Evidence-based Practice Center Systematic Review Protocol

Project Title: *Fiber Intake and Laxation Outcomes*

I. Background and Purpose of the Systematic Review

Background

Dietary fiber plays an important role in the prevention and treatment of chronic disease, particularly chronic constipation. The Dietary Reference Intake (DRI) values for the United States and Canada for dietary fiber were last reviewed in the late 1990s.[1] In preparation for an upcoming re-review of the fiber DRI values, a systematic review has been commissioned. The current DRI values for fiber, published in 2005, were based on recommended dietary targets for the management of chronic disease and established without the benefit of a systematic review. Since that time, an understanding of the complexity of ingested fibers and their diverse effects on human health has evolved. Currently, a large proportion of the United States and Canadian populations, both children and adults, consume less than the DRI values for fiber.[2, 3] Up to 20% of adults in the U.S. experience idiopathic constipation and nearly 50% use medication to assist with laxation.[4] Thus, a primary aim for the upcoming fiber DRI review will be focused on the effect of different amounts and types of dietary fiber on gut motility and laxation (hereafter referred to simply as laxation).

Fibers are defined in the CODEX 2009 as carbohydrate polymers that are not hydrolyzed by endogenous enzymes present in the human small intestine.[5] To be classified as a fiber, these polymers must either naturally occur in food, be a synthetic carbohydrate[1], or be extracted from raw materials, and they must have an established physiological health benefit,[6] such as improvement in blood cholesterol or glucose concentrations.[7] The current DRI criteria[1] define dietary fiber as nondigestible carbohydrates and lignin in plants, and defines functional fiber as "isolated, nondigestible carbohydrates that have been shown to have beneficial physiological effects in humans".[1] Total fiber is the sum of dietary and functional fibers. Fibers have traditionally be classified as "soluble" and "insoluble", but physicochemical properties such as viscosity, fermentation, and binding potential are now recognized as influential factors for their functionality in the gastrointestinal tract.[8]

In recent years, there has been substantial advancement in understanding of the diverse and multidimensional effects of dietary fibers in gastrointestinal health and management of gastrointestinal disorders related to laxation.[9] The advances are attributable to an improved capacity to characterize and classify dietary fiber, an increased understanding of the diet-gut microbiota associations in health and disease, and enhanced understanding of the influence of laxation in management of gastrointestinal disorders. In addition, understanding of the role of gut microbiota in fiber fermentation and laxation has increased since the early 2000s.[10] Elucidating

[1] Defined as "nondigestible carbohydrate polymers that are chemically synthesized and show a proven physiological benefit to health as demonstrated by generally accepted scientific evidence to competent authorities".[6]

that differential responses to diet among individuals may relate to the interplay of gut microbiota, food metabolome, and human host factors, including genetic profile and gene expression.[11-13] The proliferation of products in the marketplace with added fiber, not typically present as a natural constituent of the food, further magnifies the need to update the knowledge-base on the topic.

Purpose of the Review

This review is intended to provide a summary of evidence to serve as a foundation for the National Academies of Sciences, Engineering, and Medicine (NASEM) to review the DRI values for dietary fiber. This effort is part of a joint Working Group initiative between the United States and Canada Federal to review and update DRIs values. The U.S. Department of Agriculture (USDA) Food and Nutrition Service and U.S. Office of the Assistant Secretary for Health (OASH), within the U.S. Department of Health and Human Services (HHS), are jointly sponsoring this review by the Agency for Healthcare Research and Policy (AHRQ) Evidence-based Practice Center (EPC) Program.

The aim of this systematic review is to summarize the findings from interventional studies addressing the association between amount and type of fiber intake and laxation (i.e., gut motility) outcomes in humans in all life stages.

The initial intended audience for this review is the to-be-formed NASEM DRI review committee. The ultimate intended audiences will be nutritionists, gastroenterologists, other professionals providing nutrition and clinical care, and the general population.

II. Key Question

This systematic review will examine the Key Question as outlined below, based on the eligibility criteria presented in the next section (Table 1).

Key Question 1: What is the association between fiber intake and laxation/gut motility in the general population?

> Key Question 1a: How does the association vary among people in different life stages?

III. Methods

The systematic review will follow the EPC Program methodology, as described in its Methods Guide, particularly as it pertains to reviews of comparative effectiveness.[14]

A. Study Eligibility Criteria

Studies will be included in the review based on the study-specific inclusion and exclusion criteria described in Table 1.

Table 1. Study eligibility criteria based on Population, Intervention, Comparator, Outcome (PICO), and other elements

Element	Inclusion Criteria	Exclusion Criteria

Population	• Individuals of any age, including pregnant or lactating women
	• General population, including individuals with overweight/obese and those at elevated cardiometabolic disease risk
	  ○ Overweight/obese
	  ○ Hyperglycemia and related conditions, including type 2 diabetes
	  ○ Dyslipidemia
	  ○ Hypertension/high blood pressure
		• Those with diseases/health-related conditions or taking medications that could impact gut motility/laxation (e.g., irritable bowel syndrome; chronic constipation; lactose intolerance; use of medications that stimulate laxation or cause constipation)
		• Those with chronic constipation (100% of study population), including functional constipation
		• Study eligibility criteria includes "abnormal laxation" as defined by either a minimum or maximum number of defecations per week (or equivalent)
		• Those with other gastrointestinal-related conditions, symptoms, diagnoses
		  ○ Including diverticulosis
		• Those with diseases/health-related conditions or taking medications that could alter the gut microbiota composition/diversity (e.g., antibiotics)
		• Those with cancer, gastrointestinal disease, undernutrition, or who have had gut resection or bariatric surgery
		• Those with acute illness or injury
		• Pre-term babies (gestational age <37 weeks), babies with low birth weight (<2500 g) or small for gestational age (per study criteria)
		• Enteral/tube fed
		• Animal, *in vitro*, or other non-human studies

Interventions	• Fiber intake, including different types and sources of fiber • Fiber naturally occurring in food, enriched in food, dietary supplements, and diets that can be defined on the basis of fiber content ○ Must specify quantity of fiber intake	• Diets (or other interventions or exposures) where the fiber intake has not been quantified or explicitly specified • Combinations of fiber (from food or dietary supplements) and other entities with a purported effect on motility, digestion, or microbiota (e.g., psyllium + probiotic) • Combinations of fiber supplements and other entities (e.g., minerals, vitamins)
Comparators	• Different levels (dosages) of fiber • No added fiber or placebo • Different types or sources of fiber • Different formulations of fiber	• Other entities with a purported effect on motility, digestion, or microbiota (e.g., probiotic) • Alternative food group diets (e.g., red meat, fish, high protein)
Interventions vs. Comparators	• Fiber (supplement) vs. no fiber (supplement) • Higher fiber (diet) vs. lower fiber (diet) • Fiber vs. alternative fiber • Fiber vs. alternative fiber dose • Fiber vs. alternative fiber formulation	• Fiber + probiotic (etc.) vs. no intervention or placebo • Fiber + probiotic (etc.) vs. same probiotic (etc.) • Fiber vs. probiotic (etc.) • High-fiber diet vs. red meat diet (etc.)

Element	Inclusion Criteria	Exclusion Criteria

Outcomes	• Laxation (i.e., gut motility)
	  ○ Fecal frequency (e.g., number of defecations per week)
	  ○ Gastrointestinal transit time
	  ▪ Bristol stool scale (stool consistency)
	  ▪ Dye, marker studies
	  ○ Fecal output, weight/bulk (g/day)
	  ○ Ease of defecation (e.g., constipation)
		• Other disease or health outcomes
		• Flatulence, eructation, bloating, etc.

Subgroups of interest	• Specific life stages
	  ○ Infants
	  ○ Children and adolescents
	  ○ Adults (19-64)
	  ○ Older adults (≥65)
	  ○ Pregnant or postpartum
	  ○ Sex (male, female)
		None

Design	• Randomized controlled trials ○ Parallel or cross-over • N ≥10/group	• Observational studies • All other study designs
Timing	• Minimum duration of intervention: 2 weeks • In cross-over studies, any change in outcome measure must exclude data from the first week after end of any prior treatments. This may be accomplished by a washout period of at least 1 week.	None
Setting	• General population	• Hospital or other acute care settings
Publication	• English language • Published in peer-reviewed journals	• Non-English language text • Conference abstracts and other non-peer-reviewed data

We describe the logic for various inclusion and exclusion criteria, which were developed by the EPC based on proposed criteria from the USDA and OASH, along with discussions with a nutritionist and gastroenterologist who are members of the EPC team, our sponsors' representatives, our AHRQ Task Order Officers, and a Technical Expert Panel (TEP) of invited adult and pediatric nutritionists and gastroenterologists with knowledge in the areas of dietary fiber research and/or laxation.

To align with the purpose of DRIs, the **Population** of interest is the general population (of all ages, in all life stages), particularly from the perspective of laxation, who are not being evaluated for treatment with (or avoidance of) laxation. Thus, studies of people who are selected because of their decreased or increased laxation (including constipation and diarrhea) or who are taking other medications or supplements that have an effect on laxation or gut microbiota are excluded. To enhance applicability to the contemporary populations of the United States and Canada, the review explicitly includes studies of people with prevalent cardiometabolic conditions, including overweight/obesity, hyperglycemia and related conditions including type 2 diabetes, dyslipidemia, and hypertension.

The review focuses not only on the total amount of dietary fiber, as an **Intervention**, but the different types, forms, and formulations of fiber. To ensure a focus on the effect of fiber, the review excludes review of combinations of fiber and other entities, such as probiotics, that may affect laxation and gut health.

Given the large quantity of trial evidence regarding fiber intake that exists and known issues regarding the lack of reliability of subjective measures of food intake (e.g., food frequency

questionnaires), along with the large variability of fiber amounts in food products (e.g., wide range of fiber content in whole wheat bread), the review restricts the **Study Design** to randomized controlled trials that explicitly control and state the amount of fiber intake.

The **Timing** required for the effect on laxation to stabilize after a change in fiber intake amount or type is likely to be highly variable among individuals (and possibly due to other factors). Particularly since several outcome measures (e.g., fecal frequency) may be commonly measured over a period of 1 week, it was determined that a minimum 2-week intervention period should be required for study inclusion. In addition, there is evidence to suggest that the effect of changing diets on the microbiome may not stabilize for at least 1 week.[15-17] Cross-over studies, which are common among fiber and laxation studies, pose an additional issue related to the need for a washout period between interventions. To avoid being overly restrictive (i.e., requiring a 1-week washout for all cross-over studies), the inclusion criteria require that outcome measures in cross-over studies exclude data from the period of 1 week following the end of a prior intervention period (i.e., excluding data from the equivalent of a 1-week washout period).

Aligned with process of most DRI committees, the review's **Publications** will be restricted to published studies available in the English language.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Question

Literature Searches

We will search for studies and existing systematic reviews in Medline (via PubMed), Embase, and CINAHL. We will search index terms, along with free-text words, for concepts related to dietary fiber and laxation. Duplicate citations will be removed prior to abstract screening. Search strategies will include filters to restrict to randomized controlled trials and systematic reviews, as well as to English language publications, and to exclude conference abstracts. The search strategies for all databases will be independently peer reviewed by another experienced systematic review librarian. The PubMed search strategy (prior to peer review) is detailed in Appendix A.

The reference lists of current existing systematic reviews (published since 2015) will be screened for additional eligible studies. A Supplemental Evidence And Data for Systematic review (SEADS) portal and Federal Register Notice will be available for this review. Additional articles suggested to us from any source, including peer and public review, will be screened with the same eligibility criteria as the studies identified in the database searches.

Citation Screening

Per our EPC's standard processes, we will take advantage of the machine learning capacities for abstract screening in the Systematic Review Data Repository Plus (SRDR+) (https://srdrplus.ahrq.gov/) to limit resources spent on abstract screening. We will train the machine learning algorithm as follows:

(1) We will review the reference lists from known existing systematic reviews and clinical practice guidelines to identify potentially relevant studies, along with other known relevant citations.
(2) We will confirm this set of potentially relevant citations was adequately captured by our PubMed search.
(3) Based on recently published work by Sampson et. al.,[18] we will select the 500 "most relevant" citations from PubMed.

(4) The articles from steps (1) and (3) will be deduplicated, entered into SRDR+, and screened by all team members, with resolution of all conflicts in conference.
(5) As part of step (4), a random selection of 100 of the citations will be screened by all team members and the pilot screening and conflicts will be discussed and adjudicated in conference by the whole team. If needed, this process will be repeated with 100 or more citations. When the team is confident about eligibility criteria, screening will proceed in duplicate with adjudication of conflicts at regular team meetings.
(6) Subsequent to screening of the corpus compiled from steps (1) and (3), all citations found by the full literature searches will be added to the already-screened citations in SRDR+, and abstract screening will continue in duplicate.
(7) As screening progresses, the pretrained SRDR+ machine learning algorithm will continue to adapt and will sort the list of unscreened abstracts such that the most potentially-relevant articles are presented first. This process will make screening more efficient and will enable us to capture the preponderance of relevant articles relatively early in the abstract screening process.
(8) We will stop double screening when the predicted likelihood of the remaining unscreened papers being relevant is very low. We typically use a threshold for the prediction score of the unscreened citations of 0.40 (this threshold is based on experience with several dozen screening projects and an analysis in preparation for publication but may be lowered depending on whether we continue to find eligible abstracts near the threshold). To confirm that the selected prediction score threshold is appropriate for this literature base, when the maximum prediction score is <0.40, we will screen at least 400 additional consecutive citations (this sample size is chosen because the upper 97.5% confidence interval bound for a proportion of 0/400 is less than 1%). If any of the 400 citations are screened in (at the abstract level), we will repeat the process (restart counting of an additional 400 citations) until we have rejected at least 400 consecutive citations.

Potentially relevant citations will be retrieved to be rescreened in duplicate in full text. Searches will be updated during the draft report's public posting period.

C. Data Extraction and Data Management

Data from eligible studies will be extracted into SRDR+. Each article will be extracted by one researcher and entered data will be confirmed by a second researcher. Individual studies with multiple publications will be extracted as a single study (with a single entry in SRDR+). Articles that report multiple trials will be entered into SRDR+ separately for each study.

For each study, we will extract publication data, study design features, population characteristics (particularly related to life stages and existing cardiometabolic conditions), intervention and comparator names and descriptions, relevant outcomes and their definitions, study results, and risk of bias. All subgroup analyses or other evaluations of heterogeneity of treatment effect will be extracted.

D. Assessment of Quality and/or Methodological Risk of Bias of Individual Studies

We will evaluate each study for risk of bias and methodological quality during data extraction. Each study will be assessed by one researcher. Their assessments will be confirmed

by a second researcher. Disagreements will be discussed in conference with the team or with the Lead.

The only eligible study design is randomized controlled trials. Thus, we will complete the Cochrane Risk of Bias tool,[19] which addresses issues related to randomization and allocation concealment; blinding; deviations from intended intervention; missing data; outcome measurement; and reporting biases. We will also evaluate the adequacy of descriptions of study participants, interventions, outcomes, and study designs. In addition, we will assess the adequacy of analyses.

Each study will be given an overall risk of bias/methodological quality score (low, moderate, high) based on a standardized set of criteria:

- If randomization method or allocation concealment is at high risk of bias, the trial will be considered to be **high** risk of bias
- If randomization method, allocation concealment, and outcome assessor blinding are all unclear (with the recognition that the participant may be the outcome assessor), the trial will be considered to be at **high** risk of bias
- If one risk of bias or quality issue, other than randomization method or allocation concealment, is at high risk, then the trial will be considered to be at **moderate** risk of bias
- If two or more risk of bias or quality issues, other than randomization method or allocation concealment, is at high risk, then the trial will be considered to be at **high** risk of bias
- Trials with no identified risk of bias or quality issues will be considered to be at **low** risk of bias

If pertinent, the risk of bias for specific outcomes or analyses within studies may be downgraded.

E. Data Synthesis

Each study will be described in summary and evidence tables presenting study design features, study participant characteristics, descriptions of interventions, outcome results, and risk of bias/methodological quality. In text and tables, we will describe the characteristics of the study participants (particularly including those related to life stages) and features of the interventions or exposures.

The structure of the data synthesis (Results section) will depend in part on the characteristics of the eligible data. Ideally, there will be separate sections for each type of fiber. This will likely include separate sections for total, dietary, and functional (i.e., supplement) fiber. As feasible, this will also include separate sections for fiber from different sources (e.g., fruits, cereals, vegetables, supplements), different constituent fiber types (e.g., beta glucan, fructans, psyllium, partially hydrolyzed guar gum).

Within each section, we will organize findings by life stage and sex, including highlighting groups with no data.

Where appropriate and feasible, we will conduct random-effects meta-analyses if at least three studies are sufficiently similar in population, interventions, assessed fiber intake thresholds, and outcome. If appropriate and feasible, we will also analyze multiple intake thresholds using generalized least square models to estimate splines with knots (intake levels where the curve slope is allowed to change) at appropriate intake levels. We will then conduct multivariate meta-

analyses of the spline models (at each knot) and tabulate and graph the results to capture the threshold above which further increasing fiber intake will not significantly improve laxation measures. The goal of the meta-analyses will be to determine fiber intake thresholds above which laxation outcomes are favorable (or statistically significantly different). We may also conduct network meta-analyses, if such analyses are appropriate, feasible, and would provide further insights.

F. Grading the Strength of Evidence for Each Outcome

Following AHRQ Methods guidance,[14] the review team will consider the number of studies, their designs, limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the Key Question, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, other limitations, and the overall findings across studies, and will assign a consensus strength of evidence (SoE) rating of high, moderate, low, or insufficient to estimate an effect, addressing each outcome. All evaluated laxation outcomes will be considered to be "prioritized", and thus will be included in SoE analysis.

Outcomes with highly imprecise estimates (e.g., with 95% confidence intervals that extend beyond both 0.5 and 2.0 for categorical outcomes), highly inconsistent findings across studies (in terms of direction of effect), or with data from only one study will be deemed to have insufficient evidence to allow for a conclusion (with the exception that a single particularly large, well-conducted, and generalizable single study could provide low SoE). This approach is consistent with the concept that for imprecise evidence "any estimate of effect is very uncertain," which is the definition of Very low-quality evidence per the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.[20]

We will produce SoE tables that will provide the following for each life stage (as feasible), each analyzed fiber type, and each outcome: study types and sample sizes, overall methodological limitations, consistency, precision, directness, SoE rating, and conclusions.

Assessing Applicability

We will assess applicability in terms of generalizability to the general population as a whole and to each life stage.

IV. References

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V. Definition of Terms and Abbreviations

AHRQ	Agency for Healthcare Research and Quality
DRI	Dietary reference intake
EPC	Evidence-based Practice Center
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HHS	Department of Health and Human Services
NASEM	National Academies of Sciences, Engineering, and Medicine
OASH	(United States) Office of the Assistant Secretary for Health
SoE	Strength of evidence
SRDR+	Systematic Review Data Repository Plus
TEP	Technical Expert Panel
USDA	United States Department of Agriculture

VI. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe each change and give the rationale in this section.

VII. Review of Key Question

The Joint Canada-U.S. Dietary Reference Intakes Working Group prioritized areas for systematic review and developed the questions for the systematic review. AHRQ and Partners (HHS and USDA) finalized the Key Questions. The EPC confirmed the Key Questions with input from AHRQ and Partners to ensure that the Key Questions are specific and relevant.

VIII. Technical Expert Panel (TEP)

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. They are 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 results in 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 recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts 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 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 preparation of 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 three months after the 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 may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may 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. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators from participation in the review.

XI. Role of the Funder

This project was funded under Contract No. 75Q80120D00001/75Q80124F32011 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed 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 endorsements by 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).