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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.gov.

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Nutritional Systematic Reviews

The medical and clinical communities have effectively used systematic reviews to develop clinical and public health practice guidelines, set research agendas, and develop scientific consensus statements. However, the use of systematic reviews in nutrition applications is more recent and limited. The Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH) has been proactive and developed an evidence-based review program using the EPC Program established by AHRQ, as part of a Congressional mandate to review the current scientific evidence on the efficacy and safety of dietary supplements and identify research needs (http://ods.od.nih.gov/Research/Evidence-Based_Review_Program.aspx). To date, this program has sponsored 17 evidence reports on a range of supplement-related topics including B-vitamins, ephedra, multivitamin/mineral supplements, omega-3 fatty acids, soy, and vitamin D. ODS is currently sponsoring an augmentation of the vitamin D report published in August 2007 to provide relevant information for a pending Institute of Medicine review of the current Dietary Reference Intakes for vitamin D and calcium. The completed ODS-sponsored evidence reports have resulted in numerous associated publications in scientific journals, have formed the basis for an NIH-sponsored state-of-the-science conference, and have been used to assist in setting research agendas.

To facilitate a better understanding of the challenges involved in conducting nutrition-related systematic reviews and in integrating these reviews with nutrition applications for which such reviews have not been previously used, ODS has sponsored the development of a series of technical reports via the EPC Program. The purpose of these reports was to: a) identify the challenges, advantages, and limitations of conducting nutrition-based systematic reviews; b) work with a panel of experts to explore approaches for integrating systematic reviews into processes associated with the derivation of nutrient intake reference values; c) identify the breadth and quality of currently available nutrition-related systematic reviews against generally accepted quality guidelines within the context of the unique needs for nutrition topics; and d) critically explore the consistencies and inconsistencies in results between observational and intervention studies and evaluate how the formulation of research questions may have contributed to these discrepancies.

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Structured Abstract

**Background:** The quality of nutrition-related systematic reviews (SR) is an unstudied but important factor affecting their usefulness.

**Objective:** To evaluate reporting quality of published SRs and identify areas for improvement.

**Design:** Descriptive and exploratory analyses of reporting quality (7 nutrition items and 28 SR reporting items) of all English-language SRs published through July 2007 linking micronutrients and health outcomes in humans. Factors that may to be associated with the reporting quality were also evaluated.

**Results:** We found 141 eligible SRs of 21 micronutrients. Ninety SRs that included only interventional studies met a higher proportion of our reporting criteria (median: 62 percent, interquartile range (IQR): 51 percent, 72 percent) than 31 SRs with only observational studies (median: 53 percent, IQR: 47 percent, 60 percent) or 20 SRs with both study designs (median: 47 percent, IQR: 39 percent, 52 percent) (P<0.001). SRs published after consensus reporting standards (since 2003) met a higher proportion of the reporting criteria than earlier SRs (median: 59 percent versus 50 percent, P=0.01); however, the reporting of nutrition variables remained unchanged (median: 38 percent versus 33 percent, P=0.7). The least-reported nutrition criteria were baseline nutrient exposures (28 percent) and impacts of the measurement errors from nutrition exposures (24 percent). Only 58 SRs (41 percent) used quality scales or checklists to assess the methodological quality of the primary studies included.

**Conclusions:** The reporting quality of SRs has improved 3 years after publication of SR reporting standards (since 2003), but the reporting of nutrition variables has not. Improved adherence to consensus methods and reporting standards should improve the utility of nutrition SRs.

**Key words:** systematic review, evidence-based, critical appraisal, micronutrients.
Chapter 1. Introduction

Leading nutrition organizations are using systematic reviews (SRs) to develop evidence-based nutrition and research agendas, revise dietary guidelines, formulate public health policies and support dietetic practice guidelines with the goal of improving patient outcomes and practitioner effectiveness (1). The Office of Dietary Supplements (ODS) in collaboration with other institutes and centers of the National Institutes of Health (NIH) uses SRs to identify research needs and set research priorities (2;3). In 2001, the American Dietetic Association (ADA) began carrying out SRs on a wide range of nutrition-related diseases (Evidence Analysis Library, http://adaevidencelibrary.com/). Evidence-based guidelines are being developed to provide an additional tool for food and nutrition professionals to apply the best research results to their practice, with the goal of improving patient outcomes and practitioner effectiveness (4;5). In addition, the Food and Drug Administration (FDA) has developed a draft guidance document of an evidence-based review system to evaluate publicly available scientific evidence for health claims on food and supplement products (6). The US Preventive Services Task Force (USPSTF) uses SRs in developing clinical practice recommendations on preventive and counseling interventions including recommendations on nutrition topics (http://ahrq.gov/clinic/USpstfix.htm).

The complexity of relationships between nutrition and health and the lack of widely accepted guidance on how to address nutrition issues have impeded the transfer of evidence-based methodologies from medicine to the field of nutrition. While the concepts and methods of evidence-based medicine can be applied to nutrition questions, there are important differences between evaluations of drug therapies and nutrient-related health outcomes.(7;8) For SRs of medical interventions, there exist checklists to improve SR reporting quality (i.e., clarity and transparent reporting of SR methods and results) such as MOOSE (Meta-analysis of Observational Studies in Epidemiology) (9) and QUOROM (Quality Of Reporting Of Meta-analyses) (10). While these represent consensus guidelines to improve the quality of SRs in general, they do not provide guidance for reporting or analyses of variables unique to the field of nutrition. Standardized guidance for researchers conducting SRs on nutrition-related topics could benefit the users of these reviews (11;12).

Our aim was to examine the reporting quality of existing SRs linking micronutrients and health outcomes, and identify areas for improvement. We also performed exploratory analyses to evaluate factors that may be associated with reporting quality, such as the designs of primary studies (interventional versus observational studies), years of publications, methods of evidence syntheses (meta-analyses or qualitative synthesis), and impact factors of journals that published these reviews.
Chapter 2. Methods

Literature Search

We searched MEDLINE® from its inception through July 2007 using keywords for micronutrients, multivitamins, and antioxidants. We also searched for SRs, evidence-based reviews and meta-analyses (Supplementary Table). Citations of SRs were reviewed for additional relevant articles. The essential micronutrients included in the analysis were fat-soluble vitamins A, D, E, and K; water-soluble vitamins B (thiamin, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folate, B12) and C; macrominerals (calcium, chloride, magnesium, phosphorous, potassium, sodium and sulfur); and trace minerals (chromium, copper, fluoride, iodide, iron, manganese, molybdenum, selenium, and zinc). Multivitamins or minerals and antioxidant supplements were also included. Potentially relevant reviews included those whose abstracts described searches or eligibility criteria for study identification, or included terms such as “systematic,” “evidence,” “evidence-based,” “meta-analysis,” or “pooled analysis.”

Eligibility Criteria

Full-text articles of screened-in abstracts were retrieved and examined to confirm their eligibility according to predetermined criteria. For the purpose of this study, we defined a SR as a study that contained three components: a statement of the research questions (aims or objectives); a description of the literature search; and a listing of the study eligibility criteria. A review that lacked any of these components was excluded. We did not attempt to contact authors for clarification. The following types of reviews were excluded: reviews of foods or diets that did not quantify micronutrient intake, reviews including non-oral routes of nutrient delivery, reviews that did not relate nutrients to health outcomes, reviews of non-human data, and pooled analyses of primary databases (i.e., secondary database analyses of multiple cohorts) that did not include a SR.

Data Abstraction and Collection

The unit of analysis was the SR article. We did not analyze the primary studies within the SRs. The following data were collected from the full-text articles of eligible SRs: topics covered (exposures and outcomes), whether meta-analyses were performed, specific journal, publication date, and number of citations per SR. We categorized the outcomes examined as either clinical outcomes or intermediate outcomes. A clinical outcome was defined as a measurement of how a person feels, functions or survives, or the severity of an existing disease, or the incidence of a new diagnosis. Intermediate disease outcomes included laboratory measurements or physical signs used as surrogates for a clinical endpoint (e.g., plasma cholesterol concentrations or blood pressure for cardiovascular disease, or dark adaptation for night blindness).

A standardized form was used for data collection. From published guidelines for reporting of the meta-analyses such as MOOSE (9) and QUOROM (10), we collected and evaluated 28 reporting items regarding the search and study selection criteria; methods for assessing methodological quality of the included primary studies, methods for quantitative
syntheses, and protocols for reporting of results. The primary goal of guidelines for SR reporting is to encourage authors to provide clear and transparent reporting of the factors relating to the literature review and evidence syntheses they carried out. Most widely recognized reporting guidelines reflect consensus opinion of groups of experts in a particular field, including research methodologists and journal editors (13). Because there is no widely accepted guidance for reporting or analyses of variables unique to the field of nutrition in SRs, we included seven items in addition to those identified in MOOSE and QUOROM specific to nutrition or diet variables based on the concern that failure to adhere to the items could lead to biased syntheses and/or interpretation of results in nutrition-related SRs. The definitions and the reasons for selecting these 35 reporting items are described in Table 1.

Additional data elements collected included the number of primary studies, instruments or methods used to assess the quality of the primary studies, and the types of primary studies (interventional or observational studies). An interventional study was defined as a study with an active intervention, such as randomized or non-randomized controlled trials, crossover trials, quasi-interventional studies (or community trials), and before-and-after studies. Observational studies included cohort, case-control, cross-sectional and ecological studies, case series and case reports, where the intervention was not dictated by the investigator.

For each SR, we also collected citation counts of the SRs and impact factors of the journals that published these reviews from the Science Citation Index and the Institute for Scientific Information Journal Citation Reports® edition 2006. The impact factor of a journal is calculated based on a three-year period, and can be considered to be the average number of times articles published in the journal are cited up to two years after publication. The citation count is the number of times an article was cited by other articles published in journals indexed in Journal Citation Reports®. Citation counts were collected in February 2008. The mean yearly citation number for each SR was calculated [citation count of SR / (2008-publication year of SR)].

**Statistical Analyses**

Descriptive analyses and summary statistics were performed on the reporting characteristics of SRs, including whether the reporting followed published standards such as MOOSE (9) and QUOROM (10), reporting of nutrition variables, number and types of primary studies analyzed, whether quality assessment of primary studies were performed, and what instruments were used to assess quality or susceptibility to biases. Fishers’ exact test was used to examine differences in the proportion of SRs reporting each item, and comparing the SRs that included observational studies to those that included interventional studies.

We used the Mann-Whitney test to examine the differences in the proportion of reporting criteria met by SRs of different study types (interventional studies, observational studies, or both designs), before versus 3 years after publication of QUOROM and MOOSE (in 1999), and SRs with versus without meta-analyses. Correlation analysis was conducted to examine the association between journal impact factors and citation numbers and the proportion of reporting criteria met among SRs. The maximal number of reporting criteria is 29 (26 SR-reporting factors and 3 nutrition variables) for SRs of interventional studies alone, 30 (26+4) for SRs of observational studies alone, and 33 (26+7) for SRs of both designs. Two reporting items for SRs containing meta-analyses (reporting of models for meta-analyses and data needed to calculate the effect size) were excluded from these calculations.
Median and interquartile range (IQR) are reported when the distributions were skewed. All P-values are two-tailed and considered significant when P<0.05.
Chapter 3. Results

The MEDLINE® search identified 3,796 citations; of which 259 full-text articles were retrieved and examined to confirm their eligibility. Three additional articles were identified from citations in retrieved SRs. A total of 141 SRs (105 with and 36 without meta-analyses) were eligible (15;22-161). Among these, 90 included interventional studies alone, 31 included observational studies alone, and 20 included both types of study designs (Figure 1). Among the reviews that did not meet eligibility criteria, nine publications stated they were a SR and/or meta-analysis, or evidence-based review but that did not meet the criteria of our predetermined definition, mostly because the authors did not state the eligibility criteria for primary studies reviewed (162-170). Among the eligible reviews, alternative names used for SR included evidence-based review, evidence review, critical review, qualitative overview, overview, in-depth review of the evidence, and review.

The earliest SR identified was published in 1989 (51). Half of the SRs were published since 2003. There has been a steady increase in the number of SRs published annually; the number of published SRs tripled from 1999 to 2006 (Figure 2). The number of primary studies included in each SR ranged from 1 to 264; 60 percent of the SRs included fewer than 20 primary studies. A wide variety of potential relationships between micronutrients and health outcomes were examined (Table 2). Of 141 SRs, 88 (62 percent) evaluated clinical outcomes, 35 (25 percent) intermediate outcomes, and 18 (13 percent) both types of outcomes. CVD and cancers were the most common outcomes reported.

Factors Associated With the Reporting Quality

On average, SRs that linked micronutrients and health outcomes met 57 percent (IQR: 48 percent, 66 percent) of our reporting criteria. SRs that included only interventional studies met a higher proportion of reporting criteria (median: 62 percent, IQR: 51 percent, 72 percent) than those with only observational studies (median: 53 percent, IQR: 47 percent, 60 percent) or both study designs (median: 47 percent, IQR: 39 percent, 52 percent) (P<.001). (Figure 3) There were statistically significantly more SRs of interventional than observational studies that reported a
search for unpublished studies (40 percent versus 3 percent), described the reasons for study exclusions (64 percent versus 42 percent), used quality scales or items to assess validity (39 percent versus 3 percent), and included a flow diagram of the number of studies included and excluded (37 percent versus 6 percent). There were significantly fewer SRs of interventional than observational studies that analyzed the potential confounding or interactions of the nutrient-outcome associations (37 percent versus 71 percent) and that made specific future research recommendations (29 percent versus 52 percent).

We examined the association between the reporting quality and publication of the MOOSE and QUOROM reporting standards for SRs by testing the difference in reporting quality comparing those published before publication of these standards and SRs published 3 years after. There were 115 SRs that were published before 1999 (n=31) or since 2003 (n=84); articles published between 1999 and 2002 were excluded for being conducted too close in time to the publication of the reporting standards. Before the reporting standards, SRs met a lower proportion of our reporting criteria than after (median: 50 percent versus 59 percent, P=0.01), suggesting that the overall reporting quality of SRs linking micronutrients and health outcomes has improved since publication of the reporting standards. In contrast, the reporting of nutrition variables remained unchanged (median: 33 percent versus 38 percent, P=0.7) (Figure 4).

Of the 141 SRs, 128 were published in 84 journals with impact factors that ranged from 0.3 to 25.8; 13 SRs (8 with meta-analyses) were published in journals not indexed in the Journal Citation Reports®, therefore, they were excluded from the relevant analyses. There was a positive correlation between the proportion of reporting criteria met and the journals’ impact factors (r=0.35, P<0.001), indicating that SRs published in higher impact journals were more likely to have met a high proportion of our reporting criteria. The median yearly number of citations attributable to the SRs was 4, ranging from 0 to 100 (excluding an outlier (109) that has had 2,128 citations since 1995). The proportion of reporting criteria met was not significantly correlated with the yearly number of citation (r=0.11, P=0.18) but both correlation coefficient and statistical significance improved after excluding the outlier SR (r=0.26, P=0.003).

SRs containing meta-analyses (n=105) met a higher proportion of our reporting criteria compared to the 31 SRs without meta-analyses (median: 62 percent versus 48 percent, P<0.001). SRs containing meta-analyses were also published in journals with higher impact factors (median 4.3 versus 2.8, P=0.001) and received more yearly citations (median: 16 versus 6, P=0.001).

Quality Assessment of the Primary Studies

There were 58 SRs (49 of interventional studies, 1 of observational studies, and 8 of both designs) that used quality scales or checklists to assess the methodological quality of the primary studies. The most commonly used were Jadad (171) and Schulz (172) quality scores or checklists, which were designed to assess the adequacy in the conduct of RCTs. The one SR of observational studies used a modified quality checklist, which was originally developed to evaluate the quality of interventional studies (an unpublished thesis). Among the eight SRs of both intervention and observational studies, eight different quality scales or checklists were used. Seven of the eight SRs used single quality scales (e.g., good, fair, or poor) for both intervention and observational studies. The definitions (or the quality items considered) of these quality scales varied. One SR used separate quality checklists for intervention (Jadad) and observational studies.
Chapter 4. Discussion

The number of SRs relating micronutrient intake to health outcomes has grown rapidly in recent years. These reviews have been published in a broad range of journals, many with relatively high citation impacts. These trends suggest an increasing acceptance of SRs as a useful way to summarize the data by the nutrition community. SRs of the literature serve as the core of evidence-based guideline development. Dietary guidance issued without pre-specified and transparent evidentiary support may be more prone to errors (173) due to their greater reliance on expert opinion and the potential for omitting important data unknown to the experts. Because of the complex nature of how nutrients are handled and function in the human body, often a large number of linked questions are required for the development of nutrition guidelines.

Incorporating currently existing SRs into a new SR can be a cost-effective use of resources but also has potential risks associated with doing so (174). To ensure that future nutrition-related SRs will be of maximal value, the highest standards in their conduct and reporting must be used. Good quality SRs should minimize the likelihood of bias or misinterpretation. SRs are also helpful in identifying knowledge gaps for which specific research agenda or recommendations are needed.

Because of deficiencies in conducting and reporting of SRs in the medical literature, expert panels convened to develop guidelines for SRs. The resulting QUOROM and MOOSE lists have been adopted by SR methodologists and medical journals as standards (13). However, there are several factors that are important for interpreting nutrition research, and thus nutrition SRs, that are not included in the SR quality checklists designed for the medical literature. Thus, we developed a list of 35 items that included the potentially relevant items from QUOROM and MOOSE, along with new nutrition-specific items following the rationale described in Table 1.

Our analysis of a large cohort of nutrition SRs found that 14 of the 35 items commonly were not reported or considered in the SRs; of these, six concerned variables that are unique to the field of nutrition. Moreover, we identified deficiencies in reporting of eight (of 28) items on the clarity or transparency of methods and results (Table 3). While there is currently no consensus on nutrition quality rating issues, the reporting items used in this analysis were selected because of the likelihood that they would have generic utility across SRs conducted for different purposes. It is, however, also recognized that exceptions to generic reporting standards for nutrition SRs may be needed for specific SR applications (e.g., regulatory applications). In these cases, justification for the exceptions could be noted in the design and reporting of the SR. This standardization and transparency would clarify the applicability of a SR for purposes other than those for which it was designed and enhance comparisons of results across SRs on similar topics.

Some generic quality issues are applicable to all SRs. For example, a comprehensive and transparent search strategy, with adequate justifications for inclusion or exclusion of specific studies, is needed to ensure an unbiased selection of studies for SRs and to improve understanding of how the SR was conducted. Furthermore, searching for unpublished data and comparing them to published data could shed some insights on the potential impact of publication bias (175). There is an underlying suspicion of publication bias against studies having either null or negative outcomes (176). It is important to note that there are no reliable methods to measure publication bias. Studies have shown that the most frequently used method to assess publication bias (funnel plots) can be misleading (177-179). Quality assessment of the primary studies is essential for the evaluation of validity and the overall strength of the conclusions in a SR.
The strength of SRs and meta-analyses relies not only on the validity of the included primary studies, but also on the clarity of the reporting of the SR itself. Although good reporting does not necessarily equate valid results, good reporting provides useful information for evaluating the validity of the findings. Our analyses showed that more SRs of interventional studies than those of observational studies (54 percent versus 3 percent, respectively) used quality scales or checklists to assess the methodological quality of the primary studies included. Without quality assessments, the validity of the included primary studies is unclear and the impact of the potential biases in the primary studies on the conclusions of a SR cannot be assessed. Furthermore, SRs of interventional studies met more quality criteria than SRs of observational studies. This finding could be explained in part by the lack of reporting standards for observational studies (this is in contrast to RCTs, many of which have adopted the CONSORT reporting standards (180;181)). Recently, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (182) was developed to improve the reporting quality of observational studies. It is important to note that CONSORT and STROBE are aimed at guiding authors to report the findings of the primary studies; they were not designed as tools for assessing the quality of the primary studies included in SRs or meta-analyses. Our analyses also showed that the proportion of reporting criteria met was significantly, positively correlated with both the journals’ impact factors and yearly citation numbers. This suggests that SRs of higher reporting quality are more likely to be published on higher impact journals and had wider research dissemination.

In summary, our findings suggest that the reporting quality of SRs has improved since publication of the reporting standards but the reporting of nutrition or diet variables has not. This limits their potential value to help in formulating nutrition-related guidelines, recommendations or research agendas. Reporting standards of SRs should be tailored for specific types of research to help the users of these SRs interpret the results. An improvement in the reporting quality of meta-analyses of RCTs in the critical care literature was documented after the publication of QUOROM (183). Our analysis documents the lack of consistent standards in conducting and reporting SRs of nutrition-related topics. It also provides useful insights on key reporting items for nutrition SRs. In addition to study design features that are important in reducing bias in all studies, for nutrition-related interventional studies it is critical to report the source and dose of the intervention, such as brand names or components (or formulation) of the nutrient supplements, or foods (or recipe) in the nutrition interventions, and the amount of nutrients (or the doses) in the interventions and intervention regimens (e.g., the number of times per day). It is also important to report the baseline nutrient exposures or the background diet (i.e., baseline dietary intake levels or the levels of the biomarker of intakes) in the study population, as the background diet could be one source of heterogeneity (i.e., differential effects of nutrient supplantations on health outcomes) in a SR or meta-analysis. For the nutrition epidemiological studies, it is important to report the methods or instruments for assessing intakes of nutrient exposures, ranges or distributions of the nutrient exposures, measurement errors of the diet or nutrient variables, and the potential impact of the errors from assessing the nutrient exposures on the nutrient-outcome association.

Improving the methodological and reporting quality of nutrition SRs ought to produce more accurate, less biased summaries of the evidence and will allow users of the SRs – general readers, guideline developers, policy makers, and others – to have a better understanding of what evidence the SRs summarize and what biases may exist. While there is room for revision of the
quality items for nutrition SRs based on expert consensus, better adherence to the quality items analyzed here is likely to improve the usefulness and acceptance of nutrition SRs.
References


## List of Acronyms/Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ADA</td>
<td>American Dietetic Association</td>
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<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
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<tr>
<td>CONSORT</td>
<td>Consolidated Standard of Reporting Trials</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
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<tr>
<td>MOOSE</td>
<td>Meta-analysis of Observational Studies in Epidemiology</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>ODS</td>
<td>Office for Dietary Supplements</td>
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<tr>
<td>PICO</td>
<td>Population, Intervention (or exposure), Comparator, Outcome</td>
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<tr>
<td>QUOROM</td>
<td>Quality of Reporting of Meta-analysis</td>
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<tr>
<td>SR</td>
<td>Systematic Review</td>
</tr>
<tr>
<td>STROBE</td>
<td>Strengthening the Reporting of Observational Studies in Epidemiology</td>
</tr>
<tr>
<td>USPSTF</td>
<td>United States Preventive Services Task Force</td>
</tr>
</tbody>
</table>
### Tables

**Table 1.** Reporting items for nutrition-related systematic reviews (with or without meta-analyses)

<table>
<thead>
<tr>
<th>Reporting Item</th>
<th>Definition for Adequate Reporting</th>
<th>Rationale for Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search terms</td>
<td>Keywords for identifying relevant studies for the research questions (i.e., PI(E)COS), or complete search strategy (e.g., keywords, medical subject headings) were described or referred to elsewhere.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Searches in multiple databases</td>
<td>Search was conducted in more than one electronic database.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Search years</td>
<td>Time period of the articles searched and included was described.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Searches in multiple languages</td>
<td>Search was conducted in English and other languages.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Searching for unpublished data</td>
<td>Authors explicitly stated the efforts to include unpublished data (e.g., contact with authors, meeting abstracts or conference preceding, dissertations, or grey literature search).</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Inclusion or exclusion criteria</td>
<td>Definitions of at least two of the PI(E)COS criteria (e.g., randomized controlled trials of the vitamin E were included) were reported.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Baseline nutrition status of the population</td>
<td>Nutrition status of the population at baseline (i.e., malnutrition, normal, or mixed). Acceptable data include data from nutrition assessments, explicit interpretations or discussions of the nutrition status of the locations where the study were conducted, and inclusion/exclusion criterion for the nutrition status of the study population.</td>
<td>Malnutrition is associated with vitamins and/or mineral deficiencies. Under- or over-nutrition is associated with mechanisms that affect health outcomes (14). Therefore, baseline nutrition status is an important covariate in any studies concerning the associations between micronutrients and health.</td>
</tr>
<tr>
<td>Types of interventions/exposures</td>
<td>Nutrient interventions or exposures were described (must include dose/level and type).</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Types of comparators</td>
<td>Comparators were described (must include dose/level and type).</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Types of outcomes</td>
<td>Outcomes or endpoints were defined.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Types of study designs</td>
<td>Design of the included studies was described.</td>
<td>In QUOROM</td>
</tr>
<tr>
<td>Number of included and excluded studies</td>
<td>Number of eligible and ineligible studies identified from the search was reported.</td>
<td>In QUOROM</td>
</tr>
<tr>
<td>Reasons for exclusion</td>
<td>Reasons for exclusions were described.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Use of specific checklist for quality items</td>
<td>The list of quality items for the validity (or quality) assessment of studies were applied and reported for each included study</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Overall rating of the study given</td>
<td>A overall rating of study quality was assessed (e.g., A, B, C or Good, Fair, Poor)</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Models for meta-analyses*</td>
<td>The methods of combining estimates (e.g., fixed- and random-effects models) were reported.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td>Assessment for heterogeneity</td>
<td>Heterogeneity across studies was assessed (i.e., statistical methods) or discussed (i.e., qualitative analyses).</td>
<td>In QUOROM and MOOSE</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Reporting Item</th>
<th>Definition for Adequate Reporting</th>
<th>Rationale for Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose-response relationship of the nutrient-outcome associations/effects</strong></td>
<td>Dose-response relationships were examined using dose-response statistical models, meta-regression, or subgroup analyses by different doses (i.e., quantitative assessments), or examined qualitatively (i.e. discussions).</td>
<td>In MOOSE</td>
</tr>
<tr>
<td><strong>Assessment of publication bias</strong></td>
<td>Quantitative assessment of publication bias (e.g., funnel plot, Begg and Egger tests) was used.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td><strong>Discussion of publication bias</strong></td>
<td>Issue of publication bias was raised in Discussion.</td>
<td>In MOOSE</td>
</tr>
<tr>
<td><strong>Data sufficient to calculate the effect size</strong></td>
<td>Data needed to calculate the effect size (e.g., 2x2 table, or mean change within group) for each study were presented in the tables or figures.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td><strong>Flow diagram for the number of included and excluded studies</strong></td>
<td>A flow diagram showing the progress of study selection was presented.</td>
<td>In QUOROM</td>
</tr>
<tr>
<td><strong>The total number of primary studies included in the systematic review/meta-analysis</strong></td>
<td>The total number of studies that met inclusion criteria was reported in the text, tables, or figures.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td><strong>Graphical presentation of the results</strong></td>
<td>Graphics summarizing individual study estimates and overall estimates were presented.</td>
<td>In MOOSE</td>
</tr>
<tr>
<td><strong>Strength (e.g. effect size) of nutrient-outcome associations/effects</strong></td>
<td>The principle measures of effect (e.g., relative risk, odds ratio, risk difference, or absolute difference) were reported.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td><strong>Uncertainty of nutrient-outcome associations/effects</strong></td>
<td>Indication of statistical uncertainty of findings (e.g., confidence interval), and/or description on the ranges of estimates (e.g., SD) was reported.</td>
<td>In QUOROM and MOOSE</td>
</tr>
<tr>
<td><strong>Analysis (qualitatively or quantitatively) for potential confounding or interactions of the nutrient-outcome association</strong></td>
<td>Assessment of confounding and/or interactions (e.g., comparability of study groups) was reported, or analyzing crude and adjusted effect sizes separately.</td>
<td>In MOOSE</td>
</tr>
<tr>
<td><strong>Specific future research recommendations</strong></td>
<td>Specific suggestions for future research agenda (i.e., other than “more future research is needed”)</td>
<td>In QUOROM and MOOSE</td>
</tr>
</tbody>
</table>

**Reporting Items for nutrition-related systematic reviews that included intervention studies**

| Sources of the nutrient interventions | Brand names or components (or formulation) of the nutrient supplements, or foods (or recipes) in the nutrition interventions were reported.                                                                                       | Different forms of nutrients (e.g., all-rac-α-tocopherol (chemically synthesized form), RRR-α-tocopherol (naturally occurring form), or γ-tocopherol) may have different health benefits and/or bioavailability in the body. |
| Doses of the nutrient interventions | The amount of nutrients (or the doses) in the interventions and intervention regimens (e.g., the number of times per day) were reported.                                                                                 | High dose of nutrient supplementations may have harmful health effect (15). Also, the dose is necessary to understand what the intervention was. |
Table 1. Continued

<table>
<thead>
<tr>
<th>Reporting Item</th>
<th>Definition for Adequate Reporting</th>
<th>Rationale for Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline nutrient exposures in the study population</td>
<td>Baseline nutrient exposures or the background diet (i.e., baseline dietary intake levels or the levels of the biomarker of intakes) in the study population were reported.</td>
<td>Data suggest differential effects of nutrient supplementations on the prevention of chronic diseases depending on the background nutrient exposures (16-19).</td>
</tr>
</tbody>
</table>

**Methods/instruments for assessing intakes of nutrient exposures**

<table>
<thead>
<tr>
<th>Reporting Items for nutrition-related systematic reviews included observational studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods/instruments for assessing intakes of nutrient exposures</td>
</tr>
<tr>
<td>Ranges or distributions of the nutrient exposures</td>
</tr>
<tr>
<td>Errors in assessing nutrient exposures</td>
</tr>
<tr>
<td>Potential impacts of the errors from assessing the nutrient exposures on the nutrient-outcome association</td>
</tr>
</tbody>
</table>

PI(E)COS, Population, Intervention, Exposure, Comparator, Outcome, and Study design; QUOROM, Quality Of Reporting Of Meta-analyses; MOOSE, Meta-analysis of Observational Studies in Epidemiology; FFQ, food frequency questionnaire; SD, standard deviation

*Data were collected for systematic reviews with meta-analyses only*
<table>
<thead>
<tr>
<th>Health Outcomes</th>
<th>No. of systematic reviews</th>
<th>Clinical outcomes n (%)</th>
<th>Intermediate outcomes n (%)</th>
<th>Both n (%)</th>
<th>Age-related/neurological</th>
<th>Bone2</th>
<th>Cancer3</th>
<th>CVD4</th>
<th>Death5</th>
<th>DM6</th>
<th>Eye7</th>
<th>Infection8</th>
<th>Pregnancy/birth</th>
<th>Other10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (15;22-51)</td>
<td>30</td>
<td>14 (46)</td>
<td>11 (37)</td>
<td>5 (17)</td>
<td>0</td>
<td>15</td>
<td>5</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Vitamin A (15;26;32;52-76)</td>
<td>28</td>
<td>23 (82)</td>
<td>3 (11)</td>
<td>2 (7)</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>6</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>7</td>
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<tr>
<td>Vitamin E (15;32;52-56;59-61;66;70-72;76-89)</td>
<td>28</td>
<td>22 (79)</td>
<td>2 (7)</td>
<td>4 (14)</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5</td>
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<tr>
<td>Vitamin C (15;32;52-56;60;66;67;69-72;76-78;85;87;90-93)</td>
<td>23</td>
<td>16 (70)</td>
<td>4 (17)</td>
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<td>8</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>4</td>
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<tr>
<td>Folic acids (26;54;67;85;94-110)</td>
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<td>14 (67)</td>
<td>4 (19)</td>
<td>3 (14)</td>
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<td>2</td>
<td>0</td>
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<td>0</td>
<td>4</td>
<td>2</td>
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<tr>
<td>Vitamin D (22;29;30;32-34;36;38;39;41;111-114)</td>
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<td>10 (71)</td>
<td>1 (7)</td>
<td>3 (21)</td>
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<td>9</td>
<td>4</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<td>Vitamin B12 (54;67;85;97;101;104;105;107;108;115-117)</td>
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<td>5 (42)</td>
<td>4 (33)</td>
<td>3 (25)</td>
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<td>Vitamin B6 (26;54;85;97;101;105;107;108;115-132)</td>
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<td>5 (56)</td>
<td>3 (33)</td>
<td>1 (11)</td>
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<td>0</td>
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<td>4</td>
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<td>Iron (57;67;133-139)</td>
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<td>2 (22)</td>
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</tr>
<tr>
<td>Health Outcomes</td>
<td>No. of systematic reviews</td>
<td>Clinical outcomes n (%)</td>
<td>Intermediate outcomes n (%)</td>
<td>Both n (%)</td>
<td></td>
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<td><em>Infection</em></td>
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</tr>
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<td><em>Pregnancy/birth</em></td>
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<td><em>Other</em></td>
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</tr>
</tbody>
</table>

Vitamin K (156;157) | 2 | 1 (50) | 0 | 1 (50) | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1
Fluoride (38;158)   | 2 | 2 (100) | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1
Iodine (159;160)    | 2 | 1 (50) | 0 | 1 (50) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2
Thiamin (115)       | 1 | 1 (100) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0
Riboflavin (56)     | 1 | 1 (100) | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0
Manganese (161)     | 1 | 1 (100) | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0

88 (62%) 35 (22%) 18 (13%)

*One systematic review may have more than one micronutrients and health outcomes

1. Age-related or neurological outcomes include Alzheimer disease, Parkinson’s disease, tardive dyskinesia, cognitive function testing, and epilepsy
2. Bone outcomes include the prevalence/incidence of fracture, osteoporosis, and bone mineral density/content
3. Cancer outcomes include the prevalence/incidence/recurrence of cancers or malignant tumors, precursors of malignant tumors (e.g. cervical squamous neoplasia, colorectal adenoma), and cancer mortality
4. Cardiovascular disease (CVD) outcomes include the prevalence/incidence of cardiovascular diseases (e.g., heart diseases, vascular disease, cerebrovascular disease), blood pressure, lipid profiles, and homocysteine levels, intima media thickness, arrhythmia, and CVD mortality
5. Death outcomes include all-cause or total mortality, infant mortality, and fetal neural tube defects
6. Diabetes (DM) outcomes include the prevalence/incidence of diabetes, glycemic control, diabetic neuropathy, and glucose or insulin levels
7. Eye outcomes include cataracts, infant eye outcomes, and age-related macular disease
8. Infection outcomes include infectious diseases, common cold or respiratory infections, pneumococcal colonization, immune markers, and pneumonia-specific mortality
9. Pregnancy or birth outcomes include preeclampsia, preterm delivery or prematurity, infant growth retardation, low birthweight, retinopathy of prematurity, small for gestational age, oral cleft birth, placental abruption/infarction, congenital anomalies, and spontaneous abortion
10. Other outcomes include, falls, diarrhea, hemoglobin level, “any morbidity”, growth, healing of chronic wound, toxicity, twinning, strength or physical performance, body weight, depressive symptoms, symptoms of vitamin B12 deficiency, environment associated health disorders, premenstrual syndrome, anemia, loss of renal function, hormone levels (e.g., renin, aldosterone, catecholamines), hemorrhagic disease of newborns, dental fluorosis, goiter, thyroid-stimulating hormone, and endothelial dysfunction
<table>
<thead>
<tr>
<th>Topic</th>
<th>Reporting Item</th>
<th>QUOROM n (%)</th>
<th>MOOSE n (%)</th>
<th>Systematic reviews of study types n (%)</th>
<th>Total n (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>N=90</td>
<td>N=31</td>
<td>Both N=20</td>
<td>N=141</td>
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<td>Search</td>
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<tr>
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<td>Search terms were described or referred to elsewhere</td>
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<td>√</td>
<td>67 (74)</td>
<td>24 (77)</td>
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<tr>
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<td>Multiple databases were searched</td>
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<td>√</td>
<td>58 (64)</td>
<td>16 (52)</td>
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<td>Years searched were described</td>
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<td>√</td>
<td>76 (84)</td>
<td>27 (87)</td>
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<td>Multiple languages were included in search</td>
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<td>√</td>
<td>27 (30)</td>
<td>10 (32)</td>
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<td>Authors explicitly stated searching for unpublished data</td>
<td>√</td>
<td>√</td>
<td>36 (40)**</td>
<td>1 (3)**</td>
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<td>Inclusion or exclusion criteria were stated</td>
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<td>90 (100)</td>
<td>31 (100)</td>
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<tr>
<td></td>
<td>Nutrition status of the population at baseline was reported</td>
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<tr>
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<td>Interventions/exposures were described</td>
<td>√</td>
<td>√</td>
<td>88 (98)</td>
<td>30 (97)</td>
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<td>Comparators were described</td>
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<td>73 (81)</td>
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<td>Outcomes were described</td>
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<td>√</td>
<td>87 (97)</td>
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<td>Types of studies included were reported</td>
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<td>√</td>
<td>90 (100)</td>
<td>31 (100)</td>
</tr>
<tr>
<td></td>
<td>Number of studies included and excluded were reported</td>
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<td></td>
<td>62 (69)</td>
<td>19 (61)</td>
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<td>Reasons for exclusion were described</td>
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<td>√</td>
<td>58 (64)*</td>
<td>13 (42)*</td>
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<td></td>
<td>Quality rating were used (e.g. A, B, C or Good, Fair, Poor)</td>
<td>√</td>
<td>√</td>
<td>31 (34)**</td>
<td>0 (0)**</td>
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<td>Models for meta-analyses were reported</td>
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<td>√</td>
<td>66 (89)</td>
<td>18 (86)</td>
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<tr>
<td></td>
<td>Heterogeneity was assessed or discussed?</td>
<td>√</td>
<td>√</td>
<td>71 (79)</td>
<td>27 (87)</td>
</tr>
<tr>
<td></td>
<td>Dose-response relationship of the nutrient-outcome association/effect were examined</td>
<td>√</td>
<td></td>
<td>28 (31)</td>
<td>14 (45)</td>
</tr>
<tr>
<td></td>
<td>Publication bias was assessed</td>
<td>√</td>
<td>√</td>
<td>32 (36)</td>
<td>13 (42)</td>
</tr>
<tr>
<td></td>
<td>Publication bias was discussed</td>
<td>√</td>
<td>√</td>
<td>33 (37)</td>
<td>16 (52)</td>
</tr>
<tr>
<td></td>
<td>Data needed to calculate the effect size were given</td>
<td>√</td>
<td>√</td>
<td>54 (73)</td>
<td>16 (73)</td>
</tr>
</tbody>
</table>
Table 3. Continued

<table>
<thead>
<tr>
<th>Topic</th>
<th>Quality Criteria</th>
<th>QUOROM</th>
<th>MOOSE</th>
<th>Systematic reviews of study types n (%)</th>
<th>Total n (%) N=141</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intervention N=90</td>
<td>Observational N=31</td>
<td>Both N=20</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td>A flow diagram for the number of studies included and excluded was used</td>
<td>√</td>
<td></td>
<td>33 (37)*</td>
<td>2 (6)*</td>
</tr>
<tr>
<td></td>
<td>The total number of primary studies included in the systematic review/meta-analysis was reported</td>
<td>√</td>
<td>√</td>
<td>89 (99)</td>
<td>31 (100)</td>
</tr>
<tr>
<td></td>
<td>Results were presented graphically</td>
<td>√</td>
<td></td>
<td>61 (68)</td>
<td>18 (58)</td>
</tr>
<tr>
<td></td>
<td>Strength (e.g. effect size) of nutrient-outcome associations/effects were described</td>
<td>√</td>
<td>√</td>
<td>81 (90)</td>
<td>30 (97)</td>
</tr>
<tr>
<td></td>
<td>Uncertainty of nutrient-outcome associations/effects were described</td>
<td>√</td>
<td>√</td>
<td>77 (86)</td>
<td>27 (87)</td>
</tr>
<tr>
<td></td>
<td>Potential confounding or interactions of the nutrient-outcome association/effect were analyzed (qualitatively or quantitatively)</td>
<td>√</td>
<td></td>
<td>33 (37)*</td>
<td>22 (71)*</td>
</tr>
<tr>
<td></td>
<td>Specific future research recommendations were made</td>
<td>√</td>
<td>√</td>
<td>26 (29)*</td>
<td>16 (52)*</td>
</tr>
<tr>
<td>Nutrition Variables (Interventional studies)</td>
<td>Sources of the nutrient interventions were described</td>
<td></td>
<td></td>
<td>46 (51)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Doses of the nutrient interventions were described</td>
<td></td>
<td></td>
<td>84 (93)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Baseline nutrient exposures in the study population were described</td>
<td></td>
<td></td>
<td>24 (27)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Methods/instruments for assessing intakes of nutrient exposures were reported</td>
<td>n/a</td>
<td></td>
<td>24 (77)</td>
<td>10 (50)</td>
</tr>
<tr>
<td></td>
<td>Ranges or distributions of the nutrient exposures were described</td>
<td>n/a</td>
<td></td>
<td>14 (45)</td>
<td>3 (15)</td>
</tr>
<tr>
<td></td>
<td>Errors from assessing nutrient exposures were described or discussed</td>
<td>n/a</td>
<td></td>
<td>11 (35)</td>
<td>5 (25)</td>
</tr>
<tr>
<td></td>
<td>Potential impacts of the errors from assessing the nutrient exposures on the nutrient-outcome association were described or discussed</td>
<td>n/a</td>
<td></td>
<td>9 (29)</td>
<td>3 (15)</td>
</tr>
</tbody>
</table>

QUOROM, Quality Of Reporting Of Meta-analyses; MOOSE, Meta-analysis of Observational Studies in Epidemiology

*p<0.05, Fisher’s exact test for the difference between intervention and observational studies

**p<0.001, Fisher’s exact test for the difference between intervention and observational studies

1. Inclusion or exclusion criteria must be stated in order to be included in our analyses

2. Data were collected for systematic reviews with meta-analyses only (n=104)
**Figure 1 legend.** Selection process and the number of the included and excluded systematic reviews

**Figures 1.**

3,796 potentially relevant abstracts identified from Medline search up to July 2007

- 3,537 irrelevant abstracts were excluded

259 potentially relevant articles were retrieved for full-text screening

- 256 potentially relevant articles identified from references of the systematic reviews of systematic reviews

141 systematic reviews met inclusion criteria (105 with and 36 without meta-analyses)

- Included calcium (30 articles), vitamin A (28), vitamin E (28), vitamin C (23), folate (21), vitamin D (14), vitamin B12 (12), selenium (10), sodium (10), vitamin B6 (9), iron (9), zinc (7), magnesium (5), chromium (4), multivitamin and/or multimineral supplement (5), potassium (3), vitamin K (2), fluoride (2), thiamin (1), riboflavin (1), and manganese (1).

- Excluded updates of previous systematic reviews, reanalyses of previous meta-analysis, systematic reviews of systematic reviews, non-systematic review articles (e.g., guidelines or recommendations, pooled analyses, or narrative reviews), non-oral routes of nutrient delivery, articles that do not meet our definition of a systematic review (as determined by presence of research questions, a literature search, and study eligibility criteria), non-human data, systematic reviews with no health outcomes, with no micronutrients of interest, or with food or food groups without quantification of micronutrients, and duplicate publications (121 articles)

90 systematic reviews of interventional studies alone

31 systematic reviews of observational studies alone

20 systematic reviews of both designs

3 potentially relevant articles identified from references of the systematic reviews of systematic reviews

3 potentially relevant articles identified from references of the systematic reviews of systematic reviews

3,796 potentially relevant abstracts identified from Medline search up to July 2007

259 potentially relevant articles were retrieved for full-text screening

141 systematic reviews met inclusion criteria (105 with and 36 without meta-analyses)

90 systematic reviews of interventional studies alone

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**Figure 2 legend.** Annual publication of systematic reviews of micronutrients and health (search ended Week 2 July 2007)

**Figure 2.**
Figure 3 legend. Proportion of reporting criteria met among 141 systematic reviews of micronutrients and health

Figure 3.
**Figure 4 legend.** Proportion of reporting criteria met comparing systematic reviews published before 1999 to 3-year after publication of QOUROM and MOOSE