Infant milk-feeding practices and diabetes outcomes in offspring: a systematic review

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ABSTRACT

Background: During the Pregnancy and Birth to 24 Months Project, the US Departments of Agriculture and 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, and *4*) feeding a lower versus higher intensity of human milk to mixed-fed infants with type 1 and type 2 diabetes in offspring.

Methods: The Nutrition Evidence Systematic Review team conducted systematic reviews with external experts. We searched CINAHL, Cochrane, Embase, and PubMed for articles published January 1980–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 4 systematic reviews included 21, 37, 18, and 1 articles, respectively. Observational evidence suggests that never versus ever feeding human milk (limited evidence) and shorter versus longer durations of any (moderate evidence) and exclusive (limited evidence) human milk feeding are associated with higher type 1 diabetes risk. Insufficient evidence examined type 2 diabetes. Limited evidence suggests that the durations of any and exclusive human milk feeding are not associated with intermediate outcomes (e.g., fasting glucose, insulin resistance) during childhood.

Conclusions: Limited to moderate evidence suggests that feeding less or no human milk is associated with higher risk of type 1 diabetes in offspring. Limited evidence suggests no associations between the durations of any and exclusive human milk feeding and intermediate diabetes outcomes in children. Additional research is needed on infant milk-feeding practices and type 2 diabetes and intermediate outcomes in US populations, which may have distinct metabolic risk. *Am J Clin Nutr* 2019;109(Suppl):817S–837S.

Keywords: breastfeeding, breast milk, human milk, diabetes, fasting glucose, insulin resistance, systematic review

Introduction

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

The SRs in this article examine the relationships between infant milk-feeding practices and diabetes outcomes in offspring, including type 1 diabetes, type 2 diabetes, and some intermediate outcomes such as fasting glucose and insulin resistance. Primary

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Abbreviations used: HbA1c, hemoglobin A1c; NESR, Nutrition Evidence Systematic Review; SR, systematic review; TEC, Technical Expert Collaborative

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prevention of diabetes is a public health priority in the United States (4), where the incidences of type 1 and type 2 diabetes are increasing in children and adolescents, especially among certain racial and ethnic minorities (5, 6).

The purpose of this article is to summarize the results of 4 SRs conducted to answer the following questions:

- What is the relationship between never versus ever feeding human milk and diabetes outcomes in offspring?
- What is the relationship between shorter versus longer durations of any human milk feeding and diabetes outcomes in offspring?
- What is the relationship between shorter versus longer durations of exclusive human milk feeding and diabetes outcomes in offspring?
- What is the relationship between feeding a lower versus higher intensity, proportion, or amount of human milk to mixed-fed infants and diabetes outcomes in offspring?

Methods

NESR analysts (DG, PN, CCL, CD) and librarians (YPW, NT), 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 (SAA, LB, TJ, KMJ, LAN-R, KOO'B, EO, RP-E, EEZ), called a Technical Expert Collaborative (TEC), to complete SRs through the use of the methods that are described in detail in this supplement (7). 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, intermediate and endpoint health 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, infant formula, or both. 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. TEC members specified both intermediate and endpoint outcomes, collectively referred to in this article as *diabetes outcomes*.

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 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 the search date range 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 (8).

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 [(7), 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 *strong*, *moderate*, *limited*, or *grade not assignable* according to the NESR grading rubric [(7), 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 4 SRs on infant milk-feeding practices and diabetes outcomes in offspring comprise 53 articles. A table of articles excluded during full-text screening, with the rationale for exclusion, is available at https://nesr.usda.gov.

Only 1 of the included articles examined the intensity, proportion, or amount of human milk fed to mixed-fed infants (9). Additional information about this SR is available at https://nesr.usda.gov. Herein, we present evidence for the remaining 3 SRs:

- What is the relationship between never versus ever feeding human milk diabetes outcomes in offspring?
- What is the relationship between shorter versus longer durations of any human milk feeding and diabetes outcomes in offspring?

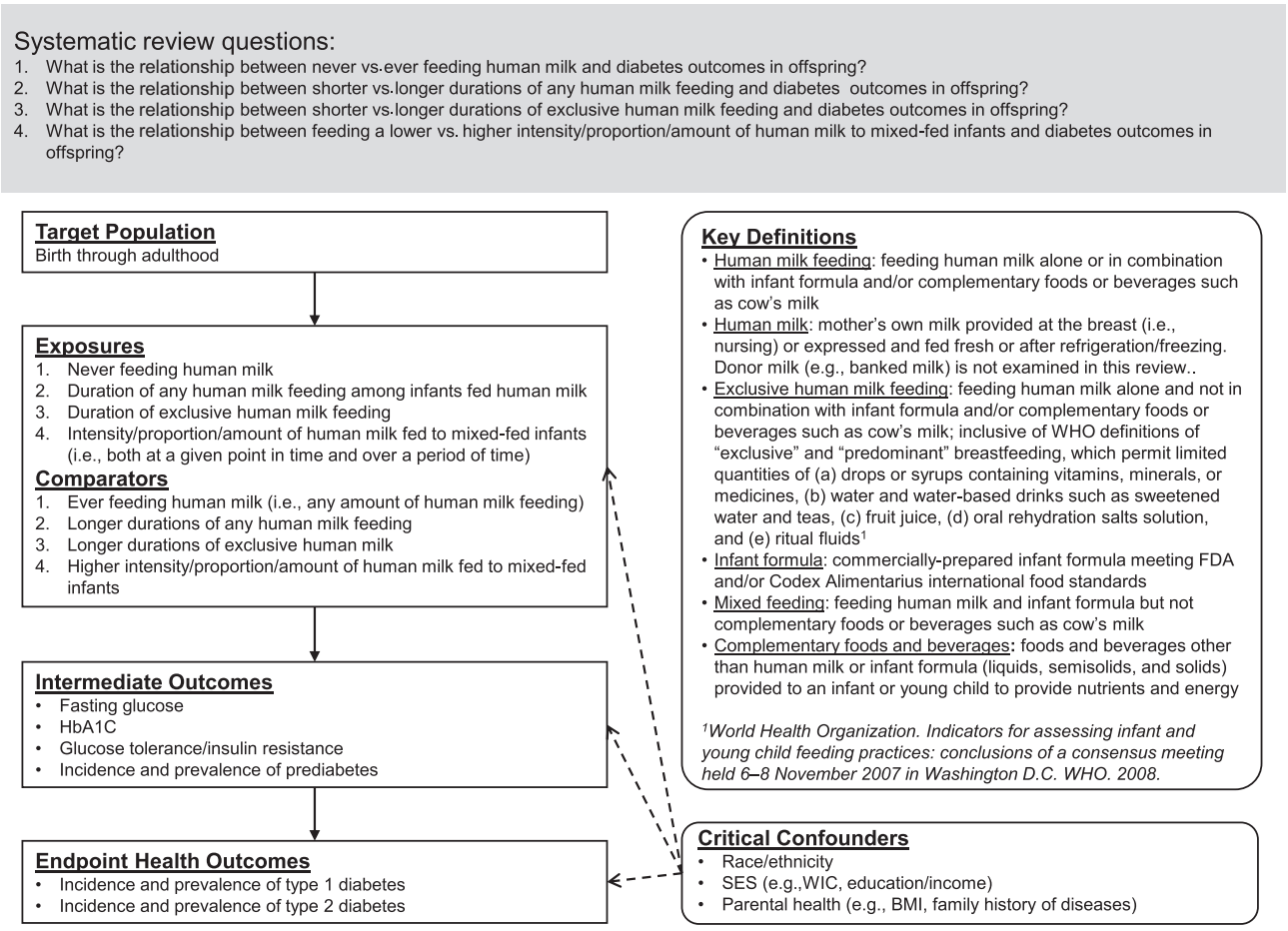

FIGURE 1 The analytic framework for SRs conducted to examine the relation of infant milk-feeding practices with diabetes outcomes in offspring. This framework illustrates the overall scope of the project, including the population, exposures and comparators, and outcomes of interest. It also includes definitions for key terms and identifies key confounders considered in the SR. SR, systematic review.

- What is the relationship between shorter versus longer durations of exclusive human milk feeding and diabetes outcomes in offspring?

Never versus ever feeding human milk and diabetes outcomes in offspring

Twenty-one articles met the inclusion criteria for this SR question; 16 examined type 1 diabetes (10–25), 2 examined type 2 diabetes (26, 27), and 3 examined intermediate outcomes, i.e., fasting glucose (28, 29), hemoglobin A1c (HbA1c) (30) or insulin resistance (28). TEC members concluded that there was insufficient evidence to determine whether or not there is a relationship between never versus ever being fed human milk and type 2 diabetes, prediabetes, fasting glucose, HbA1c, and insulin resistance or glucose tolerance (**Table 7**). Evidence about type 1 diabetes is presented below.

Type 1 diabetes.

The 16 articles that examined never versus ever being fed human milk and type 1 diabetes presented evidence from 15 independent studies (Table 2). There was 1 prospective cohort study (11) and there were 14 independent case-control studies (10, 12–25) because Dahlquist et al. (12) and Rami et al. (20) both presented evidence from the EURODIAB study.

Six of the studies reported significant associations (12, 14, 16, 18, 19, 25). The primary difference between the studies that did and did not report significant associations was statistical power. For example, all 4 studies with >200 cases (12, 14, 16, 18) reported significant associations. On the other hand, the case-control studies with nonsignificant associations (10, 13, 15, 17, 21–24) had fewer cases. The 2 studies with high-risk samples (10, 11) (which can increase statistical power) did not find significant associations. However, there was nearly universal initiation of human milk feeding by cases and controls in the sample used by Alves et al. (10) (i.e., not a lot of variation), and the comparison of interest in the prospective cohort study by Chmiel et al. (11) had a wide CI around its nonsignificant association indicative of suboptimal statistical power.

With 1 exception (19), the statistically significant associations suggested that never, compared with ever, being fed human milk is associated with higher type 1 diabetes risk. There were significant associations across heterogeneous analyses that compared never feeding human milk with ever feeding human

TABLE 1 Inclusion and exclusion criteria established for the selection of studies to include in SRs on infant milk-feeding practices and diabetes outcomes in offspring[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	Grey 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 to December 2015[2]	Published prior to 1980
Source of foods, beverages, or nutrients	Human milk: mother's own milk, 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 (31) and/or Codex Alimentarius (32) 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 (31) and/or Codex Alimentarius (32) food standards
Study setting	Countries listed as Very High or High on the 2014 Human Development Index[3] (33, 34)	Countries listed as Medium or Low on the 2014 Human Development Index (33)
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 babies
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)	
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 post-partum hospitalization of healthy babies) or malnourished participants Studies of exclusively pre-term babies (gestational age <37 wk), exclusively babies that have low birth weight (<2500 g) and/or exclusively babies that are small for gestational age

[1] SR, systematic review.
[2] In 1980 the Infant Formula Act was passed (8) 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 (35).

milk (12, 14, 18), feeding human milk for 1–3 mo (16), and feeding human milk for ≥6 mo (25), and that examined risk of type 1 diabetes at ages <15 y (12), <17 y (14), ≤18 y (16, 18), and <30 y (25). Three studies reported significant associations for some comparisons of interest and nonsignificant associations for other comparisons of interest (14, 18, 25), and the difference in significance was likely to be statistical power. For example, Kostraba et al. (14) reported that ever, compared with never, being fed human milk was associated with lower odds of type 1 diabetes in white participants (which comprised 74% of the sample), whereas the corresponding nonsignificant association in the smaller group of black participants was in the same direction but had a wide CI. Likewise, Mayer et al. (18) found that ever, compared with never, being fed human milk was associated with significantly lower odds of type 1 diabetes, whereas additional analyses that divided the group ever fed human milk into smaller groups fed human milk for ≤0.99, 1–2.99, 3–5.99, 6–11.99, and ≥12 mo had wide CIs around nonsignificant associations that were consistent in direction with the *ever compared with never* association. Finally, Tai et al. (25) reported that being fed human milk for ≥6 mo, compared with never being fed human milk, was associated with lower odds of type 1 diabetes by 30 y of age, whereas a nonsignificant association between being fed human milk for <6 mo, compared with never being fed human milk, was in the same direction but had a wide CI.

Shorter versus longer durations of any human milk feeding and diabetes outcomes in offspring

Thirty-seven articles met the inclusion criteria for this SR question; 30 examined type 1 diabetes (9, 14–20, 24, 36–56), 1 examined type 2 diabetes (27), and 6 examined the intermediate outcomes fasting glucose (28, 57, 58) and insulin resistance or glucose tolerance (28, 57–61). Intermediate outcome data were scant in adults (60, 61). TEC members concluded that there was insufficient evidence to determine the relationship between shorter versus longer durations of any human milk feeding and type 2 diabetes, prediabetes, or HbA1c throughout the lifespan,

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

Author and year	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Never vs. ever feeding human milk exposures[2]	Significant associations with type 1 diabetes	Nonsignificant associations with type 1 diabetes
Alves 2012 (10)	Case control	Brazil	$n = 123$ cases, 123 sibling controls Baseline: mean 9 y Race/ethnicity NR Risk: 100% of sibling controls had a sibling with T1D	Proportion of cases vs. controls who BF	None	94.3% vs. 99.1%, $P = 0.070$
Chmiel 2015 (11)	Prospective cohort (BABYDIAB/ BABYDIET)	Germany	$n = 2291$ Baseline: birth to 3 mo Sex NR Race/ethnicity NR Risk: 100% family history of T1D (parent)	Infant formula only before age 3 mo vs. EBF before age 3 mo	None	T1D by median 13 y: HR 0.72 (95% CI: 0.34, 1.53), $P = 0.40$
Dahlquist 2002 (12)	Case control (EURODIAB)	Austria, Latvia, Lithuania, Luxem-bourg, UK	$n = 610$ cases, 1616 controls Baseline: diagnosed <15 y but age at the study NR Sex NR Race/ethnicity NR	BF vs. not BF	T1D: OR 0.59 (95% CI: 0.35, 0.97)	None
Esfarjani 2001 (13)	Case control	Iran	$n = 52$ cases, 52 controls Baseline: <14 y Race/ethnicity NR Risk: 0% of controls with family history of IDDM	Proportion of cases vs. controls who never BF	None	17.3% vs. 23.1%, NS
Kostraba 1992 (14)	Case control	USA	$n = 211$ cases, 211 controls Baseline: diagnosed <17 y but age at the study NR Race/ethnicity: 26.1% black, 73.9% white	Ever BF vs. never BF	IDDM in white subsample: OR 0.5 (95% CI: 0.3, 0.9)	IDDM in black subsample: OR 0.5 (95% CI: 0.2, 1.4)
Kostraba 1993 (15)	Case control	USA	$n = 163$ cases, 140 controls Baseline: diagnosed <18 y but age at the study NR Race/ethnicity: 43% Hispanic, 57% non-Hispanic white	Proportion of cases vs. controls who were BF	None	52.1% vs. 54.3%, NS In Hispanic subsample: 38% vs. 35.1%, NS In non-Hispanic white subsample: 63% vs. 67.5%, NS
Malcova 2006 (16)	Case control	Czech Republic	$n = 868$ cases, 1466 controls Baseline: ≤18 y, median 13 y (IQR: 10, 16) for cases, 12 y (IQR: 9, 15) for controls Race/ethnicity NR	No BF vs. BF 1–3 mo	T1D: OR 1.93 (95% CI: 1.33, 2.80)	None
Marshall 2004 (17)	Case control	UK	$n = 196$ cases, 381 controls Baseline NR Sex NR Race/ethnicity: ∼93% white	BF vs. not BF	None	T1D: NS (data NR)
Mayer 1988 (18)	Case control	USA	$n = 268$ cases, 479 controls Baseline: diagnosed ≤18 y but age at study NR Race/ethnicity: ∼91.5% white	BF vs. no BF	IDDM: OR 0.70 (95% CI: 0.50, 0.97)	None
				BF ≤0.99 mo vs. BF 0 mo	None	IDDM: OR 0.92 (95% CI: 0.47, 1.82)
				BF 1–2.99 mo vs. BF 0 mo	None	IDDM: OR 0.68 (95% CI: 0.39, 1.18)
				BF 3–5.99 mo vs. BF 0 mo	None	IDDM: OR 0.74 (95% CI: 0.46, 1.20)
				BF 6–11.99 mo vs. BF 0 mo	None	IDDM: OR 0.67 (95% CI: 0.43, 1.04)
				BF ≥12 mo vs. BF 0 mo	None	IDDM: OR 0.54 (95% CI: 0.27, 1.08)
Meloni 1997 (19)	Case control	Italy	$n = 100$ cases, 100 controls Baseline: diagnosed at 1–15 y, but age at study NR Race/ethnicity NR Risk: 0% family history of IDDM in controls, NR in cases	No BF vs. BF BF 0 mo vs. BF >6 mo	IDDM: OR 0.41 (95% CI: 0.19, 0.91) IDDM: OR 0.36 (95% CI: 0.14, 0.94)	None None
Rami 1999 (20)	Case control (EURODIAB ACE)	Austria	$n = 114$ cases, 495 controls Baseline: <15 y Race/ethnicity NR	Proportion of cases vs. controls who BF	None	82.7% vs. 81%, $P = 0.66$

(*Continued*)

TABLE 2 (*Continued*)

Author and year	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Never vs. ever feeding human milk exposures[2]	Significant associations with type 1 diabetes	Nonsignificant associations with type 1 diabetes
Robertson 2010 (21)	Case control	UK	$n = 55$ cases, 170 controls Baseline: <15 y Race/ethnicity NR	BF vs. not BF	None	T1D: OR 1.62 (95% CI: 0.77, 3.44)
Siemiatycki 1989 (22)	Case control	Canada	$n = 128$ cases, 255 controls Baseline: 5–14 y Race/ethnicity NR	Never BF vs. BF	None	IDDM: OR 1.2 (95% CI: 0.6, 2.5)
Soltesz 1994 (23)	Case control	Hungary	$n = 130$ cases, 175 controls Baseline: 0–14 y Race/ethnicity NR	No BF vs. BF	None	IDDM: OR 1.76 (95% CI: 0.91, 3.41)
Tai 1998 (25)	Case control	China	$n = 117$ cases, 193 controls Baseline: <30 y Sex: 36.9% male Race/ethnicity NR	BF < 6 mo vs. never BF BF ≥ 6 mo vs. never BF	None T1D: OR 0.25 (95% CI: 0.09, 0.69)	T1D: OR 0.84 (95% CI: 0.45, 1.59) None
Thorsdottir 2000 (24)	Case control	Iceland	$n = 55$ cases, 165 controls Baseline: 3–19 y, mean 12.5 y Sex NR Race/ethnicity NR	Frequency of BF in cases vs. controls	None	$P > 0.1$ (data NR)

[1]BF, breastfed; EBF, exclusively breastfed; EURODIAB, European Diabetes; EURODIAB ACE, European Diabetes: Aetiology of Childhood Diabetes on an Epidemiological Basis; IDDM, insulin-dependent diabetes mellitus; NR, not reported; NS, not significant; T1D, type 1 diabetes.

[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 fasting glucose, insulin resistance, or glucose tolerance in adulthood (Table 7). Evidence about type 1 diabetes and about fasting glucose, insulin resistance, and glucose tolerance in childhood and during the transition into adolescence is presented below.

Type 1 diabetes.

The 30 articles that examined shorter versus longer durations of any human milk feeding and type 1 diabetes used prospective cohort (41, 45, 52, 56), nested case-control (9, 40, 53, 55), and case-control (14–20, 24, 36–39, 42–44, 46–51, 54) study designs (**Table 3**). There were 22 independent studies because 5 studies presented data across multiple articles [i.e., the Diabetes Autoimmunity Study in the Young with articles by Frederiksen et al. (9) and Hall et al. (56); the Swedish Childhood Diabetes Study with articles by Blom et al. (36) and Dahlquist et al. (38); the Diabetes and Environment around the Baltic Sea study with articles by Skrodeniene et al. (47) and Sadauskaite-Kuehne et al. (43); the European Diabetes: Aetiology of Childhood Diabetes on an Epidemiological Basis study with articles by Rami et al. (20) and Visalli et al. (54); and the Childhood Diabetes in Finland study with 5 articles by Virtanen et al. (49–53)].

Twelve studies reported significant associations across 16 articles (16, 36–38, 40–43, 46–51, 54, 56). A primary difference between the studies that did and did not report significant associations was statistical power. For example, 7 (16, 36–38, 42, 43, 48, 50, 51) of 10 studies with >200 cases (14, 16, 18, 36–38, 42–44, 48, 50, 51) and 4 (37, 41, 51, 56) of 6 studies that examined high-risk samples (9, 37, 39, 41, 46, 51–53, 56) found significant associations. In contrast, the 10 studies that did not find significant associations (14, 15, 17–19, 24, 39, 44, 45, 55) tended to have fewer cases (15, 17, 19, 24, 39, 55).

With 1 exception (40), the significant associations between the duration of any human milk feeding and type 1 diabetes risk were inverse associations. The significant associations were consistent in direction across prospective cohort (41, 56) and case-control study designs (16, 36–38, 42, 43, 46–51, 54), and across heterogeneous analyses that examined duration as a continuous variable (56), compared the average duration of human milk feeding in cases and controls (36, 37, 48, 51), compared heterogeneous ranges of duration [i.e., <2 wk compared with ≥5 mo (42), 1–3 compared with >12 mo (16), <2 compared with ≥2 mo (50), <2 compared with 2–7 mo (48), <2 compared with >7 mo (48), <3 compared with ≥3 mo (36, 38, 47, 50, 54), <4 compared with ≥4 mo (46), <5 compared with ≥5 mo (42), <7 compared with ≥7 mo (43, 49), <9 compared with ≥9 mo (43), and <12 compared with ≥12 mo (41)], and assessed the trend across multiple categories of duration (42). They examined risk of type 1 diabetes at ages 3–14 y (51), ≤4 y (38), <6 y (42), ≤6 y (36, 49), 6–18 y (54), <7.7 y (41), 7–14 y (50), <15 y (37), ≤15 y (43, 47, 48), ≤16 y (46), and ≤18 y (16).

The study by Kyvik et al. (40) was the only one with a significant association in a discrepant direction. However, this study has limited external validity as it included a male-only sample of cases who were both living and deceased (participants were identified from records of rejection from the mandatory military conscription or death certificates), and there were no comparable analyses in other studies in this body of evidence that would allow TEC members to examine whether the reported associations are typical among males.

Fasting glucose, insulin resistance, and glucose tolerance in childhood and the transition into adolescence.

One cluster randomized controlled trial (57) and 3 prospective cohort studies (28, 58, 59) found no associations between the duration of any human milk feeding and fasting glucose, insulin resistance, or glucose tolerance in childhood and the transition from childhood into adolescence (**Table 4**). Martin et al. (57) presented evidence from the Promotion of Breastfeeding Intervention Trial (PROBIT), a cluster randomized controlled

TABLE 3 Evidence examining the relationship between shorter versus longer durations of any human milk feeding and type 1 diabetes in offspring[1]

Author and year	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs. longer duration of any human milk feeding exposure[2]	Significant associations with type 1 diabetes	Nonsignificant associations with type 1 diabetes
Blom 1989 (36)	Case control (Swedish Childhood Diabetes Study)	Sweden	$n = 339$ cases, 527 controls Baseline: 0–14 y Race/ethnicity NR	Median BF duration in cases vs. controls	In subsample w/onset at 0–6 y: 5 mo vs. 6 mo, $P = 0.03$	4 mo vs. 4 mo, NS In subsample w/onset at 7–14 y: 3 mo vs. 3 mo, NS
				BF <3 mo vs. BF ≥3 mo	T1D in subsample w/onset at 0–6 y subsample: OR 1.7 (95% CI: 1.02, 2.89)	None
Borch-Johnsen 1984 (37)	Case control	Denmark	$n = 266$ cases, 230 controls Baseline: diagnosis <15 y, age at study NR Sex NR Race/ethnicity NR Risk: 100% sibling controls have a sibling with IDDM	Average[3] BF duration in cases vs. sibling controls	2.69 mo vs. 3.41 mo, $P < 0.01$	None
Dahlquist 1991 (38)	Case control (Swedish Childhood Diabetes Study)	Sweden	$n = 339$ cases, 528 controls Baseline: 0–14 y Sex NR Race/ethnicity NR	BF <3 mo vs. ≥3 mo	T1D in subsample w/onset at 0–4 y: OR: 3.81 (95% CI: 1.10, 13.29), $P = 0.035$	T1D: $P \geq 0.20$ (data NR)
Fort 1986 (39)	Case control	USA	$n = 95$ cases, 194 sibling controls, 95 peer controls Baseline: mean 14.8 y (SD = 5.5) Sex NR Race/ethnicity NR Risk: 100% of sibling controls had a sibling with T1D	BF duration in cases vs. sibling controls BF duration in cases vs. peer controls	None None	4.6 mo vs. 4.2 mo, NS 4.6 mo vs. 3.3 mo, NS
Frederiksen 2013 (9)	Nested case control[4] (DAISY)	USA	$n = 53$ cases, 1782 controls Baseline: Birth Race/ethnicity: 70.1% non-Hispanic white Risk: 100% at-risk genotype or family history of T1D (first-degree relative)	Mean BF duration in cases vs. controls	None	5.8 mo (SD = 7.0) vs. 6.4 mo (SD = 6.9); T1D: HR 0.97 (95% CI: 0.92, 1.01), $P = 0.17$
Hall 2015 (56)	Prospective cohort (DAISY)	USA	$n = 1783$ Baseline: birth Race/ethnicity: 70.2% non-Hispanic white Risk: 100% at-risk genotype or family history of T1D (first-degree relative)	BF duration (mo) as a continuous variable	T1D: HR 0.95 (CI: 0.90, 1.00), $P = 0.05$	None
Kostraba 1992 (14)	Case control	USA	$n = 211$ cases, 211 controls Baseline: diagnosed <17 y but age at the study NR Race/ethnicity: 26.1% black, 73.9% white	BF duration in cases vs. controls	None	In white subsample: 23 wk vs. 25 wk, $P = 0.8$ In black subsample: 17 wk vs. 28 wk, $P = 0.13$
Kostraba 1993 (15)	Case control	USA	$n = 163$ cases, 145 controls Baseline: diagnosed <18 y but age at the study NR Race/ethnicity: 43% Hispanic, 57% non-Hispanic white	BF duration in cases vs. controls	None	24.8 wk (SD = 20.4) vs. 27.8 wk (SD = 25.0), NS In Hispanic subsample: 24.3 wk (SD = 25.0) vs. 26.2 wk (SD = 18.3), NS In non-Hispanic white subsample: 25.0 wk (SD = 18.4) vs.. 28.3 wk (SD = 27.1), NS

(*Continued*)

TABLE 3 (*Continued*)

Author and year	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs. longer duration of any human milk feeding exposure[2]	Significant associations with type 1 diabetes	Nonsignificant associations with type 1 diabetes
Kyvik 1992 (40)	Nested case control	Denmark	$n = 76$ cases (including some deceased), 154 controls Baseline: birth Sex: 100% male Race/ethnicity NR	BF 0–1 mo vs. BF ≥5 mo	None	T1D (including deaths) by age 20 y: OR 0.93 (95% CI: 0.46, 1.89)
				BF 1–2 mo vs. BF ≥5 mo	T1D (including deaths) by age 20 y: OR 0.51 (95% CI: 0.29, 0.91)	None
				BF 2–3 mo vs. BF ≥5 mo	None	T1D (including deaths) by age 20 y: OR 0.58 (95% CI: 0.33, 1.02)
				BF 3–4 mo vs. BF ≥5 mo	None	T1D (including deaths) by age 20 y: OR 0.95 (95% CI: 0.51, 1.78)
				BF 4–5 mo vs. BF ≥5 mo	None	T1D (including deaths) by age 20 y: OR 0.91 (95% CI: 0.47, 1.77)
Lund-Blix 2015 (41)	Prospective cohort (MIDIA)	Norway	$n = 726$ Baseline: birth Race/ethnicity NR Risk: 100% at-risk genotype	BF duration (mo) as a continuous variable	None	T1D by age 7.70 (SD = 1.58) y: HR 0.99 (95% CI: 0.88, 1.11)
				Any BF ≥12 mo vs. <12 mo	T1D by age 7.70 (SD = 1.58) y: HR 0.37 (95% CI: 0.15, 0.93)	None
Malcova 2006 (16)	Case control	Czech Republic	$n = 868$ cases, 1466 controls Baseline: ≤18 y, median 13 y (IQR: 10, 16) for cases, 12 y (IQR: 9, 15) for controls Race/ethnicity NR	BF 4–6 mo vs. BF 1–3 mo	None	T1D: OR 1.11 (95% CI: 0.82, 1.50)
				BF 7–9 mo vs. BF 1–3 mo	None	T1D: OR .96 (95% CI: 0.65, 1.41)
				BF 10–12 mo vs. BF 1–3 mo	None	T1D: OR 0.94 (95% CI: 0.57, 1.56)
				BF >12 mo vs. BF 1–3 mo	T1D: OR 0.42 (95% CI: 0.22, 0.81)	None
Marshall 2004 (17)	Case control	UK	$n = 196$ cases, 381 controls Baseline: NR Sex NR Race/ethnicity: ~93% white	BF duration (mo) as a continuous variable	None	T1D: NS (data NR)
Mayer 1988 (18)	Case control	USA	$n = 268$ cases, 479 controls Baseline: diagnosed ≤18 y but age at study NR Race/ethnicity: ~91.5% white	BF duration in cases vs. controls	None	6.39 mo (range: 0.01–23.97 mo) vs. 7.06 mo (range: 0.20–30.33), $P = 0.11$
Meloni 1997 (19)	Case control	Italy	$n = 100$ cases, 100 controls Baseline: diagnosed 1–15 y, but age at study NR Race/ethnicity NR Risk: 0% family history of IDDM in controls, NR in cases	BF 3–5 mo vs. BF >6 mo	None	IDDM: OR 1.18 (95% CI: 0.52, 2.68)
				BF 1–2 mo vs. BF >6 mo	None	IDDM: OR 0.48 (95% CI: 0.19, 1.24)
				Per 1 mo increase in BF duration	None	IDDM: OR 1.10 (95% CI: 0.99 , 1.22)
Rami 1999 (20)	Case control (EURODIAB ACE)	Austria	$n = 114$ cases, 495 controls Baseline: <15 y Race/ethnicity NR	Median BF duration in cases vs. controls	None	2 mo (range: 0–24) vs. 2 mo (range: 0–72), $P = 0.54$

(*Continued*)

TABLE 3 (*Continued*)

Author and year	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs. longer duration of any human milk feeding exposure[2]	Significant associations with type 1 diabetes	Nonsignificant associations with type 1 diabetes
Rosenbauer 2008 (42)	Case control	Germany	$n = 719$ cases, 1735 controls Baseline: <6 y Race/ethnicity NR	BF <5 mo vs. ≥5 mo	T1D: OR 1.40 (95% CI: 1.13, 1.73), $P = 0.002$	None
				BF 2–6 wk vs. BF <2 wk	None	T1D: OR 0.97 (95% CI: 0.72, 1.31)
				BF 7 wk-4 mo vs. BF <2 wk	None	T1D: OR 0.85 (95% CI: 0.63, 1.13)
				BF ≥5 mo vs. BF <2 wk	T1D: OR 0.71 (95% CI: 0.54, 0.93), $P = 0.012$	None
				BF duration trend including categories <2 wk, 2–6 wk, 7 wk–4 mo, ≥5 mo	T1D: OR 0.89 (95% CI: 0.82, 0.97), $P = 0.008$	None
Sadauskaite-Kuehne 2004 (43)	Case control (Diabetes and Environment around the Baltic Sea)	Sweden	$n = 517$ cases, controls NR (~2 controls per case) Baseline: 0–15 y Race/ethnicity NR	Total BF ≥7 mo vs. <7 mo	T1D in subsample ages 5–9 y: OR 0.56 (95% CI: 0.38, 0.84)	NR[5]
				Total BF ≥9 mo vs. <9 mo	T1D in subsample ages 5–9 y: OR 0.61 (95% CI: 0.41, 0.92)	NR
Samuelsson 1993 (44)	Case control	Sweden	$n = 297$ cases, 792 controls Baseline: 0–14 y Sex NR Race/ethnicity NR	Mean duration of complete and partial BF in cases vs. controls	None	NS (data NR) In subsample <5 y: 8.50 mo (SD = 1.72) vs. 6.08 mo (SD = 1.06), $P = 0.33$ In subsample ages 5–9 y: 6.60 mo (SD = 0.58) vs. 6.28 mo (SD = 0.43), $P = 0.62$ In subsample >10 y: 3.85 mo (SD = 0.22) vs. 4.23 mo (SD = 0.20), $P = 0.36$
Savilahti 2009 (45)	Prospective cohort[6]	Finland	$n = 4444$ Baseline: birth Sex NR Race/ethnicity NR	Total BF ≤5.8 mo vs. >5.8 mo	None	T1D by mean 11.5 y: OR 0.95 (95% CI: 0.63, 1.42)
Sipetic 2005 (46)	Case control	Serbia	$n = 105$ cases (68 in sibling subsample), 210 outpatient controls, 68 sibling controls Baseline: 0–16 y Sex NR Race/ethnicity NR Risk: 100% of sibling controls had a sibling with T1D by 16 y	BF <4 mo vs. BF ≥4 mo	T1D: OR 2.09 (95% CI: 1.30, 3.36)	T1D in sibling subsample: OR 1.39 (95% CI: 0.75, 2.56)
Skrodenienė 2010 (47)	Case control (Diabetes and Environment around the Baltic Sea)	Lithuania	$n = 191$ cases, controls NR Baseline: 0–15 y Race/ethnicity NR	Total BF <3 mo vs. ≥3 mo	T1D: OR 3.46 (95% CI: 1.14, 10.50)	None
Thorsdottir 2000 (24)	Case control	Iceland	$n = 55$ cases, 165 controls Baseline: 3–19 y, mean 12.5 y Sex NR Race/ethnicity NR	BF duration in cases vs. controls	None	$P > 0.1$ (data NR)

(*Continued*)

TABLE 3 (*Continued*)

Author and year	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs. longer duration of any human milk feeding exposure[2]	Significant associations with type 1 diabetes	Nonsignificant associations with type 1 diabetes
Verge 1994 (48)	Case control	Australia	$n = 217$ cases, 258 controls Baseline: 0–15 y, median 9.2 y Race/ethnicity NR	Median BF duration in cases vs. controls	3 mo (IQR: 1, 9) vs. 4 mo (IQR: 1, 10), $P = 0.03$	None
				BF 2–7 mo vs. <2 mo	IDDM: OR 0.63 (95% CI: 0.40, 0.99) IDDM in subsample age <9.2 y: OR 0.33 (95% CI: 0.16, 0.69)	IDDM in subsample age ≥9.2 y: OR 0.86 (95% CI: 0.46, 1.60)
				BF >7 mo vs. <2 mo	IDDM in subsample age <9.2 y: OR 0.39 (95% CI: 0.19, 0.79)	IDDM: OR 0.68 (95% CI: 0.42, 1.09) IDDM in subsample age ≥9.2 y: OR 1.06 (95% CI: 0.51, 2.18)
Virtanen 1991 (49)	Case control (DiMe)	Finland	$n = 103$ cases, 103 controls Baseline: 0–6 y Race/ethnicity NR	Median BF duration in cases vs. controls	None	8 mo vs. 9 mo, NS
				BF ≥1 mo vs. <1 mo	None	IDDM: ∼97% in cases vs. ∼100% in controls
				BF ≥2 mo vs. <2 mo	None	IDDM: ∼94% in cases vs. ∼99% in controls
				BF ≥3 mo vs. <3 mo	None	IDDM: ∼82% in cases vs. ∼92% in controls, OR 0.45 (95% CI: 0.15, 1.32)
				BF ≥4 mo vs. <4 mo	None	IDDM: ∼79% in cases vs. ∼89% in controls, OR 0.53 (95% CI: 0.22, 1.26)
				BF ≥5 mo vs. <5 mo	None	IDDM: ∼75% in cases vs. ∼85% in controls, OR 0.68 (95% CI: 0.32, 1.44)
				BF ≥6 mo vs. <6 mo	None	IDDM: ∼69% in cases vs. ∼79% in controls, OR 0.69 (95% CI: 0.36, 1.32)
				BF ≥7 mo vs. <7 mo	IDDM: ∼52% in cases vs. ∼71% in controls, OR 0.48 (95% CI: 0.25, 0.92), $P < 0.01$	None
				BF ≥8 mo vs. <8 mo	None	IDDM: ∼50% in cases vs. ∼65% in controls, OR 0.62 (95% CI: 0.33, 1.17)
				BF ≥9 mo vs. <9 mo	None	IDDM: ∼40% in cases vs. ∼50% in controls, OR 0.73 (95% CI: 0.36, 1.50)
				BF ≥10 mo vs. <10 mo	None	IDDM: ∼33% in cases vs. ∼41% in controls
				BF ≥11 mo vs. <11 mo	None	IDDM: ∼30% in cases vs. ∼37% in controls
				BF ≥12 mo vs. <12 mo	None	IDDM: ∼23% in cases vs. ∼27% in controls
Virtanen 1992 (50)	Case control (DiMe)	Finland	$n = 426$ cases, 426 controls Baseline: 7–14 y Race/ethnicity NR	Median BF duration in cases vs. controls	None	4 mo vs. 5 mo, NS
				BF ≥1 mo vs. <1 mo	None	IDDM: ∼95% in cases vs. ∼93% in controls; OR ∼1.2 (95% CI: ∼0.6, ∼2.3)
				BF ≥2 mo vs. <2 mo	IDDM: ∼83% in cases vs. ∼89% in controls, OR 0.64 (95% CI: 0.42, 0.98), $P < 0.05$	None
				BF ≥3 mo vs. <3 mo	IDDM: ∼70% in cases vs. ∼78% in controls, OR 0.67 (95% CI: 0.48, 0.95), $P < 0.05$	None

(*Continued*)

TABLE 3 (*Continued*)

Author and year	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs. longer duration of any human milk feeding exposure[2]	Significant associations with type 1 diabetes	Nonsignificant associations with type 1 diabetes
				BF ≥4 mo vs. <4 mo	None	IDDM: ~53% in cases vs. ~60% in controls, OR ~0.8 (95% CI: ~0.6, ~1.1)
				BF ≥5 mo vs. <5 mo	None	IDDM: ~45% in cases vs. ~50% in controls, OR ~0.8 (95% CI: ~0.6, ~1.1)
				BF ≥6 mo vs. <6 mo	None	IDDM: ~38% in cases vs. ~40% in controls, OR ~0.8 (95% CI: ~0.6, ~1.2)
				BF ≥7 mo vs. <7 mo	None	IDDM: ~29% in cases vs.. ~29% in controls, OR ~1.0 (95% CI: ~0.8, ~1.4)
				BF ≥8 mo vs. <8 mo	None	IDDM: ~23% in cases vs. ~21% in controls, OR ~1.1 (95% CI: ~0.8, ~1.6)
				BF ≥9 mo vs. <9 mo	None	IDDM: ~20% in cases vs. ~17% in controls, OR ~1.3 (95% CI: ~0.8, ~1.9)
				BF ≥10 mo vs. <10 mo	None	IDDM: ~12% in cases vs. ~10% in controls, OR ~1.4 (95% CI: ~0.8, ~2.2)
Virtanen 1994 (51)	Case control (DiMe)	Finland	$n = 415$ cases, 415 sibling controls Baseline: 3–14 y Sex NR Race/ethnicity NR Risk: 100% sibling controls have a sibling with IDDM	Median BF duration in cases vs. sibling controls BF duration ≥4 mo vs. <4 mo	5 mo vs. 6 mo, $P = 0.008$ None	None IDDM: OR 1.68 (95% CI: 0.33, 8.72)
Virtanen 1998 (52)	Prospective cohort (DiMe)	Finland	$n = 725$ Baseline: 0.4–24.9 y, median 9.4 y Race/ethnicity NR Risk: 100% family risk of T1D (sibling)	Duration of total BF ≥2 mo vs. <2 mo	None	T1D within 4 y of T1D diagnosis in a sibling: HR 0.53 (95% CI: 0.2, 1.6)
Virtanen 2000 (53)	Nested Case Control (DiMe)	Finland	$n = 33$ cases, 254 controls Baseline: 1.6–16.9 y Race/ethnicity NR Risk: 100% family risk of T1D (sibling)	Duration of total BF ≥2 mo vs. <2 mo	None	T1D: OR 1.11 (95% CI: 0.3, 3.7)
Visalli 2003 (54)	Case control (EURODIAB ACE)	Italy	$n = 150$ cases, 750 controls Baseline: 6–18 y Race/ethnicity NR	BF duration <3 mo vs. ≥3 mo	T1D: OR 1.74 (95% CI: 1.40, 2.45)	None
Welander 2014 (55)	Nested case control[7] (ABIS Study)	Sweden	$n = 46$ cases, 9368 reference Baseline: birth Race/ethnicity NR	BF 0–2 mo vs. ≥11 mo BF 3–4 mo vs. ≥11 mo BF 5–6 mo vs. ≥11 mo BF 7–8 mo vs. ≥11 mo BF 9–10 mo vs. ≥11 mo	None None None None None	T1D by ~13.5 y: HR 0.7 (95% CI: 0.2, 3.1) T1D by ~13.5 y: HR 0.7 (95% CI: 0.2, 3.2) T1D by ~13.5 y: HR 1.2 (95% CI: 0.4, 3.5) T1D by ~13.5 y: HR 1.2 (95% CI: 0.5, 2.6) T1D by ~13.5 y: HR 1.4 (95% CI: 0.7, 3.0)

[1]ABIS, All Infants in Southeast Sweden; BF, breastfed; DAISY, Diabetes Autoimmunity Study in the Young; DiMe, Childhood Diabetes in Finland; EURODIAB ACE, European Diabetes: Aetiology of Childhood Diabetes on an Epidemiological Basis; IDDM, insulin-dependent diabetes mellitus; MIDIA – Environmental Triggers of Type 1 Diabetes; NR, not reported; NS, not significant; T1D, type 1 diabetes.

[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.

[3]Authors do not specify what type of average this is (e.g., mean, median).

[4]Authors call the study a prospective cohort; however, the assessment grouped participants by outcome status rather than infant feeding exposure.

[5]Authors only reported significant associations; information about nonsignificant findings were NR.

[6]Original study was a randomized controlled trial; however, the data of interest are pooled and unrelated to randomization.

[7]Authors call the study a prospective cohort; however, the assessment grouped participants by outcome status rather than infant feeding exposure.

TABLE 4 Evidence examining the relationship between shorter versus longer durations of any human milk feeding and fasting glucose, insulin resistance, and glucose tolerance in offspring in childhood and the transition from childhood into adolescence[1]

Author and year	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs. longer duration of any human milk feeding exposure[2]	Significant associations with intermediate outcomes	Nonsignificant associations with intermediate outcomes
Davis 2007 (28)	Prospective cohort (University of Southern California longitudinal SOLAR)	USA	$n = 150$ Baseline: 8–13 y Race/ethnicity: 100% Latino Risk: 100% family history of T2D (≥1 parent, sibling, or grandparent); 100% BMI ≥85th percentile	BF duration	None	Fasting glucose at Tanner pubertal stage 1: $P \geq 0.20$ (data NR) Fasting glucose across pubertal transition from Tanner pubertal stage 1 to 5: $P \geq 0.20$ (data NR) 2-h glucose during OGTT at Tanner pubertal stage 1: $P \geq 0.20$ (data NR) 2-h glucose during OGTT across pubertal transition from Tanner pubertal stage 1 to 5: $P \geq 0.20$ (data NR) Insulin sensitivity at Tanner pubertal stage 1: $P \geq 0.20$ (data NR) Insulin sensitivity across pubertal transition from Tanner pubertal stage 1 to 5: $P \geq 0.20$ (data NR) Acute insulin response at Tanner pubertal stage 1: $P \geq 0.20$ (data NR) Acute insulin response across pubertal transition from Tanner pubertal stage 1 to 5: $P \geq 0.20$ (data NR) Disposition index at Tanner pubertal stage 1: $P \geq 0.20$ (data NR) Disposition index across pubertal transition from Tanner pubertal stage 1 to 5: $P \geq 0.20$ (data NR)
Jeffery 2006 (59)	Prospective cohort (EarlyBird Diabetes Study)	UK	$n = 235$ Baseline: 5 y Race/ethnicity: 98% white	BF duration	None	HOMA-IR for boys at 8 y: NS (data NR) HOMA-IR for girls at 8 y: NS (data NR)
Martin 2014 (57)	RCT[3] or prospective cohort, depending on the analysis (PROBIT)	Belarus	$n = 13{,}616$ Baseline: birth Race/ethnicity NR	Intervention group (higher rate of any BF at 3, 6, 9, and 12 mo) vs. control group	None	Fasting glucose (mmol/L) at 11.5 y: mean difference –0.03 (95% CI: –0.16, 0.10) HOMA-IR at 11.5 y: ratio of geometric means 1.05 (95% CI: 0.85, 1.30)
				BF 3–<6 mo vs. <3 mo	None	Fasting glucose (mmol/L) at 11.5 y: mean difference 0.00 (95% CI: –0.03, 0.02) HOMA-IR at 11.5 y: ratio of geometric means 1.00 (95% CI: 0.95, 1.05)
				BF ≥6 mo vs. <3 mo	None	Fasting glucose (mmol/L) at 11.5 y: mean difference 0.01 (95% CI: –0.01, 0.03) HOMA-IR at 11.5 y: ratio of geometric means 0.97 (0.93, 1.02)
				BF duration trend according to the categories <3, 3–<6, and ≥6 mo	None	Fasting glucose (mmol/L) at 11.5 y: $P = 0.27$ HOMA-IR at 11.5 y: $P = 0.66$
Rodekamp 2005 (58)	Prospective cohort (Kaulsdorf Cohort Study)	Germany	$n = 112$ Baseline: birth Race/ethnicity NR Risk: 100% family history of T1D or GDM (mothers)	BF duration (wk)	None	Fasting glucose at 2 y: NS (data NR) 2-h glucose during OGTT at 2 y: $\beta = 0.15$, $P = 0.13$ Impaired glucose tolerance at 2 y: OR 0.99 (95% CI: 0.94, 1.06)

[1] BF, breastfed; GDM, gestational diabetes mellitus; NR, not reported; NS, not significant; OGTT, oral-glucose-tolerance test; PROBIT, Promotion of Breastfeeding Intervention Trial; RCT, randomized controlled trial; SOLAR, Study Of Latino Adolescents at Risk for Diabetes; T1D, type 1 diabetes; T2D, type 2 diabetes.

[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.

[3] RCT of an intervention to promote prolonged duration and exclusivity of breastfeeding rather than an RCT of breastfeeding per se.

trial of an intervention to promote prolonged duration and exclusivity of breastfeeding among mothers who chose to feed human milk. The primary, intention-to-treat, analysis compared the intervention group (which had higher rates of any human milk feeding measured at 3, 6, 9, and 12 mo) to the control group, and found no significant differences in fasting glucose or homeostasis model assessment of insulin resistance (HOMA-IR) at 11.5 y. Prospective cohort analyses of PROBIT study data, which compared children fed human milk 3–<6 mo and ≥6 mo with children fed human milk <3 mo and examined the trend across the 3 categories of duration (<3, 3–<6, and ≥6 mo), were also nonsignificant. Jeffery et al. (59) reported that HOMA-IR

at 8 y of age was not significantly associated with the duration of any human milk feeding in girls or in boys. Rodekamp et al. (58) found no significant associations between the duration of human milk feeding and fasting glucose, 2-h oral glucose tolerance test results, or impaired glucose tolerance [based on National Diabetes Data Group criteria for children (62)] at 2 y of age in a sample of children whose mothers had type 1 diabetes or gestational diabetes. Davis et al. (28) also enrolled a high-risk sample; participants were 8–13 y of age, Latino, had a BMI ≥85th percentile according to CDC growth standards, and had a family history of type 2 diabetes. This study found no significant associations between the duration of human milk feeding and fasting glucose, 2-h oral glucose tolerance test results, insulin sensitivity, acute insulin response, or disposition index (a measure of pancreatic β-cell function) at Tanner pubertal stage 1 or across the pubertal transition from Tanner pubertal stage 1 to 5.

Shorter versus longer durations of exclusive human milk and diabetes outcomes in offspring

Eighteen articles met the inclusion criteria for this SR question; 17 articles examined type 1 diabetes (9, 10, 13, 14, 16, 20, 41, 43, 44, 48–50, 35, 63–66), and 1 article examined fasting glucose and insulin resistance at 11.5 y of age (57). TEC members concluded that there was insufficient evidence to determine whether or not there is a relationship between shorter versus longer durations of exclusive human milk feeding and type 2 diabetes, prediabetes, HbA1c, fasting glucose at ages other than 11.5 y, and insulin resistance at ages other than 11.5 y (Table 7). Evidence about type 1 diabetes and about fasting glucose and insulin resistance at 11.5 y of age is presented below.

Type 1 diabetes.

The 17 articles that examined shorter versus longer durations of exclusive human milk feeding and type 1 diabetes presented evidence from 15 independent studies (**Table 5**). There was 1 prospective cohort study (41), 1 nested case-control study (9), and 13 independent case-control studies (10, 13, 14, 16, 20, 43, 44, 48–50, 35, 63–66) because Samuelsson et al. (44, 65) and Virtanen et al. (49, 50) each presented data for a single study across 2 articles.

Seven of the studies reported significant associations across 8 articles (10, 43, 48–50, 35, 63, 64). It is notable that the study by Alves et al. (10), which is the only study in the body of evidence that paired cases with sibling controls to minimize confounding from shared genetic and environmental factors, found a significant association. On the other hand, the studies that were more likely to have sufficient statistical power (i.e., studies with the largest numbers of cases and studies that recruited high-risk samples) reported both significant and nonsignificant associations. For example, 4 (43, 48, 50, 63) of 8 studies with >200 cases (14, 16, 43, 44, 48, 50, 63, 65, 66) found significant associations, and 1 (10) of 3 studies that examined high-risk samples (9, 10, 41) found significant associations.

All of the significant associations in the body of evidence were consistent in direction, suggesting that shorter versus longer durations of any human milk feeding are associated with higher risk of type 1 diabetes. The significant associations were from case-control studies that compared the average duration of exclusive human milk feeding in cases and controls (10, 49, 50, 35, 64) or compared heterogeneous ranges of duration [i.e., ≤7 compared with >60 d (63), <2 compared with ≥2 mo (43, 50), <3 compared with ≥3 mo (48–50), <4 compared with ≥4 mo (49), and <5 compared with ≥5 mo (43, 50)], and that examined risk of type 1 diabetes at ages ≤6 y (49), 7–14 y (50), a mean of 8 y (64), a mean of 9 y (10), a mean of 15.1 y (35), ≤15 y (43, 48) and <18 y (63).

The remaining 8 studies found nonsignificant associations between the duration of exclusive human milk feeding and type 1 diabetes (9, 13, 14, 16, 20, 41, 44, 65, 66). As noted above, some of these studies included a large number of cases (14, 16, 44, 65, 66) or high-risk samples (9, 41). The nonsignificant associations were inconsistent in direction.

Fasting glucose and insulin resistance at 11.5 y of age.

The cluster randomized controlled trial, PROBIT (described previously), was the only study to provide evidence about the duration of exclusive human milk feeding and fasting glucose and insulin resistance in childhood (**Table 6**). In the intention-to-treat analysis, Martin et al. (57) reported no significant differences in fasting glucose or HOMA-IR at 11.5 y of age between the intervention group (which had higher rates of exclusive human milk feeding measured at 3 and 6 mo) and the control group. Prospective cohort analyses of PROBIT study data found a slightly higher, but significant, fasting glucose level in children fed human milk exclusively 3–<6 mo compared with <3 mo, but no significant difference in HOMA-IR. There were no differences in fasting glucose or HOMA-IR between children fed human milk exclusively at ≥6 mo in comparison with <3 mo, and the trends across the 3 categories of duration (<3, 3–<6, and ≥6 mo) were nonsignificant.

Discussion

The conclusion statements that answer the 4 SR questions related to infant milk-feeding practices and diabetes outcomes in offspring, and the grades of the evidence underlying the conclusion statements, are listed in Table 7. TEC members used the NESR grading rubric to consider the aspects of the adequacy, consistency, generalizability, impact, and internal validity of the evidence discussed below.

The majority of evidence examined type 1 diabetes rather than type 2 diabetes or intermediate outcomes. Therefore, the adequacy of the evidence underlying the conclusion statements about the relationships of never versus ever being fed human milk (i.e., 15 studies) and shorter versus longer durations of any (i.e., 22 studies) and exclusive (i.e., 15 studies) human milk feeding with type 1 diabetes was good. On the other hand, given the low prevalence of type 1 diabetes, some of the studies likely had inadequate statistical power. For example, 7 (13, 15, 17, 21–24) of 9 (10, 11, 13, 15, 17, 21–24) studies with nonsignificant associations between never versus ever being fed human milk and type 1 diabetes, and 6 (15, 17, 19, 24, 45, 55) of 10 (14, 15, 17–19, 24, 39, 44, 45, 55) studies with nonsignificant associations between the duration of any human milk feeding and type 1 diabetes, were prospective studies or small case-control studies (i.e., <200 cases) and did not recruit high-risk samples. A similar

TABLE 5 Evidence examining the relationship between shorter versus longer durations of exclusive human milk feeding and type 1 diabetes in offspring[1]

Author and year Country	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs. longer durations of exclusive human milk feeding exposures[2]	Significant associations with type 1 diabetes	Nonsignificant associations with type 1 diabetes
Alves 2012 (10)	Case control	Brazil	$n = 123$ cases, 123 sibling controls Baseline: mean 9 y Race/ethnicity NR Risk: 100% of sibling controls had a sibling with T1D	Mean difference in EBF duration in cases vs. controls	–0.9 mo (95% CI: –1.2, –0.6), $P < 0.001$	None
Esfarjani 2001 (13)	Case control	Iran	$n = 52$ cases, 52 controls Baseline: <14 y Race/ethnicity NR Risk: 0% of controls with family history of IDDM	Mean duration of EBF in cases vs. controls	None	4.5 mo (SD = 3.1) vs. 4.1 mo (SD = 3.9), NS
Frederiksen 2013 (9)	Nested case control[3] (DAISY)	USA	$n = 53$ cases, 1782 controls Baseline: birth Race/ethnicity: 70.1% non-Hispanic white Risk: 100% at-risk genotype or family history of T1D (first-degree relative)	Mean EBF duration in cases vs. controls	None	1.4 mo (SD = 2.0) vs. 1.3 mo (SD = 1.7); T1D HR 0.97 (95% CI: 0.83, 1.14), $P = 0.73$
Gimeno 1997 (63)	Case control	Brazil	$n = 346$ cases, 346 controls Baseline: <18 y Sex NR Race/ethnicity NR	EBF 0–7 d vs. >60 d EBF 8–60 d vs. > 60 d	IDDM: OR 2.13 (95% CI: 1.28, 3.55) None	None IDDM: OR 1.14 (95% CI: 0.82, 1.58)
Kostraba 1992 (14)	Case control	USA	$n = 211$ cases, 211 controls Baseline: diagnosed <17 y but age at the study NR Race/ethnicity: 26.1% black, 73.9% white	EBF duration in cases vs. controls	None	In white subsample: 18 wk vs. 13 wk, $P = 0.4$ In black subsample: 13 wk vs. 27 wk, $P = 0.16$
Lund-Blix 2015 (41)	Prospective cohort (MIDIA)	Norway	$n = 726$ Baseline: birth Race/ethnicity NR Risk: 100% at-risk genotype	Full BF duration (mo) as a continuous variable Full BF 4–5.9 mo vs. <4 mo Full BF ≥6 mo vs. <4 mo Full BF ≤2 wk vs. >2 wk	None None None None	T1D by age 7.70 (SD = 1.58) y: HR 0.96 (95% CI: 0.78, 1.18) T1D by age 7.70 (SD = 1.58) y: HR 0.79 (95% CI: 0.32, 1.94) T1D by age 7.70 (SD = 1.58) y: HR 0.84 (95% CI: 0.26, 2.73) T1D by age 7.70 (SD = 1.58) y: HR 1.10 (95% CI: 0.36, 3.41)
Malcova 2006 (16)	Case control	Czech Republic	$n = 868$ cases, 1466 controls Baseline: ≤18 y, median 13 y (IQR: 10, 16) for cases, 12 y (IQR: 9, 15) for controls Race/ethnicity NR	Introduced to formula or other supplementary feeding at 1–3 mo vs. 4–6 mo Introduced to formula or other supplementary feeding at 7–9 mo vs. 4–6 mo Introduced to formula or other supplementary feeding at ≥ 10 mo vs. 4–6 mo	None None None	T1D: OR 1.11 (95% CI: 0.83, 1.50) T1D: OR 0.96 (95% CI: 0.69, 1.34) T1D: OR 0.90 (95% CI: 0.49, 1.67)

(*Continued*)

TABLE 5 (*Continued*)

Author and year Country	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs. longer durations of exclusive human milk feeding exposures[2]	Significant associations with type 1 diabetes	Nonsignificant associations with type 1 diabetes
Perez-Bravo 1996 (35)	Case control	Chile	$n = 80$ cases, 85 controls Baseline: mean: 15.1 y (SD = 5.6) Race/ethnicity: strata III of the sociogenetic classification (40% indigenous admixture with European genetic pools of mostly Spanish origin)	Mean EBF duration in cases vs. controls	21.55 wk (SD = 15.05) vs. 33.95 wk (SD = 20.40), $P = 0.01$	None
Perez-Bravo 2003 (64)	Case control	Chile	$n = 143$ cases, 107 controls Baseline: mean ~8 y (SD ~4 y) Race/ethnicity: 100% 2 Hispanic surnames and no Amerindian background	Mean EBF duration in cases vs. controls	5.4 mo (SD = 3.5) vs. 7.6 mo (SD = 3.6), $P < 0.02$	None
Rami 1999 (20)	Case control (EURODIAB ACE)	Austria	$n = 114$ cases, 495 controls Baseline: <15 y Race/ethnicity NR	Median EBF duration in cases vs. controls	None	2 mo (range: 0–7) vs. 2 mo (range: 0–18), $P = 0.40$
Sadauskaite-Kuehne 2004 (43)	Case control (Diabetes and Environment around the Baltic Sea)	Sweden, Lithuania	$n = 517$ Swedish cases, 286 Lithuanian cases, controls NR (~2 controls per case) Baseline: 0–15 y Race/ethnicity NR	EBF ≥5 mo vs. <5 mo	T1D in Swedish subsample ages 5–9 y: OR 0.54 (95% CI: 0.36, 0.81)	NR[4]
				EBF ≥2 mo vs. <2 mo	T1D in Lithuanian subsample ages 5–9 y: OR 0.58 (95% CI: 0.34, 0.99)	NR
Samuelsson 1993 (44)	Case control	Sweden	$n = 297$ cases, 792 controls Baseline: 0–14 y Sex NR Race/ethnicity NR	Mean duration of complete BF in cases vs. controls	None	NS (data NR) In subsample age <5 y: 4.50 mo (SD = 0.68) vs. 3.02 mo (SD = 0.47), $P = 0.17$ In subsample age 5–9 y: 3.18 mo (SD = 0.26) vs. 3.55 mo (SD = 0.25), $P = 0.34$ In subsample age >10 y: 2.17 mo (SD = 0.16) vs. 2.40 mo (SD = 0.11)
Samuelsson 2001 (65)	Case control	Sweden	$n = 297$ cases, 736 controls Baseline: 0–14 y Sex NR Race/ethnicity NR	Mean EBF duration in cases vs. controls	None	2.5 mo (95% CI: 2.2, 2.7) vs. 2.6 mo (95% CI: 2.5, 2.8)
Verge 1994 (48)	Case control	Australia	$n = 217$ cases, 258 controls Baseline: 0–15 y, median 9.2 y Race/ethnicity NR	EBF ≥3 mo vs. EBF <3 mo	IDDM: OR 0.66 (95% CI: 0.45, 0.97) IDDM in subsample age <9.2 y: OR 0.50 (95% CI: 0.28, 0.87)	IDDM in subsample age ≥9.2 y: OR 0.80 (95% CI: 0.46, 1.39)
Virtanen 1991 (49)	Case control (DiMe)	Finland	$n = 103$ cases, 103 controls Baseline: 0–6 y Race/ethnicity NR	Median EBF duration in cases vs. controls	3 mo vs. 4 mo, $P = 0.02$	None
				EBF ≥1 mo vs. <1 mo	None	IDDM: ~90% in cases vs. ~99% in controls, NS
				EBF ≥2 mo vs. <2 mo	None	IDDM: ~88% in cases vs. ~95% in controls, NS
				EBF ≥3 mo vs. <3 mo	IDDM: OR 0.36 (95% CI: 0.14, 0.93) ~73% in cases vs. ~90% in controls, $P < 0.05$	None

(*Continued*)

TABLE 5 (*Continued*)

Author and year Country	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs. longer durations of exclusive human milk feeding exposures[2]	Significant associations with type 1 diabetes	Nonsignificant associations with type 1 diabetes
				EBF ≥4 mo vs. <4 mo	IDDM: OR 0.41 (95% CI: 0.21, 0.83) ~41% in cases vs. ~61% in controls, $P < 0.05$	None
				EBF ≥5 mo vs. <5 mo	None	IDDM: OR 0.77 (95% CI: 0.36, 1.64) ~28% in cases vs. ~30% in controls, NS
				EBF ≥6 mo vs. <6 mo	None	IDDM: ~15% in cases vs. ~14% in controls, NS
Virtanen 1992 (50)	Case control (DiMe)	Finland	$n = 426$ cases, 426 controls Baseline: 7–14 y Race/ethnicity NR	Median EBF duration in cases vs. controls	2 mo vs. 2 mo,[5] $P = 0.04$	None
				EBF ≥1 mo vs. <1 mo	None	IDDM: OR ~0.8 (95% CI: ~0.5, ~1.4) ~88% in cases vs. ~90% in controls
				EBF ≥2 mo vs. <2 mo	IDDM: OR 0.60 (95% CI: 0.41, 0.89)~65% in cases vs. ~75% in controls, $P < 0.05$	None
				EBF ≥3 mo vs. <3 mo	IDDM: OR 0.63 (95% CI: 0.43, 0.93)~41% in cases vs. ~51% in controls, $P < 0.05$	None
				EBF ≥4 mo vs. <4 mo	None	IDDM: OR ~0.7 (95% CI: ~0.4, ~1.1) ~14% in cases vs. ~20% in controls
				EBF ≥5 mo vs. <5 mo	IDDM: ~7% in cases vs. ~13% in controls, $P < 0.05$	IDDM: OR ~0.6 (95% CI: ~0.3, ~1.2)
				EBF ≥6 mo vs. <6 mo	None	IDDM: OR ~0.7 (95% CI: ~0.3, ~1.7) ~4% in cases vs. ~7% in controls
Wadsworth 1997 (66)	Case control	UK	$n = 218$ cases, 324 controls Baseline: <5 y Sex NR Race/ethnicity NR	First introduction of artificial milk formula 2–6 wk vs. <2 wk	None	T1D: OR 1.42 (95% CI: 0.75, 2.70)
				First introduction of artificial milk formula 6 wk–4 mo vs. <2 wk	None	T1D: OR 0.71 (95% CI: 0.40, 1.23)
				First introduction of artificial milk formula >4 mo vs. <2 wk	None	T1D: OR 1.41 (95% CI: 0.70, 2.80)

[1]BF, breastfeeding; DAISY, Diabetes Autoimmunity Study in the Young; DiMe; Childhood Diabetes in Finland; EBF, exclusively breastfed; IDDM, insulin-dependent diabetes mellitus; MIDIA, Environmental Triggers of Type 1 Diabetes; NR, not reported; NS, not significant; T1D, type 1 diabetes.

[2]Exposures, as defined by the authors of the studies included in the body of evidence, which address shorter versus longer durations of exclusive human milk feeding or vice versa

[3]The authors call the study a prospective cohort; however, the assessment grouped participants by outcome status rather than infant feeding exposure.

[4]Authors only reported significant associations; information about nonsignificant findings was not reported.

[5]Although the medians are the same, the authors describe this as significantly shorter EBF duration in cases than controls

TABLE 6 Evidence examining the relationship between shorter versus longer durations of exclusive human milk feeding and fasting glucose and insulin resistance in offspring at 11.5 y of age[1]

Author and year	Study design (study/cohort name where applicable)	Country	Notable sample characteristics	Shorter vs. longer durations of exclusive human milk feeding exposures[2]	Significant associations with intermediate outcomes	Nonsignificant associations with intermediate outcomes
Martin 2014 (57)	RCT[3] or prospective cohort, depending on the analysis (PROBIT)	Belarus	$n = 13{,}616$ Baseline: birth Race/ethnicity NR	Intervention group (higher rate of EBF at 3 and 6 mo) vs. control group	None	Fasting glucose (mmol/L) at 11.5 y: mean difference –0.03 (95% CI: –0.16, 0.10) HOMA-IR at 11.5 y: Ratio of geometric means 1.05 (95% CI: 0.85, 1.30)
				EBF 3 to <6 mo vs. <3 mo	Fasting glucose (mmol/L) at 11.5 y (prospective cohort analysis): mean difference 0.02 (95% CI: 0.01, 0.04)	Fasting glucose (mmol/L) at 11.5 y (instrumental variable analysis): mean difference –0.09 (95% CI: –0.46, 0.29) HOMA-IR at 11.5 y (instrumental variable analysis): ratio of geometric means 1.17 (95% CI: 0.58, 2.37) HOMA-IR at 11.5 y (prospective cohort analysis): ratio of geometric means 1.00 (95% CI: 0.95, 1.05)
				EBF ≥6 mo vs. <3 mo	None	Fasting glucose (mmol/L) at 11.5 y (instrumental variable analysis): mean difference –0.15 (95% CI: –0.72, 0.42) Fasting glucose (mmol/L) at 11.5 y (prospective cohort analysis): mean difference 0.00 (95% CI: –0.05, 0.04) HOMA-IR at 11.5 y (instrumental variable analysis): ratio of geometric means 1.28 (95% CI: 0.44, 3.76) HOMA-IR at 11.5 y (prospective cohort analysis): ratio of geometric means 1.01 (95% CI: 0.91, 1.12)
				EBF duration trend according to the categories <3, 3–<6, and ≥6 mo EBF	None	Fasting glucose (mmol/L) at 11.5 y: $P = 0.38$ HOMA-IR at 11.5 y: $P = 0.94$

[1]EBF, exclusively breastfed; NR, not reported; PROBIT, Promotion of Breastfeeding Intervention Trial; RCT randomized controlled trial.
[2]Exposures, as defined by the authors of the studies included in the body of evidence, which address shorter versus longer durations of exclusive human milk feeding or vice versa.
[3]RCT of an intervention to promote prolonged duration and exclusivity of breastfeeding rather than an RCT of breastfeeding per se.

pattern did not emerge in the body of evidence that examined the duration of exclusive human milk feeding and type 1 diabetes.

The evidence related to type 1 diabetes was consistent. With 1 exception (19), the studies with significant associations between never versus ever being fed human milk and type 1 diabetes suggested that never being fed human milk is associated with higher risk of type 1 diabetes (12, 14, 16, 18, 25). Likewise, with 1 exception (40), the studies with significant associations between shorter versus longer durations of any human milk feeding and type 1 diabetes suggested that shorter durations are associated with higher risk of type 1 diabetes (16, 36–38, 41–43, 46–51, 54, 56). Notably, the only study with a significant association in the opposite direction (40) examined a sample that was entirely male and comprised of both living and deceased individuals, which hindered TEC members' ability to judge its consistency with other analyses. In the body of evidence examining shorter versus longer durations of exclusive human milk feeding and type 1 diabetes, all of the studies that reported statistically significant

TABLE 7 Systematic review questions, conclusion statements, and grades of the evidence supporting the conclusion statements

Systematic review question	Conclusion statement and grade
What is the relationship between never versus ever feeding human milk and diabetes outcomes in offspring?	Limited evidence from observational studies suggests that never versus ever being fed human milk is associated with higher risk of type 1 diabetes. (Grade: Limited). There is insufficient evidence to determine whether or not there is a relationship between never versus ever feeding human milk and type 2 diabetes, prediabetes, fasting glucose, hemoglobin A1c, insulin resistance, and glucose tolerance throughout the lifespan. (Grade: Grade not assignable)
What is the relationship between shorter versus longer durations of any human milk-feeding and diabetes outcomes in offspring?	Moderate evidence from observational studies suggests that, among infants fed some amount of human milk, shorter versus longer durations of any human milk feeding are associated with higher risk of type 1 diabetes. (Grade: Moderate). Limited but consistent evidence suggests that the duration of any human milk feeding is not associated with fasting glucose or insulin resistance in childhood or during the transition from childhood into adolescence. (Grade: Limited). There is insufficient evidence to determine whether or not there is a relationship between shorter versus longer durations of any human milk feeding and type 2 diabetes, prediabetes, or hemoglobin A1c throughout the lifespan, and fasting glucose and insulin resistance in adulthood. (Grade: Grade not assignable)
What is the relationship between shorter versus longer durations of exclusive human milk feeding and diabetes outcomes in offspring?	Limited evidence from observational studies suggests that shorter versus longer durations of exclusive human milk feeding are associated with higher risk of type 1 diabetes. Limited evidence, from a single study that used a strong design, also suggests that the duration of exclusive human milk feeding is not associated with fasting glucose or insulin resistance at 11.5 y of age. (Grade: Limited). There is insufficient evidence to determine whether or not there is a relationship between shorter versus longer durations of any human milk feeding and type 2 diabetes, prediabetes, and hemoglobin A1c throughout the lifespan, and fasting glucose and insulin resistance at ages other than 11.5 y. (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 diabetes outcomes in offspring?	There is insufficient 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 diabetes outcomes in offspring. (Grade: Grade not assignable)

associations were consistent in suggesting that shorter durations are associated with higher risk of type 1 diabetes (10, 43, 48–50, 35, 63, 64). The consistency in the direction of the significant associations across these bodies of evidence is noteworthy given that the independent variables were heterogeneous, which was a feature of not defining *longer duration*, *shorter duration*, or *ever feeding human milk*, and instead considering all analyses that compared shorter with longer durations of any or exclusive human milk feeding and never with ever feeding human milk in the synthesis of the evidence.

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. Only 3 studies described objectives to examine interventions or exposures outside of the scope of these SRs: Kostraba et al. (15) and Thorsdottir et al. (24) stated intentions to examine the consumption of cow's milk or solid foods, and the study by Savilahti et al. (45) was originally an experimental study to compare pasteurized human milk and extensively hydrolyzed formula with cow's milk formula to reduce cow's milk allergy. Qualitative methods were not used to judge clinical significance in terms of the magnitude of the risk of being fed human milk for short durations or not at all on type 1 diabetes. However, given the increasing incidence of type 1 diabetes in the United States and the social and economic consequences of this disease (5, 6), even small decreases in the risk for type 1 diabetes have the potential to be of public health importance.

The generalizability of the evidence to US populations was sound overall. There were a number of US studies that presented evidence about never versus ever being fed human milk (14, 15, 18), shorter versus longer durations of any human milk feeding (9, 14, 15, 18, 39, 56), and shorter versus longer durations of exclusive human milk feeding (9, 14) and type 1 diabetes, and they included some racial and ethnic diversity. Furthermore, all of the evidence came from countries that met the inclusion criterion of being high or very high on the Human Development Index (33), and therefore having a level of human development likely generalizable to the United States. Some of the studies recruited high-risk samples that may not be generalizable (9–11, 28, 37, 39, 41, 46, 51–53, 56, 58); yet, as previously mentioned, this had the effect of increasing the studies' statistical power, which is important given the low incidence of type 1 diabetes.

TEC members did have some concerns about internal validity related to study design. Most of the studies were case-control studies. TEC members recognized the importance of case-control studies in this area because they are useful for examining low-incident outcomes such as type 1 diabetes. However, because case-control studies rely on the retrospective collection of exposure data, differential or nondifferential misclassification of the exposure may have introduced bias. Differential misclassification from recall bias (i.e., if mothers of children with type 1 diabetes recalled or reported infant milk-feeding practices differently from mothers of children without type 1 diabetes) could have resulted in over- or underestimations of the associations, whereas nondifferential misclassification would have tended to bias the reported associations toward the null. There was no such concern related to the outcome, which was medically diagnosed and unlikely to misclassify cases or controls. Although all of the case-control studies included matching variables, and many included

additional adjustment variables, residual confounding from other variables related to infant-feeding and type 1 diabetes risk may have occurred. Residual confounding may have been less of a concern from the small number of studies that compared individuals who had type 1 diabetes with their siblings, with whom they shared genetic and environmental factors. Four such studies examined the duration of any human milk feeding (37, 39, 46, 51); 2 found significant associations between shorter compared with longer durations of any human milk feeding and higher risk of type 1 diabetes (37, 51) and a third had a nonsignificant association in the same direction with a wide CI indicative of suboptimal statistical power (46). One such study examined the duration of exclusive human milk feeding as well as never versus ever feeding human milk (10); this study found that children with type 1 diabetes were fed human milk exclusively for a significantly shorter duration from their healthy siblings but, with nearly universal initiation of human milk feeding, there was not a significant association between never versus ever being fed human milk and type 1 diabetes. Another potential source of bias was multiple comparison bias; in particular, in the bodies of evidence examining shorter versus longer durations of any and exclusive human milk feeding and type 1 diabetes, Virtanen et al. (49–53) assessed multiple comparisons across 5 articles. In addition, Sadauskaite-Kuehne et al. (43) only reported significant associations and therefore it is not possible to know how many comparisons were assessed.

TEC members graded the evidence underlying their conclusions about shorter versus longer durations of any and exclusive human milk feeding and fasting glucose, insulin resistance, and glucose tolerance during childhood and into adolescence as limited. The intention-to-treat analyses of the PROBIT study, which is a large randomized trial of an intervention to promote prolonged duration and exclusivity of breastfeeding (57), formed the basis for these conclusion statements. The PROBIT study was likely to have good internal validity because randomization mitigates selection bias and confounding. In addition, detection bias may have been reduced by collecting infant-feeding data prospectively, and an audit by PROBIT researchers found that a random subset of infant-feeding data had close agreement with data obtained by maternal interview. The bodies of evidence were small. Four studies (including PROBIT) examined shorter versus longer durations of any human milk feeding and fasting glucose, insulin resistance, and glucose tolerance; yet, the direction of the associations across the studies was consistent. The PROBIT study, alone, provided evidence about shorter versus longer durations of exclusive human milk feeding and fasting glucose and insulin resistance. TEC members had some doubts about the generalizability of the evidence to generally healthy US populations. Just 1 US sample (28) provided evidence for shorter versus longer durations of any human milk feeding and fasting glucose and insulin resistance. US populations may have higher metabolic risk than the populations from which participants were sampled in the remaining studies (e.g., the Belarusian population from which the PROBIT study was sampled). Regarding the impact of the evidence, TEC members concluded there was evidence of no association between the durations of any or exclusive human milk feeding and fasting glucose, insulin resistance, and glucose tolerance during childhood and into adolescence, which would mean there is no clinical significance.

Research recommendations

TEC members identified several areas for future research. There was insufficient evidence to answer 1 of the 4 SR questions (Table 7) because only 1 article examined the intensity, proportion, or amount of human milk fed to mixed-fed infants (9). In addition, scant evidence examined type 2 diabetes, and evidence examining intermediate outcomes tended to be from samples outside of the United States that may differ in metabolic risk from the US population. Therefore, the primary research recommendations are for future research to examine the following: *1*) the relationship between the intensity of human milk fed to mixed-fed infants and diabetes outcomes, *2*) the relationship between infant milk-feeding practices and type 2 diabetes, and *3*) intermediate and endpoint outcomes in representative and well-powered US samples. Large prospective samples could perhaps be acquired by linking surveillance systems that collect data about infant feeding and diabetes outcomes, or through the use of electronic medical record data. 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 (e.g., race and ethnicity, socioeconomic status, and family history of diabetes) should be assessed. Study designs that further minimize confounding include sib-pair analyses (e.g., comparisons of associations within sibling pairs compared with associations irrespective of sibship), analyses of cohorts with different confounding structures, and use of instrumental variables such as Mendelian randomization approaches. Researchers should incorporate effect modification into their study design whenever possible (e.g., participant race and ethnicity) because different social, demographic, and biological characteristics are likely to modify the impact of infant milk-feeding practices on the outcomes. Infant milk-feeding research should also move toward collecting infant-feeding data consistently through the use of 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).

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