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COVID-19 during pregnancy and risk of pregnancy loss (miscarriage or stillbirth): a systematic review protocol

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ABSTRACT

Introduction The COVID-19 pandemic has led to concerns about potential adverse pregnancy outcomes associated with infection, resulting in intensive research. Numerous studies have attempted to examine whether COVID-19 is associated with an increased risk of pregnancy loss. However, studies and reviews to date have drawn differing conclusions. The aim of this systematic review is to provide a summary of all quantitative research on the relationship between pregnancy loss and COVID-19 infection and, if appropriate, to synthesise the evidence into an overall effect estimate.

Methods and analysis Three publication databases (Embase, PubMed and Cochrane) and four preprint databases (medRxiv, Lancet Preprint, Gates Open Research and Wellcome Open Research) will be searched. Boolean logic will be used to combine terms associated with pregnancy loss and COVID-19. The population of interest are pregnant women. Retrieved results will be assessed in two phases: (1) abstract screening and (2) full text evaluation. All studies which compare pregnancy loss outcomes in women who had COVID-19 versus those who did not quantitatively will be included. Narrative and non-English studies will be excluded. Two reviewers will screen independently, with results compared and discrepancies resolved by the study team. Study quality and risk of bias will be assessed using a quality appraisal tool. Results will be summarised descriptively and where possible synthesised in a meta-analysis.

Ethics and dissemination This systematic review requires no ethical approval. This review will be published in a peer-reviewed journal and provide an important update in a rapidly evolving field of research.

PROSPERO registration number CRD42022327437.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review will include both published and preprint studies in an attempt to capture the very latest data and minimise publication bias.
⇒ Study selection, data extraction and quality assessment will be performed independently by two researchers, which will ensure that all relevant studies are included without personal biases.
⇒ All included studies will be assessed for quality using the National Institute for Health and Care Excellence quality appraisal checklist for quantitative studies reporting correlations and associations.
⇒ Studies which are not published in English will not be included. This limitation may cause language bias.

BACKGROUND

SARS-CoV-2 emerged as a new coronavirus at the end of 2019 spreading rapidly to cause a global pandemic of its associated illness COVID-19. Many millions of people around the world have been infected with the virus including pregnant women. However, due to the novelty of COVID-19 little is known about its potential effect on the unborn fetus and pregnancy outcomes. Aetiological hypotheses have been proposed as to ways in which COVID-19 may adversely affect pregnancy outcomes including potential increased risk of loss mediated by placental damage.[1] COVID-19 in pregnancy has therefore been the subject of intense research and there have been numerous studies which have examined any potential adverse effect leading to reviews which have attempted to summarise the evidence.[2–4]

As both the virus itself and our knowledge of its effects are constantly evolving both studies and reviews to date have drawn differing conclusions. Some have concluded an increased risk of pregnancy loss associated with COVID-19 infection[2 5–9] while others have concluded no increased risk.[10–13] Many early reviews of this question included only case reports as no comparative studies were available.[4 14–16] The latest published systematic review on this question by Pathirathna *et al* included studies published prior to June 2021 just over 1 year into the COVID-19 pandemic and like all reviews to date on this topic they noted the need for further research.[8] Since this review, there have been numerous additional studies published and there has been a global roll-out of vaccinations for COVID-19 to pregnant women. It is therefore important that we continue to review all emerging evidence in order to provide a full and current picture of any potential adverse risk.

Table 1 Inclusion and exclusion criteria

Inclusion	Exclusion
► Epidemiological studies which attempt to quantitatively assess any association between pregnancy loss and COVID-19. (Study designs may include prospective and retrospective cohort studies, case–control studies and cross-sectional studies.)	► Non-English language publications including those where the summary is in English but not the full text. ► Narrative review articles, guidelines, editorials or comments. ► Studies without a control or comparison group, for example, case reports. ► Conference presentations.

The overall aim of this study is to identify and summarise all studies to date which have quantitatively compared pregnancy loss outcomes in women who contracted COVID-19 while pregnant versus those who did not. Where possible, quantitative estimates of associations between COVID-19 and pregnancy loss will be synthesised into an overall effect estimate.

METHODS

Study registration

This protocol is prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement (online supplemental appendix 1).[17] This protocol is registered on the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42022327437).

Eligibility criteria

The review will include all studies which have attempted to quantitatively assess the potential association between having COVID-19 during pregnancy and pregnancy loss.

The population of interest are pregnant women at any maternal age or gestation of pregnancy. The exposure of interest will be COVID-19 during pregnancy. We will include all studies which attempt to ascertain COVID-19 exposure in pregnancy regardless of the method of diagnosis. The comparator population will be women who did not have COVID-19 during pregnancy. The outcome of interest will be pregnancy loss (miscarriage or stillbirth).

Table 1 gives the inclusion and exclusion criteria that will be applied to identified studies.

Information sources

Publication databases to be searched: Embase (Ovid), PubMed, Cochrane.

Table 2 Database search strategy

Database	Dates of search coverage	Miscarriage/stillbirth	COVID-19
PubMed	1 March 2020 to current date	'Abortion, Spontaneous' [MeSH] OR 'Fetal Death' [MeSH] OR 'Stillbirth' [MeSH] OR (miscarriage [MeSH Terms])) OR (miscarriages [MeSH Terms] OR Miscarriage* OR pregnancy loss* OR spontaneous abortion* OR fetal loss* OR foetal loss* OR foetal death* OR fetal death*	'coronavirus' [MeSH] OR 'coronavirus infections' [MeSH Terms] OR 'coronavirus' [All Fields] OR 'covid 2019' [All Fields] OR 'SARS2' [All Fields] OR 'SARS-CoV-2' [All Fields] OR 'SARS-CoV-19' [All Fields] OR 'severe acute respiratory syndrome coronavirus 2' [supplementary concept] OR 'coronavirus infection' [All Fields] OR 'severe acute respiratory pneumonia outbreak' [All Fields] OR 'novel cov' [All Fields] OR '2019ncov' [All Fields] OR 'sars cov2' [All Fields] OR 'cov22' [All Fields] OR 'ncov' [All Fields] OR 'covid19' [All Fields] OR 'covid 19' [All Fields] OR 'covid-19' [All Fields] OR 'coronaviridae' [All Fields] OR 'corona virus' [All Fields]
Embase	1 March 2020 to current date	spontaneous abortion/exp OR stillbirth/exp OR stillbirth.m.p OR pregnancy loss/exp OR pregnancy loss.mp OR foetal death.m.p OR fetus death OR fetus death/exp NOT [medline]/lim	'coronavirinae'/exp OR 'coronavirinae' OR 'coronaviridae infection'/exp OR 'coronaviridae infection' OR 'coronavirus disease 2019'/exp OR 'coronavirus'/exp OR coronavirus OR 'coronavirus infection'/de NOT [medline]/lim
Cochrane	1 March 2020 to current date	Search for 'stillbirth' OR 'miscarriage' OR 'foetal death rates' OR 'foetal death rate' OR 'fetal death' OR 'fetal death rate' OR 'pregnancy loss rate' OR 'pregnancy loss-rate' OR pregnancy 'loss-rates'	Search for 'coronavirus' in the Title Abstract Keyword fields

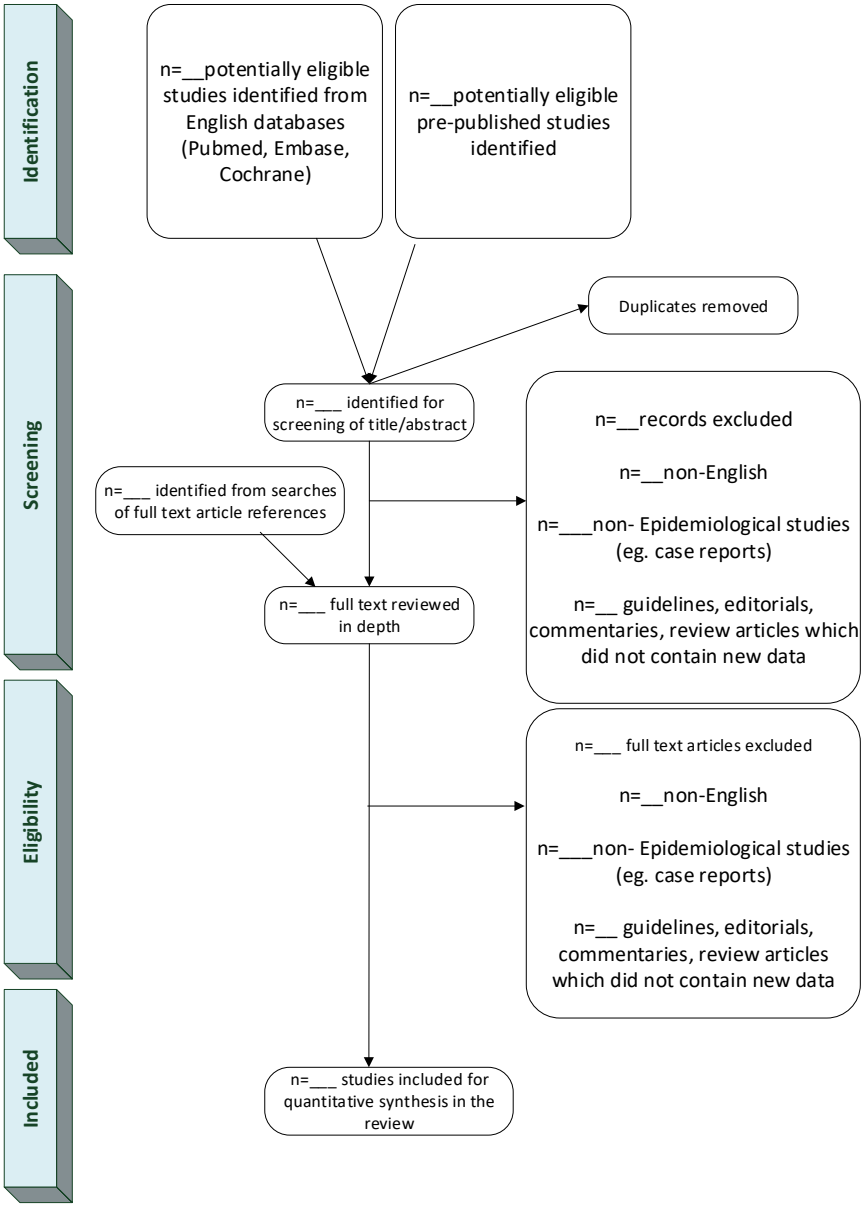

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of study selection process.

Preprint platforms to be searched: medRxiv, Lancet Preprint, Gates Open Research, Wellcome Open Research.

Search strategy

Search terms listed in table 2 will be applied in the respective databases. Terms related to pregnancy loss will be combined with terms related to COVID-19 using AND logic. Only publications after 1 March 2020 will be searched.

To further increase the sensitivity of our search, the list of references from review articles relating to COVID-19 and pregnancy loss will be screened manually to identify other potentially eligible articles.

Due to the fast-moving nature of COVID-19 research we will also search databases of preprint articles.[18] The medRxiv database will be searched via Embase using the search terms detailed above. The Lancet Preprint database will be searched for Obstetrics and Gynaecology articles which contain the term 'Covid-19'. Gates Open Research and Wellcome Open Research will also be searched for 'Covid-19' and 'Pregnancy'. Preprint databases were selected from a systematic examination of preprint platforms by Kirkham *et al*.[19] Preprint articles will be flagged as such in any presentation of results.

Data management and selection process

Searches will be performed across all databases by reviewer 1. Records of the search terms, results from the search and the date of last run will be saved. Results will be exported into Mendeley where any duplicate results will be removed.[20] Each article will be given a study ID. The remaining articles will be screened for eligibility based on titles and abstracts by two independent reviewers applying the inclusion/exclusion criteria described

Table 3 Example of data collection form

Study ID	First author, year	Study design	Location	Exposure definition	Outcome definition	Subjects (n)	Exposed (n)	Miscarriage among the exposed (n)	Stillbirth among the exposed (n)	Miscarriage among the unexposed (n)	Stillbirth among the unexposed (n)	Statistical measure and result reported in the paper	Was the study before or after vaccine roll-out?
-													

above. Discrepancies will be discussed and, where necessary, will be decided by the whole study team. Full text articles will be obtained for all articles deemed eligible for inclusion from the initial screening. Articles will be divided and assessed independently by two reviewers after which the final selection will be agreed. Any reasons for exclusion will be recorded. The study selection process is outlined in figure 1.

Data collection process

The example data capture form (table 3) will be pilot tested on a random sample of five included studies and revised if necessary. The finalised data capture form will then be completed by reviewers 1 and 2 independently for a sample of 10 studies to check concordance, after which each study will be examined by one reviewer.

Assessment of study quality

All included studies will be assessed for bias by reviewers using an adapted version of the National Institute for Health and Care Excellence (NICE) quality appraisal checklist for quantitative studies reporting correlations and associations (online supplemental appendix 2).[21] The NICE tool was chosen as it is designed for identifying rigour in observational studies that explore and generate hypotheses about causal relationships and can be used for multiple study designs. The NICE tool consists of five major items: study population and participants; selection and methods; outcomes; analysis; and summary.

Appraisal will be done using an Excel format to allow for easy compilation of responses. Decisions will be discussed and any discrepancies resolved. Each study will then be awarded an overall study quality grade for external and internal validity from one of the three categories below which are based on the checklist criteria (online supplemental appendix 1).

- ++All or most of the checklist criteria have been fulfilled, where they have not been fulfilled the conclusions are very unlikely to alter.
- +Some of the checklist criteria have been fulfilled, where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter.
- – Few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

Studies deemed to be low quality (category) will be excluded from any meta-analysis.

Data synthesis

We will use Higgins and Thompson's I^2 statistic to quantify heterogeneity, and if I^2 is >50% meta-analysis will be conducted in Stata using a random-effects model.[22] Where meta-analysis is attempted funnel plots will be used to assess publication bias.[23] Where statistical pooling is not possible, findings will be presented in narrative form using tables to aid in data presentation. If possible, we will conduct subgroup analyses of studies reporting miscarriage and stillbirth separately. We will also look at any potential impact of the widespread use of COVID-19 vaccines by grouping studies into those conducted before and after vaccine roll-out if possible. We will use 1 March 2021 as the cut-off date for studies considered to be post-vaccine roll-out. For studies after this date we will examine the national vaccine roll-out programme for the country in which the study was conducted to assess the likelihood that pregnant women within the study would have been vaccinated. We will also consider a subgroup analysis of hospitalised versus non-hospitalised COVID-19 cases if there are enough studies which consider this.

Patient and public involvement

There will be no patient or public involvement in this project.

DISCUSSION

The COVID-19 pandemic has been a challenging time for pregnant women, knowledge on the potential risks of infection to them and their unborn babies is ever evolving. With COVID-19 now circulating widely in many countries and limited risk reduction measures in place it is important to try and fully understand the risks so that pregnant women can be advised appropriately. Reviews and studies to date on whether COVID-19 increases the risk of pregnancy loss have drawn mixed conclusions.[2–4 8 13] COVID-19 research is a fast-moving area; therefore, it is important that reviews are regularly updated. This systematic review aims to provide a comprehensive overview of the latest evidence.

COVID-19 research moves very quickly, and preprint literature has become a key outlet for new research with many researchers opting to make their work available as quickly as possible. Including prepublications in this review, something which previous reviews have not done, will allow us to obtain as current a picture as possible of all

of the evidence. Inclusion of preprint literature may also help mitigate any risk of publication bias.

Vaccination against COVID-19 became widely available globally in 2021.[24] In the UK, pregnant women have been routinely advised to receive COVID-19 vaccination together with the rest of the population, according to their age and underlying health conditions since 16 April 2021.[25] The widespread introduction of COVID-19 vaccination may have led to a decrease in potential risk or pregnancy loss. We hope to identify enough studies to allow us to examine separately those which were conducted before and after the vaccination roll-out in order to provide an insight into any impact the vaccine may have had.

The results of this review can be used to inform public health messaging for pregnant women around the potential risks of COVID-19 infection. This research will also help inform any future research studies planned on this question.

Contributors This protocol was written by JC with KB, RW and MH performing critical review. JC will act as the guarantor of the review.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix 1: Prisma-P checklist

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix 2: NICE Quality appraisal checklist for quantitative studies reporting correlations and associations

Checklist items are worded so that 1 of 5 responses is possible: ++ Indicates that for that particular aspect of study design, the study has been designed or conducted in such a way as to minimise the risk of bias. + Indicates that either the answer to the checklist question is not clear from the way the study is reported, or that the study may not have addressed all potential sources of bias for that particular aspect of study design. − Should be reserved for those aspects of the study design in which significant sources of bias may persist. Not reported (NR) Should be reserved for those aspects in which the study under review fails to report how they have (or might have) been considered. Not applicable (NA) Should be reserved for those study design aspects that are not applicable given the study design under review (for example, allocation concealment would not be applicable for case–control studies).

Study identification: Include full citation details		
Study design: • Refer to the glossary of study designs (appendix D) and the algorithm for classifying experimental and observational study designs (appendix E) to best describe the paper's underpinning study design		
Assessed by:		
Section 1: Population		
1.1 Is the source population or source area well described?	++	Comments:

• Was the country (e.g. developed or non-developed, type of health care system), setting (primary schools, community centres etc), location (urban, rural), population demographics etc adequately described?	+ – NR NA	
1.2 Is the eligible population or area representative of the source population or area? • Was the recruitment of individuals, clusters or areas well defined (e.g. advertisement, birth register)? • Was the eligible population representative of the source? Were important groups underrepresented?	++ + – NR NA	Comments:
1.3 Do the selected participants or areas represent the eligible population or area? • Was the method of selection of participants from the eligible population well described? • What % of selected individuals or clusters agreed to participate? Were there any sources of bias?	++ + – NR NA	Comments:

• Were the inclusion or exclusion criteria explicit and appropriate?		
Section 2: Method of selection of exposure (or comparison) group		
2.1 Selection of exposure (and comparison) group. How was selection bias minimised? • How was selection bias minimised?	++ + – NR NA	Comments:
2.2 Was the selection of explanatory variables based on a sound theoretical basis? • How sound was the theoretical basis for selecting the explanatory variables?	++ + – NR NA	Comments:
2.3 How well were likely confounding factors identified and controlled?	++	Comments:

• Were there likely to be other confounding factors not considered or appropriately adjusted for? • Was this sufficient to cause important bias?	+ − NR NA	
2.4 Is the setting applicable to the UK? • Did the setting differ significantly from the UK?	++ + − NR NA	Comments:
Section 3: Outcomes		
3.1 Were the outcome measures and procedures reliable? • Were outcome measures subjective or objective (e.g. biochemically validated nicotine levels ++ vs self-reported smoking −)?	++ + −	Comments:

• How reliable were outcome measures (e.g. inter- or intra-rater reliability scores)? • Was there any indication that measures had been validated (e.g. validated against a gold standard measure or assessed for content validity)?	NR NA	
3.2 Were the outcome measurements complete? • Were all or most of the study participants who met the defined study outcome definitions likely to have been identified?	++ + – NR NA	Comments:
3.3 Were all the important outcomes assessed? • Were all the important benefits and harms assessed? • Was it possible to determine the overall balance of benefits and harms of the intervention versus comparison?	++ + − NR NA	Comments:

3.4 Was there a similar follow-up time in exposure and comparison groups? • If groups are followed for different lengths of time, then more events are likely to occur in the group followed-up for longer distorting the comparison. • Analyses can be adjusted to allow for differences in length of follow-up (e.g. using person-years).	++ + − NR NA	Comments:
3.5 Was follow-up time meaningful? • Was follow-up long enough to assess long-term benefits and harms? • Was it too long, e.g. participants lost to follow-up?	++ + − NR NA	Comments:
Section 4: Analyses		
4.1 Was the study sufficiently powered to detect an intervention effect (if one exists)?	++ +	Comments:

• A power of 0.8 (i.e. it is likely to see an effect of a given size if one exists, 80% of the time) is the conventionally accepted standard. • Is a power calculation presented? If not, what is the expected effect size? Is the sample size adequate?	− NR NA	
4.2 Were multiple explanatory variables considered in the analyses? • Were there sufficient explanatory variables considered in the analysis?	++ + − NR NA	Comments:
4.3 Were the analytical methods appropriate? • Were important differences in follow-up time and likely confounders adjusted for?	++ + − NR NA	Comments:

4.6 Was the precision of association given or calculable? Is association meaningful? • Were confidence intervals or p values for effect estimates given or possible to calculate? • Were CIs wide or were they sufficiently precise to aid decision-making? If precision is lacking, is this because the study is under-powered?	++ + – NR NA	Comments:
Section 5: Summary		
5.1 Are the study results internally valid (i.e. unbiased)? • How well did the study minimise sources of bias (i.e. adjusting for potential confounders)? • Were there significant flaws in the study design?	++ + –	Comments:
5.2 Are the findings generalisable to the source population (i.e. externally valid)? • Are there sufficient details given about the study to determine if the findings are generalisable to the source population?	++ + –	Comments:

• Consider: participants, interventions and comparisons, outcomes, resource and policy implications.		