

## Appendix

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

Supplemental Table 1. Embase (via Embase.com) search strategy.

Search criteria and number	Query
Patient population	
1	'premature'/exp OR premature:ab,ti OR 'low birthweight'/exp OR 'small for gestational age':ab,ti OR 'small for date':ab,ti OR lbw:ab,ti OR vlbw:ab,ti OR prematur*:ab,ti OR preterm:ab,ti OR (low:ab,ti AND (birth:ab,ti AND weight:ab,ti OR birthweight:ab,ti)) AND ('infant'/exp OR 'infant':ab,ti) OR preemie:ab,ti OR 'small for date infant'/exp OR 'small for gestational age'/exp
Long-term outcomes and clinical burden	
2	'developmental disabilities'/exp OR 'neurologic manifestations':ab,ti OR monoplegia*:ab,ti OR diplegi*:ab,ti OR hemiplegi*:ab,ti OR quadriplegi*:ab,ti OR tetraplegi*:ab,ti OR monopare*:ab,ti OR dipare*:ab,ti OR hemipare*:ab,ti OR quadripare*:ab,ti OR tetrapare*:ab,ti OR (cerebral:ab,ti AND palsy:ab,ti) OR 'cerebral palsy':ab,ti OR spastic*:ab,ti OR hypertoni*:ab,ti OR dystoni*:ab,ti OR dyskene*:ab,ti OR ataxi*:ab,ti OR chorea*:ab,ti OR choreic*:ab,ti OR choreo*:ab,ti OR athetos*:ab,ti OR athetoid*:ab,ti OR (neurodevelopmental:ab,ti OR neurologic*:ab,ti OR developmental:ab,ti OR intellectual:ab,ti OR neuromuscular:ab,ti OR motor:ab,ti OR neuromotor:ab,ti AND (disab*:ab,ti OR impair:ab,ti OR delay:ab,ti OR deviat*:ab,ti OR disorder:ab,ti OR dysfunction:ab,ti)) OR 'hypoischemic encephalopathy':ab,ti OR (brain* OR cerebral AND coagulation AND necrosis) OR (neonatal:ab,ti AND white:ab,ti AND matter AND injury:ab,ti) OR (periventricular*:ab,ti AND (encephalomalacia:ab,ti OR leukomalacia:ab,ti)) OR (cerebral*:ab,ti AND (leukomalacia:ab,ti OR encephalomalacia:ab,ti)) OR (intraventricular:ab,ti AND (hemorrhage:ab,ti OR haemorrhage:ab,ti)) OR (brain:ab,ti OR cerebral:ab,ti OR encephalopathy:ab,ti AND (hypoxi*:ab,ti OR anoxi*:ab,ti OR ischemi*:it,ab OR ischaemi*:ab,ti)) OR (central:ab,ti AND nerve:ab,ti AND system:ab,ti AND disease*:ab,ti) OR (retrolental:ab,ti AND fibroplasia:ab,ti) OR 'retinopathy of prematurity':ab,ti OR 'neonatal respiratory distress syndrome':ab,ti OR (lung:ab,ti OR bronchopulmonary:ab,ti AND dysplasia:ab,ti) OR 'growth impairment':ab,ti OR 'persistent hyperinsulinemic hypoglycemia of infancy':ab,ti OR 'congenital hyperinsulinism':ab,ti OR 'neonatal hypoglycemia':ab,ti OR 'necrotizing enterocolitis':ab,ti OR 'burden of illness':ab,ti OR 'burden of disease':ab,ti OR 'bayley scales of infant and toddler development':ab,ti OR 'bsid':ab,ti OR 'wechsler preschool and primary scale of Intelligence':ab,ti OR 'wppsi':ab,ti OR 'vineland scales of adaptive behavior':ab,ti OR 'vabs':ab,ti OR 'child behavior checklist':ab,ti OR 'cbcl':ab,ti OR 'social communication questionnaire':ab,ti OR 'scq':ab,ti OR 'adhd rating scale':ab,ti OR 'adhd-rs':ab,ti OR 'hearing impairment':ab,ti
3	epidemiology/exp OR inciden*:ab,ti OR prevalen*:ab,ti OR demograph*:ab,ti OR epidemiolog*:ab,ti OR frequen*:ab,ti OR rate:ab,ti OR distribut*:ab,ti

4	#1 AND #2 AND #3
Study design	
5	'cohort analysis'/exp OR 'cross-sectional study'/exp OR reglst*:ab,ti OR 'database':ab,ti OR 'cohort study':ab,ti OR 'cohort studies':ab,ti OR 'cohort analysis':ab,ti OR 'cohort analyses':ab,ti OR 'observational':ab,ti OR 'longitudinal':ab,ti OR 'retrospective':ab,ti OR 'prospective':ab,ti OR 'cross sectional':ab,ti OR 'real world':ab,ti
6	#4 AND #5
Interventional studies	
7	'randomized controlled trial'/exp OR 'randomization'/exp OR random*:ab,ti OR 'rct':ab,ti OR 'controlled trial':ab,ti OR 'clinical trial':ab,ti OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'cross over':ab,ti OR 'crossover':ab,ti OR 'placebo'/exp OR 'placebo':ab,ti OR (doubl* AND blind*:ab,ti) OR (singl* AND blind*:ab,ti) OR ('open':ab,ti AND label*:ab,ti)
Nonsystematic reviews	
8	'case study'/exp OR 'letter'/exp OR 'editorial'/exp OR (review:it NOT (systematic OR meta AND analy* OR (indirect OR mixed AND 'treatment comparison')))) OR ('animal'/exp NOT 'human'/exp)
9	#6 NOT #7 NOT #8
10	#9 (English language only; humans; with an abstract; 2011-2016)

Supplemental Table 2. MEDLINE (via PubMed) search strategy.

Search criteria and number	Query
Patient population	
1	“premature”[MeSH] OR premature[TIAB] OR “low birthweight”[MeSH] OR “small for gestational age”[TIAB] OR “small for date”[TIAB] OR lbw[TIAB] OR vlbw[TIAB] OR prematur*[TIAB] OR preterm[TIAB] OR (low[TIAB] AND (birth[TIAB] AND weight[TIAB] OR birthweight[TIAB])) AND (“infant”[MeSH] OR “infant”[TIAB]) OR preemie[TIAB] OR “small for date infant”[MeSH]
Long-term outcomes and clinical burden	
2	“developmental disabilities”[MeSH] OR “neurologic manifestations”[TIAB] OR monoplegia*[TIAB] OR diplegi*[TIAB] OR hemiplegi*[TIAB] OR quadriplegi*[TIAB] OR tetraplegi*[TIAB] OR monopare*[TIAB] OR dipare*[TIAB] OR hemipare*[TIAB] OR quadripare*[TIAB] OR tetrapare*[TIAB] OR (cerebral[TIAB] AND palsy[TIAB]) OR “cerebral palsy”[TIAB] OR spastic*[TIAB] OR hypertoni*[TIAB] OR dystoni*[TIAB] OR dyskene*[TIAB] OR ataxi*[TIAB] OR chorea*[TIAB] OR choreic*[TIAB] OR choreo*[TIAB] OR athetos*[TIAB] OR athetoid*[TIAB] OR (neurodevelopmental[TIAB] OR neurologic*[TIAB] OR developmental[TIAB] OR intellectual[TIAB] OR neuromuscular[TIAB] OR motor[TIAB] OR neuromotor[TIAB] AND (disab*[TIAB] OR impair[TIAB] OR delay[TIAB] OR deviat*[TIAB] OR disorder[TIAB] OR dysfunction[TIAB])) OR “hypoischemic encephalopathy”[TIAB] OR (brain* OR cerebral AND coagulation AND necrosis) OR (neonatal[TIAB] AND white[TIAB] AND matter AND injury[TIAB]) OR (periventricular*[TIAB] AND (encephalomalacia[TIAB] OR leukomalacia[TIAB])) OR (cerebral*[TIAB] AND (leukomalacia[TIAB] OR encephalomalacia[TIAB])) OR (intraventricular[TIAB] AND (hemorrhage[TIAB] OR haemorrhage[TIAB])) OR (brain[TIAB] OR cerebral[TIAB] OR

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	encephalopathy[TIAB] AND (hypoxi*[TIAB] OR anoxi*[TIAB] OR ischemi*:.it,ab OR ischaemi*[TIAB])) OR (central[TIAB] AND nerve[TIAB] AND system[TIAB] AND disease*[TIAB]) OR (retrolental[TIAB] AND fibroplasia[TIAB]) OR “retinopathy of prematurity”[TIAB] OR “neonatal respiratory distress syndrome”[TIAB] OR (lung[TIAB] OR bronchopulmonary[TIAB] AND dysplasia[TIAB]) OR “growth impairment”[TIAB] OR “persistent hyperinsulinemic hypoglycemia of infancy”[TIAB] OR “congenital hyperinsulinism”[TIAB] OR “neonatal hypoglycemia”[TIAB] OR “necrotizing enterocolitis”[TIAB] OR “burden of illness”[TIAB] OR “burden of disease”[TIAB] OR bod[TIAB] OR “bayley scales of infant and toddler development”[TIAB] OR bsid[TIAB] OR “wechsler preschool and primary scale of intelligence”[TIAB] OR wppsi[TIAB] OR “vineland scales of adaptive behaviour”[TIAB] OR vabs[TIAB] OR “child behavior checklist”[TIAB] OR cbel[TIAB] OR 'social communication questionnaire”[TIAB] OR scq[TIAB] OR “adhd rating scale”[TIAB] OR “adhd-rs”[TIAB] OR “hearing impairment”[TIAB]
3	epidemiology[MeSH] OR inciden*[TIAB] OR prevalen*[TIAB] OR demograph*[TIAB] OR epidemiolog*[TIAB] OR frequen*[TIAB] OR rate[TIAB] OR distribut*[TIAB]
4	#1 AND #2 AND #3
Study design	
5	"observational study"[TIAB] OR "observational studies"[TIAB] OR "longitudinal study"[TIAB] OR "longitudinal studies"[TIAB] OR "longitudinal studies"[Mesh] OR "retrospective"[TIAB] OR "retrospective studies"[Mesh] OR "prospective"[TIAB] OR "prospective studies"[Mesh] OR "cohort studies"[Mesh] OR "cohort study"[TIAB] OR "cohort studies"[TIAB] OR "cohort analysis"[TIAB] OR "cohort analyses"[TIAB] OR "follow up study"[TIAB] OR "follow up studies"[TIAB] OR "cross-sectional studies"[Mesh] OR "cross-sectional study"[TIAB] OR "cross-sectional studies"[TIAB] OR "cross sectional study"[TIAB] OR "cross sectional studies"[TIAB] OR survey*[TIAB] OR database*[TIAB] OR "data source"[TIAB] OR "datasource"[TIAB] OR "Registries"[Mesh] OR registry[TIAB] OR registries[TIAB] OR "chart review"[TIAB] OR "real world"[TIAB]
6	#4 AND #5
7	"Randomized Controlled Trial"[Publication Type] OR "Random Allocation"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Cross-Over Studies"[Mesh] OR "Placebos"[Mesh] OR random*[TIAB] OR “rct”[TIAB] OR “controlled trial”[TIAB] OR “clinical trial”[TIAB] OR “cross over”[TIAB] OR “crossover”[TIAB] OR “placebo”[TIAB] OR (doubl* AND blind*[TIAB]) OR (singl* AND blind*[TIAB]) OR (“open”[TIAB]AND label*[TIAB]) OR factorial*[TIAB] OR assign*[TIAB] OR allocate*[TIAB] OR volunteer*[TIAB]
8	"Case Reports" [Publication Type] OR "Letter" [Publication Type] OR "Editorial" [Publication Type]
9	review[Publication Type] NOT (systematic OR meta AND analy* OR (indirect OR mixed AND "treatment comparison"))
10	#6 NOT #7 NOT #8 NOT #9
11	#10 (English language only; humans; with an abstract; 2011-2016)

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Supplemental Table 3. MEDLINE In-Process (via PubMed) search strategy.

Search criteria and number	Query
Patient population	
1	“premature”[MeSH] OR premature[TIAB] OR “low birthweight”[MeSH] OR “small for gestational age”[TIAB] OR “small for date”[TIAB] OR lbw[TIAB] OR vlbw[TIAB] OR prematur*[TIAB] OR preterm[TIAB] OR (low[TIAB] AND (birth[TIAB] AND weight[TIAB] OR birthweight[TIAB])) AND (“infant”[MeSH] OR “infant”[TIAB]) OR preemie[TIAB] OR “small for date infant”[MeSH]
Long-term outcomes and clinical burden	
2	“developmental disabilities”[MeSH] OR “neurologic manifestations”[TIAB] OR monoplegia*[TIAB] OR diplegi*[TIAB] OR hemiplegi*[TIAB] OR quadriplegi*[TIAB] OR tetraplegi*[TIAB] OR monopare*[TIAB] OR dipare*[TIAB] OR hemipare*[TIAB] OR quadripare*[TIAB] OR tetrapare*[TIAB] OR (cerebral[TIAB] AND palsy[TIAB]) OR “cerebral palsy”[TIAB] OR spastic*[TIAB] OR hypertoni*[TIAB] OR dystoni*[TIAB] OR dyskene*[TIAB] OR ataxi*[TIAB] OR chorea*[TIAB] OR choreic*[TIAB] OR choreo*[TIAB] OR athetos*[TIAB] OR athetoid*[TIAB] OR (neurodevelopmental[TIAB] OR neurologic*[TIAB] OR developmental[TIAB] OR intellectual[TIAB] OR neuromuscular[TIAB] OR motor[TIAB] OR neuromotor[TIAB] AND (disab*[TIAB] OR impair[TIAB] OR delay[TIAB] OR deviat*[TIAB] OR disorder[TIAB] OR dysfunction[TIAB])) OR “hypoischemic encephalopathy”[TIAB] OR (brain* OR cerebral AND coagulation AND necrosis) OR (neonatal[TIAB] AND white[TIAB] AND matter AND injury[TIAB]) OR (periventricular*[TIAB] AND (encephalomalacia[TIAB] OR leukomalacia[TIAB])) OR (cerebral*[TIAB] AND (leukomalacia[TIAB] OR encephalomalacia[TIAB])) OR (intraventricular[TIAB] AND (hemorrhage[TIAB] OR haemorrhage[TIAB])) OR (brain[TIAB] OR cerebral[TIAB] OR encephalopathy[TIAB] AND (hypoxi*[TIAB] OR anoxi*[TIAB] OR ischemi*:it,ab OR ischaemi*[TIAB])) OR (central[TIAB] AND nerve[TIAB] AND system[TIAB] AND disease*[TIAB]) OR (retrolental[TIAB] AND fibroplasia[TIAB]) OR “retinopathy of prematurity”[TIAB] OR “neonatal respiratory distress syndrome”[TIAB] OR (lung[TIAB] OR bronchopulmonary[TIAB] AND dysplasia[TIAB]) OR “growth impairment”[TIAB] OR “persistent hyperinsulinemic hypoglycemia of infancy”[TIAB] OR “congenital hyperinsulinism”[TIAB] OR “neonatal hypoglycemia”[TIAB] OR “necrotizing enterocolitis”[TIAB] OR “burden of illness”[TIAB] OR “burden of disease”[TIAB] OR bod[TIAB] OR “bayley scales of infant and toddler development”[TIAB] OR bsid[TIAB] OR “wechsler preschool and primary scale of intelligence”[TIAB] OR wppsi[TIAB] OR “vineland scales of adaptive behaviour”[TIAB] OR vabs[TIAB] OR “child behavior checklist”[TIAB] OR cbcl[TIAB] OR 'social communication questionnaire”[TIAB] OR scq[TIAB] OR “adhd rating scale”[TIAB] OR “adhd-rs”[TIAB] OR “hearing impairment”[TIAB]
Limit to in-process records	
3	inprocess[SB]
Nonsystematic review	
4	review[Publication Type] NOT (systematic OR meta AND analy* OR (indirect OR mixed AND "treatment comparison"))
Combined	

Supplemental Table 4. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Study population	Humans born at $\leq 27$ weeks 6 days GA or $\leq 28$ wGA (studies with extremely preterm population only, or in which extremely preterm included as subgroups in studies with infants $> 28$ wGA)	Born at $> 27$ weeks 6 days GA  Mixed populations (preterm and term neonates) without subgroup analysis by GA at birth
	To take into account variations in the reporting of GA at birth, we allowed expanded inclusion criteria: <ul style="list-style-type: none"> <li>• <math>&lt; 29</math> wGA</li> <li>• <math>\leq 28</math> or <math>&lt; 29</math> wGA and/or BW <math>&lt; 1000</math> g</li> <li>• Upper limit of range of GA <math>&lt; 28</math> wGA in study sample, although the inclusion criteria specifically report <math>&gt; 28</math> wGA</li> </ul>	Studies in which no information on GA is provided (only information on BW)  Studies in which average values (mean, median) and variation (SD, IQR) are reported without information on upper limit
Outcomes	Neurodevelopmental impairment	Publications that report only data from <i>in vitro</i> , animal, molecular, genetic, pathologic, or pharmacokinetic/ pharmacodynamic studies
Study design	Epidemiological: population/registry  Observational: prospective cohort; retrospective cohort; cross sectional	Intervention study  Clinical trial  Meta-analyses of randomized controlled trials and interventional studies
Language	English	Non-English full text

BW, birth weight; GA, gestational age; IQR, interquartile range; SD, standard deviation; wGA, weeks gestational age.

Supplemental Table 5. NDI assessment tools used in the included studies reporting NDI.

Assessment tool	Purpose	Age group(s)	Domain(s)
Bayley scales of infant and toddler development-II <sup>16</sup>	Assess the developmental status of infants and children	1–42 mo	Cognitive development Motor development
Bayley scales of infant and toddler development-III <sup>17</sup>	Assess the developmental status of infants and children	1–42 mo	Motor development Cognition Language development Social emotion development Adaptive behavior development
Gross motor function classification system <sup>66</sup>	Categorize gross motor function of children and young people with cerebral palsy	<2 y 2–4 y 4–6 y 6–12 y 12–18 y	5 levels of classification

mo, months; NDI, neurodevelopmental impairment; y, years.

Supplemental Table 6. Prevalence of NDI and CP stratified by GA at birth.

Article*; country	Length of follow-up	Children with any <sup>a</sup> NDI stratified by GA, %						
		22 wGA	23 wGA	24 wGA	25 wGA	26 wGA	27 wGA	28 wGA
<i>North America</i>								
Zayek 2011; <sup>37</sup> USA	3.5 y	37	48	35	23	29	-	-
		37 (severe)	9 (severe)	13 (severe)	7 (severe)	12 (severe)	-	-
Goldstein 2013; <sup>22</sup> USA	18–22 mo	-	65	53	41	36	26	29
Younge 2016; <sup>24</sup> USA	18–22 mo	-	64	39	-	-	-	-
<i>Europe</i>								
Stoinska 2011; <sup>44</sup> Poland	2 y	-	-	20			15	
Camba 2012; <sup>59</sup> Spain	1–6 y	-	-	13 (moderate)	6 (moderate)	-	-	-
		-	-	25 (severe)	11 (severe)	-	-	-
De Waal 2012; <sup>45</sup> Netherlands	2 y	-	-	0	17	9	-	-
Skiöld 2012; <sup>51</sup> Sweden	2.5 y	-	-	9	3	-	-	-
<i>Rest of World</i>								
Ishii 2013; <sup>78</sup> Japan	36–42 mo	52	57	37	37	-	-	-
		30 (profound)	40 (profound)	16 (profound)	17 (profound)	-	-	-
Poon 2013; <sup>84</sup> Singapore	8 y	-	-	-	14	50	-	-
		-	-	0 (severe)	(moderate-severe) 0 (severe)	(moderate-severe) 0 (severe)	-	-
<hr/>								
Publication	Length of follow-up	Children with any <sup>a</sup> cerebral palsy stratified by GA, %						
		22 wGA	23 wGA	24 wGA	25 wGA	26 wGA	27 wGA	28 wGA
<i>North America</i>								
Zayek 2011; <sup>37</sup> USA	3.5 y	12	9	5	0	6	-	-

		12	0	3	0	3		
		(moderate-severe)	(moderate-severe)	(moderate-severe)	(moderate-severe)	(moderate-severe)		
Younge 2016; <sup>24</sup> USA	18–22 mo	-	13	18	-	-	-	-
<i>Europe</i>								
Stoinska 2011; <sup>44</sup> Poland	2 y	-	-	30			18	
Marret 2013; <sup>64</sup> France	8 y	-	-	13			9	
		-	-	7 (severe)			5 (severe)	
<i>Rest of World</i>								
Sugiura 2012; <sup>73</sup> Japan	18 mo	13 (<24 wGA)		5	9	5	6	4
Ishii 2013; <sup>78</sup> Japan	36–42 mo	22	18	8	15	-	-	-
		17 (profound)	10 (profound)	5 (profound)	9 (profound)	-	-	-
Poon 2013; <sup>84</sup> Singapore	8 y	-	-	0		50	-	-

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

<sup>a</sup>Unless indicated otherwise in parentheses.

CP, cerebral palsy; GA, gestational age; mo, months; NDI, neurodevelopmental impairment; wGA, weeks gestational age; y, years.