Global prevalence of long-term neurodevelopmental impairment following extremely preterm birth: a systematic literature review

Sujata P. Sarda[1],*, **Grammati Sarri**[2],* **and Csaba Siffel**[1,3] (iD)

Abstract

Objective: Neurodevelopmental impairment (NDI) is a major complication of extreme prematurity. This systematic review was conducted to summarize the worldwide long-term prevalence of NDI associated with extreme prematurity.

Methods: Embase and MEDLINE databases were searched for epidemiologic and observational/real-world studies, published in English between 2011 and 2016, reporting long-term prevalence of NDI (occurring from 1 year) among extremely preterm infants born at gestational age (GA) $\leq$28 weeks.

Results: Of 2406 articles identified through searches, 69 met the protocol NDI definition (24 North America, 25 Europe, 20 Rest of World). Prevalence of any severity NDI in North America was 8%–59% at 18 months to 2 years, and 11%–37% at 2–5 years; prevalence of moderate NDI in Europe was 10%–13% at 18 months to 2 years, 3% at 2–5 years, and 9%–19% at $\geq$5 years; prevalence of any NDI in Rest of World was 15%–61% at 18 months to 2 years, and 42% at 2–5 years (no North America/Rest of World studies reported any NDI at $\geq$5 years). A trend toward higher prevalence of NDI with lower GA at birth was observed.

Conclusions: Extreme prematurity has a significant long-term worldwide impact on neurodevelopmental outcomes.

[1]Global Evidence and Outcomes, Takeda, Lexington, MA, USA
[2]Evidence Synthesis, Modeling & Communication, Evidera, London, UK
[3]College of Allied Health Sciences, Augusta University, Augusta, GA, USA

*Affiliations at the time this study was performed.

Corresponding author:
Csaba Siffel, Global Evidence and Outcomes, Takeda, 300 Shire Way, Lexington, MA 02421, USA.
Email: csaba.siffel@takeda.com

Introduction

Preterm birth is one of the leading causes of infant and childhood death.[1,2] Although survival of infants born extremely preterm (birth at gestational age [GA] <28 weeks) has improved in recent decades,[3,4] premature infants remain at risk of major complications, including respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL). In particular, neurologic injury from IVH and PVL can result in lifelong neurodevelopmental impairment (NDI), imposing a significant burden on children, their caregivers, and health systems, with impacts well into adulthood.[5–9]

Major neurodevelopmental disabilities commonly associated with IVH in extremely preterm infants include cerebral palsy (CP), deafness, blindness, cognitive delay, and behavioral difficulties.[10–14] While some of these outcomes can be identified in the first 2–3 years of a child's life, neurobehavioral and emotional problems emerge later, at school age, and may persist into adulthood.

Because of variations in the way gestational age at birth is reported, variations in the definitions and reporting of NDI, and heterogeneity in the tools used to assess NDI, comparing results across studies is difficult. To the best of our knowledge, at the time this systematic literature review (SLR) was conducted, no SLRs evaluating the global prevalence of NDI in extremely preterm infants had been published.

A greater understanding of the global scope and long-term impact of neurodevelopmental morbidities associated with extreme prematurity may inform parent counseling, early interventions, and resource planning, and identify further research needs for this group of children. However, the systematic identification, collection, and synthesis of data from studies reporting such outcomes is key, to produce unbiased conclusions on the long-term impact of NDI associated with extreme prematurity and allow comparability of findings across studies. For that reason, the current SLR was designed to investigate the following research question: 'What is the global prevalence of long-term neurodevelopmental impairment in children and adults born at extremely premature gestational ages?' The aim of this SLR was to evaluate the prevalence of two long-term outcomes that are commonly associated with extreme prematurity: NDI and CP.

Methods

Overall SLR methodology

The SLR was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines,[15] and is registered in the Research Registry (https://www.research registry.com; UIN reviewregistry1155). The Embase and MEDLINE databases were searched for articles published in English between January 2011 and June

2016, reflecting a 5-year search, initiated in 2016, that was intended to capture the most current available data. Conference abstracts were excluded, unless they were available in a full-text, peer-reviewed publication format. The search strategy used a combination of free-text and controlled-vocabulary search terms relevant to long-term outcomes of extreme prematurity. Validated search terms were used where available. The full search strategy is available in Supplemental Tables 1–3. The bibliographies of SLRs and meta-analyses published from 2011 to 2016 were reviewed for additional articles. A first level of review identified relevant abstracts and excluded those meeting any of the study exclusion criteria. Publications that were not eliminated passed to the second level of review, which involved the evaluation of the full text. All abstracts were independently screened by one researcher (DM), and 30% were randomly selected for double-screening by two independent researchers (DM and SA). Any disagreement was resolved by a third researcher (GS).

Selection criteria and data extraction

Studies that reported the long-term prevalence of NDI were selected for the present analysis. Inclusion criteria were: (1) humans born at ≤27 weeks 6 days GA–although in prespecified instances, infants born at 28 weeks GA were included in the extremely preterm population to take into account variations in reporting of GA at birth (see Supplemental Table 4 for expanded inclusion criteria); (2) study outcomes that included the prevalence of long-term outcomes; (3) epidemiologic and observational/real-world studies; and (4) English-language publications.

Neurodevelopmental impairment was assessed as at least one type of neurologic (including CP) or sensory disability using the different scales reported by authors in the included studies. Data on NDI severity were extracted where available. 'Long-term' was defined as assessment for NDI at ≥12 months after birth. Studies were excluded if they presented results for mixed populations (preterm and term neonates) without a subgroup analysis by GA at birth. Clinical trials, case studies, and protocols were excluded (Supplemental Table 4). Although a study sample size may be a significant factor in determining the generalizability of its findings, no further selection criteria were applied during the present study selection in order to capture all available information on the long-term burden of extreme prematurity. For each included study, data were extracted into a standardized predesigned extraction table by one researcher (DM) and further validated for accuracy and correctness by a second researcher (SA).

Data synthesis

Data were synthesized using qualitative methods to describe the existing body of knowledge on the prevalence of NDI. Studies were grouped according to identified themes, and a narrative synthesis was used to draw on the connections between studies and the objectives of the review. For comparability purposes, data were categorized by geographic location: Europe, North America, and Rest of World. Although CP was considered part of the NDI assessment, the results are presented separately (NDI and CP) where data are available.

For studies reporting long-term outcomes or clinical burden by comparing two groups of extremely preterm infants, with and without specific characteristics (e.g. a specific mode of delivery) or comorbidities (e.g. preterm premature rupture of membranes, IVH, or sepsis), data for the group without the specific characteristics were selected and included in the current

SLR. This was done to increase comparability of results across studies and to enhance generalizability of results to the target population (i.e. extremely preterm infants). For studies that reported follow-up data on NDI at several time points, data from the oldest age cohort are presented, unless specified otherwise. Prevalence data for NDI and CP stratified by GA (where available) are presented separately.

Results

Searches identified 2406 publications. After duplicates were removed, 1937 records were reviewed, and 646 were selected for full-text evaluation. A further 563 publications that did not meet the inclusion criteria were then excluded. The main reasons for exclusion were: a mixed population without separate reporting of data for the population of interest (i.e. term and preterm infants); no outcomes of interest; short-term outcomes; and studies that excluded extremely preterm infants. In total, 69 articles relevant to NDI were included in the present analysis (Figure 1).

NDI by geographic location

Overall, there were wide variations in prevalence estimates among the included studies, particularly between North America and Europe (Figure 2). Across geographic settings, NDI was commonly assessed using the Bayley Scales of Infant Development (Supplemental Table 5).[16,17]

North America. Twenty-four North American studies reported findings for NDI (United States, 20; Canada, four) (Table 1).[18–41] Of those studies, 13 were of prospective design and 11 were
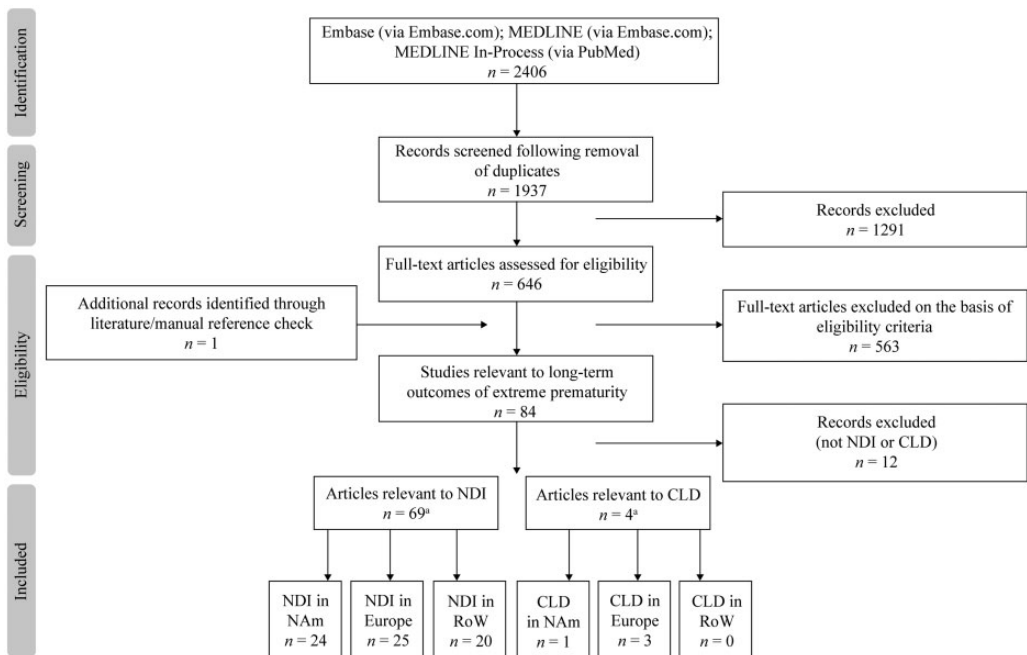
Figure 1. Study selection process for publications reporting on the prevalence of NDI (PRISMA flowchart). CLD, chronic lung disease; NAm, North America; NDI, neurodevelopmental impairment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RoW, Rest of World. (A total of 4 articles were identified relevant to CLD; these were excluded from the present SLR as not relevant to NDI).
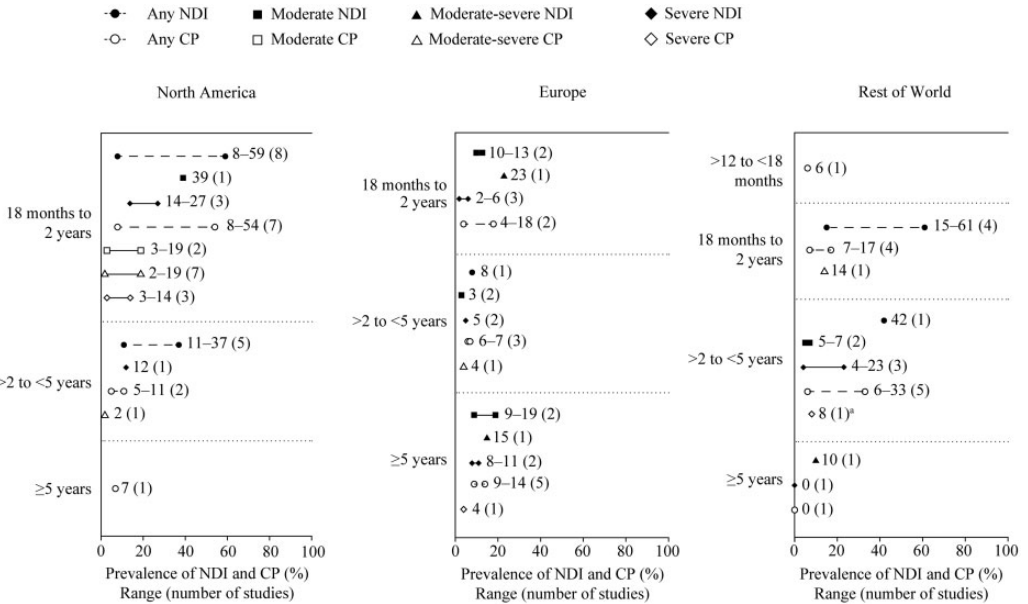
Figure 2. Reported prevalence of NDI in included studies by length of follow-up, in (left to right) North America, Europe, and Rest of World. [a]Ishii 2013 reports 'profound' CP. CP, cerebral palsy; NDI, neurodevelopmental impairment.

retrospective. Sample size varied considerably, ranging from 44 to 3608.[20,27] The reported prevalence of any NDI (in studies that reported an aggregate of NDI of any type or severity) among children born extremely preterm ranged from 8% to 59% at 18 months to 2 years follow-up,[18,26] and from 11% to 37% between 2 and 5 years follow-up (Figure 2; Table 1).[35,39] No studies reported the proportion of children with any NDI at ≥5 years follow-up. The prevalence of severe NDI ranged from 12% to 27% across all follow-up durations (reported in four studies).[23,27,28,37] The prevalence of any CP was 8%–54% at 18 months to 2 years follow-up,[19,23,31,32] 5%–11% between 2 and 5 years follow-up,[35,37] and 7% at ≥5 years follow-up.[40]

Three studies reported NDI stratified by GA, in which a trend toward a higher prevalence of NDI with lower GA at birth was observed (Supplemental Table 6).[22,24,37]

Prevalence of any NDI was 48%–65% for infants born at GA 23 weeks versus 26% for those born at GA 27 weeks.[22,24,37]

Europe. Twenty-five studies in European populations reported findings for NDI (Table 2),[8,42–65] over half of which (15/25) were database or registry-based studies. Included studies were conducted in Austria, Denmark, England, Estonia, France, the Netherlands, Norway, Poland, Spain, Sweden, and Switzerland. Sample sizes in included studies ranged considerably from 17 to 1673.[48,60] Six studies included secondary analyses of Extremely Preterm Infants in Sweden Study (EXPRESS)–a large, prospective, population-based follow-up study of infants born in Sweden at <27 weeks of GA.

The prevalence of NDI as a complication of extreme prematurity was most frequently reported as moderate or severe NDI. The prevalence of moderate NDI was 10%–13% at 18 months to 2 years follow-

Table 1. Identified articles reporting on the prevalence of NDI and CP in North America, by length of follow-up period ($n = 24$).

Article*, country	Study design; setting	Preterm population definition	Sample size	NDI, %	CP, %
18 months to 2 years follow-up ($n = 17$)[a]					
Carlo 2011;[25] USA	Prospective; multicenter	401–1000 g and 22–25 wGA	2628[g]	49 (any)	12 (moderate-severe)
Hintz 2011;[26] USA	Retrospective; multicenter	401–1000 g and <25 wGA	405[f]	59 (any)	15 (moderate-severe) 6 (severe)
Natarajan 2012;[33] USA	Prospective; multicenter	401–1000 g	556[h]	NR	2 (moderate-severe)
Stephens 2012;[18] USA	Prospective; multicenter	<27 wGA	554	8 (any)	3 (moderate)
Vohr 2012;[30] USA	Retrospective; multicenter	401–1000 g and <27 wGA	922[f]	NR	15 (any) 7 (moderate-severe)
Goldstein 2013;[22] USA	Retrospective; multicenter	401–1000 g and 23–28 wGA, with no intracranial hemorrhage or severe intracranial hemorrhage	3445	39 (any)	NR
Payne 2013;[19] USA	Prospective; multicenter	<26 weeks 6/7 days estimated GA	1021[b]	10 (NDI <70)[c] 27 (NDI <85)[d]	8 (any) 4 (moderate-severe)
Salas 2013;[28] USA	Retrospective; single center	24–29 wGA	347	18 (severe)	NR
Tsai 2013;[31] USA	Prospective; NR	Preterm infants with intraparenchymal hemorrhage	48	NR	54 (any)
Tsai 2014;[32] USA	Retrospective; single center	<1000 g or <27 wGA, with intraparenchymal hemorrhage	48	NR	54 (any) 19 (moderate) 14 (severe)
Miltaha 2015;[27] USA	Prospective; single center	23 weeks 7 days to 23 weeks 6/7 days GA	44	39 (moderate) 27 (severe)	NR

Table 1. Continued.

Article*; country	Study design; setting	Preterm population definition	Sample size	NDI, %	CP, %
Batton 2016;[21] USA	Prospective; multicenter	23–26 wGA	232	19 (any)	NR
Boghossian 2016;[20] USA	Retrospective; multicenter	22–28 wGA	3608[e]	16 (any)	12 (any) / 6 (moderate-severe)
Lefebvre 2016;[23] Canada	Retrospective; single center	≤28 wGA	160	47 (any) / 14 (severe)	8 (any) / 3 (severe)
Leviton 2016;[34] USA	Prospective; multicenter	<28 wGA	940	NR	Various[i]
VanderVeen 2016;[29] USA	Prospective; single center	<28 wGA	996	NR	11 (any)
Younge 2016;[24] USA	Retrospective; single center	22–24 wGA	187[f]	47 (any)	19 (moderate-severe)
>2 years to <5 years follow-up (n = 5)[a]					
Lodha 2011;[38] Canada	Retrospective; NR	≤28 wGA, born to older mothers	688 early maternal age 28 advanced maternal age	35 early maternal age 36 advanced maternal age	NR
Lodha 2011;[39] Canada	Prospective; single center	≤28 wGA, cesarean section versus vaginal route	251 cesarean section 274 vaginal route	37 cesarean section 36 vaginal route	NR
Zayek 2011;[37] USA	Retrospective; single center	<1000 g and 22–26 wGA	328[f]	32 (any) / 12 (severe)	5 (any) / 2 (moderate-severe)
Wickremasinghe 2012;[35] USA	Prospective; single center	≤27 weeks 6/7 days GA	96[f]	11 (any)	11 (any)
Alshaikh 2014;[36] Canada	Retrospective; single center	<29 wGA	105 CoNS 227 no CoNS	25 CoNS 15 no CoNS	NR

(continued)

Table 1. Continued.

Article*; country	Study design; setting	Preterm population definition	Sample size	NDI, %	CP, %
≥5 years follow-up (n = 2)[a]					
Sukhov 2012;[41] USA	Prospective; population based	Children with CP	924	NR	Various[i]
Durkin 2015;[40] USA	Prospective; population based	All births surviving to 1 year	3328	NR	7 (any)

*Articles are listed in each follow-up group chronologically by publication date, then alphabetically by first author.

[a]Based on maximum age at follow-up.

[b]No peri-intraventricular hemorrhage.

[c]NDI <70 = composite measure of NDI, defined in the source study as any one of the following: moderate-severe vertebral palsy, severe visual impairment, deafness, or cognitive score <70.

[d]NDI <85 = composite measure of NDI, defined in the source study as any one of the following: moderate-severe CP, severe visual impairment, deafness, or cognitive score <85.

[e]No insulin-dependent diabetes mellitus.

[f]Most recent period cohort presented in table.

[g]No antenatal corticosteroids.

[h]No bronchopulmonary dysplasia.

[i]Quadriparesis, 6%; diparesis, 4%; hemiparesis, 2%.

[j]Spasticity, 77%; ataxia, 4%; dyskinesis, 2%; hypotonia, 5%; other, 13%. Limb movement: diplegia/paraplegia, 32%; hemiplegia, 12%; monoplegia, 2%; triplegia/quadriplegia, 47%; other CP, 7%.

CP, cerebral palsy; CoNS, positive clinical signs for sepsis and positive cerebrospinal fluid cultures; GA, gestational age; NDI, neurodevelopmental impairment; NR, not reported; wGA, weeks gestational age.

Table 2. Identified articles reporting the prevalence of NDI and CP in European countries, by length of follow-up period (n = 25).

Article*; country	Study design; setting	Preterm population definition	Sample size	NDI, %	CP, %
18 months to 2 years follow-up (n = 7)[a]					
Schlapbach 2011;[46] Switzerland	Prospective; database	24–28 wGA	236[b]	23 (moderate-severe)	4 (any)
Stoinska 2011;[44] Poland	NR; single center	ELBW/VLBW infants <28 wGA	227	20 (any; 24–26 wGA) 15 (any; 27–28 wGA)	30 (any; 24–26 wGA) 18 (any; 27–28 wGA)
Von Lindern 2011;[47] the Netherlands	Retrospective; multicenter	<28 wGA	67	5 (severe)	NR
De Waal 2012;[45] the Netherlands	Prospective; database	23–27 wGA	55 (24 wGA) 104 (25 wGA) 130 (26 wGA)	0 (moderate-severe; 24 wGA) 17 (moderate-severe; 25 wGA) 9 (moderate-severe; 26 wGA)	NR
Schlapbach 2012;[43] Switzerland	Prospective; database	24 weeks 0/7 days to 27 weeks 6/7 days GA	684	13 (moderate) 6 (severe)	NR
Toome 2013;[48] Estonia	Prospective; database	Very low GA infants 22–25 wGA	17	NR	18 (any)
Morgillo 2014;[42] Switzerland	Prospective; single center	23–28 wGA	147	10 (moderate) 2 (severe)	NR
>2 years to <5 years follow-up (n = 8)[a]					
Grahn 2012;[53] Sweden	Prospective; database	<27 wGA	107	NR	6 (any)
Kerstjens 2012;[55] the Netherlands	Prospective; multicenter	≤28 wGA	150	NR	NR
Moore 2012;[8] England	Prospective; multicenter	22–26 wGA	576	3 (moderate) 5 (severe)	NR
Skiöld 2012;[51] Sweden	Prospective; database	<27 wGA	91	9 (24 wGA) 3 (25 wGA)	7 (any)
Boulet 2014;[49] France	Prospective; single center	22–28 wGA	67	3 (moderate) 5 (severe)	NR
Holmström 2014;[54] Sweden	Prospective; database	<27 wGA	411	NR	7 (any) 4 (moderate-severe)
Källén 2015;[50] Sweden	Prospective; database	<27 wGA	456	8 (any)	NR
Serenius 2015;[52] Sweden	Prospective; database	<27 wGA	456	27–30 (22–26 wGA)	NR
≥5 years follow-up (n = 10)[a]					
Leversen 2011;[56] Norway	Prospective; multicenter	22–27 wGA or BW 500–999 g	306	9 (moderate) 8 (severe)	4 (severe)

(continued)

Table 2. Continued.

Article*, country	Study design; setting	Preterm population definition	Sample size	NDI, %	CP, %
Mathiasen 2011,[65] Denmark	Retrospective; database	Infants stratified by GA	1078	NR	NR
Camba 2012,[59] Spain	Retrospective; database	<26 wGA	9 (23 wGA), 32 (24 wGA), 65 (25 wGA)	13 (moderate; 24 wGA), 6 (moderate; 25 wGA), 25 (severe; 24 wGA), 11 (severe; 25 wGA)	NR
Elgen 2012,[57] Norway	Prospective; database	<28 wGA or BW <1000 g	255	15 (moderate-severe)	NR
Klebermass-Schrehof 2012,[62] Austria	Prospective; single center	<28 wGA	320[e]	NR	14 (any)
Marret 2013,[64] France	Prospective; multicenter	22–26 wGA	610	NR	13 (moderate; 24–26 wGA), 9 (moderate; 27–28 wGA), 7 (severe; 24–26 wGA), 5 (severe; 27–28 wGA)
Mitha 2013,[63] France	Prospective; multicenter	22–28 wGA	436	NR	14 (any)
Serenius 2014,[58] Sweden	Prospective; database	<27 wGA	445	19 (moderate), 11 (severe)	9 (any)
Trønnes 2014,[60] Norway	Retrospective; registry	23–27 wGA	1673	NR	9 (any)
Skromme 2015,[61] Norway	Prospective; database	<28 wGA or BW <1000 g	281[c]	NR	9[d]

*Articles are listed in each follow-up group chronologically by publication date, then alphabetically by first author.

[a]Based on maximum age at follow-up.
[b]Uninfected (no sepsis).
[c]Pediatrician assessment.
[d]CP, blindness, or complete deafness.
[e]No intraventricular hemorrhage.

BW, birth weight; CP, cerebral palsy; ELBW, extremely low birth weight; GA, gestational age; NDI, neurodevelopmental impairment; NR, not reported; VLBW, very low birth weight; wGA, weeks gestational age.

up,[42,43] 3% between 2 and 5 years follow-up,[8,49] and 9%–19% at ≥5 years follow-up (Figure 2; Table 2).[56,58] The reported prevalence of severe NDI ranged from 2% to 11% across all follow-up durations (reported in seven studies).[8,42,43,47,49,56,58] In the included studies, CP was classified using different diagnostic criteria: the child's ability to walk without aids, by International Statistical Classification of Diseases and Related Health Problems codes, and using the Gross Motor Function Classification System (Supplemental Table 5).[66] Most studies (15/25 [including either prospective or retrospective study design]) reported follow-up at <5 years. The prevalence of any CP was 4%–18% at 18 months to 2 years follow-up,[46,48] 6%–7% between 2 and 5 years follow-up,[51,53,54] and 9%–14% at ≥5 years follow-up (Figure 2; Table 2).[58,60,62,63]

Four European studies reported NDI stratified by GA. The overall trend in findings was for a higher prevalence of NDI (any, moderate, severe) with lower GA at birth (Supplemental Table 6).[44,45,51,59] The trend for increasing NDI prevalence of any severity with lower GA was less clearly defined in European studies than in North American studies, with one study reporting 0% prevalence in infants born at 24 weeks, but 17% in those born at 25 weeks and 9% in those born at 26 weeks.[45] A decline in prevalence of NDI (any severity) with higher GA at birth was reported in two other studies, each comparing two different GA groups.[44,45,51] The prevalence of moderate or severe NDI was 13% and 25%, respectively, for infants with GA of 24 weeks versus 6% and 11%, respectively, for infants born at 25 weeks GA.[59]

Rest of World. Twenty studies from outside North America and Europe reported findings for NDI (Table 3).[12,67–85] Sample size ranged from eight (infants with focal intestinal perforation) to 2883.[73,83] Most (17/20) studies were retrospective. Just

over half of the studies (11/20) were conducted in Australia; the others were conducted in China, Japan, Singapore, and South Africa. NDI was not consistently defined across studies.

Among included studies, the prevalence of any NDI ranged from 15% to 61% at 18 months to 2 years follow-up,[68,71] and was 42% between 2 and 5 years follow-up,[78] summarized in Figure 2 and Table 3. No studies reported prevalence of any (aggregate of any severity) NDI at ≥5 years follow-up; prevalence of moderate-severe NDI was 10%.[84] The prevalence of any CP was 6% between 12 and 18 months follow-up,[67] 7%–17% at 18 months to 2 years follow-up,[68,69,74] 6%–33% between 2 and 5 years follow-up,[79,81] and 0% at ≥5 years follow-up.[84]

Two studies reported NDI stratified by GA. There was some evidence of a trend toward a higher prevalence of NDI at lower GAs, but there was variability across studies (Supplemental Table 6).[78,84]

Discussion

This SLR provides global-based evidence that children born extremely preterm are at high risk for developing long-term neurodevelopmental adverse outcomes. Overall, the search identified 69 articles that fulfilled the study criteria for NDI. The higher prevalence of NDI in North America versus Europe was notable, particularly among infants with a shorter duration of follow-up. This is likely attributable to the following factors: (1) differences in the methodology of data collection and assessment tools; (2) resuscitation practices; and (3) differences between study populations, such as GA, and neonatal and maternal comorbid conditions. An additional consideration is that studies in North America tended to report the prevalence of any NDI, whereas European studies were more likely to report NDI prevalence by severity. Across

Table 3. Identified articles reporting on the prevalence of NDI and CP from Rest of World, by length of follow-up period (n = 20).

Article*, country	Study design; setting	Preterm population definition	Sample size	NDI, %	CP, %
12 months to <18 months follow-up (n = 1)[a]					
Heald 2012;[67] Australia	Retrospective; single center	<29 wGA	97 (64[b])	NR	6 (any)[b,c]
18 months to 2 y follow-up (n = 8)[a]					
Ballot 2012;[75] South Africa	Prospective; single center	VLBW	26	NR	NR
Sugiura 2012;[73] Japan	Retrospective; multicenter	<33 wGA	2883	NR	13 (<24 wGA) 5 (24 wGA) 9 (25 wGA) 5 (26 wGA) 6 (27 wGA) 4 (28 wGA)
Cheong 2013,[68] Australia	Retrospective; NR	<28 wGA or BW <1000 g	256[d]	15 (any)	7 (any)
Chang 2015;[70] China	Retrospective; single center	ELBW[e]	45 (control)	28 (any)	14 (moderate-severe)
Hayakawa 2015;[71] Japan	Retrospective; multicenter	BW ≤1500 g; underwent laparotomy	44 (NEC) 47 (FIP)	61 (NEC) 47 (FIP)	NR
Orton 2015;[69] Australia	Retrospective; single center	<28 wGA and/or BW <1000 g	109	16 (abnormal neurologic examination)	7 (any)
Sun 2015;[74] China	Retrospective; single center	≤32 wGA, BW <1500 g	70	NR	17 (any)
Ohhashi 2016;[72] Japan	Retrospective; multicenter	<1500 g	633	NR	14 (any)
>2 y to <5 y follow-up (n = 9)[a]					
Kent 2012,[82] Australia	Retrospective; multi-center (tertiary)	<29 wGA	1473	NR	NR

(continued)

Table 3. Continued.

Article*; country	Study design; setting	Preterm population definition	Sample size	NDI, %	CP, %
Ishii 2013,[78] Japan	NR; multicenter (tertiary)	22–25 wGA	562	42 (any NDI) 23 (profound NDI)	14 (any CP) 8 (profound CP)
Abdel-Latif 2014,[80] Australia	Retrospective; multicenter (tertiary)	<29 wGA	1473	NR	9 (any)[c]
Bolisetty 2014,[12] Australia	Retrospective; multicenter (tertiary)	23–28 wGA	1472	NR	7 (any)[g]
Keir 2014,[81] Australia	Retrospective; single center	≥22 wGA and BW ≤500 g	14	NR	33 (any)
Wong 2014,[79] Australia	Retrospective; multicenter (tertiary)	<29 wGA	1472	NR	6 (any)[c,f]
Janz-Robinson 2015,[76] Australia	Retrospective; multicenter	<29 wGA	826 non-PDA 569 PDA medical 78 PDA surgery	6 (moderate [−1 SD to −2 SD]) 4 (severe [<−2 SD])	NR
Rodrigues 2015,[77] Australia	Retrospective; multicenter	<29 wGA	1205 urban 268 rural	7 (moderate; urban [−1 SD to −2 SD]) 5 (moderate; rural [−1 SD to −2 SD]) 5 (severe; urban [<−2 SD]) 5 (severe; rural [<−2 SD])	NR
Tanaka 2015,[83] Japan	Retrospective; single center	BW <1500 g; infants who underwent laparotomy for FIP or NEC	8 FIP 24 VLBW	NR	NR

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Table 3. Continued.

Article*; country	Study design; setting	Preterm population definition	Sample size	NDI, %	CP, %
≥5 y follow-up (n = 2)[a]					
Roberts 2011,[85] Australia	Prospective; multicenter	22–27 wGA or BW 500–999 g	132	NR	NR
Poon 2013,[84] Singapore	Retrospective; single center	≤26 wGA	10 (<23 wGA; n = 0 at 8 y) 23 (24 wGA; n = 6 at 8 y) 27 (25 wGA; n = 8 at 8 y) 41 (26 wGA; n = 11 at 8 y)	10 (moderate-severe; 23–25 wGA) 0 (severe; 23–26 wGA)	0 (24–25 wGA)

*Articles are listed in each follow-up group chronologically by publication date, then alphabetically by first author.
[a]Based on maximum age at follow-up.
[b]No insulin.
[c]Requiring walking aids.
[d]2005 cohort presented.
[e]Received prophylactic indomethacin.
[f]No antenatal steroids (9/143).
[g]No intraventricular hemorrhage (68/1043).
BW, birth weight; CP, cerebral palsy; ELBW, extremely low birth weight; FIP, focal intestinal perforation; NDI, neurodevelopmental impairment; NEC, necrotizing enterocolitis; NR, not reported; PDA, patent ductus arteriosus; SD, standard deviation; VLBW, very low birth weight; wGA, weeks gestational age; y, years.

follow-up ages, the prevalence of any NDI in North America was 8%–59%. The prevalence of moderate NDI was 39% in the single North American study that reported moderate NDI,[27] versus 3%–19% in included European studies. A meta-analysis that included birth cohorts in a median year of 2000 or later (median age at assessment, 28 months) estimated that 52% of surviving infants born extremely preterm worldwide develop NDI (defined as cognitive, motor, hearing, and visual impairment) to some degree;[86] this is in line with the NDI prevalence in North America found in the present SLR of more recent data.

A trend towards increased risk of NDI with decreasing GA at birth was observed in the present SLR among infants born at 23 weeks versus 27 weeks of GA (NDI prevalence, 48%–65% versus 26%, respectively). These findings are broadly consistent with data published later than the date cut-off used to identify the literature included in this study, including a 2018 meta-analysis that reported the prevalence of moderate-to-severe NDI at 18 months to 3 years (assessed using the Bayley Scales of Infant Development II or III) to be 50% among infants born at 23 weeks of GA and 17% among infants born at 27 weeks after 1994 in high-income countries.[87] Similar results were reported in a 2019 meta-analysis of studies with follow-up of extremely preterm infants (born in 1995 or later and aged 4–10 years at assessment), conducted in Australia, Europe, Japan, and the USA.[88] The risk of moderate-to-severe NDI (based on measurement of cognitive ability) significantly declined with each 1-week increase in GA, with NDI rates of 41% at 23 weeks' GA and 23% at 25 weeks' GA. However, this SLR had restricted population criteria (22–25 weeks) and looked at a later age range at follow-up, leaving a critical window of follow-up at 1–2 years after birth. Early

follow-up is important, as most clinical interventions are initiated during this early life period in an effort to improve later-life outcomes.

Compared with the present SLR, these meta-analyses were more limited regarding the overall populations studied. Furthermore, each analysis employed a different definition of NDI, all of which were more specific than the broader scope applied in the present review. The heterogeneity of our findings (>50% of included studies) precluded any follow-up statistical analysis (i.e. meta-analysis).

Retrospective and observational studies conducted in North America, South Korea, and Poland have also provided evidence that NDI prevalence increases with lower GA.[13,89,90] In these studies, NDI as well as individual cognitive and motor components, CP, and hearing impairment were reported more frequently with lower GA in extremely preterm infants. Comparison of infants born at 22–24 weeks with those born at 25–26 weeks revealed significant differences in prevalence rates for NDI (28% versus 14%), moderate-to-severe cognitive delay (35% versus 24%), and moderate-to-severe motor impairment (16% versus 6%).[13] In a study in France, moderate/severe NDI was reported in 28% and 12%, and mild NDI was reported in 38.5% and 34% of infants born at 24–26 weeks and 32–34 weeks, respectively.[91] These data indicate that the burden of NDI among extremely preterm infants is highest for infants born at the lowest GA.

The prevalence of any CP for different follow-up durations was broadly similar across geographical regions in the present SLR, with 18 months to 2 years' follow-up showing the greatest variation (4%–54%). In agreement with earlier studies,[7,30] findings from a recent US cohort study suggested that CP in extremely preterm infants may be declining in severity over time.[13] Over the four-year study period of this US

study, the percentage of infants with CP decreased from 16% to 9%, reflecting a 43% decrease in prevalence of severe CP and a 13% increase in prevalence of mild CP.

Strengths of the current study include the global focus of the review, the strict criteria used to capture the target population of extremely preterm infants and the systematic approach used to gather the data. Our findings have implications for further research, including the need for additional longitudinal studies to capture the long-term complications in children born extremely preterm, to identify risk factors associated with these outcomes and evaluate new interventions to alter the life-long trajectory of these complications. The scope of previous SLRs reporting long-term outcomes of NDI was different from the scope of the present SLR, as they have either considered a wider population focus (prematurity in general) in specific settings (low and middle-income countries only),[92] have considered a very narrow definition of extreme prematurity (e.g. those born between 22 and 25 weeks' gestation),[93] or have restricted the follow-up time frame (18–24 months).[94] The present results may be limited by variations in the tools used to assess NDI and in the definitions of NDI, which may have limited direct comparison of results across studies. A further consideration, which is inherent to observational research, is the potential bias due to patients lost to follow-up in included studies. Methodological variation and incomplete reporting are common issues encountered in studies evaluating NDI in extremely preterm children.[95] For example, in a previous evaluation of 14 cohort studies, information about several aspects of outcome assessment was lacking and most studies failed to report complete details of data analysis, including masking, subgroup analyses, and handling of missing data.[95]

Such shortfalls in reporting affect the interpretation of study results and, thus, affect the conclusions made in systematic reviews, impeding evidence-based clinical decisions.

In conclusion, children born extremely preterm experience negative long-term neurodevelopmental outcomes. Wide variations among prevalence estimates of NDI and a trend toward a higher prevalence of long-term NDI among infants born at the lowest GA were noted. Further work is needed to identify and minimize the risk of NDI in this vulnerable patient population.

ORCID iD

Csaba Siffel 🆔 https://orcid.org/0000-0002-6491-6953

Supplemental material

Supplemental material for this article is available online.

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