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Dietary Protein and Amino Acid Requirements: An Evidence Scan Protocol

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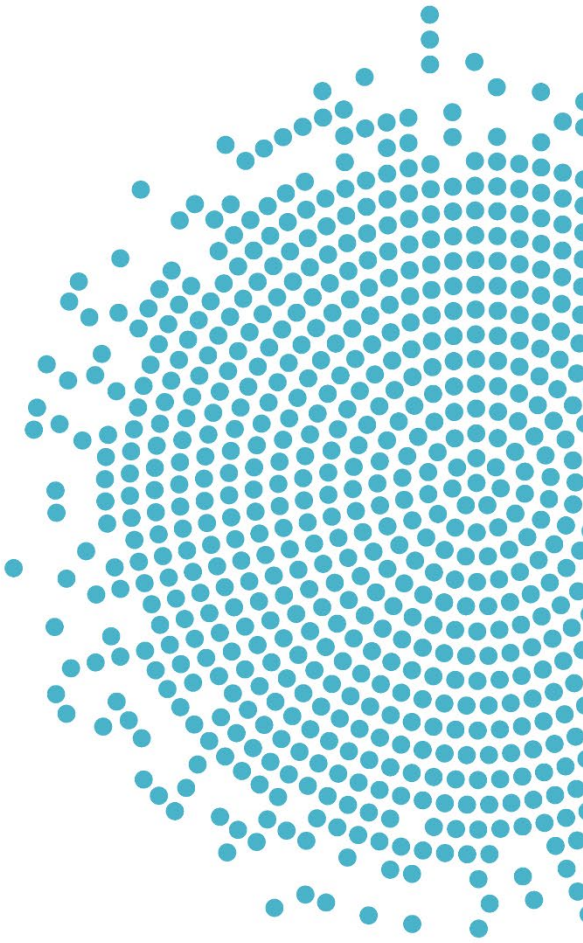

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Introduction

The Joint Canada-U.S. Dietary Reference Intakes Working Group (Working Group) has launched an effort to update the Dietary Reference Intakes for macronutrients, including protein and amino acids. The Nutrition Evidence Systematic Review (NESR) team at U.S. Department of Agriculture's (USDA), Food and Nutrition Service, Center for Nutrition Policy and Promotion was tasked with conducting an evidence scan related to average daily intake requirements for dietary protein and individual indispensable amino acids. This will augment an evidence scan conducted in 2022[*] and a systematic review conducted by the Agency for Healthcare Research and Quality (AHRQ) in 2024[†] on protein and amino acid requirements. Given that the systematic review conducted by AHRQ captured evidence published from January 2000 to May 2024, the Working Group was interested in identifying evidence published before January 2000.

The following scientific questions have been identified for this evidence scan: 1) What evidence has been published before 2000 on the average daily dietary protein intake requirements of the general population by life stage and sex? 2) What evidence has been published before 2000 on the average daily dietary individual indispensable amino acid intake requirements of the general population by life stage and sex?

Methods

NESR's methodology[‡] will be used to conduct this evidence scan. A NESR evidence scan is an exploratory evidence description project in which systematic methods are used to search for and describe the volume and characteristics of evidence available on a nutrition question or topic of public health importance. NESR evidence scans involve the following: development/refinement of the research question, protocol development, searching for and screening studies, minimal data extraction, and description of evidence. NESR evidence scans typically do not include: data extraction of study results, risk of bias assessment, synthesis of the evidence, development of conclusion statements, or grading the strength of the evidence. However, the Working Group was interested in extracting data in a way that aligns with and could be used to augment a systematic review conducted by AHRQ.[†] Thus, this evidence scan will include data extraction of study results and risk of bias assessments.

This section presents an overview of the specific methods used to answer the evidence scan questions:

1. What evidence has been published before 2000 on the average daily dietary protein intake requirements of the general population by life stage and sex?
2. What evidence has been published before 2000 on the average daily dietary individual indispensable amino acid intake requirements of the general population by life stage and sex?

[*] Nutrition Evidence Systematic Review Team. *Dietary Protein Intake: A Series of Evidence Scans on Acute Adverse Health Effects, Chronic Disease Risk, and Daily Requirements. Protein DRI Update.* Alexandria, VA: U.S. Department of Agriculture, Food and Nutrition Service, Center for Nutrition Policy and Promotion, March 2022. Available at: https://doi.org/10.52570/NESR.DRI2022.ES01

[†] Burstad K, Erickson A, Gholizadeh E, Namigga H, Claussen AM, Lamina T, Slavin J, Teigen L, Hill Gallant K, Stang J, Steffen L, Harindhanavudhi T, Kouri A, Duval S, Butler M. *Evaluation of Dietary Protein and Amino Acid Requirements: A Systematic Review*. Systematic Review. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 75Q80120D00008.) AHRQ Publication No. 24(25)-EHC030. Rockville, MD: Agency for Healthcare Research and Quality; November 2024. DOI: https://doi.org/10.23970/AHRQEPCSRPROTEINAMINO

[‡] USDA Nutrition Evidence Systematic Review Branch. USDA Nutrition Evidence Systematic Review: Methodology Manual. February 2023. U.S. Department of Agriculture, Food and Nutrition Service, Center for Nutrition Policy and Promotion, Nutrition Evidence Systematic Review. Available at: https://nesr.usda.gov/methodology-overview

Develop a protocol

An evidence scan protocol is the plan for how NESR's methodology will be used to conduct a specific evidence scan and is established by the Committee, *a priori*, before any evidence is reviewed. The protocol is designed to capture the most appropriate and relevant body of evidence to answer the evidence scan question. Development of the protocol involves discussion of the strengths and limitations of various methodological approaches relevant to the question, which then inform subsequent steps of the evidence scan process. The protocol describes all of the methods that will be used throughout the evidence scan process. Additionally, the protocol includes the following components, which are tailored to the evidence scan questions: the analytic framework, the inclusion and exclusion criteria, and the description of evidence plan. This protocol was developed to align with the protocol developed and implemented by AHRQ when conducting a systematic review on this topic.[*]

Develop an analytic framework

An analytic framework visually represents the overall scope of the evidence scan questions and depicts the contributing elements that will be examined and evaluated. **Figure 1** is the analytic framework for the evidence scan and shows that the intervention or exposure of interest is total daily protein intake level or total daily intake of indispensable amino acids (isoleucine, leucine, valine, lysine, methionine, phenylalanine, threonine, tryptophan, and histidine) in all life stages, including infants and young children (birth up to 24 months), children and adolescents (2 years up to 19 years), adults and older adults (19 years and older), pregnancy, and lactation. The comparators are different total daily protein intake levels and different total daily intake of indispensable amino acids. The outcomes are total protein requirement as defined by the following indicators or criterion of adequacy, including but not limited to: nitrogen balance method, factorial method, indicator amino acid oxidation method, and linear growth for infants, children, and adolescents (birth up to 19 years); indispensable amino acid requirement as defined by the following indicators or criterion of adequacy, including but not limited to: plasma amino acid response method, direct amino acid oxidation method, indicator amino acid oxidation method, and 24-hour amino acid balance method. Requirement is defined as the lowest daily intake value for a nutrient that will meet the need as defined by a specified indicator or criterion of adequacy, of the general population.

[*] Systematic Review: Evaluation of Dietary Protein and Amino Acid Requirements: A Systematic Review. Content last reviewed November 2024. Effective Health Care Program, Agency for Healthcare Research and Quality, Rockville, MD. https://effectivehealthcare.ahrq.gov/products/dietary-protein-intake/research

Figure 1. Analytic framework for the evidence scan questions: What evidence has been published before 2000 on the average daily dietary protein intake requirements of the general population by life stage and sex? What evidence has been published before 2000 on the average daily dietary individual indispensable amino acid intake requirements of the general population by life stage and sex?

Population	***Intervention / Exposure***	***Comparators***	***Outcomes***

All life stages, including:
• Infants and young children (birth up to 24 months)
• Children and adolescents (2 years up to 19 years)
• Adults and older adults (19 years and older)
• Pregnancy
• Lactation
	• Total daily protein intake level
	• Total daily intake of indispensable amino acids (isoleucine, leucine, valine, lysine, methionine, phenylalanine, threonine, tryptophan, and histidine)
		• Different total daily protein intake level
		• Different total daily intake of indispensable amino acids
			• Total protein requirement* as defined by the following indicators or criterion of adequacy, including but not limited to:
			  • Nitrogen balance method
			  • Factorial method
			  • Indicator amino acid oxidation method
			  • Linear growth for infants, children, and adolescents (birth up to 19 years)
			• Indispensable amino acid requirement* as defined by the following indicators or criterion of adequacy, including but not limited to:
			  • Plasma amino acid response method
			  • Direct amino acid oxidation method
			  • Indicator amino acid oxidation method
			  • 24-hour amino acid balance method

***** Requirement is defined as the lowest daily intake value for a nutrient that will meet the need as defined by a specified indicator or criterion of adequacy, of the general population.

Develop inclusion and exclusion criteria

The inclusion and exclusion criteria provide an objective, consistent, and transparent framework for determining which articles to include in the evidence scan (see **Table 1**). These criteria ensure that the most relevant and appropriate body of evidence is identified for the evidence scan questions.

Table 1. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Study design	• Randomized controlled trials • Non-randomized controlled trials* • Prospective cohort studies • Retrospective cohort studies • Nested case-control studies	• Uncontrolled trials† • Case-control studies • Cross-sectional studies • Ecological studies • Narrative reviews • Systematic reviews • Meta-analyses • Modeling and simulation studies
Publication date	• Prior to January 2000	• January 2000 - present
Population: Study participants	• Human	• Non-human

Population: Life stage	• At intervention or exposure and outcome:
	  ○ Infants and young children (birth up to 24 months)
	  ○ Children and adolescents (2 up to 19 years)
	  ○ Adults and older adults (19 years and older)
	  ○ Pregnancy
	  ○ Lactation
		• Not applicable

* Including quasi-experimental and controlled before-and-after studies

† Including uncontrolled before-and-after studies

Category	Inclusion Criteria	Exclusion Criteria
Population: Health status	• Studies that exclusively enroll participants not diagnosed with a disease[*] • Studies that enroll some participants: o with existing conditions that are known to alter protein metabolism or requirements (e.g., liver disease, kidney disease, cancer, chronic obstructive pulmonary disease, phenylketonuria, cystic fibrosis, eating disorders), or those being treated with medications that alter nutrient metabolism; o with severe undernutrition, failure to thrive/underweight, stunting, or wasting; o born preterm,[†] with low birth weight,[‡] and/or small for gestational age; o who became pregnant using Assisted Reproductive Technologies; o with multiple gestation pregnancies; o receiving pharmacotherapy to treat obesity; o pre- or post-bariatric surgery; o hospitalized for an illness, injury, or surgery;[§] o who are elite athletes (e.g., marathoners, professional or Olympic athletes); o and/or who have a baseline diet deficient in protein (i.e., below the recommended dietary allowance of protein (RDA) per age)	• Studies that exclusively enroll participants: o with existing conditions that are known to alter protein metabolism or requirements (e.g., liver disease, kidney disease, cancer, chronic obstructive pulmonary disease, phenylketonuria, cystic fibrosis, eating disorders), or those being treated with medications that alter nutrient metabolism; o with severe undernutrition, failure to thrive/underweight, stunting, or wasting; o born preterm,[†] with low birth weight,[‡] and/or small for gestational age; o who became pregnant using Assisted Reproductive Technologies; o with multiple gestation pregnancies; o receiving pharmacotherapy to treat obesity; o pre- or post-bariatric surgery; o hospitalized for an illness, injury, or surgery;[§] o who are elite athletes (e.g., marathoners, professional or Olympic athletes); o and/or who have a baseline diet deficient in protein (i.e., below the recommended dietary allowance of protein (RDA) per age)
Intervention/ exposure	• Total daily protein intake level • Total daily intake of indispensable amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine) • Multi-component intervention in which the isolated effect of the intervention of interest on the outcome(s) of interest is provided or can be determined despite multiple components	• Studies that only assess protein intake via parenteral nutrition or intravenous nutrition support • Studies that examine food products or dietary supplements not widely available to U.S. consumers • Multi-component intervention in which the isolated effect of the intervention of interest on the outcome(s) of interest is not provided or cannot be determined due to multiple components
Comparator	• Different total daily protein intake level • Different total daily intake of indispensable amino acids	• No comparator

[*] Studies that exclusively enroll participants with obesity or who are at risk for chronic disease will be included

[†] Gestational age <37 weeks and 0/7 days

[‡] Birth weight <2500g

[§] Studies that exclusively enroll participants post-cesarean section will be included

Category	Inclusion Criteria	Exclusion Criteria

Outcomes	• Total protein requirement* as defined by the following indicators or criterion of adequacy, including but not limited to:
	  ○ Nitrogen balance method
	  ○ Factorial method
	  ○ Indicator amino acid oxidation method
	  ○ Linear growth for infants, children, adolescents (birth up to 19 years)
	• Indispensable amino acid requirement* as defined by the following indicators or criterion of adequacy, including but not limited to:
	  ○ Plasma amino acid response method
	  ○ Direct amino acid oxidation method
	  ○ 24-hour amino acid balance method
	  ○ Indicator amino acid oxidation method
	
	* Requirement is defined as the lowest daily intake value for a nutrient that will meet the need as defined by a specified indicator or criterion of adequacy, of the general population
		• Not applicable

Publication status	• Peer-reviewed articles published in research journals	• Non-peer-reviewed articles, unpublished data or manuscripts, pre-prints, reports, editorials, retracted articles, and conference abstracts or proceedings
Language	• Published in English	• Not published in English
Country	• Studies conducted in any country	• Not applicable

Search for and screen studies

The NESR librarian, in collaboration with NESR analysts, will use the analytic framework and inclusion and exclusion criteria to develop a comprehensive literature search strategy. The literature search strategy will include selecting and searching the appropriate bibliographic databases, translating search using syntax appropriate for the databases being searched, and employing search refinements, such as search filters. The full literature search will be available upon request and will be fully documented in the final evidence scan.

The screening of electronic database search results will be facilitated using a web-based tool (DistillerSR, DistillerSR Inc., Ottawa, Ontario, Canada) and screening forms that will be developed based on the inclusion and exclusion criteria in this evidence scan protocol. After removal of duplicates, a re-ranking function will be utilized in DistillerSR to reorder articles by relevancy. Two NESR analysts will independently screen titles and abstracts of search results up to a 75% recall rate of citations eligible for full-text screening, as assessed by DistillerSR's natural language processing capabilities. We will then move to a single screener up to a 90% recall rate. NESR analysts will stop screening citations remaining past this 90% recall rate of citations eligible for full-text screening. Two NESR analysts will independently perform full-text screening to determine if inclusion criteria are met. Differences in screening decisions will be resolved by consultation with a third NESR analyst.

Extract data and assess the risk of bias

NESR analysts will extract the most essential data from each included article to describe key characteristics of the available evidence, such as the author, publication year, study design, population life stage, intervention/exposure, comparator, and outcomes. One NESR analyst will extract the data and a second NESR analyst will review the extracted data for accuracy. Each article included in the evidence scan will undergo a formal risk of bias assessment, with two NESR analysts independently completing the risk of bias assessment using the tool that is appropriate for the study design.[*†‡]

Describe the evidence

NESR analysts will describe the volume and characteristics of the included evidence, such as information on the population, intervention/exposure, comparator, outcomes, and risk of bias of the included evidence. The evidence may be presented in text, figures, and/or tables.

Considerations for future work

NESR analysts will identify and document research gaps and methodological limitations throughout the evidence scan process.

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[*] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366:l4898.doi: 10.1136/bmj.l4898

[†] Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016; 355:l4919; doi: 10.1136/bmj.i4919

[‡] Higgins JPT, Morgan RL, Rooney AA, et al. A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). *Environ Int* 2024; 186:108602; doi: 10.1016/j.envint.2024.108602.

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The NESR team is involved in executing and documenting the work necessary to ensure the evidence scan is completed in accordance with NESR methodology, including establishing all aspects of the protocol, which presents the plan for how they are planning to examine the scientific evidence, such as the inclusion and exclusion criteria.

The NESR team was supported by the Joint Canada-U.S. Dietary Reference Intakes Working Group, who provided input on the evidence scan question and protocol.

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