, type 1 diabetes.

<sup>2</sup> Exposures, as defined by the authors of the studies included in the body of evidence, which address shorter versus longer durations of any human milk feeding or vice versa.

<sup>3</sup> Cluster RCT of an intervention to promote prolonged duration and exclusivity of breastfeeding rather than an RCT of breastfeeding per se.

<sup>4</sup> The cohort was sampled from an RCT; however, the data of interest for this SR are unrelated to randomization.

<sup>5</sup> The cohort was sampled from a case-control study; however, the data of interest for this SR are unrelated to case/control status.

evidence of an inverse relationship between the duration of any human milk feeding and asthma because they were consistent in direction with the significant associations (18, 62, 64–67, 70, 71, 73–75, 78) and some of the nonsignificance could be attributed to inadequate power. The minority of studies had nonsignificant associations that were discrepant (32, 60, 72, 77) or did not report point estimates, so that direction could not be assessed (69).

#### *Atopic dermatitis from birth to 24 mo.*

Eight articles presented inconclusive evidence on shorter versus longer durations of any human milk feeding and atopic dermatitis during the B-24 period (32, 57, 59, 64, 81–84) (Table 7). Kramer et al. (84) provided compelling evidence from the PROBIT (a cluster randomized controlled trial described previously) that the experimental group had lower risk of atopic dermatitis at 12 mo of age than the control group (OR: 0.54; 95% CI: 0.31, 0.95). However, evidence from 7 observational studies (32, 57, 59, 64, 81–83) was inconsistent with evidence from the PROBIT study. Miyake et al. (82) found that feeding human milk for  $\geq 6$  mo, compared with  $< 6$  mo, was associated with significantly higher odds of atopic dermatitis in the absence of parental atopic history (OR: 3.39; 95% CI: 1.20, 12.36), and evidence from the remaining studies lacked statistical significance and had point estimates that were inconsistent in direction. Furthermore, TEC members had concerns about reverse causality and the specificity of detecting atopic dermatitis during the B-24 period.

#### *Atopic dermatitis in childhood.*

One cluster randomized controlled trial examined the relationship between shorter versus longer durations of any human milk feeding and atopic dermatitis in childhood (Table 8). In the PROBIT (described previously), Kramer et al. (60) found no association between group status and ever having eczema by 6.5 y, which was assessed by study pediatricians through the use of the ISAAC instrument.

There were also 6 prospective cohort studies that presented evidence across 7 articles (18, 32, 52, 64–66, 85) (Table 8) [Bergmann et al. (52, 65) presented evidence from the Multicentre Allergy Study (MAS) across 2 articles] and 1 nested case-control study (54). Data on human milk feeding were collected by parent report via interview, questionnaire, or diary. The duration of human milk feeding was assessed as a continuous variable (52, 54, 66, 85) and heterogeneous categorical variables (18, 32, 52, 54, 64, 65). Atopic dermatitis was defined based on parent responses to items from the ISAAC questionnaire (18, 54); by parent report of a physician's diagnosis or a positive SCORAD score (32); and by physical examination plus parent-reported case history (52, 65, 66), a positive skin-prick test on  $\geq 1$  occasion (64, 85) or an allergen-specific IgE concentration  $\geq 0.7$  kU/L (64). Bergmann et al. (52, 65), Sandini et al. (64), and Kusel et al. (85) specifically recruited high-risk or "risk-enriched" samples based on a combination of family history of allergic disease and IgE concentrations. The comparisons of interest by Sariachvili et al. (54), Larsson et al. (18), and Kusel et al. (85) were unadjusted, whereas the remaining studies considered a range of confounders.

Most of the associations between the duration of any human milk feeding and atopic dermatitis in childhood were nonsignificant. The only study with statistically significant associations was the MAS. Bergmann et al. (52) found a positive association between the duration of any human milk feeding (assessed as a continuous variable) and atopic eczema through 7 y of age (OR: 1.029; 95% CI: 1.002, 1.057) and between being fed human milk for  $\geq 2$  mo, compared with  $< 2$  mo, and higher odds of atopic eczema through 7 y of age (OR: 1.384; 95% CI: 1.025, 1.869). However, the significant associations were limited to 1 (52) of 2 articles (52, 65) with data from the MAS, and to 2 of the 10 relevant analyses in the article.

## Discussion

TEC members graded the evidence underlying their conclusions about 1) never versus ever being fed human milk and asthma in childhood and 2) shorter versus longer durations of any human milk feeding and asthma in childhood and adolescence as moderate (Table 9) after considering the adequacy, consistency, impact, generalizability, and internal validity of the evidence. Seventeen studies examined never versus ever being fed human milk and asthma in children, and the statistically significant associations all showed that never being fed human milk was associated with higher risk of asthma (17, 18, 23, 26–28, 30, 33, 34, 36, 62). Similarly, 20 studies examined the duration of any human milk feeding and asthma in childhood and adolescence and, with 1 exception (37), the statistically significant associations showed that shorter versus longer durations were associated with higher risk of asthma (18, 63, 68, 70, 74, 76, 78). The majority of nonsignificant associations were also consistent in suggesting higher risk with never versus ever feeding human milk and shorter versus longer durations of any human milk feeding (18, 22, 24, 26, 27, 29–31, 33, 35, 62, 64–67, 70, 71, 73–75, 78), and some of the inconsistency in statistical significance may be explained by insufficient statistical power resulting in wide CIs (18, 24, 62, 64, 75). Evidence was consistent despite heterogeneous independent variables resulting from not defining "longer," "shorter," or "ever" for the SRs and instead including all relevant comparisons. However, the consistency was limited to observational studies because the single experimental study had a nonsignificant association (60).

In the NESR grading rubric, the impact of the evidence takes into consideration the directness with which the study designs examined the link between the exposure and outcome of interest in the SR question, and the clinical significance of the evidence. Although some studies' original objectives were not explicitly stated, most studies described objectives related to examining the link between feeding human milk and asthma. Six studies with evidence about shorter versus longer durations of human milk feeding and asthma in childhood (18, 62–64, 71, 73, 75) and 4 studies with evidence about never versus ever being fed human milk and asthma in childhood (18, 19, 26, 29, 62) were indirect. Regarding clinical significance, asthma affects the quality of life for millions of children in the United States and can be life threatening (7). Therefore, even small decreases in the risk for asthma have the potential to be of public health importance.

The generalizability of the evidence to US populations had a few limitations but was sound overall. There were 2 US studies of shorter versus longer durations of any human milk feeding

**TABLE 7** Evidence examining the relationship between shorter versus longer durations of any human milk feeding and atopic dermatitis from birth to 24 mo<sup>1</sup>

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Shorter vs. longer duration of any human milk feeding exposure <sup>2</sup>	Significant associations with atopic dermatitis	Nonsignificant associations with dermatitis
Hesselmar, 2010 (57)	Prospective cohort (ALLERGYFLORA)	Sweden	<i>n</i> = 184 Baseline: 1–3 d Race/ethnicity: NR Risk: 80% family history ( $\geq 1$ parent)	Median duration of partial BF (mo) in participants with and without eczema	None	Eczema by 6 mo: 8 mo (IQR: 6.0, 9.5) vs. 7 mo (IQR: 4.5, 9.0), <i>P</i> = 0.619 Eczema by 18 mo: 6.7 mo (IQR: 6.0, 9.0) vs. 7.2 mo (IQR: 4.0, 10.0), <i>P</i> = 0.818
Kerkhof, 2003 (81)	Nested case control (PIAMA)	Netherlands	<i>n</i> = 76 cases, 228 controls Baseline: birth Race/ethnicity: NR Risk: 100% family history (mothers)	BF duration (wk)	None	Expected probability of atopic dermatitis at 12 mo: NS (data NR)
Kramer, 2001 (84)	Cluster RCT <sup>3</sup> (PROBIT)	Belarus	<i>n</i> = 16,491 Baseline: birth Race/ethnicity: NR	Experimental group (higher rates of any BF measured at 3, 6, 9, and 12 mo) vs. control group	Atopic eczema by 12 mo: OR: 0.54 (95% CI: 0.31, 0.95)	None
Kull, 2002 (59)	Prospective cohort (BAMSE)	Sweden	<i>n</i> = 3791 Baseline: birth Race/ethnicity: NR	Partial BF $\geq 6$ mo vs. $< 6$ mo	None	Atopic dermatitis by age 2 y: OR: 0.88 (95% CI: 0.72, 1.05)
Miyake, 2009 (82)	Prospective cohort (Osaka Maternal and Child Health Study)	Japan	<i>n</i> = 763, 313 in the subsample with negative parental atopic history, and 450 in the subsample with positive parental atopic history Baseline: birth Race/ethnicity: NR	Partial BF $\geq 6$ mo vs. $< 6$ mo	Atopic eczema at 16–24 mo among children without suspected atopic eczema at 2–9 mo in the subsample with negative parental atopic history: OR: 3.39 (95% CI: 1.20, 12.36)	Atopic eczema at 16–24 mo among children without suspected atopic eczema at 2–9 mo: OR: 1.66 (95% CI: 0.99, 2.92) Atopic eczema at 16–24 mo among children without suspected atopic eczema at 2–9 mo in the subsample with positive parental atopic history: OR: 1.33 (95% CI: 0.72, 2.55)
Orivuori, 2014 (32)	Prospective cohort (PASTURE)	Finland, France, Germany, Switzerland	<i>n</i> = 853 Baseline: birth Race/ethnicity: NR	BF $\leq 3$ mo vs. $> 6$ mo BF 3–6 mo vs. $> 6$ mo	None None	Atopic dermatitis up to 2 y: OR: 1.15 (95% CI: 0.69, 1.89) Atopic dermatitis up to 2 y: OR: 1.05 (95% CI: 0.65, 1.70)
Sandini, 2011 (64)	Prospective cohort <sup>4</sup>	Finland	<i>n</i> = 891 Baseline: birth Race/ethnicity: NR Risk: 100% family history ( $\geq 1$ parent)	BF $\geq 2$ mo vs. $< 2$ mo	None	Atopic eczema at 2 y: OR: 1.77 (95% CI: 0.52, 6.02)
Silvers, 2009 (83)	Prospective cohort (New Zealand Asthma and Allergy Cohort)	New Zealand	<i>n</i> = 1011 Baseline: birth Race/ethnicity: 14.6% Maori	BF duration (mo)	None	Ever had eczema by 15 mo: OR: 1.00 (95% CI: 0.98, 1.03)

<sup>1</sup>BAMSE, Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology; BF, breastfeeding/breastfed; NR, not reported; PASTURE, Protection Against Allergy Study in Rural Environments; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; PROBIT, Promotion of Breastfeeding Intervention Trial; RCT, randomized controlled trial; ref, reference; SR, systematic review.

<sup>2</sup>Exposures, as defined by the authors of the studies included in the body of evidence, which address shorter versus longer durations of any human milk feeding or vice versa.

<sup>3</sup>Cluster RCT of an intervention to promote prolonged duration and exclusivity of breastfeeding rather than an RCT of breastfeeding per se.

<sup>4</sup>The cohort was sampled from an RCT; however, the data of interest for this SR are unrelated to randomization.

and asthma in childhood and adolescence; however, they lacked racial and ethnic diversity. In addition, 1 sample was high risk for type 1 diabetes and the evidence of interest for this SR did not include any corresponding model adjustments (63). There were 5 North American studies with evidence on never versus ever feeding human milk and childhood asthma, and the 2 US studies used racially and ethnically diverse samples. Across both bodies of evidence, the samples were from countries that were high or very high on the Human Development Index (86), and therefore had a level of human development likely generalizable to the United States.

There were some concerns about internal validity. Infant milk-feeding research can be prone to detection bias because infant milk-feeding data are often collected through the use of parent-reporting methods that may not be valid and reliable; however, most studies collected these data prospectively, which reduces recall bias. Confounding can arise because differences between feeding groups are rarely mitigated by randomization (due to ethical issues around allocating infants to be fed less or no human milk) and infant-feeding decisions can be strongly socially patterned. However, most studies adjusted for confounding variables deemed important and feasible to control, although the

**TABLE 8** Evidence examining the relationship between shorter versus longer durations of any human milk feeding and atopic dermatitis in childhood<sup>1</sup>

First author, year (ref)	Study design (study/cohort name when applicable)	Country	Notable sample characteristics	Shorter vs. longer duration of any human milk feeding exposure <sup>2</sup>	Significant associations with atopic dermatitis	Nonsignificant associations with atopic dermatitis
Bergmann, 2000 (65)	Prospective cohort (MAS)	Germany	<i>n</i> = 880 Baseline: birth Sex: NR Race/ethnicity: NR Risk: "risk enriched" 38% family history (≥2 first-degree relatives or IgE concentrations)	BF >6 mo vs. ≤6 mo	None	Atopic dermatitis at 3–6 y: OR: 1.410 (95% CI: 0.959, 2.072)
Bergmann, 2002 (52)	Prospective cohort (MAS)	Germany	<i>n</i> = 939 Baseline: birth Sex: NR Race/ethnicity: NR Risk: "risk enriched" 38% family history (≥2 first-degree relatives or IgE concentrations)	BF duration (mo) BF ≥1 mo vs. BF <1 mo BF ≥2 mo vs. BF <2 mo BF ≥3 mo vs. BF <3 mo BF ≥4 mo vs. BF <4 mo BF ≥5 mo vs. BF <5 mo BF ≥6 mo vs. BF <6 mo BF ≥7 mo vs. BF <7 mo BF ≥8 mo vs. BF <8 mo BF ≥9 mo vs. BF <9 mo	Atopic eczema through 7 y: OR: 1.029 (95% CI: 1.002, 1.057), <i>P</i> = 0.034 None Atopic eczema through 7 y: OR: 1.384 (95% CI: 1.025, 1.869) None None None None None None None None	None Atopic eczema through 7 y: OR: 1.187 (95% CI: 0.854, 1.648) None Atopic eczema through 7 y: OR: 1.192 (95% CI: 0.899, 1.580) Atopic eczema through 7 y: OR: 1.292 (95% CI: 0.991, 1.685) Atopic eczema through 7 y: OR: 1.273 (95% CI: 0.977, 1.658) Atopic eczema through 7 y: OR: 1.183 (95% CI: 0.907, 1.543) Atopic eczema through 7 y: OR: 1.318 (95% CI: 0.988, 1.759) Atopic eczema through 7 y: OR: 1.294 (95% CI: 0.943, 1.776) Atopic eczema through 7 y: OR: 1.318 (95% CI: 0.943, 1.842)
Grandjean, 2010 (66)	Prospective cohort	Denmark	<i>n</i> = 464 Baseline: birth Race/ethnicity: NR	BF duration (mo) in participants with current or past history of atopic dermatitis by 5 or 7 y vs. no allergy	None	9.5 mo (IQR: 6, 12) vs. 9.9 mo (IQR: 6, 12), <i>P</i> = 0.63
Kramer, 2007 (60)	Cluster RCT <sup>3</sup> (PROBIT)	Belarus	<i>n</i> = 13,889 Baseline: birth Race/ethnicity: NR	Experimental group (higher rates of any BF measured at 3, 6, 9, and 12 mo) vs. control group	None	Ever had eczema by 6.5 y: OR: 1.0 (95% CI: 0.5, 1.8)
Kusel, 2005 (85)	Prospective cohort	Australia	<i>n</i> = 198 Baseline: birth Race/ethnicity: NR Risk: 100% family history (≥1 parent)	BF duration (wk) in participants with nonatopic eczema vs. atopic eczema by 5 y	None	~22.2 wk (95% CI: ~19.7, ~25.0) vs. ~26.0 wk (95% CI: ~23.7, ~28.5), <i>P</i> = 0.06
Larsson, 2008 (18)	Prospective cohort (DBH)	Sweden	<i>n</i> = 4779 Baseline: 1–4 y Race/ethnicity: NR	BF 3–6 mo vs. BF >6 mo BF <3 mo vs. >6 mo	None None	5-y cumulative incidence of eczema by 6–9 y: OR: 0.90 (95% CI: 0.71, 1.15) 5-y cumulative incidence of eczema by 6–9 y: OR: 0.88 (95% CI: 0.64, 1.23)
Orivuori, 2014 (32)	Prospective cohort (PASTURE)	Finland, France, Germany, Switzerland	<i>n</i> = 853 Baseline: birth Race/ethnicity: NR	BF ≤3 mo vs. BF >6 mo BF 3–6 mo vs. BF >6 mo	None None	Atopic dermatitis up to 4 y: OR: 1.14 (95% CI: 0.71, 1.85) Atopic dermatitis up to 4 y: OR: 1.25 (95% CI: 0.79, 1.98)
Sandini, 2011 (64)	Prospective cohort <sup>4</sup>	Finland	<i>n</i> = 891 Baseline: birth Race/ethnicity: NR Risk: 100% family history (≥1 parent)	BF ≥2 mo vs. BF <2 mo	None	Atopic eczema at 5 y: OR: 2.70 (95% CI: 0.79, 9.16)
Sariachvili, 2010 (54)	Nested case-control (PIPO Project)	Belgium	<i>n</i> = 252 cases, 305 controls Baseline: birth Race/ethnicity: NR	BF >4 mo vs. BF ≤4 mo Mean BF duration (wk) in cases vs. controls	None None	Eczema up to age 4 y: OR: 0.97 (95% CI: 0.67, 1.41) Eczema up to age 4 y: 13.8 wk (SE = 0.8) vs. 15.0 wk (SE = 0.8), <i>P</i> = 0.27

<sup>1</sup>BF, breastfeeding; DBH, Dampness in Buildings and Health; IgE, immunoglobulin E; MAS, Multicentre Allergy Study; NR, not reported; PASTURE, Protection Against Allergy Study in Rural Environments; PIPO Project, Prospective Study on the Influence of Perinatal factors on the Occurrence of Asthma and Allergies; PROBIT, Promotion of Breastfeeding Intervention Trial; RCT, randomized controlled trial; ref, reference; SR, systematic review.

<sup>2</sup>Exposures, as defined by the authors of the studies included in the body of evidence, which address shorter versus longer durations of any human milk feeding or vice versa.

<sup>3</sup>RCT of an intervention to promote prolonged duration and exclusivity of breastfeeding rather than an RCT of breastfeeding per se.

<sup>4</sup>The cohort was sampled from an RCT; however, the data of interest for this SR are unrelated to randomization.



**TABLE 9** Systematic review questions, conclusion statements, and grades of the evidence supporting the conclusion statements

Systematic review questions	Conclusion statements
What is the relationship between never versus ever feeding human milk and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span?	Moderate evidence suggests that never, in comparison to ever, being fed human milk is associated with higher risk of childhood asthma. (Grade: moderate) Limited evidence does not suggest a relationship between never versus ever being fed human milk and atopic dermatitis in childhood. (Grade: limited) Evidence about the relationship between never versus ever being fed human milk and atopic dermatitis from birth to 24 mo is inconclusive, and there is insufficient evidence to determine the relationship of never versus ever being fed human milk with food allergies throughout the life span, allergic rhinitis throughout the life span, asthma in adolescence or in adulthood, and atopic dermatitis in adolescence or in adulthood. (Grade: grade not assignable)
What is the relationship between shorter versus longer durations of any human milk feeding and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span?	Moderate evidence, mostly from observational studies, suggests that, among infants fed human milk, shorter versus longer durations of any human milk feeding are associated with higher risk of asthma in childhood and adolescence. (Grade: moderate) Limited evidence does not suggest a relationship between the duration of any human milk feeding and allergic rhinitis or atopic dermatitis in childhood. (Grade: limited) Evidence about the relationship between shorter versus longer durations of any human milk feeding and atopic dermatitis from birth to 24 mo is inconclusive, and there is insufficient evidence to determine the relationship of shorter versus longer durations of any human milk feeding with food allergies throughout the life span; allergic rhinitis from birth to 24 mo, in adolescence, or in adulthood; asthma in adulthood; and atopic dermatitis in adolescence or in adulthood. (Grade: grade not assignable)
What is the relationship between shorter versus longer durations of exclusive human milk feeding prior to the introduction of infant formula and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span?	There is insufficient evidence to determine the relationship between shorter versus longer durations of exclusive human milk feeding prior to the introduction of infant formula and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span. (Grade: grade not assignable)
What is the relationship between feeding a lower versus higher intensity, proportion, or amount of human milk to mixed-fed infants and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span?	There is no evidence to determine the relationship between feeding a lower versus higher intensity, proportion, or amount of human milk to mixed-fed infants and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span. (Grade: grade not assignable)
What is the relationship between feeding a higher intensity, proportion, or amount of human milk by bottle versus by breast and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span?	There is no evidence to determine the relationship between feeding a higher intensity, proportion, or amount of human milk by bottle versus by breast and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span. (Grade: grade not assignable)

specific adjustment variables varied between studies. Reverse causation can be a major concern because parents may decide, or receive medical advice, to continue or discontinue feeding human milk based on infants' symptoms and because atopic disease in parents or older siblings may influence parents' feeding decisions as they try to prevent asthma. However, the majority of studies found no baseline differences in family history of atopic disease between groups or included family history of atopic disease as an adjustment variable (18, 22–25, 27–29, 31–34, 36, 60, 62–65, 67, 68, 70, 73–78). Attrition bias, due to high attrition, differential attrition, or both, may have existed among some of the studies in the body of evidence (18, 22, 27, 31, 33, 36, 37, 62, 65, 66, 71, 77, 78); however, these studies were not more concentrated among the studies with significant compared with nonsignificant associations.

TEC members graded the evidence underlying their conclusions on 1) never versus ever being fed human milk and atopic dermatitis in childhood, 2) longer versus shorter durations of any human milk feeding and allergic rhinitis in childhood, and 3) longer versus shorter durations of any human milk feeding and atopic dermatitis in childhood as limited (Table 9). Evidence

underlying all 3 conclusion statements was consistent, with nonsignificant associations across all but 1 of the observational studies in each body of evidence (52, 53, 61). Furthermore, the inconsistency may be explainable because the significant associations were found in 1) a study that may have had limited generalizability because approximately half of the participants were born small for gestational age (53), 2) a subsample analysis of African Americans (61) with no similar analyses that TEC members could examine to assess whether the association was typical in African Americans, and 3) a study with 11 comparisons across 2 articles (52, 65) that may have been prone to multiple comparison bias.

The evidence underlying all 3 conclusion statements had limitations related to adequacy, impact, generalizability, and internal validity. The bodies of evidence were small (9, 5, and 8 studies, respectively), and some samples may have been too small for sufficient statistical power to examine the comparisons of interest (29, 32, 52, 64, 65). Regarding impact, the evidence does not suggest relationships between never versus ever being fed human milk and atopic dermatitis in childhood or between the duration of human milk feeding and allergic rhinitis or



atopic dermatitis in childhood, and with no relationship there would be no clinical significance. There are some doubts about generalizability to US populations because there was only 1 US sample with evidence about the duration of any human milk feeding and allergic rhinitis in childhood and it lacked racial and ethnic diversity (61), and there were no US samples with evidence on the duration of any human milk feeding or never versus ever being fed human milk and atopic dermatitis in childhood. In addition, in the evidence base for shorter versus longer durations of any human milk feeding and allergic rhinitis, 1 sample was from a cohort at risk for type 1 diabetes (not atopic disease) and the comparison of interest for this SR was not adjusted for any type 1 diabetes risk-related variables (63). Finally, the evidence had internal validity limitations because, as previously described, detection and selection bias may pervade infant milk-feeding research and some studies had high or differential attrition (18, 31, 52, 53, 62, 65, 66, 85).

### Research recommendations

TEC members identified several research recommendations. There was insufficient evidence to answer 3 of the 5 SR questions (Table 9). In addition, there was evidence to answer 2 of the 5 SR questions for specific age groups but not throughout the life span. Therefore, studies need to be designed and conducted to examine these gaps in evidence. Studies with representative US samples are needed to confirm current evidence. Researchers should move toward collecting infant-feeding data consistently using validated methods. We propose that researchers study the duration of human milk feeding among infants fed human milk (i.e., assess infants who were never fed human milk separately from humans who were fed human milk). Another consideration is that there may be a large degree of overlap between current literature examining the duration of exclusive human milk feeding (which may terminate with complementary feeding) and the timing of introduction of complementary foods and beverages. However, the degree of overlap is difficult to ascertain because infant-feeding variables often lack explicit and clear definitions. Precise information about what infants are fed needs to be collected and presented more consistently by the research community. Infant-feeding research will continue to rely on observational designs; however, researchers should endeavor to minimize bias through sound research design and conduct. For example, baseline differences in critical confounding variables should be assessed between comparison groups, and statistical adjustments should be made, as necessary. Studies of outcomes in the B-24 population should also address temporality. Finally, researchers should incorporate effect modification into their study design whenever possible (e.g., family history of atopic disease) because different environmental and biological characteristics may modify the impact of infant milk-feeding practices on the outcomes.

We thank Katherine Kortsmit and Kelly Mannherz for their assistance with extracting data and assessing the studies' risk of bias. We also thank Sue Anderson for serving as a TEC member until December 2015.

The authors' responsibilities were as follows—DG, PN, SAA, LB, KMJ, LAN-R, KOO'B, EO, RP-E, EEZ, and JMS: participated in establishing the research questions, analytic framework, and study inclusion and exclusion criteria; YPW and NT: developed and conducted the literature search; PN, CD, and DG: screened search results and identified studies for inclusion;

CCL, PN, and DG: conducted a manual search, extracted data, and assessed risk of bias for included studies; SAA, LB, TJ, KMJ, LAN-R, KOO'B, EO, RP-E, and EEZ: reviewed and provided substantive feedback on all SR materials, including the synthesis of the body of evidence, conclusion statement, and grade of the strength of the evidence; DG, PN, and CCL: wrote the manuscript; DG: had primary responsibility for final content; JMS: provided oversight of the project; and all authors: critically reviewed and read and approved the final manuscript. The authors declared no conflicts of interest.

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