WHAT IS THE RELATIONSHIP BETWEEN SPECIFIC NUTRIENTS FROM SUPPLEMENTS AND/OR FORTIFIED FOODS CONSUMED DURING INFANCY AND TODDLERHOOD AND GROWTH, SIZE, AND BODY COMPOSITION?: SYSTEMATIC REVIEW PROTOCOL

This document describes the protocol for a systematic review to answer the following question: What is the relationship between specific nutrients from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?

This systematic review is being conducted by the 2020 Dietary Guidelines Advisory Committee, Birth to 24 Months Subcommittee, and staff from USDA’s Nutrition Evidence Systematic Review (NESR).

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 is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews.

This document includes details about the methodology as it will be applied to the systematic review as follows:
- 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. 6) details the electronic databases and inclusion and exclusion criteria (p. 6) that will be used to search for, screen, and select articles to be included in the systematic review.
- The literature search and screening results (p. 11) 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 09/19/2019.

This version of the protocol contains updates to the following sections. The updates listed below were made but do not reflect substantive changes for this review.
- The inclusion and exclusion criteria for the date of publication was updated from May 2019 to September 2019 to reflect the anticipated date when the literature search will be conducted.
- The inclusion and exclusion criteria for the age at outcome was adjusted to include outcomes in infants through adults.
- The key confounders were edited for clarity.
- Other factors to be considered were added to the analytic framework for transparency.
**Question:** What is the relationship between specific nutrients from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?

**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 and other factors to be 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 for the relationship between iron from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition**

**Key Confounders:** Gestational age, Sex, Race/ethnicity, Socioeconomic status, Parental education, Feeding practices (e.g., human milk/infant formula history), Use of foods that are fortified or rich in the nutrient of interest (in supplements studies), Anthropometry at birth or baseline

**Other factors to be considered:** Maternal age, Prenatal vitamin-supplement use, Timing of cord-clamping, Smoking, Maternal Anthropometry

**Key definitions**

- **Dietary Supplement**— a product (other than tobacco) that is intended to supplement the diet; contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement. (O.D.S., Dietary Supplement Health and Education Act, 1994)

- **Fortification**— as defined by the U.S. Food and Drug Administration (FDA), the deliberate addition of one or more essential nutrients to a food, whether or not it is normally contained in the food. Fortification may be used to prevent or correct a demonstrated deficiency in the population or specific population groups; restore naturally occurring nutrients lost during processing, storage, or handling; or to add a nutrient to a food at the level found in a comparable traditional food. When cereal grains are labeled as enriched, it is mandatory that they be fortified with folic acid.
**Systematic review question:** What is the relationship between vitamin D from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?

<table>
<thead>
<tr>
<th>Intervention/exposure</th>
<th>Comparator</th>
<th>Health outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumption of vitamin D from supplements</td>
<td>Consumption of vitamin D:</td>
<td>• Weight, weight-for-age</td>
</tr>
<tr>
<td></td>
<td>a) at a different dosage or frequency from supplements</td>
<td>• Height, length/stature-for-age</td>
</tr>
<tr>
<td></td>
<td>b) from fortified foods</td>
<td>• BMI, BMI z-score, weight-for-length</td>
</tr>
<tr>
<td>Consumption of vitamin D from fortified foods/beverages</td>
<td>Consumption of vitamin D:</td>
<td>• Body circumferences e.g., head, arm, waist, thigh, neck</td>
</tr>
<tr>
<td></td>
<td>a) in a different amount/frequency from the same fortified food</td>
<td>• Body composition and distribution e.g., % fat mass, fat-free mass</td>
</tr>
<tr>
<td></td>
<td>b) from different fortified or unfortified foods</td>
<td>• Incidence and prevalence of:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Underweight, failure to thrive, stunting, wasting</td>
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<td></td>
<td></td>
<td>o Healthy weight</td>
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<tr>
<td></td>
<td></td>
<td>o Overweight</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Obesity</td>
</tr>
</tbody>
</table>

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

**Population:** Infants through adults, across the lifespan

**Key Confounders:** Gestational age, Sex, Race/ethnicity, Socioeconomic status, Parental education, Feeding practices (e.g., human milk/infant formula history), Use of foods that are fortified or rich in the nutrient of interest (in supplements studies), Anthropometry at birth or baseline.

**Other factors to be considered:** Sun exposure and sunscreen usage, Maternal age, Maternal vitamin-supplement use, Smoking, Maternal Anthropometry

**Key definitions**

- **Dietary Supplement**—a product (other than tobacco) that is intended to supplement the diet, contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement. (ODS, Dietary Supplement Health and Education Act, 1994)

- **Fortification**—as defined by the U.S. Food and Drug Administration (FDA), the deliberate addition of one or more essential nutrients to a food, whether or not it is normally contained in the food. Fortification may be used to prevent or correct a demonstrated deficiency in the population or specific population groups, restore naturally occurring nutrients lost during processing, storage, or handling, or to add a nutrient to a food that is not in a comparable traditional food. When cereal grains are labeled as enriched, it is mandatory that they be fortified with folic acid

**Legend**

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

**Question:** What is the relationship between specific nutrients from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?
Figure 3: Analytic framework for the relationship between vitamin B-12 from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition

Systematic review question: What is the relationship between vitamin B-12 from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?

<table>
<thead>
<tr>
<th>Intervention/exposure</th>
<th>Comparator</th>
<th>Health outcomes</th>
</tr>
</thead>
</table>
| Consumption of vitamin B-12 from supplements | Consumption of vitamin B-12: 
  a) a different dosage or frequency in supplements 
b) fortified foods | • Weight, weight-for-age  
• Height, length/stature-for-age  
• BMI, BMI z-score, weight-for-length  
• Body circumferences e.g., head, arm, waist, thigh, neck  
• Body composition and distribution e.g., % fat mass, fat-free mass  
• Incidence and prevalence of:  
  o Underweight, failure to thrive, stunting, wasting  
  o Healthy weight  
  o Overweight  
  o Obesity |
| Consumption of vitamin B-12 from fortified foods/beverages | Consumption of vitamin B-12: 
  a) in a different amount/frequency from the same fortified food 
b) different fortified or unfortified foods |

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

Key Confounders: Sex, Race/ethnicity, Socioeconomic status, Parental education, Feeding practices (e.g., human milk/infant formula history), Use of foods that are fortified or rich in the nutrient of interest (in supplements studies), Anthropometry at birth or baseline, Gestational age, Maternal vegan diet

Other factors to be considered: Maternal age, Maternal vitamin-supplement use, Smoking, Maternal Anthropometry

Key definitions

- **Dietary Supplement** — a product (other than tobacco) that is intended to supplement the diet; contains one or more dietary ingredients (including vitamins, minerals, herbs or other botanicals, amino acids, and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement. (ODS, Dietary Supplement Health and Education Act, 1994)

- **Fortification** — as defined by the U.S. Food and Drug Administration (FDA), the deliberate addition of one or more essential nutrients to a food, whether or not it is normally contained in the food. Fortification may be used to prevent or correct a demonstrated deficiency in the population or specific population groups; restore naturally occurring nutrients lost during processing, storage, or handling; or to add a nutrient to a food at the level found in a comparable traditional food. When cereal grains are labeled as enriched, it is mandatory that they be fortified with folic acid

Legend

- The relationship of interest in the systematic review
- Factors that may impact the relationship of interest in the systematic review
Figure 4: Analytic framework for the relationship between omega-3 fatty acids from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition.

**Systematic review question:** What is the relationship between omega-3 fatty acids from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?

<table>
<thead>
<tr>
<th>Intervention/exposure</th>
<th>Comparator</th>
<th>Health outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumption of omega-3 fatty acids from supplements</td>
<td>Consumption of omega-3 fatty acids: a) at a different dosage or frequency from supplements, b) from fortified foods</td>
<td>• Weight, weight-for-age&lt;br&gt;• Height, length/stature-for-age&lt;br&gt;• BMI, BMI z-score, weight-for-length&lt;br&gt;• Body circumferences e.g., head, arm, waist, thigh, neck&lt;br&gt;• Body composition and distribution e.g., % fat mass, fat-free mass&lt;br&gt;• Incidence and prevalence of:&lt;br&gt;  o Underweight, failure to thrive, stunting, wasting&lt;br&gt;  o Healthy weight&lt;br&gt;  o Overweight&lt;br&gt;  o Obesity</td>
</tr>
<tr>
<td>Consumption of omega-3 fatty acids from fortified foods/beverages</td>
<td>Consumption of omega-3 fatty acids: a) in a different amount/frequency from the same fortified food, b) different fortified or unfortified foods</td>
<td>Population: Infants and toddlers (birth to 24 months); full-term, healthy and/or at risk for chronic disease</td>
</tr>
</tbody>
</table>

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

**Key Confounders:** Gestational age, Sex, Race/ethnicity, Socioeconomic status, Parental education, Feeding practices (e.g., human milk/infant formula history), Use of foods that are fortified or rich in the nutrient of interest (in supplements studies), Anthropometry at birth or baseline

**Other factors to be considered:** Maternal age, Maternal vitamin-supplement use, Smoking, Maternal Anthropometry

**Legend**
- The relationship of interest in the systematic review
- Factors that may impact the relationship of interest in the systematic review

**Key definitions**
- **Dietary Supplement**—a product (other than tobacco) that is intended to supplement the diet, contains one or more dietary ingredients (including vitamins, minerals, herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement. (ODS, Dietary Supplement Health and Education Act, 1994)
- **Fortification**—as defined by the U.S. Food and Drug Administration (FDA), the deliberate addition of one or more essential nutrients to a food, whether or not it is normally contained in the food. Fortification may be used to prevent or correct a demonstrated deficiency in the population or specific population groups; restore naturally occurring nutrients lost during processing, storage, or handling; or to add a nutrient to a food at the level found in a comparable traditional food. When cereal grains are labeled as enriched, it is mandatory that they be fortified with folic acid.
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 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
- PubMed
- Cochrane
- Embase

Inclusion and exclusion criteria

This table provides the inclusion and exclusion criteria for the 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>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</td>
<td>• Case-control studies</td>
</tr>
<tr>
<td></td>
<td>before and after studies</td>
<td>• Cross-sectional studies</td>
</tr>
<tr>
<td></td>
<td>• Prospective cohort studies</td>
<td>• Uncontrolled before-and-after studies</td>
</tr>
<tr>
<td></td>
<td>• Retrospective cohort studies</td>
<td>• Narrative reviews</td>
</tr>
<tr>
<td></td>
<td>• Nested case-control studies</td>
<td>• Systematic reviews</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Meta-analyses</td>
</tr>
</tbody>
</table>
### Question
What is the relationship between specific nutrients from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?

### Category Inclusion Criteria
- Studies that examine consumption of iron, vitamin D, vitamin B-12, or omega-3 fatty acids from:
  - supplements
  - fortified foods/beverages
- Studies that specify the dosage/amount/fortification level received of the specific nutrient
- Studies that examine animal products that contain added nutrients as a result of feeding the animal a specialized diet

### Exclusion Criteria
- Studies that do not specify the dosage/amount/fortification level received of the specific nutrient
- Studies that vary nutrients other than the nutrient of interest without controlling for that variation

### Category Inclusion Criteria
- Studies that compare consumption of iron, vitamin D, vitamin B-12, or omega-3 fatty acids:
  - at a different dosage or frequency from supplements
  - in a different amount/frequency from the same fortified food/beverages
  - from different fortified or unfortified foods

### N/A
Question: What is the relationship between specific nutrients from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?

<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
</table>
| **Outcomes** | • Weight, weight-for-age  
• Height, length/stature-for-age  
• BMI, BMI z-score, weight-for-length  
• Body circumferences e.g., head, arm, waist, thigh, neck  
• Body composition and distribution e.g., % fat mass, fat-free mass, skinfold thickness  
• Incidence and prevalence of:  
  o Underweight, failure to thrive, stunting, wasting  
  o Healthy weight  
  o Rapid infant weight gain  
  o Overweight  
  o Obesity | N/A |

**Date of publication**  
January 2000 – September 2019  
Articles published prior to 2000

**Publication status**  
Articles that have been peer-reviewed  
Articles that have not been peer-reviewed and are not published in peer-reviewed journals (e.g., unpublished data, manuscripts, pre-prints, reports, abstracts, and conference proceedings)

**Language of publication**  
Articles published in English  
Articles published in languages other than English

**Country**  
Studies conducted in countries ranked as high or higher human development  
Studies conducted in countries ranked as medium or lower human development

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1 The Human Development classification was based on the Human Development Index (HDI) ranking from the year the study intervention occurred or data were collected (UN Development Program. HDI 1990-2017 HDRO calculations based on data from UNDESA (2017a), UNESCO Institute for Statistics (2018), United Nations Statistics Division (2018b), World Bank (2018b), Barro and Lee (2016) and IMF (2018). Available from: http://hdr.undp.org/en/data). If the study did not report the year in which the intervention occurred or data were collected, the HDI classification for the year of publication was applied. HDI values are available from 1980, and then from 1990 to present. If a study was conducted prior to 1990, the HDI classification from 1990 was applied. If a study was conducted in 2018 or 2019, the most current HDI classification was applied. When a country was not included in
<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study participants</td>
<td>• Human participants</td>
<td>Non-human participants (i.e., animals)</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:</td>
<td>• Age at intervention or exposure:</td>
</tr>
<tr>
<td></td>
<td>o Infants and toddlers (0-24 months)</td>
<td>o Children and adolescents (2-18 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Adults (19 -64 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Older adults (65 years and older)</td>
</tr>
<tr>
<td></td>
<td>• Age at outcome:</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>o Infants and toddlers (0-24 months)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o Children and adolescents (2-18 years)</td>
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<td>o Adults (19 -64 years)</td>
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<tr>
<td></td>
<td>o Older adults (65 years and older)</td>
<td></td>
</tr>
<tr>
<td>Health status of</td>
<td>• Studies that enroll participants who are healthy and/or at risk for chronic disease</td>
<td>• Studies that exclusively enroll participants diagnosed with a disease.</td>
</tr>
<tr>
<td>study participants</td>
<td>• Studies that enroll some participants diagnosed with a disease</td>
<td>• Studies that exclusively enroll participants classified as underweight, stunted, wasted, or obese (i.e., studies that aim to treat participants who have already been diagnosed with the outcome of interest)</td>
</tr>
<tr>
<td></td>
<td>• Studies that enroll some participants classified as underweight, stunted, wasted, or obese.</td>
<td>• Studies that exclusively enroll infants born preterm (gestational age &lt;37 weeks and 0/7 days), infants with low birth weight (&lt;2500g), and/or infants born small for gestational age</td>
</tr>
<tr>
<td></td>
<td>• Studies that enroll infants born full-term (≥37 weeks and 0/7 days gestational age)</td>
<td></td>
</tr>
<tr>
<td>Study Duration</td>
<td>• Studies regardless of length</td>
<td>N/A</td>
</tr>
</tbody>
</table>

the HDI ranking, the current country classification from the World Bank was used instead (The World Bank. World Bank country and lending groups. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-country-and-lending-groups).

Question: What is the relationship between specific nutrients from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?
<table>
<thead>
<tr>
<th>Category</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of Study Groups</td>
<td>• Studies regardless of group size</td>
<td>• N/A</td>
</tr>
<tr>
<td>Source of Foods, Beverages, or Nutrients</td>
<td>• Vitamin and mineral supplements (e.g., iron drops)</td>
<td>• Donor or banked milk</td>
</tr>
<tr>
<td></td>
<td>• Fortified foods/beverages</td>
<td>• Unfortified or fortified human milk</td>
</tr>
<tr>
<td></td>
<td>• Commercially prepared infant formula meeting FDA (^\text{ii}) and/or Codex Alimentarius (^\text{iii}) international food standards (e.g., milk-based, soy, partially-hydrolyzed, extensive-hydrolyzed, amino acid-based)</td>
<td></td>
</tr>
</tbody>
</table>


Question: What is the relationship between specific nutrients from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?
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 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 5: Flow chart of literature search and screening results (To be added)

Included Articles (To be added)
1. Ref

Excluded Articles (To be added)

The table below 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>

Question: What is the relationship between specific nutrients from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?