Academy of Nutrition and Dietetics
Evidence Analysis Center

Methodology: The Guideline Development Process

According to the Institute of Medicine (National Academy of Sciences), "Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options". This chapter describes the process and methods used to conduct comprehensives systematic reviews and how the findings from these systematic reviews were used to develop clinical practice nutrition guidelines for patients with chronic kidney disease. These guidelines were developed according to the Standards for Developing Trustworthy Clinical Practice Guidelines as stated by Institute of Medicine.

Development of these guidelines was a collaborative process between National Kidney Foundation (NKF) and the Academy of Nutrition and Dietetics (Academy). Nutrition and its' management is an integral aspect of care for patients with kidney disease. Due to recent developments in the literature regarding treatment and assessment of CKD, the Academy and NKF collaborated to merge, update and expand the current 2010 Evidence Analysis Library® (EAL®) CKD guidelines and the Kidney Disease Outcomes Quality Initiative (KDOQI) Nutrition Guidelines. Hence, the objective of this initiative is to provide medical nutrition therapy (MNT) guidelines for patients with chronic kidney disease (CKD) to assess, prevent and treat protein-energy wasting, mineral and electrolyte disorders, and other metabolic co-morbidities associated with CKD.

Overview of the Guideline Development Process

Guideline development is a detailed and comprehensive process. The steps followed to develop this guideline are below (some steps were completed concurrently):

1. Select the Work group or expert panel that works with the evidence review team.
2. Orient the work group the 5-step systematic review process of the Academy of Nutrition and Dietetics' Evidence Analysis Center.
3. Develop research questions, inclusion and exclusion criteria and a detailed search plan as well as identify interventions and outcomes of interest.
4. Search multiple databases based on search plan.
5. Screen abstracts and full text articles based on *a priori* eligibility criteria.
6. Extract data and critically assess the quality of included studies (risk of bias of studies)
7. Synthesize evidence narratively (evidence summary and conclusion statements) and in table format (Study characteristics and findings table). Grade the quality of evidence for each outcome and provide GRADE tables.
8. Develop recommendation statements based on the findings of the systematic review and other important considerations and assign "strength of recommendation".
9. Write a guideline manuscript.
10. Conduct internal, external, and public review of the guideline.
11. Respond to reviewer comments and update the guideline before publication.

Workgroup Selection Process

The Academy of Nutrition and Dietetics led the process of work group member recruitment. To assure appropriate expertise and limit bias, the Evidence Based Practice Committee Work Group Selection sub-committee followed a transparent process of selecting work group members. An open recruitment message with a link to online application was circulated via stakeholders for experts in the topic area of chronic kidney disease. Interested candidates provided: signed Disclosure and Conflict of Interest From, curriculum vitae, and personal statements indicating interest and qualifications that related to the topic. The workgroup selection committee then evaluated each candidate based on set criteria. Higher scoring

candidates were considered for position of workgroup chair /co-chair. A total of 15 workgroup members were selected to develop these guidelines. Two co-chairs were appointed, and the work group consisted of physicians, registered dietitians or nutritionists, researchers, and methodologists with expertise in the renal nutrition field. The selected members, according to their experiences and skill sets, were assigned to corresponding subtopics. The work group participated in all steps of systematic review process, which included developing research questions, agreeing on inclusion and exclusive criteria, developing the search plan, evaluating the evidence, and approving and grading the evidence and developing recommendation statements. All workgroup members and the evidence review team (ERT) met twice for 2-day face to face meetings as well as a teleconference calls once a month for the duration of the project.

Guideline Focus

During the first meeting the work group defined the scope for the guideline. The co-chairs developed the first draft of the scope which was discussed and refined by the work group members. It was determined that the guideline would focus on Nutrition in all stages of CKD in adults and would cover the subtopics of macronutrient, micronutrient, and electrolyte management in CKD. Both assessment and intervention question under these subtopics were proposed. Three workgroups were developed, with five members assigned to each workgroup and a Chair appointed to help lead the workgroup.

Systematic Review Process

Question Development, Literature Search and Study Selection

This guideline followed the Academy of Nutrition and Dietetics systematic review methodology. An analytical framework was developed by the ERT and refined by the work group members to help guide question development. During the initial teleconference calls and first face to face meeting, the workgroup developed a list of questions that were deemed important for clinicians and patients (Table 1). The workgroup developed the *a priori* inclusion and exclusion criteria as listed in Table 2.

A comprehensive search of literature was conducted using PubMed, MEDLINE, EMBASE, and CINAHL search engines. A first literature search was conducted to identify studies addressing assessment questions and a second search was conducted to identify studies addressing intervention questions in order to identify studies that answered more than one question. Inclusion criteria included in the search plan included: human adults with CKD aged 19 years and older published between 1985 and December 2016. hu Search terms included terms to identify relevant nutrition interventions assessment tools in adult CKD patients.

The first literature search focused on assessment questions identified 4,857 potential studies. The PRISMA diagram illustrating the study selection process are presented in Figure 1. The second comprehensive search to answer all the intervention questions in order identified 11,017 potential studies. The PRISMA diagram illustrating study selection process for intervention questions is in Figure 2.

After the search was completed, studies were systematically screened based additional *a priori* inclusion/exclusion criteria. For intervention questions, only randomized controlled trials that had at least 6 individuals per arm were included. Included studies investigated an intervention of interest (e.g. protein restrictions, phosphorus intake, sodium intake etc) in comparison with no intervention or minimal intervention. For assessment questions, only studies that tested the validity, reliability or relationship of an assessment tool against a comparative tool (reference standard) or mortality were included in this review.

The list of titles and abstracts were independently reviewed and marked for inclusion or exclusion (along with the reason) and any differences were resolved by discussion with a third reviewer. Full texts of articles meeting inclusion criteria were ordered and reviewed for inclusion. 225 studies met the inclusion

criteria for Intervention questions and 125 for assessment articles. A list of excluded articles with reason for exclusion was also created to maintain transparency (available of Academy of Nutrition and Dietetics Evidence Analysis Center website).

Data Extraction and Study Quality Assessment
Relevant data was extracted from the included articles using a standardized online data extraction tool. Key information extracted from each study included: Authors information; year of publication; type of study design; details of intervention: type of intervention, duration of the intervention, who delivered the intervention, setting, number of centers; Participants: sample size, mean age, age range, gender, study inclusion and exclusion criteria, comorbidities; Interventions: intervention details, comparison group details, medication use; Outcomes: reported primary and secondary outcomes, time points of reported outcomes; other details such as funding source.

All included studies were critically appraised for risk of bias. Two independent reviewers assessed the quality or studies using the Academy's online risk of bias tool, the Quality Criteria Checklist (QCC). The questions of the QCC are based on quality constructs and risk of bias domains identified by the Cochrane Collaboration and the Agency for Healthcare Research ad Quality (AHRQ). Questions examine sampling bias, performance bias, detection bias, attrition bias, and reporting bias. Any discrepancies between the two reviewers were resolved by consensus or by a third reviewer.

Data Synthesis and Grading the Evidence
Descriptive synthesis of evidence was conducted for all identified outcomes for which there were included studies. When possible, meta-analysis was conducted using random-effects model. For continuous data, results were summarized as mean difference (MD) between treatment groups (intervention v/s control/placebo) with 95% confidence interval (CI) or standardized mean differences (SMD). Dichotomous outcomes were reported as odds ratio (OR) or risk ratios (RR) with 95% CI. The I^2 statistic was used to determine the degree of heterogeneity in the calculated effect size, and 25%, 50%, and 75% were considered low, moderate, high, respectively. Sub-group analysis was conducted as appropriate to manage clinical heterogeneity.

After completion of the data extraction and data synthesis, the ERT provided the systematic review results in the following formats for the workgroup to review, edit, and approve: 1) Evidence summary: a narrative summary of all included trials for each identified outcome was drafted for each research question in the systematic review. A conclusion statement was developed for each proposed question /outcome. The conclusion statement is a clear, simple and to the point answer to the proposed questions.; 2) Study characteristics table: provided information regarding study characteristics, sample size, population, intervention details and quality of each included study; 3) Quality of evidence (strength of evidence): Each of the conclusion statements were assigned a GRADE (reference) to reflect the quality of studies, inconsistency of results, imprecision, indirectness of the evidence, and publication bias. Using this method, the evidence for each outcome of interest was graded as A (high), B (moderate), C (low), or D (very low). A GRADE table was generated using GradePro and demonstrated how the strength of evidence (GRADE) was derived for each outcome of interest.

Guideline Development
The workgroup members drafted comprehensive recommendations for nutrition care for adults with CKD. During this phase, the role of the work group member was to translate the available evidence into action statements that were clear, concise, and ready to be implemented by practitioners. The workgroup and ERT used the GRADE method for development of recommendations. The GRADE method involves two major components: a rating for quality of evidence (described above) and rating the strength of

recommendations. The evidence grades are reported at the end of the recommendation statements (e.g A, B, C, or D) and reflect the confidence in the estimated effects (Table 3).

The second component is rating the strength of the recommendation statement. This rating reflects the extent to which one is confident that desirable effects of an intervention outweigh undesirable effects. The grade for strength of the recommendation can be assigned Level 1 or Level 2. Table 4 shows the implication of each level for practitioners, clinicians, and policy makers. Level 1 recommendations use the terminology "We recommend", which means that this course of action should be applied to most people and practitioners can have confidence that implementing this recommendation has more benefit than risk. Level 2 recommendations use the terminology "We suggest".

When providing the level for the strength of the recommendation, a number of factors besides the quality of evidence are taken into consideration, inlcuding: patient values and preferences, quality of evidence, benefits and harms, cost/resources to implement the recommendation, acceptability, feasibility, and health equity. In addition to evidence-based recommendations, in certain scenarios "Opinion" statements were developed. These statements were developed when there was not enough evidence or evidence had too low of quality to write a graded recommendation, but the workgroup determined it was important to provide some guidance to patients and practitioners. These recommendations are ungraded, and usually refer to general or routine practice.

Once the full draft of recommendation statements was ready, it was reviewed and edited multiple times by all the workgroup members and the ERT. The workgroup participated in a final blinded vote of recommendation statements, and a majority of votes approving the statement was necessary for each statement to be accepted into the final guideline.

Draft Report with Supporting Rationale

Once the recommendation statements were developed, the work group members drafted a guideline manuscript that included the supporting materials for each topic, including: rationale, detailed justification (evidence summary), special discussions, implementation considerations, risks and harms, costs, and need for future research. In these sections the work group members also cited additional references important to the respective topic, including discussion of studies published after our search dates or other systematic reviews on the topic.

Peer Review Process

These guidelines underwent a systematic peer review process. The first phase of review was an internal review conducted by KDOQI leadership and the National Kidney Foundation Scientific Advisory Board. Feedback from this internal review were reviewed and incorporated in the guideline as appropriate. The second phase of the review was an external review conducted by 12 experts in this field. The AGREE II tool (Appraisal of Guidelines for Research and Evaluation) criteria was used to assess the quality of guideline reporting. The third phase was an open, public review phase. Reviewer comments from all phases were collated by staff and sent to workgroup members for discussion and possible edits. Work group chairs coordinated the final revision of the guideline document based on review comments and the final guideline manuscript will be submitted for publication.

Table 1. Questions for each Subtopic	Questions
Assessment: Nutritional status	What composite nutritional indices should be used to assess nutritional status, and/or protein-energy wasting in adults with CKD 1-5D, non-dialysis and transplant?
	What technical devices and anthropometric measures should be used to assess body composition in adults with CKD 1-5D, non-dialyzed and transplant?
	What laboratory measures should be used to assess nutritional status in adults with CKD 1-5D, non-dialysis and transplant?
	Is there evidence to support the use of hand-grip strength for assessing nutritional status in adults with CKD 1-5D, non-dialyzed and transplant?
Assessment: Macronutrients	What methods should be used to assess dietary intake of energy and protein in adults with CKD 1-5D, non-dialysis and transplant?
	What methods should be used assess energy and protein requirements in adults with CKD 1-5D, non-dialysis and transplant?
Assessment: Micronutrients	What methods should be used to assess micronutrient intake in adults with CKD 1-5D, non-dialysis and transplant?
	What methods should be used to assess micronutrient needs in adults with CKD 1-5, non-dialysis and transplant?
	What methods should be to assess micronutrient status in adults with CKD 1-5, non-dialysis and transplant?
Assessment: Electrolytes	What are the methods should be used to assess dietary electrolyte intake in adults with CKD 1-5D, non-dialysis and transplant?
	What methods should be used to assess electrolyte needs in adults with CKD 1-5, non-dialysis and transplant?
	3. What methods should be used to assess electrolyte status in adults with CKD 1-5, non-dialysis and transplant?
Medical Nutrition Therapy	What is the effect of MNT provided by a registered dietitian or international equivalent on outcomes in adult patients with CKD 1-5D, non-dialysis and transplant?
Macronutrient: Protein restriction and type	What is the effect of protein restriction, with or without ketoanalogues of amino acids, intake on outcomes in adults with CKD 1-5D, non-dialysis and transplant?
	What is the effect of protein type (animal vs plant) intake on outcomes in adults with CKD 1-5D, non-dialysis and transplant?
Macronutrient: Dietary patterns	What is the effect of specific dietary patterns on outcomes in patients with CKD 1-5, non-dialysis and transplant?
Macronutrient: Omega-3 supplementation	What is the effect of omega 3 supplementation on outcomes in adults with CKD 1-5D, non-dialysis and transplant?

Macronutrient: Oral Nutrition supplements	What is the effect of oral nutritional supplementation on outcomes in adults with CKD 1-5, non-dialysis and transplant?
Macronutrient: Dialysate supplements	What is the effect of nutritional supplementation via dialysate on outcomes in adults with CKD 1-5D, non-dialysis and transplant?
Macronutrient: IDPN supplements	What is the effect of nutritional supplementation via IDPN on outcomes in adults with CKD 1-5D, non-dialysis and transplant?
Micronutrients: intervention questions	What is the effect of micronutrient intake (B vitamins, vitamins C, D, E and K and selenium and zinc) on outcomes in adults with CKD 1-5D, non-dialysis and transplant?
Electrolytes: intervention questions	What is the effect of dietary intake of (acid-base, calcium, phosphorus, potassium, magnesium, sodium) on (electrolyte) biomarkers and other health outcomes in adults with CKD 1-5D, non-dialysis and transplant?

Table 2. Inclusion and Exclusion criteria

Assessment Research Questions		
	Inclusion	**Exclusion**
Age	Adults (age 18 and older)	Young adults ≤18 years of age, infants, children and adolescents.
Setting	Clinical or outpatient	Other than clinical or outpatient
Health Status	CKD of any stage, nephrotic syndrome, maintenance hemodialysis chronic peritoneal dialysis, and kidney transplantation with different CKD stages, with or without dyslipidemia and diabetes; kidney transplant recipients	Cancer or any other terminal condition or serious condition
Nutrition Related Problem/Condition	Chronic kidney disease	None
Study Design Preferences	• Diagnostic, validity, reliability studies, prediction, and/or correlation studies • Studies need to have a comparative tool/method included	• Review article; meta-analysis (Pertinent review articles will be hand searched) • Not a research study: Poster session, commentary, letter to editor, "grey" literature: technical reports from government agencies or scientific research groups, working papers from research groups or committees, white papers, position papers, abstracts, conference reports or preprints.

Outcomes	• Evaluates validity, agreement and reliability of the screening tool
	• Reports one or more of the following outcomes:
	  • Validity [e.g., construct (convergent, divergent) criterion (concurrent or predictive)]
	  • Reliability (e.g., inter- or intra-rater)
	  • Sensitivity / Specificity
	  • Positive and/or negative predictive value Agreement [kappa].
		• No evaluation of validity, agreement or reliability of the screening tool
		• Does not report on at least one of the outcomes of interest.
		• Tools evaluated as predictors of morbidity and mortality outcomes.

Study Drop out rate	20% for studies <1 year and 30% for studies > 1 year.	>20% for studies <1 year and >30% for studies >1 year
Year Range	1985 to December 2016	Published prior to 1985

Authorship	• If an author is included on more than one primary research article that is similar in content, the most recent review or article will be accepted and earlier versions will be rejected. • If an author is included on more than one Review Article or primary research article and the content is different, then both reviews may be accepted.	Studies by same author similar in content.
Language	Limited to articles in English	Languages other than English
Subjects	Humans	Animals
Publication	Published in peer-reviewed journal.	Not published in peer-reviewed journal.
Intervention Research Questions		
	Inclusion	**Exclusion**
Age	Adults (age 18 and older)	Young adults ≤18 years of age, infants, children and adolescents.
Setting	Clinical or outpatient	Other than clinical or outpatient
Health Status	CKD of any stage, nephrotic syndrome, maintenance hemodialysis chronic peritoneal dialysis, and kidney transplantation with different CKD stages, with or without dyslipidemia and diabetes; kidney transplant recipients	Cancer or any other terminal condition or serious condition
Nutrition Related Problem/Condition	Chronic kidney disease	None
Study Design Preferences	RCT or Clinical Controlled Studies	• Observational studies • Review article; meta-analysis (Pertinent review articles will be hand searched) • Not a research study: Poster session, commentary, letter to editor, "grey" literature: technical reports from government agencies or scientific research groups, working papers from research groups or committees, white papers, position papers, abstracts, conference reports or preprints.
Outcomes	Mortality, renal replacement therapy, quality of life, nutritional status outcomes, dietary intake outcomes, inflammation outcomes, anthropometrics, micronutrient biomarkers, electrolyte biomarkers, CKD progression, comorbidity	• Does not report on at least one of the outcomes of interest.

	outcomes (lipid profile, blood pressure)	
Size of Study Groups	For controlled trials at least 6 subjects in each arm	• <6 individuals for each study group
Study Drop-out rate	20% for studies <1 year and 30% for studies > 1 year.	>20% for studies <1 year and >30% for studies >1 year
Year Range	1985 to December 2016	Published prior to 1985
Authorship	• If an author is included on more than one primary research article that is similar in content, the most recent review or article will be accepted and earlier versions will be rejected. • If an author is included on more than one Review Article or primary research article and the content is different, then both reviews may be accepted.	Studies by same author similar in content.
Language	Limited to articles in English	Languages other than English
Subjects	Humans	Animals
Publication	Published in peer-reviewed journal.	Not published in peer-reviewed journal.

Figure 1. Flow diagram of identified studies for Assessment questions

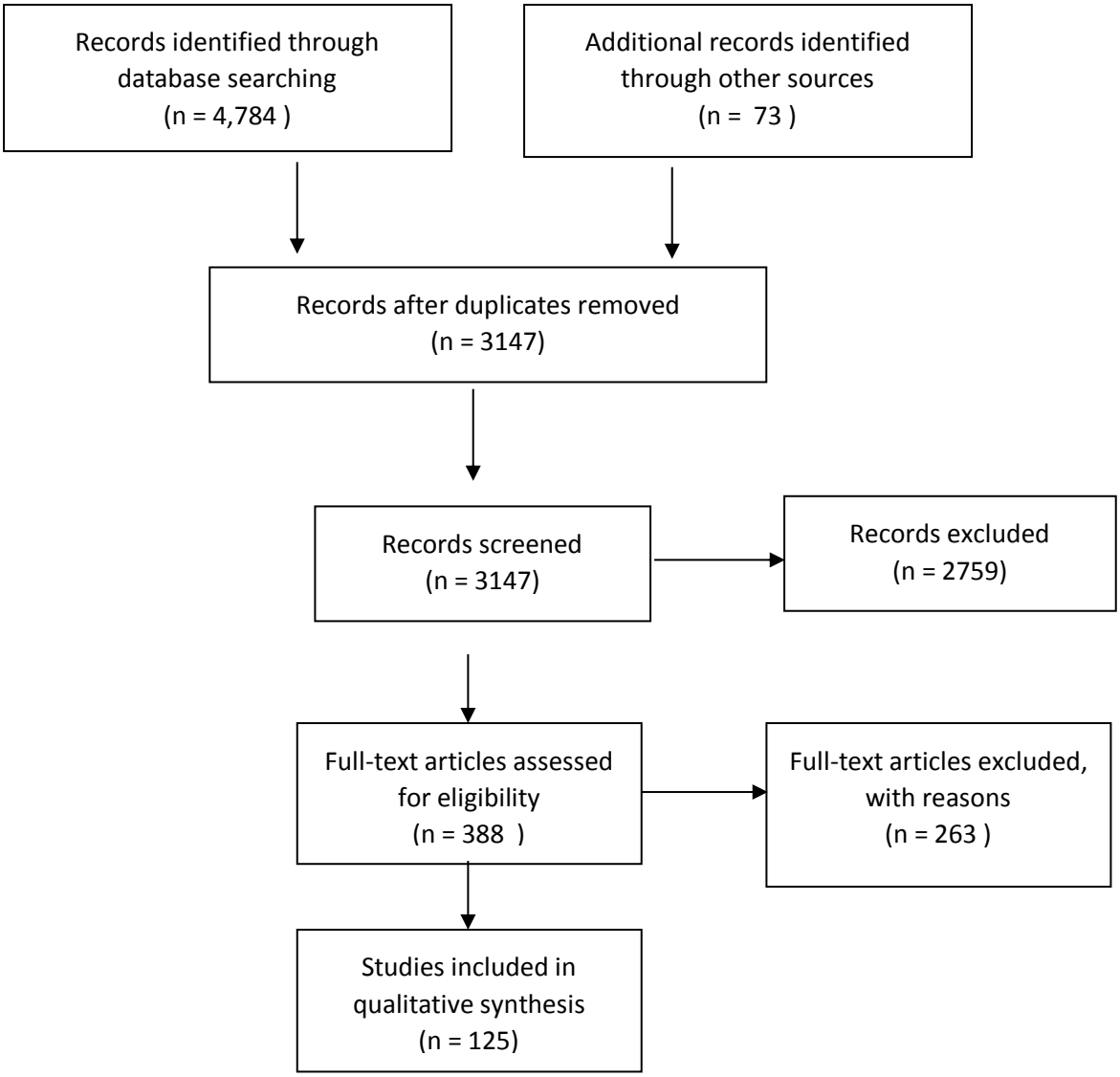

Figure 2. Flow diagram of identified studies for Intervention questions

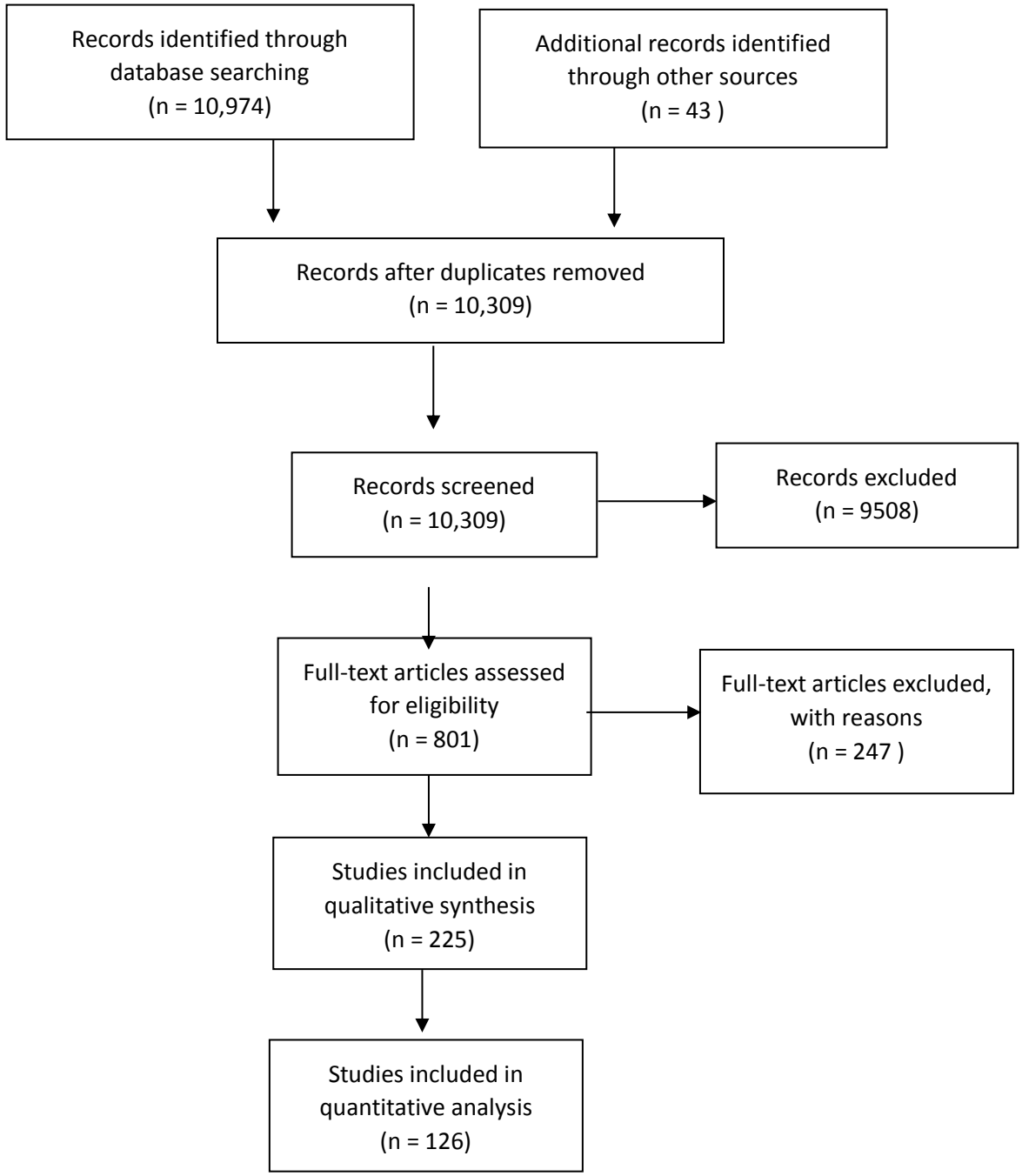

Table 3. Quality of Evidence Grades

Grade	Definition
High (A)	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate (B)	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low (C)	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low (D)	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Source: GRADE handbook

Table 4. Implications of strong and weak recommendations for different users of guidelines

	Strong Recommendation (Level 1 = We recommend)	**Weak Recommendation (Level 2 = We suggest)**
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Source: GRADE handbook