Title

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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/nqy371

Peer reviewed

Infant milk-feeding practices and diagnosed celiac disease and inflammatory bowel disease in offspring: a systematic review

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ABSTRACT

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

Objective: The aim of these systematic reviews was to examine the relationships of never versus ever feeding human milk, shorter versus longer durations of any and exclusive human milk feeding, and feeding a lower versus a higher intensity of human milk to mixed-fed infants with diagnosed celiac disease and inflammatory bowel disease (IBD).

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

Results: We included 9 celiac disease and 17 IBD articles. Limited case-control evidence suggests never versus ever being fed human milk is associated with higher risk of celiac disease, but concerns about reverse causality precluded a conclusion about the relationship of shorter versus longer durations of any human milk feeding with celiac disease. Evidence examining never versus ever feeding human milk and IBD was inconclusive, and limited, but consistent, case-control evidence suggests that, among infants fed human milk, shorter versus longer durations of any human milk feeding are associated with higher risk of IBD. For both outcomes, evidence examining the duration of exclusive human milk feeding was scant and no articles examined the intensity of human milk fed to mixed-fed infants.

Conclusion: Limited case-control evidence suggests that feeding human milk for short durations or not at all associates with higher risk of diagnosed IBD and celiac disease, respectively. The small number of studies and concern about reverse causality and recall bias prevent stronger conclusions. *Am J Clin Nutr* 2019;109(Suppl):838S–851S.

Keywords: breastfeeding, breast milk, human milk, celiac disease, inflammatory bowel disease, Crohn disease, ulcerative colitis, systematic review

Introduction

The Pregnancy and Birth to 24 Months Project was an initiative of the USDA and US Department of Health and Human Services (1–3). During the Project, the USDA Nutrition Evidence Systematic Review (NESR) team (formerly the Nutrition Evidence Library or NEL) collaborated with external experts to complete a series of systematic reviews (SRs) that examined nutrition topics relevant to women during pregnancy and offspring during the first 2 y of life.

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: ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; IBD, inflammatory bowel disease; NESR, Nutrition Evidence Systematic Review; SR, systematic review; TEC, Technical Expert Collaborative.

First published online March 28, 2019; doi: https://doi.org/10.1093/ajcn/nqy371.

The SRs in this article examine the relationships of infant milk-feeding practices with diagnosed celiac disease and inflammatory bowel disease (IBD) in offspring. In 2003, researchers from the Center for Celiac Research at the University of Maryland School of Medicine estimated that the prevalence of celiac disease in the United States was 0.7–0.8% (4). According to the CDC, in 2015 the prevalence of IBD (specifically, Crohn disease or ulcerative colitis) in the United States was 1.3% among individuals 18 y of age and older (5). Celiac disease and IBD can both cause severe gastrointestinal symptoms and complications such as malnutrition (6, 7) and bowel cancer (8, 9); therefore, they are important areas of public health research.

The purpose of this article is to summarize 8 SRs conducted to answer the following questions:

- What is the relationship between never versus ever feeding human milk and *1*) celiac disease and *2*) IBD in offspring?
- What is the relationship between shorter versus longer durations of any human milk feeding and *1*) celiac disease and *2*) IBD in offspring?
- What is the relationship between shorter versus longer durations of exclusive human milk feeding and *1*) celiac disease and *2*) IBD in offspring?
- What is the relationship between feeding a lower versus a higher intensity, proportion, or amount of human milk to mixed-fed infants and *1*) celiac disease and *2*) IBD in offspring?

Methods

NESR 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 (10). 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 SRs

TEC members specified the target population, exposures and comparators, outcomes, critical confounding variables, and key definitions for the SRs using the analytic framework shown in **Figure 1**. In the SRs, "infant milk-feeding practices" referred to the feeding of human milk and/or infant formula. 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 the 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 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. Similarly, for the comparison of never with ever feeding human milk, TEC members did not define any minimum amount for ever feeding human milk. They examined all comparisons of shorter with longer durations (or vice versa) and of never with ever feeding human milk (or vice versa) as defined by the authors of the studies included in the SRs.

The SRs included evidence about diagnosed celiac disease and IBD, only. This ensured that the SRs address the relationships of infant milk-feeding practices with celiac disease and IBD and not the relationships of infant milk-feeding practices with the many other diseases and conditions with similar symptoms.

Literature search, screening, and selection

The librarians developed a literature search strategy that used exposure terminology but not outcome terminology (available from https://nesr.usda.gov) so that 1 search could be used to identify literature in support of SRs examining infant milk-feeding practices with several different outcomes (3). The librarians conducted a broad search in CINAHL, Cochrane, Embase, and PubMed using a search date range of January, 1980 to March, 2016. The search excluded articles published before 1980 because the US Congress passed the Infant Formula Act in 1980, which established minimum nutrient requirements for commercial infant formulas in the United States and thus health effects associated with formula consumption before 1980 may be different (11). The search was restricted to primary research; existing systematic reviews and meta-analyses were not included in the review. The search was not updated before publication.

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 (10) (available from 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. 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 implications, nor should they be interpreted to be dietary guidance. The strength of the evidence underlying each conclusion statement was graded as strong, moderate, limited, or grade not assignable using the NESR grading rubric (10) (available from https://nesr.usda.gov) which takes into consideration the internal validity, consistency,

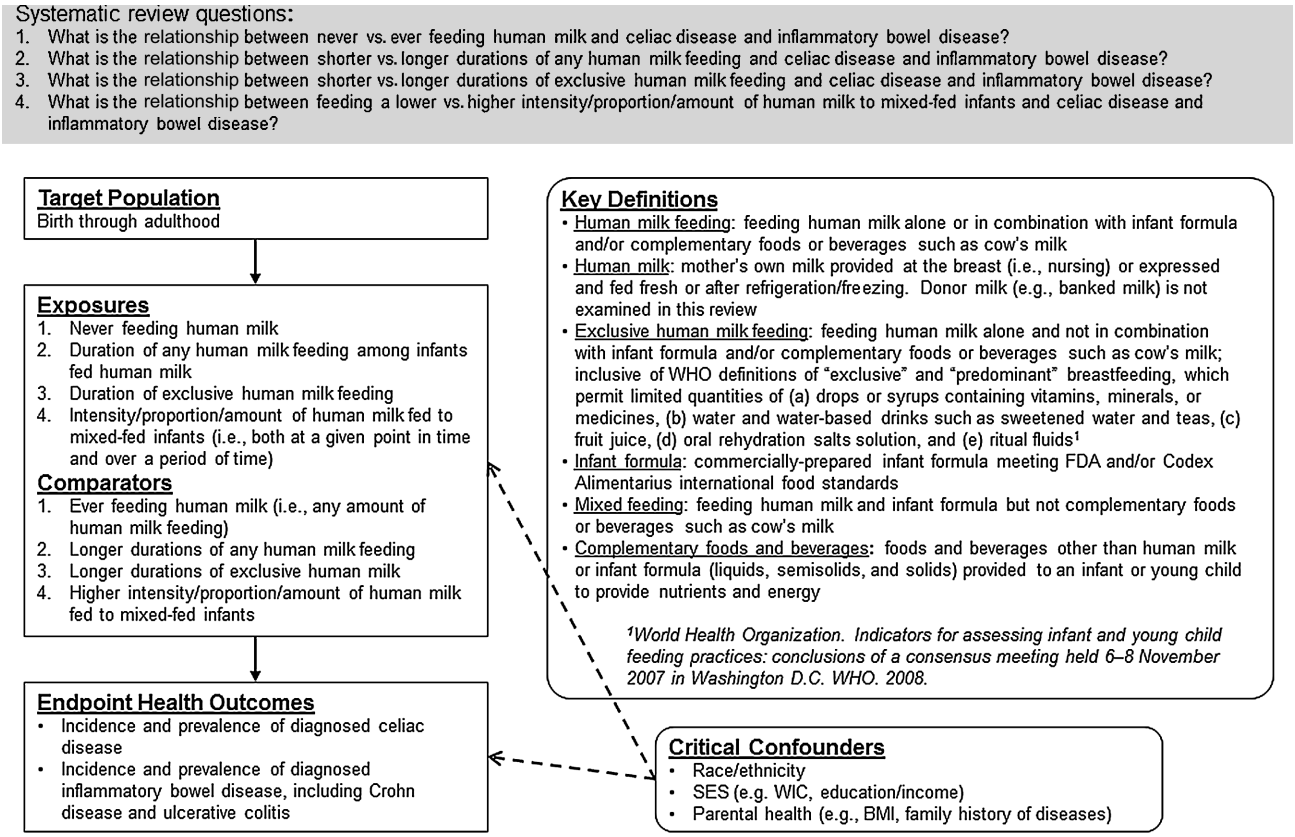

FIGURE 1 The analytic framework for systematic reviews conducted to examine the relationships of infant milk-feeding practices with celiac disease and inflammatory bowel disease in offspring. This framework illustrates the overall scope of the project, including the population, exposures, comparators, and outcomes of interest. It also includes definitions of key terms. FDA, Food and Drug Administration; SES, socioeconomic status; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

adequacy, impact, and generalizability of the evidence. Finally, TEC members identified research recommendations.

Results

The literature search yielded 31,335 articles. The evidence for the 4 SRs on infant milk-feeding practices and celiac disease comprised 9 articles (12–20) whereas the evidence for the 4 SRs on infant milk-feeding practices and IBD comprised 17 articles (14, 21–36). A literature search and screening flowchart and table of articles excluded during full-text screening, with the rationale for their exclusion, is available from https://nesr.usda.gov.

Infant milk-feeding practices and celiac disease in offspring

There was insufficient evidence to determine the relationship between the duration of exclusive human milk feeding and celiac disease (12, 18) and no evidence to determine the relationship between the intensity, proportion, or amount of human milk fed to mixed-fed infants and celiac disease. Additional information about these topics is available at https://nesr.usda.gov. Evidence about never versus ever feeding human milk and shorter versus longer durations of any human milk feeding is presented below.

Never versus ever feeding human milk.

Four articles met the inclusion criteria for the SR examining the relationship between never versus ever feeding human milk and celiac disease (**Table 2**). These articles presented evidence from 2 case-control studies from Italy (13, 15) and 2 case-control studies from Germany (14, 18).

Auricchio et al. (13) matched cases with sibling controls, which minimizes confounding from family-level variables (including the critical confounding variables identified by TEC members in Figure 1). Cases' median age at diagnosis was 15 mo (range: 6 mo–14 y). Infant milk-feeding data were collected by maternal recall via interview and, for a subset of cases who had infant milk-feeding data recorded in their medical records, there was good agreement between the data reported by mothers and the data recorded in cases' medical records at the time of their diagnosis. Celiac disease was diagnosed using criteria from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (37). Children who were fed formula from birth were compared with 4 categories of children who were fed human milk for different durations (i.e., <30, 30–59, 60–89, and ≥90 d). The authors reported that, for each categorical increase in the duration of human milk feeding compared with never human milk feeding, there was a significant decrease in the RR of celiac disease.

TABLE 1 Inclusion and exclusion criteria established for the selection of studies to include in systematic reviews on infant milk-feeding practices and celiac disease and inflammatory bowel disease[1]

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 from 1980–December, 2015[2]	Published before 1980
Source of foods, beverages, or nutrients	Human milk: mother's own milk, that is, human milk fed at the breast, or expressed and fed fresh or after refrigeration/freezing Infant formula: commercially-prepared infant formula meeting FDA (38) or Codex Alimentarius (39) 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 (38) or Codex Alimentarius (39) food standards
Study setting	Countries listed as Very High or High on the 2014 Human Development Index[3] (40, 41)	Countries listed as Medium or Low on the 2014 Human Development Index (40)
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), toddlers (12–24 mo), children (2–12 y), adolescents (13–18 y), adults (19 y and older)	—
Size of study groups	Studies with ≥30 participants per study group or a power analysis indicating that the study is appropriately powered for the outcomes of interest	Studies with <30 participants per study group with no power analysis indicating that the study is appropriately powered for the outcomes of interest
Health status of study participants	Studies done in generally healthy populations Studies done in populations where infants were full term (gestational age ≥37 and 0/7 wk) 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 of exclusively preterm infants (gestational age <37 wk), exclusively infants that have low birth weight (<2500 g), or exclusively infants that are small for gestational age

[1]FDA, Food and Drug Administration.
[2]In 1980 the Infant Formula Act (11) was passed and December, 2015 was when the literature search occurred.
[3]When a country was not included in the Human Development Index ranking, country classification from the World Bank was used instead.

Decker et al. (14) compared cases with age-matched controls. Cases' mean ± SD age at diagnosis was 5.5 ± 4.2 y. Significantly more controls than cases were male and significantly more cases than controls were born by cesarean delivery; however, these differences were not adjusted for in the analyses. Infant milk-feeding data were collected by parent recall via questionnaire or interview. Celiac disease was diagnosed medically (cases were patients at pediatric gastrointestinal outpatient clinics) with histological confirmation for 87.9% of cases. In this study, significantly more cases than controls were fed human milk and, in an unadjusted analysis, there was a significant association between ever being fed human milk, in comparison with never being fed human milk, and higher odds of celiac disease.

Greco et al. (15) compared cases with controls who were matched by age and geographic location. Cases' mean ± SD age at diagnosis was 2.14 ± 2.6 y. Infant milk-feeding data were collected by parent recall via interview, and the study authors completed a quality control check that found good agreement with exposure data collected longitudinally at well-baby clinics for a subset of controls. Celiac disease was diagnosed using ESPGHAN criteria (37). The percentage of infants fed human milk at birth did not differ significantly between cases and controls.

Peters et al. (18) compared cases with sex- and age-matched controls. Cases' median age at the onset of symptoms was 13.0 mo (range: 1.0–84.0 mo). Infant milk-feeding data were collected by parent recall via questionnaire. Celiac disease was diagnosed medically using ESPGHAN criteria (42), with 93% of the diagnoses confirmed by biopsy. The analyses compared 3 durations of human milk feeding (i.e., >0–<3, ≥3–<7, and ≥7 mo) with never feeding human milk, and included family history of celiac disease as an adjustment variable (i.e., 1 of the 3 critical confounding variables identified by TEC members in Figure 1). The study found significant associations between being fed human milk for ≥3–<7 mo and ≥7 mo, compared with never being fed human milk, and lower odds of celiac disease. In addition, when being fed human milk for >0–<3 mo was compared with never being fed human milk, the association was

TABLE 2 Evidence examining the relationship between never versus ever feeding human milk and celiac disease in offspring[1]

Author and year, study design, country	Notable sample characteristics	Never vs. ever feeding human milk exposure[2]	Significant associations with celiac disease	NS associations with celiac disease
Auricchio 1983 (13), case control, Italy	$n = 216$ cases, 289 sibling controls Baseline: median 5–8 y depending on study site Race/ethnicity NR	FF vs. BF <30, 30–59, 60–89, and ≥90 d	RR: 1.6 (95% CI: 1.2, 1.7)	None
Decker 2010 (14), case control, Germany	$n = 123$ cases, 743 controls Baseline: mean ± SD 9.1 ± 4.5 y for cases and 10.0 ± 4.5 y for controls Race/ethnicity NR	% BF in cases vs. controls BF vs. not BF	86.6% vs. 76.5%, $P = 0.015$ OR: 1.99 (95% CI: 1.12, 3.51)	None None
Greco 1988 (15), case control, Italy	$n = 201$ cases, 1949 controls Baseline: mean ± SD 2.14 ± 2.6 y Sex NR Race/ethnicity NR	% BF at birth in cases vs. controls	None	~65% vs. ~70%, OR: 1.16 (95% CI NR)
Peters 2001 (18), case control, Germany	$n = 143$ cases, 137 controls Baseline: mean 6.4 y, median 6.2 y Sex NR Race/ethnicity NR	BF >0–<3 mo vs. never BF BF ≥3–<7 mo vs. never BF BF ≥7 mo vs. never BF	None OR: 0.22 (95% CI: 0.08, 0.59) OR: 0.18 (95% CI: 0.06, 0.52)	OR: 0.39 (95% CI: 0.15, 1.02) None None

[1] BF, breastfeeding/breastfed; FF, formula feeding/formula fed; NR, not reported; NS, nonsignificant.
[2] 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.

in the same direction but the CI was wider and included the null.

In summary, 4 case-control studies examined the relationship between never versus ever being fed human milk and celiac disease. The 2 studies, which controlled for confounding (13, 18), reported associations that were consistent in direction, suggesting that never versus ever being fed human milk is associated with higher risk of celiac disease. The remaining 2 studies found no difference in the percentage of cases and controls fed human milk at birth (15), or found that ever versus never being fed human milk was associated with a significant increase in celiac disease risk (14); however, these analyses did not include statistical adjustments, including for variables found to differ between cases and controls in the study by Decker et al. (14). TEC members concluded that this limited evidence suggests that never versus ever being fed human milk is associated with higher risk of celiac disease.

Shorter versus longer durations of any human milk feeding.

Nine articles met the inclusion criteria for the SR examining the relationship between shorter versus longer durations of any human milk feeding and celiac disease (12–20). Four articles presented nested case-control or prospective cohort data analyses (12, 17, 19, 20) and the remaining 5 were case-control studies (13–16, 18).

When TEC members began assessing the evidence, they identified that the diagnosis of celiac disease preceded the time some infants stopped receiving human milk; that is, there was not time ordering in which the exposure definitively came before the outcome. Owing to this reverse causality concern, the SR question about shorter versus longer durations of any human milk feeding and celiac disease could not be answered because it was not clear that the exposure was affecting the outcome, rather than the opposite.

Infant milk-feeding practices and IBD in offspring

Two of the 17 articles included for the infant milk-feeding practices and IBD SRs examined shorter versus longer durations of exclusive human milk feeding (27, 28) and none examined the intensity, proportion, or amount of human milk fed to mixed-fed infants. TEC members concluded this was insufficient evidence to answer these 2 SR questions. Additional information about these topics is available from https://nesr.usda.gov. Evidence about never versus ever feeding human milk and shorter versus longer durations of any human milk feeding is presented below.

Never versus ever feeding human milk.

Thirteen articles examined the relationship between never versus ever feeding human milk and IBD (**Table 3**). They presented evidence from 1 nested case-control study from the United Kingdom (34), 11 independent case-control studies from the United States (33), Canada (27–29), France (30), Italy (31), Germany (14), Denmark (23), China (36), Japan (35), and New Zealand (32), and a multinational study (i.e., United States, Canada, United Kingdom, Sweden, Denmark, Holland, France, Italy, and Israel) (22). Two articles by Koletzko et al. (27, 28) were related to each other, but presented evidence on distinct outcomes (i.e., Crohn disease and ulcerative colitis).

The nested case-control study by Roberts et al. (34) included 114 cases with Crohn disease, 66 cases with ulcerative colitis, and 248,479 controls from the Oxford Record Linkage Study. The study collected data about participants beginning at birth,

TABLE 3 Evidence examining the relationship between never versus ever feeding human milk and IBD in offspring[1]

Author and year, study design (study/cohort name when applicable), country	Notable sample characteristics	Never vs. ever feeding human milk exposure[2]	Significant associations with IBD	NS associations with IBD
Amre 2006 (29), case control, Canada	$n = 194$ Crohn disease cases, 194 controls Baseline: mean ± SD: 12.26 ± 4.0 y in cases, 8.63 ± 5.0 y in controls Race/ethnicity: NR; 93% French-Canadian	Ever BF vs. never BF	None	Crohn disease: OR: 0.8 (95% CI: 0.5, 1.3)
Baron 2005 (30), case control, France	$n = 222$ Crohn disease cases, 222 Crohn disease controls; 60 ulcerative colitis cases, 60 ulcerative colitis controls Baseline: median 13.5 y (IQR: 11, 15 y) for Crohn disease, 14 y (IQR: 11, 15 y) for ulcerative colitis Race/ethnicity NR	BF vs. no BF	Crohn disease: OR: 2.1 (95% CI: 1.3, 3.4), $P = 0.003$	Ulcerative colitis: NS (data NR)
Castiglione 2012 (31), case control, Italy	$n = 468$ Crohn disease cases, 527 ulcerative colitis cases, 562 controls Baseline: median ~37 y (range: 16–66 y) Race/ethnicity NR	BF vs. no BF	None	Crohn disease: OR: 1.04 (95% CI: 0.78, 1.39) Ulcerative colitis: OR: 1.27 (95% CI: 0.96, 1.69)
Decker 2010 (14), case control, Germany	$n = 374$ Crohn disease cases, 169 ulcerative colitis cases, 743 controls Baseline: mean ± SD 13.9 ± 3.5 y for Crohn disease cases, 13.5 ± 4.0 y for ulcerative colitis cases, 10.0 ± 4.5 y for controls Race/ethnicity NR	BF vs. no BF	None	Crohn disease: OR: 0.93 (95% CI: 0.69, 1.25) Ulcerative colitis: OR: 1.01 (95% CI: 0.66, 1.55)
Gearry 2010 (32), case control (Canterbury IBD Study), New Zealand	$n = 638$ Crohn disease cases, 653 ulcerative colitis cases, 600 controls Baseline: 13.5% 20–29 y, 23.0% 30–39 y, 20.9% 40–49 y, 16.7% 50–59 y, 25.9% >59 y Race/ethnicity: 96.8% Caucasian, 2% Maori, 1.5% Asian, 0.1% Pacific Islander	BF vs. no BF	Crohn disease: OR: 0.55 (95% CI: 0.41, 0.74) Ulcerative colitis: OR: 0.71 (95% CI: 0.52, 0.96)	None
		BF 0–2 mo vs. no BF	None	Crohn disease: OR: ~1.0 (95% CI: ~0.7, ~1.5) Ulcerative colitis: OR: ~1.1 (95% CI: ~0.8, ~1.7)
		BF 3–6 mo vs. no BF	Crohn disease: OR: ~0.5 (95% CI: ~0.4, ~0.8) Ulcerative colitis: OR: ~0.6 (95% CI: ~0.4, ~0.9)	None
		BF 6–12 mo vs. no BF	Crohn disease: OR: ~0.5 (95% CI: ~0.4, ~0.8) Ulcerative colitis: OR: ~0.6 (95% CI: ~0.5, ~0.9)	None
		BF >12 mo vs. no BF	Crohn disease: OR: ~0.4 (95% CI: ~0.3, ~0.8) Ulcerative colitis: OR: ~0.4 (95% CI: ~0.1, ~0.9)	None
Gilat 1987 (22), case control, United States, Canada, United Kingdom, Sweden, Denmark, Holland, France, Italy, and Israel	$n = 302$ Crohn diseases cases, 197 ulcerative colitis cases, 998 controls Baseline: mean ± SD 20.0 ± 5.2 y; all participants <25 y Race/ethnicity NR	BF frequency in cases vs. controls	None	Crohn disease: NS (data NR) Ulcerative colitis: NS (data NR)

(*Continued*)

TABLE 3 (*Continued*)

Author and year, study design (study/cohort name when applicable), country	Notable sample characteristics	Never vs. ever feeding human milk exposure[2]	Significant associations with IBD	NS associations with IBD
Hansen 2011 (23), case control, Denmark	$n = 123$ Crohn disease cases, 144 ulcerative colitis cases, 267 controls Baseline: median ~38 y (range: 10–95 y) Race/ethnicity: 100% Caucasian	BF vs. no BF	None	IBD: OR: 1.07 (95% CI: 0.52, 2.16) Crohn disease: OR: 1.80 (95% CI: 0.60, 5.38) Ulcerative colitis: OR: 0.70 (95% CI: 0.27, 1.84)
Koletzko 1989 (27), case control, Canada	$n = 114$ Crohn disease cases, 180 controls Baseline: mean ~17 y Race/ethnicity NR	No BF vs. BF	Crohn disease: RR 3.8 (95% CI: 1.5, 9.5), $P = 0.005$	None
Koletzko 1991 (28), case control, Canada	$n = 93$ ulcerative colitis cases, 138 controls Baseline: mean ~15 y Sex NR Race/ethnicity NR	No BF vs. BF	None	Ulcerative colitis: RR: 1.7 (95% CI: 0.77, 3.65), $P = 0.19$
Rigas 1993 (33), case control, United States	$n = 68$ Crohn diseases cases, 39 ulcerative colitis cases, 202 controls Baseline: <17 y Race/ethnicity: 94.2% white	BF ≤5 mo vs. BF 0 mo	None	Crohn disease: RR: 0.7 (95% CI: 0.3, 1.5) Ulcerative colitis: RR: 0.7 (95% CI: 0.3, 1.6)
		BF 6–11 mo vs. BF 0 mo	None	Crohn disease: RR: 0.6 (95% CI: 0.2, 1.5) Ulcerative colitis: RR: 0.5 (95% CI: 0.2, 1.5)
		BF ≥12 mo vs. BF 0 mo	None	Crohn disease: RR: 0.1 (95% CI: 0.01, 1.1) Ulcerative colitis: RR: 0.2 (95% CI: 0.03, 2.2)
Roberts 2011 (34), nested case control (Oxford Record Linkage Study), United Kingdom	$n = 114$ Crohn disease cases, 66 ulcerative colitis cases, 248,479 controls Baseline: birth Race/ethnicity NR	Proportion of artificial-fed infants vs. BF infants with subsequent disease status	None	Crohn disease by mean 18 y (range: 10–30 y): 0.031% vs. 0.033%, $P = 0.89$ Ulcerative colitis by mean 18 y (range: 10–30 y): 0.015% vs. 0.020%, $P = 0.67$
Urashima 1999 (35), case control, Japan	$n = 42$ Crohn disease cases, 133 ulcerative colitis cases, 392 controls Baseline: mean ~10.7 y (range: 2 mo–15 y 10 mo) Race/ethnicity NR	BF only plus mixed feeding from birth to 4 mo vs. artificial feeding only from birth to 4 mo	Crohn disease: OR: 0.30 (95% CI: 0.13, 0.70) Ulcerative colitis: OR: 0.53 (95% CI: 0.31, 0.89)	None
Wang 2013 (36), case control, China	$n = 1308$ ulcerative colitis cases, 1308 controls Baseline: average ~41.5 y (range: 16–70 y) Race/ethnicity NR	BF vs. no BF	None	Ulcerative colitis: OR: 1.08 (95% CI: 0.79, 1.48), $P = 0.628$

[1] BF, breastfed; IBD, inflammatory bowel disease; NR, not reported; NS, nonsignificant.
[2] 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.

and the follow-up period was a mean of 18 y (range: 10–30 y). Data about whether or not participants were fed human milk came from mothers' maternity medical records, and data about whether participants were diagnosed with Crohn disease or ulcerative colitis came from participants' inpatient and outpatient medical records. There was no significant difference between the proportion of participants who were never fed human milk and developed Crohn disease and the proportion of participants who were ever fed human milk and developed Crohn disease. Likewise, there was no significant difference between the proportion of participants who were never fed human milk and developed ulcerative colitis and the proportion of participants who were ever fed human milk and developed ulcerative colitis.

The analytic sample sizes of the case-control studies ranged from 68 Crohn disease cases, 39 ulcerative colitis cases, and 202 controls (33) to 638 Crohn disease cases, 653 ulcerative colitis

cases, and 600 controls (32). Participants were both male and female and, in the 3 studies that reported race or ethnicity, nearly all participants were white [97% in the study by Gearry et al. (32), 100% in the study by Hansen et al. (23), and 94% in the study by Rigas et al. (33)].

Most of the studies collected infant-feeding data retrospectively by parent report (14, 27–30, 35) or by self-report (22, 23, 31, 32, 36), in some instances with instructions to participants to corroborate responses with parental recall (32) or with information recorded prospectively in participants' *carnet de santé* (30) or "child health book" (32) (i.e., booklets into which pediatric health information is recorded by health professionals for families in France and New Zealand, respectively). Rigas et al. (33) extracted infant-feeding data from participants' medical records. The outcomes, Crohn disease and ulcerative colitis, were medically diagnosed. All of the studies used matching variables and 5 used additional adjustment variables (14, 27, 28, 30, 32, 33). Most studies matched cases with controls using sex and age (22, 23, 30, 32, 35, 36) and geographic location (22, 23, 30–32, 35). Koletzko et al. (27, 28) matched cases with sibling controls to account for family-level variables such as genetic and environmental factors. The studies by Amre et al. (29), Decker et al. (14), and Rigas et al. (33) matched cases with controls based on their status as patients at the time of the study rather than by sex and age; hence, in the studies by Amre et al. (29) and Decker et al. (14), cases were significantly older than controls, and in the study by Decker et al. (14) more of the Crohn disease cases than controls were male. Rigas et al. (33) did not indicate whether cases differed significantly from controls with regard to typical matching variables. Decker et al. (14) and Rigas et al. (33) subsequently controlled for age and sex in their statistical analyses, but Amre et al. (29) did not adjust for these variables. Five of the studies accounted for variables identified by TEC members as critical confounders for this SR (Figure 1) by including family history of IBD (32), race (33), ethnicity (32), and measures of socioeconomic status [i.e., maternal education (30), social class at birth (32)] as adjustment variables, conducting analyses in homogeneous racial or ethnic groups (23), or matching cases with sibling controls (27, 28).

Four of the 11 case-control studies reported statistically significant associations between never versus ever being fed human milk and IBD outcomes (27, 30, 32, 35). The associations were consistent in direction across 3 of these studies (27, 32, 35) and suggested that never versus ever being fed human milk is associated with a higher risk of IBD outcomes.

Specifically, Gearry et al. (32) examined the prevalence of Crohn disease and of ulcerative colitis in a sample of participants ≥20 y of age. The first analysis compared ever being fed human milk with never being fed human milk and found that ever being fed human milk was associated with significantly lower odds of Crohn disease and of ulcerative colitis. Next, the group ever fed human milk was divided into 4 categories of duration (i.e., 0–2, 3–6, 6–12, and >12 mo). The odds of Crohn disease and of ulcerative colitis were close to the null when 0–2 mo of human milk feeding was compared with never being fed human milk; however, when 3–6, 6–12, and >12 mo of human milk feeding were compared with never being fed human milk, the study found significantly lower odds of Crohn disease and of ulcerative colitis among those fed human milk.

Koletzko et al. (27, 28) examined the associations of never compared with ever feeding human milk with Crohn disease (27) and with ulcerative colitis (28) in children and adolescents (mean 16.1 and 14.2 y of age, respectively) using comparisons with healthy siblings. In comparison with ever being fed human milk, never being fed human milk was associated with a significantly higher RR of Crohn disease. When Koletzko et al. (28) conducted the same analysis to examine the RR of ulcerative colitis, the RR was in the same direction but was nonsignificant with a wide CI.

Urashima et al. (35) examined Crohn disease and ulcerative colitis in children and adolescents (age range: 2 mo–15 y 10 mo). The study compared participants who were ever fed human milk (i.e., participants who were fed human milk only or who were mixed-fed) with participants who were never fed human milk from birth to 4 mo of age. Ever compared with never being fed human milk was associated with significantly lower odds of Crohn disease and of ulcerative colitis.

The study by Baron et al. (30) found an association that was inconsistent in direction with the previous 3 studies. The study examined risk of Crohn disease and of ulcerative colitis in childhood and adolescence. In participants <17 y of age, being fed human milk, compared with not being fed human milk, was associated with significantly higher odds of Crohn disease. The corresponding analysis for ulcerative colitis was not statistically significant, and the point estimate was not reported so the direction could not be examined.

In summary, across 1 nested case-control study and 11 case-control studies, there were 4 case-control studies that reported statistically significant associations. Three of the 4 studies reported statistically significant associations that suggest that never versus ever feeding human milk is associated with higher risk of Crohn disease (27, 32, 35) and of ulcerative colitis (32, 35), and the remaining study reported a statistically significant association that suggests that never versus ever feeding human milk is associated with a lower risk of Crohn disease (30). The analyses in 1 of these studies (35) did not account for any of the critical confounding variables identified by TEC members (Figure 1); on the other hand, Koletzko et al. (27) matched cases with sibling controls, Gearry et al. (32) included adjustments for all 3 critical confounders, and Baron et al. (30) adjusted for a measure of socioeconomic status. Across the body of evidence, 3 of the studies had nonsignificant associations with wide CIs indicative of suboptimal statistical power (23, 28, 33); all but 1 of the nonsignificant associations across these 3 studies were in the direction of never versus ever feeding human milk being associated with higher risk of IBD outcomes. The remaining 4 studies with nonsignificant associations had reasonably narrow CIs, suggesting that they had sufficient statistical power (14, 29, 31, 36). TEC members concluded that this evidence examining the relationship between never versus ever feeding human milk and IBD risk was inconclusive.

Shorter versus longer durations of any human milk feeding.

Nine articles examined the relationship between shorter versus longer durations of any human milk feeding and IBD (**Table 4**). They presented evidence from 8 independent case-control studies because Koletzko et al. (27, 28) addressed Crohn disease (27) and ulcerative colitis (28) in the same population in separate articles. The studies were from Canada (27, 28), Sweden (21),

TABLE 4 Evidence examining the relationship between shorter versus longer durations of any human milk feeding and IBD[1]

Author and year, study design, country	Notable sample characteristics	Shorter vs. longer duration of any human milk feeding exposure[2]	Significant associations with IBD	NS associations with IBD
Bergstrand 1983 (21), case control, Sweden	$n = 308$ Crohn disease cases, 308 controls Baseline: NR; adulthood Sex NR Race/ethnicity NR	Mean difference in BF duration in cases vs. controls	Crohn disease: −1.17 mo (SE: −0.25 mo), $P < 0.01$	None
Decker 2010 (14), case control, Germany	$n = 374$ Crohn disease cases, 169 ulcerative colitis cases, 743 controls Baseline: mean ± SD 13.9 ± 3.5 y for Crohn disease cases, 13.5 ± 4.0 y for ulcerative colitis cases, 10.0 ± 4.5 y for controls Race/ethnicity NR	Average BF duration in cases vs. controls	Ulcerative colitis: 3.53 mo vs. 5.25 mo, OR: 0.93 (95% CI: 0.89, 0.98), $P = 0.006$	Crohn disease: 4.24 mo vs. 5.25 mo, OR: 0.99 (95% CI: 0.96, 1.01), $P = 0.335$
Gilat 1987 (22), case control, United States, Canada, United Kingdom, Sweden, Denmark, Holland, France, Italy, and Israel	$n = 302$ Crohn diseases cases, 197 ulcerative colitis cases, 998 controls Baseline: mean ± SD 20.0 ± 5.2 y; all participants <25 y Race/ethnicity NR	BF duration in cases vs. controls	None	Crohn disease: NS (data NR) Ulcerative colitis: NS (data NR)
Hansen 2011 (23), case control, Denmark	$n = 123$ Crohn disease cases, 144 ulcerative colitis cases, 267 controls Baseline: median ~38 y (range: 10–95 y) Race/ethnicity: 100% Caucasian	BF >6 mo vs. BF ≤6 mo	None	IBD: OR: 0.50 (95% CI: 0.23, 1.11) Crohn disease: OR: 0.63 (95% CI: 0.20, 1.91) Ulcerative colitis: OR: 0.40 (95% CI: 0.13, 1.28)
Hlavaty 2013 (24), case control, Slovakia	$n = 129$ Crohn disease cases, 96 ulcerative colitis cases, 293 controls Baseline: median ~30 y (range: 14–87 y) Race/ethnicity NR	BF <6 mo vs. BF ≥6 mo	Crohn disease: OR: 2.72 (95% CI: 1.67, 4.41), $P = 0.00$ Ulcerative colitis: OR: 1.69 (95% CI: 1.02, 2.80), $P = 0.04$	None
Jakobsen 2013 (25), case control, Denmark	$n = 59$ Crohn disease cases, 56 ulcerative colitis cases, 477 controls Baseline: range 3.1–17.2 y Race/ethnicity NR	BF >3 mo vs. BF ≤3 mo	None	IBD: OR: 0.5 (95% CI: 0.3, 1.0), $P = 0.058$ Crohn disease: NS (data NR) Ulcerative colitis: OR: 0.5 (95% CI: 0.2, 1.0), $P = 0.06$
Ko 2015 (26), case control, Australia	$n = 75$ Crohn disease Middle East migrant cases, 153 Middle East migrant controls, 85 Crohn disease Caucasian cases, 79 ulcerative colitis Middle East migrant cases, 77 ulcerative colitis Caucasian cases Baseline: ~35–45 y Race/ethnicity: 42.1% Caucasian, 57.9% Middle Eastern	Sustaining BF 0–2 mo vs. not	None	Crohn disease in Middle East migrant subsample: OR: ~0.3 (95% CI: ~0.1, ~2.5) Crohn disease in Caucasian subsample: OR: ~0.8 (95% CI: ~0.5, ~2.6) Ulcerative colitis in Middle East migrant subsample: OR: ~0.3 (95% CI: ~0.1, ~2.5) Ulcerative colitis in Caucasian subsample: OR: ~0.5 (95% CI: ~0.3, ~1.6)
		Sustaining BF 3–6 mo vs. not	Crohn disease in Middle East migrant subsample: OR: ~0.1 (95% CI: ~0.0, ~0.8) Crohn disease in Caucasian subsample: OR: ~0.1 (95% CI: ~0.0, ~0.8)	Ulcerative colitis in Middle East migrant subsample: OR: ~0.2 (95% CI: ~0.1, ~2.4) Ulcerative colitis in Caucasian subsample: OR: ~0.4 (95% CI: ~0.2, ~1.2)

(*Continued*)

TABLE 4 (*Continued*)

Author and year, study design, country	Notable sample characteristics	Shorter vs. longer duration of any human milk feeding exposure[2]	Significant associations with IBD	NS associations with IBD
		Sustaining BF 6–12 mo vs. not	Crohn disease in Middle East migrant subsample: OR: ∼0.1 (95% CI: ∼0.0, ∼0.5) Crohn disease in Caucasian subsample: OR: ∼0.1 (95% CI: ∼0.0, ∼0.6) Ulcerative colitis in Middle East migrant subsample: OR: ∼0.1 (95% CI: ∼0.0, ∼0.5) Ulcerative colitis in Caucasian subsample: OR: ∼0.1 (95% CI: ∼0.0, ∼0.6)	None
		Sustaining BF >12 mo vs. not	Crohn disease in Middle East migrant subsample: OR: ∼0.0 (95% CI: ∼0.0, ∼0.3) Crohn disease in Caucasian subsample: OR: ∼0.0 (95% CI: ∼0.0, ∼0.3) Ulcerative colitis in Middle East migrant subsample: OR: ∼0.1 (95% CI: ∼0.0, ∼0.3) Ulcerative colitis in Caucasian subsample: OR: ∼0.0 (95% CI: ∼0.0, ∼0.2)	None
Koletzko 1989 (27), case control, Canada	$n = 114$ Crohn disease cases, 180 controls Baseline: mean ∼17 y Race/ethnicity NR	Total length of BF in cases vs. controls	None	Crohn disease: NS (data NR)
Koletzko 1991 (28), case control, Canada	$n = 93$ ulcerative colitis cases, 138 controls Baseline: mean ∼15 y Sex NR Race/ethnicity NR	Total length of BF in cases vs. controls	None	Ulcerative colitis: NS (data NR)

[1]BF, breastfeeding/breastfed; IBD, inflammatory bowel disease; NR, not reported; NS, nonsignificant.
[2]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.

Germany (14), Denmark (23, 25), Slovakia (24), Australia (26), and a multinational study (i.e., United States, Canada, United Kingdom, Sweden, Denmark, Holland, France, Italy, and Israel) (22). The analytic sample sizes ranged from 114 Crohn disease cases, 93 ulcerative colitis cases, and 138–180 controls (27, 28) to 302 Crohn disease cases, 197 ulcerative colitis cases, and 998 controls (22). Only 2 studies reported participants' race or ethnicity; Hansen et al. (23) reported having a sample that was 100% Caucasian and Ko et al. (26) had a sample that was 57.9% Middle Eastern and 42.1% Caucasian. One study did not report participants' sex (21), but all other samples included both males and females.

The studies collected data about the duration of any human milk feeding retrospectively by parent report (14, 27, 28) or by self-report (21–26), in some instances with instructions to participants to corroborate their responses with parental recall (21, 22, 26). The outcomes, Crohn disease and ulcerative colitis, were medically diagnosed. All studies included matching variables and half included additional adjustment variables (14, 24, 25, 27, 28). Most studies matched cases with controls using participants' age and geographic location (21–26), and some studies also used participants' sex (21–24, 26) and ethnicity (23) as matching variables. Koletzko et al. (27, 28) matched cases with sibling controls to account for family-level variables such as genetic and environmental factors. Decker et al. (14) matched cases with controls based on their status as an outpatient at the time of the study; however, Crohn disease and ulcerative colitis cases were significantly older than controls and more of the Crohn disease cases than controls were male (both of these variables were subsequently controlled for in the statistical analyses). Half of the studies accounted for variables identified by TEC members as critical confounders for this SR (i.e., family history of IBD, race/ethnicity, and socioeconomic status, see Figure 1) by including ethnicity and socioeconomic status as adjustment variables (25), conducting analyses in homogeneous racial or ethnic groups (23, 26), or matching cases with sibling controls (27, 28).

Four of the 8 studies reported statistically significant inverse associations between the duration of any human milk feeding and IBD outcomes (14, 21, 24, 26) and a fifth study had CIs in which the upper limit was at the null (25).

Specifically, Bergstrand and Hellers (21) compared the mean duration of any human milk feeding in cases with Crohn disease and controls. On average, individuals with Crohn disease were fed human milk for 1.17 mo less than controls, and this difference was significant.

Decker et al. (14) also compared the average duration of any human milk feeding between cases and controls. Although the average duration of any human milk feeding was 1.72 mo shorter for cases with ulcerative colitis and 1.01 mo shorter for cases with Crohn disease than for controls, the difference was only significant for ulcerative colitis; the odds of Crohn disease were closer to the null.

Hlavaty et al. (24) examined the duration of any human milk feeding as a categorical variable. Being fed human milk for <6 compared with ≥6 mo was associated with significantly higher odds of Crohn disease and of ulcerative colitis.

Ko et al. (26) also examined the duration of any human milk feeding as a categorical variable (i.e., 0–2, 3–6, 6–12, and ≥12 mo), and assessed risk in subsamples of participants who were Middle Eastern migrants and who were Caucasian. In both subsamples, being fed human milk for 0–2 mo was not significantly associated with odds of Crohn disease or of ulcerative colitis. However, in both subsamples, there were significantly lower odds of Crohn disease when human milk feeding was sustained for 3–6, 6–12, and >12 mo. In addition, in both subsamples, there were significantly lower odds of ulcerative colitis when human milk feeding was sustained for 6–12 and >12 mo.

Jakobsen et al. (25) compared being fed human milk for >3 against ≤3 mo and assessed the odds of IBD, generally, and of Crohn disease and of ulcerative colitis, specifically. Although this study did not find any significant associations, the odds of IBD and of ulcerative colitis had CIs in which the upper limit was the null. The point estimate associated with Crohn disease was not reported.

In summary, 4 of the 8 case-control studies in this body of evidence reported statistically significant associations that are consistent in direction, suggesting that shorter versus longer durations of any human milk feeding are associated with higher risk of Crohn disease (21, 24, 26) and of ulcerative colitis (14, 24, 26). The analyses in 3 of these studies (14, 21, 24) did not account for any of the critical confounding variables identified by TEC members (Figure 1). The analyses in the study by Jakobsen et al. (25), which were well-controlled, found associations of >3 compared with ≤3 mo of any human milk feeding with both IBD and ulcerative colitis in which the upper limits of the CIs were at the null. Furthermore, it is notable that all of the studies in this body of evidence that reported point estimates (i.e., significant and nonsignificant) had associations that were consistent in direction (14, 21, 23–26) and, in some cases, the CIs around the nonsignificant point estimates were wide and indicative of suboptimal statistical power (23, 26). TEC members concluded that limited but consistent evidence suggests that shorter versus longer durations of any human milk feeding are associated with higher risk of IBD.

Discussion

The SR questions and conclusion statements are listed in **Table 5**. TEC members graded as limited the evidence underlying the conclusion statements about *1*) never versus ever feeding human milk and celiac disease, and *2*) shorter versus longer durations of any human milk feeding and IBD. A grade of limited is assigned when "the conclusion statement is substantiated by insufficient evidence, and the level of certainty is seriously restricted by limitations in the evidence, such as the amount of evidence available, inconsistencies in the findings, or methodological or generalizability concerns" (10). TEC members used the NESR grading rubric to consider aspects of the adequacy, consistency, generalizability, internal validity, and impact of the evidence described below.

The adequacy of the evidence related to never versus ever feeding human milk and celiac disease was hindered because the body of evidence consisted of just 4 case-control studies. The evidence was consistent across the 2 studies that included adjustment variables to minimize confounding (13, 18); both found statistically significant associations that suggested that never versus ever being fed human milk is associated with higher risk of celiac disease.

The body of evidence related to shorter versus longer durations of any human milk feeding and IBD consisted of 8 studies, including some that may have had inadequate sample sizes for sufficient statistical power, as reflected by wide CIs (23, 26). Across the 4 studies with statistically significant associations, there was consistency in the direction of the associations that suggested that shorter versus longer durations of any human milk feeding are associated with higher risk of Crohn disease (21, 24, 26) and of ulcerative colitis (14, 24, 26). In addition, a fifth study that was well-controlled found nonsignificant associations in the same direction and had a CI with an outer limit at the null (25). Furthermore, the nonsignificant associations reported across the body of evidence were consistent in direction with the significant associations. The consistency in direction across this body of evidence is noteworthy given that the independent variables were heterogeneous, which was a feature of not defining longer duration or shorter duration, and instead considering together all analyses that compared shorter with longer durations of any human milk feeding.

Across the 2 SR questions, TEC members had some concerns about the generalizability of the evidence because there were no US studies about never versus ever feeding human milk and celiac disease and the United States was only represented within a multinational study (22) in the body of evidence for shorter versus longer durations of any human milk feeding and IBD. The majority of the evidence came from Europe. However, all of the evidence in these SRs came from countries that met the inclusion criterion of being high or very high on the Human Development Index (40) and therefore having a level of human development likely generalizable to the United States.

TEC members did have some concerns about internal validity related to study design. Almost all of the studies were case-control studies. TEC members recognized the importance of case-control studies because they are useful for examining low-incident outcomes such as celiac disease and IBD. However, because case-control studies rely on the retrospective collection

TABLE 5 Systematic review questions, conclusion statements, and grades of the evidence supporting the conclusion statements[1]

Infant milk-feeding practices and celiac disease systematic reviews
What is the relationship between never versus ever feeding human milk and celiac disease in offspring?
Limited evidence from a small number of case-control studies suggests that never versus ever being fed human milk is associated with higher risk of celiac disease. (Grade: Limited)
What is the relationship between shorter versus longer durations of any human milk feeding and celiac disease in offspring?
A conclusion about the relationship between shorter versus longer durations of any human milk feeding and celiac disease could not be drawn owing to concerns about reverse causality across the body of evidence. (Grade: Grade not assignable)
What is the relationship between shorter versus longer durations of exclusive human milk feeding and celiac disease in offspring?
There is insufficient evidence to determine whether or not there is a relationship between shorter versus longer durations of exclusive human milk feeding and celiac disease in offspring. (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 celiac disease in offspring?
There is no evidence to determine whether or not there is a relationship between feeding a lower versus higher intensity, proportion, or amount of human milk to mixed-fed infants and celiac disease outcomes in offspring. (Grade: Grade not assignable)
Infant milk-feeding practices and inflammatory bowel disease systematic reviews
What is the relationship between never versus ever feeding human milk and inflammatory bowel disease in offspring?
Evidence about the relationship between never versus ever being fed human milk and inflammatory bowel disease in offspring is inconclusive. (Grade: Grade not assignable)
What is the relationship between shorter versus longer durations of any human milk feeding and inflammatory bowel disease in offspring?
Limited but consistent evidence from case-control studies suggests that, among infants fed human milk, a shorter versus longer duration of any human milk feeding is associated with higher risk of inflammatory bowel disease. (Grade: Limited)
What is the relationship between shorter versus longer durations of exclusive human milk feeding and inflammatory bowel disease in offspring?
There is insufficient evidence to determine whether or not there is a relationship between shorter versus longer durations of exclusive human milk feeding and inflammatory bowel disease in offspring. (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 inflammatory bowel disease in offspring?
There is no evidence to determine whether or not there is a relationship between feeding a lower versus higher intensity, proportion, or amount of human milk to mixed-fed infants and inflammatory bowel disease outcomes in offspring. (Grade: Grade not assignable)

[1] A grade of "limited" is assigned when "the conclusion statement is substantiated by insufficient evidence, and the level of uncertainty is seriously restricted by limitations in the evidence, such as the amount of evidence available, inconsistencies in findings, or methodological or generalizability concerns" and "grade not assignable" is assigned when "a conclusion statement cannot be drawn because of a lack of evidence, or the available evidence has serious inconsistencies and/or methodological concerns" (10).

of exposure data, differential or nondifferential misclassification of the exposure may have introduced bias. Differential misclassification from recall bias (e.g., if mothers of children and adolescents with Crohn disease recalled or reported infant milk-feeding practices differently from mothers of children and adolescents without Crohn disease) could have resulted in over- or underestimations of the associations, whereas nondifferential misclassification would have tended to bias the reported associations toward the null. Two studies, both of which were from the body of evidence examining the relationship between never versus ever being fed human milk and celiac disease, validated infant-feeding data using information recorded prospectively by health professionals (13, 15). The outcome was medically diagnosed and unlikely to misclassify cases or controls; however, because we included studies of diagnosed celiac disease and IBD, and these diseases may be underdiagnosed (43, 44), the reported effects of infant feeding on the outcomes may be over- or underestimations of the true effects. [Studies that examine the feeding of human milk and the development of antibodies, with or without symptomatic disease, have been conducted (45), but include high-risk samples that may not be generalizable to the broader population.] Although all of the case-control studies included matching variables, and many included additional adjustment variables, a minority of studies across the 2 SRs accounted for the critical confounding variables identified by TEC members in Figure 1 (13, 18, 23, 25–28). In addition, residual confounding from other variables related to infant feeding and the outcomes may have occurred.

Regarding impact, TEC members did not use qualitative methods to judge the magnitude of the risk of being fed human milk for short durations or not at all on celiac disease or IBD. However, both celiac disease and IBD have serious consequences, so even small decreases in risk have the potential to be of public health importance.

Research recommendations

TEC members identified several areas for future research. There was insufficient evidence to answer some of the SR questions (Table 5). In addition, the evidence that examined never versus ever being fed human milk and celiac disease, shorter versus longer durations of any human milk feeding and IBD, and never versus ever being fed human milk and IBD was either limited or inconclusive and predominantly from outside of the United States. Therefore, future researchers should expand the available evidence about the relationships between infant milk-feeding practices and celiac disease and IBD using representative US samples. Infant-feeding research will continue to rely on observational designs; however, researchers should endeavor to minimize bias through sound research design and conduct such as controlling for baseline differences in critical confounding variables. The use of study designs such as sib-pair analyses (e.g., comparisons of associations within sibling pairs

with associations irrespective of sibship), analyses of cohorts with different confounding structures, and use of instrumental variables such as Mendelian randomization approaches could also be helpful in minimizing confounding. Researchers should incorporate effect modification into their study design whenever possible (e.g., participant sex, race, and ethnicity) because different environmental and biological characteristics are likely to modify the impact of human milk on the outcomes. Infant milk-feeding research should also move toward collecting infant-feeding data consistently using validated methods, and 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 infants who were fed human milk).

We thank Katherine Kortsmit and Kelly Mannherz for their assistance with extracting data and assessing risk of bias for included studies. 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: has primary responsibility for final content; JMS: provided oversight of the project; and all authors: critically reviewed and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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