WHAT IS THE RELATIONSHIP BETWEEN THE DURATION OF EXCLUSIVE HUMAN MILK AND/OR INFANT FORMULA CONSUMPTION AND LONG-TERM HEALTH OUTCOMES?: SYSTEMATIC REVIEW PROTOCOL

This document describes the protocol for a systematic review to answer the following question: What is the relationship between the duration of exclusive human milk and/or infant formula consumption and long-term health outcomes?

The 2020 Dietary Guidelines Advisory Committee, Birth to 24 Months Subcommittee, will be answering this question by conducting a systematic review with support from USDA's Nutrition Evidence Systematic Review (NESR) part of which involves updating six existing NESR systematic reviews.

NESR methodology for answering a systematic review question involves:

- searching for and selecting articles,
- extracting data and assessing the risk of bias of results from each included article,
- synthesizing the evidence,
- developing a conclusion statement,
- grading the evidence underlying the conclusion statement, and
- recommending future research.

More information about NESR's systematic review methodology, which will be used in this systematic review update, is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews.

The existing NESR systematic reviews that will be updated as part of this work were conducted during the Pregnancy and Birth to 24 Months Project by the Infant Milk-Feeding Practices Technical Expert Collaborative and staff from USDA's NESR. Complete documentation of the existing systematic reviews is available on the NESR website:

- https://nesr.usda.gov/what-relationship-between-never-versus-ever-feeding-human-milk-and-cardiovascular-disease-outcomes#full-review
- https://nesr.usda.gov/what-relationship-between-shorter-versus-longer-durations-any-human-milk-feeding-and-cardiovascular#full-review
- https://nesr.usda.gov/what-relationship-between-shorter-versus-longer-durations-exclusive-human-milk-feeding-and-0#full-review
- https://nesr.usda.gov/what-relationship-between-never-versus-ever-feeding-human-milk-and-diabetes-outcomes-offspring#full-review
- https://nesr.usda.gov/what-relationship-between-shorter-versus-longer-durations-any-human-milk-feeding-and-diabetes#full-review
- https://nesr.usda.gov/what-relationship-between-shorter-versus-longer-durations-exclusive-human-milk-feeding-and-diabetes#full-review

In addition, more information about the systematic review methodology used during the Pregnancy and Birth to 24 Months Project is available on the NESR website:

- https://nesr.usda.gov/pregnancy-and-birth-24-months-project-nutrition-evidence-systematic-review-methodology

This document describes the protocol, or plan, for how the update to the existing systematic reviews will be conducted. The protocol provides:

- The analytic framework (p. 3) illustrates the overall scope of the question, including the population, the interventions and/or exposures, comparators, and outcomes of interest.
- The literature search and screening plan (p. 4) details the electronic databases and inclusion and exclusion criteria (p. 4) that will be used to search for, screen, and select articles to be included in the systematic review. The following inclusion and exclusion criteria from the existing systematic reviews were updated:
    - Date of publication
    - Study design
    - Outcomes
- The literature search and screening results (p. 8) includes a list of included articles, and a list of excluded articles with the rationale for exclusion.

This protocol is up-to-date as of: 10/22/2019.

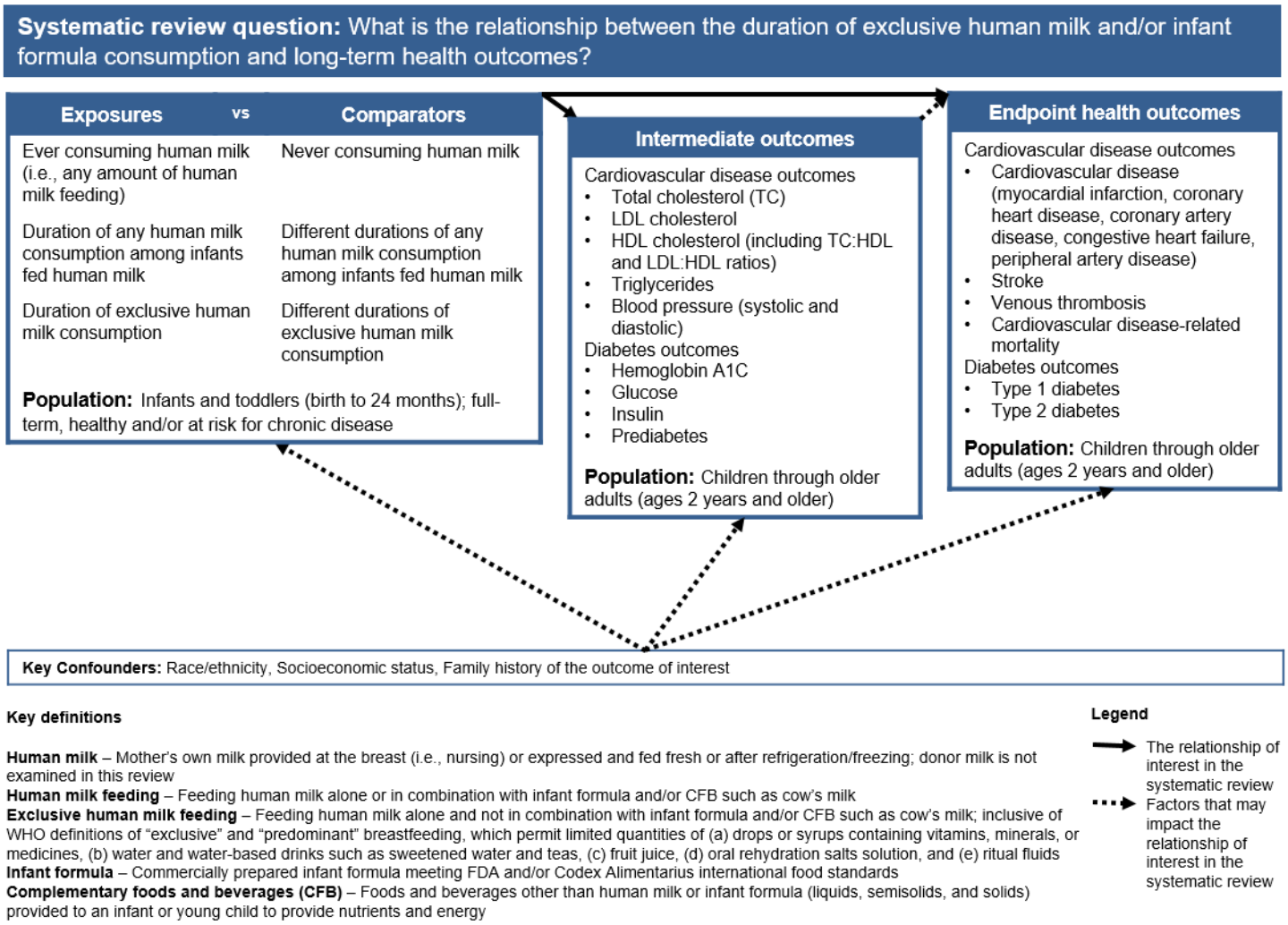
This version of the protocol contains updates to the following sections. These changes do not reflect a substantive change in the intent or conduct of the review.

- On the analytic framework and in the inclusion and exclusion criteria table, the exposure and comparator related to the duration of exclusive human milk consumption were updated to be consistent with the existing reviews.
- In the inclusion and exclusion criteria table, the date of publication criterion now reflects that the literature search was conducted in September 2019.

ANALYTIC FRAMEWORK

The analytic framework (**Figure 1**) illustrates the overall scope of the systematic review, including the population, the interventions and/or exposures, comparators, and outcomes of interest. It also includes definitions of key terms and identifies key confounders considered in the systematic review. The inclusion and exclusion criteria that follow provide additional information about how parts of the analytic framework will be defined and operationalized for the review.

Figure 1: Analytic framework



Key definitions

Human milk – Mother's own milk provided at the breast (i.e., nursing) or expressed and fed fresh or after refrigeration/freezing; donor milk is not examined in this review
Human milk feeding – Feeding human milk alone or in combination with infant formula and/or CFB such as cow's milk
Exclusive human milk feeding – Feeding human milk alone and not in combination with infant formula and/or CFB such as cow's milk; inclusive of WHO definitions of "exclusive" and "predominant" breastfeeding, which permit limited quantities of (a) drops or syrups containing vitamins, minerals, or medicines, (b) water and water-based drinks such as sweetened water and teas, (c) fruit juice, (d) oral rehydration salts solution, and (e) ritual fluids
Infant formula – Commercially prepared infant formula meeting FDA and/or Codex Alimentarius international food standards
Complementary foods and beverages (CFB) – Foods and beverages other than human milk or infant formula (liquids, semisolids, and solids) provided to an infant or young child to provide nutrients and energy

Legend

→ The relationship of interest in the systematic review
⇢ Factors that may impact the relationship of interest in the systematic review

LITERATURE SEARCH AND SCREENING PLAN

Electronic databases

Listed below are the databases that will be searched to identify all potentially relevant articles that have been published to address the update for this systematic review question. Additional details regarding the search strategy will be published upon completion of the review, and are available upon request prior to publication.

- **CINAHL**
- **Cochrane**
- **Embase**
- **PubMed**

Inclusion and exclusion criteria

Table 1 provides the inclusion and exclusion criteria for the update to this systematic review. The inclusion and exclusion criteria are a set of characteristics that will be used to determine which articles identified in the literature search will be included or excluded in the systematic review.

Table 1. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Publication status	Articles that have been peer-reviewed	Articles that have not been peer-reviewed and are not published in peer-reviewed journals, including unpublished data, manuscripts, reports, abstracts, and conference proceedings
Date of publication	January 1980 to March 2016 (existing NESR systematic reviews) March 2016 to September 2019 (update)	Articles published prior to or after January 1980-September 2019
Language of publication	Articles published in English	Articles published in languages other than English
Study design	Randomized controlled trials Non-randomized controlled trials, including quasi-experimental and controlled before-and-after studies Prospective cohort studies Retrospective cohort studies Nested case-control studies Case-control studies (type 1 diabetes only)	Uncontrolled trials Case-control studies (outcomes other than type 1 diabetes[i]) Cross-sectional studies Uncontrolled before-and-after studies Narrative reviews Systematic reviews Meta-analyses

[i] The existing NESR systematic reviews included case-control studies. The update will exclude case-control studies for all outcomes other than type 1 diabetes. The rationale is that case-control studies are primarily beneficial for increasing statistical power when outcomes have a low incidence, and there is likely to be sufficiently powered evidence for this

Category	Inclusion Criteria	Exclusion Criteria
Interventions/ exposures	Duration of exclusive human milk and/or infant formula consumption:	
	a) Ever consuming human milk (i.e., any amount of human milk feeding)	
	b) Duration of any human milk consumption among infants fed human milk	b) Variables that include infants who were never fed human milk
	c) Duration of exclusive human milk consumption	
Comparators	Different durations of exclusive human milk and/or infant formula consumption:	
	a) Never consuming human milk	a) Variables that include any amount of human milk feeding (e.g., very short-term or token) or the feeding of infant formula that does not meet the definition below
	b) Different durations of any human milk consumption among infants fed human milk	b) Variables that include infants who were never fed human milk
	c) Different durations of exclusive human milk consumption	
Sources of foods, beverages, or nutrients	Human milk: Mothers' own milk (MOM), that is, human milk fed at the breast (i.e., nursing) or expressed and fed fresh or after refrigeration/freezing	Human milk from third parties (e.g., banked/donor milk)
	Infant formula: commercially prepared infant formula meeting FDA[ii] and/or Codex Alimentarius[iii] international food standards	Infant formulas that are not commercially prepared or that do not meet FDA and/or Codex Alimentarius international food standards

systematic review that comes from studies that use stronger designs for outcomes other than type 1 diabetes.

[ii] U.S. Food and Drug Administration. Version 19 December 2013. Internet: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/InfantFormula/ucm136118.htm#manufacture (accessed March 23, 2018).

[iii] Food and Agriculture Organization of the United Nations. World Health Organization. Codex Alimentarius. International Food Standards. Standard for infant formula and formulas for special medical purposes intended for infants. Codex Stan 72-1981. 2007.

Category	Inclusion Criteria	Exclusion Criteria

Outcomes	Cardiovascular disease outcomes
	• Intermediate outcomes
	  o Total cholesterol (TC)
	  o LDL cholesterol
	  o HDL cholesterol (including TC:HDL, LDL:HDL)
	  o Triglycerides
	  o Blood pressure (systolic and diastolic)
	• Endpoint health outcomes[iv]
	  o Cardiovascular disease (myocardial infarction, coronary heart disease, coronary artery disease, congestive heart failure, peripheral artery disease)
	  o Stroke
	  o Venous thrombosis
	  o Cardiovascular disease-related mortality
	Diabetes outcomes
	• Intermediate outcomes
	  o Hemoglobin A1C
	  o Glucose
	  o Insulin
	  o Prediabetes
	• Endpoint health outcomes
	  o Type 1 diabetes
	  o Type 2 diabetes	

[iv] The existing NESR systematic reviews included arterial stiffness/intima-media thickness and metabolic syndrome. The update will not include these outcomes. The rationale is that there is unlikely to be a lot of evidence about arterial stiffness/intima-media thickness, and the components of metabolic syndrome (i.e., blood pressure, blood sugar, blood lipids, and waist circumference) are already addressed by this systematic review and the systematic review on growth, size, and body composition.

Category	Inclusion Criteria	Exclusion Criteria
Country	Studies conducted in countries ranked as high or very high human development[v]	Studies conducted in countries ranked as medium or lower human development
Study participants	Human participants Males Females	Non-human participants (e.g., animal and in-vitro studies)
Age of study participants	Age at intervention or exposure: infants and toddlers (birth to 24 months) Age at outcome: children and adolescents (ages 2-18 years), adults (ages 19-64 years), older adults (ages 65 years and older)	Age at outcome: infants and toddlers (birth to 24 months)
Health status of study participants	Studies that enroll participants: • born full-term (≥37 weeks and 0/7 days gestational age) • who are healthy and/or at risk for chronic disease Studies that enroll *some* participants: • born preterm (gestational age <37 weeks and 0/7 days), with low birth weight (<2500g), or small for gestational age • diagnosed with a disease • diagnosed with the outcomes of interest	Studies that *exclusively* enroll participants: • born preterm (gestational age <37 weeks and 0/7 days), with low birth weight (<2500g), or small for gestational age • diagnosed with a disease or hospitalized with an illness or injury • with the outcomes of interest (i.e., studies that aim to treat participants with the outcomes of interest)
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

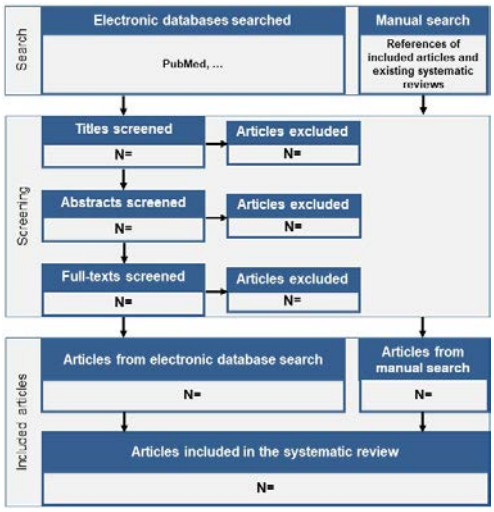
[v] The human development classification from the existing reviews will be applied to the update for consistency. During the existing reviews, the human development classification was the Human Development Index (HDI) from the most recent Human Development Report (United Nations Development Programme. Human Development Report 2014. New York, 2014.)

LITERATURE SEARCH AND SCREENING RESULTS

This protocol will be updated with the literature search and screening results after the search and screening plan has been finalized and implemented.

The flow chart (**Figure 2**) below illustrates the literature search and screening results for articles examining the update to this systematic review question. The results of the electronic database searches, after removal of duplicates, were screened independently by two NESR analysts using a step-wise process by reviewing titles, abstracts, and full-texts to determine which articles met the inclusion criteria. A manual search was done to find articles that were not identified when searching the electronic databases; all manually identified articles are also screened to determine whether they meet criteria for inclusion.

Figure 2: Flow chart of literature search and screening results (To be added)



Included Articles (To be added)

1. Ref

Excluded Articles (To be added)

Table 2 lists the articles excluded after full-text screening. At least one reason for exclusion is provided for each article, which may not reflect all possible reasons. Information about articles excluded after title and abstract screening is available upon request.

Table 2. Excluded articles

	Citation	Rationale
1		