2015 Dietary Guidelines Advisory Committee (DGAC) Nutrition Evidence Library Methodology

USDA's Nutrition Evidence Library supported the 2015 Dietary Guidelines Advisory Committee as it conducted systematic reviews on diet and health. This document includes archives from www.NEL.gov describing the systematic review methodology used by the 2015 Dietary Guidelines Advisory Committee. The NEL systematic review methodology is also outlined in *Part C: Methodology* of the *Scientific Report of the 2015 Dietary Guidelines Advisory Committee*.

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OVERVIEW

The USDA's Nutrition Evidence Library (NEL), housed within the Center for Nutrition Policy and Promotion, was responsible for assisting the 2015 Dietary Guidelines Advisory Committee (DGAC) in reviewing the science and supporting development of the 2015 DGAC Report. The NEL used state-of-the-art methodology informed by the Agency for Healthcare Research and Quality (AHRQ) [1], the Cochrane Collaboration [2], the Academy of Nutrition and Dietetics (AND) [3], and the 2011 Institute of Medicine (IOM) systematic review (SR) standards [4] to review, evaluate, and synthesize published, peer-reviewed food and nutrition research. The NEL's rigorous, protocol-driven methodology is designed to maximize transparency, minimize bias, and ensure SRs are relevant, timely, and high quality. Using the NEL evidence-based approach enables HHS and USDA to comply with the Data Quality Act, which states that federal agencies must ensure the quality, objectivity, utility, and integrity of the information used to form federal guidance.

DGAC members developed the SR questions and worked with NEL staff to complete the SRs. The following represents overarching principles for the NEL process:

- The DGAC made all substantive decisions required during the process
- NEL staff provided facilitation and support to ensure that the process was implemented consistently across DGAC Subcommittees in accordance with NEL methodology
- NEL used document templates, which served as a starting point and were tailored to each specific review
- The DGAC's Science Review Subcommittee provided oversight to the DGAC's work throughout the deliberative process, ensuring that the Subcommittees used consistent and transparent approaches when reviewing the evidence from the NEL SRs.

The NEL employed a six-step SR process, which leveraged a broad range of expert inputs:

- Step 1: Develop systematic review questions and analytic frameworks
- Step 2: Search, screen, and select studies to review
- Step 3: Extract data and assess the risk of bias of the research
- Step 4: Describe and synthesize the evidence
- Step 5: Develop conclusion statements and grade the evidence
- Step 6: Identify research recommendations

Each step of the process was documented to ensure transparency and reproducibility. Specific information about each review is available at www.cnpp.usda.gov/NEL-2015-DGAC, including the research questions, the related literature search protocol, literature selection decisions, an assessment of the methodological quality of each included study, evidence summary materials, evidence tables, a description of key findings, graded conclusion statements, and identification of research limitations and gaps. These steps are described in the following sections:

- Develop Systematic Review Questions and Analytic Frameworks
- Literature Search, Screen, and Select Studies to Review
- Extract Data and Assess the Risk of Bias

- Evidence Synthesis, Conclusion Statements, Grading of the Evidence, and Research Recommendation

Once complete, the evidence portfolio including the description of evidence, evidence synthesis, conclusion, grade, and research recommendations, is used to inform the *Scientific Report of the 2015 Dietary Guidelines Advisory Committee*. Information in the report was vetted by the full committee and presented at public meetings; more detailed supporting information on each specific systematic review is available the 2015 DGAC systematic review project page.

References

[1] Methods Guide for Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2014. Available from: www.effectivehealthcare.ahrq.gov.

[2] Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: The Cochrane Collaboration; 2011 [updated March 2011]. Available from: http://handbook.cochrane.org/.

[3] American Dietetic Association. Research and Strategic Business Development. Evidence Analysis Manual Chicago, IL: American Dietetic Association; 2012 [updated January 2012]. Available from: http://www.andeal.org/files/Docs/2012_Jan_EA_Manual.pdf.

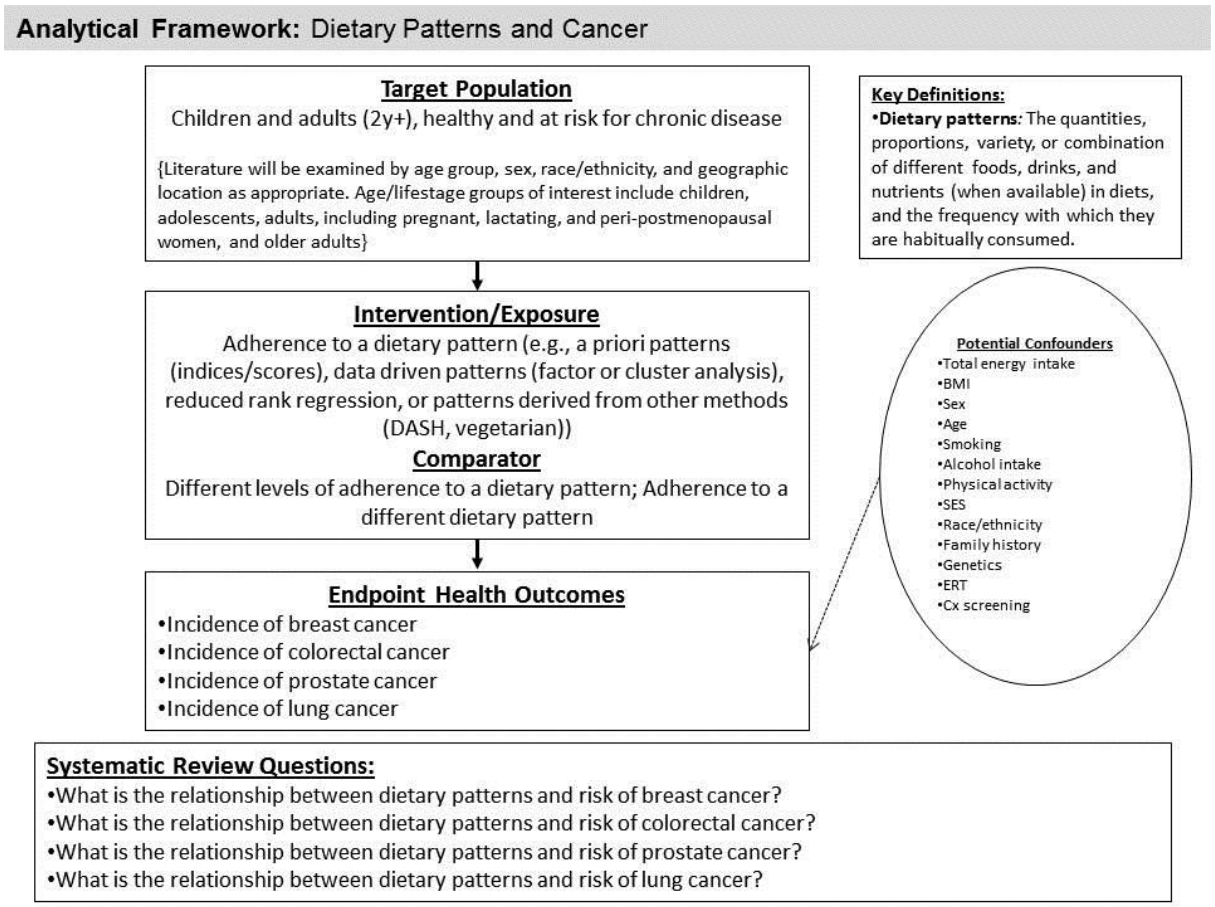
[4] Institute of Medicine. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academies Press; 2011. Available from: http://books.nap.edu/openbook.php?record_id=13059.

DEVELOP SYSTEMATIC REVIEW QUESTIONS AND ANALYTIC FRAMEWORKS

The DGAC identified, refined, and prioritized the most relevant topics and then developed clearly focused systematic review (SR) questions that were appropriate in scope, objective, and targeted important policy relevant to public health issue(s). SR questions must be specific enough to be researchable using NEL methodology, but broad enough to not overly limit the scope of the literature search. Once topics and SR questions were generated, the DGAC developed an analytic framework for each topic in accordance with NEL methodology. These frameworks clearly identified the core elements of the SR question/s, key definitions, and potential confounders to inform development of the SR protocol.

The core elements of an SR question include Population, Intervention or Exposure, Comparator, and Outcomes (PICO). These elements represent key aspects of the topic that are considered in developing a SR framework. An analytic framework is a type of evidence model that defines and links the PICO elements and key confounders. The analytical framework serves as a visual representation of the overall scope of the project, provides definitions for key SR terms, helps to ensure that all contributing elements in the causal chain will be examined and evaluated, and aids in determining inclusion and exclusion criteria and the literature search strategy.

EXAMPLE OF AN NEL SYSTEMATIC REVIEW ANALYTIC FRAMEWORK



LITERATURE SEARCH, SCREEN, AND SELECT STUDIES TO REVIEW

To minimize bias, inclusion and exclusion criteria were established for each SR question prior to searching the literature to guide the screening and selection process. Standard inclusion and exclusion criteria were established by the NEL and approved by the DGAC to promote consistency across reviews and to ensure that the evidence being considered in NEL SRs was most relevant to the U.S. population. These standard criteria were revised by the DGAC *a priori* as needed to ensure that they were appropriate for the specific SR being conducted. In general, criteria were established based on the analytic framework to ensure that each study included the appropriate population, intervention/exposure, comparator(s), and outcomes. They were typically established for the following study characteristics:

- Study design
- Date of publication
- Publication language
- Study setting
- Study duration
- Publication status (i.e., peer reviewed)
- Type, age, and health status of study subjects
- Size of study groups
- Study dropout rate

Once inclusion and exclusion criteria were determined, they were used to guide the literature search process. Searching, screening, and selecting scientific literature was an iterative process that sought to objectively identify the most complete and relevant body of evidence to answer a SR question. The NEL librarians created and implemented search strategies that included identifying the most appropriate databases and search terms to answer each SR question. To optimize each search, NEL librarians peer review each other's search strategies.

Existing high-quality literature reviews, including SRs and/or MAs, that addressed the topic or SR questions posed were identified by the NEL using a process called a duplication assessment. Existing SRs and MAs were valuable sources of evidence and were used for two main purposes in the NEL SR process:

- To augment a NEL SR as an additional source of evidence, but not as an included study in the review (in this case, the studies in the existing SR or MA would not be included individually in the NEL review that was conducted); or
- To replace a *de novo* NEL SR.

The NEL also used existing SRs to provide background and context for current reviews, inform SR methodology (e.g., inclusion and exclusion criteria, search strategy), and cross-check the literature search for completeness.

If relevant, low risk of bias, and timely existing SRs or MA were available, the reviews were compared and a decision was made by the DGAC as to whether an existing SR/MA would be used, or whether a *de novo* SR would be conducted. This decision was made based on the relevancy of the review in relation to the SR question and, when more than one review was identified, the consistency of the findings. If existing SRs/MA addressed different aspects of the outcome, more than one SR/MA may have been be used to replace a *de novo* SR.

Once the literature search was complete, the resulting articles were screened by two NEL analysts independently, beginning with titles, followed by abstracts, and then full-text articles, to determine which articles met the criteria for inclusion in the review. Articles that met the inclusion criteria and relevant existing SR were hand searched in an effort to find additional pertinent articles not identified through the electronic search.

The DGAC provided direction throughout this process to ensure that the inclusion and exclusion criteria were applied appropriately and the final list of included articles was complete and captured all research available to answer a SR question. Each step of the process was documented to ensure transparency and reproducibility.

EXTRACT DATA AND ASSESS THE RISK OF BIAS

Key information from each study included in a systematic review (SR) was extracted and a risk of bias assessment was performed by a NEL abstractor. NEL abstractors are National Service Volunteers from across the United States with advanced degrees in nutrition or a related field, who were trained to review individual research articles included in NEL systematic reviews. From the evidence grids, summary tables are created for each SR that highlight the most relevant data from the reviewed papers.

The risk of bias (i.e., internal validity) for each study was assessed using the NEL Bias Assessment Tool (BAT). This tool helped in determining whether any systematic error existed to either over- or underestimate the study results. This tool was developed in collaboration with a panel of international SR experts.

NEL staff reviewed the work of abstractors, resolved inconsistencies, and generated a draft of a descriptive summary of the body of evidence. The DGAC reviewed this work and used it to inform their synthesis of the evidence.

NUTRITION EVIDENCE LIBRARY BIAS ASSESSMENT TOOL (BAT)

The NEL BAT is used to assess the risk of bias of each individual primary study included in a SR.

Types of bias addressed in the NEL BAT

Type of bias	Description
Selection Bias	Systematic differences between baseline characteristics of the groups that are compared; error in choosing the individuals or groups taking part in a study
Performance Bias	Systematic differences between groups in the intervention/exposure received, or in experience with factors other than the interventions/exposures of interest
Detection Bias	Systematic differences between groups in how outcomes are determined; outcomes are more likely to be observed or reported in certain subjects
Attrition Bias	Systematic differences between groups in withdrawals from a study, particularly if those who drop out of the study are systematically different from those who remain in the study

Adapted from: Cochrane Bias Methods Group: http://bmg.cochrane.org/assessing-risk-bias-included-studies

The NEL BAT is tailored by study design, with different sets of questions applying to randomized controlled trials (RCTs) (14 questions), non-randomized controlled trials (14 questions), and observational studies (12 questions). Abstractors complete the

NEL BAT after data extraction for each article. There are four response options:

- Yes: Information provided in the article is adequate to answer “yes” (score=0)
- No: Information provided in the article clearly indicates an answer of “no” (score=2)
- Cannot Determine: No information or insufficient information is provided in the article, so an answer of “yes” or “no” is not possible (score=1)
- N/A: The question is not applicable to the article (score=0)

The NEL BAT

Risk of Bias Questions	Study Designs	Type of Bias
Were the inclusion/exclusion criteria similar across study groups?	Controlled trials Observational studies	Selection Bias
Was the strategy for recruiting or allocating participants similar across study groups?	Controlled trials Observational studies	Selection Bias
Was the allocation sequence randomly generated?	RCTs	Selection Bias
Was the group allocation concealed (so that assignments could not be predicted)?	RCTs	Selection Bias Performance Bias
Was distribution of health status, demographics, and other critical confounding factors similar across study groups at baseline? If not, does the analysis control for baseline differences between groups?	RCTs Controlled trials Observational studies	Selection Bias
Did the investigators account for important variations in the execution of the study from the proposed protocol or research plan?	RCTs Controlled trials Observational studies	Performance Bias

Was adherence to the study protocols similar across study groups?	RCTs Controlled trials Observational studies	Performance Bias
Did the investigators account for the impact of unintended/unplanned concurrent interventions or exposures that were differentially experienced by study groups and might bias results?	RCTs Controlled trials Observational studies	Performance Bias
Were participants blinded to their intervention or exposure status?	RCTs Controlled trials	Performance Bias
Were investigators blinded to the intervention or exposure status of participants?	RCTs Controlled trials	Performance Bias
Were outcome assessors blinded to the intervention or exposure status of participants?	RCTs Controlled trials Observational studies	Detection Bias
Were valid and reliable measures used consistently across all study groups to assess inclusion/exclusion criteria, interventions/exposures, outcomes, participant health benefits and harms, and confounding?	RCTs Controlled trials Observational studies	Detection Bias
Was the length of follow-up similar across study groups?	RCTs Controlled trials Observational studies	Attrition Bias

In cases of high or differential loss to follow-up, was the impact assessed (e.g., through sensitivity analysis or other adjustment method)?	RCTs Controlled trials Observational studies	Attrition Bias
Were other sources of bias taken into account in the design and/or analysis of the study (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	RCTs Controlled trials Observational studies	Attrition, Detection, Performance, and Selection Bias
Were the statistical methods used to assess the primary outcomes adequate?	RCTs Controlled trials Observational studies	Detection Bias

The completed NEL BAT is used to rate the overall risk of bias for the article by tallying the responses to each question. Each “Yes” response receives 0 points, each “Cannot Determine” response receives 1 point, each “No” response receives 2 points, and each “N/A” response receives 0 points. Since 14 questions are answered for RCTs and non-randomized controlled trials, they will be assigned a risk of bias rating out of a maximum of 28 points; while observational studies will be out of 24 points. The lower the number of points received, the lower the risk of bias.

EVIDENCE SYNTHESIS, CONCLUSION STATEMENTS, GRADING EVIDENCE, AND RESEARCH RECOMMENDATIONS

DESCRIBE AND SYNTHESIZE THE EVIDENCE

Evidence synthesis is the process by which the DGAC compared, contrasted, and combined evidence from multiple studies to develop key findings and a graded conclusion statement that answered the SR question. This qualitative synthesis of the body of evidence involved identifying overarching themes or key concepts from the findings, identifying and explaining similarities and differences between studies, and determining whether certain factors affected the relationships being examined. To facilitate the DGAC's review and analysis of the evidence, staff prepared a "Key Trends" template for each SR question. This document was customized for each question and included questions related to major trends, key observations, themes for conclusion statements and key findings. It also addressed methodological problems or limitations, magnitude of effect, generalizability of results, and research recommendations. DGAC members used the description of the evidence, along with the full data extraction grid, and full-text manuscripts to complete the "Key Trends" questions. The responses were compiled and used to draft the qualitative evidence synthesis and the conclusion statement.

DEVELOP CONCLUSION STATEMENTS, EVIDENCE GRADE, AND RESEARCH RECOMMENDATIONS

The conclusion statement is a brief summary statement worded as an answer to the SR question. It must be tightly associated with the evidence, focused on general agreement among the studies around the independent variable(s) and outcome(s), and may acknowledge areas of disagreement or limitations, where they exist. The conclusion statement reflects the evidence reviewed and does not include information that is not addressed in the studies. The conclusion statement also may identify a relevant population, when appropriate. In addition, "key findings" (approximately 3 to 5 bulleted points) were drafted for some questions to provide context and highlight important findings that contributed to conclusion statement development (e.g., brief description of the evidence reviewed, major themes, limitations of the research reviewed or results from intermediate biomarkers).

The DGAC used predefined criteria to evaluate and grade the strength of available evidence supporting each conclusion statement. The grade communicates to decision makers and stakeholders the strength of the evidence supporting a specific conclusion statement. The grade for the body of evidence and conclusion statement was based on five elements outlined in the table below: quality, quantity, consistency, impact, and generalizability.

Based on the existing body of evidence, research gaps, and limitations, the DGAC formulated several research recommendations that could advance knowledge related to the SR question. These recommendations can be used to inform research agendas and further inform policymakers.

USDA NUTRITION EVIDENCE LIBRARY CONCLUSION STATEMENT EVALUATION CRITERIA

Criteria for judging the strength of the body of evidence supporting the Conclusion Statement

Elements	Grade I: Strong	Grade II: Moderate	Grade III: Limited	Grade IV: Grade Not Assignable*
Risk of bias (as determined using the NEL Bias Assessment Tool)	Studies of strong design free from design flaws, bias, and execution problems	Studies of strong design with minor methodological concerns OR only studies of weaker study design for question	Studies of weak design for answering the question OR inconclusive findings due to design flaws, bias, or execution problems	Serious design flaws, bias, or execution problems across the body of evidence
Quantity •Number of studies •Number of subjects in studies	Several good quality studies; Large number of subjects studied; Studies have sufficiently large sample size for adequate statistical power	Several studies by independent investigators; Doubts about adequacy of sample size to avoid Type I and Type II error	Limited number of studies; Low number of subjects studied and/or inadequate sample size within studies	Available studies do not directly answer the question OR no studies available
Consistency of findings across studies	Findings generally consistent in direction and size of effect or degree of association, and statistical significance with very minor exceptions	Some inconsistency in results across studies in direction and size of effect, degree of association, or statistical significance	Unexplained inconsistency among results from different studies	Independent variables and/or outcomes are too disparate to synthesize OR single small study unconfirmed by other studies
Impact •Directness of studied outcomes •Magnitude of effect	Studied outcome relates directly to the question; Size of effect is clinically meaningful	Some study outcomes relate to the question indirectly; Some doubt about the clinical significance of the effect	Most studied outcomes relate to the question indirectly; Size of effect is small or lacks clinical significance	Studied outcomes relate to the question indirectly; Size of effect cannot be determined
Generalizability to the US population of interest	Studied population, intervention and outcomes are free from serious doubts about generalizability	Minor doubts about generalizability	Serious doubts about generalizability due to narrow or different study population, intervention or outcomes studied	Highly unlikely that the studied population, intervention AND/OR outcomes are generalizable to the population of interest

*Standard conclusion statement is used to communicate that there is either insufficient evidence or no evidence available to answer the question.

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The USDA Nutrition Evidence Library (NEL), housed within the Center for Nutrition Policy and Promotion, assisted the 2015 Dietary Guidelines Advisory Committee (DGAC) in conducting the 2015 DGAC systematic reviews. For a list of 2015 Dietary Guidelines Advisory Committee Membership and Acknowledgment lists, see: *Membership* and *Appendix E-10: Dietary Guidelines Advisory Committee Report Acknowledgments*.

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