

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Not applicable
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	Not applicable
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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 1 & 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 9
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Not applicable



## APPENDIX 2

### NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

#### **Selection**

- 1) Is the case definition adequate?
  - a) yes, with independent validation \*
  - b) yes, eg record linkage or based on self reports
  - c) no description
- 2) Representativeness of the cases
  - a) consecutive or obviously representative series of cases \*
  - b) potential for selection biases or not stated
- 3) Selection of Controls
  - a) community controls \*
  - b) hospital controls
  - c) no description
- 4) Definition of Controls
  - a) no history of disease (endpoint) \*
  - b) no description of source

#### **Comparability**

- 1) Comparability of cases and controls on the basis of the design or analysis
  - a) study controls for \_\_\_\_\_ (Select the most important factor.) \*
  - b) study controls for any additional factor \* (This criteria could be modified to indicate specific control for a second important factor.)

#### **Exposure**

- 1) Ascertainment of exposure
  - a) secure record (eg surgical records) \*
  - b) structured interview where blind to case/control status \*
  - c) interview not blinded to case/control status
  - d) written self report or medical record only
  - e) no description
- 2) Same method of ascertainment for cases and controls
  - a) yes \*
  - b) no
- 3) Non-Response rate
  - a) same rate for both groups \*
  - b) non respondents described
  - c) rate different and no designation

## NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

### Selection

- 1) Representativeness of the exposed cohort
  - a) truly representative of the average \_\_\_\_\_ (describe) in the community \*
  - b) somewhat representative of the average \_\_\_\_\_ in the community \*
  - c) selected group of users eg nurses, volunteers
  - d) no description of the derivation of the cohort
- 2) 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
- 3) Ascertainment of exposure
  - a) secure record (eg surgical records) \*
  - b) structured interview \*
  - c) written self report
  - d) no description
- 4) Demonstration that outcome of interest was not present at start of study
  - a) yes \*
  - b) no

### Comparability

- 1) Comparability of cohorts on the basis of the design or analysis
  - a) study controls for \_\_\_\_\_ (select the most important factor) \*
  - b) study controls for any additional factor \* (This criteria could be modified to indicate specific control for a second important factor.)

### Outcome

- 1) Assessment of outcome
  - a) independent blind assessment \*
  - b) record linkage \*
  - c) self report
  - d) no description
- 2) Was follow-up long enough for outcomes to occur
  - a) yes (select an adequate follow up period for outcome of interest) \*
  - b) no
- 3) Adequacy of follow up of cohorts
  - a) complete follow up - all subjects accounted for \*
  - b) subjects lost to follow up unlikely to introduce bias - small number lost - > \_\_\_\_ % (select an adequate %) follow up, or description provided of those lost) \*
  - c) follow up rate < \_\_\_\_ % (select an adequate %) and no description of those lost
  - d) no statement

### APPENDIX 3: Tool for evaluating the methodological quality of case reports and case series

Domains	Leading explanatory questions
Selection	1. Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?
Ascertainment	2. Was the exposure adequately ascertained? 3. Was the outcome adequately ascertained?
Causality	4. Were other alternative causes that may explain the observation ruled out? 5. Was there a challenge/rechallenge phenomenon? 6. Was there a dose-response effect? 7. Was follow-up long enough for outcomes to occur?
Reporting	8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

- Questions 4, 5 and 6 are mostly relevant to cases of adverse drug events.

#### Methodological quality and synthesis of case series and case reports

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Author	Yes	No	Na	Tool caser OR Observational
ALZAMORA	1,2,3,8		4,5,6,7	CR
CUIFANG	1,2,3,8		4,5,6,7	CS
DEHAN LUI	1,2,3,8		4,5,6,7	CS
KAMALI ADHDAN	1-3,8		4,5,6,7	CR
LINGKONG	1-3,8		4-7	CR
MI SEON	1-3,8		4-7	CR
MUNOUZ	1-3,8		4-7	CR
PENG Z	1-3,8		4-7	CR
PU YANG	1-3,8		4-7	CS
SHAOSHUAI WANG	1-3,8		4-7	CS
SIYU CHEN	1-3,8		4-7	CS
XIALI XIONG	1-3,8		4-7	CR
YAN CHEN	1-3,8		4-7	CS
Xiaolin	1-3, 8		4-7	CS
Alonso	1-3,8		4-7	CR
Igbal	1-3,8		4-7	CR
Khan	1-3,8		4-7	CS
Belinda	1-3, 8		4-7	CR
Zamaniyan	1-3,8		4-7	CR
Lu D	1-3,8		4-7	CR
Sun	1-3,8		4-7	CS
Y Wu	1-3,8		4-7	CS
Piersigilli	1-3,8		4-7	CR

Xiaotong Wang	1-3,8		4-7	CR
Zhi Jiang Zhang	1-3,8		4-7	CS
Zeng H	1-3,8		4-7	CS
Dong Lan	1-3,8		4-7	CR
Buonsenso	1-3,8		4-7	CS
Eun-Kyung Lee	1-3,8		4-7	CR
Fatemeh Eghbalian	1-3,8		4-7	CR
Gregorio-Hernández	1-3,8		4-7	CS
Serafina Perrone	1-3,8		4-7	CR
Mahdavi	1-3,8		4-7	CR
Rishi Lumba	1-3,8		4-7	CR
Rocio	1-3,8		4-7	CR
Salik	1-3,8		4-7	CR
Soumeth	1-3,8		4-7	CR
Ying Xiong	1-3,8		4-7	CR

CS:Case series, CR: Case report

APPENDIX 4

**Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies**

Criteria	No of articles		
	Yes	No	Other(CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	10		
2. Was the study population clearly specified and defined?	10		
3. Was the participation rate of eligible persons at least 50%?	10		
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	10		
5. Was a sample size justification, power description, or variance and effect estimates provided?			10
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			10
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			10
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			10
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	7		3
10. Was the exposure(s) assessed more than once over time?			10
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	7		3
12. Were the outcome assessors blinded to the exposure status of participants?			10
13. Was loss to follow-up after baseline 20% or less?			10
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship			10

\*CD, cannot determine; NA, not applicable; NR, not reported