Evidence-based Practice Center Systematic Review Protocol

Project Title: Digestible Carbohydrate Intake and Maternal-Infant Outcomes: A Systematic Review

I. Background and Objectives for the Systematic Review

This review aims to identify and summarize the available evidence linking digestible carbohydrate intake and outcomes for pregnant people and infants from birth to two years of age.[1-3] Although the scope of this review is limited to outcomes during pregnancy, at birth, and up to the first 24 months of age, nutrition during these life stages has long-term effects extending into adolescence and adulthood.[4,5]

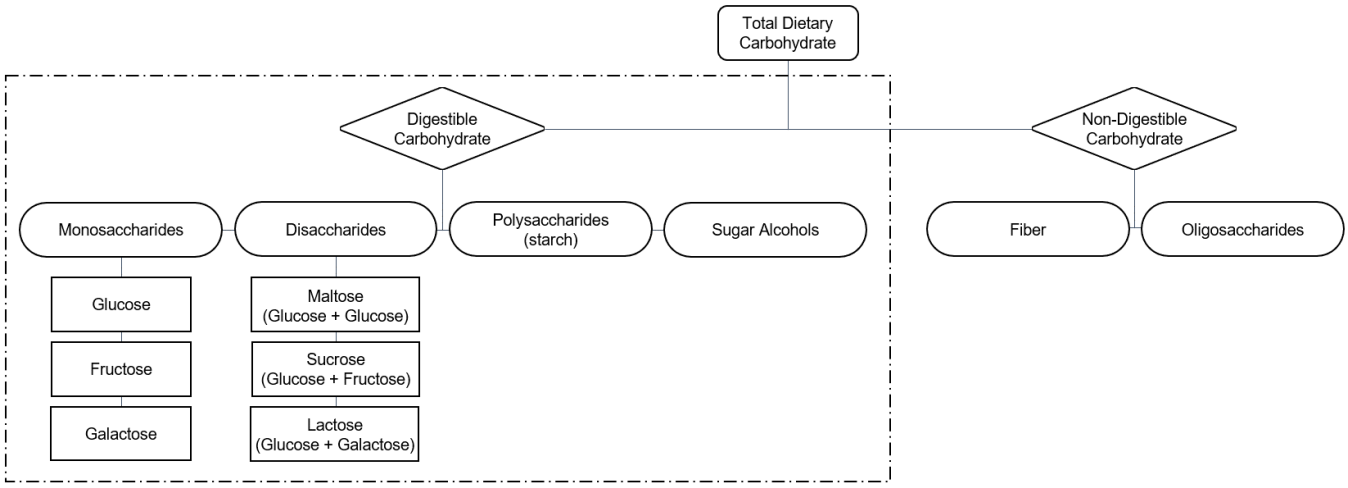
Current dietary guidelines for pregnant individuals and infants birth up to 24 months old

The 2020-2025 Dietary Guidelines for Americans cites the Dietary Reference Intake (DRI)[6] for total carbohydrate intake for pregnant individuals of at least 175 grams of carbohydrate per day (g/d), and a usual dietary pattern that meets the Acceptable Macronutrient Distribution Range (AMDR) for total carbohydrate of 45% to 65% of total energy intake. The DRI for total carbohydrate was published in 2005 and based on the estimated amount of carbohydrate needed to support physiological function of the brain of children one year of age and older and adults (130 g/d). Lacking sufficient evidence to determine a DRI for carbohydrate for infants 0–12 months of age, an adequate intake (AI) was established based on the average amount of carbohydrate consumed from human milk and supplementary foods. For infants 0 to 6 months of age the AI for carbohydrate is 60 g/d, while for infants 6 to 12 months of age the AI for carbohydrate is 95 g/d.

Dietary recommendations including DRIs, Recommended Dietary Allowances, and AIs are the foundation of guidelines and policies designed to inform people and promote healthy food choices

As illustrated in Figure 1, digestible carbohydrate is comprised of sugars (monosaccharides [e.g., glucose, fructose, galactose]; disaccharides [e.g., sucrose (glucose-fructose), maltose (glucose-glucose), lactose (glucose-galactose)]; starches, which are polysaccharides most commonly of glucose molecules; and some sugar alcohols [e.g., xylitol, erythritol, maltitol, sorbitol, etc.]). Once consumed, digestible carbohydrate is broken down into its composite molecular units, primarily monosaccharides, which are absorbed, transported into the circulation, metabolized, or converted to glucose, and stored as glycogen or, when consumed in excess, converted into fat.

Figure 1. Components of Total Dietary Carbohydrate



The dotted line indicates the area of interest, i.e., digestible carbohydrate, for this review.

Monosaccharides derived from digestible carbohydrate serve as substrates for a multitude of metabolic and physiologic mechanisms, including serving as the primary substrate to generate energy in the form of adenosine triphosphate (ATP). Mono- and di-saccharides and the glucose derived from starches yield about 4 kilocalories (kcal) per g; sugar alcohols yield between 1.5–3 kcal/g.[7] Glucose is an important source of energy for the pregnant individual, and is the primary source of energy for the placenta, and the developing fetus and contributes to fetal and newborn outcomes.[8-10] After birth, glucose and fat—the most energy-dense macronutrient—comprise the predominant sources of energy for the infant as evidenced by the macronutrient distribution of mature human milk, which is about 50% fat, 40% carbohydrate, and 10% protein and yields an energy density of 65–70 kcal/100 milliliters.[11]

Physiological Factors Impacting Diet and Nutrition Research in Pregnant Persons

Assessing usual food and nutrient intake during pregnancy is complicated by transitional and physiological 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, which are also influenced by social and cultural norms and expectations.[12] Nausea, heartburn, constipation, and fatigue influence food and nutrient intake during pregnancy. Food intake during early gestation, when nausea and fatigue are common, is likely different than food intake in late gestation when heartburn, bloating, constipation, and early satiety are frequent. Also, prenatal vitamin/mineral dietary supplements, while increasing the intake of essential micronutrients, can impact food intake by worsening nausea and constipation. For these reasons, the timing and mode of nutritional assessment including supplement use matters,[13] making data collection and analyses more complex.

Gestational Weight Gain. Recommendations for weight gain during pregnancy based on pre-pregnancy Body Mass Index (BMI), as defined by the World Health Organization (WHO) [14] and Centers for Disease Control and Prevention (CDC),[15] were released by the Institute of Medicine in 2009[16] and later modified by the Committee on Obstetric Practice of the American College of

Obstetricians and Gynecologists.[17] Excessive gestational weight gain in some studies has been associated with higher risk to the pregnant person, the fetus, and the neonate. Reported risks to the pregnant person include gestational diabetes, hypertension, cesarean section, and post-partum weight retention.[18-20] Risks to the developing fetus include larger birth size (macrosomia), higher body fat percentage at birth, preterm delivery, and impaired glucose tolerance.[21-26] Risks to the newborn include increased risk of obesity and its co-occurring conditions throughout childhood and into adulthood.[26-29] Outside of pregnancy, higher carbohydrate intake, especially simple carbohydrate intake, has been associated with higher weight and BMI, and hence some individuals enter pregnancy on restricted carbohydrate diets for the purpose of weight loss or to maintain weight loss. Gaining a better understanding of the relationship between gestational weight gain and dietary intake, specifically digestible carbohydrate intake, will allow for the development of more specific guidelines to inform clinicians, public health experts, policymakers, and government and non-governmental agencies involved in translating the science into actionable strategies for the public.

Restrictive Dietary Patterns During Pregnancy. Equally as important as understanding the relationships between gestational weight gain and dietary intake is understanding the impact of dietary patterns that severely restricts one of the major classes of macronutrients (fat, protein, or carbohydrate) and the subsequent higher consumption of the other two classes of macronutrients. Examples of these dietary patterns include low-carbohydrate, high protein, high-fat Atkins-type or ketogenic diets and high carbohydrate, lower protein, very low-fat diets like the Pritikin or Ornish diets. Importantly, not only does following a restrictive dietary pattern influence macronutrient consumption, but it can also impact key micronutrient consumption. For instance, low carbohydrate diets are known to contain inadequate amounts of folate/folic acid and to be associated with a slightly higher risk of having a child with a neural tube defect.[30]

Infant Feeding Recommendations

The CDC,[31] WHO,[14] American Academy of Pediatrics (AAP),[32] Dietary Guidelines of America,[33] and other professional medical organizations recommend that infants are exclusively fed human milk until 6 months of age and thereafter as mutually desired by the lactating parent and infant. According to these recommendations, when an infant is not fed human milk, the best alternative is a commercially prepared and regulated standard infant formula during the first year of life. The AAP states that other beverages, including cow milk, other mammalian milks (e.g., goat milk), and fruit juice, should not be provided during the first year of life, and that infants and children should not consume sugar-sweetened beverages.[32] The WHO, CDC, and AAP encourage the sequential introduction of complementary foods when nutritional needs of infants who exclusively consume human milk or infant formula or a combination of the two are no longer met, around 6 months of age. Gaining a better understanding of usual food and nutrient intake, including digestible carbohydrate intake, among infants and young children and its impact on growth, size, body composition, and other health outcomes is needed to better inform evidence-based recommendations and guidelines for this vulnerable population during a critical developmental window.

Assessing Nutritional Composition and Consumption of Human Milk and Human Milk Substitutes/Standard Infant Formulas. The composition of human milk changes over the course of lactation from the secretion of colostrum to transitional milk to mature milk, and varies throughout

a feeding and throughout the day.[34] When collected over 24 hours and mixed, mature human milk is comprised of about 87% water and 13% milk solids, which include about 7% carbohydrate, 4% fat, 1% protein, and <1% vitamins and minerals.[35] The carbohydrate component of human milk is predominantly lactose,[34] a disaccharide, with small amounts of monosaccharides (glucose, fructose), and nondigestible oligosaccharides.[36] The lactose concentration remains relatively constant over time to stabilize osmolality and to prevent osmotic diarrhea.[37] Significantly higher concentrations of fructose in human milk have been reported after consumption of a beverage sweetened with high-fructose corn syrup compared to baseline or a control beverage,[38] and short-term controlled cross-over feeding studies of higher sugar and higher fat diets resulted in significant differences in breast milk triglycerides, cholesterol, protein and lactose concentrations.[34,39-41] These results demonstrate that infants consuming human milk can be exposed to exogenously derived 'added sugars' as a result of their lactating parent's diet.

The nutritional composition of standard infant formulas is designed to be as similar to human milk as possible and is established and strictly regulated by the Federal Food, Drug, and Cosmetic Act.[42] The most common types of standard infant formula are derived from cow milk, with the primary carbohydrate being lactose, or from soy with carbohydrates typically derived from corn syrup solids and sugar.[43]

Purpose of the Review

The goal is to identify research available since the last DRI guidelines were established that can inform updated recommendations for total digestible carbohydrate intake during pregnancy and for infants aged up to 24 months of age.

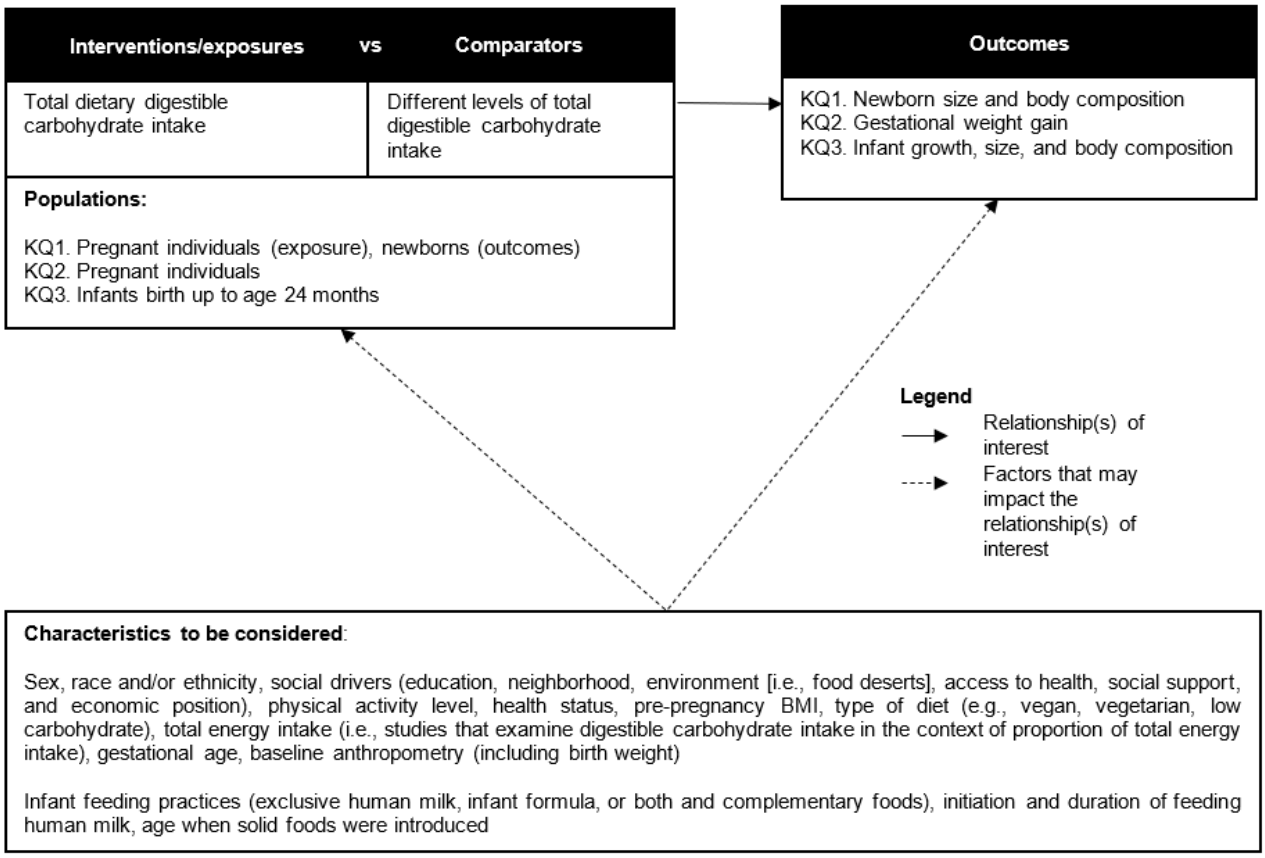
To achieve this goal, the systematic review will answer the Key Questions (KQs) outlined below. It will aim to summarize and synthesize the best available evidence linking consumption of specific amounts and proportions of digestible carbohydrate intake to important health outcomes for pregnant people and their offspring from birth through 24 months of age. The review will be used to inform the work by the National Academies of Sciences, Engineering, and Medicine (NASEM) that will support the development of the upcoming U.S. and Canadian government DRIs for digestible carbohydrate intake during pregnancy and by infants from birth to 24 months of age.

II. Key Questions

1. What is the association between dietary digestible carbohydrate intake by a person during pregnancy and the weight, length, head circumference, and other measures of size and body composition of the infant obtained at birth? How are these associations affected by characteristics of the pregnant person?
2. What is the association between dietary digestible carbohydrate intake during pregnancy and gestational weight gain? How are these associations affected by characteristics of the pregnant person?
3. What is the association between infant dietary digestible carbohydrate intake, including digestible carbohydrate intake from human milk, and measures of growth, size, and body composition in individuals from birth to 24 months of age?

Please see **Table 1** for inclusion and exclusion criteria by PICOTS (Population, Intervention, Comparator, Outcomes, Timing, Settings)[44] framework.

III. Logic Model



IV. Methods

This review will adhere to the international PRISMA[45] (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines and will follow standard methods for systematic reviews based on Agency for Healthcare Research and Quality's (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[46] ("AHRQ Methods Guide"). The final protocol will be registered in PROSPERO.[47]

A. 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	**KQ1 and KQ2:** • Pregnant individuals and newborns not affected by a disease	**All KQs:** • Non-human participants (e.g., animal studies, in-vitro models)

	or health-related condition that impacts carbohydrate absorption and/or metabolism **KQ3:** • Infants from birth to 24 months of age not affected by a disease or health-related condition that impacts carbohydrate absorption and/or metabolism	• Studies that enroll participants with diseases/health-related conditions that impact carbohydrate absorption or metabolism (e.g., cancer, malabsorption syndromes, diabetes) • Studies that exclusively enroll participants hospitalized with 1) an illness or injury; or 2) undernourished, underweight, stunted, or wasted participants • 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 **KQ1 and KQ2:** • Individuals who are not pregnant • Studies that enroll participants that are pre- or post-bariatric surgery **KQ3:** • Children older than 24 months of age • Studies of exclusively pre-term babies (gestational age <37 weeks), exclusively babies that have low birth weight (<2500g) and /or exclusively babies that are small for gestational age
Intervention (Exposure)	• Studies that report total dietary digestible carbohydrate intake[a] from foods, beverages, and dietary supplements[b] or report values that allow total digestible carbohydrate intake to be calculated, and percentage of dietary intake consisting of total dietary carbohydrate with or without the % from other macronutrients (protein and fat) • A dietary pattern that describes and quantifies intake of total dietary digestible	• Studies that do not specify the amount of total digestible carbohydrate intake (e.g., studies that only report type or source of digestible carbohydrate or report only total carbohydrate, but not digestible carbohydrate) • Studies that do not provide percentage of dietary intake from total digestible carbohydrates or enough data to allow this to be calculated • Studies that only assess digestible carbohydrate intake via infusions • Studies that only assess exposure to digestible carbohydrate 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. and/or Canadian consumers

	carbohydrate and total energy intake, with or without total fat, and total dietary protein content (e.g., low/high-fat diet; low/high-carbohydrate diet; high-protein; ketogenic diet; Atkins diet; Zone diet; Pritikin diet; Ornish diet)	• Multi-component interventions that do not isolate the effect of, or association with, digestible carbohydrate
Comparator	• Consumption of different levels of total dietary digestible carbohydrate intake	• Studies that do not attempt to control for energy intake of participants such that comparisons are not made on an isocaloric basis. Comparisons of digestible carbohydrate exposure should not be confounded by differences in participants' energy intake.
Outcome	**KQ1:** <u>Newborn size and body composition</u> • Birth weight, weight-for-age and percentile or Z-score adjusted for gestational age • Low birth weight • Small-for-gestational age • Large-for-gestational age; fetal macrosomia • Birth length, length-for-age and percentile and Z-score adjusted for gestational age • Head circumference and percentile and Z-score adjusted for gestational age • BMI, BMI z-score, weight-for-length percentile, and Z-score • Ponderal index or other composite measures • Body composition and distribution (e.g.,	

	% fat mass, fat-free mass, skin fold thicknesses, circumferences) **KQ2:** <u>Gestational weight gain</u> • Change in pregnant individual's body weight from baseline (before or during 1st trimester of pregnancy) to a later time point during pregnancy and/or right before delivery • Weight gain in relationship to weight gain recommendations, based on pre-pregnancy BMI **KQ3:** <u>Infant (up to 24 months of age) growth, size, and body composition</u> • Weight-for-age and percentile or Z-score adjusted for gestational age • Length-for-age and percentile and Z-score adjusted for gestational age • Head circumference and percentile and Z-score adjusted for gestational age • BMI, BMI z-score, weight-for-length percentile, and Z-score • Body composition and distribution (e.g., % fat mass, fat-free mass, skin fold thicknesses, circumferences)	

	• Incidence and prevalence of underweight, failure to thrive, stunting, wasting, healthy weight, overweight, obesity	
Timing	• All exposure or intervention durations will be included • KQ1 and KQ2: exposure during pregnancy • KQ3: exposure from birth to 24 months of age	
Setting	• Outpatient; all settings except hospital and acute care will be included	• Hospital and acute care
Study Design	• Randomized controlled trials • Non-randomized controlled trials, including quasi-experimental and controlled before-and-after studies • Prospective cohort studies • Nested case-control studies	• Narrative reviews • Systematic reviews • Meta-analyses • Scoping reviews • Umbrella reviews • Retrospective cohort 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, including those rated high and very high on the Human Development Index (HDI)[c]	• Locations not rated high or very high on the HDI

Study Size	• Studies with N ≥ 30 participants (for randomized clinical trials [RCTs]): ≥ 10 participants analyzed per study arm)	• Studies with N < 30 participants (for RCTs: < 10 participants analyzed per study arm), and without power calculation
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] Total dietary digestible carbohydrate intake defined as collective starch and sugar intake; carbohydrate intake not including dietary fiber.

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

B. 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®, and the Cochrane Library. Our initial sample search strategy, developed by a research librarian with expertise in conducting searches for systematic reviews, is in Appendix 1. The final search strategy will be peer-reviewed by a second research librarian.

Preliminary searches and our review of search strategies and protocols for related topics found that they return many in vivo and in vitro animal and biochemical studies. These will be excluded, but we want to do this quickly and accurately, to allow more time to focus on relevant studies and other technical and clinical issues. However, as relying on the PubMed filters for humans and animals is discouraged by the Evidence-based Practice Center (EPC) librarian group and other experts,[48] who have demonstrated that relevant articles may be missed or excluded, we will not use these filters but will triage abstracts as described in the Study Selection below.

We will limit search dates to articles published in 2000 or later, consistent with other reviews on DRI currently underway.[49-53] The most recent DRI guidelines were published in 2005[6] 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 citations identified will be imported to a reference management system (EndNote® Version 21; Thomson Reuters, Philadelphia, PA). References 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, or others such as the United States Department of Agriculture's (USDA) National

Agricultural Library (AGRICOLA). 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. 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: In accordance with the AHRQ Methods Guide,[46] we will use the pre-defined criteria described in **Table 1** to screen citations (titles and abstracts) identified through our searches to determine eligibility for full-text review. To facilitate faster identification of relevant studies yet adhere to standards and assure the search is comprehensive and the triage accurate, we will customize our approach. In accordance with documented issues[48] with use of specific filters in databases, and with the advice of the EPC librarian group, the medical research librarian will use the words and phrases for animals, biochemical terms, and journal titles (e.g., Journal of Dairy Science) identified during our preliminary search to triage a subset of references that are very likely to not be relevant. This group of citations will be reviewed by one research staff member, and those that are confirmed to be animal and biochemical studies will be excluded with that one review. All other abstracts will be reviewed by two team members according to our normal process. 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 study selection process. 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.

C. Data Abstraction and Data Management

At the beginning of data abstraction, we will develop a standardized data form in Microsoft Excel® for each Key Question that includes study characteristics (e.g., author, year, 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 mapped to one unique study.

D. Assessment of Risk of Bias for Individual Studies

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 chapter, Assessing the Risk of Bias of Individual Studies, described in AHRQ Methods Guide.[46] Criteria will be tailored to study design and will be based on the U.S. Preventive Services Task Force (USPSTF) methods and guidance.[54] 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.[55] 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.

Table 2. Criteria for grading the risk of bias of individual studies.[46]

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

E. Data Synthesis

Findings 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.

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 growth, size, or body composition (including points in time of use as well as organization or country norms); measurements of dietary digestible carbohydrate intake; and different time periods of outcome assessment (e.g., first trimester, 37 weeks, etc.). 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.[46,56,57] 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.

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

Similar to the approach for assessing risk of bias for individual studies, the strength of evidence (SOE) for each outcome will be initially assessed by one researcher for prioritized outcomes by using the approach described in the AHRQ Methods Guide.[46] 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. Patient centered outcomes are considered direct.
- Precision (precise or imprecise)
    - 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)
    - Publication bias, selective outcome reporting, and selective analysis reporting are types of reporting bias. 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.

Strength of Evidence	Description
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.[46] Where both RCTs and observational studies are included for a given 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.[46]

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.

G. Assessing Applicability

Applicability will be assessed in accordance with the AHRQ's Methods Guide,[46] using the PICOTS framework. 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, 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, perinatal stage), clinical characteristics (e.g., diet-related condition), intervention factors (e.g., intensity and frequency of engagement, use of co-interventions), outcomes (e.g., use of unvalidated or nonstandardized outcomes), and settings (e.g., clinical 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 clinical practice in typical U.S. settings. We will provide a qualitative summary of our assessment.

V. References

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VI. Definition of Terms

Acronym/Abbreviation	Definition
AAP	American Academy of Pediatrics
AHRQ	Agency for Healthcare Research and Quality
AI	Adequate Intake
AMRD	Acceptable Macronutrient Distribution Range
ATP	Adenosine triphosphate
BMI	Body mass index
CDC	The Centers for Disease Control and Prevention
DCI	Digestible Carbohydrate Intake
DRI	Dietary Reference Intake
EPC	Evidence-based Practice Center
HDI	Human Development Index
KQ	Key Question
NASEM	National Academies of Sciences, Engineering, and Medicine (NASEM)
NRSI	Nonrandomized studies of intervention
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Setting/Study Design

PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT	Randomized controlled trials
RDA	Recommended Dietary Allowance
SEADS	Supplemental Evidence and Data for Systematic Reviews
SOE	Strength of Evidence
TEP	Technical Expert Panel
TOO	Task Order Officer
U.S.	United States
USDA	United States Department of Agriculture
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

VII. Summary of Protocol Amendments

If the EPC needs to amend the protocol, it should give the date of each amendment, describe the change, and give the rationale in this section. Changes will not be incorporated into the protocol.

Table 1 below illustrates the format:

Date	Section	Original	Revised	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in language in the revised protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use as justification "because the AE/TOO/TEP/peer reviewer told us to" but explain what the change hopes to accomplish.

VIII. 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 Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

IX. 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.

X. 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.

Any team member involved in a study will not contribute to decisions about including or excluding the study, data abstraction, or risk of bias assessment for that study. While we do not anticipate that this will be necessary, if the search returns more than a small number or percentage of studies that involve a team member, we will develop a formal conflict management plan which will be shared with AHRQ.

XI. 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.

XII. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).[47]

Appendix 1. Example Search Strategy

Ovid MEDLINE® Search Strategy for Protocol

1 Dietary Carbohydrates/ or Dietary Sugars/ or Starch/
2 "Diet, Carbohydrate-Restricted"/
3 Recommended Dietary Allowances/
4 "Nutritional Status"/
5 "Nutritive Value"/
6 carbohydrate*.tw,kf.
7 (3 or 4 or 5) and 6
8 ((total and carbohydrate*) or (diet* and carbohydrate*)).tw.
9 1 or 2 or 7 or 8
10 exp Pregnancy/
11 exp Pregnancy Outcome/
12 exp Pregnancy Complications/
13 Gestational Weight Gain/
14 *"Birth Weight"/
15 Failure to Thrive/
16 ((gestation* or pregnant or pregnancy or antenatal or ante-natal or prenatal or pre-natal or perinatal or peri-natal or postnatal or post-natal or antepartum or ante-partum or peripartum or peri-partum or postpartum or post-partum or maternal or "puerperal") and (weight or "body mass" or BMI)).tw.
17 ((infant* or infancy or baby or babies or newborn* or neonat*) and (growth or weight or size or circumference or length or height or stature or macrosomia or underweight or "failure to thrive" or fat or (body adj3 (mass or composition)) or BMI or stunting or wasting or overweight or obes*)).tw.
18 or/10-17
19 9 and 18
20 limit 19 to yr="2000 -Current"
21 limit 20 to english language