Universitat Autònoma de Barcelona

Sex and gender considerations in clinical research on sepsis: sex-and gender-based analysis and prognostic effect

Alba Antequera Martín

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P.h.D in Methodology of Biomedical Research and Public Health
Department of Paediatrics, Obstetrics & Gynaecology and Preventative Medicine
Faculty of Medicine, 2021

Doctoral thesis
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Directors
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Cover credit: Julia Campello Coll.

Une personne qui tombe d'un immeuble de 50 étages. Le mec, au fur et à mesure de sa chute, elle se répète sans cesse pour se rassurer: " Jusqu'ici tout va bien... Jusqu'ici tout va bien... Jusqu'ici tout va bien " Mais l'important, c'est pas la chute. C'est l'atterrissage.

La Haine

To Encarna, Elena, and Juan, who write me letters,

Abstract

Background: Historically, western-oriented research knowledge and approaches have often reproduced the dynamics of different structural oppression systems. The evidence derived from these methodologies is at risk of disregarding the needs of health care and values and preferences of most of the population that, in turn, is composed of a mosaic in which groups experiencing multiple axes of disadvantage. Sepsis is a leading cause of mortality worldwide. The degree of sex- and gender-related inclusion analysis and reporting in studies underpinning clinical recommendations for sepsis, as well as the role of sex as an independent prognostic factor for mortality among critically ill adults with sepsis, remain unclarified.

Objective: To synthesise and evaluate the role of sex and gender in clinical research on sepsis and elaborate a methodological approach to sex-and gender-based analysis in systematic reviews (SR).

Methods: Article-based thesis composed of three main studies. First study: A bibliometric study examining the female Participation–to–Prevalence Ratio (PPR) in primary studies underpinning recommendations from clinical guidelines and SRs for sepsis. Second study: A revision process of sex and gender appraisal tool for SR (SGAT-SR). We revised the items to consider additional factors associated with health inequities and appraised sex and gender considerations using the SGAT-SR-2 and PPR in Cochrane sepsis reviews. Third study: SR and meta-analysis. We included studies evaluating independent associations between sex and mortality in critically ill adults with sepsis controlling for at least one of five core covariate domains pre-specified following a literature search and consensus amongst experts.

Results: Among 277 sepsis primary studies examined, females were under-enrolled. Among 71 Cochrane reviews assessed, possible similarities and differences across sex and gender were rarely appraised. Prognostic SR included 13 studies. Meta-analysis found no sex-based differences in all-cause hospital mortality and all-cause ICU mortality (very low-certainty evidence). Females presented higher 28-day all-cause mortality (very low-certainty evidence) and lower 1-year all-cause mortality (low-certainty evidence).

Interpretation: Representation of participants by sex in sepsis studies can be assessed by using PPR. The SGAT-SR-2 tool can support the design and appraisal of SR to assess sex and gender considerations. Clinical research should embrace sex- and gender-based analysis to understand

to whom the evidence applies, given the potential implications for clinical practice, research, and policy-making. High-quality research is needed to test the adjusted prognostic value of sex for predicting mortality in critically ill adults with sepsis.

Resum

Rerefons: Històricament la recerca i el coneixement produïts des d'occident sovint han reproduït les dinàmiques de diferents sistemes d'opressió estructural. L'evidència derivada d'aquestes metodologies córre el risc d'ignorar les necessitats de l'atenció sanitària i els valors i preferències de la majoria de la població que, alhora, està formada per un mosaic de grups atravessats per múltiples eixos de desigualtat. La sepsia és una de les principals causes de mortalitat mundial. L'inclusió i l'anàlisi per sexe i gènere en els estudis que sustenten les recomanacions clíniques sobre sèpsia, així com el rol del sexe com un factor pronòstic independent de mortalitat entre els adults en estat crític amb sèpsia segueix sense estar clar.

Objectiu: Sintetitzar i avaluar el rol del sexe i el gènere en la recerca clínica sobre sèpsia i elaborar un enfoc metodològic per a les anàlisis basades en sexe i gènere en les revisions sistemàtiques (RS).

Mètode: Tesi basada en articles composta per tres estudis principals. Primer estudi: Estudi bibliomètric examinant la Ràtio Participació-Prevalença (PPR) en estudis primaris que sustenten les recomanacions de les guies clíniques i revisions sistemàtiques sobre la sèpsia. Segon estudi: Revisió de l'eina d'avaluació de sexe i gènere per a RS (SGAT-SR). Hem analitzat els items per a tenir en compte factors adicionals associats a les inequitats en salut i hem valorat les consideraciones de sexe i gènere utilitzant l'SGAT-SR-2 i el PPR en RS Cochrane sobre sèpsia. Tercer estudi: RS i meta-anàlisis. Hem inclòs estudis que evaluen les associcacions independents entre sexe i mortalitat en adults en estat crític amb sèpsia control·lant almenys un dels cinc dominis de covariables pre-especificades després d'una recerca bibliogràfica i un consens d'experts.

Resultats: Les dones estan infra-representades en els 277 estudis primaris sobre sèpsia. Entre 71 revisions Cochrane avaluades, rara vegada han estat avaluades possibles similituds i diferències entre sexe i gènere. La RS pronòstica va incloure 13 estudis. La metanàlisi no va trobar diferències per sexe en la mortalitat hospitalària per totes les cases i mortalitat per totes les causes a l'UCI (molt baix nivell d'evidència). Les dones presenten una mortalitat més alta per totes les causes al dia 28 (molt baix nivell d'evidència) i menor mortalitat per totes les causes a l'any (baix nivell d'evidència).

Interpretació: La representació dels participants per sexe en estudis sobre sèpsia es pot avaluar utilitzant PPR. SGAT-SR-2 pot donar suport al disseny i avaluació de RS en relació amb les consideracions de sexe i gènere. La recerca clínica necessita integrar l'anàlisi basats en sexe i gènere per comprendre qui són inclosos (i exclosos) a l'evidència. És necessària recerca d'alta qualitat per avaluar i ajustar el valor pronòstic del sexe per a predir la mortalitat en adults en estat crític degut a la sèpsia.

Resumen

Antecedentes: Históricamente, la tradición científica occidental ha reproducido los sistemas de estructuras opresivas. Este conocimiento corre el riesgo de desatender las necesidades de atención en salud y los valores y preferencias de la mayoría de la población que, a su vez, está formada por un mosaico de grupos atravesados por múltiples ejes de desventaja. La sepsis es una de las principales causas de mortalidad en todo el mundo. El grado de inclusión, análisis y presentación de resultados en relación al sexo y género en los estudios que sustentan las recomendaciones clínicas para la sepsis, así como el papel del sexo como factor pronóstico independiente para la mortalidad en pacientes críticos con sepsis, están sin clarificar.

Objetivo: Sintetizar y evaluar el papel del sexo y el género en la investigación clínica sobre sepsis y elaborar una propuesta metodológica para los análisis de sexo y género en las revisiones sistemáticas (RS).

Métodos: Tesis por compendio de publicaciones compuesta por tres estudios principales. Primer estudio: Estudio bibliométrico que examina la Ratio Participación-Prevalencia (PPR) por sexo en los estudios primarios que sustentan las recomendaciones de las guías clínicas y RS de sepsis. Segundo estudio: Revisión de la herramienta para la valoración de las categorías sexo y género en RS (SGAT-SR, por sus siglas en inglés). Revisamos los ítems considerando otros factores adicionales asociados con las inequidades en salud y evaluamos los ejes de sexo y género utilizando SGAT-SR-2 y PPR en revisiones Cochrane de sepsis. Tercer estudio: RS y metaanálisis. Incluimos estudios que evaluaban asociaciones independientes entre sexo y mortalidad en adultos críticos con sepsis ajustando, al menos, por uno de los cinco dominios de covariables preespecificados tras el proceso de búsqueda bibliográfica y consenso de expertos.

Resultados: Las mujeres estuvieron infrarrepresentadas en los 277 estudios primarios de sepsis. Las 71 revisiones Cochrane raramente evaluaron las posibles similitudes y diferencias entre sexos y géneros. La RS pronóstica incluyó 13 estudios. El metanálisis no encontró diferencias por sexo en la mortalidad hospitalaria y mortalidad en UCI (muy baja certeza de la evidencia). Las mujeres presentaron una mayor mortalidad a los 28 días (muy baja certeza de la evidencia) y una mortalidad por todas las causas al año más baja (baja certeza de la evidencia).

Interpretación: La representación de los participantes por sexo en los estudios de sepsis puede evaluarse con el PPR. SGAT-SR-2 puede apoyar el diseño y evaluación de RS en relación a las consideraciones de sexo y género. La investigación clínica necesita integrar el análisis basado en sexo y género para comprender quiénes son incluidos (y excluidos) en la evidencia. Se necesita investigación de alta calidad para evaluar el valor pronóstico independiente del sexo en la mortalidad en adultos críticos con sepsis.

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Conflict of interest

The author declares no conflict of interest.

Ethical approval

Ethics permission was not necessary as this thesis used only published data.

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List of abbreviations

AIDS Acquired immunodeficiency syndrome

APACHE Acute Physiology and Chronic Health Evaluation

CHARMS-PF Checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies for prognostic factors

CDC Centers for Disease Control and Prevention

CDSR Cochrane Database of Systematic Reviews

CI Confidence interval

CONSORT Consolidated standards of reporting trials

COVID-19 Coronavirus disease 2019

F Females

GRADE Grading of recommendations assessment, development, and evaluation

HIV Human immunodeficiency viruses

HKSJ Hartung-Knapp-Sidik-Jonkman

ICU Intensive care unit

M Males

N/A Not applicable

NIH National Institutes of Health

OR Odds ratio

PI Prediction interval

PICOd Population, intervention, comparator, outcome, design

PICOTS Population, index, comparator, outcome(s), timing, setting

PF Prognosis factor

PPR Participation–to–Prevalence Ratio

PRISMA Preferred reporting items for systematic reviews and meta-analyses

PROGRESS-Plus 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

QUIPS Quality in prognosis studies

RCT Randomised clinical trials

REMARK Reporting recommendations for tumour marker prognostic studies

RoB Risk of bias

SAPS Simplified acute physiology score

SDI Socio-demographic index

SGAT Sex and gender appraisal tool – systematic reviews

SGBA Sex- and gender-based analysis

SOFA Sequential organ failure assessment score

SR Systematic review

SSC Surviving sepsis campaign

WHO World Health Organisation

01 Background

1. Background

1.1. Description of the condition: Sepsis

Sepsis, a preventable life-threatening response to infection marked by severe organ dysfunction, remains a substantial public health burden globally [1,2]. In 2017, an overall estimated 49 million incident cases of sepsis, 41% of them among children under five years old, and 11 million sepsis-related deaths were recorded, accounting for one of five deaths worldwide [3]. Significant geographical disparities are found in sepsis incidence since 85% of new cases were among people living in regions with a low or middle socio-demographic index (SDI) [3]. Regarding our context, in 2017, age-standardised sepsis incidence in Western Europe and Spain was 67.8 and 162.2 per 100,000 population, respectively [3]. Hospitalisations due to sepsis have risen over time in Spain and Catalonia [4,5]. Sepsis-related deaths differ markedly across locations. Although the highest age-standardised sepsis-related mortality also occurred in countries with the lowest SDI, the inverse relation with SDI is stronger for mortality than for incidence [3]. Hospital mortality occurs in one-third of adults with sepsis, and it is the leading cause of death in critically ill patients [6–8]. Moreover, among adults who survive after admission for sepsis, more than one in five die in the next two years [9], and one in six experience significant, long-term morbidity [2]. Readmissions within 90 days of discharge for sepsis are also common (an estimated 40% among adults aged 50 years or older) [9].

Sepsis is a heterogeneous syndrome shaped by pathogen factors and host factors that lead to organ dysfunction [1]. The pathogenesis involves a complex and dynamic chain of interactions from the host response, with early activation of both pro-inflammatory and anti-inflammatory mechanisms, to major modifications in the neuroendocrine system, cardiovascular response, coagulation pathways, and neurological and autonomic disturbances [1,10–12]. Accurate identification of sepsis among patients with suspected or confirmed infection is challenging. There is currently no *gold standard* diagnostic test for sepsis [13]. Since 2016, a consensus definition of sepsis for adults (Sepsis-3) has been “life-threatening organ dysfunction caused by a dysregulated host response to infection”, where organ dysfunction is identified as an acute increase in the total organ failure relative to baseline score [1,14]. Septic shock refers to a subset of sepsis characterised by a cardiovascular dysfunction and cellular abnormalities in which patient requiries vasopressors to maintain the arterial pressure and tissue perfusion (i.e., targeting markers of mean arterial pressure of ≥65 mm Hg and serum lactate level < 2 mmol/L, respectively) in the absence of hypovolemia [1]. Septic shock associates a higher likelihood of death than sepsis alone [1]. The analyses to

evaluate the validity of clinical criteria for diagnosis sepsis outside of the intensive care units (ICU), based on the qSOFA [quick Sequential (Sepsis-related) Organ Failure Assessment] score, were conducted on exclusively cohorts from Germany and the United States [13,14] and validated retrospectively in Low- and Middle-Income Countries (LMIC) [15]. However, it should be noted that no decision rule has been evaluated prospectively in low-resources settings [13]. Additionally, although the task force for Sepsis-3 specified no possible causes of sepsis [13,16], the major sources of infections potentially leading to organ failure encompass lower respiratory tract infections (including critical coronavirus disease 2019, COVID-19), diarrhoeal diseases, bacterial bloodstream infections, severe malaria, complicated dengue, and systemic fungal infections [2,10,17]. The definition of sepsis for the paediatric population is also challenging. The last consensus criteria of paediatric sepsis in 2005 relied on the adult sepsis definition at that time (Sepsis-1 1991), which considered suspected infection alongside values of the systemic inflammatory response syndrome criteria adapted to age [18]. Formal revisions to the 2005 paediatric sepsis definitions are awaiting, especially those constraints related to requirements for laboratory tests in resource-limited environments [13,18,19]. Lastly, there is a lack of unified criteria for neonatal sepsis [20].

Risk factors for developing sepsis focus on a patient's predisposition to infection and the likelihood of organ dysfunction. Exposure to an epidemic, extremes of age (<2 years and >55 years), host genetic factors, underlying immunosuppression (such as HIV, diabetes, cancer, drug-mediated immune suppression, and alcohol abuse), chronic diseases (e.g., chronic obstructive pulmonary disease, and protein-calorie malnutrition), and breach of natural barriers (e.g., trauma, burn, surgical injury, catheterization, and intubation) all predispose patients to infection [10–12]. Risk factors for developing organ dysfunction among patients with infections are less well defined, but probably include the infecting pathogen, comorbidities, host genetic factors, male sex, black race, and timeliness of treatment [11,12,21–23].

Advances in our understanding of sepsis over the last decades have not led to substantial improvements in outcomes [24]. The patient care strategies that have shown effectiveness include early diagnosis, the completion of an initial bundle of management (providing cardiorespiratory resuscitation and appropriate and timely empirical antimicrobial therapy and source control), and a management bundle for critically ill patients (e.g., the recommendation of lung-protective ventilation) [12,16,25].

1.2. Description of the sex and gender as social determinants of health

1.2.1 Sex and gender constructs

Understanding sex and gender variables and drawing attention to their operationalisation is the first step to integrating sex and gender in medical research. Sex and gender are distinct constructs, though often used interchangeably in the scientific literature on health and public discourse [26]. Yet even though there are no single agreed-upon definitions, sex is commonly understood to refer to biological attributes 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) [27–29]. Sex is associated with physical and physiological features, including chromosomes, gene expression, and hormonal levels, but it is typically assigned at birth (or before during ultrasound) based on the appearance of external genitalia [30]. Gender is associated with socially constructed roles, relationships, behaviours, and identities of women, men, transgender, and other gender-diverse people, and relative power that societies ascribe according to such genders [26,27]. *Cisgender* people represent individuals whose sex assigned at birth is congruent with their gender identity [30]. *Trans* (transgender, transsexual, and other gender diverse people) term encompass a broad spectrum of nonconforming identities of persons who self-identify or are categorised as having gender other than that labelled at birth [27,31]. It is worth noting that the terminology used to denote sex and gender categories varies across societal contexts (e.g., *bantut* in the Philippines, *muxes* in Mexico, or *hijra* in India) [32,33]. Lastly, in contrast to biological essentialism, where gender is fixed and determined by biological sex [33], biosocial, relational, and intersectional approaches understand sex and gender are distinguishable social categories that reflect complex biological, genetic, and social processes closely intertwined [34–36]. Thus, other social constructs permeate the biological sex. For example, several studies suggest that smoking and low socioeconomic status are associated with earlier natural menopause [37–39].

Understanding differences between sex and gender terms expands beyond a linguistic issue but enabling researchers to consider them separately, when appropriate, and accurately discuss the clinical implications of the findings [40]. It also can contribute to reducing the stigma of non-binary individuals [40–42]

1.2.2 Historical perspective on sex and gender in health research

In the Western tradition, until the Enlightenment, the one-sex model prevailed categorising the sex of individuals into a single one. While all individuals had the same sexual and reproductive organs (and consequently, the same "sex"), females' organs were envisioned as inverted (within the body) [43,44]. Throughout the 19th century, the two-sex model emphasised the biological differences between female and male individuals [43,45]. Along with the growing recognition of scientific authority in controversial social matters, biological differences were argued to support social hierarchies [46]. Thus, sociopolitical struggles over human inequities shaped the conceptualisation of sex as a biomedical category [46]. Later, the discovery of chromosomal sex determination (1905) and the isolation of sex hormones (the 1920s-1930s) reinforced the idea of the role of biological traits as social and individual behaviours determinants of health [44,46,47]. Sex come to be used interchangeably in research reports to referring to either biological and social processes until during the late 1950s through the 1970s when the concept of gender emerged from theory and research in gender development [44,48,49]. Women's health was relegated to obstetrics and gynaecology (including sexually transmitted infections), and maternal and child health programmes for a long period [46,50]. The omission of sex and gender categories in other fields of medical and public health research, alongside the conceptualisation of race, has been broadly interpreted as the assumption of the Caucasian male subject as the standard default [44,46]. However, Krieger pointed out an alternative explanation that emphasises the acceptance of difference, which justifies the Caucasian male norm for all health conditions, except Caucasian females for reproductive health and non-Caucasians for measure degrees of racial difference [46]. Over the last decades, women's right movements, scholars, healthcare providers, and institutions (such as the WHO Commission of Social Determinants of Health) have moved sex and gender considerations beyond reproductive health and recognised them to be important to an accurate understanding of health and disease [26,51]. Exploring both potential similarities and differences across sex and gender and among diverse groups within specific sex or gender is essential to move toward precision medicine [46,52]. For example, studies found that chronic obstructive pulmonary disease incidence in Sweden was highest in native women with low income and low education who lived alone [53], that the schistosomiasis prevalence in Nigeria was highest in young men [54], and that statin therapy has similar effectiveness for the prevention of major vascular events across sexes [55], while aspirin was not beneficial for primary prevention[1] among females younger than 65 years old [56].

[1] This randomized clinical trial was published in 2005. Current clinical practice guidelines [289] (2019) reflect that aspirin has questionable benefits in the primary prevention of cardiovascular diseases, either sex.

1.2.3 Sex and gender approaches in health research

Table 1 summarises sex and gender approaches in health research [i.e., sex and gender blind research, sex and gender differences, SGBA (sex- and gender-based analysis), SGBA+, and intersectionality] according to the typology described by Hammarström, McCarthy and colleagues, and Brabete and colleagues [44,48,57,58]. SGBA is a framework that helps researchers explore 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. Additionally, either SGBA+ or intersectional frameworks rest on the premise of heterogeneity within individuals belonging to a particular sex or gender group, drawing attention to simultaneous social dimensions that overlap and interact with each other to drive health outcomes [59]. SGBA+ calls attention to the importance of addressing other social determinants of health that interact with sex and gender by operating under an additive assumption, while an intersectional framework helps researchers examine the potential impacts of interlocking systems of inequities and oppression exploring multi-faceted interactions in which categories take their meaning from others [44,51,57,60]. For example, in the Ebola outbreak, context-specific vulnerabilities related to different levels of exposure for women and men intersect with poverty and low social status [61–63]. Bauer and colleagues [64] illustrated the problems of ignoring intersectional relationships pointing out a study of cardiac catheterization referrals that received extensive coverage in the media [65]. The ensuing discussion focused on those individuals who were female and who were black (as independent categories) were less likely to be referred for catheterization [66], whereas analysis revealed that the reduced referrals rate was limited entirely to black female participants, and this interaction resulted in overall effects across sex and race [67].

Health equity is defined as the absence of avoidable and unfair differences in health [68]. 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 [69–73]. The PROGRESS-Plus framework provides a conceptual and practical framework that researchers can use to improve the reporting of social determinants of health. In short, PROGRESS-Plus is comprised of **P**lace of residence, **R**ace/ethnicity/culture/language, **O**ccupation, **G**ender or sex, **R**eligion, **E**ducation, **S**ocioeconomic status, **S**ocial capital, and other contextual factors that facilitate disadvantage, such as age, sexual orientation, and disability [74–76]. Equity extensions of reporting guidelines for systematic reviews (preferred reporting items for systematic reviews and meta-analyses, PRISMA-Equity) and randomised trials (consolidated standards of reporting trials, CONSORT-Equity) as well as Cochrane recommend the

PROGRESS-Plus framework as a reminder to consider the social determinants of health in clinical and epidemiological research [77,78] .

Table 1. Models to considering sex and gender in health research

Research phase/ Model	Sex and gender blind research	Sex and gender differences	SGBA	SGBA+	Intersectional
Epistemology of medicine	Not questioned	Not questioned	Questioned	Questioned	Questioned
Terms sex and gender	"Static difference" perspective: sex and gender as dichotomous variables on an individual level Lack of definition. Terms are used interchangeably	"Static difference" perspective: sex and gender as dichotomous variables on an individual level Sex and gender may be defined. Terms may be used interchangeably. Focus (if any) is on biological characteristics	Sex and gender defined. The interplay between them is emphasised	Sex and gender defined. The interplay between them is emphasised	Sex and gender defined. The interplay between them is emphasised
Literature review	Sex/gender-specific literature non-considered	Sex/gender-specific literature non-considered	Sex/gender-specific literature considered	Sex/gender-specific literature considered alongside other social stratifiers (e.g., ethnicity, age, disability)	Interdisciplinary literature, Sex/gender-specific literature considered alongside other social stratifiers
Research question	Sex/gender-related research questions non-stated	Sex/gender-related research questions non-stated, or differences only	Sex/gender-related research questions stated	Sex/gender-related research questions stated, and additional social stratifiers included	Specific groups and identities-related research questions stated (gender is not necessarily the focus of the study)
Methods					
Data analysis	Sex as confounder (e.g., included in a multivariate analyses)	Sex as confounder (e.g., included in a multivariate analyses). Main outcomes: disaggregated by sex/gender or analysed controlling for sex/gender	Sex/gender as analysis category. Main outcomes: differences across sex/gender by testing for interaction	Sex/gender as analysis category, additional social stratifiers included. Main outcomes: differences across sex/gender and other factors by testing for interaction, but as independent analyses (not combined into a single analysis)	Analysed on multiple levels - interactive analysis (e.g., comparing irregular migrant status and regular migrant status and native young and old women to the same groups in men)
Methodology	Quantitative methods dominant; lack of reflexivity	Quantitative methods dominant; lack of reflexivity	Quantitative and Qualitative; argues for reflexivity	Quantitative and Qualitative; argues for reflexivity	Quantitative and Qualitative; reflexivity is key

Continued

Research phase/ Model	Sex and gender blind research	Sex and gender differences	SGBA	SGBA+	Intersectional
Differences within and similarities across sex/gender	Seldom analysed (except for age)	Seldom analysed (except for age)	Often analysed	Often analysed	Analysed on multiple levels
Results	Sex/gender-blind results	Sex/gender not necessarily reported It may lead to new knowledge about sex/gender differences providing data on female participants to the already-existing knowledge about male participants	Sex/gender reported	Sex/gender reported in relation to other social stratifiers	Sex/gender and other social stratifiers given equal prominence
Interpretation of findings	Sex/gender-blind discussion	Sex/gender-related findings may be non-discussed. Differences reported in the results section may be non-interpreted or non-explained	Sex/gender-related findings are discussed. Differences reported in the results section are interpreted and explained	Sex/gender-related findings are discussed in relation to, at least, another social stratifier	Sex/gender-related findings are discussed in relation to other social stratifiers. Differences reported in the results section are interpreted and explained
		Risk of exaggeration of sex/gender differences observed	Greater awareness of the risk of exaggerating sex/gender differences	Greater awareness of the risk of exaggerating sex/gender differences	Greater awareness of the risk of exaggerating sex/gender differences

Abbreviations: SGBA, sex- and gender-based analysis

Adapted from: Hammarström, McCarthy et al and Braberte et al [44,48,57,58]

1.3. Evaluate outcomes by sex and gender as health research priority

1.3.1 General aspects

Studying similarities and differences of effects across sex and gender is a recognised health research priority [79,80].The lack of consideration for sex and gender in research hampers our understanding of health conditions, fails to detect specific needs, and undermines the care provided [44,80,81]. For example, the current COVID-19 crisis has brought into sharp focus the relevant role that biological sex and gender norms have on health outcomes, exposure, access to the health system, and the impact of policies [82]. It has been hypothesised that COVID health outcomes are associated with either biological susceptibility (e.g., stronger immune response in females) or gender-related behaviours (e.g., higher likelihood of smoking and drinking among men) [83–85] . Severe adverse effects following COVID-19 vaccination occur more frequently in female subjects [86]. Gendered differences in exposure relate to intersecting factors, for example, occupation risk in a gendered distribution of work, wherein women are highly represented on the essential occupations during the COVID-19 outbreak, including the health workforce [87–89]. Gender norms impact on barriers to healthcare systems, for example, men can be more reluctant to seek care, and women can lose autonomy in decision-making [90]. Gender-diverse people can experience greater challenges regarding their mental health and those who are undergoing transition-related treatment can face accessibility constraints [91]. Pandemic policies and public health measures have different implications by gender. For instance, during lockdowns, violence against women has intensified [92,93], and the gap in the distribution of unpaid care work has increased [94].

The Commission's Women and Gender Equity Knowledge Network report [95] posed how gender imbalances permeate content and process perspectives of the health research as follows:

Gender imbalances in research content:

- Delayed recognition of health issues more prevalent among females: for example, the evolution of the AIDS (acquired immunodeficiency syndrome) definition by CDC (Centers for Disease Control and Prevention) underscores the resistance to include female disorders [46,96].
- Blinded approaches to specific health needs: for example, to set criteria for osteoporosis in male subjects until 1997 according to a female cohort, rather than

establishing a male reference population [97], or underestimation of depression and anxiety among men because of traditional assumptions related to gender and mental health, as well as measurement and clinician bias [98].

- Little attention to vulnerabilities shaped by gender and other intersecting social factors: for instance, in Yemen, gender, age, and occupation intersect, resulting in a raised exposure to sand-fly bites, and consequently risk of Leishmaniasis infection, for women and boys who work on agriculture and animal care [61].

Gender imbalances in research process:

- Sex and gender representation in clinical trials: until the early 1990s, women in general, the elderly, and diverse sub-populations were broadly excluded from clinical trials [58,99]. Since then, guidelines developed by regulatory agencies increasingly mandate that study populations in trials evaluating therapeutic interventions should reflect the target patient populations [13,14]. However, evidence still reveals under-representation of women in cancer, cardiovascular, visceral leishmaniasis, and HIV trials [100–105].Limited sex- and gender-disaggregated data: for example, few countries currently provide sex-disaggregated data on COVID-19 disease [106].
- Lack of sex- and gender-based analysis: several studies have pointed to the lack of sex-related reporting in both primary studies, systematic reviews, and clinical practice guidelines [107–113]. However, personalised healthcare approaches must account for sex, gender, and other intersecting factors to determine possible differential health and drug outcomes [114]. For instance, a systematic review found that male patients with 50-69% symptomatic carotid stenosis appeared to gain higher benefit from endarterectomy than female patients [115].
- Gender-sensitive methodologies to capture nuances: for example, in Malawi, men are more likely to be lost along the care-seeking pathway than women [61].
- Gender imbalance in the research communities: barriers to women scientists remain widespread worldwide since they tend to be underrepresented and relatively receive less funding, and their contributions are more likely to be under-recognised than their men colleagues [116–118]. Moreover, it has been argued that broadening research communities, involving more voices and genders, may contribute to integrating equity in health research [50,52]. In that regard, various studies have demonstrated that women investigators may be more likely to include female participants and sex-related reporting [119–122].

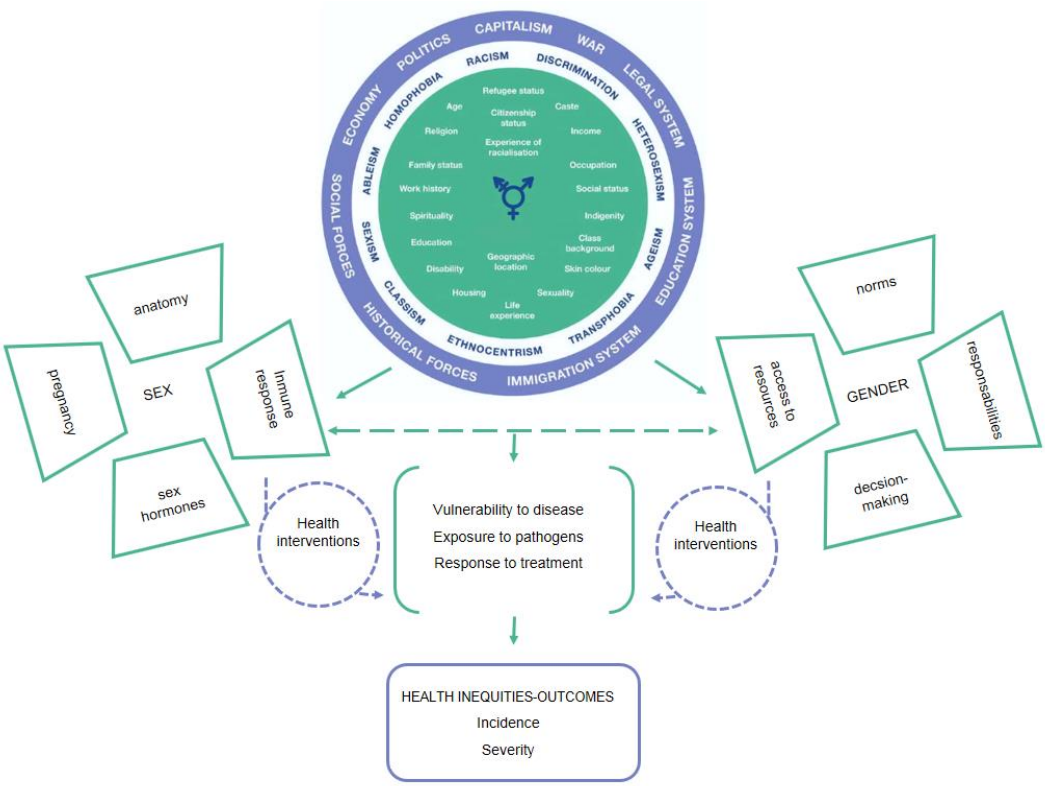
Several guidance and mandates have been developed to integrate assessment of sex and gender into health research [72,73,117,123–126]. For example, Sex and Gender Equity in

Research (SAGER) guidelines were elaborated by the European Association of Science Editors to provide a systematic approach to sex and gender reporting in research across disciplines [72]. Notwithstanding these resources, there is limited uptake in many research areas, including sepsis [111,112,120,127,128].

1.3.2 Sex and gender considerations in sepsis research

Traditionally, sex and gender differences have focused relatively little attention on infectious diseases, although they have a role in the incidence and severity of such illnesses [129]. The World Health Organisation (WHO) analytical framework for public health sets up direct and indirect mechanisms whereby sex and gender impact the transmission model through its critical elements (i.e., vulnerability to illness, exposure to pathogens, and treatment response) [129] (Figure 1). Firstly, sex and gender directly affect each critical element of the model, which influences disease incidence and severity. Secondly, the interplay between sex and gender and health interventions determine incidence and severity, and these, in turn, on the critical elements of the transmission model. The WHO also calls for integrating an intersectional lens to better understand infectious diseases and generating evidence about possible similarities and differences to be addressed through policies and programmes [61]. To help investigators to this end, WHO has developed a toolkit for incorporating an intersectional framework into research on infectious diseases of poverty [61]. However, despite the acknowledged importance of integrating sex and gender in infectious diseases research, studies focusing on HIV, healthcare-associated infections, tuberculosis, and COVID-19, revealed an imbalance in terms of representation in trials and an inadequate sex-and gender-based analysis and reporting in the publications [102,110,127,130,131]. It is also worth noting that the European Commission convened the Gendered Innovations 2 Expert Group to develop a policy report addressing sex and gender impact on COVID-19 [132].

Figure 1. The WHO analytical framework and intersectional framework to understand the impact of sex and gender on infectious disease



Adapted from WHO 2011 [61].

Accounting for sex and gender in sepsis research content can overcome the potential contributions of sex and gender bias involved in the failures of translational research [133]. Evidence on sex as a risk factor for community-onset sepsis is inconclusive [134], while it has been hypothesised that sex may have a prognostic effect on outcomes among patients with sepsis (See 3.2. section). Furthermore, there is a scarcity of sex and gender considerations in sepsis management. High-impact clinical guidelines do not include clinical implications related to the sex or gender of patients, except recommendations for maternal sepsis [16,135]. Studies have found women 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 [136,137]. No previous studies have assessed the representation of participants by sex (i.e. Participation–to–Prevalence Ratio, PPR) nor sex-and gender-based analysis in primary studies underpinning sepsis treatment recommendations. Thus, the work detailed in the first study compiled in this thesis examines these research questions.

Sepsis management, service provision, and policy-making are also expected to be based on the best available evidence [138–140]. Cochrane systematic reviews are used worldwide to

inform decisions on sepsis care. Therefore, a shortage of analysis and reporting may limit their scope [141]. The work described in the second study presented as part of this thesis revises the Sex and Gender Appraisal Tool – Systematic Reviews (SGAT-SR) tool incorporating additional factors associated with health inequities and applies it to Cochrane reviews of interventions on sepsis. It also presents explanatory and supporting material in the use of the SGAT-SR-2 to assist systematic review authors and end-users. The second study also assesses the PPR at review-level. This work 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 [142]. Finding no SGBA appraisal tool to apply to systematic reviews, they designed the SGAT-SR and later revised it as a planning tool [143]. In 2018, Lopez-Alcalde and colleagues pointed out the value of revising the SGAT-SR to make it consistent with new developments in reviews [127], and in keeping with evolving knowledge about sex and gender.

1.4. Description of the impact on sepsis outcomes: Prognosis

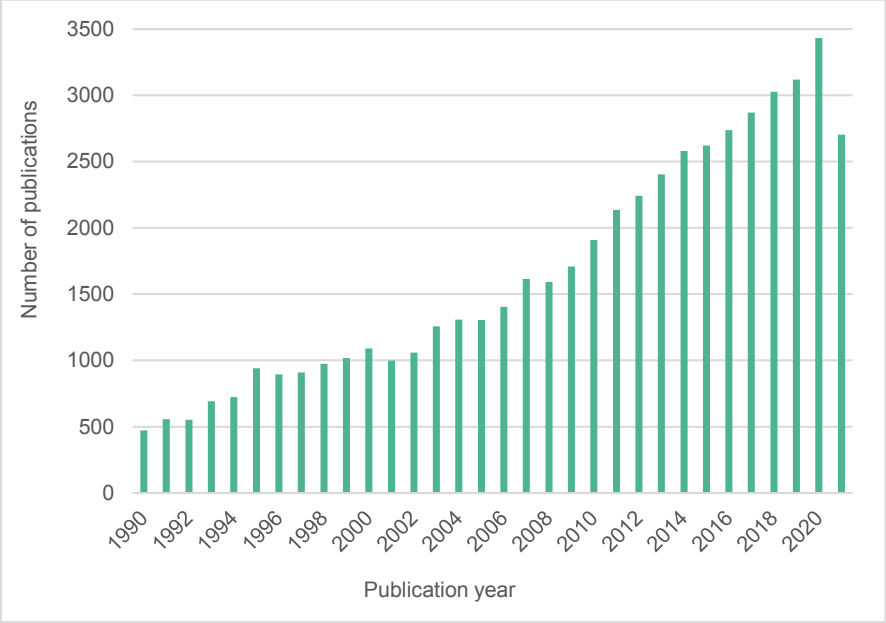
1.4.1 What is the prognosis?

Prognosis research in medicine provides information on the likelihood of future outcomes in people with a particular health condition based on their clinical and non-clinical characteristics [78,144,145]. Prognostication is not restricted to predicting survival, yet often studied, but it may also forecast changes in symptoms (e.g., pain), restoration of function, recurrence, or quality of life, nor it is limited to ill individuals (e.g., use of APGAR score in newborns) [145,146]. Prognosis research serves several purposes, including determining the risk in a broad population over time, identifying patient characteristics associated with poor outcomes, building prognostic models, and selecting target groups for treatment.

Although prognostic concerns were prominent until the nineteenth century, social science has described an ellipsis of prognostic thinking in the first half of the twentieth century partially due to the development of accurate diagnosis and effective therapies for previously fatal diseases, which reduced the variability of possible outcomes illness might have [147]. Over the past two decades, there has been an increasing interest in prognostication within modern medicine due to the highest global burden of diseases than at any previous time alongside the efforts for providing personalized medicine (e.g., biomarker-guided therapies) [144,148] (Figure 2). The Prognosis Research Strategy partnership outlined a framework of four interrelated key themes:

- Fundamental prognosis research: describing the likely course of conditions or outcome probability in the context of the current diagnosis and treatment (i.e., “What is the prognosis of people with a given disease?”) [144].
- Prognostic factor research: identifying specific factors that are associated with future outcomes (e.g., biomarkers) [149].
- Prognostic model research: developing, validating and investigating the clinical impact of statistical models that predict individual probability or futures outcomes by combining multiple prognostic factors (e.g., APACHE score for critically ill patients) [150].
- Stratified medicine research: identifying factors that predict an individual’s response to treatment, which helps to tailor therapeutic decisions in order to maximise benefit and reduce harm [151].

Figure 2. Prognosis research on sepsis by year



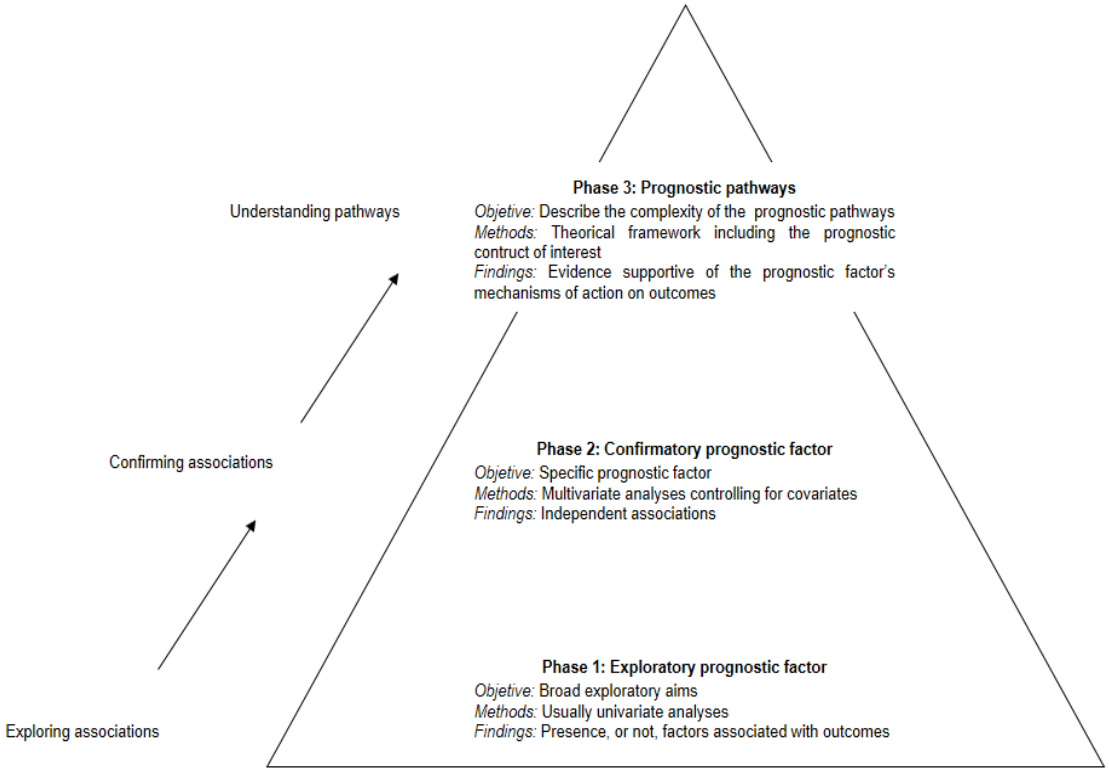
Footnotes: Data source: PubMed, accessed 3 November 2021. Search strategy: (sepsis) AND (Prognosis/Broad [filter]).

According to the scope of this thesis, the subsequent section addresses the characteristics of the prognostic factor research.

1.4.2 What is prognostic factor research?

A prognostic factor is any variable in people living with a particular condition (a start point) that is associated with a subsequent clinical outcome (an endpoint) [149]. Prognostic variables can be obtained from patient demographics, patient history (e.g., comorbidities), clinical history (e.g., onset of symptoms), physical examination (e.g., breathing rate), disease characteristics (e.g., biomarkers), test results, and previous treatment [145]. For acceptance in clinical practice, studied factors require to be fully defined, reproducible and widely available, have therapeutic implications, and results based on independent associations [152]. The optimal design for prognostic purposes is a prospective cohort study. Although case-control design can be used, investigator-based selection of ratio can manipulate the absolute probabilities [153]. This flaw may be overcome by using a nested case-control in an existing predefined source of population with a known sample [154]. Experimental designs can also be considered, but different strategies are needed: either analysing only the comparison arm or both groups after controlling for intervention when the intervention is effective and pooling both groups when the intervention is ineffective [145,155]. Hayden and colleagues [156] described a framework to conceptualise prognostic factors studies based on the phase of investigation as follows: phase 1, the study aimed to describe associations between promising prognostic factors and the outcome; phase 2, the study aimed to confirm independent associations between a prognostic factor and the outcome; and phase 3, the study aimed to understand prognostic pathways (Figure 3). New studies of prognostic factors should rely on the results of the previous prognosis research and additional sources of information (e.g., clinical observation or basic science) [156,157].

Figure 3.Framework of prognostic factors studies by phase of investigation



Adapted from Hayden and colleagues 2008 [156].

Whereas prognostic and aetiological studies have similarities regarding design and analysis, they address different research questions. Prognosis research attempts to predict, as accurately as possible, among people with a particular condition the probability of a future outcome. Aetiological research seeks to explain if a risk factor is associated with causing a condition [145,158]. Although prognostic studies may contribute to the knowledge of the pathophysiology of the outcome, causality is neither a primary aim nor a requirement [145].

Implications of prognostic factor evidence for clinical practice and research can be discussed separately [149]. For clinical decision-making, prognostic factor research can help to:
i) Redefine health conditions (e.g., the inclusion of CD4+ count in the classification of HIV infection stages).
ii) Monitor disease progression (e.g., targeting HbA1c in patients with diabetes control).
iii) Build multivariable prognostic models [150].
iv) Inform treatments and identify response predictors [151].

For research, prognostic factor studies can contribute to:

i) Develop interventions for modifiable prognostic factors. However, caution is required since most prognostic factors are not causal, but they are associated with the true causal factors (frequently unknown).
ii) Design of interventions studies (i.e., prognostic factors are potential confounding factors).

While well accepted methodological guidelines have evolved for conducting and reporting for intervention and diagnosis studies [159,160], no similar recommendations exist for prognostic factor studies [149,152]. There are concerns about the poor quality of prognostic studies, lack of protocol registrations, inadequate analysis (i.e., using subjective cut-points for continuous variables instead of analysing on continuous scales, ignoring non-linear relations, and conducting only univariate analysis) reporting bias, and scant data sharing [149]. The Prognosis Research Strategy group has elaborated recommendations for improving transparency (Table 2) [161], although, as yet, no general standard has been embraced.

Table 2.Recommendations of the prognosis research strategy group for improving the transparency of prognosis research

Recommendation	Description
1. Develop reporting guidelines	Develop extensions of REMARK guidelines for tumour marker studies [162].
2. Facilitate data sharing	Encourage evidence-synthesis and meta-analysis of individual patient data.
3. Routine registration of prognostic studies	Establish a minimal dataset (start point, list of candidate factors). Description of the analysis plan.
4. Accessible study protocol	Encourage public and early accessibility (e.g., registry or journal publication). Time-stamped electronic protocols.
5. Promote systematic evaluation of methods for transparency	Evaluate critically and systematically methods in achieving transparency for public accountability.

Abbreviations: REMARK, reporting recommendations for tumour marker prognostic studies.

Despite every year thousands of studies researching prognostic factors are published, they often differ regarding the methodological quality, misleading the prognostic value of the examined factor [157]. Therefore, an evidence-based approach to prognostic factors is needed to ascertain findings from prognosis studies and enable informed decisions for patients/, clinicians, and healthcare providers [157]. However, conducting reviews in the area of prognosis is in its early stages compared with systematic reviews of the effects of interventions and diagnostic test accuracy [78]. The Cochrane Prognosis Methods Group has developed guidance to support reviews of prognostic factor studies [163,164].

1.4.3 Sex as prognostic factor in patients with sepsis

Biological mechanisms concerning sex hormones and immune responses have been hypothesised to explain differences in survival by sex for patients with sepsis [165–168]. For example, a study found that mortality in patients with septic shock was associated with high 17β-estradiol and progesterone levels in male patients, but with high 17β-estradiol and testosterone levels in female patients [169]. Although, there continues to be a gap between findings of sex-based differences in preclinical trials and clinical settings that hampers our understanding of underlying mechanisms [170]. As well, individual studies evaluating the relationship between sex and outcome of sepsis report conflicting and imprecise findings [134,171,172].

Prognostic research can be collated in evidence syntheses to examine the role of sex in mortality among patients with sepsis. It may help in risk stratification of these patients by combining independent prognostic factors within prognostic models, which contribute to the selection of the most appropriate therapeutic options [149]. Using a systematic review search filter in PubMed, two potentially relevant citations can be found [173,174]. Their detailed assessment showed several weaknesses. For example, there was no definition of eligibility criteria concerning studies that capture independent associations, a feature that is critical for focussing the review on prognostic evidence [156]. In addition, specific tools [175] for the assessment of risk of bias in prognostic studies were not applied. Therefore, an evidence synthesis tailored to the specific methodological requirements of prognostic research is required to help delineate the significance of sex in sepsis outcomes in critically ill patients. The work described in the third study of this thesis addresses this gap of knowledge.

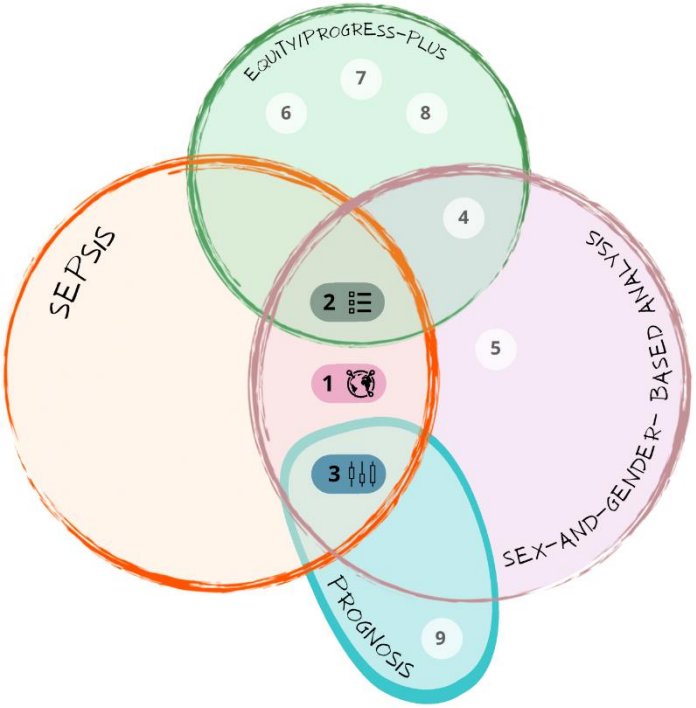
1.5. Which insight can this thesis provide into sepsis research?

The evidence-based healthcare decision process is informed by the stages of evidence development. First, formulating the research question, defining eligibility criteria, collecting and analysing data, and discussing the applicability of findings and limitations of the study. Next, the publication of results, which, later on, decision-makers interpret [176]. This *scientific action* is embedded in sociopolitical frames of reference [58,177]. Krieger defined the social production of scientific knowledge as “the ways in which social institutions and beliefs affect recruitment, training, practice, and funding of scientists, thereby shaping what questions we, as scientists, do and do not ask, the studies we do and do not conduct, and the ways in which we analyse and interpret data, consider their likely flaws, and disseminate results” [178]. Interpretations of biological and social phenomena have been shaped by scientific racism, sexism, heterosexism, and other axes of oppression. For example, evolutionary biology implicitly assumed that different-sex sexual behaviour was the norm across animals [179], or dominant white physicians explained the social hierarchy based on racialised differences in health outcomes (e.g., poorer health of enslaved people) in the eighteenth century [180].

High-quality clinical research is essential to achieve the highest level of health for all people. Two questions arise from this goal: who are "all persons"? How to produce meaningful knowledge that applies to the entire population? Study participants should reflect on the characteristics of the population affected by a particular health condition to identify underlying biological and social factors that may influence the variability in effectiveness and safety of interventions [181,182]. The diversity among groups involved in clinical studies also has ethical and social implications, as more people can potentially benefit at the individual and population level, in the case of subgroups systematically underrepresented [181,182]. Nevertheless, diversity in clinical evidence is conflicting with the homogeneity of the population to be studied, which is the dominant paradigm and ensures its internal validity [183]. Indeed, most reports of randomised clinical trials (RCT) fail to provide demographic data, and elderly people, women, and ethnic minorities tend to be underrepresented [184]. To expand potential benefits from the research also goes far beyond overcoming the lack of diversity in studies. To generate diversity-sensitive clinical knowledge requires exploring diverse issues that are relevant for health outcomes by using hypothesis-generating (e.g., subgroups in individual participant data meta-analysis, observational studies, databases of routine healthcare, and qualitative studies) and hypothesis-testing research (e.g., aetiological studies, subgroups in RCTs) [183].

Thus, this dissertation is a methodological proposal that aims at embracing sex and gender in research for clinical conditions, such as sepsis (Figure 4). This thesis explores the integration of sex and gender and the extent to which other PROGRESS-Plus factors interacting with sex and gender are considered across primary studies and evidence synthesis on sepsis and assesses sex as an independent prognostic factor for mortality among critically ill patients with sepsis. The theoretical underpinnings rest on the sex- and gender-based analysis model, PROGRESS-Plus and intersectional frameworks, and the prognosis methodology detailed above.

Figure 4. Diagram article-based thesis



Footnotes: 1-3 main studies conducted for the article-based thesis, 4-10 additional studies.

02 Objectives

2. Objectives

2.1. General objective

To synthesise and evaluate the role of sex and gender in clinical research on sepsis, and elaborate a methodological approach to sex-and gender-based analysis in systematic reviews.

2.2. Specific objectives

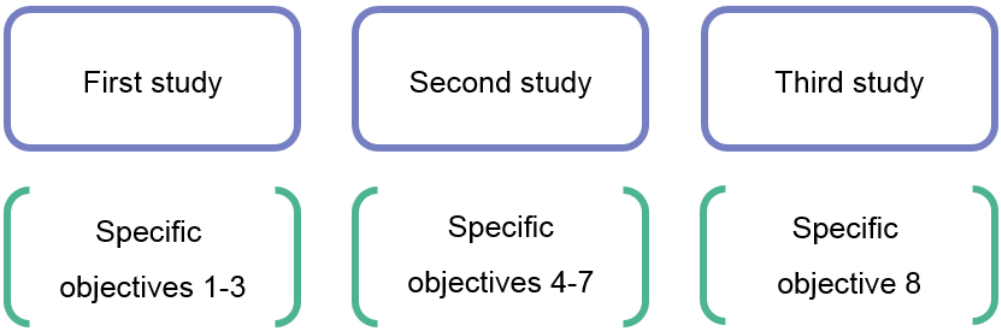
1. To assess the level of representation by sex relative to the sex-disaggregated incidence of sepsis in the overall population in primary studies underpinning recommendations from guidelines and systematic reviews for sepsis treatment in adults.
2. To describe the extent to which sex is analysed and reported in primary studies underpinning recommendations from guidelines and systematic reviews for sepsis treatment in adults.
3. To examine factors associated with sex inclusion and reporting in primary studies underpinning recommendations from guidelines and systematic reviews for sepsis treatment in adults.
4. To revise a sex and gender appraisal tool for systematic reviews (SGAT-SR) incorporating additional factors associated with health inequities.
5. To apply the SGAT-SR-2 tool to Cochrane systematic reviews on sepsis.
6. To elaborate on explanatory and supporting material in the use of the SGAT-SR-2 to assist systematic review authors and end-users.
7. To assess the level of representation by sex relative to the sex-disaggregated incidence of sepsis in the overall population at the Cochrane sepsis review level.
8. To summarise the available evidence to assess the role of sex as an independent prognostic factor for mortality in patients with sepsis admitted to intensive care units.

03 Methods

3. Methods

This is an article-based thesis composed of three main studies addressing the specific objectives referred to above (Figure 5).

Figure 5. Matching thesis objectives and studies



3.1. Methods of the first study

Protocol

PROSPERO registration number CRD42020148157, registered on 7 January 2020.

Eligibility criteria

Studies

We considered randomised clinical trials (RCT) and quasi-randomised trials on sepsis treatment with primary clinical outcomes included in systematic reviews (SR) published in the Cochrane Database of Systematic Reviews (CDSR) or in leading medical journals. We also considered observational studies included in sepsis treatment recommendations of clinical guidelines. We excluded studies whose recruitment was restricted to one sex, because they addressed sex-specific diseases, cancer and neutropenic populations. We excluded unpublished trial data, letters to editors and conference abstracts because they provided insufficient details on study methodology and findings.

Participants

We included studies on adults (using the age threshold defined by the study authors) with a sepsis diagnosis admitted to a hospital ward, emergency department or intensive care unit (ICU). Studies of both adult and paediatric populations were eligible provided adults accounted for at least 80% of the sample. We accepted the sepsis and shock septic definitions used by

the study authors. In this research, we accepted the sex and gender terminology used by the study author, which, when applicable, we also appraised for appropriacy. Moreover, we used the "sex" term for participants selected and the "gender" term for investigators.

Interventions

We considered studies whose interventions addressed sepsis treatments, grouped into four categories as follows: initial resuscitative treatment, failure of initiative therapy, supportive therapies and investigational therapies (See Supplementary material A.1). We excluded studies focusing on therapeutic drug monitoring, antibiotic susceptibility testing or prophylactic therapies.

Search strategy and selection process

We searched SRs on sepsis treatment published in the CDSR and leading medical journals and clinical guidelines on sepsis treatment (See Supplementary material A.1). We imposed no language restriction. To retrieve RCTs and quasi-randomised trials, we used the advanced search options in the CDSR (from 1995 to August 2019) and MEDLINE Ovid (from 1946 to August 2019) to select SRs that used "sepsis" either as MeSH term or as a term in the title. The MEDLINE search strategy was based on the core journals set combined with the top 15 critical care and intensive care medicine journals in Scimago. To identify relevant observational studies, using the term "sepsis" we searched for high-impact guidelines in the UpToDate and Trip Database, retrieving the NG51 NICE guideline [135] and the Surviving Sepsis Campaign international guidelines [16], both dating from 2016. We removed duplicates with the assistance of Mendeley reference management software [185]. Records were screened using Covidence online software [186]. We used Excel to identify further duplicates, select studies, build data extraction templates and extract data. If we retrieved several publications that referred to the same study, we selected the publication that offered the most complete data.

Two authors screened titles and abstracts for all the retrieved references, scanning first the SRs and guidelines and then the primary studies. We piloted eligibility criteria using a sample of studies. We resolved disagreements by discussion. Two authors screened full-text similarly.

Data extraction

We piloted 20 studies to ensure the data extraction form. Three authors independently extracted data and examined a random sample of 10% studies for accuracy assessment.

We extracted the following information from each study:

1. Gender of the first and last study authors, journal, publication year, location of authors (country of affiliated institution), and language.
2. Registration or protocol published.
3. Study design.
4. Study setting: ward, emergency department, or ICU.
5. Participant characteristics: total number, number of participants disaggregated by sex, data on social health determinants.
6. Main results: sex-disaggregated, sex-adjusted data, sex-disaggregated dropout data, and sex subgroup analyses where appropriate.
7. Sponsorship source: non-profit, profit, mixed, none, or not stated.
8. Terminology used for sex and gender [27,72].

In relation to point 1 above, we assigned gender to authors using the gender algorithm designed by Larivière and colleagues [116]. When given names were initials, we tracked information on gender by searching PubMed for the researcher's name in double quotes tagged with [Author] and matching the results with the institutional affiliation.

Sex-related reporting and analysis

Three authors assessed sex-related reporting and analysis approaches in the studies according to amended Sex and Gender Equity in Research (SAGER) guidelines [72], with information responding to the following questions extracted from each study:

1. Is sex relevant to the study topic?
2. Has the rationale for sex representation, or lack of it, been provided in the study design?
3. Have the main outcomes been reported disaggregated by sex? Have drop-out data been reported by sex (adapted from Schulz 2010 [160])? If subgroups were analysed by sex, have they been rigorously conducted? Rigorous sex subgroup analysis was defined as follows: subgroup analysis was stated a priori, a rationale was provided, a hypothesis was offered regarding the outcome of the subgroup analysis, P values were adjusted for the number of comparisons made, and overall findings were emphasised more than subgroup analysis findings (adapted from McGregor 2016 [187]).

4. Has sex based on analysis, or lack thereof, been mentioned and discussed in the discussion section?

Data analysis

We compared the female representation in studies relative to their representation in the overall sepsis population using the Participation–to–Prevalence Ratio (PPR) [188–191]. 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)]. We determined sepsis incidence by sex on the basis of a comprehensive bibliographic search of peer-reviewed journals and infectious disease databases [192]. We used as a benchmark figure for sex-stratified sepsis incidence reported by Martin [193], as reflecting the largest cohort and longest study period. We established different temporary cut-off points for the analyses according to historical landmarks: 1993, when the NIH (National Institutes of Health) Revitalization Act mandated the adequate inclusion of women in NIH-sponsored clinical research to determine sex-based differences; and 2007 and 2010, when guidelines on reporting observational studies and RCTs were endorsed, respectively [99,160,194]. Those temporary cut-off points were adjusted for our study in terms of the median period between study completion and publication as determined from a literature review (33 months) [195–197].

We performed the same analyses within subgroups to explore PPR behaviour according to the following:

- Study design. Observational studies versus RCTs.

- Study setting. ICU studies versus non-ICU studies. The ICU sepsis incidence was based on data reported by Sakr [198] (study period May 2012, N=2,973 patients admitted to the ICU).

- Study sample size. Threshold defined by the upper quartile of our cohort.

- Sepsis epidemiological changes over time. Studies published in or before 2003 versus studies published in or after 2005. We established two sepsis incidences based on data reported by Martin [193] (study period 1979-2000, N=13,319,418 participants)

and Stoller [199] (study period 2008-2012, N=6,067,789 participants), adjusting the research period as described above.

Secondary analyses were as follows:

1. Appropriate use of the terms “sex” and “gender” according to SAGER guidelines [72,127].

2. Sex-related analyses and reporting.

3. Description of social determinants of health: place of residence (e.g., urban/rural area, high, low and middle-income country), race/ethnicity/culture/language, occupation, gender and sex, religion, education, socioeconomic status, and social capital (PROGRESS acronym) [76].

4. Factors associated with female participation and sex-related analysis and reporting.

The unit of analysis was the primary study. We performed a descriptive analysis and a bibliometric analysis. We limited the assessment of appropriate use of “sex” and “gender” to studies published in English. We reported data as medians, percentages and interquartile ranges (IQRs). We conducted univariate analyses for the female participation proportion and publication year, funding source, author gender, author's country of affiliation categorised by the World Bank income classification [200], study design, study sample size and ICU setting. We established statistical significance at a P value of 0.05. We carried out multivariate analyses to characterise independent associations between the above-mentioned study characteristics and sex-related reporting. We performed statistical analyses using STATA statistical software (version 15.1; STATA Corporation, College Station, TX, USA).

3.2. Methods of the second study

Protocol

Protocol registered with Open Science Framework on 24 December 2020 [201].

Revision of the Sex and Gender Appraisal Tool – Systematic Reviews (SGAT–SR)

The development of the original SGAT-SR tool was described elsewhere [142,143]. 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 A.2).

We tracked citations on Doull and colleagues [142], 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 [127,202], evaluating the most recent guidance on sex- and gender-based analysis and equity considerations [72,78,187,203,204], and on intersectionality [34,76,77]. We convened an advisory board composed of nine experts in SGBA (RSH, JL-A, VR, ST, PT, MD, JH-R, ZM, and JP), equity in health research, and evidence synthesis. The Cochrane Handbook was used as the reference for issues related to methodological standards [78].

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 A.2). 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) [112]. 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 [27], 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 the three questions assessing the use of the terms, the possible responses are those defined by Adisso and colleagues [112] as follows: binary, non-binary, or unclear use (#17); appropriate, inappropriate, or unclear (#18); and interchangeable, non-interchangeable, or unclear use (#19). For three questions (#5.a, #8.a, #12.a), we also asked whether the authors provided a rationale. Two authors 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. Supplementary material A.2 details criteria for assessing each item and provides examples.

Appraisal of systematic reviews on sepsis

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 A.2). 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.

Search strategy and selection process

We used the advanced search option within the CDSR (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 A.2).

Two authors 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.

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 [205] 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 A.2).

- 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).

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 (2016) [72], 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) [103,188,204]. A PPR between 0.8 and 1.2 reflects adequate or bias-free enrolment, while values below or above suggest underrepresentation and overrepresentation, respectively. We calculated the PPR by dividing the percentage of female study participants by the percentage of females in the overall sepsis population. 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 [192,193,198,206–209]. Table S1 (Supplementary material A.2) details population descriptors used for sex-stratified incidence estimates [193,198,206–209]. 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.

3.3. Methods of the third study

Protocol

We registered the protocol with PROSPERO (CRD42019145054) and published it in full [210]. Supplemental Table 1 (Supplementary material A.3) details the differences between the protocol and the review. We adhered to the PRISMA statement [211].

Eligibility criteria

We included studies (experimental or any observational design) that sought to confirm the independent prognostic effect of sex on mortality in critically ill adults with sepsis controlling for covariates (called phase 2-confirmatory studies, which means the objective statement outlined sex as a prognostic factor of interest and analyses adjusted for covariates) [156]. We included patients aged 16 years and older with a sepsis diagnosis, as defined by the study authors, treated in an ICU. Studies including both adult and paediatric patients were eligible if adults represented more than 80% of the study sample. Sex and gender are distinct concepts, though often erroneously interchanged in the medical research reports [27] . We accepted any assessment of sex as a biological characteristic. We also appraised operational concepts of sex and gender provided by the study authors using the classification detailed in Table S2 (Supplemental material A.3) [127]. After a literature search and consensus amongst experts (Table S3, Supplemental material A.3), we pre-specified 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, or alcohol dependence), non-urinary source of infection, and inappropriate or late antibiotic coverage. The co-primary outcomes were all-cause hospital mortality and 28-day all-cause mortality. Secondary outcomes were 7-day all-cause hospital mortality, 1-year all-cause mortality, and all-cause ICU mortality. Table 3 describes the review question according to the PICOTS (population, index, comparator, outcome(s), timing, setting).

Table 3. PICOTS system

Population	Index prognostic factor	Comparator	Outcome(s)	Timing	Setting
Adults with sepsis	Sex	Non-applicable to this review[1]	*Primary outcomes*		Intensive care units
			All-cause hospital mortality	The longest follow-up provided by the study authors (until death of hospital discharge)	
			28-day all-cause hospital mortality	28 days from sepsis diagnosis	
			Secondary outcomes:		
			7-day all-cause hospital mortality	7 days from sepsis diagnosis	
			1-year all-cause mortality	1 year from sepsis diagnosis	
			All-cause ICU mortality	The longest follow-up provided by the study authors (until death of ICU discharge)	

[1] 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, or alcohol dependence), non-urinary source of infection, and inappropriate or late antibiotic coverage.

Search strategy and selection process

We searched MEDLINE Ovid, Embase Elsevier, and Web of Science for studies published from inception to 17 July 2020, and ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform for unpublished and ongoing studies, regardless of language. The search strings included terms related to the population (sepsis), the prognostic factor (sex), prognostic study methods, and the outcome (mortality). Furthermore, we handsearched conference proceedings from 2010 to 2019 of the foremost critical care and infectious diseases symposia. Table S4 (Supplemental material A.3) presents the full search strategy.

We used the online software EPPI-Reviewer 4 to manage the study selection process [212]. Pairs of review authors independently screened the title and abstracts, and when appropriate, full-texts to determine their eligibility. We used a consensus method and consulted a third author if disagreement remained.

Data extraction and risk of bias assessment

Two authors independently extracted data and reached a consensus using electronic extraction templates in EPPI-Reviewer 4. We used the CHARMS-PF (checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies for

prognostic factors) guidance for data collection [164]. We contacted all study authors for missing information. Two authors independently assessed the risk of bias of the included studies, agreed on ratings, and a third author participated when required. We applied an outcome-level approach and amended the QUIPS (quality in prognosis studies) tool using four categories (low, moderate, high, or unclear risk) [164,175,213]. We defined studies controlling for less than three of the aforementioned covariates as "minimally adjusted for other prognostic factors or moderate risk", and those controlling for at least three of these covariates as "adequately adjusted or low risk of bias" for the QUIPS adjustment domain [214]. We assessed selective reporting bias by: 1) searching for a prospective study protocol or registration; 2) dealing with related conference abstracts; and 3) carefully examining the study methods section [175].

Data synthesis

For each study and prognostic factor estimate, we extracted the measures of associations alongside its confidence intervals (CIs). We transformed association measures into an odds ratio (OR) with its 95% CIs to allow statistical pooling whenever adequate [215]. We estimated no data from Kaplan-Meier curves because of the risk of overestimation of events and censorship concerns [216]. We presented results consistently, so associations above one indicated a higher mortality for female participants. We pooled estimates in meta-analyses when valid data were available. For the primary analyses, we used estimates from the model that adjusted for more covariates from the core of adjustment factors. We performed random-effects meta-analyses applying the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment [217], using RevMan 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and the template for conversion provided by IntHout (31). We examined statistical heterogeneity computing prediction intervals when the meta-analysis contained at least three studies [217,218]. We also calculated I-squared and Tau-squared statistics to provide further quantifications of statistical heterogeneity. We planned to explore possible methodological causes of heterogeneity performing subgroup analyses. We undertook a single prespecified subgroup analysis for prospective versus retrospective studies when appropriate. We compared differences between subgroups by performing a test of interaction [219]. We carried out no subgroup analyses based on other study characteristics because there were insufficient studies. We conducted sensitivity analyses accounting for the risk of bias excluding studies with either a high or moderate risk of bias in one of the following QUIPS key domains: study attrition, prognostic factor measurement, outcome measurement, and adjustment for other prognostic factors. Additionally, we explored potential differences between meta-analyses based on unadjusted (crude) and adjusted estimates, and the impact of the unique information

reported in abstract conferences [220]. We could not perform further sensitivity analyses as no other comparisons met the predefined criteria. Although we planned to assess publication bias for each meta-analysis including ≥10 studies by funnel plot representation and Peter's test at a 10% level [221], no meta-analysis met this criterion.

Assessment of the certainty of evidence

We assessed the certainty of evidence using the GRADE (grading of recommendations assessment, development, and evaluation) approach and guidance for prognosis studies (Table S5, Supplemental material A.3) [214,222–227]. We tabulated our findings for each outcome using the GRADEpro GDT software [228]. We described results for prognostic effect estimate considering the certainty of evidence and its clinical importance (important effect, slight effect, and little or no effect). As we found no well-established clinically important thresholds for prognostic effects, we agreed *a priori* on an absolute risk difference of at least ± 10‰ as clinically important difference;

04 Results

4. Results

This section separately presents the results of each of the three studies involved in this thesis. Firstly, a summary is described, and then the full text of the publication is available for providing further details.

4.1. Results of the first study

Antequera A, Madrid-Pascual O, Solà I, Roy-Vallejo E, Petricola S, Plana MN, et al. Female under-representation in sepsis studies: a bibliometric analysis of systematic reviews and guidelines. J Clin Epidemiol 2020;126:26-36. doi:10.1016/j.jclinepi.2020.06.014

Impact factor. 6.437 (2020 Journal Citation Reports®)

We included 277 studies published between 1973 and 2017. For the 246 studies for which sex data were available, the share of female participation was 40%. Females overall were underrepresented relative to their share of the sepsis population (PPR 0.78). Disaggregated results were reported by sex in 57 studies. In univariate analyses, non-ICU setting and consideration of other social health determinants were significantly associated with greater female participation ($P<0.001$ and $P=0.023$, respectively). In regression models, studies published in 1996 or later were likely to report sex, whilst RCTs were unlikely to do so ($P=0.019$ and $P<0.001$, respectively).

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ORIGINAL ARTICLE

Female under-representation in sepsis studies: a bibliometric analysis of systematic reviews and guidelines

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Abstract

Objectives: The objective of the study was to assess female representation in primary studies underpinning recommendations from clinical guidelines and systematic reviews for sepsis treatment in adults.

Study Design and Setting: We conducted a bibliometric study. We removed studies pertaining to sex-specific diseases and included quasirandomized, randomized clinical trials (RCTs), and observational studies. We analyzed the female participation-to-prevalence ratio (PPR).

Results: We included 277 studies published between 1973 and 2017. For the 246 studies for which sex data were available, the share of female participation was 40%. Females overall were under-represented relative to their share of the sepsis population (PPR 0.78). Disaggregated results were reported by sex in 57 studies. In univariate analyses, non–intensive care unit setting and consideration of other social health determinants were significantly associated with greater female participation ($P < 0.001$ and $P = 0.023$, respectively). In regression models, studies published in 1996 or later were likely to report sex, while RCTs were unlikely to do so ($P = 0.019$ and $P < 0.001$, respectively).

Conclusion: Our study points to female underenrollment in sepsis studies. Primary studies underpinning recommendations for sepsis have poorly reported their findings by sex.

Keywords: Sepsis; Sex; Gender; Participation-to-prevalence ratio; Sex-related reporting; Systematic reviews; Clinical guidelines

1. Introduction

Sepsis, accounting for around 6 million deaths every year and with an overall incidence of around one case per 1000 patients [1,2], continues to be a significant burden on society. Some studies suggest that while incidence is rising, mortality is falling [3–5]. Sepsis, defined as a life-threatening organ dysfunction caused by a dysregulated host response to inflammation [6], is a heterogeneous syndrome affecting both females and males, yet the impact of sex on outcomes remains unclear [7,8]. Social and contextual interactions as well as biological factors may affect health outcomes for sepsis [9,10].

Until around the mid-1980s, women were broadly excluded as participants in biomedical research [11,12]. In recent decades, research and governmental organizations have endeavored to ensure proper female participation in clinical trials except when a rationale is provided for their exclusion [13,14]. Notwithstanding these measures, the medical

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Ethical approval: Ethical permission was not necessary as this study used only published data.

Conflict of interest: None.

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What is new?

Key findings

- Female participation in primary studies underpinning recommendations for treating sepsis from systematic reviews and guidelines is below their representation in the sepsis population. Less than half of studies published in English used "sex" and "gender" terminology properly and only around a fifth of studies reported by sex or included other health determinants.

What this adds to what was known?

- We highlight the female representation gap in the sepsis field and the lack of sex-related reporting and analysis.

What is the implication and what should change now?

- Sex-based participation disparities and the lack of sex-related analyses and reporting limit the generalizability of research and hamper the external validity of the effectiveness of clinical interventions. Academics, researchers, journal editors, and funding agencies need to encourage to report disaggregated data and discuss the influence of sex and gender on research findings, aimed at addressing the biological and social diversity of patient populations.

literature still reflects disparities in female participation in several fields [15–19]. A number of studies also point to the lack of sex-related reporting in both primary studies and systematic reviews (SRs) [20–24]. Furthermore, recent studies have demonstrated that women investigators may be more likely to include female participants and sex-related reporting [25–27]. We assessed the level of female representation in sepsis treatment primary studies underpinning recommendations from guidelines and SRs, described the extent to which sex is analyzed and reported, and examined factors associated with sex inclusion and reporting.

2. Materials and methods

2.1. Protocol

We registered the protocol with PROSPERO on 7 January 2020 (CRD42020148157) [28].

2.2. Search methods

We searched SRs on sepsis treatment published in the Cochrane Database of Systematic Reviews (CDSR) and leading medical journals and clinical guidelines on sepsis treatment (see Supplementary material). We imposed no language restriction.

To retrieve randomized clinical trials (RCTs) and quasirandomized trials, we used the advanced search options in the CDSR (from 1995 to August 2019) and MEDLINE Ovid (from 1946 to August 2019) to select SRs that used "sepsis" either as a MeSH term or as a term in the title. The MEDLINE search strategy was based on the core journal set combined with the top 15 critical care and intensive care medicine journals in Scimago. To identify relevant observational studies, using the term "sepsis," we searched for high-impact guidelines in the UpToDate and Trip Database, retrieving the NG51 NICE guideline [29] and the Surviving Sepsis Campaign international guidelines [30], both dating from 2016.

2.3. Eligibility criteria

2.3.1. Studies

We considered RCTs and quasirandomized trials on sepsis treatment with primary clinical outcomes included in SRs published in the CDSR or in leading medical journals. We also considered observational studies included in sepsis treatment recommendations of clinical guidelines. We excluded studies whose recruitment was restricted to one sex because they addressed sex-specific diseases and/or cancer or neutropenic populations. We excluded unpublished trial data, letters to editors, and conference abstracts because they provided insufficient details on study methodology and findings.

2.3.2. Participants

We included studies on adults (using the age threshold defined by the study authors) with a sepsis diagnosis admitted to a hospital ward, emergency department, or intensive care unit (ICU). Studies of both adult and pediatric populations were eligible provided adults accounted for at least 80% of the sample. We accepted the sepsis and shock septic definitions used by the study authors. Sex—a biological characteristic that distinguishes females and males—and gender—reflecting socially constructed roles, behaviors, and identities of women, men, and gender-diverse individuals—are distinct concepts [31], yet tend to be interchangeably used in the medical literature. In this research, we accepted the sex and gender terminology used by the study author, which, when applicable, we also appraised for appropriacy. Moreover, we used the "sex" term for participants selected and the "gender" term for investigators.

2.3.3. Interventions

We considered studies whose interventions addressed sepsis treatments and grouped into four categories as follows: initial resuscitative treatment, failure of initiative therapy, supportive therapies, and investigational therapies

(see Supplementary material). We excluded studies focusing on therapeutic drug monitoring, antibiotic susceptibility testing, or prophylactic therapies.

2.4. Study selection and screening

We removed duplicates with the assistance of Mendeley reference management software [32]. Records were screened using Covidence online software [33]. We used Excel to identify further duplicates, select studies, build data extraction templates, and extract data. If we retrieved several publications that referred to the same study, we selected the publication that offered the most complete data.

Two authors (A.A.M. and O.M-P.) screened titles and abstracts for all the retrieved references, scanning first the SRs and guidelines and then the primary studies. We classified studies into excluded and included categories. We piloted eligibility criteria using a sample of studies. We resolved disagreements by discussion. Two authors (A.A.M. and O.M-P.) screened full-text similarly.

2.5. Data extraction and management

We piloted 20 studies to ensure the data extraction form. Three authors (A.A.M., O.M-P., and E.R-V.) independently extracted data and examined a random sample of 10% studies for accuracy assessment.

We extracted the following information from each study:

1. Gender of the first and last study authors, journal, publication year, location of authors (country of affiliated institution) and language.
2. Registration or protocol published.
3. Study design.
4. Study setting: ward, emergency department, or ICU.
5. Participant characteristics: the total number, number of females, and data on social health determinants.
6. Main results: sex-disaggregated data, sex-adjusted data, sex-disaggregated dropout data, and sex subgroup analyses where appropriate.
7. Sponsorship source: nonprofit, profit, mixed, none, or not stated.
8. Terminology used for sex and gender [31,34].

In relation to point 1 mentioned previously, we assigned gender to authors using the gender algorithm designed by Larivière et al [35]. When given names were initials, we tracked information on gender searching PubMed for the researcher's name in double quotes tagged with [Author] and matching the results with the institutional affiliation.

2.5.1. Sex-related reporting and analysis

Three authors (A.A.M., O.M-P., and E.R-V.) assessed sex-related reporting and analysis approaches in the studies according to amended Sex and Gender Equity in Research (SAGER) guidelines [34], with information responding to the following questions extracted from each study:

1. Is sex relevant to the study topic?
2. Has the rationale for sex representation, or lack of it, been provided in the study design?
3. Have the main outcomes been reported disaggregated by sex? Have drop-out data been reported by sex (adapted from Schulz, 2010 [36])? If subgroups were analyzed by sex, have they been rigorously conducted? Rigorous sex subgroup analysis was defined as follows: subgroup analysis was stated a priori, a rationale was provided, a hypothesis was offered regarding the outcome of the subgroup analysis, *P* values were adjusted for the number of comparisons made, and overall findings were emphasized more than subgroup analysis findings (adapted from McGregor, 2016 [37]).
4. Has sex based on analysis, or lack thereof, been mentioned and discussed in the discussion section?

2.6. Data analysis

We compared the female representation in studies relative to their representation in the overall sepsis population using the participation-to-prevalence ratio (PPR) [17,19,38,39]. A PPR between 0.8 and 1.2 reflects adequate or bias-free enrollment, whereas values less or greater suggest under-representation and over-representation, respectively.

We calculated the PPR by dividing the percentage of female study participants by the percentage of females in the overall sepsis population. We determined sepsis incidence by sex on the basis of a comprehensive bibliographic search of peer-reviewed journals and infectious disease databases [40]. We used as a benchmark figure for sex-stratified sepsis incidence that reported by Martin [41], as reflecting the largest cohort and longest study period. We established different temporary cutoff points for the analyses according to historical landmarks: 1993, when the National Institutes of Health (NIH) Revitalization Act mandated the adequate inclusion of women in NIH-sponsored clinical research to determine sex-based differences; 2007 and 2010, when guidelines on reporting observational studies and RCTs were endorsed, respectively [12,36,42]. Those temporary cutoff points were adjusted for our study in terms of the median period between study completion and publication as determined from a literature review (33 months) [43–45].

We performed the same analyses within subgroups to explore PPR behavior according to the following:

- Study design: observational studies vs. RCTs.
- Study setting: ICU studies vs. non-ICU studies. The ICU sepsis incidence was based on data reported by Sakr [46] (study period May 2012, $N = 2{,}973$ patients admitted to the ICU).

- Study sample size: Threshold defined by the upper quartile of our cohort.
- Sepsis epidemiological changes over time: Studies published in or before 2003 vs. studies published in or after 2005. We established two sepsis incidences based on data reported by Martin [41] (study period 1979−2000, N = 13,319,418 participants) and Stoller [5] (study period 2008−2012, N = 6,067,789 participants), adjusting the research period as described previously.

Secondary analyses were as follows:

1. Appropriate use of the terms "sex" and "gender" according to SAGER guidelines [24,34].
2. Sex-related analyses and reporting.
3. Description of the place of residence, race, ethnicity, culture, and language, occupation, gender and sex, religion, education, socioeconomic status, and social capital (PROGRESS) health determinants [47].
4. Factors associated with female participation and sex-related analysis and reporting.

The unit of analysis was the individual study. We performed a descriptive analysis and a bibliometric analysis. We limited the assessment of appropriate use of "sex" and "gender" to studies published in English. We reported data as medians, percentages, and interquartile ranges (IQRs). We conducted univariate analyses for the female participation proportion and publication year, funding source, author gender, author's country of affiliation categorized by the World Bank income classification [48], study design, study sample size, and ICU setting. We established statistical significance at a P value of 0.05. We carried out multivariate analyses to characterize independent associations between the aforementioned study characteristics and sex-related reporting. We performed statistical analyses using STATA statistical software (version 15.1; STATA Corporation, College Station, TX).

3. Results

3.1. Description of studies

3.1.1. Search results

We conducted a search on 2 August 2019. The search strategy yielded 106 SRs and two clinical guidelines, composed of 1,582 references on sepsis interventions for adult participants (Figure 1). A two-stage screening process—first of SRs and guidelines and then of primary studies—identified 277 studies. We excluded two Chinese studies after failed attempts to locate them in searches of MEDLINE, Embase, CENTRAL, CNKI, and Google Scholar [49,50].

3.1.2. Included studies

The included 277 studies (Table 1) had a total of 168,879 participants, for a median (IQR) of 128 (62−420) participants per study, with 17 studies contributing almost two-thirds (56.68%) of the sample. All participants were adults, and all studies were published between 1973 and 2017 (half after 2005). Most studies were published in English (88.81%). Most studies were RCTs (71.84%) and nearly half addressed initial resuscitative treatment (44.77%).

Funding details were available for 164 (59.21%) studies, with nearly half (47.56%) of those studies reporting nonprofit sources. Of studies published after milestone dates for reporting recommendations on funding, 65 studies included funding information, and just over a third (66.15%) of those were funded by nonprofit sources.

We identified 543 dominant authorship positions; four collaborative research groups in four papers were considered as single signatures and seven publications were signed by a single author. We could not clarify the gender of either the first or last author for 45 positions. Men and women accounted for 76.53% (415/543) and 13.44% (73/543) of authorships, respectively, with a similar gender distribution between first and last authors. Six last-position authors were groups. Thirty-eight authors (three women and 34 men) signed over one-third of the manuscripts (98/277 studies, 35.38%).

Although authorship was widely distributed in geographic terms (Europe, North and South America, Asia, and Oceania), only 14.36% (78/543) belonged to middle-income countries and none to low-income countries. While U.S. affiliations predominated by country (148/543 authorships, 27.25%), European affiliations predominated by continent (230/543 authorships, 42.36%). Eight countries contributed with a single study (Argentina, Malaysia, Poland, the Philippines, Russia, Saudi Arabia, Thailand, and Uruguay).

3.2. Participation-to-prevalence ratio

We withdrew studies for which no data were available on the sex of participants, leaving 246 studies with 131,342 participants providing information on female participants, that is, 40.44% (N = 53,110) of the sample, with a median (IQR) of 39.22% (32.00−43.75%). We included one study with 61 participants on treatment for acute pyelonephritis that recruited only female participants because this disease is not sex specific. The PPR was 0.78, indicating that women were represented at a level below their share of the sepsis population. Figures 2 and 3 depict results for the PPR and female participation proportion by authors' gender and country of affiliation, respectively. Table 2 shows subgroup analyses.

3.3. Secondary analyses

3.3.1. Appropriate use of the terms "sex" and "gender" according to SAGER guidelines

Of the 245 included studies published in English, and excluding the 6% of studies that did not use either "sex"

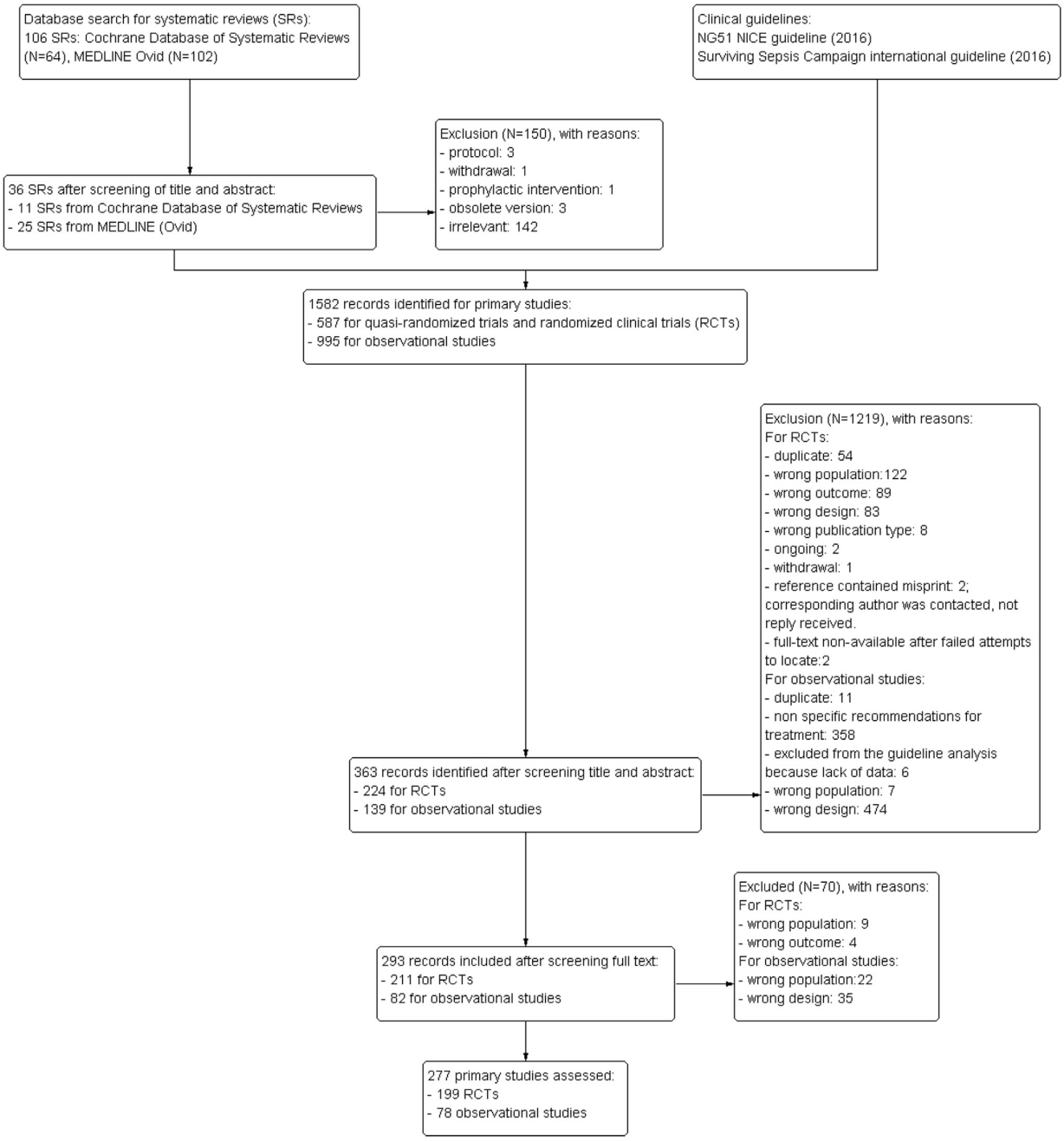

Fig. 1. Study flow diagram. SR, systematic review.

or ''gender'', 230 studies used at least one of the terms. Of those, we judged that 98 (40.00%) studies used the terminology properly, 83 (33.88%) studies used inaccurate terms, and the remaining 49 (20.00%) studies used terms inconsistently or were unclear because of a lack of the corresponding definitions.

3.3.2. Sex-related analysis and reporting

Details on sex-related reporting according to SAGER guidelines for all 277 studies are summarized in Tables 3 and 4. Overall, 57 (20.57%) studies included sex-related reporting for at least one SAGER checklist item. Twenty-five (9.02%) studies took sex into account in study design. Only

Table 1. Characteristics of the included studies

Characteristics	Included studies, $N = 277$
Design (*N*, %)	
Observational	86 (28.16)
Retrospective	50 (18.05)
Prospective	28 (10.11)
RCT	199 (71.84)
Single centre	140 (50.54)
Multicentre	137 (49.46)
Research topic (*N*, %)	
Initial resuscitative treatment	124 (44.77)
Failure of initiative therapy	43 (15.52)
Supportive therapies	56 (22.22)
Investigational therapies	52 (17.77)
Combination of previous categories	2 (0.72)
Funding (*N*, %)	All studies after guidelines[a]
Nonprofit	78 (28.16) 43 (47.25)
Profit	54 (19.49) 7 (7.69)
Mixed	23 (8.30) 9 (9.89)
None	9 (3.25) 6 (6.51)
Not stated	113 (40.79) 26 (28.57)

Abbreviation: RCT, randomized clinical trial.

[a] The STROBE and CONSORT guidelines, with reporting recommendations on funding for observational and RCT studies, published in 2007 and 2010, respectively. The analysis combined observational studies and RCTs published in 2007 and 2010 or later, respectively, after adjusting the research period as described in the Section 2 ($N = 91$).

30 (10.83%) studies reported sex-disaggregated main outcomes. As for drop-out data, 81 (21.24%) studies were unclear because they included neither a narrative mention nor a participant flowchart, whereas 108 (38.99%) studies reported no drop-outs and, of the remaining 88 (31.77%) studies, 22 reported a drop-out rate more than 10% and only one study reported drop-out rates by sex. For the adjusted analyses, 157 (56.68%) studies performed no adjusted analyses. When performed, 28/120 (23.34%) studies included sex, whereas 92/120 (76.67%) studies excluded sex as a covariate in the model, with most of the latter (56/92 studies; 60.77%) providing a statistical rationale. Only six (2.17%) studies conducted sex subgroup analyses, although only one of those studies complied with the full set of criteria proposed by McGregor [33]. Finally, very few authors (6/277 studies; 2.17%) discussed the potential implications of sex of the lack of such for the interpretation of study findings.

3.3.3. Description of PROGRESS health determinants

Details on at least one of the PROGRESS components, excluding sex and gender, were available in 44 studies with 68,783 participants. In terms of participant baseline characteristics, three studies reported place of residence and 34 studies reported racial and/or ethnic background. For disaggregated data by PROGRESS health determinants, subgroup analyses or regression models, five studies reported place of residence and a further five reported racial and/or ethnic background. Three studies reported the racial background for both baseline characteristics and analyses. High-income countries were significantly associated with reporting of place of residence and racial and/or ethnic background ($P = 0.011$). No study provided information on occupation, religion, education, socioeconomic status, or social capital.

3.3.4. Factors associated with female participation and sex-related analysis and reporting

Positively associated with an increased likelihood of female participation were a non-ICU setting ($P < 0.001$) and consideration of PROGRESS components ($P = 0.023$). Studies published in or after 1996 were also positively associated with an increased likelihood of sex-related reporting ($P = 0.019$). Moreover, RCTs compared with observational studies were less likely to report sex ($P < 0.001$). All results controlled for single-center or multicenter studies, publication year, study sample size, and consideration of PROGRESS components (see Supplementary material Table S1 and Table S2). Finally, the data did not suggest any effect of publication year, author's gender, author's country of affiliation categorized by income, funding source, sample size, or study design on the female participation level.

4. Discussion

Our analysis of primary studies underpinning sepsis treatment recommendations in SRs and guidelines revealed the female participation level to be less than that of female representation in the sepsis population. Secondary analyses indicated that fewer than half of studies published in English used "sex" and "gender" terminology properly and that only around a fifth reported by sex or included other health determinants.

To our knowledge, no previous studies have assessed the female participation in sepsis treatment studies. Nonetheless, our findings corroborate results in other fields that found female underenrollment [18,19,51], which may be explained by several factors. Female enrollment in RCTs may be affected by exclusion criteria based on age and comorbidities, as females with sepsis tend to be older and to exhibit more comorbidities than males [41,52,53]. To overcome such methodological constraints, Tannenbaum and Day proposed calculating the sample size to examine between- and within-group sex and age differences as defined in preliminary data [54]. Another factor is that, independently of the patient's clinical features, their sex may influence care provider perceptions and recommendations [55–57] and adversely affect the probability of recruitment for clinical trials.

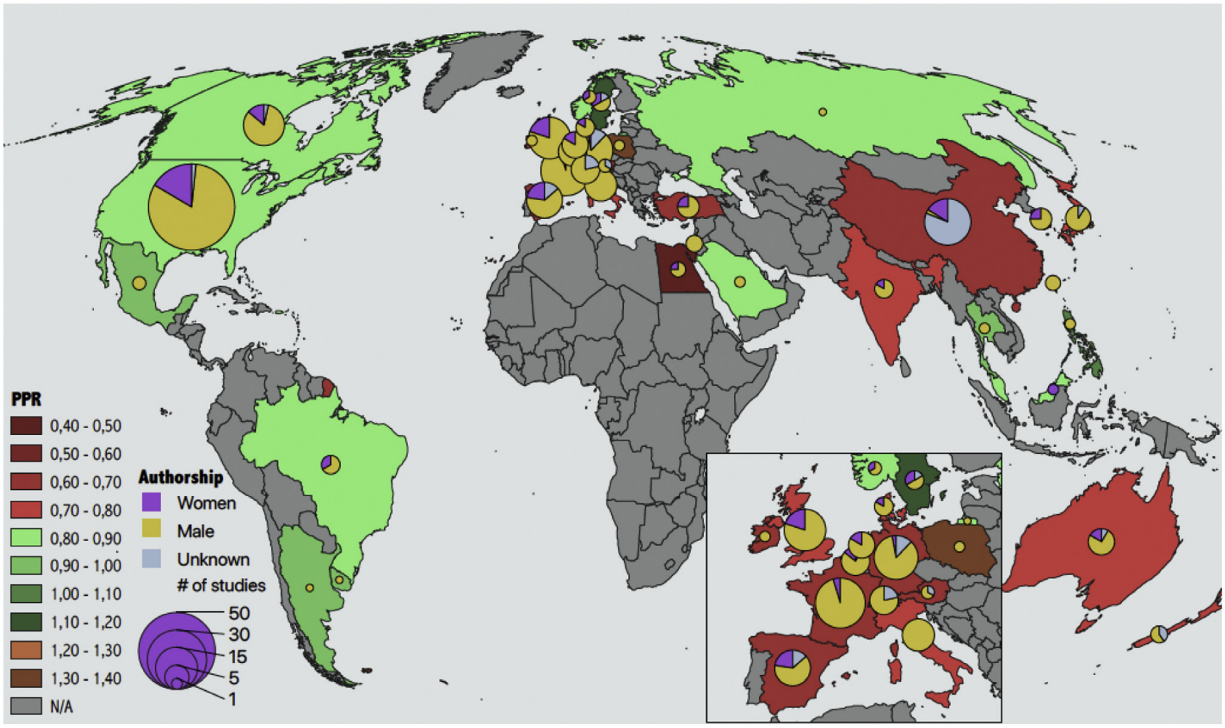

Fig. 2. Participation-to-prevalence ratio by author gender and country of affiliation. PPR, participation-to-prevalence ratio.

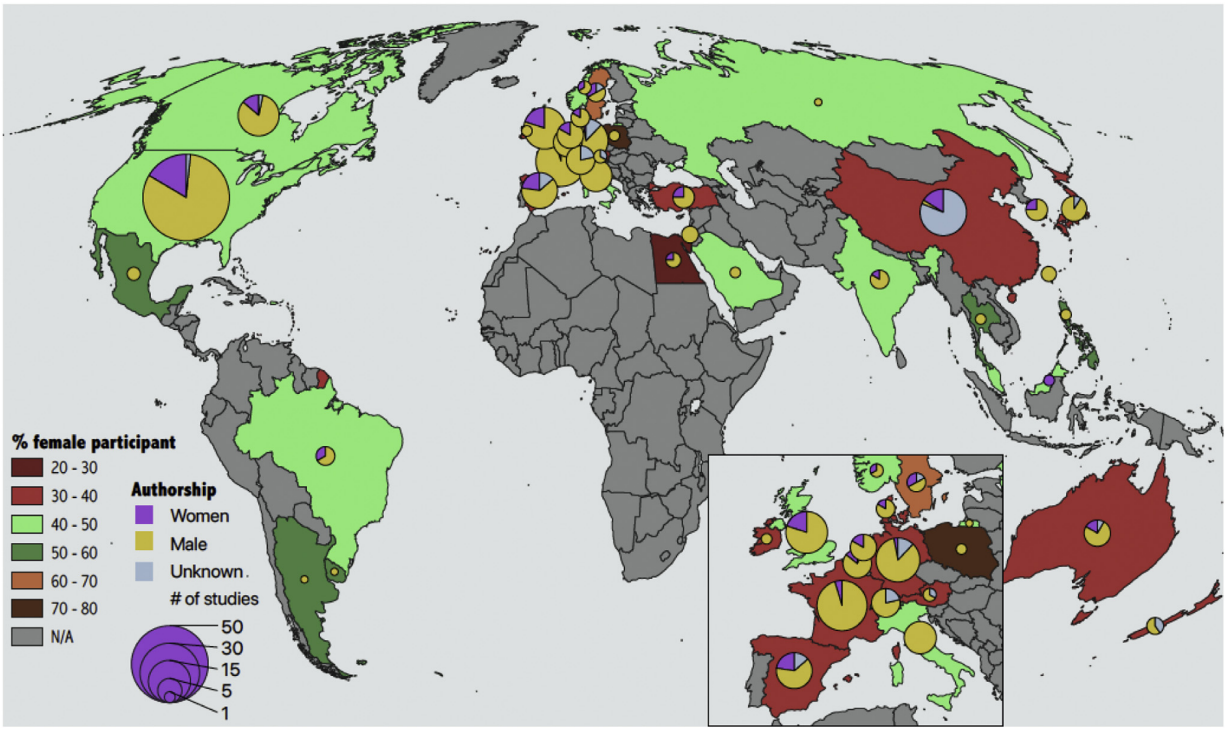

Fig. 3. Female participants as a percentage of study participants by author gender and the country of affiliation.

Table 2. Prevalence-to-participation ratio by subgroup

Characteristics	Studies (*N*)	Sample (*N*)	Females (*N*)	PPR
Design				
Observational	65	68,625	28,412	0.8
RCT	181	62,717	24,698	0.76
Setting				
ICU	156	92,754	36,827	1.02
Non-ICU	90	38,588	16,283	0.81
Sample size				
≥500 participants	57	105,328	42,892	0.78
<500 participants	189	26,014	10,216	0.76
Publication year				
2003 or before	108	25,647	10,432	0.78
2005 or after	136	101,858	41,156	0.81

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

Our findings point to adequate female participation in ICU settings that needs to be interpreted with care. Data on sepsis by sex in the ICU setting reflect a lower female sepsis incidence than in the non-ICU setting [46]. Nevertheless, Dodek and Fowler reported a higher prevalence of male patients receiving ICU care after adjusting for diagnosis and comorbidities. Those authors suggested that sex-related differences may be explained by biological plausibility related to current comorbidity scales may not reliably predict illness severity and because biases (including gender bias) may influence decision-making about ICU admission [56,58].

The fact that we found no associations between author gender and female enrollment or between author gender and sex-related reporting contradicts findings reported in other recent studies [25–27]. One possible explanation may be that the findings of those other studies were based on larger data sets. The fact that we found that social health determinants were rarely reported corroborates other findings that racial and/or ethnicity reporting remains uncommon [59–61].

We were unable to analyze data on sex in 31 (22.23%) studies because sex was not reported. This proportion contrasts with the 2% to 9% reported by Canadian trials and RCTs that supported FDA approval [17,62–64]. This difference may be explained by the heterogeneity of our sample in terms of publication year, design, and author country of affiliation. Our findings for sex-related analysis and reporting data are consistent with the findings of previous studies that addressed this question (14, 56–58). Regarding sex-related analysis, the medical literature reflects a wide range of prespecified analyses (0–57%), performed analyses (0–8%), and properly performed subgroup analyses (5–35%) [60,64–66]. Reporting solely aggregated outcomes may mask differences by sex [67–70]. Wallach et al evaluated sex-treatment interactions in RCTs included in Cochrane SRs, finding that only 41 (4%) SRs properly described sex-disaggregated treatment outcomes and, of those, 10% detected differential effects for the sexes [71]. Our results highlight the gap of knowledge about potential implications for the clinical practice of sex-related treatment response.

A number of initiatives are underway to tackle the poor integration of sex and gender in medical research, but a prerequisite is a better understanding of the rationale behind current research practices. Basic science lacks evidence of sex- or gender-based differences as pointed out in a qualitative analysis of health research fund applications [72]; indeed, as pointed out by Clayton [73], most preclinical research is performed exclusively on male animals. Second, grant agencies have begun to develop policies to close the sex and gender gap [73–75]. It is suggested that an explicit request to include sex and gender considerations might boost accountability regarding sex and gender [72]. Third, several journals and editors have elaborated guidelines and editorial policies for sex and gender reporting in submitted manuscripts, although, as yet, no general standard has been embraced [34,76,77], while universities have also begun to develop resources that foster the consideration of sex and gender in research [78].

The strengths of the study include the fact that we imposed no language restrictions. We contacted review authors to request further information on records that could not retrieve but received no response. We assessed inclusion criterion in relation to the primary clinical outcome using the study's protocol or register when available and otherwise the methods section. We established sex-

Table 3. Sex-related reporting according to SAGER guidelines

Studies (*N* = 277)	Criteria fulfilled	Criteria not fulfilled
Study topic (*N*, %)	1 (0.36)	276 (99.64)
Study design (*N*, %)	25 (9.06)	251 (90.94)
Data: outcomes disaggregated by sex (*N*, %)[a]	30 (10.87)	244 (88.41)
Data: outcomes adjusted by sex (*N*, %)[b]	28 (23.34)	92 (76.67)
Discussion (*N*, %)	6 (2.17)	270 (97.83)

Abbreviations: SAGER, Sex and Gender Equity in Research.
[a] Data outcomes disaggregated by sex, *N* = 275 studies after removing single-sex studies addressing non–sex-specific medical conditions.
[b] Data adjusted by sex, *N* = 120 studies after removing studies with no adjusted analyses.

Table 4. Sex-related reporting by gender of first-last authors

Sex reported?	Studies (*N*)	Female-female (*N*)	Male-male (*N*)	Female-male or male-female (*N*)
Yes	57	5	38	14
No	220	27	138	55

stratified incidence of sepsis through broad bibliographic search and conducted several subgroup analyses by temporal, design, and setting subsets. As for limitations, because we used a search strategy designed to retrieve only high-impact sepsis treatment evidence, our sample does not represent the full spectrum of literature on which recommendations are based. Another issue is the inherent constraint to the PPR, specifically that it is challenging to reliably ascertain the sex-stratified incidence of sepsis. Another limitation is the lack of reported data by geographical regions and the limited data available for low-resource settings, bearing in mind that most sepsis-related deaths occur in low- and middle-income countries [2]. The largest cohorts come from the United States, while incidence by sex is reported inconsistently in European data records [3,5,41,79]. A further limitation is that the PPR thresholds for adequate enrollment (1 ± 0.20) seem defined by convention. We could locate no bibliography that supported these cutoffs and, although we contacted corresponding authors of previous publications [17,19,38] to request further details, we received no reply. Given that the thresholds are possibly unjustifiably wide, we may have overestimated bias-free enrollment. Moreover, our regression model included as covariate an adjusted NIH cutoff point (the year 1996), although most affiliations (as a proxy for study country) belonged no to the United States. Finally, we considered no other primary study factors (e.g., the risk of bias) that may have affected the certainty of recommendations.

In conclusion, we found that females were underenrolled in sepsis studies and that sepsis studies failed to include sex-related analysis and reporting. The lack of sex-related inclusion, analysis, and reporting may jeopardize the external validity of those studies.

CRediT authorship contribution statement

Alba Antequera: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing - original draft, Visualization. **Olaya Madrid-Pascual:** Validation, Investigation, Resources, Writing - review & editing. **Ivan Solà:** Methodology, Resources, Writing - review & editing. **Emilia Roy-Vallejo:** Validation, Investigation, Resources, Writing - review & editing. **Sami Petricola:** Validation, Formal analysis, Visualization, Writing - review & editing. **Maria Nieves Plana:** Formal analysis, Writing - review & editing. **Xavier Bonfill:** Methodology, Writing - review & editing, Funding acquisition.

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Supplementary data

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4.2. Results of the second study

Antequera A, Stallings E, Henry RS, Lopez-Alcalde J, Runnels V, Tudiver S, et al. Sex and Gender Appraisal Tool-Systematic Reviews-2 and Participation-to-Prevalence Ratio assessed to whom the evidence applies in sepsis reviews. J Clin Epidemiol 2021, in press. doi.org/10.1016/j.jclinepi.2021.11.006

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Sex and Gender Appraisal Tool for Systematic Reviews–2 (SGAT-SR-2) consists of 19 questions appraising the review's sections and use of the terms sex and gender (Table 4). Supplementary material A.2 details criteria for assessing each item and provides examples.

Table 4. Sex and Gender Appraisal Tool for Systematic Reviews –2(SGAT-SR-2)

Review section	Question	Reviews meeting the criteria				
		Yes	No	Probably yes	Probably no	NA
Abstract	1. Did the abstract report on sex or gender?					
Plain language summary	2. Did the plain language summary report on sex or gender?					
Background	3.a. Did the background discuss the relevance of sex or gender to the review question?					
	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?					
Objectives	4. Were sex, gender or related terms used in objectives?‡					
Methods	5.a. Did the review’s eligibility criteria consider sex or gender differences?*					
	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?					
	6. Did the review plan to collect characteristics of participants by sex or gender at the study-level?					
	7. Did the review plan to collect missing participant data by sex or gender at the study-level (e.g., attrition from the study)?					
	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)?†					
	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?					
Results	9. Did the review report characteristics of participants by sex or gender at the study-level (or state that no data were available)?					
	10. Did the review report missing participant data by sex or gender at the study-level (or state that no data were available)?					
	11. Did the review report characteristics of participants by sex or gender at the review-level (or state that no data were available)?					
	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)?†					
	12.b. If 12.a. “Yes” or “Probably yes”, Did the review analyse or report results accounting for any other					

Continued

	PROGRESS-Plus characteristics interacting with sex or gender?	
	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 outcome (i.e., indirectness)?	
Discussion and Authors' conclusions	14. Did the review discuss the limitations related to sex or gender of the population of interest?	
	15. Did the review discuss the implications of evidence for practice or research related to sex or gender of the population of interest?	
	16. Did the review discuss the applicability of evidence related to sex or gender of the population of interest?	

Questions	**Reviews meeting the criteria**
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* Binary use (female/male) Non-binary use (person with DSD/female/male) Unclear *Gender* Binary use (woman/man or girl/boy)) Non-binary use (woman/man/gender diverse/etc.) Unclear	
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* Appropriate (person with DSD/female/male) Inappropriate (girl/boy/woman/man/gender diverse/etc.) Unclear *Gender* Appropriate (girl/boy/woman/man/gender diverse/etc.) Inappropriate (person with DSD/female/male) Unclear	
19. Non-interchangeable use (N=48) Explanation: When authors mention sex, gender, or related terms, did they use them interchangeably? Yes No Unclear	

Abbreviations: NA, non-applicable, DSD, differences of sex development.
* "Yes" response required to specify if a rationale was provided.
† "No" response required to specify if a rationale was provided.
‡ [Sex or gender] Related terms refer to female, male, individuals with differences of sex development girls, women, boys, men, transgender, and other gender diverse people.

Among 71 systematic reviews 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 PROGRESS-Plus 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).

Title: Sex and Gender Appraisal Tool-Systematic Reviews-2 and Participation-to-Prevalence Ratio assessed to whom the evidence applies in sepsis reviews

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Conflict of interest: None.

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 and 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 being 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 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 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

[1] In this manuscript, we used definitions of sex, gender, and related terms (i.e., female, male, individuals with differences of sex development girls, women, boys, men, transgender, and other gender diverse people) as proposed by the Canadian Institutes of Health Research (CIHR) [12].

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 218 records. 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.

Figure 1. Study flow diagram

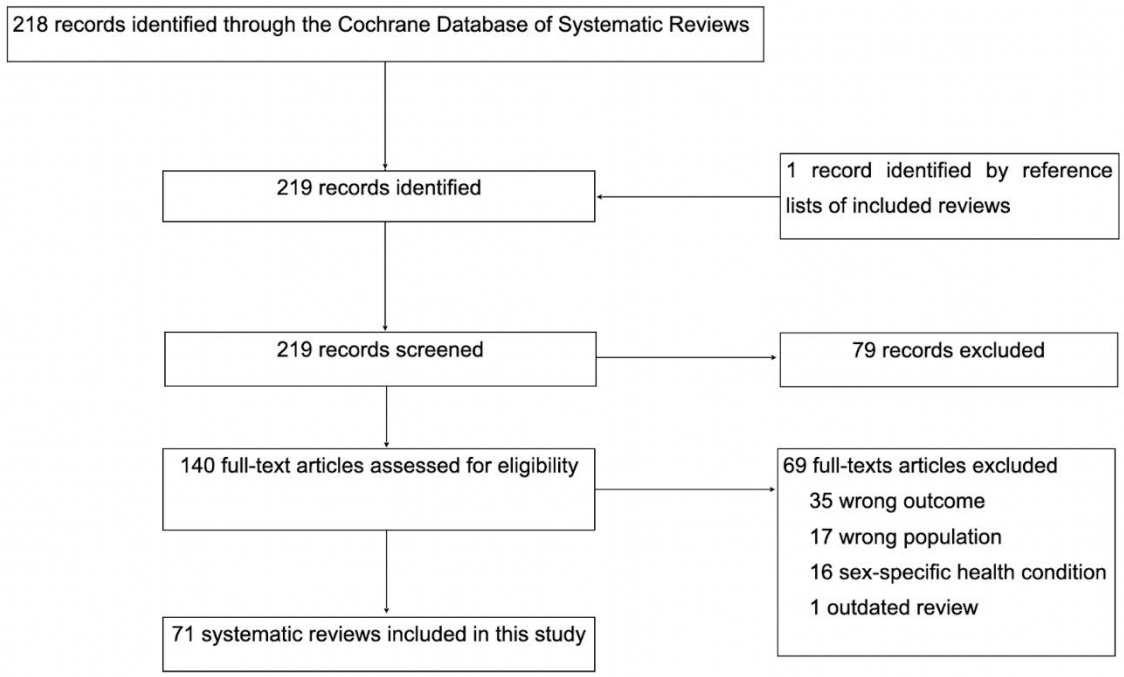

Table 1. Characteristics of the included reviews

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.

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 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
Methods	5.a. Did the review's eligibility criteria consider sex or gender differences?*	1 RP 4 RNP	66	0	0	0
	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
Results	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
	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

Continued

Review section	Question	Reviews meeting the criteria				
		Yes	No	Probably yes	Probably no	NA
Discussion and Authors' conclusions	14. Did the review discuss the limitations related to sex or gender of the population of interest?	2	63	0	0	6
	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; NRP, non-rationale provided.
* "Yes" response required to specify if a rationale was provided.
† "No" response required to specify if a rationale was provided.
‡ [Sex or gender] Related terms refer to female, male, individuals with differences of sex development girls, women, boys, men, transgender, and other gender diverse people.

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.

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.

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

Figure 2 shows disaggregated data by the inclusion of at least one of theSGAT-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).

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

Abbreviations: SGBA, sex-and gender-based analysis.

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).

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.

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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4.3. Results of the third study

Lopez-Alcalde J, Antequera Martín A, Stallings E, Muriel A, Fernández-Félix B, Solà I, 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(5):e035927. doi:10.1136/bmjopen-2019-035927

Antequera A, Lopez-Alcalde J, Stallings E, Muriel A, Fernández-Félix B, del Campo R, et al. Sex as a prognostic factor for mortality in critically ill adults with sepsis: a systematic review and meta-analysis. BMJ Open. 2021;11(9):e048982. doi: 10.1136/bmjopen-2021-048982.

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From 14,304 records, 13 studies [229–239] (80,520 participants) were included. Meta-analysis did not find sex-based differences in all-cause hospital mortality (OR 1.02, 95% CI 0.79 to 1.32; very low-certainty evidence), and all-cause ICU mortality (OR 1.19, 95% CI 0.79 to 1.78; very low-certainty evidence). However, females presented higher 28-day hospital mortality (OR 1.18, 95% CI 1.05 to 1.32; very low-certainty evidence) and lower 1-year mortality (OR 0.83, 95% CI 0.68 to 0.98, low-certainty evidence). There was a moderate risk of bias in the domain adjustment for other prognostic factors in six studies, and the certainty of evidence was further affected by inconsistency and imprecision. Table 5 displays “Summary of findings” for each review outcome.

Table 5. Summary of findings

Outcomes	Anticipated absolute prognostic effects*			Effect estimate (95% CI) [95% prediction interval]	№ of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk in males	Risk in females (95% CI)	ARD in females(95% CI)**			
All-cause hospital mortality (; median observed length of stay ranged from 6 to 26 days)	303 per 1 000 [a]	307 per 1 000 (255 to 364)	4 more per 1000 (47fewer to 62 more)	OR 1.02 (0.79 to 1.32) [0.5 to 2.08]	28,915 (4 observational phase 2 studies)	⨁◯◯◯ VERY LOW [b,c,d]
28-day all-cause mortality	240 per 1 000 [a]	271 per 1 000 (249 to 294)	31 more per 1000 (9 more to 54 more)	OR 1.18 (1.05 to 1.32) [0.56 to 2.50]	12,579 (3 observational phase 2 studies)	⨁◯◯◯ VERY LOW [b,d,e,f]
1-year all-cause mortality	505 per 1 000 [a]	459 per 1 000 (410 to 500)	46 fewer per 1000 (95 fewer to 5 fewer)	OR 0.83 (0.68 to 0.98) N/M	6,134 (1 observational phase 2 study)	⨁⨁◯◯ LOW [d,e,g,h]
All-cause ICU mortality (median observed length of stay ranged from 2.7 to 13 days)	200 per 1 000 [a]	229 per 1 000 (167 to 308)	29 more per 1000 (33 fewer to 108 more)	OR 1.19 (0.80 to 1.78) [0.49 to 2.89]	31,562 (5 observational phase 2 studies)	⨁◯◯◯ VERY LOW [b,c,d]

Abbreviations: ARD: Absolute risk difference; ARI: Absolute risk increase; ARR: Absolute risk reduction; CI: Confidence interval; ICU: Intensive care unit; N/M: Not meaningful; OIS: Optimal information size; OR: Odds ratio; OSS: Observed sample size.

*The risk in the female group (and its 95% confidence interval) is based on the assumed risk in the male participants group and the estimated effect of sex (OR and its 95% CI)** We considered an ARD of at least ± 10‰ as large enough to be clinically meaningful. Thus, we defined the clinical importance of the absolute prognostic effect for all the review outcomes as follows: important improvement (ARR of at least 10‰), slight improvement (10‰ < ARR ≤ 5‰), minimal or no effect (-5‰ < ARD < 5‰), slight worsening (5‰ ≤ ARI < 10‰), and important worsening (ARI of at least 10‰).

Not meaningful: < 3 studies for computing of the 95% prediction interval a meaningful estimate.

Explanations

a. The assumed risk in male participants is based on the median risk amongst the male participants in the included studies. We consider this risk reflects the context of ICUs in high-resource countries adequately. Downgraded by two levels for very serious inconsistency due to a wide 95% prediction interval ranging from an increased mortality in male sex to an increased mortality in female sex that could not be explained for any reason.
c. Downgraded by two levels for very serious imprecision because the CI 95% of the ARD in our assumed risk scenario ranges from an important improvement to an important worsening in the prognosis of female participants compared with male participants. Besides, the OSS was smaller than the OIS required.
d. Publication bias not assessed because of the scarce number of included studies (< 10).
e. Downgraded by one level for serious imprecision because the CI 95% of the ARD in our assumed risk scenario exceeds one of our clinical importance thresholds (i.e., it is compatible with an important or a slight prognostic effect). The OSS was greater than the OIS.
f. Downgraded by one level for serious indirectness because one study.(52) was responsible for 85% of the weight reported in- and out-hospital mortality

g. Downgraded by one level for serious risk of bias because the effect estimate comes from a study with moderate and unclear risk of bias for half of the QUIPS domains.
h. Inconsistency not assessed because a single study was considered.

BMJ Open

Sex as a prognostic factor for mortality in critically ill adults with sepsis: a systematic review and meta-analysis

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ABSTRACT

Objective To assess the role of sex as an independent prognostic factor for mortality in patients with sepsis admitted to intensive care units (ICUs).

Design Systematic review and meta-analysis.

Data sources MEDLINE, Embase, Web of Science, ClinicalTrials.gov and the WHO Clinical Trials Registry from inception to 17 July 2020.

Study selection Studies evaluating independent associations between sex and mortality in critically ill adults with sepsis controlling for at least one of five core covariate domains prespecified following a literature search and consensus among experts.

Data extraction and synthesis Two authors independently extracted and assessed the risk of bias using Quality In Prognosis Studies tool. Meta-analysis was performed by pooling adjusted estimates. The Grades of Recommendations, Assessment, Development and Evaluation approach was used to rate the certainty of evidence.

Results From 14 304 records, 13 studies (80 520 participants) were included. Meta-analysis did not find sex-based differences in all-cause hospital mortality (OR 1.02, 95% CI 0.79 to 1.32; very low-certainty evidence) and all-cause ICU mortality (OR 1.19, 95% CI 0.79 to 1.78; very low-certainty evidence). However, females presented higher 28-day all-cause mortality (OR 1.18, 95% CI 1.05 to 1.32; very low-certainty evidence) and lower 1-year all-cause mortality (OR 0.83, 95% CI 0.68 to 0.98; low-certainty evidence). There was a moderate risk of bias in the domain adjustment for other prognostic factors in six studies, and the certainty of evidence was further affected by inconsistency and imprecision.

Conclusion The prognostic independent effect of sex on all-cause hospital mortality, 28-day all-cause mortality and all-cause ICU mortality for critically ill adults with sepsis was uncertain. Female sex may be associated with decreased 1-year all-cause mortality.

PROSPERO registration number CRD42019145054.

Strengths and limitations of this study

- ► To our knowledge, this systematic review is the first addressing the prognostic independent effect of sex on mortality for patients with sepsis following the recommended standards for reviews of prognostic factor studies.
- ► The meta-analysis pooled adjusted estimates for at least one of five core covariate domains prespecified following a literature search and consensus among experts.
- ► The certainty of the evidence was evaluated using the Grades of Recommendations, Assessment, Development and Evaluation approach.
- ► Heterogeneity was substantial between the included studies.

INTRODUCTION

Sepsis, a life-threatening organ dysfunction produced by a dysregulated host response to inflammation,[1] is a leading cause of death in intensive care units (ICUs) and accounts for one of five deaths worldwide.[2–4] It is a heterogeneous illness affecting males more often than females.[5] Evaluating if outcomes differ by sex is a recognised health research priority.[6] It has been hypothesised that sex may have a prognostic effect on sepsis outcomes. Biological mechanisms concerning the relation between sex hormone metabolism and immune responses are known to underpin this hypothesis.[7–11] However, individual studies evaluating the relationship between sex and outcome of sepsis report conflicting and imprecise findings.[12–14]

Prognostic research that identifies patient characteristics associated with outcomes in people with a particular condition[15] can be collated in evidence syntheses to examine the role of sex in mortality among patients with sepsis. It may help in risk stratification of these patients by combining independent prognostic factors within prognostic models, which contribute to the selection of the most appropriate therapeutic options.[15] Using a

systematic review search filter in PubMed, we found two potentially relevant citations.[16 17] Their detailed assessment showed several weaknesses. For example, there was no definition of eligibility criteria concerning studies that capture independent associations, a feature that is critical for focussing the review on prognostic evidence.[18] In addition, specific tools[19] for the assessment of risk of bias in prognostic studies were not applied. Therefore, an evidence synthesis tailored to the specific methodological requirements of prognostic research is required to help delineate the significance of sex in sepsis outcomes in critically ill patients.

We conducted a systematic review and meta-analysis to summarise the available evidence to assess the role of sex as an independent prognostic factor for mortality in patients with sepsis admitted to the ICU.

METHODS

We registered the protocol with PROSPERO (CRD42019145054) and published it in full.[20] Online supplemental table 1 details the differences between the protocol and the review. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[21]

Eligibility criteria

We included studies (experimental or any observational design) that sought to confirm the independent prognostic effect of sex on mortality in critically ill adults with sepsis controlling for covariates (called phase 2-confirmatory studies, which means the objective statement outlined sex as a prognostic factor of interest and analyses adjusted for covariates).[18] We included patients aged 16 years and older with a sepsis diagnosis, as defined by the study authors, treated in an ICU. Studies including both adult and paediatric patients were eligible if adults represented more than 80% of the study sample. Sex and gender are distinct concepts, though often erroneously interchanged in the medical research reports.[22] We accepted any assessment of sex as a biological characteristic. We also appraised operational concepts of sex and gender provided by the study authors using the classification detailed in online supplemental table 2.[23] After a literature search and consensus among experts (online supplemental table 3), we prespecified the following core set of adjustment factors: age, severity score (Sequential Organ Failure Assessment score, Simplified Acute Physiology Score II or Acute Physiologic Assessment and Chronic Health Evaluation II), comorbidities (immunosuppression, pulmonary diseases, cancer, liver diseases or alcohol dependence), non-urinary source of infection, and inappropriate or late antibiotic coverage. The coprimary outcomes were all-cause hospital mortality and 28-day all-cause mortality. Secondary outcomes were 7-day all-cause hospital mortality, 1-year all-cause mortality and all-cause ICU mortality. Table 1 describes the review question according to the population, index, comparator, outcome(s), timing, setting.

Search strategy and selection process

We searched MEDLINE Ovid, Embase Elsevier and Web of Science for studies published from inception to 17 July 2020, and ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform for unpublished

Table 1 PICOTS system

Population	Index prognostic factor	Comparator	Outcome(s)	Timing	Setting
Adults with sepsis	Sex	Non-applicable to this review*	Primary outcomes		ICUs
			All-cause hospital mortality	The longest follow-up provided by the study authors (until death of hospital discharge)	
			28-day all-cause mortality	28 days from sepsis diagnosis	
			Secondary outcomes		
			7-day all-cause hospital mortality	7 days from sepsis diagnosis	
			1-year all-cause mortality	1 year from sepsis diagnosis	
			All-cause ICU mortality	The longest follow-up provided by the study authors (until death of ICU discharge)	

*Core set of adjustment factors: age, severity score (Sequential Organ Failure Assessment score, Simplified Acute Physiology Score II or Acute Physiologic Assessment and Chronic Health Evaluation II), comorbidities (immunosuppression, pulmonary diseases, cancer, liver diseases or alcohol dependence), non-urinary source of infection and inappropriate or late antibiotic coverage.
ICUs, intensive care units; PICOTS, population, index, comparator, outcome(s), timing, setting.

and ongoing studies, regardless of language. The search strings included terms related to the population (sepsis), the prognostic factor (sex), prognostic study methods and the outcome (mortality). Furthermore, we handsearched conference proceedings from 2010 to 2019 of the foremost critical care and infectious diseases symposia. Online supplemental table 4 presents the full search strategy.

We used the online software EPPI-Reviewer V.4 to manage the study selection process.[24] Pairs of review authors independently screened the title and abstracts, and when appropriate, full texts to determine their eligibility. We used a consensus method and consulted a third author if disagreement remained.

Data extraction and risk of bias assessment

Two authors independently extracted data and reached a consensus using electronic extraction templates in EPPI-Reviewer V.4. We used the checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies for prognostic factors guidance for data collection.[25] We contacted all study authors for missing information. Two authors independently assessed the risk of bias of the included studies, agreed on ratings and a third author participated when required. We applied an outcome-level approach and amended the Quality In Prognosis Studies (QUIPS) tool using four categories (low, moderate, high or unclear risk).[19 25 26] We defined studies controlling for less than three of the aforementioned covariates as 'minimally adjusted for other prognostic factors or moderate risk', and those controlling for at least three of these covariates as 'adequately adjusted or low risk of bias' for the QUIPS adjustment domain.[27] We assessed selective reporting bias by: (1) searching for a prospective study protocol or registration, (2) dealing with related conference abstracts and (3) carefully examining the study methods section.[19]

Data synthesis

For each study and prognostic factor estimate, we extracted the measures of associations alongside its CIs. We transformed association measures into an OR with its 95% CIs to allow statistical pooling whenever adequate.[28] We estimated no data from Kaplan-Meier curves because of the risk of overestimation of events and censorship concerns.[29] We presented results consistently, so associations above one indicated a higher mortality for female participants. We pooled estimates in meta-analyses when valid data were available. For the primary analyses, we used estimates from the model that adjusted for more covariates from the core of adjustment factors. We performed random-effects meta-analyses applying the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment,[30] using RevMan V.5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and the template for conversion provided by IntHout.[31] We examined statistical heterogeneity computing prediction intervals when the random-effects meta-analysis contained at least three studies.[30 32] We also calculated I^2 and τ^2 statistics to provide further quantifications of statistical heterogeneity. We planned to explore possible methodological causes of heterogeneity performing subgroup analyses. We undertook a single prespecified subgroup analysis for prospective vs retrospective studies when appropriate. We compared differences between subgroups by performing a test of interaction.[33] We carried out no subgroup analyses based on other study characteristics because there were insufficient studies. We conducted sensitivity analyses accounting for the risk of bias excluding studies with either a high or moderate risk of bias in one of the following QUIPS key domains: study attrition, prognostic factor measurement, outcome measurement and adjustment for other prognostic factors. Additionally, we explored potential differences between meta-analyses based on unadjusted (crude) and adjusted estimates, and the impact of the unique information reported in abstract conferences.[34] We could not perform further sensitivity analyses as no other comparisons met the predefined criteria. Although we planned to assess publication bias for each meta-analysis including ≥10 studies by funnel plot representation and Peter's test at a 10% level,[35] no meta-analysis met this criterion.

Assessment of the certainty of evidence

We assessed the certainty of evidence using the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach and guidance for prognosis studies (online supplemental table 5).[27 36–41] We tabulated our findings for each outcome using the GRADEpro GDT software.[42] We described results for prognostic effect estimate considering the certainty of evidence and its clinical importance (important effect, slight effect and little or no effect). As we found no well-established clinically important thresholds for prognostic effects, we agreed a priori on an absolute risk difference of at least ±10‰ as clinically important difference.

Patient and public involvement

No patients or the general public involved.

RESULTS

Our searches threw a total of 14 304 records. After removing duplicates, we screened 13 115 titles and abstracts and identified 146 full texts for further examination. Finally, the review included 13 studies[43–55] (figure 1). One study included[55] was reported as a conference abstract. Thus, we examined database information published elsewhere[56] to obtain further details on study methods. The included studies involved a total of 80 520 adult participants (45.25% females). Table 2 and online supplemental table 6 display their characteristics. Online supplemental table 7 and online supplemental table 8 show the sepsis definition and covariates included in the adjusted models of each study, respectively. Although four studies[47 50 53 54] had phase 2 designs and provided adjusted data on mortality, their time frames differed from ours and/or reported unadjusted estimates for some of the review outcomes. Hence, we only used those data for sensitivity analyses.

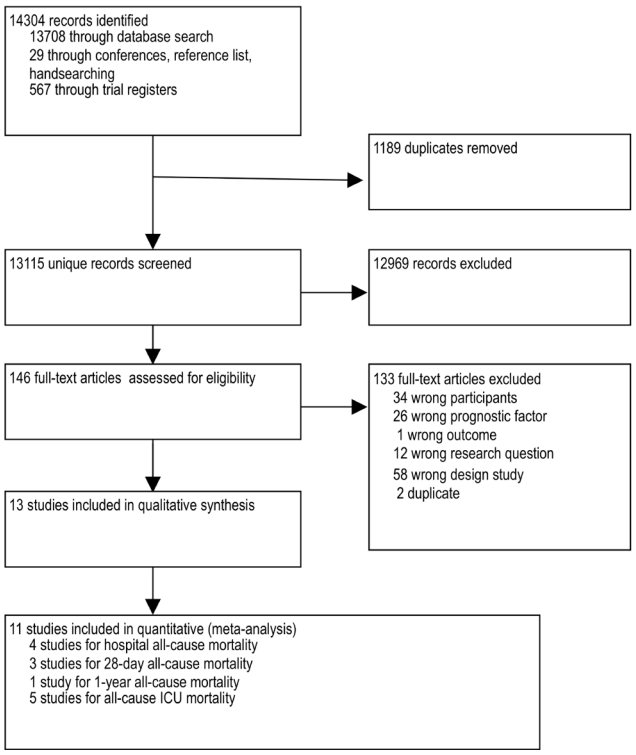

Figure 1 Flow diagram. ICU, intensive care unit.

Online supplemental figure 1 depicts the risk of bias assessment at outcome level of each included study using QUIPS. Over half of the studies[43 45 46 48–50 54] were at low risk for study participation, study attrition, and outcome measurement domains. While three studies[51 52 55] described baseline characteristics inadequately, and another two[44 47] provided insufficient data on drop-outs. All studies were at unclear risk for the prognostic factor domain, given that none defined sex. The risk of bias for the adjustment for other prognosis factors domain was low for half of the studies[43 44 47 52 54 55] and moderate for the others[45 46 48–51] because of an acceptable or minimal adjustment, respectively. Three studies[45 50 55] were at unclear risk for the statistical analysis and reporting domain, while the remaining studies were at low risk of bias.

Evidence synthesis

Online supplemental table 9 presents the summary outcome estimates for each study. Table 3 displays 'Summary of findings' for each review outcome.

Primary outcomes

We investigated the independent prognostic effect of sex on all-cause hospital mortality. We found seven studies[43–45 47 50 53 55] (38 016 recruited participants) addressing this question. Among the five studies[43–45 47 55] (30 349 analysed participants) that provided adjusted results, four of them[43 44 47 55] (28 915 analysed participants) presented sufficiently similar data allowing quantitative synthesis. Meta-analysis showed inconclusive results on sex-based differences in all-cause hospital mortality (OR 1.02, 95% CI 0.79 to 1.32; I^2=64%; very low-certainty evidence) (figure 2A). The 95% prediction interval ranged from 0.5 to 2.08. Sensitivity analyses results remained unaltered either excluding the study[55] only reported as a conference abstract (OR 0.95, 95% CI 0.55 to 1.64), or using unadjusted estimates (OR 1.00, 95% CI 0.88 to 1.14) (online supplemental figure 2 and online supplemental figure 3, respectively).

We examined sex-based differences in 28-day all-cause mortality. We found six studies[44 49 50 52–54] (20 930 recruited participants) addressing this question. Three studies[44 49 52] (12 579 analysed participants) provided adjusted results. Meta-analysis found higher 28-day all-cause mortality in the female group (OR 1.18, 95% CI 1.05 to 1.32; I^2=0%; very low-certainty evidence) (figure 2B). Considering a risk of 24% for 28-day all-cause mortality in male patients, 31 more female patients per 1000 will die (95% CI from 9 to 54 more), as compared with male patients. The 95% prediction interval ranged from 0.56 to 2.5. Sensitivity analysis results were inconclusive either pooling only studies with low or uncertain risk of bias for all key QUIPS domains (OR 1.17, 95% CI 0.88 to 1.56) or unadjusted estimates (OR 1.05, 95% CI 0.84 to 1.32) (online supplemental figure 4).

Secondary outcomes

No study evaluated the prognostic role of sex on 7-day all-cause hospital mortality. We sought sex-related differences in 1-year all-cause mortality. Of two studies[50 53] investigating this question, only one[50] (6134 analysed patients) provided adjusted estimates reporting as Cox proportional hazard regression with OR (95% CI). We were unable to get further clarification from the study authors; therefore, we considered this a misspelling error, and so we transformed their estimate (assumed HR) into OR. This study showed lower 1-year all-cause mortality in the female group (OR 0.83, 95% CI 0.68 to 0.98; low-certainty of evidence). Considering a risk of 50.5% for 1-year all-cause mortality in male patients, 46 fewer female patients per 1000 will die (95% CI from 95 to 5 fewer), as compared with male patients. Sensitivity analysis results using unadjusted estimates were inconclusive (OR 0.86, 95% CI 0.54 to 1.37) (online supplemental figure 5).

We evaluated sex-related all-cause ICU mortality. We found seven studies[43 46–48 51 53 54] (51 936 recruited participants) addressing this question. Five studies[43 46 48 51 54] (31 562 analysed participants) provided adjusted estimates. One of them[48] reported adjusted OR stratified by age, and after failing to get an overall adjusted estimate from the study author, we considered it as two substudies. Pooled adjusted estimates found inconclusive results on sex-based differences in all-cause ICU mortality (OR 1.19, 95% CI 0.79 to 1.78; I^2=69%; very low-certainty evidence) (online supplemental figure 6). The 95% prediction interval ranged from 0.49 to 2.89. Results of analyses comparing subgroups by longitudinal designs showed no differences (p=0.83). Sensitivity analysis results including only studies with low or uncertain risk of bias for all key

Table 2 Characteristics of included studies

Study	Study dates	Study design	Sites	Population	Primary outcome	Sample size N of study participants (N with outcome)	Inclusion criteria	Exclusion criteria
Adrie *et al* 2007[43]	1997–2005	Prospective nested case–control	12	Adults admitted to the ICU for severe community-acquired sepsis	ICU mortality Post-ICU mortality	1692 (1608)	>16 years old; ICU stays >24 hours; community-acquired severe sepsis	NS
Caceres *et al* 2013[44]	2006–2007	Retrospective cohort	4	Adults admitted to the ICU for hospital-acquired pneumonia	All-cause mortality	416 (319)	≥18 years old; ICU admission; clinical suspicion of pneumonia	None
Dara *et al* 2012[55]	1998–2007	Retrospective cohort	28	Adults admitted to the ICU for septic shock	Hospital mortality	8670 (8670)	Consecutive adults with septic shock patients	NS
Luethi *et al* 2010[48]	2008–2014	Post hoc analysis of an RCT	51	Adults presented to the ED with septic shock. Data were available for ICU setting	90-day all-cause illness severity-adjusted mortality	1387 (1387)	≥18 years old; septic shock	NS
Madsen *et al* 2014[45]	2005–2012	Retrospective cohort	1	Adults admitted to the ICU for severe sepsis or septic shock	SSC resuscitation bundle completion	814 (814)	>18 years old presenting to the ED with criteria for severe sepsis/septic shock	Only comfort measures within the first 24 hours; non-ICU admission
Mahmood *et al* 2012[51]	2004–2008	Retrospective cohort	NS*	Adults admitted to the ICU (sepsis subgroup)	ICU mortality	27 935 (27 935)	Consecutive adults in the APACHE IV database; sepsis subgroup	Readmission to the ICU
Nachtigall *et al* 2011[46]	January/March 2006; February/May 2007	Prospective cohort	1	Adults admitted to mixed ICUs with a special focus on sepsis patients (sepsis subgroup)	ICU mortality	327 (327)	Consecutive adults (≥18 years); ICU stays >36 hours; sepsis criteria for at least 1 day during the ICU stay	NS
Pietropaoli *et al* 2010[47]	2003–2006	Retrospective cohort	98	Adults admitted to the ICU for severe sepsis or septic shock	Hospital mortality	18 757 (18 318)	≥16 years old; severe sepsis/septic shock patients; data from the first ICU admission	If gender, age, or hospital mortality was missing
Sakr *et al* 2013[54]	April/Sep 2006[14]	Post hoc analysis of a prospective cohort	24	Adults admitted to the medical and/or surgical ICU for severe sepsis	ICU mortality	305 (305)	>18 years old; severe sepsis; data from the first ICU admission	NS
Samuelsson *et al* 2015[52]	2008–2012	Retrospective cohort	65	Adults admitted to the ICU (sepsis subgroup)	30-day mortality	9830 (9830)	Consecutive SAPS III–scored adults ICU (>15 years old); validated mortality data in the registry; sespsis subgroup	Reasons for not being able to obtain mortality data: non-Swedish residency and patients with concealed identity

Continued

Table 2 Continued

Study	Study dates	Study design	Sites	Population	Primary outcome	Sample size N of study participants (N with outcome)	Inclusion criteria	Exclusion criteria
Sunden-Cullberg *et al* 2020[49]	2008–2015	Retrospective cohort	42	Adults admitted to the ICU for sepsis or shock septic via the ED within 24 hours	Sepsis bundle completion; 30-day mortality	2720 (2430)	≥18 years old; ICU admission within 24 hours of arrival to an ED; community-acquired severe sepsis or septic shock	Data non-registered simultaneously in two selected registries, alongside SAPS3 data. Multiple registrations.
van Vught *et al* 2017[53]	2011–2014	Prospective cohort	2	Adults admitted to the ICU for sepsis	90-day mortality	1533 (1815 admissions†)	Consecutive patients >18 years old; sepsis; expected ICUs stay >24 hours; data from multiple ICU admission‡	Transfer from other ICUs
Xu *et al* 2019[50]	2001–2012	Retrospective cohort	1	Adults admitted to the ICU for sepsis	1 year mortality	6134 (6134)	All adults diagnosed with sepsis, severe sepsis, or septic shock in the database	<18 years old

*Information reported as 'large number of ICUs'.
†van Vught analysed 1815 admissions for its primary outcome. Data were available at the patient level for the review outcomes.
‡ICU demographic and long-term follow-up data from the first ICU admission, host response data from overall admissions.
APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; ED, emergency department; ICU, intensive care unit; NS, not stated; RCT, randomised controlled trial; SAPS, Simplified Acute Physiology Score; SSC, surviving sepsis campaign.

Table 3 Summary of findings

Outcomes	Anticipated absolute prognostic effects*			Effect estimate (95% CI) (95% prediction interval)	No of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk in males	Risk in females (95% CI)	ARD in females (95% CI)†			
All-cause hospital mortality (median observed length of stay ranged from 6 to 26 days)	303 per 1 000‡	307 per 1 000 (255 to 364)	4 more per 1000 (47 fewer to 62 more)	OR 1.02 (0.79 to 1.32) (0.5 to 2.08)	28 915 (4 observational phase 2 studies)	⊕◯◯◯ VERY LOW§¶**
28-day all-cause mortality	240 per 1 000‡	271 per 1 000 (249 to 294)	31 more per 1000 (9 more to 54 more)	OR 1.18 (1.05 to 1.32) (0.56 to 2.50)	12 579 (3 observational phase 2 studies)	⊕◯◯◯ VERY LOW§**††‡‡
1-year all-cause mortality	505 per 1 000‡	459 per 1 000 (410 to 500)	46 fewer per 1000 (95 fewer to 5 fewer)	OR 0.83 (0.68 to 0.98) N/M	6134 (1 observational phase 2 study)	⊕⊕◯◯ LOW**††§§¶¶
All-cause ICU mortality (median observed length of stay ranged from 2.7 to 13 days)	200 per 1 000‡	229 per 1 000 (167 to 308)	29 more per 1000 (33 fewer to 108 more)	OR 1.19 (0.80 to 1.78) (0.49 to 2.89)	31 562 (5 observational phase 2 studies)	⊕◯◯◯ VERY LOW§¶**

Not meaningful: <3 studies for computing of the 95% prediction interval a meaningful estimate.
*The risk in the female group (and its 95% CI) is based on the assumed risk in the male participants group and the estimated effect of sex (OR and its 95% CI).
†We considered an ARD of at least ±10‰ as large enough to be clinically meaningful. Thus, we defined the clinical importance of the absolute prognostic effect for all the review outcomes as follows: important improvement (ARR of at least 10‰), slight improvement (10‰<ARR≤5‰), minimal or no effect (–5‰<ARD<5‰), slight worsening (5‰≤ARI<10‰), and important worsening (ARI of at least 10‰).
‡The assumed risk in male participants is based on the median risk among the male participants in the included studies. We consider this risk reflects the context of ICUs in high-resource countries adequately.
§Downgraded by two levels for very serious inconsistency due to a wide 95% prediction interval ranging from an increased mortality in male sex to an increased mortality in female sex that could not be explained for any reason.
¶Downgraded by two levels for very serious imprecision because the 95% CI of the ARD in our assumed risk scenario ranges from an important improvement to an important worsening in the prognosis of female participants compared with male participants. Besides, the OSS was smaller than the OIS required.
**Publication bias not assessed because of the scarce number of included studies (<10).
††Downgraded by one level for serious imprecision because the CI 95% of the ARD in our assumed risk scenario exceeds one of our clinical importance thresholds (ie, it is compatible with an important or a slight prognostic effect). The OSS was greater than the OIS.
‡‡Downgraded by one level for serious indirectness because one study[52] was responsible for 85% of the weight reported in-hospital and out-hospital mortality.
§§Downgraded by one level for serious risk of bias because the effect estimate comes from a study with moderate and unclear risk of bias for half of the QUIPS domains.
¶¶Inconsistency not assessed because a single study was considered.
ARD, absolute risk difference; ARI, absolute risk increase; ARR, absolute risk reduction; GRADE, Grades of Recommendations, Assessment, Development and Evaluation; ICU, intensive care unit; N/M, not meaningful; OIS, optimal information size; OSS, observed sample size; QUIPS, Quality In Prognosis Studies.

QUIPS domains were inconclusive (OR 1.24, 95% CI 0.001 to 1223). Sensitivity analysis results using unadjusted estimates remained unaltered (OR 1.15, 95% CI 0.87 to 1.52) (online supplemental figure 7).

DISCUSSION

Main findings

Our systematic review assessed whether sex is an independent prognostic factor for mortality among adults with sepsis admitted to ICUs. We are uncertain of the independent prognostic effect of sex for all-cause hospital mortality, 28-day all-cause mortality and all-cause ICU mortality in critically patients, as the certainty of the evidence was very low. Female sex may be associated with an important reduction in 1-year all-cause mortality (low-certainty evidence). However, the CI of the absolute reduction is also compatible with a slight protective effect.

Strengths and weaknesses of the study

Strengths of our review include a comprehensive and non-language-restricted search strategy covering unpublished resources, the inclusion of observational phase 2 explanatory studies, which initially provide high certainty of the evidence for prognosis,[18] and an available published protocol to which we adhered.[20] We also prespecified a core set of adjustment factors based on a literature review, the consensus among clinician review authors, and inputs from reviewers during the protocol publication process.[20] We handled the unique information from a conference abstract by contacting the study authors, examining register details published elsewhere,

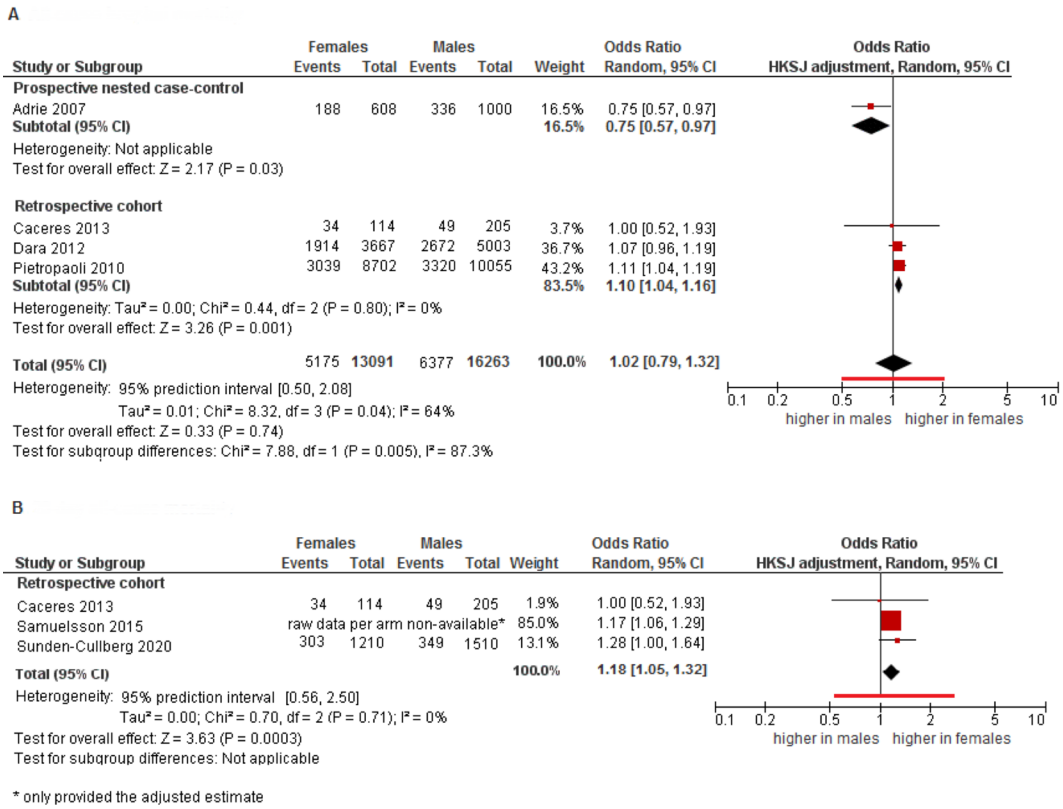

Figure 2 Forest plots of adjusted analyses for association between sex and all-cause hospital mortality (A) and 28-day all-cause mortality (B). HKSJ, Hartung-Knapp-Sidik-Jonkman.

and exploring sensitivity analysis without these results.[34] We performed the HKSJ procedure, which yields a wider and more rigorous confidence interval,[30] and applied the GRADE framework adaptations for prognostic factor research to rate the certainty in pooled estimates.[25 38–40] We established a clinical threshold based on the premise that sex is a non-modifiable factor that affects the entire population; therefore, an absolute risk difference of 10‰ on mortality may lead to a clinically important impact. Besides, a more demanding threshold, for example, ±20‰, would not modify the certainty of evidence assessment.

Some limitations of this review arise from poor reporting in the included studies. First, included studies referred to an unclear or inadequate definition of sex. Although we anticipated no biological assessments, we expected at least a statement based on sexual dimorphism observed by healthcare staff. Although we meta-analysed studies providing all-cause hospital mortality to improve precision, additional analyses to explore potential differences between short and medium/long-term outcomes could not be performed because only two out of four included studies reporting the length of stay.[43 44] Another issue is the ambiguous definitions used for the 28-day mortality outcome. Some studies provided a clear description linked to in-hospital mortality, while others combined in-hospital and out-hospital events or omitted further details. After requesting additional clarifications, only Samuelsson *et al* replied.[52] We pooled these studies and downgraded evidence certainty for indirectness. As well, clinical heterogeneity was substantial between the included studies, which differed regarding the sepsis definition used (ie, diagnostic criteria and sepsis and/or septic shock), illness severity measurements and score ratings, comorbidity burden, as well as in clinical practice (ie, treatment protocols). We quantified statistical heterogeneity using 95% prediction intervals, which help to assess the inconsistency criteria in GRADE, where usually large study sample sizes may result in narrow CIs alongside high I^2.[39 57 58] However, these intervals are still imprecise when meta-analysis includes few studies.[58] For hospital mortality, 28-day mortality, and ICU mortality, prediction intervals contained the value of null effect, suggesting that sex may not be prognostic in at least some situations.[30 57] Also, most prespecified subgroup analyses were not feasible because of the scarcity of studies. Another limitation is that we cannot provide information about the cause of death, which is particularly relevant for late mortality. Lastly, the included studies were mainly conducted in North America and Western Europe.

Implications for clinical practice

The certainty of evidence for all-cause hospital mortality, 28-day all-cause mortality and ICU mortality was very low. Consequently, the available evidence to inform healthcare providers is limited. Female sex may be associated with an important reduction in 1-year all-cause mortality (low-certainty evidence). Based on a risk of 50.5% for

1-year all-cause mortality among male patients, 46 fewer female patients per 1000 will die (95% CI from 95 to 5 fewer). Studies examining long-term mortality after sepsis suggest that epigenetic regulation may cause post-sepsis immunosuppression and atherosclerosis phenomena.[59] Thus, sex as an independent prognostic factor for late mortality may suggest the development of targeted interventions.[15]

Implications for research

Our systematic review and meta-analysis offer information for future research in this field. To our knowledge, this is the first synthesis on sex and mortality in adults with sepsis admitted to ICUs following the recommended standards for systematic reviews of prognosis factors. Our core set of adjustment factors may be a supporting source for prognostic factors selection in multivariable modelling in further study designs. This review also contributes to identifying knowledge gaps. Our meta-analysis failed to provide definitive evidence on all-cause hospital mortality, 28-day all-cause mortality and all-cause ICU mortality in critically ill patients with sepsis. These inconclusive results showed a lack of evidence supporting sex as an independent prognostic factor in these patients, not as evidence of a lack of prognostic effect. Moreover, no studies looked at 7-day mortality and a single study investigated long-term mortality. Therefore, well-designed prospective studies are needed to test the adjusted prognostic role of sex in patients with sepsis admitted to ICUs. Finally, addressing the architecture for tracking of prognosis research is required. Academics, journals, editors and librarians may boost preregistering protocols to help both reduce the risk of publication bias and detect selective outcome reporting bias. Also, they may encourage a proper indexing process in electronic databases to enhance the reliability of searches.

CONCLUSIONS

Our systematic review and meta-analysis found uncertain evidence as to whether sex has an independent prognostic impact on all-cause hospital mortality, 28-day all-cause mortality and all-cause ICU mortality among critically ill adults with sepsis since the certainty of the evidence was very low. Female sex may be associated with decreased 1-year all-cause mortality (low-certainty evidence). High-quality research is needed to test the adjusted prognostic value of sex for predicting mortality in adults with sepsis admitted to ICUs.

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05 Discussion

This thesis is a methodological proposal for integrating sex and gender in research for clinical conditions, such as sepsis. This work addresses whether and how sex-and gender-based analysis is applied in clinical research on sepsis and the extent to which other PROGRESS-Plus factors interacting with sex and gender are considered. As well, it evaluates the independent prognostic effect of sex on mortality among critically ill patients.

This section discusses general insight gained from this thesis about the challenges and implications of integrating sex and gender into clinical research. Additional pieces of research in which the doctoral candidate has collaborated also are discussed to enrich the reflection (Supplementary material B).

5.1. Summary of main findings

First study

The analysis of primary studies underpinning sepsis treatment recommendations in systematic reviews (SRs) and guidelines revealed the female participation level to be below that of female representation in the sepsis population. Secondary analyses indicated that fewer than half of studies published in English used “sex” and “gender” terminology properly and that only around a fifth reported by sex or included other health determinants.

Second study

The SGAT-SR-2 (Sex and Gender Appraisal Tool – Systematic Reviews-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 (Participation–to–Prevalence Ratio) were unavailable in the reviews, they were extracted directly from the included randomised clinical trials (RCT). 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.

Third publication

This systematic review assessed whether sex is an independent prognostic factor for mortality amongst adults with sepsis admitted to intensive care units (ICUs). We are uncertain of the independent prognostic effect of sex for all-cause hospital mortality, 28-day all-cause hospital mortality, and all-cause ICU mortality in critically patients, as the certainty of the evidence was very low. Female sex may be associated with an important reduction in 1-year all-cause mortality (low-certainty evidence). However, the confidence interval of the absolute reduction is also compatible with a slight protective effect.

5.2. Agreements and disagreements with other studies

Representation of participants by sex in studies on sepsis [First and second publication]

To the best of our knowledge, these are the first studies assessing the representation of participants by sex (i.e., PPR) involved in sepsis research at both the study level and systematic review level. Among the reviews on paediatric populations, PPR indicated adequate representation in one SR and ranged from under to bias-free enrolment in another. Although some clinical areas, such as dermatology [189], point out a sex-balanced of adequate representation, our results are in line with findings of other fields that showed bias-enrolment in adults [102-104,240]. One possible explanation may be that as females with sepsis tend to be older and to have more medical comorbidities than males [193,229,241,242], 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) [243]. To overcome such methodological constraints, Tannenbaum and colleagues proposed calculating sample size to examine between- and within-group sex and age differences as defined in preliminary data [70]. Another factor is that, independently of the patient's clinical features, their sex may influence care provider perceptions and recommendations and adversely affect the probability of recruitment for clinical trials [65,244,245]. 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 [204,246,247].

Our findings point to adequate female participation in ICU settings that needs to be interpreted with care. Data on sepsis by sex in the ICU setting reflect a lower female sepsis incidence than in the non-ICU setting [198]. Nevertheless, Dodek and Fowler reported a higher prevalence of male patients receiving ICU care after adjusting for diagnosis and comorbidities; those authors suggested that sex-related differences may be explained by biological plausibility related to current comorbidity scales may not reliably predict illness severity and because biases (including gender bias) may influence decision-making about ICU admission [244,248].

Sex-and gender-based analysis and reporting [First and second publication]

The scarcity of sex- and gender-based analysis and reporting across sepsis research corroborates results in other fields [109,127,142,249]. 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 in systematic reviews. Furthermore, six of the primary studies (2.17%) conducted sex subgroup analyses [first publication], although only one complied with the full set of criteria proposed by McGregor [187], while none of the pre-defined subgroup analyses by sex in sepsis reviews was undertaken [second publication]. Regarding sex-related analysis, the medical literature reflects a wide range of pre-specified analyses (0%-57%), performed analyses (0%-8%) and properly performed subgroup analyses (5%-35%) [111,250–252]. Reporting solely aggregated outcomes may mask differences by sex [253–256]. Wallach and colleagues evaluated sex-treatment interactions in RCTs included in Cochrane SRs, finding that only 41 SRs (4%) properly described sex-disaggregated treatment outcomes and, of those, 10% detected differential effects for the sexes [257]. 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 [70,72,73,258].

I also worked on a study researching on sex considerations in the heart failure. The fourth manuscript [259] examined the prevalence of sex considerations and temporal patterns in 252

cohort studies assessing the effectiveness of cardiac resynchronization therapy in patients with heart failure. Whereas reporting shortcomings remain prevalent in this topic, temporal analysis displayed a change in the consideration of sex in statistical models, background, study design, and knowledge translation.

Factors associated with female participation and sex-related analysis and reporting [First publication]

Primary studies published in or after 1996 were also positively associated with an increased likelihood of sex-related reporting (P=0.019). Moreover, RCTs compared with observational studies were less likely to report sex (P<0.001).

The fact that we found no associations between author gender and female enrolment or between author gender and sex-related reporting contradicts findings reported in other recent studies [25–27]. One possible explanation may be that the findings of those other studies were based on larger datasets. The fifth study [260] was a thoroughly collaborative work resulting from inspiration after a cooperative translation and dissemination of the special theme issue of The Lancet on Advancing women in science, medicine, and global health [261]. The fifth study assessed the association between sex-and gender-based analysis and reporting and gender of authors using a cross-section of 516 Cochrane systematic reviews of interventions published in 2018. Women represented 53.1% and 42.2% of first and last authorships, respectively. When first and last authors were women, there was higher possibility of sex- and gender-related reporting.

The fact that we found that social determinants of health were rarely reported corroborates other findings that racial and/or ethnicity reporting remains uncommon [59–61]. The sixth publication [262] evaluated how and to what extent health equity considerations are assessed in WHO guidelines, and results of the cross-sectional survey showed suboptimal evidence to support equity judgments in WHO guidelines published from 2014 to 2019. The seventh work investigated what methods systematic reviewers apply to consider health equity in SRs of effectiveness. This updated Cochrane systematic review included 158 studies, in which most comment PROGRESS-Plus factors were age (43/158 studies), socioeconomic status (35/158 studies), place of residence (24/158 studies), gender or sex (22/158 studies), and race or ethnicity (17/158 studies). Review authors who considered health equity used the following methodological approaches: i) descriptive assessment of analysis and reporting at review level (151/158 studies), ii) descriptive assessment of analysis and reporting at primary study level (74/158 studies), iii) analytic approaches examining differential effects across one or more PROGRESS-Plus factors (16/158 studies), iv) applicability assessment (25/158 studies), and v) stakeholder engagement. Further work is needed to clarify the definition of health equity

used by authors, to describe in detail the analytic approaches (including subgroup analyses), and to report transparently on which applicability assessments are based.

Use of the terms sex and gender [Second and third publication]

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 [112,127,263]. Although the peer-reviewed scientific literature has documented health outcomes on gender diverse people, substantial gaps in research remain [264,265]. More inclusive data collection approaches will hopefully expand sex- and gender-reporting beyond binary categories [266].

Furthermore, in the systematic review assessing sex as a prognostic factor, it was particularly striking that all included studies referred to an unclear or inadequate definition of sex. Although we anticipated no biological assessments, we expected, at least, a statement based on sexual dimorphism observed by healthcare staff.

Sex as an independent prognostic factor for mortality in critically ill patients with sepsis [Third publication]

To the best of our knowledge, this systematic review is the first synthesis on sex and mortality in adults with sepsis admitted to ICUs following the recommended standards for systematic reviews of prognosis factors. Failla [173] and Papathanassoglou [174] conducted other systematic reviews that examined the influence of sex on outcomes in adults with sepsis and found inconclusive findings and a small disadvantage for survival amongst female patients, respectively. However, as noted above, both suffer from methodological flaws that render questionable findings. While there is no tool to assess the quality of systematic reviews of prognosis, AMSTAR-2-(a measurement tool to assess systematic reviews) is practical critical appraisal instrument to assess the quality of conduct of systematic reviews of randomised controlled trials of interventions [267]. Table 6 depicts a revised AMSTAR-2 for prognostic factors (AMSTAR-2-PF) only for exploratory purposes. This revised tool is a proposal developed by our team in the context of master's degree dissertations on prognostic factor overviews that I was pleased to co-supervise (Table S1, Supplementary material C).

Table 6. Revised AMSTAR-2-PF judgements for other systematic reviews

Revised AMSTAR-2-PF	**Failla 2017** [173]	**Papathanassoglou 2017** [174]
1. Did the research questions and inclusion criteria for the review include the components of PICOTS?	No Quote: "Article were included if the following criteria were met: peer-reviewed journals; English language; original research and data analysis; and published from 2006 to 2016"	Yes Quote: "Inclusion criteria targeted: a) studies addressing critically ill adult patients specifically; (b) studies specifically addressing outcomes of sepsis among their primary aims; (c) studies having sex comparisons among their primary outcomes".
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?*	No	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	No
4. Did the review authors use a comprehensive literature search strategy?*	Partial Yes Quote: "MedlinePlus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), EBSCO, and PubMed databases were accessed"	Partial Yes Quote: "Studies were located through searches of on-line databases with the assistance of a health-sciences expert librarian. CINAHL, PubMed, EMBASE and COHRANE databases. Reference lists of identified articles were also checked for pertinent studies"
5. Did the review authors perform study selection in duplicate?	Yes Quote: "Both authors independently selected studies for eligibility by title and abstract. (…) the full-text articles were thoroughly reviewed and consensus was reached through discussion"	Yes Quote: "Study titles were screened independently by two reviewers to identify pertinent studies. Subsequently, abstracts and the full text of retrieved articles were read and compared against inclusion and exclusion criteria independently"
6. Did the review authors perform data extraction in duplicate?	No	Yes Quote: "Data from studies which met the eligibility criteria were verified by two of the authors"
7. Did the review authors provide a list of excluded studies and justify the exclusions?*	Partial Yes Provided aggregated reasons for exclusion at the full-text stage	No
8. Did the review authors describe the included studies in adequate detail?	Partial Yes Described population, index PF, outcomes, study design, adjusting PFs where appropriate	Yes Described population (in detail), index PF, outcomes, study design, adjusting PFs (in detail), study setting, statistical analysis method and modelling

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?*	No No tool	No Quote: "STROBE checklist and the Cochrane Tool to Assess Risk of Bias in Cohort Studies"
10. Did the review authors report on the sources of funding for the studies included in the review?	No Likely, little relevance to SRs assessing sex as PF	No Likely, little relevance to SRs assessing sex as PF
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?*	NMA	Yes Quote: "There was very large heterogeneity between study estimates. This fact, together with the very small number of studies identified and deemed appropriate for meta-analysis, raises doubts as to the usefulness or appropriateness of a pooled effect. Nevertheless, a forest plot of study estimates is provided [by using] fixed-effect-model and random-effect model"
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	NMA	No
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?*	No	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?*	NMA	No †
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No Likely, little relevance to SRs assessing sex as PF	No Likely, little relevance to SRs assessing sex as PF
Overall	Critically low	Critically low

Abbreviations: NMA, no meta-analysis conducted, PICOTS, Population, Index prognostic factor, Comparator prognostic factors, Outcome, Timing, Setting, PF, prognostic factor, RoB, risk of bias, SR, systematic review, STROBE Strengthening the reporting of observational studies in epidemiology

* AMSTAR 2 critical domains

† Five studies meta-analysed

5.3. Strengths and limitations

This thesis has been formulated and produced within well-established frameworks of sex-and gender-based analysis, PROGRESS-Plus and intersectionality, and prognosis research, by combing them to appraise the extent to which sex and gender dimensions are integrated into clinical research on sepsis and to evaluate the independent prognostic factor of sex among patients with sepsis admitted to intensive care units. The development process of this work has been systematic, transparent (i.e., each protocol was registered prospectively and publicly available), and thoroughly discussed (i.e., each publication was peer-reviewed in journals of the first quartile, and the second study was informed by feedback from an expert advisory board). This article-based thesis also included non-language and non-date-restricted search strategies, which in the case of the systematic review of prognostic factor studies also covered unpublished resources. Protocols and registers were used to assess the eligibility criteria and possible selective reporting bias. Corresponding authors of included studies and reviews, as appropriate, in two out of three publications were contacted to request further information.

Some of the limitations of this thesis arise from the quality of reporting in the included studies and reviews. This problem is particularly acute for studies of prognostic factors without a clear definition of sex and 28-day mortality outcome. Some studies provided a clear description linked to in-hospital mortality, while others combined in- and out-hospital events or omitted further details. After requesting additional clarifications, only Samuelsson replied [268]. We pooled these studies and downgraded evidence certainty for indirectness. Another limitation is the lack of reported data by geographical regions and the limited data available for low-resources settings, bearing in mind that most sepsis-related deaths occur in low- and middle-income countries [269]. The included studies were mainly conducted in North America and Western Europe. Another potential concern might point out the overlap between primary studies included in the PPR calculation between the first and second publications. There were differences in eligibility criteria (e.g., adults vs. adults and children, treatment intervention vs. any intervention) and the unit of analysis (i.e., primary studies vs. SRs). Twelve studies overlapped, of which nine were involved in a single SR [270]. Moreover, as sex, gender and intersectionality theories are evolving constructs, this thesis should be interpreted in light of current efforts to enhance sex-and gender-based analysis and draw attention to the need for integrating the social determinants of health into clinical research. Lastly, Table 7 displays the specific strengths and limitations by research question and study.

Table 7. Description of specific strengths and limitations by research question and study

Research question	Specific strengths	Specific limitations
Representation of participants by sex [First and second publication]	- Examine the level of representation by sex relative to the sex-disaggregated incidence of sepsis in the overall population by calculating Participation–to–Prevalence Ratio. - Establish sex-stratified incidence of sepsis through broad bibliographic search and conducted several subgroup analyses by population, temporal, design, and setting subsets.	- The regression model included as covariate an adjusted NIH cut-off point (the year 1996), although most affiliations (as a proxy for study country) belonged no to the USA [First study].
Revised SGAT-SR-2 tool [Second publication]	- 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. - Elaborate on a summary providing explanations, rationales, and, when available, good practice examples on SGBA that may serve as a resource for planning SRs (Supplementary material)	- Sex, gender and intersectionality theories are evolving constructs.
Sex-and gender-based analysis [First and second publication]	- Receive feedback from almost half of the Co-ordinating Editors of the included Cochrane Groups [Second publication].	- Search strategy design to retrieve only high-impact sepsis treatment evidence. - 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 these studies. - Our studies was limited to what reviews and primary studies and systematic reviews reported.
Sex as an independent prognostic factor for mortality in critically ill patients with sepsis [Third publication]	- Eligibility study criterion limited to phase 2 studies, which initially provide high certainty of the evidence for prognosis [156]. - Pre-specify a core set of adjustment factors based on a literature review, the consensus amongst clinician review authors, and inputs from reviewers during the protocol publication process [210]. - Handle the unique information from a conference abstract by contacting the study authors, examining register details published elsewhere, and exploring sensitivity analysis [220]. - Perform the HKSJ procedure, which yields a wider and more rigorous confidence interval [217]. - Apply the GRADE framework adaptations for prognostic factor research to rate the certainty in pooled estimates [164,224–226]. - Establish a clinical threshold based on the premise that sex is a non-modifiable factor that affects the entire population; therefore, an absolute risk difference of 10‰ on mortality may lead to a clinically important impact. Besides, a more demanding threshold, e.g., ± 20‰, would not modify the certainty of evidence assessment.	- Substantial clinical heterogeneity between the included studies, which differed regarding the sepsis definition used (i.e., diagnostic criteria, and sepsis and/or septic shock), illness severity measurements and score ratings, comorbidity burden, as well as in clinical practice (i.e., treatment protocols). We quantified statistical heterogeneity using 95% prediction intervals, which help to assess the inconsistency criteria in GRADE, where usually large study sample sizes may result in narrow CIs alongside high I^2 [225,271,272]. However, these intervals are still imprecise when meta-analysis includes few studies [272]. For hospital mortality, 28-day mortality, and ICU mortality, prediction intervals contained the value of null effect, suggesting that sex may not be prognostic in at least some situations [217,271]. Additionally, most pre-specified subgroup analyses were not feasible because of the scarcity of studies.

5.4. Implications for clinical practice

Despite the methodological nature of this thesis, its findings lay out several directions for future clinical work. The certainty of evidence for all-cause hospital mortality, 28-day all-cause mortality, and ICU mortality was very low. Consequently, the available evidence to inform healthcare providers is limited. Female sex may be associated with an important reduction in 1-year all-cause mortality (low-certainty evidence). Based on a risk of 50.5% for 1-year all-cause mortality among male patients, 46 fewer female patients per 1000 will die (95% CI from 95 to 5 fewer). Studies examining long-term mortality after sepsis suggest that epigenetic regulation may cause post-sepsis immunosuppression and atherosclerosis phenomena [9]. Thus, sex as an independent prognostic factor for late mortality may suggest the development of targeted interventions [149]. It is important that healthcare providers adopt a sex- and gender- informed perspective regarding possible similarities and differences across sex and gender in patients with sepsis, which may contribute to improve patient care. The most common prognostic scores rely on physiological measures, which usually differ between sexes, and modelling development processes accounted for neither sex nor other demographic variables, albeit SAPS II and APACHE II included age [273–275]. Thus, the scoring models may require sex adjustments for a reliable prediction of illness severity

5.5. Implications for researchers and stakeholders

Three broad headings for discussion related to future research emerge from this thesis: 1) How the integration of sex and gender into clinical research enables to explore the causes of heterogeneity, 2) How sex and gender considerations provide insights into the argumentation on the applicability of the findings, and 3) How to address gaps of knowledge related to the role of sex as a possible prognostic factor for sepsis.

How the integration of sex and gender into clinical research enables to explore the causes of heterogeneity

Incorporation of sex and gender in primary studies and systematic reviews for clinical conditions, such as sepsis, enables to explore the causes of heterogeneity among studies and to assess the findings [115,276]. Assessment of differential impacts of both exposures and interventions across sex (biological variability) and gender and other social interacting forces can help to identify sources of heterogeneity [78]. Analysing sex-and gender-disaggregated data should be driven by existing literature. However, a prerequisite is a better understanding

of the rationale behind current research practices. Basic science lacks evidence of sex- or gender-based differences as pointed out in a qualitative analysis of health research fund applications [277]; indeed, as pointed out by Clayton [278], most preclinical research is performed exclusively on male animals. Description of the methods used to determining sex and gender and systematic data collection by sex and gender allow hypothesis-generating and -testing procedures by pooling data across studies. Otherwise, compelling rationales should be provided for disregarding them [124]. Supplementary material of the third publication provides a comprehensive summary of definitions, rationales, and when available, good practice examples on SGBA that may serve as a resource for planning systematic reviews. Several journals and editors have elaborated guidelines and editorial policies for sex-and gender-reporting in submitted manuscripts, although, as yet, no general standard has been embraced [72,73,123], while universities have also begun to develop resources that foster the consideration of sex and gender in research [279].

Many observational studies adjust for PROGRESS-Plus factors and do not examine the association of PROGRESS-Plus characteristics with outcomes, which omits the fact that these variables could also explain effects variations [280]. The eighth publication [82] proposes rapid, interim guidance on transparency in assessing health equity in observational studies related to COVID-19. We aim to extend the well-known STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines [194] to enhance transparent reporting of health equity considerations. We engaged with Indigenous stakeholders and others groups experiencing health inequities to co-produce this guidance and to bring an intersectional lens. We identified 14 areas in the STROBE checklist that need additional detail to encourage transparent reporting of health equity (Figure 6).These items include description of the population across relevant health equity characteristics using the PROGRESS-Plus factors as well as sampling methods to reach and include populations who experience vulnerability. As with CONSORT-Equity, informed consent, research accountability, and ethics procedures need to be reported for all studies that include populations who experience vulnerability and health inequities. Studies that include people experiencing inequity need to report methods to determine the relevance of outcomes for these populations and collect relevant socio-demographic and contextual information for analysis. Methods to analyse differential exposure, differential susceptibility and differential capacity to respond need to be planned and described. Finally, implications of exclusion, missingness, or exclusion of people experiencing inequities need to be discussed.

Figure 7. Possible equity extension items for STROBE

We searched for examples of COVID-19 observational studies with an explicit focus on evaluating effects across one or more social determinants of health using the PROGRESS-Plus framework. Figure 7 summarises the risk for COVID-19 disease (exposure or susceptibility –i.e., differential effect including infection and recovery-) and implications for healthcare access for each PROGRESS-Plus factor.

Figure 6. Risk for COVID-19 infection and implications for healthcare access across PROGRESS-Plus factor

Plus refers to other context-specific factors that generate health inequities, such as disability,age, or people in prisons

How sex and gender considerations provide insights into the argumentation on the applicability of the findings

Over the last years, grant agencies have begun to develop policies to close the sex and gender gap [278,281,282]. It is suggested that an explicit request to include sex and gender considerations might boost accountability regarding sex and gender [277]. As mentioned above, an adequate representation of participants in trials and clinical practice guidelines according to the sex-and gender-stratified prevalence, as appropriate, in the disease population can be examined using the PPR [204,246,247]. While PRISMA and Cochrane state systematic reviews should present the demographics of contributing studies [283,284], this recommendation could benefit from specifying further details. Thus, PRR metric could be a valuable tool for systematic reviews to assist users in making decisions about to whom the evidence applies. For example, Benstoem and colleagues downgraded the certainty of the evidence of their findings for chronic heart failure due to male predominance [285]. 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 [265,286,287]. Stakeholders leading evidence synthesis, such as Cochrane Collaboration, can enhance accountability by asking critical questions about the applicability of findings [143,203].

How to address gaps of knowledge related to the role of sex as a possible prognostic factor for sepsis

The systematic review and meta-analysis of the third publication offer information for future research in this field. Our core set of adjustment factors may be a supporting source for prognostic factors selection in multivariable modelling in further study designs. This review also contributes to identifying knowledge gaps. Our meta-analysis failed to provide definitive evidence on all-cause hospital mortality, 28-day all-cause hospital mortality, and all-cause ICU mortality in critically ill patients with sepsis. These inconclusive results showed a lack of evidence supporting sex as an independent prognostic factor in these patients, not as evidence of a lack of prognostic effect. Moreover, no studies looked at 7-day mortality and a single study investigated long-term mortality. Therefore, well-designed prospective studies are needed to test the adjusted prognostic role of sex in patients with sepsis admitted to ICUs. Finally, there is a need for improvement in the tracking of prognosis research. Academics, journals, editors, and librarians may promote pre-registering protocols to help both reduce the risk of publication bias and detect selective outcome reporting bias. In addition, they may encourage a proper indexing process in electronic databases to enhance the reliability of searches.

I contributed to another systematic review evaluating sex as an independent prognostic factor for mortality in patients with pulmonary thromboembolism [155]. Our experience conducting these two reviews investigating sex as index prognostic factor led us to summarise the methodological challenges and lessons learned as well to propose how reviews assessing a similar question, regardless of the clinical area, can address them. [288]. The nine publication [288] provides specific insight into data extraction and risk of bias assessment (Table 8).

Table 8. Challenges and lesson learned in systematic reviews evaluating sex as a prognostic factor

Review step	Default description	Adjustment for SRs addressing sex as PF and rationale
Data extraction	CHARMS-PF includes a specific domain for characteristics of the index PF (definition and method for measurement, timing of PF measurement, if PF was assessed blinded for outcome, handling of PF in the analysis)	Any definition of sex and any method of sex measurement given by the authors were accepted. However, information on the use of sex, gender, and related terms were collected and evaluated if terms were being used adequately according to the current international definitions. We anticipated that the study authors, even assessing biological dimension (i.e., sex), could use incorrect terms. To report the lack of literacy surrounding the terms for sex and gender should be highlighted in the SR. The timing of the PF measurement does not matter when studying sex in primary studies nor reviews as it is not normally a temporal variable that may change.
Assessment risk of bias	QUIPS includes six assessment domains that are rated as low, moderate, or high risk of bias.	Amended the QUIPS tool using four categories (low, moderate, high, or unclear risk) [164,175,213]. In SRs investigating sex as a PF, the unclear category may be especially relevant since some signalling items of QUIPS, such as those related to PF domains with a high likelihood of lack of sex definition, have a limited value for the assessment and rating. We slightly modified three QUIPS domains: 1) Study participation to examine if the baseline was clearly described and is reported separately for females and males participants. 2) Study attrition to examine if key characteristics of participants lost to follow-up were provided separately for female and males participants. 3) Prognostic factor measurement, we considered non-applicable for signalling questions b-f (Table S1, Supplementary material B).
Data analysis	Ideally a meta-analysis of adjusted data should ensure that all included estimates are adjusted for the same set of other prognostic (i.e., core set of adjustment factors)	Delphi panel (expert input) to aid in this decision-making process

Abbreviations, CHARMS-PF, Critical appraisal and data extraction for systematic reviews of prediction modelling studies for prognostic factors; PF, prognostic factor; QUIPS, Quality in prognosis studies; SR; systematic review
Adapted from Stalling 2021 [288].

Lastly, according to implications previously discussed, this thesis poses some methodological approaches to make progress towards sex and gender integration into clinical research:

- Representation of participants by sex or gender in both primary studies and systematic reviews relative to their representation in the disease population can be assessed by using Participation–to–Prevalence Ratio.
- Efforts to facilitate an adequate demographic enrolment among clinical study participants must be supported to ensure that results rely on representative population samples.
- Review authors should provide data on the sex or gender, as appropriate, of participants to allow readers to assess the applicability of findings.
- Academics, researchers, stakeholders leading evidence synthesis, such as Cochrane Collaboration, editors, and funding agencies need 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.
- Well-designed, adequately powered and reported prospective studies are needed to test independent associations between sex and mortality in patients with sepsis admitted to intensive care units.
- Our core set of adjustment factors can assist researchers who conduct prognostic factor studies and systematic reviews assessing sex as an independent prognostic factor for critically ill adults with sepsis.
- There is a need for improvement in the tracking of prognosis research.
- There is a need for guidance on how to address heterogeneity between prognostic factor studies.

06 Conclusions

6. Conclusion

- There is a need for adequate sex-specific enrolment among primary studies underpinning recommendations on sepsis to ensure that efficacy and safety findings are drawn from representative population samples.
- Study and 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 findings.
- There is a need for better integration of sex-and gender-based analysis to understand to whom the evidence on sepsis applies, given the potential implications for clinical practice, research, and policy-making.
- The SGAT-SR-2 tool and the Participation–to–Prevalence Ratio may be useful in designing systematic reviews to assess sex and gender considerations, interaction with PROGRESS-Plus factors, and the applicability of evidence.
- The independent prognostic effect of sex on mortality for critically ill adults with sepsis was uncertain.
- There is a need for high-quality research to address the adjusted prognostic value of sex for predicting mortality in adults with sepsis admitted to intensive care units.

07 References

7. References

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08 Supplementary material

8.1. Supplementary material A. Supplementary material of article-based studies

8.1.1 Supplementary material of the first publication

Female under-representation in sepsis studies: a bibliometric analysis of systematic reviews and guidelines

Authors: Alba Antequera Martín, Olaya Madrid-Pascual, Ivan Solà, Emilia Roy-Vallejo, Sami Petricola, Maria Nieves Plana, Xavier Bonfill.

Supplementary material

Search strategies

Search strategy for MEDLINE Ovid (Accessed 02/08/2019)

#1	“Search (((sepsis[MeSH Terms]) OR septic shock[MeSH Terms]) OR sepsis[Title]) OR septic[Title]"	132,483
#2	"Search ((((""Am J Respir Crit Care Med""[Journal] OR ""Intensive Care Med""[Journal] OR ""Crit Care Med""[Journal] OR ""Clin J Am Soc Nephrol""[Journal] OR ""Chest""[Journal] OR ""Crit Care""[Journal] OR ""Clin Nutr""[Journal] OR ""J Trauma Acute Care Surg""[Journal] OR ""Eur Heart J Acute Cardiovasc Care""[Journal] OR ""Ann Intensive Care""[Journal] OR ""Shock""[Journal] OR ""Crit Care Resusc""[Journal] OR ""J Crit Care""[Journal] OR ""Neurocrit Care""[Journal] OR ""J Intensive Care""[Journal] OR ""Curr Opin Crit Care""[Journal] OR ""Crit Care Clin""[Journal] OR ""Burns""[Journal] OR ""Adv Wound Care (New Rochelle)""[Journal] OR ""Semin Respir Crit Care Med""[Journal] OR ""Emerg Med J""[Journal] OR ""Heart Lung""[Journal] OR ""J Clin Monit Comput""[Journal] OR ""Anaesth Crit Care Pain Med""[Journal] OR ""Respir Care""[Journal] OR ""Scand J Trauma Resusc Emerg Med""[Journal] OR ""Curr Opin Support Palliat Care""[Journal] OR ""J Intensive Care Med""[Journal] OR ""Crit Care Res Pract""[Journal] OR ""Ren Fail""[Journal] OR ""Ther Hypothermia Temp Manag""[Journal] OR ""HERD""[Journal] OR ""Anaesth Intensive Care""[Journal] OR ""Anesthesiol Res Pract""[Journal] OR ""Anaesthesiol Intensive Ther""[Journal] OR ""Ann Burns Fire Disasters""[Journal] OR ""Eur J Trauma Emerg Surg""[Journal] OR ""Omega (Westport)""[Journal] OR ""Arch Trauma Res""[Journal] OR ""Rev Bras Ter Intensiva""[Journal] OR ""Indian J Crit Care Med""[Journal] OR ""Med Intensiva""[Journal] OR ""Turk J Emerg Med""[Journal] OR ""J Intensive Care Soc""[Journal] OR ""Int J Crit Illn Inj Sci""[Journal] ""Rev Esp Anestesiol Reanim""[Journal] OR ""Tanaffos""[Journal] OR ""Med Klin Intensivmed Notfmed""[Journal] OR ""Crit Care Shock""[Journal] OR ""Zhonghua Wei Zhong Bing Ji Jiu Yi Xue""[Journal] OR ""Acute Med""[Journal] OR ""Tuberk Toraks""[Journal] OR ""Trauma""[Journal] OR ""Perioper Care Oper Room Manag""[Journal] OR ""Clin Pulm Med""[Journal] OR ""Enferm Intensiva""[Journal] OR ""Zhongguo Wei Zhong Bing Ji Jiu Yi Xue""[Journal] OR ""Rom J Anaesth Intensive Care""[Journal] OR ""Anasthesiol Intensivmed Notfallmed Schmerzther""[Journal] OR ""Trauma Case Rep""[Journal] OR ""Zhonghua Shao Shang Za Zhi""[Journal]))) OR jsubsetaim[text]"	2,242,415
#3	"Search (((((sepsis[MeSH Terms]) OR septic shock[MeSH Terms]) OR sepsis[Title]) OR septic[Title])) AND ((((""Am J Respir Crit Care Med""[Journal] OR ""Intensive Care Med""[Journal] OR ""Crit Care Med""[Journal] OR ""Clin J Am Soc Nephrol""[Journal] OR ""Chest""[Journal] OR ""Crit Care""[Journal] OR ""Clin Nutr""[Journal] OR ""J Trauma Acute Care Surg""[Journal] OR ""Eur Heart J Acute Cardiovasc Care""[Journal] OR ""Ann Intensive Care""[Journal] OR ""Shock""[Journal] OR ""Crit Care Resusc""[Journal] OR ""J Crit Care""[Journal] OR ""Neurocrit Care""[Journal] OR ""J Intensive Care""[Journal] OR ""Curr Opin Crit Care""[Journal] OR ""Crit Care Clin""[Journal] OR ""Burns""[Journal] OR ""Adv Wound Care (New Rochelle)""[Journal] OR ""Semin Respir Crit Care Med""[Journal] OR ""Emerg Med J""[Journal] OR ""Heart Lung""[Journal] OR ""J Clin Monit Comput""[Journal] OR ""Anaesth Crit Care Pain Med""[Journal] OR ""Respir Care""[Journal] OR ""Scand J Trauma Resusc Emerg Med""[Journal] OR ""Curr Opin Support Palliat Care""[Journal] OR ""J Intensive Care Med""[Journal] OR ""Crit Care Res Pract""[Journal] OR	22,207

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#5	"Search (((((sepsis[MeSH Terms]) OR septic shock[MeSH Terms]) OR sepsis[Title]) OR septic[Title])) AND ((((""Am J Respir Crit Care Med""[Journal] OR ""Intensive Care Med""[Journal] OR ""Crit Care Med""[Journal] OR ""Clin J Am Soc Nephrol""[Journal] OR ""Chest""[Journal] OR ""Crit Care""[Journal] OR ""Clin Nutr""[Journal] OR ""J Trauma Acute Care Surg""[Journal] OR ""Eur Heart J Acute Cardiovasc Care""[Journal] OR ""Ann Intensive Care""[Journal] OR ""Shock""[Journal] OR ""Crit Care Resusc""[Journal] OR ""J Crit Care""[Journal] OR ""Neurocrit Care""[Journal] OR ""J Intensive Care""[Journal] OR ""Curr Opin Crit Care""[Journal] OR ""Crit Care Clin""[Journal] OR ""Burns""[Journal] OR ""Adv Wound Care (New Rochelle)""[Journal] OR ""Semin Respir Crit Care Med""[Journal] OR ""Emerg Med J""[Journal] OR ""Heart Lung""[Journal] OR ""J Clin Monit Comput""[Journal] OR ""Anaesth Crit Care Pain Med""[Journal] OR ""Respir Care""[Journal] OR ""Scand J Trauma Resusc Emerg Med""[Journal] OR ""Curr Opin Support Palliat Care""[Journal] OR ""J Intensive Care Med""[Journal] OR ""Crit Care Res Pract""[Journal] OR ""Ren Fail""[Journal] OR ""Ther Hypothermia Temp Manag""[Journal] OR ""HERD""[Journal] OR ""Anaesth Intensive Care""[Journal] OR ""Anesthesiol	102

Res Pract""[Journal] OR ""Anaesthesiol Intensive Ther""[Journal] OR ""Ann Burns Fire Disasters""[Journal] OR ""Eur J Trauma Emerg Surg""[Journal] OR ""Omega (Westport)""[Journal] OR ""Arch Trauma Res""[Journal] OR ""Rev Bras Ter Intensiva""[Journal] OR ""Indian J Crit Care Med""[Journal] OR ""Med Intensiva""[Journal] OR ""Turk J Emerg Med""[Journal] OR ""J Intensive Care Soc""[Journal] OR ""Int J Crit Illn Inj Sci""[Journal] ""Rev Esp Anestesiol Reanim""[Journal] OR ""Tanaffos""[Journal] OR ""Med Klin Intensivmed Notfmed""[Journal] OR ""Crit Care Shock""[Journal] OR ""Zhonghua Wei Zhong Bing Ji Jiu Yi Xue""[Journal] OR ""Acute Med""[Journal] OR ""Tuberk Toraks""[Journal] OR ""Trauma""[Journal] OR ""Perioper Care Oper Room Manag""[Journal] OR ""Clin Pulm Med""[Journal] OR ""Enferm Intensiva""[Journal] OR ""Zhongguo Wei Zhong Bing Ji Jiu Yi Xue""[Journal] OR ""Rom J Anaesth Intensive Care""[Journal] OR ""Anasthesiol Intensivmed Notfallmed Schmerzther""[Journal] OR ""Trauma Case Rep""[Journal] OR ""Zhonghua Shao Shang Za Zhi""[Journal]))) OR jsubsetaim[text) Filters: Systematic Reviews

Search string for the Cochrane Database of Systematic Reviews via The Cochrane Library (http://www.cochranelibrary.com/. Issue 7 2019; Accessed 02/08/2019)

#1	MeSH descriptor: [Sepsis] explode all trees	4,080
#2	(sepsis OR septic):ti	4,009
#3	#1 OR #2	6,530
#4	#1 OR #2 in Cochrane Reviews, Cochrane Protocols	64

Intervention types

We classified interventions into four categories:

1. Initial resuscitative treatment: fluid therapy and antimicrobial therapy.
2. Failure of initiative therapy: vasopressors and inotropic agents, glucocorticoids and blood products.
3. Supportive therapies: anticoagulants, mechanical ventilation, sedation and analgesia, glucose control, renal replacement therapy, bicarbonate therapy, blood purification, N-acetylcysteine, antipyretic therapy and nutrition.
4. Investigational therapies: immunotherapy, recombinant human activated protein C, statins and selenium.

Table S1: Univariate analysis of female participation in the study population (N= 246 studies).

Characteristic	% Female participation, median (IQR)	P value
Setting		0.0002
ICU	37.93 (30.98- 42.72)	
Non-ICU	41.34 (36.67- 47.50)	
PROGRESS components?†		0.0227
Yes	41.41 (38.46- 43.75)	
No	38.77 (31.48- 43.75)	

† Excluding the sex and gender component. IQR: interquartile range.

Table S2: Multivariate analysis of sex-related reporting (N=277 studies).

Characteristic	OR	SE	P value	95% CI
Publication year				
<1996	3.33	1.70	0.019	1.22 to 9.05
PROGRESS components*				
(non-inclusion)	1.96	0.78	0.089	0.90 to 4.26
Study design				
RCT	2.43	1.19	0.000	1.73 to 6.78
Study design: participating centres	0.52	0.19	0.077	0.25 to 1.07
Multicentre				
Study sample size				
≥500 participants	1.40	0.54	0.378	0.66 to 2.98

* Excluding the sex and gender component. CI: confidence interval; OR: odds ratio; PROGRESS: place of residence-race/ethnicity/culture/language-occupation-gender/sex-religion-education-socioeconomic status-social capital; RCT: randomised clinical trial; SE: standard error.

8.1.2 Supplementary material of the second publication

Title: Sex and Gender Appraisal Tool-Systematic Reviews-2 and Participation-to-Prevalence Ratio assessed to whom the evidence applies in sepsis reviews

Authors: Antequera A, Stallings E, Henry RS, Lopez-Alcalde J, Runnels V, Tudiver S, Tugwell P, Welch V.

Supplementary material

Contents:

The original tool: Sex and Gender Appraisal Tool for Systematic Reviews (SGAT-SR)

Sex and Gender Appraisal Tool for Systematic Reviews – 2 (SGAT-SR-2)

The SGAT-SR-2 tool: Glossary, Response options, and Criteria for applying the revised tool and examples.

Differences between the protocol and the study

Search strategy

Intervention types

References to included Cochrane Systematic Reviews

References to included primary studies in the subset of Cochrane Systematic Reviews

Supplementary tables

Table S1. Population descriptors used for sex-stratified incidence of sepsis in the Participation-to-Prevalence-Ratio calculation.

Table S2. Data provided by reviews reporting sex or gender of participants at the study-level.

The original tool: Sex and Gender Appraisal Tool for Systematic Reviews (SGAT-SR)

The original SGAT-SR tool was designed by Doull and colleagues: Doull M, Runnels VE, Tudiver S, Boscoe M. Appraising the evidence: applying sex- and gender-based analysis (SGBA) to Cochrane systematic reviews on cardiovascular diseases. J Women's Health (Larchmt) 2010;19,997-1003.

The original SGAT-SR: Appraisal tool

Review section: Background

Are the terms sex/gender used in background?*

Are sex/gender identified as relevant or not to review question?

Does background discuss why sex/gender differences may be expected?

Review section: Objectives

Are the terms sex, gender, male, or female used in objectives?

Review section: Criteria for inclusion/exclusion

Does the review's inclusion/exclusion criteria consider sex/gender differences?

Was there justification or explanation for the exclusion of some groups?

Review section: Methods

Does the review examine whether outcome measures are different for males and females?

Did the review extract data by sex?

Did the review extract data on sex of withdrawals and dropouts?

In cases where sex/gender is used as a proxy for other measures (i.e., weight), is there an explanation for this approach?

Were any subgroup analyses completed?

Were subgroup analyses by sex completed?

Review section: Results and analysis

Do results distinguish between findings for males/females?

Does the review report conclusions (of effectiveness, efficacy, safety) that are different for men and women?

If adverse effects are reported, is information sex disaggregated?

Does review note that subgroup analyses by sex could not be done?

Review section: Discussion and conclusions

Does the review report that primary studies analysed or failed to analyse results by sex?

Does the review address sex/gender implications for clinical practice?

Does the review address sex/gender implications for policy and regulation?

Does the review address sex/gender implications for research?

Review Section: Table of included studies

Does the description of included studies give detailed information on study samples?

* Note: Sex/gender is used here to mean sex and/or gender.

Possible responses: “Yes, review met criteria”; “No, review did not met criteria”; “Item was not applicable to review”; and “Unable to determine”

The original SGAT-SR: Planning tool

The SGAT- SR was also utilised as the basis for a systematic review planning tool. Available at https://methods.cochrane.org/sites/methods.cochrane.org.equity/files/public/uploads/SRTool_PlanningVersionSHORTFINAL.pdf

Sex and Gender Appraisal Tool-Systematic Reviews-2 and Participation-to-Prevalence Ratio assessed to whom the evidence applies in sepsis reviews

Sex and Gender Appraisal Tool for Systematic Reviews – 2 (SGAT–SR–2)

Review section	Question	Reviews meeting the criteria				
		Yes	No	Probably yes	Probably no	NA
Abstract	1. Did the abstract report on sex or gender?					
Plain language summary	2. Did the plain language summary report on sex or gender?					
Background	3.a. Did the background discuss the relevance of sex or gender to the review question?					
	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?					
Objectives	4. Were sex, gender or related terms used in objectives?‡					
Methods	5.a. Did the review’s eligibility criteria consider sex or gender differences?*					
	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?					
	6. Did the review plan to collect characteristics of participants by sex or gender at the study-level?					
	7. Did the review plan to collect missing participant data by sex or gender at the study-level (e.g., attrition from the study)?					
	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)?†					
	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?					
Results	9. Did the review report characteristics of participants by sex or gender at the study-level (or state that no data were available)?					
	10. Did the review report missing participant data by sex or gender at the study-level (or state that no data were available)?					
	11. Did the review report characteristics of participants by sex or gender at the review-level (or state that no data were available)?					
	12.a. Did the review analyse or report results across sex or gender for the most important outcomes (e.g.,					

Sex and Gender Appraisal Tool-Systematic Reviews-2 and Participation-to-Prevalence Ratio assessed to whom the evidence applies in sepsis reviews

	analyses to investigate heterogeneity, such as subgroup analysis)?†	
	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?	
	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 outcome (i.e., indirectness)?	
Discussion and Authors' conclusions	14. Did the review discuss the limitations related to sex or gender of the population of interest?	
	15. Did the review discuss the implications of evidence for practice or research related to sex or gender of the population of interest?	
	16. Did the review discuss the applicability of evidence related to sex or gender of the population of interest?	

Questions	**Reviews meeting the criteria**
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* Binary use (female/male) Non-binary use (person with DSD/female/male) Unclear *Gender* Binary use (woman/man or girl/boy)) Non-binary use (woman/man/gender diverse/etc.) Unclear	
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* Appropriate (person with DSD/female/male) Inappropriate (girl/boy/woman/man/gender diverse/etc.) Unclear *Gender* Appropriate (girl/boy/woman/man/gender diverse/etc.) Inappropriate (person with DSD/female/male) Unclear	
19. Non-interchangeable use (N=48) Explanation: When authors mention sex, gender, or related terms, did they use them interchangeably? Yes No Unclear	

Abbreviations, NA, non-applicable, DSD, differences of sex development.

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

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

‡ [Sex or gender] Related terms refer to female, male, individuals with differences of sex development girls, women, boys, men, transgender, and other gender diverse people

The SGAT-SR-2 tool: Glossary, Response options, and Criteria for applying the revised tool and examples

Glossary

- Sex, typically assigned at birth, refers to a set of biological traits that distinguish females, males, and individuals with differences of sex development [1–3].
- Differences of sex development (DSD): variations in chromosomal expressions or physiological characteristics that have not been categorised into the female-male dichotomy DSD replaces “intersex” term after the 2006 Consensus Statement [4].
- Gender reflects socially constructed roles, behaviours, and identities of girls, women, boys, men, transgender, gender diverse individuals, etc [1–3].
- Acronym PROGRESS-Plus: Place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socio-economic status and social capital, and ‘Plus’ refers to additional categories such as age, sexual orientation and disability which may influence opportunities for health of individuals and populations [5–7].
- Intersectional analysis takes into account simultaneous interactions between different components of social identity, and the influence of systems of oppression [8].
- Missing participant data (MPD): Any outcome data from individual participants that are unavailable to the investigator(s). There are many potential sources of MPD in a systematic review, for example, losses to follow-up, exclusions from analysis, selective reporting bias, incomplete reporting, characteristics not measured. The two latter are particularly relevant to questions addressing heterogeneity based on sex or gender because they affect missing study-level characteristics (for subgroup analysis or meta-regression) [9,10].
- GRADE (grading of recommendations assessment, development and evaluation): System for grading the certainty of evidence of systematic reviews and clinical guidelines through assessment of five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. For evidence from non-randomized studies and rarely randomized studies, evidence can be upgraded by three further domains (large effect, dose response, and opposing plausible residual bias and confounding). GRADE assessment are usually presented in Summary of Findings (SoF) tables [9,11,12].
- Indirectness domain assesses if studies contributing to the review meet eligibility criteria but examine a restricted version of the main review question in terms of population, intervention or outcomes [9,13].

Response options

For questions #1 - #16, the possible responses are:

- Yes
- No
- Probably yes: To denote situations where review authors provided insufficient details but it would be reasonable to respond “probably yes” (which implies that a judgment was made) [14].
- Probably no: To denote situations where review authors provided insufficient details but it would be reasonable to respond “probably no” (which implies that a judgment was made) [14].
- Non-applicable: To denote three possible situations: a) either the health condition of interest was limited to specific sex (e.g., prostate biopsy-related sepsis) or the scope of the research question was gender-segregated (e.g., examining research gaps when specific-gender patients have been understudied); b) reviews found no eligible studies (neither qualitative nor quantitative synthesis) for those questions related to the results sections (i.e., #9 - #12) and applicability and limitations (i.e., #14 and #16); c) questions in which the answer to the preceding question was different to "Yes" or "Probably yes" (i.e., #3.b, #5.b, #8.b, and #12.b).

For questions #17 - #19, the specific responses and related explanations are described below the corresponding questions.

Criteria for applying the SGAT-SR-2 tool and examples

Abstract section

1. Did the abstract report on sex or gender?

Review authors used sex, gender, or related terms to report “Background”, “Objectives”, “Selection criteria”, “Data collection and analysis”, “Main results” or “Authors’ conclusions”.
Rationale: Abstract is a key section for readers. Summarising the study characteristics provides readers of the Abstract with important information about the applicability of the included studies.

- Yes

Example: “There are long-term complications of galactosaemia, despite treatment, including learning disabilities and female infertility” [15]

- No
- Probably yes
- Probably no
- Non-applicable

Plain language summary

2. Did the plain language summary (PLS) report on sex or gender?

Review used sex, gender, or related terms to report PLS.
Rationale: PLS, which is aimed towards the general public, is the key dissemination product for each Cochrane Review. Summarising the study characteristics provides readers of the PLS with important information about the applicability of the included studies.

- Yes

Example:
“Unfortunately, despite treatment, long-term complications for people with galactosaemia include learning difficulties and fertility problems (in females)” [15]

- No
- Probably yes
- Probably no
- Non-applicable

Background

3.a. Did the background discuss the relevance of sex or gender to the review question?

Review considered whether sex or gender differences may be expected in discussing the context, population, intervention, comparator, or outcomes.
Rationale, SAGER guidelines [16]: Authors should respond if sex and gender are relevant to the topic, or justify why not, where appropriate. Authors should report prior studies that point out presence or lack of sex or gender similarities or differences. When such references are lacking, authors should explain whether sex or gender differences may be expected.

- Yes

Review mentioned sex or gender may have a role in the incidence or severity of the condition, or sex or gender may have an influence on accessibility, adherence, safety, or effectiveness of the intervention. Otherwise, review justified why sex or gender was not relevant to the review question.

Examples:

“Suggested risk factors for poor prognosis include male sex, prematurity or being small-for-gestational age, and septic delivery” [17]

“Advanced age, male sex, and lower socioeconomic class are associated with higher incidence of acute pancreatitis” [18]

- No

None mention related to sex or gender considerations.

- Probably yes
- Probably no
- Non-applicable

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?

Review discussed if interactions may be expected between sex or gender and other PROGRESS-Plus characteristics in the context of the review question.

- Yes

Review mentioned an interrelationship between sex or gender and other PROGRESS-Plus characteristics.

Examples:

“It is estimated that almost 10% of American men will suffer from duodenal ulcer in their lifetime, although its incidence varies within a country as it is more frequent in men and the incidence increases with age” [19]

“Advanced age, male sex, and lower socioeconomic class are associated with higher incidence of acute pancreatitis”[18]

- No

None mention an interrelationship between sex or gender and any other PROGRESS-Plus characteristics.

- Probably yes
- Probably no
- Non-applicable

Objectives

4. Were sex or gender-related terms used in objectives?

Review used sex, gender, or related terms to describe objectives.

- Yes

Example Cochrane review (non-included in our sample study):

“To determine the effects of vitamin D or related compounds, with or without calcium, for preventing fractures in post-menopausal women and older men” [20]

- No
- Probably yes
- Probably no
- Non-applicable

Methods

5.a. Did the review’s eligibility criteria consider sex or gender differences?

Review described eligibility criteria on the basis of sex or gender. In those cases, examining if review described the rationale for including or excluding particular populations related to sex or gender considerations.

- Yes. Is the rationale provided?: Yes, rationale provided; Yes, non-rationale provided

Example “Yes, rationale provided”:

“We planned to exclude paediatric patients and pregnant women as other confounding factors such as microbial heterogeneity may obscure the results” [21]

Examples “Yes, non- rationale provided”:

“Types of participants: We excluded pregnant women” [22]

"We excluded...women undergoing caesarean section" [23]

“Exclusion criteria: Pregnant women” [24]

- No

The review’s eligibility criteria considered any sex or gender without differentiating them.

Example:
"Types of participants: People of any age or gender (...) admitted to any unit in the hospital setting, or treated in an outpatient setting" [25]

- Probably yes
- Probably no
- Non-applicable

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?

Review described eligibility criteria on the basis of other PROGRESS-Plus characteristics that interact with sex or gender in the context of the review question. Rationale, WHO [8]: Intersecting categories may result in effects on outcomes in infectious diseases.

- Yes

Example non-Cochrane review (non-included in our sample study): "To be included in the review, studies had to be (...) Studies that explored barriers to early presentation and diagnosis with symptomatic breast cancer in black women of 18 years or over of African or Caribbean descent" [26]

- No

The review's eligibility criteria considered no other PROGRESS-Plus characteristics in relation to the sex or gender criterion.

- Probably yes
- Probably no
- Non-applicable

6. Did the review plan to collect characteristics of participants by sex or gender at the study-level?

Assessing this question requires reading the main text in the methods section, data extraction template where available, and protocol if needed. An affirmative response may include instances where the information is inferred across methods description.
Rationale, Cochrane Handbook [9]: "Collecting data: (…)Characteristics of participants at the beginning (or baseline) of the study (e.g., age, sex, comorbidity, socio-economic status)"
SAGER guidelines [16]: "Data should be reported disaggregated by sex and gender"

ICMJE [27]: “Researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these [age, sex, or ethnicity] and other relevant demographic variables.

- Yes

Examples:

“Participants (total number, gestational age, sex, country, socioeconomic and ethnic groups, diagnosis, status)” [28]

Appendix: “Sex of participants (M/F numbers or %)” [29]

“No. of males: No. of females” [21]

Information inferred: “Data synthesis: We examined clinical and methodological heterogeneity with reference to the study population (gender, age and TBSA percentage), intervention and outcome” [30]

- No

Examples: “The following parameters were extracted: Number of deaths, SIRS [Systemic inflammatory response syndrome], MOF [Multiple organ failure], operative interventions, local septic complications (pancreatic abscess formation, infected necrosis), other local complications (fluid collection, pseudocyst, sterile pancreatic necrosis, fistula), systemic infection (septicemia, UTI, pneumonia, line infection), protection of gut mucosal barrier parameters, and length of hospital stay in days” [31]

“We extracted the following data for each trial: authors; year of publication; country; level of care; human resources used; inclusion and exclusion criteria; study characteristics; mean or median weight and gestational age at birth, and infant age at enrollment by group; description of interventions; co-interventions; mean or median duration of KMC; criteria for infant discharge from the hospital; scheme for follow-up of infants after discharge; numbers randomized and analyzed; numbers of and reasons for withdrawal; and outcomes.“ [32]

- Probably yes
- Probably no

“The review authors performed data extraction independently using specifically designed paper forms” [33]. No additional information elsewhere.

- Non-applicable

7. Did the review plan to collect missing participant data by sex or gender at the study-level (e.g., attrition from the study)?

Assessing this question requires reading the main text in the methods section, data extraction template where available, and protocol if needed. An affirmative response may include instances where the information is inferred across methods description.
Rationale, Cochrane handbook [9]: definition, types of missing data, and implications.

- Yes

Example: “We extracted the following data: withdrawals, reasons for withdrawals; age, gender…” [25].

- No

Example:
“Loss of follow-up (dropouts) before the end of the study in each group” [34]

- Probably yes
- Probably no

Example: “The review authors performed data extraction independently using specifically designed paper forms” [33]. No additional information elsewhere.

- Non-applicable

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)?

Review planned to analyse or report outcomes by sex or gender (e.g., performing subgroup analysis or meta-regression, narrative synthesis, etc.). Assessing this question requires reading the main text of the methods section, and protocol if needed. A negative response requires examining if the review explained the reasons.
Rationale, ICMJE [27]: “Results: Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.”

- Yes

Examples:
“We planned to perform the following subgroup analyses; they were not feasible because stratified/subgroup data were unavailable...Sex” [35]
“We considered the following groups for subgroup analysis where specific subgroup data are available (...) sex" [36]

- No. Is the rationale provided? “No, rationale provided”, “No, non-rationale provided”.
- Probably yes

- Probably no
- Non-applicable

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?

Review planned to explore differences by sex or gender using PROGRESS-Plus characteristics. Assessing this question requires reading the main text (methods section) and protocol, if needed. Rationale, WHO [8]: Intersecting categories may result in effects on outcomes in infectious diseases. For example, Intersectional sex-disaggregated analysis: Explore within group differences among males and females using one or two PROGRESS-Plus characteristics (e.g., in a hypothetical intervention to prevent sepsis in patients with stroke, author may disaggregate sepsis incidence by race and sex [37])

- Yes
- No
- Probably yes
- Probably no
- Non-applicable

Results

9. Did the review report characteristics of participants by sex or gender at the study-level (or state that no data were available)?

Review reported characteristics of participants by sex or gender (i.e., absolute number or percentage by arms) at the study-level in the main text (results section) or table of included studies, or stated that data were not available. The item tries to capture the review authors’ effort to report on sex or gender, including whether they were unable to do so or reported insufficient details because of lack of reporting in the included studies.

Of note, the best scenario would be where the review reported characteristics of participants by sex or gender to both randomised and analysed patients per each arm of comparison at study-level.

- Yes

Examples:

Table of included studies: “Gender (male/female): intervention=125:95; control = 118:104”. “Gender: not stated” [38]

“EN group (standard) Gender, M/F: 10/0 (...) “Gender: not reported” [23]

- No
- Probably yes
- Probably no
- Non-applicable

Example: “No published RCTs testing de-escalation of antimicrobial treatment for adult patients diagnosed with sepsis, severe sepsis or septic were included in this review” [39]

10. Did the review report missing participant data by sex or gender at the study-level (or state that no data were available)?

Review reported missing participant data by sex or gender in the main text (results section) or table of included studies, or stated that data were not available. The item tries to capture the review authors’ effort to report on sex or gender, including whether they were unable to do so because of lack of reporting in the included studies.

- Yes

Example:

“Withdrawals: Group 2: 5 (8.6%) (2 males and 3 females)” [25]

- No

Examples:

Table of included studies: “n = 23; some early participant loss but study authors did not report to which group these participants belonged; use of ITT analysis” [23]

“Table 1: Characteristics of included studies [18]

Study name	No of participants randomised	Postrandomisation dropouts	No of participants for whom outcome was reported”

- Probably yes
- Probably no
- Non-applicable

Example:

"No published RCTs testing de-escalation of antimicrobial treatment for adult patients diagnosed with sepsis, severe sepsis or septic were included in this review" [39]

11. Did the review report characteristics of participants by sex or gender at the review-level (or state that no data were available)?

Review reported characteristics of participants by sex or gender (i.e., absolute number or percentage by arms) at the review-level in the main text (results section), preferably by outcome assessed, Summary of Findings tables, or stated that data were not available. The item tries to capture the review authors' effort to report on sex or gender and whether they were unable to do so because of lack of reporting in the included studies (in both scenarios, the response would be "Yes").

Of note, the best scenario would be where the review reported the sex or gender characteristics of the body of the evidence for each outcome in the following sections: main text (results section), and Summary of Findings Tables.

- Yes

Examples:

"The approximate mean proportion of men was 64%" [40]

"Nine studies reported the male-to-female ratio…The percentage of males ranged from 60% to 90%, with a mean of 72%" [30]

"Only one included trial reported on proportions of male and female participants, including 1689 males and 1452 females. The other two trials did not offer details on patient gender" [41]

- No
- Probably yes
- Probably no

To denote situations where review authors provided insufficient details on sample composition by sex or gender at the review level.

Examples:

"All the trials included males and females except one trial that included only males" [31]

"Seven trials were restricted to participants with urinary tract infection, all hospitalized, mainly women" [34]

- Non-applicable

.

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)?

Review analysed or reported outcomes by sex or gender in the main text of the results section (e.g., performing subgroup analysis or meta-regression, narrative synthesis, etc.). A negative response requires examining if the review explained the reasons (for example, no available data, or sex or gender stated as no relevant to the research question).
Rationale, SAGER guidelines [16]: “Data should be reported disaggregated by sex and gender”
ICMJE [27]: “Separate reporting of data by demographic variables, such as age and sex (...) should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.”

Of note, the best scenario would be where the review attempted to explain the heterogeneity in the results by sex or gender, where appropriate. This would imply conducting subgroup analyses by performing meta-analyses (MA) for each sex or gender and a test of interaction between those MAs.

- Yes

Example:
"[in the Sebag-Montefiore 2009 trial] At six months' follow-up, male sexual dysfunction was significantly increased following surgery in the group that received PRT (…) [in the van Gijn 2011 trial] sexual function was significantly worse for both males and females" [42]

- No. Is the rationale provided?: “No, rationale provided”;” No, non-rationale provided”

Example “No, rationale provided”:
“We could not perform the planned subgroup analyses based on birth weight and sex due to lack of stratified data” [35]

- Probably yes
- Probably no
- Non-applicable

.

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?

Review explored differences by sex or gender across PROGRESS-Plus characteristics.

- Yes

Hypothetical example:

Overcrowded living conditions increase the risk of transmission of ebola [8]. An intervention addressing epidemiological monitoring of cases may examine the number of new cases by gender in the subset of the lower-income regions in Democratic Republic of Congo.

- No
- Probably yes
- Probably no
- Non-applicable

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)?

Review considered the sex or gender characteristics of the study participants to assess if they differed from those of the population that the review posed.(i.e., indirectness domain of GRADE). Information for assessing this item is expected to be found in the main text (results section) or the Summary of Findings tables.

Rationale, Cochrane Handbook [9]: One type of indirectness evidence is situations in which "the evidence may be regarded as indirect in relation to the broader question of interest because the population is primarily related to [a specific subset of population]. The opposite scenario can equally apply [examining intervention to a specific subset of population taking into account a broader population]"

GRADE equity guidelines [43]: Evaluate indirectness of evidence to vulnerable populations or settings is one of the methods to assess health equity with the GRADE framework "Direct evidence maybe lacking because some populations may not represent a large proportion of trial populations (e.g., migrants and refugees), and data are unlikely to be disaggregated for specific subgroups…also because some populations are explicitly excluded from trials, such as pregnant women (…) certainty of the evidence should not be rated down for indirectness for population differences unless there are compelling reasons to anticipate differences in effect due to biology/physiology, sociocultural influences, or setting-specific resource issues that impact the effectiveness or harms of the intervention.(...) rating down for indirectness could in itself increase inequities if this leads to less use of an effective intervention by disadvantaged groups".

- Yes

Example Cochrane review (non-included in our sample study):

"We found evidence of no difference in cardiovascular mortality and serious adverse events between long-term treatment with ivabradine and placebo/usual care/no treatment in participants with heart failure with HFrEF. Nevertheless, due to indirectness (male predominance), the certainty of the available evidence is rated as moderate" [44]

- No
- Probably yes
- Probable no
- Non-applicable

Discussion and Authors' conclusions

14. Did the review discuss the limitations related to sex or gender of the population of interest?

Review discussed limitations related to sex or gender of the population of interest at study-level (e.g.,, included studies failed to analyse outcomes by sex or gender, exclusion of some groups for specific reasons related to sex or gender, reporting bias of subgroup analyses by sex or gender) or at review-level (e.g., implications of lack of reporting of withdrawals by sex or gender)
Rationale, PRISMA [45]: "Discuss limitations at study and outcome-level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)"
CONSORT-Equity 2017 Extension [46]: "Report any limitations related to assessing effect on health equity"

- Yes

Example: "female representation was lower in the included studies, and data were not presented disaggregated by sex" [47]

- No
- Probably yes
- Probably no
- Non-applicable

15. Did the review discuss the implications of evidence for practice or research related to sex or gender of the population of interest?

Review discussed implications of the evidence for practice or research related to sex or gender of population of interest. Additionally, review could discuss implications for program implementation; in this case, an affirmative response is also valid.

Rationale, Cochrane Handbook [9]: "It is helpful to consider the population, intervention, comparison and outcomes that could be addressed, or addressed more effectively in the future, in the context of the certainty of the evidence in the current review (Brown et al 2006): P (Population): (…) sex."

MECIR [48]: "Recommendations for future research should offer constructive guidance on addressing the remaining uncertainties identified by the review. This is particularly important for reviews that identify few or no studies. Include any information about completed or ongoing studies that are likely to address the review question."

- Yes

Examples: "Implications for research: Sex as a relevant prognostic factor for critically ill conditions remains a question to be resolved" [47]

Example Cochrane review (non-included in our sample study): "There were no studies which looked at (…) pregnant women. We would like to see research done in this area to determine the most advantageous treatment and regimen for these particularly vulnerable groups to reduce the significant morbidity and mortality associated with them" [49]

- No
- Probably yes
- Probably no
- Non-applicable

16. Did the review discuss the applicability of evidence related to sex or gender of the population of interest?

Review discussed the applicability of the evidence related to sex or gender of the population of interest based on potential biological variations between sexes that may affect responsiveness to an intervention (e.g., a differential risk of adverse effects related to pharmacokinetic and drug concentrations), or socially constructed behaviours or identities and power and resource distribution between genders that may affect adherence (e.g.,adherence to interventions that aim to change health-related behaviours[50]) and values and preferences. Additionally, review could discuss if the representation of sexes or genders of the review population matches with the sex or gender distribution of the disease in the population of interest, and even if there are concerns

about indirectness related to the population (i.e., population of the included studies did not fully represent the review question).

Rationale, Cochrane Handbook [9]: “A description of the identifying prognostic or baseline risk factors in a brief scenario (e.g., age or gender) will help users of a review further (..) biological variation that may affect the applicability of a result to a reader or population include divergence in pathophysiology (e.g., biological differences between women and men that may affect responsiveness to an intervention) (...) Predictable differences in adherence can be due to divergence in how recipients of care perceive the intervention (e.g., the importance of side effects), economic conditions or attitudes that make some forms of care inaccessible in some settings (...) The importance placed on outcomes, together with other factors, will influence whether the recipients of care will or will not accept an option that is offered (...) GRADE’s certainty domains include a judgement about ‘indirectness’ to describe all of these aspects including the concept of direct versus indirect comparisons of different interventions”

Sex-specific consideration in guidelines generation and application [51]: “Consider if studies include adequate representation of females and males”.

- Yes

Example: “We found that clinical heterogeneity, especially relating to the intervention, but also to the population and setting...the percentage of males versus females spanned from 49%, Jakkula 2018, to 84%, Lång 2018”[40]

“Heparin-induced thrombocytopaenia (HIT) is an adverse event that may be life-threatening. It is more common after intraoperative or perioperative administration of heparin. Its incidence is reported at between 0.1% and 5%. Risk factors for HIT include type of heparin used (greater risk with unfractionated heparin), duration of exposure, patient setting, and patient gender (1.5 to 2 times higher among women)” [52]

“Overall completeness and applicability of evidence: Study data did not allow for subgroup analysis based on gender” [35]

- No
- Probably yes
- Probably no
- Non-applicable

Use of sex, gender and related terms

17. Non-binary use of sex and gender

Item assessed when the review used sex or gender. We considered a binary operationalisation of sex or gender, if review authors used the terms sex or gender and applied them by distinguishing two categories, even when these categories were inferred. We considered as non-binary if review authors used the terms sex or gender and applied them using a third category (e.g., individuals with differences of sex development, gender diverse, or not specified). We considered unclear to denote when review authors used the terms sex or gender without specifying further categories.

Rationale: Criteria based on the framework developed by Adisso and colleagues [53]

- Yes (=binary use)

Examples: “All three studies enrolled infants of both sexes" [54] And no sex-related terms used. “Sex (M/F): treatment group 30/19; control group; 39/9 (...) M/F - male/female” [24] Non (=non-binary use)

- Unclear
- Non- applicable

Terms sex or gender were not used.

18. Use of appropriate categories

Item assessed when the review used sex or gender. We considered an appropriate use when review authors consistently mentioned the categories female/male/individuals with differences of sex development or girl/woman/boy/man/gender diverse/etc. for sex and gender, respectively, according to commonly held definitions of sex and gender [1–3]. We considered an inappropriate use if review authors used sex and gender terms but applied categories related to sex to depict gender, and vice versa. We used unclear to denote situations in which sex and gender terms were used without subsequent categories.

Rationale: Criteria based on the framework developed by Adisso and colleagues [53]

- Yes (=appropriate use)
- No (=inappropriate)

Example: “Gender (male/female): intervention=125:95; control = 118:104”. “Gender: not stated” [38]

- Unclear
- Non-applicable

Terms sex or gender were not used.

19. Non-interchangeable use

Item assessed when the review used sex, gender, or related terms. We considered as an interchangeable use when sex-and gender-related terms were used to refer to either sex or gender in the same review. We considered as a non-interchangeable use when sex and gender were used to describe biological features and sociocultural traits, respectively. We considered an unclear use in other scenarios where this criterion is applicable.

Rationale: Criteria based on the framework developed by Adisso and colleagues [53]

- Yes (=interchangeably)

Examples: “Sex APC group: 56.1% men; placebo group 58.0% men (...) Sex: APC group, male 59.6%; placebo group, male 48.5%” [55]

“Table of included studies: control group: 9 cases (7 males, 2 females) (...) 30 patients (16 men and 14 women)” [56]

- No (=non-interchangeably)
- Unclear use
- Non-applicable

Terms sex, gender or related terms were not used.

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Differences between the protocol and the study

- Responses to the SGAT-SR-2 tool.

We described in the protocol the following possible responses: “Yes, review met criteria”, “No, review did not meet criteria with rationale”, “No, review did not meet criteria without rationale”, “Not applicable”, or “Unclear”.

We used the following responses in the SGAT-SR-2 tool: “Yes”, “No”, “Probably yes”, “Probably no”, and “Not applicable”.

During the piloting process, we noted that requesting a rationale i) might not be needed for all questions, ii) may increase the complexity across the tool with a marginal benefit for characterisation of sex- and gender-based analysis and reporting, iii) certain “Yes” responses also may benefit from providing a rationale. Therefore, those responses that require a rationale were specified across the tool.

- Duplicate independent application of the SGAT-SR-2 tool to the whole sample

The protocol specified that two authors would independently apply the revised tool to the whole sample of eligible sepsis Cochrane reviews.

The piloting process was done by duplicate (22% of eligible reviews). However, one author rated the tool to the remaining appraisals, and another cross-checked the results because of time constraints and also because the piloting process reflected a strong level of agreement in our ratings

- Country data were not extracted due to substantial heterogeneity in reporting noted during the piloting process.

- Indirectness domain assessment in GRADE: No reviews assessed the certainty of evidence taking into consideration the sample composition by sex or gender at the review-level. Hence, we were unable to explore this question.

Search strategy

Search string for the Cochrane Database of Systematic Reviews via The Cochrane Library (http://www.cochranelibrary.com/. Issue 1 2021; Accessed 07/01/2021)

#1	MeSH descriptor: [Sepsis] explode all trees	4,563
#2	MeSH descriptor: [Shock,Septic] explode all trees	974
#3	(sepsis OR septic):ti,ab,kw	13,383
#4	#1 OR #2 OR #3	14,925
#5	#4 in Cochrane Reviews, Cochrane Protocol	226

Intervention types

We classified interventions into the following categories:

1. Initial resuscitative treatment: fluid therapy and antimicrobial therapy.
2. Failure of initiative therapy: vasopressors and inotropic agents, glucocorticoids, and blood products.
3. Supportive therapies: anticoagulants, mechanical ventilation, sedation and analgesia, glucose control, renal replacement therapy, bicarbonate therapy, blood purification, stress ulcer prophylaxis, N-acetylcysteine, antipyretic therapy, and nutrition.
4. Investigational therapies: immunotherapy, granulocyte transfusions, recombinant human activated protein C, statins, and selenium.
5. Prevention: any intervention to prevent sepsis.

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Supplementary tables

Table S1. Population descriptors used for sex-stratified incidence of sepsis in the Participation-to-Prevalence-Ratio calculation.

Population Setting	Sample size (N)	Females (%)	Year	Country	Reference
Neonates* ICU	2,521,249	43.3	1988-2006	United States	Lukacs SL, Schrag SJ. Clinical sepsis in neonates and young infants, United States, 1988-2006. J Pediatr 2012;160(6):960-5.e1.
	567	53.3	2013-2014	26 countries: 59 in North America, 39 in Europe, 10 in South America, 10 in Asia, 7 in Australia/New Zealand, 3 in Africa	Weiss SL, Fitzgerald JC, Pappachan J, *et al.* Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med 2015 15;191(10):1147-57.
Adults ICU	2,978	49	2012	84 countries: Europe 54% participants, Asia 19%, America 17%, other continents 10%	Sakr Y, Jaschinski U, Wittebole X, *et al.* Sepsis in intensive care unit patients: Worldwide data from the intensive care over nations audit. Open forum Infect Dis 2018;5:ofy313
Adults Hospital	10,319,418	51.9	1979-2000	United States	Martin GS, Mannino DM, Eaton S, *et al.* The epidemiology of sepsis in the United States from 1979through 2000. NEJM 2003;16:1546-1554.
Children* Hospital	325	58.7	2016	Kenya	Vekaria-Hirani V, Kumar R, Musoke RN, *et al*. Prevalence and management of septic shock among children admitted at the Kenyatta National Hospital, longitudinal survey. Int J Pediatr 2019;2019:1502963.
	854 BSI-episodes	42.6	2008-2013	South Africa	Dramowski, A., Cotton, M.F., Rabie, H. *et al.* Trends in paediatric bloodstream infections at a South African referral hospital. BMC Pediatr 15, 33 (2015).

Abbreviations: BSI, bloodstream infection; ICU, intensive care unit.

*Sex-stratified incidence of sepsis in these populations and settings had substantial heterogeneity, so, two data sources were used.

Table S2. Data provided by reviews reporting sex or gender of participants at the study-level.

Review	Total RCTs included (N)	RCTs with lack of data (N)	RCTs reported data as sex or gender (N)	RCTs reported data as male or men (N)	RCTs reported data as female or women (N)
Brand 2010	9	3	6	0	0
Barajas-Nava 2013	36	16	20	0	0
Wong 2005	40	38	2	0	0
Kelly 2017	4	0	0	4	0
Shah 2009	3	0	3	0	0
Allingstrup 2016	30	6	24	0	0
Warttig 2018	3	2	1	0	0
Antequera 2019	21	2	0	0	19
Lewis 2018	69	16	53	0	0
Shiu 2013	29	3	1	25	0
Lewis 2018	25	6	19	0	0
Al-Omran 2010	8	0	8	0	0
Borthwick 2017	4	0	0	4	0
Barbateskovic 2019	10	1	0	9	0
Mutter 2013	42	5	7	30	0
Li 2018	3	2	1	0	0
Kapoor 2019a	29	4	0	25	0
Kapoor 2019b	9	3	0	6	0
Boeuf 2003	6	4	2	0	0
Chan 2020	8	2	6	0	0
Moggia 2017	78	15	0	0	63
Abraha 2018	4	3	1	0	0
Breederveld 2014	13	4	9	0	0
Lai 2016	13	7	0	6	0
Total	496	142	163	109	82

8.1.3 Supplementary material of the third publication

Supplemental material

Sex as a prognostic factor for mortality in critically ill adults with sepsis: a systematic review and meta-analysis

Alba Antequera, Jesús López-Alcalde, Elena Stallings, Alfonso Muriel, Borja Manuel Fernández-Félix, Rosa del Campo, Manuel Ponce-Alonso, Pilar Fidalgo, Ana Verónica Halperin, Olaya Madrid-Pascual, Noelia Álvarez-Díaz, Ivan Solà, Federico Gordo, Gerard Urrútia, Javier Zamora.

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Supplemental Table 1. Differences between the protocol and the review

Modified element	Explanation
Wording primary outcomes	We modify the wording for primary outcomes for clarity purposes, following the suggestion of peer reviewers. "All-cause hospital mortality" and "28-day all-cause mortality", instead of All-cause mortality (the longest follow-up provided by study authors)" and 28-day all-cause hospital mortality", respectively.
All-cause ICU mortality	We added all-cause ICU mortality as secondary outcome. We considered all-cause ICU mortality as a relevant outcome and non-subsidiary of pooling with hospital mortality outcomes.
Subgroup analyses	We were not able to undertake subgroup analyses comparing cohort versus case-control studies because there were insufficient studies.
Sensitivity analyses	We added sensitivity analysis after excluding the unique data from conference abstracts. We also carried out sensitivity analyses by pooling crude estimates. We were not able to perform the following sensitivity analyses specified in the protocol as no comparisons met the predefined criteria: - Excluding only studies with a high risk of bias in one QUIPS key domain. - Excluding studies that provided an adjusted estimated but did not adjusted for all our core set of additional prognostic factors.

Supplemental Table 2. Assessment of the use of terms sex and gender in the included studies

Adequate (any of the following):	Inadequate (any of following):
- Sex for biological characteristics. - Gender for socially constructed roles, behaviours, and identities. - Females or males for sex. - Women or men for gender.	- Gender for biological characteristics. - Sex for socially constructed roles, behaviours, and identities. - Females or males for gender. - Women or men for sex.

Supplemental Table 3. Process of defining the core set of adjustment factors

Step	Method	Potential additional prognostic factors identified
1. Preliminary searches to identify potential prognostic factors on mortality in patients with sepsis	1. PubMed search: (sepsis[Title]) AND "prognostic factor"[Title] 2. Embase: 'prognostic factor':ti AND 'sepsis':ti 3. Search in Uptodate 4. Initial discussion with review team members	1. Hypertriglyceridemia 2. Positive fluid balance 3. Red cell distribution width 4. Duration of SIRS before organ failure 5. Heart-type fatty acid-binding protein 6. D-dimer 7. Low serum level of high-density lipoprotein colesterol 8. Serum N-terminal pro-brain natriuretic peptide level 9. Immunosuppression 10. Cancer 11. Liver diseases 12. Alcohol dependence 13. Non-urinary source of infection 14. Inappropriate or late antibiotic coverage
2. Identify prognostic models for mortality in patients with sepsis	We considered factors included in the SOFA prognostic model	1. PaO2 2. FiO2 3. On mechanical ventilation 4. Platelets, $\times 10^3/\mu L$ 5. Glasgow Coma Scale 6. Bilirubin, mg/dL (µmol/L) 7. Mean arterial pressure OR administration of vasoactive agents required 8. Creatinine, mg/dL (µmol/L) (or urine output
3. Final list of key additional prognostic factors	We defined the final list of core set of adjustment factors by consensus	1. Age 2. Severity score at baseline (SOFA, SAPS II, APACHE II score) 3. Comorbidities: immunosuppression, pulmonary diseases, cancer, liver diseases, alcohol dependence 4. Non-urinary source of infection 5. Inappropriate or late antibiotic coverage

Supplemental Table 4. Search strategy

Full search string for MEDLINE Ovid (consulted 17th July 2020)
1. exp Sepsis/
2. exp Shock, Septic/
3. (septic* or sepsis* or SIRS).ti,ab.
4. "septic shock".ti,ab.
5. "endotoxic shock".ti,ab.
6. "toxic shock".ti,ab.
7. "severe sepsis".ti,ab.
8. "blood stream infection".ti,ab.
9. (septic?emia or "systemic inflammatory response syndrome" or py?emia).ti,ab.
10. (multi?organ adj5 failure).ti,ab.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp Sex Factors/
13. exp Sex Characteristics/
14. exp Sex Distribution/
15. exp Sex/
16. exp Sex Ratio/
17. exp Women's Health/
18. exp Men's Health/
19. boy*.ti,ab.
20. female*.ti,ab.
21. gender.ti,ab.
22. girl*.ti,ab.
23. male*.ti,ab.
24. men.ti,ab.
25. sex.ti,ab.
26. women.ti,ab.
27. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 11 and 27
29. exp Mortality/
30. mortality.ti,ab.
31. dead.ti,ab.
32. death*.ti,ab.
33. died.ti,ab.
34. fatality.ti,ab.
35. fatalities.ti,ab.
36. survivor.ti,ab.
37. survival.ti,ab.
38. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 28 and 38
40. incidence.sh.
41. follow up studies.sh.
42. "prognos*".ab,ti.
43. "predict*".ab,ti.
44. "course*".ab,ti.
45. 40 or 41 or 42 or 43 or 44
46. 39 and 45
47. exp Animals/ not humans.sh.

48. 46 not 47

Full search string for Embase Elsevier (consulted 17th July 2020)

#1	'sepsis'/mj
#2	'septic shock'/mj
#3	septic*:ab,ti OR sepsis*:ab,ti OR sirs:ab,ti
#4	'septic shock':ab,ti
#5	'endotoxic shock':ab,ti
#6	'toxic shock':ab,ti
#7	'severe sepsis':ab,ti
#8	'blood stream infection':ab,ti
#9	septic?emia:ab,ti OR 'systemic inflammatory response syndrome':ab,ti OR py?emia:ab,ti
#10	multi$organ NEAR/5 failure
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	'sex factor'/mj
#13	'sexual characteristics'/mj
#14	'sex ratio'/mj
#15	'sex'/mj
#16	'women`s health'/mj
#17	'men`s health'/mj
#18	boy*:ab,ti
#19	female*:ab,ti
#20	gender:ab,ti
#21	girl*:ab,ti
#22	male*:ab,ti
#23	men:ab,ti
#24	sex:ab,ti
#25	women:ab,ti
#26	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
#27	#11 AND #26
#28	'mortality'/mj
#29	mortality:ab,ti
#30	dead:ab,ti
#31	death:ab,ti
#32	died:ab,ti
#33	'fatality':ab,ti
#34	fatalities:ab,ti
#35	survivor:ab,ti
#36	survival:ab,ti
#37	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
#38	#27 AND #37
#39	'disease course'/mj
#40	risk:kw
#41	diagnos*:kw
#42	'follow-up':kw
#43	epidemiology:lnk
#44	outcome:ab,ti
#45	#39 OR #40 OR #41 OR #42 OR #43 OR #44
#46	#38 AND #45
#47	'animal'/exp
#48	'human'/exp

#49 #47 NOT #48

#50 #46 NOT #49 AND ([embase]/lim OR [pubmed-not-medline]/lim)

Full search string for Web of Science (consulted 17th July 2020)

1 TOPIC: (sepsis) OR TOPIC: ("septic shock") OR TOPIC: ("Systemic inflammatory response syndrome") OR TOPIC: ("multiple organ failure")

2 TITLE: ("septic shock") OR TITLE ("endotoxic shock") OR TITLE: ("toxic shock") OR TITLE: ("severe sepsis") OR TITLE: ("blood stream infection") OR TITLE: (septic?emia) OR TITLE: (py?emia) OR TITLE: (septic*) OR TITLE: (sepsis*) OR TITLE: (SIRS)

3 #2 OR #1

4 TOPIC: ("sex factors" OR "sex distribution" OR "Sex characteristics" OR "Sex ratio" OR sex OR "women's health" OR "men's health") OR TITLE: (boy* OR male* OR girl* OR female* OR gender OR women OR men OR sex)

5 #4 AND #3

6 TOPIC: (mortality) OR TITLE: (mortality OR death OR dead OR died OR fatality OR fatalities OR survivor OR survival)

7 #6 AND #5

8 TOPIC: (incidende OR "follow up studies") OR TITLE: (prognos* OR predict* OR course*)

9 #8 AND #7

Trials registries (consulted 12th December 2019)

- ClinicalTrials.gov www.clinicaltrials.gov

- World Health Organization International Clinical Trials Registry Platform apps.who.int/trialsearch/

Hand-searched conference proceedings

- Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 50th edition 2010 to 59th edition 2019.

- European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 20th edition 2010 to 29th edition 2019.

- Society for Healthcare Epidemiology of America (SHEA): IDWeek 2012 to 2019 editions.

- International Conference on Prevention and Infection Control (ICPIC): 2011, 2013, 2015, 2017, 2019

- Society of Critical Care Medicine (SCCM): 39th edition 2010 to 48th edition 2019.

- International Symposium on Intensive Care and Emergency Medicine (ISICEM): 30th edition 2010 to 39th edition 2019.

- European Society of Intensive Care Medicine (ESICM): 23rd edition 2010 to 32nd edition 2019.

Supplemental Table 5. Guide to judge the certainty of evidence for prognostic factors GRADE

We initially assigned high certainty of the evidence for phase-2 confirmatory designs, i.e., studies that sought to test independent associations between the prognostic factor and outcomes	
We considered that the following factors may downgrade the certainty of evidence:	
Risk of bias	We rated as having: 1) serious limitations when most evidence was from studies at moderate or unclear risk of bias for most of the QUIPS domains; 2) very serious limitations when most evidence was from studies at high risk of bias for most of the QUIPS domains.
Inconsistency	We judged inconsistency relying on variability in point estimates using prediction intervals, extent of overlap of these intervals, and considering where point estimates lie in relation to clinical decision thresholds. We pre-specified subgroup analyses to explore differences across categories. In case of a single study within the existing body of evidence estimated the effect, we considered this criterion as "not applicable".
Indirectness	We downgraded the certainty of evidence whether participant population, prognostic factor, and/or outcomes fully represented no the review question. We judged indirectness for the prognostic factor based on characteristics of the primary independent variable, regardless of the adequacy of used terms, since we assessed insufficient details of sex and gender definitions provided or non-stated in the prognostic factor measurement QUIPS domain.
Imprecision	We judged imprecision considering: - Optimal information size - Compatibility of the 95% confidence interval of the absolute risk difference with our pre-defined clinical thresholds (minimal prognostic effects that were considered as clinically relevant for decision-making)
Publication bias	We planned 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.
We considered that the following factors may upgrade the certainty of evidence:	
Large effect estimate	We assessed size effect estimate considering: i) For meta-analysis: We considered upgrading the certainty of evidence for moderate or large pooled effects. Arbitrary thresholds define moderate odds ratio (1.5 ≤ OR ≤ 2), or large (OR > 2) ii) For narrative summary: We considered upgrading the certainty of evidence for moderate or large effects reported by most of the primary studies.
Dose response	We considered no dose response because of the feature of our prognostic factor of interest (dichotomous)

Abbreviations: OR: Odds ratio; QUIPS: Quality in prognosis studies.

Supplemental Table 6. Descriptive summary of included studies

	Adrie 2017	Caceres 2013	Dara 2012	Luethi 2020	Madsen 2014	Mahmood 2012	Nachtigall 2011
Methods							
Study design	Nested case-control	Cohort	Cohort	Post-hoc analysisis	Cohort	Cohort	Cohort
Database	OutcomeRea	IMPACT-HAP	CATSS	ARISE	SSC Database	APACHE IV	Not reported
Sample size calculation	Not reported	Not reported	Not reported	Not reported	Reported	Not reported	Not reported
Participants*							
Females; Males	631 (37); 1,061 (63)	145 (35); 271 (65)	3667 (42.3); 5003 (57.7)	562 (40.5); 825 (54)	365 (45); 449 (55)	13221 (47.3); 14714 (52.7)	130 (40); 197 (60)
Sociodemographics							
Age	69 (57-77); 65 (51-75)	62.4 (16.9); 55.7 (16.5)	62.8 (15.9) ; 62.3 (16.6)	62 (17.1); 63.5 (15.8)	66.2 (18); 66.3 (16.2)	Not reported §	68 (57-78); 64 (50-72)
Race	Not reported	Not reported		Not reported	284 (78.5); 370 (82.4)	Not reported §	Not reported
Caucasian							
African-American							
Latin							
Other/unknown							
Socioeconomic status	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Comorbidities						Not reported §	
Respiratory	123 (19.5); 266 (25)	37 (25.5); 54 (20.2)	Not reported	53 (8.3); 90 (9.5)	Not reported		20 (15.4); 27 (13.7)
Cardiac	71 (11.2); 123 (11.6)	32 (22.1); 58 (21.6)	(9.9) ; (11.2)	46 (7.2); 128 (13.5)	77 (21.1); 97 (21.6)		Not reported
Renal	19 (3); 29 (2.7)	31 (21.4); 45 (16.9)	Not reported	21 (3.3); 43 (4.5)	Not reported		24 (18.5); 37 (18.8)
Diabetes	Not reported	46 (31.7); 74 (27.6)	Not reported	27 (4.2); 58 (6.1)	Not reported		Not reported
Immunosuppression	119 (18.9); 207 (19.5)	60 (41.4); 101 (37.8)	(1.8) ; (3.3)	Not reported	Not reported		18 (13.8); 11 (5.6)
Liver disease	28 (4.4); 66 (6.2)	Not reported	(10) ; (16.9)	26 (4.1); 57 (6)	Not reported		8 (6.2); 17 (8.6)
Cancer	Not reported	Not reported	Not reported	87 (13.6); 161 (16.9)	Not reported		Not reported
Severity score							
APACHE II	19 (14-24); 19 (14-24)	22.1 (7.6); 19.9 (7.2)	25.9 (8.2) ; 25.5 (8.1)	48.1 (20.4); 50.2 (20.0) ‡	Not reported		Not reported
SAPS II	44 (33-58); 45 (34-60)	Not reported	Not reported	Not reported	Not reported		40 (29-53); 39 (28-51)
SOFA	6 (4-9); 6 (4-9)	Not reported	Not reported	3.7 (2.7); 4.2 (2.8)	6.2 (2.9); 7.2 (3.2)		5 (3-7); 6 (4-9)
Infection site							
Urinary source of infection	68 (10.8); 51 (4.8)	N/A	Not reported	138 (21.6); 170 (17.9)	Not reported	Not reported §	31 (23.8); 14 (7.1)
Prognosis factor							
Independent variable	Gender	Gender	Gender	Gender	Gender	Gender	Gender
Sex/ gender definition	Not reported	Not reported	Not reported	Reported	Not reported	Not reported	Not reported
Terms used	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men	Gender, female, male	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men	Gender, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men
Appropriateness of terms use	Inadequate	Inadequate	Inadequate	Unclear	Inadequate	Inadequate	Inadequate

Extracted outcomes							
Primary outcomes							
All-cause hospital mortality	Yes	Yes	Yes	No	Yes	No	No
28-day all-cause mortality	No	Yes	No	No	No	No	No
Secondary outcomes							
7-day all-cause hospital mortality	No	No	No	No	No	No	No
1-year all-cause mortality	No	No	No	No	No	No	No
All-cause ICU mortality	Yes	No	Yes	Yes	No	Yes	Yes
Follow-up	Not reported	Hospital discharge, death or 28 days after penumonia diagnosis, whichever ocurred first	Not reported	Not reported	Not reported	Not reported	Not reported
Identification							
Country	France	United States	Canada, United States, Saudi Arabia	Australia, New Zealand, Finland, Hong Kong, Ireland	United States	United States	Germany
Funding source	Educational grants from Aventis Pharma, France, and Wyeth; and public funds	Pfizer. University of Lousville Foundation responsible for project oversight	Unrestricted grants from Eli-Lilly, Pfizer, Bayer, Astellas, Merck, Mantioba Research Council, Health Sciences Centre Foundation, Innovations and Opportunities Foundation, Deacon Foundation	National Health and Medical Research Council	Alpert Medical School of Brown University	Not reported	Not reported
Conflict of interest	None	Declared	Declared	Declared	Not reported	None	Declared
Identifier or protocol	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Notes	Authors used conditional logistic regression with matching on age, death propensity score, and center. Email sent to study authors in May 2020; no reply received.	28-day mortality reported, authors were contacted for clarification in May 2020; no reply received.	Email sent to study authors in March 2020; no reply received	Baseline data available only for main cohort (N=1,591 participants). Email sent to study authors in May 2020; reply received but we were unable to get additional data.	Email sent to study authors in May 2020; no reply received.	Baseline data available only for main cohort (N=261,255 participants) Email sent to study authors in June 2020; no reply received.	Email sent to study authors in May 2020; no reply received.

Continued

	Pietropaoli 2010	Sakr 2013	Samuelsson 2015	Sunden-Cullberg 2020	van Vught 2017	Xu 2019
Methods						
Study design	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort
Database	Cerner Project IMPACT	Piademont Intensive Care Unit Network	SIR	NQSR and SIR	MARS	MIMIC-III
Sample size calculation	Reported	Not reported	Not reported	Not reported	Not reported	Not reported
Participants*						
Females; Males	8,702 (46); 10,055 (54)	85 (27.9); 220 (72.1)	Not reported §	1,210 (44.5); 1,510 (55.5)	595 (38.8); 938 (61.2)	2,677 (43.6); 3,457 (56.4)
Sociodemographics						
Age	68 (54-75); 65 (52-76)	67.7 (14.3); 63.1 (15)	Not reported §	68 (56–77); 68(58–77)	59.4 (16.2); 60.8 (14.8)	65-89 (50.4); 65-89 (51.1)‖
Race		Not reported	Not reported §	Not reported		
Caucasian	6,439 (74); 7,541 (75)				510 (85.7); 839 (89.4)	1,915 (71.5); 2,597 (75.1)
African-American	1,218 (14); 1,207 (12)					369 (13.8);273 (7.9)
Latin	435 (5); 603 (6)					70 (2.6); 143 (4.1)
Other/unknown	610 (7); 704 (7)					238 (8.9); 325 (9.4)
Socioeconomic status	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Comorbidities			Not reported §	Not reported		Not reported
Respiratory	870 (10); 1005 (10)	3 (3.5); 18 (8.2)			72 (12.1); 138 (14.7)	
Cardiac	522 (6); 704 (7)	8 (9.4); 17 (7.7)			131 (22); 232 (24.7)	
Renal	522 (6); 603 (6)	16 (18.8); 40 (18.2)			86 (14.5); 131 (14)	
Diabetes	Not reported	18 (21.2); 34 (15.5)			124 (20.8); 183 (19.5)	
Immunosuppression	1,131 (13); 1,307 (13)	Not reported			Not reported	
Liver disease	261 (3); 402 (4)	Not reported			Not reported	
Cancer	1,218 (14); 1,709 (17)	4 (4.7); 6 (2.7)			136 (22.9); 245 (26.1)	
Severity score						
APACHE II	21 (15-27); 21 (15-27)	Not reported		Not reported	79 (62-99); 76 (58-98)†	Not reported
SAPS II	35 (15-64); 33 (14-64)	55 (18.8); 55.3(17.5)		64 (55–73); 65 (56–75)¶	Not reported	21.39 (5.73); 21.06 (5.6)
SOFA	Not reported	9.1 (3.3); 9.8 (3.7)		Not reported	7 (5-9); 7 (4-9)	6.97 (3.52); 7.29 (3.75)
Infection site						
Urinary source of infection	2,698 (31); 1,910 (19)	5 (5.9); 13 (5.9)	Not reported §	258 (21.3); 301(19.9)	Not reported	Not reported
Prognosis factor						
Independent variable	Gender	Gender	Gender/Sex	Sex	Gender	Sex
Sex/ gender definition	Reported	Not reported	Not reported	Reported	Not reported	Not reported
Terms used	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men
Appropriateness of terms use	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
Extracted outcomes						
Primary outcomes						
All-cause hospital mortality	Yes	No	No	No	Yes	Yes

28-day all-cause mortality	No	Yes	Yes	Yes	Yes	Yes
Secondary outcomes						
7-day all-cause hospital mortality	No	No	No	No	No	No
1-year all-cause mortality	No	No	No	No	Yes	Yes
All-cause ICU mortality	Yes	Yes	No	No	Yes	No
Follow-up	Not stated	Death or ICU discharge	30 days	30 days	1 year	1 year
Identification						
Country	Brazil, Canada, US	Italy	Sweden	Sweden	Netherlands	United States
Funding source	National Heart, Lung and Blood Institute	Regione Piamonte, *progetti finalizzati di ricerca*	Regional Health Care Authorities in the Halland and Skåne regions of Sweden	Karolinska Institute, Swedish Government Funds for Clinical Research	Center for Translational Molecular Medicine, project MARS	Guangzhou Science and Technology Programs, the Guangdong Provincial Key Laboratory Construction Projection on Organ and Transplant Immunology, and the Guangdong Provincial International Cooperation Base of Science and Technology
Conflict of interest	None	None	None	None	Declared	None
Identifier or protocol	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Notes	Email sent to study authors in April 2020; no reply received.	ICU mortality mismatched published data, authors were contacted for clarification in April 2020; reply received. 28-day mortality reported, authors were contacted again for clarification in May 2020; no reply received.	30-day mortality reported, authors were contacted for clarification in June 2020; reply received (outcome included 30-day in- and out-hospital mortality). Sepsis subgroup comparison was adjusted at P<0.001.	30-day mortality reported, authors were contacted for clarification in June 2020; no reply received.	30-day mortality reported, authors were contacted for clarification in May 2020; no reply received.	Cox analyes reported as OR without additional clarification, and 30-day mortality reported, authors were contacted for clarification in July 2020; no reply received.

*Categorical variables expressed as numerical values and percentages, and continuous variables expressed as median and IQR, or mean and standard deviation as the study may be.

† APACHE IV

‡ APACHE III

§ Participant characteristics only available for whole ICU cohort

¶ SAPS III

|| Age reported by the study authors as percentage of participants in different age groups. Age expressed as age group (percentage).

Abbreviations: APACHE: Acute Physiology and Chronic Health Evaluation; ARISE: Australasian resuscitation in sepsis evaluation; CATSS: Cooperative antimicrobial therapy of septic shock; ICU: Intensive care unit; IMPACT: abbreviation not detailed; IMPACT- HAP: Improving medicine through pathway assessment of critical therapy in hospital-acquired pneumonia; F: Females; M: Males; MARS: Molecular diagnosis and risk stratification of sepsis; MIMIC: Medical information mart for intensive care III; N/A: Not applicable; NQSR: National quality sepsis registry; SAPS: Simplified Acute Physiology Score; SIR: Swedish intensive care registry; SOFA: Sequential Organ Failure Assessment score; SSC: Surviving sepsis campaign.

Supplemental Table 7. Sepsis definition provided by the study authors

Study	Sepsis-related term for defining health condition	Operational definition
Adrie 2007*	Sepsis severe	Severe sepsis was defined as infection with two or more criteria for systemic inflammatory response syndrome and at least one criterion for organ dysfunction
Caceres 2013	Severe infection, hospital-acquired pneumonia	Severe infection was defined as hospital-acquired pneumonia, including ventilator-associated pneumonia and health-care associated pneumonia
Dara 2012	Sepsis shock	Non-provided
Luethi 2010	Septic shock	Septic shock was defined as two or more criteria for systemic inflammatory response syndrome and refractory hypotension (systolic blood pressure of b90 mmHg or a mean arterial pressure of 65 mmHg after an intravenous fluid challenge), or hyperlactatemia (blood lactate level of ≥4.0 mmol/L), or both.
Madsen 2014	Severe sepsis and septic shock	Severe sepsis or septic shock as defined by Surviving Sepsis Campaign.
Mahmood 2012	Sepsis	Non-provided
Nachtigall 2011	Sepsis	Sepsis, severe sepsis, and septic shock was defined according to the national and international sepsis guidelines, requering two or more criteria for systemic inflammatory response syndrome associated with an infection
Pietropaoli 2010	Severe sepsis and septic shock	Severe sepsis was defined as development of at least one severe acute organ dysfunction within 3 days of a presumed infection.
Sakr 2013	Severe sepsis	Sepsis syndromes were diagnosed according to the criteria proposed by the American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference [Severe sepsis: sepsis associated with organ dysfunction, hypoperfusion, or hypotension]
Samuelsson 2015	Sepsis	Non-provided
Sunden-Cullberg 2020	Severe sepsis and septic shock	Severe sepsis and septic shock were diagnosed using a modified version of the 1992 sepsis definition, in practice accepting a diagnosis of severe sepsis on the basis of infection plus organ dysfunction
van Vught 2017†	Sepsis	Sepsis was defined as an infection diagnosed with a "probable" or "definite" likelihood, plus at least one additional variable as described in the 2001 International Sepsis Definitions. Shock was defined by the use of vasopressors.
Xu 2019‡	Sepsis, severe sepsis and shock septic	Non-provided

Supplemental Table 8. Prognostic factors in adjusted models for mortality in included studies

Study	Prognostic factors included in adjusted analyses
Adrie 2007*	Chronic respiratory failure; metastatic cancer; immunocompromised status; emergency surgery; acute respiratory failure and shock at hospital admission; urinary tract infection as a cause of sepsis; type of microorganism (*E coli, S pneumoniae*, and *Enterobacter* species)
Caceres 2013	Age; APACHE II; HCAP; white race; history of cardiac/renal/vascular/diabetes/respiratory disease; severe sepsis; hospital LOS; ICU LOS; MV after diagnosis of MRSA; CPIS at baseline
Dara 2012	APACHE II; age; site of infection; source of admission ; inappropriate antibiotics; other variables related to organ dysfunction
Luethi 2010	Illness severity (APACHE III score); pre-existing comorbidities (Charlson comorbidity index); cardiac arrhythmia; intravenous resuscitation fluid (per kilogram) administered before ICU admission
Madsen 2014	Age; race; SOFA; CHF; coagulopathy
Mahmood 2012	Acute physiology score; age; ethnicity; pre-ICU length of stay; pre-ICU location and hospital teaching status
Nachtigall 2011	Age; TISS-28 on admission (nursing workload); occurrence of pneumonia; septic shock; fungi detected; septic shock
Pietropaoli 2010	Age; dependent functional status at admission; African-American race; type of admittance; medical versus surgical patient; type of insurance; CPR within 24h of admission; comorbidities (chronic liver disease, active cancer within 5 years, chronic cardiovascular disease, chronic respiratory disease, immunocompromised status); illness severity (neurological dysfunction, cardiovascular dysfunction, elevated serum lactate, acute renal failure, hepatic dysfunction, hematologic dysfunction; SAPS II score); source of infection; processes of care; hospital characteristics
Sakr 2013	Age; comorbidities (renal failure with dialysis, chronic obstructive pulmonary disease); SAPS II; type of admission (elective surgery, emergency surgery, medical admission); initial SOFA sub-scores; referring facility; source of infection (abdominal)
Samuelsson 2015	Age; comorbidity (scored as in the Simplified Acute Physiology III); hospital LOS in days; location prior to ICU admission; therapy prior to ICU admission; reason for ICU admission; surgical status; presence of nosocomial or lower-airway infection; physiologic derangement (scored as in the Simplified Acute Physiology III); hospital characteristics
Sunden-Cullberg 2020	Temperature-adjusted SAPS3; body temperature; incorrect antibiotics; treatment limitations
van Vught 2017†	Age; body mass index; comorbidity; source of infection; acute physiology score
Xu 2019‡	Age; race; first ICU service; marital status; insurance; admission location; SAPS; SOFA

* Adrie 2007 reported adjusted analyses using a conditional logistic regression after matching on age, death propensity score, and centre.

† van Vught 2017 reported adjusted analyses only for 90-day mortality.

‡ Xu 2019 reported adjusted analyses using a Cox proportional hazard regression model.

Abbreviations: APACHE: Acute Physiology and Chronic Health Evaluation; CHF: Congestive heart failure; CPIS: Clinical Pulmonary Infection Score; CPR: Cardiopulmonary resuscitation; HCAP: Health care-associated pneumonia; ICU: Intensive care unit; MRSA: methicillin-resistant *Staphylococcus aereus;* MV: Mechanical ventilation; LOS: Length of stay; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment score; TISS-28: Therapeutic Intervention Scoring System-28.

Supplemental Table 9. Summary outcome estimates for each included study

Study	Unadjusted OR, 95%CI*				Adjusted OR, 95%CI*			
	Hospital mortality	28-day mortality	1-year mortality	ICU mortality	Hospital mortality	28-day mortality	1-year mortality	ICU mortality
Adrie 2007	0.88 (0.71-1.10)	N/A	N/A	0.87 (0.69-1.09)	0.75 (0.57-0.97)	N/A	N/A	0.75 (0.58-0.98)
Caceres 2013	1.35 (0.81-2.26)	1.35 (0.81-2.26)	N/A	N/A	0.99 (0.52-1.93)	0.99 (0.52-1.93)	N/A	N/A
Dara 2012	0.95 (0.87-1.04)	N/A	N/A	N/A	1.07 (0.96-1.19)	N/A	N/A	N/A
Luethi 2010	N/A	N/A	N/A	1.14 (0.82-1.58)	N/A	N/A	N/A	<50y: 1.18 (0.47-2.86) >50y: 1.33 (0.90-1.96)
Madsen 2014	1.10 (0.80-1.52)	N/A	N/A	N/A	"Multivariable analysis…Gender was not associated with in-hospital survival"	N/A	N/A	N/A
Mahmood 2012	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.07 (0.99-1.16)
Nachtigall 2011	N/A	N/A	N/A	1.89 (1.06-3.36)	N/A	N/A	N/A	1.91 (1.00-3.64)
Pietropaoli 2010	1.09 (1.02-1.16)	N/A	N/A	1.09 (1.02-1.17)	1.11 (1.04-1.19)	N/A	N/A	N/A
Sakr 2013	N/A	"Kaplan-Meier analysis showed reduced 28-day survival in female compared with male patients"	N/A	2.01 (1.20-3.37)	N/A	N/A	N/A	2.23 (1.17-4.24)

Samuelsson 2015	N/A	N/A	N/A	N/A	N/A	1.17 (1.06-1.29)†	N/A	N/A
Sunden-Cullberg 2020	N/A	1.11 (0.91-1.36)	N/A	N/A	N/A	1.28 (1.00-1.64)	N/A	N/A
van Vught 2017‡	1.02 (0.81-1.27)	1.13 (0.90-1.43)	0.92 (0.74-1.13)	1.14 (0.89-1.45)	N/A	N/A	N/A	N/A
Xu 2019	0.89 (0.80-0.99)	0.91 (0.82-1.01)	0.84 (0.76-0.93)	N/A	N/A	N/A	0.83 (0.68-0.98)§	N/A

***** Prognostic effect reported as OR (95% CI).

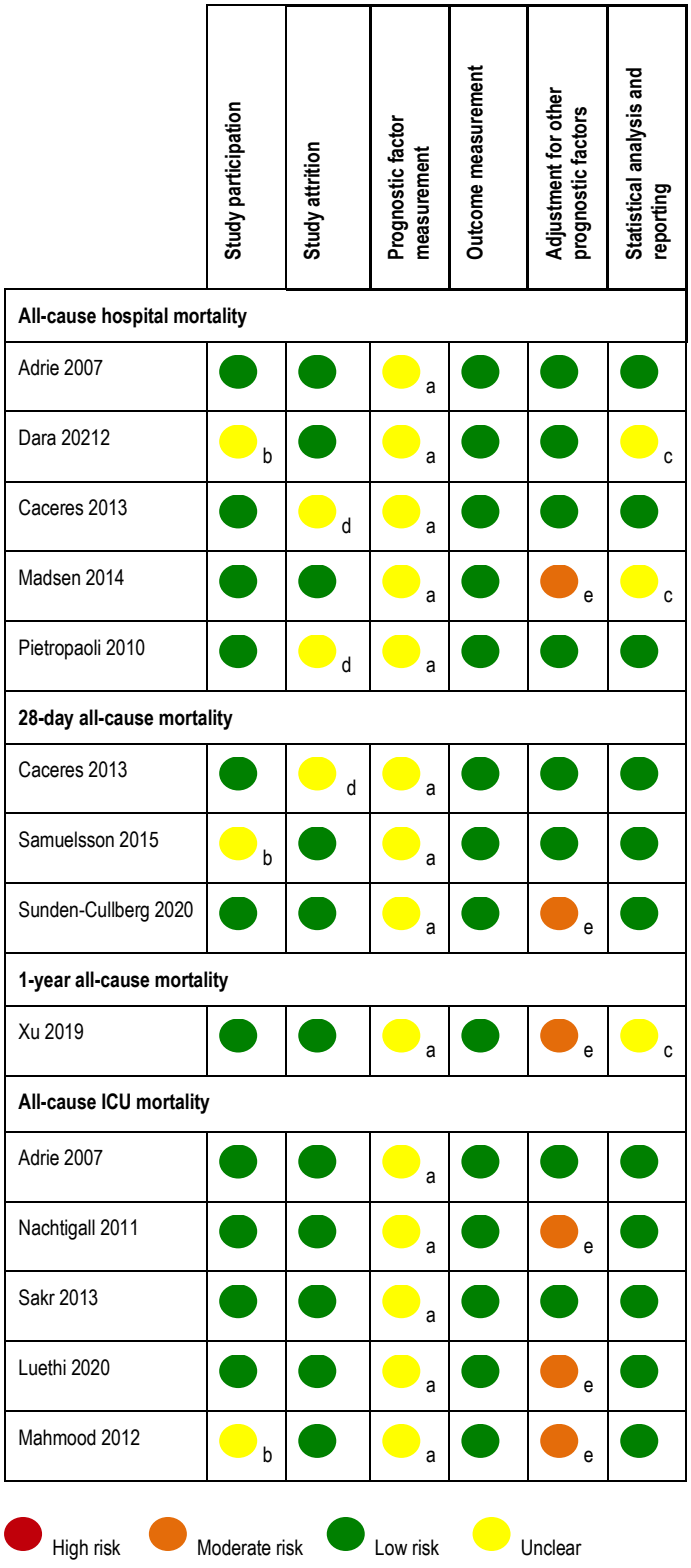
† Prognostic effect reported by the study authors as OR (99% CI), 1.17 (1.03- 1.33). We transformed it into OR (95% CI).

‡ van Vught 2017 reported adjusted analyses only for 90-day mortality.

§ Xu 2019 reported adjusted analyses using a Cox proportional hazard regression model as OR (95% CI), 1.08 (1.01-1.17), without additional clarifications. After contacting the study authors and no reply received, we assumed that they reported Cox analyses as hazard ratios (HR). We transformed HR into OR (95% CI)

Abbreviations: CI: Confidence interval; N/A: Not available; OR: Odds ratio; Y: Years old.

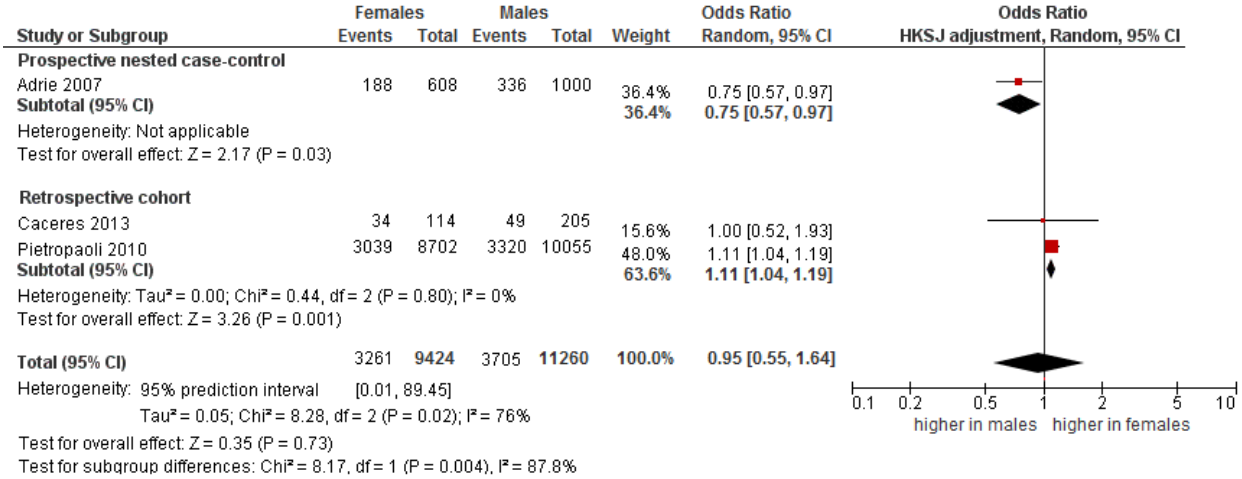
Supplemental Figure 1. QUIPS Risk of bias domain summary by outcome



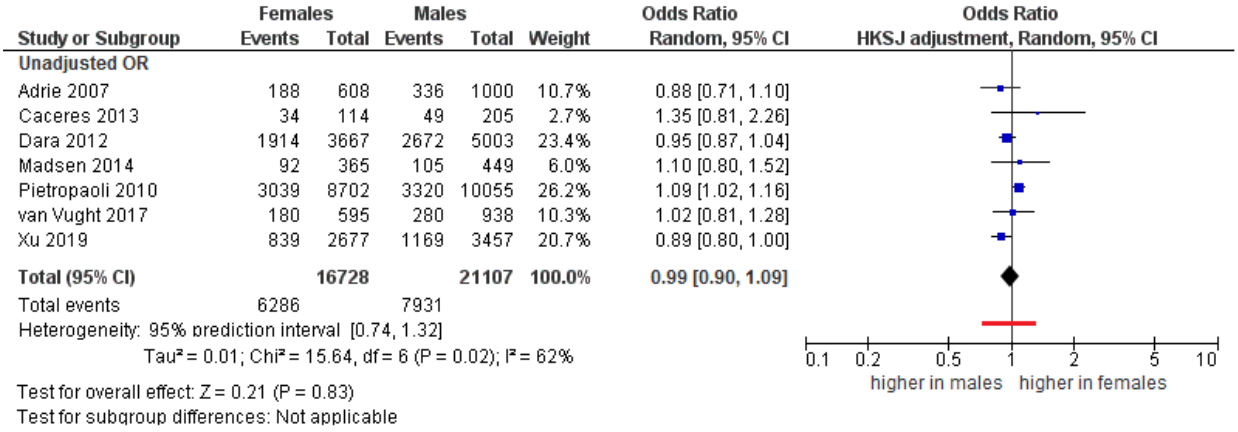
Explanations:

a. Unclear or not stated a definition of sex or gender.
b. Insufficient data on baseline description for sepsis subgroup.
c. Insufficient presentation of data to assess the adequacy of the analytic strategy.
d. Inadequate description of dropouts to judge the risk of important differences between participants analysed and those who were not.
e. Minimal adjustment for covariates as defined in our review core set of adjustment factors.

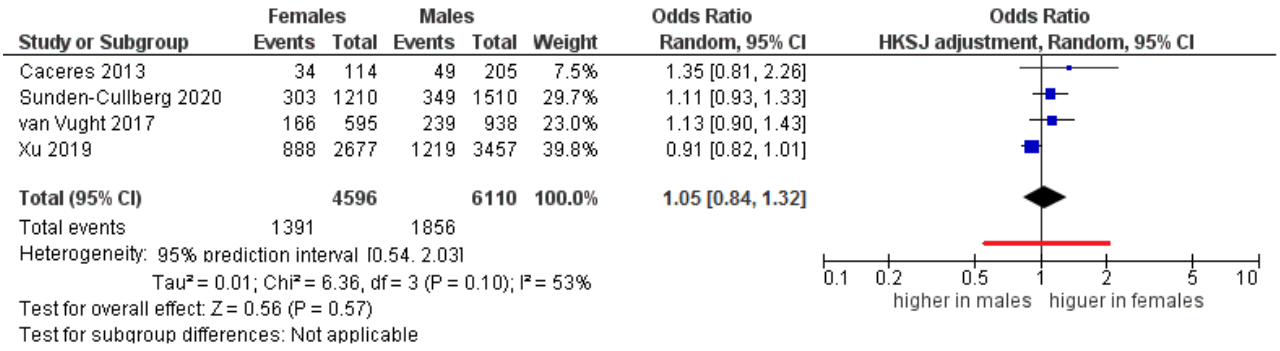
Supplemental Figure 2. Sensitivity analysis of adjusted analyses for association between sex and all-cause hospital mortality after excluding unique data from conference abstracts



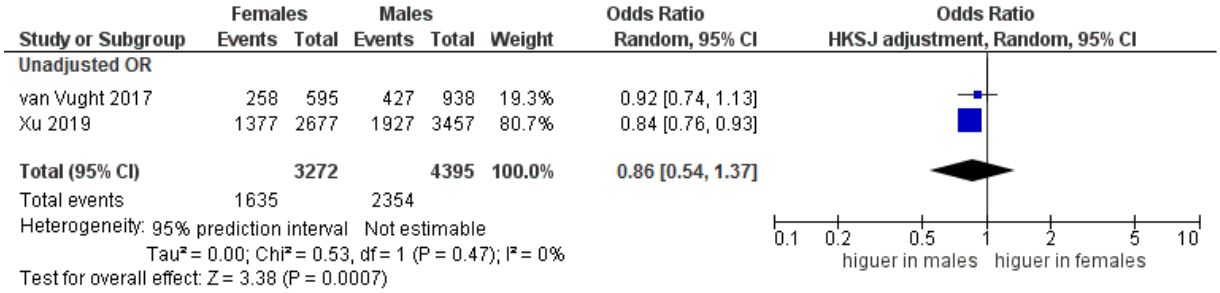
Supplemental Figure 3. Forest plot of unadjusted analyses for association between sex and all-cause hospital mortality



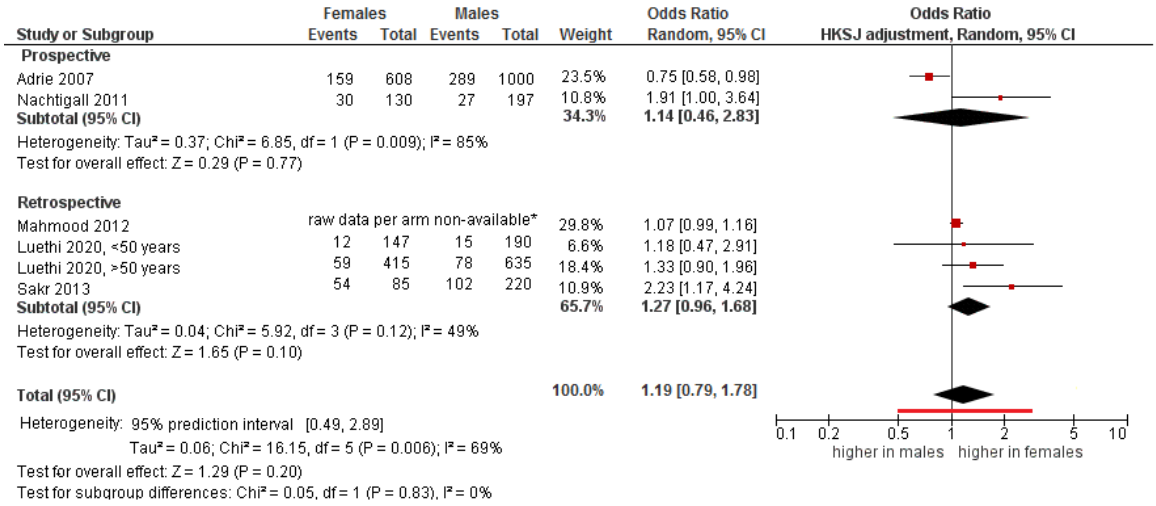
Supplemental Figure 4. Forest plot of unadjusted analyses for association between sex and 28-day all-cause mortality



Supplemental Figure 5. Forest plot of unadjusted analyses for association between sex and 1-year all-cause mortality

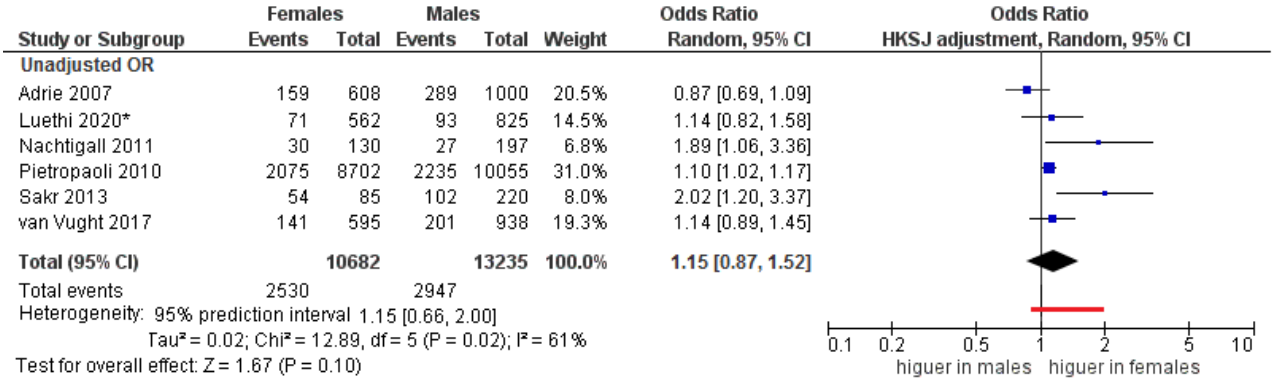


Supplemental Figure 6. Forest plot of adjusted analyses for association between sex and all-cause ICU mortality



* only provided the adjusted estimate

Supplemental Figure 7. Forest plot of unadjusted analyses for association between sex and all-cause ICU mortality



* Luethi 2020 reported an overall unadjusted odds ratio.

8.2. Supplementary material B. Additional studies

Fourth study

Omar Dewidar, Irina Podinic, Victoria Barbeau, Dilan Patel, Alba Antequera, David Birnie, et al. Sex and gender in studies of cardiac resynchronization therapy: a systematic review. ESC Heart Fail 2021, in press. doi.org/10.1016/j.jclinepi.2021.11.006.

Impact factor: 4.411 (2020 Journal Citation Reports®)

Abstract

Rationale: Cohort studies contribute to the understanding of sex differences in the effectiveness of cardiac resynchronization therapy (CRT) in heart failure patients as women are underrepresented in trials. Suboptimal reporting contributes to hindering the advances we take to understand these differences which may lead to under recognition of biological and social differences that affect health outcomes.

Objective: To examine the prevalence of sex considerations and temporal patterns in cohort studies assessing the effectiveness of CRT devices in heart failure patients.

Methods: We searched studies indexed in Medline, Embase and Web of Science from January 2000 to June 2020, regardless of their language. Heart failure and cohort study design filters were applied. Screening and extraction of studies was conducted in duplicate.

Results: Our search yielded 11909 studies and 7518 were screened after deduplication. Of those, 252 met our eligibility criteria and were assessed for sex considerations. Over half (62%) of the studies were published in Q1 ranked journals, but only 6 studies (2%) reported the use of STROBE guidelines. Sex was described mostly (33%) in the abstract of the studies. Almost half (48%) of the studies described the sex of study participants by male sex only. Only 14% of the studies considered sex in the study design and analysis plan. Outcome data disaggregated by sex was only reported in 42 studies (17%). Of the studies that had statistical models (n=173), 120 studies (69%) adjusted for sex. Over half (60%) of those studies reported an effect size. Temporal analysis displayed a change in the consideration of sex in statistical models, background, study design and knowledge translation.

Conclusions: Reporting shortcomings remain prevalent with missed opportunities to understand sex differences in the treatment of patients with heart failure. Further guidance needs to be developed to assist researchers in improving the completeness of reporting.

Fifth study

Antequera A, Cuadrado-Conde A, Roy-Vallejo E, Montoya-Martínez M, León-García M, Madrid-Pascual O, *et al*. Lack of sex-related reporting and analysis in Cochrane Reviews: a cross-sectional study. Manuscript submitted for publication 2020.

Abstract

Background: Sex-specific analysis and reporting may allow a better understanding of intervention effects and can support the decision-making process. Well-conducted systematic reviews (SRs), like those carried out by the Cochrane Collaboration, provide clinical responses transparently and stress gaps of knowledge. This study aimed to describe the extent to which sex is analysed and reported in a cross-section of Cochrane SRs of interventions, and assess the association with the gender of main authorships.

Methods: We searched SRs published during 2018 within the Cochrane Database of Systematic Reviews. An investigator appraised the sex-related analysis and reporting across sections of SRs and collected data on gender and country of affiliation of the review first and last authors, and a second checked for accuracy. We conducted descriptive statistics and bivariate logistic regression to explore the association between the gender of the authors and sex-related analysis and reporting.

Results: Six hundred and ten Cochrane SRs were identified. After removing those that met no eligibility criteria, 516 reviews of interventions were included. Fifty-six reviews included sex-related reporting in the abstract, 90 considered sex in their design, 380 provided sex-disaggregated descriptive data, 142 reported main outcomes or performed subgroup analyses by sex, and 76 discussed the potential impact of sex or the lack of such on the interpretations of findings. Women represented 53.1% and 42.2% of first and last authorships, respectively. Women authors (in first and last position) had a higher possibility to report sex in at least one of the review sections (OR 2.05; CI 95% 1.12- 3.75, P=0.041) than having none.

Conclusions: Sex consideration among Cochrane SRs was frequently missing. Structured guidance to sex-related analysis and reporting is needed to enhance the external validity of findings. Likewise, including gender diversity within the research workforce and relevant authorship positions may foster equity in the evidence generated.

Sixth study

Dewidar O, Tsang P, León-García M, Mathew C, Antequera A, Badeh T, et al. Over half of the WHO guidelines published from 2014 to 2019 explicitly considered health equity issues: A cross sectional survey. J Clin Epidemiol 2020;S0895-4356(20)30472-8. doi:10.1016/j.jclinepi.2020.07.012

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ELSEVIER

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Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Over half of the WHO guidelines published from 2014 to 2019 explicitly considered health equity issues: a cross-sectional survey

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Abstract

Objective: To evaluate how and to what extent health equity considerations are assessed in World Health Organization (WHO) guidelines.

Study Design and Setting: We evaluated WHO guidelines published between January 2014 and May 2019. Health equity considerations were assessed in relation to differences in baseline risk, importance of outcomes for socially disadvantaged populations, inclusion of health inequity as an outcome, equity-related subgroup analysis, and indirectness in each recommendation.

Results: We identified 111 WHO guidelines, and 54% (60 of 111) of these used the Evidence to Decision (EtD) framework. For the 60 guidelines using an EtD framework, the likely impact on health equity was supported by research evidence in 28% of the recommendations (94 of 332). Research evidence was mostly provided as differences in baseline risk (23%, 78/332). Research evidence less frequently addressed the importance of outcomes for socially disadvantaged populations (11%, 36/332), considered indirectness of the evidence for socially disadvantaged populations (2%, 5/332), considered health inequities as an outcome (2%, 5/332) and considered differences in the magnitude of effect in relative terms between disadvantaged and more advantaged populations (1%, 3/332).

Conclusion: The provision of research evidence to support equity judgements in WHO guidelines is still suboptimal, suggesting the need for better guidance and more training.

Keywords: WHO; Health equity; GRADE; Guidelines; Guideline development; Evidence to decision

Transparency declaration: The manuscript's guarantor (O.D.) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding: The authors received no financial support for the research or the publication of this article.

Ethics approval: Not required.

Competing interest statement: All authors have completed the ICMJE uniform disclosure format http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; Holger Schunemann is the co-chair of the GRADE working group and reports no financial conflict of interest, Peter Tugwell is the recipient of Canada Research Chair in Health Equity (Tier 1—2016 to 2024) from the Canadian Institutes of Health Research, Vivian Welch reports grants from World Health Organization, outside the submitted work; no other relationships or activities could have influenced this work.

Contribution: V.W., Peter Tugwell, E.A., P.C., K.P., and H.S. conceived the study. O.D., V.W., Philip Tsang, J.P., and T.P. developed the screening and data extraction forms. O.D., Philip Tsang, M.L., C.M., A.A., and T.B. screened the reviews and extracted data. O.D. conducted data quality check, analyzed the data, and wrote the first draft of the manuscript. V.W., Peter Tugwell, E.A., P.C., K.P., H.S., A.A., M.L., and T.P. suggested revisions to the manuscript. All authors approved the final version of the manuscript.

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Seventh study

Welch V, Dewidar O, Tanjong Ghogomu E, Abdisalam S, Al Ameer, Barbeau VI, *et al*. How effects on health equity are assessed in systematic reviews of interventions. Manuscript submitted for publication 2021.

Abstract

Background: Enhancing health equity is endorsed in the Sustainable Development Goals. The failure of systematic reviews to consider potential differences in effects across equity factors.effects is cited by decision-makers as a limitation to their ability to inform policy and program decisions.

Objectives: To explore what methods systematic reviewers use to consider health equity in systematic reviews of effectiveness.

Search methods: We searched the following databases up to February 26, 2021: MEDLINE, PsycINFO, the Cochrane Methodology Register, CINAHL, Education Resources Information Center, Education Abstracts, Criminal Justice Abstracts, Hein Index to Foreign Legal Periodicals, PAIS International, Social Services Abstracts, Sociological Abstracts, Digital Dissertations and the Health Technology Assessment Database. We searched SCOPUS to identify articles that cited any of the included studies on June 10, 2021. We contacted authors and searched the reference lists of included studies to identify additional potentially relevant studies.

Selection criteria: We included empirical studies of cohorts of systematic reviews that assessed methods for measuring effects on health inequalities. We define health inequalities as unfair and avoidable differences across socially stratifying factors that limit opportunities for health. We operationalize this by assessing studies which evaluated differences in health across any component of the PROGRESS-Plus acronym, which stands for Place of residence, Race/ethnicity/culture/language, Occupation, Gender or sex, Religion, Education, Socioeconomic status, Social capital. Plus stands for other factors associated with discrimination, exclusion, marginalization or vulnerability How effects on health equity are assessed in systematic reviews of interventions 20-Oct-2021 Review Manager 5.4.1 3 such as personal characteristics (e.g., age, disability), relationships that limit opportunities for health (e.g. children in a household with smoking parents) or environmental situations which provide limited control of opportunities for health (e.g., school food environment).

Data collection and analysis: Data were extracted using a pre-tested form by two independent reviewers. Risk of bias was appraised for included studies according to the potential for bias in selection and detection of systematic reviews.

Main results: A total of 48,814 studies were screened at title and abstract in duplicate. In this updated review, we identified an additional 124 methodological studies published in the 10 years since the first version of this review, which included 34 studies. Thus, 158 methodological studies met our criteria for inclusion. The methods used by these studies focused on evidence relevant to populations experiencing inequity (108 out of 158 studies), assess subgroup analysis across PROGRESS-Plus (26 out of 158 studies), assess analysis of a gradient in effect across PROGRESS-Plus (2 out of 158 studies) or use a combination of subgroup analysis and focused approaches (20 out of 158 studies). The most common PROGRESS-Plus factors assessed were age (43 studies), socioeconomic status in 35 studies, low and middle income countries in 24 studies, gender or sex in 22 out of 158 studies, race or ethnicity in 17 studies, and four studies assessed multiple factors across which health inequity may exist. Only sixteen studies provided a definition of health inequity. Five methodological approaches to consider health equity in systematic reviews of effectiveness were identified: 1) descriptive assessment of reporting and analysis in systematic reviews (151 of 158 studies used a type of descriptive method); 2) descriptive assessment of reporting and analysis in original trials (74 out of 158 studies); 3) analytic approaches which assessed differential effects across one or more PROGRESS-Plus factors (16/158 studies); and 4) applicability assessment (25/158 studies) and 5) stakeholder engagement. Reporting for both approaches (analytic and applicability) lacked transparency and was insufficiently detailed to enable the assessment of credibility.

A new finding in this update is the appraisal of whether relevant stakeholders with lived experience of health inequity were included in the design of systematic reviews or design and delivery of interventions, which was assessed by 28 out of 158 studies.

Authors' conclusions: There is a need for improvement in conceptual clarity about the definition of health equity, describing sufficient detail about analytic approaches (including subgroup analyses) and transparent reporting of judgments required for applicability assessments in order to consider health equity in systematic reviews of effectiveness.

Eighth publication

Antequera A, Lawson DO, Noorduyn SG, Dewidar O, Avey M, Bhutta ZA, Chamberlain C, et al. Improving social justice in COVID-19 health research. Interim reporting guidelines for observational studies. Int J Environ Res Public Health. 2021;18(17):9357. doi: 10.3390/ijerph18179357

Impact Factor: 3.390 (2020, Journal Citation Reports®)

Int. J. Environ. Res. Public Health **2021**, *18*, 9357. https://doi.org/10.3390/ijerph18179357

International Journal of *Environmental Research and Public Health*

MDPI

Article

Improving Social Justice in COVID-19 Health Research: Interim Guidelines for Reporting Health Equity in Observational Studies

Alba Antequera [1,*], Daeria O. Lawson [2], Stephen G. Noorduyn [2], Omar Dewidar [3], Marc Avey [4], Zulfiqar A. Bhutta [5,6], Catherine Chamberlain [7,8], Holly Ellingwood [9,10], Damian Francis [11], Sarah Funnell [12,13], Elizabeth Ghogomu [14], Regina Greer-Smith [15], Tanya Horsley [3,16], Clara Juando-Prats [17,18], Janet Jull [19], Elizabeth Kristjansson [20], Julian Little [3], Stuart G. Nicholls [21], Miriam Nkangu [3], Mark Petticrew [22], Gabriel Rada [23,24], Anita Rizvi [19], Larissa Shamseer [25], Melissa K. Sharp [26], Janice Tufte [27], Peter Tugwell [3,14,21], Francisca Verdugo-Paiva [23,24], Harry Wang [28], Xiaoqin Wang [29], Lawrence Mbuagbaw [2,†] and Vivian Welch [3,14,†]

Abstract: The COVID-19 pandemic has highlighted the global imperative to address health inequities. Observational studies are a valuable source of evidence for real-world effects and impacts of implementing COVID-19 policies on the redistribution of inequities. We assembled a diverse global multi-disciplinary team to develop interim guidance for improving transparency in reporting health equity in COVID-19 observational studies. We identified 14 areas in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist that need additional detail to encourage transparent reporting of health equity. We searched for examples of COVID-19 observational studies that analysed and reported health equity analysis across one or more social determinants of health. We engaged with Indigenous stakeholders and others groups experiencing health inequities to co-produce this guidance and to bring an intersectional lens. Taking health equity and social determinants of health into account contributes to the clinical and epidemiological understanding of the disease, identifying specific needs and supporting decision-making processes. Stakeholders are encouraged to consider using this guidance on observational research to help provide evidence to close the inequitable gaps in health outcomes.

Ninth publication

Stallings E, Antequera A, López-Alcalde J, García-Martín M, Urrútia G, Zamora J. Sex as a Prognostic Factor in Systematic Reviews: Challenges and Lessons Learned. J Pers Med. 2021;11(6):441. doi: 10.3390/jpm11060441.

Impact factor: 4.945 (2020 Journal Citation Reports®)

Journal of *Personalized Medicine*

MDPI

Article

Sex as a Prognostic Factor in Systematic Reviews: Challenges and Lessons Learned

Elena Stallings [1,2,*], Alba Antequera [3], Jesús López-Alcalde [1,2,4,5], Miguel García-Martín [2,6], Gerard Urrútia [2,3] and Javier Zamora [1,2,7]

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Abstract: Sex is a common baseline factor collected in studies that has the potential to be a prognostic factor (PF) in several clinical areas. In recent years, research on sex as a PF has increased; however, this influx of new studies frequently shows conflicting results across the same treatment or disease state. Thus, systematic reviews (SRs) addressing sex as a PF may help us to better understand diseases and further personalize healthcare. We wrote this article to offer insights into the challenges we encountered when conducting SRs on sex as a PF and suggestions on how to overcome these obstacles, regardless of the clinical domain. When carrying out a PF SR with sex as the index factor, it is important to keep in mind the modifications that must be made in various SR stages, such as modifying the PF section of CHARMS-PF, adjusting certain sections of QUIPS and extracting data on the sex and gender terms used throughout the studies. In this paper, we provide an overview of the lessons learned from carrying out our reviews on sex as a PF in different disciplines and now call on researchers, funding agencies and journals to realize the importance of studying sex as a PF.

Keywords: sex; gender; prognosis; prognostic factor; systematic review; methods

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1. Introduction

People are living longer, with one or more health problems; prognosis research is thus vital for explaining and predicting future clinical outcomes in people with existing health conditions. Prognosis research aims to summarize and predict relevant outcomes such as death, recovery, recurrence, disability, or quality of life. In the past 10 years, research on prognosis has rapidly increased [1–4] along with many novel studies and new methods being developed. However, results from different studies are often contradictory, making it difficult to assess a specific prognostic factor (PF). This is where systematic reviews come into play. Nevertheless systematic reviews of PFs have received little attention by scientists to date. In clinical medicine, we are starting to see a transition from a universal medicine that has a one-size-fits-all approach to personalized medicine. Personalized medicine is a unique individualized approach to treatment based on a patient's diagnosis and prognosis [5]. This intertwinement has led to theragnostics, which is the connection of diagnosis and therapeutics addressed to people on an individual basis [6]. This novel connection can provide better prognoses relying on specific features, i.e., PFs. Genetic information plays an important role in theragnostics and pharmacogenetics—which is the

Table S1. QUIPS modifications for studying sex as a prognostic factor

Domains	QUIPS	QUIPS modified for sex as PF	Comments
1. Study participation	Description of the baseline study sample	Baseline number and characteristics of participants by sex are clearly described and reported separately for males and females	The regular QUIPS refers to a description of the baseline sample in general (both sexes combined); however, we specified that it was necessary to have the participants characteristics described by sex. Example: Females (N): race of females (N), obesity in females (N). Males (N): race of males (N), obesity in males (N).
2. Study attrition	Adequate description of participants lost to follow-up	Key characteristics of participants lost to follow-up are provided separately for males and females	The key characteristics of the lost-to-follow-up participants must be recorded by sex. N of females and N of males per characteristic. However, this was never reported.
3. Prognostic factor measurement	a. Clear definition or description of the PF	Clear definition or description of sex	The authors must provide an adequate definition for the prognostic factor, in this case sex .
	b. Adequately valid and reliable method of measurement	Not applicable	We do not anticipate specific sex measurement for this type of research question.
	c. Continuous variables reported or appropriate cut points used	Not applicable	Sex measurement is not a continuous variable.
	d. Same method and setting of measurement used in all study participants	Not applicable	We do not anticipate method and setting measurement for this type of research question.
	e. Adequate proportion of the study sample had complete data	Not applicable	We do not anticipate missing data of sex measurement for this type of research question.
	f. Appropriate methods of imputation were used for missing data	Not applicable	We do not anticipate missing data of sex measurement for this type of research question.
4.Outcome measurement		No differences	
5. Adjustment for other prognostic factors		No differences	
6. Statistical analysis and reporting		No differences	

Abbreviations, QUIPS, quality in prognosis studies.
Adapted from Stalling 2021 [288].

8.3. Supplementary material C. AMSTAR-2 vs AMSTAR-2-PF

Table S1. Differences between AMSTAR-2 and AMSTAR-2.PF

AMSTAR-2 [267]	Responses to AMSTAR-2	Responses to AMSTAR-2-PF	Rationale
1. Did the research questions and inclusion criteria for the review include the components of PICO?	For Yes: ☐ Population ☐ Intervention ☐ Comparator group ☐ Outcome Optional (recommended) ☐ Timeframe for follow-up ☐ Yes ☐ No	For Yes: ☐ Population ☐ Index PF ☐ Comparator factor ☐ Outcome Optional (recommended) ☐ Timeframe for follow-up ☐ Setting ☐ Purpose of the study /phase (phase I confirmatory study vs phase 2 exploratory study) ☐ Yes ☐ No	Studies that address the review question on prognostic factor defined by the PICOTS (Population, Index prognostic factor, Comparator prognostic factors, Outcome, Timing, Setting) framework [164] and the phase of investigation [156]. Comparator be considered in a review in various ways: "to compare the prognostic ability of a certain index factor with two or more other (that is, comparator) PFs; or to review the adjusted prognostic value of a particular index factor" [164]
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?*	For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ a risk of bias assessment For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, and ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol ☐ Yes ☐ Partial Yes ☐ No	Idem	

AMSTAR-2 [267]	Responses to AMSTAR-2	Responses to AMSTAR-2-PF	Rationale
3. Did the review authors explain their selection of the study designs for inclusion in the review?	For Yes, the review should satisfy ONE of the following: □ Explanation for including only RCTs □ OR Explanation for including only NRSI □ OR Explanation for including both RCTs and NRSI □ Yes □ No	For Yes, the review should satisfy ONE or MORE of the following: □ Explanation for including only longitudinal studies (cohort studies) □ Explanation for including non-longitudinal observational case-control (only or in addition to longitudinal studies) □ Explanation for including cross-sectional studies (only or in addition to longitudinal studies) □ Explanation for including RCTs (only or in addition to longitudinal studies)	The best design to address prognostic questions is a cohort study. Other designs can be used, but a rational is required [145]
4. Did the review authors use a comprehensive literature search strategy?*	For Partial Yes (all the following): □ Searched at least 2 databases (relevant to research question) □ Provided key word and/or search strategy □ Justified publication restrictions (e.g., language) For Yes, should also have (all the following): □ Searched the reference lists/bibliographies of included studies □ Searched trial/study registries □ Included/consulted content experts in the field □Ssearched for grey literature □ Conducted search within 24 months of completion of the review □ Yes □ Partial Yes □ No	The following item is removed: □ Searched trial/study registries	The best design to address prognostic questions is a cohort study [145]
5. Did the review authors perform study selection in duplicate?	For Yes, either ONE of the following: □ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include □ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder selected by one reviewer □ Yes □ No	Idem	

AMSTAR-2 [267]	Responses to AMSTAR-2	Responses to AMSTAR-2-PF	Rationale
6. Did the review authors perform data extraction in duplicate?	For Yes, either ONE of the following: □ At least two reviewers achieved consensus on which data to extract from included studies □ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder extracted by one reviewer □ Yes □ No	Idem	
7. Did the review authors provide a list of excluded studies and justify the exclusions?*	For Partial Yes: □ Provided a list of all potentially relevant studies that were read in full text form but excluded from the review For Yes, must also have: □ Justified the exclusion from the review of each potentially relevant study □ Yes □ Partial Yes □ No	For Partial Yes: □ Provided a list of all potentially relevant studies that were read in full text form but excluded from the review □Pprovided aggregated reason for exclusion of studies that were read in full text form For Yes, must also have: □ Justified the exclusion from the review of each potentially relevant study read in full text, providing individual reasons for exclusion □ Yes □ Partial Yes □ No	Exclusion reasons are very relevant to inform the reader about the application of the eligibility criteria. As search strategy for prognostic factor reviews often retrieves a considerable number of records, to describe reasons for exclusion at the full-text stage is needed. However, it may be more informative for the reader to provide the aggregated exclusion reasons rather than providing raw data.
8. Did the review authors describe the included studies in adequate detail?	For Partial Yes (ALL the following): □ Described populations □ Described interventions □ Described comparators □ Described outcomes □ Described research designs For Yes, should also have ALL the following: □ Described population in detail (participant description, eligibility and recruitment methods, dates, details of treatment received if relevant) □ Described intervention and comparator in detail (including doses where relevant) □ Described study's setting □ Timeframe for follow-up □ Yes □ Partial Yes □ No	For Partial Yes (ALL the following): □ Described populations □ Described index PF □ Described comparator factors □ Described outcomes □ Described research designs For Yes, should also have ALL the following: □ Described population in detail (participant description, eligibility and recruitment methods, dates, details of treatment received if relevant) □ Described PF and comparator in detail □ Described study's setting □ Timeframe for follow-up □ Describe statistical analysis method and modelling □ Yes □ Partial Yes □ No	CHARMS-PF (checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies modified for reviews of prognostic factor studies) checklist of key items to be extracted from primary studies of prognostic factors [164]

AMSTAR-2 [267]	Responses to AMSTAR-2	Responses to AMSTAR-2-PF	Rationale
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?*	RCTs For Partial Yes, must have assessed RoB from □ Unconcealed allocation, and □ Lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality) For Yes, must also have assessed RoB from: □ Allocation sequence that was not truly random, and □ Selection of the reported result from among multiple measurements or analyses of a specified outcome □ Yes □ Partial Yes □ No □ Includes only NRSI NRSI For Partial Yes, must have assessed RoB: □ From confounding, and □ From selection bias, and For Yes, must also have assessed RoB: □ Methods used to ascertain exposures and outcomes, and □ Selection of the reported result from among multiple measurements or analyses of a specified outcome □ Yes □ Partial Yes □ No □ Includes only RCTs	Removed criteria for RCTs. NRSI For Partial Yes, must have assessed RoB: □ From confounding (i.e., adjustment for other prognostic factors), and □ From selection bias, and For Yes, must also have assessed RoB: □ methods used to ascertain exposures and outcomes, and □ From outcome measurement □ From study attrition, and □ Statistical analysis and reporting □ Yes □ Partial Yes □ No	QUIPS to assess risk of bias [164,175]
10. Did the review authors report on the sources of funding for the studies included in the review?	For Yes □ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies □ Yes □ No	Idem	
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?*	RCTs For Yes: □ The authors justified combining the data in a meta-analysis	Removed criteria for RCTs. For Yes: □ The authors justified combining the data in a meta-analysis □ AND they used an appropriate weighted technique to combine study results (random	If a meta-analysis is conducted, a random effects model is essential to allow for unexplained heterogeneity across studies [164]

	□ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present □ AND investigated the causes of any heterogeneity □ Yes □ No □ NMA For NRSI For Yes: □ The authors justified combining the data in a meta-analysis □ AND they used an appropriate weighted technique to combine study results adjusting for heterogeneity if present □ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available □ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review □ Yes □ No □ NMA	effects model), adjusting for heterogeneity if present □ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available □ Yes □ No □ NMA	
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	For Yes: □ Included only low risk of bias RCTs □ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect □ Yes □ No □ NMA	"RCTs" replaced by "studies". For Yes: □ Included only low risk of bias studies □ OR, if the pooled estimate was based on NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect □ Yes □ No □ NMA	
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?*	For Yes: □ Included only low risk of bias RCTs □ OR, if RCTs with moderate or high RoB, or NRSI were included, the review provided a discussion of the likely impact of RoB on the results □ Yes □ No	For Yes: □ Included only low risk of bias studies □ OR, if studies with moderate or high RoB were included, the review provided a discussion of the likely impact of RoB on the results □ OR the authors assessed the certainty of evidence with the GRADE system □ Yes □ No	The assessment of the certainty of the summary results using GRADE considers the impact of RoB on the certainty of evidence [214,222–227].

AMSTAR-2 [267]	Responses to AMSTAR-2	Responses to AMSTAR-2-PF	Rationale
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	For Yes: □ There was no significant heterogeneity in the results □ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review □ Yes □ No	For Yes: □ There was no significant heterogeneity in the results □ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review □ OR the authors assessed the certainty of evidence with the GRADE system □ Yes □ No	The assessment of the certainty of the summary results using GRADE considers the impact of heterogeneity (the inconsistency domain) on the certainty of evidence [214,222–227].
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?*	For Yes: □ Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias □ Yes □ No □ NMA	For Yes: □ Performed graphical or statistical tests for publication bias where appropriate, and discussed the likelihood and magnitude of impact of publication bias □ OR the authors assessed the certainty of evidence with the GRADE system □ Yes □ No □ NMA	The assessment of the certainty of the summary results using GRADE considers the impact of publication bias on the certainty of evidence [214,222–227].
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	For Yes: □ The authors reported no competing interests OR □ The authors described their funding sources and how they managed potential conflicts of interest □ Yes □ No	Idem	

Abbreviations: GRADE, grades of recommendation, assessment, development, and evaluation, PF, prognostic factor, QUIPS, quality in prognosis studies, RCT, randomised clinical trial, RoB, risk of bias, NMA, no meta-analysis conducted, NRSI, non-randomized studies

* AMSTAR 2 critical domains.

Rating overall confidence in the results of the review:

- High: No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
- Moderate: More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.
- Low: One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.
- Critically low: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

8.4. Supplementary material D. Other publications in which the candidate was co-author during the doctoral programme

Santero M, Pérez-Bracchiglione J, Acosta-Dighero R, Meade AG, Antequera A, Auladell-Rispau A, *et al*. Efficacy of systemic oncological treatments in patients with advanced esophageal or gastric cancers at high risk of dying in the middle and short term: an overview of systematic reviews. BMC Cancer 2021;21(1):712. doi: 10.1186/s12885-021-08330-5.

Salazar J, Pérez-Bracchiglione J, Salas-Gama K, Antequera A, Auladell-Rispau A, Dorantes-Romandía R, *et al*. Systemic treatments for advanced digestive cancer research. Efficacy of systemic oncological treatments in patients with advanced pancreatic cancer at high risk of dying in the short or medium-term: overview of systematic reviews. Eur J Cancer 2021;154:82-91. doi: 10.1016/j.ejca.2021.05.034.

Rodríguez-Grijalva G, Pérez-Bracchiglione J, Salas-Gama K, Antequera A, Auladell-Rispau A, Dorantes-Romandía R, *et al*. Systemic oncological treatments for patients with advanced hepatobiliary cancers at high risk of dying in the short and middle term: an overview of systematic reviews. Manuscript submitted for publication 2021.