REVIEW ARTICLE

Stress ulcer prophylaxis in adult intensive care unit patients – a protocol for a systematic review

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Conflict of interests
Marija Barbateskovic: PhD student at the Centre for Research in Intensive Care and Copenhagen Trial Unit. Søren Marker: PhD student at the Centre for Research in Intensive Care and the department of intensive care at Rigshospitalet. Coordinating investigator of the randomized clinical trial 'Stress Ulcer Prophylaxis in the Intensive Care Unit' (SUP-ICU). Janus Christian Jakobsen: Director of Research, Chief Physician, Department of Cardiology, Holbæk Sygehus, Holbæk, Denmark. Mette Krag: Coordinating investigator of SUP-ICU. Anders Granholm: Coordinating investigator of SUP-ICU. Carl Thomas Anthon: Coordinating investigator of SUP-ICU. Anders Perner: Head of Research in the intensive care unit at Rigshospitalet. The intensive care unit receives support for research from CSL Behring, Fresenius Kabi and Ferring Pharmaceuticals. Dr Perner is initiator of SUP-ICU. Jørn Wetterslev: Member of the Copenhagen Trial Unit task force for developing trial sequential analysis theory, manual and software. Dr Wetterslev is member of the SUP-ICU steering group. Morten Hylander Møller: Sponsor and initiator of SUP-ICU.

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Background: In the intensive care unit (ICU), stress ulcer prophylaxis with proton pump inhibitors or histamine-2-receptor antagonists is standard of care although gastrointestinal bleeding remains uncommon. It remains unknown whether its use is associated with benefits or harms and the quality of evidence supporting the use of stress ulcer prophylaxis has been questioned. Accordingly, the objective of this systematic review was to critically assess the evidence from randomized clinical trials on the benefits and harms of stress ulcer prophylaxis vs. placebo or no prophylaxis in adult ICU patients.
Methods: We will systematically search for randomized clinical trials in major international databases. Two authors will independently screen and select trials for inclusion, extract data and assess the methodological quality using the Cochrane risk of bias tool. Any disagreement will be resolved by consensus. We will perform conventional meta-analyses using Review Manager, and STATA 15, and we will assess the risk of random errors using Trial Sequential Analysis. Also, we will assess and report the overall quality of evidence for all outcomes according to GRADE.
Discussion: The evidence on the benefits and harms of stress ulcer prophylaxis in adult ICU patients is unclear and an updated systematic review is warranted as new trials have been published. To control risks of systematic and random errors, we will use Cochrane and GRADE methodology and Trial Sequential Analysis. Our ambition with this systematic review is to provide updated, reliable and precise data to better inform decision makers on the use of stress ulcer prophylaxis in adult ICU patients.

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Background

Description of the condition

Patients admitted to the intensive care unit (ICU) are at risk of stress-related gastrointestinal mucosal damage that may evolve to ulceration and bleeding.[1] Decreased mucosal blood flow, mucosal ischaemia and reperfusion injury may contribute to the pathophysiology, but the exact mechanisms are not completely understood.[2,3] The majority of ICU patients are believed to develop endoscopically visible signs of gastrointestinal ulcerations after 3 days in the ICU.[4,5] Typically, these ulcerations are superficial and asymptomatic and only a small proportion of these ulcerations will progress to overt gastrointestinal bleeding.[6,7] The reported prevalence of gastrointestinal bleeding varies between 2% and 5% and they are associated with an increased risk of death and increased length of stay in the ICU.[7–12] However, the studies showing these associations generally include all conditions resulting in gastrointestinal bleeding and not exclusively stress ulcers and other bleedings prevented by acid suppressants.[13] It has been suggested that less than 50% of patients with gastrointestinal bleeding are entirely caused by stress ulceration.[14]

Several risk factors for developing gastrointestinal bleeding have been suggested, including mechanical ventilation and coagulopathy.[8] In addition, acute and chronic disease severity, hepatic failure and acute kidney injury have been proposed as other important risk factors.[7,11,15]

Description of the intervention

Stress ulcer prophylaxis was introduced in the 1970's to prevent gastrointestinal bleeding. Antacids followed by sucralfate were initially the preferred agents.[16] A randomized clinical trial from 1998 on sucralfate vs. histamine-2-receptor antagonists (H2RAs) in ICU patients, reported a lower rate of gastrointestinal bleeding in the H2RA group.[17] Subsequently, proton pump inhibitors (PPIs) were introduced and they are currently together with H2RAs the most frequently used acid suppressants.[7,18]

How the intervention might work

Increasing pH on the luminal side of the gastric mucosa is likely protective against ulcerations.[3]

H2RAs decreases gastric acid secretion by inhibiting stimulation of the H^+-K^+-adenosine triphosphatase (ATPase) by binding to the H2-receptor on the parietal cells.[19]

Proton pump inhibitors inhibit the secretion of gastric acid by forming irreversible disulphide bonds with the H^+-K^+-ATPase pump. PPIs provide a stronger and more prolonged reduction in acid secretion compared to H2RAs due to the irreversible bond.[19]

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Why it is important to do this review

Stress ulcer prophylaxis is regarded as standard of care in the ICU and the administration of stress ulcer prophylaxis is recommended by international guidelines.[20] Nonetheless, as a result of limited data and methodological flaws in some trials, the quantity and quality of evidence supporting the use of stress ulcer prophylaxis in adult ICU patients is low with no firm evidence for benefit or harm.[21,22] Importantly, increased rates of myocardial ischaemia, *Clostridium difficile* enteritis and hospital-acquired pneumonia with the use of stress ulcer prophylaxis has been suggested.[1,21,23,24]

Several randomized clinical trials and systematic reviews have compared the effects of PPIs and H2RAs,[23,25–28] but neither PPIs nor H2RAs have demonstrated its superiority as compared to placebo or no prophylaxis. New trials have been published and others are expected to be published soon.[29–31] These new trial estimates are important to include in an up-to-date systematic review.

Objectives

The objective of the study was to assess the benefits and harms of stress ulcer prophylaxis vs. placebo or no prophylaxis in adult ICU patients.

Methods

This protocol was written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist (Appendix S1). Our methodology is based on the recommendations by the Cochrane Collaboration,[32] the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA),[33] Keus et al,[34] the eight-step assessment suggested by Jakobsen et al,[35] and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[36]

The protocol is registered in the PROSPERO database (CRD42018089151).

Criteria for considering studies for this review

Types of studies

We will include randomized clinical trials, irrespective of publication status, reported outcomes, publication date and language. We will not specifically search for observational studies (quasi-randomized studies; cohort studies; case–control studies and case series), and we will not include observational studies in any meta-analyses. However, we will provide a narrative account of observational data if we identify observational studies reporting rare adverse events during the literature search.[32]

We will include unpublished trials only if methodological descriptions and trial data are provided by direct contact with trial authors or in written form.

Types of participants

We will include any adult ICU patients (as defined by trialists).

Types of interventions

We will include any randomized clinical trial comparing stress ulcer prophylaxis with either PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole) or H2RAs (cimetidine, famotidine, nizatidine and ranitidine). We will accept any dose, formulation and duration.

Intervention group. The intervention group will be defined as those receiving PPIs or H2RAs.

Control group. The control group will be defined as those receiving placebo or no prophylaxis.

Types of outcome measures

Primary outcomes

1. All-cause mortality (dichotomous outcome).
2. Proportion of participants with any gastrointestinal bleeding as defined by trialists.

Secondary outcomes

1. Proportion of participants with one or more serious adverse event (dichotomous outcome). We will include the data if the trialists use the term 'serious adverse event', 'severe adverse event', 'serious adverse reaction', 'serious complication', 'severe

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complication' or similar terms (including events fulfilling the criteria of ICH-GCP definition)[64]
2. Health related quality of life (any valid scale used by trialists)
3. Proportion of participants with myocardial ischaemia (dichotomous outcome), as defined by trialists
4. Proportion of participants with hospital-acquired pneumonia (dichotomous outcome), as defined by trialists
5. Proportion of participants with *Clostridium difficile* enteritis (dichotomous outcome), as defined by triallists

We will estimate all continuous and dichotomous outcomes at two time points.

1. The time point closest to 90 days. This will be our assessment time point of primary interest.
2. Maximum follow-up, as reported by the included trials.

Search methods for identification of studies

Electronic searches

Randomized clinical trials that fulfil the inclusion criteria will be identified through literature searching with systematic and sensitive search strategies specifically designed to identify relevant randomized clinical trials without restrictions to language, publication year and journal.

The following databases will be searched from inception:

1. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (latest issue)
2. Ovid MEDLINE (from 1946 to date of search)
3. Ovid Embase (from 1974 to date of search)
4. Science Citation Index Expanded (Web of Science) (from 1900 to date of search)
5. Biosis Previews (Web of Science) (from 1969 to date of search)

For details on the full search strategies, see Appendix S2.

Searching other resources

Reference lists of reviews, relevant papers, randomized and non-randomized trials as well as editorials will be screened manually for potentially relevant trials. Furthermore, authors of the identified trials and experts within the area and pharmaceutical companies (if relevant) will be contacted and asked for additional (unpublished) trials.

In addition, ongoing and unpublished trials will be searched for in the following trial registers:

1. ClinicalTrials.gov
2. WHO International Clinical Trials Registry Platform (ICTRP)
3. EU clinical trial register
4. Australian New Zealand Clinical Trials Registry (ANZCTR)

Furthermore, we will search for unpublished trials on:

1. U.S. Food and Drug Administration (FDA)
2. European Medicines Agency (EMA)
3. Websites of medical companies producing PPIs and H2RAs.

Data collection and analysis

The following methods on data collection and data analyses will be used.

Selection of studies

Two authors (SM or AG or CTA) will independently screen the titles and abstracts of all reports identified by the searches. Reports that are not deemed potentially irrelevant will be obtained in full-text, and the same two reviewers will independently assess these for inclusion. Any disagreement will be resolved by consensus.

Data extraction and management

MB and SM will independently extract predefined data of the included trials using a data collection form, which will be specifically designed and piloted by the review team. Any disagreement concerning the extracted data will be discussed between the two authors. If no agreement can be reached, a third author (JW, JCJ or MHM) will resolve the issue. Whenever

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necessary, corresponding authors will be contacted to clarify issues related to data reporting or if further trial details are needed. We will extract the following data:

1. Trial: country, duration of the trial, date of publication and class of trial (single vs. multi-centre)
2. Participants: number randomized, number analysed, number lost to follow-up/withdrawn, type of population, mean/median age, sex, inclusion criteria and exclusion criteria
3. Interventions: intervention, comparator and concomitant medications
4. Outcomes: primary and secondary outcomes specified and collected and time points reported
5. Risk of bias

Assessment of risk of bias in included studies

MB and SM will independently assess the risk of systematic errors of each included trial. We will assess the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting and other bias including baseline imbalance, early stopping and bias due to vested financial interest or academic bias. Any disagreement will be discussed between the two authors. We will assess the risk of bias according to the Cochrane Handbook for systematic Reviews of interventions.[32]

Based on the risk of bias assessment, the included trials will be defined as overall low risk of bias if all bias domains are judged as low risk of bias. For additional details on how we will assess the risk of bias, see Appendix S3.

In addition, we will assess all domains for each outcome. Only 'blinding of outcome assessment', 'incomplete outcome data' and 'selective outcome reporting' will vary between outcomes. Thus, we will assess the bias risk for each outcome assessed in addition to each trial. Our primary conclusions will be based on the results of both our primary and secondary outcome results with overall low risk of bias. If no results with overall low risk of bias are found, we will base our primary conclusions on the outcome results irrespective of overall risk of bias. We will present our primary conclusions in the 'Summary of Findings' table.

Measures of treatment effect

Risk ratios (RRs) with 95% confidence intervals (CIs) and Trial Sequential Analysis adjusted CIs[37] will be calculated for dichotomous outcomes.

We will calculate the mean difference (MD) with 95% CI and Trial Sequential Analysis adjusted CI[37] for continuous outcomes. We will secondly use standardized mean difference (SMD) when trials assess the same outcome but measure it in a variety of ways, e.g. using different scales.

Unit of analysis issues

If multi-arm trials are included and they compare PPI vs. H2RA vs. placebo or no intervention, we will separate the two groups getting a PPI and H2RA and divide the placebo/no intervention group with two. If multi-arm trials are included and compare a PPI or H2RA in two different doses vs. placebo or no intervention, we will combine the two pharmacological interventions into a single group and compare these to the placebo/no intervention group.

If cluster-randomized trials are included, we will define the ICU as the unit of allocation. We will use the generic inverse variance method in RevMan to calculate effect estimates for these trials.[32]

Dealing with missing data

We will contact trial investigators for important missing data, including "unclear" risk of bias ratings and missing outcomes.

For both dichotomous and continuous outcomes, we will not be imputing missing data for any outcomes in the primary analysis and intention-to-treat data will not be used if the original report did not contain such data.

If standard deviations (SD) are not reported, the SDs will be calculated using data from the trial if possible.

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In the sensitivity analysis best-worst case scenario and worst-best case scenario for dichotomous and continuous outcomes, imputed data will be used, see 'Sensitivity analysis' Appendix S4.

Assessment of heterogeneity

We will primarily assess signs of heterogeneity by visual inspection of the forest plots.

We will assess presence of statistical heterogeneity by χ^2 test with significance set at $P < 0.10$ and by measuring the quantities of heterogeneity by I^2 statistic.[38] We will interpret statistical heterogeneity according to the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions[32]: 0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity and 75–100%: considerable heterogeneity.

We will explore potential clinical heterogeneity by conducting pre-specified subgroup analyses, see 'Subgroup analysis and investigation of heterogeneity', which may explain the statistical heterogeneity.

Assessment of reporting biases

We will visually assess funnel plots for signs of asymmetry if ten or more trials are included in an analysis.[32,35]

We will test asymmetry within dichotomous outcomes with the Harbord test[39] and for continuous outcomes regression asymmetry test.[40] Adjusted rank correlation will also be used.[41]

Data synthesis

Meta-analysis

We will perform conventional meta-analysis of outcomes with comparable effect measures where more than one trial is included. If clinical and statistical heterogeneity are large or unexpected, we will re-consider performing the meta-analysis. The statistical software Review Manager[42] provided by the Cochrane Collaboration, STATA 15, the Trial Sequential Analysis software provided by Copenhagen Trial Unit[43] and GRADEpro[44] will be used.

We will report the results narratively if a quantitative synthesis is not appropriate.

Assessment of significance

We will assess our intervention effects with both random-effects model meta-analyses[45,46] and fixed-effect model meta-analyses.[46,47] We will use the more conservative point estimate of the two, which is the point estimate closest to no effect (highest P value). If the estimates from the two models are approximately equal, we will use the estimate with the widest CI.

We will adjust our thresholds for statistical significance because of multiplicity problems due to multiple outcomes by dividing the pre-specified P value threshold with the value halfway between 1 (no adjustment) and the number of primary or secondary outcome comparisons (Bonferroni adjustment).[35,48] We have defined two co-primary outcomes and five secondary outcomes, thus we will consider a P value of 0.033 or less as significant for the primary outcomes and a P value of 0.017 or less as significant for the secondary outcomes. We will report Trial Sequential Analysis adjusted CIs which means that these CIs are adjusted for multiple outcomes, sparse data and multiple updating of meta-analyses. We will report 95% CIs as well. We will use the eight-step procedure to assess if the thresholds for significance are crossed, which include choosing the most appropriate meta-analysis model being the one with the most conservative result, performing subgroup analyses and sensitivity analyses to explore statistical heterogeneity, adjusting the threshold for statistical significance, performing trial sequential analysis, calculating Bayes factor, assessing the potential impact of bias, assessing the risk of publication bias and assessing clinical significance.[35]

Trial sequential analysis

Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data[49–57] therefore trial sequential analysis[43] can be applied to assess this risk.[58] The required information size and the required number of trials[59] (that is the number of participants and trials needed in a meta-analysis to detect or reject an a priori pre-

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specified realistic intervention effect) can be calculated to minimize random errors.[60] The required information size takes into account the event proportion in the control group, the assumption of a plausible relative risk (RR) reduction and the heterogeneity variance[61] of the meta-analysis.[60] Trial sequential analysis enables testing for significance to be conducted each time a new trial is included in the meta-analysis. On the basis of the required information size and the required number of trials, trial sequential monitoring boundaries can be constructed. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the required information size.[52,53,55,57]

Firm evidence for benefit or harms may be established if the trial sequential monitoring boundary is crossed before reaching the required information size, in which case further trials may turn out to be superfluous. In contrast, if the boundary is not surpassed one may conclude that it is necessary to continue with further trials before a certain intervention effect can be detected or rejected. Firm evidence for lack of the postulated intervention effect can also be assessed with trial sequential analysis. This occurs when the cumulative z-score crosses the trial sequential monitoring boundaries for futility.

We will use conservative estimations of the anticipated intervention effect estimates to reduce the risk of random error.[35] Large anticipated intervention effects lead to small required information sizes and the thresholds for significance will be less strict after the information size has been reached.[35]

We will provide trial sequential analysis adjusted summary estimates for all outcomes. We will estimate the diversity-adjusted required information size[60] based on the proportion of patients with an outcome in the control group. In addition we will use a family wise error rate (FWER) of 5%[35] leading to a statistical significance level of 2.5% for each of the co-primary outcomes, a beta of 20%, and a diversity (D^2)[60] suggested by the trials in the meta-analysis[35]. As a sensitivity analysis, we will use a diversity of 20% if the actual measured heterogeneity is in fact zero because in this case heterogeneity will most likely increase when further trials are added until the required information size is reached. As anticipated intervention effects for the primary and secondary outcomes in the trial sequential analysis we will use realistic a priori relative risk reductions (RRRs) of 20% or a 20% relative risk increase (RRI). Furthermore, we will use a RRR or a RRI based on the confidence limit closest to null effect in the 95% Cl in the traditional meta-analyses.

Subgroup analysis and investigation of heterogeneity

We will seek to determine if the efficacy and safety of the prevention options are influenced by types of ICU populations and type of intervention and comparator by conducting the following subgroup analyses:

1. Comparing estimates of the pooled intervention effect in trials with overall 'low risk of bias' vs. overall 'high risk of bias'. Hypothesized direction of subgroup effect: increased beneficial intervention effect in the trials with overall high risk of bias.
2. Comparing estimates of the pooled intervention effect in the included subpopulations of adult ICU patients: medical ICU patients vs. surgical ICU patients vs. mixed ICU patients. Hypothesized direction of sub-group effect: increased beneficial intervention effect in some sub-ICU-populations.
3. Comparing estimates of the pooled intervention effect in the included subpopulations of adult ICU patients: patients with any type of shock vs. patients without shock. Hypothesized direction of sub-group effect: increased beneficial intervention effect in patients with any type of shock.
4. Comparing estimates of the pooled intervention effect in the included subpopulations of adult ICU patients: patients treated with renal replacement therapy (RRT) at baseline vs. patients not receiving RRT. Hypothesized direction of sub-group effect: increased beneficial intervention effect in patients treated with RRT.

1. Comparing estimates of the pooled intervention effect in the included subpopulations of adult ICU patients: invasive mechanically ventilated patients vs. patients not mechanically ventilated. Hypothesized direction of

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sub-group effect: increased beneficial intervention effect in mechanically ventilated patients.
2. Comparing estimates of the pooled intervention effect in trials using PPIs vs. trials using H2RAs. Hypothesized direction of the sub-group effect: increased beneficial intervention effect in trials using PPI.
3. Comparing estimates of the pooled intervention effect in trials using placebo vs. trials using no prophylaxis. Hypothesized direction of the sub-group effect: increased beneficial intervention effect in trials using no prophylaxis.

Sensitivity analysis

We will perform sensitivity analyses to assess the potential impact of reporting bias by performing meta-analyses where we will exclude trials not reporting on 'clinically important bleeding (as reported by trialists)'.

We define 'clinically important bleeding' as any episode in the ICU of overt gastrointestinal bleeding and at least one of the following four features within 24 h of gastrointestinal bleeding (in the absence of other causes)[8,10,14] (or similar terms):

1. Spontaneous drop of systolic blood pressure, mean arterial pressure or diastolic blood pressure of 20 mmHg or more.
2. Start of vasopressor or a 20% increase in vasopressor dose.
3. Decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l).
4. Transfusion of 2 units of packed red blood cells or more.

Additionally, we will perform sensitivity analyses to assess the potential impact of missing data by performing best–worst and worst–best case scenarios.[35] For additional details on how we will perform this sensitivity analysis, see Appendix S4.

Summary of findings

We will use the GRADE system[62] to assess the overall quality of evidence for all outcomes by constructing summary of findings tables using the GRADE software.[44] For each primary and secondary outcome, firstly we will present summary of findings in RCTs with overall low risk of bias and secondarily results in all trials.

The GRADE approach appraises the overall quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality measure of a body of evidence considers within-study risk of bias, inconsistency (unexplained heterogeneity), indirectness (inclusion of other patient groups or use of surrogate outcomes), imprecision (wide confidence interval around the effect estimate) and risk of publication bias. Accordingly, the overall quality of evidence will be rated 'high', 'moderate', 'low' or 'very low'.

Discussion

Proton pump inhibitors are some of the most prescribed drugs in the world.[19] Stress ulcer prophylaxis is regarded as standard of care in ICU patients and its use is recommended in international guidelines.[20] Nonetheless, the quantity and quality of evidence of supporting the use of stress ulcer prophylaxis in ICU patients is low, with no firm evidence for benefit and harm.[63]

With the outlined systematic review, we aim to update the systematic review by Krag et al[63] and evaluate the benefits and harms of stress ulcer prophylaxis in adult ICU patients. An updated systematic review is highly needed as new trials may provide important new data on the potential benefit and harm of stress ulcer prophylaxis, including *Clostridium difficile* infections, hospital-acquired infections and cardiovascular events.

This protocol has strengths. It has been prepared in accordance with the PRISMA-P statement.[64] We have pre-defined the methodology for the coming systematic review based on the Cochrane Handbook for Systematic Reviews of Interventions,[32] the eight-step assessment suggested by Jakobsen et al,[35] Trial Sequential Analysis,[58] and the GRADE methodology.[62] Hence, this protocol takes into account the risks of both random and systematic errors. In addition, by applying trial sequential analysis to the data, this allows us to conclude whether firm

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evidence has been reached or if additional trials are needed.[52,53,55,57]

Neither critical illness nor gastrointestinal bleeding is restricted to ICU patients. Whether stress ulcer prophylaxis is associated with benefits or harms in critically ill patients in general (including patients outside the ICU) is another important question, which also needs to be assessed in the future.[13]

As uncertainty over whether routine use of stress ulcer prophylaxis is indicated in ICU patients, there is a need to assess the balance between the benefits and harms. Our ambition with this systematic review is to provide reliable, updated and precise data to better inform decision makers on clinical practice on the use of stress ulcer prophylaxis.

Contributions of authors

MB, SM, JCJ, MK, AG, CTA, AP, JW and MHM: Contributed to the conception of the study protocol.

MB: Drafted the manuscript, performed the search strategies and registered the protocol in PROSPERO.

All authors critically contributed to the manuscript and all authors read and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. PRISMA-P 2015 Checklist.
Appendix S2. Search strategies for systematic review.
Appendix S3. Details on the assessment of risk of bias.
Appendix S4. Details on the sensitivity analysis.

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