**Search Strategies for all databases queried**
**Ovid MEDLINE(R) ALL <1946 to January 20, 2022>**

1 Clostridioides difficile/ 10462
2 (clostridioides difficile or clostridium difficile or txid1496 or c diff or cdiff or c difficile or bacillus difficilis or clostridium difficilis or peptoclostridium difficile).mp. 17996
3 1 or 2 17996
4 ((predict* or risk*) and (model* or tool*)).mp. 1237226
5 3 and 4 960

**Embase <1974 to 2022 January 20>**

1 clostridioides difficile/ 2559
2 (clostridioides difficile or clostridium difficile or txid1496 or c diff or cdiff or c difficile or bacillus difficilis or clostridium difficilis or peptoclostridium difficile).mp. 35578
3 1 or 2 35578
4 ((predict* or risk*) and (model* or tool*)).mp. 1617120
5 3 and 4 1975

**Cochrane Database of Systematic Reviews &**
**Cochrane Central Register of Controlled Trials**
**January 2022 (77 results)**

ID Search Hits
#1 MeSH descriptor: [Clostridioides difficile] this term only 207
#2 (("clostridioides difficile" or "clostridium difficile" or "txid1496" or "c diff" or "cdiff" or "c NEXT difficile" or "bacillus difficilis" or "clostridium difficilis" or "peptoclostridium difficile")):ti,ab,kw 1548
#3 #1 or #2 1548
#4 ((predict* or risk*) and (model* or tool*)):ti,ab,kw 74874
#5 #3 and #4 77

**Table S1** – Test types included in event definition by study.

| | | (+) result was included in CDI case definition | | |
|---|---|---|---|---|
| | | **EIA** | **NAAT** | **CTA** |
| **Chandra et al.** | *Index model (2012)* | Yes | No | No |
| | *External validation (2014)* | Yes | No | No |
| Cooper et al. (2013) | | Yes | Yes | No |
| Davis et al. (2018) | | No | Yes | No |
| Garey et al. (2008) | | No | No | Yes |
| Press et al. (2016) | | No | Yes | No |
| Tabak et al. (2015) | | Yes | No | No |
| **Oh et al. (2018)** | *MGH model* | Yes | *Yes | No |
| | *UM model* | Yes | Yes | No |
| **Tilton et al.** | *Index model (2019)* | No | Yes | No |
| | *Validation model (2021)* | No | Yes | No |
| **Voicu et al. (2021)** | *Model 1* | Yes | No | No |
| | *Model 2* | Yes | No | No |

*Oh et al only used NAAT for discordant cases between GDH and toxin EIA

Cytotoxicity assay (CTA); enzyme immunoassay (EIA) for toxins; nucleic acid amplification test (NAAT) for toxin gene;

**Table S2**– Eligibility criteria by study.

| | | (+) result was included in CDI case definition | | |
|---|---|---|---|---|
| | | **Time from admission until considered HO-CDI** | **Criteria to receive laboratory test of CDI** | **Exclusion criteria** |
| **Chandra et al.** | *Index model (2012)* | ≥ 48h | Unformed stool | CDI in last 3 months |
| | *External validation (2014)* | ≥ 48h | | |
| Cooper et al. (2013) | | | | |
| Davis et al. (2018) | | ≥ 48h | Liquid stool | Patients readmitted for primarily for CDI infection |
| Garey et al. (2008) | | ≥ 48h | Clinical suspicion | |
| Press et al. (2016) | | ≥ 72h | Unformed stool | CDI <3 days, history of CDI |
| Tabak et al. (2015) | | ≥ 48h | | |
| **Oh et al. (2018)** | *MGH model* | ≥ 48h | | Positive in the 14 days prior to admission |
| | *UM model* | ≥ 48h | | Positive in the 14 days prior to admission or admitted to inpatient psychiatric unit. |
| **Tilton et al.** | *Index model (2019)* | ≥ 48h | | Prior CDI diagnosis, pregnant, incomplete medical records, IBS, IBD, or diarrhea < 48 hours into admission |
| | *Validation model (2021)* | ≥ 72h | Receipt of systemic antibiotics | CDI within 90 days prior to admission, pregnant, length of stay < 72 hrs, a diagnosis of IBS or IBD, receipt of metronidazole or vancomycin prior to CDI diagnosis, diarrhea before day 4 of admission |
| **Voicu et al. (2021)** | *Model 1* | ≥ 48h | Diagnosis of variceal bleed secondary to liver cirrhosis | Receipt of metronidazole or vancomycin, recent CDI, CDI treatment prior to testing, antibiotics prior to CDI dignosis, admission from other hospital with different upper GI bleeding protocol |
| | *Model 2* | ≥ 48h | Diagnosis of variceal bleed | |

| | | (+) result was included in CDI case definition | |
|---|---|---|---|
| | **Time from admission until considered HO-CDI** | **Criteria to receive laboratory test of CDI** | **Exclusion criteria** |
| | | secondary to liver cirrhosis | |

**Table S3** – List of predictors by study

| | | Predictors |
|---|---|---|
| **Chandra et al.** | *Index model (2012)* | New-onset unformed stool, hospital length of stay >7 days, age >65 years, long-term care facility resident, high-risk antibiotic use, hypoalbuminemia (<30g/L) |
| | *External validation (2014)* | Same as index model, see above. |
| Cooper et al. (2013) | | Multiple antibiotics, stool, admission from other facility, prior C. difficile infection |
| Davis et al. (2018) | | Number of high risk antibiotics (0-5), age (<40, 40-55, >55), Charlson comorbidity index (0, 1, >=2), proton pump inhibitor |
| Garey et al. (2008) | | Age (50-80, >80), hemodialysis, non-surgical admission, intensive care unit length of stay |
| Press et al. (2016) | | Age, admission in past 60 days, mechanical vent, dialysis, CHF, antibiotics |
| Tabak et al. (2015) | | CO-CDI pressure >60-percentile, age >64, trasfer from other hospital or skilled nursing facility, mechanical ventilation present on admission, CIM on admission, previous CDI, discharge in last 30 days, admission to intensive care unit, hypoalbuminemia (≤30mg/L), hypercreatininemia (>2 mg/dL), increased bands (>32%), abnormal platelets (<=150k or >420k), and leukocytosis (> 11k). |
| **Oh et al. (2018)** | *MGH* | Risk factors: Medicine service, CDI in the prior year, propofol, Age 77-89, Chlorhexidine, MICU, ceruloplasmin (.0126-.0214), prescribed metronidazole, prescribed dextrose, prescribed cefepime. Protective factors: OBGYN service, ceruloplasmin (< .001), Surgery service, age (41-56), prescribed simvastatin, prescribed oxycodone, Obstetrics service, Age (18-41), prescribed docusate, admitted from ED. |

| | | Predictors |
|---|---|---|
| | *UM* | Risk factors: CDI in prior year, ED location, tachycardia, prescribed cefoxitin, prescribed fluconazole, prescribed ondansetron, prescribed prochlorperazine, prescribed an antifungal, prescribed an antiemetic, admit hold. Protective factors: prescribed warfarin, age (35-51), prescribed NSAIs, prescribed hydrocodone, on the neurology unit, on the orthopedic surgery unit, on the OB unit, prescribed ibuprofen, living in Washtenaw County, age (18-35). |
| **Tilton et al.** | *Index model (2019)* | Age (>70), hospitalization (past 90 days) |
| | *Validation model (2021)* | History of hematologic mallignancy, history of solid tumor malignancy, hospitalization (past 90 days) |
| **Voicu et al. (2021)** | *Model 1* | Age, days of admission, Charlson comorbidity index, Child-Pugh score |
| | *Model 2* | History of hepatocellular carcinoma, prescribed proton-pump inhibitor, creatinine, urea |

Oh et al. used an EMR based ML model and the full list of predictors includes over 1000 variables. Predictors presented reflect the top 10 positive and negative predictors in the model.

**Table S4** - Model performance on derivation and validation sets.

| | | Performance | |
|---|---|---|---|
| | | **Derivation** | **Validation** |
| **Chandra et al.** | *Index model (2012)* | 0.93 (95% CI: 0.92, 0.95) | 0.95 (95% CI: 0.93, 0.96) |
| | *External validation (2014)* | | 0.94 (95% CI: 0.93, 0.96) |
| Cooper et al. (2013) | | 0.93 (95% CI: 0.93, 0.93) | 0.91 (95% CI: 0.90, 0.91) |
| Davis et al. (2018) | | 0.75 (95% CI: NR) | 0.77 (95% CI: NR) |
| Garey et al. (2008) | | 0.73 (95% CI: NR) | 0.68 (95% CI: NR) |
| Press et al. (2016) | | 0.85 (95% CI: NR) | 0.85 (95% CI: NR) |
| Tabak et al. (2015) | | 0.79 (95% CI: 0.76, 0.81) | 0.79 (95% CI: 0.76, 0.81) |
| **Oh et al. (2018)** | *MGH model* | | 0.75 (95% CI: 0.73, 0.78) |
| | *UM model* | | 0.82 (95% CI: 0.8, 0.84) |
| **Tilton et al.** | *Index model (2019)* | | 0.7 (95% CI: NR) |
| | *Validation model (2021)* | | 0.74 (95% CI: NR) |
| **Voicu et al. (2021)** | *Model 1* | | 0.84 (95% CI: 0.76, 0.92) |
| | *Model 2* | | 0.82 (95% CI: 0.75, 0.90) |

Value presented in Tilton et al. 2021 is for the new model developed in that paper. The validation performance of the index model in the 2021 Tilton paper is .62.

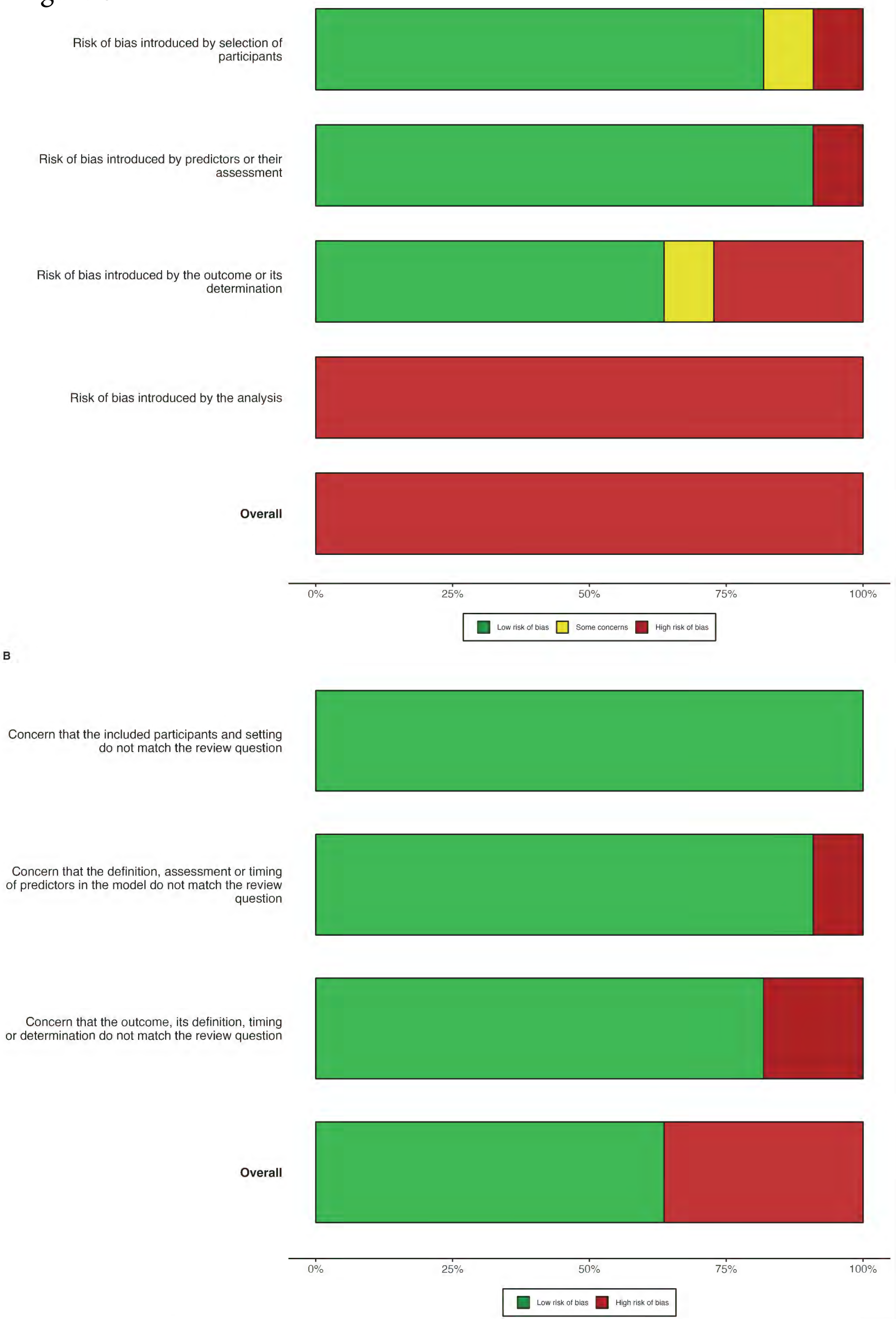
**Table S5** - Model performance on derivation and validation sets.

| Paper | Model | Estimated study prevalence (per 1000 persons) | Sensitivity | Specificity | PPV | NPV | LR+ | LR- |
|---|---|---|---|---|---|---|---|---|
| **Chandra et al.** | *Index model (2012)* | 5.5 | 0.94 | 0.80 | 0.03 | 1.00 | 4.70 | 0.08 |
| | *External validation only (2014)* | 8.8 | 0.98 | 0.85 | 0.06 | 1.00 | 6.64 | 0.02 |
| Cooper et al. (2013) | | 11 | 0.92 | 0.87 | 0.07 | 1.00 | 7.03 | 0.10 |
| Davis et al. (2018) | | 15.2 | 0.82 | 0.52 | 0.03 | 0.99 | 1.73 | 0.34 |
| Garey et al. (2008) | | 7.2 | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* |
| Press et al. (2016) | | 4.6 | 0.82 | 0.76 | 0.02 | 1.00 | 3.37 | 0.24 |
| Tabak et al. (2015)* | | 4.1 | 0.75 | 0.71 | 0.01 | 1.00 | 2.59 | 0.35 |
| **Oh et al. (2018)** | *MGH model* | 8.4 | 0.23 | 0.95 | 0.04 | 0.99 | 4.83 | 0.81 |
| | *UM model* | 11.2 | 0.28 | 0.95 | 0.06 | 0.99 | 5.79 | 0.76 |
| **Tilton et al.** | *Index model (2018)* | *NA* | 0.44 | 0.80 | *NA* | *NA* | 2.20 | 0.70 |
| | *Validation & model (2021)* | *NA* | 0.63 | 0.78 | *NA* | *NA* | 2.42 | 0.67 |
| **Voicu et al. (2021)*** | *Model 1* | 68.1 | 0.68 | 0.88 | 0.29 | 0.97 | 5.67 | 0.36 |
| | *Model 2* | 68.1 | 0.68 | 0.74 | 0.16 | 0.97 | 2.62 | 0.43 |

Study prevalence calculated from population information provided in manuscript.
Tilton et al. only provided information on their case-control sample.
*Sensitivity and specificity estimated from ROC figure.

A

# Figure S1


Risk of bias introduced by selection of participants
Risk of bias introduced by predictors or their assessment
Risk of bias introduced by the outcome or its determination
Risk of bias introduced by the analysis
Overall
0%
25%
50%
75%
100%
Low risk of bias
Some concerns
High risk of bias

B


Concern that the included participants and setting do not match the review question
Concern that the definition, assessment or timing of predictors in the model do not match the review question
Concern that the outcome, its definition, timing or determination do not match the review question
Overall
0%
25%
50%
75%
100%
Low risk of bias
High risk of bias

# PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | 1 |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 3 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 3-4 |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 4-5 |
| 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. | 4 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | 4-5, supplement |
| 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. | 5 |
| 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. | 5-6 |
| 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. | 5 |
| | 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. | 5 |
| 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. | 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. | NA |
| 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)). | NA |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | NA |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | NA |
| | 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. | NA |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | NA |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | NA |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 6 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | NA |

# PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **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. | 7 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | 7 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | 7 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | 10 |
| 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. | 7-8 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | NA |
| | 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. | NA |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | NA |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | NA |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | 10 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | NA |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | 11 |
| | 23b | Discuss any limitations of the evidence included in the review. | 13-14 |
| | 23c | Discuss any limitations of the review processes used. | 13-14 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | 14 |
| **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. | Not registered |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | NA |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | NA |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | 15 |
| Competing interests | 26 | Declare any competing interests of review authors. | 15 |
| 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. | 15 |

*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

# TRIPOD-SRMA Checklist for reporting systematic reviews of prediction model studies

| Section and topic | Item No | Checklist item | Page |
|---|---|---|---|
| **Title** | | | |
| Title | 1 | Identify the report as a systematic review or meta-analysis (or both) of diagnostic or prognostic model studies. Specify the target population and outcome(s) predicted as relevant to the review question. | 1 |
| **Abstract** | | | |
| Abstract | 2 | See the TRIPOD-SRMA Checklist for Abstracts | 1 |
| **Introduction** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 3 |
| Objectives | 4 | Provide an explicit statement of the objective(s) being addressed with reference to: target population, index and comparator models (as relevant), outcome(s), time (prediction horizon and intended moment of using the model), and setting. | 3 |
| **Methods** | | | |
| Study eligibility criteria | 5 | Specify study characteristics used as eligibility criteria, including any prediction models of specific interest, and whether development or validation studies (or both) were eligible. | 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. | 4 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Supplement |
| Study 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. | 4-5 |
| Data collection process | 9 | Specify the methods used to collect data from study 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. | 5-6 |
| Data Items | 10a | List and define all items for which data were sought from each study. | 5 |
| | 10b | State the model performance measures that were sought (e.g., measures of calibration, discrimination, overall model fit, clinical utility). | 5-6 |
| | 10c | Describe how any desired but unreported data items (items 10a, 10b) were handled (e.g., contacted authors, calculated from other reported information). | 5-6 |
| Risk of bias and applicability assessment | 11 | Specify the methods used to assess risk of bias in the included studies and their applicability to the review question. This should be done separately for each model development and validation. Include details of any tool(s) used, how many reviewers assessed each study and whether they worked independently. | 6 |
| Synthesis methods | 12a | Describe any methods for synthesising estimates of performance measures for each model. If meta-analysis was carried out, describe the methods used, including any transformations of data prior to pooling, how any heterogeneity in model performance was quantified and handled, and software package(s) used. | NA |
| | 12b | Describe any methods used to explore possible causes of heterogeneity in model performance (e.g., subgroup analysis, meta-regression), including whether or not they were planned. | NA |

| Section and topic | Item No | Checklist item | Page |
|---|---|---|---|
| | 12c | Describe any sensitivity analyses conducted to assess robustness of the synthesised results. | NA |
| Certainty assessment | 13 | Describe any methods used to assess certainty (or confidence) in the body of evidence for a prediction model. | NA |
| **Results** | | | |
| Study selection | 14 | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies and models included in the review, ideally using a flow diagram. | 7 |
| Study and model characteristics | 15 | Present study characteristics and model details extracted (as per Item 10a), and cite the study reports. | 7-9 |
| Risk of bias and applicability | 16 | Present results of risk of bias and applicability assessment. This should be done separately for each model development and validation in each included study. | 10 |
| Results of model performance in individual studies | 17 | Present performance estimates and confidence intervals for each model and all evaluations, including whether they relate to the internal or external validation performance. If internal, give details of the method. | 9 |
| Results of syntheses | 18a | Present the results of any synthesis of model performance, together with details of which study estimates contributed. If meta-analysis was carried out, then for each model and performance measure, present summary results, confidence/credible intervals and measures of heterogeneity. Forest plots may be useful. | NA |
| | 18b | For each model, present results of all investigations of possible causes of heterogeneity in model performance. | NA |
| | 18c | Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results. | NA |
| Certainty of evidence | 19 | Present any assessments of certainty (or confidence) in the body of evidence for each prediction model of interest. | NA |
| **Discussion** | | | |
| Summary of evidence | 20 | Summarise the main findings including the strengths and limitations of the evidence. | 11 |
| Limitations | 21 | Discuss the strengths and limitations of the review process. | 13-14 |
| Implications | 22 | Discuss implications of the results in the context of other evidence and for practice, policy, and future research. | 11-13 |
| **Other information** | | | |
| Registration and protocol | 23a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Not registered |
| | 23b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | NA |
| | 23c | Describe and explain any amendments to information provided at registration or in the protocol. | NA |
| Support | 24 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | 15 |
| Competing interests | 25 | Declare any competing interests of review authors. | 15 |

| Section and topic | Item No | Checklist item | Page |
|---|---|---|---|
| Availability of data, code, and other materials | 26 | 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. | 15 |

This checklist appears in appendix 2 of Snell KIE, Levis B, Damen JAA, et al. Transparent reporting of multivariable prediction models for individual prognosis or diagnosis: checklist for systematic reviews and meta-analyses (TRIPOD-SRMA). *BMJ* 2023;381:e073538. doi:10.1136/bmj-2022-073538.