BMJ Open Evaluation of the role of sex as a prognostic factor in critically ill adults with sepsis: systematic review protocol

Jesús Lopez-Alcalde ^{1,2,3}, Alba Antequera Martín ^{4,5}, Elena Stallings,² Alfonso Muriel ^{2,3,6}, Borja Fernández-Félix,^{2,3} Ivan Solà ^{5,7,8}, Rosa del Campo ⁹, Manuel Ponce-Alonso ⁹, Federico Gordo,^{1,10} Pilar Fidalgo,^{1,11} Ana Verónica Halperin,⁹ Noelia Álvarez-Díaz ¹², Olaya Madrid-Pascual ¹³, Gerard Urrutia,^{5,7,8} Javier Zamora ^{2,3}

To cite: Lopez-Alcalde J, Antequera Martín A, Stallings E, *et al*. Evaluation of the role of sex as a prognostic factor in critically ill adults with sepsis: systematic review protocol. *BMJ Open* 2020;**10**:e035927. doi:10.1136/bmjopen-2019-035927

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-035927>).

JL-A and AAM contributed equally.

Received 22 November 2019
Revised 21 February 2020
Accepted 07 April 2020

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Alba Antequera Martín, Department of Epidemiology and Public Health, Biomedical Research Institute Sant Pau, Sant Antoni Maria Claret 167, building 18, 08025 Barcelona, Spain; alba.antequera.martin@gmail.com

ABSTRACT

Introduction Sepsis is a leading cause of mortality in critically ill patients. Recently, it has been recognised that sex may contribute to a differential risk for developing sepsis and it remains uncertain if the prognosis of sepsis varies between the sexes. The aim of this systematic review is to summarise the available evidence to assess the role of sex as a prognostic factor in patients with sepsis managed in the intensive care unit (ICU).

Methods and analysis This is a systematic review protocol of prognostic studies of sex in patients with sepsis managed in the ICU. The primary outcomes include all-cause hospital mortality and all-cause hospital mortality during the first 28 days. The secondary outcomes include all-cause hospital mortality during the first 7 days and all-cause mortality at 1 year. We will conduct a search strategy based on the population (sepsis), the prognostic factor (sex), the outcome of interest (mortality) and prognostic study methods. We will search in the following databases up to December 2019: MEDLINE Ovid (from 1976), Embase Elsevier (from 1974), Web of Science and two trial registries. We will impose no language restrictions. Two authors will independently screen titles, abstracts and full-text articles for eligibility of studies, and subsequently extract data. Two authors will independently assess the risk of bias of each study using the Quality in Prognostic Studies (QUIPS) tool. If possible, we will carry out a meta-analysis to provide a pooled prognostic effect estimate for each outcome. We will use the Grading of Recommendations Assessment, Development and Evaluation system to assess the quality of evidence. **Ethics and dissemination** Ethical approval will not be required. Findings from this review will be reported in a peer-reviewed scientific journal. Additionally, the results will be disseminated at conferences and in the mass media.

PROSPERO registration number CRD42019145054.

INTRODUCTION

Sepsis is currently defined as life-threatening organ dysfunction resulting from a dysregulated host response to inflammation.¹ Sepsis is a major health problem with a worldwide incidence of about 1 case per 1000 patients,

Strengths and limitations of this study

- To our knowledge, this systematic review will be the first addressing sex as a prognostic factor for sepsis and its findings may help to stratify patients for treatment.
- This systematic review will examine mortality outcomes, which are critical for patients and decision making.
- There may be challenges for meta-analysing the results due to heterogeneity among primary studies.

making it the main cause of admission to an intensive care unit (ICU) in high-income countries.^{2–3} Moreover, despite advances in healthcare, sepsis remains a leading cause of death every year and is the most common cause of death within the ICU.^{4–6}

Sepsis is a heterogeneous disease affecting both male and female individuals.⁷ Recently, it has been recognised that sex may contribute to a differential risk for developing sepsis; and it remains uncertain if the prognosis of sepsis varies between the sexes.^{8–14} Prognosis factors are relevant in clinical care as they can identify risk groups in which clinical practice may be tailored to the aim of reducing morbidity and mortality.¹⁵ The aim of this systematic review is to summarise the available evidence to assess the role of sex as a prognostic factor for mortality in patients with sepsis managed in the ICU.

METHODS

Registration

We registered the protocol with an International Prospective Register of Systematic Reviews (PROSPERO) on 12 November 2019. Possible amendments will be updated on PROSPERO. The protocol is reported

according to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols statement.¹⁶ The review will be reported according to the PRISMA statement.¹⁷

Eligibility criteria

Type of studies

We will include experimental studies, randomised or not, and any observational study investigating the prognostic significance of sex in adults with sepsis managed in the ICU. Regarding prognostic factor studies, we will only include phase II confirmatory studies.

Type of participants

Adults (male and female individuals, which allow determining the role of sex) aged ≥ 16 years with a diagnosis of sepsis. We will accept the study authors' definition of sepsis and septic shock. For a study to be eligible, the sepsis must be managed in an ICU. Studies including adults, children and/or adolescents will be eligible if adults represent $>80\%$ of the study sample.

Type of prognostic factors

We will include studies that assess sex as a prognostic factor. We will accept any assessment of sex as provided by the study authors. The concepts of sex and gender are distinct. Sex is a biological characteristic and gender refers to the socially constructed roles, behaviours and identities of women, men and gender-diverse individuals.¹⁸ This review will not assess the association between gender and the outcomes of patients with sepsis in the ICU.

We will assess the role of sex as a prognostic factor after adjustment for additional covariates. After a literature search and a consensus process with clinician review authors, and as suggested during peer review of our protocol (online supplementary appendix 1), we agreed on the following core set of adjustment factors: age, severity score (Sequential Organ Failure Assessment score (SOFA), Simplified Acute Physiology Score II (SAPS II) or Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II)), comorbidities (immunosuppression, pulmonary diseases, cancer, liver diseases and alcohol dependence), non-urinary source of infection, inappropriate or late antibiotic coverage.^{19–26} We may modify this list if we find new evidence that justifies the changes.

Type of outcomes

Primary outcomes

- ▶ All-cause hospital mortality (the longest follow-up provided by the study authors).
- ▶ All-cause hospital mortality during the first 28 days.

Secondary outcomes

- ▶ All-cause hospital mortality during the first 7 days.
- ▶ All-cause mortality at 1 year.

Information sources

We will search the following databases:

- ▶ MEDLINE Ovid (from 1946 onwards).
- ▶ Embase Elsevier (from 1974 onwards).
- ▶ Web of Science (WoS).

Search methods

The search strings will be based on terms related to the population (sepsis), the prognostic factor (sex), the outcome (mortality) and prognostic study methods.²⁷ For 'sex' we will use a search string adapted from Lorenzetti, Moerman, Song and Stewart^{28–31} (online supplementary appendix 2). We will not apply publication date or language restrictions.

Moreover, we will check the bibliographic references for additional relevant studies. We will also scan ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/) for unpublished and ongoing studies.

Furthermore, we will search for conference abstracts of major critical care and infectious diseases symposia from 2010.

1. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 50th edition 2010 to 59th edition 2019.
2. European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 20th edition 2010 to 29th edition 2019.
3. Society for Healthcare Epidemiology of America (SHEA): IDWeek 2012 to 2019 editions.
4. International Conference on Prevention and Infection Control (ICPIC): 2011, 2013, 2015, 2017, 2019
5. Society of Critical Care Medicine (SCCM): 39th edition 2010 to 48th edition 2019.
6. International Symposium on Intensive Care and Emergency Medicine (ISICEM): 30th edition 2010 to 39th edition 2019.
7. European Society of Intensive Care Medicine (ESICM): 2010 onwards.

Apart from that, we will contact experts on the topic to ask for any ongoing, missing or unreported studies.

STUDY RECORDS

Data management

We will eliminate duplicates with Endnote 7.8 reference management software.³² We will manage the resultant unique references with the online software EPPI-Reviewer to identify additional duplicates, select studies, build the data extraction templates and extract the data.³³

Study selection and data collection

Two of six review authors (AAM, AH, MPA, OM, RdC, PF) will independently screen retrieved results according to the best practice guidelines to determine whether they fulfil the eligibility criteria of this review.³⁴ We will use a consensus method, and a third author (JL-A, AAM, ES) will be consulted if there are disagreements. We will pilot

eligibility criteria on a sample of references to ensure their reproducibility. Assessment of the eligibility of full texts will be undertaken similarly. Two of seven authors (JL-A, AAM, AH, MP, OM, RdC, PF) will independently extract data according to a pre-defined form and a third author will resolve the discrepancies (JL-A, AAM, ES). We will pilot the data extraction template with three studies to ensure its suitability. We will compare results and resolve discrepancies by discussion or by referring to a third review author.

Data items

We will use CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies for prognostic factor (CHARMS-PF) guidance for data collection.³⁵ This tool modifies the original CHARMS checklist for prediction model studies.³⁶ We will extract the following data from each eligible study:

1. Publication date, country and setting in which the study was conducted.
2. Study design: experimental study or observational study.
3. Registration: presence of registration or protocol published (yes/no).
4. Sepsis definition used by authors.
5. Participant characteristics: participant description, eligibility criteria and details of treatment received (if applicable).
6. Sex definition used by authors.
7. Review outcomes reported in the study: mortality; type of measures (binary); follow-up period (the first 7 days, the first 28 days and the longest follow-up provided by the study authors).
8. Missing data: attrition (quantification and reasons), handling of missing data by the study authors (available case analysis or imputation).
9. Analysis: univariate analysis/logistic regression/Cox regression/other.
10. Estimates reported between the prognostic factor and each review outcome: (a) unadjusted estimate: association between sex and mortality with no covariate; (b) adjusted estimates: association/s between sex and mortality with at least one covariate.
11. Type of measure of association: odds ratio (OR), risk ratio (RR) or hazard ratio (HR).
12. List of adjustment factors that were used. We will contact authors of individual studies for additional information if required.

Assessment of methodological quality and risk of bias

We will use the QUIPS (Quality In Prognosis Studies) tool to assess risk of bias.³⁵ Two review authors will independently assess the following six domains of the QUIPS tool: (1) study participation; (2) study attrition; (3) prognostic factor measurement; (4) outcome measurement; (5) adjustment for other prognostic factors; (6) statistical analysis and reporting.

We will make a judgement for every criterion, using one of four categories (low, moderate, high risk and unclear), adapting the QUIPS guidelines.^{35 37 38} We will resolve disagreements by discussion, and a third author will be consulted if it is required.

We will evaluate the impact of risk of bias from primary studies by performing sensitivity analyses (see the Sensitivity analyses section).

Data synthesis

For each study and prognostic effect estimate, we will extract the measures of association reported in each study (OR, RR, HR) along with its standard error (SE) or confidence intervals (CIs). We will transform association measures into OR with its 95% CI in order to allow statistical pooling whenever adequate.³⁹ We acknowledge that the studies providing the adjusted prognostic effect of a particular factor can differ in the set of adjustment factors. We will define a core set of adjustment factors for each review outcome.

If the study provides a set of adjustment factors that differ from our core set, we will meta-analyse the study but the estimate will be penalised as part of the risk of bias assessment. If the same study presents different estimates for the same outcome, each of them adjusted for different factors, we will extract the estimate that has adjusted for the maximum number of our key confounders for meta-analysis. If there are several estimations, all of them having adjusted for the same key confounders, we will consider the estimate adjusted for more confounders in total. We assume that this will minimise the risk of confounding bias in the estimation.

We plan to combine the results from individual studies in a meta-analysis to provide a pooled prognostic effect estimate for each outcome. We will carefully evaluate the censoring mechanisms assumed in the studies that have been analysed using time-to-event procedures (i.e., Cox proportional hazard models). If we conclude that there is a risk of bias due to informative censoring (e.g., when patients with better prognosis are discharged for the ICU), we will disregard HRs obtained in such studies. We plan to use the Hartung-Knapp-Sidik-Jonkman (HKSJ) method for random-effects meta-analysis. We will use the Cochrane statistical package Review Manager 5.3 for organising the text of the review, and if the meta-analysis is possible, we will use the metareg command in Stata (Stata V.15.1) for performing the meta-analysis with the HKSJ method.⁴⁰

Heterogeneity between studies

When there are at least three studies, we will examine heterogeneity by calculating prediction intervals in order to inform how the effect varies across populations. The prediction interval is an index of dispersion that describes the range of effect sizes in which we would expect that the true effect size will fall.⁴¹ We will use the spreadsheet provided by Borenstein *et al* for computing the prediction interval.⁴²

If we judge that the meta-analysis is inappropriate for other reasons, we will not combine results and we will undertake a narrative analysis of studies.

To better understand the sources of heterogeneity, we plan to conduct the following subgroup analyses:

- Trials versus cohort studies versus case-control studies.
- Prospective studies (all the study parts were prospective) versus retrospective studies (all the study parts were retrospective).

Sensitivity analyses

We will undertake the following sensitivity analyses:

- Evaluate the impact of risk of bias from individual trials in the overall effect. We will consider the following risk of bias domains as key domains for the analyses: study attrition, prognostic factor measurement, outcome measurement and adjustment for other prognostic factors.
- We will exclude studies with a high risk of bias in at least one key domain.
- We will exclude studies with a high or moderate risk of bias in at least one key domain.
- Assess the effect of excluding studies that have provided an adjusted estimate, but that did not adjust for all our core set of additional prognostic factors.

Publication bias

We will attempt to assess the presence of publication bias for each meta-analysis containing ≥ 10 studies by funnel plot representation and Peter's test at a 10% level.⁴³

Confidence in cumulative evidence

We will attempt to use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and will present our results for each main outcome in a 'Summary of findings' table, although we acknowledge that the GRADE approach has not been widely used to assess the certainty of the evidence of prognostic factors.^{44 45} We will follow the principles suggested in Hughton *et al* and Iorio *et al* for prognostic questions.^{46 47} We will use GRADE profiler (GRADEpro GDT) for designing a 'Summary of findings'.⁴⁸

Patients and public involvement

Patients and the general public will not be involved in the process of conducting this systematic review. We will not plan to involve patients in the dissemination of the results of this systematic review.

Ethics and dissemination

Ethical permission is not necessary as this study summarises published data. This review is part of the SEXCOMPLEX project (Influence of sex and sex hormones on human chronic disorders of complex aetiology), a 2-year project (2017–2019) coordinated by Hospital Ramón y Cajal (Madrid, Spain). We shall disseminate our findings through peer-reviewed publication, at conferences, and in the mass media.

Author affiliations

¹Faculty of Health Sciences, Universidad Francisco de Vitoria, Pozuelo de Alarcón, Spain

²Clinical Biostatistics Unit, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain

³Epidemiology and Public Health Networking Biomedical Research Centre (CIBERESP), Madrid, Spain

⁴Autonomous University of Barcelona, Barcelona, Spain

⁵Biomedical Research Institute Sant Pau, Hospital Santa Cruz y San Pablo, Barcelona, Spain

⁶Department of Nursing and Physiotherapy, Universidad de Alcalá, Madrid, Spain

⁷Epidemiology and Public Health Networking Biomedical Research Centre (CIBERESP), Barcelona, Spain

⁸Iberoamerican Cochrane Centre, Barcelona, Spain

⁹Department of Microbiology, Hospital Universitario Ramón y Cajal, Madrid, Spain

¹⁰Department of Intensive Care, Hospital Universitario del Henares, Coslada, Madrid, Spain

¹¹Department of Internal Medicine, Hospital Universitario del Henares, Coslada, Madrid, Spain

¹²Medical Library, Hospital Universitario Ramón y Cajal, Madrid, Madrid, Spain

¹³Arztpraxis Kalkbreite, Zurich, Switzerland

Twitter Jesus Lopez-Alcalde @JLopezAlcalde

Acknowledgements The authors thank Centro de Investigación Biomédica en Red (CIBER) for its support.

Contributors Guarantor: JL-A. Conceiving of the review: JZ, JL-A, AAM. Designing protocol: JL-A, AAM, ES, JZ, IS. PROSPERO registration: AAM, JL-A. Designing research strategies: NA-D, IS, JL-A, AAM. Drafting of the manuscript; contributed equally to this work as first authors: AAM, JL-A. Methodological approach: JL-A, AAM, AM, IS, JZ, ES, GU. Clinical perspective: RdC, MP-A, FG, PF, AH, AAM. Screening search results: RdC, MP-A, PF, AH, OM-P, AAM, JL-A, FG. Analysing data: AM, AAM, JL-A, JZ, BF-F. Interpreting data: AAM, JL-A, AM, IS, JZ. Securing funding for the review: JL-A, JZ, GU. Critical revision of the manuscript for important intellectual content: All authors. Alba Antequera Martín is a doctoral candidate in Public Health and Methodology of Biomedical Research, at the Department of Pediatrics, Obstetrics, Gynaecology and Preventive Medicine at Universitat Autònoma de Barcelona (Spain) and this work is part of her PhD.

Funding The SEXCOMPLEX project was supported by Instituto de Salud Carlos III (Plan Estatal de I + D + i 2013–2016) and co-financed by the European Development Regional Fund 'A way to achieve Europe' (ERDF) grant number PIE16/00050. AAM was funded by the Instituto de Salud Carlos III through the "Acción Estratégica en Salud 2013–2016 / Contratos Río Hortega call 2018/CM18/00141" (Co-funded by European Social Fund 2014–2020, "Investing in your future"). BF-F was funded by Networking Biomedical Research Centre (CIBER). Publishing costs were provided by Networking Biomedical Research Centre (CIBER). These funding sources had no role in the design of this review, its execution, analyses, interpretation of the data, or decision to submit results.

Disclaimer The funding sources had no role in the design of this review, its execution, analyses, interpretation of the data or decision to submit results.

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 required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Jesus Lopez-Alcalde <http://orcid.org/0000-0002-1598-8790>

Alba Antequera Martín <http://orcid.org/0000-0002-1670-6302>

Alfonso Muriel <http://orcid.org/0000-0002-4805-4011>

Ivan Solà <http://orcid.org/0000-0003-0078-3706>

Rosa del Campo <http://orcid.org/0000-0003-1147-7923>

Manuel Ponce-Alonso <http://orcid.org/0000-0002-3239-9373>
 Noelia Álvarez-Díaz <http://orcid.org/0000-0002-5904-3609>
 Olaya Madrid-Pascual <http://orcid.org/0000-0002-2861-0121>
 Javier Zamora <http://orcid.org/0000-0003-4901-588X>

REFERENCES

- Singer M, Deutschman CS, Seymour CW, et al. The third International consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801.
- Linde-Zwirble WT, Angus DC. Severe sepsis epidemiology: sampling, selection, and society. *Crit Care* 2004;8:222–6.
- Perner A, Gordon AC, De Backer D, et al. Sepsis: frontiers in diagnosis, resuscitation and antibiotic therapy. *Intensive Care Med* 2016;42:1958–69.
- Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of global incidence and mortality of Hospital-treated sepsis: current estimates and limitations. *Am J Respir Crit Care Med* 2016;193:259–72.
- Reinhart K, Daniels R, Kisson N, et al. Recognizing Sepsis as a Global Health Priority - A WHO Resolution. *N Engl J Med* 2017;377:414–7.
- Moskowitz A, Omar Y, Chase M, et al. Reasons for death in patients with sepsis and septic shock. *J Crit Care* 2017;38:284–8.
- Pinheiro da Silva F, César Machado MC. Personalized medicine for sepsis. *Am J Med Sci* 2015;350:409–13.
- Esper AM, Moss M, Lewis CA, et al. The role of infection and comorbidity: factors that influence disparities in sepsis. *Crit Care Med* 2006;34:2576–82.
- Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546–54.
- Tsertsvadze A, Royle P, Seedat F, et al. Community-Onset sepsis and its public health burden: a systematic review. *Syst Rev* 2016;5:81.
- Papathanassoglou E, Middleton N, Benbenishty J, et al. Systematic review of gender-dependent outcomes in sepsis. *Nurs Crit Care* 2017;22:284–92.
- Sakr Y, Elia C, Mascia L, et al. The influence of gender on the epidemiology of and outcome from severe sepsis. *Crit Care* 2013;17:R50.
- Eachempati SR, Hydo L, Barie P. Bending gender rules for septic patients: are host responses positioned equally for all critically ill patients? *Crit Care Med* 2009;37:2649–50.
- Croce MA, Fabian TC, Malhotra AK, et al. Does gender difference influence outcome? *J Trauma* 2002;53:889–94.
- Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis research strategy (progress) 2: prognostic factor research. *PLoS Med* 2013;10:e1001380.
- Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- Johnson JL, Greaves L, Repta R. Better science with sex and gender: facilitating the use of a sex and gender-based analysis in health research. *Int J Equity Health* 2009;8:14.
- Vincent J-L, Moreno R, Takala J, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996;22:707–10.
- Tolsma V, Schwebel C, Azoulay E, et al. Sepsis severe or septic shock: outcome according to immune status and immunodeficiency profile. *Chest* 2014;146:1205–13.
- Danai PA, Moss M, Mannino DM, et al. The epidemiology of sepsis in patients with malignancy. *Chest* 2006;129:1432–40.
- O'Brien JM, Lu B, Ali NA, et al. Alcohol dependence is independently associated with sepsis, septic shock, and hospital mortality among adult intensive care unit patients. *Crit Care Med* 2007;35:345–50.
- Krieger JN, Kaiser DL, Wenzel RP. Urinary tract etiology of bloodstream infections in hospitalized patients. *J Infect Dis* 1983;148:57–62.
- Paul M, Shani V, Muchtar E, et al. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrob Agents Chemother* 2010;54:4851–63.
- Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010;38:1045–53.
- Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med* 2014;42:1749–55.
- Wilczynski NL, Haynes RB, Hedges Team. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med* 2004;2:23.
- Lorenzetti DL, Lin Y. Locating sex- and gender-specific data in health promotion research: evaluating the sensitivity and precision of published filters. *J Med Libr Assoc* 2017;105:216–225.
- Moerman CJ, Deurenberg R, Haaftkens JA. Locating sex-specific evidence on clinical questions in MEDLINE: a search filter for use on OvidSP. *BMC Med Res Methodol* 2009;9:25.
- Song MM, Simonsen CK, Wilson JD, et al. Development of a PubMed based search tool for identifying sex and gender specific health literature. *J Womens Health* 2016;25:181–7.
- Stewart F, Fraser C, Robertson C, et al. Are men difficult to find? identifying male-specific studies in MEDLINE and Embase. *Syst Rev* 2014;3:78.
- Endnote X7. *Endnote X7 computer program*. Version X 7.8. Philadelphia: Clarivate Analytics, 2018.
- Thomas J, Brunton JGS. *EPPI-Reviewer 4: software for research synthesis*. 2010.
- Polanin JR, Pigott TD, Espelage DL, et al. Best practice guidelines for Abstract screening large-evidence systematic reviews and meta-analyses. *Res Synth Methods* 2019;10:330–42.
- Riley RD, Moons KGM, Snell KIE, et al. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ* 2019;364:k4597.
- Moons KGM, de Groot JAH, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the charms checklist. *PLoS Med* 2014;11:e1001744.
- Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280.
- Aldin A, Umlauff L, Estcourt LJ, et al. Interim PET-results for prognosis in adults with Hodgkin lymphoma: a systematic review and meta-analysis of prognostic factor studies. *Cochrane Database Syst Rev* 2019;9:CD012643.
- Symons MJ, Moore DT. Hazard rate ratio and prospective epidemiological studies. *J Clin Epidemiol* 2002;55:893–9.
- The Nordic Cochrane Centre. *Review Manager (RevMan) [Computer program]*. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
- Borenstein M, Higgins JPT, Hedges LV, et al. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. *Res Synth Methods* 2017;8:5–18.
- Borenstein M. *Common Mistakes in Meta-Analysis and How to Avoid Them*. First edn. Englewood: Biostat, Inc, 2019.
- Peters JL, Sutton AJ, Jones DR, et al. Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 2006;295:676.
- Guyatt G, Oxman AD, Akl EA, et al. Grade guidelines: 1. Introduction- GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
- Schünemann H, Brozek J, et al. The GRADE Working Group. *Grade Handbook for grading quality of evidence and strength of recommendations*, 2019. from <http://guidelinedevelopment.org/app/handbook/handbook.html>
- Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the grade framework. *Syst Rev* 2013;2:71.
- Iorio A, Spencer FA, Falavigna M, et al. Use of grade for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ* 2015;350:h870.
- GRADEpro GDT, McMaster University. *Guideline development tool [computer program]*. Evidence Prime, Inc, 2015. <http://grade.pro.org/>