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Impact of neonatal sepsis on neurocognitive outcomes: a systematic review and meta-analysis

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Abstract

Introduction Sepsis is associated with neurocognitive impairment among preterm neonates but less is known about term neonates with sepsis. This systematic review and meta-analysis aims to provide an update of neurocognitive outcomes including cognitive delay, visual impairment, auditory impairment, and cerebral palsy, among neonates with sepsis.

Methods We performed a systematic review of PubMed, Embase, CENTRAL and Web of Science for eligible studies published between January 2011 and March 2023. We included case–control, cohort studies and cross-sectional studies. Case reports and articles not in English language were excluded. Using the adjusted estimates, we performed random effects model meta-analysis to evaluate the risk of developing neurocognitive impairment among neonates with sepsis.

Results Of 7,909 studies, 24 studies ($n=121,645$) were included. Majority of studies were conducted in the United States ($n=7$, 29.2%), and all studies were performed among neonates. 17 (70.8%) studies provided follow-up till 30 months. Sepsis was associated with increased risk of cognitive delay [adjusted odds ratio, aOR 1.14 (95% CI: 1.01—1.28)], visual impairment [aOR 2.57 (95%CI: 1.14- 5.82)], hearing impairment [aOR 1.70 (95% CI: 1.02–2.81)] and cerebral palsy [aOR 2.48 (95% CI: 1.03–5.99)].

Conclusion Neonates surviving sepsis are at a higher risk of poorer neurodevelopment. Current evidence is limited by significant heterogeneity across studies, lack of data related to long-term neurodevelopmental outcomes and term infants.

Keywords Sepsis, Neonatal sepsis, Infantile sepsis, Neurocognitive outcomes, Systematic review

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Introduction

Sepsis is a major cause of mortality and morbidity among neonates [1–4]. Young infants especially neonates, defined by age < 28 days old, have a relatively immature immune system and are susceptible to sepsis [5, 6]. Annually, there are an estimated 1.3 to 3.9 million cases of infantile sepsis worldwide and up to 700,000 deaths [7]. Low-income and middle-income countries bear a disproportionate burden of neonatal sepsis cases and deaths [7, 8]. While advances in medical care over the past decade have reduced mortality, neonates who survive sepsis are at risk of developing neurocognitive complications, which affect the quality of life for these children and their caregivers [9].

Previous reviews evaluating neurocognitive outcomes in neonates with infections or sepsis have focused on specific types of pathogens (e.g., Group B streptococcus or nosocomial infections [10]), or are limited to specific populations such as very low birth weight or very preterm neonates [11], and there remains paucity of data regarding neurocognitive outcomes among term and post-term neonates. There remains a gap for an updated comprehensive review which is not limited by type of pathogen or gestation. In this systematic review, we aim to provide a comprehensive update to the current literature on the association between sepsis and the following adverse neurocognitive outcomes (1) mental and psychomotor delay (cognitive delay (CD)), (2) visual impairment, (3) auditory impairment and (4) cerebral palsy (CP) among neonates [11].

Methods

We performed a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [12]. This study protocol was registered with Open Science Framework (https://doi.org/10.17605/OSF.IO/B54SE).

Eligibility criteria

We identified studies which evaluated neurocognitive outcomes in neonates less than 90 days old (regardless of gestational age) with sepsis. While the neonatal period is traditionally defined to be either the first 28 days postnatally for term and post-term infants, or 27 days after the expected date of delivery for preterm infants [13], serious late onset infections in the young infant population can present beyond the neonatal period [14], hence we defined the upper age limit as 90 days old to obtain a more complete picture of the burden of young infantile sepsis [15]. Post-term neonates was defined as a neonate delivered at > = 42 weeks of gestational age in this study [16]. We included studies that either follow international sepsis definitions such as Surviving Sepsis Campaign guidelines definitions [17], or if they fulfilled clinical, microbiological and/or biochemical criteria for sepsis as defined by study authors. The primary outcome of interest was impaired neurocognitive outcome defined by the following domains of neurodevelopmental impairment (NDI) [11]: (1) CD, (2) visual impairment, (3) auditory impairment and (4) CP. We selected these domains because they were highlighted as key neurocognitive sequelae after intrauterine insults in a landmark review by Mwaniki et al. [18]. The authors' definitions of these outcomes and their assessment tools were captured, including the use of common validated instruments (e.g., a common scale used for CD is the Bayley Scales of Infant Development (BSID) [19] while a common instrument used for CP was the Gross Motor Function Classification System (GMFCS) [20]. Specifically for BSID, its two summative indices score – Mental Development Index (MDI) and Psychomotor Development Index (PDI) were collected. The MDI assesses both the non-verbal cognitive and language skills, while PDI assess the combination of fine and gross motor skills. The cut-off points for mild, moderate and severe delay for MDI and PDI were < 85 or < 80, < 70 and < 55 respectively [21]. There were no restrictions on duration of follow-up or time of assessment of neurocognitive outcomes to allow capturing of both short- and long-term neurocognitive outcomes.

Case–control, cohort studies and cross-sectional studies published between January 2011 and March 2023 were included. Because the definition and management of sepsis has evolved over the years [22], we chose to include studies published from 2011 onwards. Case reports, animal studies, laboratory studies and publications that were not in English language were excluded. Hand-searching of previous systematic reviews were performed to ensure all relevant articles were included. To avoid small study effects, we also excluded studies with a sample size of less than 50 [23].

Information sources and search strategy

Four databases (PubMed, Cochrane Central, Embase and Web of Science) were used to identify eligible studies. The search strategy was developed in consultation with a research librarian. The first search was conducted on 4 December 2021 and an updated search was conducted on 3 April 2023. The detailed search strategy can be found in Supplementary Tables 1A and B.

Study selection process

Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) [24] was utilized during this review. Five reviewers (WJO, BJY, NM, CLN and GH) independently conducted the database search and screened the title and abstracts for relevance. Following

training on inclusion and exclusion eligibility, 4 reviewers (WJO, NM, CLN and GH) subsequently assessed the full text of shortlisted articles for eligibility. All full texts were independently assessed by at least 2 reviewers. Any conflict related to study eligibility were resolved in discussion with the senior author (S-LC). We recorded the reason(s) for exclusion of each non-eligible article.

Data collection process and data items

Four reviewers (WJO, NM, CLN and GH) independently carried out the data extraction using a standardized data collection form, and any conflict was resolved by discussion, or with input from the senior author (S-LC). A pilot search was performed for the first 200 citations to evaluate concordance among reviewers and showed good concordance among reviewers of 94%. For studies with missing data required for data collection or meta-analyses, we contacted the corresponding authors of articles to seek related information. If there was no reply from the authors, the data were labelled as missing.

Study risk of *bias* assessment

Three reviewers (BJY, GH and WJO) independently carried out the assessment of risk of bias using the Newcastle–Ottawa Scale (NOS) for all observational studies [25]. Studies were graded based on three domains namely, selection, comparability and outcomes. Studies were assigned as low, moderate and high risk of bias if they were rated 0–2 points, 3–5 points and 6–9 points respectively. Any conflict was resolved by discussion or with input from the senior author (S-LC).

Statistical analysis

All outcomes (i.e. CD, visual impairment, auditory impairment and CP) were analysed as categorical data. Analyses were done for each NDI domain separately. To ensure comparability across scales, results from different studies were only pooled if the same measurement tools were used to assess the outcomes and hence sub-group analyses were based on different scales and/or different definitions of neurocognitive outcomes used by authors. Both unadjusted and adjusted odds ratios (aOR) and/or relative risk (RR) for each NDI domain were recorded. Where source data were present, we calculated the unadjusted OR if the authors did not report one, together with the 95% confidence interval (CI). For adjusted odds ratio, these were extracted from individual studies and variables used for adjustment were determined at the individual study level.

Meta-analysis was conducted for all outcomes that were reported by at least 2 independent studies or cohorts. Studies were included in the meta-analysis only if they reported outcomes for individual NDI domains within 30 months from sepsis occurrence. For each domain, all selected studies were pooled using DerSimonian-Laird random effects model due to expected heterogeneity. Studies were pooled based on adjusted and unadjusted analyses. Case–control and cohort studies were pooled separately. The pooled results were expressed as unadjusted odds ratio (OR) or adjusted odds ratio (aOR) with corresponding 95% confidence interval (95% CI). If there was more than 1 study that utilized the same population, we only analysed data from the most recent publication or from the larger sample size, to avoid double counting. Standard error (SE) from studies with multiple arms with same control group were adjusted using $SE = \sqrt{(K/2)}$, where K refers to number of treatment arms including control [26]. Heterogeneity across studies was evaluated using the I^2 statistic, for which $\geq 50\%$ is indicative of significant heterogeneity. With regards to publication bias, this was performed using Egger's test and funnel plots only if the number of studies pooled were 10 or more for each outcome.

For neurocognitive related outcomes, subgroup analyses were performed based on the severity of the NDI domain outcomes and distinct, non-overlapping populations of septic infants (such as late onset vs early onset sepsis, culture positive sepsis vs clinically diagnosed sepsis, term and post term patients).

All analyses were done using 'meta' library from R software (version 4.2.2) [27]. The statistical significance threshold was a two tailed P-value < 0.05.

Certainty of evidence

The certainty of evidence for outcomes in this review was performed during the GRADE criteria [28] which is centred on the study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations.

Results

Study selection

From 7,909 studies identified, a total of 24 articles were included (Fig. 1) [29–52]. A total of 101,657 and 19,988 preterm and term infants were included in this review.

Study characteristics

There were 2 case–control studies and 22 cohort studies, with a total of 121,645 infants (Table 1). Studies were conducted in 16 different countries (Fig. 2), with the most studies conducted in the United States of America (USA) (7 studies, $n = 92{,}358$ patients) [30, 33, 37, 41, 42, 47, 52]. There were no studies that were conducted solely on term infants. 5 studies reported data specifically on ELBW infants (27,078 infants) and 6 studies on VLBW infants (3,322 infants). All studies were performed among neonates.

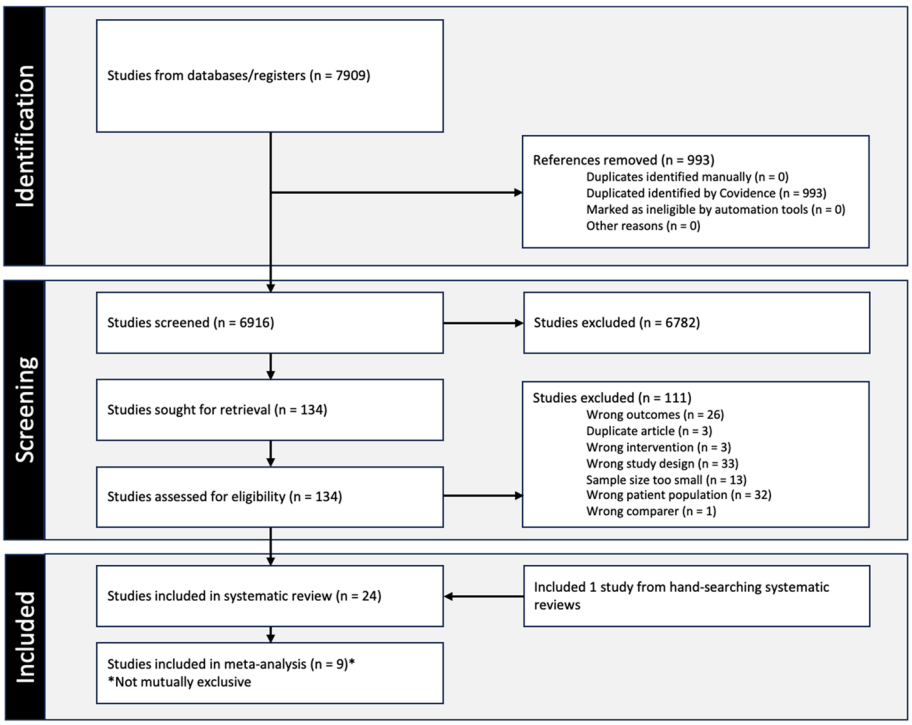

Fig. 1 PRISMA flowchart of the study selection process for search

Risk of bias

Overall, all 24 studies were classified as low risk (Supplementary Table 2). 5 papers scored high risk for outcome bias for having greater than 10% of initial population being lost to follow-up [29, 32, 40–42].

Outcome measures reported by domain

As the number of studies pooled for each outcome was less than 10, publication bias was not analysed in the meta-analyses.

Cognitive delay (CD)

Among 24 studies that assessed for CD, 16 studies reported either the incidence of CD among young infants with sepsis compared to those without, and/or the odds ratio (adjusted and/or unadjusted) comparing the two populations [29, 31–38, 40–42, 45, 46, 48, 49]. The scales used, authors' definition of CD, incidence of CD among those with sepsis and those without are described in Table 2. The most common tools used for assessment of CD were the Bayley Scales of Infant Development (BSID) ($n=13$) and Denver Development Screening Test II ($n=2$).

Infantile sepsis was associated with increased risk of overall CD delays [aOR 1.14 (95%CI: 1.01, 1.28)], overall PDI delay (aOR 1.73 (95%CI: 1.16, 2.58)) and moderate PDI delay [aOR 1.85 (95%CI: 1.01, 3.36)]. Conversely, infantile sepsis was not associated with increased risk for severe PDI delay nor overall MDI delay [aOR 1.30 (95%CI: 0.99, 1.71)] or its subgroups. There were no significant differences in outcomes between different subgroups of infections as well as culture-proven or clinically defined sepsis for either MDI or PDI (Table 8, Fig. 3A and B).

Visual impairment

Seven studies reported data on visual impairment (Table 3) [31, 33, 41, 42, 47, 49]. The most common definition of visual impairment utilized was "visual acuity of < 20/200" ($n=4$, 66.7%).

In the meta-analysis, infantile sepsis was associated with significantly increased risk of visual impairment [aOR 2.57 (95%CI: 1.14, 5.82)] but there were no statistically significant differences in visual impairment between subgroups of early or late onset sepsis, and blood culture negative conditions as compared to the non-septic population (Table 8, Fig. 3A and B).

Hearing impairment

Seven studies reported data on hearing impairment (Table 4) [31, 33, 41, 42, 47, 49]. Two studies defined hearing impairment as permanent hearing loss affecting communication with or without amplification [42, 47]. Other definitions included "sensorineural hearing loss

Table 1 Study characteristics

First author, Year	Country	Population	Study design	Gestational Age	Birth weight	Sample size, total (sepsis)	Duration of follow-up	Causative organisms	Sepsis definition	Composite NDI?
Schlapbach, 2011 [29]	Switzerland	Extreme preterm, ELBW	Cohort study	Sepsis: 26.4 (25.7–27.1) Suspected sepsis: 26.6 (25.7–27.3)	Sepsis: 820 (700–959) Suspected sepsis: 850 (740–995)	541 (305)	21 to 25 months	Gram positive bacteria (80%) CONS (51%) Staphylococcus aureus (15%)	Proven sepsis: Positive result on 1 or more bacterial or fungal cultures obtained from blood or cerebrospinal fluid in an infant with clinical signs of infection (temperature instability, irritability, apathia, feeding difficulties, prolonged capillary refill, apnea, tachycardia, and tachypnea) treated with antibiotics for 5 or more days or until death pathogens that may represent contaminations were considered as proven sepsis only if laboratory signs of infection such as elevated CRP, left shift, or leukopenia, were present and if the sepsis episode had been treated for 5 or more days or until death Suspected sepsis: an episode with clinical and/or laboratory signs of infection in the absence of a positive bacterial or fungal culture from a normally sterile site in an infant who received treatment with antibiotics for 5 or more days or until death	No

Table 1 (continued)

First author, Year	Country	Population	Study design	Gestational Age	Birth weight	Sample size, total (sepsis)	Duration of follow-up	Causative organisms	Sepsis definition	Composite NDI?
Adams-Chapman, 2013 [30]	United states	ELBW	Cohort study	NR	Birthweight < 750g: 257	1317 (1037)	18–22 months	Candida	Positive blood culture and antibiotic therapy for > = 5 days	Yes
de Haan, 2013 [31]	Netherlands	Preterm	Cohort study	< 30 weeks gestation: Neonatal candida sepsis: 27.1 ± 1.4 Gram negative sepsis: 27.0 ± 1.5	NCS: 936.6 ± 208.2 GNS: 933.3 ± 197.8	204 (84)	24 months	Candida sepsis: - C. albicans: 52% - C. parapsilosis: 48% Gram negative sepsis: - Klebsiella pneumonia: 24% - E. coli: 18% - Enterobacter cloacae: 18%	1. Gram-negative bacteria or candida species found in peripheral blood cultures 2. Clinical sepsis: At least 2 of the following symptoms - Increase in frequency or duration of apnoea or bradycardia (not related to feeding problems or airway obstruction) necessitating an increase in ventilatory support - Hypothermia or hyperthermia - Circulatory compromise: Systolic blood pressure < P5	No
Mitha, 2013 [32]	France	Preterm	Cohort study	NR	NR	2665 (955)	60 months	EOS (only 84% had causative organisms identified) - GBS (34%) - E coli (33%) LOS (only 75% had causative organisms identified) - CoNS (46%) - Staph aureus (20%)	Early-onset sepsis (EOS) was defined as confirmed infection of maternal origin (vertically transmitted), on the basis of medical records. Late-onset sepsis (LOS) was defined as a postnatally acquired infection (horizontally acquired) treated with antibiotics for at least 7 days, also on the basis of medical records.	No

Table 1 (continued)

First author, Year	Country	Population	Study design	Gestational Age	Birth weight	Sample size, total (sepsis)	Duration of follow-up	Causative organisms	Sepsis definition	Composite NDI?
Alshaikh, 2014 [33]	United states	Preterm	Cohort study	25.9 ± 1.7	834 ± 211g	332 (105)	37.1 ± 2.1 months	Coagulase negative streptococcus	Combination of: - Suggestive clinical signs - Positive single-organism sterile body fluids culture for coagulase-negative staphylococcus (CoNS)	No
Ferreira, 2014 [34]	Brazil	Preterm, VLBW	Cohort study	29.1 ± 2 weeks	1015 ± 256	194 (86)	12 months	NA	1. Presence of a positive blood culture 2. Presence of clinical and laboratory signs suggestive of infection	No
Hentges, 2014 [35]	Brazil	Preterm, VLBW	Cohort study	29.06 ± 1.84	1024 ± 228	411 (94)	18 and 24 months	Coagulase negative Staphylococcus S. aureus Candida	Late onset sepsis: presence of positive blood cultures over 72 h of life, followed by clinical signs - changes in breathing pattern - hypothermia or hyperthermia - circulatory symptoms - GIT symptoms	No
Dangor, 2015 [36]	South Africa	Preterm and term	Case–control study	NR	NR	384 (122)	3 and 6 months	Group B Streptococcus	1. > 90 days of age in whom GBS was cultured from blood, CSF or other normally sterile sites 2. GBS identified in CSF by latex agglutination	No
Bright, 2017 [52]	United States	Preterm	Cohort study	23–24 weeks: 187 25–26 weeks: 399 27 weeks or more: 298	< = 750g: 331 751-1000g: 382 > 1000g: 171	894 (362)	10 years	NR	Documented late bacteremia: Recovery of an organism from blood drawn during week 2, 3, or 4. Specific organisms were not identified. Suspected infections: Culture-negative, but the infants received antibiotics for more than 72 h.	No

Table 1 (continued)

First author, Year	Country	Population	Study design	Gestational Age	Birth weight	Sample size, total (sepsis)	Duration of follow-up	Causative organisms	Sepsis definition	Composite NDI?
Savioli, 2018 [37]	United States	Preterm and term	Cohort study	NR	Over 2500g Known sepsis: 97 Suspected sepsis: 2858 1500-2499g Known sepsis: 28 Suspected sepsis: 455 1000-1499g Known sepsis: 23 Suspected sepsis: 109 < 1000g Known sepsis: 42 Suspected sepsis: 27	65,938 (3639)	Within 60 months	NR	Criteria for sepsis: documented clinical symptoms, five or more days of antibiotic use, and a positive laboratory screening test (positive microbial growth in the blood, urine, or CSF). Suspected sepsis: clinical symptoms of sepsis and five or more days of antibiotic use without a positive laboratory screening test, consistent with other studies' definition of suspected sepsis	No
Singh, 2018 [38]	India	Preterm, VLBW	Cohort study	< 32: 40 (50%) 32–36: 37 (46.3%) 34–36: 7 (8.8%) 36–38: 3 (3.8%)	1000–1200: 37 (43.6%) 1201–1400: 29 (36.3%) 1401–1500: 14 (17.5%)	160 (80)	6 months	Klebsiella pneumoniae (33.8%) Escherichia coli (15%) Candida species (13.8%)	Postive blood culture	No
Zonnenberg, 2019 [39]	The Netherlands	Preterm, VLBW	Cohort study	28 + 0 (15 SD) days	1078 ± 322	117 (85)	24 months	Coagulase-negative staphylococci (82.3%) Staphylococcus aureus (16.4%) Escherichia coli (2.3%)	Late-onset sepsis was defined as a positive blood culture after 72 h of life. If the blood culture did not turn positive but clinical signs implied antibiotic treatment for 7 days, late-onset sepsis was considered probable but not proven. If in one of the episodes a causal microorganism was found, the infant was classified as proven infection.	No

Table 1 (continued)

First author, Year	Country	Population	Study design	Gestational Age	Birth weight	Sample size, total (sepsis)	Duration of follow-up	Causative organisms	Sepsis definition	Composite NDI?
Nakwa, 2020 [40]	South Africa	Preterm and term	Case–control study	NR	NR	571 (122)	12 months	NR	GBS sepsis was defined as isolation of GBS from blood culture in infants < 90 days of age. GBS meningitis was defined through identification of GBS in cerebrospinal fluid (CSF) by culture or latex agglutination (irrespective of whether GBS was cultured on blood); or in cases where the CSF was sterile but the blood culture was GBS-positive, a pleocytosis of ≥ 20 cells/mm 3 for < 28-day olds and ≥ 10 cells/mm 3 for 29–89-day olds (with no adjustment made for traumatic taps) was taken as evidence for GBS meningitis.	No
Mukhopadhyay, 2020 [42]	United States	Extreme preterm, ELBW	Cohort study	24.4 ± 1.1	713 ± 131	6565 (153)	18–22 months (for births before 1st July 2012) 22–26 months (for births on or after 1st July 2012)	Gram positive (27.5%) Gram negative (65.4%) Fungi (1.3%)	EOS was defined as blood or cerebrospinal fluid (CSF) culture obtained ≤ 72 h of age that grew pathogenic bacteria or fungi, for which the infant received antibiotics ≥ 5 days or died with intent to receive antibiotics ≥ 5 days	No

Table 1 (continued)

First author, Year	Country	Population	Study design	Gestational Age	Birth weight	Sample size, total (sepsis)	Duration of follow-up	Causative organisms	Sepsis definition	Composite NDI?
a) Horváth-Puhó, 2021 [43]	Denmark	Preterm and term	Cohort study	NR	NR	16,470 (1525)	14 years (7–18)	GBS	Exposed children were defined as having a history of iGBS disease (sepsis, meningitis, or pneumonia) by the age of 89 days. GBS meningitis, sepsis, and pneumonia were defined on the basis of discharge diagnoses with the use of International Classification of Diseases (ICD)-10 codes	Yes
b) Horváth-Puhó, 2021 [44]	The Netherlands	Preterm and term	Cohort study	NR	NR	7658 (697)	9 years (6–11)	GBS	Exposed children were defined as having a history of iGBS disease (sepsis, meningitis, or pneumonia) by the age of 89 days. Sepsis was defined as a positive blood culture only.	Yes
Mukhopadhyay, 2021 [41]	United States	Extreme preterm, ELBW	Cohort study	24.7 ± 1.0	708 ± 135	3940 (2387)	18–22 months (for births before 1st July 2012) 22–26 months (for births on or after 1st July 2012)	CoNS (52%) Staph aureus (13%) E coli (7%)	Late onset sepsis (LOS) defined as isolation of a pathogen from blood or CSF obtained > 72 h of age and appropriate therapy for ≥ 5 days (≥ 7 days for CSF growth) or death before completed treatment	No
Ortgies, 2021 [45]	Germany	Preterm, VLBW	Cohort study	NR	NR	342 (54)	21–27 months	NR	Culture-proven EOS was defined as a positive result of one or more bacterial or fungal blood cultures obtained from patients and antimicrobial treatment for at least 5 days Clinical EOS was defined using established laboratory parameters and persistent clinical presentation	No

Table 1 (continued)

First author, Year	Country	Population	Study design	Gestational Age	Birth weight	Sample size, total (sepsis)	Duration of follow-up	Causative organisms	Sepsis definition	Composite NDI?
Shim, 2021 [46]	Korea	Preterm, VLBW	Cohort study	(27 + 2) ± (2 + 2)	927.3 ± 239.3	2098 (419)	18–24 months	Coagulase-negative Staphylococcus (48.8%) Gram negative (19%) Gram positive bacteria (79.5%)	LOS was defined as a postnatally acquired infection which occurred after the third postnatal day of life. Only sepsis confirmed by blood culture was considered.	No
Brumbaugh, 2022 [47]	United States	Extreme preterm	Cohort study	25.0 (24.1–25.9)	700 (600–810)	13,372 (4731)	18—26 months	NR	LOS was defined as isolation of a bacterial or fungal pathogen from blood obtained more than 72 h after birth and accompanied by treatment for at least 5 days or death before completed treatment.	No
Golin, 2022 [48]	Brazil	Preterm	Cohort study	31.22 (24–36)	1419 (550–2300)	100 (50)	Corrected gestational age between 37 and 42 weeks	Gram positive in 1 Streptococcus b in1 Bacillus gram negative + Klebsiella pneumoniae in 1 Escherichia coli in 3 E.coli + E faecalis in 1 E. coli + Bacillus in 1 (hemoculture only performed in 84% and only positive in 9%)	Neonatal sepsis was considered in the presence of a positive blood culture and/or clinical and laboratory signs suggestive of infection.	No
a) Horváth-Puhó, 2022 [43]	Denmark	Preterm and term	Cohort study	NR	NR	15,643 (1432)	Up till 18 years	GBS	Having a history of GBS sepsis or meningitis by age 89 days as identified based on International Classification of Diseases. 10th revision (ICD-10) codes of discharge diagnosis from the Danish National Patent Registry	Yes

Table 1 (continued)

First author, Year	Country	Population	Study design	Gestational Age	Birth weight	Sample size, total (sepsis)	Duration of follow-up	Causative organisms	Sepsis definition	Composite NDI?
b) Horváth-Puhó, 2022 [44]	The Netherlands	Preterm and term	Cohort study	NR	NR	7658 (697)	Up to 12 years	GBS	Having cerebrospinal fluid and/or a blood culture positive for GBS, identified through the Netherlands Reference Laboratory for Bacterial Meningitis	Yes
Humberg, 2022 [49]	Germany	Extreme preterm and ELBW	Cohort study	No LOS: 26.3 (25.1–27.4) One LOS: 25.7 (24.4–26.9) Recurrent LOS: 25.3 (24.1–26.6) Total including no sepsis: 26.1 (25.0–27.3)	No LOS: 780 (640–900) One LOS: 725 (630–860) Recurrent LOS: 660 (575–790) Total including no sepsis: 748 (630–890)	1343 (263)	5–6 years	S. hominis S. agalactiae VRE ESBL-positive Klebsiella spp Enterobacter spp	Neonatal sepsis was confirmed using a positive culture, which was defined as any sample of blood or cerebrospinal fluid which tested positive for bacterial growth	No
Kartam, 2022 [50]	Kuwait	Preterm	Cohort study	No sepsis: 29.5 (28.1–31.4) EOS: 27.0 (25.8–28.7) LOS: 25.9 (25.0–27.7)	No sepsis: 1190 (1020–1380) EOS: 1045 (832–1335) LOS: 840 (695–966)	203 (109)	36 months CA	Klebsiella pneumonia (31.3%) Streptococcus agalactia (25.0%) Escherichia coli (18.8%)	Neonatal sepsis was confirmed using a positive culture, which was defined as any sample of blood or cerebrospinal fluid which tested positive for bacterial growth. A blood culture was considered contaminated if the presence of gram-positive cocci in it was negated by another culture drawn 30-min apart. Earlyonset sepsis (EOS) was described by a positive blood culture occurring ≤ 72 h after birth, and LOS as an infection contracted after this period. A case of sepsis was considered severe if associated with hemodynamic instability and disseminated intravascular coagulation (DIC)	No

Table 1 (continued)

First author, Year	Country	Population	Study design	Gestational Age	Birth weight	Sample size, total (sepsis)	Duration of follow-up	Causative organisms	Sepsis definition	Composite NDI?
Paul, 2022[51]	LMIC (South Africa, India, Mozambique, Kenya and Argentina)	Preterm and term	Cohort study	NR	NR	577 (159)	1–18 years	NR	GBS-meningitis was diagnosed by GBS-positive cerebrospinal fluid (CSF) culture in most cases (67¢4%), but five cases defined as meningitis had suggestive CSF leucocyte count of > 20 £ 106/l plus GBS-positive blood culture and nine had GBS-positive blood culture plus suggestive clinical symptoms of meningitis.	*Yes*

Preterm ≤ 37 gestational weeks, *VLBW* Very low birth weight (VLBW) < 1500 g, *ELBW* extremely low birth weight (ELBW) < 1000 g, *EOS* Early Onset Sepsis, *LOS* Late Onset Sepsis, *NCS* Neonatal Candida Sepsis, *GBS* Group B Streptococcus, *NR* Not Reported, *CONS* Coagulase-negative Staphylococcus, *VRE* vancomycin-resistant enterococcus, *ESBL* extended spectrum beta-lactamase

Foot note: Results from studies are specified as frequencies (percentages) unless not reported in the study

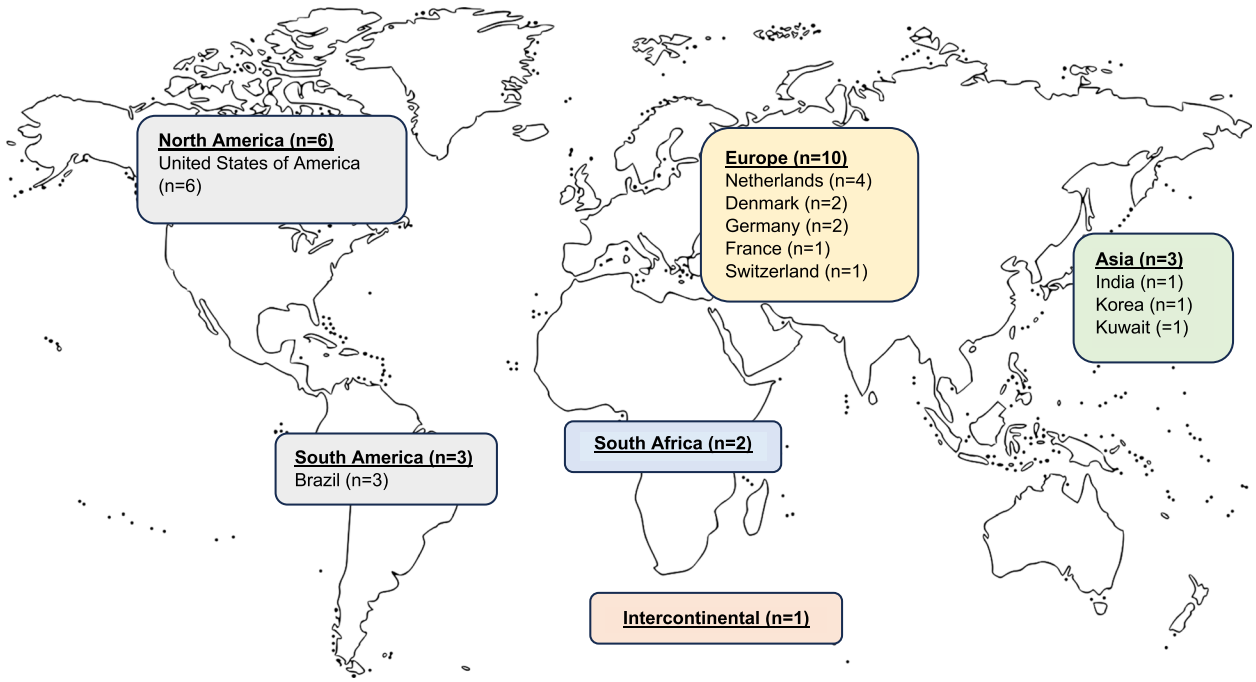

Fig. 2 World map depicting distribution of studies that evaluate neurocognitive outcomes in infantile and neonatal sepsis

requiring amplification" ($n=1$), "bilateral hearing impairment with no functional hearing (with or without amplification)" ($n=1$), "clinical hearing loss" ($n=1$).

In the meta-analysis, sepsis was associated with increased risk of hearing impairment [aOR 1.70 (95% CI: 1.02–2.81)]. However, in the subgroup analyses, there were no differences in risk of hearing impairment between patients with late onset sepsis as compared to the non-septic population (Table 8, Fig. 3A and B).

Cerebral palsy

Nine studies [29, 32, 33, 41, 42, 47–50] reported data on CP (Table 5), of which 5 studies [41, 42, 45, 49, 50] used the GMFCS scale. In the meta-analysis, infantile sepsis was associated with significantly increased risk of CP [aOR 2.48 (95%CI: 1.03; 5.99)]. There was no difference in rates of CP among patients with proven or suspected sepsis, as compared with infants with no sepsis (Table 8, Fig. 3A and B).

Differences in neurocognitive outcomes between neonates with culture-proven or clinically diagnosed sepsis as well as early or late onset sepsis

Tables 6 and 7 showed data related to differences in neurocognitive outcomes between neonates with culture-proven or clinically diagnosed sepsis as well as early or late onset sepsis. Meta-analyses were not be performed due to significant heterogeneity in definitions of sepsis, time of assessment of outcomes.

Differences in neurocognitive outcomes between term and post-term neonates

There were no studies which evaluated neurocognitive outcomes between term and post-term neonates and infants.

Certainty of evidence

We found that the certainty of evidence to be very low to low for the four main neurocognitive outcomes selected. (Supplementary File 3).

Discussion

In this review involving more than 121,000 infants, we provide an update to the literature regarding young infant sepsis and neurocognitive impairment. Current collective evidence demonstrate that young infant sepsis was associated with increased risk of developing neurocognitive impairment in all domains of CD, visual impairment, auditory impairment and cerebral palsy.

Cognitive delay

In this review, higher rates of cognitive delay were noted among infants with sepsis [29, 31, 33–38, 40–42, 45, 46, 48, 49, 52]. We found that infants with sepsis reported lower PDI scores (Table 8), which measures

Table 2 Cognitive delay assessment and definition

First author, Year	Scale used	Cognitve delay definition	Sepsis incidence	No sepsis incidence	Ratios	Adjusted for (if any)
Schlapbach, 2011 [29]	Bayley's Scales of Infant Development (BSID) II	MDI and/or PDI scores < 70	PDI < 70: Proven sepsis: 32/128 (25%) Suspected sepsis: 38/164 (23%) MDI < 70: Proven sepsis: 30/132 (23%) Suspected sepsis: 30/166 (18%) MDI or PDI scores between 70 and 84: Proven sepsis: 43/134 (32%) Suspected sepsis: 49/167 (29%)	PDI < 70: Uninfected: 29/193 (15%) MDI < 70: Uninfected: 39/229 (17%) MDI or PDI scores between 70 and 84: Uninfected: 68/232 (29%)	Multivariable OR (95% CI) for PDI < 70: Proven sepsis vs uninfected: 1.80 (0.95–3.41), *P*-value = 0.073 Suspected sepsis vs uninfected: 1.36 (0.72–2.59), *P*-value = 0.341 Multivariable OR (95% CI) for MDI < 70: Proven sepsis vs uninfected: 1.37 (0.73–2.58), *P*-value = 0.325 Suspected sepsis vs uninfected: 0.70 (0.36–1.35), *P*-value = 0.286 Multivariable OR (95% CI) for MDI or PDI between 70 and 84: Proven sepsis vs uninfected: 0.96 (0.57–1.59), *P*-value = 0.863 Suspected sepsis vs uninfected: 1.23 (0.75–2.01), *P*-value = 0.419	Center, year of birth, gender, gestational age, birth weight, brain injury, BPD, ROP, socioeconomic status, and postnatal growth.
Adams-Chapman, 2013 [30]	Bayley Scales of Infant Development II (Evaluated prior to 1 October 2007)	MDI < 70 or PDI < 70	NR	NR	NR	NA
	Bayley Scales of Infant Development III (Evaluated after 1 October 2007)	BSID-III cognitive < 70				
de Haan, 2013 [31]	Bayley Scales of Infant Development (Second Edition-Dutch version)	- Mildly delayed: MDI and PDI scores between 70 to 84 - Severely delayed: MDI or PDI scores below 70	Mildly abnormal Neonatal Candida Sepsis (NCS) = 9/17 (53%) Gram negative sepsis (GNS) = 8/33 (24%) Severely abnormal NCS = 1/17 (6%) GNS = 7/33 (21%)	Mildly abnormal Uncomplicated (UC) = 13/102 (13%) Severely abnormal UC = 2/102 (2%)	NR	NA

Table 2 (continued)

First author, Year	Scale used	Cognitve delay definition	Sepsis incidence	No sepsis incidence	Ratios	Adjusted for (if any)
Mitha, 2013 [32]	Kaufman Assessment Battery for Children	Mental processing composite (MPC) score < 70	NR	NR	Adjusted OR (95% CI) EOS: 0.98 (0.47–2.04), *P*-value = 0.95 LOS: 0.79 (0.50–1.24), *P*-value = 0.31	For cerebral palsy, models were adjusted for maternal and neonatal variables selected in the univariate analysis (preterm rupture of membranes, spontaneous preterm labor, gender, gestational age, and small for gestational age) and other factors previously reported to be associated with short- and long-term outcomes (eg, antenatal corticosteroid therapy) For cognitive impairment, models were adjusted for maternal and neonatal variables selected in the univariate analysis (maternal age at birth, maternal level of education, parity, preterm rupture of membranes, gender, gestational age, small for gestational age, and duration of central venous catheter use) and other factors previously reported to be associated with short- and long-term outcomes (eg, antenatal corticosteroid therapy)

Table 2 (continued)

First author, Year	Scale used	Cognitve delay definition	Sepsis incidence	No sepsis incidence	Ratios	Adjusted for (if any)
AL Shaikh, 2014 [33]	- Wechsler Preschool and Primary Scale of Intelligence-Revised - Bayley Scales of Infant Development II - Stanford-Binet IV	> 2 standard deviation below the mean on standardized assessment	NR	NR	Adjusted OR (95% CI): 2.23 (1.01–4.9), *P*-value = 0.048	Because of small event numbers in deafness and blindness, their association with CoNS sepsis were adjusted for GA only For CP, cognitive delay and major disabilities, which had a greater number of outcome events, the associations were adjusted for GA, chorioamnionitis, severe intraventricular hemorrhage and use of postnatal steroids
Ferreira, 2014 [34]	Bayley Scale of Infant Development (Second edition)	Altered: MDI or PDI scores < 85 - Mildly delayed: MDI and PDI scores between 70 to 84 - Severely delayed: MDI or PDI scores below 70	Altered PDI at 12 months: 48/86 (55.8%) Neuromotor impairment at 12 months: 29/86 (33.7%) Neuromotor impairment and/or altered PDI at 12 months: 51/86 (59.3%) Altered MDI at 12 months: 41/86 (47.7%)	Altered PDI at 12 months: 25/108 (23.1%) Neuromotor impairment at 12 months: 10/108 (9.3%) Neuromotor impairment and/or altered PDI at 12 months: 28/108 (25.9%) Altered MDI at 12 months: 35/108 (32.4%)	NR	NA
	Amiel-Tison and Grenier protocol	Changes associated with one or more of several body segments at clinical/neurological evaluation, such as: change in muscle tone, abnormal posture, abnormal spontaneous movements, altered neurological examination, and motor developmental delay				
	Motor development milestones	Did not reach age-appropriate motor milestones				

Table 2 (continued)

First author, Year	Scale used	Cognitve delay definition	Sepsis incidence	No sepsis incidence	Ratios	Adjusted for (if any)
Hentges, 2014 [35]	Bayley Scales of Infant and Toddler Development II	Mildly delayed: MDI and PDI scores between 70 to 84 Severely delayed: MDI or PDI scores below 70	Cognitive Impairment: Coagulase negative Staphylococcus: 17/36 (47.2%) Gram Positive: 12/16 (75.0%) Gram negative and fungi: 5/10 (50%) Motor deficit: Coagulase negative Staphylococcus: 6/36 (16.7%) Gram Positive: 11/16 (68.8%) Gram negative and fungi: 4/10 (40.0%)	Cognitive Impairment: Non-Septic: 76/164 (46.3%) Motor deficit Non-Septic: 48/164 (29.3%)	Severe motor deficit adjusted OR (CI) Coagulase negative Staphylococcus: 0.6 (0.1–4.1), *P*-value = 0.68 Other gram positive: 4.1 (0.88–19), *P*-value = 0.071 Gram negative bacteria and fungi: 1.3 (0.2–8), *P*-value = 0.74 Severe and moderate motor deficit adjusted OR (CI) Coagulase negative Staphylococcus: 0.5 (0.1–1.6), *P*-value = 0.24 Other gram positive: 6 (1.6–21), *P*-value = 0.006 Gram negative bacteria and fungi: 0.8 (0.1–3.9), *P*-value = 0.8 Severe cognitive impairment adjusted OR (CI) Coagulase negative Staphylococcus: 0.9 (0.1–5.6), *P*-value = 0.99 Other gram positive: 1.9 (0.4–8.9), *P*-value = 0.39 Gram negative bacteria and fungi: 1.5 (0.2–10.2), *P*-value = 0.67 Severe and moderate cognitive impairment adjusted OR (CI) Coagulase negative Staphylococcus: 0.9 (0.3–2.4), *P*-value = 0.91 Other gram positive: 3.9 (0.96–16), *P*-value = 0.06 Gram negative bacteria and fungi: 0.3 (0.03–3), *P*-value = 0.33	Logistic regression adjusted for type of delivery, maternal preeclampsia, use of antenatal corticosteroids, CHAD transfusion, leukomalacia, retinopathy of prematurity, length of stay, SNAPPE II, gestational Age

Table 2 (continued)

First author, Year	Scale used	Cognitve delay definition	Sepsis incidence	No sepsis incidence	Ratios	Adjusted for (if any)
Dangor, 2015 [36]	Denver Development Screening Test II	Abnormal test for any of the four domains (gross motor, fine motor, language and personal-social) or hypertonia and/or hyperreflexia detected on examination	Evaluated at 3 months Overall: 9/68 (13.2%) - Abnormal Denver-II assessment: 3/68 (4.4%) - Hypertonia/hyperreflexia: 6/68 (8.9%) Evaluated at 6 months Overall: 9/68 (13.2%) - Abnormal Denver-II assessment: 5/68 (7.4%) - Hypertonia/hyperreflexia: 4/68 (5.9%)	Evaluated at 3 months Overall: 1/262 (0.4%) - Abnormal Denver-II assessment: 1/262 (0.4%) - Hypertonia/hyperreflexia: 0/262 (0%) Evaluated at 6 months Overall: 1/232 (0.4%) - Abnormal Denver-II assessment: 1/232 (0.4%) - Hypertonia/hyperreflexia: 0/232 (0%)	Evaluated at 3 months: Multivariate OR: 21.48 (2.58–179.15), *P*-value = 0.005 Evaluated at 6 months: Multivariate OR: 13.18 (1.44–120.95), *P*-value = 0.023	Gender, gestational age, birth weight < 2500 g, perinatal asphyxia, mechanical ventilation, infant HIV exposure status and previous non-GBS related hospitalizations
Bright, 2017 [52]	- School-Age Differential Ability Scales, Second Edition (DASII) - Verbal and Nonverbal Reasoning scale - Oral and Written Language Scales (OWLS) - NEPSY-II (A Developmental NEuroPSYchological Assessment, Second Edition) - TheWechsler Individual Achievement Test, Third Edition (WIAT-III) - Gross Motor Function Classification System - Manual Ability Classification System.	- Sensorimotor function Manual Ability Classification system > = 3 - Gross motor function classification system > = 3 - Processing speed NEPSY-II Inhibition Naming (1) Z score = < -2 (2) Z score > -2, = < -1 - Fine motor function NEPSY-II Visuomotor Precision (1) Z score = < -2 (2) Z score > -2, = < -1	Sensorimotor function: - Suspected late onset bacteremia: 12 - Definite late onset bacteremia: 12 Gross motor function classification system: - Suspected late onset bacteremia: 5 - Definite late onset bacteremia: 6 Processing speed: (1) Z score = < -2 - Suspected late onset bacteremia: 33 - Definite late onset bacteremia: 35 (2) Z score > -2, = < -1 - Suspected late onset bacteremia: 21 - Definite late onset bacteremia: 19 Fine motor function NEPSY-II Visuomotor Precision (1) Z score = < -2 - Suspected late onset bacteremia: 22 - Definite late onset bacteremia: 22 (2) Z score > -2, = < -1 - Suspected late onset bacteremia: 33 - Definite late onset bacteremia: 35	Sensorimotor function: - No late onset bacteremia: 8 Gross motor function classification system: - No late onset bacteremia: 5 Processing speed: (1) Z score = < -2 - No late onset bacteremia: 29 (2) Z score > -2, = < -1 - No late onset bacteremia: 20 Fine motor function NEPSY-II Visuomotor Precision (1) Z score = < -2 - No late onset bacteremia: 20 (2) Z score > -2, = < -1 - No late onset bacteremia: 35	NR	NA

Table 2 (continued)

First author, Year	Scale used	Cognitve delay definition	Sepsis incidence	No sepsis incidence	Ratios	Adjusted for (if any)
Savioli, 2018 [37]	The Agency for Healthcare Quality and Research (AHQR) Clinical Classification System (CCS)	Diagnosis within the following two CCS subcategories within the first 5 years of life - ICD-9 diagnostic code for developmental disorders - ICD-9 diagnostic code for disorders usually diagnosed in infancy, childhood, or adolescence	Known sepsis: 96/190 (50.5%) Suspected sepsis: 971/3,449 (28.2%)	No sepsis: 13,802/62,299 (22.2%)	OR (95% CI) for any developmental delay Known sepsis: 3.59 (2.70–4.77) Known sepsis – Preterm infants: 1.80 (1.09–2.98)[a] Known sepsis – Term infants: 1.71 (1.10–2.65)[a] Suspected sepsis: 1.38 (1.28–1.49) Suspected sepsis – Preterm infants: 1.18 (1.00–1.40)[a] Suspected sepsis – Term infants: 1.08 (0.98–1.19)	Preterm birth, low birth weight, retinopathy of prematurity, chronic lung disease, patent ductus arteriosus, intra-ventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, and hearing loss
Singh, 2018 [38]	Differential Ability Scales, Second Edition (DASII)	Measurement of neurodevelopmental outcomes Significantly delayed development: DASII score < 70	11/47 (23.4%)	2/66 (3%)	NR	NA
Zonnenberg, 2019 [39]	- Bayley's Scales of Infant and Toddler Development II (BSID-II) - Lexiquotient - Child Behavior Checklist (CBCL)	No definition of impairment given. Mean scores were compared between sepsis and non-sepsis groups for statistical significance	NR	NR	NR	NA
Nakwa, 2020 [40]	Denver II developmental scale	Mild delay: Delay (i.e. fail or refusal of the item) in 1 out of 4 domains (gross motor, fine motor, language, personal-social) Moderate-to-severe delay: Any of the following - Delay in > 1 domain - Blindness - Cerebral palsy	Overall delay: 15/65 (23.1%) Mild delay: 9/65 (13.9%) Moderate to severe delay: 6/65 (9.2%)	Overall delay: 11/207 (5.3%) Mild delay: 11/207 (5.3%) Moderate to severe delay: 0/207 (0%)	Adjusted OR (95% CI): Overall: 4.23 (1.65–10.83), *P*-value = 0.003 Sepsis only: 3.51 (1.23–10.04), *P*-value = 0.019 Meningitis only: 8.29 (0.88–78.3), *P*-value = 0.065	Variables with a $P < 0.2$ in the univariable analysis

Table 2 (continued)

First author, Year	Scale used	Cognitve delay definition	Sepsis incidence	No sepsis incidence	Ratios	Adjusted for (if any)
Mukhopadhyay, 2020 [42]	Bayley Scales of Infant Development, Third Edition	Bayley-3 cognitive composite score < 85	EOS: 38/90 (42.2%)	Unaffected infants with prolonged antibiotics: 745/2,270 (33.1%) Unaffected infants without prolonged antibiotics: 695/2,333 (30.0%)	Adjusted RR (95% CI) EOS vs prolonged antibiotics: 1.26 (0.98–1.63), *P*-value = 0.07 EOS vs prolonged antibiotics: 1.34 (1.04–1.74), *P*-value = 0.02	Maternal education, maternal insurance, maternal race/ethnicity, maternal hypertension, antepartum hemorrhage, antenatal steroids, maternal antibiotics received during the delivery admission, clinical chorioamnionitis, membrane rupture > 18 h, caesarean delivery, infant GA (categorical), BW (continuous), male sex, intubation at birth, temperature < 60 min of birth, severe intraventricular hemorrhage ≤ 7 days age and start of enteral feeds ≤ 3 days age
a) Horváth-Puhó, 2021 [43] (Denmark)	ICD-10 codes for mental, behavioural, and nervous system disorders	NDI: impairment in any domain Multidomain NDI: impairment in more than one domain	NR	NR	No ratios available for cognitive delay alone	NA
b) Horváth-Puhó, 2021 [44] (The Netherlands)	Special educational support	Mild NDI: Children who received additional support in regular schools Moderate or severe NDI: Children who received education in special needs schools	NR	NR	No ratios available for cognitive delay alone	NA

Table 2 (continued)

First author, Year	Scale used	Cognitve delay definition	Sepsis incidence	No sepsis incidence	Ratios	Adjusted for (if any)
Mukhopadhyay, 2021 [41]	Bayley Scales of Infant Development, Third Edition	Bayley-3 cognitive composite score < 85	LOS: 35/579 (6.1%) LOCNC: 130/1,395 (9.3%)	Unaffected: 54/1,387 (3.9%)	Adjusted RR (95% CI) LOS vs unaffected: 1.12 (0.96–1.31), *P*-value = 0.14 LOCNC vs unaffected: 1.15 (1.01–1.30), *P*-value = 0.03	Maternal education, insurance, race/ethnicity, antenatal antibiotics, antenatal steroids, antepartum haemorrhage, infant GA, birth weight, sex, temperature at < = 60 min of birth, intubation at birth, maximum respiratory support < = 24 h of age, enteral feeds started < = 3 days of birth, receipt of antibiotics for > = 5 days starting < = 72 h of age, severe IVH diagnosed < = 7 days of birth and centre
Ortgies, 2021 [45]	Bayley Scales of Infant Development II (German translation)	MDI and/or PDI scores < 70	PDI < 70: 6/31 (19.35%) PDI < 85: 8/31 (25.81%) MDI < 70: 3/31 (9.68%) MDI < 85: 7/31 (23.58%)	PDI < 70: 3/135 (1.65%) PDI < 85: 18/135 (13.33%) MDI < 70: 6/135 (4.44%) MDI < 85: 37/135 (27.41%)	OR (95% CI) for PDI < 70: 10.56 (2,476–45,035), *P*-value = 0.001 OR (95% CI) for PDI < 85: 2.261 (0.879–5,818), *P*-value = 0.091 OR (95% CI) for MDI < 70: 2.304 (0.543–9,771), *P*-value = 0.318 OR (95% CI) for MDI < 85: 0.773 (0.307–1,944), *P*-value = 0.584	Variables showing significant differences in the univariate analysis: High CRIB score for MDI < 70 and high CRIB scores and chorioamnionitis for PDI < 70
Shim, 2021 [46]	Bayley scales of infant development (BSID) second edition Bayley scales of infant development (BSID) third edition	Both motor and cognitive delay: Scores < 70 Both motor and cognitive delay: Scores < 80	Motor delay: 111/347 (32.0%) Cognitive delay: 124/392 (31.6%)	Motor delay: 308/1,751 (17.6%) Cognitive delay: 295/1,706 (17.3%)	Adjusted OR (95% CI) for cognitive delay: 1.48 (1.02–2.16), *P*-value = 0.042	
Brumbaugh, 2022 [47]	BSID II and BSID III	BSID-II MDI < 70 BSID cognitive composite score < 85	NR	NR	NR	NA
Golin, 2022 [48]	HHNE: Hammersmith Infant Neurological Examination	Significant differences in the domains of the HNNE	NR	NR	OR (95% CI) for effect of neonatal sepsis on clinical neurological alterations: 7.08 (2.13–23.53)	

Table 2 (continued)

First author, Year	Scale used	Cognitve delay definition	Sepsis incidence	No sepsis incidence	Ratios	Adjusted for (if any)
a) Horváth-Puhó, 2022 [43] (Denmark)	ICD-10 codes for mental, behavioural, and nervous system disorders	NR	NR	NR	No ratios available for cognitive delay alone	NA
b) Horváth-Puhó, 2022 [44] (The Netherlands)	Special educational support recorded in national school registries	Mild NDI: Children who received additional support in regular schools Moderate or severe NDI: Children who received education in special needs schools	NR	NR	No ratios available for cognitive delay alone	NA
Humberg, 2022 [49]	1. Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI I-III, German) 2. Movement Assessment Battery for Children – Second Edition (MABC-2)	NR	IQ < 85: One LOS: 31 (19.7 [14.1–26.5]) Recurrent LOS: 24 (38.7 [27.3–51.1])[a] Manual dexterity difficulties: One LOS: 36 (34.6 [26.0–44.1]) Recurrent LOS: 19 (48.7 [33.6–64.0])[a] Aim and catching difficulties: One LOS: 39 (37.1 [28.4–46.6])[a] Recurrent LOS: 16 (40.0 [25.9–55.4])[a] Balance difficulties: One LOS: 16 (15.2 [9.3–23.0])[a] Recurrent LOS: 15 (35.7 [22.6–50.8])[a]	IQ < 85: No LOS: 174 (19.0 [16.6–21.7]) Manual dexterity difficulties: No LOS: 226 (33.1 [29.6–36.7]) Aim and catching difficulties: No LOS: 183 (26.9 [23.6–30.3]) Balance difficulties: No LOS: 79 (11.7 [9.4–14.3])	NR	Gestational age, birth weight, female gender, antenatal administration of steroids, small for gestational age, any intra-cranial hemmorhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, treatment of retinopathy of prematurity (operation, laser, or use of anti-vascular endothelial growth factor), and highest maternal education level

Table 2 (continued)

First author, Year	Scale used	Cognitve delay definition	Sepsis incidence	No sepsis incidence	Ratios	Adjusted for (if any)
Kartam, 2022 [50]	Bayley scales of infant and toddler development-III (BSID-III)	Moderate developmental delay: Score of 70–84 in ≥ 1 of the 3 domains Severe developmental delay: Score < 70 for any domain or unable to assign score due to severe mental deficiency or cerebral palsy	NR	NR	Adjusted beta coefficient values: Motor composite score: - EOS: −0.1 (−7.7 to 7.5), *P*-value = 0.938 - LOS: -9.5 (−16.4 to −2.7), *P*-value = 0.007 Cognitive composite score: - EOS: 2.0 (−5.0 to 9.1), *P*-value = 0.569 - LOS: −4.7 (−11.2 to 1.7), *P*-value = 0.146 Language composite score: - EOS: 3.9 (−7.8 to 15.6), *P*-value = 0.507 - LOS: 0.82 (−8.3 to 6.6), *P*-value = 0.829	Birth weight, gestational age, severe sepsis, and necrotizing enterocolitis
Paul, 2022 [51]	Various tools (Each site used various neurodevelopmental assessments, with 26 tools in total across the 5 study sites. Each site selected assessment tools for their setting based on child's age, cultural appropriateness, validation of instrument for their population, and technical capacity.)	Scored 2 standard deviations (SD) below the standardized reference mean in cognition AND/OR motor composite measures	NR	NR	NR	NA

BSID III Bayley Scales of Infant and Toddler Development 3rd edition, *BSID II* Bayley Scales Of Infant and Toddler Development 2nd edition, *GMFCS* Gross Motor Function Classification System, *NDI* neurodevelopmental impairment, *MDI* Mental Developmental Index, *PDI* Psychomotor Developmental Index, *NR* Not recorded

[a] Statistically significant

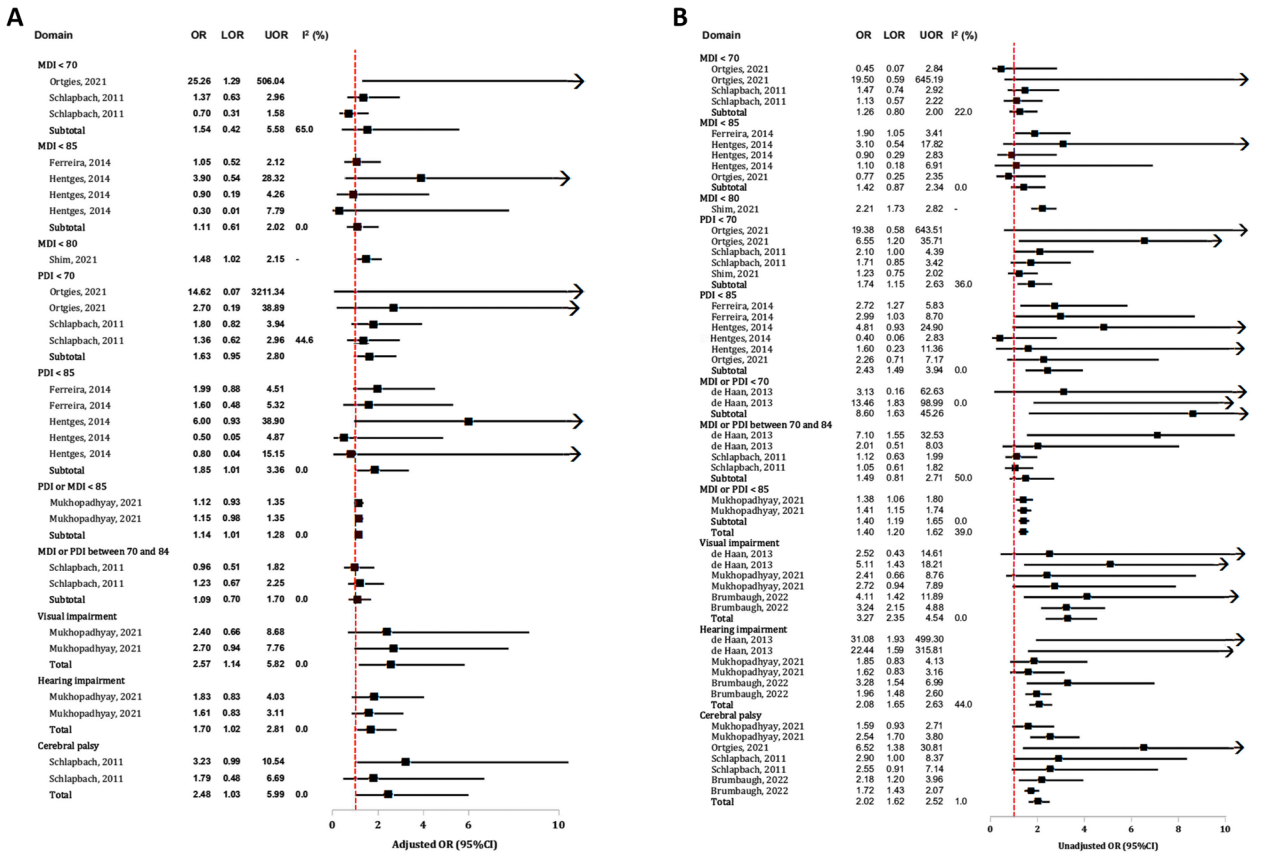

Fig. 3 **A** Forest plot on adjusted odds ratios for neurocognitive outcomes related to MDI, PDI, visual impairment, hearing impairment and cerebral palsy. **B** Forest plot on unadjusted odds ratios for neurocognitive outcomes related to MDI, PDI, visual impairment, hearing impairment and cerebral palsy. Legend: MDI: Mental Developmental Index; PDI: Psychomotor Developmental Index. Foot note: Mild MDI or PDI: < 85 or < 80; Moderate MDI or PDI < 70; Severe MDI or PDI < 55

mainly neuromotor development. On the other hand, young infant sepsis was not associated with lower MDI scores (Table 8), which assesses cognitive and language development. The pathophysiological mechanism of young infant sepsis and its preferential impact on PDI remains unclear. Postulated mechanisms include development of white matter lesions which may arise from the susceptibility of oligodendrocyte precursors to inflammatory processes such as hypoxia and ischemia [53]. Future studies should look into evaluating the causes of the above findings. A majority of included studies focused on early CD outcomes while no studies evaluated long-term outcomes into adulthood. CD is known to involve complex genetic and experiential interactions [54] and may evolve overtime with brain maturation. Delays in speech and language, intellectual delay and borderline intellectual functioning are shown to be associated with poorer academic or employment outcomes in adulthood [55, 56], and early assessment of CD may not fully reveal the extent of delays. The only study with follow-up to the adolescent phase showed a progressive increase in NDI rate as the participants aged, which provides evidence of incremental long-term negative outcomes associated with infantile sepsis [44]. Moving forward, studies with longer follow-up may allow for further examination of the long-term effects of neonatal sepsis on CD.

There were different versions of the BSID instrument (BSID-II and BSID-III) [19, 57, 58]. BSID-II lacked subscales in PDI and MDI scores, leading to the development of BSID-III with the segregation of PDI into fine and gross motor scales and MDI into cognitive, receptive language, and expressive language scales [59]. Although we pooled results of both BSID-II and BSID-III in our study, we recognize that comparisons between BSID-II and BSID-III are technically challenging due to differences in standardised scores [59, 60]. In addition, the BSID-IV was created in 2019 which has fewer items, However, none of our studies utilized this instrument. Future studies should consider this instrument, as well as standardising the timepoints for assessment of CD.

Table 3 Visual impairment assessment and definition

First author, year	Definition of visual impairment	Outcome	Variables adjusted for
de Haan, 2013 [31]	Visual Handicaps	Neonatal Candida Sepsis = 3/17 (18%) Gram Negative Sepsis = 10/33 (30%) Uncomplicated = 8/102 (8%)	NA
Alshaikh, 2014 [33]	Visual acuity < 20/200 following refractive correction	Adjusted OR (95% CI): 0.35 (0.03–3.37), *P*-value = 0.36	NA
Bright, 2017 [52]	Child is legally blind in both eyes	No late onset bacteremia:2 Suspected late onset bacteremia: 6 Definite late onset bacteremia: 7	NA
Mukhopadhyay, 2020 [42]	Corrected vision < 20/200 in both eyes	Adjusted RR (95% CI): 1. EOS vs prolonged antibiotics: -0.40 2. EOS vs no prolonged antibiotics: -0.62	NA
Mukhopadhyay, 2021 [41]	Corrected vision < 20/200 in both eyes	Adjusted RR (95% CI): LOS vs unaffected: 2.40 (0.84–6.80), *P*-value = 0.14 LOCNC vs unaffected: 2.70 (1.14–6.41), *P*-value = 0.03	Maternal education, insurance, race/ethnicity, antenatal antibiotics, antenatal steroids, antepartum haemorrhage, infant GA, birth weight, sex, temperature at < = 60 min of birth, intubation at birth, maximum respiratory support < = 24 h of age, enteral feeds started < = 3 days of birth, receipt of antibiotics for > = 5 days starting < = 72 h of age, severe IVH diagnosed < = 7 days of birth and centre
Brumbaugh, 2022 [47]	Bilateral blindness (visual acuity < 20/200)	Infants with LOM: 4/97 (4%) Infants with LOS and no LOM: 95/2893 (3%) Infants with no LOS or LOM: 62/5982 (1%)[a]	NA
Humberg, 2022 [49]	Visus < 0.8 in the best-performing eye without glasses	No LOS: 181 (18.2 [15.9–20.7]) One LOS: 38 (21.6 [16.0–28.1]) Recurrent LOS: 21 (31.8 [21.5–43.6])[a]	NA

OR Odds Ratio, *RR* Risk Ratio, *NCS* Neonatal Candida Sepsis, *GNS* Gram-Negative Sepsis, *UC* Uncomplicated Sepsis

[a] Statistically significant

Visual impairment

Young infant sepsis was associated with increased risk of developing visual impairment. This was similar to results noted by a previous systematic review published in 2014 [61] and 2019 [62] which showed that neonatal sepsis was associated with twofold risk of developing retinopathy of prematurity in preterm infants. Specifically, meningitis was associated with a greater risk of visual impairment compared to just sepsis alone [47]. The mechanism of visual impairment has not been fully described although various theories have been suggested, including sepsis mediated vascular endothelial damage, increased body oxidative stress response as well as involvement of inflammatory cytokines and mediators [63, 64].

Hearing impairment

Our meta-analysis showed an increased risk of hearing impairment for young infants with young infants with sepsis. This is consistent with a previous report that found an association between neonatal meningitis and sensorineural hearing loss [65]. One potential confounder which we were unable to account for may have been the use of ototoxic antimicrobial agents such as aminoglycosides. Additional confounders include very low birth weight, patient's clinical states (e.g. hyperbilirubinemia requiring exchange transfusion) and use of mechanical ventilation or extracorporeal membrane support. To allow for meaningful comparisons of results across different study populations, it is imperative that a standardised definition of hearing impairment post neonatal sepsis be established for future studies.

Cerebral palsy

Our meta-analysis found an association between neonatal sepsis and an increased risk of developing CP. This is also consistent with previous systematic reviews which had found a significant association of sepsis and CP in VLBW and early preterm infants [11]. One study found that infants born at full term and who experienced neonatal infections were at a higher risk of developing a spastic triplegia or quadriplegia phenotype of CP [66]. The pathophysiology and mechanism of injury to white

Table 4 Hearing impairment assessment and definition

First author, year	Definition of hearing impairment	Outcome	Variables adjusted for
de Haan, 2013 [31]	Clinical hearing loss	Neonatal Candida Sepsis = 4/17 (24%) Gram Negative Sepsis = 6/33 (18%) Uncomplicated = 1/102 (1%)	NA
Alshaikh, 2014 [33]	Deafness: Sensorineural hearing loss requiring amplification	Adjusted OR (95% CI): 2.24 (0.64–7.73), *P*-value = 0.20	NA
Bright, 2017 [52]	Child has hearing aids or a cochlear implant and/or receives special services for the hearing-impaired	No late onset bacteremia: 3 Suspected late onset bacteremia: 3 Definite late onset bacteremia: 7	NA
Mukhopadhyay, 2020 [42]	Permanent hearing loss affecting communication with or without amplification	Adjusted RR (95% CI): EOS vs prolonged antibiotics: 0.67 (0.17–2.69), *P*-value = 0.77 EOS vs no prolonged antibiotics: 0.88 (0.22–3.54), *P*-value = 1.0	NA
Mukhopadhyay, 2021 [41]	Permanent hearing loss with or without amplification	Adjusted RR (95% CI): LOS vs unaffected: 1.83 (0.96–3.47), *P*-value = 0.07 LOCNC vs unaffected: 1.61 (0.94–2.76), *P*-value = 0.10	Maternal education, insurance, race/ethnicity, antenatal antibiotics, antenatal steroids, antepartum haemorrhage, infant GA, birth weight, sex, temperature at < = 60 min of birth, intubation at birth, maximum respiratory support < = 24 h of age, enteral feeds started < = 3 days of birth, receipt of antibiotics for > = 5 days starting < = 72 h of age, severe IVH diagnosed < = 7 days of birth and centre
Brumbaugh, 2022 [47]	Bilateral hearing impairment with no functional hearing (with or without amplification)	Infants with LOM: 8/96 (8%) Infants with LOS and no LOM: 148/2880 (5%) Infants with no LOS or LOM: 159/5940 (3%)[a]	NA
Humberg, 2022 [49]	NR	No LOS: 501 (53.2 [50.0–56.4]) One LOS: 95 (56.5 [49.0–63.9]) Recurrent LOS: 44 (66.7 [54.8–77.1])[a]	NA

OR Odds Ratio, *RR* Risk Ratio, *NCS* Neonatal Candida Sepsis, *GNS* Gram-Negative Sepsis, *UC* Uncomplicated Sepsis

[a] Statistically significant

matter resulting in increased motor dysfunction remains unclear and more research is required in this area.

Limitations and recommendations for future research

The main limitation of this review lies in the heterogeneity in the definitions of sepsis, exposures and assessment of outcomes across studies. This is likely attributed to the varying definition of sepsis used in different countries as well as lack of gold standard definitions or instruments for assessment of each component of NDI. A recent review of RCTs [67] also reported similar limitations where 128 different varying definitions of neonatal sepsis were used in literature. Notably, there is a critical need for developing international standardized guidelines for defining neonatal sepsis as well as assessment of NDI such as hearing and visual impairment. Another important limitation relates to the inability to assess quality of neonatal care delivered as well as temporal changes in medical practices which could have affected neurocognitive outcomes for neonates with sepsis. Improving quality of neonatal care has been shown to significantly reduce mortality risk among neonates with sepsis, especially in resource-poor countries [68]. We performed a comprehensive search strategy (PubMed, Embase, Web of Science and CENTRAL) coupled with hand searching of references within included systematic reviews, but did not evaluate grey literature. Future studies should include additional literature databases and grey literature. Another area of research gap lies in the paucity of data related to differences in neurocognitive outcomes between term and post-term neonates with sepsis and future research is required to bridge this area of research gap. Likewise, there are few studies which evaluated differences in neurocognitive outcomes between early or late onset sepsis and outcomes assessed were significantly heterogenous which limits meaningful meta-analyses. Similarly, there was significant heterogeneity in study outcomes, causative organisms and severity of disease.

We found a lack of long-term outcomes and recommend that future prospective cohorts include a longer follow-up duration as part of the study design. This is important given the implication of NDI on development

Table 5 Cerebral palsy assessment and definition

First author, year	Scale used	Definition of impairment	Outcome	Variables adjusted for
Schlapbach, 2011 [29]	Palisano et al. classification	Non progressive motor disorder characterized by abnormal tone in at least 1 extremity and abnormal control of movement and posture	**Incidence:** Proven sepsis: 14/136 (10%) Suspected sepsis: 17/169 (10%) No sepsis: 10/236 (4%) **OR (95% CI) comparing proven sepsis and uninfected:** Univariable model: 2.90 (1.22–6.89), *P*-value = 0.016 Multivariable model: 3.23 (1.23–8.48), *P*-value = 0.017 **OR (95% CI) comparing suspected sepsis and uninfected:** Univariable model: 2.55 (1.10–5.93), *P*-value = 0.030 Multivariable model: 1.79 (0.61–5.25), *P*-value = 0.287	Center, year of birth, gender, gestational age, birth weight, brain injury, BPD, ROP, socioeconomic status, and postnatal growth.
Mitha, 2013 [32]	European Cerebral Palsy Network	Presence of at least 2 of the following: - Abnormal posture or movement - Increased tone - Hyperreflexia	**Adjusted OR (95% CI):** EOS alone: 1.70 (0.84–3.45), *P*-value = 0.03 LOS alone: 1.71 (1.14–2.56), *P*-value = 0.03 EOS & LOS: 2.33 (1.02–5.33), *P*-value = 0.03	**NA**
Alshaikh, 2014 [33]	NR	Non-progressive motor impairment characterized by abnormal muscle tone in at least one extremity and decreased range or control of movements	Adjusted OR (95% CI): 0.63 (0.24—1.64), *P*-value = 0.34	NA
Mukhopadhyay, 2020 [42]	Gross motor function classification system (GMFCS)	Mild: Level ≤ 1 Moderate: Level 2–3 Severe: Level 4–5	**Adjusted RR (95% CI) for GMFCS level: ≥ 2:** EOS vs prolonged antibiotics: 1.50 (0.91–2.46), *P*-value = 0.11 EOS vs no prolonged antibiotics: 1.74 (1.05–2.88), *P*-value = 0.03	**NA**
Mukhopadhyay, 2021 [41]	Gross motor function classification system (GMFCS)	Mild: Level ≤ 1 Moderate: Level 2–3 Severe: Level 4–5	**Adjusted RR (95% CI) for GMFCS level: ≥ 2:** LOS vs unaffected: 1.16 (0.77–1.76), *P*-value = 0.48 LOCNC vs unaffected: 1.91 (1.40–2.60), *P*-value = < 0.001	**NA**
Ortgies, 2021 [45]	Gross motor function classification system (GMFCS)	NR	**Incidence:** EOS: 4/31 (12.09%) No-EOS: 3/135 (1.65%) *P*-value = 0.014 **OR (95% CI):** 6.519 (1379–30,809), *P*-value: 0.018	**NA**
Brumbaugh, 2022 [47]	Palisano Gross Motor Function Classification System	Gross motor function level ≥ 2	Infants with LOM: 13/97 (13%) Infants with LOS and no LOM: 314/2887 (11%) Infants with no LOS or LOM: 395/5981 (7%)[a]	NA
Humberg, 2022 [49]	Gross motor function classification system (GMFCS)	GMFCS ≥ 1	No LOS: 82 (7.8 [6.3–9.5]) One LOS: 22 (12.0 [7.9–17.3]) Recurrent LOS: 10 (13.0 [6.9–21.8])	NA
Kartam, 2022 [50]	Gross motor function classification system (GMFCS)	NR	No sepsis: 8 (9.6) EOS: 0 (0.0)[a] LOS: 21 (28.0)[a]	NA

GMFCS Gross Motor Function Classification System, *OR* Odds ratio, *RR* Risk ratio, *NR* Not reported

[a] Statistically significant

Table 6 Characteristics of study categorised by early vs late onset sepsis

Authors, year of study	Sample size	Definition of early or late onset sepsis	Outcomes
Late vs early onset sepsis			
Mitha, 2013 [32]	2665 (955)	Early-onset sepsis (EOS) was defined as confirmed infection of maternal origin (vertically transmitted), on the basis of medical records. Late-onset sepsis (LOS) was defined as a postnatally acquired infection (horizontally acquired) treated with antibiotics for at least 7 days, also on the basis of medical records.	1. There was no association between neonatal infection and cognitive impairment 2. The frequency of cerebral palsy was higher in infants with isolated EOS (odds ratio [OR]: 1.70 [95% confidence interval (CI): 0.8423.45]) or isolated LOS (OR: 1.71 [95% CI: 1.1422.56]) than in uninfected infants, and this risk was even higher in cases of combined EOS and LOS (OR: 2.33 [95% CI: 1.0225.33])
Kartam, 2022 [50]	203 (109)	Neonatal sepsis was confirmed using a positive culture, which was defined as any sample of blood or cerebrospinal fluid which tested positive for bacterial growth. A blood culture was considered contaminated if the presence of gram-positive cocci in it was negated by another culture drawn 30-min apart. Early onset sepsis (EOS) was described by a positive blood culture occurring ≤ 72 h after birth, and LOS as an infection contracted after this period. A case of sepsis was considered severe if associated with hemodynamic instability and disseminated intravascular coagulation (DIC)	1. The relationship between LOS and lower motor scores remained significant (adjusted $\beta = -9.5$, 95% CI: −16.4 to −2.7; $p = 0.007$), whereas the association with cognitive and language scores were no longer significant at 3 years of age after adjustment
Early onset sepsis			
Mukhopadhyay, 2020 [42]	6565 (153)	EOS was defined as blood or cerebrospinal fluid (CSF) culture obtained ≤ 72 h of age that grew pathogenic bacteria or fungi, for which the infant received antibiotics ≥ 5 days or died with intent to receive antibiotics ≥ 5 days.	1. Risk of NDI was higher for infants with early onset sepsis (EOS) compared with culture-negative infants who received prolonged early antibiotics and compared with infants who did not receive prolonged early antibiotics 2. Among those without culture-confirmed EOS, the administration of prolonged antibiotics was not associated with any significant difference in outcomes of death and/or NDI
Late onset sepsis			
Hentges, 2014 [35]	411 (94)	Late onset sepsis: presence of positive blood cultures over 72 h of life, followed by clinical signs - changes in breathing pattern - hypothermia or hyperthermia - circulatory symptoms - GIT symptoms	1. VLBW infants with Gram-positive infection showed motor deficit when compared to the non-septic group, 68.8% vs. 29.3%, respectively (OR 6; 1.6–21.8, $p = 0.006$); the cognitive development was similar between the groups 2. However, no differences were observed in cognitive and motor scores for newborns who presented with late-onset sepsis by coagulase-negative Staphylococcus (CNS)
Zonnenberg, 2019 [39]	117 (85)	Late-onset sepsis was defined as a positive blood culture after 72 h of life. If the blood culture did not turn positive but clinical signs implied antibiotic treatment for 7 days, late-onset sepsis was considered probable but not proven. If in one of the episodes a causal microorganism was found, the infant was classified as proven infection	1. No significant differences were found in cognitive, motor, and behavioral scores or lexiquotient comparing patients with versus no proven infection at 2 years correct age
Mukhopadhyay, 2021 [41]	3940 (2387)	Late onset sepsis (LOS) defined as isolation of a pathogen from blood or CSF obtained > 72 h of age and appropriate therapy for ≥ 5 days (≥ 7 days for CSF growth) or death before completed treatment	1. Risk for NDI did not differ between late-onset sepsis (LOS) and late-onset, antibiotic treated, blood culture-negative conditions (LOCNC) 2. Risk for NDI was higher for LOCNC infants compared with unaffected infants (RR 1.17 (1.04–1.31)) 3. Risk for NDI was not significantly higher for LOS compared with unaffected infants (might be due to smaller numbers of LOS)

Table 6 (continued)

Authors, year of study	Sample size	Definition of early or late onset sepsis	Outcomes
Shim, 2021 [46]	2098 (419)	LOS was defined as a postnatally acquired infection which occurred after the third postnatal day of life. Only sepsis confirmed by blood culture was considered.	1. LOS had a significant association with cognitive delay (adjusted odds ratio, 1.48; 95% confidence interval, 1.02–2.16), but no association with motor delay in VLBWIs at 18–24 months of correct age
Brumbaugh, 2022 [47]	13,372 (4731)	LOS was defined as isolation of a bacterial or fungal pathogen from blood obtained more than 72 h after birth and accompanied by treatment for at least 5 days or death before completed treatment.	1. NDI was present in 42% (95%CI, 32%-52%) of children with LOM and in 43% (95%CI, 41%-45%) of children with LOS without LOM compared with only 33% (95%CI, 32%-34%) of children with neither infection ($P < .001$) 2. The incidences of cerebral palsy (24%; 95% CI, 3%-14%), abnormal visual acuity (24%; 95%CI, 15%-32%), and bilateral hearing impairment (8%; 95%CI, 3%-14%) were highest among infants with a history of LOM

CI confidence interval, *EOS* early onset sepsis, *LOS* late onset sepsis, *LOCNC* late-onset, antibiotic treated, blood culture-negative conditions, *NDI* neurodevelopmental impairment, *OR* odds ratio, *RR* Relative risk, *VLBW* very low birth weight

Table 7 Characteristics of study categorised by culture positive vs clinical sepsis

Authors, year of study	Sample size	Definition of sepsis	Outcomes
Culture positive vs culture negative sepsis			
Schlapbach, 2011 [29]	541 (305)	Proven sepsis: Positive result on 1 or more bacterial or fungal cultures obtained from blood or cerebrospinal fluid in an infant with clinical signs of infection (temperature instability, irritability, apathia, feeding difficulties, prolonged capillary refill, apnea, tachycardia, and tachypnea) treated with antibiotics for 5 or more days or until death pathogens that may represent contaminations were considered as proven sepsis only if laboratory signs of infection such as elevated CRP, left shift, or leukopenia, were present and if the sepsis episode had been treated for 5 or more days or until death Suspected sepsis: an episode with clinical and/or laboratory signs of infection in the absence of a positive bacterial or fungal culture from a normally sterile site in an infant who received treatment with antibiotics for 5 or more days or until death	1. Proven sepsis independently increased the risk of CP (OR: 3.23 [95% CI: 1.23– 8.48]; $P=0.017$) and NDI (OR: 1.69 [95% CI: 0.96 –2.98]; $P=0.067$) 2. Suspected sepsis was not associated with neurodevelopmental outcome ($P>0.05$)
de Haan, 2013 [31]	204 (84)	1. Gram-negative bacteria or candida species found in peripheral blood cultures 2. Clinical sepsis: At least 2 of the following symptoms - Increase in frequency or duration of apnoea or bradycardia (not related to feeding problems or airway obstruction) necessitating an increase in ventilatory support - Hypothermia or hyperthermia - Circulatory compromise: Systolic blood pressure < P5	1. No difference in adverse outcome (death or severe NDI) between GNS and NCS infants, and between NCS and uncomplicated group 2. Significantly adverse outcomes between GNS and UC group (OR 4.8 (1.5–15.9))
Ferreira, 2014 [34]	194 (86)	1. Presence of a positive blood culture 2. Presence of clinical and laboratory signs suggestive of infection	1. Preterm infants with very low birthweight that had neonatal sepsis are 2.5 times more likely to have altered neuromotor development at 12 months of corrected age, regardless of other risk factors
Bright, 2017 [52]	894 (362)	Documented late bacteremia: Recovery of an organism from blood drawn during week 2, 3, or 4. Specific organisms were not identified. Suspected infections: Culture-negative, but the infants received antibiotics for more than 72 h	1. Late-onset bacteremia was not associated with executive or motor dysfunctions 2. Participants with bacteremia during the second to fourth postnatal week of life were at increased risk for intellectual impairment (low IQ) at age 10 years 3. Children with either suspected or definite bacteremia were more likely than their peers without bacteremia to be legally blind in both eyes. 4. Children with definite bacteremia were slightly more likely than other children to have a hearing impairment

Table 7 (continued)

Authors, year of study	Sample size	Definition of sepsis	Outcomes
Savioli, 2018 [37]	65,938 (3639)	Criteria for sepsis: documented clinical symptoms, five or more days of antibiotic use, and a positive laboratory screening test (positive microbial growth in the blood, urine, or CSF). Suspected sepsis: clinical symptoms of sepsis and five or more days of antibiotic use without a positive laboratory screening test, consistent with other studies' definition of suspected sepsis	1. After adjustment for known developmental risk factors, sepsis and suspected sepsis were associated with increased risk for any developmental delay, (1.48 (1.05–2.09) and 1.09 (1.01–1.18)), respectively, and multiple developmental delay sub-types - Preterm infants with suspected sepsis: Significantly increased risks of communication and developmental delay - Preterm infants with known sepsis: Significantly increased risks of developmental delay - Term infants with suspected sepsis: Significantly increased risks of developmental, learning and pervasive developmental disorders (PDD) delay - Term infants with known sepsis: Significantly increased risks of communication, developmental, learning, motor and PDD delay 2. Suspected sepsis did not appear to confer as great a risk as known sepsis, suspected sepsis was significantly associated with multiple categories of neurodevelopmental delay in unadjusted and adjusted models
Zonnenberg, 2019 [39]	117 (85)	Late-onset sepsis was defined as a positive blood culture after 72 h of life. If the blood culture did not turn positive but clinical signs implied antibiotic treatment for 7 days, late-onset sepsis was considered probable but not proven. If in one of the episodes a causal microorganism was found, the infant was classified as proven infection.	1. No significant differences were found in cognitive, motor, and behavioral scores or lexiquotient comparing patients with versus no proven infection at 2 years correct age
Ortgies, 2021 [45]	342 (54)	Culture-proven EOS was defined as a positive result of one or more bacterial or fungal blood cultures obtained from patients and antimicrobial treatment for at least 5 days Clinical EOS was defined using established laboratory parameters and persistent clinical presentation	1. EOS among VLBW-infants significantly impaired the neurodevelopment at 2 years corrected age 2. BSIDII examinations were carried out at a median of 24 months (Range 23 – 31 months) corrected age with no significant difference between the study groups 3. MDI values were similar in both study groups, however PDI values were significantly lower in the EOS group - In particular, PDI values < 70 showed a significant association with infection while PDI values < 85 only showed a weak association 4. Occurrence of cerebral palsy was significantly higher in the EOS group
Culture positive			
Adams-Chapman, 2013 [30]	1317 (1037)	Positive blood culture and antibiotic therapy for > = 5 days	1. Candida infected had significantly higher odds of NDI compared with uninfected NRN registry infants with no history of suspected sepsis or proven sepsis (OR (95% CI) = 1.83 (1.01,3.33, $p = 0.047$) 2. Survivors with systemic candidiasis had a similar risk of poor neurologic outcome as those infected with other pathogens, which suggests that the pathophysiologic pathways resulting in CNS injury in infected preterm neonates may not be pathogen specific 3. Duration of positive cultures did not predict the risk for NDI

Table 7 (continued)

Authors, year of study	Sample size	Definition of sepsis	Outcomes
Hentges, 2014 [35]	411 (94)	Late onset sepsis: presence of positive blood cultures over 72 h of life, followed by clinical signs - changes in breathing pattern - hypothermia or hyperthermia - circulatory symptoms - GIT symptoms	1. VLBW infants with Gram-positive infection showed motor deficit when compared to the non-septic group, 68.8% vs. 29.3%, respectively (OR 6; 1.6–21.8, $p = 0.006$); the cognitive development was similar between the groups 2. However, no differences were observed in cognitive and motor scores for newborns who presented with late-onset sepsis by coagulase-negative Staphylococcus (CNS)
Singh, 2018 [38]	160 (80)	Positive blood culture	1. At the six-month follow-up, there is a statistically significant difference ($P = 0.001$) in neurodevelopmental impairment (NDI) between the culture-positive infants and the controls 2. There is also a statistically significantly lower median developmental ($P = 0.001$), motor ($P \leq 0.001$), and mental ($P = 0.002$) quotients in infants with culture-positive sepsis compared to controls
Mukhopadhyay, 2020 [42]	6565 (153)	EOS was defined as blood or cerebrospinal fluid (CSF) culture obtained ≤ 72 h of age that grew pathogenic bacteria or fungi, for which the infant received antibiotics ≥ 5 days or died with intent to receive antibiotics ≥ 5 days.	1. Risk of NDI was higher for infants with early onset sepsis (EOS) compared with culture-negative infants who received prolonged early antibiotics and compared with infants who did not receive prolonged early antibiotics 2. Among those without culture-confirmed EOS, the administration of prolonged antibiotics was not associated with any significant difference in outcomes of death and/or NDI
Mukhopadhyay, 2021 [41]	3940 (2387)	Late onset sepsis (LOS) defined as isolation of a pathogen from blood or CSF obtained > 72 h of age and appropriate therapy for ≥ 5 days (≥ 7 days for CSF growth) or death before completed treatment	1. Risk for NDI did not differ between late-onset sepsis (LOS) and late-onset, antibiotic treated, blood culture-negative conditions (LOCNC) 2. Risk for NDI was higher for LOCNC infants compared with unaffected infants (RR 1.17 (1.04–1.31)) 3. Risk for NDI was not significantly higher for LOS compared with unaffected infants (might be due to smaller numbers of LOS)
Shim, 2021 [46]	2098 (419)	LOS was defined as a postnatally acquired infection which occurred after the third postnatal day of life. Only sepsis confirmed by blood culture was considered.	1. LOS had a significant association with cognitive delay (adjusted odds ratio, 1.48; 95% confidence interval, 1.02–2.16), but no association with motor delay in VLBWIs at 18–24 months of correct age
Brumbaugh, 2022 [47]	13,372 (4731)	LOS was defined as isolation of a bacterial or fungal pathogen from blood obtained more than 72 h after birth and accompanied by treatment for at least 5 days or death before completed treatment.	1. NDI was present in 42% (95%CI, 32%-52%) of children with LOM and in 43% (95%CI, 41%-45%) of children with LOS without LOM compared with only 33% (95%CI, 32%-34%) of children with neither infection ($P < .001$) 2. The incidences of cerebral palsy (24%; 95% CI, 3%-14%), abnormal visual acuity (24%; 95%CI, 15%-32%), and bilateral hearing impairment (8%; 95%CI, 3%-14%) were highest among infants with a history of LOM

Table 7 (continued)

Authors, year of study	Sample size	Definition of sepsis	Outcomes
Humberg, 2022 [49]	1343 (263)	Neonatal sepsis was confirmed using a positive culture, which was defined as any sample of blood or cerebrospinal fluid which tested positive for bacterial growth	1. Recurrent sepsis to be significantly associated with adverse motor development (critical MABC-2 testing: 3.3 [1.5–7.3], $p = 0.003$, pB = 0.012) 2. No significant impact of recurrent LOS was found on intelligence quotient and behavioral difficulties 3. Odds of having critical motor testing results for infants with recurrent LOS were 1.7 times (95% confidence interval 1.4–2.3) that of infants with one LOS 4. The study could not demonstrate that infants with single events or recurrent episodes of neonatal LOS had an higher likelihood for CP, intelligence, or behavioral difficulties when all cases were pooled and adjusted for important neonatal risk factors
Kartam, 2022 [50]	203 (109)	Neonatal sepsis was confirmed using a positive culture, which was defined as any sample of blood or cerebrospinal fluid which tested positive for bacterial growth. A blood culture was considered contaminated if the presence of gram-positive cocci in it was negated by another culture drawn 30-min apart. Early onset sepsis (EOS) was described by a positive blood culture occurring ≤ 72 h after birth, and LOS as an infection contracted after this period. A case of sepsis was considered severe if associated with hemodynamic instability and disseminated intravascular coagulation (DIC)	1. The relationship between LOS and lower motor scores remained significant (adjusted β = −9.5, 95% CI: −16.4 to −2.7; $p = 0.007$), whereas the association with cognitive and language scores were no longer significant at 3 years of age after adjustment
Paul, 2022 [51]	577 (159)	GBS-meningitis was diagnosed by GBS-positive cerebrospinal fluid (CSF) culture in most cases (67¢4%), but five cases defined as meningitis had suggestive CSF leucocyte count of > 20 £ 106/l plus GBS-positive blood culture and nine had GBS-positive blood culture plus suggestive clinical symptoms of meningitis.	1. GBS disease is on average associated with a higher risk of moderate/severe NDI (adjusted odds ratio: 1.27 (95% CI: 0.65, 2.45)) 2. Mild impairment was also more frequent in GBS (27.6% (95% CI: 20.3 – 35.5%)) compared to non-GBS children (12.9% (95% CI: 9.7% -16.4%)) 3. The risk of emotional-behavioural problems was similar irrespective of GBS exposure (aRR = 0.98 (95% CI: 0.55, 1.77))

CI confidence interval, *CP* cerebral palsy, *CSF* cerebrospinal fluid, *EOS* early onset sepsis, *GBS* Group B streptococcus, *GNB* gram negative bacteremia, *IQ* intellectual quotient, *LOS* late onset sepsis, *NDI* neurodevelopmental impairment, *NCS* neonatal candida sepsis, *OR* odds ratio, *RR* Relative risk, *VLBW* very low birth weight

Table 8 Meta analysis related to neurocognitive outcomes among infants with sepsis

Parameter	Study	Subgroup by scale and cut-off	Unadjusted OR (95%CI)	Adjusted OR (95% CI)
MDI	Ortgies, 2021 [45]	MDI < 70	0.45 [0.07; 2.84]	-
	Ortgies, 2021 [45]	MDI < 70	19.50 [0.59; 645.19]	**25.56 [1.29; 506.04]**
	Schlapbach, 2011 [29]	MDI < 70	1.47 [0.74; 2.92]	1.37 [0.63; 2.96]
	Schlapbach, 2011 [29]	MDI < 70	1.13 [0.57; 2.22]	0.70 [0.31; 1.58]
	Subtotal	**MDI < 70**	**1.26 [0.80; 2.00]**	1.54 [0.42; 5.58]
	Ferreira, 2014 [34]	MDI < 85	1.90 [1.05; 3.41]	1.05 [0.52; 2.12]
	Hentges, 2014 [35]	MDI < 85	3.10 [0.54; 17.82]	3.90 [0.54; 28.32]
	Hentges, 2014 [35]	MDI < 85	0.90 [0.29; 2.83]	0.90 [0.19; 4.26]
	Hentges, 2014 [35]	MDI < 85	1.10 [0.18; 6.91]	0.30 [0.01; 7.79]
	Ortgies, 2021 [45]	MDI < 85	0.77 [0.25; 2.35]	-
	Subtotal	**MDI < 85**	**1.42 [0.87; 2.34]**	1.11 [0.61; 2.02]
	Shim, 2021 [46]	MDI < 80	2.21 [1.73; 2.82]	**1.48 [1.02; 2.15]**
	Total		**1.57 [1.14; 2.16]**	1.30 [0.99; 1.71]
PDI	Ortgies, 2021 [45]	PDI < 70	19.38 [0.58; 643.51]	14.62 [0.07; 3211.34]
	Ortgies, 2021 [45]	PDI < 70	6.55 [1.20; 35.71]	2.70 [0.19; 38.89]
	Schlapbach, 2011 [29]	PDI < 70	2.10 [1.00; 4.39]	1.80 [0.82; 3.94]
	Schlapbach, 2011 [29]	PDI < 70	1.71 [0.85; 3.42]	1.36 [0.62; 2.96]
	Shim, 2021 [46]	PDI < 70	1.23 [0.75; 2.02]	-
	Subtotal	**PDI < 70**	**1.74 [1.15; 2.63]**	1.63 [0.95; 2.80]
	Ferreira, 2014 [34]	PDI < 85	2.72 [1.27; 5.83]	1.99 [0.88; 4.51]
	Ferreira, 2014 [34]	PDI < 85	2.99 [1.03; 8.70]	1.60 [0.48; 5.32]
	Hentges, 2014 [35]	PDI < 85	4.81 [0.93; 24.90]	6.00 [0.93; 38.90]
	Hentges, 2014 [35]	PDI < 85	0.40 [0.06; 2.83]	0.50 [0.05; 4.87]
	Hentges, 2014 [35]	PDI < 85	1.60 [0.23; 11.36]	0.80 [0.04; 15.15]
	Ortgies, 2021 [45]	PDI < 85	2.26 [0.71; 7.17]	-
	Subtotal	**PDI < 85**	**2.43 [1.49; 3.94]**	**1.85 [1.01; 3.36]**
	Total		**1.98 [1.42; 2.74]**	**1.73 [1.16; 2.58]**
MDI or PDI	de Haan, 2013 [31]	MDI or PDI < 70	3.13 [0.16; 62.63]	-
	de Haan, 2013 [31]	MDI or PDI < 70	13.46 [1.83; 98.99]	-
	Subtotal	**MDI or PDI < 70**	**8.60 [1.63; 45.26]**	**-**
	de Haan, 2013 [31]	MDI or PDI between 70 and 84	7.10 [1.55; 32.53]	-
	de Haan, 2013 [31]	MDI or PDI between 70 and 84	2.01 [0.51; 8.03]	-
	Schlapbach, 2011 [29]	MDI or PDI between 70 and 84	1.12 [0.63; 1.99]	0.96 [0.51; 1.82]
	Schlapbach, 2011 [29]	MDI or PDI between 70 and 84	1.05 [0.61; 1.82]	1.23 [0.67; 2.25]
	Subtotal	**MDI or PDI between 70 and 84**	**1.49 [0.81; 2.71]**	1.09 [0.70; 1.70]
	Mukhopadhyay, 2021 [41]	MDI or PDI < 85	1.38 [1.06; 1.80]	1.12 [0.93; 1.35]
	Mukhopadhyay, 2021 [41]	MDI or PDI < 85	1.41 [1.15; 1.74]	1.15 [0.98; 1.35]
	Subtotal	**MDI or PDI < 85**	**1.40 [1.19; 1.65]**	**1.14 [1.01; 1.28]**
	Total		**1.40 [1.20; 1.62]**	**1.13 [1.01; 1.28]**
Visual impairment	de Haan, 2013 [31]		2.52 [0.43; 14.61]	-
	de Haan, 2013 [31]		5.11 [1.43; 18.21]	-
	Mukhopadhyay, 2021 [41]		2.41 [0.66; 8.76]	2.40 [0.66; 8.68]
	Mukhopadhyay, 2021 [41]		2.72 [0.94; 7.89]	2.70 [0.94; 7.76]
	Brumbaugh, 2022 [47]		4.11 [1.42; 11.89]	-
	Brumbaugh, 2022 [47]		3.24 [2.15; 4.88]	-
	Total		**3.27 [2.35; 4.54]**	**2.57 [1.14; 5.82]**

Table 8 (continued)

Parameter	Study	Subgroup by scale and cut-off	Unadjusted OR (95%CI)	Adjusted OR (95% CI)
Hearing impairment	de Haan, 2013 [31]		31.08 [1.93; 499.30]	-
	de Haan, 2013 [31]		22.44 [1.59; 315.81]	-
	Mukhopadhyay, 2021 [41]		1.85 [0.83; 4.13]	1.83 [0.83; 4.03]
	Mukhopadhyay, 2021 [41]		1.62 [0.83; 3.16]	1.61 [0.83; 3.11]
	Brumbaugh, 2022 [47]		3.28 [1.54; 6.99]	-
	Brumbaugh, 2022 [47]		1.96 [1.48; 2.60]	-
	Total		**2.08 [1.65; 2.63]**	**1.70 [1.02; 2.81]**
Cerebral palsy	Mukhopadhyay, 2021 [41]		1.59 [0.93; 2.71]	-
	Mukhopadhyay, 2021 [41]		2.54 [1.70; 3.80]	-
	Ortgies, 2021 [45]		6.52 [1.38; 30.81]	-
	Schlapbach, 2011 [29]		2.90 [1.00; 8.37]	3.23 [0.99; 10.54]
	Schlapbach, 2011 [29]		2.55 [0.91; 7.14]	1.79 [0.48; 6.69]
	Brumbaugh, 2022 [47]		2.18 [1.20; 3.96]	-
	Brumbaugh, 2022 [47]		1.72 [1.43; 2.07]	-
	Total		**2.02 [1.62; 2.52]**	**2.48 [1.03; 5.99]**

Legend: *MDI* Mental Developmental Index, *PDI* Psychomotor Developmental Index

Foot note: Mild MDI or PDI: < 85 or < 80; Moderate MDI or PDI < 70; Severe MDI or PDI < 55

into adulthood. Most data were reported for preterm infants with low birth weight, and there was a paucity of data for term infants in our literature review. Since prematurity itself is a significant cause of NDI [69], future studies should consider how gestational age and/or birth weight can be adequately adjusted for in the analysis.

Apart from the domains of NDI we chose to focus on in this review, there are other cognitive domains classified by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) [70] and/or recommended by the Common Data Elements (CDE) workgroup [71]. Future studies may wish to look into the implications of sepsis on other neuro-cognitive domains related to executive function, complex attention and societal cognition which are studied for other types of acquired brain injury [71, 72].

Conclusion

Our systematic review and meta-analysis found that neonates surviving sepsis are at a higher risk of poorer neurodevelopment. However, the evidence is limited by significant heterogeneity and selection bias due to differing definitions used for NDI and for sepsis. There is also a lack of long-term follow-up data, as well as data specific for term and post-term infants. Future prospective studies should be conducted with long-term follow-up to assess the impact of neurodevelopmental impairment among all populations of neonates with sepsis.

Supplementary Information

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Supplementary Material 1.

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Conflict of interest

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Authors' contribution

SLC and JHL were the study's principal investigators and were responsible for the conception and design of the study. WJO, JJBS, BY, GE, NAM and CLN were the co-investigators. WJO, JJBS, BY, GE, NAM and CLN were responsible for the screening and inclusion of articles and data extraction. All authors contributed to the data analyses and interpretation of data. WJO, JJBS, BY, GE, NAM and CLN prepared the initial draft of the manuscript. All authors revised the draft critically for important intellectual content and agreed to the final submission. All authors had access to all study data, revised the draft critically for important intellectual content and agreed to the final submission.

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Availability of data and materials

All data generated or analyzed in the study are found in the tables and supplementary materials.

Declarations

Ethics approval and consent to participate
As this was a systematic review with no access to patient data, ethical approval from the institutional review board was exempted.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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