SYSTEMATIC REVIEW

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Sex Differences in Pediatric Sepsis Mortality: A Systematic Review and Meta-Analysis

Uchenna K. Kennedy, MD[1]
Juliette Moulin[2]
Lea Bührer, MSc[3]
Joanne Lim Fang Nian[4]
Leyla Halter[2]
Luzius Böhni[2]
Melisa Güzelgün[2]
Kusum Menon, MD, MSc[5]
Jan Hau Lee, MBBS, MCI[6]
Luregn J. Schlapbach, MD, PhD, FCICM[2,7,8]
Ulrike Held, PhD[3]

OBJECTIVES: Pediatric sepsis remains a leading cause of childhood mortality worldwide. Sex differences have been shown to modify risk factors, treatment, and outcome of various diseases, and adult studies revealed sex differences in pathophysiological responses to septic shock. We aimed to perform a systematic review and meta-analysis on the association of sex with outcomes in hospitalized children with sepsis.

DATA SOURCES: Medline and Embase databases were searched for studies of children < 18 years with sepsis published between January 01, 2005, and March 31, 2022.

STUDY SELECTION: We included cohort studies, and randomized controlled trials in children greater than or equal to 37-week-old postconception to 18 years which included sepsis, severe sepsis or septic shock, and mortality as an outcome.

DATA EXTRACTION: Study characteristics, patient demographics, and illness severity scores were extracted from eligible articles. Random-effects meta-analysis was performed.

DATA SYNTHESIS: We screened 14,791 studies, with 912 full-text reviews and inclusion of 124 studies. The total population involved 426,163 patients, of which 47% (201,438) were girls. Meta-regression showed moderate evidence for a higher mortality in boys compared with girls. The estimated risk difference of mortality between boys and girls with all types of sepsis was −0.005 (95% CI, −0.0099 to −0.00001; $p = 0.049$), indicating slightly higher mortality for boys. When including the World Bank income level as a moderator, the effect was −0.008 (95% CI, −0.013 to −0.002; $p = 0.005$).

CONCLUSIONS: This large systematic review and meta-analysis on sex differences in pediatric sepsis mortality showed moderate evidence for a higher sepsis mortality in boys compared with girls. The effect persisted when adjusting for country's income level.

KEYWORDS: child; gender; infection; mortality; sex

Despite advances in modern medicine, sepsis remains a major contributor to childhood mortality and morbidity worldwide, with more than 3 million deaths annually (1–5). Population-based studies demonstrated differences in pediatric sepsis outcomes according to age groups, socioeconomic status, comorbidities, and pathogen, while the contribution of sex and gender as key biological and social determinants of health have been less focused on (1, 6–9). Sex is a biological categorization that relates to sexual anatomy, sex hormones, sex chromosomes, and sex-specific gene expression from autosomes (10, 11). Gender is a socially constructed definition, which encompasses cultural aspects, behaviors, and identities (12, 13). Sex and gender differences can affect outcomes through multiple mechanisms, such as differences in biological vulnerability, differences in biological response to treatment, or socioeconomic differences. The importance of including sex and gender as

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RESEARCH IN CONTEXT

- Pediatric sepsis is a leading cause of childhood morbidity and mortality worldwide.
- There is limited knowledge of sex differences in children with sepsis, even though sex and gender have been shown to influence risk factors and treatment outcomes of various diseases.
- This is a systematic review and meta-analysis of all pediatric sepsis literature published between January 01, 2005, and March 31, 2022, including over 14,000 abstracts and a study population of more than 420,000 patients.

determinants of health in clinical research has been increasingly recognized and guidelines on how to incorporate this into clinical research have been developed (Sex and Gender Equity in Research [SAGER] Guidelines) (14). In adults, studies revealed distinct differences in pathophysiological responses to septic shock when comparing male and female patients (15), including the response to corticosteroid treatment, as well as a possible protective effect of estrogens on critical illness (16, 17), which may translate to different risks of sepsis hospitalization, sepsis-related ICU admission, death, and readmission to hospital (18). Women with sepsis have been reported to receive less timely initiation of antibiotics (19, 20) and less vital organ support compared with men (21).

Despite known sex-specific differences in the immunological response and the maturation of host defenses across pediatric age groups (22), there is limited literature on the role of sex and gender in outcomes of sepsis in children (23, 24). To address this gap, we aimed to quantify the association of sex with hospital mortality in children with sepsis through a systematic review and meta-analysis.

METHODS

We performed a systematic literature review and meta-analysis of the association of sex with hospital mortality in children with sepsis. Even though most pediatric critical care studies use the terms sex and gender interchangeably, the majority of them refer to the biological variable, sex. In the pediatric sepsis literature, there is practically no reporting on "gender" specifically, as defined earlier. As it was not possible to determine on what basis sex was defined in individual studies (e.g., self-reporting or assigned following examination of external or internal body characteristics or by other means), we used the term "sex" to reflect the presented data and equated sex and gender for this work. To describe male and female study participants, we used the gender-affirming terminology "boy" and "girl" (25, 26). The study protocol including the search strategy was registered on PROSPERO (CRD42022315753) and has been published (27).

Search Strategy and Selection Criteria

The databases MEDLINE and Embase were searched for relevant studies published between January 01, 2005, and March 31, 2022, using the following search terms: "sepsis, severe sepsis, septic shock, child, pediatric, mortality" (**eFig. 1**, http://links.lww.com/CCX/B480). We chose this time frame due to the publication of the International Pediatric Sepsis Definition Consensus Conference statement in 2005 (28), which for the first time provided age-specific criteria for sepsis in children. Inclusion criteria for studies were: 1) prospective or retrospective cohort studies or randomized trials; 2) study population of children greater than or equal to 37 weeks post gestational age to less than 18 years; 3) study population with sepsis, severe sepsis or septic shock; and 4) primary study setting: hospitalized children.

Exclusion criteria were: 1) abstracts, case studies, narrative reviews, systematic reviews, and meta-analysis; 2) studies including adults, preterm infants, full-term neonates that never left the hospital or a study population including more than 20% neonates; 3) cohort studies with fewer than 20 children with sepsis, severe sepsis or septic shock; as smaller studies would not be adequately powered to detect a difference in outcome between the sexes; 4) primary study setting outpatient or neonatal ICU; 5) studies that do not mention mortality; 6) mortality not analyzed according to sex; 7) clearly overlapping study populations, determined by the reviewers during full-text screening; 8) article not available; and 9) article not in English or no English translation available.

Data Extraction

Each abstract and subsequently full text from the search were screened for eligibility using the systematic review platform Covidence (29) by two separate reviewers (U.K.K., J.M., J.L., L.B., M.G., L.H.). At each screening level, conflicts were resolved by discussion with a third reviewer (L.J.S.) (27). Data from the included full-text articles were extracted by two separate reviewers (J.M., J.L.) using a Research Electronic Data Capture platform (30) hosted at the Children's Hospital of Zurich, Switzerland. A third reviewer (U.K.K.) checked for errors and merged the data to create a single dataset. For some studies reporting odds ratios or risk differences for sex regarding mortality or for large sepsis studies that did not report mortality according to sex, authors were contacted to provide the missing raw data.

To assess the quality of the articles, we used the first four domains of the "Quality In Prognosis Studies" tool for each study (31). The final two domains relate to confounding factors and statistical analysis, which were not relevant to the unadjusted data in our meta-analysis. Risk of bias assessment was reported as "low risk," "intermediate risk," or "high risk" (**eFig. 2**, http://links.lww.com/CCX/B480). The following parameters were extracted and further analyzed: on a study level, we analyzed demographic data including sample size, study region, income level of the study site according to according to the World Bank classification of 2019–2020 (32) and year of publication. With regards to the study population, we collected demographic data (ethnicity), data on sepsis severity (sepsis, severe sepsis, septic shock as defined by respective study authors), comorbidities, type of infection, sepsis severity scores (Pediatric Index of Mortality, Pediatric Risk of Mortality, pediatric Sequential Organ Failure Assessment score, Pediatric Logistic Organ Dysfunction Score), and age/age categories of the study population.

Outcomes

The primary outcome was all-cause hospital mortality. Hospital mortality was reported as 28- or 30-day mortality, ICU mortality, in-hospital or unspecified mortality. For our analysis, we included all forms of mortality that were reported (**eTable 1**, http://links.lww.com/CCX/B480). The effect measure was the risk difference in hospital mortality, measured as risk of girls minus risk of boys for all analyses. Negative risk differences indicated higher hospital mortality in boys as compared with girls. The risk difference was reported together with its 95% CI.

Data Analysis

We analyzed the data using the R programming language (33) in combination with dynamic reporting with knitr (34) following a fully scripted approach for reproducibility. For descriptive statistics, we reported frequencies with percentages for all categorical variables. For the meta-analysis, a random-effects model was assumed due to the anticipated large between-study heterogeneity among the individual studies. Study-specific results and pooled estimates were visualized using forest plots. We used meta-regression for specific questions, treating certain variables (age, main site study region, World Bank income classification) as moderators, and exploring their associations with sepsis-related deaths. We assessed statistical heterogeneity of the random-effects model using the parameter τ^2 estimated with the restricted maximum likelihood method and with the DerSimonian–Laird method (35) in a sensitivity analysis. Additionally, I^2 and χ^2 statistics were calculated, and CIs, as well as prediction intervals, both at 95% level were reported (36). Funnel plots were used for the assessment of publication bias.

RESULTS

Our literature search resulted in 14,791 publications of which 917 underwent full-text review. Of these, 793 were excluded, leaving 124 studies included in our meta-analysis (**Fig. 1**) (8, 23, 37–157). Study demographics and patient characteristics of included studies are shown in **Table 1** and **eTable 2** (http://links.lww.com/CCX/B480). The setting for most studies was a PICU ($n = 112$), followed by the general ward ($n = 14$). Nine studies included both settings. The total studied population involved 426,163 patients, of whom 201,438 (47%) were girls and 224,719 (53%) were boys. A total of 408,809 patients (96%) were from high-income countries (32). A total of 21,846 patients (9,711 girls and 12,135 boys) had severe sepsis and 9,412 patients (4,465 girls and 4,947 boys) had septic shock (Fig. 1). Overall mortality across all included studies was 10.6% (44,988 deaths) with a mortality of 10.3% (20,684 deaths) in the female population and a mortality of 10.8% (24,304 deaths) in the male population.

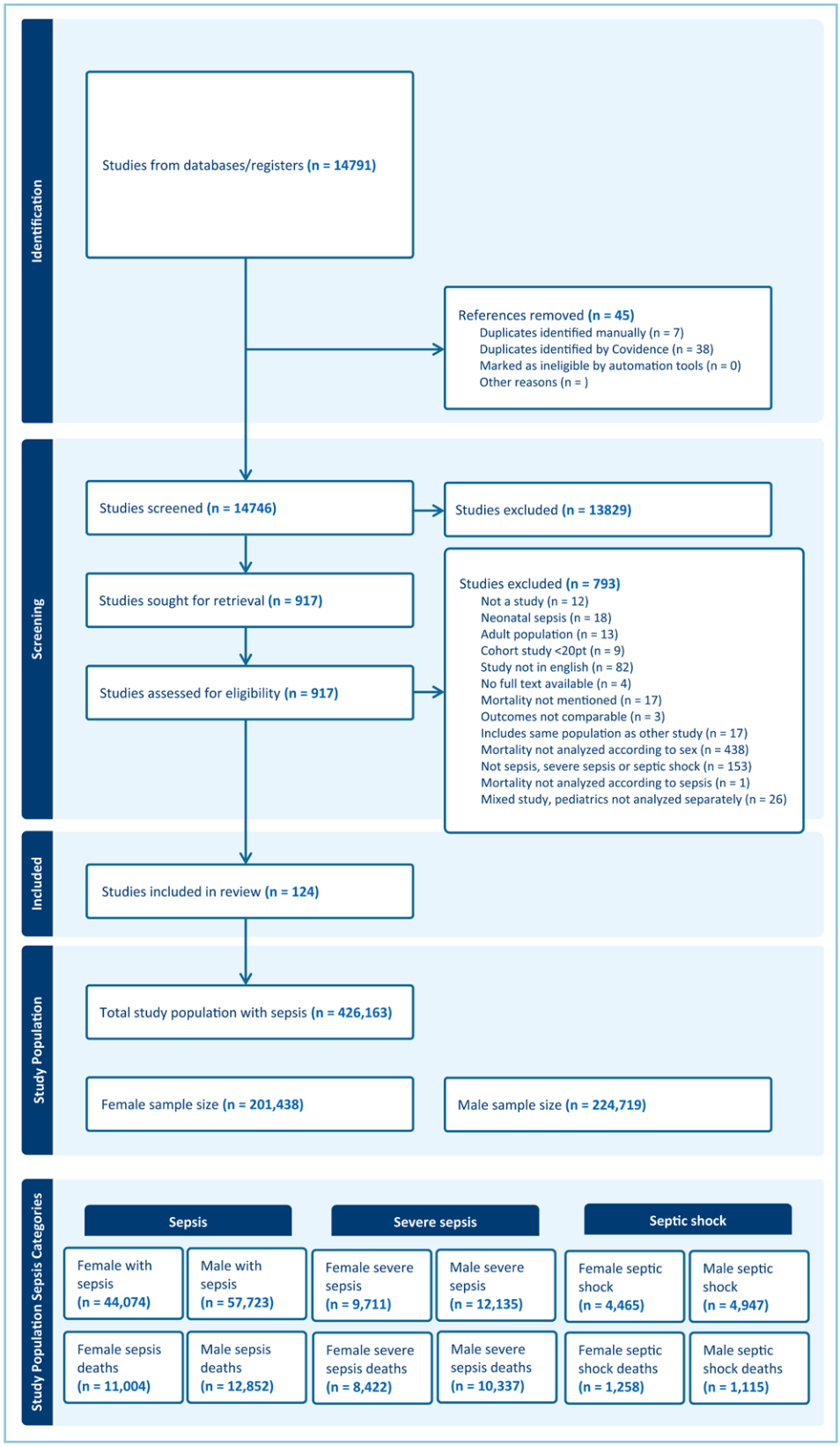

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart with illustration of the patient collectives used in the meta-analysis.

The meta-analysis to estimate the pooled risk difference of sepsis mortality between girls and boys showed moderate evidence for a higher mortality in boys compared with girls. Specifically, the estimated risk difference of mortality between boys and girls with all types of sepsis was −0.005 (95% CI, −0.0099 to −0.00001, 95% prediction interval −0.024 to 0.014; $p = 0.049$).

Mortality across all sepsis categories was analyzed and is shown as forest plot in **Figure 2**, which only includes studies with a sample size of more than 1000 patients. **eFigure 3** (http://links.lww.com/CCX/B480) illustrates the corresponding funnel plot. In the studies with a sample size above 1000 patients, the risk difference was −0.0063 (95% CI, −0.0115 to −0.0010, 95% prediction interval −0.024 to 0.011; $p = 0.02$). In the subgroups of sepsis, severe sepsis and septic shock, the risk difference was −0.0060, (95% CI, −0.0103 to −0.0018, 95% prediction interval −0.0159 to 0.0038; $p = 0.005$), −0.0036 (95% CI, −0.0264 to 0.0192, 95% prediction interval, −0.048 to 0.040, $p = 0.76$), and −0.0130 (95% CI, −0.1047 to 0.0787, 95% prediction interval, −0.333 to 0.307; $p = 0.78$), respectively (**eFigs. 4–7**, http://links.lww.com/CCX/B480). Only 79 studies could be included in this subgroup analysis, as the remaining studies included multiple subgroups without providing exact numbers for these subgroups.

TABLE 1.
Study Characteristics Including Main Site Location, Study Design, and Patient Characteristics

Demographic Data	Studies in the Meta-Analysis (Total *n* = 124), *n* (%)	Patients in the Meta-Analysis (Total *n* = 426,163), *n* (%)
Main site location		
Africa	3 (2.4)	2,087 (0.5)
America: Central/South	19 (15.3)	5,086 (1.2)
America: North	21 (16.9)	298,052 (69.9)
Asia: East	20 (16.1)	3,676 (0.9)
Asia: Rest	28 (22.6)	3,691 (0.9)
Europe	18 (14.5)	112,161 (26.3)
Middle East	15 (12.1)	1,410 (0.3)
Study design		
Case–control	3 (2.4)	321 (0.1)
Other	4 (3.2)	505 (0.1)
Prospective cohort	59 (47.6)	28,170 (6.6)
Randomized controlled trial	2 (1.6)	99 (< 0.1)
Retrospective cohort	56 (45.2)	397,068 (93.2)
Patient characteristics		
Comorbidities		
Cardiovascular	28 (22.9)	16,867 (4.0)
Respiratory	23 (18.5)	5,665 (1.3)
Gastrointestinal (including hepatic)	22 (17.7)	4,454 (1.0)
Renal/urologic	20 (16.1)	15,827 (3.7)
Neurologic/neuromuscular	31 (25.0)	33,452 (7.8)
Endocrinologic	4 (3.2)	45 (0,01)
Hematologic/immunologic	10 (8.1)	10,226 (2.4)
Immunologic	16 (12.9)	3,232 (0.8)
Hematologic: non-specified	3 (2.4)	59 (0.01)
Metabolic	13 (10.5)	10,181 (2.4)
Oncology	39 (31.5)	26,782 (6.3)
Congenital or genetic	21 (16.9)	587 (0.1)
All transplants	2 (1.6)	5,400 (1.3)
Solid organ transplant	6 (4.8)	878 (0.2)
Bone marrow transplant	6 (4.8)	1,143 (0.3)
Surgical	6 (4.8)	178 (0.04)
Burn patients	2 (1.6)	589 (0.1)
Any chronic complex condition	9 (7.3)	18,709 (4.4)
Scoring systems		
Pediatric Index of Mortality II	18 (14.5)	6,334 (1.5)
Pediatric Risk of Mortality	30 (24.2)	6,586 (1.5)
Pediatric Sequential Organ Failure Assessment score	6 (4.8)	819 (0.2)
Pediatric Logistic Organ Dysfunction Score	17 (13.7)	3,734 (0.9)

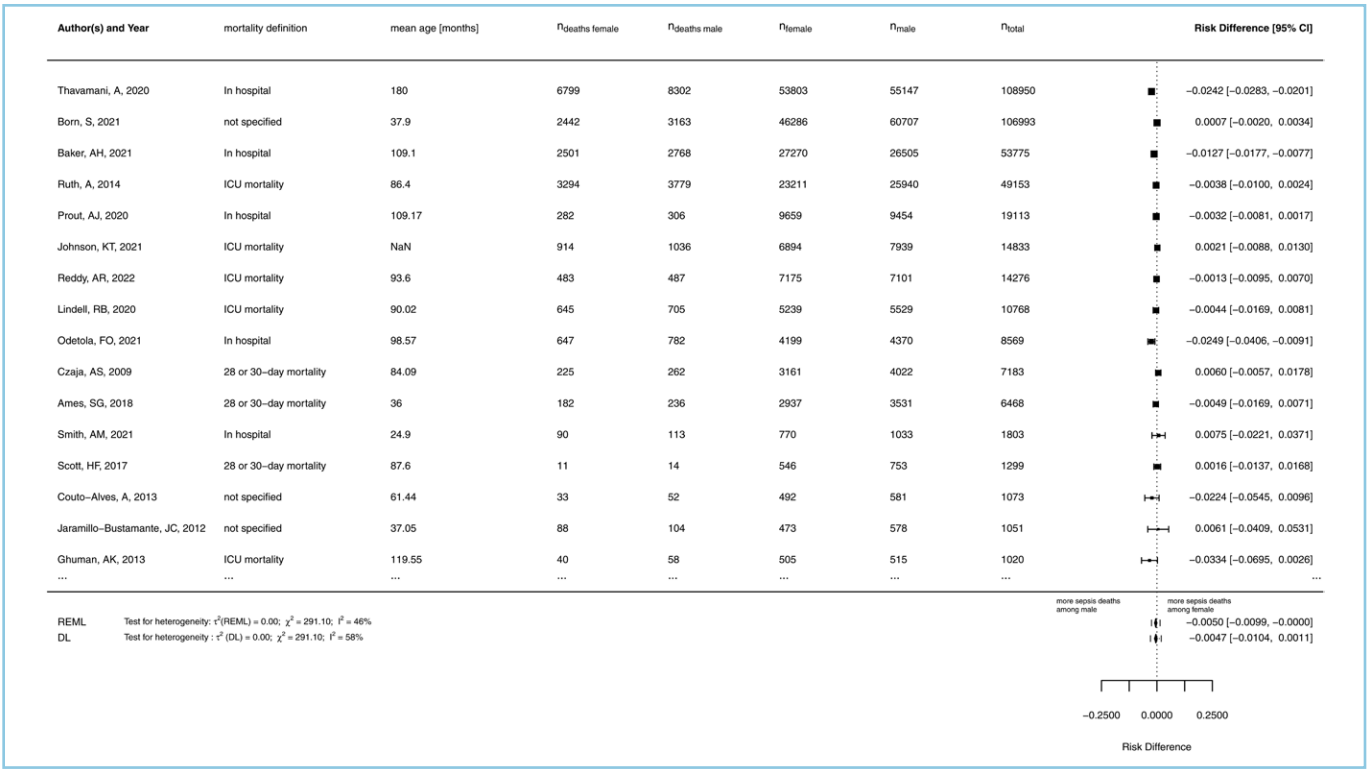

Figure 2. Forest plot of mortality of all sepsis types for all studies with more than 1,000 patients. In this plot, the estimate and heterogeneity parameters for the overall effect correspond to the evaluation of all 124 studies. For visualization purposes, the forest plot is additionally divided into subgroups regarding sample size: up to 50, > 50 to < 100, ≥ 100 to < 200, 200 to < 500, and 500 and more (see **Supplementary Material**, http://links.lww.com/CCX/B480). DL = DerSimonian-Laird method, REML = restricted maximum likelihood method.

An analysis addressing sepsis mortality according to publication year showed no evidence of a moderating effect of time on sex-specific mortality (**eFig. 8**, http://links.lww.com/CCX/B480). Data on type of infection, comorbidities, extracorporeal membrane oxygenation (ECMO), mechanical ventilation, renal replacement therapy, sepsis severity scores, and PICU length of stay were not reported by sex and could therefore not be analyzed.

We performed additional meta-regression analyses with World Bank income classification, age, and study region as moderators. The effect on the primary outcome when including the income level of the country as moderator in meta-regression was −0.008 (95% CI, −0.013 to −0.002, 95% prediction interval −0.027 to 0.011; p = 0.005) (**Fig. 3**; and **eTable 3**, http://links.lww.com/CCX/B480).

We found no evidence that age affected sex-specific sepsis mortality (**Fig. 4**; and **eFig. 9**, http://links.lww.com/CCX/B480) when analyzing results overall and on a study level. In a meta-regression fitted to adjust for main site location per study (**eTables 4** and **5**, http://links.lww.com/CCX/B480), no association between study region and risk for sepsis deaths could be found.

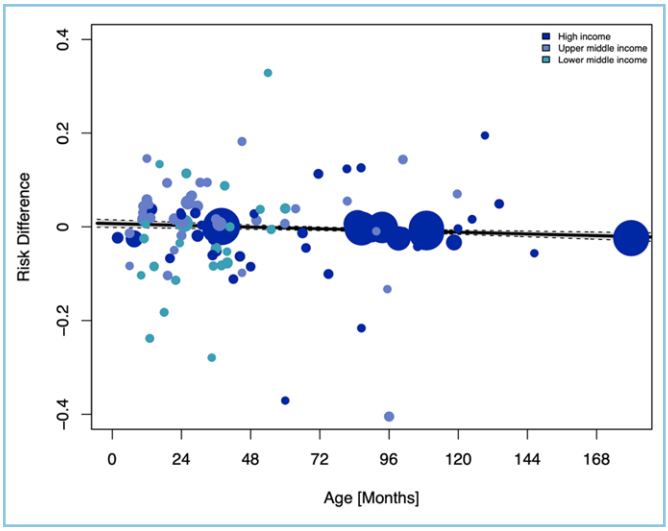

Figure 3. Mortality risk difference of girls vs. boys for age per income level. The estimated total risk difference is printed in *black*, the corresponding 95% CI in *gray*. A negative risk difference indicates higher mortality risk in males.

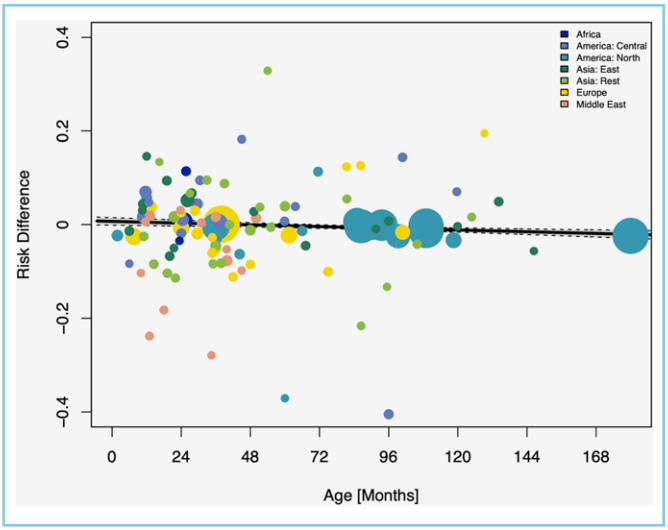

Figure 4. Mortality risk difference of girls vs. boys for age per study by main site location.

WHAT THIS STUDY MEANS

- This study is the first systematic review on sex differences in pediatric sepsis mortality including the entire published literature since publication of the Pediatric Sepsis Consensus Statement in 2005.
- Our study revealed moderate evidence for a higher mortality in boys compared with girls.
- This knowledge serves as foundation for studying outcomes in the pediatric sepsis literature including sex differences as important determinants of health.

DISCUSSION

In this systematic review and meta-analysis on the association of sex with mortality in sepsis in children, a total of 124 studies including over 400,000 patients across all continents were included with a predominance of ICU studies. The evidence synthesis showed moderate evidence for a higher sepsis mortality in boys compared with girls. This effect was confirmed when including the income level of the country as a moderator.

To the best of our knowledge, this is the first meta-analysis on sex differences in pediatric sepsis mortality. In recent years, there has been increasing interest to examine social determinants of health and their impact on health and well-being. These might be even more relevant in the particularly vulnerable pediatric population. Sex differences may modify disease associations at multiple levels such as biological mechanisms, differences in response to treatment, or gender-related and socioeconomic factors. For sepsis and sepsis mortality, there are well-known biological and socioeconomic risk factors, such as age, region, and income level of the country, which were included as moderators in this review (4, 6).

From a biological perspective, males appear to have a higher susceptibility for many pathogens, which could be explained by a stronger CD4+ T-cell response in females (22, 158). This translated into a higher neonatal mortality and worse clinical long-term outcomes and survival in male neonates compared with females (159, 160).

Our main finding of a slightly higher sepsis mortality in boys corresponds to previous pediatric studies, in which boys were shown to have increased susceptibility to infections and to severe infections during early childhood (161). When looking at the full-text studies included in our review, most larger studies with study populations > 1000 showed a slight tendency for a higher sepsis mortality in boys. Overall, the effect size is small but consistent across the main sepsis group, the severe sepsis, and septic shock groups; however, the threshold for statistical significance was not met in the smaller subgroups. The sepsis group makes up for the majority of the studied population.

However, a recently published study evaluating sex differences in mortality in 389 children with septic shock did not reveal a mortality difference between the sexes (162). This difference as compared with our findings might be explained by the smaller cohort size.

A recent systematic review analyzing sex differences in overall PICU mortality showed that males were more likely to be admitted to the PICU, whereas overall female mortality was higher (163). However, when identifying the studies evaluating sex-specific differences in the pediatric sepsis population, these showed a higher male mortality, corresponding to the results of our review (23, 95).

The adult literature on this topic shows conflicting results: Several studies reported a higher risk for sepsis hospitalization, sepsis-related ICU admission, death, and readmission to hospital within 1 year after a sepsis hospitalization in adult men (18). A multicenter cohort

study involving more than 2000 patients observed a higher 30-day mortality in men with sepsis (17), which is in line with our findings. However, a recent meta-analysis involving 130,000 patients across 89 studies showed women to be at higher risk of death from Staphylococcal infections (164). It remains unclear if these differences correspond to true biological differences or rather reflect the effect of sociodemographic factors (165).

In order to increase knowledge and understanding in the field of pediatric sepsis, more in-depth studies on the host response in sepsis by sex and their interaction with other disease-modifying factors are needed. Underreporting of social determinants of health in the field of pediatric sepsis has been shown to be an issue in understanding the role these factors play in sepsis development and severity (166). Thus, larger datasets with more specific reporting of social determinants of health, including sex and gender, will lead to an improved understanding of pediatric sepsis and a more individualized diagnostic and therapeutic approach.

An important limitation of our study is the over-representation of high-income countries in included studies. Patients from high-income countries, such as Europe, North America, and Australia made up for 96% of the studied population and therefore our results might not be generalizable to upper- and lower-middle income (UMIC and LMIC) and lower-income countries (LIC) on which a scarcity of high-quality epidemiological data on sepsis persists. As 85% of sepsis cases and deaths worldwide involve LIC, LMIC, and UMIC settings (4), this search result is strikingly disproportional to the global epidemiology and reflects the over-representation of literature from high-income countries with a predominance of ICU settings.

Our study has several additional limitations: We excluded studies that were not in English, which may have led to underrepresentation of certain study regions. Sepsis coding might be inaccurate and we were unable to confirm the correct coding of sepsis categories within papers. As this review is not based on an individual data analysis, we cannot rule out that certain patients were included multiple times in our analysis due to overlapping datasets.

As many studies did not report on sex-specific outcomes, this led to the exclusion of a considerable proportion of pediatric sepsis studies which might have biased the effect estimate. Finally, while the review included publications following the release of the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) definitions, these eminence-based criteria have been shown to be inconsistently applied (167), and the recently published data-driven Phoenix criteria for sepsis in children were not yet available. It should also be noted that studies published within the first year after publication of the 2005 IPSCC criteria might not have used this definition yet. In addition to the challenges of applying the 2005 IPSCC criteria robustly across studies, there is increasing recognition of the heterogeneity of sepsis as a syndrome (165). Future studies should investigate whether gender-specific information may help identifying treatable traits in this population.

CONCLUSIONS

In conclusion, this large systematic review and meta-analysis studying the association of sex with pediatric sepsis mortality showed moderate evidence for a higher pediatric sepsis mortality in boys compared to girls. Our review provides an important foundation for studying outcomes in the pediatric sepsis literature with the inclusion of social determinants of health. This will pave the way for a more individualized approach to research in this field.

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1 *Children's Research Center, Division of Pediatric Urology, Department of Pediatric Surgery, University Children's Hospital Zurich, Zurich, Switzerland.*

2 *Faculty of Medicine, University of Zurich, Zurich, Switzerland.*

3 *Department of Biostatistics at Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland.*

4 *Faculty of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Queenstown, Singapore.*

5 *Department of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada.*

6 *Children's Intensive Care Unit, Department of Intensive Care, KK Women's and Children's Hospital, Duke National University Singapore, Singapore, Singapore.*

7 *Department of Intensive Care and Neonatology, and Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland.*

8 *Child Health Research Centre, The University of Queensland, Brisbane, QLD, Australia.*

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Dr. Kennedy, project lead, was involved in data collection and extraction, preparation and revision of the article. Ms. Moulin was involved in equal contribution as UK to data collection and extraction, and preparation of the article. Ms. Bührer, co-author, was involved in statistical analysis and interpretation; and article revision. Prof. Schlapbach, co-author, was involved as supervisor of the project, supervision of data collection and extraction, and article revision. Dr. Menon, co-author, was involved as supervisor of the project, systematic review expertise, conceptual advice, and article revision. Assoc. Prof. Lee, co-author, was involved in conceptual advice and article revision. Ms. Lim Fang Nian, co-author, was involved in abstract and full-text screening. Ms. Halter, co-author, was involved in abstract screening. Mr. Böhni, co-author, was involved in abstract screening. Ms. Güzelgün, co-author, was involved in abstract screening. Prof. Held, last author, was involved in statistical expertise and article revision.

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Drs. Kennedy and Moulin are first co-authors and contributed equally.

For information regarding this article, E-mail: uchenna.kennedy@kispi.uzh.ch

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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