| **Section and Topic**  | **Item #** | **Checklist item**  | **Location where item is reported**  |
| --- | --- | --- | --- |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review. | n/a |
| **ABSTRACT**  |  |
| Abstract  | 2 | See the PRISMA 2020 for Abstracts checklist. | Abstract, paragraph 1 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of existing knowledge. | Background, paragraph 5 |
| Objectives  | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Background, paragraph 5 |
| **METHODS**  |  |
| Eligibility criteria  | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Literature parsing, paragraphs 2,3, 4Literature database construction, paragraphs 3,4 |
| 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. | Literature parsing, paragraphs 1,3Literature database construction, paragraph 3 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Literature parsing, paragraphs 1, 2, 3, 4Literature database construction, paragraphs 1, 3 |
| 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. | Literature parsing, paragraph 2, 4Literature database construction, paragraph 3 |
| 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. | Literature parsing, paragraphs 1, 2, 3Literature database construction, paragraph 3 |
| 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. | n/a |
| 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. | Definition of genes, paragraph 1Loss of function intolerance, paragraph 1Phenotype databases, paragraphs 1,2Citation analysis, paragraph 1Identification of NIH supported research organizations, paragraph 1Definition of genome biology, paragraphs 1, 2Definition of genome-wide association study, paragraphs 1, 2 |
| 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. | Literature database construction, paragraphs 4, 5, 6 |
| 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. | Statistical analysis, paragraph 1Corresponding figure legends |
| 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)). | Literature parsing, paragraphs 1, 2, 3Literature database construction, paragraph 3 |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Literature parsing, paragraphs 1, 2, 3Literature database construction, paragraph 3 |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Statistical analysis, paragraphs 2, 3 |
| 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. | Statistical analysis, paragraphs 2, 3 |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | none |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Statistical analysis, paragraph 3 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Statistical analysis, paragraph 3 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Statistical analysis, paragraph 3 |
| **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. | Accompanying PRISMA flow diagram |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | n/a |
| Study characteristics  | 17 | Cite each included study and present its characteristics. | n/a |
| Risk of bias in studies  | 18 | Present assessments of risk of bias for each included study. | n/a |
| 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. | n/a |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | n/a |
| 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. | Each figure has confidence intervals that are explained in figure legends. Further we deposited metrics at https://doi.org/10.21985/n2-b5bm-3b17 |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | n/a |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | n/a |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Literature database construction, paragraphs 4, 5, 6Study limitations, paragraph 1 |
| Certainty of evidence  | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | n/a |
| **DISCUSSION**  |  |
| Discussion  | 23a | Provide a general interpretation of the results in the context of other evidence. | Discussion, paragraphs 1-10 |
| 23b | Discuss any limitations of the evidence included in the review. | Study limitations, paragraphs 1, 2, 3Literature database construction, paragraphs 4, 5, 6 |
| 23c | Discuss any limitations of the review processes used. | Study limitations, paragraphs 1, 2, 3Literature database construction, paragraphs 4, 5, 6 |
| 23d | Discuss implications of the results for practice, policy, and future research. | Discussion, paragraphs 2-10  |
| **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. | Other Information, paragraph 1 |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Other Information, paragraph 1 |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Other Information, paragraph 1 |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Other Information, paragraph 1 |
| Competing interests | 26 | Declare any competing interests of review authors. | Other Information, paragraph 1 |
| 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. | Other Information, paragraph 1 |

*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

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