Chapter 2
Systematic Reviews in the Field of Nutrition

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Key Points

- Systematic reviews are valuable tools for staying abreast of evolving nutrition and aging-related topics, formulating dietary guidelines, establishing nutrient reference intakes, formulating clinical practice guidance, evaluating health claims, and setting research agendas.
- Basic steps of conducting a systematic review include identifying a review team, developing an analytic framework, formulating key questions, selecting inclusion/exclusion criteria, identifying search terms, searching the literature, selecting publications for inclusion, extracting and summarizing data, rating the methodological quality of the included studies, and if adequate data is available, conducting a meta-analysis.
- Unique issues specific to nutrition-related topics include baseline exposure, nutrient status, nutrient bioavailability, nutrient bioequivalence, biological stores, multiple biological functions, undefined nature of nutrient intervention, and uncertainties in assessing dose–response relationships
- Conclusions of systematic reviews or meta-analysis are helpful tools that can contribute to decisions but do not in themselves establish guidelines or research agendas.

Keywords Nutrition • Diet • Systematic review • Key questions • Analytic framework • Evidence tables • Meta-analysis • Bioavailability • Bioequivalence • Dietary supplements • Older adults

The amount of scientific literature published each year increases exponentially. Very few individuals have the time to keep abreast of the latest findings, and even fewer have the time to integrate the latest findings into prior work. For topics unaligned with one's primary area of expertise or research focus the task can become insurmountable. Under these circumstances, review articles can serve an important function.

There are two general types of reviews; narrative and systematic. Both summarize the literature on a specific topic. For the most part, narrative reviews do not use a consistent methodological approach to accomplish this task. Unclear are the criteria used to include or exclude studies, making it difficult to determine whether the review is a comprehensive and unbiased evaluation of the literature.

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A systematic review specifies inclusion/exclusion criteria and follows a relatively standard format designed to provide an impartial and complete assessment of all the literature available on the topic. This chapter will focus on the latter type, systematic review, and the unique considerations that should be addressed when performing a review of nutrition-related topics.

Background

Systematic review methodology was first developed in the field of medicine as an approach to formulate clinical practice guidelines [1–3]. The approach has been used to not only establish guidelines [4, 5] but also set research agendas [6] and formulate scientific consensus statements [7, 8]. More recently systematic review methodology has been applied to the field of nutrition [9–11]. In addition to helping professionals stay abreast of evolving topics, the reviews also serve as the basis for formulating dietary guidelines [12], establishing nutrient reference intakes [13], formulating clinical practice guidance [14], evaluating health claims [15], and setting research agendas [16].

Steps to Conducting Systematic Reviews

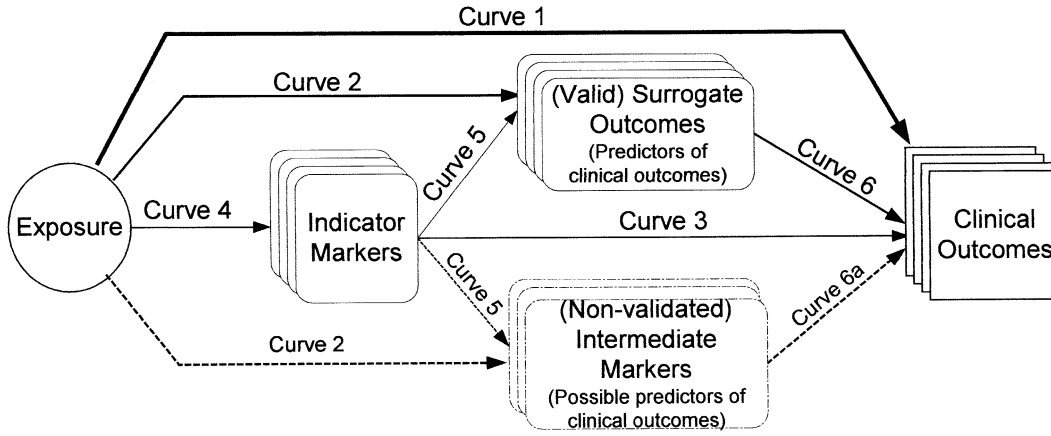
There are basic components that are integral to the systematic review process [17–19]. Critical is the ability to identify and synthesize all the available data in an unbiased manner to answer prespecified questions. A key component of conducting a systematic review is to thoroughly document all aspects of the process. This latter point is important not only to ensure validity and reproducibility but to also facilitate cost-effective periodic updates as new data emerge. Cochrane Collaboration [20] and the Agency for Healthcare Research and Quality [21] are two organizations that have developed guidelines for conducting systematic reviews.

Review Team

Prior to commencing work on a systematic review, it is important to identify the individuals who will be working on the project and their roles. The size of the team will depend on expertise of those involved, the range, number, and detailed nature of research questions to be addressed, and the scope of available literature. In addition to those individuals who will be responsible for conducting the actual systematic review, there may be others involved. These individuals are domain experts, commonly referred to as a technical expert panel. Particularly in the field of nutrition, it is important to include domain experts who represent multiple disciplines. Domain experts provide guidance in terms of refining the research questions and identifying search terms. They typically are not involved in the actual review process so as to ensure independence of those conducting the systematic review and to avoid potential bias or the appearance of bias according to prior publications or public statements. Once the systematic review is completed it is not uncommon for the technical expert panel to serve as reviewers.

Analytic Framework

An analytic framework provides a graphic representation of the organizational structure of a systematic review and includes the basic elements of the review: exposure(s), indicator marker(s), surrogate outcome(s), and clinical outcome(s) of interest. A generic analytic framework is depicted in Fig. 2.1 [11].



Curve 1. Association of exposure with clinical outcomes of interest
Curve 2. Association of exposure with surrogate outcomes or intermediate markers (with good or possible evidence for linkage with clinical outcomes)
Curve 3. Association of indicator markers to clinical outcomes
Curve 4. Association between exposure and indicator markers
Curve 5. Association of indicator markers to surrogate outcomes or intermediate markers (with good or possible evidence for linkage with clinical outcomes)
Curve 6. Association between surrogate outcomes and clinical outcomes ("good" evidence for linkage)
6a. Association between intermediate markers and clinical outcomes (uncertain linkage)

Fig. 2.1 Generic analytic framework of dietary reference intakes [22]. Reprinted with permission of the Agency for Healthcare Research and Quality from M. Chung, et al. Vitamin D and Calcium: A Systematic Review of Health Outcomes, p. 23

In general, solid lines indicate established paths between exposure, and indicator markers, surrogate markers, or clinical outcomes. The dashed lines indicate possible or yet to be validated relationships. Some component of each research question should be included in the analytical framework. The complexity of the analytic framework depends on the breadth of the topic and the number of questions to be addressed. For example, Fig. 2.2 depicts an analytical framework developed to address five key questions involving two nutrients, vitamin D and calcium [22]. This analytic framework was developed jointly by the methodologists and domain experts, prior to starting the systemic literature review.

Research (Key) Questions

The initial research questions, henceforth referred to as key questions, are drafted by either the sponsor or researchers. These questions are carefully reviewed, and frequently modified, by the research team to improve clarity or increase specificity. For example, a single question may be divided into multiple questions, each defined by specific criteria. The essential components of each key question are summarized by the acronym PICO. PICO is an abbreviation for population/patient (P), intervention/independent variable (I), comparator (C), and outcome (O). In some cases, PICO-D is used, with the D representing study design. Key questions must be carefully formulated to match the intent of the systemic review because they will define the literature search terms, inclusion criteria, and exclusion criteria. Prior to finalizing the key questions it is helpful to evaluate the available resources for the project and potential extent of the literature (horizon scan). This information may lead to a reassessment of the project scope and/or modifications in the PICO criteria.

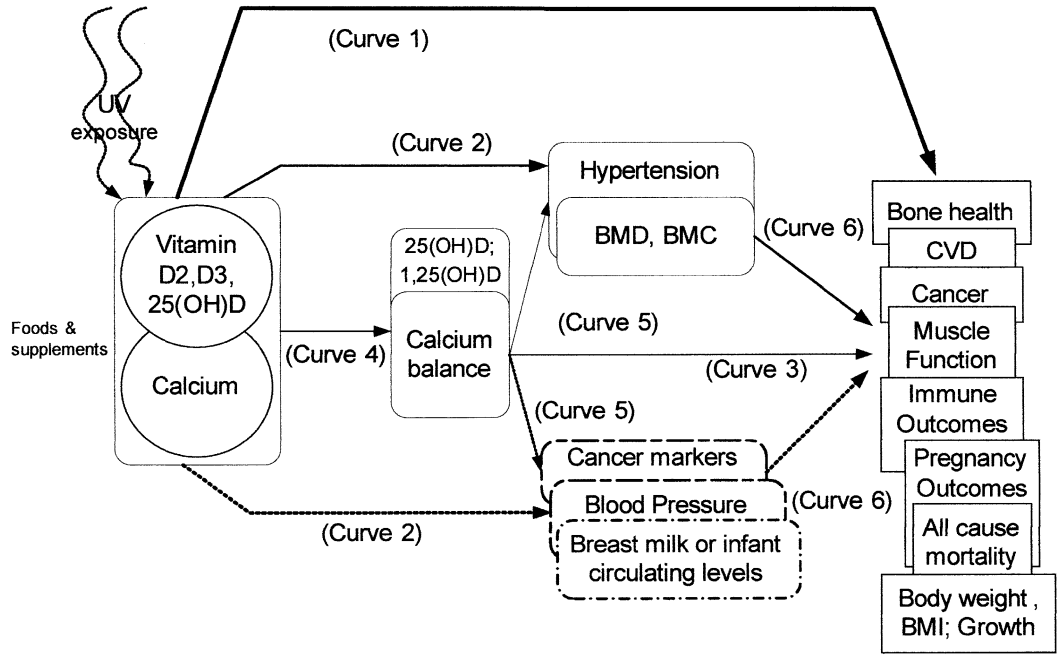


Fig. 2.2 Analytic framework for vitamin D and/or calcium estimated average requirement [22]. Reprinted with permission of the Agency for Healthcare Research and Quality from M. Chung, et al. Vitamin D and Calcium: A Systematic Review of Health Outcomes, p. 23

Inclusion/Exclusion Criteria

After the key questions are finalized, the next step in the systematic review process is to define the inclusion/exclusion criteria. These decisions should be made on the basis of the PICO components. The population will be defined by specific characteristics, e.g., age range, sex, health status. The intervention will be defined by the specific dietary component(s) (in the case of nutrition-related systematic reviews), dose, chemical form, and duration of intervention. For example, if the area of interest is omega-3 fatty acids, the intervention could be all omega-3 fatty acids, alpha-linolenic acid, eicosapentaenoic acid or docosahexaenoic acid, fish oil or fish, or some combination thereof. The dose could have minimum and maximum daily limits and the duration could be limited in terms of minimum/maximum length of time. To carry the omega-3 fatty acids example forward, the comparator(s) could be a placebo, such as another vegetable oil or, if the intervention is fish, an alternate food that has an equivalent amount of protein. The outcomes could be broad, e.g., all-cause mortality; narrow, e.g., coronary heart disease and stroke; or limited to indicator biomarkers, e.g., plasma triglyceride or C-reactive protein concentrations. For some topics if the analytical methodologies for the indicator biomarker have changed over time or the number of publications that appear to address the key questions is large, a cut-off publication date can be used as an inclusion criterion.

Search Terms

Search terms are identified on the basis of the key question components. Both the methodologists and domain experts should participate in identifying the search terms to ensure they are comprehensive enough to adequately capture all the available literature and specific enough to minimize identifying extraneous literature that does not address the key questions. Filtering out extraneous literature can be a time-consuming burden.

Literature Search

At this point the domain experts step back from the systematic review process and the remaining members of the research team should conduct the literature search. This division of labor is necessary to avoid potential bias or the appearance of bias during the review process. To ensure that all literature meeting the inclusion criteria is identified, multiple databases should be searched (e.g., Medline, CAB Abstracts, and Cochrane Library Central) and citations of recent publications should be reviewed to ensure the most relevant literature was identified by the search strategy. If more than a few relevant articles are identified using the latter approach the search terms should be reassessed by the research team. At all stages of the literature search it is critical to meticulously document the methodology.

Literature Selection

As a general rule, the majority of publications identified during the literature search will not meet the inclusion criteria. Screening is initially done on the basis of abstracts. Reasons for excluding publications are dictated by the inclusion/exclusion criteria. Typical reasons for exclusion include the type of article (e.g., editorials, reviews, case studies), study design (e.g., inadequate statistical analysis, lack of control group), and not meeting the inclusion criteria (relevant exposure or outcome measures, inadequate intervention period, study subject characteristics out of range). During the screening process it is important to generate a flow diagram that documents information for the total number of publications identified, and the number remaining during the preliminary screening process, with particular attention to documenting publications filtered out. The next step is to retrieve full texts of the remaining publications. As for the prior screening step, the reasons for screening out studies should be fully documented. One example of a flow diagram is shown in Fig. 2.3 [23].

Extract and Summarize Data

A system must be developed to accurately and comprehensively extract data from the included publications. This is assisted by the development of an evidence table template. The format can be unique to each systematic review. Critical components may include participant characteristics, study design, intervention, methods used to measure compliance, results, statistical significance, and outcomes. It is important to include all the information necessary to answer the key questions in a format that will facilitate comparisons among studies. Data extraction is time consuming and every effort should be made to avoid having to re-extract data due to an omission. Some systematic reviews include publications of studies with very different designs, such as clinical interventions and observation cohorts. In

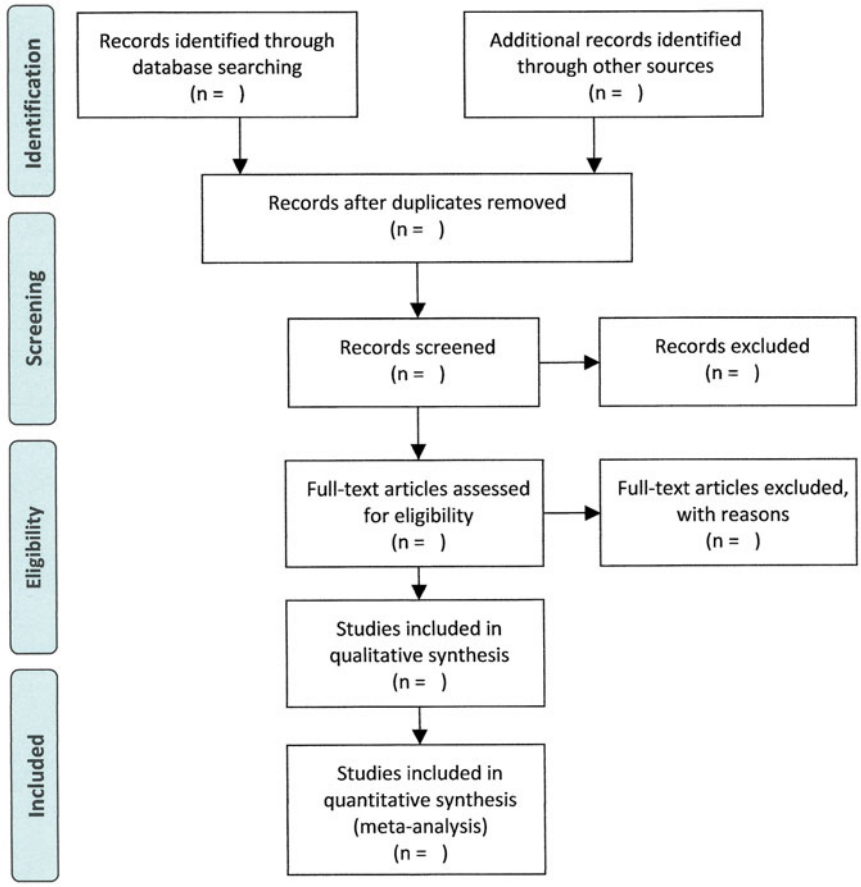


Fig. 2.3 Flow diagram (PRISMA) [23]

those cases separate evidence tables may be constructed to ensure the critical components of each type of study design is adequately captured. Evidence tables tend to be large in size and cumbersome to work with. Comparison among studies is facilitated by using the evidence tables to construct summary evidence tables that capture the specific elements necessary to synthesize the data.

Methodological Quality and Applicability of Studies

Some type of quality assessment is usually part of a systematic review. Table 2.1 proves a simple example with some common elements [17]. A number of quality assessment tools are available, for example, Cochrane Collaboration [20], the U.S. Preventive Services Task Force [21] and the Grading Recommendations Assessment, Development and Evaluation working group [24]. The choice of which to use depends on the topic and characteristics of the review.

Table 2.1 One approach to assessing methodological quality and applicability of studies[a]

Methodological quality
A Least bias; results are valid.
B Susceptible to some bias, but not sufficient to invalidate the results.
C Significant bias that may invalidate the results.
Applicability
I Sample is representative of the target population. It should be sufficiently large to cover both sexes, a wide age range, and other important features of the target population (e.g., diet).
II Sample is representative of a relevant subgroup of the target population, but not the entire population.
III Sample is representative of a narrow subgroup of subjects only, and is of limited applicability to other subgroups.
Overall effect
++ Clinically meaningful benefit demonstrated.
+ A clinically meaningful beneficial trend exists but is not conclusive.
0 Clinically meaningful effect not demonstrated or is unlikely.
– Harmful effect demonstrated or is likely.

[a]Adapted from [17]

Meta-analysis

Meta-analysis use statistical approaches to combine the data from multiple studies to derive a conclusion about the totality of the data. Frequently the result of a meta-analysis is to calculate an overall effect estimate. In some cases, a meta-regression can be performed to evaluate discrepancies among studies and to explore factors such as dose–response relationships. The major concern when performing and interpreting a meta-analysis is the appropriateness of combining studies that did not use identical experimental protocols. Decisions on whether it is appropriate to combine studies must be made on a case by case basis. Meta-analysis should not be confused with a pooled analysis. For a pooled analysis primary data from multiple individual studies are combined and analyzed. For a meta-analysis mean data derived from published studies are combined and analyzed.

Unique Issues Related to Nutrition-Related Systematic Reviews

Methodological approaches to performing systematic reviews were first developed to address questions in the field of medicine [25]. The literature on pharmaceutical interventions tends to be more straightforward than that related to nutrition. There are a number of unique factors that must be accounted for when performing systematic reviews of nutrition-related topics (Table 2.2). It is important to be aware of these prior to starting the review process so that accommodations, when necessary, can be made.

Baseline Exposure

There is a baseline exposure for all essential nutrients. This exposure can be the variable of interest, as for observational studies, or a starting point to be accounted for in interventional studies. For interventional studies this information is used as a starting point from which to increase or decrease intake. Inaccurate accounting for potential differences in baseline exposure among study subjects can alter the conclusions drawn from the data. Baseline exposure most commonly comes from foods and

Table 2.2 Unique issues related to nutrition-related systematic reviews

• Baseline exposure
• Nutrient status at baseline
• Nutrient bioavailability
• Nutrient bioequivalence
• Biological stores
• Multiple and interrelated biological functions
• Undefined nature of nutrient/food intervention
• Uncertainty in assessing dose–response relationships

beverages, nutrient and herbal supplements, endogenous synthesis (e.g., vitamin D, vitamin K), and/or environmental contamination (e.g., iron cooking pot). Limitations in accurately quantifying baseline nutrient exposure include factors such as the subjective nature of self-reported food and beverage intake, incomplete data bases with which to analyze the data, subject burden associated with collecting intake data, and inadequate methodology for quantifying in vivo synthesis. Currently, few biomarkers to characterize baseline nutrient exposure are available. Information on how the baseline food/nutrient intake is assessed should be included in the systematic review methodology section.

Nutrient Status

The nutrient status of an individual or population at baseline will impact on the ability to assess potential relationships between intake and outcomes within a cohort, and the response to altering the intake after an intervention. There is a wide range of approaches used to determine nutrient status, including, but not limited to concentrations in blood-borne cells, hard tissue concentrations (hair, nails), activity of enzymes for which the nutrient is a cofactor, saturation of carrier proteins, and nutrient or metabolite excretion. Homeostatic mechanisms, trafficking of nutrients to different tissues and storage capacity for the nutrient of interest precludes, with rare exceptions, the use of plasma concentrations as an indicator of nutrient status.

Nutrient Bioavailability

Not all forms of a nutrient are absorbed to the same degree of efficiency, otherwise referred to as bioavailability. Many factors determine nutrient bioavailability. These include, but are not limited to ionic state (e.g., ferric [Fe^{3+}]/ferrous [Fe^{2+}]); chemical form (e.g., folic acid/folate); nutrient–nutrient interactions (e.g., vitamin C and non-heme iron); nutrient–food interactions (e.g., dietary fat facilitates fat-soluble vitamin absorption, phytic acid/oxalic acid-containing foods impedes zinc absorption); nutrient–drug interactions (e.g., isoniazid and vitamin B_6, coumadin and vitamin K, folate and metformin); mineral salts (e.g., calcium carbonate, calcium citrate, calcium malate); single versus multiple daily doses (e.g., calcium, iron), and habitual intake (e.g., iron, vitamin C). Additional factors that may alter nutrient bioavailability include biological status (e.g., iron and pregnancy, vitamin B_{12} and achlorhydria), food processing (e.g., particle size and dietary fiber, lye-treatment [corn] and tryptophan, heat treatment and carotenoids), and for nutrient supplements completeness or rate of release (e.g., coatings, excipients, surfactants).

Nutrient Bioequivalence

Many nutrients occur in multiple forms that have different biological activity, commonly referred to as bioequivalence. The general approach used to address this issue is to calculate nutrient equivalents as was done when setting the recommended dietary allowances for vitamin A (preformed vitamin A and carotenoids), folate (folate and folic acid), vitamin K (phylloquinone and menaquinone), and niacin (niacin and tryptophan) [26–28]. The challenge of determining accurate conversion factors for the calculation of nutrient equivalents has recently been demonstrated for beta-carotene [27].

Nutrient Availability from Biological Stores

In humans, release of nutrients from storage depots can be unrelated to biological need. The release of vitamin A from hepatic stores is dependent on protein nutriture. The release or deposition in adipocytes of fat-soluble vitamins can be determined by changes in tissue mass rather than biological need for the nutrients.

Multiple and Interrelated Biological Functions of Nutrients

Most nutrients have multiple biological functions. The key questions define the nutrient-specific scope of the systematic review. This is often accomplished by narrowing the range of the work (e.g., vitamin D and bone health or breast cancer risk, vitamin A and infectious disease or xerophthalmia). Some biological functions of nutrients are dependent on the biological status of other nutrients (e.g., folate/vitamin B_{12}/vitamin B_6, vitamin D/calcium) and must be accounted for.

Undefined Nature of Nutrient Intervention

Food-based interventions, in contrast to supplement-based interventions, present unique challenges in accurately attributing a cause and effect to an individual nutrient or group of nutrients. For example, one approach to increasing very long-chain n-3 fatty acid (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) intake is to provide or instruct study participants to increase fish intake. However, there is considerable variability in the levels of EPA and DHA in different fish, within species of the same type of fish [29], season the fish was caught and animal husbandry practices for farm-raised fish. In addition, there are other compounds in fish, in addition to EPA and DHA, that could alter the biological outcomes assessed. Evaluating the effect of EPA and DHA using nutrient supplements is not without similar challenges due to the wide range of fatty acid profiles in available fish oil, potential changes in absolute levels during prolonged storage or heat exposure, and different chemical forms of the fatty acids (e.g., triglyceride, ethyl esters). Documentation of nutrient intake assessment is important to record.

Uncertainties in Assessing Dose–Response Relationships

It is difficult to accurately assess food, hence, nutrient intakes. In some cases systematic bias is unavoidable using currently available dietary instruments. This can be particularly important for systematic reviews designed to assess absolute rather than relative dose–response relationships. In general, food frequency questionnaires underestimate energy and protein intakes with greater biases than 24-h recall [30]. Potential biases for other nutrient intake estimates are not adequately documented but likely exist. Assay procedures for biomarkers of nutritional status can also significantly affect the mean and distribution of reported values and need to be factored into data interpretation [31, 32].

Strengths and Limitations of Systematic Review Approach for Nutrition Applications

Applying the systematic review approach to nutrition applications has both strengths and limitations (Table 2.3).

Strengths

Strengths of the systematic review process include representing an objective process while avoiding the appearance of bias, summarizing a comprehensive assessment of the available literature, defining the scope of the review as reflected in key questions, documenting the search strategy in a detailed manner, allowing for flexibility to customize searches by each topic without compromising rigorousness, generating a report that can be updated in a cost effective manner, identifying a transparent process of review, enhancing statistical power by simultaneously assessing multiple and frequently small studies, incorporating some ability to detect publication bias, providing an assessment of methodological quality, applicability and overall effect, and facilitating identification of research gaps.

Table 2.3 Strengths and limitations of the systematic review process

Strengths
• Represents an objective process and avoids the appearance of bias
• Summarizes a comprehensive assessment of the available literature
• Defines scope of the review as reflected in key questions
• Documents search strategy in a detailed manner
• Allows for flexibility to customize searches by each topic without compromising rigorousness
• Generates a report that can be updated in cost effective manner
• Identifies a transparent process of review
• Enhances statistical power by simultaneously assessing multiple and frequently small studies
• Incorporates some ability to detect publication bias
• Provides an assessment of methodological quality, applicability and overall effect
• Facilitates identification of research gaps
Limitations
• Confines imposed by key questions in terms of population, intervention, comparator and outcome measures
• Restrictions impact on the number of studies meeting the inclusion criteria
• Limitations imposed by the quality and scope of available data (e.g., poor study design, missing data, publication bias)

The detailed level of documentation is an integral part of the systematic review process. A beneficial byproduct of the systematic reviews is the ability to identify needed improvements in the quality and nature of data reporting. This is particularly valuable in the field of nutrition where the number of studies available to answer a key question is often limited.

Limitations

Limitations of the systematic review process include confines imposed by the key questions in terms of population, intervention, comparator and outcome measures, restrictions that impact on the number of studies meeting the inclusion criteria, and limitations imposed by the quality and scope of available data (e.g., poor study design, missing data, publication bias).

Confusion can be caused when multiple systematic reviews addressing what appear to be on the same topic come to different conclusions [9, 33, 34]. Such discrepancies can usually be attributed to differences in the key questions, study inclusion/exclusion criteria, evolution of available data, and changes in the analytical approaches used to generate the data or quality of the data. Meticulous documentation of the process can avoid confusion.

Contribution of Systematic Reviews to Nutritional Status of Older Adults

It is difficult to isolate an independent contribution of systematic reviews in defining the nutritional status specifically of older adults or understanding their unique nutritional challenges. However, the contribution of systematic reviews to the understanding of health outcomes, particularly in terms of chronic disease risk, has had a marked effect.

In 2013, it was reported that the prevalence of multi-morbidity, the concurrent existence of two or more chronic disorders, is increasing in the United States, paralleling the increased life-span and demographic shift in the population to the older aged groups [35]. The rates of multi-morbidity in individuals aged <65 years, 65–74 years, 75–84 years, and >85 years is 50 %, 62 %, 76 %, and 82 %, respectively. These data were corroborated using previously published systematic reviews [35]. It can be difficult to address the nutritional needs of individuals with multi-morbidities. To be most efficacious intervention approaches may need to be tailored to different age groups. However, a systematic review of nutrition and health literacy literature concluded that health literacy was a stronger predictor of health status than age, income, employment, education, and race [36]. This type of information is critical when designing intervention programs to improve health status of older adults.

Evaluating the nutritional status of older adults is an important component when assessing health status. A challenge is determining which nutritional screening tool is the best predictor of status for older adults and most likely to provide useful information to optimize health outcomes. A systematic review of the instruments available was used to address this issue [37]. In addition to providing valuable information on the relative strengths of each instrument for which data were available, research gaps that would benefit from being addressed were also identified. The most recent iteration of the Dietary Reference Intakes for calcium and vitamin D relied heavily on a systemic review of the evidence [13, 22]. The conclusions of the review resulted in changes in the vitamin D dietary reference intakes for most age groups, including individuals >70 years [22].

Multivitamins use is common in older adults [38, 39]. Strikingly, use is most prevalent among those with the most nutrient adequate diets [40, 41]. Conclusions of a systematic review indicate the most prominent motivator for nutrient supplement use among all U.S. adults is desire to improve overall health [42]. However, for older adults this is not the case, their motivations stem more from

specific health concerns and nutrient supplement use parallels engaging in more favorable health and lifestyle behaviors [42]. Recently, concern has been raised that multivitamin–multimineral supplement use in older adults is associated with increased mortality [43–45]. A systematic review was conducted to address this issue. The totality of the data indicated that there was no trend of multivitamin–multimineral supplement use with all-cause mortality, and there was a trend for reduced mortality from vascular and cancer causes [46]. In addition, no statistically significant evidence for heterogeneity or publication bias in the data was identified by the systematic review. Only an unbiased approach that considered all the data together could have adequately addressed this issue.

Conclusion

Systematic reviews are by their very nature an objective assessment of the available literature on a defined topic. The availability of systematic reviews that have addressed nutrition-related questions is extremely useful. The process is flexible, allowing for a wide range of topics to be addressed and facilitates periodic updates as new data emerge. However, it is important to note that by definition, systematic reviews are limited in scope as defined by the key question and restricted to what is frequently a less than complete dataset. The key questions answered are discrete units rather than interrelated entities. The conclusions of systematic reviews or meta-analysis do not in themselves establish guidelines or research agendas. They are an important tool that can contribute to decisions in these areas. A well-documented transparent process is critical for reviewing the data, and if inadequate data are available and expert opinion impacts on the final recommendations, there is a clear indication of when that occurred and within what context.

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