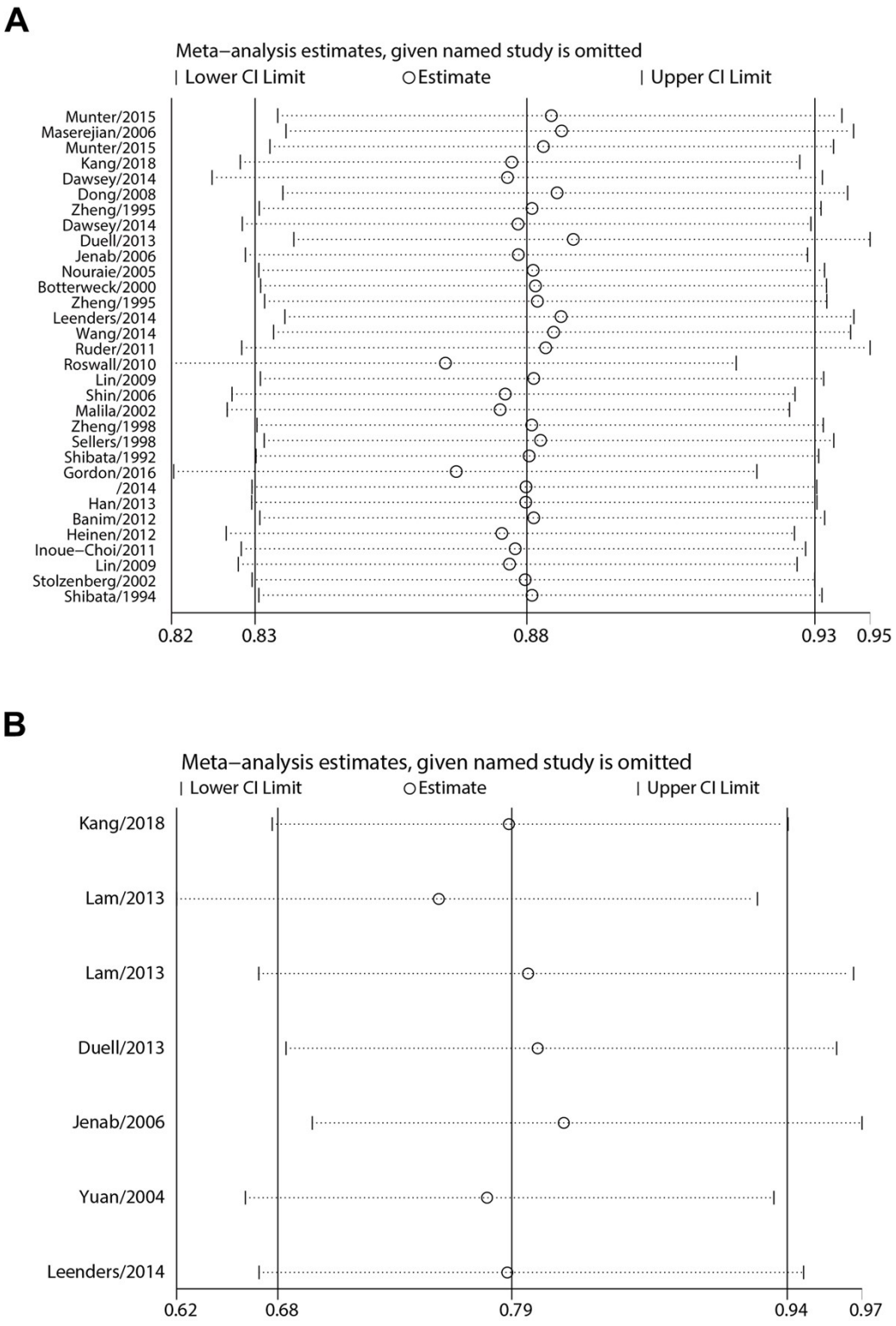
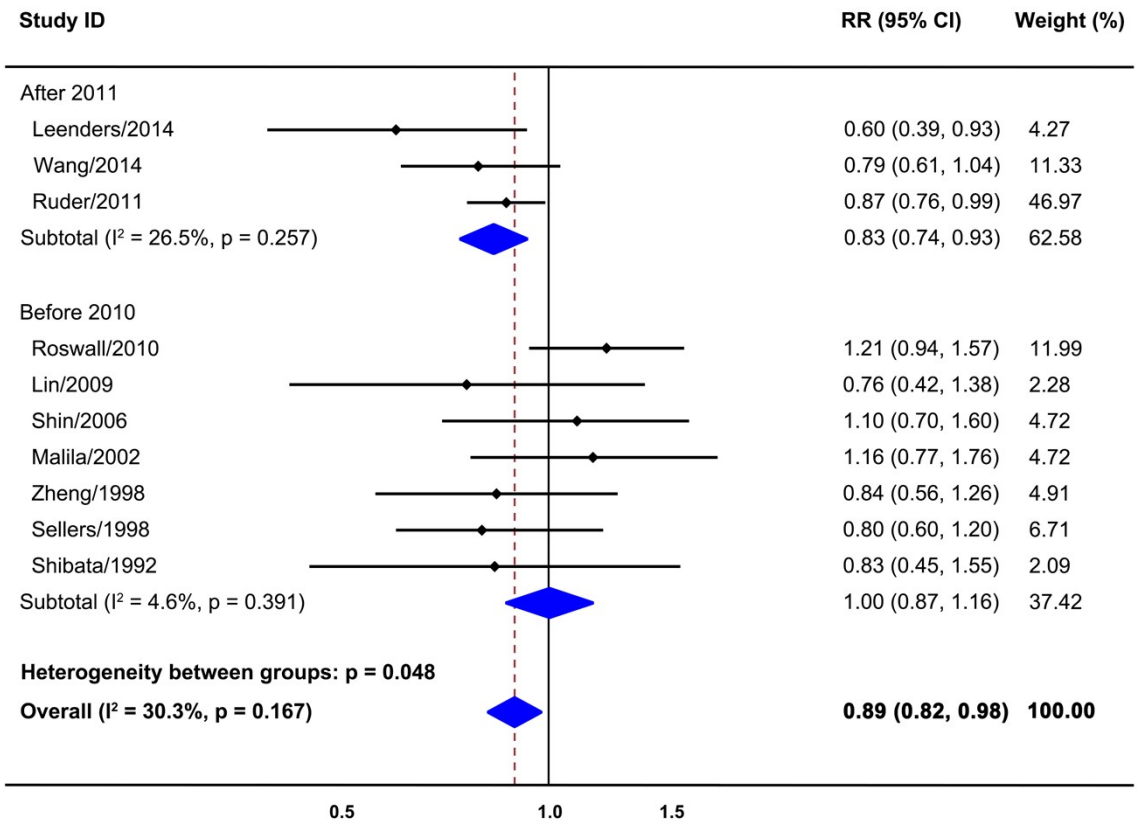
**Supplementary Figure 1.** Sensitivity analysis performed by including studies related to dietary vitamin C intake (A) and blood vitamin C level (B).



**Supplementary Figure 2.** Forest plot of the time series analysis on vitamin C intake and colorectal cancer incidence.



**Supplementary Figure 3.** GRADE assessment: A comprehensive evaluation of outcomes.

| | Group | Study | Certainty assessment | | | | | Certainty |
|---|---|---|---|---|---|---|---|---|
| | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | |
| Vitamin C intake | OPE cancer | Munter/2015① | Not serious | Serious | Not serious | Not serious | None | ⊗⊗⊗○ Moderate |
| | | Maserejian/2006 | | | | | | |
| | | Munter/2015② | | | | | | |
| | | Kang/2018 | | | | | | |
| | | Dawsey/2014 | | | | | | |
| | | Dong/2008 | | | | | | |
| | | Zheng/1995 | | | | | | |
| | Gastric cancer | Dawsey/2014 | Not serious | Not serious | Not serious | Not serious | None | ⊗⊗⊗⊗ High |
| | | Duell/2013 | | | | | | |
| | | Jenab/2006 | | | | | | |
| | | Nouraie/2005 | | | | | | |
| | | Botterweck/2000 | | | | | | |
| | | Zheng/1995 | | | | | | |
| | Colorectal Cancer | Leenders/2014 | Not serious | Not serious | Not serious | Not serious | None | ⊗⊗⊗⊗ High |
| | | Wang/2014 | | | | | | |
| | | Ruder/2011 | | | | | | |
| | | Roswall/2010 | | | | | | |
| | | Lin/2009 | | | | | | |
| | | Shin/2006 | | | | | | |
| | | Malila/2002 | | | | | | |
| | | Zheng/1998 | | | | | | |
| | | Sellers/1998 | | | | | | |
| | | Shibata/1992 | | | | | | |
| | Pancreatic Cancer | Gordon/2016 | Not serious | Not serious | Not serious | Not serious | None | ⊗⊗⊗⊗ High |
| | | Wang/2014 | | | | | | |
| | | Han/2013 | | | | | | |
| | | Banim/2012 | | | | | | |
| | | Heinen/2012 | | | | | | |
| | | Inoue-Choi/2011 | | | | | | |
| | | Lin/2009 | | | | | | |
| | | Stolzenberg/2002 | | | | | | |
| | | Shibata/1994 | | | | | | |
| Plasma vitamin C | Colorectal Cancer | Leenders/2014 | Not serious | Not serious | Serious | Serious | None | ⊗⊗○○ Low |
| | Gastric Cancer | Lam/2013 | Not serious | Not serious | Not serious | Not serious | None | ⊗⊗⊗⊗ High |
| | | Duell/2013 | | | | | | |
| | | Jenab/2006 | | | | | | |
| | | Yuan/2004 | | | | | | |
| | Esophageal Cancer | Kang/2018 | Not serious | Not serious | Not serious | Serious | None | ⊗⊗⊗○ Moderate |
| | | Lam/2013 | | | | | | |

Evidence Quality

Moderate Quality

High Quality

**Supplementary Table 1.** Quality assessment for cohort studies according to Newcastle-Ottawa Scale.

| Study | Selection | | | | Comparability[a] | Outcome | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | | Q6 | Q7[b] | Q8 | |
| Munter/2015 | * | * | * | * | ** | * | * | * | 9 |
| Maserejian/2006 | | * | * | * | ** | * | * | * | 8 |
| Kang/2018 | * | * | | | ** | * | * | * | 7 |
| Dong/2008 | | * | * | | ** | * | * | * | 7 |
| Dawsey/2014 | * | * | * | * | ** | * | * | * | 9 |
| Duell/2013 | * | * | * | * | * | * | | * | 7 |
| Jenab/2006 | * | | * | * | * | * | * | * | 7 |
| Nouraie/2005 | | * | * | | ** | * | * | * | 7 |
| Yuan/2004 | * | * | * | * | ** | * | * | * | 9 |
| Botterweck/2000 | * | * | * | * | ** | * | | * | 8 |
| Zheng/1995 | * | * | * | | ** | * | | * | 7 |
| Leenders/2014 | | * | * | | * | * | | * | 5 |
| Ruder/2011 | * | * | * | * | ** | * | * | * | 9 |
| Roswall/2010 | * | * | * | * | * | * | * | * | 8 |
| Lin/2009 | | * | * | * | ** | * | * | * | 8 |
| Shin/2006 | * | * | * | * | ** | * | | * | 8 |
| Malila/2002 | | * | * | * | ** | * | * | * | 8 |
| Zheng/1998 | * | * | * | * | ** | * | * | * | 9 |
| Sellers/1998 | * | * | * | * | | * | * | * | 7 |
| Shibata/1992 | * | * | * | * | * | * | * | * | 8 |
| Gordon/2016 | * | * | * | * | * | * | * | * | 8 |
| Han/2013 | * | * | * | * | ** | * | * | * | 9 |
| Banim/2012 | * | * | * | * | ** | * | * | * | 9 |
| Heinen/2012 | * | * | * | * | ** | * | * | * | 9 |
| Inoue-Choi/2011 | | * | * | * | * | * | * | * | 7 |
| Stolzenberg/2002 | * | * | * | * | ** | * | * | * | 9 |
| Shibata/1994 | * | * | * | * | ** | * | * | * | 9 |
| Kurahashi/2009 | * | * | * | | ** | * | | * | 7 |
| Makiuchi/2017 | * | * | * | * | ** | * | | * | 8 |
| Egnell/2017 | * | * | * | * | ** | * | * | * | 9 |

A maximum of 9 stars(points) can be allotted to each study. The NOS scale can be adapted to better suit the specific circumstances of a study by modifying the scores for each aspect. In general, a score of 7-9 is indicative of high-quality research, while a score of 4-6 suggests moderate-quality research. Scores below 4 are considered

low-quality research.

[a] A maximum of 2 stars can be allotted in category Q5, one for age and sex, the other for other related controlled factors.

[b] The 25$^{th}$ percentile follow-up year of all included articles was 7.775. Therefore, a follow-up year longer than 7.775 was deemed to be sufficiently long.

Selection

Q1: Representativeness of the exposed cohort: (a) truly representative *, (b) somewhat representative *, (c) selected group, (d) no description of the derivation of the cohort.

Q2: Selection of the non-exposed cohort: (a) drawn from the same community as the exposed cohort *, (b) drawn from a different source, (c)no description of the derivation of the non-exposed cohort.

Q3: Ascertainment of exposure: (a) secure record (e.g., surgical record) *, (b) structured interview *, (c) written self report, (d) no description, (e) other.

Q4: Demonstration that outcome of interest was not present at start of study: (a) yes *, (b) no.

Comparability

Q5: Comparability of cohorts on the basis of the design or analysis controlled for confounders: (a) the study controls for age and sex *, (b) study controls for other related factors (e.g., BMI or waist-hip ratio, smoking status, education) *, (c) cohorts are not comparable on the basis of the design or analysis controlled for confounders.

Outcome

Q6: Assessment of outcome: (a) independent blind assessment *, (b) record linkage *, (c) self report, (d) no description, (e) other.

Q7: Was follow-up long enough for outcomes to occur: (a) yes *, (b) no.

Q8: Adequacy of follow-up of cohorts: (a) complete follow up——all subject accounted for *, (b) subjects lost to follow up unlikely to introduce bias-number lost

less than or equal to 20% or description of those lost suggested no different from those followed *, (c) follow up rate less than 80% and no description of those lost, (d) no statement.

**Supplementary Table 2.** Risk of bias assessment for RCTs according to the Cochrane Collaboration Risk of Bias Tool.

| Study | Random Sequence Generation | Allocation Concealment | Blinding of Participants and Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Reporting | Other Bias |
|---|---|---|---|---|---|---|---|
| Lam/ 2013 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear |
| Wang/ 2014 | Low risk | Low risk | Low risk | Low risk | Unclear | Low risk | Unclear |

**Supplementary Table 3.** Egger's test and Begg's test for studies reporting on the relationship between vitamin C intake (A) or plasma vitamin C (B) and digestive system cancer risk.

**A**

Egger's test

| Std_Eff | Coef. | Std. Err. | t | P>\| t \| | 95% CI |
|---|---|---|---|---|---|
| **slope** | -0.0309569 | 0.0707593 | -0.44 | 0.665 | -0.1754665, 0.1135528 |
| **bias** | -0.6531181 | 0.4183731 | -1.56 | 0.129 | -1.50755, 0.2013138 |

Begg's test

| | |
|---|---|
| **adj. Kendall's Score (P-Q)** | -111 |
| **Std. Dev. of Score** | 61.66 (corrected for ties) |
| **Number of Studies** | 32 |
| **z** | -1.80 |
| **Pr > \| z \|** | 0.072 |
| **z (continuity corrected)** | 1.78 |
| **Pr > \| z \| (continuity corrected)** | 0.074 |

**B**

Egger's test

| Std_Eff | Coef. | Std. Err. | t | P>\| t \| | 95% CI |
|---|---|---|---|---|---|
| **slope** | -0.0906224 | 0.1865969 | -0.49 | 0.648 | -0.5702851, 0.3890403 |
| **bias** | -0.6638078 | 0.8458848 | -0.78 | 0.468 | -2.838224, 1.510608 |

Begg's test

| | |
|---|---|
| **adj. Kendall's Score (P-Q)** | -5 |
| **Std. Dev. of Score** | 6.66 |
| **Number of Studies** | 7 |
| **z** | -0.75 |
| **Pr > \| z \|** | 0.453 |
| **z (continuity corrected)** | 0.60 |
| **Pr > \| z \| (continuity corrected)** | 0.548 |

## MOOSE checklist

| Section and Topic | Item # | Location where item is reported |
|---|---|---|
| **Reporting of background should include** | | |
| Problem definition | 1 | Page 3 & Table 1 |
| Hypothesis statement | 2 | Page 3 & Table 1 |
| Description of study outcome(s) | 3 | Page 3 & Table 1 |
| Type of exposure or intervention used | 4 | Page 3 & Table 1 |
| Type of study designs used | 5 | Page 3 & Table 1 |
| Study population | 6 | Page 3 & Table 1 |
| **Reporting of search strategy should include** | | |
| Qualifications of searchers (eg, librarians and investigators) | 7 | Page 8 |
| Search strategy, including time period included in the synthesis and keywords | 8 | Page 7 |
| Effort to include all available studies, including contact with authors | 9 | Page 8 |

| | | |
|---|---|---|
| Databases and registries searched | 10 | Page 7 |
| Search software used, name and version, including special features used (eg, explosion) | 11 | Page 7 |
| Use of hand searching (eg, reference lists of obtained articles) | 12 | Page 7-8 & Figure 1 |
| List of citations located and those excluded, including justification | 13 | Figure 1 |
| Method of addressing articles published in languages other than English | 14 | Page 7-8 |
| Method of handling abstracts and unpublished studies | 15 | Page 7-8 |
| Description of any contact with authors | 16 | NA |
| **Reporting of methods should include** | | |
| Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | 17 | Table 1 |
| Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | 18 | Page 8 |
| Documentation of how data were classified and coded (eg, multiple raters, | 19 | Page 9-10 |

| | | |
|---|---|---|
| blinding, and interrater reliability) | | |
| Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) | 20 | Page 9-10 |
| Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | 21 | Page 8 & Supplementary table 1 & Supplementary table 2 |
| Assessment of heterogeneity | 22 | Page 9 |
| Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | 23 | Page 9-10 |
| Provision of appropriate tables and graphics | 24 | Figure 1 & Table 2 |
| **Reporting of results should include** | | |
| Graphic summarizing individual study estimates and overall estimate | 25 | Figure 2 & Figure 3 |

| | | |
|---|---|---|
| Table giving descriptive information for each study included | 26 | Table 1 |
| Results of sensitivity testing (eg, subgroup analysis) | 27 | Table 3 & Supplementary figure 1 |
| Indication of statistical uncertainty of findings | 28 | Page 27-28 |
| **Reporting of discussion should include** | | |
| Quantitative assessment of bias (eg, publication bias) | 29 | Supplementary figure 3 |
| Justification for exclusion (eg, exclusion of non–English-language citations) | 30 | Page 8 & Table 1 |
| Assessment of quality of included studies | 31 | Page 8 & Supplementary table 1 & Supplementary table 2 |
| **Reporting of conclusions should include** | | |
| Consideration of alternative explanations for observed results | 32 | Page 18-28 |
| Generalisation of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | 33 | Page 28 |

# PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | Page 1 |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Page 3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Page 3 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Page 3 |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Page 6-7 & Table 1 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Page 6 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Page 6 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Page 8 & Table 1 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Page 7-8 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Page 8 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Page 8 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 8 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Page 8 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Page 9-10 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Page 9-10 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Page 9-10 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Page 9-10 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Page 9-10 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Page 9-10 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Page 9-10 |
| Certainty | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Page 9-10 |

# PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| assessment | | | |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Figure 1 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Figure 1 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Table 2 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Figure 5 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Figure 2& Figure 3 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Table 2 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Figure 2& Figure 3 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Page 27-28 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Supplementary figure 1 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Figure 5 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Figure 2 & Figure 3 |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Page 18-28 |
| | 23b | Discuss any limitations of the evidence included in the review. | Page 28 |
| | 23c | Discuss any limitations of the review processes used. | Page 28 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Page 28 |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Page 6 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Page 6-7 |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Page 6-7 |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Page 29 |
| Competing interests | 26 | Declare any competing interests of review authors. | Page 29 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Page 29 |

# PRISMA 2020 Checklist

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71