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 the use of, and update to, existing NESR systematic reviews 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 using and updating six existing NESR systematic reviews. The existing NESR systematic reviews 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 Nutrition Evidence Systematic Review (NESR). Complete documentation of the six existing systematic reviews is available on the NESR website:


Information about the systematic review methodology used during the Pregnancy and Birth to 24 Months Project is also available on the NESR website:


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. 2) 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. 3) details the electronic databases and inclusion and exclusion criteria (p. 3) 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: 07/02/19.
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

**Systematic review question:** What is the relationship between the duration of exclusive human milk and/or infant formula consumption and long-term health outcomes?

**Exposures** vs **Comparators**
- Ever consuming human milk (i.e., any amount of human milk feeding)
- Duration of any human milk consumption among infants fed human milk
- Duration of exclusive human milk consumption prior to the introduction of infant formula

**Population:** Infants and toddlers (birth to 24 months); full-term, healthy and/or at risk for chronic disease

**Intermediate outcomes**
- Cardiovascular disease outcomes
  - Total cholesterol (TC)
  - LDL cholesterol
  - HDL cholesterol (including TC:HDL and LDL:HDL ratios)
  - Triglycerides
  - Blood pressure (systolic and diastolic)
- Diabetes outcomes
  - Hemoglobin A1C
  - Glucose
  - Insulin
  - Prediabetes

**Population:** Children through older adults (ages 2 years and older)

**Endpoint health outcomes**
- Cardiovascular disease outcomes
  - Cardiovascular disease (myocardial infarction, coronary heart disease, coronary artery disease, congestive heart failure, peripheral artery disease)
  - Stroke
  - Venous thrombosis
  - Cardiovascular disease-related mortality
- Diabetes outcomes
  - Type 1 diabetes
  - Type 2 diabetes

**Population:** Children through older adults (ages 2 years and older)

**Key Confounders:** Race/ethnicity, Socioeconomic status, Family history of the outcome of interest

**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
- **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

Question: What is the relationship between the duration of exclusive human milk and/or infant formula consumption and long-term health outcomes?
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

<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication status</td>
<td>Articles that have been peer-reviewed</td>
<td>Articles that have not been peer-reviewed and are not published in peer-reviewed journals, including unpublished data, manuscripts, reports, abstracts, and conference proceedings</td>
</tr>
<tr>
<td>Date of publication</td>
<td>Original systematic review: January 1980 to March 2016</td>
<td>Articles published prior to 1980 and after (Month of literature search) 2019</td>
</tr>
<tr>
<td></td>
<td>Update to the systematic review: March 2016- (Month of literature search) 2019</td>
<td></td>
</tr>
<tr>
<td>Language of publication</td>
<td>Articles published in English</td>
<td>Articles published in languages other than English</td>
</tr>
</tbody>
</table>

Question: What is the relationship between the duration of exclusive human milk and/or infant formula consumption and long-term health outcomes?
<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomized controlled trials</td>
<td>Uncontrolled trials</td>
</tr>
<tr>
<td></td>
<td>Non-randomized controlled trials, including quasi-experimental and controlled before-and-after studies</td>
<td>Case-control studies (outcomes other than type 1 diabetes)</td>
</tr>
<tr>
<td></td>
<td>Prospective cohort studies</td>
<td>Cross-sectional studies</td>
</tr>
<tr>
<td></td>
<td>Retrospective cohort studies</td>
<td>Uncontrolled before-and-after studies</td>
</tr>
<tr>
<td></td>
<td>Nested case-control studies</td>
<td>Narrative reviews</td>
</tr>
<tr>
<td></td>
<td>Case-control studies (type 1 diabetes only)</td>
<td>Systematic reviews</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meta-analyses</td>
</tr>
</tbody>
</table>

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
- c) Duration of exclusive human milk consumption prior to the introduction of infant formula

b) Variables that include infants who were never fed human milk

c) Duration of exclusive human milk consumption prior to the introduction of complementary foods and beverages or the concurrent introduction of complementary foods and beverages and infant formula (including when a study does not specify what follows exclusive human milk feeding)

---

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

Question: What is the relationship between the duration of exclusive human milk and/or infant formula consumption and long-term health outcomes?
**Question:** What is the relationship between the duration of exclusive human milk and/or infant formula consumption and long-term health outcomes?

<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparators</strong></td>
<td>Different durations of exclusive human milk and/or infant formula consumption:</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>a) Never consuming human milk</td>
<td>b) Variables that include infants who were never fed human milk</td>
</tr>
<tr>
<td></td>
<td>b) Different durations of any human milk consumption among infants fed human milk</td>
<td>c) Durations of exclusive human milk consumption prior to the introduction of complementary foods and beverages or the concurrent introduction of complementary foods and beverages and infant formula (including when a study does not specify what follows exclusive human milk feeding)</td>
</tr>
<tr>
<td></td>
<td>c) Different durations of exclusive human milk consumption prior to the introduction of infant formula</td>
<td></td>
</tr>
<tr>
<td><strong>Sources of foods, beverages, or nutrients</strong></td>
<td>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</td>
<td>Human milk from third parties (e.g., banked/donor milk)</td>
</tr>
<tr>
<td></td>
<td>Infant formula: commercially prepared infant formula meeting FDA(^ii) and/or Codex Alimentarius(^iii) international food standards</td>
<td>Infant formulas that are not commercially prepared or that do not meet FDA and/or Codex Alimentarius international food standards</td>
</tr>
</tbody>
</table>


**Question:** What is the relationship between the duration of exclusive human milk and/or infant formula consumption and long-term health outcomes?
### Outcomes

**Cardiovascular disease outcomes**

- **Intermediate outcomes**
  - Total cholesterol (TC)
  - LDL cholesterol
  - HDL cholesterol (including TC:HDL, LDL:HDL)
  - Triglycerides
  - Blood pressure (systolic and diastolic)

- **Endpoint health outcomes**
  - Cardiovascular disease (myocardial infarction, coronary heart disease, coronary artery disease, congestive heart failure, peripheral artery disease)
  - Stroke
  - Venous thrombosis
  - Cardiovascular disease-related mortality

**Diabetes outcomes**

- **Intermediate outcomes**
  - Hemoglobin A1C
  - Glucose
  - Insulin
  - Prediabetes

- **Endpoint health outcomes**
  - Type 1 diabetes
  - Type 2 diabetes

---

**Question:** What is the relationship between the duration of exclusive human milk and/or infant formula consumption and long-term health outcomes?

---

**Footnote:** 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.
<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>Studies conducted in countries ranked as high or very high human development(^v)</td>
<td>Studies conducted in countries ranked as medium or lower human development</td>
</tr>
<tr>
<td>Study participants</td>
<td>Human participants</td>
<td>Non-human participants (e.g., animal and in-vitro studies)</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>Age of study participants</td>
<td>Age at intervention or exposure: infants and toddlers (birth to 24 months)</td>
<td>Age at outcome: infants and toddlers (birth to 24 months)</td>
</tr>
<tr>
<td></td>
<td>Age at outcome: children and adolescents (ages 2-18 years), adults (ages 19-64 years), older adults (ages 65 years and older)</td>
<td></td>
</tr>
<tr>
<td>Health status of study participants</td>
<td>Studies that enroll participants:</td>
<td>Studies that exclusively enroll participants:</td>
</tr>
<tr>
<td></td>
<td>• born full-term (≥37 weeks and 0/7 days gestational age)</td>
<td>• born preterm (gestational age &lt;37 weeks and 0/7 days), with low birth weight (&lt;2500g), or small for gestational age</td>
</tr>
<tr>
<td></td>
<td>• who are healthy and/or at risk for chronic disease</td>
<td>• diagnosed with a disease or hospitalized with an illness or injury</td>
</tr>
<tr>
<td></td>
<td>Studies that enroll some participants:</td>
<td>• with the outcomes of interest (i.e., studies that aim to treat participants with the outcomes of interest)</td>
</tr>
<tr>
<td></td>
<td>• born preterm (gestational age &lt;37 weeks and 0/7 days), with low birth weight (&lt;2500g), or small for gestational age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• diagnosed with a disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• diagnosed with the outcomes of interest</td>
<td></td>
</tr>
<tr>
<td>Size of study groups</td>
<td>Studies with ≥30 participants per study group or a power analysis indicating that the study is appropriately powered for the outcome(s) of interest</td>
<td>Studies with &lt;30 participants per study group with no power analysis indicating that the study is appropriately powered for the outcome(s) of interest</td>
</tr>
</tbody>
</table>

\(^v\) 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.)

Question: What is the relationship between the duration of exclusive human milk and/or infant formula consumption and long-term health outcomes?
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

<table>
<thead>
<tr>
<th>Citation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>