UNITED STATES DEPARTMENT OF AGRICULTURE

Dietary Protein Intake: A Series of Evidence Scans on Acute Adverse Health Effects, Chronic Disease Risk, and Daily Requirements

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Introduction

The Joint Canada-US Dietary Reference Intakes Working Group has launched an effort to update the Dietary Reference Intakes (DRIs) for macronutrients in the coming years, including protein. The USDA Nutrition Evidence Systematic Review team is supporting this effort by conducting a series of evidence scans related to total dietary protein intake. These evidence scans will inform potential future systematic reviews (SRs) that will be conducted to update the macronutrient (including protein) DRIs.

Current DRIs[a] for dietary protein include Estimated Average Requirements (EAR) and Recommended Dietary Allowance (RDA) values for apparently healthy children age 7 months to 18 years and apparently healthy adults age 19 years and older, based on a meta-analysis of nitrogen balance studies. Adequate Intake (AI) values for apparently healthy infants 0 to 6 months, are based on the average consumption of protein from human milk. There was not enough information to establish specific Tolerable Upper Intake levels (UL) for dietary protein or the indispensable amino acids.

Acceptable Macronutrient Distribution Ranges (AMDR), defined as "a range of intakes for a particular energy source that is associated with reduced risk of chronic diseases while providing adequate intakes of essential nutrients," are set for protein and the other macronutrients.[a] Protein requirements (expressed as a percentage of total energy intake) are not independent of other energy sources or the total energy requirement of the individual. However, the upper range for total protein intake from diet as a percent of total energy intake was set at no more than 35% in adults to decrease risk of chronic disease. In 2005, there was insufficient evidence to support a recommendation for total protein intake or to suggest an upper limit for an AMDR for protein intake based on chronic disease risk specifically. It was acknowledged, however, that high total protein intake or high animal protein intake is implicated in the following health conditions: osteoporosis, renal stones, renal insufficiency, coronary artery disease, and obesity.

Since the 2005 DRIs for macronutrients and energy were published, further research has been completed on the relationship between protein intake and health, including adverse health effects, chronic disease risk, and protein intake requirements overall. To address the update to the evidence base around protein intake and to aid in informing future work on the DRIs, the following evidence scans were completed:

The first evidence scan (Chapter 1) addresses the following questions:

- **What is the relationship between high dietary protein intake and acute adverse health effects?**
- **What is the relationship between high amino acid intake and acute adverse health effects?**

The second evidence scan (Chapter 2) addresses the following question:

What is the relationship between dietary protein intake and risk of chronic disease[b]?

The third evidence scan (Chapter 3) addresses the following questions:

- **What is the average daily dietary protein intake requirement[c] of apparently healthy individuals by life stage and sex?**
- **What is the average daily intake requirement for individual indispensable amino acids of apparently healthy individuals by life stage and sex?**

[a] Institute of Medicine 2005. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: The National Academies Press. https://doi.org/10.17226/10490.

[b] i.e., bone outcomes; sarcopenia; renal outcomes; cardiovascular disease risk; diabetes risk; growth, size, and body composition; developmental milestones; dementia/cognitive decline; all-cause moratlity

[c] Requirement: lowest daily intake value for a nutrient that will meet the need as defined by a specified indicator or criterion of adequacy, of apparently healthy individuals

Project methods

This section provides an overview of the methodology utilized to conduct this series of evidence scans. Detailed methodology for each evidence scan can be found in each of the three specific methods sections below.

An evidence scan is a systematic and exploratory process used to describe the volume and characteristics of research available on a topic or question and to identify evidence gaps. They are characterized by the following:

- Providing objective data to support topic and question development, refinement, and prioritization, and inform protocol development
- Not answering the research question, but giving a description of available evidence
- Not involving risk of bias assessment, synthesis, or grading the strength of the evidence

Develop a protocol

For each evidence scan, the NESR team collaborated with the Working Group to develop a protocol. An evidence scan protocol is a plan for how a specific review or scan will be conducted. The protocol includes:

- Analytic framework
- Literature search and screening plan
    - Inclusion and exclusion criteria
    - Electronic databases and search terms

The evidence scan protocols were established up-front, and designed to capture the most appropriate, relevant, and direct body of evidence related to the topic or question of interest. Specific methods and any variations to protocols that occurred during the course of the evidence scans are documented in the three chapters of this report.

A description of NESR's methodology for developing an analytic framework is below. NESR's methodology for developing inclusion and exclusion criteria and the search strategy, as well as processes related to screening and selecting studies for inclusion in the evidence scan, is described, below, in "**Search for, screen, and select literature**."

Develop analytic frameworks

Analytic frameworks were developed for each evidence scan question. An analytic framework defines the core elements of the scan question, includes definitions for key terms, and helps to ensure that important contributing elements in the causal chain will be considered. The analytic framework serves as the foundation for the rest of the evidence scan process and informs the inclusion/exclusion criteria, literature search strategy, and data extraction.

A standard framework, called the PICO framework, was used to define core elements of each evidence scan question. The elements of the PICO framework are the Population (for both the intervention/exposure and for the outcome), Intervention and/or exposure, Comparator (i.e., the alternative being compared to the intervention or exposure), and Outcomes. Key terms, key confounders, and other factors to be considered (i.e., mediators, moderators, covariates) were also identified and included in the analytic framework where appropriate.

Search for, screen, and select literature

Systematic searching, screening, and selecting the scientific literature is a process through which NESR sought to identify the most complete and relevant body of evidence related to the evidence scan questions. The process started with defining inclusion and exclusion criteria *a priori*, followed by developing and implementing literature search strategies, and finally screening and identifying search results. The entire process was documented, including a complete list of articles that met criteria for inclusion in each scan, and a list of excluded articles, with the rationale for exclusion.

Define inclusion and exclusion criteria

Inclusion and exclusion criteria provide an objective, consistent, and transparent framework for determining which articles to include in each evidence scan. These criteria were developed to guide selection of the most relevant and appropriate body of evidence for each evidence scan. Additionally, these criteria were framed to increase the utility of the scans for the upcoming protein DRI process. Any revisions to the criteria that occurred during the evidence scan are documented in the individual chapters in this report.

NESR analysts collaborated with the Working Group to establish inclusion and exclusion criteria that were tailored to the specific scan question addressed.

Developing and implementing the literature search strategy

Once the inclusion and exclusion criteria were set, the NESR librarian used the analytic framework and inclusion/exclusion criteria to guide development of a comprehensive literature search strategy. The librarian worked in collaboration with NESR staff to construct a preliminary search strategy using PubMed operators and search terms. This was used to conduct a test search, preview the results, and correct any syntax, spelling, or grammatical errors. Each search strategy underwent multiple revisions to refine and adjust the search before it was finalized for use. The search strategies are included in this report for all evidence scans completed (Chapters 1-3).

Identify bibliographic databases

In Chapters 1 and 2, the librarian searched PubMed alone. In Chapter 3, the librarian used Scopus and Web of Science to map citations.

Develop search terms and apply search filters

NESR analysts helped identify initial key terms and/or relevant articles to ensure that the NESR librarian understood the scope and intent of the evidence scan question. The librarian was responsible for drafting the search and incorporating feedback from NESR analysts in finalizing the search.

Individual evidence scan search strategies are detailed in the report chapters below.

Screen and select studies

The screening of search results was facilitated by the use of a web-based tool (i.e., DistillerSR) and screening forms that were developed based on the inclusion and exclusion criteria identified for each evidence scan. All search results were dual screened by two NESR analysts. The goal of screening was to review the search results and exclude those that did not meet the inclusion criteria. Screening was completed at three levels. The first level of screening was completed using only the title of each article. If an article was not excluded at this level, it moved forward to the second level, where the abstract was screened. Finally, if an article passed the first two levels, it moved to the third level, where the full text of the article was screened. Any disagreements between analysts were reconciled between the two screenings. If necessary, a third analyst was consulted to resolve differences. Any deviations from this screening process are noted in each chapter of this report.

Document the search results

After the electronic searches were completed, NESR analysts and the librarian documented the literature search and screening results by compiling lists of the included and excluded citations, along with the rationale for exclusion at the full-text level.

Extract data

NESR analysts extracted and summarized data from each included article to objectively describe the body of evidence available for each evidence scan. To expedite data extraction, only the most essential data for answering the question were extracted. Specific elements extracted for each evidence scan are detailed in subsequent chapters.

Once the types of data to be extracted were determined, an electronic data extraction form was developed and used to facilitate accurate, consistent, and efficient data extraction. This form ensured that the same information from each article was formatted consistently, which made the content easier to compare and contrast during synthesis. NESR analysts used DistillerSR to extract data.

One NESR analyst extracted data from each included article using the data extraction form. In some cases, the required data were not reported in the article. In those situations, the data were recorded as “not reported.” Next, a second analyst reviewed only the extracted results for completeness, accuracy, and consistent presentation and formatting. Evidence tables were created by NESR analysts using the extracted data.

Description of the evidence

NESR analysts described the volume and characteristics of the evidence identified using text and tables considerations were noted that could potentially be useful for future DRI systematic reviews.

Identifying considerations for future DRI work

Points that could be of note to the Working Group were summarized as considerations for their future work and future contributions to the macronutrient DRI process. These noted considerations were completed after describing the volume and characteristics of the evidence, and they were based on the gaps and limitations observed during data extraction.

Chapter 1 – High dietary protein intake (including amino acid intake) and acute adverse health effects

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Specific methods to conduct this evidence scan

Develop a protocol

The research questions, "What is the relationship between high dietary protein intake and acute adverse health effects?" and "What is the relationship between high amino acid intake and acute adverse health effects?", were explored with an evidence scan. The following section describes the protocol developed for this evidence scan.

The analytic framework for the evidence scan examining the relationships between total protein intake and amino acid intake and acute adverse health effects is presented in **Figure 1-a**. The analytic framework visually represents the overall scope of the evidence scan question and depicts the contributing elements that were considered. The first intervention or exposure of interest was any level of total protein intake defined as elevated or high, or compared to a lower level of protein intake. The comparator was a lower protein intake or no comparator. The next intervention or exposure of interest was any level of amino acid intake defined as elevated or high, or compared to a lower level of amino acid intake. The comparator was a lower amino acid intake or no comparator. The included amino acids were as follows: histidine, isoleucine, leucine, lysine, methionine, cysteine, phenylalanine, tyrosine, threonine, tryptophan, valine, arginine, and glutamine. The comparator was a lower level of amino acid intake or no comparator. For both intervention/exposures, the outcomes were any acute adverse health effects, especially those with a focus on toxicity. General outcomes were listed in the analytic framework but were not limited to this list. There were no key confounders noted due to the limited data extraction completed in evidence scans.

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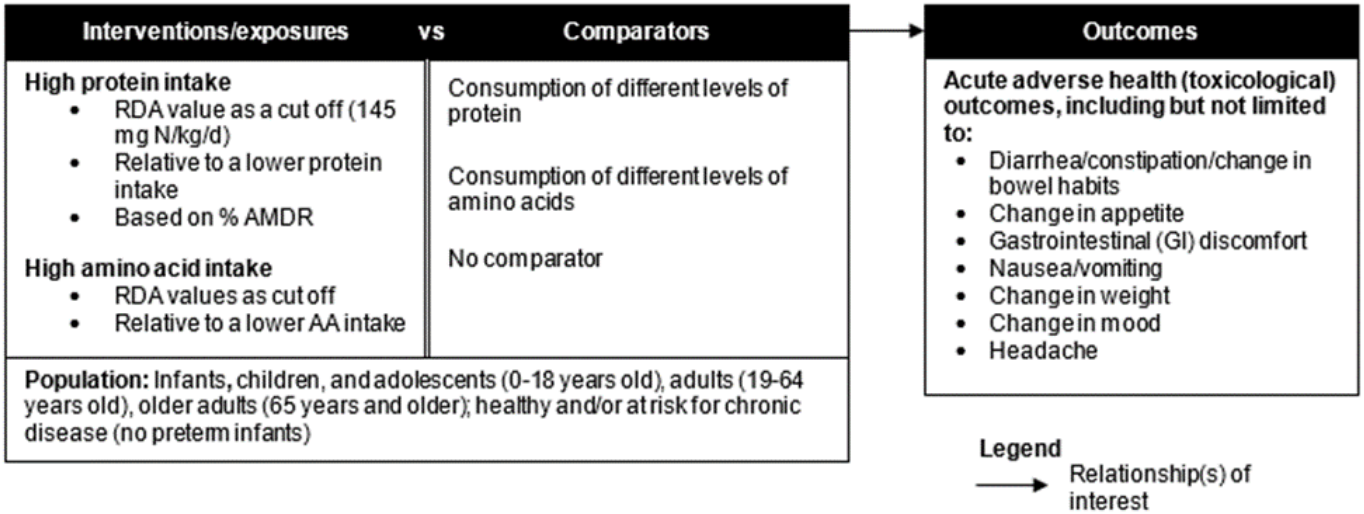
Figure 1-a. Analytic framework for high protein intake and acute adverse health effects



Search for and select studies

NESR analysts worked with the Working Group to finalize the inclusion and exclusion criteria and the literature search strategy, which are detailed in **Table 1-a** and **Appendix 1-a**, respectively**.** The study designs of interest for this specific scan included SRs, meta-analyses (MAs) and narrative reviews in order to streamline the literature search.

Table 1-a. Inclusion and exclusion criteria for high protein intake and acute adverse health effects

Category	Inclusion Criteria	Exclusion Criteria
Study design	• Systematic reviews • Meta-analyses • Narrative reviews	• Primary literature including: ○ Randomized controlled trials ○ Non-randomized controlled trials (including quasi-experimental and controlled before and after studies) ○ Prospective cohort studies ○ Retrospective cohort studies ○ Nested case-control studies ○ Case-control studies ○ Case studies ○ Brief reports ○ Uncontrolled trials ○ Cross-sectional studies ○ Uncontrolled before and after studies

Category	Inclusion Criteria	Exclusion Criteria

Intervention/ exposure	• **High dietary total protein intake from food, beverages, and protein supplements**
	  ○ RDA value as a cut off (145 mg N/kg/d)
	  ○ Relative to a lower protein intake
	  ○ Based upon percentage of energy intake (AMDR)
	
	• **High amino acid (AA) intake (Histidine, isoleucine, leucine, lysine, methionine, cysteine, phenylalanine, tyrosine, threonine, tryptophan, valine, arginine**Error! Bookmark not defined.**, glutamine*)**
	  ○ RDA and EAR values as a cut off
	  ○ Relative to lower AA intake
		• Studies that **only** assess protein intake via infusions (rather than the GI track)

Comparator	• Consumption of different levels of total dietary protein • Consumption of different levels of amino acids • No comparator	• Co-exposures (i.e., same protein intake level but varying supplementation or physical activity)
Outcomes	**Acute adverse health effects (toxicological outcomes), including but not limited to:** • Diarrhea/constipation/change in bowel habits • Change in appetite • GI discomfort • Nausea/vomiting • Change in weight • Change in mood • Headache	• Chronic disease outcomes related to protein intake (renal disease, bone health outcomes, diabetes, etc.)
Study duration	• Observational studies: Any duration • Trials: Up to 8 weeks	• Trials: >8 weeks

Publication date	• Review Papers
	  ○ 2016 to present
		• Review Papers
		  ○ Prior to 2016

Publication status	• Articles published in peer-reviewed journals	• Articles that have not been peer reviewed and are not published in peer-reviewed journals (e.g., unpublished data, manuscripts, pre-prints, reports, abstracts, conference proceedings)
Language	• Articles published in English	• Articles published in languages other than English
Country	• Studies conducted in any country	

Study participants	• Human participants
	  ○ Males
	  ○ Females
		• Non-human participants (e.g., animal studies, in-vitro models)

* Amino acids included in addition to indispensable amino acids that were of interest to the Joint Canada-US Dietary Reference Intakes Working Group

Category	Inclusion Criteria	Exclusion Criteria
Age of study participants	• Age at intervention or exposure: ○ Infants, children, and adolescents (0-18 years) ○ Adults (19-64 years) ○ Older adults (65 years and older)	N/A
Health status of study participants	• Studies that enroll participants who are healthy and/or at risk for chronic disease, including those with obesity • Studies that enroll **some** participants diagnosed with a disease or hospitalized with and illness or injury • Studies that enroll **some** participants diagnosed with a disease or with the health outcome of interest • Studies which exclusively recruit athletes and/or highly active individuals	• Studies that *exclusively* enroll participants diagnosed with a disease or hospitalized with an illness or injury (for this criterion, studies that exclusively enroll participants with obesity will not be excluded) • Studies that exclusively enroll undernourished participants • Studies that exclusively enroll participants with a baseline diet deficient in protein • Studies that exclusively enroll pre-term infants.

The final search terms and number of search results are included in **Appendix 1-a**.

Standard screening and selection processes were utilized for this scan, however handsearching was completed in addition to the electronic database search. Handsearching of the citations from each included review was completed in order to verify the comprehensiveness of the literature search for this evidence scan.

The included citations for each evidence scan can be found in **References for all three evidence scan chapters**.

Extract data

NESR analysts extracted data from each included review to objectively describe the body of evidence available in the last 5 years about high protein and high amino acid intake. Data extraction was completed in DistillerSR by one analyst for each review and a second analyst checked the extracted data for accuracy. The following data elements were extracted from each included review:

- Publication author and publication year
- Study design
- Purpose of review or research question answered by the review
- Population studied (life stage/age group)
- Adverse health effects discussed or outlined in the review
    - Dosage of high protein and/or high amino acid intake (if noted)
    - Duration of high protein and/or high amino acid intake (if noted)
- If study noted no adverse health effects
    - Dosage of high protein and/or high amino acid intake (if noted)
    - Duration of high protein and/or high amino acid intake (if noted)

No effect estimates or measures of statistical validity were extracted from the included reviews and no quality assessments were completed.

Describe the evidence

NESR analysts summarized the volume and characteristics of included studies to inform the following two questions:

1. **What is the relationship between high dietary protein intake and acute adverse health effects?**
2. **What is the relationship between high amino acid intake and acute adverse health effects?**

The extracted data were summarized in written form, as well as presented visually in a table. The extracted information helped analysts and the Working Group understand the following:

- The volume and characteristics of research examining the levels of protein intake (total protein and amino acids) at which acute adverse health outcomes do or do not occur
- Which acute adverse health outcomes occur as a result of high protein or amino acid intake and how they are defined
- How 'high protein intake' and 'high/excess amino acid intake' are defined in the literature

Considerations for future DRI work

Considerations for future SRs completed to inform the DRI process across acute adverse health effects were included in this evidence scan.

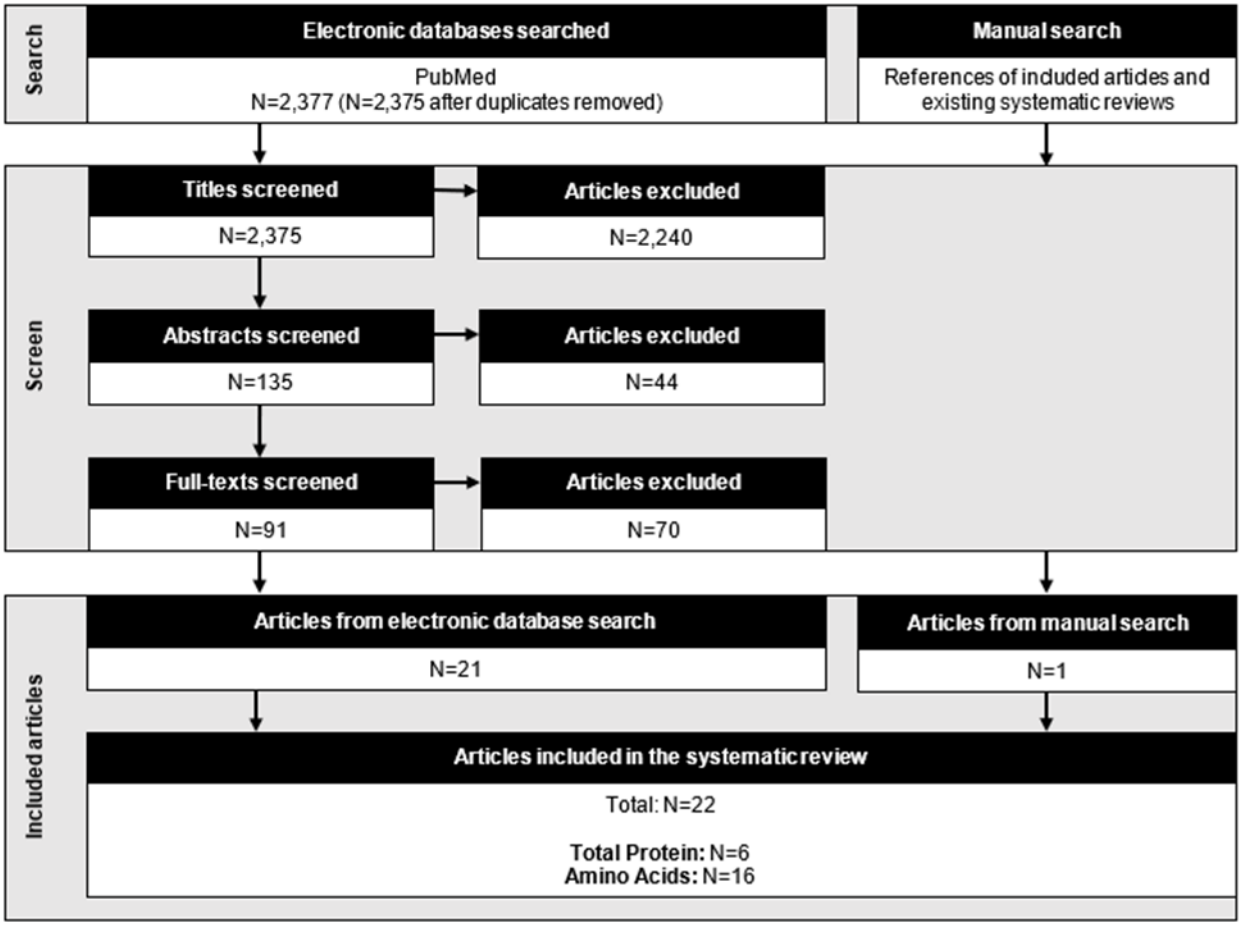
Results

Literature search and screening results

The literature search yielded 2,375 search results after the removal of duplicates (see **Figure 2**). Dual-screening resulted in the exclusion of 2,240 titles, 44 abstracts, and 70 full-text articles. Reasons for full-text exclusion are in **Appendix 1-b**. One additional review was identified from the manual search. The body of evidence included 22 reviews:

- 6 reviews provided evidence on total dietary protein
- 16 reviews provided evidence on amino acids

Figure 1-b. Literature search and screen flowchart for high protein intake and acute adverse health effects



Description of the evidence

This evidence scan included 22 reviews.

- Six reviews included some information regarding high dietary protein intake and acute adverse health effects (three narrative reviews,[1-3] two SRs,[4,5] and one SR with MA[6]).
- Sixteen reviews included some information regarding high dietary amino acid intake and acute adverse health effects (13 narrative reviews[7-19] and 3 SRs with MAs[20-22]).

Population characteristics

Total Protein Reviews

The populations studied for adverse effects in all included reviews were adults, aside from one review where age was not reported.[3] Three of the six protein reviews included studies with adult and older adult participants,[2,4,5] one focused on adults,[1] and one focused on older adults.[6]

Table 2 shows the full extraction table with population, intervention/exposure, and outcome data of the total protein reviews.

Amino Acid Reviews

The populations studied for adverse effects in the amino acid reviews ranged from adolescents to older adults, aside from the four reviews in which age was not reported or unclear.[10,16-18] Two reviews included adolescent, adult, and older adult populations,[20,21] three reviews focused on adults only,[7,13,19] and seven reviews focused on adults and older adults.[8,9,11,12,14,15,22]

Table 3 shows the full extraction table with population, intervention/exposure, and outcome data of the amino acid reviews.

Intervention/exposure characteristics

Total Protein Reviews

While six reviews were found total, three were narrative reviews describing the landscape of evidence available regarding high protein intake, and none of the included SRs were designed specifically to review evidence on protein toxicity. The extracted data from the reviews demonstrates gaps in the evidence available to determine specific and generalizable UL values.

Amino Acid Reviews

The 16 reviews identified that met the inclusion/exclusion criteria provided information about 7 amino acids. Multiple reviews suggested methods for establishing UL values in the future as more evidence becomes available. While most reviews evaluated the safety of amino acid supplementation, noted adverse effects from high amino acid intake were supported by only a few studies with limited data. The dosage and duration of amino acid intake/supplementation were not clearly defined or were not reported.

One review evaluated amino acids generally,[18] four reviews evaluated arginine,[8,15,17,22] three reviews evaluated glutamine,[9,10,17] two reviews evaluated histidine,[13,19] four reviews evaluated leucine,[7,8,11,17] three reviews evaluated lysine,[17,20,21] one review evaluated methionine,[14] and four reviews evaluated tryptophan.[8,12,16,17] Two reviews had information about multiple amino acids.[8,17]

Outcome assessment

Total Protein Reviews

Three reviews mentioned or discussed acute adverse effects occurring as a result of high protein intake and three reviews discussed instances of high protein intake without adverse effects.

Adverse effects

1. One SR reported suppressed appetite with high protein intake (dosage/duration of intervention not reported).[6]
2. Another SR reported changes in urinary biomarkers (increased urinary calcium and decreased urinary pH) with 27 g per day of whey protein for 3 days.[5]
3. The same SR reported exacerbation of acne lesions when consuming a high level of protein for 60 days.[5]
4. A narrative review provided a general list of possible adverse effects of high protein intake (no duration or dosage information provided): intestinal discomfort, hyperaminoacidemia, hyperammonemia, hyperinsulinemia, dehydration, irritation, nausea, diarrhea, liver and kidney injuries, fatigue, headache, seizures, high risk of cardiovascular disease, or even death.[3]

No adverse effects

1. One narrative review reported no harmful effects (including changes in blood parameters and clinical side effects) with protein intake of 3.0-4.4 g/kg/d over 8 weeks in healthy resistance-trained adults.[1]

2. Another narrative review noted that there have been no previously reported adverse effects of protein intake above the RDA (within the AMDR).[2]
3. One SR reported no pattern of abnormality among blood variables or blood pressure in studies with protein intake under 35% of total energy intake.[4] One study compared intake of 0.8 g/kg to 3.6 g/kg in a 12-week crossover and found significantly increased blood urea nitrogen concentrations. Another study found changes in a number of renal lab values with 1 week of high protein, but the clinical significance was unclear and not viewed as ‘adverse’.

Amino Acid Reviews

Fourteen reviews mentioned or discussed acute adverse effects occurring as a result of high amino acid intake and 3 reviews discussed instances of high protein intake without adverse effects. Some reviews discussed both instances of adverse effects and instances without any serious effects.

Adverse effects

1. Nausea/vomiting/GI discomfort
    - Varying high doses of leucine in an unspecified duration[7]
    - At above 7.5 g of tryptophan in an unspecified duration[12]
    - Varying high doses of lysine in an unspecified duration[20,21]
    - At 24-64 g of histidine per day for 4 weeks[19]
2. Change in biomarkers (e.g., markers of liver function, blood ammonia, serum urea nitrogen)
    - Varying high doses of leucine in an unspecified duration[7]
    - Varied high doses of leucine per day (single day)[11]
    - Varying high doses of leucine, tryptophan, and arginine in an unspecified duration[8]
    - At 0.5g/kg/day of glutamine over 14 days[9]
    - Varying high doses of glutamine in an unspecified duration[10]
    - At 6 g/d of lysine for 14 days[21]
    - Varying high doses of histidine in an unspecified duration[13]
    - At 4-16 g histidine per day for 4 weeks[19]
    - Varying high doses of methionine in an unspecified duration[14]
3. Headache
    - At 4-16 g histidine per day for 4 weeks[19]
    - At 4.8 g lysine per day for 56 days[21]
    - At 1,500 mg of arginine per day for 17 days to 5,000 mg of arginine per day for 6 weeks[22]
4. Skin rash, dizziness
    - At 4.8 g lysine per day for 56 days[21]
5. Itching, insomnia

- At 1,500 mg of arginine per day for 17 days to 5,000 mg of arginine per day for 6 weeks[22]

6. Appetite change, mood changes, weakness, drowsiness, painful eyes, visual acuity, mental confusion, poor memory
    - At 24-64 g of histidine per day for 4 weeks[19]
7. Smell/taste change
    - At 65 mg of histidine per day for 24 days[19]
8. Eosinophilia-myalgia syndrome
    - 1989 incident involving high dose tryptophan[16]

No adverse effects

1. Acute or chronic doses of tryptophan ranging from 1-15 g per day had no effects of GI pain/discomfort, diarrhea, or constipation[12]
2. No reports of signs of toxicity or mutagenic activity in subjects treated with histidine (dose and duration not specified)[13]
3. Varying dosages of methionine in a crossover study (9.2-91 mg/kg/day for 2 weeks with 2-week washout) showed no signs of intolerance or changes in body composition at lowest observed adverse effect level[14]
4. In doses of arginine ranging from 3-42 g per day, no adverse effects were noted overall[15]
5. Several clinical studies were submitted to FDA for GRAS determination showing a lack of adverse effects[17]
6. Contaminated amino acid supplements have been shown to cause adverse effects but no peer-reviewed literature documents severe adverse reactions to an amino acid overdose, even in subgroups suspected of frequently consuming dietary supplements[17,18]

Considerations for future DRI work

As the DRI process moves forward at the guidance of the Working Group, the following may be important to consider as a result of this completed evidence scan:

1. This evidence scan found little evidence to support a systematic review on the acute adverse health effects resulting from high dietary protein intake. There were no reviews focused specifically on protein and adverse health effects, only a few select sentences or cited studies within the reviews.
2. A large proportion of the data extracted in this evidence scan came from narrative reviews. Although narrative reviews can help provide an overview of potentially relevant evidence, they involve less rigorous methodology compared to systematic reviews (including those with meta-analyses), which are considered the gold standard of evidence synthesis.
3. Since the previous edition of DRIs were published, more research has been completed on amino acid intake. However, much of this research was conducted in animals or was focused on chronic health outcomes. Further exploration of amino acid intake, especially supplementation of high doses, is needed to inform potential future UL values.

Table 1-b. Evidence examining the relationship between high protein intake and acute adverse health effects [a]

Author, Year and Review Type	Purpose of review or research question	Life Stage (Population studied)	High protein intake without adverse effects	Adverse effects noted as a result of high protein intake
Ben-Harchache, 2021[6] Systematic review and meta-analysis	Aimed to determine the effects of protein supplementation on appetite and/or energy intake in healthy older adults.	Older adults, 60+ y	N/A	• Appetite change (In acute studies (n = 8), appetite ratings were suppressed in 7 out of 24 protein arms) • Intervention varied and duration/dosing were not specified)
Jager, 2017[1] Narrative review	An updated position stand addressing the most important dietary protein categories that affect physically active individuals across domains such as exercise performance, body composition, protein timing, recommended intakes, protein sources and quality, and the preparation methods of various proteins.	Adults, 19-59 y	• No harmful effects at ~3.4–4.4 g/kg/day (duration NR) • No harmful effects at 4.4 g/kg/day over 8 weeks in healthy resistance trained individuals • No changes in any assessed blood parameters at 3.4 g/kg/day over 8 weeks while following a prescribed resistance training program • No clinical side effects or body composition changes at >3.0 g/kg/day over 8 weeks.	N/A

Author, Year and Review Type	Purpose of review or research question	Life Stage (Population studied)	High protein intake without adverse effects	Adverse effects noted as a result of high protein intake
Van Elswyk, 2018[4] Systematic review	To examine published literature investigating the relation of protein intake and indicators of kidney function in healthy adults, with the purpose of understanding if levels of intake above the currently established US RDA of 0.8 g/kg body weight, but within the AMDR, are consistent with normal kidney health and function	Adults, 19-59 y Older adults, 60+ y	• Evidence reported suggests that protein intake above the US RDA has no adverse effect on blood pressure. • In studies with protein intake of up to 1.8–2.5 g/kg daily, no pattern of abnormality among blood variables, suggestive of adverse effects of increased protein intake, was observed. • One exception was in a study of 5 young men participating in a 12-week crossover study comparing “low” (0.8 g/kg), “moderate” (1.8 g/kg), and “high” (3.6 g/kg) protein intake. In this study, protein intake of 3.6 g/kg significantly increased blood urea nitrogen concentrations beyond the UL of the normal range. • A one week crossover study with “high-protein" diet in healthy young men induces significant changes in the GFR, the filtration fraction, albuminuria, serum uric acid, and urinary pH values, whereas other indicators of renal function remained unchanged. • The clinical significance of these findings is unclear and all studies in this review had protein intake of under 35% total energy intake.	N/A

Author, Year and Review Type	Purpose of review or research question	Life Stage (Population studied)	High protein intake without adverse effects	Adverse effects noted as a result of high protein intake
Vasconcelos, 2021[5] Systematic Review	To find documents dealing with harmful and/or adverse and/or deleterious effects of whey protein supplementation on animals and/or humans (only human studies were extracted)	Adults, 19-59 y Older adults, 60+ y	N/A	• Change in biomarkers (27 g/d of whey protein alone for 3 days) • Exacerbation of acne lesions (dose not specified, high protein intake for 60 days)
Wolfe, 2017[2] Narrative Review	The discussion in this review describes limitations to the derivation and practical application of the RDA compared with the use of the AMDR to help maximize health benefits associated with higher protein intake by using flexible calories inherent in different dietary patterns.	Adults, 19-59 y Older adults, 60+ y	• To the knowledge of the review authors, there has never been a study in which the RDA for protein intake was compared with a higher level of protein intake, and the RDA was found to be superior in terms of any endpoint • In contrast to the scenario of increasing either the fat or carbohydrate portion of the diet to satisfy the total requirement for energy intake, consumption of dietary protein in excess of the RDA but within the AMDR guidelines is not known to cause adverse responses. There have been no reported adverse effects of protein intake above the RDA	N/A

Author, Year and Review Type	Purpose of review or research question	Life Stage (Population studied)	High protein intake without adverse effects	Adverse effects noted as a result of high protein intake
Wu, 2016[3] Narrative review	To highlight historic studies of dietary protein intake by humans and recent issues concerning the effects of protein nutrition on health, particularly the preservation of skeletal-muscle mass and function in adults.	NR/Unclear	N/A	• This review provided a general list of potential adverse effects of protein intake (duration of exposure not provided) • Intestinal discomfort, hyperaminoacidemia, hyperammonemia, hyperinsulinemia, dehydration, irritation, nausea, diarrhea, liver and kidney injuries, fatigue, headache, seizures, high risk of cardiovascular disease, or even death

[a] Abbreviations: AMDR: Acceptable Macronutrient Distribution Range; g; gram(s); GFR: glomerular filtration rate; kg: kilogram(s); N/A: not applicable or not available; NR: not reported; RDA: Recommended Dietary Allowance; UL: Tolerable Upper Limit; y: year(s)

Table 1-c. Evidence examining the relationship between high amino acid intake and acute adverse health effects[a]

Author, Year and Review Type	Amino Acid(s) studied	Purpose of review	Life Stage (Population studied)	High amino acid intake without adverse effects	Adverse effects noted as a result of high amino acid intake
Borack, 2016[7] Narrative Review	Leucine	To describe the efficacy and safety of leucine supplementation in the elderly.	Adults, 19-59 y	N/A	• Nausea/Vomiting/GI discomfort (Varying dosages, duration NR) • Change in biomarkers (Varying dosages, duration NR) • Note - although focus on review was the elderly, evidence in humans regarding acute effects was in healthy young men)
Cynober, 2016[8] Narrative Review	Leucine Tryptophan Arginine	This conference workshop supplement paper proposes a no observed adverse effect level for diet-added arginine (30 g/day) and diet-added tryptophan (4.5 g/day) in young adults and an upper limit of safe intake for total dietary leucine (500 mg/kg/day) in elderly adults.	Adults, 19-59 y Older adults, 60+ y	N/A	Change in biomarkers (dose of amino acids and duration varied)
Davani-Davari, 2019[9] Narrative Review	Glutamine	To review the available experimental and clinical data on the renal safety of several amino acids (carnitine, arginine, glutamine) used by athletes and bodybuilders.	Adults, 19-59 y Older adults, 60+ y	N/A	Change in biomarkers (0.5 g/kg/day over 14 days)

Author, Year and Review Type	Amino Acid(s) studied	Purpose of review	Life Stage (Population studied)	High amino acid intake without adverse effects	Adverse effects noted as a result of high amino acid intake
Durante, 2019[10] Narrative Review	Glutamine	This review describes the metabolism and function of glutamine in cardiovascular physiology and pathology, and highlights potential therapeutic approaches targeting glutamine in cardiovascular disease.	NR/Unclear	N/A	Change in biomarkers (dose of amino acids and duration varied)
Elango, 2016[11] Narrative Review	Leucine	To describe 2 current studies to determine the UL for leucine in young and elderly men	Adults, 19-59 y Older adults, 60+ y	N/A	Biomarkers change (varied doses of 50, 150, 250, 500, 750, 1000, 1250 mg per kg per day/single day)
Fernstrom, 2016[12] Narrative Review	Tryptophan	To examine pathways of tryptophan metabolism and their effects on target body functions.	Adults, 19-59 y Older adults, 60+ y	• No effects of acute/chronic intake of tryptophan in doses of 1-15 g on GI pain/discomfort, diarrhea, or constipation • The relatively modest increase in melatonin production and secretion that accompanies tryptophan supplementation would also be expected to be safe as a result of high oral doses of melatonin supplementation that has been shown to be safe. • Serotonin-related effects on gut function appear to be minor or absent after tryptophan ingestion, at doses that can be quite high in relation to normal daily tryptophan ingestion in dietary protein	Nausea/vomiting/GI discomfort (at above 7.5 g tryptophan/dose, duration not reported)

Author, Year and Review Type	Amino Acid(s) studied	Purpose of review	Life Stage (Population studied)	High amino acid intake without adverse effects	Adverse effects noted as a result of high amino acid intake
Hayamizu, 2019[20] Meta-analysis	Lysine	To evaluate the safety of oral ingestion of lysine	Adolescents, 13-18 y Adults, 19-59 y Older adults, 60+ y	N/A	Change in bowel habits and nausea/vomiting/GI discomfort (varied doses and durations across studies)
Hayamizu, 2020[21] Meta-analysis	Lysine	To assess clinical safety of lysine supplementation.	Adolescents, 13-18 y Adults, 19-59 y Older adults, 60+ y	N/A	• Bowel habits change and nausea/vomiting/GI discomfort (dosage and duration varied) • Change in biomarkers (6 g lysine/d/14d) • Skin rash, dizziness, headache (4.8 g lysine/day/56 days)
Holecek, 2020[13] Narrative Review	Histidine	To review histidine metabolism and the results of studies examining the benefits and therapeutic potential of histidine.	Adults, 19-59 y	N/A	• Change in biomarkers (dosing of histidine supplementation and duration NR) • Although some adverse effects appear to be reported, paper states that there are no reports of signs of toxicity or mutagenic activity in subjects treated with histidine.
Ligthart-Melis, 2020[14] Narrative Review	Methionine	This narrative review discusses the importance and potentially harmful effects of Methionine supplementation from clinical studies performed in humans over the past 20 years.	Adults, 19-59 y Older adults, 60+ y	No signs of intolerance or changes in body composition at lowest observed adverse effect level in healthy older adults after consuming varied doses of Met supplements; dosages were 9.2, 22.5, 46.3, and 91 mg Met/kg/day for two weeks with 2-week washout periods between intakes (Deutz).	Change in biomarkers (Dosage and duration varied)

Author, Year and Review Type	Amino Acid(s) studied	Purpose of review	Life Stage (Population studied)	High amino acid intake without adverse effects	Adverse effects noted as a result of high amino acid intake
McNeal, 2016[15] Narrative Review	Arginine	The purpose of this review is to summarize the current knowledge with regard to the safety of Arg, especially noting data from recent studies in animals and humans pertinent to the effects of Arg on adipose tissue and the metabolic derangements associated with adiposity.	Adults, 19-59 y Older adults, 60+ y	• Doses of Arg range from 3-42 g/day • In a previous review, studies included had some populations exclusively with chronic conditions, but no adverse effects were noted overall (Shao and Hathcock). There is an absence of any pattern in the adverse effects that are attributable to Arg, and therefore the literature demonstrates a substantial level of safety for supplemental Arg. • The current review did evaluate adverse effects in other studies, but those 8 weeks or shorter had only participants with chronic conditions (T2D, eclampsia)	N/A
Oketch-Rabah, 2016[16] Narrative Review	Tryptophan	Examines 2 amino acids that have been associated with in-market adverse events to show how quality specifications might have helped prevent the adverse clinical outcomes.	NR/Unclear	N/A	Mentioned incident in 1989 involving tryptophan and eosinophilia-myalgia syndrome

Author, Year and Review Type	Amino Acid(s) studied	Purpose of review	Life Stage (Population studied)	High amino acid intake without adverse effects	Adverse effects noted as a result of high amino acid intake
Rhim, 2019[22] Meta-analysis	Arginine	To evaluate the potential role of arginine/citrulline alone or arginine combined with other supplements in erectile dysfunction of mild to moderate severity.	Adults, 19-59 y Older adults, 60+ y	N/A	The adverse effects included headache, itching, and insomnia, and no severe adverse effect was observed. However, these arginine supplements were in some cases given in combination with other supplements. (1500 mg/day/17 days; 5000 mg/day/4 weeks; 5000 mg/day/6 weeks) Arginine alone had even fewer adverse effects
Roberts, 2016[17] Narrative Review	Leucine Lysine Tryptophan Arginine Glutamine	This conference workshop supplement paper discusses the safety and regulatory process of long-term amino acid supplementation in Europe and the United States; it highlights the need for human studies as opposed to classical animal toxicological studies.	NR/Unclear	Review mentions several clinical studies that were submitted to FDA for GRAS determination showing a lack of adverse effects.	Review mentioned one article that found "adverse events" resulting from consumption of L-tryptophan contaminated with 1,1'-ethylene-bis (tryptophan) but did not discuss duration.
Smriga, 2020[18] Narrative Review	Amino acids	In International regulation of AAs argue that controlling the standards of purity and ingredient quality are the key safety issues	NR/Unclear	While there have been adverse effects triggered by contaminated amino acid supplements, no peer-reviewed literature documents severe adverse reactions to an amino acid supplement overdose, even in subgroups suspected of frequently consuming dietary supplements	N/A

Author, Year and Review Type	Amino Acid(s) studied	Purpose of review	Life Stage (Population studied)	High amino acid intake without adverse effects	Adverse effects noted as a result of high amino acid intake
Thalacker-Mercer, 2020[19] Narrative Review	Histidine	To examine existing research on the benefits of histidine intake, adverse effects of excess histidine, and upper tolerance level for histidine.	Adults, 19-59 y	N/A	• Appetite change, GI discomfort/nausea/vomiting, mood changes, headache, weakness, drowsiness, painful eyes, visual acuity, mental confusion, poor memory (24-64 g histidine/day for 4 wks) • Smell/taste change (65 g histidine/day for 24 days) • Change in biomarkers (varied doses 4-16 g histidine/day for 4 wks)

[a] Abbreviations: AA: Amino acid; Arg: Arginine; FDA: Food and Drug Administration; g: gram(s); GI: Gastrointestinal; GRAS: Generally recognized as safe; kg: kilogram(s); mg: milligram(s); N/A: not available or not applicable; NR: Not reported; T2D: Type 2 Diabetes; UL: Tolerable Upper Limit; wks: weeks; y: year(s)

Chapter 2 – Protein intake and chronic disease risk

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Specific methods to conduct this evidence scan

Develop a protocol

The research question, "What is the relationship between protein intake and chronic disease risk?", was explored using an evidence scan.

The analytic framework for the evidence scan examining the relationship between dietary protein intake and risk of chronic disease is presented in **Figure 2-a**. The analytic framework visually represents the overall scope of the evidence scan question and depicts the contributing elements that were considered. The intervention or exposure of interest was total protein intake from foods, beverages, and dietary supplements. The comparator was consumption of different levels of total protein intake or no comparator. The outcomes were chronic disease outcomes, including: bone outcomes, sarcopenia, renal outcomes, risk of cardiovascular disease (CVD), risk of diabetes, growth/size/body composition, neurocognitive development, dementia/cognitive decline, and all-cause mortality (ACM). General outcomes were listed in the analytic framework but were not limited to this list. There were no key confounders noted due to the limited data extraction completed in evidence scans.

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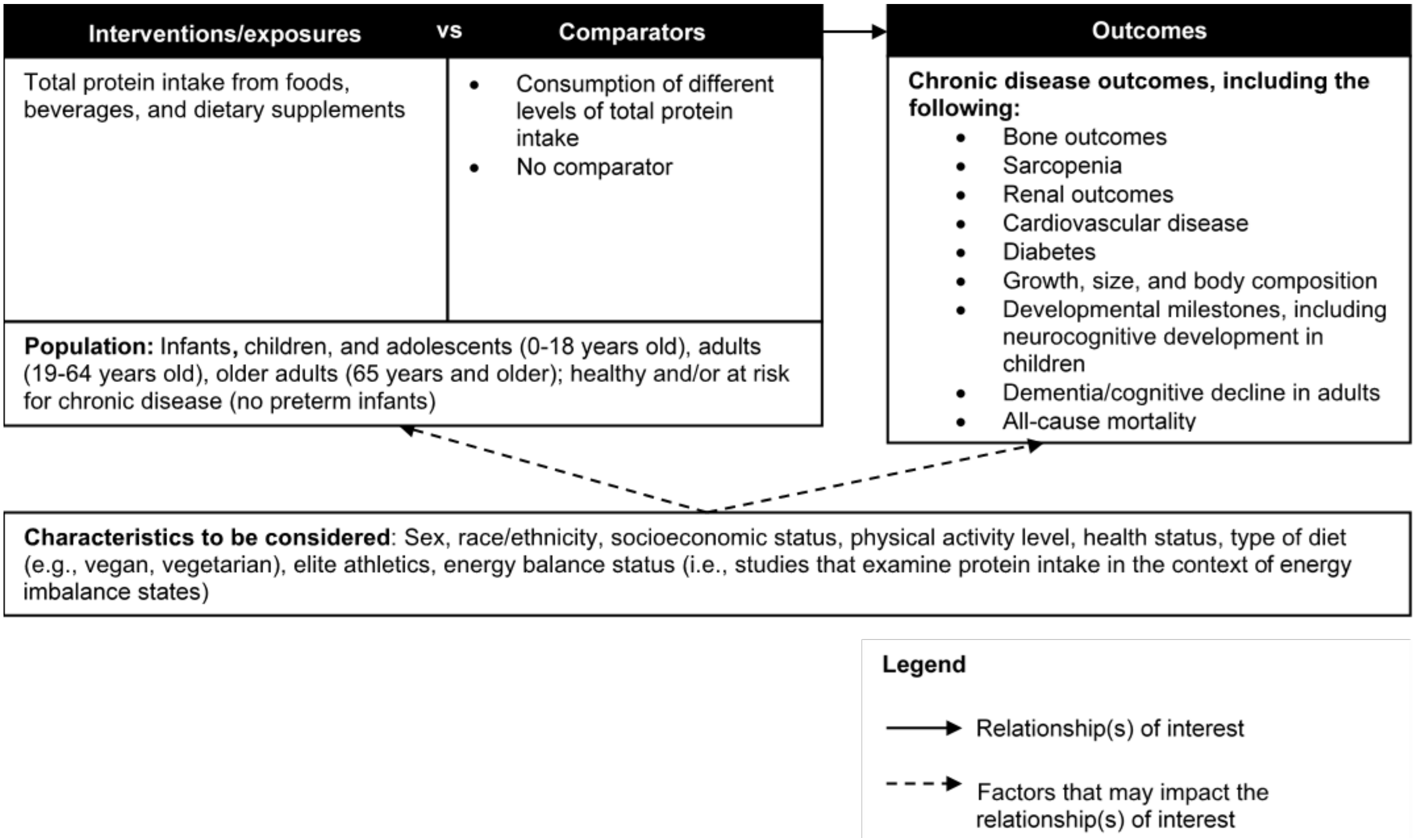
[a] Lead for protein intake and chronic disease risk evidence scan and project lead (Chapters 2 and 3), NESR team, NGAD, CNPP, FNS, USDA,

[b] Analyst, NESR team; Panum Group, under contract with the FNS, USDA,

[c] Librarian, NESR team; Panum Group, under contract with the FNS, USDA

Figure 2-a. Analytic framework for protein intake and chronic disease risk



Search for and select studies

NESR analysts worked with the Working Group to finalize the inclusion and exclusion criteria and the literature search strategy, which are detailed in **Table 2-a** and **Appendix 2-a,** respectively. The study designs of interest for this specific scan included SRs, MAs, scoping reviews and umbrella reviews in order to streamline the literature search. Supplemental searches were completed to evaluate protein intake and length of sleep (search strategy detailed in **Appendix 2-b**), as well as protein intake and appetite/satiety (search strategy detailed in **Appendix 2-c**). Articles were screened by two NESR analysts independently for inclusion based on these pre-determined criteria and disagreements were reconciled by a third analyst. The DRI Protein WG desired information on the number articles that evaluated animal and/or protein intake. A bibliography of articles that evaluated protein intake from animal or plant sources but were excluded because analysis did not include an assessment of total protein intake is found in **Appendix 2-d.**

Table 2-a. Inclusion and exclusion criteria for protein intake and chronic disease risk

Category	Inclusion Criteria	Exclusion Criteria
Study design	• Systematic reviews • Meta-analyses • Scoping reviews • Umbrella reviews	• Narrative reviews • Systematic reviews or meta-analyses that exclusively include cross-sectional and/or uncontrolled studies • All other study designs
Intervention/ exposure	• Total dietary protein intake from food, beverages, and dietary supplements	• Studies that do not specify the amount of protein intake (e.g., studies that only report type of protein or source of protein) • Studies that assess %AMDR, but do not describe the entire macronutrient distribution of the diet (i.e., studies that only examine a single macronutrient in relation to outcomes) • Studies that **only** assess protein intake via infusions (rather than the GI tract) • Studies that examine food products or dietary supplements not widely available to U.S. consumers • Multi-component interventions that do not isolate the effect or association of protein (including protein and exercise combinations)
Comparator	• Consumption of different levels of total dietary protein intake • No comparator	• Co-exposures (i.e., same protein intake level or source, but varying supplementation or physical activity)

Chronic Disease Risk Outcomes	• Bone outcomes: ○ Osteoporosis ○ Osteopenia ○ Fracture ○ Bone mass including bone mineral density, bone mineral content • Sarcopenia • Renal outcomes: ○ Incidence of kidney stones or ureteral stones ○ Incidence of chronic kidney disease, renal insufficiency • Incidence of cardiovascular disease ○ Blood pressure ○ Hypertension • Diabetes ○ Incidence of type 2 diabetes ○ Incidence of gestational diabetes ○ HbA1C, glucose tolerance (not post-prandial measures) • Growth, size, and body composition ○ Weight, weight-for-age, weight-for-gestational age ○ Length or height, length/stature-for-age ○ BMI, BMI z-score, weight-for-length ○ Body circumferences (e.g., head, arm, waist, thigh, neck) ○ Body composition and distribution (e.g., % fat mass, fat-free mass, skinfold thickness, DEXA, BEI, MRI) ○ Gestational weight change, postpartum weight change ○ Incidence and prevalence of: ▪ Underweight, failure to thrive, stunting, and wasting ▪ Healthy weight ▪ Rapid infant weight gain ▪ Infant macrosomia ▪ Overweight ▪ Obesity • Developmental milestones, including neurocognitive development (i.e., examined via milestone achievement and/or scales/indices) in children • Dementia/cognitive decline in adults	• Incidence of type 1 diabetes, prediabetes, insulin levels, post-prandial assessments

Category	Inclusion Criteria	Exclusion Criteria

	• All-cause mortality
	• Additional factors considered
	  • Appetite and satiety
	  • Sleep duration	

Publication date	• Review Papers
	  ○ 2016 to present
	• *Primary Research (only if no relevant review papers are identified)*
	  ○ *2002 to present*
		• Review Papers
		  ○ Prior to 2016
		• *Primary Research*
		  ○ *Prior to 2002*

Publication status	• Articles published in peer-reviewed journals	• Articles that have not been peer reviewed and are not published in peer-reviewed journals (e.g., unpublished data, manuscripts, pre-prints, reports, abstracts, conference proceedings)
Language	• Articles published in English	• Articles published in languages other than English
Country[a]	• Studies conducted in high or very high human development countries	• Studies conducted in low or medium human development countries

Study participants	• Human participants
	  ○ Males
	  ○ Females
		• Non-human participants (e.g., animal studies, in-vitro models)

Age of study participants	• Age at intervention or exposure:
	  ○ Infants, children, and adolescents (0-18 years)
	  ○ Adults (19-64 years)
	  ○ Older adults (65 years and older)
		N/A

[a] The Human Development classification was based on the Human Development Index (HDI) ranking from the year the study intervention occurred or data were collected. If the study did not report the year in which the intervention occurred or data were collected, the HDI classification for the year of publication was applied. HDI values are available from 1980, and then from 1990 to present. If a study was conducted prior to 1990, the HDI classification from 1990 was applied. When a country was not included in the HDI ranking, the current country classification from the World Bank is used instead.

Category	Inclusion Criteria	Exclusion Criteria
Health status of study participants	• Studies that enroll participants who are healthy and/or at risk for chronic disease, including those with obesity and/or sarcopenia • Studies that enroll **some** participants diagnosed with a disease or hospitalized or in a long-term care facility with an illness or injury • Studies that enroll **some** participants diagnosed with a disease or with the health outcome of interest • Studies that exclusively recruit athletes and/or highly active individuals	• Studies that *exclusively* enroll participants diagnosed with a disease or hospitalized or in a long-term care facility with an illness or injury (for this criterion, studies that exclusively enroll participants with obesity will not be excluded) • Studies that aim to treat participants who have already been diagnosed with the outcome of interest (except weight loss interventions in overweight or obese subjects and studies in subjects with sarcopenia) • Studies that exclusively enroll undernourished participants • Studies that exclusively enroll participants with a baseline diet deficient in protein • Studies that exclusively enroll pre-term infants. • Studies that exclusively enroll post-bariatric surgery subjects

Extract data

NESR analysts extracted data from each included review to objectively describe the body of evidence available in the last 5 years about protein intake and risk of chronic disease. Data extraction was completed in DistillerSR by one analyst for each review and a second analyst checked the extracted data for accuracy. The following data elements were extracted from each included review:

- Publication author and publication year
- Study design
- Purpose of review or research question answered by the review
- Population studied (life stage/age group)
- Intervention/exposure and comparator
- Outcomes examined in the review
- Direction of the relationship between the intervention/exposure and outcome (inverse, positive, null)

No effect estimates or measures of statistical validity were extracted from the included reviews.

Describe the evidence

NESR analysts summarized the volume and characteristics of included studies to inform the following question:

- **What is the relationship between dietary protein intake and risk of chronic disease?**

The extracted data were summarized in written form, as well as presented visually in a table. The extracted information helped analysts and the Working Group understand the following:

- The volume and characteristics of research examining the levels of protein intake (total protein and amino acids) associated with increased chronic disease risk
- Which chronic disease outcomes occur as a result of total protein intake

Quality and duplication assessment

The Working Group reviewed results from the evidence scans conducted as described above and identified the following outcomes as warranting further investigation: ACM, bone health, CVD, diabetes, renal health and sarcopenia. For each identified study within these topic areas, NESR analysts conducted a formal assessment to evaluate the methodological quality of the review, noted the source of funding, and conducted a duplication assessment to identify the number of unique studies within the body of evidence. The following topics were excluded from further evaluation due to insufficient evidence (dementia/cognitive decline; neurocognitive development) or were considered beyond the scope of chronic disease (growth, size, and body composition). Below is a brief description of each assessment.

AMSTAR 2 assessment and documentation of funding source

NESR analysts conducted a dual, independent assessment for each review using AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews),[a] a 16-item critical appraisal tool for assessing the quality of SRs that include randomized and/or non-randomized studies. Critical domains were defined *a priori* based on the needs of the Working Group. Responses were compared, and any disagreements were discussed and reconciled. To address the potential for conflict of interest and bias, NESR analysts also noted the funding source of each included review.

Duplication assessment

NESR analysts identified the component studies within each review that addressed specific outcomes, constructing tables to illustrate citation overlap across the body of evidence and identified the number of unique studies included within the identified reviews for each topic area.

Considerations for future DRI work

Considerations for future SRs completed to inform the DRI process across chronic disease outcomes were were included in this evidence scan.

Results

Literature search and screening results

The chronic disease risk literature search yielded 3,850 search results (see **Figure 2-b**). Dual-screening resulted in the exclusion of 3,397 titles, 270 abstracts, and 138 full-text articles. Reasons for full-text exclusion are in **Appendix 2-e**. The body of evidence included 45 reviews and meta-analyses:

- 3 reviews provided evidence on ACM
- 7 reviews provided evidence on bone health
- 10 reviews provided evidence on CVD risk
- 2 reviews provided evidence on dementia/cognitive decline (adults)

[a] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008. Published 2017 Sep 21. doi:10.1136/bmj.j4008

- 6 reviews provided evidence on diabetes risk
- 17 reviews provided evidence on growth, size, and body composition
- 0 reviews provided evidence on neurocognitive development (children)
- 2 reviews provided evidence on renal health
- 5 reviews provided evidence on sarcopenia

Separate literature searches were conducted for sleep duration and appetite/satiety. The sleep duration literature search yielded 74 search results and dual-screening resulted in the exclusion of 64 titles, 3 abstract and 7 full-text; no reviews met inclusion criteria for sleep duration (see **Figure 2-c**). Reasons for full-text exclusion are in **Appendix 2-f**. The appetite and satiety literature search identified 87 search results (see **Figure 2-d**) and dual-screening resulted in exclusion of 41 titles, 28 abstracts and 14 full-text articles; four SRs met inclusion criteria for appetite and satiety. Reasons for full-text exclusion are in **Appendix 2-g**.

Figure 2-b. Literature search and screen flowchart for total dietary protein intake and chronic disease risk

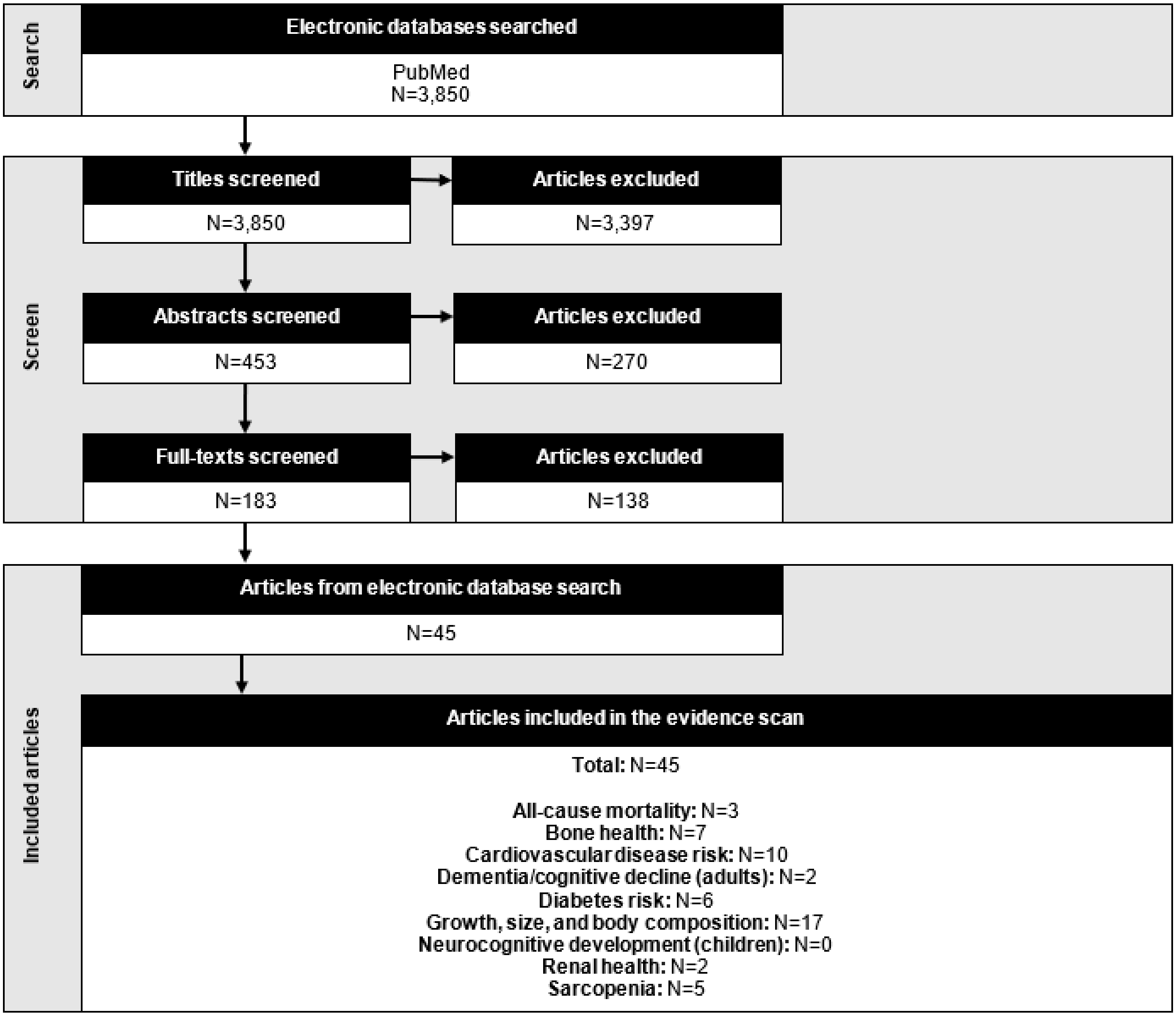


Figure 2-c. Literature search and screen flowchart for protein intake and sleep duration

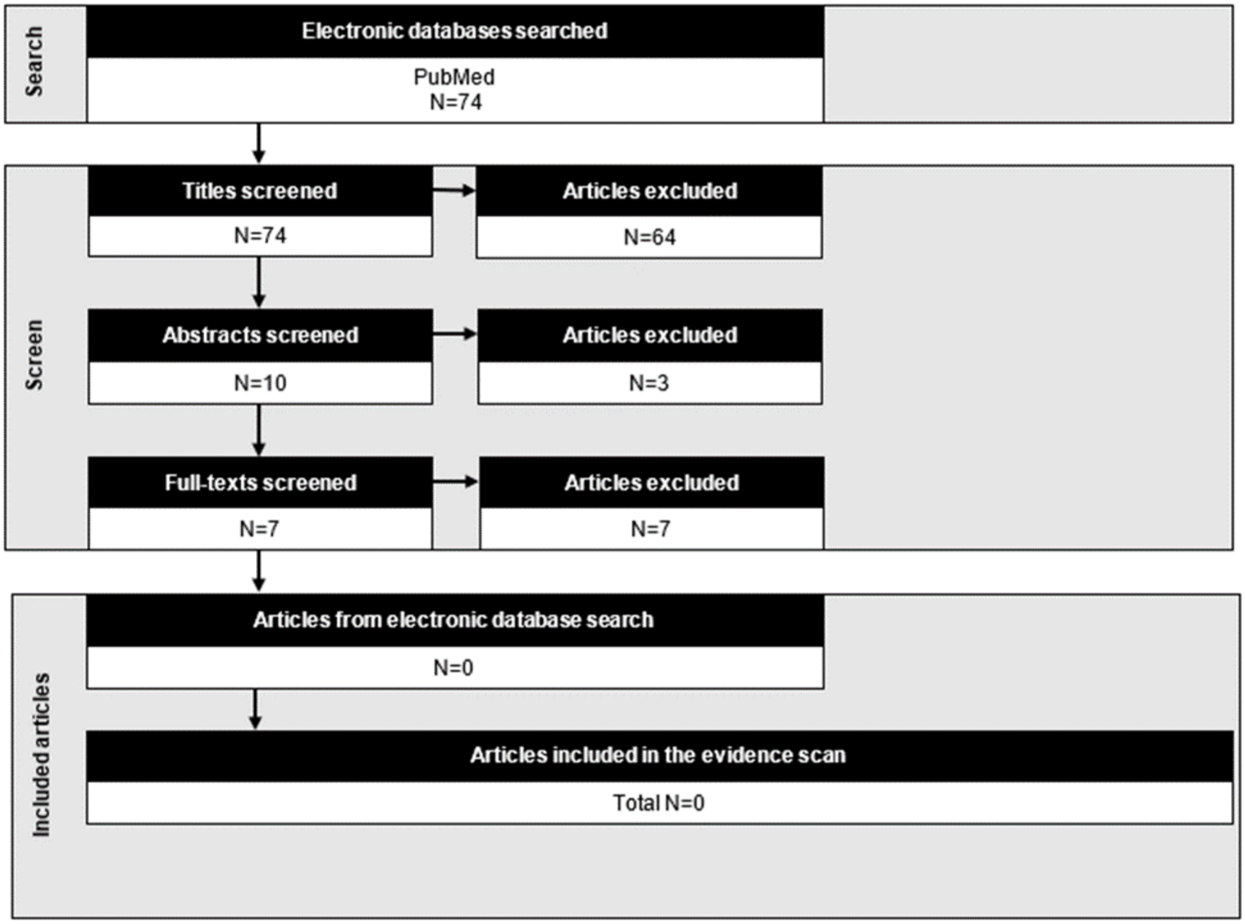
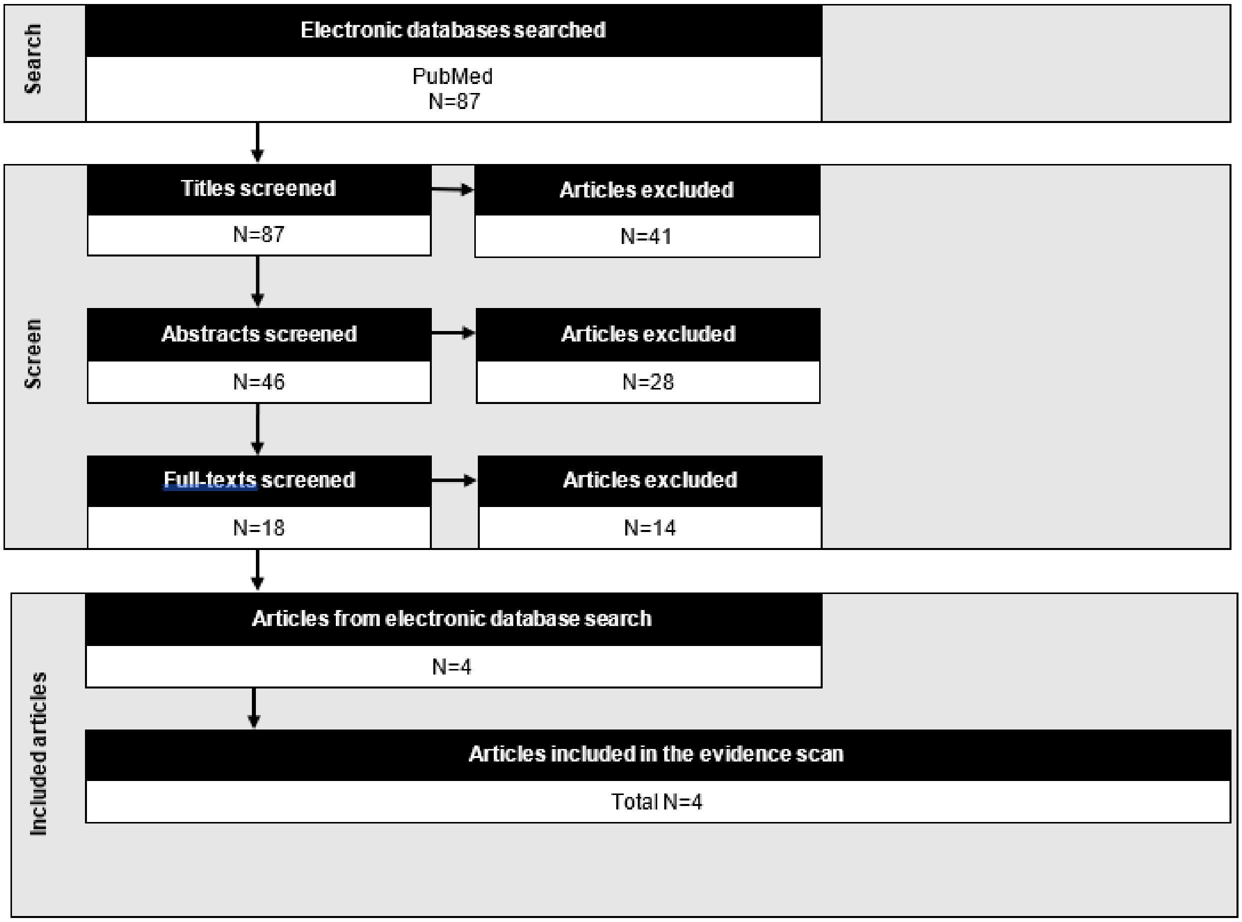


Figure 2-d. Literature search and screen flowchart for protein intake and appetite/satiety



Description of the evidence

All-cause mortality

Three SRs examined the relationship between protein intake and ACM risk.[23-25] **Table 2-b** shows the full extraction table with population, intervention/exposure, and outcome data for SRs reporting on the all-cause mortality outcome.

Review and population characteristics

All three SRs on ACM risk were conducted with MA. The number of included studies within each SR ranged from 8[23] to 29 studies.[24] All three articles included only prospective cohort studies (PCSs). There was considerable overlap of included studies between the three reviews with 31 unique studies (**Appendix 2-i**). Adults were studied in the three articles, with two reviews also including older adults.[23,25] The AMSTAR 2 ratings for the included SRs were moderate[23,25] and low[24] (**Appendix 2-h**).

Intervention/exposure characteristics

All the included studies in the three reviews evaluated habitual protein intake as the exposure (one continuously,[25] one categorically,[23] and one with both[24]). Follow-up varied across these observational studies ranging from 3.4 years to 27 years.

Outcome characteristics and trends

All three reviews and meta-analyses evaluated ACM as an outcome alongside other cause-specific outcomes. For ACM, effect estimates were broken down according to the following exposures: total protein intake, plant protein intake, and animal protein intake. There were mixed results (inconsistent) found for the relationship between total protein intake and ACM risk. Two reviews found null associations between animal protein intake and ACM risk[24,25] and one with a positive relationship.[23] All three reviews found an inverse relationship between plant protein intake and ACM (increased intake of plant protein was associated with lower ACM risk).

Bone health

Seven SRs examined the relationship between protein intake and bone outcomes.[26-32] **Table 2-c** shows the full extraction table with population, intervention/exposure, and outcome data for systematic reviews reporting on bone outcomes.

Review and population characteristics

Of the seven SRs on bone outcomes, five were conducted with MA[27-29,31,32] and two were conducted without MA.[26,30] The number of included studies within each SR primarily ranged from 13 studies with relevant outcomes[28] to 34 studies with relevant outcomes.[32] However, one review included 103 studies with relevant outcomes (many of which were cross-sectional studies).[27] Most reviews had considerable overlap in studies that provided data on relevant outcomes, with 149 unique articles represented in total (**Appendix 2-j**). Of these, 124 reported on bone mass (bone mineral density [BMD] and/or bone mineral content [BMC]), 25 reported on fracture, and 6 reported on osteoporosis/osteopenia. Older adults were studied in all seven SRs and adults were studied in six SRs.[27-32] Children and adolescents, 2 to 18 years old, were studied in one SR.[27] The population of one SR focused on participants with overweight or obesity.[32] The AMSTAR 2 ratings for the included SRs were moderate,[28] low,[27,29,32] and critically low[26,30,31] (**Appendix 2-h**).

Intervention/exposure characteristics

All reviews on bone health included interventions that altered protein intake and six reviews included studies that assessed habitual protein intake (reported continuously and categorically).[26-31] The included studies of one SR also had a primary focus on interventions designed to induce weight loss and interventions that were multi-component (but isolated the effect of total protein).[32] The duration of interventions varied across the studies in the reviews, ranging from 4 days to 2 years. Similarly, the duration of follow-up for included observational studies varied across the reviews, ranging from no follow-up (cross-sectional studies) to 32 years.

Outcome characteristics and trends

All seven SRs examined outcomes related to bone mass, specifically BMD and BMC. The relationship between protein intake and bone mass varied across the reviews and by site examined, with positive, mixed, and null results reported. A variety of sites were examined within and across the reviews, such as hip, femoral neck, lumbar spine, and total body.

Five SRs examined fractures as an outcome.[26-29,31] The review conclusions tended towards null and inverse (higher protein, lower risk) for hip fracture. For other fracture sites, such as the spine and the forearm, the review conclusions tended to be null, mixed, or inconclusive.

Finally, one SR assessed osteoporosis as an outcome, reporting mixed results.[27]

Cardiovascular disease risk

Ten SRs examined the relationship between protein intake and CVD outcomes.[23-25,33-39] **Table 2-d** shows the full extraction table with population, intervention/exposure, and outcome data for SRs reporting on CVD outcomes.

Review and population characteristics

Of the 10 included reviews, two were umbrella reviews[33,39] and 8 were SRs, 5 of which were conducted with MA.[23-25,34,36] Four reviews included only RCTs[33-35,39] and the other six included only PCSs.[23-25,36-38] The 2 umbrella reviews each had 6 meta-analyses of RCTs with 8 relevant unique studies due to considerable overlap, and the 8 SRs had 71 relevant unique studies with minimal overlap by outcome. (**Appendix 2-k**) One review included individuals during pregnancy,[37] one review included adults (age 19-59 years of age),[33] and the remaining reviews included adults and older adults.[23-25,34-36,38,39] The AMSTAR 2 ratings for the included SRs were high,[33,37,39] moderate,[23,25,34,38] low,[24,35] and critically low.[36] (**Appendix 2-h**)

Intervention/exposure characteristics

Of the four reviews evaluating trials, all evaluated interventions that altered protein intake.[33-35,39] Of the six reviews evaluating observational studies (PCS in all), the studies were evaluating habitual protein intake, both categorical and continuous.[23-25,36-38]

The four reviews containing only RCTs ranged in intervention duration from 0.8 months to 52 months in those studies that reported intervention duration.[33,34] Of the reviews including only PCSs, follow-up duration ranged from 2.3 years to 32 years in those reviews that reported follow-up duration.[23-25,36,38]

Outcome characteristics and trends

There were 4 categories of CVD outcomes within the 10 included reviews evaluating total protein intake and CVD risk. Five reviews evaluated blood pressure, including hypertension[33-35,38,39]; one review evaluated the protein intake of pregnant persons and the blood pressure of their offspring.[37] Cardiovascular disease mortality was detailed in three reviews.[23-25] One review evaluated stroke mortality[23] and one review evaluated stroke risk.[36] Finally, one review focused on protein intake and coronary heart disease risk.[38]

Of the five total reviews evaluating protein intake and blood pressure, results were mixed, including null and inverse results. In the review evaluating protein intake in pregnancy, there was a null association with offspring blood pressure. Total protein intake was not consistently associated with cardiovascular disease mortality. Null and positive associations with total protein and animal protein was observed with CVD mortality; null and inverse associations were observed with plant protein. Both reviews evaluating stroke related outcomes found null associations, as did the review evaluating coronary heart disease risk.

Dementia/cognitive decline (adults)

Two SRs examined the relationship between protein intake and dementia/cognitive decline outcomes.[40,41] **Table 2-e** shows the full extraction table with population, intervention/exposure, and outcome data for SRs reporting on dementia/cognitive decline outcomes.

Review and population characteristics

Both SRs on dementia and cognitive decline outcomes were conducted without MA and primarily included cross-sectional studies: one review included eight cross-sectional studies and one PCS,[40] while the other review included five cross-sectional studies and two RCTs.[41] There was minimal overlap in studies included across the two reviews. The populations studied included adults and older adults in one review[41] and older adults alone in the other review.[40]

Intervention/exposure characteristics

Both reviews on dementia and cognitive decline outcomes assessed habitual intake or protein (reported continuously and categorically).[40,41] The observational studies that assessed habitual intake of protein were predominantly cross-sectional, but the one included PCS reported a follow-up duration of 8.5 months.[40] One SR assessed an intervention (3 weeks in duration) that altered protein intake.[41]

Outcome characteristics and trends

A variety of cognitive outcomes were assessed across the two reviews including: abstract reasoning, digit subtraction, fluid intelligence, global cognition/cognitive function, immediate and delayed learning ability, inhibition control, memory, nonverbal learning, problem-solving ability, processing speed, reaction time, risk of mild cognitive impairment, short-term memory, sustained attention, verbal fluency, verbal and nonverbal memory, and working memory.[40,41] Few studies within each review assessed the same aspect of cognition. One review reported predominantly null associations between protein intake and cognitive decline,[40] while the other review reported mixed results with some positive associations.[41]

Diabetes risk

Five SRs with MA,[42-46] and one umbrella review of MAs[33] examined the relationship between protein intake and risk of type 2 diabetes. **Table 2-f** shows the full extraction with population, intervention/exposure, outcome data and AMSTAR 2 rating for systematic and umbrella reviews reporting on diabetes outcomes.

Review and population characteristics

The 5 SRs with MA each included 6 to 9 PCSs, but there was significant overlap among included studies, with 12 unique studies in total across the reviews (see **Appendix 2-I**). The umbrella review included six meta-analyses of RCTs. All the SRs included adults and older adults, while the umbrella review reported subject age as greater than or equal to 18 years. The AMSTAR 2 ratings for the included SRs were high,[33] moderate,[42,43,45,46] and critically low[44] (**Appendix 2-h**).

Intervention/exposure characteristics

All SRs included interventions that assessed higher verses lower habitual intake reported categorically, and four also examined a continuous measure of habitual protein intake.[42,43,45,46] The one umbrella review examined meta-analyses which examined interventions that altered the quantity of protein intake.[33]

Outcome characteristics and trends

Five SRs with MA found total protein intake and animal protein intake was positively associated with type 2 diabetes. Results for plant protein intake and type 2 diabetes were inconsistent, with studies reporting null,[43] inverse,[42] or U-shaped curve associations[46] or results which differed by gender[44] or level of protein intake.[45]

The umbrella review which included six meta-analyses found higher compared to lower protein intake had a weak or null effect on Hemoglobin A1c (HbA1c).[33]

Growth, size, and body composition

Fifteen systematic reviews[47-61] and two umbrella reviews[33,62] examined the relationship between protein intake and outcomes related to growth, size, and body composition. **Table 2-g** summarizes the population, intervention/exposure, and outcome data for reviews reporting on protein intake and growth, size, and body composition.

Review and population characteristics

Of the 15 SRs, 11 were conducted with MA[47,49-53,56,58-61] and 4 were conducted without MA.[48,54,55,57] Most SRs included only RCTs,[47,49-53,56,58-61] two only included PCSs,[55,57] one included RCTs and PCSs,[48] and one included RCTs and non-randomized controlled trials (NRCTs).[54] The number of included studies within the systematic reviews ranged from two[60] to 66.[56] Of the two umbrella reviews, one included two systematic reviews[62] and one included seven meta-analyses.[33] Four reviews studied infant populations,[48,54,55,62] two of which also included toddlers 12-23 months and/or children 2-12 years.[48,55] Thirteen reviews studied adult populations,[33,47,49-53,56-61] 10 of which also included older adults.[33,47,50-53,56,58-60]

Intervention/exposure characteristics

Fifteen reviews included interventions that altered protein intake,[33,47-54,56-62] nine of which also included interventions designed to induce weight loss.[47,49-52,56,59-61] Two reviews included interventions with supplements designed to enhance athletic performance.[53,58] Three reviews assessed habitual intake (reported continuously and/or categorically).[48,55,57]

Outcome characteristics

Six reviews examined outcomes related to growth,[48,54,55,57,59,62] including weight gain,[48,54] gestational weight gain,[57] incidence or prevalence of overweight and/or obesity,[48,54,55,62] and weight loss maintenance.[59] The relationship between protein intake during the first 2 years of life and risk of overweight and/or obesity later in childhood was a mix of positive and null results.

Seven reviews examined outcomes related to size,[33,48,49,54,55,61] including weight/weight z-score,[33,49,54,61] length,[54] BMI/BMI z-score,[33,48,49,54,55,61,62] head circumference,[54] and waist circumference.[49,61] For protein intake and BMI/BMI z-score, reviews tended to show a positive relationship for infants and an inverse relationship in adults.

Thirteen reviews examined outcomes related to body composition,[47-56,58,60,61] including muscle mass,[50] muscle thickness,[58] lean mass,[47,51-53,56,58] fat-free mass or fat-free mass index,[54,55,60,61] fat mass or fat mass index,[47-50,52-55,58,61] body mass,[47] and body fat percentage.[55] For fat mass, reviews tended to be a mix of positive and null results for infants, and a mix of inverse and null results for adults. For fat-free mass, reviews tended to report null results in both infants and adults. For lean mass, reviews tended to be a mix of positive and null results for adults.

Neurocognitive development (children)

No reviews were found that met the inclusion/exclusion criteria for this outcome.

Renal health

Two SRs examined the relationship between protein intake and renal outcomes.[35,63] **Table 2-h** shows the full extraction table with population, intervention/exposure, and outcome data for SRs reporting on renal outcomes.

Review and population characteristics

Of the two SRs on renal outcomes, one was conducted with MA[63] while one was conducted without MA.[35] The SR with MA included 28 RCTs.[63] The SR without MA included 13 RCTs, 5 cross-sectional studies, and 2 PCSs with data relevant to the evidence scan's included outcomes.[35] There was some overlap in the included studies between the 2 reviews, with 41 unique articles with relevant outcome data represented in total (**Appendix 2-m**). The populations studied in both SRs were adults and older adults (19 years old and older). The AMSTAR 2 rating was moderate for one SR[63] and low for the other SR[35] (**Appendix 2-h**).

Intervention/exposure characteristics

Both SRs on renal outcomes assessed interventions that altered protein intake.[35,63] The SR that included observational studies also examined habitual intake of protein (measured and reported continuously and in categories).[35] The duration of included trials across reviews ranged from 1 day to 104 weeks,[35,63] while the time to follow-up of included observational studies ranged from no follow-up (cross-sectional studies) to 21 years.[35]

Outcome characteristics and trends

Both SRs examined glomerular filtration rate (GFR) or estimated GFR (eGFR).[35,63] While mixed results were reported, there was a tendency toward positive relationships between protein intake and GFR. One SR reported on kidney disease incidence and the reported association with protein intake was null; however, this outcome was assessed in only one of the review's included studies.[35]

Sarcopenia

Five SRs examined the relationship between protein intake and sarcopenia outcomes.[53,64-67] **Table 2-h** shows the full extraction table with population, intervention/exposure, and outcome data for SRs reporting on sarcopenia outcomes.

Review and population characteristics

Of the five SRs on total protein intake and sarcopenia outcomes, three were conducted with MA.[53,64,67] The majority of studies included in the five reviews are PCSs and RCTs, though a few cross-sectional, case-control, and NRCTs were included as well. Between the 3 outcome categories (muscle strength, muscle mass, and sarcopenia) there were 100 relevant articles found in each of the reviews with no overlap present (**Appendix 2-n**). All five reviews included studies with older adult participants with one review that also included adults age 19 to 59 years of age.[53] The AMSTAR 2 ratings for the included SRs were low[53,67] and critically low[64-66] (**Appendix 2-h**).

Intervention/exposure characteristics

Three reviews included studies assessing habitual intake (reported continuously and categorically),[64-66] three reviews included interventions that altered protein intake,[53,66,67] and one included multi-component interventions that isolated the effect of total protein.[53] Two reviews evaluating trials had intervention durations of 4.5 to 24 weeks[53] and 10 to 104 weeks.[67] The third review evaluating trials did not report intervention duration.[66] One review that evaluated observational studies had a follow-up range of up to 6 years.[65] The other two reviews that included observational studies did not report follow-up duration.[64,66]

Outcome characteristics and trends

For this evidence scan, sarcopenia itself was included as an outcome, as well as muscle mass and muscle strength outcomes that make up the definition of sarcopenia. Four reviews evaluated muscle strength outcomes,[64,66,67] four reviews evaluated muscle mass outcomes,[53,65-67] and one review evaluated sarcopenia overall.[66] There were all null results across reviews for upper-limb and lower-limb muscle strength[53,64,66,67] aside from a positive relationship in one review for handgrip strength (but only when combined with exercise in frail/sarcopenic populations).[67] Two reviews had trends towards a positive relationship for lean muscle mass gain and for skeletal muscle mass[53,65] and the other two muscle mass reviews found only null relationships.[66,67] The review evaluating protein intake and sarcopenia overall found inconclusive/mixed results.[66]

Supplemental scans

Sleep duration

No reviews were found that met the inclusion/exclusion criteria for this supplemental scan.

Appetite and satiety

Four SRs examined the relationship between protein intake and appetite and satiety outcomes.[68-71] **Table 2-j** shows the full extraction table with population, intervention/exposure, and outcome data for SRs reporting on appetite and satiety outcomes.

Review and population characteristics

Of the four SRs on appetite and satiety outcomes, two were conducted with MA[68,70] and two were conducted without MA.[69,71] All of the reviews predominantly included RCTs, with the number of relevant included studies ranging from 2[71] to approximately 41.[70] The populations studied included adults and older adults in three reviews[69-71] and older adults alone in one review.[68] Two reviews focused on studies where 100 percent of participants were with overweight or obesity.[69-71]

Intervention/exposure characteristics

All reviews predominantly assessed interventions that altered protein intake.[68-71] The two reviews focusing on individuals with overweight or obesity included interventions that were designed to induce weight loss.[69-71] Two of the SRs assessed studies with acute intervention durations, ranging from immediate assessment of appetite and satiety following protein intake to approximately 3 hours following protein intake.[68,70] All four SRs reported on longer-term interventions with durations ranging from 2 days to 34 months.

Outcome characteristics and trends

A variety of appetite and satiety related outcomes were assessed, including hunger, fullness, desire to eat, prospective food consumption, thoughts about food, satiety, and composite appetite score.[68-71] For acute studies, the reviews reported mixed findings but there was a tendency towards higher protein intake increasing satiety and decreasing appetite.[68,70] For longer-term studies, the reviews reported mixed findings – primarily null or a positive effect of protein on satiety.

Considerations for future DRI work

As the DRI process moves forward at the guidance of the Working Group, the following may be important to consider as a result of this completed evidence scan:

1. This evidence scan describes a broad range of evidence related to total dietary protein intake and chronic disease risk. It is difficult to know how pivotal the role of protein intake is to these relationships and it is challenging to isolate the effect of protein from the effect of other macronutrients, micronutrients, and bioactive substances.
2. Evidence was derived from existing systematic reviews, meta-analyses, and umbrella reviews identified by a literature search in PubMed. Use of a broader range of bibliographic databases may have identified additional reviews.
3. Completing duplication assessment of the relevant studies included in each review according to the reported outcome provided a rough estimate of the potentially included unique primary research articles. However, future systematic reviews would need to consider differences in intervention/exposure, database coverage, and assess the full inclusion/exclusion criteria used to identify and evaluate primary evidence.
4. Modifying the inclusion and exclusion criteria for each outcome would influence the strength and size of the reviews. This includes modifications to the following criteria: date range; study design; health status of the participants; characteristics or scope of the intervention/exposure (e.g., weight loss interventions, expanding scope to include protein source, duration of intervention, study/sample size); range of validated intermediate and health outcomes; and potential sources of confounding (e.g., studies that assess percent AMDR or describe full macronutrient distribution of the diet).

Table 2-b. Evidence examining the relatonship between protein intake and all-cause mortality[a]

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure and comparator	Outcomes Examined and Brief Results (Directly from source article)
Chen, 2020[23] Systematic Review and Meta-analysis 8 PCS Date range: Through 2019	To further clarify the current evidence from previous studies, researchers systematically reviewed and meta-analyzed their findings with those from previous prospective studies to evaluate the association of dietary protein intake with mortality.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: NA Observational: 9.4 y to 27 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories)	**All-cause Mortality:** Total Protein: Positive (Higher total protein intake was associated with higher risk of all-cause mortality) Animal Protein: Positive Plant Protein: Inverse
Naghshi, 2020[24] Systematic Review and Meta-analysis 29 PCS Date range: Through 2019	To examine and quantify the potential dose-response relation between intake of total, animal, and plant protein and the risk of mortality from all causes, cardiovascular disease, and cancer.	Adults, 19-59 y	**Duration:** Trials: NA Observational: 3.4 y to 22 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous)	**All-cause Mortality**: Total Protein: Inverse (lower risk associated with higher total protein intake) Plant Protein: Inverse Animal protein: Null
Qi, 2020[25] Systematic Review and Meta-analysis 10 PCS Date range: Through 2020	To summarize the evidence of the relationships between dietary protein intake and risk of all-cause, cardiovascular disease, and cancer mortality.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: NA Observational: 4.8 y to 27 y **Intervention/Exposure:** Habitual intake (Continuous)	**All-cause Mortality:** Total Protein: Null Animal protein: Null Plant protein: Inverse

[a] Abbreviations: NA, not applicable; PCS, prospective cohort study; y, years

Table 2-c. Evidence examining the relatonship between protein intake and bone health[a]

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure	Outcomes Examined and Brief Results (Directly from source article)
Curneen, 2018[26] Systematic Review 20 studies (study designs not reported consistently) Date range: Through 2018	To review the evidence of a relationship between BMD and protein quantity in animal subjects and individuals >50 years of age. To assess the association between the concentration of protein consumed in the diet and bone fracture (hip fracture).	Adults, 60+ y	**Duration:** Trials: Unclear Observational: Unclear **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous); Interventions that alter protein intake	**Fracture:** Total fracture and hip fracture: primarily inverse (decreased fracture) but some null **Bone Mass:** Femoral neck BMD, lumbar spine BMD, total hip BMD, total body BMD: primarily positive but some null
Darling, 2019[27] Systematic Review and Meta-analysis 13 RCT, 22 PCS, 62 CS, and 13 CC (some overlap in studies across designs) Date range: 1976 to 2016	To perform a systematic review and meta-analysis of evidence published the past 40 years on dietary protein intake and all indices of bone health across the life-course.	Children, 2-12 y Adolescents, 13-18 y Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 4 d to 9 mo Observational: 0 y (CS) to 22 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous); Interventions that alter protein intake	**Osteoporosis**: Mixed **Fracture**: Osteoporotic Fractures: Null (for total, animal and plant protein) Low trauma Fractures: Null **Bone Mass:** Lumbar Spine BMD: Null Femoral Neck BMD: Null
Groenendijk, 2019[28] Systematic Review and Meta-analysis 1 RCT and 12 PCS Date Range: Through 2018	To assess the impact of dietary protein intake above the RDA (0.8 g/kg/d) on BMD/BMC, bone turnover markers, and fracture risk in older adults compared to a lower dietary protein intake.	Adults, 60+ y	**Duration:** Trials: 2 y Observational: 1 y to 32 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous); Interventions that alter protein intake	**Fracture:** Hip fractures: Inverse (decreased fracture) Total fractures: Null Spine fractures: Null **Bone Mass:** Total hip BMD: Primarily positive but mixed Femoral neck BMD: Primarily positive but mixed Total body BMD: Mixed Lumbar spine BMD: Mixed Total body BMC: Mixed

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure	Outcomes Examined and Brief Results (Directly from source article)
Shams-White, 2017[29] Systematic Review and Meta-analysis 11 RCT and 18 PCS Date range: Through 2016	To clarify the impact of dietary protein and dietary protein and calcium with or without vitamin D on bone health outcomes in healthy adults.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 6 mo to 24 mo Observational: 1 y to 17 y **Intervention/Exposure:** Habitual intake (continuous and categorical); Interventions altering protein intake	**Fracture:** Hip fractures: Null Spine, forearm, and overall: Insufficient or inconsistent data **Bone Mass:** Lumbar spine BMD: Positive (small effect) Total hip BMD, femoral neck BMD: Null Total body BMD, total body BMC: Inconclusive data
Tsagari, 2020[30] Systematic Review 11 RCT and 7 PCS Date range: Through 2019	To clarify the impact of dietary protein on bone health outcomes (BMD, bone biomarkers, fractures) in healthy adults.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 12 mo to 24 mo Observational: 2.5 y to 5 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous); Interventions that alter protein intake	**Bone Mass:** Lumbar spine BMD: Trends towards positive (RCTs) Femoral neck BMD: Null Total hip BMD: Null Total body BMD: Null, but trends towards positive (PCS)
Wallace, 2017[31] Systematic Review and Meta-analysis 5 RCT and 15 PCS Date range: Through 2017	To assess whether there is an independent relationship between dietary protein intake above the current RDA (0.8 g/kg/d) and fractures, BMD/BMC, or markers of bone turnover.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 0.6 wk to 104 wk Observational: 1 y to 32 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous); Interventions that alter protein intake	**Fracture:** Hip fractures: Primarily inverse (higher protein, fewer fractures) Total fractures: Mixed Spine fractures: Null Forearm fractures: Inverse (only 1 study) **Bone Mass:** BMC, Cortical bone BMD, trabecular bone BMD, femoral neck BMD, hip/total hip BMD, intertrochanter/trochanter BMD, spine/lumbar spine BMD, proximal femur BMD, radius and radial shaft/midshaft BMD, total body BMD, Ward's area BMD, tibia/total tibia BMD, total body BMD: Tendency toward positive relationships in PCS, mixed results in RCTs

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure	Outcomes Examined and Brief Results (Directly from source article)
Wright, 2019[32] Systematic Review and Meta-analysis 27 RCT, 6 'longitudinal intervention' studies, 1 CC Date range: Through 2019	To conduct a systematic review and meta-analysis assessing the effect of dietary protein quantity (high protein vs normal protein) on energy-restriction-induced changes in BMD and BMC in healthy adults.	Adults, 19-59 y Adults, 60+ y 100% of participants were overweight or obese	**Duration:** Trials: 3 mo to 2 y Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions designed to induce weight loss; Multi-component interventions (isolates effect of total protein)	**Bone Mass:** Total BMD and Lumbar spine BMD: Tendency toward positive relationship but clinical significance questionable Femoral neck BMD, Hip BMD: results NR Total BMC, Lumbar spine BMC, Femoral neck BMC, Hip BMC: Mixed with tendency toward null

[a] Abbreviations: BMC, bone mineral content; BMD, bone mineral density; CC, case-control study; CS, cross-sectional study; d, days; g, grams; kg, kilograms; mo, months; NA, not applicable; NR, not reported; PCS, prospective cohort study; RCT, randomized controlled trial; RDA, recommended daily allowance; wk, weeks; y, years

Table 2-d. Evidence examining the relatonship between protein intake and cardiovascular disease risk[a]

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure and comparator	Outcomes Examined and Brief Results (Directly from source article)
Chen, 2020[23] Systematic Review and meta-analysis 5 PCS (3 additional studies that looked at plant or animal protein only) Date Range: Through Aug 27, 2019	To examine associations of dietary protein from different sources with all-cause and cause-specific mortality.	Adults, 19-59 y Adults, 60+ y	**Duration:** Observational: median ~13 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories)	**CVD mortality, and non-stroke CVD mortality:** Total protein and animal protein intake associated with higher risk; null association with plant protein **Stroke mortality:** Null association with protein intake or animal protein intake (found as part of primary research done for systematic review, not the MA)
Dinu, 2020[33] Umbrella Review 6 meta-analyses of RCTs Date range: Through April 2019	To describe and critically evaluate the impact of different diets and/or dietary patterns on human health, by considering their effects on anthropometric parameters and cardiometabolic risk factors.	Adults, 19-59 y	**Duration:** 0.8 mo to 52 mo **Intervention/Exposure:** Interventions that alter protein intake	**Blood pressure:** Weak or no evidence with high protein diet
Mousavi, 2020[38] Systematic Review 13 PCS (8 on CHD; 5 on HTN) Date Range: Through April 2020	To summarize previous investigations on the association between total, animal and plant proteins intake and the risk of coronary heart disease and hypertension in adults.	Adults, 19-59 y Adults, 60+ y	**Duration:** Observational: 2.3 y to 22 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous)	**CHD:** No significant relationship with protein intake **HTN:** No significant relationship with protein intake
Naghshi, 2020[24] Systematic Review and Meta-analysis 14 PCS (10 in meta-analysis) Date range: Through Dec 2019	To examine and quantify the potential dose-response relation between intake of total, animal, and plant protein and the risk of mortality from all causes, cardiovascular disease, and cancer.	Adults, 19-59 y Adults, 60+ y	**Duration:** Observational: 5 y to 32 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous)	**CVD mortality:** Null association with total protein and animal protein; lower risk associated with plant protein

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure and comparator	Outcomes Examined and Brief Results (Directly from source article)
Qi, 2020[25] Systematic Review and Meta-analysis 8 PCS Date range: Through Feb 2020	To assess the relationships between total, animal, and plant protein intakes and risk of all-cause, CVD, and cancer mortality in the general population.	Adults, 19-59 y Adults, 60+ y	**Duration:** Observational: 4.8 y to 27 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous)	**CVD mortality:** Null association with total protein; animal protein associated with higher risk; plant protein associated with lower risk
Schwingshackl, 2019[34] Systematic Review and Meta-analysis 12 high-protein RCTs Date range: Through June 2017	To establish a clinically meaningful hierarchy of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients in a systematic review through the synthesis of available evidence from randomized trials.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 3 mo to 15 mo **Intervention/Exposure:** Interventions that alter protein intake	**Blood pressure:** High protein diets were more effective in reducing SBP and DBP compared to control diets; the effects compared to low fat diets were not statistically significant
Sukhato, 2020[39] Umbrella Review 6 MAs of RCTs (high protein diet) Date Range: Through June 2020	To provide an update on the available evidence for the efficacy of different dietary patterns on blood pressure lowering.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: NR **Intervention/Exposure:** Habitual intake (Continuous)	**Blood Pressure:** Small beneficial effect of high protein diets on lowering blood pressure. **DBP:** Small beneficial effect of high protein diets lowering DBP. **SBP:** SBP in the high-protein diet groups was significantly lower than SBP in the low-protein diet groups
Van Elswyk, 2018[35] Systematic Review 9 RCT Date range: Through 2017	To examine published literature investigating the relation of protein intake and indicators of kidney function in healthy adults with the purpose of understanding whether levels of intake above the currently established US RDA of 0.8 g/kg body weight, but within the AMDR, are consistent with normal kidney health and function.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: NR **Intervention/Exposure:** Interventions that alter protein intake	**Blood pressure:** Null association with total protein intake

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure and comparator	Outcomes Examined and Brief Results (Directly from source article)
van Elten, 2019[37] Systematic Review 8 PCS Date Range: Through June 30, 2017	To synthesize evidence examining the association of maternal diet and physical activity before and during pregnancy with offspring's blood pressure and vascular health.	Pregnancy	**Duration:** Trials: NR Observational: NR **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous); Interventions that alter protein intake	**Offspring blood pressure:** Predominately null association
Zhang, 2016[36] Systematic Review and meta-analysis 12 PCS Date Range: Through June 27, 2016	To quantitatively estimate dietary protein intake and risk of stroke, using the most recent data.	Adults, 19-59 y Adults, 60+ y	**Duration:** Observational: 5 y to 26 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous)	**Stroke risk:** Null association between protein intake and stroke risk (both total risk and individual stroke types)

[a] Abbreviations: AMDR, acceptable macronutrient distribution range; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; g, grams; HTN, hypertension; kg, kilograms; MA, meta-analysis; NR, not reported; PCS, prospective cohort study; RCT, randomized controlled trial; RDA, recommended daily allowance; SBP, systolic blood pressure; US, United States; y, years;

Table 2-e. Evidence examining the relatonship between protein intake and dementia/cognitive decline (adults)[a]

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure	Outcomes Examined and Brief Results (Directly from source article)
Coelho-Júnior, 2021[40] Systematic Review 8 CS, 1 PCS Date range: 1983 to 2020	To investigate the available evidence on the association between protein intake and cognitive function in older adults	Adults, 60+ y	Trials: NA Observational: 0 mo (CS) to 8.5 mo **Intervention/Exposure:** Habitual intake (Continuous)	**Dementia/Cognitive Decline (adults):** Global cognitive function, immediate and delayed learning ability, nonverbal learning, verbal and nonverbal memory, short-term memory, working memory, verbal fluency, processing speed, problem-solving ability, sustained attention, abstract reasoning: Predominantly null
Muth, 2021[41] Systematic Review 2 RCT, 5 CS Date range: ~1998 to 2018	To synthesize previous research addressing the effects of macronutrients from acute, intervention, and long-term whole meal studies on cognitive functioning in healthy young and old adults.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 3 wk Observational: All CS **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous); Interventions that alter protein intake	**Dementia/Cognitive Decline (adults):** Inhibition control, reaction time, fluid intelligence, working memory, memory, global cognition, digit subtraction, risk of mild cognitive impairment: Mixed but some positive associations

[a] Abbreviations: CS, cross-sectional study; mo, months; NA, not applicable; PCS, prospective cohort study; RCT, randomized controlled trial; wk, weeks; y, years

Table 2-f. Evidence examining the relatonship between protein intake and diabetes risk[a]

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure and Comparator	Outcomes Examined and Brief Results (Directly from source article)
Dinu, 2020[33] Umbrella review of meta-analyses 6 MA Date range: Through 2019	The aim was to describe and critically evaluate the impact of different diets and/or dietary patterns on human health, by considering their effects on anthropometric parameters and cardiometabolic risk factors.	Adults, 19-59 y Adults, 60+ y 3 of 6 included meta-analyses examined participants with T2D	**Duration:** Trials: 1 mo to 52 mo Observational: NA **Intervention/Exposure:** Interventions that alter protein intake	**HbA1c**: Weak or null
Fan, 2019[42] Systematic Review and Meta-analysis 6 PCS Date range: Through 2019	To explore the relations between dietary protein consumption and the risk of T2D	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: NA Observational: 7.2 y to 20 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous)	**Type 2 Diabetes**: Total Protein: Positive Animal Protein: Positive Plant Protein: Inverse Meta-analyses showed the same results.
Shang, 2016[43] Systematic Review and Meta-analysis 9 PCS Date range: Through 2016	Prospectively examined the relations of total, animal and plant protein intakes with incidence of T2D.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: NA Observational: 5 y- 24 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous)	**Type 2 Diabetes:** Total Protein: Positive Animal Protein: Positive Plant Protein: Null
Tian, 2017[44] Systematic Review and Meta-analysis 9 PCS Date range: Through 2017	To clarify the association of protein consumption with risk of T2DM.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: NA Observational: 5 y to 24 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories)	**Type 2 Diabetes:** Total Protein: Positive (high protein intake, high risk of T2D) Animal Protein: Positive Plant Protein: Mixed (Null in males, negative in females)

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure and Comparator	Outcomes Examined and Brief Results (Directly from source article)
Ye, 2019[45] Systematic Review and Meta-analysis 8 PCS Date range: Until 2018	To evaluate the association between dietary proteins and the risk of T2DM.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: NA Observational: 5 y to 24 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous)	**Type 2 Diabetes:** High total protein: Positive Moderate total protein: Null High animal protein: Positive Moderate animal protein: Null High plant protein: Null Moderate plant protein: Inverse
Zhao, 2019[46] Systematic Review and Meta-analysis 8 PCS Date range: Through 2018	To quantitatively assess whether dietary total, animal, and plant protein would be associated with type 2 diabetes risk.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: NA Observational: 5 y to 24 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous)	**Type 2 Diabetes:** Total protein: Positive Animal protein: Positive Plant Protein: U-shaped curve indicating protective effect

[a] Abbreviations: HbA1c, hemoglobin A1c; MA, meta-analysis; mo, months; NA, not applicable; PCS, prospective cohort study; T2D, type 2 diabetes; y, years

Table 2-g. Evidence examining the relatonship between protein intake and growth, size, and body composition[a]

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure	Outcomes Examined and Brief Results (Directly from source article)
Bergia, 2018[47] Systematic Review and Meta-analysis 8 RCT Date range: Through 2017	To assess effects of whey protein supplementation with or without energy restriction and resistance training on changes in body mass, lean mass, and fat mass in women.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 6 wk to 12 mo Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions with supplements; Interventions designed to induce weight loss	**Body composition:** Lean mass: Positive Fat mass: Null Body mass: Null
Dinu, 2020[33] Umbrella review of meta-analyses 7 meta-analyses (7 on Weight; 2 on BMI) Date range: Through 2019	The aim was to describe and critically evaluate the impact of different diets and/or dietary patterns on human health, by considering their effects on anthropometric parameters and cardiometabolic risk factors.	Adults, 19-59 y Adults, 60+ y (NR)	**Duration:** Trials: 1 mo to 52 mo Observational: NA **Intervention/Exposure:** Interventions that alter protein intake	**Size**: Weight: Weak or null BMI: Weak or null
Ferré, 2021[48] Systematic Review 8 PCS and 1 RCT Date range: Through 2020	To evaluate the effects of protein intake during the second year of life on weight and fat mass gain and the subsequent risk of obesity development later in childhood.	Infants, <12 mo Toddlers, 12-23 mo	**Duration:** Trials: 1 y Observational: 1 mo to 11 y **Intervention/Exposure:** Interventions that alter protein intake; Higher vs Lower habitual intake (Categories); Habitual intake (Continuous)	**Growth:** Risk of overweight or obesity: Null Rapid weight gain: Mixed **Size**: BMI z-score: Positive and null **Body composition**: Fat mass: Positive
Hansen, 2021[49] Systematic Review and Meta-analysis 37 RCT Date range: Through 2021	To summarize the current evidence investigating if dietary interventions rich in protein lead to improved body weight management in adults with excessive body weight.	Adults, 19-59 y	**Duration:** Trials: 8 wk to 104 wk Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions designed to induce weight loss	**Size:** Weight: Inverse BMI: Inverse Waist circumference: Null **Body composition**: Fat mass: Inverse

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure	Outcomes Examined and Brief Results (Directly from source article)
Hsu, 2019[50] Systematic Review and Meta-analysis 2 RCT Date range: Through 2019	To investigate the effects of exercise or nutrition on body composition, metabolic health, and physical performance in individuals with sarcopenic obesity and (2) to determine if exercise combined with nutrition provides additional benefits for body composition, metabolic health, and physical performance, compared to exercise or nutrition alone, in individuals with sarcopenic obesity.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 12 wk and 16 wk **Intervention/Exposure:** Interventions that alter protein intake; Interventions designed to induce weight loss	**Body composition:** Fat mass: Inverse Muscle mass: Null
Hudson, 2020[51] Systematic Review and Meta-analysis 18 RCT (15 without resistance training) Date range: Through 2018	To conduct a systematic review and meta-analysis to assess the effects of protein intakes greater than the RDA, compared with at the RDA, on changes in whole-body lean mass.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 8 wk to 52 wk Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions designed to induce weight loss	**Body composition:** Lean mass: Null
Kim, 2016[52] Systematic Review and Meta-analysis 20 RCT Date range: Through 2015	To assess the effects of protein intake on energy restriction-induced changes in body mass, lean mass, and fat mass in adults older than 50 years.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 8 wk to 104 wk Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions designed to induce weight loss; Multi-component interventions (isolates effect of total protein)	**Body composition**: Lean mass: Positive Fat mass: Inverse
Lin, 2021[53] Systematic Review and Meta-analysis 11 RCT Date range: Through 2020	To determine the impact of protein supplementation during endurance training on aerobic capacity, body composition, and exercise performance in healthy and clinical populations.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 4.5 wk to 24 wk Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions with supplements; Interventions designed to enhance athletic performance	**Body composition**: Lean mass gain: Positive Fat mass: Null

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure	Outcomes Examined and Brief Results (Directly from source article)
Patro-Gołąb, 2016[54] Systematic Review 10 RCT and 2 NRCT Date range: Through 2014	To investigate current evidence on the effects of infant formulas and follow-on formulas with different protein concentrations on infants 'and children's growth, body composition, and later risk of overweight and obesity.	Infants, <12 mo	**Duration:** Trials: 3 mo to 12 mo Observational: NA **Intervention/Exposure:** Interventions that alter protein intake	**Growth:** Weight gain: Null Risk of obesity: Positive **Size**: Weight/Weight z-score: Positive at age ~6-12mo, Null at later ages BMI/BMI z-score: Positive Length: Null Head circumference: Null **Body composition**: Fat mass: Null Fat-free mass: Null
Patro-Gołąb, 2016[62] Umbrella Review 2 systematic reviews Date range: Through 2015	To provide a systematic review of systematic reviews on the effects of nutritional interventions or exposures in children (up to three years of age) on the subsequent risk of obesity, overweight, and adiposity.	Infants, <12 mo	**Duration:** Trials: NR Observational: NA **Intervention/Exposure:** Interventions that alter protein intake (Infant formula)	**Growth:** Obesity prevalence: Positive **Size**: BMI: Positive
Stokes, 2021[55] Systematic Review 8 PCS Date range: Through 2020	To review and appraise studies that explored the long-term associations between intakes of total protein and protein from different sources during the first 2 y of life and subsequent obesity outcomes in childhood and adolescence.	Infants, < 12 mo Toddlers, 12-23 mo Children, 2-12 y	**Duration:** Trials: NA Observational: 5 y to 11 y **Intervention/Exposure:** Habitual intake (Continuous)	**Growth:** Risk of overweight: Positive and null **Size**: BMI/BMI z-score: Positive; mixed results by protein source **Body composition**: % Body Fat: Positive; mixed results by protein source Fat mass index: Positive; mixed results by protein source Fat-free mass index: Null
Tagawa, 2020[56] Systematic Review and Meta-analysis 105 RCT (66 without resistance training) Date range: Through 2019	To evaluate the dose-response relationship of the effects of protein intake on lean body mass.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 2 wk to 18 mo Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions designed to induce weight loss	**Body composition:** Lean mass: Positive

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure	Outcomes Examined and Brief Results (Directly from source article)
Tielemans, 2016[57] Systematic Review 19 PCS Date range: Through 2015	To evaluate the effects of energy intake and macronutrient intake on gestational weight gain.	Adults, 19-59 y	**Duration:** Trials: NA Observational: Through 3rd trimester **Intervention/Exposure:** Habitual intake (Continuous)	**Growth:** Gestational weight gain: Mixed (total and by protein source)
Valenzuela, 2019[58] Systematic Review and Meta-analysis 7 RCT Date range: Through 2019	To compare the effects of beef protein, whey protein, or no protein supplementation combined with exercise training on body composition and exercise performance.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 8 wk to 16 wk Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions with supplements; Interventions designed to enhance athletic performance; Multi-component interventions (isolates effect of total protein)	**Body composition**: Lean mass: Positive Fat mass: Null Muscle thickness: Mixed
van Baak, 2019[59] Systematic Review and Meta-analysis 3 RCT Date range: NR (but included studies ranged from 1997-2017)	To review what is currently known about dietary strategies for weight loss maintenance, focusing on nutrient composition.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 26 wk and 12 mo **Intervention/Exposure:** Interventions that alter protein intake; Interventions designed to induce weight loss	**Growth** Weight loss maintenance: Positive
Yin, 2020[60] Systematic Review and Meta-analysis 2 RCT Date range: Through 2019	To describe the criteria used to identify people with sarcopenic obesity and the components of the non-pharmacological interventions used to manage it, and to evaluate the effectiveness of those interventions.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 3 mo and 4 mo Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions designed to induce weight loss	**Body composition:** Fat-free mass: Null
Zhang, 2020[61] Systematic Review and Meta-analysis 9 RCT Date range: Through 2019	To quantitatively estimate dietary protein intake and risk of stroke, using the most recent data.	Adults, 19-59 y	**Duration:** Trials: 12 wk to 12 mo Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions designed to induce weight loss	**Size**: Weight: Inverse BMI: Inverse Waist circumference: Null **Body composition**: Fat mass: Inverse Fat-free mass: Null

[a] Abbreviations: BMI, body mass index; mo, months; NA, not applicable; NR, not reported; NRCT, non-randomized controlled trial; PCS, prospective cohort study; RCT, randomized controlled trial; wk, weeks; y, years; %, percent

Table 2-h. Evidence examining the relatonship between protein intake and renal health[a]

Author, Year; Relevant Included Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure	Outcomes Examined and Brief Results (Directly from source article)
Devries, 2018[63] Systematic Review and Meta-analysis 28 RCT Date range: Through 2017	To examine whether GFR increase to a greater extent after a high protein diet as compared with a normal or lower protein diet in individuals without CKD.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 4 d to 104 wk Observational: NA **Intervention/Exposure:** Interventions that alter protein intake	**Renal Insufficiency**: GFR post-intervention: Positive (increased protein, increased GFR) GFR change: Null
Van Elswyk, 2018[35] Systematic Review 13 RCT, 5 CS, 2 PCS Date range: Through 2017	To examine published literature investigating the relation of protein intake and indicators of kidney function in healthy adults with the purpose of understanding whether levels of intake above the currently established US RDA of 0.8 g/kg body weight, but within the AMDR, are consistent with normal kidney health and function.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 1 d to 4 mo Observational: 0 y (CS) to 21 y **Intervention/Exposure:** Higher vs Lower habitual intake (Categories); Habitual intake (Continuous); Interventions that alter protein intake	**Renal Insufficiency:** GFR and eGFR: Primarily positive but mixed Kidney disease incidence: Null

[a] Abbreviations: AMDR, acceptable macronutrient distribution range; CKD, chronic kidney disease; CS, cross-sectional study; d, days; eGFR, estimated glomerular filtration rate; g, grams; GFR, glomerular filtration rate; kg, kilograms; mo, months; NA, not applicable; PCS, prospective cohort study; RCT, randomized controlled trial; RDA, recommended daily allowance; US, United States; wk, weeks; y, years

Table 2-i. Evidence examining the relatonship between protein intake and sarcopenia[a]

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure and comparator	Outcomes Examined and Brief Results (Directly from source article)
Coelho-Júnior, 2018[64] Systematic Review and Meta-analysis 4 PCS, 2 CS, 1 CC Date range: Through 2018	To conduct a systematic review and meta-analysis of observational studies investigating the association of relative protein intake and physical function in older adults.	Adults, 60+ y	**Duration:** Trials: NA Observational: NR **Intervention/Exposure:** Higher vs Lower habitual intake (Categories)	**Upper-limb muscle strength** (isometric handgrip): Null for high vs low protein intake **Lower-limb muscle strength** (chair-rise, knee extensor strength): Null for high vs low protein intake
Kirwan, 2021[67] Systematic Review and Meta-analysis 28 RCT Total (9 without resistance exercise) Date range: 1990 to 2021	To complete a systematic review and meta-analysis of RCTs assessing the effect of protein supplementation or higher-protein diets, without the use of essential amino acids or supplements known to to stimulate hypertrophy, with or without concomitant resistance exercise interventions on lean body mass, appendicular lean mass, and strength in older adults.	Adults, 60+ y	**Duration:** Trials: 10 wk to 104 wk Observational: NA **Intervention/Exposure**: Interventions that alter protein intake	**Appendicular lean mass**: Null; positive relationship when combined with exercise in frail/sarcopenic populations **Handgrip strength**: Null; positive relationship when combined with exercise in frail/sarcopenic populations **Total lean body mass:** Null **Knee extension strength**: Null
Lin, 2021[53] Systematic Review and Meta-analysis 14 RCT and 1 NRCT Date range: Through 2020	To determine the impact of protein supplementation during endurance training on aerobic capacity, body composition, and exercise performance in healthy and clinical populations.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials: 4.5 wk to 24 wk Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions with supplements; Interventions designed to enhance athletic performance; Multi-component interventions (isolates effect of total protein)	**Lean muscle mass gain**: Trended toward Positive **Muscle strength**: Null

Author, Year; Included Relevant Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure and comparator	Outcomes Examined and Brief Results (Directly from source article)
Naseeb, 2017[66] Systematic Review 2 CS, 7 RCT and 1 PCS Date range: 2010 to 2015	To discuss the role of protein and exercise in slowing the progression of sarcopenia.	Adults, 60+ y	**Duration:** Trials: NR Observational: NR **Intervention/Exposure**: Higher vs Lower habitual intake (Categories); Habitual intake (Continuous); Interventions that alter protein intake	**Muscle mass**: Null **Muscular strength**: Null **Sarcopenia**: Only one study, results inconclusive
Yaegashi, 2021[65] Systematic Review 6 PCS and 11 CS Date range: Through 2021	To investigate the association of dietary protein intake with skeletal muscle mass in older adults.	Adults, 60+ y	**Duration:** Trials: NA Observational: 0 y (cross-sectional) to 6 y **Intervention/Exposure**: Higher vs Lower habitual intake (Categories); Habitual intake (Continuous)	**Appendicular skeletal muscle mass and whole skeletal muscle mass**: 70% of studies had a positive association but the other studies contained null and inverse associations

[a] Abbreviations: CC, case-control; CS, cross-sectional; NA, not applicable; NR, not reported; PCS, prospective cohort study; RCT, randomized controlled trial; wk, weeks; y, years; %, percent

Table 2-j. Evidence examining the relatonship between protein intake and appetite/satiety[a]

Author, Year; Relevant Included Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure	Outcomes Examined and Brief Results (Directly from source article)
Ben-Harchache, 2021[68] Systematic Review and Meta-analysis 10 RCT (8 acute and 2 longer-term) Date range: Through 2020	To determine the effects of protein supplementation (supplements or whole foods) on appetite and energy intake in healthy older adults.	Adults, 60+ y	**Duration:** Trials (acute): 0 h (immediately after protein intake) to 3 h Trials (longer-term): 18 d to 11 wk Observational: NA **Intervention/Exposure:** Interventions that alter protein intake	**Appetite and Satiety**: Acute Composite appetite score, hunger, fullness, desire to eat, prospective food consumption: Mixed, some positive (higher protein, greater satiety), some null Longer-term Hunger, desire to eat: Mixed
de Carvalho, 2020[69] Systematic Review 9 RCT, 1 NRCT (all longer-term) Date range: Through 2019	To synthesize the best available evidence on effect of high protein diets (longer than 7 days) on appetite among individuals with overweight or obesity.	Adults, 19-59 y Adults, 60+ y 100% of participants with overweight or obesity	**Duration:** Trials (longer-term): 7 d to 34 mo Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions designed to induce weight loss	**Appetite and Satiety**: Longer-term Hunger, desire to eat, thoughts about food, fullness, fullness after meals, satiety, prospective food consumption: Mixed, some positive (higher protein, greater satiety), some null
Kohanmoo, 2020[70] Systematic Review and Meta-analysis ~41 RCT (~28 acute and ~ 13 longer-term; individual studies not reported clearly) Date range: Through 2019	To evaluate the effect of protein intake on appetite and gastrointestinal hormones involved in appetite regulation, and to assess if the effect of protein on these outcomes differs between acute and longer-term intake.	Adults, 19-59 y Adults, 60+ y	**Duration:** Trials (acute): ~3 h (time varied but range NR) Trials (longer-term) 3 d to 9 mo Observational: NA **Intervention/Exposure:** Interventions that alter protein intake	**Appetite and Satiety**: Acute Hunger, fullness, satiety, desire to eat, prospective food consumption: Positive (higher protein, greater satiety) based on meta-analysis Longer-term Hunger, fullness, satiety, desire to eat, prospective food consumption: Null based on meta-analysis

Author, Year; Relevant Included Studies; and Review Date Range	Purpose of the review	Populations and/or Life-Stages	Study duration; Intervention/Exposure	Outcomes Examined and Brief Results (Directly from source article)
Zhao, 2017[71] Systematic Review 2 RCT (both longer-term) Date range: Through 2016	To assess evidence exploring alterations of gut hormones during diet-induced weight changes.	Adults, 19-59 y Adults, 60+ y 100% of participants with overweight or obesity	**Duration:** Trials (longer-term): 5 wk to 12 wk Observational: NA **Intervention/Exposure:** Interventions that alter protein intake; Interventions designed to induce weight loss	**Appetite and Satiety**: Longer-term Hunger, desire to eat, fullness: Positive (higher protein, greater satiety)

[a] Abbreviations: d, days; h, hours; mo, months; NA, not applicable; NRCT, non-randomize controlled trial; RCT, randomized controlled trial; wk, weeks; y, years, %, percent

Chapter 3 – Average daily dietary protein intake (including amino acid intake) requirement

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Specific methods to conduct this evidence scan

Develop a protocol

The research questions, “What is the average daily dietary protein intake requirement of apparently healthy individuals by life stage and sex”? and “What is the average daily intake requirement for individual indispensable amino acids of apparently healthy individuals by life stage and sex”? are explored with this evidence scan.

In order to answer the research questions, a protocol was written to clarify the areas of interest and structure the questions in more detail.

The analytic framework for the evidence scan examining protein intake requirements is presented in **Figure 3-a**. The analytic framework visually represents the overall scope of the evidence scan question and depicts the contributing elements that were considered. The intervention or exposure of interest was total daily protein intake level or total daily intake of indispensable amino acids (AAs; histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine). The comparator was a different levels of total daily protein intake level or a different total daily intake of indispensable AAs. The outcomes were: total protein requirement as defined by the following indicators or criteria of adequacy – nitrogen balance method, factorial method, indicator amino acid method, mean protein intake of infants fed principally human milk [0-6 months], mean protein content of human milk [0-6 months]; indispensable AA requirement as defined by the following indicators or criteria of adequacy – plasma AA response method, direct AA oxidation method, 24-hour AA balance method, indicator AA oxidation method, mean AA intake of infants fed principally human milk [0-6 months], mean AA content of human milk [0-6 months]. There were no key confounders noted due to the limited data extraction completed in evidence scans.

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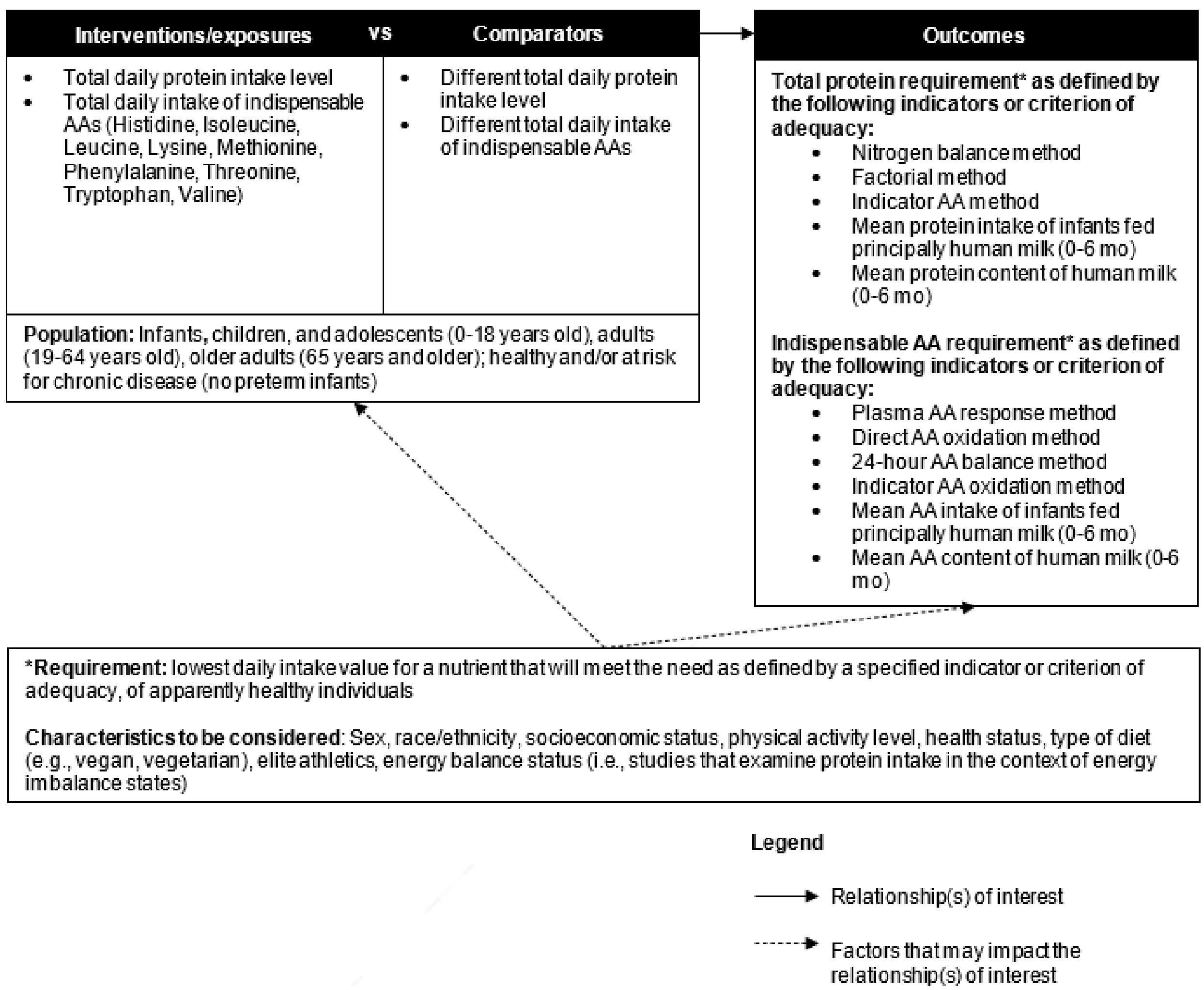
[c] Librarian, NESR team; Panum Group, under contract with the FNS, USDA,

[d] Project lead, NESR team, NGAD, CNPP, FNS, USDA

Figure 3-a. Analytic framework for protein intake requirements



Search for and select studies

NESR analysts worked jointly with the Working Group to establish the final inclusion and exclusion criteria and literature search strategy, which are detailed in **Table 3-a** and **Appendix 3-a,** respectively.

In this evidence scan, initial searches had low precision, leading the team to choose to identify articles through citation mining, rather than a systematic search.

The librarian identified a set of six relevant reports and systematic reviews on protein intake.[a] Then, using Scopus and Web of Science, the librarian extracted all of the articles cited in those six papers (one level of backward citation mining) and all of those articles which cited those papers (one level of forward citation mining). These extracted articles were checked for relevance (those which mentioned dietary, macronutrient, energy, protein, or amino acid intake or interventions); date (published after 2000); and publication type (proceedings and conference abstracts excluded).

Using this method, the librarian identified 372 articles in the backward citation mining and 1,228 articles in the forward citation mining after de-duplication.

Citation mining, while a useful strategy for mapping evidence in a subject area, searches within a small, contained sample, and is not an exhaustive search method.

Table 3-a. Inclusion and exclusion criteria for protein intake requirements

Category	Inclusion Criteria	Exclusion Criteria
Study design	• Systematic reviews • Meta-analyses • Scoping reviews • Umbrella reviews • Randomized controlled trials • Non-randomized controlled trials, including quasi-experimental and controlled before-and-after studies • Prospective cohort studies • Retrospective cohort studies • Nested case-control studies	• International and government reports • Narrative reviews • Systematic reviews or meta-analyses that exclusively include cross-sectional and/or uncontrolled studies • Uncontrolled trials • Case-control studies • Uncontrolled before-and-after studies

[a] Deutz, N. E., Bauer, J. M., Barazzoni, R., Biolo, G., Boirie, Y., Bosy-Westphal, A., ... & Calder, P. C. (2014). Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. *Clinical nutrition*, *33*(6), 929-936. Guidelines: https://www.espen.org/guidelines-home/espen-guidelines

Bauer, J., Biolo, G., Cederholm, T., Cesari, M., Cruz-Jentoft, A. J., Morley, J. E., ... & Boirie, Y. (2013). Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. *Journal of the American Medical Directors association*, *14*(8), 542-559.

Hörnell, A., Lagström, H., Lande, B., & Thorsdottir, I. (2013). Protein intake from 0 to 18 years of age and its relation to health: a systematic literature review for the 5th Nordic Nutrition Recommendations. *Food & nutrition research*, *57*(1), 21083. Guidelines: http://norden.diva-portal.org/smash/get/diva2:704251/FULLTEXT01.pdf

Joint FAO/WHO/UNU Expert Consultation on Protein and Amino Acid Requirements in Human Nutrition (2002 : Geneva, Switzerland), Food and Agriculture Organization of the United Nations, World Health Organization & United Nations University. (2007). Protein and amino acid requirements in human nutrition: report of a joint FAO/WHO/UNU expert consultation. World Health Organization. https://apps.who.int/iris/handle/10665/43411

Pedersen A, Cederholm T. Health effects of protein intake in healthy elderly populations: a systematic literature review. Food Nutr Res 2014;58:23364. http://dx.doi.org/10.3402/fnr.v58.23364.

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2012. Scientific Opinion on Dietary Reference Values for protein. EFSA Journal;10(2). https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2012.2557

Category	Inclusion Criteria	Exclusion Criteria
Intervention/ exposure	• Total daily protein intake level • Total daily intake of indispensable AAs (Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Threonine, Tryptophan, Valine)	• Studies that **only** assess protein intake via infusions (rather than the GI tract) • Studies that examine food products or dietary supplements not widely available to U.S. consumers • Multi-component interventions that do not isolate the effect or association of protein (including protein and exercise combinations)
Comparator	• Different total daily protein intake level • Different total daily intake of indispensable AAs	• No comparator
Protein requirement outcome	Total protein requirement* as defined by the following indicators or criterion of adequacy: • Nitrogen balance method • Factorial method • Indicator AA oxidation method • Mean protein intake of infants fed principally human milk (0-6 mo) • Mean protein content of human milk (0-6 mo) Indispensable AA requirement* as defined by the following indicators or criterion of adequacy: • Plasma AA response method • Direct AA oxidation method • 24-hour AA balance method • Indicator AA oxidation method • Mean AA intake of infants fed principally human milk (0-6 mo) • Mean protein content of human milk (0-6 mo)	N/A
Publication date	• 2000 to present	• Prior to 2000
Publication status	• Reports published by international and government entities • Articles published in peer-reviewed journals	• Articles that have not been peer reviewed and are not published in peer-reviewed journals (e.g., unpublished data, manuscripts, pre-prints, reports, abstracts, conference proceedings)
Language	• Articles and reports published in English	• Articles and reports published in languages other than English
Country	• Studies conducted in any country	
Study participants	• Human participants • Subjects who are pregnant	• Non-human participants (e.g., animal studies, in-vitro models)

Category	Inclusion Criteria	Exclusion Criteria

Age of study participants	• Age at intervention or exposure:
	  o Infants, children, and adolescents (0-18 years)
	  o Adults (19-64 years)
	  o Older adults (65 years and older)
		N/A

Health status of study participants	• Studies that enroll participants who are healthy and/or at risk for chronic disease, including those with obesity • Studies that enroll some participants diagnosed with a disease or hospitalized or in a long-term care facility with an illness or injury • Studies that enroll some participants diagnosed with a disease or with the health outcome of interest • Studies that exclusively recruit athletes and/or highly active individuals	• Studies that *exclusively* enroll participants diagnosed with a disease or hospitalized or in a long-term care facility with an illness or injury (for this criterion, studies that exclusively enroll participants with obesity will not be excluded) • Studies that aim to treat participants who have already been diagnosed with the outcome of interest (except weight loss interventions in overweight or obese subjects) • Studies that exclusively enroll undernourished participants • Studies that exclusively enroll participants with a baseline diet deficient in protein • Studies that exclusively enroll pre-term infants • Studies that exclusively enroll post-bariatric surgery subjects

Extract data

NESR analysts extracted data from each included review to objectively describe the body of evidence. Data extraction was completed in DistillerSR by two analysts for each article. Any conflicts between analysts were reconciled between the two screeners. If necessary, a third analyst was consulted to resolve differences. The following data elements were extracted from each included article:

- Publication author and publication year
- Study design
- Population studied (life stage/age group)
- Outcome assessment method
- Outcome assessed (total protein or select AAs)

No results were extracted from the included articles and no quality assessments were completed.

Describe the evidence

NESR analysts summarized the volume and characteristics of included studies to inform the following question:

- **What is the average daily dietary protein intake requirement of apparently healthy individuals by life stage and sex?**
- **What is the average daily intake requirement for individual indispensable amino acids of apparently healthy individuals by life stage and sex?**

The extracted data were summarized in written form, as well as presented visually in a table. The extracted information helped analysts and the Working Group understand the following:

- The volume and characteristics of research examining protein intake requirements
- The volume and characteristics of research examining indispensable AA intake requirements

Considerations for future DRI work

Considerations for future systematic reviews completed to inform the DRI process were were included in this evidence scan.

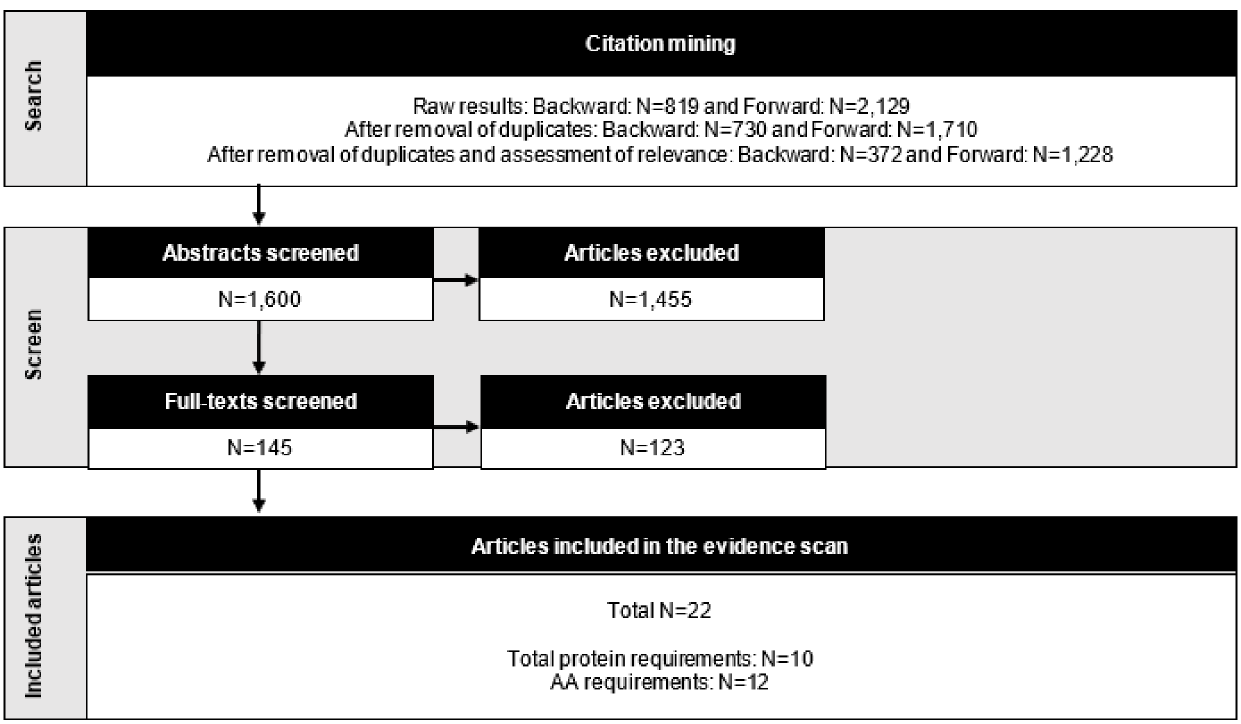
Results

Literature search and screening results

Citation mining for the protein requirements evidence scan yielded 1,600 search results after the removal of duplicates and assessment of relevance (see **Figure 3-b**). Dual-screening resulted in the exclusion of 1,455 abstracts, and 123 full-text articles. Reasons for full-text exclusion are in **Appendix 3-b**. The body of evidence included 22 articles:

- 10 articles on total protein requirements
- 12 articles on indispensable AA requirements

Figure 3-b. Literature search and screen flowchart for protein intake requirements



Description of evidence

Total protein requirement

Ten articles examined total protein requirements.[72-81] Of these, one article[78] was found to have been cited in the 2005 IOM report on protein[a]. The evidence on total protein requirements is organized by age of the participants. **Table 3-b** shows the full extraction table with citation, protein requirement(s) assessed, outcome assessment method(s), population(s) examined, and study design(s) for articles reporting on total protein requirements.

Children (2-12 years)

One RCT examined total protein requirements in children (2-12 years).[73] Total protein requirements in this study were assessed using the indicator AA oxidation (IAAO) method.

Adults (19-59 years)

Two RCTs examined total protein requirements in adults (19-59 years).[74,81] One RCT was conducted with female participants only,[81] whereas one was conducted with male participants only.[74] Both studies utilized the IAAO method to assess total protein requirements. Additionally, one of the RCTs included a MA of 29 studies that utilized the nitrogen balance method to assess total protein requirements.[74]

Adults (19-59 years) and older adults (60+ years)

Two studies, one RCT[72] and one SR with MA,[78] examined total protein requirements in a combined population of adults (19-59 years) and older adults (60+ years). Both studies utilized the nitrogen balance method to assess total protein requirements. As previously noted, the SR with MA, which included 27 studies in the SR and 19 studies in the MA, was cited in the 2005 IOM report.[78]

Older adults (60+ years)

Four studies, three RCTs[75,77,80] and one SR,[76] examined total protein requirements in older adults (60+ years). Among the RCTs, two were conducted with female participants,[75,80] whereas one was conducted with male participants.[77] Further, two RCTs utilized the IAAO method to determine total protein requirements,[77,80] whereas one utilized the nitrogen balance method.[75] The SR assessed studies that determined total protein requirements using the nitrogen balance and included one MA and 4 additional individual studies.

All age groups

One SR reported on total protein requirements across all age groups from infancy to older adulthood.[79] The number of included studies in the SR was not reported. Methods used to determine protein requirements that were summarized by the SR included the mean protein content of human milk, the factorial method, and the nitrogen balance method.

Indispensable AA requirements

Twelve articles examined indispensable AA requirements.[82-93] Of these, six articles[82,83,85-88] were found to have been cited in the 2005 IOM report on protein[b]. The evidence on indispensable AA requirements is organized by the type of AA. **Table 3-c** shows the full extraction table with citation, population, intervention/exposure, and outcome data for articles reporting on indispensable AA requirements.

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[a] Institute of Medicine 2005. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington, DC: The National Academies Press. https://doi.org/10.17226/10490.

[b] Institute of Medicine 2005. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington, DC: The National Academies Press. https://doi.org/10.17226/10490.

Leucine

One RCT examined leucine requirements in adult (19-59 years) males.[86] This RCT used the 24-hour AA balance method, the direct AA oxidation method, and the nitrogen balance method to determine leucine requirements. This RCT was cited in the 2005 IOM report on protein.

Lysine

Four studies, three RCTs[84,85,87] and 1 NRCT,[83] examined lysine requirements in adults (19-59 years). One RCT had not been previously cited in the 2005 IOM report on protein.[84] In this study, lysine requirements were assessed using the IAAO method and participants were limited to females.[84] Of the three studies that had been cited in the 2005 IOM report on protein, two were conducted with male participants and utilized the IAAO and 24-hour indicator AA balance methods to determine lysine requirements, whereas one was conducted with both male and female participants and utilized the 24-hour AA balance and direct AA oxidation methods to determine lysine requirements.

Methionine

Two RCTs examined methionine requirements in adult (19-59 years) males.[89,90] Both RCTs utilized the IAAO and 24-hour AA balance methods to determine methionine requirements. Neither study was cited in the 2005 IOM report on protein.

Threonine

Two RCTs examined threonine requirements in adults (19-59 years),[82,88] both of which were cited in the 2005 IOM report. Both RCTs utilized the IAAO and 24-hour indicator AA balance methods to determine threonine requirements. One RCT was conducted with male participants,[88] whereas one RCT included both male and female participants.[82]

Valine

One RCT examined valine requirements in adult (19-59 years) males.[91] This RCT utilized the IAAO and 24-hour indicator AA balance methods to determine valine requirements. This RCT was cited in the 2005 IOM report on protein.

Total branched-chain AAs (BCAAs)

Two RCTs examined the total requirement for BCAAs (isoleucine, leucine, valine) in adult (19-59 years) males.[92,93] Both RCTs utilized the IAAO method to determine BCAA requirements. Neither study was cited in the 2005 IOM report on protein.

Considerations for future DRI work

As the DRI process moves forward at the guidance of the Working Group, the following may be important to consider as a result of this completed evidence scan:

1. Relatively few studies or systematic reviews have been published on the topic of total protein or individual indispensable AA requirements since the completion of the 2005 IOM report on protein DRIs. Most new evidence was focused on total protein requirements and assessed adults (19-59 years) and older adults (60+ years). Fewer new studies were available on individual indispensable AA requirements (6 RCTs) or in children (2-12 years; 1 RCT). No new evidence was identified for adolescents, toddlers, or infants except as part of a systematic review on total protein requirements across the lifespan.

2. Citation mining, while a useful strategy for mapping evidence in a subject area, searches within a small, contained sample, and is not an exhaustive search method. Therefore, it is possible that there are

additional, relevant studies that have been published since the completion of the 2005 IOM report on protein DRIs that were not captured by this evidence scan.

3. A full systematic review to fully explore this topic may be beneficial to inform future DRI work. The information found through citation mining was thorough but was part of an abbreviated evidence scan procedure. A systematic review would potentially provide a stronger body of evidence on protein requirements.

Table 3-b. Protein requirements bibliography with study characteristics: total protein[a]

Citation	Protein Requirement(s) Assessed	Outcome Assessment Method(s)	Population(s) Examined	Study Design(s)
Children (2-12 y)				
Elango, R, Humayun, MA, Ball, RO, Pencharz, PB. Protein requirement of healthy school-age children determined by the indicator amino acid oxidation method. American Journal of Clinical Nutrition. 2011. 94(6):1545-1552. doi:10.3945/ajcn.111.012815.[73]	Total Protein	Indicator AA oxidation method	Children (2-12 y)	RCT
Adults (19-59 y)				
Humayun, MA, Elango, R, Ball, RO, Pencharz, PB. Reevaluation of the protein requirement in young men with the indicator amino acid oxidation technique. American Journal of Clinical Nutrition. 2007. 86(4):995-1002. doi:10.1093/ajcn/86.4.995.[74]	Total Protein	Indicator AA oxidation method, Nitrogen balance method	Adults (19-59 y), Males Alone	RCT, Meta-Analysis (29 studies)
Tian, Y, Liu, J, Zhang, Y, Piao, J, Gou, L, Tian, Y, Li, M, Ji, Y, Yang, X. Examination of chinese habitual dietary protein requirements of chinese young female adults by an indicator amino acid method. Asia Pacific Journal of Clinical Nutrition. 2011. 20(3):390-396. https://apjcn.nhri.org.tw/server/APJCN/20/3/390.pdf. Accessed February 9, 2022.[81]	Total Protein	Indicator AA oxidation method	Adults (19-59 y), Females Alone	RCT
Adults (19-59 y) and Older Adults (60+ y)				
Campbell, WW, Johnson, CA, McCabe, GP, Carnell, NS. Dietary protein requirements of younger and older adults. American Journal of Clinical Nutrition. 2008. 88(5):1322-1329. doi:10.3945/ajcn.2008.26072.[72]	Total Protein	Nitrogen balance method	Adults (19-59 y), Older Adults (60+ y)	RCT

Citation	Protein Requirement(s) Assessed	Outcome Assessment Method(s)	Population(s) Examined	Study Design(s)
[b]Rand, WM, Pellett, PL, Young, VR. Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults. American Journal of Clinical Nutrition. 2003. 77(1):109-127. doi:10.1093/ajcn/77.1.109.[78]	Total Protein	Nitrogen balance method	Adults (19-59 y), Older Adults (60+ y)	Systematic Review (27 studies), Meta-Analysis (19 studies)
Older Adults (60+ y)				
Morse, MH, Haub, MD, Evans, WJ, Campbell, WW. Protein requirement of elderly women: Nitrogen balance responses to three levels of protein intake. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2001. 56(11):M724-M730. doi:10.1093/gerona/56.11.M724.[75]	Total Protein	Nitrogen balance method	Older Adults (60+ y), Females Alone	RCT
Pedersen, AN, Cederholm, T. Health effects of protein intake in healthy elderly populations: A systematic literature review. Food and Nutrition Research. 2014. 58. doi:10.3402/fnr.v58.23364.[76]	Total Protein	Nitrogen balance method	Older Adults (60+ y)	Systematic Review (1 meta-analysis [Rand 2003] with 19 included studies, 4 studies)
Rafii, M, Chapman, K, Elango, R, Campbell, WW, Ball, RO, Pencharz, PB, Courtney-Martin, G. Dietary protein requirement of men > 65 years old determined by the indicator amino acid oxidation technique is higher than the current estimated average requirement. Journal of Nutrition. 2016. 146(4):681-687. doi:10.3945/jn.115.225631.[77]	Total Protein	Indicator AA oxidation method	Older Adults (60+ y), Males Alone	RCT

Citation	Protein Requirement(s) Assessed	Outcome Assessment Method(s)	Population(s) Examined	Study Design(s)
Tang, M, McCabe, GP, Elango, R, Pencharz, PB, Ball, RO, Campbell, WW. Assessment of protein requirement in octogenarian women with use of the indicator amino acid oxidation technique. American Journal of Clinical Nutrition. 2014. 99(4):891-898. doi:10.3945/ajcn.112.042325.[80]	Total Protein	Indicator AA oxidation method	Older Adults (60+ y), Females Alone	RCT
All Age Groups				
Richter, M, Baerlocher, K, Bauer, JM, Elmadfa, I, Heseker, H, Leschik-Bonnet, E, Stangl, G, Volkert, D, Stehle, P. Revised Reference Values for the Intake of Protein. Annals of Nutrition and Metabolism. 2019. 74(3):242-250. doi:10.1159/000499374.[79]	Total Protein	Factorial method, Mean protein content of human milk, Nitrogen balance method	Infants (0-6 mo), Infants (7-11 mo), Toddlers (12-23 mo), Children (2-12 y), Adolescents (13-18 y), Adults (19-59 y), Older Adults (60+ y)	Systematic Review (number of included studies NR)

[a] Abbreviations: AA, amino acid; BCAA, branched-chain amino acid; NRCT, non-randomized controlled trial; RCT, randomized controlled trial; y, year

[b] Included in: Institute of Medicine 2005. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington, DC: The National Academies Press. https://doi.org/10.17226/10490.

Table 3-c. Protein requirements bibliography with study characteristics: individual amino acids[a]

Citation	Protein Requirement(s) Assessed	Outcome Assessment Method(s)	Population(s) Examined	Study Design(s)
Leucine				
[b]Kurpad, AV, Raj, T, El-Khoury, A, Kuriyan, R, Maruthy, K, Borgonha, S, Chandukudlu, D, Regan, MM, Young, VR. Daily requirement for and splanchnic uptake of leucine in healthy adult Indians. American Journal of Clinical Nutrition. 2001. 74(6):747-755. doi:10.1093/ajcn/74.6.747.[86]	Leucine	24-hour AA balance method, Direct AA oxidation method, Nitrogen balance method	Adults (19-59 y), Males Alone	RCT
Lysine				
[b]El-Khoury, AE, Pereira, PCM, Borgonha, S, Basile, A, Beaumier, L, Wang, SY, Metges, CC, Ajami, AM, Young, VR. Twenty-four-hour oral tracer studies with L-[1-C-13]lysine at a low (15 mg center dot kg(-1)center dot d(-1)) and intermediate (29 mg-kg(-1)center dot d(-1)) lysine intake in healthy adults. American Journal of Clinical Nutrition. 2000. 72(1):122-130. doi:10.1093/ajcn/72.1.122.[83]	Lysine	24-hour AA balance method, Direct AA oxidation method	Adults (19-59 y)	NRCT
Kriengsinyos, W, Wykes, LJ, Goonewardene, LA, Ball, RO, Pencharz, PB. Phase of menstrual cycle affects lysine requirement in healthy women. American Journal of Physiology-Endocrinology and Metabolism. 2004. 287(3):E489-E496. doi:10.1152/ajpendo.00262.2003.[84]	Lysine	Indicator AA oxidation method	Adults (19-59 y), Females Alone	RCT
[b]Kurpad, AV, Raj, T, El-Khoury, A, Beaumier, L, Kuriyan, R, Srivatsa, A, Borgonha, S, Selvaraj, A, Regan, MM, Young, VR. Lysine requirements of healthy adult Indian subjects, measured by an indicator amino acid balance technique. American Journal of Clinical Nutrition. 2001. 73(5):900-907. doi:10.1093/ajcn/73.5.900.[85]	Lysine	Indicator AA oxidation method, 24-hour indicator AA balance method	Adults (19-59 y), Males Alone	RCT

Citation	Protein Requirement(s) Assessed	Outcome Assessment Method(s)	Population(s) Examined	Study Design(s)
[b]Kurpad, AV, Regan, MM, Raj, T, El-Khoury, A, Kuriyan, R, Vaz, M, Chandakudlu, D, Venkataswamy, VG, Borgonha, S, Young, VR. Lysine requirements of healthy adult Indian subjects receiving long-term feeding, measured with a 24-h indicator amino acid oxidation and balance technique. American Journal of Clinical Nutrition. 2002. 76(2):404-412. doi:10.1093/ajcn/76.2.404.[87]	Lysine	Indicator AA oxidation method, 24-hour indicator AA balance method	Adults (19-59 y), Males Alone	RCT
Methionine				
Kurpad, AV, Regan, MM, Varalakshmi, S, Gnanou, J, Lingappa, A, Young, VR. Effect of cystine on the methionine requirement of healthy Indian men determined by using the 24-h indicator amino acid balance approach. American Journal of Clinical Nutrition. 2004. 80(6):1526-1535. doi:10.1093/ajcn/80.6.1526.[90]	Methionine	Indicator AA oxidation method, 24-hour indicator AA balance method	Adults (19-59 y), Males Alone	RCT
Kurpad, AV, Regan, MM, Varalakshmi, S, Vasudevan, J, Gnanou, J, Raj, T, Young, VR. Daily methionine requirements of healthy Indian men, measured by a 24-h indicator amino acid oxidation and balance technique. American Journal of Clinical Nutrition. 2003. 77(5):1198-1205. doi:10.1093/ajcn/77.5.1198.[89]	Methionine	Indicator AA oxidation method, 24-hour indicator AA balance method	Adults (19-59 y), Males Alone	RCT
Threonine				
[b]Borgonha, S, Regan, MM, Oh, SH, Condon, M, Young, VR. Threonine requirement of healthy adults, derived with a 24-h indicator amino acid balance technique. American Journal of Clinical Nutrition. 2002. 75(4):698-704. doi:10.1093/ajcn/75.4.698.[82]	Threonine	Indicator AA oxidation method, 24-h indicator AA balance method	Adults (19-59 y)	RCT

Citation	Protein Requirement(s) Assessed	Outcome Assessment Method(s)	Population(s) Examined	Study Design(s)
[b]Kurpad, AV, Raj, T, Regan, MM, Vasudevan, J, Caszo, B, Nazareth, D, Gnanou, J, Young, VR. Threonine requirements of healthy Indian men, measured by a 24-h indicator amino acid oxidation and balance technique. American Journal of Clinical Nutrition. 2002. 76(4):789-797. doi:10.1093/ajcn/76.4.789.[88]	Threonine	Indicator AA oxidation method, 24-hour indicator AA balance method	Adults (19-59 y), Males Alone	RCT
Valine				
Kurpad, AV, Regan, MM, Raj, TDS, Gnanou, JV, Rao, VN, Young, VR. The daily valine requirement of healthy adult Indians determined by the 24-h indicator amino acid balance approach. American Journal of Clinical Nutrition. 2005. 82(2):373-379. doi:10.1093/ajcn/82.2.373.[91]	Valine	Indicator AA oxidation method, 24-hour indicator AA balance method	Adults (19-59 y), Males Alone	RCT
Total BCAAs				
Riazi, R, Rafii, M, Wykes, LJ, Ball, RO, Pencharz, PB. Valine may be the first limiting branched-chain amino acid in egg protein in men. Journal of Nutrition. 2003. 133(11):3533-3539. doi:10.1093/jn/133.11.3533.[92]	Isoleucine, Leucine, Valine (Assessed together as BCAAs)	Indicator AA oxidation method	Adults (19-59 y), Males Alone	RCT
Riazi, R, Wykes, LJ, Ball, RO, Pencharz, PB. The total branched-chain amino acid requirement in young healthy adult men determined by indicator amino acid oxidation by use of L-[1-C-13]phenylalanine. Journal of Nutrition. 2003. 133(5):1383-1389. doi:10.1093/jn/133.5.1383.[93]	Isoleucine, Leucine, Valine (Assessed together as BCAAs)	Indicator AA oxidation method	Adults (19-59 y), Males Alone	RCT

[a] Abbreviations: AA, amino acid; BCAA, branched-chain amino acid; NRCT, non-randomized controlled trial; RCT, randomized controlled trial; y, year

[b] Included in: Institute of Medicine 2005. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Ar
National Academies Press. https://doi.org/10.17226/10490.

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The NESR team members were involved in: establishing all aspects of the protocol, which presented the plan for how they would examine the scientific evidence, including the inclusion and exclusion criteria; reviewing all studies that met the criteria they set; and describing the body of evidence for each question. The NESR team facilitated, executed, and documented the work necessary to ensure the evidence scan was completed in accordance with NESR methodology.

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Appendices

Appendix 0: Abbreviations

Abbreviation	Full name
AA	Amino acid(s)
ACM	All-cause mortality
AI	Adequate Intake
AMDR	Acceptable Macronutrient Distribution Range
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
ARS	Agricultural Research Service
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body Mass Index
CNPP	Center for Nutrition Policy and Promotion
CVD	Cardiovascular disease
d	Day(s)
DRI	Dietary Reference Intakes
EAR	Estimated Average Requirement
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FDA	Food and Drug Administration
FNS	Food and Nutrition Service
g	Gram(s)
GFR	Glomerular filtration rate
GI	Gastrointestinal
GRAS	Generally recognized as safe
HbA1c	Hemoglobin A1c
HDI	Human Development Index
HHS	Health and Human Services

Abbreviation	Full name
IAAO	Indicator amino acid oxidation
IOM	Institute of Medicine
kg	Kilogram(s)
MA	Meta-analysis
mg	Milligram(s)
N	Nitrogen
NESR	Nutrition Evidence Systematic Review
NGAD	Nutrition Guidance and Analysis Division
NIH	National Institutes of Health
NRCT	Non-randomized controlled trial
ODPHP	Office of Disease Prevention and Health Promotion
PCS	Prospective cohort study
PICO	Population, Intervention/exposure, comparator, outcome
RCT	Randomized controlled trial
RDA	Recommended Dietary Allowance
SR	Systematic Review
UL	Tolerable Upper Limit
USDA	United States Department of Agriculture
WG	DRI Protein Working Group
Working Group	Joint Canada-US Dietary Reference Intakes Working Group
y	Year(s)

Appendix 1-a: Literature search strategy for high protein intake and acute adverse health effects evidence scan

Database: PubMed
Provider: U.S. National Library of Medicine
Date(s) Searched: October 26, 2021

Search #	Concept	String	Results
#1	Dietary Proteins and Amino Acids	“dietary proteins”[MeSH] OR “Amino Acids”[MeSH] OR “Diet, High Protein”[MeSH] OR “protein intake”[TIAB] OR “high protein”[TIAB] OR “protein consumption”[TIAB] OR “protein supplement*”[TIAB] OR “increased protein”[tiab] OR “amino acid*”[tiab] OR Histidine[tiab] OR isoleucine[tiab] OR leucine[tiab] OR lysine[tiab] OR methionine[tiab] OR cysteine[tiab] OR phenylalanine[tiab] OR tyrosine[tiab] OR threonine[tiab] OR tryptophan[tiab] OR valine[tiab]	1,593,139
#2	Upper Limits	"No-Observed-Adverse-Effect Level"[Mesh] OR “Upper limit*”[tiab] OR “upper reference level*”[tiab] OR toxicity[tiab] OR “upper safe limit*”[tiab] OR “tolerance”[tiab] OR “tolerable upper intake level”[tiab] OR “excessive intake”[tiab] OR “adverse effect*”[tiab] OR “excessive”[tiab]	971,557
#3	Review	review[ptyp] OR scoping review[ti] OR narrative review[ti] OR qualitative review[ti] OR evidence review[ti] OR quantitative review[ti] OR meta-review[ti] OR critical review[ti] OR mixed studies review[ti] OR mapping review[ti] OR integrative review[ti] OR (literature[ti] AND review[ti]) OR systematic review[ptyp] OR systematic review[ti] OR meta-analysis[ptyp] OR meta-analysis[ti] OR meta-analyses[ti]	3,104,796
#4	#1 AND #2 AND #3		8,193
#5	Limiters	NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) Language: English Publication Date: 2016-present	2,377

Appendix 1-b: Excluded articles for high protein intake and acute adverse health effects evidence scan

The following table lists the articles excluded after full-text screening for this evidence scan. At least one reason for exclusion is provided for each article, though this may not reflect all possible reasons. Information about articles excluded after title and abstract screening is available upon request.

#	Citation	Exclusion reason #1	Exclusion reason #2	Exclusion reason #3
1	Ancu, O.,Mickute, M.,Guess, N. D.,Hurren, N. M.,Burd, N. A.,Mackenzie, R. W.. Does high dietary protein intake contribute to the increased risk of developing prediabetes and type 2 diabetes?. Appl Physiol Nutr Metab. 2021. 46:1-9. doi:10.1139/apnm-2020-0396 .	Outcome	-	-
2	Andreeva, E.,Tkeshelashvili, B.. Women dealing with hot flushes: the role of beta-alanine. Eur Rev Med Pharmacol Sci. 2020. 24:5148-5154. doi:10.26355/eurrev_202005_21209 .	Outcome	Health status	-
3	Antonio, J.,Candow, D. G.,Forbes, S. C.,Gualano, B.,Jagim, A. R.,Kreider, R. B.,Rawson, E. S.,Smith-Ryan, A. E.,VanDusseldorp, T. A.,Willoughby, D. S.,Ziegenfuss, T. N.. Common questions and misconceptions about creatine supplementation: what does the scientific evidence really show?. J Int Soc Sports Nutr. 2021. 18:13. doi:10.1186/s12970-021-00412-w .	IV/E	-	-
4	Arrieta-Cruz, I.,Gutierrez-Juarez, R.. The Role of Circulating Amino Acids in the Hypothalamic Regulation of Liver Glucose Metabolism. Adv Nutr. 2016. 7:790S-7S. doi:10.3945/an.115.011171 .	IV/E	Outcome	-
5	Backus, K. M.. Applications of Reactive Cysteine Profiling. Curr Top Microbiol Immunol. 2019. 420:375-417. doi:10.1007/82_2018_120 .	IV/E	Outcome	-
6	Badawy, A. A.,Namboodiri, A. M.,Moffett, J. R.. The end of the road for the tryptophan depletion concept in pregnancy and infection. Clin Sci (Lond). 2016. 130:1327-33. doi:10.1042/CS20160153 .	Outcome		-
7	Balestrino, M.. Role of Creatine in the Heart: Health and Disease. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13041215	IV/E		-
8	Barkovich, E.,Gropman, A. L.. Late Onset Ornithine Transcarbamylase Deficiency Triggered by an Acute Increase in Protein Intake: A Review of 10 Cases Reported in the Literature. Case Rep Genet. 2020. 2020:7024735. doi:10.1155/2020/7024735 .	Outcome	Health status	-

#	Citation	Exclusion reason #1	Exclusion reason #2	Exclusion reason #3
9	Bird, J. A.,Barni, S.,Brown-Whitehorn, T. F.,du Toit, G.,Infante, S.,Nowak-Wegrzyn, A.. Food protein-induced enterocolitis syndrome oral food challenge: Time for a change?. Ann Allergy Asthma Immunol. 2021. 126:506-515. doi:10.1016/j.anai.2021.02.022 .	IV/E	-	-
10	Blachier, F.,Blais, A.,Elango, R.,Saito, K.,Shimomura, Y.,Kadowaki, M.,Matsumoto, H.. Tolerable amounts of amino acids for human supplementation: summary and lessons from published peer-reviewed studies. Amino Acids. 2021. 53:1313-1328. doi:10.1007/s00726-021-03054-z .	Outcome	Non-human	-
11	Cava, E.,Yeat, N. C.,Mittendorfer, B.. Preserving Healthy Muscle during Weight Loss. Adv Nutr. 2017. 8:511-519. doi:10.3945/an.116.014506 .	Outcome	-	-
12	Curran, C. P.,Marczinski, C. A.. Taurine, caffeine, and energy drinks: Reviewing the risks to the adolescent brain. Birth Defects Res. 2017. 109:1640-1648. doi:10.1002/bdr2.1177 .	IV/E	-	-
13	D'Arcy, E.,Rayner, J.,Hodge, A.,Ross, L. J.,Schoenaker, Dajm. The Role of Diet in the Prevention of Diabetes among Women with Prior Gestational Diabetes: A Systematic Review of Intervention and Observational Studies. J Acad Nutr Diet. 2020. 120:69-85 e7. doi:10.1016/j.jand.2019.07.021 .	Outcome	-	-
14	Davani-Davari, D.,Karimzadeh, I.,Ezzatzadegan-Jahromi, S.,Sagheb, M. M.. Potential Adverse Effects of Creatine Supplement on the Kidney in Athletes and Bodybuilders. Iran J Kidney Dis. 2018. 12:253-260. doi:#electronic resource number# .	IV/E	-	-
15	De Bandt, J. P.. Leucine and Mammalian Target of Rapamycin-Dependent Activation of Muscle Protein Synthesis in Aging. J Nutr. 2016. 146:2616S-2624S. doi:10.3945/jn.116.234518 .	IV/E	Outcome	-
16	De Waele, E.,Jakubowski, J. R.,Stocker, R.,Wischmeyer, P. E.. Review of evolution and current status of protein requirements and provision in acute illness and critical care. Clin Nutr. 2021. 40:2958-2973. doi:10.1016/j.clnu.2020.12.032 .	Health status	-	-
17	Dimina, L.,Mariotti, F.. The Postprandial Appearance of Features of Cardiometabolic Risk: Acute Induction and Prevention by Nutrients and Other Dietary Substances. Nutrients. 2019. 11:#pages#. doi:10.3390/nu11091963 .	IV/E	-	-
18	Ding, X.,Bin, P.,Wu, W.,Chang, Y.,Zhu, G.. Tryptophan Metabolism, Regulatory T Cells, and Inflammatory Bowel Disease: A Mini Review. Mediators Inflamm. 2020. 2020:9706140. doi:10.1155/2020/9706140 .	Outcome	Health status	-

#	Citation	Exclusion reason #1	Exclusion reason #2	Exclusion reason #3
19	Djuric, D.,Jakovljevic, V.,Zivkovic, V.,Srejovic, I.. Homocysteine and homocysteine-related compounds: an overview of the roles in the pathology of the cardiovascular and nervous systems. Can J Physiol Pharmacol. 2018. 96:991-1003. doi:10.1139/cjpp-2018-0112 .	Outcome	-	-
20	Dolan, E.,Swinton, P. A.,Painelli, V. S.,Stephens Hemingway, B.,Mazzolani, B.,Infante Smaira, F.,Saunders, B.,Artioli, G. G.,Gualano, B.. A Systematic Risk Assessment and Meta-Analysis on the Use of Oral beta-Alanine Supplementation. Adv Nutr. 2019. 10:452-463. doi:10.1093/advances/nmy115 .	IV/E	-	-
21	Dubo, S.,Gallegos, D.,Cabrera, L.,Sobrevia, L.,Zuniga, L.,Gonzalez, M.. Cardiovascular Action of Insulin in Health and Disease: Endothelial L-Arginine Transport and Cardiac Voltage-Dependent Potassium Channels. Front Physiol. 2016. 7:74. doi:10.3389/fphys.2016.00074 .	IV/E	Outcome	-
22	Esse, R.,Barroso, M.,Tavares de Almeida, I.,Castro, R.. The Contribution of Homocysteine Metabolism Disruption to Endothelial Dysfunction: State-of-the-Art. Int J Mol Sci. 2019. 20:#pages#. doi:10.3390/ijms20040867 .	Outcome	-	-
23	Franceschi, N.,Paraskevopoulos, K.,Waigmann, E.,Ramon, M.. Predictive Protein Toxicity and Its Use in Risk Assessment. Trends Biotechnol. 2017. 35:483-486. doi:10.1016/j.tibtech.2017.03.010 .	IV/E	Outcome	-
24	Galvan, E.,Arentson-Lantz, E.,Lamon, S.,Paddon-Jones, D.. Protecting Skeletal Muscle with Protein and Amino Acid during Periods of Disuse. Nutrients. 2016. 8:#pages#. doi:10.3390/nu8070404 .	Outcome	-	-
25	Haleem, D. J.. Improving therapeutics in anorexia nervosa with tryptophan. Life Sci. 2017. 178:87-93. doi:10.1016/j.lfs.2017.04.015 .	Health status	-	-
26	Hansen, T. T.,Astrup, A.,Sjodin, A.. Are Dietary Proteins the Key to Successful Body Weight Management? A Systematic Review and Meta-Analysis of Studies Assessing Body Weight Outcomes after Interventions with Increased Dietary Protein. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13093193 .	Outcome	-	-
27	Harvey, Cjdc,Schofield, G. M.,Williden, M.. The use of nutritional supplements to induce ketosis and reduce symptoms associated with keto-induction: a narrative review. PeerJ. 2018. 6:e4488. doi:10.7717/peerj.4488 .	IV/E	Outcome	-
28	Herring, C. M.,Bazer, F. W.,Johnson, G. A.,Wu, G.. Impacts of maternal dietary protein intake on fetal survival, growth, and development. Exp Biol Med (Maywood). 2018. 243:525-533. doi:10.1177/1535370218758275 .	Outcome	-	-

#	Citation	Exclusion reason #1	Exclusion reason #2	Exclusion reason #3
29	Hoffmann, N. V.,Ahmed, A.,Fortunato, J. E.. Food protein-induced enterocolitis syndrome: Dynamic relationship among gastrointestinal symptoms, immune response, and the autonomic nervous system. Ann Allergy Asthma Immunol. 2021. 126:498-505. doi:10.1016/j.anai.2021.02.004 .	IV/E	-	-
30	Holecek, M.. Branched-chain amino acids in health and disease: metabolism, alterations in blood plasma, and as supplements. Nutr Metab (Lond). 2018. 15:33. doi:10.1186/s12986-018-0271-1 .	Design	Health status	-
31	Kang, J.,Ratamess, N. A.,Faigenbaum, A. D.,Bush, J. A.. Ergogenic Properties of Ketogenic Diets in Normal-Weight Individuals: A Systematic Review. J Am Coll Nutr. 2020. 39:665-675. doi:10.1080/07315724.2020.1725686 .	IV/E	- -	-
32	Kim, J.,Kim, H.,Roh, H.,Kwon, Y.. Causes of hyperhomocysteinemia and its pathological significance. Arch Pharm Res. 2018. 41:372-383. doi:10.1007/s12272-018-1016-4	Outcome		-
33	Kozich, V.,Stabler, S.. Lessons Learned from Inherited Metabolic Disorders of Sulfur-Containing Amino Acids Metabolism. J Nutr. 2020. 150:2506S-2517S. doi:10.1093/jn/nxaa134 .	Health status	-	-
34	Lancha, A. H., Jr.,Zanella, R., Jr.,Tanabe, S. G.,Andriamihaja, M.,Blachier, F.. Dietary protein supplementation in the elderly for limiting muscle mass loss. Amino Acids. 2017. 49:33-47. doi:10.1007/s00726-016-2355-4 .	Outcome	-	-
35	Lehotsky, J.,Tothova, B.,Kovalska, M.,Dobrota, D.,Benova, A.,Kalenska, D.,Kaplan, P.. Role of Homocysteine in the Ischemic Stroke and Development of Ischemic Tolerance. Front Neurosci. 2016. 10:538. doi:10.3389/fnins.2016.00538 .	Outcome	-	-
36	Lekawanvijit, S.,Kompa, A. R.,Krum, H.. Protein-bound uremic toxins: a long overlooked culprit in cardiorenal syndrome. Am J Physiol Renal Physiol. 2016. 311:F52-62. doi:10.1152/ajprenal.00348.2015 .	IV/E	Health status	-
37	Ma, N.,Tian, Y.,Wu, Y.,Ma, X.. Contributions of the Interaction Between Dietary Protein and Gut Microbiota to Intestinal Health. Curr Protein Pept Sci. 2017. 18:795-808. doi:10.2174/1389203718666170216153505 .	Outcome	Non-human	-
38	Mastrorilli, C.,Santoro, A.,Procaccianti, M.,Pagliaro, G.,Caffarelli, C.. New insights into food protein-induced enterocolitis in children. Minerva Pediatr. 2020. 72:416-423. doi:10.23736/S0026-4946.20.05976-9 .	IV/E		-

#	Citation	Exclusion reason #1	Exclusion reason #2	Exclusion reason #3
39	Matthews, J. J.,Dolan, E.,Swinton, P. A.,Santos, L.,Artioli, G. G.,Turner, M. D.,Elliott-Sale, K. J.,Sale, C.. Effect of Carnosine or beta-Alanine Supplementation on Markers of Glycemic Control and Insulin Resistance in Humans and Animals: A Systematic Review and Meta-analysis. Adv Nutr. 2021. #volume#:#pages#. doi:10.1093/advances/nmab087 .	Outcome	-	-
40	Mazzucato, M.,Fioretto, P.,Avogaro, A.. High-protein diet: A barrier to the nephroprotective effects of sodium-glucose co-transporter-2 inhibitors?. Diabetes Obes Metab. 2020. 22:1511-1515. doi:10.1111/dom.14071 .	Outcome	-	-
41	Meftah, A.,Hasegawa, H.,Kantrowitz, J. T.. D-Serine: A Cross Species Review of Safety. Front Psychiatry. 2021. 12:726365. doi:10.3389/fpsyt.2021.726365 .	IV/E	-	-
42	Mirzaei, H.,Raynes, R.,Longo, V. D.. The conserved role of protein restriction in aging and disease. Curr Opin Clin Nutr Metab Care. 2016. 19:74-9. doi:10.1097/MCO.0000000000000239 .	IV/E	-	-
43	Moon, J.,Koh, G.. Clinical Evidence and Mechanisms of High-Protein Diet-Induced Weight Loss. J Obes Metab Syndr. 2020. 29:166-173. doi:10.7570/jomes20028 .	Outcome	-	-
44	Moore, D. R.. Maximizing Post-exercise Anabolism: The Case for Relative Protein Intakes. Front Nutr. 2019. 6:147. doi:10.3389/fnut.2019.00147 .	Outcome	-	-
45	Moulle, V. S.,Parnet, P.. Effects of Nutrient Intake during Pregnancy and Lactation on the Endocrine Pancreas of the Offspring. Nutrients. 2019. 11:#pages#. doi:10.3390/nu11112708 .	Outcome	-	-
46	Mousa, A.,Naqash, A.,Lim, S.. Macronutrient and Micronutrient Intake during Pregnancy: An Overview of Recent Evidence. Nutrients. 2019. 11:#pages#. doi:10.3390/nu11020443 .	Outcome	-	-
47	Moussa, M.,Papatsoris, A. G.,Abou Chakra, M.,Moussa, Y.. Update on cystine stones: current and future concepts in treatment. Intractable Rare Dis Res. 2020. 9:71-78. doi:10.5582/irdr.2020.03006 .	IV/E	Health status	-
48	Nurul Adilah, Z.,Mohd Redzwan, S.. Effect of dietary macronutrients on aflatoxicosis: a mini-review. J Sci Food Agric. 2017. 97:2277-2281. doi:10.1002/jsfa.8234 .	IV/E	Non-human	-
49	Osborn, D. A.,Schindler, T.,Jones, L. J.,Sinn, J. K.,Bolisetty, S.. Higher versus lower amino acid intake in parenteral nutrition for newborn infants. Cochrane Database Syst Rev. 2018. 3:CD005949. doi:10.1002/14651858.CD005949.pub2 .	Health status	-	-

#	Citation	Exclusion reason #1	Exclusion reason #2	Exclusion reason #3
50	Pereira-da-Silva, L.,Rego, C.,Pietrobelli, A.. The Diet of Preschool Children in the Mediterranean Countries of the European Union: A Systematic Review. Int J Environ Res Public Health. 2016. 13:#pages#. doi:10.3390/ijerph13060572 .	IV/E	Outcome	-
51	Phillips, S. M.,Paddon-Jones, D.,Layman, D. K.. Optimizing Adult Protein Intake During Catabolic Health Conditions. Adv Nutr. 2020. 11:S1058-S1069. doi:10.1093/advances/nmaa047 .	Outcome	-	-
52	Popova, A. A.,Koksharova, O. A.. Neurotoxic Non-proteinogenic Amino Acid beta-N-Methylamino-L-alanine and Its Role in Biological Systems. Biochemistry (Mosc). 2016. 81:794-805. doi:10.1134/S0006297916080022 .	IV/E	Outcome	-
53	Roberts, A.,Lynch, B.,Rietjens, Imcm. Risk Assessment Paradigm for Glutamate. Ann Nutr Metab. 2018. 73 Suppl 5:53-64. doi:10.1159/000494783 .	IV/E	-	-
54	Saito, M.,Marumo, K.. The Effects of Homocysteine on the Skeleton. Curr Osteoporos Rep. 2018. 16:554-560. doi:10.1007/s11914-018-0469-1 .	IV/E	Outcome	-
55	Shams-White, M. M.,Chung, M.,Du, M.,Fu, Z.,Insogna, K. L.,Karlsen, M. C.,LeBoff, M. S.,Shapses, S. A.,Sackey, J.,Wallace, T. C.,Weaver, C. M.. Dietary protein and bone health: a systematic review and meta-analysis from the National Osteoporosis Foundation. Am J Clin Nutr. 2017. 105:1528-1543. doi:10.3945/ajcn.116.145110 .	Outcome	-	-
56	Shiao, S. P. K.,Lie, A.,Yu, C. H.. Meta-analysis of homocysteine-related factors on the risk of colorectal cancer. Oncotarget. 2018. 9:25681-25697. doi:10.18632/oncotarget.25355 .	IV/E	Outcome	-
57	Sivashanmugam, M.,J, J.,V, U.,K, N. S.. Ornithine and its role in metabolic diseases: An appraisal. Biomed Pharmacother. 2017. 86:185-194. doi:10.1016/j.biopha.2016.12.024 .	IV/E	-	-
58	Skovierova, H.,Vidomanova, E.,Mahmood, S.,Sopkova, J.,Drgova, A.,Cervenova, T.,Halasova, E.,Lehotsky, J.. The Molecular and Cellular Effect of Homocysteine Metabolism Imbalance on Human Health. Int J Mol Sci. 2016. 17:#pages#. doi:10.3390/ijms17101733 .	Design	Outcome	-
59	Slater, G. J.,Sygo, J.,Jorgensen, M.. SPRINTING. . . Dietary Approaches to Optimize Training Adaptation and Performance. Int J Sport Nutr Exerc Metab. 2019. 29:85-94. doi:10.1123/ijsnem.2018-0273 .	Outcome	-	-
60	Strasser, B.,Fuchs, D.. Diet Versus Exercise in Weight Loss and Maintenance: Focus on Tryptophan. Int J Tryptophan Res. 2016. 9:9-16. doi:10.4137/IJTR.S33385 .	IV/E	Outcome	-

#	Citation	Exclusion reason #1	Exclusion reason #2	Exclusion reason #3
61	Thompson, M. E.,Noel, M. B.. Issues in Nutrition: Dietary Supplements. FP Essent. 2017. 452:18-25. doi:#electronic resource number# .	IV/E	Outcome	-
62	Tielemans, M. J.,Garcia, A. H.,Peralta Santos, A.,Bramer, W. M.,Luksa, N.,Luvizotto, M. J.,Moreira, E.,Topi, G.,de Jonge, E. A.,Visser, T. L.,Voortman, T.,Felix, J. F.,Steegers, E. A.,Kiefte-de Jong, J. C.,Franco, O. H.. Macronutrient composition and gestational weight gain: a systematic review. Am J Clin Nutr. 2016. 103:83-99. doi:10.3945/ajcn.115.110742 .	Outcome	-	-
63	Tome, D.. Admissible daily intake for glutamate. Curr Opin Clin Nutr Metab Care. 2020. 23:133-137. doi:10.1097/MCO.0000000000000624 .	IV/E	-	-
64	Torre-Villalvazo, I.,Aleman-Escondrillas, G.,Valle-Rios, R.,Noriega, L. G.. Protein intake and amino acid supplementation regulate exercise recovery and performance through the modulation of mTOR, AMPK, FGF21, and immunity. Nutr Res. 2019. 72:1-17. doi:10.1016/j.nutres.2019.06.006 .	Outcome	-	-
65	Turkozu, D.,Sanlier, N.. L-theanine, unique amino acid of tea, and its metabolism, health effects, and safety. Crit Rev Food Sci Nutr. 2017. 57:1681-1687. doi:10.1080/10408398.2015.1016141 .	IV/E	Outcome	-
66	Volterman, K. A.,Atkinson, S. A.. Protein Needs of Physically Active Children. Pediatr Exerc Sci. 2016. 28:187-93. doi:10.1123/pes.2015-0257 .	IV/E	Outcome	-
67	Wade, F.,Belhaj, K.,Poizat, C.. Protein tyrosine phosphatases in cardiac physiology and pathophysiology. Heart Fail Rev. 2018. 23:261-272. doi:10.1007/s10741-018-9676-1 .	IV/E	Outcome	-
68	Wang, J.,Ji, H.. Influence of Probiotics on Dietary Protein Digestion and Utilization in the Gastrointestinal Tract. Curr Protein Pept Sci. 2019. 20:125-131. doi:10.2174/1389203719666180517100339 .	Outcome	-	-
69	Zhang, S.,Zeng, X.,Ren, M.,Mao, X.,Qiao, S.. Novel metabolic and physiological functions of branched chain amino acids: a review. J Anim Sci Biotechnol. 2017. 8:10. doi:10.1186/s40104-016-0139-z .	IV/E	Outcome	-
70	Zhuo, D. X.,Ragosta, M., 3rd,Patterson, B.. Tyrosine kinase inhibitor toxicity manifesting as comorbid Moyamoya syndrome and obstructive coronary artery disease: A case report and review of the literature. Catheter Cardiovasc Interv. 2019. 94:117-119. doi:10.1002/ccd.28189 .	Design	IV/E	Health status

Appendix 2-a: Literature search strategy for protein intake and chronic disease risk evidence scan

Database: PubMed
Provider: U.S. National Library of Medicine
Date(s) Searched: December 17, 2021

Search #	Concept	String	Results
#1	Protein	“dietary proteins”[MeSH] OR “Amino Acids”[MeSH] OR “Diet, High Protein”[MeSH] OR “protein intake”[TIAB] OR “high protein”[TIAB] OR “protein consumption”[TIAB] OR “protein supplement*”[TIAB] OR “increased protein”[tiab]	938,484
#2	GSBC	"Adipose Tissue"[Mesh] OR "Body Composition"[Mesh] OR "Body Weights and Measures"[MeSH:NoExp] OR "Body Fat Distribution"[Mesh] OR "Body Mass Index"[Mesh] OR "Body Size"[Mesh] OR "Skinfold Thickness"[Mesh] OR "Waist-Hip Ratio"[Mesh] OR "Overnutrition"[Mesh] OR "Growth"[Mesh:NoExp] OR anthropometr*[tiab] OR body fat[tiab] OR fat mass[tiab] OR fat free mass[tiab] OR lean mass[tiab] OR obese[tiab] OR obesity[tiab] OR underweight[tiab] OR overweight[tiab] OR weight status[tiab] OR head circumference[tiab] OR arm circumference[tiab] OR calf circumference[tiab] OR neck circumference[tiab] OR thigh circumference[tiab] OR waist circumference[tiab] OR waist to hip ratio[tiab] OR waist hip ratio[tiab] OR body mass index[tiab] OR BMI[tiab] OR adipos*[tiab] OR body weight[tiab] OR body height[tiab] OR body size[tiab] OR body composition[tiab] OR overnutrition[tiab] OR wasting[tiab] OR healthy weight[tiab] OR skin fold[tiab] OR skin folds[tiab] OR skinfold[tiab] OR skinfolds[tiab] OR "Weight Reduction Programs"[Mesh] OR "Body-Weight Trajectory"[Mesh] OR "Weight Gain"[MeSH] OR "Weight Loss"[MeSH:NoExp] OR “Diet, Reducing"[Mesh] OR weight gain[tiab] OR diet reduc*[tiab] OR weight cycling[tiab] OR weight decreas*[tiab] OR weight watch*[tiab] OR weight control*[tiab] OR weight retention[tiab] OR weight management[tiab] OR (weight[tiab] AND (maint*[tiab] OR reduc*[tiab] OR loss*[tiab] OR chang*[tiab])) OR “Growth Charts”[Mesh] OR growth chart*[tiab]OR stunting[tiab] OR stunted[tiab] OR weight for height[tiab] OR stature for age[tiab] OR weight for age[tiab] OR height for age[tiab] OR length for age[tiab] OR weight for length[tiab] OR failure to thrive[tiab]	1,394,632
#3	CVD	"Cardiovascular Diseases"[Mesh:NoExp] OR "cardiovascular disease*"[tiab] OR "coronary artery disease"[tiab] OR "heart disease*"[tiab] OR "Heart Failure"[Mesh] OR "heart failure"[tiab] OR "myocardial infarction*"[tiab] OR "Myocardial Ischemia"[Mesh] OR "myocardial ischemia*"[tiab] OR "Stroke"[Mesh] OR "stroke*"[tiab] OR "angina"[tiab] OR "heart attack*"[tiab] OR "Venous Thrombosis"[Mesh] OR "venous thrombosis"[tiab] OR "hypertension"[tiab] OR Blood Pressure[Mesh:NoExp] OR "high blood pressure"[tiab] OR "Lipids/blood"[Mesh] OR "Cholesterol, HDL"[Mesh] OR "HDL cholesterol"[tiab] OR "Cholesterol, LDL"[Mesh] OR "LDL cholesterol"[tiab] OR	2,173,208

		"total cholesterol"[tiab] OR “blood cholesterol”[tiab] OR "Triglycerides"[Mesh] OR "triglycerides"[tiab] OR "Hypertension"[Mesh:NoExp] OR hypertensi*[tiab] OR "Hypertension, Pregnancy-Induced"[Mesh] OR "Pre-Eclamp*"[tiab] OR preeclamp*[tiab] OR Eclamp*[tiab]	
#4	T2D	"Diabetes Mellitus"[Mesh:NoExp] OR "Diabetes Mellitus, Type 2"[Mesh] OR "type 2 diabet*"[tiab] OR "T2D"[tiab] OR "adult onset diabetes"[tiab] OR "Prediabetic State"[Mesh] OR "prediabet*"[tiab] OR "pre diabet*"[tiab] OR "Insulin Resistance"[Mesh] OR "insulin resistance"[tiab] OR "insulin resistant"[tiab] OR "glucose intolerance"[tiab] OR “glucose intolerant”[tiab] OR "glucose tolerance"[tiab] OR “glucose tolerant”[tiab] OR "Glycated Hemoglobin A"[Mesh] OR "hemoglobin A1c"[tiab] OR hba1c[tiab] OR "hba 1c"[tiab] OR “haemoglobin A1c”[tiab] OR "Hyperglycemia"[Mesh] OR "hyperglycemia"[tiab] OR hyperglycaemia[tiab] OR "Hypoglycemia"[Mesh] OR "hypoglycemia"[tiab] OR hypoglycaemia[tiab] OR ((impaired[tiab] OR glucose[tiab]) AND fasting[tiab]) OR "blood glucose"[MeSH] OR "blood glucose"[tiab] OR “plasma glucose”[tiab] OR “serum glucose”[tiab] OR "glycemi*"[tiab] OR glycaemi*[tiab] OR "blood sugar"[tiab] OR dysglycemi*[tiab] OR dysglycaemi*[tiab] OR hyperinsulinism[MeSH] OR hyperinsulin*[tiab] OR "Diabetes, Gestational"[Mesh] OR (gestation*[tiab] AND diabet*[tiab]) OR ("Maternal Nutritional Physiological Phenomena"[Mesh] AND diabet*[tiab])	660,434
#5	Bone Health	"Bone Density"[Mesh] OR “bone density”[tiab] OR bone mineral density[tiab] OR "Bone Development"[Mesh] OR “bone development"[tiab] OR "Fractures, Bone"[Mesh] OR "Bone Diseases"[Mesh] OR bone disease*[tiab] OR bone turnover[tiab] OR bone loss[tiab] OR osteoporosis[tiab] OR “Osteoporosis”[Mesh] OR osteopen*[tiab] OR osteitis[tiab] OR osteolysis[tiab] OR "Rickets"[Mesh] OR Rickets[tiab] OR bone mineral*[tiab] OR “bone mass”[tiab] OR bone health*[tiab] OR "Bone Demineralization, Pathologic"[Mesh] OR bone demineral*[tiab] OR "Bone Remodeling"[Mesh] OR bone strength[tiab] OR bone formation[tiab] OR bone accretion[tiab] OR bone mineral accretion[tiab] OR ((bone[tiab] OR bones[tiab] OR "Bone and Bones"[Mesh]) AND (fracture*[tiab] OR remodel*[tiab] OR ossification[tiab] OR resorption[tiab] OR BMC[tiab] OR BMD[tiab] OR "Biomarkers"[Mesh] OR biomarker*[tiab]))	918,688
#6	Sarcopenia	"Muscular Atrophy"[MesH] OR "sarcopen*"[tiab] OR "presarcopen*"[tiab] OR "muscular atroph*"[tiab] OR "Muscle Fatigue"[Mesh] OR "muscle fatigue"[tiab] OR "Muscle Strength"[Mesh] OR "muscle strength*"[tiab] OR "muscle wast*"[tiab] OR "muscle weak*"[tiab] OR "muscle loss*"[tiab] OR "muscle function*"[tiab] OR "muscle mass"[tiab] OR "hand strength*"[tiab] OR "grip strength*"[tiab] OR "handgrip*"[tiab] OR "pinch strength*"[tiab] OR "Physical Functional Performance"[Mesh] OR "physical performance*"[tiab]	150,647
#7	Chronic Kidney Disease	"Kidney Diseases"[MeSH:NoExp] OR "Renal Insufficiency"[MeSH] OR "Nephrolithiasis"[MeSH] OR ((renal[tiab] OR kidney[tiab]) AND (insufficiency[tiab] OR disease[tiab] OR failure[tiab] OR chronic[tiab] OR endstage[tiab] OR end stage[tiab])) OR CKF[tiab] OR CKD[tiab] OR CRF[tiab] OR CRD[tiab] OR ESKD[tiab] OR ESRD[tiab] OR ESKF[tiab] OR ESRF[tiab] OR	564,081

		nephrolith[tiab] OR kidney stone*[tiab] OR kidney calcul*[tiab] OR renal stone*[tiab] OR renal calcul*[tiab] OR glomerular filtration rate[tiab] OR GFR[tiab]	
#8	Dementia and Cognitive Decline	"Cognition Disorders"[Mesh] OR "Cognition"[Mesh] OR cognition[tiab] OR metacognition[tiab] OR neurocognitive[tiab] OR "Dementia"[Mesh] OR dementia[tiab] OR Alzheimer*[tiab] OR senility[tiab] OR senile[tiab] OR presenile[tiab] OR (cognit*[tiab] AND (function*[tiab] OR dysfunction*[tiab] OR declin*[tiab] OR deteriorat* OR degenerat*[tiab] OR disorder*[tiab] OR dysfunction*[tiab] OR reduct*[tiab] OR impair*[tiab] OR deficit*[tiab] OR deficien* OR progress*[tiab] OR perform*[tiab] OR abilit*[tiab]))	727,154
#9	Neurocognitive Health and Development	"Mental Disorders"[Mesh:NoExp] OR “Anxiety Disorders”[Mesh] OR “Mood disorders”[Mesh] OR “Motor Disorders”[Mesh] OR “Neurocognitive disorders”[Mesh:NoExp] OR “Cognition Disorders”[Mesh] OR “Neurodevelopmental disorders”[Mesh] OR "mental disorder*"[tiab] OR "Cognition"[Mesh] OR "cogniti*"[tiab] OR "metacogniti*"[tiab] OR "neurocogniti*"[tiab] OR "neurodevelop*"[tiab] OR "neurologic*"[tiab] OR "Depression"[Mesh] OR "depression"[tiab] OR "anxiety"[tiab] OR "Psychomotor Performance"[Mesh] OR “Psychomotor Disorders”[Mesh] OR psychomotor[tiab] OR "motor skill*"[tiab] OR "Executive Function"[Mesh] OR "executive function*"[tiab] OR "attention deficit disorder*"[tiab] OR "ADHD"[tiab] OR “attention deficit hyperactivity disorder”[tiab] OR "developmental disorder*"[tiab] OR "Autism"[tiab] OR “autistic”[tiab] OR "Asperger*"[tiab] OR “Communication Disorders”[Mesh] OR communication disorder*[tiab] OR "language processing"[tiab] OR "language delay*"[tiab] OR "Child Development"[Mesh] OR "child develop*"[tiab] OR "developmental delay*"[tiab] OR "developmental disabilit*"[tiab] OR "Problem Solving"[Mesh] OR "developmental domain*"[tiab] OR "Mental Processes"[Mesh:NoExp] OR "mental process*"[tiab] OR “Social development”[tiab] OR “emotional development”[tiab] OR “Visual Acuity”[MeSH:NoExp] OR "Aptitude"[Mesh] OR "Aptitude tests"[Mesh] OR "Achievement"[Mesh] OR “Intelligence”[MeSH] OR “Neuropsychological Tests”[MeSH] OR “visual acuity”[tiab] OR aptitude[tiab] OR intelligence[tiab] OR neuropsychologic*[tiab] OR (child health[tiab] AND wellbeing[tiab]) OR “educational status”[tiab] OR ((academic[tiab] OR education*[tiab] OR school[tiab]) AND (performance[tiab] OR achievement[tiab] OR attainment[tiab] OR failure[tiab] OR success[tiab]))	2,298,792
#10	ACM	("Mortality"[Mesh] OR "mortality"[Subheading] OR mortality[tiab] OR death[ti])	1,492,965
#11	Chronic Disease	"Chronic Disease"[Mesh] OR "chronic disease*"[tiab]	637,337
#12	Review	review[ptyp] OR scoping review[ti] OR qualitative review[ti] OR evidence review[ti] OR quantitative review[ti] OR meta-review[ti] OR critical review[ti] OR mixed studies review[ti] OR mapping review[ti] OR integrative review[ti] OR (literature[ti] AND review[ti]) OR systematic review[ptyp] OR systematic review[ti] OR meta-analysis[ptyp] OR meta-analysis[ti] OR meta-analyses[ti]	3,136,213

#13	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) AND #12		19,679
#14	Limiters	#13 NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) Language: English Publication Date: 2016-present	3,859

Appendix 2-b: Literature search strategy for protein intake and length of sleep evidence scan (supplemental to chronic disease risk scan)

Database: PubMed
Provider: U.S. National Library of Medicine
Date(s) Searched: December 15, 2021

Search #	Concept	Search String	# of Results
#1	Protein	“dietary proteins”[MeSH] OR “Amino Acids”[MeSH] OR “Diet, High Protein”[MeSH] OR “protein intake”[TIAB] OR “high protein”[TIAB] OR “protein consumption”[TIAB] OR “protein supplement*”[TIAB] OR “increased protein”[tiab]	936,791
#2	Sleep	"sleep"[MeSH] OR "total sleep time"[tiab] OR "tst"[tiab] OR ((sleep*[tiab] OR nap[tiab] OR naps[tiab] OR napping[tiab]) AND (time[tiab] OR duration[tiab] OR quality[tiab] OR length[tiab] OR hour*[tiab]))	181,296
#3	Review	review[ptyp] OR scoping review[ti] OR qualitative review[ti] OR evidence review[ti] OR quantitative review[ti] OR meta-review[ti] OR critical review[ti] OR mixed studies review[ti] OR mapping review[ti] OR integrative review[ti] OR (literature[ti] AND review[ti]) OR systematic review[ptyp] OR systematic review[ti] OR meta-analysis[ptyp] OR meta-analysis[ti] OR meta-analyses[ti]	3,134,720
#4	#1 AND #2 AND #3		355
#5	Limiters	NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) Language: English Publication Date: 2016-present	74

Appendix 2-c: Literature search strategy for protein intake and appetite/satiety evidence scan (supplemental to chronic disease risk scan)

Database: PubMed
Provider: U.S. National Library of Medicine
Date(s) Searched: January 5, 2022

Search #	Concept	String	Results
#1	Protein	“dietary proteins”[MeSH] OR “Amino Acids”[MeSH] OR “Diet, High Protein”[MeSH] OR “protein intake”[TIAB] OR “high protein”[TIAB] OR “protein consumption”[TIAB] OR “protein supplement*”[TIAB] OR “increased protein”[tiab]	939,469
#2	Satiety	"Satiation"[Mesh] OR Satiet*[tiab] OR Satiat*[tiab] OR Appetite[tiab] OR Fullness[tiab] OR “Hunger”[MeSH] OR Hunger[tiab] OR “Desire to eat”[tiab]	57,416
#3	#1 AND #2		3,023
#4	Limiters	#3 AND (review[ptyp] OR scoping review[ti] OR qualitative review[ti] OR evidence review[ti] OR quantitative review[ti] OR meta-review[ti] OR critical review[ti] OR mixed studies review[ti] OR mapping review[ti] OR integrative review[ti] OR (literature[ti] AND review[ti]) OR systematic review[ptyp] OR systematic review[ti] OR meta-analysis[ptyp] OR meta-analysis[ti] OR meta-analyses[ti]) NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) Language: English Publication Date: past 5 years	87

Appendix 2-d: Bibliography of excluded reviews identified that evaluated plant and/or animal protein intake (not total protein intake)

#	Brief Citation	Full citation
1	Chalvon-Demersay, 2017	Chalvon-Demersay, T, Azzout-Marniche, D, Arfsten, J, Egli, L, Gaudichon, C, Karagounis, LG, Tomé, D. A Systematic Review of the Effects of Plant Compared with Animal Protein Sources on Features of Metabolic Syndrome. J Nutr. 2017. 147:281-292. doi:10.3945/jn.116.239574
2	Shams-White, 2018	Shams-White, MM, Chung, M, Fu, Z, Insogna, KL, Karlsen, MC, LeBoff, MS, Shapses, SA, Sackey, J, Shi, J, Wallace, TC, Weaver, CM. Animal versus plant protein and adult bone health: A systematic review and meta-analysis from the National Osteoporosis Foundation. PLoS One. 2018. 13:e0192459. doi:10.1371/journal.pone.0192459
3	Nachvak, 2019	Nachvak, SM, Moradi, S, Anjom-Shoae, J, Rahmani, J, Nasiri, M, Maleki, V, Sadeghi, O. Soy, Soy Isoflavones, and Protein Intake in Relation to Mortality from All Causes, Cancers, and Cardiovascular Diseases: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. J Acad Nutr Diet. 2019. 119:1483-1500.e17. doi:10.1016/j.jand.2019.04.011
4	Lonnie, 2020	Lonnie, M, Laurie, I, Myers, M, Horgan, G, Russell, WR, Johnstone, AM. Exploring Health-Promoting Attributes of Plant Proteins as a Functional Ingredient for the Food Sector: A Systematic Review of Human Interventional Studies. Nutrients. 2020. 12. doi:10.3390/nu12082291
5	Zhao, 2020	Zhao, H, Song, A, Zheng, C, Wang, M, Song, G. Effects of plant protein and animal protein on lipid profile, body weight and body mass index on patients with hypercholesterolemia: a systematic review and meta-analysis. Acta Diabetol. 2020. 57:1169-1180. doi:10.1007/s00592-020-01534-4
6	Pimpin, 2019	Pimpin, L, Kranz, S, Liu, E, Shulkin, M, Karageorgou, D, Miller, V, Fawzi, W, Duggan, C, Webb, P, Mozaffarian, D. Effects of animal protein supplementation of mothers, preterm infants, and term infants on growth outcomes in childhood: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr. 2019. 110:410-429. doi:10.1093/ajcn/nqy348
7	Guasch-Ferre, 2019	Guasch-Ferré, M, Satija, A, Blondin, SA, Janiszewski, M, Emlen, E, O'Connor, LE, Campbell, WW, Hu, FB, Willett, WC, Stampfer, MJ. Meta-Analysis of Randomized Controlled Trials of Red Meat Consumption in Comparison With Various Comparison Diets on Cardiovascular Risk Factors. Circulation. 2019. 139:1828-1845. doi:10.1161/circulationaha.118.035225

Appendix 2-e: Excluded articles for protein intake and chronic disease risk evidence scan

The following table lists the articles excluded after full-text screening for this evidence scan. At least one reason for exclusion is provided for each article, though this may not reflect all possible reasons. Information about articles excluded after title and abstract screening is available upon request.

#	Citation	Exclusion reason #1	Exclusion reason #2
1	Adeva-Andany, MM, González-Lucán, M, Fernández-Fernández, C, Carneiro-Freire, N, Seco-Filgueira, M, Pedre-Piñeiro, AM. Effect of diet composition on insulin sensitivity in humans. Clin Nutr ESPEN. 2019. 33:29-38. doi:10.1016/j.clnesp.2019.05.014	Study Design	-
2	Adeva-Andany, MM, Rañal-Muíño, E, Vila-Altesor, M, Fernández-Fernández, C, Funcasta-Calderón, R, Castro-Quintela, E. Dietary habits contribute to define the risk of type 2 diabetes in humans. Clin Nutr ESPEN. 2019. 34:8-17. doi:10.1016/j.clnesp.2019.08.002	Study Design	-
3	Ahnen, RT, Jonnalagadda, SS, Slavin, JL. Role of plant protein in nutrition, wellness, and health. Nutr Rev. 2019. 77:735-747. doi:10.1093/nutrit/nuz028	Study Design	-
4	Al-Nimr, RI. Optimal Protein Intake during Weight Loss Interventions in Older Adults with Obesity. J Nutr Gerontol Geriatr. 2019. 38:50-68. doi:10.1080/21551197.2018.1544533	Study Design	-
5	Amirani, E, Milajerdi, A, Reiner, Ž, Mirzaei, H, Mansournia, MA, Asemi, Z. Effects of whey protein on glycemic control and serum lipoproteins in patients with metabolic syndrome and related conditions: a systematic review and meta-analysis of randomized controlled clinical trials. Lipids Health Dis. 2020. 19:209. doi:10.1186/s12944-020-01384-7	Intervention/Exposure	-
6	Ancu, O, Mickute, M, Guess, ND, Hurren, NM, Burd, NA, Mackenzie, RW. Does high dietary protein intake contribute to the increased risk of developing prediabetes and type 2 diabetes?. Appl Physiol Nutr Metab. 2021. 46:1-9. doi:10.1139/apnm-2020-0396	Study Design	-
7	Anton, SD, Hida, A, Mankowski, R, Layne, A, Solberg, LM, Mainous, AG, Buford, T. Nutrition and Exercise in Sarcopenia. Curr Protein Pept Sci. 2018. 19:649-667. doi:10.2174/1389203717666161227144349	Study Design	-
8	Aragon, AA, Schoenfeld, BJ, Wildman, R, Kleiner, S, VanDusseldorp, T, Taylor, L, Earnest, CP, Arciero, PJ, Wilborn, C, Kalman, DS, Stout, JR, Willoughby, DS, Campbell, B, Arent, SM, Bannock, L, Smith-Ryan, AE, Antonio, J. International society of sports nutrition position stand: diets and body composition. J Int Soc Sports Nutr. 2017. 14:16. doi:10.1186/s12970-017-0174-y	Study Design	-
9	Artaza-Artabe, I, Sáez-López, P, Sánchez-Hernández, N, Fernández-Gutierrez, N, Malafarina, V. The relationship between nutrition and frailty: Effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review. Maturitas. 2016. 93:89-99. doi:10.1016/j.maturitas.2016.04.009	Intervention/Exposure	Outcome
10	Badely, M, Sepandi, M, Samadi, M, Parastouei, K, Taghdir, M. The effect of whey protein on the components of metabolic syndrome in overweight and obese individuals; a systematic review and meta-analysis. Diabetes Metab Syndr. 2019. 13:3121-3131. doi:10.1016/j.dsx.2019.11.001	Intervention/Exposure	-
11	Bai, GH, Tsai, MC, Tsai, HW, Chang, CC, Hou, WH. Effects of branched-chain amino acid-rich supplementation on EWGSOP2 criteria for sarcopenia in older adults: a systematic review and meta-analysis. Eur J Nutr. 2021. #volume#:#pages#. doi:10.1007/s00394-021-02710-0	Intervention/Exposure	-
12	Batsis, JA, Villareal, DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. Nat Rev Endocrinol. 2018. 14:513-537. doi:10.1038/s41574-018-0062-9	Study Design	-

#	Citation	Exclusion reason #1	Exclusion reason #2
13	Beaudart, C, Dawson, A, Shaw, SC, Harvey, NC, Kanis, JA, Binkley, N, Reginster, JY, Chapurlat, R, Chan, DC, Bruyère, O, Rizzoli, R, Cooper, C, Dennison, EM. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporos Int. 2017. 28:1817-1833. doi:10.1007/s00198-017-3980-9	Intervention/Exposure	-
14	Beaudart, C, Rabenda, V, Simmons, M, Geerinck, A, Araujo De Carvalho, I, Reginster, JY, Amuthavalli Thiyagarajan, J, Bruyère, O. Effects of Protein, Essential Amino Acids, B-Hydroxy B-Methylbutyrate, Creatine, Dehydroepiandrosterone and Fatty Acid Supplementation on Muscle Mass, Muscle Strength and Physical Performance in Older People Aged 60 Years and Over. A Systematic Review on the Literature. J Nutr Health Aging. 2018. 22:117-130. doi:10.1007/s12603-017-0934-z	Intervention/Exposure	-
15	Bilancio, G, Cavallo, P, Ciacci, C, Cirillo, M. Dietary Protein, Kidney Function and Mortality: Review of the Evidence from Epidemiological Studies. Nutrients. 2019. 11:#pages#. doi:10.3390/nu11010196	Study Design	-
16	Boirie, Y, Guillet, C. Fast digestive proteins and sarcopenia of aging. Curr Opin Clin Nutr Metab Care. 2018. 21:37-41. doi:10.1097/mco.0000000000000427	Study Design	-
17	Bray, GA, Siri-Tarino, PW. The Role of Macronutrient Content in the Diet for Weight Management. Endocrinol Metab Clin North Am. 2016. 45:581-604. doi:10.1016/j.ecl.2016.04.009	Study Design	-
18	Camargo, LDR, Doneda, D, Oliveira, VR. Whey protein ingestion in elderly diet and the association with physical, performance and clinical outcomes. Exp Gerontol. 2020. 137:110936. doi:10.1016/j.exger.2020.110936	Intervention/Exposure	-
19	Cao, JJ. High Dietary Protein Intake and Protein-Related Acid Load on Bone Health. Curr Osteoporos Rep. 2017. 15:571-576. doi:10.1007/s11914-017-0408-6	Study Design	-
20	Castro-Barquero, S, Ruiz-León, AM, Sierra-Pérez, M, Estruch, R, Casas, R. Dietary Strategies for Metabolic Syndrome: A Comprehensive Review. Nutrients. 2020. 12:#pages#. doi:10.3390/nu12102983	Study Design	-
21	Chapman, S, Chung, HC, Rawcliffe, AJ, Izard, R, Smith, L, Roberts, JD. Does Protein Supplementation Support Adaptations to Arduous Concurrent Exercise Training? A Systematic Review and Meta-Analysis with Military Based Applications. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13051416	Intervention/Exposure	-
22	Cheng, H, Kong, J, Underwood, C, Petocz, P, Hirani, V, Dawson, B, O'Leary, F. Systematic review and meta-analysis of the effect of protein and amino acid supplements in older adults with acute or chronic conditions. Br J Nutr. 2018. 119:527-542. doi:10.1017/s0007114517003816	Intervention/Exposure	Health status
23	Daly, RM. Exercise and nutritional approaches to prevent frail bones, falls and fractures: an update. Climacteric. 2017. 20:119-124. doi:10.1080/13697137.2017.1286890	Study Design	-
24	de Sousa, MV, da Silva Soares, DB, Caraça, ER, Cardoso, R. Dietary protein and exercise for preservation of lean mass and perspectives on type 2 diabetes prevention. Exp Biol Med (Maywood). 2019. 244:992-1004. doi:10.1177/1535370219861910	Study Design	-
25	Deane, CS, Bass, JJ, Crossland, H, Phillips, BE, Atherton, PJ. Animal, Plant, Collagen and Blended Dietary Proteins: Effects on Musculoskeletal Outcomes. Nutrients. 2020. 12:#pages#. doi:10.3390/nu12092670	Study Design	-
26	Dewansingh, P, Melse-Boonstra, A, Krijnen, WP, van der Schans, CP, Jager-Wittenaar, H, van den Heuvel, Eghm. Supplemental protein from dairy products increases body weight and vitamin D improves physical performance in older adults: a systematic review and meta-analysis. Nutr Res. 2018. 49:1-22. doi:10.1016/j.nutres.2017.08.004	Intervention/Exposure	-
27	Dirks, ML, Wall, BT, van Loon, LJC. Interventional strategies to combat muscle disuse atrophy in humans: focus on neuromuscular electrical stimulation and dietary protein. J Appl Physiol (1985). 2018. 125:850-861. doi:10.1152/japplphysiol.00985.2016	Study Design	-

#	Citation	Exclusion reason #1	Exclusion reason #2
28	Dos Reis Padilha, G, Sanches Machado d'Almeida, K, Ronchi Spillere, S, Corrêa Souza, G. Dietary Patterns in Secondary Prevention of Heart Failure: A Systematic Review. Nutrients. 2018. 10:#pages#. doi:10.3390/nu10070828	Health status	-
29	Drummen, M, Tischmann, L, Gatta-Cherifi, B, Adam, T, Westerterp-Plantenga, M. Dietary Protein and Energy Balance in Relation to Obesity and Co-morbidities. Front Endocrinol (Lausanne). 2018. 9:443. doi:10.3389/fendo.2018.00443	Study Design	-
30	Elmadfa, I, Meyer, AL. Animal Proteins as Important Contributors to a Healthy Human Diet. Annu Rev Anim Biosci. 2017. 5:111-131. doi:10.1146/annurev-animal-022516-022943	Study Design	-
31	Eriksen, KG, Lind, MV, Larnkjær, A, Mølgaard, C, Michaelsen, KF. Early Nutrition and Its Effect on Growth, Body Composition and Later Obesity. World Rev Nutr Diet. 2018. 117:111-128. doi:10.1159/000484502	Study Design	-
32	Eyre, S, Faxén-Irving, G, Attman, PO, Evans, M, Windahl, K, Wegener, S, Andersén, C, Nykvist-Raanaes, K, Einemo, S, Carrero, JJ. A practical approach to low protein diets in Sweden- 45 years of clinical use. BMC Nephrol. 2016. 17:89. doi:10.1186/s12882-016-0295-6	Study Design	-
33	Ezquerro, S, Rodríguez, A, Portincasa, P, Frühbeck, G. Effects of Diets on Adipose Tissue. Curr Med Chem. 2019. 26:3593-3612. doi:10.2174/0929867324666170518102340	Study Design	Intervention/Exposure
34	Feart, C. Nutrition and frailty: Current knowledge. Prog Neuropsychopharmacol Biol Psychiatry. 2019. 95:109703. doi:10.1016/j.pnpbp.2019.109703	Study Design	-
35	Fekete Á, A, Givens, DI, Lovegrove, JA. Can milk proteins be a useful tool in the management of cardiometabolic health? An updated review of human intervention trials. Proc Nutr Soc. 2016. 75:328-41. doi:10.1017/s0029665116000264	Study Design	Intervention/Exposure
36	Ferraro, PM, Bargagli, M, Trinchieri, A, Gambaro, G. Risk of Kidney Stones: Influence of Dietary Factors, Dietary Patterns, and Vegetarian-Vegan Diets. Nutrients. 2020. 12:#pages#. doi:10.3390/nu12030779	Study Design	Intervention/Exposure
37	Franzke, B, Neubauer, O, Cameron-Smith, D, Wagner, KH. Dietary Protein, Muscle and Physical Function in the Very Old. Nutrients. 2018. 10:#pages#. doi:10.3390/nu10070935	Study Design	-
38	Gielen, E, Beckwée, D, Delaere, A, De Breucker, S, Vandewoude, M, Bautmans, I. Nutritional interventions to improve muscle mass, muscle strength, and physical performance in older people: an umbrella review of systematic reviews and meta-analyses. Nutr Rev. 2021. 79:121-147. doi:10.1093/nutrit/nuaa011	Intervention/Exposure	-
39	Gimeno-Mallench, L, Sanchez-Morate, E, Parejo-Pedrajas, S, Mas-Bargues, C, Inglés, M, Sanz-Ros, J, Román-Domínguez, A, Olaso, G, Stromsnes, K, Gambini, J. The Relationship between Diet and Frailty in Aging. Endocr Metab Immune Disord Drug Targets. 2020. 20:1373-1382. doi:10.2174/1871530320666200513083212	Study Design	-
40	Grant, WB. Using Multicountry Ecological and Observational Studies to Determine Dietary Risk Factors for Alzheimer's Disease. J Am Coll Nutr. 2016. 35:476-89. doi:10.1080/07315724.2016.1161566	Study Design	Intervention/Exposure
41	Grote, V, Theurich, M, Luque, V, Gruszfeld, D, Verduci, E, Xhonneux, A, Koletzko, B. Complementary Feeding, Infant Growth, and Obesity Risk: Timing, Composition, and Mode of Feeding. Nestle Nutr Inst Workshop Ser. 2018. 89:93-103. doi:10.1159/000486495	Study Design	-
42	Guasch-Ferré, M, Satija, A, Blondin, SA, Janiszewski, M, Emlen, E, O'Connor, LE, Campbell, WW, Hu, FB, Willett, WC, Stampfer, MJ. Meta-Analysis of Randomized Controlled Trials of Red Meat Consumption in Comparison With Various Comparison Diets on Cardiovascular Risk Factors. Circulation. 2019. 139:1828-1845. doi:10.1161/circulationaha.118.035225	Intervention/Exposure	-
43	Hanach, NI, McCullough, F, Avery, A. The Impact of Dairy Protein Intake on Muscle Mass, Muscle Strength, and Physical Performance in Middle-Aged to Older Adults with or without Existing Sarcopenia: A Systematic Review and Meta-Analysis. Adv Nutr. 2019. 10:59-69. doi:10.1093/advances/nmy065	Intervention/Exposure	-

#	Citation	Exclusion reason #1	Exclusion reason #2
44	Haschke, F, Grathwohl, D, Detzel, P, Steenhout, P, Wagemans, N, Erdmann, P. Postnatal High Protein Intake Can Contribute to Accelerated Weight Gain of Infants and Increased Obesity Risk. Nestle Nutr Inst Workshop Ser. 2016. 85:101-9. doi:10.1159/000439492	Study Design	-
45	Hellmuth, C, Uhl, O, Kirchberg, FF, Grote, V, Weber, M, Rzehak, P, Carlier, C, Ferre, N, Verduci, E, Gruszfeld, D, Socha, P, Koletzko, B. Effects of Early Nutrition on the Infant Metabolome. Nestle Nutr Inst Workshop Ser. 2016. 85:89-100. doi:10.1159/000439491	Study Design	-
46	Hertzler, SR, Lieblein-Boff, JC, Weiler, M, Allgeier, C. Plant Proteins: Assessing Their Nutritional Quality and Effects on Health and Physical Function. Nutrients. 2020. 12:#pages#. doi:10.3390/nu12123704	Study Design	-
47	Hidayat, K, Chen, GC, Wang, Y, Zhang, Z, Dai, X, Szeto, IMY, Qin, LQ. Effects of Milk Proteins Supplementation in Older Adults Undergoing Resistance Training: A Meta-Analysis of Randomized Control Trials. J Nutr Health Aging. 2018. 22:237-245. doi:10.1007/s12603-017-0899-y	Intervention/Exposure	-
48	Hidayat, K, Du, HZ, Yang, J, Chen, GC, Zhang, Z, Li, ZN, Qin, LQ. Effects of milk proteins on blood pressure: a meta-analysis of randomized control trials. Hypertens Res. 2017. 40:264-270. doi:10.1038/hr.2016.135	Intervention/Exposure	-
49	Hou, L, Lei, Y, Li, X, Huo, C, Jia, X, Yang, J, Xu, R, Wang, X. Effect of Protein Supplementation Combined with Resistance Training on Muscle Mass, Strength and Function in the Elderly: A Systematic Review and Meta-Analysis. J Nutr Health Aging. 2019. 23:451-458. doi:10.1007/s12603-019-1181-2	Intervention/Exposure	-
50	Huang, LP, Condello, G, Kuo, CH. Effects of Milk Protein in Resistance Training-Induced Lean Mass Gains for Older Adults Aged ≥ 60 y: A Systematic Review and Meta-Analysis. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13082815	Intervention/Exposure	-
51	Inaba, M, Okuno, S, Ohno, Y. Importance of Considering Malnutrition and Sarcopenia in Order to Improve the QOL of Elderly Hemodialysis Patients in Japan in the Era of 100-Year Life. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13072377	Study Design	Health status
52	Ispoglou, T, Witard, OC, Duckworth, LC, Lees, MJ. The efficacy of essential amino acid supplementation for augmenting dietary protein intake in older adults: implications for skeletal muscle mass, strength and function. Proc Nutr Soc. 2021. 80:230-242. doi:10.1017/s0029665120008010	Study Design	-
53	Joshi, S, Hashmi, S, Shah, S, Kalantar-Zadeh, K. Plant-based diets for prevention and management of chronic kidney disease. Curr Opin Nephrol Hypertens. 2020. 29:16-21. doi:10.1097/mnh.0000000000000574	Study Design	-
54	Kirk, B, Prokopidis, K, Duque, G. Nutrients to mitigate osteosarcopenia: the role of protein, vitamin D and calcium. Curr Opin Clin Nutr Metab Care. 2021. 24:25-32. doi:10.1097/mco.0000000000000711	Study Design	-
55	Kitada, M, Ogura, Y, Monno, I, Koya, D. The impact of dietary protein intake on longevity and metabolic health. EBioMedicine. 2019. 43:632-640. doi:10.1016/j.ebiom.2019.04.005	Study Design	-
56	Ko, GJ, Obi, Y, Tortorici, AR, Kalantar-Zadeh, K. Dietary protein intake and chronic kidney disease. Curr Opin Clin Nutr Metab Care. 2017. 20:77-85. doi:10.1097/mco.0000000000000342	Study Design	-
57	Ko, GJ, Rhee, CM, Kalantar-Zadeh, K, Joshi, S. The Effects of High-Protein Diets on Kidney Health and Longevity. J Am Soc Nephrol. 2020. 31:1667-1679. doi:10.1681/asn.2020010028	Study Design	Intervention/exposure
58	Koliaki, C, Spinos, T, Spinou, M, Brinia M, E, Mitsopoulou, D, Katsilambros, N. Defining the Optimal Dietary Approach for Safe, Effective and Sustainable Weight Loss in Overweight and Obese Adults. Healthcare (Basel). 2018. 6:#pages#. doi:10.3390/healthcare6030073	Study Design	-
59	Labata-Lezaun, N, Llurda-Almuzara, L, López-de-Celis, C, Rodríguez-Sanz, J, González-Rueda, V, Hidalgo-García, C, Muniz-Pardos, B, Pérez-Bellmunt, A. Effectiveness of Protein Supplementation Combined with Resistance Training on Muscle Strength and Physical Performance in Elderly: A Systematic Review and Meta-Analysis. Nutrients. 2020. 12:#pages#. doi:10.3390/nu12092607	Intervention/Exposure	-

#	Citation	Exclusion reason #1	Exclusion reason #2
60	Lancha, AH, Jr, Zanella, R, Jr, Tanabe, SG, Andriamihaja, M, Blachier, F. Dietary protein supplementation in the elderly for limiting muscle mass loss. Amino Acids. 2017. 49:33-47. doi:10.1007/s00726-016-2355-4	Study Design	-
61	Le Couteur, DG, Solon-Biet, S, Cogger, VC, Mitchell, SJ, Senior, A, de Cabo, R, Raubenheimer, D, Simpson, SJ. The impact of low-protein high-carbohydrate diets on aging and lifespan. Cell Mol Life Sci. 2016. 73:1237-52. doi:10.1007/s00018-015-2120-y	Study Design	-
62	Li, M, Liu, F. Effect of whey protein supplementation during resistance training sessions on body mass and muscular strength: a meta-analysis. Food Funct. 2019. 10:2766-2773. doi:10.1039/c9fo00182d	Intervention/Exposure	-
63	Liao, CD, Chen, HC, Huang, SW, Liou, TH. The Role of Muscle Mass Gain Following Protein Supplementation Plus Exercise Therapy in Older Adults with Sarcopenia and Frailty Risks: A Systematic Review and Meta-Regression Analysis of Randomized Trials. Nutrients. 2019. 11:#pages#. doi:10.3390/nu11081713	Intervention/Exposure	-
64	Liao, CD, Lee, PH, Hsiao, DJ, Huang, SW, Tsauo, JY, Chen, HC, Liou, TH. Effects of Protein Supplementation Combined with Exercise Intervention on Frailty Indices, Body Composition, and Physical Function in Frail Older Adults. Nutrients. 2018. 10:#pages#. doi:10.3390/nu10121916	Intervention/Exposure	Comparator
65	Liao, CD, Tsauo, JY, Wu, YT, Cheng, CP, Chen, HC, Huang, YC, Chen, HC, Liou, TH. Effects of protein supplementation combined with resistance exercise on body composition and physical function in older adults: a systematic review and meta-analysis. Am J Clin Nutr. 2017. 106:1078-1091. doi:10.3945/ajcn.116.143594	Intervention/Exposure	-
66	Liao, CD, Wu, YT, Tsauo, JY, Chen, PR, Tu, YK, Chen, HC, Liou, TH. Effects of Protein Supplementation Combined with Exercise Training on Muscle Mass and Function in Older Adults with Lower-Extremity Osteoarthritis: A Systematic Review and Meta-Analysis of Randomized Trials. Nutrients. 2020. 12:#pages#. doi:10.3390/nu12082422	Intervention/Exposure	-
67	Lim, MT, Pan, BJ, Toh, DWK, Sutanto, CN, Kim, JE. Animal Protein versus Plant Protein in Supporting Lean Mass and Muscle Strength: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13020661	Intervention/exposure	-
68	Lind, MV, Larnkjær, A, Mølgaard, C, Michaelsen, KF. Dietary protein intake and quality in early life: impact on growth and obesity. Curr Opin Clin Nutr Metab Care. 2017. 20:71-76. doi:10.1097/mco.0000000000000338	Study Design	-
69	Lombardo, M, Bellia, C, Moletto, C, Aulisa, G, Padua, E, Della-Morte, D, Caprio, M, Bellia, A. Effects of Quality and Quantity of Protein Intake for Type 2 Diabetes Mellitus Prevention and Metabolic Control. Curr Nutr Rep. 2020. 9:329-337. doi:10.1007/s13668-020-00324-2	Study Design	Outcome
70	Lonnie, M, Laurie, I, Myers, M, Horgan, G, Russell, WR, Johnstone, AM. Exploring Health-Promoting Attributes of Plant Proteins as a Functional Ingredient for the Food Sector: A Systematic Review of Human Interventional Studies. Nutrients. 2020. 12:#pages#. doi:10.3390/nu12082291	Intervention/Exposure	Outcome
71	Magkos, F. Protein-Rich Diets for Weight Loss Maintenance. Curr Obes Rep. 2020. 9:213-218. doi:10.1007/s13679-020-00391-0	Study Design	-
72	Magkos, F. The role of dietary protein in obesity. Rev Endocr Metab Disord. 2020. 21:329-340. doi:10.1007/s11154-020-09576-3	Study Design	-
73	Mareschal, J, Genton, L, Collet, TH, Graf, C. Nutritional Intervention to Prevent the Functional Decline in Community-Dwelling Older Adults: A Systematic Review. Nutrients. 2020. 12:#pages#. doi:10.3390/nu12092820	Intervention/Exposure	-
74	Marshall, RN, Smeuninx, B, Morgan, PT, Breen, L. Nutritional Strategies to Offset Disuse-Induced Skeletal Muscle Atrophy and Anabolic Resistance in Older Adults: From Whole-Foods to Isolated Ingredients. Nutrients. 2020. 12:#pages#. doi:10.3390/nu12051533	Study Design	-

#	Citation	Exclusion reason #1	Exclusion reason #2
75	Martin-Cantero, A, Reijnierse, EM, Gill, BMT, Maier, AB. Factors influencing the efficacy of nutritional interventions on muscle mass in older adults: a systematic review and meta-analysis. Nutr Rev. 2021. 79:315-330. doi:10.1093/nutrit/nuaa064	Intervention/Exposure	-
76	Martínez-Amat, A, Aibar-Almazán, A, Fábrega-Cuadros, R, Cruz-Díaz, D, Jiménez-García, JD, Pérez-López, FR, Achalandabaso, A, Barranco-Zafra, R, Hita-Contreras, F. Exercise alone or combined with dietary supplements for sarcopenic obesity in community-dwelling older people: A systematic review of randomized controlled trials. Maturitas. 2018. 110:92-103. doi:10.1016/j.maturitas.2018.02.005	Intervention/Exposure	-
77	Master, PBZ, Macedo, RCO. Effects of dietary supplementation in sport and exercise: a review of evidence on milk proteins and amino acids. Crit Rev Food Sci Nutr. 2021. 61:1225-1239. doi:10.1080/10408398.2020.1756216	Study Design	-
78	Matonti, L, Blasetti, A, Chiarelli, F. Nutrition and growth in children. Minerva Pediatr. 2020. 72:462-471. doi:10.23736/s0026-4946.20.05981-2	Study Design	-
79	McCarthy, D, Berg, A. Weight Loss Strategies and the Risk of Skeletal Muscle Mass Loss. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13072473	Study Design	-
80	Mendonça, N, Hengeveld, LM, Visser, M, Presse, N, Canhão, H, Simonsick, EM, Kritchevsky, SB, Newman, AB, Gaudreau, P, Jagger, C. Low protein intake, physical activity, and physical function in European and North American community-dwelling older adults: a pooled analysis of four longitudinal aging cohorts. Am J Clin Nutr. 2021. 114:29-41. doi:10.1093/ajcn/nqab051	Study Design	Outcome
81	Molino, S, Dossena, M, Buonocore, D, Verri, M. Sarcopenic Obesity: An Appraisal of the Current Status of Knowledge and Management in Elderly People. J Nutr Health Aging. 2016. 20:780-8. doi:10.1007/s12603-015-0631-8	Study Design	-
82	Morales, Ms FE, Tinsley, GM, Gordon, PM. Acute and Long-Term Impact of High-Protein Diets on Endocrine and Metabolic Function, Body Composition, and Exercise-Induced Adaptations. J Am Coll Nutr. 2017. 36:295-305. doi:10.1080/07315724.2016.1274691	Study Design	-
83	Morgan, PT, Harris, DO, Marshall, RN, Quinlan, JI, Edwards, SJ, Allen, SL, Breen, L. Protein Source and Quality for Skeletal Muscle Anabolism in Young and Older Adults: A Systematic Review and Meta-Analysis. J Nutr. 2021. 151:1901-1920. doi:10.1093/jn/nxab055	Intervention/exposure	Comparator
84	Morton, RW, Murphy, KT, McKellar, SR, Schoenfeld, BJ, Henselmans, M, Helms, E, Aragon, AA, Devries, MC, Banfield, L, Krieger, JW, Phillips, SM. A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. Br J Sports Med. 2018. 52:376-384. doi:10.1136/bjsports-2017-097608	Intervention/Exposure	-
85	Mu, Y, Kou, T, Wei, B, Lu, X, Liu, J, Tian, H, Zhang, W, Liu, B, Li, H, Cui, W, Wang, Q. Soy Products Ameliorate Obesity-Related Anthropometric Indicators in Overweight or Obese Asian and Non-Menopausal Women: A Meta-Analysis of Randomized Controlled Trials. Nutrients. 2019. 11:#pages#. doi:10.3390/nu11112790	Intervention/Exposure	-
86	Nachvak, SM, Moradi, S, Anjom-Shoae, J, Rahmani, J, Nasiri, M, Maleki, V, Sadeghi, O. Soy, Soy Isoflavones, and Protein Intake in Relation to Mortality from All Causes, Cancers, and Cardiovascular Diseases: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. J Acad Nutr Diet. 2019. 119:1483-1500.e17. doi:10.1016/j.jand.2019.04.011	Intervention/Exposure	-
87	Naclerio, F, Larumbe-Zabala, E. Effects of Whey Protein Alone or as Part of a Multi-ingredient Formulation on Strength, Fat-Free Mass, or Lean Body Mass in Resistance-Trained Individuals: A Meta-analysis. Sports Med. 2016. 46:125-137. doi:10.1007/s40279-015-0403-y	Intervention/Exposure	-
88	Narasaki, Y, Rhee, CM, Kramer, H, Kalantar-Zadeh, K. Protein intake and renal function in older patients. Curr Opin Clin Nutr Metab Care. 2021. 24:10-17. doi:10.1097/mco.0000000000000712	Study Design	-

#	Citation	Exclusion reason #1	Exclusion reason #2
89	O'Bryan, KR, Doering, TM, Morton, RW, Coffey, VG, Phillips, SM, Cox, GR. Do multi-ingredient protein supplements augment resistance training-induced gains in skeletal muscle mass and strength? A systematic review and meta-analysis of 35 trials. Br J Sports Med. 2020. 54:573-581. doi:10.1136/bjsports-2018-099889	Intervention/Exposure	-
90	O'Connell, ML, Coppinger, T, McCarthy, AL. The role of nutrition and physical activity in frailty: A review. Clin Nutr ESPEN. 2020. 35:1-11. doi:10.1016/j.clnesp.2019.11.003	Study Design	-
91	O'Keefe, JH, Bergman, N, Carrera-Bastos, P, Fontes-Villalba, M, DiNicolantonio, JJ, Cordain, L. Nutritional strategies for skeletal and cardiovascular health: hard bones, soft arteries, rather than vice versa. Open Heart. 2016. 3:e000325. doi:10.1136/openhrt-2015-000325	Study Design	-
92	Oktaviana, J, Zanker, J, Vogrin, S, Duque, G. The effect of protein supplements on functional frailty in older persons: A systematic review and meta-analysis. Arch Gerontol Geriatr. 2020. 86:103938. doi:10.1016/j.archger.2019.103938	Intervention/Exposure	Outcome
93	Parackal, S. Dietary Transition in the South Asian Diaspora: Implications for Diabetes Prevention Strategies. Curr Diabetes Rev. 2017. 13:482-487. doi:10.2174/1573399812666160901094741	Study Design	-
94	Pedro, RN, Aslam, AU, Bello, JO, Bhatti, KH, Philipraj, J, Sissoko, I, Vasconcellos, GS, Trinchieri, A, Buchholz, N. Nutrients, vitamins, probiotics and herbal products: an update of their role in urolithogenesis. Urolithiasis. 2020. 48:285-301. doi:10.1007/s00240-020-01182-x	Intervention/Exposure	-
95	Petroni, ML, Caletti, MT, Dalle Grave, R, Bazzocchi, A, Aparisi Gómez, MP, Marchesini, G. Prevention and Treatment of Sarcopenic Obesity in Women. Nutrients. 2019. 11:#pages#. doi:10.3390/nu11061302	Study Design	-
96	Pimpin, L, Kranz, S, Liu, E, Shulkin, M, Karageorgou, D, Miller, V, Fawzi, W, Duggan, C, Webb, P, Mozaffarian, D. Effects of animal protein supplementation of mothers, preterm infants, and term infants on growth outcomes in childhood: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr. 2019. 110:410-429. doi:10.1093/ajcn/nqy348	Intervention/Exposure	-
97	Pinto, CL, Botelho, PB, Pimentel, GD, Campos-Ferraz, PL, Mota, JF. Creatine supplementation and glycemic control: a systematic review. Amino Acids. 2016. 48:2103-29. doi:10.1007/s00726-016-2277-1	Intervention/Exposure	-
98	Piri Damaghi, M, Mirzababaei, A, Moradi, S, Daneshzad, E, Tavakoli, A, Clark, CCT, Mirzaei, K. Comparison of the effect of soya protein and whey protein on body composition: a meta-analysis of randomised clinical trials. Br J Nutr. 2021. #volume#:1-11. doi:10.1017/s0007114521001550	Intervention/Exposure	Comparator
99	Poscia, A, Milovanovic, S, La Milia, DI, Duplaga, M, Grysztar, M, Landi, F, Moscato, U, Magnavita, N, Collamati, A, Ricciardi, W. Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis. Eur J Public Health. 2018. 28:275-283. doi:10.1093/eurpub/ckx199	Intervention/Exposure	-
100	Reidy, PT, Rasmussen, BB. Role of Ingested Amino Acids and Protein in the Promotion of Resistance Exercise-Induced Muscle Protein Anabolism. J Nutr. 2016. 146:155-83. doi:10.3945/jn.114.203208	Study Design	-
101	Richter, M, Baerlocher, K, Bauer, JM, Elmadfa, I, Heseker, H, Leschik-Bonnet, E, Stangl, G, Volkert, D, Stehle, P. Revised Reference Values for the Intake of Protein. Ann Nutr Metab. 2019. 74:242-250. doi:10.1159/000499374	Study Design	Outcome
102	Rizzoli, R, Biver, E, Bonjour, JP, Coxam, V, Goltzman, D, Kanis, JA, Lappe, J, Rejnmark, L, Sahni, S, Weaver, C, Weiler, H, Reginster, JY. Benefits and safety of dietary protein for bone health-an expert consensus paper endorsed by the European Society for Clinical and Economical Aspects of Osteopororosis, Osteoarthritis, and Musculoskeletal Diseases and by the International Osteoporosis Foundation. Osteoporos Int. 2018. 29:1933-1948. doi:10.1007/s00198-018-4534-5	Study Design	-
103	Roberts, JL, Stein, AD. The Impact of Nutritional Interventions beyond the First 2 Years of Life on Linear Growth: A Systematic Review and Meta-Analysis. Adv Nutr. 2017. 8:323-336. doi:10.3945/an.116.013938	Intervention/Exposure	-

#	Citation	Exclusion reason #1	Exclusion reason #2
104	Rus, GE, Porter, J, Brunton, A, Crocker, M, Kotsimbos, Z, Percic, J, Polzella, L, Willet, N, Huggins, CE. Nutrition interventions implemented in hospital to lower risk of sarcopenia in older adults: A systematic review of randomised controlled trials. Nutr Diet. 2020. 77:90-102. doi:10.1111/1747-0080.12608	Intervention/Exposure	Health status
105	Russell, WR, Baka, A, Björck, I, Delzenne, N, Gao, D, Griffiths, HR, Hadjilucas, E, Juvonen, K, Lahtinen, S, Lansink, M, Loon, LV, Mykkänen, H, Östman, E, Riccardi, G, Vinoy, S, Weickert, MO. Impact of Diet Composition on Blood Glucose Regulation. Crit Rev Food Sci Nutr. 2016. 56:541-90. doi:10.1080/10408398.2013.792772	Study Design	Intervention/Exposure
106	Santos, J, Leitão-Correia, F, Sousa, MJ, Leão, C. Dietary Restriction and Nutrient Balance in Aging. Oxid Med Cell Longev. 2016. 2016:4010357. doi:10.1155/2016/4010357	Study Design	-
107	Severo, JS, da Silva Barros, VJ, Alves da Silva, AC, Luz Parente, JM, Lima, MM, Moreira Lima, AÂ, Dos Santos, AA, Matos Neto, EM, Tolentino, M. Effects of glutamine supplementation on inflammatory bowel disease: A systematic review of clinical trials. Clin Nutr ESPEN. 2021. 42:53-60. doi:10.1016/j.clnesp.2020.12.023	Intervention/Exposure	Outcome
108	Shad, BJ, Thompson, JL, Breen, L. Does the muscle protein synthetic response to exercise and amino acid-based nutrition diminish with advancing age? A systematic review. Am J Physiol Endocrinol Metab. 2016. 311:E803-e817. doi:10.1152/ajpendo.00213.2016	Intervention/Exposure	-
109	Shams-White, MM, Chung, M, Fu, Z, Insogna, KL, Karlsen, MC, LeBoff, MS, Shapses, SA, Sackey, J, Shi, J, Wallace, TC, Weaver, CM. Animal versus plant protein and adult bone health: A systematic review and meta-analysis from the National Osteoporosis Foundation. PLoS One. 2018. 13:e0192459. doi:10.1371/journal.pone.0192459	Intervention/exposure	-
110	Siddique, N, O'Donoghue, M, Casey, MC, Walsh, JB. Malnutrition in the elderly and its effects on bone health - A review. Clin Nutr ESPEN. 2017. 21:31-39. doi:10.1016/j.clnesp.2017.06.001	Study Design	-
111	Simonson, M, Boirie, Y, Guillet, C. Protein, amino acids and obesity treatment. Rev Endocr Metab Disord. 2020. 21:341-353. doi:10.1007/s11154-020-09574-5	Study Design	-
112	Singhal, A. Obesity in Toddlers and Young Children: Causes and Consequences. Nestle Nutr Inst Workshop Ser. 2020. 95:41-51. doi:10.1159/000511510	Study Design	-
113	Solfrizzi, V, Agosti, P, Lozupone, M, Custodero, C, Schilardi, A, Valiani, V, Sardone, R, Dibello, V, Di Lena, L, Lamanna, A, Stallone, R, Bellomo, A, Greco, A, Daniele, A, Seripa, D, Sabbà, C, Logroscino, G, Panza, F. Nutritional Intervention as a Preventive Approach for Cognitive-Related Outcomes in Cognitively Healthy Older Adults: A Systematic Review. J Alzheimers Dis. 2018. 64:S229-s254. doi:10.3233/jad-179940	Intervention/Exposure	-
114	Soultoukis, GA, Partridge, L. Dietary Protein, Metabolism, and Aging. Annu Rev Biochem. 2016. 85:5-34. doi:10.1146/annurev-biochem-060815-014422	Study Design	-
115	Spence, JD. Nutrition in Stroke Prevention. Semin Neurol. 2017. 37:259-266. doi:10.1055/s-0037-1603470	Study Design	-
116	Strasser, B, Wolters, M, Weyh, C, Krüger, K, Ticinesi, A. The Effects of Lifestyle and Diet on Gut Microbiota Composition, Inflammation and Muscle Performance in Our Aging Society. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13062045	Study Design	-
117	Tang, M. Protein Intake during the First Two Years of Life and Its Association with Growth and Risk of Overweight. Int J Environ Res Public Health. 2018. 15:#pages#. doi:10.3390/ijerph15081742	Study Design	-
118	Ten Haaf, DSM, Nuijten, MAH, Maessen, MFH, Horstman, AMH, Eijsvogels, TMH, Hopman, MTE. Effects of protein supplementation on lean body mass, muscle strength, and physical performance in nonfrail community-dwelling older adults: a systematic review and meta-analysis. Am J Clin Nutr. 2018. 108:1043-1059. doi:10.1093/ajcn/nqy192	Intervention/Exposure	-

#	Citation	Exclusion reason #1	Exclusion reason #2
119	Thomas, DK, Quinn, MA, Saunders, DH, Greig, CA. Protein Supplementation Does Not Significantly Augment the Effects of Resistance Exercise Training in Older Adults: A Systematic Review. J Am Med Dir Assoc. 2016. 17:959.e1-9. doi:10.1016/j.jamda.2016.07.002	Intervention/Exposure	Outcome
120	Tieland, M, Franssen, R, Dullemeijer, C, van Dronkelaar, C, Kyung Kim, H, Ispoglou, T, Zhu, K, Prince, RL, van Loon, LJC, de Groot, Lcpgm. The Impact of Dietary Protein or Amino Acid Supplementation on Muscle Mass and Strength in Elderly People: Individual Participant Data and Meta-Analysis of RCT's. J Nutr Health Aging. 2017. 21:994-1001. doi:10.1007/s12603-017-0896-1	Intervention/Exposure	-
121	Travers, J, Romero-Ortuno, R, Bailey, J, Cooney, MT. Delaying and reversing frailty: a systematic review of primary care interventions. Br J Gen Pract. 2019. 69:e61-e69. doi:10.3399/bjgp18X700241	Intervention/Exposure	Outcome
122	Tsuboi, M, Momosaki, R, Vakili, M, Abo, M. Nutritional supplementation for activities of daily living and functional ability of older people in residential facilities: A systematic review. Geriatr Gerontol Int. 2018. 18:197-210. doi:10.1111/ggi.13160	Intervention/Exposure	Outcome
123	Tu, DY, Kao, FM, Tsai, ST, Tung, TH. Sarcopenia among the Elderly Population: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Healthcare (Basel). 2021. 9:#pages#. doi:10.3390/healthcare9060650	Intervention/Exposure	-
124	Turton, J, Brinkworth, GD, Field, R, Parker, H, Rooney, K. An evidence-based approach to developing low-carbohydrate diets for type 2 diabetes management: A systematic review of interventions and methods. Diabetes Obes Metab. 2019. 21:2513-2525. doi:10.1111/dom.13837	Health status	-
125	van Wijngaarden, JP, Wojzischke, J, van den Berg, C, Cetinyurek-Yavuz, A, Diekmann, R, Luiking, YC, Bauer, JM. Effects of Nutritional Interventions on Nutritional and Functional Outcomes in Geriatric Rehabilitation Patients: A Systematic Review and Meta-Analysis. J Am Med Dir Assoc. 2020. 21:1207-1215.e9. doi:10.1016/j.jamda.2020.04.012	Intervention/Exposure	-
126	Vasconcelos, Qdjs, Bachur, TPR, Aragão, GF. Whey protein supplementation and its potentially adverse effects on health: a systematic review. Appl Physiol Nutr Metab. 2021. 46:27-33. doi:10.1139/apnm-2020-0370	Intervention/Exposure	-
127	Veena, SR, Gale, CR, Krishnaveni, GV, Kehoe, SH, Srinivasan, K, Fall, CH. Association between maternal nutritional status in pregnancy and offspring cognitive function during childhood and adolescence; a systematic review. BMC Pregnancy Childbirth. 2016. 16:220. doi:10.1186/s12884-016-1011-z	Intervention/Exposure	-
128	Walrand, S. Dietary supplement intake among the elderly: hazards and benefits. Curr Opin Clin Nutr Metab Care. 2018. 21:465-470. doi:10.1097/mco.0000000000000512	Study Design	-
129	Westerterp-Plantenga, MS. Challenging energy balance - during sensitivity to food reward and modulatory factors implying a risk for overweight - during body weight management including dietary restraint and medium-high protein diets. Physiol Behav. 2020. 221:112879. doi:10.1016/j.physbeh.2020.112879	Study Design	-
130	Wirth, J, Hillesheim, E, Brennan, L. The Role of Protein Intake and its Timing on Body Composition and Muscle Function in Healthy Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Nutr. 2020. 150:1443-1460. doi:10.1093/jn/nxaa049	Intervention/Exposure	-
131	Wirunsawanya, K, Upala, S, Jaruvongvanich, V, Sanguankeo, A. Whey Protein Supplementation Improves Body Composition and Cardiovascular Risk Factors in Overweight and Obese Patients: A Systematic Review and Meta-Analysis. J Am Coll Nutr. 2018. 37:60-70. doi:10.1080/07315724.2017.1344591	Intervention/Exposure	-
132	Witard, OC, McGlory, C, Hamilton, DL, Phillips, SM. Growing older with health and vitality: a nexus of physical activity, exercise and nutrition. Biogerontology. 2016. 17:529-46. doi:10.1007/s10522-016-9637-9	Study Design	-

#	Citation	Exclusion reason #1	Exclusion reason #2
133	Witard, OC, Wardle, SL, Macnaughton, LS, Hodgson, AB, Tipton, KD. Protein Considerations for Optimising Skeletal Muscle Mass in Healthy Young and Older Adults. Nutrients. 2016. 8:181. doi:10.3390/nu8040181	Study Design	Outcome
134	Wu, G. Dietary protein intake and human health. Food Funct. 2016. 7:1251-65. doi:10.1039/c5fo01530h	Study Design	-
135	Ye, J, Yu, Q, Mai, W, Liang, P, Liu, X, Wang, Y. Correction to: Dietary protein intake and subsequent risk of type 2 diabetes: a dose-response meta-analysis of prospective cohort studies. Acta Diabetol. 2019. 56:871. doi:10.1007/s00592-019-01365-y	Study Design	Pub. status
136	Yue, H, Zhou, P, Xu, Z, Liu, L, Zong, A, Qiu, B, Liu, W, Jia, M, Du, F, Xu, T. Effect of low-protein diet on kidney function and nutrition in nephropathy: A systematic review and meta-analysis of randomized controlled trials. Clin Nutr. 2020. 39:2675-2685. doi:10.1016/j.clnu.2019.11.039	Health status	-
137	Zanini, B, Simonetto, A, Zubani, M, Castellano, M, Gilioli, G. The Effects of Cow-Milk Protein Supplementation in Elderly Population: Systematic Review and Narrative Synthesis. Nutrients. 2020. 12:#pages#. doi:10.3390/nu12092548	Intervention/Exposure	-
138	Zhang, J, Yu, Y, Wang, J. Protein Nutritional Support: The Classical and Potential New Mechanisms in the Prevention and Therapy of Sarcopenia. J Agric Food Chem. 2020. 68:4098-4108. doi:10.1021/acs.jafc.0c00688	Study Design	-

Appendix 2-f: Excluded articles for protein intake and sleep duration evidence scan (supplemental to chronic disease risk scan)

The following table lists the articles excluded after full-text screening for this evidence scan. At least one reason for exclusion is provided for each article, though this may not reflect all possible reasons. Information about articles excluded after title and abstract screening is available upon request.

#	Citation	Exclusion reason #1	Exclusion reason #2
1	Doherty, R, Madigan, S, Warrington, G, Ellis, J. Sleep and Nutrition Interactions: Implications for Athletes. Nutrients. 2019. 11:#pages#. doi:10.3390/nu11040822	Study design	-
2	Fenton, S, Burrows, TL, Skinner, JA, Duncan, MJ. The influence of sleep health on dietary intake: a systematic review and meta-analysis of intervention studies. J Hum Nutr Diet. 2021. 34:273-285. doi:10.1111/jhn.12813	Intervention/exposure	Outcome
3	Gratwicke, M, Miles, KH, Pyne, DB, Pumpa, KL, Clark, B. Nutritional Interventions to Improve Sleep in Team-Sport Athletes: A Narrative Review. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13051586	Study design	Intervention/exposure
4	Kay-Stacey, M, Attarian, H. Advances in the management of chronic insomnia. Bmj. 2016. 354:i2123. doi:10.1136/bmj.i2123	Intervention/exposure	-
5	Laudisio, D, Barrea, L, Pugliese, G, Aprano, S, Castellucci, B, Savastano, S, Colao, A, Muscogiuri, G. A practical nutritional guide for the management of sleep disturbances in menopause. Int J Food Sci Nutr. 2021. 72:432-446. doi:10.1080/09637486.2020.1851658	Study design	-
6	Reis, CEG, Loureiro, LMR, Roschel, H, da Costa, THM. Effects of pre-sleep protein consumption on muscle-related outcomes - A systematic review. J Sci Med Sport. 2021. 24:177-182. doi:10.1016/j.jsams.2020.07.016	Outcome	-
7	Zhao, M, Tuo, H, Wang, S, Zhao, L. The Effects of Dietary Nutrition on Sleep and Sleep Disorders. Mediators Inflamm. 2020. 2020:3142874. doi:10.1155/2020/3142874	Study design	-

Appendix 2-g: Excluded articles for protein intake and appetite/satiety evidence scan (supplemental to chronic disease risk scan)

The following table lists the articles excluded after full-text screening for this evidence scan. At least one reason for exclusion is provided for each article, though this may not reflect all possible reasons. Information about articles excluded after title and abstract screening is available upon request.

#	Citation	Exclusion reason #1	Exclusion reason #2
1	Chapman, I, Oberoi, A, Giezenaar, C, Soenen, S. Rational Use of Protein Supplements in the Elderly-Relevance of Gastrointestinal Mechanisms. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13041227	Study Design	-
2	Dela Cruz, J, Kahan, D. Pre-Sleep Casein Supplementation, Metabolism, and Appetite: A Systematic Review. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13061872	Intervention/Exposure	-
3	Freire, RH, Alvarez-Leite, JI. Appetite control: hormones or diet strategies?. Curr Opin Clin Nutr Metab Care. 2020. 23:328-335. doi:10.1097/MCO.0000000000000675	Study Design	-
4	Hansen, TT, Astrup, A, Sjodin, A. Are Dietary Proteins the Key to Successful Body Weight Management? A Systematic Review and Meta-Analysis of Studies Assessing Body Weight Outcomes after Interventions with Increased Dietary Protein. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13093193	Outcome	-
5	Li, M, Zhao, S, Wu, S, Yang, X, Feng, H. Effectiveness of Oral Nutritional Supplements on Older People with Anorexia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13030835	Intervention/Exposure	-
6	Lonnie, M, Hooker, E, Brunstrom, JM, Corfe, BM, Green, MA, Watson, AW, Williams, EA, Stevenson, EJ, Penson, S, Johnstone, AM. Protein for Life: Review of Optimal Protein Intake, Sustainable Dietary Sources and the Effect on Appetite in Ageing Adults. Nutrients. 2018. 10:#pages#. doi:10.3390/nu10030360	Study Design	-
7	Lonnie, M, Laurie, I, Myers, M, Horgan, G, Russell, WR, Johnstone, AM. Exploring Health-Promoting Attributes of Plant Proteins as a Functional Ingredient for the Food Sector: A Systematic Review of Human Interventional Studies. Nutrients. 2020. 12:#pages#. doi:10.3390/nu12082291	Intervention/Exposure	-
8	Magkos, F. The role of dietary protein in obesity. Rev Endocr Metab Disord. 2020. 21:329-340. doi:10.1007/s11154-020-09576-3	Study Design	-
9	Mollahosseini, M, Shab-Bidar, S, Rahimi, MH, Djafarian, K. Effect of whey protein supplementation on long and short term appetite: A meta-analysis of randomized controlled trials. Clin Nutr ESPEN. 2017. 20:34-40. doi:10.1016/j.clnesp.2017.04.002	Intervention/Exposure	-
10	Moon, J, Koh, G. Clinical Evidence and Mechanisms of High-Protein Diet-Induced Weight Loss. J Obes Metab Syndr. 2020. 29:166-173. doi:10.7570/jomes20028	Study Design	-
11	Morales, Ms FE, Tinsley, GM, Gordon, PM. Acute and Long-Term Impact of High-Protein Diets on Endocrine and Metabolic Function, Body Composition, and Exercise-Induced Adaptations. J Am Coll Nutr. 2017. 36:295-305. doi:10.1080/07315724.2016.1274691	Study Design	Outcome
12	Ojha, U. Protein-induced satiation and the calcium-sensing receptor. Diabetes Metab Syndr Obes. 2018. 11:45-51. doi:10.2147/DMSO.S156597	Study Design	-

#	Citation	Exclusion reason #1	Exclusion reason #2
13	Qiu, M, Zhang, Y, Long, Z, He, Y. Effect of Protein-Rich Breakfast on Subsequent Energy Intake and Subjective Appetite in Children and Adolescents: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13082840	Intervention/Exposure	-
14	Zhang, Y, Chen, X, Allison, DB, Xun, P. Efficacy and safety of a specific commercial high-protein meal-replacement product line in weight management: meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr. 2020. #volume#:1-12. doi:10.1080/10408398.2020.1829539	Outcome	-

Appendix 2-h: AMSTAR 2 assessment of review quality and funding source by outcome category[a,b]

Article	AMSTAR 2																Overall rating	Funding
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16		
All-cause mortality																		
Chen, 2020[23]	Y	PY	Y	PY	Y	N	PY	Y	PY	N	Y	Y	Y	Y	Y	Y	Moderate	None
Naghshi, 2020[24]	Y	N	N	PY	N	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Low	Tehran University of Medical Sciences
Qi, 2020[25]	Y	PY	Y	PY	Y	N	Y	PY	PY	N	Y	Y	Y	N	Y	Y	Moderate	None
Bone health																		
Curneen, 2018[26]	N	N	N	PY	N	N	N	Y	N	N	NM	NM	N	Y	NM	Y	Critically low	None
Darling, 2019[27]	Y	N	Y	N	Y	N	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Low	Not reported
Groenendijk, 2019[28]	Y	N	Y	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Moderate	Jaap Schouten Foundation
Shams-White, 2017[29]	Y	Y	Y	Y	Y	Y	PY	Y	Y	Y	Y	N	Y	Y	N	Y	Low	National Osteoporosis Foundation through support of Egg Nutrition Center and Dairy Management Inc
Tsagari, 2020[30]	Y	N	Y	N	N	N	N	N	N	N	NM	NM	N	N	NM	Y	Critically low	Not reported
Wallace, 2017[31]	Y	N	Y	Y	Y	Y	N	Y	N	N	Y	N	N	Y	N	Y	Critically low	Beef Checkoff through National Cattleman’s Beef Association
Wright, 2019[32]	Y	Y	Y	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	N	Y	Low	NIH; Purdue University

Article	AMSTAR 2																Overall rating	Funding
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16		
Cardiovascular disease risk																		
Chen, 2020[23]	Y	PY	Y	PY	Y	N	PY	Y	PY	N	Y	Y	Y	Y	Y	Y	Moderate	None
Dinu, 2020[33]	Y	Y	Y	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	High	None
Mousavi, 2020[38]	Y	PY	Y	PY	N	Y	Y	Y	PY	N	Y	Y	Y	Y	Y	Y	Moderate	Not reported
Naghshi, 2020[24]	Y	N	N	PY	N	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Low	Tehran University of Medical Sciences
Qi, 2020[25]	Y	PY	Y	PY	Y	N	Y	PY	PY	N	Y	Y	Y	N	Y	Y	Moderate	None
Schwingshackl, 2019[34]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Moderate	None
Sukhato, 2020[39]	Y	Y	Y	PY	Y	Y	PY	Y	Y	N	NM	NM	Y	Y	NM	Y	High	Prince Mahidol Award Foundation; Thai Health Promotion Foundation; International Decision Support Initiative; Thailand Research Fund
Van Elswyk, 2018[35]	Y	N	Y	N	N	N	Y	Y	Y	N	NM	NM	Y	Y	NM	Y	Low	Beef Checkoff
van Elten, 2019[37]	Y	Y	Y	Y	Y	Y	PY	Y	Y	N	NM	NM	Y	Y	NM	Y	High	Dutch Heart Foundation; European Commission
Zhang, 2016[36]	N	N	N	PY	N	N	N	PY	PY	N	Y	Y	Y	Y	Y	Y	Critically low	Not reported
Diabetes risk																		
Dinu, 2020[33]	Y	Y	Y	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	High	None
Fan, 2019[42]	Y	N	Y	Y	N	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Moderate	National Key Research and Development Program of

Article	AMSTAR 2																Overall rating	Funding
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16		
																		China; National Natural Science Foundation of China
Shang, 2016[43]	Y	N	Y	PY	N	N	Y	Y	PY	N	Y	Y	Y	Y	Y	Y	Moderate	VicHealth; Cancer Council Victoria; Australian National Health and Medical Research Council
Tian, 2017[44]	Y	N	Y	PY	N	N	PY	N	N	N	Y	N	N	Y	Y	Y	Critically low	National Natural Science Foundation of China; Harbin Medical University
Ye, 2019[45]	Y	N	Y	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Moderate	Not reported
Zhao, 2019[46]	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Moderate	State Key Laboratory of Oncogenes and Related Genes
Renal health																		
Devries, 2018[63]	Y	N	Y	PY	N	N	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Moderate	US National Dairy Council; Dairy Farmers of Canada; US National Beef Cattlemen's Association
Van Elswyk, 2018[35]	Y	N	Y	N	N	N	Y	Y	Y	N	NM	NM	Y	Y	NM	Y	Low	Beef Checkoff
Sarcopenia																		
Coelho-Junior, 2018[64]	Y	N	Y	PY	Y	Y	PY	PY	N	N	Y	N	N	Y	N	Y	Critically low	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; Fundação de Amparo à Pesquisa do Estado de São Paulo; CNPq
Kirwan, 2021[67]	Y	PY	Y	PY	Y	Y	PY	Y	Y	N	Y	N	N	Y	Y	Y	Low	Institute for Health Research at Liverpool John Moores University

Article	AMSTAR 2																Overall rating	Funding
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16		
Lin, 2021[53]	Y	Y	Y	PY	Y	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Low	Ministry of Science and Technology, Taiwan
Naseeb, 2017[66]	N	N	N	N	N	N	N	PY	N	N	NM	NM	N	N	NM	Y	Critically low	Not reported
Yaegashi, 2021[65]	Y	N	N	PY	Y	Y	N	Y	N	Y	NM	NM	N	Y	NM	Y	Critically low	Not reported

[a] **Q1***: Did the research questions and inclusion criteria for the review include the components of PICO?; **Q2**: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?; **Q3**: Did the review authors explain their selection of the study designs for inclusion in the review?; **Q4***: Did the review authors use a comprehensive literature search strategy?; **Q5**: Did the review authors perform study selection in duplicate?; **Q6**: Did the review authors perform data extraction in duplicate?; **Q7***: Did the review authors provide a list of excluded studies and justify the exclusions?; **Q8***: Did the review authors describe the included studies in adequate detail?; **Q9***: Did the review authors use a satisfactory technique for assessing the risk of bias [RoB] in individual studies that were included in the review?; **Q10**: Did the review authors report on the sources of funding for the studies included in the review?; **Q11**: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?; **Q12**: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?; **Q13***: Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?; **Q14**: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?; **Q15***: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias [small study bias] and discuss its likely impact on the results of the review?; **Q16***: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

*** denotes questions that were considered critical domains**

[b] Abbreviations: N: No; NM: No meta-analysis; PY: Probably yes; Q: Question; Y: Yes

Appendix 2-i: Duplication assessment for protein intake and all-cause mortality evidence

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Argos M, Int J Cancer 2013	All-cause mortality	Naghshi, 2020
Bates CJ, Br J Nutr 2010	All-cause mortality	Naghshi, 2020; Qi, 2020; Chen, 2020
Borugian MJ, Cancer Epidemiol Biomarkers Prev 2004	All-cause mortality	Naghshi, 2020
Budhathoki S, JAMA Intern Med 2019	All-cause mortality	Naghshi, 2020; Qi, 2020; Chen, 2020
Campmans-Kuijpers MJ, Cardiovasc Diabetol 2015	All-cause mortality	Naghshi, 2020
Chan R, J Nutr Health Aging 2019	All-cause mortality	Naghshi, 2020; Qi, 2020
Chen Z, Eur J Epidemiol 2020	All-cause mortality	Qi, 2020; Chen, 2020
Courand PY, Hypertension 2016	All-cause mortality	Naghshi, 2020
Dehghan M, Lancet 2017	All-cause mortality	Naghshi, 2020; Qi, 2020
Dwyer JT, Am J Public Health 1994	All-cause mortality	Naghshi, 2020
Esrey KL, J Clin Epidemiol 1996	All-cause mortality	Naghshi, 2020
Halbesma N, J Am Soc Nephrol 2009	All-cause mortality	Naghshi, 2020
Hernandez Alonso P, Clin Nutr 2016	All-cause mortality	Naghshi, 2020; Qi, 2020
Holmes MD, Cancer 1999	All-cause mortality	Naghshi, 2020
Holmes MD, J Clin Oncol 2017	All-cause mortality	Naghshi, 2020
Kelemen LE, Am J Epidemiol 2005	All-cause mortality	Naghshi, 2020; Qi, 2020; Chen, 2020
Kurihara A, J Atheroscler Thromb 2019	All-cause mortality	Chen, 2020
Levine ME, Cell Metab 2014	All-cause mortality	Naghshi, 2020; Qi, 2020; Chen, 2020
Mendonca N, Eur J Nutr 2019	All-cause mortality	Naghshi, 2020
Nagata C, J Nutr 2015	All-cause mortality	Naghshi, 2020
Palli D, Cancer 2000	All-cause mortality	Naghshi, 2020
Papanikolaou Y, Curr Dev Nutr 2019	All-cause mortality	Naghshi, 2020
Payette H, J Gerontol A Biol Sci Med Sci 1999	All-cause mortality	Naghshi, 2020
Preis SR, Am J Clin Nutr 2010	All-cause mortality	Naghshi, 2020
Rohan TE, Nutr Cancer 1993	All-cause mortality	Naghshi, 2020
Sauvaget C, Stroke 2004	All-cause mortality	Naghshi, 2020

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Smit E, Nutr Cancer 2007	All-cause mortality	Naghshi, 2020
Song M, JAMA Intern Med 2016	All-cause mortality	Naghshi, 2020; Qi, 2020; Chen, 2020
Song M, JNCI Cancer Spectr 2018	All-cause mortality	Naghshi, 2020
Virtanen HEK, Am J Clin Nutr 2019	All-cause mortality	Naghshi, 2020; Qi, 2020; Chen, 2020
Zaslavsky O, Am J Clin Nutr 2017	All-cause mortality	Naghshi, 2020

Appendix 2-j: Duplication assessment for protein intake and bone health evidence

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Abelow BJ, Calcif Tissue Int, 1992	Fracture (hip)	Darling 2019
Alekel DL, Am J Clin Nutr, 2000	BMD/BMC	Darling 2019
Alexy U, Am J Clin Nutr, 2005	BMC	Darling 2019
Alissa EM, J Am Coll Nutr, 2014	BMD	Darling 2019
Alissa EM, J Bone Miner Metab, 2011	BMD, Osteopenia	Darling 2019
Aoe S, Biosci Biotechnol Biochem, 2001	BMD	Darling 2019
Aoe S, Osteoporos Int, 2005	BMD	Darling 2019; Wallace 2017
Avenell A, Eur J Clin Nutr, 1994	BMD	Wright 2019
Backx EMP, Int J Obes, 2016	BMD/BMC	Wright 2019
Ballard TLP, Bone, 2006	BMD/BMC	Wallace 2017
Beasley JM, Am J Clin Nutr, 2010	BMD	Darling 2019
Beasley JM, Am J Clin Nutr, 2014	BMD, Fracture (any, hip, spine, forearm)	Darling 2019; Groenendijk 2019; Shams-White 2017; Tsagari 2020; Wallace 2017
Bounds W, J Am Diet Assoc, 2005	BMD/BMC	Darling 2019
Bowen J, J Nutr, 2004	BMD	Wright 2019
Brehm BJ, J Clin Endocrinol Metab, 2005	BMC	Wright 2019
Budek AZ, Osteoporos Int, 2007	BMC	Darling 2019
Cauley JA, J Bone Miner Res, 2016	Fracture (hip)	Groenendijk 2019; Shams-White 2017
Chan R, Food Nutr Bull, 2009	BMD	Darling 2019
Chan R, J Nutr Health Aging, 2011	BMD	Darling 2019
Chevalley T, J Bone Miner Res, 2014	BMD/BMC	Cureneen 2018; Darling 2019; Groenendijk 2019
Chevalley T, J Clin Endocrinol Metab, 2011	Fracture (any)	Darling 2019
Chevalley, J Bone Miner Res, 2008	BMC	Darling 2019
Chiu JF, Calcif Tissue Int, 1997	BMD, Osteopenia	Darling 2019
Clifton PM, Am J Clin Nutr, 2008	BMD/BMC	Wright 2019
Coin A, Eur J Clin Nutr, 2008	BMD	Darling 2019

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Cooper C, Calcif Tissue Int, 1996	BMD	Darling 2019
Courteix D, PloS One, 2015	BMD/BMC	Wright 2019
Dargent-Molina P, J Bone Miner Res, 2008	Fracture (any)	Cureneen 2018; Darling 2019; Shams-White 2017
Dawson-Hughes, Am J Clin Nutr, 2002	BMD	Cureneen 2018; Darling 2019; Groenendijk 2019; Shams-White 2017; Tsagari 2020
Devine A, Am J Clin Nutr, 2005	BMD	Cureneen 2018; Darling 2019; Groenendijk 2019; Wallace 2017
Ekbote VH, J Bone Miner Metab, 2011	BMC	Darling 2019
Evans EM, Menopause, 2007	BMD	Darling 2019
Fairweather-Tait SJ, Am J Clin Nutr, 2011	BMD	Darling 2019
Farrin N, Saudi Med J, 2008	Osteoporosis/Osteopenia	Darling 2019
Feskanich D, Am J Epidemiol, 1996	Fracture (forearm, hip)	Darling 2019; Shams-White 2017
Flodin L, Clin Interv Aging, 2014	BMD	Shams-White 2017; Tsagari 2020
Frassetto LA, J Gerontol A Biol Sci Med Sci, 2000	Fracture (hip)	Darling 2019
Freudenheim JL, Am J Clin Nutr, 1986	BMC	Darling 2019
Fung TT, Osteopporos Int, 2017	Fracture (hip)	Groenendijk 2019; Wallace 2017
Geinoz G, Osteoporos Int, 1993	BMD	Cureneen 2018; Darling 2019
Genaro PD, Nutr Clin Pract, 2015	BMD/BMC	Darling 2019
Gregg EW, Osteoporos Int, 1999	BMD	Darling 2019
Gunn CA, J Nutr Health Aging, 2014	BMD, Osteoporosis	Darling 2019
Hannan MT, J Bone Miner Res, 2000	BMD	Cureneen 2018; Darling 2019; Groenendijk 2019; Shams-White 2017; Tsagari 2020; Wallace 2017
Henderson NK, J Bone Miner Res, 1995	BMD	Darling 2019
Hernandezavila M, Epidemiology, 1993	BMD	Darling 2019
Hinton PS, Eur J Clin Nutr, 2010	BMD/BMC	Wright 2019
Hinton PS, Eur J Clin Nutr, 2012	BMD/BMC	Wright 2019
Hirota T, Am J Clin Nutr, 1992	BMD	Darling 2019
Ho SC, Osteoporos Int, 2003	BMD/BMC	Darling 2019
Ho SC, Osteoporos Int, 2008	BMD/BMC	Darling 2019; Shams-White 2017; Tsagari 2020

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Ho-Pham LT, Eur J Clin Nutr, 2012	BMD/BMC	Darling 2019; Wallace 2017
Ho-Pham LT, Osteoporos Int, 2009	BMD	Darling 2019
Hoppe C, Osteoporos Int, 2000	BMC	Darling 2019
Horiuchi T, Osteoporos Int, 2000	BMD	Darling 2019
Hu T, Brit J Nutr, 2014	BMD	Darling 2019
Ilich JZ, Eur J Clin Nutr, 2003	BMD/BMC	Cureneen 2018; Darling 2019
Isanejad M, J Nutr Health Aging, 2017	BMC	Groenendijk 2019
Iuliano-Burns S, Osteoporos Int, 2005	BMC	Darling 2019
Jaime PC, Sao Paulo Med J, 2006	BMD	Darling 2019
Jesudason D, Am J Clin Nutr, 2013	BMD	Shams-White 2017; Tsagari 2020; Wright 2019
Jones G, Am J Clin Nutr, 2001	BMD	Darling 2019
Jones KW, Eur J Clin Nutr, 2013	BMD/BMC	Wright 2019
Josse AR, J Clin Endocr Metab, 2012	BMD/BMC	Wright 2019
Kenny AM, Am J Clin Nutr, 2009	BMD	Darling 2019
Kerstetter JE, Calcif Tissue Int, 2000	BMD	Cureneen 2018;
Kerstetter JE, J Clin Endocrinol Metab, 2015	BMD	Cureneen 2018; Darling 2019; Shams-White 2017; Tsagari 2020; Wallace 2017
Key TJ, Public Health Nutr, 2007	Fracture (any)	Darling 2019
Kim J, Asia Pac J Clin Nutr, 2008	Osteoporosis	Cureneen 2018; Darling 2019
Knurick JR, Nutrients, 2015	BMD	Darling 2019
Koh WP, Am J Epidemiol, 2009	Fracture (hip)	Shams-White 2017
Kukuljan S, Osteoporos Int, 2009	BMD	Shams-White 2017; Tsagari 2020
Kumar A, J Bone Miner Metab, 2010	BMD	Darling 2019
Labouesse MA, Bone, 2014	BMD/BMC	Wright 2019
Lacey JM, J Bone Miner Res, 1991	BMC	Darling 2019
Langsetmo L, J Bone Miner Res, 2017	BMD	Groenendijk 2019; Wallace 2017
Langsetmo L, J Nutr Health Aging, 2015	BMD, Fracture (any)	Darling 2019; Shams-White 2017; Wallace 2017
Lau EMC, Eur J Clin Nutr, 1998	BMD	Darling 2019

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Li Z, Nutr J, 2010	BMD	Shams-White 2017; Tsagari 2020; Wright 2019
Libuda L, Am J Clin Nutr, 2008	BMC	Darling 2019
Libuda L, Br J Nutr, 2011	BMC	Darling 2019
Liu X, Br J Nutr, 2013	BMD	Wright 2019
Loenneke JP, Ann Nutr Metab, 2010	BMD/BMC	Darling 2019
Macdonald HM, Am J Clin Nutr, 2005	BMD	Darling 2019
Martinez-Ramirez MJ, Clin Nutr, 2012	Fracture (any)	Cureneen 2018; Darling 2019
Meng X, J Bone Miner Res, 2009	BMC	Darling 2019; Groenendijk 2019; Wallace 2017
Metz JA, Am J Clin Nutr, 1993	BMD/BMC	Darling 2019
Meyer HE, Am J Epidemiol, 1997	Fracture (hip)	Darling 2019; Shams-White 2017
Michaelsson K, Calcif Tissue Int, 1995	BMD	Darling 2019
Misra D, Osteoporos Int, 2011	Fracture (hip)	Cureneen 2018; Darling 2019; Groenendijk 2019; Shams-White 2017; Wallace 2017
Munger RG, Am J Clin Nutr, 1999	Fracture (hip)	Cureneen 2018; Darling 2019; Shams-White 2017; Wallace 2017
Mussolino ME, J Bone Miner Res, 1998	Fracture (hip)	Darling 2019; Shams-White 2017; Wallace 2017
Nakata Y, J Bone Miner Metab, 2008	BMD/BMC	Wright 2019
Neville CE, Calcif Tissue Int, 2002	BMD	Darling 2019
New SA, Am J Clin Nutr, 1997	BMD	Darling 2019
Nieves JW, Osteoporos, 1992	Fracture (hip)	Darling 2019
Orozco Lopez P, An Med Interna, 1998	BMD	Darling 2019
Orwoll ES, Am J Clin Nutr, 1987	BMC	Darling 2019
Park YJ, J Korean Acad Nurs, 2014	BMD	Darling 2019
Pedone C, Bone, 2010	BMD	Wallace 2017
Perez Durillo FT, Aten Primaria, 2011	Fracture (hip)	Darling 2019
Pop LC, Am J Clin Nutr, 2015	BMD/BMC	Wright 2019
Pop LC, Osteoporos Int, 2017	BMD/BMC	Wright 2019
Preisinger E, Wien Klin Wochenschr, 1995	Osteoporosis	Darling 2019
Pritchard JE, Int J Obes, 1996	BMD/BMC	Wright 2019

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Promislow JH, Am J Epidemiol, 2002	BMD	Darling 2019; Shams-White 2017; Tsagari 2020
Quintas ME, Eur J Clin Nutr, 2003	BMD	Darling 2019
Ramsdale SJ, Clin Sci, 1994	BMD/BMC	Wright 2019
Rapuri PB, Am J Clin Nutr, 2003	BMD	Cureneen 2018; Darling 2019; Groenendijk 2019; Wallace 2017
Recker RR, JAMA, 1992	BMD	Shams-White 2017; Tsagari 2020
Ricci TA, J Bone Miner Res, 1998	BMD/BMC	Wright 2019
Riedt CS, J Bone Miner Res, 2005	BMD/BMC	Wright 2019
Rosado JL, J Am Diet Assoc, 2011	BMC	Wright 2019
Rubinacci A, Minerva Med, 1992	BMC	Darling 2019
Sahni S, J Bone Miner Res, 2010	Fracture (hip)	Darling 2019; Shams-White 2017
Sahni S, Public Health Nutr, 2014	BMD	Darling 2019; Shams-White 2017; Tsagari 2020; Wallace 2017
Samieri C, Osteoporos Int, 2013	Fracture (hip, spine, wrist)	Darling 2019
Schurch MA, Ann Intern Med, 1998	BMD	Darling 2019; Shams-White 2017; Tsagari 2020
Schwingel A, Revista Brasileira de Cineantropometria & Desempenho Humano, 2006	BMC	Wright 2019
Sellmeyer DE, Am J Clin Nutr, 2001	Fracture (hip)	Cureneen 2018; Darling 2019
Shapses SA, J Bone Miner Res, 2001	BMD/BMC	Wright 2019
Skov AR, Obes Res, 2002	BMD/BMC	Wright 2019
Sukumar D, J Bone Miner Res, 2011	BMD	Shams-White 2017; Tsagari 2020; Wright 2019
Svendsen OL, Am J Med, 1993	BMD	Wright 2019
Tang M, Nutr Res, 2013	BMD/BMC	Wright 2019
Teegarden D, Am J Clin Nutr, 1998	BMD/BMC	Darling 2019
Tengstrand B, Clin Nutr, 2007	BMD	Shams-White 2017; Tsagari 2020
Thomas DT, J Am Coll Nutr, 2010	BMD	Wright 2019
Thorpe M, J Nutr, 2008	BMD	Cureneen 2018; Darling 2019; Shams-White 2017; Tsagari 2020; Wright 2019
Tirosh A, J Clin Endocrinol Metab, 2015	BMD	Shams-White 2017; Tsagari 2020; Wright 2019

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Tkatch L, J Am Coll Nutr, 1992	BMD	Darling 2019
Tucker KL, Eur J Nutr, 2001	BMD	Wallace 2017
Tylavsky FA, Am J Clin Nutr, 1988	BMD/BMC	Darling 2019
Uenishi K, Osteoporos Int, 2007	BMD	Darling 2019
Van Loan MD, Am J Clin Nutr, 1998	BMD/BMC	Wright 2019
Vatanparast H, J Nutr, 2007	BMD/BMC	Darling 2019
Villareal DT, Arch Intern Med, 2006	BMD	Wright 2019
Vupadhyayula PM, Menopause, 2009	BMD	Darling 2019
Wang MC, Oseoporos Int, 1997	BMD/BMC	Cureneen 2018; Darling 2019
Weiss EP, Med Sci Sports Exerc, 2017	BMD	Wright 2019
Wengreen HJ, J Bone Miner Res, 2004	Fracture (hip)	Cureneen 2018; Darling 2019
Whiting SJ, J Am Coll Nutr, 2002	BMD	Darling 2019
Yamamura J, Biosci Biotechnol Biochem, 2002	BMD	Darling 2019
Yazdanpanah N, Bone, 2007	BMD	Darling 2019
Zhang Q, Brit J Nutr, 2010	BMC	Darling 2019
Zhang X, Arch Intern Med, 2005	Fracture (any)	Darling 2019; Shams-White 2017
Zhong Y, Nutrition, 2009	Fracture (any)	Cureneen 2018; Darling 2019
Zhu K, J Bone Miner Res, 2011	BMD	Cureneen 2018; Darling 2019; Groenendijk 2019; Shams-White 2017; Tsagari 2020; Wallace 2017
Zou ZY, Eur J Nutr, 2009	BMD	Darling 2019; Wallace 2017

Appendix 2-k: Duplication assessment for protein intake and cardiovascular disease risk evidence

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Aaltonen J, J Pediatr. 2008	Offspring BP	van Elten, 2019
Adair LS, Circulation. 2001	Offspring BP	van Elten, 2019
Alonso A, Archives of Medical Research 2006	Hypertension/Blood pressure	Mousavi, 2020
Altorf-van der Kuil W, Journal of Hypertension 2010	Hypertension/Blood pressure	Mousavi, 2020
Altorf-van der Kuil W, British Journal of Nutrition 2012	Hypertension/Blood pressure	Mousavi, 2020
Bates CJ, Br J Nutr 2010	CVD Mortality	Naghshi, 2020
Bernstein AM, Stroke 2012	Stroke risk	Zhang, 2016
Blumfield M, Nutrients 2015	Offspring BP	van Elten, 2019
Brinkworth GDM, Diabetologia 2004b	Blood pressure	Schwingshackl, 2019
Brinkworth GDM, International Journal of Obesity and Related Metabolic Disorders 2004a	Blood pressure	Schwingshackl, 2019
Budhathoki S, JAMA Intern Med 2019	CVD Mortality	Naghshi, 2020; Qi, 2020; Chen, 2020
Buendia JR, American Journal of Hypertension 2015	Hypertension/Blood pressure	Mousavi, 2020
Campans-Kuijpers MJ, Cardiovasc Diabetol 2015	CVD Mortality	Naghshi, 2020
Campbell DD, British Journal of Nutrition 2012	Blood pressure	Schwingshackl, 2019
Chan R, J Nutr Health Aging 2019	CVD Mortality	Naghshi, 2020; Qi, 2020
Chen Z, Eur J Epidemiol 2020	CVD Mortality	Qi, 2020; Chen, 2020
Clifton PM, Nutr Metab Cardiovasc Dis 2014	Blood pressure	Dinu, 2020
Courand PY, Hypertension 2016	CVD Mortality	Naghshi, 2020
Dalle Grave R, Obesity (Silver Spring) 2013	Blood pressure	Schwingshackl, 2019
Dansinger ML, JAMA 2005	Blood pressure	Schwingshackl, 2019
Dehghan M, Lancet 2017	CVD Mortality	Naghshi, 2020; Qi, 2020
Dehghan M, The Lancet 2017	Coronary heart diesease	Mousavi, 2020
Delbridge EA, American Journal of Clinical Nutrition 2009	Blood pressure	Schwingshackl, 2019
Dong YJ, Br J Nutr 2013	Blood pressure	Dinu, 2020; Sukhato, 2020

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Doorenbos CJ, Clin Sci (Lond) 1990	Blood pressure	van Elswyk, 2018
Esrey KL, J Clin Epidemiol 1996	CVD Mortality	Naghshi, 2020
Frank H, Am J Clin Nutr 2009	Blood pressure	van Elswyk, 2018
Gross JL, Diabetes Care 2002	Blood pressure	van Elswyk, 2018
Halton TL, The New England Journal of Medicine 2006	Coronary heart diesease	Mousavi, 2020
Haring B, PLoS One 2014	Coronary heart diesease	Mousavi, 2020
Haring B, Stroke 2015	Stroke risk	Zhang, 2016
Hernandez Alonso P, Clin Nutr 2016	CVD Mortality	Naghshi, 2020; Qi, 2020
Huh SY, Int J Epidemiol 2005	Offspring BP	van Elten, 2019
Iso H, Am. J. Epidemiology 2003	Stroke risk	Zhang, 2016
Iso H, Circulation 2001	Stroke risk	Zhang, 2016
Jacobs DR Jr, Am J Kidney Dis 2009	Blood pressure	van Elswyk, 2018
Jenkins DJ, Am J Clin Nutr 2001	Blood pressure	van Elswyk, 2018
Juraschek SP, Am J Kidney Dis 2013	Blood pressure	van Elswyk, 2018
Kelemen LE, Am J Epidemiol 2005	Coronary heart diesease; CVD Mortality	Mousavi, 2020; Naghshi, 2020 Chen, 2020
Khaw KT, N. Engl. J. Med. 1987	Stroke risk	Zhang, 2016
Kim HH, Journal of Diabetes Investigation 2014	Blood pressure	Schwingshackl, 2019
Kitazato H, Nephron 2002	Blood pressure	van Elswyk, 2018
Krebs JD, Diabetologia 2012	Blood pressure	Schwingshackl, 2019
Kurihara A, Journal of Atherosclerosis and Thrombosis 2019	Coronary heart diesease	Mousavi, 2020
Lagiou P, BMJ 2012	Stroke risk	Zhang, 2016
Larsson SC, Atherosclerosis 2012	Stroke risk	Zhang, 2016
Leary SD, Arch Dis Child. 2005	Offspring BP	van Elten, 2019
Leary SD, J Epidemiol Community Health. 2013	Offspring BP	van Elten, 2019
Lelong H, Hypertension 2017	Hypertension/Blood pressure	Mousavi, 2020
Levine ME, Cell Metabol 2014	CVD Mortality	Naghshi, 2020; Qi, 2020; Chen, 2020
Luger M, Experimental and Clinical Endocrinology & Diabetes 2013	Blood pressure	Schwingshackl, 2019

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Nagata C, J. Nutr. 2015	CVD Mortality; Stroke risk	Naghshi, 2020; Zhang, 2016
Normia J, J Hum Nutr Diet. 2013	Offspring BP	van Elten, 2019
Nuttall FQ, Metabolism 2006	Blood pressure	van Elswyk, 2018
Preis SR, AJCN 2010	CVD Mortality; Stroke risk; Coronary heart diesease	Naghshi, 2020; Zhang, 2016; Mousavi, 2020
Prentice RL, Epidemiology 2011	Stroke risk; Coronary heart diesease	Zhang, 2016; Mousavi, 2020
Rebholz CM, Am J Epidemiol 2012	Blood pressure	Sukhato, 2020
Santesso, N Eur J Clin Nutr 2012	Blood pressure	Dinu, 2020; Sukhato, 2020
Sauvaget C, Stroke 2004	CVD Mortality; Stroke risk	Naghshi, 2020; Zhang, 2016
Schwingshackl L, Nutr J 2013	Blood pressure	Dinu, 2020; Sukhato, 2020
Song M, JAMA Intern Med 2016	CVD Mortality	Qi, 2020; Chen, 2020
Sun Y, Curr Dev Nutr 2019	CVD Mortality	Naghshi, 2020
Talaei M, J Nutr 2014	Stroke risk	Zhang, 2016
Tang M, Obesity (Silver Spring) 2013	Blood pressure	Schwingshackl, 2019
Tharrey M, Int J Epidemiol 2018	CVD Mortality	Qi, 2020
Tielemans S, J Hum Hypertens 2013	Blood pressure	Sukhato, 2020
van den Hil LCL, Br J Nutr. 2013	Offspring BP	van Elten, 2019
Velazquez LL, Nutr Hosp 2008	Blood pressure	van Elswyk, 2018
Wallstrom P, PLoS One 2012	Coronary heart disease	Mousavi, 2020
Watson N, Nutrients 2016	Blood pressure	Schwingshackl, 2019
Wycherley TP, Am J Clin Nutr 2012	Blood pressure	Dinu, 2020
Wycherley TP, Diabetes Care 2010	Blood pressure	Schwingshackl, 2019
Zhao WT, Medicine 2018	Blood pressure	Dinu, 2020; Sukhato, 2020

Appendix 2-I: Duplication assessment for protein intake and diabetes risk evidence

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Alhazmi A, Public Health Nutr 2014	Type 2 Diabetes	Shang, 2016; Ye, 2019; Zhao, 2019
Bao W, Diabetes Care 2013	Type 2 Diabetes	Tian, 2017
Chen Z, Clin Nutr 2019	Type 2 Diabetes	Fan, 2019
Ericson U, Br J Nutr 2013	Type 2 Diabetes	Fan, 2019; Shang, 2016; Tian, 2017
Malik VS, Am J Epidemiol 2016	Type 2 Diabetes	Fan, 2019; Shang, 2017; Tian, 2017; Ye, 2019; Zhao, 2019
Nanri A, PLoS One, 2015	Type 2 Diabetes	Shang, 2018; Tian, 2017; Ye, 2019; Zhao, 2019
Shang X, Am J Clin Nutr 2016	Type 2 Diabetes	Fan, 2019; Shang, 2019; Tian, 2017; Ye, 2019; Zhao, 2019
Sluijs I, Diabetes Care 2010	Type 2 Diabetes	Fan, 2019; Shang, 2020; Tian, 2017
Song Y, Diabetes Care 2004	Type 2 Diabetes	Shang, 2020; Ye, 2019; Zhao, 2019
Tinker LF, Am J Clin Nut. 2011	Type 2 Diabetes	Shang, 2020; Tian, 2017; Ye, 2019; Zhao, 2019
Van Nielen M, Diabetes Care 2014	Type 2 Diabetes	Shang, 2020; Tian, 2017; Ye, 2019; Zhao, 2019
Virtanen HEK, Br J Nutr 2017	Type 2 Diabetes	Fan, 2019; Tian, 2017; Ye, 2019; Zhao, 2019

Appendix 2-m: Duplication assessment for protein intake and renal health evidence[a]

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Antonio J, J Int Soc Sports Nutr, 2016	GFR	Devries 2018
Antonio J, J Nutr Metab, 2016	GFR	Devries 2018
Bergstrom J, Acta Med Scand, 1985	GFR	Devries 2018
Berryman CE, Am J Clin Nutr, 2016	GFR	van Elswyk 2018
Brinkworth GD, Int J Obes Relat Metab Disord, 2004	GFR	Devries 2018
Brinkworth GD, J Am Diet Assoc, 2010	GFR	Devries 2018
Chu J, Am J Clin Nutr, 1975	GFR	Devries 2018
Doorenbos CJ, Clin Sci (Lond), 1990	GFR	van Elswyk 2018
Frank H, Am J Clin Nutr, 2009	GFR	Devries 2018; van Elswyk 2018
Friedman A, Clin J Am Soc Nephrol, 2012	GFR	Devries 2018
Gross J, Diabetes Care, 2002	GFR	Devries 2018; van Elswyk 2018
Hegsted M, J Nutr, 1981	GFR	Devries 2018
Herber-Gast GM, Am J Clin Nutr, 2016	GFR	van Elswyk 2018
Jenkins D, Am J Clin Nutr, 2001	GFR	Devries 2018; van Elswyk 2018
Johnston C, J Nutr, 2004	GFR	Devries 2018
Juraschek SP, Am J Kidney Dis, 2013	GFR	Devries 2018; van Elswyk 2018
Kerstetter JE, Am J Clin Nutr, 1997	GFR	van Elswyk 2018
Kerstetter JE, Am J Clin Nutr, 1998	GFR	Devries 2018; van Elswyk 2018
Kerstetter JE, Am J Clin Nutr, 2000	GFR	van Elswyk 2018
Kerstetter JE, J Nutr, 2006	GFR	van Elswyk 2018
Kim Y, J Nutr, 1979	GFR	Devries 2018
Kitazato H, Nephron, 2002	GFR	van Elswyk 2018
Larsen R, Diabetologia, 2011	GFR	Devries 2018
Leidy H, Obesity, 2007	GFR	Devries 2018
Longland T, Am J Clin Nutr, 2016	GFR	Devries 2018

[a] GFR; Glomerular filtration rate

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Luger M, Exp Clin Endocrinol Diabetes, 2013	GFR	Devries 2018
Luscombe-Marsh ND, Am J Clin Nutr, 2005	GFR	Devries 2018
Noakes M, Am J Clin Nutr, 2005	GFR	Devries 2018
Ogna A, Eur J Nutr, 2016	GFR	van Elswyk 2018
Poortmans JR, Int J Sport Nutr Exerc Metab, 2000	GFR	van Elswyk 2018
Rebholz CM, Am J Nephrol, 2015	Kidney disease incidence	van Elswyk 2018
Roughead Z, J Nutr, 2003	GFR	Devries 2018; van Elswyk 2018
Skov A, Int J Obes Relat Metab Disord, 1999	GFR	Devries 2018
Tay J, Medicine, 2015	GFR	Devries 2018
Teo BW, Ann Acad Med Singapore, 2015	GFR	van Elswyk 2018
Teunissen-Beekman K, Phys Rep, 2016	GFR	Devries 2018
Velazquez Lopez L, Nutr Hosp, 2008	GFR	van Elswyk 2018
Wagner E, J Am Diet Assoc, 2007	GFR	Devries 2018
Walrand S, Am J Physiol Endocrinol Metab, 2008	GFR	Devries 2018; van Elswyk 2018
Wycherley T, Nutr Diabetes, 2012	GFR	Devries 2018
Zykova SN, Nutr J, 2015	GFR	van Elswyk 2018

Appendix 2-n: Duplication assessment for protein intake and sarcopenia evidence

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Aguiar AF, Eur J Appl Physiol 2013	Muscle mass; Muscle strength	Naseeb, 2017
Ahnfeldt-Mollerup P, Eur J Phys Rehabil 2015	Muscle strength	Lin, 2021
Aleman-Mateo H, Clin Interv Aging 2012	Lean body mass; Appendicular lean mass; Handgrip strength	Kirwan, 2021
Aleman-Mateo H, Clin Interv Aging 2014	Lean body mass; Appendicular lean mass; Handgrip strength	Kirwan, 2021
Antonio J, Nutrition 2000	Lean muscle mass gain	Lin, 2021
Arnarson A, Eur J Clin Nutr 2013	Lean body mass	Kirwan, 2021
Beasley JM, J Nutr Health Aging 2016	Whole skeletal muscle mass	Yaegashi, 2021
Bjorkman MP, Eur Geriatr Med 2012	Skeletal muscle mass	Kirwan, 2021
Campbell WW, Am J Clin Nutr 1994	Lean body mass	Kirwan, 2021
Carlsson M, J Nutr Health Aging 2011	Lean body mass	Kirwan, 2021
Chale A, J Gerontol A Biol Sci Med Sci 2013	Lean body mass	Kirwan, 2021
Chan R, J Nutr Health Aging 2014	Appendicular skeletal muscle mass; Lower-limb Muscle functioning/strength	Yaegashi, 2021; Coelho-Júnior, 2018
Cheng YH, Clin Nutr 2019	Lean muscle mass gain	Lin, 2021
Cramer JT, J Strength Cond Res 2012	Lean muscle mass gain	Lin, 2021
Daly RM, Am J Clin Nutr 2014	Muscle mass; Muscle strength	Naseeb, 2017
Dirks ML, J Am Med Dir Assoc 2017	Lean body mass; Appendicular lean mass; Handgrip strength; Knee ext. strength	Kirwan, 2021
Dirks ML, J Nutr 2014	Muscle mass; Muscle strength	Naseeb, 2017
Elstgeest LEM, Am J Clin Nutr 2020	Appendicular skeletal muscle mass	Yaegashi, 2021
Englund DA, J Gerontol A Biol Sci Med Sci 2017	Lean muscle mass gain; Muscle strengh	Lin, 2021
Ferguson-Stegall L, J Nutr Metab 2011	Lean muscle mass gain	Lin, 2021
Flakoll PJ, J Appl Physiol 2004	Lean muscle mass gain	Lin, 2021
Genaro Pde S, Nutr Clin Pract 2015	Appendicular skeletal muscle mass	Yaegashi, 2021
Gingrich A, Nutrients 2017	Whole skeletal muscle mass	Yaegashi, 2021
Gregorio L, J Nutr Health Aging 2014	Appendicular skeletal muscle mass; Upper-limb Muscle Strength; Lower-limb Muscle Strength	Yaegashi, 2021; Coelho-Júnior, 2018
Gryson C, J Am Med Dir Assoc 2014	Lean body mass; Appendicular lean mass	Kirwan, 2021
Gualano B, Exp Gerontol 2014	Muscle mass; Muscle strength	Naseeb, 2017
Hashemi R, Nutrition 2015	Sarcopenia	Naseeb, 2017
Houston DK, Am J Clin Nutr 2008	Appendicular skeletal muscle mass	Yaegashi, 2021
Huang RY, Nutrients 2016	Whole skeletal muscle mass	Yaegashi, 2021

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
Iglay HB, J Nutr Health Aging 2009	Lean body mass	Kirwan, 2021
Isanejad M, Br J Nutr 2016	Upper-limb Muscle Strength; Lower-limb Muscle Strength	Coelho-Júnior, 2018
Isanejad M, J Nutr Sci 2015	Appendicular skeletal muscle mass	Yaegashi, 2021
Jonvik KL, Med Sci Sports Exerc 2019	Lean muscle mass gain; Muscle strength	Lin, 2021
Jyvakorpi SK, Eur Geriatr Med 2020	Appendicular skeletal muscle mass	Yaegashi, 2021
Kephart WC, Amino Acids 2016	Lean muscle mass gain	Lin, 2021
Kim H, J Am Med Dir Association 2016	Lean muscle mass gain; Muscle strength	Lin, 2021
Kim HK, J Am Geriatri Soc 2012	Muscle mass; Muscle strength	Naseeb, 2017
Kim SH, Arch Gerontol Geriatr 2013	Appendicular skeletal muscle mass; Sarcopenia	Yaegashi, 2021; Naseeb, 2017
Knuiman P, Am J Clin Nutr 2019	Lean muscle mass gain	Lin, 2021
Larocque SC, J. Nutr. Gerontol. Geriatr 2015	Upper-limb muscle strength	Coelho-Júnior, 2018
Leenders M, Med Sci Sports Exerc 2013	Lean body mass	Kirwan, 2021
Li C, J Acad Nutr Diet 2021	Lean body mass; Appendicular lean mass; Handgrip strength	Kirwan, 2021
Liao YH, NeuroRehabiliation 2019	Lean muscle mass gain; Muscle strength	Lin, 2021
Markofski MM, J Gerontol A Biol Sci Med Sci 2019	Lean muscle mass gain; Muscle strength	Lin, 2021
Meng X, J Bone Miner Res 2009	Appendicular skeletal muscle mass	Yaegashi, 2021
Mitchell CJ, Am J Clin Nutr 2017	Lean body mass; Appendicular lean mass; Handgrip strength	Kirwan, 2021
Nabuco HCG, Clin Nutr ESPEN 2019	Lean body mass; Appendicular lean mass; Knee ext. strength	Kirwan, 2021
Nabuco HCG, J Aging Phys Act 2019	Appendicular lean mass	Kirwan, 2021
Nabuco HCG, Nutrients 2018	Knee ext. strength	Kirwan, 2021
Nahas PC, Nutrients 2019	Lean body mass; Knee ext. strength	Kirwan, 2021
Nilsson A, Nutrients 2018	Whole skeletal muscle mass	Yaegashi, 2021
Oh C, Nutr Res 2018	Appendicular skeletal muscle mass	Yaegashi, 2021
Ormsbee MJ, Int J Sport Nutr Exerc Metab 2018	Lean muscle mass gain; Muscle strength	Lin, 2021
Otsuka R, Public Health Nutr 2020	Appendicular skeletal muscle mass	Yaegashi, 2021
Ottestad I, J Nutr Health Aging 2017	Lean body mass	Kirwan, 2021
Rahi B, Eur. J. Nutr 2016	Lower-limb Muscle Strength	Coelho-Júnior, 2018
Rossato LT, Nutrients 2017	Lean body mass	Kirwan, 2021
Scott D, J Am Geriatr Soc 2010	Muscle mass; Muscle strength	Naseeb, 2017
Shahar S, Clin Interv Aging 2013	Lean body mass; Handgrip strength	Kirwan, 2021
Sugihara Junior P, Int J Sport Nutr Exerc Metab 2018	Knee ext. strength	Kirwan, 2021

Articles included in reviews	Relevant outcome(s) assessed	Source review(s)
ten Haaf D, Nutrients 2018	Upper-limb muscle strength; Lower-limb Muscle Strength	Coelho-Júnior, 2018
Ten Haaf DSM, J Cachexia Sarcopenia Muscle 2019	Lean body mass; Handgrip strength	Kirwan, 2021
Thomson RL, Clin Nutr 2016	Lean body mass; Handgrip strength	Kirwan, 2021
Tieland M, J Am Med Dir Assoc 2012 (a)	Lean body mass; Appendicular lean mass; Handgrip strength; Knee ext. strength; Muscle mass; Muscle strength	Kirwan, 2021; Naseeb, 2017
Tieland M, J Am Med Dir Assoc 2012 (b)	Lean body mass; Appendicular lean mass; Handgrip strength; Knee ext. strength; Muscle mass; Muscle strength	Kirwan, 2021; Naseeb, 2017
Valenzuela RE, Clin Interv Aging 2013	Appendicular skeletal muscle mass	Yaegashi, 2021
Verdijk LB, Am J Clin Nutr 2009	Lean body mass; Knee ext. strength	Kirwan, 2021
Verlaan S, Clin Nutr 2015	Upper-limb muscle strength	Coelho-Júnior, 2018
Walker TB, Int J Sport Nutr Exerc Metab 2010	Lean muscle mass gain	Lin, 2021
Yaegashi A, Nutrients 2021	Appendicular skeletal muscle mass	Yaegashi, 2021
Zdzieblik D, Br J Nutr 2015	Lean body mass	Kirwan, 2021
Zhu K, J Nutr 2015	Lean body mass	Kirwan, 2021

Appendix 3-a: Literature search strategy for the protein requirements evidence scan

Backward Citation Mining, Level 1
Date(s) Searched: January 27, 2022

Article	Database Used	Results	Results after Deduplication
Deutz	Scopus	91	91
Bauer	Scopus	252	205
Hörnell	WoS	52	51
FAO/WHO	WoS	130	124
Pedersen	Scopus	42	27
EFSA	Scopus	252	232
Total		819	730

In Hörnell, there were 10 references which WoS could not export, due to the nature of their citations (reports not in English, not in the WoS database).

Forward Citation Mining, Level 1
Date(s) Searched: January 28, 2022

Article	Database Used	Results	Results after Deduplication
Deutz	Scopus	702	701
Bauer	Scopus	1,128	782
Hörnell	WoS	65	64
FAO/WHO	WoS	12	12
Pedersen	Scopus	49	15
EFSA	Scopus	174	136
Total		2,129	1,710

Appendix 3-b: Excluded articles for the protein requirements evidence scan

The following table lists the articles excluded after full-text screening for this evidence scan. At least one reason for exclusion is provided for each article, though this may not reflect all possible reasons. Information about articles excluded after title and abstract screening is available upon request.

#	Citation	Exclusion reason #1	Exclusion reason #2
1	Agergaard, J, Hansen, ET, van Hall, G, Holm, L. Postprandial amino acid availability after intake of intact or hydrolyzed meat protein in a mixed meal in healthy elderly subjects: a randomized, single blind crossover trial. Amino Acids. 2021. 53:951-959. doi:10.1007/s00726-021-03000-z	Intervention/exposure	-
2	Agostoni, C, Scaglioni, S, Ghisleni, D, Verduci, E, Giovannini, M, Riva, E. How much protein is safe?. INTERNATIONAL JOURNAL OF OBESITY. 2005. 29:S8-S13. doi:10.1038/sj.ijo.0803095	Study design	-
3	Al-Nimr, RI. Optimal Protein Intake during Weight Loss Interventions in Older Adults with Obesity. Journal of Nutrition in Gerontology and Geriatrics. 2019. 38:50-68. doi:10.1080/21551197.2018.1544533	Outcome	-
4	Arnal, MA, Mosoni, L, Boirie, Y, Houlier, ML, Morin, L, Verdier, E, Ritz, P, Antoine, JM, Prugnaud, J, Beaufrère, B, Patureau Mirand, P. Protein feeding pattern does not affect protein retention in young women. Journal of Nutrition. 2000. 130:1700-1704. doi:10.1093/jn/130.7.1700	Comparator	Outcome
5	Bauer, J, Biolo, G, Cederholm, T, Cesari, M, Cruz-Jentoft, AJ, Morley, JE, Phillips, S, Sieber, C, Stehle, P, Teta, D, Visvanathan, R, Volpi, E, Boirie, Y. Evidence-based recommendations for optimal dietary protein intake in older people: A position paper from the prot-age study group. Journal of the American Medical Directors Association. 2013. 14:542-559. doi:10.1016/j.jamda.2013.05.021	Study design	-
6	Bauer, JM, Diekmann, R. Protein and Older Persons. Clinics in Geriatric Medicine. 2015. 31:327-338. doi:10.1016/j.cger.2015.04.002	Study design	-
7	Beasley, JM, Wertheim, BC, Lacroix, AZ, Prentice, RL, Neuhouser, ML, Tinker, LF, Kritchevsky, S, Shikany, JM, Eaton, C, Chen, Z, Thomson, CA. Biomarker-calibrated protein intake and physical function in the women's health initiative. Journal of the American Geriatrics Society. 2013. 61:1863-1871. doi:10.1111/jgs.12503	Outcome	-
8	Berryman, CE, Lieberman, HR, Fulgoni, VL, III, Pasiakos, SM. Protein intake trends and conformity with the Dietary Reference Intakes in the United States: Analysis of the National Health and Nutrition Examination Survey, 2001-2014. American Journal of Clinical Nutrition. 2018. 108:405-413. doi:10.1093/ajcn/nqy088	Outcome	-
9	Bonnefoy, M, Gilbert, T. Frailty and nutrition — the current state of play and outlook for the future. Cahiers de l'Annee Gerontologique. 2015. 7:8-12. doi:10.1007/s12612-015-0445-7	Pub. language	-
10	Brestenský, M, Nitrayová, S, Patráš, P, Nitray, J. Dietary requirements for proteins and amino acids in human nutrition. Current Nutrition and Food Science. 2019. 15:638-645. doi:10.2174/1573401314666180507123506	Study design	-

#	Citation	Exclusion reason #1	Exclusion reason #2
11	Campbell, WW, Leidy, HJ. Dietary Protein and Resistance Training Effects on Muscle and Body Composition in Older Persons. Journal of the American College of Nutrition. 2007. 26:696S-703S. doi:10.1080/07315724.2007.10719650	Study design	-
12	Campbell, WW, Trappe, TA, Jozsi, AC, Kruskall, LJ, Wolfe, RR, Evans, WJ. Dietary protein adequacy and lower body versus whole body resistive training in older humans. Journal of Physiology. 2002. 542:631-642. doi:10.1113/jphysiol.2002.020685	Intervention/exposure	Comparator
13	Campbell, WW, Trappe, TA, Wolfe, RR, Evans, WJ. The recommended dietary allowance for protein may not be adequate for older people to maintain skeletal muscle. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2001. 56:M373-M380. doi:10.1093/gerona/56.6.M373	Comparator	-
14	Chevalier, S, Gougeon, R, Nayar, K, Morais, JA. Frailty amplifies the effects of aging on protein metabolism: Role of protein intake. American Journal of Clinical Nutrition. 2003. 78:422-429. doi:10.1093/ajcn/78.3.422	Intervention/exposure	Outcome
15	Chew, STH, Kayambu, G, Lew, CCH, Ng, TP, Ong, F, Tan, J, Tan, NC, Tham, SL. Singapore multidisciplinary consensus recommendations on muscle health in older adults: assessment and multimodal targeted intervention across the continuum of care. BMC Geriatrics. 2021. 21:#pages#. doi:10.1186/s12877-021-02240-8	Study design	Outcome
16	Chouraqui, JP, Tavoularis, G, Simeoni, U, Ferry, C, Turck, D. Food, water, energy, and macronutrient intake of non-breastfed infants and young children (0-3 years). European Journal of Nutrition. 2020. 59:67-80. doi:10.1007/s00394-018-1883-y	Intervention/exposure	Outcome
17	Dangin, M, Boirie, Y, Garcia-Rodenas, C, Gachon, P, Fauquant, J, Callier, P, Ballèvre, O, Beaufrère, B. The digestion rate of protein is an independent regulating factor of postprandial protein retention. American Journal of Physiology - Endocrinology and Metabolism. 2001. 280:E340-E348. doi:10.1152/ajpendo.2001.280.2.e340	Intervention/exposure	Outcome
18	Dangin, M, Guillet, C, Garcia-Rodenas, C, Gachon, P, Bouteloup-Demange, C, Reiffers-Magnani, K, Fauquant, J, Ballèvre, O, Beaufrère, B. The rate of protein digestion affects protein gain differently during aging in humans. Journal of Physiology. 2003. 549:635-644. doi:10.1113/jphysiol.2002.036897	Intervention/exposure	Outcome
19	Dardevet, D, Mosoni, L, Savary-Auzeloux, I, Peyron, MA, Polakof, S, Rémond, D. Important determinants to take into account to optimize protein nutrition in the elderly: Solutions to a complex equation. Cahiers de Nutrition et de Dietetique. 2021. 56:333-349. doi:10.1016/j.cnd.2021.10.002	Study design	-
20	Dato, S, Hoxha, E, Crocco, P, Iannone, F, Passarino, G, Rose, G. Amino acids and amino acid sensing: implication for aging and diseases. Biogerontology. 2019. 20:17-31. doi:10.1007/s10522-018-9770-8	Study design	-
21	De Vries-Ten Have, J, Owolabi, A, Steijns, J, Kudla, U, Melse-Boonstra, A. Protein intake adequacy among Nigerian infants, children, adolescents and women and protein quality of commonly consumed foods. Nutrition Research Reviews. 2020. 33:102-120. doi:10.1017/S0954422419000222	Outcome	-
22	Deer, RR, Volpi, E. Protein intake and muscle function in older adults. Current Opinion in Clinical Nutrition and Metabolic Care. 2015. 18:248-253. doi:10.1097/MCO.0000000000000162	Study design	-

#	Citation	Exclusion reason #1	Exclusion reason #2
23	Deutz, NEP, Bauer, JM, Barazzoni, R, Biolo, G, Boirie, Y, Bosy-Westphal, A, Cederholm, T, Cruz-Jentoft, A, Krznariç, Z, Nair, KS, Singer, P, Teta, D, Tipton, K, Calder, PC. Protein intake and exercise for optimal muscle function with aging: Recommendations from the ESPEN Expert Group. Clinical Nutrition. 2014. 33:929-936. doi:10.1016/j.clnu.2014.04.007	Study design	-
24	Dickinson, JM, Volpi, E, Rasmussen, BB. Exercise and nutrition to target protein synthesis impairments in aging skeletal muscle. Exercise and Sport Sciences Reviews. 2013. 41:216-223. doi:10.1097/JES.0b013e3182a4e699	Study design	-
25	Dideriksen, K, Reitelseder, S, Holm, L. Influence of amino acids, dietary protein, and physical activity on muscle mass development in humans. Nutrients. 2013. 5:852-876. doi:10.3390/nu5030852	Study design	-
26	Diekmann, R, Bauer, JM. Protein requirements of elderly people. Deutsche Medizinische Wochenschrift. 2014. 139:239-242. doi:10.1055/s-0033-1359989	Pub. language	-
27	Drummond, MJ. A practical dietary strategy to maximize the anabolic response to protein in aging muscle. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2015. 70:55-56. doi:10.1093/gerona/glu157	Study design	-
28	Efsa Panel on Dietetic Products, Nutrition, Allergies, . Scientific Opinion on nutrient requirements and dietary intakes of infants and young children in the European Union. EFSA Journal. 2013. 11:#pages#. doi:10.2903/j.efsa.2013.3408	Study design	-
29	Elango, R, Ball, RO, Pencharz, PB. Individual amino acid requirements in humans: An update. Current Opinion in Clinical Nutrition and Metabolic Care. 2008. 11:34-39. doi:10.1097/MCO.0b013e3282f2a5a4	Study design	-
30	Emery, PW. Protein requirements in nutrition support. Advanced Nutrition and Dietetics in Nutrition Support. 2018. #volume#:127-134. doi:10.1002/9781118993880	Study design	-
31	Evans, WJ. Protein Nutrition, Exercise and Aging. Journal of the American College of Nutrition. 2004. 23:601S-609S. doi:10.1080/07315724.2004.10719430	Study design	-
32	Franz, K, Müller-Werdan, U, Norman, K. Nutrition and malnutrition in old age: Interdisciplinary measures for the optimization of nutrition. Klinikarzt. 2017. 46:620-623. doi:10.1055/s-0043-122588	Pub. language	-
33	Franzke, B, Neubauer, O, Cameron-Smith, D, Wagner, KH. Dietary protein, muscle and physical function in the very old. Nutrients. 2018. 10:#pages#. doi:10.3390/nu10070935	Study design	-
34	Gaffney-Stomberg, E, Insogna, KL, Rodriguez, NR, Kerstetter, JE. Increasing dietary protein requirements in elderly people for optimal muscle and bone health. Journal of the American Geriatrics Society. 2009. 57:1073-1079. doi:10.1111/j.1532-5415.2009.02285.x	Study design	-
35	Gaillard, C, Alix, E, Boirie, Y, Berrut, G, Ritz, P. Are elderly hospitalized patients getting enough protein?. Journal of the American Geriatrics Society. 2008. 56:1045-1049. doi:10.1111/j.1532-5415.2008.01721.x	Health status	-
36	Gaspareto, N, Previdelli, ÁN, Laurentino, GC, de Aquino, RC. Protein Consumption: Inadequacy in Amount, Food Sources, and Mealtime Distribution in Community-Dwelling Older Adults. Ageing International. 2021. #volume#:#pages#. doi:10.1007/s12126-021-09465-3	Outcome	-

#	Citation	Exclusion reason #1	Exclusion reason #2
37	Grote, V, Von Kries, R, Closa-Monasterolo, R, Scaglioni, S, Gruszfeld, D, Sengier, A, Langhendries, JP, Koletzko, B. Protein intake and growth in the first 24 months of life. Journal of Pediatric Gastroenterology and Nutrition. 2010. 51:S117-S118. doi:10.1097/MPG.0b013e3181f96064	Outcome	-
38	Han, JH, Kang, LL, Liang, D, Li, HZ, Su, YX, Zhang, YM, Yang, YX. Composition requirements of follow-up formula for 6-12-month-old infants: recommendations of a Chinese expert group. Asia Pacific Journal of Clinical Nutrition. 2019. 28:347-355. doi:10.6133/apjcn.201906_28(2).0017	Outcome	-
39	Harris, S. Nutrition and exercise: A personalised approach. The Art and Science of Personalising Care with Older People with Diabetes. 2018. #volume#:81-98. doi:10.1007/978-3-319-74360-8_5	Study design	-
40	Hermanky, M, Korninger, C, Fuchs, D, Strasser, B. Effects of a Protein Optimized Diet Combined with Moderate Resistance Training on the Postoperative Course in Older Patients with Hip Fracture. Aktuelle Ernahrungsmedizin. 2017. 42:180-187. doi:10.1055/s-0043-105466	Pub. language	-
41	Hilbig, A, Kersting, M. Effects of age and time on energy and macronutrient intake in German infants and young children: Results of the DONALD study. Journal of Pediatric Gastroenterology and Nutrition. 2006. 43:518-524. doi:10.1097/01.mpg.0000229548.69702.aa	Outcome	-
42	Hoffer, LJ, Bistrian, BR. Appropriate protein provision in critical illness: A systematic and narrative review. American Journal of Clinical Nutrition. 2012. 96:591-600. doi:10.3945/ajcn.111.032078	Health status	-
43	Houston, DK, Nicklas, BJ, Ding, J, Harris, TB, Tylavsky, FA, Newman, AB, Jung, SL, Sahyoun, NR, Visser, M, Kritchevsky, SB. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: The Health, Aging, and Body Composition (Health ABC) study. American Journal of Clinical Nutrition. 2008. 87:150-155. doi:10.1093/ajcn/87.1.150	Outcome	-
44	Iizaka, S, Kaitani, T, Nakagami, G, Sugama, J, Sanada, H. Clinical validity of the estimated energy requirement and the average protein requirement for nutritional status change and wound healing in older patients with pressure ulcers: A multicenter prospective cohort study. Geriatrics and Gerontology International. 2015. 15:1201-1209. doi:10.1111/ggi.12420	Health status	-
45	Isanejad, M, Sirola, J, Mursu, J, Kröger, H, Tuppurainen, M, Erkkilä, AT. Association of protein intake with bone mineral density and bone mineral content among elderly women: The OSTPRE fracture prevention study. Journal of Nutrition, Health and Aging. 2017. 21:622-630. doi:10.1007/s12603-016-0800-4	Outcome	-
46	Jordan, LY, Melanson, EL, Melby, CL, Hickey, MS, Miller, BF. Nitrogen balance in older individuals in energy balance depends on timing of protein intake. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2010. 65 A:1068-1076. doi:10.1093/gerona/glq123	Intervention/exposure	Comparator
47	Juillet, B, Fouillet, H, Bos, C, Mariotti, F, Gausserès, N, Benamouzig, R, Tomé, D, Gaudichon, C. Increasing habitual protein intake results in reduced postprandial efficiency of peripheral, anabolic wheat protein nitrogen use in humans. American Journal of Clinical Nutrition. 2008. 87:666-678. doi:10.1093/ajcn/87.3.666	Outcome	-
48	Jun, S, Cowan, AE, Dwyer, JT, Campbell, WW, Thalacker-Mercer, AE, Gahche, JJ, Bailey, RL. Dietary Protein Intake Is Positively Associated with Appendicular Lean Mass and Handgrip Strength among Middle-Aged US Adults. Journal of Nutrition. 2021. 151:3755-3763. doi:10.1093/jn/nxab288	Outcome	-

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49	Jung, HW, Kim, SW, Kim, IY, Lim, JY, Park, HS, Song, W, Yoo, HJ, Jang, HC, Kim, K, Park, Y, Park, YJ, Yang, SJ, Lee, HJ, Won, CW, Sarcopenia-Frailty Study Group of the Korean Geriatric, Society, the Korean Nutrition, Society. Protein intake recommendation for korean older adults to prevent sarcopenia: Expert consensus by the korean geriatric society and the korean nutrition society. Annals of Geriatric Medicine and Research. 2018. 22:167-175. doi:10.4235/agmr.18.0046	Study design	-
50	Khanal, P, He, L, Degens, H, Stebbings, GK, Onambele-Pearson, GL, Williams, AG, Thomis, M, Morse, CI. Dietary protein requirement threshold and micronutrients profile in healthy older women based on relative skeletal muscle mass. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13093076	Outcome	-
51	Kiesswetter, E, Sieber, CC, Volkert, D. Protein intake in older people: Why, how much and how?. Zeitschrift fur Gerontologie und Geriatrie. 2020. 53:285-289. doi:10.1007/s00391-020-01723-4	Study design	-
52	Kiesswetter, E. Nutrition and sarcopenia. Osteologie. 2017. 26:28-31. doi:10.1055/s-0037-1622078	Pub. language	-
53	Koletzko, B, Broekaert, I, Demmelmair, H, Franke, J, Hannibal, I, Oberle, D, Schiess, S, Baumann, BT, Verwied-Jorky, S, Childhood Obesity Project EU. Protein intake in the first year of life: A risk factor for later obesity? The EU Childhood Obesity project. EARLY NUTRITION AND ITS LATER CONSEQUENCES: NEW OPPORTUNITIES: PERINATAL PROGRAMMING OF ADULT HEALTH - EC SUPPORTED RESEARCH. 2005. 569:69-79. doi:#electronic resource number#	Study design	Outcome
54	Koopman, R, Wagenmakers, AJM, Manders, RJF, Zorenc, AHG, Senden, JMG, Gorselink, M, Keizer, HA, Van Loon, LJC. Combined ingestion of protein and free leucine with carbohydrate increases postexercise muscle protein synthesis in vivo in male subjects. American Journal of Physiology - Endocrinology and Metabolism. 2005. 288:E645-E653. doi:10.1152/ajpendo.00413.2004	Outcome	-
55	Koopman, R, Walrand, S, Beelen, M, Gijsen, AP, Kies, AK, Boirie, Y, Saris, WHM, Van Loon, LJC. Dietary protein digestion and absorption rates and the subsequent postprandial muscle protein synthetic response do not differ between young and elderly men. Journal of Nutrition. 2009. 139:1707-1713. doi:10.3945/jn.109.109173	Intervention/exposure	Outcome
56	Krok-Schoen, JL, Archdeacon Price, A, Luo, M, Kelly, OJ, Taylor, CA. Low Dietary Protein Intakes and Associated Dietary Patterns and Functional Limitations in an Aging Population: A NHANES Analysis. Journal of Nutrition, Health and Aging. 2019. 23:338-347. doi:10.1007/s12603-019-1174-1	Outcome	-
57	Kurpad, AV, Regan, MM, Raj, T, Maruthy, K, Gnanou, J, Young, VR. Intravenously infused C-13-leucine is retained in fasting healthy adult men. Journal of Nutrition. 2002. 132:1906-1908. doi:10.1093/jn/132.7.1906	Intervention/exposure	Outcome
58	Kurpad, AV, Regan, MM, Raj, T, Varalakshmi, S, Gnanou, J, Thankachan, P, Young, VR. Leucine requirement and splanchnic uptake of leucine in chronically undernourished adult Indian subjects. American Journal of Clinical Nutrition. 2003. 77:861-867. doi:10.1093/ajcn/77.4.861	Health status	-
59	Lancha Jr, AH, Zanella Jr, R, Tanabe, SGO, Andriamihaja, M, Blachier, F. Dietary protein supplementation in the elderly for limiting muscle mass loss. Amino Acids. 2017. 49:33-47. doi:10.1007/s00726-016-2355-4	Study design	-
60	Layman, DK. A protein-centric perspective for skeletal muscle metabolism and cardiometabolic health. Nutrition and Cardiometabolic Health. 2017. #volume#:333-347. doi:10.1201/9781315119410	Study design	-

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61	Leser, S. The 2013 FAO report on dietary protein quality evaluation in human nutrition: Recommendations and implications. Nutrition Bulletin. 2013. 38:421-428. doi:10.1111/nbu.12063	Study design	-
62	Linn, T, Santosa, B, Grönemeyer, D, Aygen, S, Scholz, N, Busch, M, Bretzel, RG. Effect of long-term dietary protein intake on glucose metabolism in humans. Diabetologia. 2000. 43:1257-1265. doi:10.1007/s001250051521	Outcome	-
63	Liu, Z, Jahn, LA, Wei, L, Long, W, Barrett, EJ. Amino acids stimulate translation initiation and protein synthesis through an Akt-independent pathway in human skeletal muscle. Journal of Clinical Endocrinology and Metabolism. 2002. 87:5553-5558. doi:10.1210/jc.2002-020424	Intervention/exposure	Outcome
64	Lonnie, M, Hooker, E, Brunstrom, JM, Corfe, BM, Green, MA, Watson, AW, Williams, EA, Stevenson, EJ, Penson, S, Johnstone, AM. Protein for life: Review of optimal protein intake, sustainable dietary sources and the effect on appetite in ageing adults. Nutrients. 2018. 10:#pages#. doi:10.3390/nu10030360	Study design	-
65	Martinez, JA, Wertheim, BC, Thomson, CA, Bea, JW, Wallace, R, Allison, M, Snetselaar, L, Chen, Z, Nassir, R, Thompson, PA. Physical Activity Modifies the Association between Dietary Protein and Lean Mass of Postmenopausal Women. Journal of the Academy of Nutrition and Dietetics. 2017. 117:192-203.e1. doi:10.1016/j.jand.2016.10.009	Outcome	-
66	Mathewson, SL, Gordon, AL, Smith, K, Atherton, PJ, Greig, CA, Phillips, BE. Determining the influence of habitual dietary protein intake on physiological muscle parameters in youth and older age. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13103560	Outcome	-
67	McCarthy, D, Berg, A. Weight loss strategies and the risk of skeletal muscle mass loss. Nutrients. 2021. 13:#pages#. doi:10.3390/nu13072473	Study design	-
68	Mendonça, N, Hengeveld, LM, Visser, M, Presse, N, Canhão, H, Simonsick, EM, Kritchevsky, SB, Newman, AB, Gaudreau, P, Jagger, C. Low protein intake, physical activity, and physical function in European and North American community-dwelling older adults: A pooled analysis of four longitudinal aging cohorts. American Journal of Clinical Nutrition. 2021. 114:29-41. doi:10.1093/ajcn/nqab051	Outcome	-
69	Michaelsen, KF. Protein requirements and intake. PEDIATRICS. 2000. 106:1293-1294. doi:#electronic resource number#	Study design	-
70	Millward, DJ, Fereday, A, Gibson, NR, Cox, MC, Pacy, PJ. Efficiency of utilization of wheat and milk protein in healthy adults and apparent lysine requirements determined by a single-meal [1-C-13]leucine balance protocol. American Journal of Clinical Nutrition. 2002. 76:1326-1334. doi:10.1093/ajcn/76.6.1326	Intervention/exposure	Outcome
71	Millward, DJ, Fereday, A, Gibson, NR, Pacy, PJ. Human adult amino acid requirements: [1-13C]leucine balance evaluation of the efficiency of utilization and apparent requirements for wheat protein and lysine compared with those for milk protein in healthy adults. American Journal of Clinical Nutrition. 2000. 72:112-121. doi:10.1093/ajcn/72.1.112	Intervention/exposure	Outcome
72	Millward, DJ. An adaptive metabolic demand model for protein and amino acid requirements. British Journal of Nutrition. 2003. 90:249-260. doi:10.1079/BJN2003924	Study design	-

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73	Mirzaei, H, Suarez, JA, Longo, VD. Protein and amino acid restriction, aging and disease: From yeast to humans. Trends in Endocrinology and Metabolism. 2014. 25:558-566. doi:10.1016/j.tem.2014.07.002	Study design	-
74	Mojtahedi, M, De Groot, LCPGM, Boekholt, HA, Van Raaij, JMA. Nitrogen balance of healthy Dutch women before and during pregnancy. American Journal of Clinical Nutrition. 2002. 75:1078-1083. doi:10.1093/ajcn/75.6.1078	Intervention/exposure	Outcome
75	Morais, JA, Chevalier, S, Gougeon, R. Protein turnover and requirements in the healthy and frail elderly. Journal of Nutrition, Health and Aging. 2006. 10:272-283. doi:#electronic resource number#	Study design	-
76	Morens, C, Bos, C, Pueyo, ME, Benamouzig, R, Gausserès, N, Luengo, C, Tomé, D, Gaudichon, C. Increasing habitual protein intake accentuates differences in postprandial dietary nitrogen utilization between protein sources in humans. Journal of Nutrition. 2003. 133:2733-2740. doi:10.1093/jn/133.9.2733	Outcome	-
77	Morley, JE, Argiles, JM, Evans, WJ, Bhasin, S, Cella, D, Deutz, NEP, Doehner, W, Fearon, KCH, Ferrucci, L, Hellerstein, MK, Kalantar-Zadeh, K, Lochs, H, MacDonald, N, Mulligan, K, Muscaritoli, M, Ponikowski, P, Posthauer, ME, Fanelli, FR, Schambelan, M, Schols, AMWJ, Schuster, MW, Anker, SD. Nutritional recommendations for the management of sarcopenia. Journal of the American Medical Directors Association. 2010. 11:391-396. doi:10.1016/j.jamda.2010.04.014	Study design	-
78	Morley, JE, Bauer, JM. Nutrition and aging successfully. Current Opinion in Clinical Nutrition and Metabolic Care. 2017. 20:1-3. doi:10.1097/MCO.0000000000000330	Study design	-
79	Morris, S, Cater, JD, Green, MA, Johnstone, AM, Brunstrom, JM, Stevenson, EJ, Williams, EA, Corfe, BM. Inadequacy of protein intake in older UK adults. Geriatrics (Switzerland). 2020. 5:#pages#. doi:10.3390/geriatrics5010006	Outcome	-
80	Murphy, MM, Higgins, KA, Bi, X, Barraj, LM. Adequacy and sources of protein intake among pregnant women in the United States, NHANES 2003–2012. Nutrients. 2021. 13:1-13. doi:10.3390/nu13030795	Outcome	-
81	Mustafa, J, Ellison, RC, Singer, MR, Bradlee, ML, Kalesan, B, Holick, MF, Moore, LL. Dietary Protein and Preservation of Physical Functioning among Middle-Aged and Older Adults in the Framingham Offspring Study. American Journal of Epidemiology. 2018. 187:1411-1419. doi:10.1093/aje/kwy014	Outcome	-
82	Nilsson, A, Rojas, DM, Kadi, F. Impact of meeting different guidelines for protein intake on muscle mass and physical function in physically active older women. Nutrients. 2018. 10:#pages#. doi:10.3390/nu10091156	Outcome	-
83	Nowicki, GJ, Ślusarska, B, Bartoszek, A, Kocka, K, Deluga, A, Kachaniuk, H, Łuczyk, M. Moderation and mediation analysis of the relationship between total protein concentration and the risk of depressive disorders in older adults with function dependence in home care. Nutrients. 2018. 10:#pages#. doi:10.3390/nu10101374	Outcome	-
84	Nowson, C, O'Connell, S. Protein requirements and recommendations for older people: A review. Nutrients. 2015. 7:6874-6899. doi:10.3390/nu7085311	Study design	-

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85	Nygren, J, Nair, KS. Differential regulation of protein dynamics in splanchnic and skeletal muscle beds by insulin and amino acids in healthy human subjects. Diabetes. 2003. 52:1377-1385. doi:10.2337/diabetes.52.6.1377	Intervention/exposure	Outcome
86	Overdevest, E, Dorhout, BG, Nicolaou, M, van Valkengoed, IGM, Haveman-Nies, A, Oztürk, H, de Groot, LCPGM, Tieland, M, Weijs, PJM. Dietary protein intake in older adults from ethnic minorities in the Netherlands, a mixed methods approach. Nutrients. 2021. 13:1-12. doi:10.3390/nu13010184	Outcome	-
87	Paddon-Jones, D, Leidy, H. Dietary protein and muscle in older persons. Current Opinion in Clinical Nutrition and Metabolic Care. 2014. 17:5-11. doi:10.1097/MCO.0000000000000011	Study design	-
88	Paddon-Jones, D, Rasmussen, BB. Dietary protein recommendations and the prevention of sarcopenia. Current Opinion in Clinical Nutrition and Metabolic Care. 2009. 12:86-90. doi:10.1097/MCO.0b013e32831cef8b	Study design	-
89	Paddon-Jones, D, Sheffield-Moore, M, Katsanos, CS, Zhang, XJ, Wolfe, RR. Differential stimulation of muscle protein synthesis in elderly humans following isocaloric ingestion of amino acids or whey protein. Experimental Gerontology. 2006. 41:215-219. doi:10.1016/j.exger.2005.10.006	Outcome	-
90	Patro-Golab, B, Zalewski, BM, Kolodziej, M, Kouwenhoven, S, Poston, L, Godfrey, KM, Koletzko, B, van Goudoever, JB, Szajewska, H. Nutritional interventions or exposures in infants and children aged up to 3 years and their effects on subsequent risk of overweight, obesity and body fat: a systematic review of systematic reviews. Obesity Reviews. 2016. 17:1245-1257. doi:10.1111/obr.12476	Outcome	-
91	Paul, C, Leser, S, Oesser, S. Significant amounts of functional collagen peptides can be incorporated in the diet while maintaining indispensable amino acid balance. Nutrients. 2019. 11:#pages#. doi:10.3390/nu11051079	Outcome	-
92	Phillips, SM, Paddon-Jones, D, Layman, DK. Optimizing adult protein intake during catabolic health conditions. Advances in Nutrition. 2020. 11:S1058-S1069. doi:10.1093/ADVANCES/NMAA047	Study design	-
93	Phillips, SM, Tang, JE, Moore, DR. The role of milk- and soy-based protein in support of muscle protein synthesis and muscle protein accretion in young and elderly persons. Journal of the American College of Nutrition. 2009. 28:343-354. doi:10.1080/07315724.2009.10718096	Study design	-
94	Phillips, SM. Current Concepts and Unresolved Questions in Dietary Protein Requirements and Supplements in Adults. Frontiers in Nutrition. 2017. 4:#pages#. doi:10.3389/fnut.2017.00013	Study design	-
95	Pillai, RR, Kurpad, AV. Amino acid requirements in children and the elderly population. British Journal of Nutrition. 2012. 108:S44-S49. doi:10.1017/S0007114512002401	Study design	-
96	Prentice, P, Ong, KK, Schoemaker, MH, van Tol, EAF, Vervoort, J, Hughes, IA, Acerini, CL, Dunger, DB. Breast milk nutrient content and infancy growth. Acta Paediatrica. 2016. 105:641-647. doi:10.1111/apa.13362	Intervention/exposure	Outcome
97	Protein and amino acid requirements in human nutrition. World Health Organization technical report series. 2007. #volume#:1-265, back cover. doi:#electronic resource number#	Study design	-

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98	Raiha, NCR, Fazzolari-Nesci, A, Cajozzo, C, Puccio, G, Monestier, A, Moro, G, Minoli, I, Haschke-Becher, E, Bachmann, C, Van't Hof, M, Fassler, ALC, Haschke, F. Whey predominant, whey modified infant formula with protein/energy ratio of 1.8 g/100 kcal: Adequate and safe for term infants from birth to four months. JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION. 2002. 35:275-281. doi:10.1097/01.MPG.0000024570.18154.C7	Outcome	-
99	Reidy, PT, Walker, DK, Dickinson, JM, Gundermann, DM, Drummond, MJ, Timmerman, KL, Fry, CS, Borack, MS, Cope, MB, Mukherjea, R, Jennings, K, Volpi, E, Rasmussen, BB. Protein blend ingestion following resistance exercise promotes human muscle protein synthesis. Journal of Nutrition. 2013. 143:410-416. doi:10.3945/jn.112.168021	Outcome	-
100	Rennie, MJ. Anabolic resistance: The effects of aging, sexual dimorphism, and immobilization on human muscle protein turnover. Applied Physiology, Nutrition and Metabolism. 2009. 34:377-381. doi:10.1139/H09-012	Study design	-
101	Report of the scientific committee on food on the revision of essential requirements of infant formulae and follow-on formulae. Report of the Scientific Committee on Food on the Revision of Essential Requirements of Infant Formulae and Follow-on Formulae. 2003. #volume#:#pages#. doi:#electronic resource number#	Study design	-
102	Rieu, I, Balage, M, Sornet, C, Giraudet, C, Pujos, E, Grizard, J, Mosoni, L, Dardevet, D. Leucine supplementation improves muscle protein synthesis in elderly men independently of hyperaminoacidaemia. Journal of Physiology. 2006. 575:305-315. doi:10.1113/jphysiol.2006.110742	Outcome	-
103	Roberts, SA, Thorpe, JM, Ball, RO, Pencharz, PB. Tyrosine requirement of healthy men receiving a fixed phenylalanine intake determined by using indicator amino acid oxidation. American Journal of Clinical Nutrition. 2001. 73:276-282. doi:#electronic resource number#	Intervention/exposure	-
104	Rodriguez, NR, Miller, SL. Effective translation of current dietary guidance: Understanding and communicating the concepts of minimal and optimal levels of dietary protein. American Journal of Clinical Nutrition. 2015. 101:1353S-1358S. doi:10.3945/ajcn.114.084095	Study design	-
105	Rosenberger, C, Rechsteiner, M, Dietsche, R, Breidert, M. Energy and protein intake in 330 geriatric orthopaedic patients: Are the current nutrition guidelines applicable?. Clinical Nutrition ESPEN. 2019. 29:86-91. doi:10.1016/j.clnesp.2018.11.016	Health status	-
106	Rousset, S, Mirand, PP, Brandolini, M, Martin, JF, Boirie, Y. Daily protein intakes and eating patterns in young and elderly French. British Journal of Nutrition. 2003. 90:1107-1115. doi:10.1079/BJN20031004	Outcome	-
107	Shad, BJ, Thompson, JL, Breen, L. Does the muscle protein synthetic response to exercise and amino acid-based nutrition diminish with advancing age? a systematic review. American Journal of Physiology - Endocrinology and Metabolism. 2016. 311:E803-E817. doi:10.1152/ajpendo.00213.2016	Outcome	-
108	Soriano, G, Rossi, F, Sourdet, S. Protein intake and physical functioning in frail older subjects. Cahiers de Nutrition et de Dietetique. 2019. 54:61-68. doi:10.1016/j.cnd.2018.09.006	Pub. language	-
109	Suominen, MH, Jyvakorpi, SK, Pitkala, KH, Finne-Soveri, H, Hakala, P, Mannisto, S, Soini, H, Sarlio-Lahteenkorva, S. Nutritional guidelines for older people in Finland. Journal of Nutrition, Health and Aging. 2014. 18:861-867. doi:10.1007/s12603-014-0509-1	Study design	Outcome

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110	Unni, US, Raj, T, Sambashivaiah, S, Kuriyan, R, Uthappa, S, Vaz, M, Regan, MM, Kurpad, AV. The effect of a controlled 8-week metabolic ward based lysine supplementation on muscle function, insulin sensitivity and leucine kinetics in young men. Clinical Nutrition. 2012. 31:903-910. doi:10.1016/j.clnu.2012.03.008	Outcome	-
111	van Zwienen-Pot, JI, Visser, M, Kruizenga, HM. Predictors for achieving adequate protein and energy intake in nursing home rehabilitation patients. Aging Clinical and Experimental Research. 2018. 30:799-809. doi:10.1007/s40520-017-0850-4	Outcome	Health status
112	Volpi, E, Campbell, WW, Dwyer, JT, Johnson, MA, Jensen, GL, Morley, JE, Wolfe, RR. Is the optimal level of protein intake for older adults greater than the recommended dietary allowance?. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2013. 68:677-681. doi:10.1093/gerona/gls229	Study design	-
113	Volpi, E, Kobayashi, H, Sheffield-Moore, M, Mittendorfer, B, Wolfe, RR. Essential amino acids are primarily responsible for the amino acid stimulation of muscle protein anabolism in healthy elderly adults. American Journal of Clinical Nutrition. 2003. 78:250-258. doi:10.1093/ajcn/78.2.250	Intervention/exposure	Outcome
114	Walrand, S, Boirie, Y. Optimizing protein intake in aging. Current Opinion in Clinical Nutrition and Metabolic Care. 2005. 8:89-94. doi:10.1097/00075197-200501000-00014	Study design	-
115	Walrand, S, Short, KR, Bigelow, ML, Sweatt, AJ, Hutson, SM, Nair, KS. Functional impact of high protein intake on healthy elderly people. American Journal of Physiology - Endocrinology and Metabolism. 2008. 295:E921-E928. doi:10.1152/ajpendo.90536.2008	Outcome	-
116	Weijs, PJM, Wolfe, RR. Exploration of the protein requirement during weight loss in obese older adults. Clinical Nutrition. 2016. 35:394-398. doi:10.1016/j.clnu.2015.02.016	Outcome	-
117	Wirth, R, Volkert, D. Nutritional medicine in elderly patients: Advances and challenges. Zeitschrift fur Gerontologie und Geriatrie. 2017. 50:666-668. doi:10.1007/s00391-017-1278-3	Pub. language	-
118	Witard, OC, McGlory, C, Hamilton, DL, Phillips, SM. Growing older with health and vitality: a nexus of physical activity, exercise and nutrition. Biogerontology. 2016. 17:529-546. doi:10.1007/s10522-016-9637-9	Study design	-
119	Wolfe, RR, Miller, SL, Miller, KB. Optimal protein intake in the elderly. Clinical Nutrition. 2008. 27:675-684. doi:10.1016/j.clnu.2008.06.008	Study design	-
120	Yang, Y, Churchward-Venne, TA, Burd, NA, Breen, L, Tarnopolsky, MA, Phillips, SM. Myofibrillar protein synthesis following ingestion of soy protein isolate at rest and after resistance exercise in elderly men. Nutrition and Metabolism. 2012. 9:#pages#. doi:10.1186/1743-7075-9-57	Outcome	-
121	Yeung, SSY, Trappenburg, MC, Meskers, CGM, Maier, AB, Reijnierse, EM. Inadequate energy and protein intake in geriatric outpatients with mobility problems. Nutrition Research. 2020. 84:33-41. doi:10.1016/j.nutres.2020.09.007	Outcome	-
122	Yoshii, N, Sato, K, Ogasawara, R, Kurihara, T, Hamaoka, T, Fujita, S. Relationship between dietary protein or essential amino acid intake and training-induced muscle hypertrophy among older individuals. Journal of Nutritional Science and Vitaminology. 2017. 63:379-388. doi:10.3177/jnsv.63.379	Outcome	-

#	Citation	Exclusion reason #1	Exclusion reason #2
123	Zalewski, BM, Patro, B, Veldhorst, M, Kouwenhoven, S, Crespo Escobar, P, Calvo Lerma, J, Koletzko, B, van Goudoever, JB, Szajewska, H. Nutrition of infants and young children (one to three years) and its effect on later health: A systematic review of current recommendations (EarlyNutrition project). Critical Reviews in Food Science and Nutrition. 2017. 57:489-500. doi:10.1080/10408398.2014.888701	Outcome	-