Evidence-based Practice Center Systematic Review Protocol

Project Title: ***Dietary Total Fat Intake and Dietary Polyunsaturated Fatty Acid Intake and Child Growth and Development Outcomes: A Systematic Review***

I. Background and Objectives for the Systematic Review

Importance of Diet and Fats in Human Development

This review aims to identify and summarize available evidence linking the impact of total dietary fat, but in particular polyunsaturated fatty acids (PUFA), consumed by infants, children, and adolescents on their growth and development, by individuals during pregnancy on their risk of preterm birth, and by individuals during pregnancy and lactation on the growth and cognitive development of their offspring during infancy, childhood, and adolescence.[1-8] Although the scope of this review is limited to outcomes for individuals through 18 years of age , as described by the Developmental Origins of Health and Disease (DOHaD),[9-11] and supported by the '1st 1000 Days' initiative,[12,13] nutrition at early life stages has longer-term effects extending into young adulthood, our next generations of parents, and older adults.

Dietary fat and the different types of fatty acids serve essential roles in establishing and maintaining health including as a source of energy, essential fatty acids, fat-soluble vitamins and other compounds; as a reserve of energy to draw from under acute and chronic energy deficit conditions; as structural components of cellular and intracellular membranes; and as regulatory factors for appetite and other mechanisms essential for growth and cognitive development.[14,15] Since the publication of the joint U.S. and Canadian Dietary Reference Intakes (DRIs) for dietary fat in 2005, a substantial amount of scientific evidence has been added to our knowledge base that has led to changes in: (1) formulations of food and dietary supplements to add omega-3 fatty acids (e.g., docosahexaenoic acid, DHA) to infant formula and prenatal vitamins;[16-18] (2) fish, poultry, and animal herd feeds (adding specific fatty acids),[19] grazing practices (grass-fed),[20] and aquaculture (wild-caught-vs-farm raised)[21] to modify fatty acid profiles of harvested meat[22] and eggs;[23] and (3) dietary guidelines including recommendations to increase consumption of fish and seafood to increase omega-3 fatty acid consumption and to replace solid fats with vegetable and seed oils.[24,25] Identifying evidence to inform and substantiate how recommendations for fat intake, especially omega-3 and omega-6 PUFA intake should: (1) differ during pregnancy and lactation to optimize fetal development and birth outcomes and to reduce the risk of preterm birth, and (2) differ to support physical growth and cognitive development among infants, children, and adolescents, is essential to optimizing their present health and future wellbeing.

Role of Dietary Intake Recommendations

Dietary recommendations are the foundation of guidelines, policies, and practices designed to promote healthy food choices. They are used in consumer education materials, such as the nutrition facts panels on food packaging, in medical nutrition therapy and patient education, and in community settings to establish policy and refine programs, and for client counseling.

Nutrition and diet receive more attention in healthcare during pregnancy and infancy than at other stages of life but are receiving increased attention in childhood and adolescence. Synthesizing the evidence to inform these recommendations requires understanding (1) the metabolic and physiologic roles of dietary fats and PUFAs, (2) key aspects of nutrition during pregnancy, lactation, infancy, and childhood through adolescence to optimize physical and cognitive development, and (3) research methods and data specific to nutrition, growth, and cognitive assessment research. The joint U.S.-Canada Dietary Reference Intake (DRI) Working Group allows the two governments to more efficiently coordinate discussions and use resources, as well as expand the evidence base and scientific expertise needed to set priorities and inform recommendations related to DRIs.

Assessing Dietary Intake during Pregnancy, Lactation, Infancy, Childhood, and Adolescence

Assessing usual food and nutrient intake during pregnancy is complicated by changes that occur to support the developing placenta, fetus, and the pregnant person. Pregnancy-related hormonal changes affect nutrient absorption and metabolism, energy and nutrient needs, appetite, taste, food preference and avoidance, and meal patterns.[26] Intake during the first trimester, when nausea and fatigue are common, is different than in the third trimester when heartburn and constipation are frequent. Prenatal vitamin/mineral supplements are routinely recommended but vary widely in composition with some preparations now including DHA. Despite their nutritional benefits, prenatal supplements are known to impact food intake during pregnancy by causing nausea and constipation. For these reasons, timing of nutritional assessment during pregnancy matters and completion of multiple nutritional assessments including assessment of dietary supplement use is needed to estimate usual dietary intake throughout pregnancy.[27]

Another challenge is assessing the nutritional composition of human milk which changes over the course of lactation from the secretion of colostrum to transitional milk, to mature milk and varies throughout a feeding (higher in carbohydrate at the beginning; higher in fat at the end) and throughout the day.[28] The energy density of mature human milk is between 65-70 kcal/100 ml with a macronutrient distribution of about 10% protein, 40% carbohydrate, and 50% fat, primarily in the form of triacylglycerides, of which palmitic acid (C16:0), a saturated fatty acid, contributes to 10-12% of the total energy density.[29] The fatty acid composition of human milk does not vary significantly by demographic factors,[28] but is influenced by the lactating person's diet[30] and dietary supplement use,[31] by the fatty acid composition of adipose tissue stores of the lactating individual who is losing weight, and through maternal lipid metabolism.[31] Measuring human milk consumption by a breastfed infant is commonly done by weighing the infant immediately before and after a feeding session,[32,33] and nutrient intake is estimated by multiplying volume of milk consumed by established human milk nutrient concentrations[34] that are standardized, despite these acknowledged variations.

When human milk is not provided, the best alternative source of nutrition for infants is commercially prepared and regulated standard infant formula during the first year of life.[35,36] The nutritional composition of standard infant formulas is designed to be as similar to human milk as possible[37] and is established and strictly regulated by the Federal Food, Drug, and Cosmetic Act,

21 USC 321 et seq., as published in Title 21 of the Code of Federal Regulations.[36] The most common types of standard infant formula are derived from cow milk or soybeans with the primary source of fat derived from vegetable oils (soy, coconut, safflower). And, since 2002, long-chain n-3 and n-6 polyunsaturated fatty acids [arachidonic (ARA), eicosapentaenoic (EPA), and DHA] have been added to many formula preparations.[38] Around 6 months of age, sequential introduction of complementary foods including variety of vegetables, fruits, cereal and grain products, legumes and pulses, and dairy and meat products is recommended to meet the infant's expanding nutritional requirements. Additional sources of fat (e.g., butter, margarine, oils);[39] juice and cow milk, regardless of milk fat content, should not be included in an infant's diet until after 1 year of age; and sugar-sweetened beverages should not be provided until after two years of age and then only sparingly or not at all. Methodology used to assess food and beverage intake of children and adults depends on the circumstance and includes completing 5-step multi-pass 24-hour recalls (in person, by telephone, or on a computer),[40,41] multiple-day diet records, weighed diet records, weighed research diets, and validated food frequency questionnaires (FFQs) among other techniques. Information is collected from young children through surrogate reporters (e.g., parents, childcare providers), from older children, from the child themselves with support from a parent or responsible adult, and from adolescents and adults themselves. Information collected is reviewed for accuracy and completeness, entered into a computer-based nutrient analysis system, check by a second analyst for accuracy, evaluated for plausibility using defined upper and lower limits for outliers or other standardized methods such as the Goldberg method to identify under- or over-reporters.[42,43] The expected heterogeneity in the studies (e.g., exposure and outcome measures) that may reflect that these life stages inherently involve change and measurement changes over time will require careful consideration in analysis and evaluation of the available literature.

Nutrient Databases Used to Assess Food and Nutrient Intakes

Despite the limitations addressed above, once collected, food consumption data is entered into and analyzed using a standardized database and nutrient analysis system often specific to the country(ies) in which the study was performed.[44,45] The Canadian government maintains a comprehensive, computerized bilingual database with updates every 2 to 3 years,[46] derived from U.S. Department of Agriculture (USDA) Nutrient Database for Standard Reference and including Canadian-specific standards and foods. Similarly, the USDA Food Surveys Research Group maintains an extensive and continuously updated food and nutrient database for dietary studies (FNDDS) with updated versions released every 2 years.[47] The FNDDS is used to convert amounts of foods and beverages consumed by individuals into standard units to determine their nutrient values.[48] Information on total energy (kcal), total protein (g), total carbohydrate (g), total fat (g), individual fatty acids (g), and other nutrients is available. Studies of large, nationally representative, community-dwelling individuals, including individuals who are pregnant or lactating and children and adolescents in the U.S. (e.g., National Health and Nutrition Examination Survey), use this database to estimate usual nutrient intake for health surveillance and disease-risk correlational studies,[47] providing consistency.

Purpose of the Review

The goal of this review is to identify peer-reviewed and published research available since the

last joint DRI guidelines were established regarding effects of total fat and PUFAs on generally healthy populations at different life stages with diverse genetic backgrounds, health statuses, and nutritional needs. This review will enable dietary recommendations to be aligned with the most current and comprehensive evidence and that the recommendations lead to health behaviors that enhance pregnancy outcomes and optimize physical growth and cognitive development from conception through adolescence, ultimately maximizing health and wellbeing.

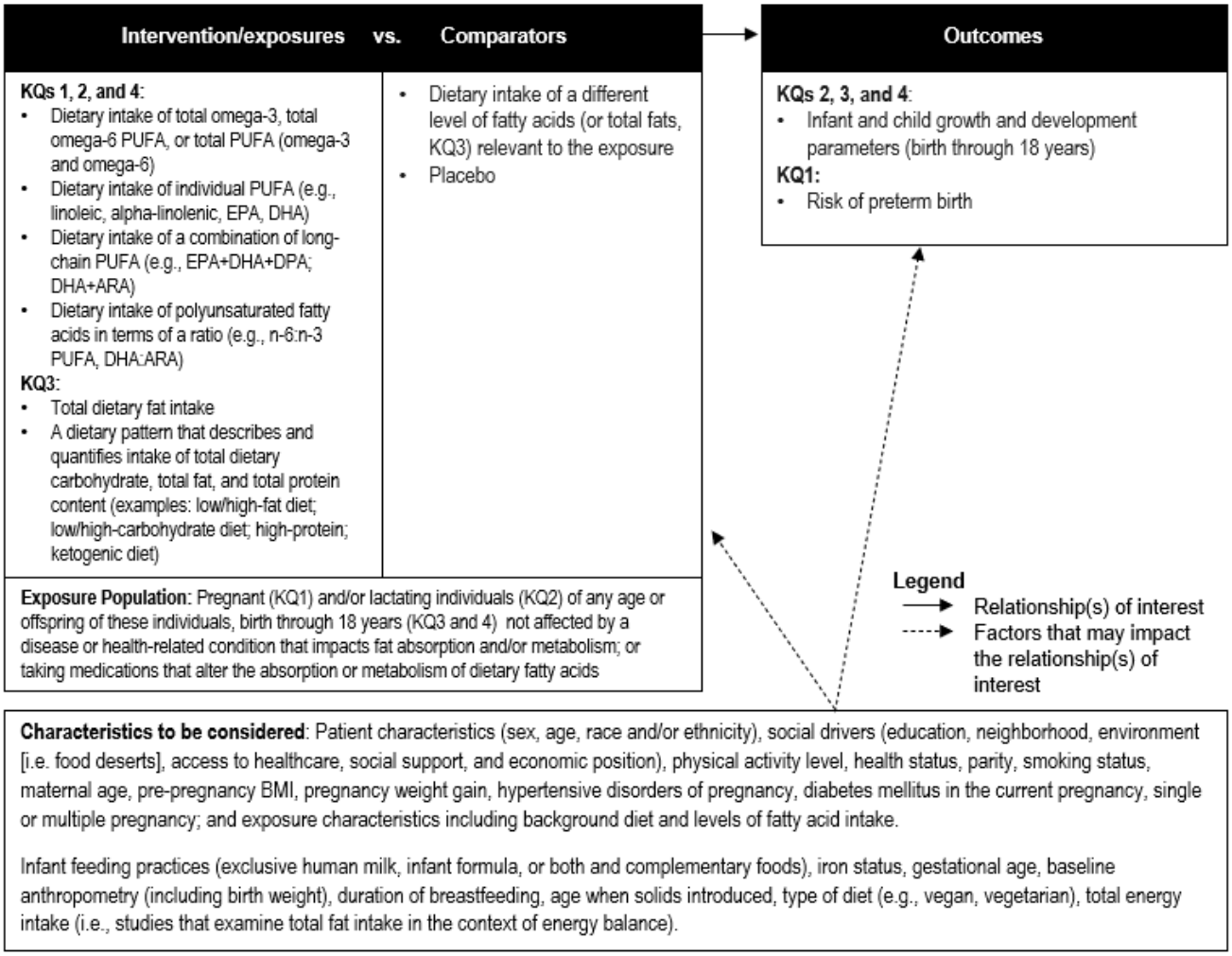
To achieve this goal, the systematic review will answer the Key Questions (KQs) outlined below. The review will be used to inform forthcoming work by the National Academies of Sciences, Engineering, and Medicine (NASEM) to update the U.S. and Canadian DRIs for macronutrients. These updated DRI values in turn will inform a wide range of decisions from food choices made by individuals to public health programs and policies.

II. Key Questions

1. What is the association between dietary intake of omega-6 and/or omega-3 polyunsaturated fatty acids during pregnancy and risk of preterm birth?
    a. How are these associations affected by intervention/exposure characteristics (for example, the ratio of different fatty acids)?
2. What is the association between dietary intake of omega-6 and/or omega-3 polyunsaturated fatty acids during pregnancy and/or lactation and infant/child growth and developmental outcomes?
    a. How are these associations affected by intervention/exposure characteristics (for example, the ratio of different fatty acids)?
3. What is the association between dietary intake of total fat in individuals birth through 18 years of age and measures of growth and development?
4. What is the association between dietary intake of omega-6 and/or omega-3 polyunsaturated fatty acids in individuals birth through 18 years of age and measures of growth and development?

Please see **Table 1** for inclusion and exclusion criteria arranged using the PICOTS (Population, Intervention, Comparator, Outcomes, Timing, Settings)[49] framework.

III. Logic Model



IV. Methods

This review will follow standard methods for conducting systematic reviews based on Agency for Healthcare Research and Quality's (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[51] ("AHRQ Methods Guide") and will adhere to the international PRISMA[50] (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines for reporting. The final protocol will be registered in the international prospective register of systematic reviews (PROSPERO).[52]

Criteria for Inclusion/Exclusion of Studies in the Review

We will apply the following inclusion and exclusion criteria (**Table 1**) to the abstracts and full text of studies identified in the literature search.

Table 1. Inclusion and Exclusion Criteria by Population, Intervention, Comparator, Outcome, Timing, Setting/Study Design (PICOTS)

Element	Inclusion Criteria	Exclusion Criteria
Population	**Exposure population:** • Individuals who are pregnant (KQ1) and/or lactating (KQ2) of any age or individuals from birth through 18 years of age (KQ3 and 4) from the general population (including those with overweight/obesity) not affected by a disease or health-related condition that impacts fat absorption and/or metabolism; or taking medications that alter the absorption or metabolism of dietary fatty acid **Outcome population:** • Offspring of the pregnant individual (birth through 18 years) not taking medications or affected by a disease or health-related condition that impacts fat absorption and/or metabolism Note: given the distinction between chronological age versus pubertal stage, as well as heterogeneity in enrollment across age ranges, for studies meeting all other eligibility criteria, we will consider exceptions	• Non-human participants (e.g., animal studies, in-vitro models) • Studies that enroll participants taking medications or with diseases/health-related conditions that impact fatty acid absorption or metabolism (e.g., Crohn's disease, ulcerative colitis, short-gut syndrome, cystic fibrosis, celiac). This includes cancer and malabsorption syndromes. • Studies that exclusively enroll participants hospitalized with an illness or injury • Studies designed to induce weight loss or treat overweight and obesity through energy restriction or hypocaloric diets for the purposes of treating additional or other medical conditions • Studies that exclusively enroll participants with severe undernourishment, underweight, stunting, or wasting • Studies that enroll participants who are pre- or post-bariatric surgery • Studies with enrollment <u>exclusively</u> of: pre-term babies (gestational age <37 weeks), babies admitted to the NICU, babies that have low birth weight (<2500g) and /or babies that are small for gestational age (for assessment of infant and child growth parameters and developmental outcomes) • Studies that enroll infants with conditions treated/prevent by dietary supplementation (e.g., G- or GJ-tubes, fatty acid oxidation disorders, necrotizing enterocolitis, attention deficit (and/or hyperactivity) disorder, ADHD, autism, etc.)

Element	Inclusion Criteria	Exclusion Criteria
	to the age criterion.[a]	
Intervention (Exposure)	**KQ1, 2, and 4** • Dietary intake of total omega-3 PUFA, total omega-6 PUFA, or total PUFA (omega-3 and omega-6) • Dietary intake of individual PUFA (examples: linoleic, alpha-linolenic, EPA, DHA) • Dietary intake of a combination of long-chain PUFA (example: EPA+DHA+DPA; DHA+ARA) • Dietary intake of polyunsaturated fatty acids in terms of a ratio (example, n-6:n-3 PUFA, DHA:ARA) **KQ3:** • Total dietary fat intake (as either grams/day or % of total energy intake from fat) • A dietary pattern that describes and quantifies intake of total dietary carbohydrate, total fat, and total protein content (examples: low/high-fat diet; low/high-carbohydrate diet; high-protein; ketogenic diet) *Note: Dietary intake can be from foods, supplements, and/or supplemented foods*[b]	**KQ1, 2, and 4** • Studies that do not quantify PUFA intake as either grams/day or % of total energy intake from PUFA (e.g., studies where exposure is number of fish servings per week) • Studies that do not provide absolute intake of fatty acids included in ratios • Studies that only assess fatty acid biomarker wt% of total or concentrations • Studies that only assess fatty acid intake via infusions (parenteral [intralipid] or stable isotope) • Studies that only assess exposure to fatty acids from a single meal, or eating occasion such that usual intake cannot be inferred • Studies that examine food products or dietary supplements not widely available to U.S. consumers • Multi-component interventions that do not isolate the effect or association of the PUFA exposure • Observational studies that do not account for any confounders • Studies designed to induce weight loss or treat participants who are determined to be overweight and obese through energy restriction or hypocaloric diets for the purposes of treating additional or other medical conditions **KQ3** • Studies that do not describe the energy and entire macronutrient distribution of the diet (i.e., studies that do not report total carbohydrate, total fat, and total protein contents of experimental or baseline diets)

Element	Inclusion Criteria	Exclusion Criteria

Comparator	**KQ1, 2, and 4**
	• Placebo
	• Dietary intake of a different amount of fatty acids relevant to the exposure:
	  o Total omega-3
	  o Total omega-6
	  o Individual PUFA
	  o Combination of long-chain PUFA
	  o Intake of PUFA in terms of a ratio
	
	KQ3
	• Dietary intake of a different amount of total fat
		• Diet(s) with an energy intake that is statistically significantly higher or lower than the intervention/exposure diet (e.g., not isocaloric comparison)
		• Studies that do not have a statistically significant difference between groups in PUFA or total fat intake
		• Studies comparing undefined exposures (e.g., comparisons of undefined quartiles)

Outcome	**KQ2, 3, and 4** Infant and child (birth through 18 years) growth parameters • Birth weight • Weight and Weight-for-age percentile or Z-score adjusted for gestational age • Length or Height and Length-for-age or Height-for-age percentile and Z-score adjusted for gestational age • Head circumference and Head circumference percentile and Z-score adjusted for gestational age Infant and child (birth through 18 years) developmental outcomes[c] • Cognitive /	• BMI, BMI z-score • Body composition and distribution (e.g., % fat mass, fat-free mass, skin fold thicknesses) • Incidence and prevalence of overweight, obesity

Element	Inclusion Criteria	Exclusion Criteria
	neurological • Language / communication • Movement / physical • Visual function / acuity • Social / emotional learning **KQ1** • Risk of preterm birth	
Timing	• All exposure or intervention durations will be included	•
Setting	• Outpatient; all settings except hospital and acute care will be included	• Inpatient; hospital and acute care
Study Design	• Randomized controlled trials • Prospective cohort studies • Nested case-control studies	• Narrative reviews • Systematic reviews • Meta-analyses • Scoping reviews • Umbrella reviews • Retrospective cohort studies • Non-randomized controlled trials, including quasi-experimental and controlled before-and-after studies • Cross-sectional studies • Case-control studies • All other study designs
Geographic Location	• Locations with food products or dietary supplements widely available to U.S. and/or Canadian consumers • Countries rated very high on the Human Development Index (HDI)[d] at the time of data collection	• Locations not rated very high on the HDI
Study Size	• Studies including	• Studies with N < 30 participants (for RCTs:

Element	Inclusion Criteria	Exclusion Criteria
	power calculations or effect sizes • Studies with N ≥ 30 participants (for randomized clinical trials [RCTs]): ≥ 10 participants analyzed per study arm)	< 10 participants analyzed per study arm), without power calculations or effect sizes • Case studies and n=1 samples • Non-randomized studies that do not account for any potential confounders
Language	• Articles published in English	• Articles published in languages other than English
Publication Dates	• Articles published during or after 2000	• Articles published prior to 2000

[a] For studies meeting all other eligibility criteria, studies enrolling populations aged 0 to older than 19 years will be included if: a) results are stratified by age group, allowing extraction of data for participants aged through 18 years; or b) 85% of the population is aged through 18 years, if results are not stratified by age group. The one exception is studies of adolescents; for those meeting all other eligibility criteria, studies enrolling adolescents through age 26, regardless of result stratification or percentage of population aged through 18 years, will be included. See the Study Selection section.

[b] Dietary supplement is defined as a product intended to supplement the diet that contains one or more dietary ingredients (including vitamins, minerals, herbs or other botanicals, amino acids, and other substances) intended to be taken by mouth as a pill, capsule, table, or liquid, and that is labeled on the front panel as being a dietary supplement.

[c] See Section IV for an example table of measures with periodicity.

[d] United Nations Development Programme Human Development Reports, **https://hdr.undp.org/data-center/human-development-index#/indicies/HDI**

Literature Search Strategies to Identify Relevant Studies to Answer the Key Questions

Literature Databases

We will conduct a comprehensive database search, including Ovid MEDLINE®, EMBASE® or CINAHL, and the Cochrane Library. Our initial sample search strategy will be developed by a research librarian with expertise in conducting searches for systematic reviews. The final search strategy will be peer-reviewed by a second research librarian.

Based on prior experience with related topics, search strategies return many publications of in vivo and in vitro animal and biochemical studies, respectively. However, the Evidence-based Practice Center (EPC) librarian group and other experts have discouraged relying on PubMed filters for humans and animals,[53] as relevant articles may be missed or excluded. We will triage abstracts using a modified review approach, described in the Study Selection section below.

We will limit search dates to articles published in 2000 or later, consistent with other reviews on DRI currently underway.[54-57] The most recent DRI guidelines were published in 2005[58] but were not developed using systematic reviews for the topics covered in this review. If older, seminal studies or studies cited in the prior guideline are needed for context we will provide them and explain the context they provide, but they will not be presented as evidence.

All identified citations will be imported to a reference management system (EndNote® Version 21; Thomson Reuters, Philadelphia, PA). Reference lists of included studies will be reviewed to identify other relevant publications. Sources for gray literature may include reports produced by federal and state agencies, healthcare provider organizations, specialty or quality organizations and societies. We will search for clearinghouses that aggregate, or reports that summarize research across different organizations and we will follow up on the suggestions made by Technical Expert Panel (TEP) members.

Electronic literature searches will be updated while the draft report is posted for public comment to capture any new publications. Abstracts and full texts will be assessed using the same process of dual review as all other studies considered for inclusion (see Study Selection below). If any pertinent new literature is identified for inclusion in the report, it will be incorporated into the final version of the report.

Supplemental Evidence and Data for Systematic review (SEADS)

AHRQ will publish an announcement in the Federal Register to notify interested individuals or organizations about the opportunity to submit additional study-specific information via the SEADS portal on the Effective Health Care website. We will review any submission using the same inclusion and exclusion criteria used for the published literature.

Study Selection

We will use pre-defined criteria described in **Table 1** to screen citations (titles and abstracts) identified through our searches, in accordance with the AHRQ Methods Guide,[51] to determine eligibility for full-text review. Abstracts will be independently reviewed by two team members, with the exception of triaged animal and biochemical abstracts; these citations, identified in preliminary searches by the medical research librarian using words and phrases for animals, biochemical terms, and journal titles (e.g., Journal of Dairy Science),[49] will be reviewed by one team member and excluded or moved back into the general review set. We will retrieve full text articles for all abstracts deemed appropriate for consideration by at least one reviewer. Each full-text article will be independently reviewed for eligibility by two team members, including any articles suggested by the TEP or peer reviewers, or that result from the public posting process. Any disagreements will be resolved by consensus among investigators. If consensus cannot be reached, a third reviewer will resolve the difference. We will use a web-based systematic review software, DistillerSR® (Evidence Partners Incorporated, Ottawa, Canada), to facilitate the study selection process. No Artificial Intelligence or Machine Learning will be used in study selection or other processes in this review. A record of studies excluded at the full-text level with reasons for exclusion will be maintained and made available as an appendix to the final report.

We acknowledge the distinction between chronological age versus pubertal stage, as well as heterogeneity in enrollment across age ranges. Studies enrolling mixed ages beyond our inclusion criterion (through age 18 years) and meeting all other eligibility criteria will be included if a) results are stratified by age group such that results can be extracted for participants through 18 years separately from older ages, or b) 85% of participants fall within our age

criterion, if data for eligible age groups are not reported separately. A specific exception will be made for studies of adolescents; those meeting all other eligibility criteria and enrolling participants beginning in adolescence through age 26 years will be included regardless of results stratification or percentage of participants aged through 18 years.

Data Abstraction and Data Management

We will develop a standardized data form in Microsoft Excel® for data extraction for each Key Question that includes study characteristics (e.g., author, year of publication and data collection, country, study design, inclusion and exclusion criteria), population characteristics (e.g., age, sex, social drivers, BMI, type of diet, energy intake), exposure or intervention, comparisons, and outcomes. The standardized form will be pilot tested by all study team members using 10 studies. We will iteratively continue testing the form until no additional items or unresolved questions exist. After we finalize the form, reviewers will work independently, and a second team member will review the data for accuracy. In case the included studies do not report all necessary information (e.g., methods and results), we may attempt to contact authors directly when feasible. Multiple publications relating to the same study will be counted as one unique study, but the information from multiple publications will be included.

Assessment of Methodological Risk of Bias of Individual Studies

In accordance with the AHRQ Methods Guide,[51] we will use predefined criteria to assess the risk of bias, or internal validity, of each included study. Controlled trials and observational studies will be assessed using a priori established criteria consistent with the approach recommended in the Methods Guide chapter Assessing the Risk of Bias of Individual Studies.[51] Criteria will be tailored to study design and will be based on the U.S. Preventive Services Task Force (USPSTF) methods and guidance.[51] For randomized controlled trials (RCTs), we will downgrade studies that do not provide randomization, allocation concealment, and/or blinding details, have a high rate of loss to follow-up, or demonstrate selective reporting or other bias accordingly. For nonrandomized studies of intervention (NRSI), these criteria will include methods of study subject selection (e.g., consecutive, use of an inception cohort) and appropriate control for confounding of relevant factors.[51] Any modifications to the USPSTF criteria or specific criteria added for this topic will be documented in the methods sections of the systematic review report and its appendices. To address the potential for publication bias, we will conduct appropriate statistical tests (e.g., funnel plots, statistical tests for Egger's small sample effects) if we have a sufficient number (≥10) of similar RCTs. Otherwise, we will qualitatively assess the literature for indications of publication bias. Studies will be rated as being "low," "moderate," or "high" risk of bias as described below in **Table 2**. Each study will be independently evaluated for risk of bias by two team members. Any disagreements will be resolved by discussion and consensus. Studies rated high risk of bias will not be excluded from the evidence synthesis (see Data Synthesis section below); however, they may be summarized separately.

Table 2. Criteria for assessing the risk of bias of individual studies[51]

Rating	Description and Criteria
Low	• Least risk of bias, results generally considered valid • Employ valid methods for selection, inclusion, and when relevant, allocation of subjects to exposure; report similar baseline characteristics in different treatment groups; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinding of participants, care providers, and outcomes assessors); and use appropriate analytic methods (e.g., intention-to-treat analysis)
Moderate	• Susceptible to some bias but not enough to necessarily invalidate results • May not meet all criteria for low risk of bias, but no flaw is likely to cause major bias; the study may be missing information related to attrition, blinding, or analytic methods, making it difficult to assess limitations and potential problems • Category is broad; studies with this rating will vary in strengths and weaknesses; some studies rated moderate risk of bias are likely to be valid, while others may be only possibly valid
High	• Significant flaws that imply biases of various kinds that may invalidate results; "fatal flaws" in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems with intervention delivery • Studies are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions • Considered to be less reliable than studies rated moderate or low risk of bias when synthesizing the evidence, particularly if discrepancies between studies are present

Data Synthesis

Data will be synthesized by Key Question, both qualitatively (e.g., ranges and descriptive analysis, with interpretation of results) and quantitatively (meta-analysis) when appropriate. We will construct evidence tables identifying the study characteristics, including risk of bias, and results of interest in summary tables. Studies will be described using a hierarchy-of-evidence approach, where the best evidence will be the focus of our synthesis. Studies rated high risk of bias may be analyzed separately when appropriate (e.g., sensitivity analyses, narrative synthesis), but will not be excluded from the included body of evidence.

To address anticipated heterogeneity in reported outcomes, variation in their definitions and criteria for what constitutes response, we will specify outcome measures to assess infant. child, and adolescent growth and developmental outcomes (including points in time of use, validation of surveys in other languages, organization or country norms); measurements of dietary fats and fatty acids; and different time periods of outcome assessment (e.g., months or years of the infant or child, specific timepoints of sensitivity and vulnerability in brain development, COVID-19 restrictions, etc.). We will capture specific information to facilitate

assessment of effect modifiers and confounders, as well as additional detail regarding characteristics of populations, exposures, and outcomes (spontaneous, iatrogenic, not specified preterm birth; maternal populations age ≤16 or ≥35 years who are particularly at risk for SGA; multiple gestation; duration between exposure and outcome; human milk collection and analysis factors; formula composition). We will prioritize validated measures conducted by trained evaluators, ideally with a reference to a standard, along with constructs and subscales of global measures (e.g., Bayley Scales of Infant and Toddler Development, Wechsler Preschool and Primary Scale of Intelligence, specific tests for recognition memory). We also recognize that exposure is likely continuous, modified by intake of other nutrients, and varies in quality, quantity, and effects by age and sex, particularly within critical brain development periods (e.g., DHA within first 2 years, PUFA during puberty), and will identify to the extent possible. We will classify the magnitude of effects for measures (e.g., ≤ SS = 85 as clinically significant, ≤ T-score = 40 as clinically significant for behavioral measures). We will evaluate the proportion of participants meeting thresholds for clinically important differences as 0.5 SD or higher when reported. Where possible, we will pool adjusted estimates (e.g., standardized mean differences for outcome measures with 95% confidence intervals), but this requires that variables included in these models are reported and that the same or similar adjustment variables were used across studies.

We will consider pooling studies if there are at least two clinically and methodologically comparable studies.[51,59,60] Meta-analyses using profile-likelihood random effect models will be conducted to summarize data and obtain more precise estimates. For nonrandomized studies of intervention (NRSI), we will use pooled estimates adjusted for key confounders as reported by authors. We will assess statistical heterogeneity of sensitivity and subgroup analyses (e.g., differences by study risk of bias, study design, exposure differences, participant characteristics, outcome measurements, timepoints) using the I^2 statistic and visual assessment of overlap of 95% confidence intervals in forest plots.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

Outcomes to be assessed for strength of evidence (SOE) will be prioritized based on input from the Technical Expert Panel during protocol development, and in discussion with partners after data extraction. Based on this prioritized list, the SOE for exposure/intervention-outcome pairs within each KQ will initially be assessed by one researcher for prioritized outcomes by using the approach described in the AHRQ Methods Guide.[51]

To ensure consistency and validity of the evaluation, the initial assessment will be independently reviewed by at least one other experienced investigator using the following criteria:

- Study limitations (low, medium, or high level of study limitations)
    - This is the degree to which studies for a given outcome are likely to have reduced bias based on study design, analysis, and conduct. The aggregate risk of bias across individual studies reporting an outcome is considered.
- Consistency (consistent, inconsistent, or unknown/not applicable)
    - This is the degree to which studies report similar magnitudes of effect (i.e., range

sizes are similar) or same direction of effect (i.e., effect sizes have the same sign).

- Directness (direct or indirect)
    - This is the degree to which the outcome is directly or indirectly related to health outcomes of interest. Participant-centered outcomes are considered direct.
- Precision (precise or imprecise)
    - This describes the level of certainty of the effect estimate for a particular outcome with a precise estimate being one that allows a clinically useful conclusion. This may be based on sample size sufficiency and number of events. If these are adequate, the interpretation of the confidence interval is also considered. When quantitative synthesis is not possible, sample size and assessment of variance within individual studies will be considered.
- Reporting bias (suspected or undetected)
    - This describes publication bias, selective outcome reporting, and selective analysis reporting. If sufficient numbers of RCTs (≥10) are available, quantitative funnel plot analysis may be done.

The strength of evidence will be assigned an overall grade of high, moderate, low, or insufficient (**Table 3**) by evaluating and weighing the combined results of the five primary domains.

Table 3. Description of the strength of evidence grades

Strength of Evidence	Description
High	Very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. The findings are stable, i.e., another study would not change the conclusions.
Moderate	Moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. The findings are likely to be stable, but some doubt remains.
Low	Limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). Additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	Investigators are unable to estimate an effect or have no confidence in the estimate of effect for this outcome. The body of evidence has unacceptable deficiencies, precluding reaching a conclusion. If no evidence is available, it will be noted as "no evidence."

The strength of the evidence may be downgraded based on the limitations described above. There are also situations where the observational evidence may be upgraded (e.g., large magnitude of effect, presence of dose-response relationship or existence of plausible unmeasured confounders), if there are no downgrades on the primary domains, as described in the AHRQ

Methods Guide.[51] Where both RCTs and observational studies are included for a given exposure/intervention-outcome pair, we follow the additional guidance on weighing RCTs over observational studies, assessing consistency across the two bodies of evidence, and determining a final rating.[51]

A Summary of Findings table will be constructed for each comparison in each Key Question, with quantitative (meta-analyses) or qualitative (narrative) data where appropriate.

Assessing Applicability

Applicability will be assessed using the PICOTs framework, in accordance with the AHRQ's Methods Guide.[51] Applicability refers to the degree to which study participants are similar to people with similar exposures, particularly populations of interest to the users of the review. If participant, environmental, clinical, and intervention characteristics are similar, then it is expected that outcomes associated with the intervention for study participants will likely be similar to outcomes in real-world setting and people with similar exposures. Multiple factors identified *a priori* that are likely to impact applicability include characteristics of enrolled populations (e.g., age), environmental or clinical characteristics (e.g., diet-related condition), intervention factors (e.g., provisioned diets vs. self-prepared, intensity and frequency of engagement, use of co-interventions), outcomes (e.g., use of unvalidated or nonstandardized outcomes or outcome assessment tools), and settings (e.g., research or community setting, country). Review of abstracted information on these factors will be used to assess situations for which the evidence is most relevant and to evaluate applicability to real-world application in typical U.S. and Canadian settings. We will provide a qualitative summary of our assessment.

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VI. Definition of Terms

Table 4. Acronyms and Abbreviations

Acronym/Abbreviation	Definition
AHRQ	Agency for Healthcare Research and Quality
ARA	Arachidonic acid (omega-6)
BMI	Body mass index

DHA	Docosahexaenoic acid (omega-3)
DPA	Docosapentaenoic acid (intermediate omega-3)
EPA	Eicosapentaenoic acid (omega-3)
HDI	Human Development Index
KQ	Key Question
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Setting/Study Design
RCT	Randomized controlled trials
U.S.	United States

Table 5. HDI – Countries Rated Very High (2022)

Andorra	Greece	Poland
Antigua and Barbuda	Hong Kong, China (SAR)	Portugal
Argentina	Hungary	Qatar
Australia	Iceland	Romania
Austria	Ireland	Russian Federation
Bahamas* (20-21)	Israel	Saint Kitts and Nevis
Bahrain	Italy	San Marino
Barbados* (12-15)	Japan	Saudi Arabia
Belarus	Kazakhstan* (12-16)	Serbia* (12-15)
Belgium	Korea (Republic of)	Seychelles* (12-17, 20-21)
Brunei Darussalam	Kuwait	Singapore
Canada	Latvia	Slovakia
Chile	Liechtenstein	Slovenia
Costa Rica* (12-16)	Lithuania	Spain
Croatia	Luxembourg	Sweden
Cyprus	Malaysia* (12-16, 21)	Switzerland
Czechia	Malta	Thailand* (12-18, 21)
Denmark	Montenegro	Trinidad and Tobago* (12)
Estonia	Netherlands	Türkiye* (12)
Finland	New Zealand	United Arab Emirates
France	Norway	United Kingdom
Georgia* (12-15)	Oman	United States
Germany	Panama* (12-14)	Uruguay* (12)

Countries indicated with an asterisk were ranked as 'high' at least once during the years 2012-2022; years rated as high are indicated in the parentheses as 20xx.

Table 6. Example Measures with Periodicity

Category	Scale	2 mos	6 mos	12 mos	18 mos	24 mos	3y	4y	5y	6y	7y	8y	9y	10y	11y	12y	13y	14y	15y	16y	17y	18y
Cognitive	Bayley III	x	x	x	x	x	x															
	Bayley IV	x	x	x	x	x	x															

Category	Scale	2 mos	6 mos	12 mos	18 mos	24 mos	3y	4y	5y	6y	7y	8y	9y	10y	11y	12y	13y	14y	15y	16y	17y	18y
	BRIEF *(executive function*)								x	x	x	x	x	x	x	x	x	x	x	x	x	x
	BRIEF-2 *(executive function*)								x	x	x	x	x	x	x	x	x	x	x	x	x	x

BRIEF, Behavior Rating Inventory of Executive Function

VII. Summary of Protocol Amendments

If the EPC needs to amend the protocol, provide a numbered list of versions with the date of posting, which will be hyperlinked to previous versions, and a table with the date of each amendment, description of the change, and the rationale. Changes will be incorporated into the protocol.

VIII. Previous Versions of the Protocol

- None

IX. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The Technical Expert Panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts.

Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparing the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

XI. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

XII. Role of the Funder

This project was funded under Contract No. 75Q80120D00006 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed the EPC response to contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by either the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIII. Registration

This protocol will be registered in PROSPERO.