

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 describes the protocol, or plan, for how the systematic review will be conducted. The protocol provides:

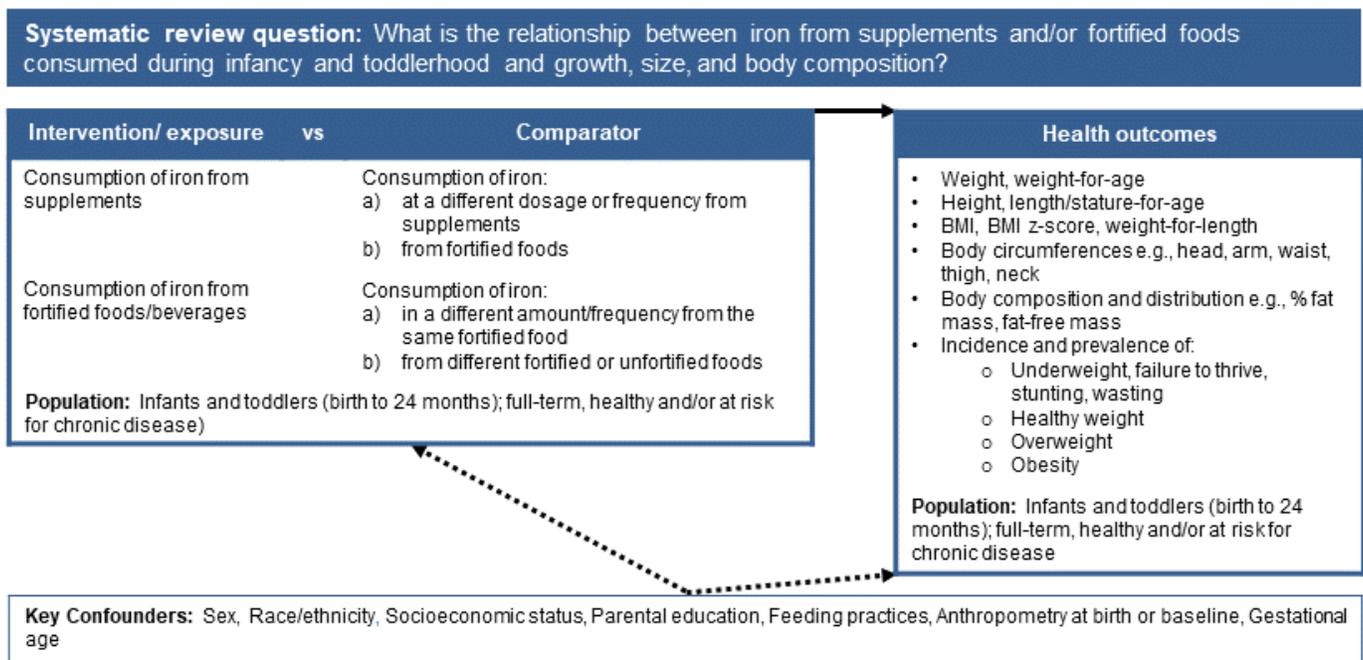
- The [analytic framework](#) (p. 2) illustrates the overall scope of the question, including the population, the interventions and/or exposures, comparators, and outcomes of interest.
- The [literature search and screening plan](#) (p. 6) details the electronic databases and [inclusion and exclusion 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: 07/02/2019.

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



Key definitions

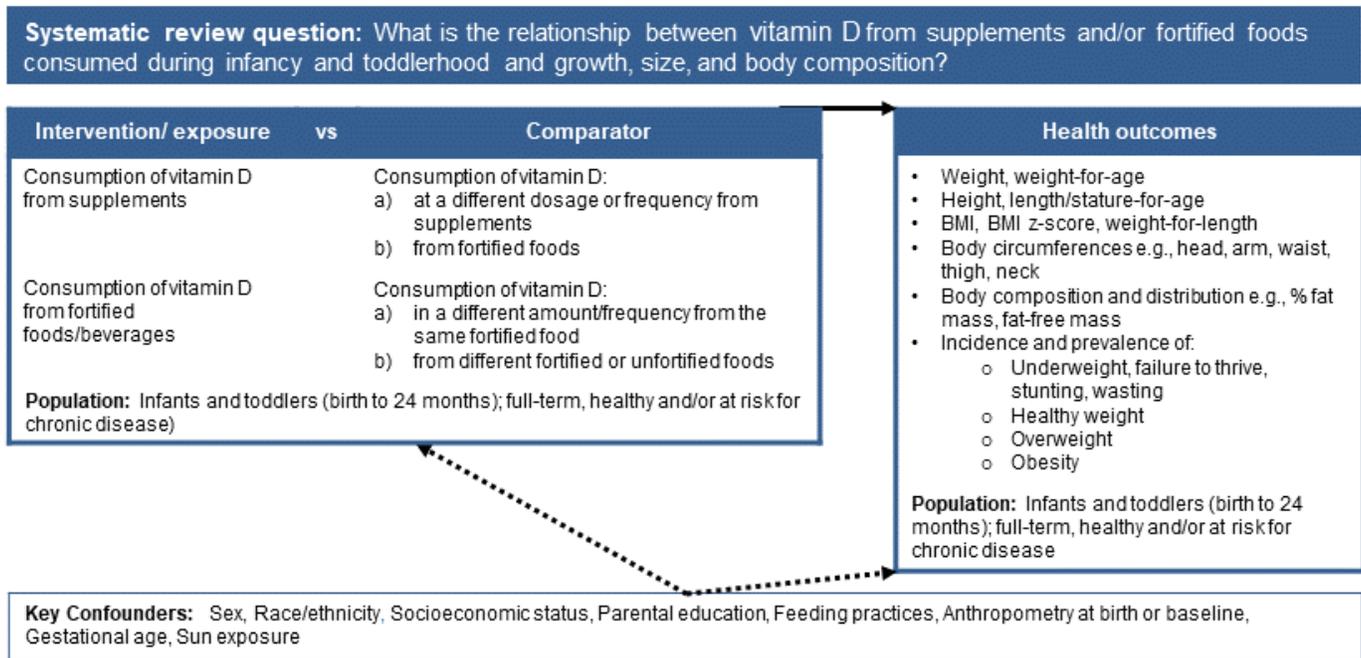
- **Dietary Supplement**— a product (other than tobacco) that: is intended to supplement the diet; contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, 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

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 2: Analytic framework for the relationship between vitamin D from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition



Key definitions

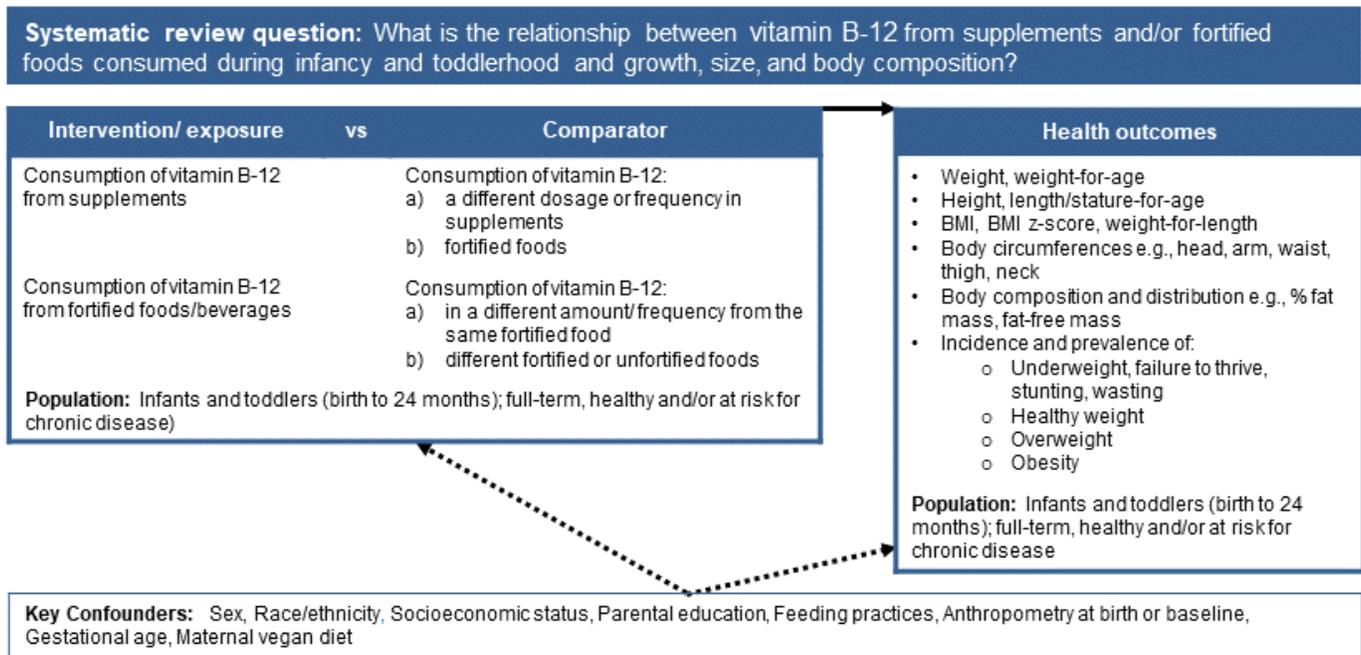
- **Dietary Supplement**— a product (other than tobacco) that: is intended to supplement the diet; contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule,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



Key definitions

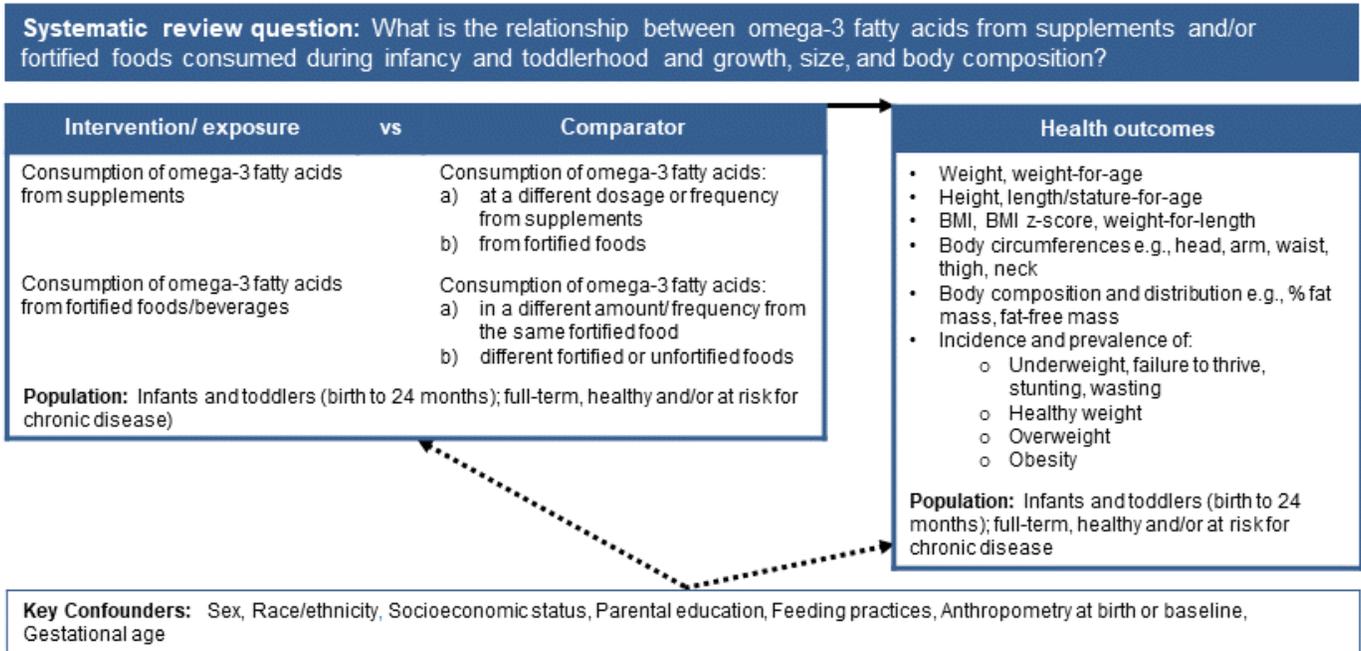
- **Dietary Supplement**— a product (other than tobacco) that: is intended to supplement the diet; contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, 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

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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 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



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

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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 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

Category	Inclusion Criteria	Exclusion Criteria
Study design	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Uncontrolled trials • Case-control studies • Cross-sectional studies • Uncontrolled before-and-after studies • Narrative reviews • Systematic reviews • Meta-analyses

Category	Inclusion Criteria	Exclusion Criteria
Intervention/ exposure	<ul style="list-style-type: none"> • Studies that examine consumption of iron, vitamin D, vitamin B-12, or omega-3 fatty acids from: <ul style="list-style-type: none"> ○ 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 	<ul style="list-style-type: none"> • 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
	<ul style="list-style-type: none"> • Studies that compare consumption of iron, vitamin D, vitamin B-12, or omega-3 fatty acids: <ul style="list-style-type: none"> ○ 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

Category	Inclusion Criteria	Exclusion Criteria
Outcomes	<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> ○ Underweight, failure to thrive, stunting, wasting ○ Healthy weight ○ Rapid infant weight gain ○ Overweight ○ Obesity 	N/A
Date of publication	January 2000 – May 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
Countryⁱ	Studies conducted in countries ranked as high or higher human development	Studies conducted in countries ranked as medium or lower human development

ⁱ 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

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	Exclusion Criteria
Study participants	<ul style="list-style-type: none"> • Human participants • Males • Females 	Non-human participants (i.e., animals)
Age of study participants	<ul style="list-style-type: none"> • Age at intervention or exposure: <ul style="list-style-type: none"> ○ Infants and toddlers (0-24 months) • Age at outcome: <ul style="list-style-type: none"> ○ Infants and toddlers (0-24 months) 	<ul style="list-style-type: none"> • Age at intervention or exposure: <ul style="list-style-type: none"> ○ Children and adolescents (2-18 years) ○ Adults (19 -64 years) ○ Older adults (65 years and older) • Age at outcome: <ul style="list-style-type: none"> ○ Children and adolescents (2-18 years) ○ Adults (19 -64 years) ○ Older adults (65 years and older)
Health status of study participants	<ul style="list-style-type: none"> • Studies that enroll participants who are healthy and/or at risk for chronic disease • Studies that enroll some participants diagnosed with a disease • Studies that enroll some participants classified as underweight, stunted, wasted, or obese. • Studies that enroll infants born full-term (≥ 37 weeks and 0/7 days gestational age) 	<ul style="list-style-type: none"> • Studies that exclusively enroll participants diagnosed with a disease. • 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) • Studies that exclusively enroll infants born preterm (gestational age < 37 weeks and 0/7 days), infants with low birth weight (< 2500g), and/or infants born small for gestational age
Study Duration	<ul style="list-style-type: none"> • Studies regardless of length 	<ul style="list-style-type: none"> • N/A

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?

Category	Inclusion Criteria	Exclusion Criteria
Size of Study Groups	<ul style="list-style-type: none"> • Studies regardless of group size 	<ul style="list-style-type: none"> • N/A
Source of Foods, Beverages, or Nutrients	<ul style="list-style-type: none"> • Vitamin and mineral supplements (e.g., iron drops) • Fortified foods/beverages • Commercially prepared infant formula meeting FDAⁱⁱ and/or Codex Alimentariusⁱⁱⁱ international food standards (e.g., milk-based, soy, partially-hydrolyzed, extensive-hydrolyzed, amino acid-based) 	<ul style="list-style-type: none"> • Donor or banked milk • Unfortified or fortified human milk

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.

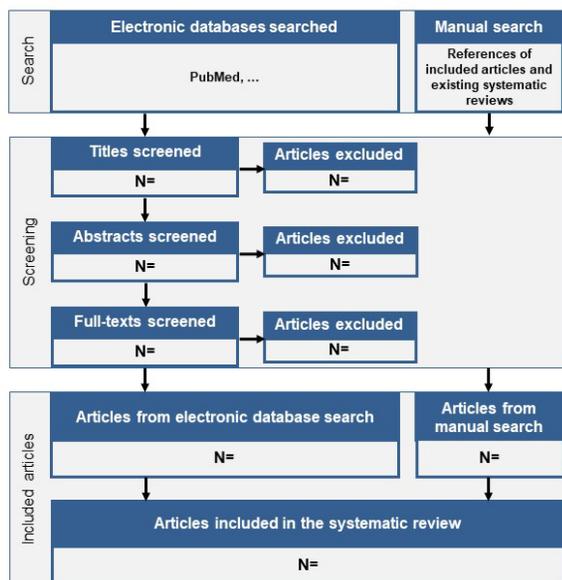
Question: What is the relationship between specific nutrients from supplements and/or fortified foods consumed during infancy and toddlerhood and growth, size, and body composition?

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

Citation	Rationale
1	

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?