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The Collaborative IPD of Sleep and Stillbirth (Cribss) - an Individual Participant Data Meta-Analysis study protocol

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ABSTRACT

Introduction: Accumulating evidence has shown an association between maternal supine going-to-sleep position and stillbirth in late pregnancy. Advising women not to go to sleep on their back can potentially reduce late stillbirth rate by 9%. However, the association between maternal right-sided going-to-sleep position and stillbirth is inconsistent across studies. Furthermore, individual studies are underpowered to investigate interactions between maternal going-to-sleep position and fetal vulnerability, which is potentially important for producing clear and tailored public health messages on safe going-to-sleep position. We will use individual participant data (IPD) from existing studies to assess whether right-side and supine going-to-sleep positions are independent risk factors for late stillbirth and test the interaction between going-to-sleep position and fetal vulnerability.

Methods and Analysis: An IPD meta-analysis approach will be utilised using the Cochrane Collaboration-endorsed methodology. We will identify case-control and prospective cohort studies and randomised trials which collected maternal going-to-sleep position data and pregnancy outcome data that included stillbirth. The primary outcome is stillbirth. A one stage procedure meta-analysis, stratified by study with adjustment of a priori confounders will be carried out.

Ethics and dissemination: The IPD meta-analysis has obtained central ethics approval from the New Zealand Health and Disability Ethics Committee, ref: NTX/06/05/054/AM06. Individual studies should also have ethical approval from relevant local ethics committees. Interpretation of the results will be discussed with consumer representatives. Results of the study will be published in peer-reviewed journals and presented at international conferences.

Systematic review registration: PROSPERO registration number: CRD42017047703

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Late stillbirth is a rare event in high-income countries, and individual participant data meta-analysis of several studies can yield a sufficiently large sample size for exploring interactions and subgroup analysis that are difficult to undertake within a single study.

- There is no restriction on language or countries where the study was conducted, therefore the results from this study are likely to be generalisable.
- It is the first IPD meta-analysis examining the association between maternal going-to-sleep position in late pregnancy and the risk of stillbirth, and the potential interactions with other stillbirth risk factors. The results from this study are likely to contribute important messages for a public health intervention.
- Service users will oversee the conduct of the study. Their involvement will help to design appropriate research questions and will help the implementation and translation of the research outcomes.
- One limitation of the study is that the maternal going-to-sleep positions are likely to be self-reported.

INTRODUCTION

Stillbirth, the death of a baby before birth, is a major global burden affecting more than 2.6 million families per year [1]. In high-income countries, the rate of late stillbirth (28 weeks or greater) varies widely from 1.3 to 8.8 per 1,000 births [2] and is approximately twice as common as neonatal death [3]. Importantly, the annual rate of reduction for neonatal death is twice that of stillbirth [2]. The variations between countries suggest it is possible to further reduce late stillbirth. Importantly, maternal characteristics present in early pregnancy only explain a small amount of the risk for late stillbirth [4]. Therefore, significant reductions in late stillbirth require identification of additional maternal risk factors amenable to modification during pregnancy [5].

Accumulating evidence suggests that supine going-to-sleep position may be a modifiable risk factor for stillbirth in late pregnancy. Stacey *et al.* first reported an association between going-to-sleep position and late stillbirth, with women who did not go-to-sleep on their left side, the night before the baby was suspected to have died, having an increased odds of stillbirth [6]. Among non-left sided sleepers, the odds were greater in women who went to sleep supine; and there was also a borderline increase in odds in women who went to sleep on their right side [6]. Similar associations between supine going-to-sleep position and late stillbirth have since been reported by several studies [7-9]. In addition to the epidemiologic evidence, a number of physiological studies have suggested that the relationship between supine going-to-sleep position and late stillbirth is biologically plausible. Significant hemodynamic changes in maternal and fetal circulation have been observed in relation to maternal position in late pregnancy, with decreased maternal cardiac output and uterine blood flow [10], and pulsatility index in the fetal middle cerebral artery (a surrogate for fetal hypoxia) [11] seen in maternal supine position when compared to left position. A recent study by Stone *et al*. has shown that when the mother is in the supine position, the fetus spends more time in behavioural state 1 (fetal quiescence) and less time in active fetal behavioural state 4, compared to when the mother is on her left side, indicating supine

position may be a mild hypoxic stressor [12]. It was hypothesised that these physiological changes associated with supine position are related to the direct compression of the inferior vena cava by the gravid uterus [13]. Furthermore, supine sleep position is also associated with sleep disturbed breathing and obstructive sleep apnoea [14], which have also been associated with pregnancy complications such as pre-eclampsia, fetal growth restriction [15], and gestational diabetes [15, 16]. These pregnancy complications are known risk factors for stillbirth [17], and might represent another mechanism that contributes to the association between supine going-to-sleep position and late stillbirth.

The findings from the epidemiological studies combined with the supportive physiological evidence suggest that the association between supine sleep position and late stillbirth is likely to be causal. Informing pregnant women and their healthcare providers about optimal going-to-sleep position in late pregnancy is a strategy that may reduce stillbirth and is potentially harmless. Therefore, there is an urgent need to assess the accumulated evidence to develop a public health campaign. However, there are some unanswered questions that are critical for developing clear public health messages. Firstly, it is unclear whether right sided going-to-sleep position is a risk factor for late stillbirth. A borderline increase in risk was reported with right side compared to left side going-to-sleep position in the Stacey *et al.* study. However, this association was not found in other studies [7, 9]. The inconsistent finding of right side going-to-sleep position warrants further clarification so that clear advice about whether women should be advised to go-to-sleep on either side or only on their left side can be developed. Secondly, there is no evidence whether there are groups of women who are at elevated risk when they go-to-sleep in a suboptimal position (such as those who smoke, are overweight or have small babies etc.) and how other stillbirth risk factors interact with sleep position. Stillbirth is the end point of diverse pathological processes. Multiple risk factors and pathological events can contribute at different time points and cumulatively lead to the final event. Our research group has hypothesised a triple-risk framework for late stillbirth that cannot be explained by one risk factor or condition alone [18]. We speculate

that three groups of factors namely maternal factors (eg, obesity, smoking), fetal and placental factors (eg, a small for gestational age (SGA) fetus) and an additional stressor(s) (eg, reduced uterine blood flow associated with supine position) in themselves may be insufficient to cause the death, but their combination may have a lethal effect [18]. Individual stillbirth case control studies published to date have insufficient power to explore fully the interactions between supine going-to-sleep position, markers of fetal vulnerability and adverse maternal factors. Furthermore, it is important to explore other factors that may also be associated with supine sleep position such as SGA, reduced fetal movements and sleep disturbed breathing, as this may provide insights into the potential mechanism of risk associated with the supine position.

The Collaborative IPD Sleep and Stillbirth (Cribss) group was established in December 2016. We aim to synthesise the current evidence about going-to-sleep position and stillbirth risk. Additionally we will address the above unanswered questions by combining and analysing the individual participant data from all available studies in an individual participant data (IPD) meta-analysis. IPD meta-analysis is considered the gold standard approach to evidence synthesis as it has the potential to improve the precision and reliability of the results obtained from individual studies [19]. In contrast to the traditional approach of meta-analysis, which extracts summary (aggregate) data from study publications, an IPD meta-analysis uses line-by-line original data sourced directly from the researchers responsible for the relevant studies. An IPD meta-analysis involves the central collection, checking, harmonisation and re-analysis of the original data of all eligible participants from each of the available studies. With proper quality assessment and standardisation processes, an IPD meta-analysis can model complex relationships, which traditional meta-analyses are not able to do [20]. It is particularly useful in evaluating multi-factorial frameworks by evaluating critical outcome determinants and their interactions.

OBJECTIVES

The main questions to be addressed by the Cribss IPD meta-analysis are:

1. Is maternal going-to-sleep position associated with late stillbirth?
2. Are indicators of fetal vulnerability, including: maternal obesity, SGA, maternal smoking, maternal second-hand tobacco exposure, substance use, alcohol consumption, maternal medical conditions (including pre-existing hypertension and diabetes), and maternal perception of fetal movements associated with late stillbirth?
3. Does maternal going-to-sleep position interact with indicators of fetal vulnerability to influence the risk of late stillbirth?

Secondary questions to be addressed by the first cycle of Cribss IPD meta-analysis are:

1. Is sleep disturbed breathing associated with late stillbirth? Is (are) going-to-sleep position(s) associated with greater risk of late stillbirth in women with sleep disturbed breathing?
2. Are factors that may influence vena caval compression (eg, long sleep duration, sleeping during the day, restless legs,) associated with risk of late stillbirth? Do these factors interact with going-to-sleep position?
3. Do women who report they received advice about sleep position have lower risk of late stillbirth compared with women who did not receive such advice?
4. Do women who report they received advice about awareness of fetal movements have a lower risk of late stillbirth than women who did not receive such advice?

METHODS AND ANALYSIS

This study will apply an IPD meta-analysis approach, and will follow the methodology endorsed by the Cochrane Collaboration where applicable [21, 22]. We will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) IPD statement for reporting findings. The study will be conducted by the Collaborative IPD Sleep and Stillbirth (Cribss) group which comprises the participating study investigators, an IPD expert, and consumer representatives. The coordination centre is located in the department

of Obstetrics and Gynaecology at the University of Auckland, Auckland, New Zealand. We have registered the IPD Study with the PROSPERO international prospective register of systematic reviews (CRD42017047703).

Eligibility criteria

Study inclusion criteria (regardless of whether the study is published or unpublished):

1. Case-control and prospective cohort studies which collected:
    - Maternal going-to-sleep position during pregnancy and
    - Pregnancy outcome that included stillbirth and
    - Aimed to recruit controls with an on-going pregnancy at similar gestation to the cases
2. Randomised controlled trials which collected:
    - Maternal going-to-sleep position during pregnancy and
    - Pregnancy outcome data that included stillbirth and
    - Did not test an intervention that might have an impact on going-to-sleep position

Participant level exclusion criteria:

- Multiple pregnancy in the third trimester
- Major congenital abnormality at study entry or major congenital abnormality as a cause of death found post study entry or post-randomisation in randomised controlled trials
- Gestation less than 28 weeks when last sleep position data during pregnancy was collected
- Termination of pregnancy at greater than or equal to 28 weeks

Information sources and search strategy

We will develop the search strategy according to the Cochrane Collaboration guidelines prior to the initial literature search. A search of the databases: MEDLINE, EMBASE, LILACS, Web of Science, OpenGrey, and Google Scholar, will be conducted, for the purpose of locating

published research about an association between maternal sleep position and late pregnancy stillbirth. We will also access the WHO International Clinical Trials Registry Platform to identify any ongoing and registered trials. Proceedings from International Stillbirth Alliance (ISA) annual conferences and The International Society for the Study and Prevention of Perinatal and Infant Death (ISPID) international conferences. Published perinatal conference abstracts will also be identified through the above database searches. Experts in the field and the collaborative group will be asked about their knowledge of any unpublished studies. To increase the likelihood of identifying all relevant studies, the reference lists of all retrieved articles will be hand searched. No language restriction will be applied.

Four search terms will be used to search the databases with the article title, abstracts and body all searched. The search terms are: 'stillbirth', 'fetal death', 'perinatal death' and 'sleep' and synonyms. The search terms will be tested to check that they effectively located the types of articles that are consistent with the inclusion criteria prior to conducting the search in all engines. An example of a detailed MEDLINE search strategy is presented in supplementary appendix 1.

Selection process

Study eligibility will be assessed independently by two members of the Cribss group, any disagreements will be adjudicated by a third member. Eligibility assessment will be based on published protocols, method sections from publications, and unpublished protocols and, or study information requested from potential eligible study investigators. All potential eligible study investigators will be contacted to verify eligibility. Participant level exclusion criteria will be applied during the analysis. The main investigator and/or the corresponding author from any eligible study will be approached via email to participate in the Cribss IPD meta-analysis study. If there is no reply, other co-authors of the published manuscript will be subsequently approached.

Data acquisition and data management

The data centre is located in the Department of Obstetrics and Gynaecology at the University of Auckland, New Zealand, who will manage transferring and sharing of data. A detailed data management plan has been reviewed and agreed by all Cribss members.

Each eligible study lead investigator will be asked to provide de-identified individual level participant data for each participant enrolled in their study. Some indirect potential identifiers (eg, age, ethnicity) are essential demographic characteristics, and will be required. A study ID for each participant will be retained as this is essential for data integrity checking and data cleaning. Each study investigator will also be asked to provide metadata (such as questionnaires, data collection forms, data dictionaries) and study-level data to explain the variables, and data on the study representativeness (Table 1).

The anonymised data in a common format (eg, cvs., xls. or other formats that can be converted by the Cribss data centre) will be requested for transfer via the University of Auckland institutional Seafile file syncronisation and share platform or equivalent secure means. The Seafile platform has built-in file encryption. Files are encrypted before syncing to the server. User authentication is needed to access the files [23].

The anonymised dataset from each participating study will be checked for data integrity. This will include: 1) checking data range and outliers, 2) clarifying missing data, 3) identifying invalid values, 4) detecting duplicates, and 5) verifying internal consistency where appropriate. Reports of discrepancies will be generated and sent to each participating study investigator for further verification or correction where necessary.

After appropriate data cleaning, the individual participating study investigators will confirm and sign-off on their own dataset before it is merged into the IPD database. New variables

will be generated following a set of consistent harmonisation rules that will be decided by the Cribss group. An IPD data dictionary will be created to document the details of variables (including variable names, type, explanation, and validation rules) to help other users to understand the dataset.

Data items

We aim to collect the following data items from each participating study (Table 1).

Table 1 Data items will be requested from participating studies

Study level information
1. Study inclusion and exclusion criteria 2. Matching method of cases and controls 3. Time period of recruitment 4. Number of cases and controls 5. Informed consent procedure 6. Study participant representativeness (eg, minimal demographic data comparison between participant and eligible non-participant, or between participants and a relevant comparison of a maternity care population)
Participant level information
A. Maternal characteristics
1. Unique study ID 2. Maternal demographic details including: age, ethnicity 3. Past obstetric history 4. Maternal height 5. Earliest available maternal weight in the study pregnancy 6. Gestation at earliest available weight 7. Last available maternal weight in current pregnancy

8. Gestation at last available weight 9. Study centre (if the study was conducted in more than one centre) 10. Highest completed education level at the time of recruitment 11. Marital status at the time of recruitment 12. Pre-existing medical conditions and medical conditions during the study pregnancy 13. Smoking status before and during the study pregnancy 14. Exposure to second-hand smoke before and during the study pregnancy 15. Alcohol consumption before and during the study pregnancy 17. Recreational drug usage before and during the study pregnancy
B. Maternal sleep practices and fetal movement data in every available time frame
1. Going-to-sleep position 2. Sleep duration 3. Number of times getting up during the night (eg, to go to the toilet) 4. Frequency of daytime napping 5. Bed size 6. Number of people shared bed with 7. Self-reported details of snoring behaviour 8. Insomnia 9. Sleep quality as measured by validated questionnaire 10. Maternal perception of fetal movement 11. Advice received on fetal movement 12. Advice received on sleep position
C. Antenatal care and pregnancy outcomes
1. Gestation (gestation at enrolment for controls, and gestation at diagnosis of stillbirth for cases) 2. Baby sex 3. Baby birthweight

4. Gestation for calculating birthweight centile 5. Birthweight centile per original study standards 6. Type of facility of baby's birth 7. Gestation at earliest ultrasound 8. Blood pressure and gestation at measurement 9. Type of maternity provider 10. Number of antenatal visits in each trimester 11. Ultrasound scans (first trimester scan, anatomy scan and third trimester growth scan(s)) 12. Antenatal vaginal bleeding 13. Hospital admission(s) 14. Use of antibiotics 15. Nutritional supplements 16. Clinical suspicion of fetal growth restriction (FGR) /SGA 17. Management of clinically suspected FGR/SGA 18. Laboratory tests for glucose metabolism (including polycose glucose challenge test, haemoglobin A1c and oral glucose tolerance test), hepatitis B status and blood group and the gestation that the tests were conducted.
D. Stillbirth cases specific data
1. Time of day mother thought the baby died 2. The reason that the mother thought something was wrong with the pregnancy 3. The reason that the mother saw a health practitioner at the diagnosis of stillbirth 4. Maternal decision on postmortem 5. Placental pathology results 6. The Perinatal Society of Australia and New Zealand (PSANZ) coding for classification of cause of stillbirth

Outcome measures

The primary outcome is late stillbirth, using the WHO recommended definition for stillbirth for international comparison: “a baby born with no signs of life at or after 28 weeks' gestation” [24]. Intrapartum stillbirth will be included in the analysis with the rationale that supine going-to-sleep position may result in a vulnerable baby that is unable to tolerate labour.

Risk of bias assessment

Risk of bias for non-randomised studies will be assessed in duplicate and independently by two investigators from the Cribss group, using Risk of Bias In Non-randomized Studies – of Exposure (ROBINS-E) assessment tool [25]. The assessment results will be compared. Any disagreement will be resolved by discussion or by a third reviewer.

Statistical analysis plan

A detailed statistical analysis plan will be prepared by the Cribss data centre group and reviewed, agreed upon and published by the Cribss group prior to the analysis. All going-to-sleep positions will be compared to left sided going-to-sleep position as the reference group. The last available going-to-sleep position during pregnancy (within two weeks before stillbirth in cases) will be harmonised and used for the primary objectives.

An individual participant data (IPD) analysis will be performed. A one stage approach to analysis will be taken so that the individual participant data from all eligible studies are included in a single model. Logistic regression models will be used for the binary outcome (late stillbirth). A fixed study effect and a study site effect will be included in the model specification as strata. Univariable analysis will be performed to evaluate the association between sleep position and late stillbirth risk. The interaction between sleep position and factors indicating a vulnerable pregnancy will be assessed in bi-variable models. A multivariable model will be developed incorporating previously reported confounders and any significant interaction terms, once it has been established what cofounders can be controlled

for consistently across studies. Estimate of risk will be reported as odds ratio and 95% confidence intervals.

If an important confounder is not available for one or more studies, sensitivity analysis will be conducted, with and without these studies, to compare risk estimates. If there are any controls who reported their pregnancy going-to-sleep position after they have given birth, sensitivity analysis will be conducted without these controls. Where sufficient data exist, all analysis will be also conducted in term and preterm subgroups. For missing data in each individual study, no imputation will be carried out. Statistical analyses will be performed using SAS (SAS Institute Inc., Cary NC USA).

ETHICS AND DISSEMINATION

The IPD meta-analysis has obtained central ethics approval from the New Zealand Health and Disability Ethics Committee, ref: NTX/06/05/054/AM06. The participating studies retain the right to withdraw their data from the analysis at any time.

Final IPD results will be presented to the nominated representative from each participating study prior to publication and public dissemination. Interpretation of the results will be discussed with the Cribss consumer representatives. Results of the study will be published in peer-reviewed journals and presented at national and international conferences. For the publications from the main questions, every Cribss member will participate in the manuscript preparation and editing. Authorship will be guided by the recommendations of the International Committee of Medical Journal Editors.

CONCLUSION

Cribss is the first IPD meta-analysis to evaluate the current evidence of the relationship between maternal going-to-sleep position and late stillbirth. The study will allow assessment of important interactions that cannot be tested in standard, aggregate data meta-analysis.

The overall goal of Cribss is to reduce late stillbirth by developing high quality data based evidence- to inform public health messages about optimal late pregnancy sleep practices. This IPD meta-analysis may identify sub-groups of women at greater risk (such as those with known SGA fetuses, who continue to smoke during pregnancy or are overweight) and thus develop evidence that can be used to tailor public health messages.

AUTHORS' CONTRIBUTION: ML, JMDT, RSC, AG, CRG, AEPH, TS, EAM, LMEM, LA conceptualised the study. ML, JMDT, RSC, AG, CRG, AEPH, TS, VC, VB, EAM, LMEM, LA have participated in study design and funding application. ML drafted the manuscript. RSC drafted appendix1. LA, JMDT, RSC, AG, CRG, AEPH, TS, EAM, LMEM, critically revised the manuscript. ML, JMDT, RSC, AG, CRG, AEPH, TS, VC, VB, EAM, LMEM, LA have read and approved submission of the final manuscript. LMEM is the guarantor of the review.

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COMPETING INTERESTS STATEMENT: The authors declare that they have no competing interests.

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Appendix 1:

Search strategy for the Collaborative IPD of Sleep and Stillbirth (Cribss) study

Databases or search engines that will be used

A search of the databases: MEDLINE, EMBASE, LILACS, Web of Science, OpenGrey, and Google Scholar, will be conducted, for the purpose of locating published research about an association between maternal sleep position and late pregnancy stillbirth. We will also access WHO International Clinical Trials Registry Platform to identify any ongoing and registered trials. Proceedings from International Stillbirth Alliance (ISA) annual conferences and The International Society for the Study and Prevention of Perinatal and Infant Death (ISPID) international conferences will be manually searched. Published perinatal conference abstracts will be identified through the above database searches. Experts in the field and the collaborative group will be asked for their knowledge of any unpublished studies.

Limits applied

To increase the likelihood of identifying all relevant studies, the reference lists of all retrieved articles will be hand searched. No language restriction will be applied.

List the search terms used

Three search terms will be used to search the databases with the article title, abstracts and body all searched. The search terms are:

- stillbirth
- fetal death
- sleep

and synonyms. The search terms will be tested to check that they effectively located the types of articles that are consistent with the inclusion criteria prior to conducting the search in all engines.

Document the search process

The following search was conducted sequentially using the search terms in MEDLINE on 20th November 2016.

Search engine		Search terms	# Retrieved:
MEDLINE			
MEDLINE	1	Stillbirth/	3851
MEDLINE	2	(stillbirth* or still-birth* or stillborn* or still-born*).ti,ab,kf.	13691
MEDLINE	3	Fetal Death/	24585
MEDLINE	4	((fetal or foetal or fetus or foetus) adj death*).ti,ab,kf.	8769
MEDLINE	5	((fetal or foetal or fetus or foetus) adj3 (loss or losses)).ti,ab,kf.	4804
MEDLINE	6	Perinatal Death/	860
MEDLINE	7	((perinatal or peri-natal) adj death*).ti,ab,kf.	4007
MEDLINE	8	((prenatal or pre-natal or intrauterine or intra-uterine or antepartum or ante-partum or antenatal or ante-natal) adj death*).ti,ab,kf.	2026
MEDLINE	9	or/1-8	46353
MEDLINE	10	Sleep/	46957
MEDLINE	11	((sleep or sleeping) adj (position* or practice* or posture*)).ti,ab,kf.	1354
MEDLINE	12	maternal sleep*.ti,ab,kf.	139
MEDLINE	13	or/10-12	47711
MEDLINE	14	9 and 13	23

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	Check
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Yes, P1, line 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	na
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes, P3, line 60
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes, P2, line 4-36
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes, P17, line 346-350
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	na
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Yes, P17, line 353
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes, P17, line 353
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes, P17, line 353
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes, P5, line 80-166
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes, P8, line 163
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	Yes, P9, line 195
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	Yes, P9-10, line 214

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	Yes, P9-10, line 214 and appendix 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes, P11, line 247-277
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)	Yes, P10, line 236
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	Yes, P11, line 247-277
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	Yes, line 279-283 (table 1)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes, P14-15, line 284
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	Yes, P15, line 290
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes, P15, line 296
	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)	Yes, P15, line 296
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes, P16, line 315
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	na
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes, P16, line 315
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	na

*** 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.**

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