

Title: Sex and Gender Appraisal tool for Systematic Reviews-2 (SGAT-SR-2) and Participation-to-Prevalence Ratio: methods to assess to whom the evidence applies in Cochrane sepsis reviews

Authors: Antequera A ¹, Stallings E ², Henry RS ^{3,4}, Lopez-Alcalde J ^{2,5,6}, Runnels V ⁷, Tudiver S ⁸, Tugwell P ^{9,10,11}, Welch V ^{12,13}.

¹ Biomedical Research Institute Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

² Clinical Biostatistics Unit, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain. CIBER Epidemiología y Salud Pública (CIBERESP), Spain.

³ Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada.

⁴ Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

⁵ Institute for Complementary and Integrative Medicine, University Hospital Zurich and University of Zurich, Zurich, Switzerland.

⁶ Faculty of Health Sciences, Universidad Francisco de Vitoria, Pozuelo de Alarcón, Spain.

⁷ Faculty of Social Sciences, University of Ottawa, Ottawa, Ontario, Canada.

⁸ Researcher/Consultant - Gender and Health, Ottawa, Ontario, Canada.

⁹ Department of Medicine, and School of Epidemiology and Public Health, University of Ottawa Faculty of Medicine, Ottawa, Ontario, Canada.

¹⁰ Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

¹¹ WHO Collaborating Centre for Knowledge Translation and Health Technology Assessment in Health Equity, Bruyère Research Institute, Ottawa, Ontario, Canada.

¹² Bruyère Research Institute, University of Ottawa, Ottawa, Ontario, Canada.

¹³ School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada.

Corresponding author: Alba Antequera. Street: Sant Antoni Maria Claret 167, building 18, 08025 Barcelona (Spain). E-mail: alba.antequera.martin@gmail.com. Telephone: (0034) 935537814. Fax: (0034) 935537809

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Abstract

Objectives: To revise a sex and gender appraisal tool for systematic reviews (SGAT-SR) and apply it to Cochrane sepsis reviews.

Study design and setting: The revision process was informed by existing literature on sex, gender, intersectionality, and feedback from an expert advisory board. We revised the items to consider additional factors associated with health inequities. We appraised sex and gender considerations using the SGAT-SR-2 and female Participation-to-Prevalence Ratio (PPR) in Cochrane sepsis reviews.

Results: SGAT-SR-2 consists of 19 questions appraising the review's sections and use of the terms sex and gender. Among 71 SRs assessed, 50.7% included at least one tool item. The most frequent item was the number of participants by sex or gender at included study-level (24/71 reviews). Only four reviews provided disaggregated data for the full set of included trials, while two considered other equity-related factors. Reviews rarely appraised possible similarities and differences across sex and gender. In at least half of a subset of reviews, female participants were under-represented relative to their share of the sepsis population (PPR<0.8).

Conclusion: The SGAT-SR-2 tool and the PPR can support the design and appraisal of systematic reviews to assess sex and gender considerations, address to whom evidence applies, and determine future research needs.

Keywords: Equity; Sex- and gender-based analysis; Systematic reviews; Sepsis; SGAT-SR-2; Participation-to-Prevalence Ratio.

What is new?

Key findings

- The SGAT-SR-2 tool addresses whether and how sex- and gender-based analysis is applied to Cochrane reviews on sepsis and the extent to which other PROGRESS-Plus factors interacting with sex and gender are considered.

What this adds to what was known?

- Reviews on sepsis rarely appraised possible similarities and differences across sex and gender.
- The level of representation by sex relative to the sex-disaggregated incidence of sepsis in the overall population (i.e. Participation-to-Prevalence Ratio) was examined.

What is the implication and what should change now?

- Review authors should provide information on the sex or gender of study populations (or state when data are unavailable) to enable users to assess the applicability of the review's findings.
- Representation of participants by sex or gender in a systematic review relative to their representation in the disease population can be assessed by using Participation-to-Prevalence Ratio.
- Cochrane needs to embrace sex- and gender-based analysis to understand to whom the evidence applies, given the potential implications for clinical practice, research, and policy- making.

1. Introduction

Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to inflammation [1], is a major health problem and represents around 20% of worldwide deaths [2]. Traditionally, sex and gender differences have received little attention in infectious diseases, although they may have a role in the incidence and severity of such illnesses [3]. Biological mechanisms have been hypothesised to explain differences in survival by sex for patients with sepsis [4–7]. As well, studies have found women with sepsis may receive less invasive procedures and delayed antibiotic administration that may be explained by biological factors related to the reliability of severity score estimations, and implicit bias of health care providers [8,9]. Regarding treatment response, high-impact guidelines for sepsis management do not include clinical implications related to the sex or gender of patients, except recommendations for maternal sepsis [10,11].

A first step for integrating sex and gender in medical research involves understanding these terms and drawing attention to their operationalization. Sex, typically assigned at birth, refers to a set of biological traits that distinguish females, males, and individuals with differences of sex development (i.e., variations in chromosomal expressions or physiological characteristics that differ from the female-male dichotomy), while gender reflects socially constructed roles, behaviours, and identities, not necessarily based on biological sex, of girls, women, boys, men, transgender, and other gender diverse people [12–15]. Although sex and gender are distinguishable social categories, they reflect complex biological, genetic, and social processes that are closely intertwined [16,17]¹. Until the early 1990s, women in general, the elderly, and diverse sub-populations were broadly excluded from clinical trials [18]. Since then, guidelines developed by regulatory agencies increasingly mandate that study populations in trials evaluating therapeutic interventions should reflect the target patient populations [19,20]. Sex- and gender-based analysis (SGBA) is a framework that helps researchers explore

¹ In this manuscript, we used definitions of sex, gender, and related terms as proposed by the Canadian Institutes of Health Research (CIHR) [12].

potential sex and gender differences and similarities in a particular subject of interest, for example, by testing sex- and gender-intervention interactions, and discussing potential similarities and differences and their implications for practice, research, and policy-making. SGBA+ calls attention to the importance of addressing other social determinants of health that interact with sex and gender, while an intersectional framework helps researchers examine the potential impacts of interlocking systems of inequities and oppression [21,22]. For example, the World Health Organization has developed a toolkit for incorporating an intersectional gender lens into research on infectious diseases of poverty that considers the vulnerability to illness, exposure to pathogens, and treatment responses [23]. However, despite guidance and mandates to apply such frameworks [24–30], there is limited uptake in many research areas, including sepsis [31–35]. Since the early 2000s, a number of initiatives have been undertaken in health equity research, in parallel with advances in knowledge of sex, gender and intersectionality [23,25,26,36–40]. For example, the PROGRESS-Plus framework (place of residence, race/ethnicity/culture/language, occupation, gender or sex, religion, education, socio-economic status and social capital, and other context-specific factors that facilitate disadvantage, such as age, sexual orientation, and disability) identifies socially stratifying forces that drive variations in health [41–43]. PRISMA-Equity extension and Cochrane recommend its use as a reminder to consider the social determinants of health in systematic reviews [37,44]. Sepsis management, service provision, and policy-making are also expected to be based on the best available evidence [45–47]. The work described in this article draws on the efforts of Doull and colleagues (2010) who sought to determine whether Cochrane reviews of cardiovascular diseases addressed issues related to sex and gender [48]. Finding no SGBA appraisal tool to apply to systematic reviews, they designed the Sex and Gender Appraisal Tool – Systematic Reviews (SGAT-SR) and later revised it as a planning tool [49]. In 2018, Lopez-Alcalde and colleagues pointed out the value of revising the SGAT-SR to make it consistent with new developments in reviews [33], and in keeping with evolving knowledge about sex and gender. Consequently, we revised the SGAT-SR tool and applied it to Cochrane reviews of interventions on sepsis. We elaborated on explanatory and supporting material in the use of the SGAT-SR-2 to assist systematic review authors and end-users. We also assessed the female Participation-to-Prevalence Ratio (PPR).

2. Material and methods

2.1. Protocol

We registered the protocol with Open Science Framework on 24 December 2020 [50]. Supplementary material details differences between the protocol and the study.

2.2. Revision of the SGAT-SR tool

The development of the original SGAT-SR tool was described elsewhere [48,49]. Briefly, the tool consisted of 21-questions whose answers denoted the presence or absence of sex and gender considerations across the sections of Cochrane reviews at that time: Background, Objectives, Inclusion/Exclusion criteria, Methods, Results and Analysis, Discussion and Conclusions, and Table of included studies (See Supplementary material).

We tracked citations on Doull and colleagues [48], searching PubMed for its PMID data to identify potential studies that applied the SGAT-SR tool. We revised the SGAT-SR tool by reviewing previous comments on its use relevant to this study [33,51], evaluating the most recent guidance on sex- and gender-based analysis and equity considerations [26,44,52–55], and on intersectionality [16,23,37,40,43]. We convened an advisory board composed of nine experts in SGBA, equity in health research, and evidence synthesis (RSH, JL-A, VR, ST, PT, MD, JH-R, ZM, and JP). The Cochrane Handbook was used as the reference for issues related to methodological standards [44].

The main changes to the SGAT-SR-2 tool were: 1) adding a section on use of the terms sex and gender; 2) changing response categories, and 3) adding assessment of whether additional factors interacting with sex and gender were considered using the PROGRESS-Plus framework. The SGAT-SR-2 tool comprises 19 questions appraising the following sections: Abstract, Plain language summary, Background, Methods, Results, Discussion and Authors' conclusions, and the use of the sex and gender terms (See Supplementary material). We described the findings as review authors mentioned sex and gender, and the SGAT-SR-2 tool assessed the use of terms by applying the framework proposed by Adisso and colleagues (questions #17, #18, #19) [34]. This framework establishes criteria to evaluate the operationalisation of sex and gender, the use of appropriate categories to describe sex and gender according to the current international definitions [12], and the non-interchangeable use of terms. We structured the items to be able to capture when authors explicitly addressed sex and gender considerations, including when they noted a lack of available data, and when they failed to do so. The possible responses to items #1 to #16 of the SGAT-SR-2 tool are: "Yes", "No", "Probably yes", "Probably no", and "Non-applicable". For three questions (#5.a, #8.a, #12.a), we also asked whether the authors provided a rationale. For the three questions assessing the use of the terms, the possible responses are those defined by Adisso and colleagues [34] as follows: binary, non-binary, or unclear use (#17); appropriate, inappropriate, or unclear (#18); and interchangeable, non-interchangeable, or unclear use (#19). Two authors (AA, ES) independently examined the consistency of the revised tool by piloting a sample, using the Excel random function, of 22% of eligible reviews. The advisory board

members were presented with the updated literature review, the findings of the piloting process, resulting in rewording items for clarity, and the draft of the manuscript for review and revision. Supplementary material details criteria for assessing each item and provides examples.

2.3. Appraisal of systematic reviews on sepsis

2.3.1. Eligibility criteria

We formulated the research question according to the PICOd (population, intervention, comparator, outcome, design) tool. We considered as population adults and paediatric patients with sepsis, including severe sepsis and septic shock, or at the risk of developing sepsis. Reviews on mixed populations (e.g., critically ill patients) involving participants with sepsis were also eligible. Because our focus was on analysis across sex (e.g., to determine if there were any sex differences/similarities), reviews addressing sex-specific health conditions (e.g., prostate biopsy-related sepsis) were excluded. We included any intervention to prevent or treat sepsis (See Supplementary material). We included any comparator to prevent or treat sepsis. For reviews assessing interventions in patients with sepsis, we considered any outcome. For reviews evaluating interventions in populations at the risk of developing sepsis, we included those in which sepsis was a designated main outcome (e.g., sepsis incidence or sepsis-related mortality included in Summary of Findings table). We included Cochrane systematic reviews (SR). We excluded protocols and reviews withdrawn from the Cochrane Library.

2.3.2. Search method and selection process

We used the advanced search option within the Cochrane Database of Systematic Reviews (from inception to 31st December 2020) to retrieve SRs that used “sepsis” either as a MeSH term or as a term in the title, abstract, or keyword (Supplementary material).

Two authors (AA, ES) independently screened titles and abstracts for all retrieved SRs against the eligibility criteria and resolved disagreements by consensus. We used Excel to organise a database of SRs, build data extraction templates, and collect data.

2.3.3. Data extraction

After the duplicate piloting test, one author continued collecting data, while the second cross-checked them, resolving possible discrepancies by discussion. These authors were not involved in the writing or editorial management of the eligible SRs, except in one review [56] evaluated by a third party.

We extracted the following information from each SR:

- Review information: Publication year, Cochrane Group, number of included studies, population, setting, and type of intervention (Supplementary material).
- Participant information: Sample size analysed (total and by sex or gender) when available and otherwise as provided by the review authors (e.g., randomised, enrolled).
- Sex-stratified disease incidence (See Data analysis).

2.4. Data analysis

We tabulated the responses to the tool by simple counts and summarised results numerically to describe overall responses for each question. We calculated the percentage of SRs fulfilling each question when appropriate. We documented sex- and gender-related analysis and reporting trends over time, as well as the potential impact of guidelines proposed by SAGER (Sex and Gender Equity in Research) (2016) [26], based on its supra-national scope and broad dissemination, by comparing proportions using chi-square testing. The temporary cut-off point of the SAGER publication was adjusted to 2017 as the Cochrane policy establishes a period up to one year between the publication of the review protocol and the SR submission.

Additionally, we assessed representation of participants by sex in the reviews using the Participation-to-Prevalence Ratio (PPR) [54,57,58]. The PPR is a metric that compares the representation of a specific population in studies relative to their proportion in the overall disease population. By convention, a PPR between 0.8 and 1.2 suggests bias-free enrolment, whereas values lower or greater reflect under-representation or over-representation, respectively. We calculated the PPR by dividing the percentage of female participants at review-level by the percentage of females at sepsis population-level [i.e., (female participants/total participants)/ (sepsis incidence among females/total sepsis incidence)]. As no review reported sex-stratified incidence or accurate sex-disaggregated data at review-level, we determined sepsis incidence by sex through a comprehensive literature search of infectious disease databases and peer-reviewed journals, accounting for the type of population, setting, country, study execution date, and largest cohort when feasible [59–65]. Table S1 (Supplementary material) details population descriptors used for sex-stratified incidence estimates [54-59]. According to the protocol, we reviewed primary studies included in a subset of 10% of eligible SRs to extract the total participants by sex at review outcome-level.

We performed statistical analyses using STATA statistical software (version 15.1; STATA Corporation, College Station, TX). Lastly, we contacted the 13 Co-ordinating Editors of

Cochrane groups of eligible reviews to comment on the interpretation of findings and considered their feedback on the challenges of SGBA in sepsis reviews.

3. Results

3.1. Description of reviews

The search strategy yielded 226 records of which eight were protocols. One further review was retrieved by checking the reference list of the included SRs. We identified 71 SRs that met our eligibility criteria (Figure 1). The included reviews contained 1,055 studies (432,570 participants). Six reviews found no eligible studies. Most of the SRs (60.56%) assessed the effect of interventions to prevent sepsis, and over half (54.93%) focused on the paediatric population. All reviews were published between 2000 and 2020 (half after 2014). Table 1 and Supplementary material depict characteristics of the included reviews and the reference list, respectively.

3.2. Sex-and gender-based analysis and reporting

Table 2 displays sex- and gender-based analysis and reporting by applying the SGAT-SR-2 tool to the 71 included reviews. Overall, 36 (50.70%) reviews met at least one of the tool items, while no review met all requirements. A single review reported the relevance of female fertility complications in the abstract and plain language summary. Five SRs discussed the relevance of sex or gender to the review question in the background, and two of these considered other PROGRESS-Plus factors interacting with sex or gender. No review used sex, gender, or related terms to describe its objectives. Among five reviews that excluded a particular population based on sex or gender-related criteria, only one provided a rationale. As for planning data collection, 15 (21.13%) SRs pre-specified data extraction of participants by sex or gender, whereas one planned to collect missing data for participants by gender, and 47 reviews provided insufficient details and were rated as “Probably no” for both questions (i.e., #6-#7). As for planning analysis, three reviews defined *a priori* sex subgroup analyses. In the results section, the sex or gender of participants was reported by 24 (33.80%) reviews at the study-level, yet only four provided disaggregated data for the full set of included randomised clinical trials (RCT) (Table S2, Supplementary material). Nine (12.68%) SRs provided inaccurate sex or gender-disaggregated data at the review-level (e.g., “Nine studies [of 13] reported the male-to-female ratio [and] the percentage of males ranged from 60% to 90%, with a mean of 72%” [66]), whilst only one reported sex-disaggregated missing participant data. One SR conducted a narrative synthesis by describing sex-related results. Pre-specified sex subgroup analyses by three of the SRs were not conducted, but two reviews provided a

rationale. Among the four reviews that included sex or gender considerations in the discussion section, one discussed implications for research related to sex, another the applicability of the reviews' findings based on potential variations between sexes, and two others stated limitations due to availability of data by sex or gender and either the implications for research or applicability of the findings. The questions relating to the results and discussion of the findings (i.e., #9-13, -#14, and #16, respectively) were non-applicable for the six reviews that found no eligible studies.

Table 3 summarises the questions of the SGAT-SR-2 about the review authors' use of sex, gender, and related terms (#17-19). Data for these items are presented in a separate table only for clarity purposes as their possible responses are different from the rest of the questions. Out of 71 reviews, the term sex was mentioned in 24 (33.81%) reviews, gender in 16 (22.53%), and terms related to sex and gender (e.g., female, male, women, men, girl, boy) in 42 (59.15%) reviews. Neither sex, gender nor related terms were used in 23 (32.39%) reviews. Non-binary use of sex and gender and use of appropriate categories to refer to sex and gender were assessed only in the reviews that mentioned sex or gender. Most authors treated sex (17/24 reviews; 70.84%) and gender (11/16 reviews; 68.75%) as binary variables, and the remaining as unclear. The use of categories to characterise sex was evenly distributed into appropriate (8/24 reviews) (e.g., "Sex: female/male" [67]), inappropriate (e.g., "Sex: 58.5% men" [68]) and unclear use (i.e., authors mentioned the term sex without subsequent categories), whereas to describe gender, most authors used inappropriate categories (10/16 reviews; 62.5%) (e.g., "Gender: male/female" [69]). Of the 48 SRs that mentioned sex, gender, or related terms, almost two-thirds (30/48 reviews; 62.5%) used sex and gender interchangeably.

3.3. Sex- and gender-based analysis and reporting over time

Figure 2 shows disaggregated data by the inclusion of at least one of the SGAT-SR-2 questions over the publication years. Overall, there were no substantial trend changes. The data did not suggest an association between the publication year of SAGER guidelines (2017 onwards) with the likelihood of sex- and gender-based analysis and reporting in sepsis reviews ($P= 0.071$).

3.4. Participation-to-Prevalence Ratio (PPR)

We examined the level of representation by sex of participants in seven (10%) reviews [63,65–70] involving 65 RCTs (18,909 participants) (See References to RCTs, Supplementary material). Three SRs were conducted in adults, two in children, and two included both groups.

Of the latter, we withdrew 16 RCTs from PPR analyses: three trials (202 participants) that enrolled children because sex-stratified incidence of sepsis differs by age [2] and 13 RCTs (1,224 participants) for which no data were available on the sex of participants, leaving 49 RCTs (17,483 participants) that provided sex-disaggregated information. The PPR was <0.8 in the samples of pooled trials assessing primary outcomes of three reviews that included adults [72–74], indicating that females were represented at a level lower than their share of the sepsis population and relatively close to 1 in a further three reviews that included either adults [69,71] and neonates [70], indicating that the sex ratio approximated that of the sepsis population. PPR ranged from 0.79 to 1.08 in one review that included children [67], whose incidence by sex based on available data presented a substantial heterogeneity (Table 4).

4. Discussion

The SGAT-SR-2 tool provides insight into sex and gender considerations and assesses reporting of other PROGRESS-Plus factors associated with health inequities. Our analysis of Cochrane reviews on sepsis interventions revealed that half met at least one item addressing sex-and gender-based analysis and reporting. The most frequently reported item was the number of participants by sex or gender at study-level, and only two reviews mentioned other PROGRESS-Plus characteristics interacting with sex or gender. Most authors treated sex and gender as binary variables, used the terms interchangeably, and described gender by applying sex-related categories. The female representation was assessed in a subset of eligible reviews. As the necessary data for calculating PPR were unavailable in the reviews, they were extracted directly from the included RCTs. PPR indicated that the female representation level was less than the female incidence proportion for sepsis at the review outcome-level in three out of seven reviews, and similar to their share of the sepsis population in another three, while the female participation ranged from under to adequate representation in a further review.

The scarcity of sex- and gender-based analysis and reporting across sepsis reviews corroborates results in other fields [33,48,75,76]. Our analysis makes an additional contribution by exploring the interaction of sex and gender with other PROGRESS-Plus factors. Despite increasing awareness of the impact of sex and gender on treatment response and disease management, it is disappointing that we found no time trends for SGBA. Furthermore, none of the pre-defined subgroup analyses by sex was undertaken in sepsis reviews. It is worth noting that inclusion criteria of sepsis studies based on specific diseases hinder the interpretation of sex or gender subgroup analyses. For sex- or gender-specific conditions (e.g. post-caesarean-related sepsis), such interpretations might be straightforward. However, for those specific diseases not related to sex- or gender-specific conditions, it may be difficult to differentiate between sex-or gender-specific and disease-specific (e.g.,

urosepsis) effect modification. Bearing in mind biological plausibility and social constructs, such differentiation requires discussing if differences accounted for sex or gender may be expected *a priori*, collecting data (e.g., raw sex- and gender-disaggregated outcomes from primary studies, which allows performing individual patient data meta-analyses), exploring specific interactions, and interpreting the findings [25,26,38,77].

Among the two-thirds of reviews that mentioned sex, gender, and related terms, most authors applied binary categories and used sex and gender interchangeably. This is consistent with the findings of previous studies [33,34,78]. Although the peer-reviewed scientific literature has documented health outcomes on gender diverse people, substantial gaps in research remain [79,80]. More inclusive data collection approaches will hopefully expand sex- and gender-reporting beyond binary categories [81].

To our knowledge, this is the first study assessing the representation of participants by sex involved in sepsis systematic reviews (i.e., PPR). Among the reviews involving paediatric populations, PPR indicated adequate representation in one SR and ranged from under to bias-free enrolment in another. Nevertheless, our results confirm findings in other fields that showed bias-enrolment in adults [82–84]. One possible explanation may be that as females with sepsis tend to be older and to have more medical comorbidities than males [59,85–87], RCTs may be more likely to exclude them due to age, comorbidities, and conditions related to female sex (e.g., pregnancy, lactation, or lack of contraception use) [88]. The PPR tackles challenges conflated by the difficulty in establishing accurate estimates of disease prevalence/incidence, particularly for low- and middle-income countries, and the variation in relative disease prevalence/incidence by sex across age. Some sex-specific considerations for developing clinical trials and guidelines suggest that, at minimum, the participation of each sex should reflect the sex-stratified prevalence in the disease population and suggest exploring sex-specific bias using the PPR [19,54,89]. Similarly, this metric could be a valuable tool for systematic reviews to assist users in making decisions about to whom the evidence applies.

Integration of sex and gender in reviews for clinical conditions, such as sepsis, enables researchers to explore the causes of heterogeneity among studies and to assess the findings [90,91]. For example, Benstoem and colleagues downgraded the certainty of the evidence of their findings for chronic heart failure due to male predominance [92]. Moreover, while PRISMA and Cochrane state SRs should present the demographics of contributing studies [93,94], this recommendation could benefit from specifying further details. Identifying outstanding gaps or missing groups through evidence synthesis sheds light on “who may be left out” and may stimulate research to address these gaps [80,95,96]. Stakeholders leading

evidence synthesis, such as Cochrane, can enhance accountability by asking critical questions about the applicability of findings [49,52].

The strengths of the study include a registered protocol and an advisory board of topic experts. Some members either designed the original tool or applied it in previous studies, providing added insights about premises underlying the original tool and challenges. We developed a summary providing explanations, rationales, and, when available, good practice examples on SGBA that may serve as a resource for planning SRs (Supplementary material). We also analysed the sex representation by calculating PPRs in a subset of reviews. We received feedback from almost half of the Co-ordinating Editors of the included Cochrane Groups. As for limitations, since we designed a Cochrane-restricted search strategy, our sample does not cover the entire spectrum of SRs on sepsis interventions. Another limitation is the exclusion criterion of sex-specific conditions, which may be closely intertwined with gender identities, such as transgender. As well as a definitional issue for systematic reviewers, this is an important societal issue raised by discussions of definitions of sex and gender, which continue to be fluid but exceed the scope of this study. As well, our study was limited to what reviews reported. Finally, as sex, gender and intersectionality theories are evolving constructs, this study should be interpreted in light of current efforts to enhance SGBA and draw attention to the need for integrating the social determinants of health into clinical research.

In conclusion, Cochrane reviews on sepsis rarely addressed sex-and gender-based analysis or considered other interacting PROGRESS-Plus characteristics. The SGAT-SR-2 tool and the PPR can support the design and appraisal of systematic reviews for sepsis and other health conditions to assess sex and gender considerations, interaction with PROGRESS-Plus, and the applicability of evidence. Addressing to whom the evidence applies and what uncertainties remain can have transformative implications for clinical practice, research, and policy-making.

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CRedit authorship contribution statement

Alba Antequera: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing-Original Draft, Writing-Review & Editing. Elena Stalling Validation, Investigation, Writing-Review & Editing. Richard S. Henry: Methodology, Advisory Board, Writing-Review & Editing. Jesus Lopez-Alcalde: Conceptualization, Methodology, Advisory Board, Writing-Review & Editing. Vivien Runnels: Conceptualization, Methodology, Advisory Board, Writing-Review & Editing. Sari Tudiver: Conceptualization, Methodology, Advisory Board, Writing-Review & Editing. Peter Tugwell: Methodology, Advisory Board, Writing-Review & Editing. Vivian Welch: Conceptualization, Methodology, Writing-Review & Editing, Supervision.

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Figures

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Figure 1. Study flow diagram

Figure 2. Sex- and gender-based analysis and reporting in Cochrane systematic reviews of sepsis from 2000-2020.

Tables

Table 1. Characteristics of the included reviews

Characteristics	Included reviews, N=71	Sex or gender considerations
		N reviews including sex or gender considerations: N reviews not including sex or gender considerations
Cochrane review groups (N,%)		
Colorectal Cancer Group	3 (4.22)	3:0
Cystic Fibrosis and Genetic Disorders Group	1 (1.41)	1:0
Emergency and Critical Care Group	18 (25.35)	13:5
Gut Group	2 (2.82)	2:0
Gynaecological, Neuro-oncology and Orphan Cancer Group	1 (1.41)	0:1
Hepato-Biliary Group	1 (1.41)	1:0
Infectious Diseases Group	2 (2.82)	0:2
Injuries Group	3 (4.22)	3:0

Kidney and Transplant Group	2 (2.82)	2:0
Neonatal Group	33 (46.48)	5:28
Pregnancy and Childbirth Group	1 (1.41)	1:0
Vascular Group	1 (1.41)	1:0
Wounds Group	3 (4.22)	3:0
Type of population (N,%)		
Adult	17 (23.94)	16:1
Paediatric	39 (54.93)	9:30
Neonates	34 (47.89)	7:27
Children	5 (7.04)	2:3
Mixed: Adult and paediatric	15 (21.13)	10:5
Type of intervention (N,%)		
Prevention of sepsis	43 (60.56)	21:22
Treatment of sepsis	27 (38.03)	14:13
Initial resuscitative treatment	13 (18.31)	8:5
Failure of initiative therapy	2 (2.82)	1:1
Supportive therapies	7 (9.86)	5:2
Investigational therapies	5 (7.04)	0:5
Mixed: Prevention and treatment	1 (1.41)	0:1
Setting (N,%)		
Hospital	59 (83.10)	29:30
Admitted to ICU	30 (42.25)	15:15
Admitted to non- ICU department	2 (2.82)	2:0
Admitted to any department (ICU or non-ICU)	27 (38.03)	12:15
Out-of-hospital	3 (4.22)	0:3
Mixed: Hospital and out-of-hospital	7 (9.86)	4:3
Not stated	2 (2.82)	2:0

Abbreviations: ICU, intensive care unit.

Table 2. Responses to the questions #1-#16 of the SGAT-SR-2 tool

Review section	Question	Reviews meeting the criteria				
		Yes	No	Probably yes	Probably no	NA
Abstract	1. Did the abstract report on sex or gender?	1	70	0	0	0
Plain language summary	2. Did the plain language summary report on sex or gender?	1	70	0	0	0
Background	3.a. Did the background discuss the relevance of sex or gender to the review question?	5	66	0	0	0
	3.b. If 3.a. "Yes" or "Probably yes", Did the background discuss if sex or gender interact with other PROGRESS-Plus characteristics in the context of the review question?	2	4	0	0	65
Objectives	4. Were sex, gender or related terms used in objectives?	0	71	0	0	0
	5.a. Did the review's eligibility criteria consider sex or gender differences?*	1 RP 4 RNP	66	0	0	0
Methods	5.b. If 5.a "Yes" or "Probably yes", Did the review's eligibility criteria consider any other PROGRESS-Plus characteristics interacting with sex or gender?	0	5	0	0	66
	6. Did the review plan to collect characteristics of participants by sex or gender at the study-level?	15	9	0	47	0
	7. Did the review plan to collect missing participant data by sex or gender at the study-level (e.g., attrition from the study)?	1	23	0	47	0
	8.a. Did the review plan to analyse or report results across sex or gender for the most important outcomes (e.g., analyses to investigate heterogeneity, such as subgroup analysis)?†	3	68 RNP	0	0	0
	8.b. If 8.a. "Yes" or "Probably yes", Did the review plan to analyse or report results accounting for any other PROGRESS-Plus characteristics interacting with sex or gender?	0	3	0	0	68
	9. Did the review report characteristics of participants by sex or gender at the study-level (or state that no data were available)?	24	41	0	0	6
	10. Did the review report missing participant data by sex or gender at the study-level (or state that no data were available)?	1	64	0	0	6
	11. Did the review report characteristics of participants by sex or gender at the review-level (or state that no data were available)?	9	54	0	2	6

Results	12.a. Did the review analyse or report results across sex or gender for the most important outcomes (e.g., analyses to investigate heterogeneity, such as subgroup analysis)?†	1	2 RP 62 RNP	0	0	6
	12.b. If 12.a. "Yes" or "Probably yes", Did the review analyse or report results accounting for any other PROGRESS-Plus characteristics interacting with sex or gender?	0	1	0	0	70
	13. Did the review consider the characteristics of participants by sex or gender to assess the certainty of the body of the evidence for review outcomes (i.e., indirectness)?	0	65	0	0	6
	14. Did the review discuss the limitations related to sex or gender of the population of interest?	2	63	0	0	6
Discussion and Authors' conclusions	15. Did the review discuss the implications of evidence for practice or research related to sex or gender of the population of interest?	2	69	0	0	0
	16. Did the review discuss the applicability of evidence related to sex or gender of the population of interest?	2	63	0	0	6

Abbreviations: NA, non-applicable; RP, rationale provided; RNP, non-rationale provided.

* "Yes" response required to specify if a rationale was provided.

† "No" response required to specify if a rationale was provided.

Table 3. Responses to the questions #17-19 of the SGAT-SR-2 tool: the use of sex, gender and related terms

Questions	Reviews meeting the criteria (N, %)
17. Non-binary use of sex and gender Explanation: When authors mentioned the terms sex or gender, did they describe them by using two or more categories?	
Sex (N=24)	
Binary use (female/male)	17 (70.83)
Non-binary use (person with DSD/female/male)	0 (0)
Unclear	7 (29.17)
Gender (N=16)	
Binary use (woman/man or girl/boy)	11 (68.75)
Non-binary use (woman/man/gender diverse/etc.)	0 (0)
Unclear	5 (31.25)
18. Use of appropriate categories Explanation: When authors mentioned the terms sex or gender, did they use consistently the corresponding related-categories, according to the current international definitions?	
Sex (N=24)	
Appropriate (person with DSD/female/male)	8 (33.34)
Inappropriate (girl/boy/woman/man/gender diverse/etc.)	8 (33.34)
Unclear	8 (33.34)
Gender (N=16)	
Appropriate (girl/boy/woman/man/gender diverse/etc.)	2 (12.50)
Inappropriate (person with DSD/female/male)	10 (62.50)
Unclear	4 (25.00)
19. Non-interchangeable use (N=48) Explanation: When authors mention sex, gender, or related terms, did they use them interchangeably?	
Yes	30 (62.50)
No	8 (16.67)
Unclear	10 (20.83)

Abbreviations: DSD, differences of sex development.

Table 4. Participation-to-Prevalence Ratio for a subset of eligible reviews

Review	Outcome assessed	Population Setting	RCTs (N)	Publication year range	Sample (N)	Females (N)	PPR
Shah 2009 [70]	Incidence of Staphylococcal infections	Neonates ICU	3	2005-2007	2,694	1,358	1.08;1.16*
Warttig 2018 [69]	Time to initiation of antimicrobial therapy	Adults ICU	3	2012	442	199	0.92
Paul 2014 [71]	Mortality at follow-up	Adults Hospital†	12	1979-2006	1,114	474	0.82
Annane 2019 [72]	28-day mortality	Adults Hospital†	30	1984-2018	9,044	3,507	0.75
Borthwick 2017 [73]	28-day mortality	Adults ICU	2	2008-2013	159	61	0.78
Li 2018 [67]	Mortality at follow-up	Children Hospital‡	1	2011	3,141	1,452	0.79; 1.08*
Szakmany 2012 [74]	30-day mortality	Adults ICU	11	1994-2008	889	291	0.67

Abbreviations: ICU, intensive care unit; PPR, participation-to-prevalence ratio; RCT, randomised clinical trial.

* PPR estimated using two data sources for the sex-stratified incidence of sepsis due to substantial heterogeneity among available estimates.

† Data displayed represents adults, after removing RCTs on paediatric population.

‡ Review setting: Admission to the hospital or ICU. However, for mortality at follow-up, authors considered a single RCT that included participants treated on general wards.