Lead Article

Are systematic reviews addressing nutrition for cancer prevention trustworthy? A systematic survey of quality and risk of bias

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Context: *The last 30 years have yielded a vast number of systematic reviews and/or meta-analyses addressing the link between nutrition and cancer risk.* ***Objective:*** *The aim of this survey was to assess overall quality and potential for risk of bias in systematic reviews and meta-analyses (SRMAs) that examined the role of nutrition in cancer prevention.* ***Data Sources:*** *MEDLINE, Embase, and the Cochrane Library databases were searched (last search performed November 2018).* ***Study Selection:*** *Studies identified as SRMAs that investigated a nutritional or dietary intervention or exposure for cancer prevention in the general population or in people at risk of cancer and in which primary studies had a comparison group were eligible for inclusion. Screening, data extraction, and quality assessment were conducted independently by 2 reviewers.* ***Data Extraction:*** *Altogether, 101 studies were randomly selected for analysis. The methodological quality and risk of bias were evaluated using the AMSTAR-2 and ROBIS tools, respectively.* ***Results:*** *Most SRMAs included observational studies. Less than 10% of SRMAs reported a study protocol, and only 51% of SRMAs assessed the risk of bias in primary studies. Most studies conducted subgroup analyses, but only a few reported tests of interaction or specified subgroups of interest a priori. Overall, according to AMSTAR-2, only 1% of SRMAs were of high quality, while 97% were of critically low quality. Only 3% had a low risk of bias, according to ROBIS.* ***Conclusions:*** *This systematic survey revealed substantial limitations with respect to quality and risk of bias of SRMAs. SRMAs examining nutrition and cancer prevention cannot be considered trustworthy, and results should be interpreted with caution. Peer reviewers as well as users*

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of SRMAs should be advised to use the AMSTAR-2 and/or ROBIS instruments to help to determine the overall quality and risk of bias of SRMAs.
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INTRODUCTION

A systematic review aims to answer a well-defined research question on the basis of available evidence, using systematic methods. Evidence should be identified, selected, appraised in duplicate, and synthesized on the basis of a prespecified protocol.[1,2] A meta-analysis, on the other hand, is a statistical method for combining the results of individual studies included in a systematic review.[1,2] According to a recent study, however, overviews and meta-epidemiological studies often do not use consistent definitions of a systematic review.[3] Systematic reviews are perceived not only as a very efficient strategy for summarizing evidence on a particular clinical or public health question but also as a reliable tool for assessing the methods of primary and secondary studies and for generating new hypotheses.[4,5] Since literature reviews are typically characterized as retrospective observational studies of primary studies, they are prone to bias.[1] The results of a biased systematic review may be misleading to those who use such results as evidence.[6] In the last 30 years, the number of studies published as systematic reviews or meta-analyses (SRMAs) has increased substantially. While SRMAs are considered the highest level of evidence for informing clinical practice and policy, several publications have raised considerable concerns over the quality and credibility of SRMA results as the number of reviews increases.[7,8]

Certain steps can be undertaken to minimize bias in reviews, including prespecification of the methods using a study protocol and adherence to methodological guidelines issued by reputed organizations such as the Cochrane Collaboration and the Joanna Briggs Institute.[2,9–11] However, despite available guidance, published articles in various health science fields have shown that SRMAs often do not use recognized methodology, resulting in misleading or false conclusions.[7,12–19]

Structured instruments for the assessment of the methodological quality of reviews, such as AMSTAR (A Measurement Tool to Assess Systematic Reviews)[20–23] or ROBIS,[24] have been used only in the assessment of reviews on selected topics in nutrition.[25,26] For instance, a recent publication examined the extent of the risk of bias due to potential conflicts of interest of the authors of reviews on artificially sweetened beverages, while another review focused on the association between industry sponsorship and outcomes of nutritional studies.[27,28] Another review used the ROBIS instrument to examine the quality of systematic reviews on observational studies in nutritional epidemiology in general.[29] However, the quality of SRMAs published in the field of nutrition for cancer prevention has not been evaluated systematically.[30,31]

Herein, the overall quality and potential for risk of bias of articles published as SRMAs on nutritional interventions or exposures in cancer prevention was examined, the aim being to inform users of such reviews and to make recommendations for improving future research in this field.[32,33]

METHODS

Following a scoping review that aimed to identify the types and characteristics of interventions or exposures that have been studied for cancer prevention, a protocol for this systematic survey was developed and registered in the PROSPERO database (no. CRD42019121116).

Using keywords for the interventions or exposures identified in the scoping review, along with additional keywords generated with the help of a librarian (for the search strategy, see Appendix S1 in the Supporting Information online), the MEDLINE, Embase, and Cochrane Library databases were searched for SRMAs that examined nutritional interventions or exposures for cancer prevention. The last search was performed on November 3, 2018. The research question was defined according to the PICOS (Participants, Intervention, Comparison, Outcomes, Study design) scheme presented in Table 1.

The search yielded 24 739 references published between 2010 and 2018. After deduplication, 20 413 references were screened. Following a calibration exercise to ensure an agreement of 80% or higher among all reviewers, pairs of reviewers independently screened titles and abstracts using the Covidence software (covidence.org). A total of 1586 full-text articles were found suitable for further assessment. Subsequently, upon completing a similar calibration exercise, investigators screened the full-text articles identified. Any conflicts were resolved by discussion or by consultation with a

Table 1 **PICOS criteria for inclusion and exclusion of studies.**

Parameter	Criteria
Participants	Population in the study constituted the general population or people at risk of cancer. Studies on populations with diagnosed cancer under treatment or on patients with specific diseases were excluded.
Intervention	Studies of interest had to investigate a nutritional or dietary intervention or exposure for cancer prevention, while those that aimed to assess different lifestyle factors or exposures were excluded. Nutritional or dietary interventions or exposures were defined as changes in the intake or different intake of any type of foods (eg., meat, fruits, vegetables, salt, pepper, sugar, tea, coffee, alcohol) or supplements (including supplements with vitamins, minerals, or other substances) or as changes in or different dietary constituents. Studies that examined only serum levels of a particular nutrient in relation to cancer risk were excluded. Cancer prevention referred to lower risk of cancer with increasing the intake/higher intake of foods connected with a protective effect and decreasing the intake/lower intake of or avoiding those that were connected with a higher risk of cancer.
Comparison	Any intervention or exposure or no intervention or exposure used for comparison and studies which compared different intakes of foods in relation to cancer risk.
Outcomes	Any cancer incidence or any cancer mortality.
Study design	Articles published from 2010 onward and identified as systematic reviews and meta-analyses (SRMAs) as described in the title, abstract, or full text, were eligible for inclusion, if they included primary studies with a comparison group (interventional studies with a control group, such as randomized or nonrandomized controlled trials, and observational studies comparing different intake or exposure levels). Overviews of systematic reviews as well as studies published as conference abstracts only (which do not contain enough information to assess study quality or risk of bias), were excluded.

third reviewer. Screening of full texts provided 737 studies published as 746 records for inclusion (Figure 1). Finally, 101 randomly selected studies were analyzed further, in proportion to the number of records identified per year of the specified range of publication dates (see Appendix S2 in the Supporting Information online for the list of studies). Since the study was exploratory in nature, a sample size of 100 was defined and, on the basis of the total number of studies included, the proportion of articles published each year was calculated. Using that proportion, the sample size per each year as a proportion of 100 was defined, and the RAND procedure in Microsoft Excel was used to randomly select the prespecified number of studies per year. Because there were equal proportions in 2 publication years, the same number of studies for both years was taken, which resulted in a sample size of 101.

In the next step, pairs of reviewers independently extracted data using abstraction forms developed in Microsoft Excel (version 2016). The extraction phase also included an assessment of the methodological quality and the risk of bias of eligible SRMAs. For this purpose, AMSTAR-2[23] (an updated version of original AMSTAR tool) and ROBIS[24](Risk of Bias in Systematic Reviews) were used, respectively. In the assessments, published guidance available for each tool was followed. Any conflicts were resolved by discussion, and if necessary, a third reviewer was involved. For quality control, a random sample of 10% of extractions (using the RAND procedure in Excel as described above) was verified by the third independent reviewer. The AMSTAR-2 tool was designed to assess the quality of SRMAs, including randomized or nonrandomized studies. It contains 16 questions for which judgments "yes" or "no" can be applied. For 5 questions, "partially yes" can also be selected. Of the 16 questions, 7 are considered to be critical items: protocol registered before the commencement of the review (item 2); adequacy of the literature search (item 4); justification of exclusion of individual studies (item 7); assessment of the risk of bias of individual studies included in the review (item 9); use of appropriate meta-analytical methods (item 11); consideration of risk of bias when interpreting the results (item 13); and assessment of the presence of publication bias and its impact (item 15). With the publication of the AMSTAR-2 tool, the authors offered the following guidance on its application: The review is considered high quality if no or one non-critical flaw is found, moderate quality if more than one non-critical flaw is found, low quality if one critical flaw is found, regardless of non-critical flaws, and critically low quality if more than one critical flaw is found, regardless of non-critical ones.[24]

The ROBIS tool was designed specifically to assess the risk of bias in systematic reviews. This instrument consists of 3 phases. Phase 1 includes the following: (i) relevance assessment (optional); (ii) identification of concerns connected with the review process; and (iii) judgment of the risk of bias. Phase 2 includes

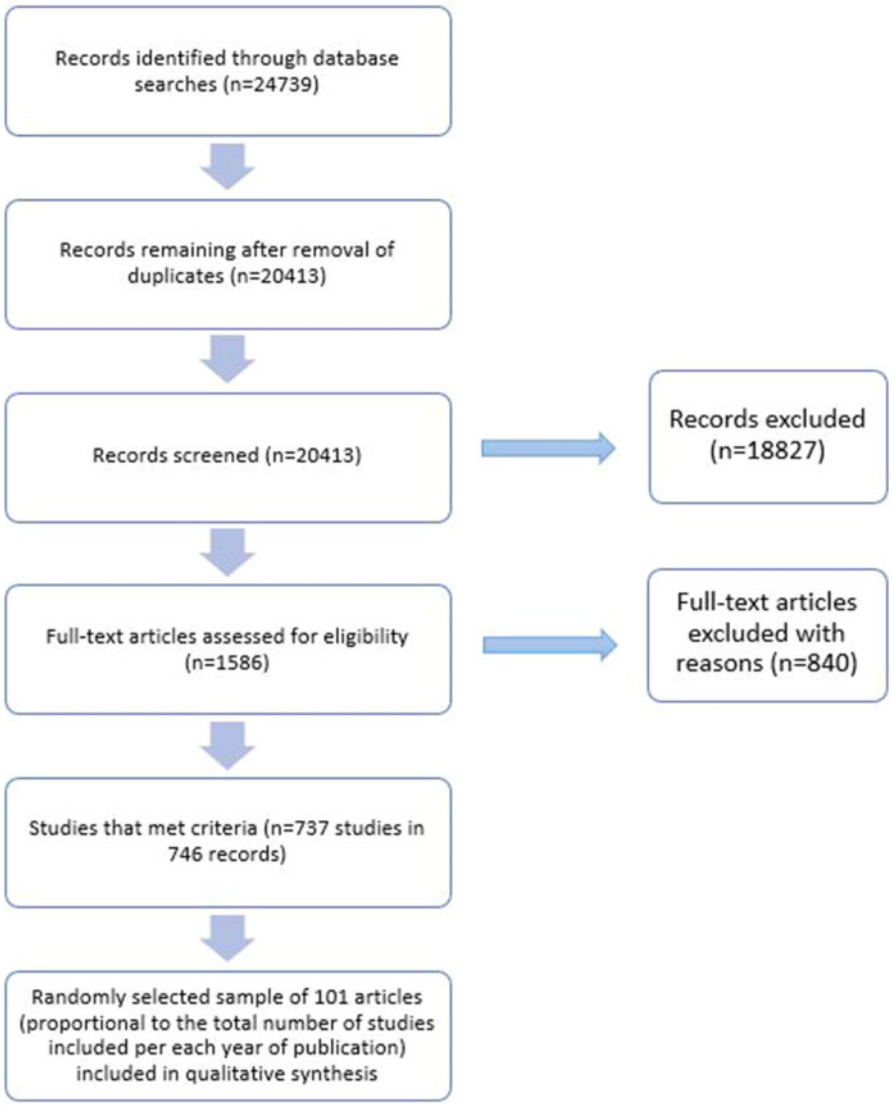

Figure 1 **Flow diagram of the literature search process.**

assessment of 4 domains that may introduce the risk of bias: (i) study eligibility criteria; (ii) identification and selection of studies; (iii) data collection and study appraisal; and (iv) data synthesis and findings. Phase 3 focuses on the risk of bias in the overall interpretation of review findings while considering limitations identified in any of the phase 2 domains.

The data extraction form was designed to retrieve all data necessary for the description of study characteristics and analyses, including population, intervention or exposure, outcomes analyzed, bibliographic data, and methods used. The collected data were summarized descriptively. Continuous data were analyzed using median values and ranges, and categorical data using frequencies. The results of quality and risk-of-bias assessments were summarized for each item separately as well as overall for all reviews.

RESULTS

General characteristics of included SRMAs

Forty-nine percent of the included systematic reviews or meta-analyses published their results within 9 months of the time of their literature searches, while 70% published their results within 12 months, with the period between the search and the publication of the review ranging from 1 to 31 months. Most SRMAs searched standard databases such as MEDLINE (98%), Embase (54%), and the Cochrane Library (29%), while only 13% of SRMAs searched unpublished studies/data. The main types of eligible study design were cohort studies (93%) and case-control studies (81%). Randomized controlled trials were included in 21% of the SRMAs, while controlled clinical trials were included in 8%. Other study designs, such as

Table 2 **General characteristics of systematic reviews and meta-analysis (SRMAs) included in the analysis. Data are presented as median (range) values unless otherwise indicated.**

Item		Value
Impact factor of the journal		3.53 (0–51.27)
No. of authors		6 (1–48)
No. of included studies, by type	Any type	18 (5–572)
	RCT	0 (0–108)
	Controlled clinical trial	0 (0–1)
	Cohort	6 (0–163)
	Case-control	9 (0–409)
	Other	0 (0–12)
No. of participants		539 607 (74 498–99 413 386)
No. of people with cancer outcomes		8414.5 (11 846–486 538)
Total no. of meta-analyses reported in the study		3 (0–64)
No. of meta-analyses with significant results for cancer incidence or mortality		1 (0–31)
Databases searched (%)		
MEDLINE		98
Embase		54
The Cochrane Library		29
Unpublished studies/data		13
Country of the corresponding author (%)		
China		49
United States		10
Italy		9
United Kingdom		6
Korea		5
Other		22
Conflicts of interests and funding (%)		
Conflicts of interest statement provided		81
Reported any funding		64
Public funding		55
No funding		6
Meta-analysis used as a method of synthesis (%)		
Performed any meta-analysis		95
Only reported high vs low intake meta-analysis		49
Only reported dose-response meta-analysis		4
Reported both high vs low and dose-response meta-analysis		38
Other (vs placebo/no intervention)		5
Reported the use of GRADE method or other methods to assess overall quality or certainty of the evidence		5

Abbreviation: GRADE, Grading of Recommendations, Assessment, Development and Evaluations.

ecological studies and cross-sectional studies, were included in 13% of SRMAs (Table 2).

Only 9% of SRMAs had study protocols available. If the SRMA provided information about the protocol, this information was retrieved and reviewed as part of the AMSTAR-2 and ROBIS assessment. The remaining studies did not report publishing a protocol or omitted any mention of methods designed a priori in a protocol. The eligible studies examined a variety of interventions or exposures, which were subsequently grouped into broader categories, as shown in Figure 2. The study duration or follow-up period in the included studies ranged from 3 months to 65 years.

In general, the most common health outcome described in the SRMAs was cancer incidence (71%), and both cancer incidence and mortality were reported in 14%. In 11% of SRMAs, the cancer outcome was not clearly stated. Authors focused primarily on a single type of cancer (73%), with 21% of studies describing multiple types of cancer.

Characteristics of methods used in included SRMAs

Of the included SRMAs, 49% did not report on the use of any quality or risk-of-bias assessment of primary studies, while only 13% covered all elements listed in AMSTAR-2 item 9a/b (ie, risk-of-bias assessment at the individual study level) in their assessment. The vast majority (95%) of included SRMAs performed one or more meta-analyses, with the most frequent comparison being higher vs lower intake of nutritional interventions or exposures (86%). Most SRMAs (94%) measured heterogeneity between the included primary studies. They explored heterogeneity using a subgroup analysis (80%) or meta-regression (30%); however, only 17% of SRMAs that performed subgroup analyses used a test for interactions. Only 2 SRMAs reported a priori hypotheses for subgroups analyses.

Statistical approaches for measuring heterogeneity varied, with the most common being *I2* alone (28%) or a combination of *I2* and the Q test (59%). Among

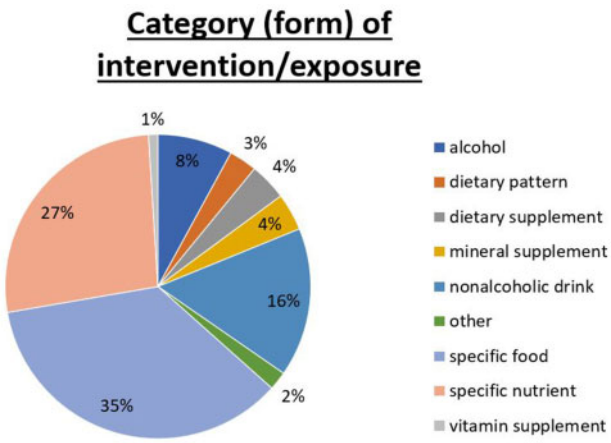

Figure 2 **Food and dietary categories analyzed in included systematic reviews or meta-analyses (categories are mutually exclusive).**

SRMAs that performed subgroup analyses, the median number of subgroups was 6, and the maximum was 84. Moreover, 65% of SRMAs performed a sensitivity analysis to check the robustness of the findings (leave-one-out analysis, used in 50 of 66 studies [76%] with sensitivity analysis) and/or other sensitivity analyses such as exclusion of studies for various reasons, quality assessment of included studies, adjustment for confounding, method of data collection in primary studies (self-reported or derived from cancer registry, 18 of 66 studies [27%]). Furthermore, 82% of SRMAs analyzed potential publication bias or small-study effects (Table 3), and 45% of those analyses used the test of statistical significance when the number of primary studies included was less than 10. Eighteen SRMAs did not analyze publication or small-study bias, only 2 of which provided a reason for not assessing publication bias.

Characteristics of quality and risk-of-bias assessment

Of the 101 SRMAs, 98 (97%) were of critically low quality as assessed using the AMSTAR-2 tool.[32] This indicates that their results and conclusions may not provide an accurate and comprehensive summary of the review question. Only one study was judged to be of high quality, and 2 studies were judged to be of low quality. The detailed assessment of the critical items is summarized in Figure 3, and the detailed assessment for each AMSTAR-2 item is summarized in Table S1 in the Supporting Information online.

The noncritical items in the AMSTAR-2 tool that most often scored low were item 10 ("Did the review authors report on the sources of funding for the studies included in the review?" [3% of studies]) and item 3 ("Did the review authors explain their selection of the study designs for inclusion in the review?" [7% of studies]). On the other hand, the best reporting compliance was achieved for item 16 ("Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?" [77% of studies]) and item 14 ("Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?" [66% of studies]).

Table 3 **Evaluation of publication bias or small-study effects in included systematic reviews and/or meta-analyses (n = 83)**

Type of publication bias/small-study effects analysis	Percentage of studies
Funnel plot asymmetry	82
Egger test	90
Begg test	63
Begg and Egger test	61
Reviews or meta-analyses for which statistical analysis was conducted for < 10 studies	45

The overall assessment with the ROBIS tool showed that 97% of included SRMAs had a high overall risk of bias, while only 3% had a low risk of bias. The third domain (data collection and study appraisal) had the lowest percentage of SRMAs with "high concern for risk of bias" assessments (87%). The percentages of SRMAs with "high concern for risk of bias" assessments reached 92% or more for the other domains. (Figure 4).

The ROBIS signaling questions that most often raised concerns (ie, highest rates of "no" or "probably no" responses) were Q2.1 ("Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?"), Q1.3 ("Were eligibility criteria unambiguous?"), and Q3.2 ("Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?"), with 89%, 82%, and 74% of studies at high concern, respectively. The ROBIS signaling questions with the highest reporting compliance (ie, highest rates of "yes" and "probably yes" responses) were Q3.3 ("Were all relevant study results collected for use in the synthesis?"), Q4.1 ("Did the synthesis include all studies that it should?"), and Q4.4 ("Was between-studies variation [heterogeneity] minimal or addressed in the synthesis?"), with 93%, 91%, and 81% of studies at low concern, respectively.

DISCUSSION

Main findings

A total of 737 SRMAs were included in the systematic survey, of which a subsample of 101 was randomly selected for a detailed analysis. The overall results indicated that only 1% of SRMAs were of high quality

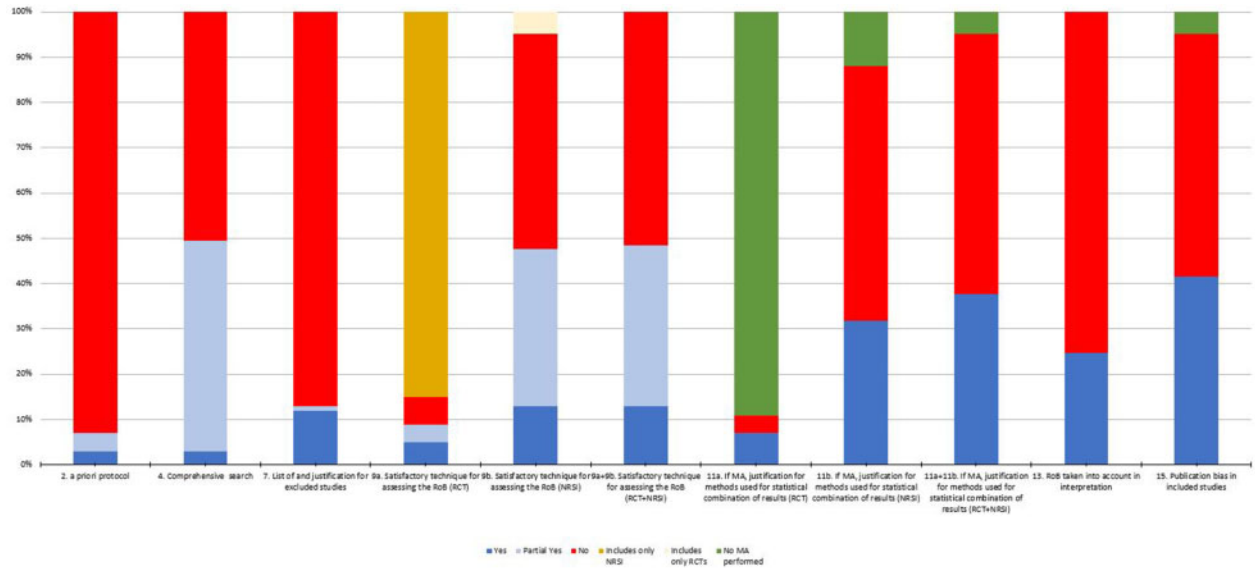

Figure 3 **Assessment of critical items (numbers 2, 4, 7, 9a, 9b, 9a+9b, 11a, 11b, 11a+11b, 13, and 15) in the AMSTAR-2 tool.** Bars show percentages of the ratings "yes," "no," "partial yes," "includes only NRCT," "includes only RCT," and "no MA performed" for each critical item. *Abbreviations*: MA, meta-analysis; NRSI, nonrandomized studies of intervention/exposure; RCT, randomized clinical trial; RoB, risk of bias.

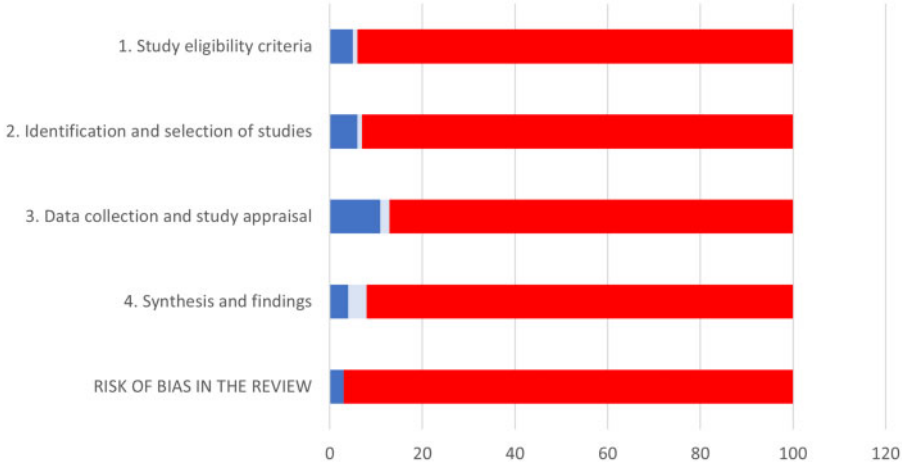

Figure 4 **Assessment of risk of bias in the ROBIS tool.** Bars show percentages of the ratings "low," "unclear," and "high" for each domain, as well as the overall assessment of risk of bias.

according to AMSTAR-2, and 3% were of low risk of bias according to ROBIS. This demonstrates that 97% of the analyzed SRMAs addressing nutritional interventions or exposures for cancer prevention had major flaws. Undoubtedly, this calls for caution when interpreting the results and conclusions of SRMAs. The main problems included the absence of a reference to an SRMA study protocol and the lack of a clear, prespecified, structured review question. Furthermore, only 51% of SRMAs reported on the assessment of risk of bias among the included primary studies, and only 13% of SRMAs covered all the subcriteria listed in item 9 of the AMSTAR-2 checklist.

Besides overlooking items that were specified in the AMSTAR-2 and ROBIS tools, which led to numerous methodological flaws, authors of SRMAs seemed to use methods without having adequate knowledge of their proper usage. For example, publication bias or small-study effects were sometimes analyzed with the test of statistical significance when the number of primary studies was less than 10, which is a widely accepted threshold for statistical tests to determine publication bias or small-study effects.[34]

Results within the context of previous studies

To the best of knowledge, no previous study has comprehensively assessed the methodological quality of SRMAs addressing nutrition interventions or exposures for cancer prevention.[29,31,35] A previous systematic

review focused on the quality of all nutrition-related systematic reviews published only in the Cochrane Database of Systematic Reviews showed that most studies (51%) were of high quality (receiving 9–11 out of 11 points in the previous AMSTAR tool[20–22]), with a median AMSTAR score of 9 (interquartile range, 7–10).[35] The remaining studies (49%) were assessed to be of moderate quality (receiving 5–8 points). The discrepancy in the results regarding quality obtained in that study and the present study is probably because Naude et al[35] searched Cochrane reviews only. Cochrane reviews undergo a thorough editorial and publishing process, including obligatory a priori publication of a protocol, and that process appears to improve the methods and quality in terms of the a priori design, the identification of studies, the assessment of quality or risk of bias, and the presence of a meta-analysis, as compared with non-Cochrane reviews.[36]

In contrast, the findings of a recent publication assessing 150 SRMAs of cohort studies in nutrition using the ROBIS instrument were similar to those of the present study.[29] Zeraatkar et al[29] found that more than 75% of SRMAs had important flaws related to study eligibility criteria (mainly the lack of prespecified eligibility criteria), and nearly all included studies had limitations related to identification and selection of studies, data collection and study appraisal, and synthesis of findings; moreover, notably, all reviews were rated as having a high risk of bias.[29]

Finally, another study focused on various vitamin interventions and tested the quality of reviews obtained from 4 Chinese databases. Again, the authors reported the mean quality according to AMSTAR (as opposed to AMSTAR-2) as a score of 6.10 ± 1.20 (out of 11 points).[37] Overall, they reported high adherence to the items considered critical in AMSTAR, namely, the use of appropriate methods for the evidence synthesis (98%), as well as assessment and documentation of the quality/risk of bias of the included studies (93.0%). However, similar to the present study, the study reported noncompliance with the domains of (i) a priori design (0%); (ii) providing a list of included and excluded studies (0%); and (iii) conducting a search for gray literature ($< 10\%$). The discrepancy between the results of their study and the results of the present study might be related to their use of a previous version of the AMSTAR tool, which had different response options and guidance, their use of a different sample of studies (studies published only in Chinese journals), and their focus on a different scope of interventions or exposures (vitamins vs any nutritional interventions or exposures).

Studies on the quality of reviews in other fields also concluded that, in many cases, the overall validity of SRMAs was unsatisfactory,[12–19,38,39] with authors using questionable methods to assess methodological quality or the risk of bias of primary studies[39] or not performing such assessments altogether.[40] A previous study that examined the quality and the risk of bias of studies published as SRMAs in the field of bariatric surgery and in which the same methodological tools were used (AMSTAR-2 and ROBIS) revealed similar drawbacks, including the lack of a priori design as well as poor reporting of excluded studies and lack of justification for the exclusion of studies.[18]

It has been estimated that only about 10% to 20% of systematic reviews register their protocols a priori.[7] In the present study, the frequency was even lower (9%). However, preregistration of protocols does not guarantee that the protocol is complete, that the methods used in the systematic review are appropriate, or that the conduct, analyses, and reporting of systematic reviews are methodologically correct. Nonetheless, preregistration of protocols can help increase the quality and the transparency of SRMAs.[7,36]

It might be argued that detailed study protocols and methodological training in conducting SRMAs are the foundation of good SRMAs. For instance, possible explanations for the low quality of SRMAs could be the lack of a prespecified, registered protocol, which is suggested to improve the quality of SRMAs,[2,41,42] and poor methodological training in the preparation and conduct of SRMAs (eg, lack of training in risk-of-bias assessment and the use of calibration exercises, and failure to include a statistician or methodologist).[43] Journal requirements for a priori study protocols, preferably those that are publicly available (eg, PROSPERO), and the use of reporting guidelines such as PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[44] and MOOSE (Meta-Analysis of Observational Studies in Epidemiology),[45] along with encouragement to use critical appraisal tools (eg, AMSTAR-2 or ROBIS) during the editorial process are likely to improve the quality of SRMAs.[8,34] It may be that low-quality SRMAs are linked to institutional pressures to publish articles in any journal, regardless of its impact factor. However, 50% of studies that were assessed in detail were published in journals with an impact factor above 3.53 (range: 0–51.27).[46]

Finally, carefully prepared SRMAs should be summarized with transparent assessment of the certainty/strength of the evidence for each reported outcome. In the present overview, only 5% of the 101 included SRMAs used an approach or system to assess the overall certainty of the evidence, such as GRADE (Grading of Recommendations, Assessments, Development and Evaluations), which is consistent with a recently published study indicating that, among 800 SRMAs

published in higher impact journals in the field of nutrition, only 5.9% used GRADE to assess the certainty of the evidence.[47] The results of the present study, together with the results of other recent reviews, leave no doubt that there is a need to promote the use of study protocols, methodological tools for risk-of-bias assessment, guidelines to assess the certainty of evidence (eg, GRADE), and checklists (eg, PRISMA) that can help to improve the reporting and validity of SRMAs in the field of nutrition in general.

Strengths and limitations

The strengths of this study include the use of the following: a prespecified and preregistered protocol; an exhaustive and comprehensive search with no language restrictions; clearly specified inclusion and exclusion criteria; and procedures for the study processes, such as study selection, data extraction, and quality assessment performed by 2 people independently (see Appendix S3 in the Supporting Information online). This is the first comprehensive systematic survey in which internationally endorsed assessment tools (ROBIS and AMSTAR-2) were used to assess the quality and risk of bias of studies published as SRMAs on a variety of nutritional or dietary interventions or exposures for cancer prevention.

The limitations of this survey include the narrow window for inclusion of published SRMAs, from 2010 to 2018. However, such a timespan allows examination of the current practice and quality of SRMAs. Another limitation is the inclusion of only a subsample of studies; however, the subsample was drawn randomly and proportionally to the number of articles published per year. It should be emphasized that there is no perfect tool to assess the quality and risk of bias of SRMAs. For instance, AMSTAR-2 contains not only items to assess methodological quality but also those to assess only the quality of reporting. Further, it insufficiently addresses the issue of certainty of effect estimates for each outcome, it has limited guidance about subgroup analysis to explore effect modification, and it does not emphasize the need to present summary data as absolute estimates rather than relative estimates, given that absolute estimates are recommended.[48]

CONCLUSION

Results from studies published as SRMAs on nutrition interventions or exposures for cancer prevention should be interpreted with caution, given the substantial methodological drawbacks that were detected in this systematic survey. Journal editors, peer reviewers, and users of SRMAs should be encouraged to assess the risk of bias and quality of reviews (eg, using AMSTAR-2 and ROBIS), paying particular attention to the methodological aspects considered critical for ensuring the validity of SRMAs, including prespecified study protocols, comprehensive literature searches, assessment of quality and risk of bias of individual studies, thorough assessment of heterogeneity (explored through subgroup analysis), and assessment of the certainty of evidence for each outcome.

Author contributions. All authors contributed significantly to the work as follows: conceptualization (M.M.B.), design (J.Z., D.S., M.K., M.J.S., B.C.J., M.M.B.), data acquisition (J.Z., D.S., M.J.S., M.K., P.W., W.S., M.G., A.S., A.W., K.K., J.B.C., M.M.B.), data interpretation and analysis (J.Z., D.S., M.J.S., M.K., B.C.J., M.M.B.), drafting of the manuscript (J.Z., M.M.B., B.C.J.), and critical revision of the manuscript (D.S., M.J.S., M.K., P.W., W.S., M.G., A.S., A.W., K.K., J.B.C., B.C.J., M.M.B.). All authors approved the final version of the manuscript submitted.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1 **Search strategy.**
Appendix S2 **List of included systematic reviews and meta-analyses.**
Appendix S3 **PRISMA checklist.**
Table S1 **Detailed results of AMSTAR-2.**

Acknowledgments

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