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School-age outcomes of children after perinatal brain injury: a systematic review and meta-analysis

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Complete List of Authors:	Rees, Philippa; University College London Institute of Child Health, Population policy and Practice Callan, Caitriona; University of Oxford Nuffield Department of Primary Care Health Sciences Chadda, Karan; Cambridge University Hospitals NHS Foundation Trust, Department of Paediatrics Vaal, Meriel; University College London Institute of Child Health, University College London and Great Ormond Street Institute of Child Health Diviney, James; Great Ormond Street Hospital for Children NHS Foundation Trust, Paediatric Intensive Care Unit Sabti, Shahad; King's College London Harnden, Fergus; Chelsea and Westminster Hospital NHS Foundation Trust Gardiner, Julian; University College London Institute of Child Health, University College London and Great Ormond Street Institute of Child Health Battersby, Cheryl; Imperial College London, Neonatal Medicine Gale, Chris; Imperial College London Institute of Child Health, University College London and Great Ormond Street Institute of Child Health, University College London and Great Ormond Street Institute of Child Health					
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School-age outcomes of children after perinatal brain injury: a systematic review and meta-analysis

Philippa Rees¹ MPhil MBBCh, Caitriona Callan² MB BChir, Karan R Chadda³ MB BChir, Meriel Vaal MRes MBChB¹, James Diviney⁴ MB BChir, Shahad Sabti⁵ MBBS, Fergus Harnden⁶ MBChB, Julian Gardiner¹PhD, Cheryl Battersby⁷ PhD, Chris Gale⁷ PhD, Alastair Sutcliffe¹ PhD

Affiliations:

- 1. Population Policy and Practice, Great Ormond Street UCL Institute of Child Health, London, UK.
- 2. Nuffield Department of Primary Care Health Sciences, University of Oxford.
- 3. Department of Paediatrics, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.
- 4. Paediatric Intensive Care Unit, Great Ormond Street Hospital, London, UK
- 5. Kings College London, UK.
- 6. Chelsea and Westminster Hospital NHS Foundation Trust, London, UK.
- 7. Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London, London, UK.

Address correspondence to: Dr Philippa Rees, Population Policy Practice, UCL Institute of Child Health, 1st Floor 30 Guilford Street, London, WC1N 1EH, p.rees@ucl.ac.uk

School-age outcomes of children after perinatal brain injury: a systematic review and meta-analysis

Background

Over 3,000 children suffer a perinatal brain injury in England every year according to national surveillance. The childhood outcomes of infants with perinatal brain injury are however unknown.

Methods

A systematic review and meta-analyses were undertaken to explore school-aged neurodevelopmental outcomes of children after perinatal brain injury compared to those without perinatal brain injury. The primary outcome was neurodevelopmental impairment which included cognitive, motor, speech and language, behavioural, hearing, or visual impairment after 5 years of age.

Results

This review included 42 studies. Preterm infants with intraventricular haemorrhage (IVH) grade 3-4 were found to have a three-fold greater risk of moderate-severe neurodevelopmental impairment at school age OR 3.69 (95%CI: 1.7, 7.98). Infants with perinatal stroke had an increased incidence of hemiplegia 61% (95%CI: 39.2, 82.9) and an increased risk of cognitive impairment (difference in full scale IQ -24.2 (95%CI: -30.73, -17.67). Perinatal stroke was also associated with poorer academic performance; and lower receptive -20.25 (95%CI: -34.36, -6.13) and expressive language scores -20.25 (95%CI: -34.36, -6.13). Studies reported an increased risk of persisting neurodevelopmental impairment at school age after neonatal meningitis. Cognitive impairment and special educational needs were highlighted after moderate-severe HIE. However, there were limited comparative studies providing school-aged outcome data across neurodevelopmental domains and few provided adjusted data. Findings were further limited by the heterogeneity of studies.

Conclusions

Longitudinal population studies exploring childhood outcomes after perinatal brain injury are urgently needed to better enable clinicians to prepare affected families, and to facilitate targeted developmental support to help affected children reach their full potential.

School-age outcomes of children after perinatal brain injury: a systematic review and meta-analysis

What is already known on this topic

Thousands of children suffer a brain injury around the time of birth every year in England. Many of these injuries are associated with neurodevelopmental impairment at two years of age. However, two-year outcomes are not necessarily representative of later childhood outcomes and function, which are a priority for parents.

What this study adds

This review provides an overview of existing evidence of childhood outcomes after perinatal brain injury. It indicates that there is some evidence of on-going impairment throughout childhood for different types of perinatal brain injury but that there are considerable gaps in knowledge.

How this study might affect research, practice or policy

for detailed high-, mes after perinatal bran. This review shows the need for detailed high-quality longitudinal population studies exploring childhood outcomes after perinatal brain injury

School-age outcomes of children after perinatal brain injury: a systematic review and meta-analysis

Perinatal brain injuries can have wide-ranging deleterious consequences for children, families and broader society.(1-4) Over 3,000 infants experience perinatal brain injury in England annually¹ and the Department of Health and Social Care (DHSC) has committed to halving the rate of perinatal brain injuries by 2030 as part of the national maternity ambition.(5) To monitor progress towards this goal, a standardised definition of perinatal brain injury was developed. This definition – which encompasses moderate to severe Hypoxic Ischaemic Encephalopathy (HIE), perinatal stroke, central nervous system infections (CNS), kernicterus, intraventricular haemorrhage (IVH) grade 3-4, and cystic periventricular leukomalacia – includes 'indicators' of such injuries during the neonatal period.(6) The degree to which this definition captures and represents true perinatal brain injuries is unclear and requires us to look beyond the neonatal period.(6)

Focusing on the childhood outcomes of infants with perinatal brain injury provides a fuller understanding of the population captured by the DHSC definition. Despite their importance to families, school-aged outcomes following neonatal care have been an overlooked research priority. Neonatal studies typically focus on two-year composite outcomes which have less meaning for parents, may mask the true neurodevelopmental burden of injuries, and are known to be poorly predictive of future functioning.(7-10) As such, our understanding of childhood developmental trajectories after brain injuries – and whether any sequelae are fixed, stable or amenable to interventions – is limited. We therefore undertook a systematic review to explore the school-age neurodevelopmental outcomes of children following perinatal brain injury.

METHODS

Study selection

The review was conducted as per the pre-registered protocol (CRD 42021278572) and the PRISMA statement.(11) We included observational comparative studies exploring neurodevelopmental outcomes of children over five years of age after perinatal brain injury, published between 2000-2021 (Table 1). For inclusion, studies were required to have a non-brain injured comparator group. The primary outcome of interest was neurodevelopmental impairment as defined by study authors; secondary outcomes included motor, cognitive, speech and language, behavioural and neuropsychological, visual and hearing outcomes and seizures.

A search strategy incorporating 99 key terms and mesh headings was developed in Medline Ovid, adapted and run across 10 databases to identify published and grey literature. Snowballing techniques were used to augment search sensitivity (Supplement 1 & 2). All titles were screened independently by two reviewers. The full-texts of all potentially relevant titles were retrieved, reviewed and their risk of bias assessed by two trained reviewers independently (PR, CC, MV, JD, SS). Disagreements were arbitrated by a third reviewer.

Data extraction and synthesis

Studies were stratified by brain injury type, sub-stratified by age of outcome assessment and outcome type, and summarised in a narrative synthesis. Where sufficient suitable data were available from contextually and clinically comparable studies, data were pooled in random effects meta-analyses using RevMan 5.4. Continuous data were pooled using the inverse variance method; dichotomous data were pooled using the Mantel-Haenszel method; and analysis data from studies which did not provide raw data were pooled with dichotomous data

from other studies using the generic inverse variance method.(12) Where studies provided insufficient comparative data for a particular outcome, the combined incidence figures for that outcome within the brain injured population was calculated across studies using the Fisher exact test for binomial data.(13) Statistical heterogeneity was assessed using the I² statistic and substantial heterogeneity (>85%) was explored further in sub-group analyses.

Quality assessment

The Newcastle Ottawa Tool was used to assess risk of bias across three domains: population selection, the comparability of the 'brain injured' and 'non brain injured' comparator groups, and outcome assessment.(14) Studies were classed as poor, fair, or good for each domain and given an overall risk of bias classification.

Patient and Public Involvement

Patients or the public were not involved in the design or conduct of this review. However the review's findings will be used to shape the larger CHERuB study in partnership with our parent advisory panel.

RESULTS

Searches identified 14,210 records and 42 studies were included (Supplement 3). Studies focused on intraventricular haemorrhage (n=27), white matter injury (WMI) amongst preterm infants (n=15), perinatal stroke (n=8), neonatal meningitis (n=4), and HIE (n=3); these were not mutually exclusive (Supplement 4). Most studies were undertaken in the USA (n=10), the UK (n=8), the Netherlands (n=5) or Australia (n=4). These were prospective (n=27) or retrospective cohort studies (n=14). Included studies were deemed to be moderate (n=17) or low risk of bias (n=27) (Supplement 5).

Preterm injuries

The 29 studies exploring outcomes after IVH or WMI mostly included infants born <32 weeks' gestation (n=22) after the year 2000 (n=18) (Supplement 4). Most studies confirmed injury on ultrasound or MRI imaging (n=22) these were reviewed by radiologists (n=6), neonatologists (n=3) or both (n=1); 14 studies used the Papile classification; only 2 studies stratified results by laterality.

Nine studies explored neurodevelopmental impairment at 5-14 years of age after preterm brain injury including IVH (n=9) and WMI (n=6).(15-23) Two comparable studies highlighted a considerably increased pooled crude risk of moderate-severe neurodevelopmental impairment after IVH grade 3-4 at 8 years of age OR 3.69 (95%CI: 1.7, 7.98) $I^2 = 0\%$ (Figure 1, Supplement 6).(17, 20)

Six studies explored motor outcomes after IVH grade 3-4: they consistently highlighted an increased risk of motor impairment at 5-12 years of age.(20, 23-27) Additionally, two

comparable studies reported an 8-fold increased crude risk of cerebral palsy after IVH grade 3-4 OR 8.13 (95%CI: 4.64, 14.22) *I*²=0% (Figure 2).

Cognitive outcomes at school-age after preterm brain injuries were reported by 16 studies using 25 different cognitive assessment tools - limiting the potential for meta-analysis (Supplement 4).(15, 16, 20, 21, 23-34) Educational outcomes were reported by 5 studies.(20, 21, 25, 29, 34)

Studies consistently reported lower cognitive scores at school-age following IVH grade 3-4. (15, 20, 21, 24-26, 30, 34) Hollebrandse 2021 reported an increased risk of cognitive impairment at 8 years of age OR 2.68 (95%CI: 1.21, 5.94).(25) Van de Bor 2000 and Hollebrandse 2021 reported that the cognitive impact of IVH grade 3-4 affected educational needs.(21, 25) Van de Bor 2000 reported increased special educational needs at 5, 9 and 14 years: the adjusted risk at 14 years of age was marked, aOR 3.99 (95%CI: 1.36, 11.69).(21) Studies reported no significant differences in language scores after IVH grade 3-4.(20, 21) However, an association with reading OR 3.62 (95%CI: 1.59, 8.24), spelling OR 4.48 (95%CI: 1.8, 11.2), and arithmetic OR 2.79 (95%CI: 1.2, 6.48) impairment was demonstrated.(25) Most studies highlighted cognitive effects after WMI.(16, 29, 32, 34)

Studies exploring behavioural outcomes after IVH 3-4 did not find any associations with attention deficits, conduct issues or autism spectrum disorder (Supplement 6).(15, 24, 35) However, there was conflicting evidence around the mental health effects of WMI.(16, 36)

Studies exploring hearing impairment after IVH and/or WMI were small or not comparable. 10 studies explored visual impairment after IVH or WMI, 4 provided meaningful outcome data.(15, 20-22, 26, 27, 32, 33, 37, 38) An increased prevalence of visual impairment after IVH grade 3-4 (45.4% and 90.9%) compared to controls (7.5%) was reported in addition to significantly lower visual motor integration scores.(26)

Perinatal stroke

Eight comparative studies explored school-age outcomes after perinatal stroke, these included 177 children with perinatal stroke (100 left-sided and 54 right-sided – not all studies specified laterality) and 232 comparator children (Supplement 4).(39-46) Infants' gestation age was largely unspecified. Five studies presented a combined incidence of childhood seizures after perinatal stroke of 40.1% (95%CI: 26.8-53.3% I^2 =56%) (Supplement 7).(39, 42, 43, 45, 46) The combined incidence of hemiparesis after perinatal stroke was 61% (95%CI: 39.2, 82.9 I^2 =88%). There was considerable heterogeneity across studies, and likely detection bias as only symptomatic children would have undergone diagnostic investigations (Supplement 8).(39, 41-44)

Five studies identified a significant combined mean difference in full scale IQ scores at 7-13 years of age after perinatal stroke: -24.2 (95%CI: -30.73, -17.67) I^2 =80% (Figure 3).(39, 41, 44-46) There was heterogeneity across studies in terms of assessment timing, assessment tools, and combining those with left and right-sided strokes.

Differences in stroke laterality partially explained the heterogeneity. The combined mean difference in full scale IQ following left-sided strokes was -26.1 (95%CI: -29.1, -22.93)

*I*²=0%; compared to -26.7 (95%CI: -39.38. -14.02) *I*²=76% for right-sided strokes. No significant differences in cognitive outcomes were found by laterality.(39, 41, 44-46) Kolk 2011 reported significantly lower scores across all NEPSY domains other than executive function after perinatal stroke, including attention, visuo-spacial function, memory, and learning.(42)

Two studies presented educational outcomes after perinatal stroke. Although Northam 2018 found that most children with perinatal stroke were in mainstream education (n=28, 93%), they also highlighted that additional educational support was often required (n=12, 40%). This was in keeping with Ballantyne 2008 reporting lower mean scores for reading (p<0.0001), spelling (p=0.001) and arithmetic (p<0.0001) after perinatal stroke compared to controls at 7-8 years of age, persisting on re-assessment at 10-12 years.

Kolk 2011 reported significantly lower scores compared to controls across most NEPSY language domains following perinatal stroke. (42) Significantly lower receptive and expressive language scores were also reported across studies: -20.88 (95%CI: -36.66, -5.11) $I^2=88\%$ and -20.25 (95%CI: -34.36, -6.13) $I^2=87\%$ respectively (Supplement 9, 10). (39, 44) Statistical heterogeneity may have been as a result of studies combining left and right-sided strokes and the varying age of outcome assessment. Studies highlighted that deficits in receptive language scores present at 7-8 years persisted at 10-12 years but that expressive language scores improved (p=0.012). (39, 40)

Meningitis

Studies consistently reported an increased risk of neurodevelopmental impairment after neonatal meningitis (Supplement 6).(47-49) An increased likelihood of neuromotor disability

at 5 years of age (n=45/274, 16%) compared to controls (n=2/1391, 0.1%) was reported (Supplement 4).(47) On re-assessment of the same population at 9-10 years, this increased risk of severe disability persisted (n=12, 10.8% compared to n=0, 0%).(49) An increased risk of any neurodevelopmental impairment at 5 years after neonatal *Group-B Streptococcal* meningitis was also reported in the Netherlands, RR 5.30 (95%CI: 2·57-10·89), and in Denmark, RR 7.80 (95%CI: 4·42-13·77).(48) This increased risk persisted on subsequent assessment: at 11 years of age in the Netherlands, RR 2.99 (95%CI: 1.83, 4.88) and at 15 years of age in Denmark RR, 3.15 (95%CI: 1.82, 5,46).(48)

Hypoxic-ischaemic encephalopathy

Two comparative studies (of the same cohort) explored outcomes of term-born infants with moderate-severe HIE, but without cerebral palsy, at school age (Supplement 4).(50, 51) They highlighted significantly lower full scale IQ scores after HIE (mean difference –13.62 (95%CI: –20.53 to –6.71)).(50) This difference in cognition was also seen for perceptual reasoning, working memory, and processing speed. Children with HIE were also more likely than controls to receive additional classroom support: OR 10 (95%CI: 1.16, 86) although the confidence interval for this risk estimate was wide.(50) Children with HIE (without cerebral palsy) also had significantly lower motor scores (mean difference –2.12 (95%CI: –3.93, –0.30)) and verbal comprehension scores (mean difference –8.8 (95%CI: –14.25, –3.34)).(50) They were also noted to have higher behavioural difficulty scores especially for emotional problems.(50)

DISCUSSION

This review brings together the existing evidence on the later childhood outcomes of infants with perinatal brain injury. Although 42 studies were included, small study populations, limited data on injury severity and laterality, and the heterogeneity of outcome measures limited the potential power of results. However, studies did demonstrate a three-fold higher risk of moderate-severe neurodevelopmental impairment at school age following IVH grade 3-4. Studies consistently report cognitive impairment after IVH grade 3-4 but suggest that speech and language is relatively preserved. A higher risk of hemiplegia, cognitive impairment and poorer academic performance after perinatal stroke is reported in addition to poorer receptive and expressive language scores. Studies consistently report a higher risk of persisting neurodevelopmental impairment after neonatal meningitis – however few studies address this question. Few comparative studies explore school-age outcomes after HIE.

This is the first systematic review to focus on school-age outcomes after perinatal brain injury using the DHSC definition.(6) An extensive search strategy was employed alongside a rigorous review process. Most studies were deemed to be of low risk of bias. Due to our strict inclusion criteria (especially requiring a non-brain injured comparator group) many pertinent studies were excluded. Heterogeneity in terms of outcomes assessed, outcome assessment tools, and timing of outcome assessment limited the comparability of studies and the potential for meta-analyses. This review was also limited by the size of available studies and how studies presented data for extraction. Few studies presented adjusted data or explored childhood trajectories after perinatal brain injury.

Previous reviews were limited by a lack of comparable studies, heterogeneity across studies, the inclusion of much older cohorts (from the pre-surfactant era for example) or by including

non-comparative studies.(4, 52-54) Whilst this review was also limited by studies' heterogeneity and the quality of available data, new and important findings - for example the risk of neurodevelopmental impairment - at school age after IVH 3-4 were identified. Our finding of a higher risk of cerebral palsy after IVH and motor impairments after preterm brain injuries is echoed by previous studies.(52, 53, 55)

Lynch 2001 highlighted that 60% of infants have neurological sequelae that emerge over time following perinatal stroke. This was in-keeping with our findings of a higher risk of hemiparesis, cognitive impairment, and speech and language impairment at school age.(56) Several large non-comparative population-based studies also mirror these findings.(57-60)

Although previous reviews highlight an increased risk of various neurodevelopmental impairments after neonatal meningitis in early childhood – we are unaware of any focusing on school-age outcomes after neonatal meningitis.(4, 61)

The review's findings of potential on-going impairments across cognitive, speech and language, and behavioural domains - in addition to a need for increased school support – after HIE are mirrored by other studies.(62-66) Shankaran 2012 and Azzopardi 2014 highlight ongoing neurodevelopmental sequelae at school age amongst children who received therapeutic hypothermia for moderate-severe HIE.(62, 63, 65) Unfortunately these studies were not powered to explore individual (non-composite) developmental outcomes or school-age outcomes.(63, 66, 67)

Implications

Considerable gaps in the evidence are highlighted, particularly around the risk of specific outcomes following different types of injury, the precision around risk estimates, the impact of different factors (such as injury laterality), and the developmental trajectories of these children i.e. whether outcomes are fixed, deteriorate, or improve over time. This information is key to prepare families for the future, inform enhanced developmental surveillance, and enable targeted multidisciplinary support to help affected children to reach their full potential. As such, this review highlights a pressing need for high-quality, comparative studies which use the 'Core Outcomes In Neonatology' to explore long-term outcomes after perinatal brain injury and permit future meta-analyses. (10) Additionally, to meet the DHSC ambition to reduce perinatal brain injury, real-time longitudinal population data, extending beyond the neonatal period to childhood, are necessary as the current definition is limited to 'indicators' of injury from the neonatal period. This could be achieved through linkage of existing population datasets within the UK and would enable monitoring of progress towards the DHSC goal and evaluation of the impact of national Quality Improvement efforts targeting 7.04 perinatal brain injuries.(68, 69)

CONCLUSION

This review provides an overview of existing evidence that perinatal brain injuries can have a lasting impact throughout childhood. Considerable gaps in the evidence are highlighted and studies' heterogeneity significantly limited the potential for evidence synthesis. Longitudinal population studies are needed to robustly explore childhood trajectories after perinatal brain injury.

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Contributors' statement

Dr Rees conceptualised and designed the review, reviewed and appraised studies, undertook data extraction and synthesis, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Callan conceptualized and designed the review, designed and oversaw the search strategy, reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Chadda reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Vaal reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Diviney reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Sabti reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Harnden reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Gardiner was the lead statistician for the review, he advised on and oversaw the data analysis, and reviewed and revised the manuscript.

Dr Battersby oversaw and supervised the review and critically revised the manuscript for important intellectual content.

Professor Gale oversaw and supervised the review and critically revised the manuscript for important intellectual content.

Professor Sutcliffe oversaw and supervised the review and critically revised the manuscript for important intellectual content.

All authors approve the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Autions: The authors would

pplemental file 7 and 8. **Additional Contributions:** The authors would like to thank Dr Roxanna Short for creating the figures in supplemental file 7 and 8.

- Figure 1: Crude risk of neurodevelopmental impairment at 8 years of age after IVH grade 3-4
- neurodev,
 sk of cerebral palsy
 Jed mean difference in IQ s.
 stroke

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 ad.nhs.uk/mat-transformatio THIS.Institute. Avoiding Brain Injury in Childbirth (ABC) collaboration 2022 [Available from: https://www.thisinstitute.cam.ac.uk/research-projects/avoiding-brain-injuryin-childbirth-
- collaboration/#:~:text=The%20Avoiding%20Brain%20Injury%20in,to%20suspected%20intr apartum%20fetal%20deterioration.
- NHS England. Maternity and Neonatal Safety Improvement Programme [Available from: https://www.england.nhs.uk/mat-transformation/maternal-and-neonatal-safetycollaborative/.

Table 1 Inclusion and exclusion criteria	
Inclusion Criteria	Exclusion Criteria
Peer-reviewed observational studies (cohort, case-control, cross-sectional)	Non-comparative studies; opinions; commentaries; reviews; case-reports; lab studies
Studies in all languages	Studies where the population includes adults and children and the data for children cannot be extracted
Studies published after 2000	Studies focused on children with IVH grade 1-2, neonatal seizures, hypoglycaemic brain injury, or neonatal abstinence syndrome
Children with a diagnosis of brain injury occurring at or around the time of birth (including during the neonatal period) as defined by the DHSC (including those with any white matter injury but not including those with isolated seizures)	Studies which include infants with brain injuries diagnosed during the neonatal and infancy period where most were diagnosed outside of the neonatal period
Studies including infants with moderate to severe HIE born in the post therapeutic hypothermia era (i.e. where infants received therapeutic hypothermia)	Studies including infants with moderate-severe HIE born during the pre-therapeutic hypothermia era or in low- or middle-income countries that do not offer therapeutic hypothermia
Studies focused on school-aged neurodevelopmental outcomes (of children between 5-18 years of age)	Studies of infants with mild HIE

Secondary outcome(s):

parental interview/ survey)

Primary outcome(s):

including:

1. Any cognitive impairment, as defined by authors (direct testing)

Neurodevelopmental impairment, as defined by authors

(including direct testing, clinical record review, and

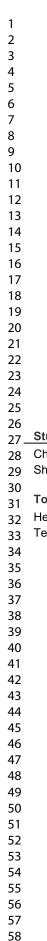
- 2. Mild cognitive impairment (intelligence or developmental quotient 1-2 standard deviations below the mean)
- 3. Moderate-severe cognitive impairment (intelligence or developmental quotient more than 2 standard deviations below the mean)
- 4 Executive dysfunction, as defined by authors (direct testing)
- 5. Low numeracy, as defined by authors (by direct testing or educational achievement tests)
- 6. Low literacy, as defined by authors (by direct testing or educational achievement tests)
- 7. Special educational needs as defined by authors (school or parental report)
- 8. Motor impairment, as defined by authors (including direct testing, clinical record review, and reporting)
- 9. Visual-motor impairment, as defined by authors (on direct testing)

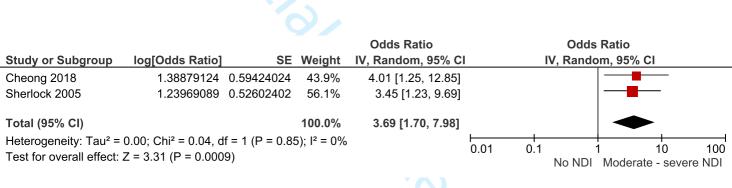
- 10. Emotional-behavioural difficulty, as defined by authors (including direct testing, clinical record review, and parental reporting
- 11. Speech and language impairment, as defined by authors (on direct testing)
- 12. Visual impairment, as defined by authors (including direct testing, clinical record review, and parental reporting)
- 13. Hearing impairment, as defined by authors (including direct testing, clinical record review, and parental reporting)
- b. Stuc. and wit. 14. Epilepsy/seizures, as defined by authors (including medical history taking, clinical record review and parental reporting

Studies reporting outcomes for children diagnosed with

Studies where comparable outcome data from those with and without perinatal brain injury cannot be extracted







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)		IVH grad	e 3-4	No IV	Ή		Odds Ratio	Odds	Ratio	
) 7 –	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Rand	lom, 95% CI	
2	Beaino 2010	9	38		1153	48.5%	7.47 [3.34, 16.69]			
))	Hollebrandse 2021	15	35	26	331	51.5%	8.80 [4.03, 19.19]		_	
)	Total (95% CI)		73		1484	100.0%	8.13 [4.64, 14.22]		•	
	Total events	24		72						
3	Heterogeneity: Tau ² = Test for overall effect:				= 0.77);	I ² = 0%		0.01 0.1 No cerebral palsy	1 10 Cerebral palsy	100
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5		Perinatal stroke							Mean Difference		Mean Difference				
б-	Study or Subgroup	Mean		Total			Total		IV, Random, 95% CI		IV,	Random, 9	5% CI		
7	Ballayntyne 2008	94.7	20.4	29	123	15	38	18.2%	-28.30 [-37.12, -19.48]		_				
8	Gold 2014	88	4	27	117	2.7	19	26.6%	-29.00 [-30.94, -27.06]		-				
9	Northam 2017	99	14	30	112	16	40	20.7%	-13.00 [-20.05, -5.95]		_				
n	Tilema 2008	80	14.1	10		11.7	10		-28.00 [-39.36, -16.64]			_			
1	Trauner 2001	93.4	22	39	116.2	13	54	19.7%	-22.80 [-30.53, -15.07]		_	-			
1 2	Total (95% CI)			135			161	100.0%	-24.20 [-30.73, -17.67]		•	•			
3	Heterogeneity: Tau ² =	40.85; C	hi ² = 20).00, df	= 4 (P =	0.000)5); l² =	80%		-100	-5 0	0	 50	100	
4	Test for overall effect:	Z = 7.26	(P < 0.0)	00001)						-100	-30	U	50	100	
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Supplement 1: databases searched

Cochrane Central Register of Controlled Trials

EBSCO-CINAHL (Cumulative Index to Nursing and Allied Health Literature)

Google Scholar

Ovid-EMBASE

Ovid-MEDLINE

Ovid-MEDLINE E-pub ahead of print

Ovid-MEDLINE In-Process and Other Non-Indexed Citations

PubMed

Scopus

1 Index Expandex Web of Knowledge (Science Citation Index Expanded and Conference Proceedings Citation Index Science)

Supplement 2: Medline Ovid Search Strategy

- 1. exp CHILD/
- 2. exp Child, Preschool/
- 3. exp ADOLESCENT/
- 4. exp INFANT/ or exp INFANT, NEWBORN/
- 5. (child* or toddler* or baby or infant* or adolescent*).mp.
- 6. 1 or 2 or 3 or 4 or 5
- 7. exp Educational Status/
- 8. exp Child Development/
- 9. exp Learning Disorders/
- 10. exp Educational Measurement/
- 11. exp SCHOOLS/
- 12. exp Academic Performance/
- 13. school performance.mp.
- 14. exp COGNITION/
- 15. exp LEARNING/
- 16. exp SPATIAL LEARNING/
- 17. exp VERBAL LEARNING/
- 18. exp SOCIAL LEARNING/
- 19. exp Intelligence Tests/
- 20. exp INTELLIGENCE/
- 21. exp Intellectual Disability/
- 22. exp Neurodevelopmental Disorders/
- 23. neurodevelopm*.mp.
- 24. (nervous system dys* or CNS dys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 25. (nervous system abnorm* or CNS abnorm*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 26. (nervous system malform* or CNS malform*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 27. (nervous system dis* or CNS dis*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 28. (mental health condi* or mental health dis*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 29. mental health outcome.mp.
- 30. behaviour* abnorm*.mp.
- 31. cognitive impairment.mp. or exp Cognitive Dysfunction/
- 32. visual impairment.mp. or exp Vision Disorders/
- 33. visual develop*.mp.
- 34. (visual dis* or visual dys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

- 35. (nystagmus or strabismus).mp.
- 36. (visual acuity or refractive error*).mp.
- 37. hearing impairment.mp. or exp Hearing Loss/
- 38. exp Deafness/
- 39. exp DEAF-BLIND DISORDERS/
- 40. exp Hearing Loss, Sensorineural/
- 41. exp Movement Disorders/
- 42. exp Cerebral Palsy/
- 43. motor impairment.mp.
- 44. (seizure* or convulsi*).mp.
- 45. exp EPILEPSY/ or epilepsy.mp.
- 46. exp Executive Function/
- 47. visual-motor impairment.mp.
- 48. numeracy.mp.
- 49. literacy.mp. or exp LITERACY/
- 50. jaundice.mp.
- 51. exp Language Development Disorders/ or exp Child Language/ or language impairment.mp. or exp Reading/ or exp Dyslexia/ or reading impairment.mp.
- 52. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
- 36 01 37 01 40 01 41 01 42 01 43
- 53. 49 or 50 or 51
- 54. 52 or 53
- 55. exp JAUNDICE, NEONATAL/
- 56. exp JAUNDICE/
- 57. exp Hyperbilirubinemia, Neonatal/
- 58. exp Hyperbilirubinemia/
- 59. hyperbilirubin*.mp.
- 60. exp Hyperbilirubinemia, Hereditary/
- 61. bilirubin encephalopathy.mp.
- 62. bilirubin-induced neuro*.mp.
- 63. exchange transfusion.mp.
- 64. exp ASPHYXIA NEONATORUM/
- 65. (exp ASPHYXIA/ or asphyxia.mp.) and neonat*.mp.
- 66. exp Hypoxia-Ischemia, Brain/ and neonat*.mp.
- 67. perinatal asphyxia.mp.
- 68. birth asphyxia.mp.
- 69. (hypoxic-ischemic encephalopathy or hypoxic-ischaemic encephalopathy).mp.
- 70. neonatal encephalopathy.mp.
- 71. (exp Cerebral Hemorrhage/ or exp Intracranial Hemorrhages/ or exp Brain Ischemia/ or intracranial haemorrhage.mp. or exp Subarachnoid Hemorrhage/ or exp Stroke/) and neonat*.mp.
- 72. perinatal stroke.mp.
- 73. (central nervous system infection.mp. or exp Central Nervous System Infections/) and neonat*.mp.
- 74. (exp Meningoencephalitis/ or meningo-encephalitis.mp.) and neonat*.mp.
- 75. (MENINGITIS/ or meningitis.mp.) and neonat*.mp.

- 76. exp MENINGITIS, VIRAL/ and neonat*.mp.
- 77. (meningoencephalitis and neonat*).mp.
- 78. (encephalitis.mp. or exp ENCEPHALITIS, VIRAL/ or exp INFECTIOUS

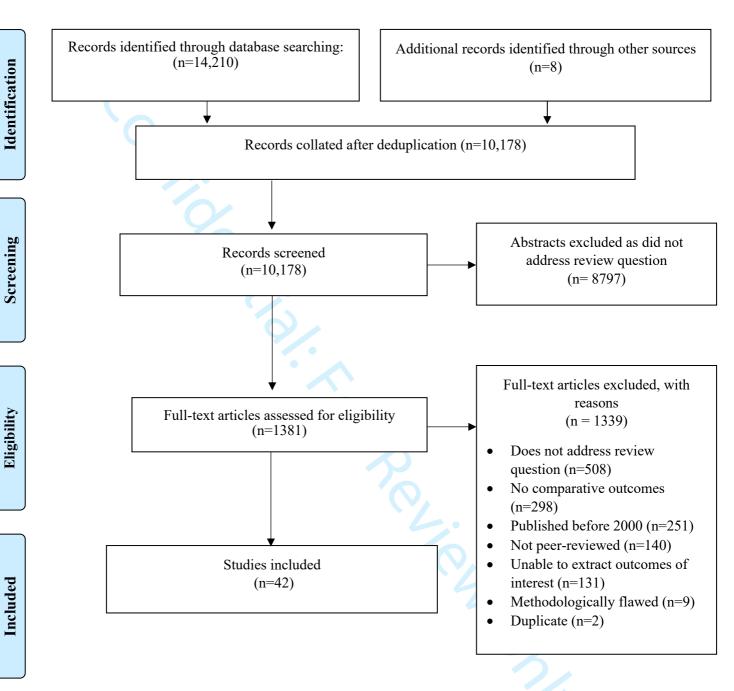
ENCEPHALITIS/ or exp ENCEPHALITIS/) and neonat*.mp.

- 79. kernicterus.mp. or exp KERNICTERUS/
- 80. preterm white matter disease.mp.
- 81. (periventricular leukomalacia.mp. or exp Leukomalacia, Periventricular/) and neonat*.mp.
- 82. (therapeutic hypothermia.mp. or exp Hypothermia, Induced/) and neonat*.mp.
- 83. ((subdural haemorrhage or subdural hemorrhage) and neonat*).mp.
- 84. (exp Hematoma, Subdural/ or subdural haemorrhage.mp. or exp Craniocerebral Trauma/) and neonat*.mp.
- 85. (intraventricular haemorrhage and neonat*).mp.
- 86. (tentorial tear and neonat*).mp.
- 87. (parenchymal haemorrhage and neonat*).mp.
- 88. (ventriculoperitoneal shunt.mp. or exp Cerebrospinal Fluid Shunts/ or exp Ventriculoperitoneal Shunt/) and neonat*.mp.
- 89. ((ventricular drain or Rickham reservoir or CSF shunt) and neonat*).mp.
- 90. neonatal stroke.mp.
- 91. (cerebrovascular accident and neonat*).mp.
- 92. neonatal cerebral ischaemia.mp.
- 93. (exp Intracranial Thrombosis/ or cerebral venous thrombosis.mp.) and neonat*.mp.
- 94. (seizure.mp. or exp Seizures/) and neonat*.mp.
- 95. 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85
- or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94
- 96. exp Cohort Studies/
- 97. exp Retrospective Studies/
- 98. (cohort* or (case\$ and control\$)).tw.
- 99. exp Cross-Sectional Studies/
- 100. exp Randomized Controlled Trial/
- 101. 96 or 97 or 98 or 99 or 100
- 102. exp "REVIEW"/
- 103. exp Case Reports/
- 104. Animals/
- 105. animal stud*.mp.
- 106. 102 or 103 or 104 or 105
- 107. 6 and 52 and 95 and 101
- 108. 107 not 106

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PRISMA 2009 Flow Diagram



Supplement 4: included studies of school-aged outcomes after perinatal brain injury

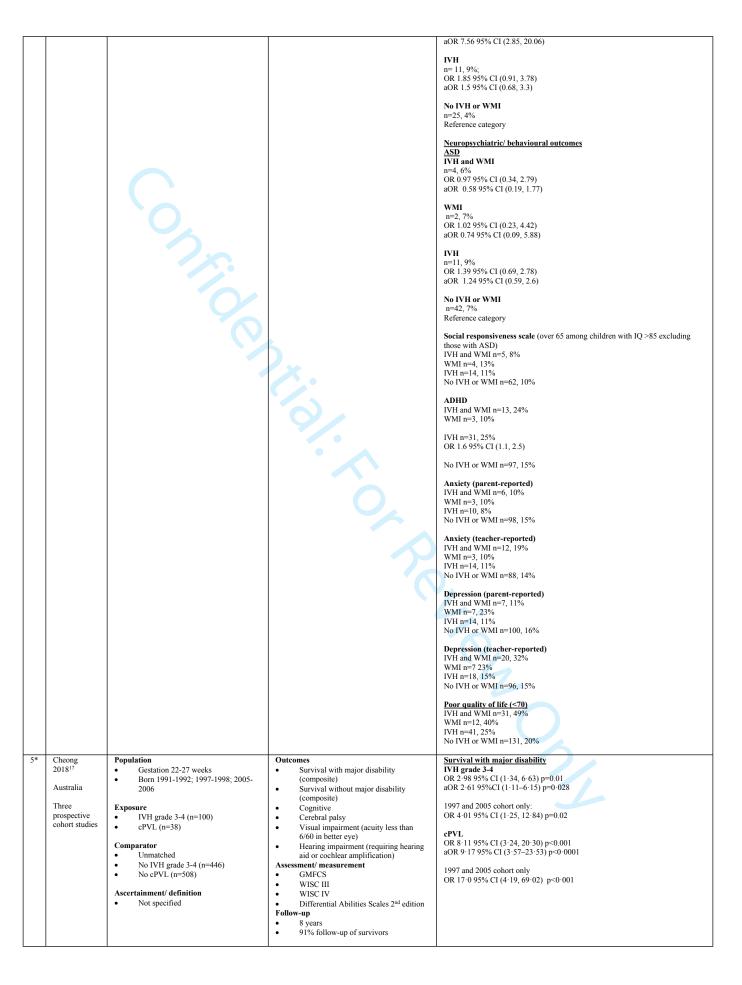
Supplement 4: included studies of school-aged outcomes after perinatal brain injury

* overlapping study data; \(\Omega \) potential error in manuscript, Adjusted Odds Ratio (aOR); Attention Deficit Hyperactivity Disorder (ADHD); Autism Spectrum Disorder (ASD); Bayley Scale of Infant
Development (BSID); Child Behaviour Checklist (CBCL); Clinical Evaluation of Language Fundamentals (CELF); Cystic Periventricular leukomalacia (cPVL); Gross Motor Function Classification System,
(GMFCS); Haemorrhagic parenchymal infarction (HPI); Hazard Ratio (HR); International Classification of Disease (ICD); Intraventricular haemorrhage (IVH); Intelligence Quotient (IQ); Kaufman Assessment
Battery for Children (K-ABC); Mental Developmental Index (MDI); Peabody Picture Vocabulary Test (PPVT); Periventricular (PV); Periventricular leukomalacia (PVL); National Institute of Child Health and
Human Development (NICHD); Neonatal Intensive Care Unit (NICU); Psychomotor Development Index (PDI); Retinopathy of Prematurity (ROP); Small for Gestational Age (SGA); Spontaneous Intestinal
Perforation (SIP); Standard Deviation (SD); Standard Error (SE); Test of Motor Impairment (TOMI); Very low birthweight (VLBW); Visuomotor integration (VMI); Wechsler Abbreviated Scale of Intelligence
(WASI); Wechsler Intelligence Scale for Children (WISC); Wechsler Preschool & Primary Scale of Intelligence (WPPSI); White Matter Injury (WMI); Wide Range Achievement Test (WRAT)

Belgium Retrospective cohort Retrospective cohort Exposure (n=19) IVH grade 3-4 Comparator (n=44) • Gestation ≤32 weeks with and without spontaneous intestinal perforation (SIP) • Functional disability (composite) • Cognitive • Motor • Wisual • Behavioural/ mental health • Wellbeing • Quality of life • Physical health Cognitive • Cognitive • Motor • Visual • Behavioural/ mental health • Wellbeing • Quality of life • Physical health Cognitive • Cognitive • Cognitive • Motor • Wellbeing • Quality of life • Physical health Cognitive	Author	Population	Outcomes	Main result(s)
Study type Ascertainment/ definition Adaptation For population Gestation 523 weeks with and without spontaneous intestinal perforation (SIP) Belgium For population Gestation 521 weeks with and without spontaneous intestinal perforation (SIP) Bom 1994-2014 Fixposure (n=19) Wellbeing Behavioural/ mental health Wellbeing Behavioural/ mental health Wellbeing Disabilities and 8 8.79 95%CI (1.61, 22.15) Subgraph Disa	Year	Exposures		
Adamt 2019 ¹² Belgium Retrospective cohort Page 17th grade 3-4 Comparator (n=4) No IVH Ascertainment/ definition Clinical record review Prospective cohort Prospective cohort Beaino 2010 ¹² France Prospective cohort Prospective cohort				
Belgium Retrospective cohort Results (Retrospective cohort) Retrospective cohort Retr	Study type	Ascertainment/ definition		
Belgium Retrospective cohort Separation (SIP) Born 1994-2014 Sepostre (n=19) IV grade 3-4 Comparator (n=44)	Adant 2019 ¹⁵	Population		Outcomes of those with SIP compared to controls without SIP – by IVH
Retrospective cohort Retrospective cohort Retrospective cohort Population Retrospective cohort Regular educational needs school and R 7.9 9%CI (2.1, 5.672) Reduction, Retrospective cohort in a special educational needs school and R 7.9 9%CI (2.1, 5.672) Reduction, Retrospective cohort in a special educational needs school and R 7.9 9%CI (2.1, 5.672) Reduction, Retrospective cohort in a special educational needs school and R 7.9 9%CI (2.1, 5.672) Reduction, Retrospective cohort in a special educational needs school and R 7.9 9%CI (2.1, 5.672) Retrospective retrospective cohort in a special education				subgroup
Retrospective cohort Prospective cohort Beaino 2010 ⁷³ Prospective cohort Prospec	Belgium			D: 125
Exposure (n=19) • IVH grade 3-4 Comparator (n=44) • Matched on gender, gestational age, date of birth (multiples matched to sibling without SIP) • No IVH Ascertainment/ definition • Clinical record review Beaino 2010 ²³ Beaino 2010 ²³ Prospective cohort Prospective cohort Prospective cohort IVI grade 2 (n=173) • IVI grade 2 (n=173) • IVI grade 2 (n=173) • IVI grade 2 (n=17) • IVI grade 3 (n=22) • IVI grade 3 (n=123) • IVI grade 3 (n=12) • IVI grade 3 (n=12) • IVI grade 3 (n=12) • IVI grade 3 (n=13) • IVI grade 3 (n=12) • IVI grade 3 (n=12) • IVI grade 3 (n=13) • Unmatched • No IVI Ascertainment/ definition • Ultrassound maging undertaken and reviewed by neonatologists or residuation and reviewed by neonatologists or residuation and reviewed by neonatologists or residuation and residuation with well has been also with the substitution of the problems and substitution problems and substitut	D			
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Finne Population Population Cerebral palsy Cere	COHOIT	Evanguage (n=10)		Multiple disabilities
Comparator (n=44)				
Measurement/ assessment Sill pill		• IVH glade 3-4		uoit 5.57 55 /vol (1.01, 22.15)
Matched on gender, gestational age, date of birth (multiples) matched to sibling without SIP) No IVH		Comparator (n=44)	Physical health	Cognitive
date of birth (multiples matched to sibling without SIP) No IVH Ascertainment/ definition Clinical record review Follow-up 6 7% follow-up at 7-11 months 4 41% follow-up at 4-10 years 4 45% follow-up at 4-10 years 86% follow-up at 4-10 years 86% follow-up telephone survey Follow-up 6 6 7% follow-up at 4-10 years 7 86% follow-up at 4-10 years 86% follow-up telephone survey Follow-up 1 8eaino 2010 ⁷³ France France Follow-up 1 Population Gestation <33 weeks France 1 Gestation <33 weeks 1 Follow-up 1 Vil grade 1 (n=173) 1 Vil grade 2 (n=117) 1 Vil grade 2 (n=117) 1 Vil grade 2 (n=117) 1 Vil grade 3 (m=32) 1 Vil grade 3 (m=32) 1 Vil grade 3 (m=32) 1 Vil grade 4 (n=173) 2 Vil grade 3 Vil (n=66) Persistent echodensities or ventricular dilatation (m=241) 2 Comparator (n=1133) 1 Unmatched No IVH Ascertainment/ definition Ultrasound imaging undertaken and reviewed by neonatologists or			Mossuroment/assessment	Regular education system (not a special educational needs school)
Soling without SIP) No IVH Ascertainment/ definition PepedsOL Peped				aOR 8.73 95%CI (2.1, 36.72)
PedsOL IQ testing		sibling without SIP)		
Ascertainment/ definition Clinical record review Follow-up 67% follow-up at 7-11 months 41% follow-up at 18-22 months 49% follow-up at 4-10 years 86% follow-up telephone survey Prospective cohort Prosp		No IVH		
Ascertaiment/ definition Clinical record review Follow-up 67% follow-up at 18-22 months 4 Mys follow-up at 18-10 years 86% follow-up telephone survey Follow-up 67% follow-up at 18-22 months 4 Mys follow-up at 4-10 years 86% follow-up telephone survey PedsOL low physical health disorder (including attention problems problems and autism spectrum disorders) a OR 0.87 95%CI (0.61, 0.10) PedsOL low physical health score a OR 0.87 95%CI (0.61, 0.10) PedsOL low physical health score a OR 0.87 95%CI (0.61, 0.10) Cerebral palsy Measurement/assessment Standardised questionnaires completed by physicians Follow-up 1VH grade 2 (n=17) 1VH grade 3 (n=13) 1VH grade 3 (n=12) 1VH grade 3 (n=32) 1VH grade 3 (n=32) 1VH grade 3 (n=22) 1VH grade 3 (n=22) 1VH grade 3 (n=22) 1VH grade 3 (n=22) 1VH grade 3 (n=24) 1VH grade 3 (n=173) 1VH grade 1 (n=173) 1VH gra				aOR 0.474 95%C1 (0.13, 1.69)
Follow-up at 7-11 months • 14% follow-up at 18-22 months • 49% follow-up at 4-10 years • 86% follow-up telephone survey Prospective cohort Prospective cohort Prospective cohort Prospective cohort Comparator (n=1153) • Ummatched • No IVH Ascertainment/ definition • Ultrasound imaging undertaken and reviewed by neonatologists or designed and content of the follow-up at 4-10 years • 67% follow-up at 4-10 years • 86% follow-up at 4-10 years • 86% follow-up telephone survey Prospective cohort Pros			TQ testing	Debayianual/mantal haalth disanday (in alvding attention maklama anndy
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Beaino 2010 ⁷³ Population Gestation < 33 weeks Gerebral palsy Cerebral palsy Grade 3 IVH OR 3.75 95%CI (2.04–5.85)				uor 1.24 /3/001 (0.32, 4.0)
Beaino 2010 ⁷³ Population Gestation <33 weeks France Prospective cohort Prospectiv				PedsQL low quality of life score
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Population Contraction of 22 weeks					
Netherlands Prospective closert Experience ready outstream charge ventricular distantion after Viril grade. 4 me, 33%, all unilinears spanise cerebral pulsy Deschaementhage ventricular distantion after Viril grade. 4 me, 13%, and in the VIVI grade. 4 me, 13%, and in the VIVI grade and seasoners No IVI Comparator (n=23) Macked on gentiation, brithweight. No IVI Acceptalment (definition) Pepile classification Pepile classification Pepile classification Till grade 4 me, 33%, all unilinears spanise cerebral pulsy Measurement AIC Comparator (n=23) No IVII and 4 me, 13%, all unilinears spanise cerebral pulsy Measurement and seasoners No IVII and 4 me, 13%, all unilinears spanise cerebral pulsy Measurement AIC Comparator (n=23) No IVII and 4 me, 13%, all unilinears spanise cerebral pulsy Measurement AIC Comparator (n=23) No IVII and 4 me, 13%, all unilinears spanise cerebral pulsy Measurement AIC Comparator (n=23) No IVII and 4 me, 13%, all unilinears spanise cerebral pulsy Measurement AIC Comparation can be problemed. Measurement and the matter except for those without cerebral pulsy No IVII and 4 me, 13%, all unilinears spanise cerebral pulsy Measurement AIC Comparation can be problemed. Measurement AIC No IVII and 4 me, 13%, all unilinears spanise cerebral pulsy Measurement AIC Comparation can be problemed. Measurement AIC No IVII and 4 me, 13%, all unilinear spanise cerebral pulsy No IVII and 5 me, 2 me,	3				
Notice transport (n=23)		201224			
Prospecies		Notherlands	Born 1999-2004		
Prospective colloid Possible content of the High 2-14 requiring necrosorgical intervention		1 tourer lands	Exposure (n=32)		GMFCS level 2, n=2
Properties Properties			Post-haemorrhagic ventricular	Benavioural	GMFCS level 3, n=1
No FVL Comparator (ne-23)		cohort			Mayamant ABC mater seems (for those without conclude males)
WPFSL (34 definition Dates) versions					
Revise Amsterdams Kinder Machelo on gestation, birthweight, and set			NOTVE		IVH grade 3 n=6, 26%
Matched on gestation, birthweight, and sees			Comparator (n=23)		
No IVH				Intelligentietest	No IVH n=0
CICCL Teacher Report Form					Score p 5-15 (borderline motor function)
** Teacher Report Form ** Ultracound diagnoss** ** Papile classification ** Papile classification ** Follow-up ** 4-8 years (median 5.7) ** 97% follow-up ** 4-8 years (median 5.7) ** 97% follow-up ** Cognition ** Weehaler intelligence test (mean ±5D) ** Verbal scale ** Verbal scale ** Performance scale ** IVI = 22., 57=13 ** IVI			NOTVII		
Pollow-up					
4.4 years (median 5.7) 1. 97% follow-up 1. 97% follow-up 1. 197% fo					101111 (ii 3, 25.470)
■ 97% follow-up VIH grade 4 n=0, 0%			rapite classification		
No IVH n=12, 70.6% Cognition					
Wechsler intelligence test (mean ±SD)				•	
Wechsler intelligence test (mean ±SD)					
Verbal scale IVI IVI -30 weeks gestation m=16, 94=13 No IVI -30 -30 -31 No IVI -30					
IVH = 30weeks' gestation n=16, 94±13 No IVH n=24, 96=13, Performance scale IVH, n=23, 94±16, IVH, n=23, 94±16, IVH, n=23, 94±16, IVH n=24, 10±14, Production scale IVH n=23, 87±22, IVH n=24, 95±14 IVH m=24, 95±14 IVH m=24, 95±14 IVH m=24, 95±14 IVH m=24, 95±14 IVH m=25, 95±16, IVH m=15, IQ 9±15, IVH m=10, 1Q 9±10, IQ 85 n=9 (64 3%) IVH =30 weeks' gestation n=23, IQ 9±17, IQ-85 n=17 (74%) IVH =30 weeks' gestation m=23, IQ 9±17, IQ-85 n=17 (74%) IVH =30 weeks' gestation m=23, IQ 9±17, IVH =30 weeks' gestation m=3, m=1, m=1, m=1, m=1, m=1, m=1, m=1, m=1					
No IVH ==24, 96:13; Performance scale IVH, ==23, 94:216, IVH =30weeks' gestation n=16, 93±15 No IVH ==24, 103±14; Production scale IVH ==24, 103±14; Production scale IVH =23, 87:22; IVH =30weeks' gestation n=16, 85±24 No IVH ==24, 93:14 Intelligence quotient (n; mean ±/sD) IVH grads 3 n=17, 10, 96:15; IQP-85 n=17, 10, 90:15 IQP-85 n=16, 63, 2%) IVH IV n=15; IQ 91±10; IQP-85 n=16, 63, 2%) No IVH n=23, 10, 98±15, IQP-85 n=17, (74%) Behavioural outcomes CBCL parental score: mean T score ±8D, n in subclinical range (%) IVH =26:48, ±8.4, n=3, (12%) IVH =26:48, ±8.4, n=3, (12%) IVH =30 weeks' gestation n=20:46, 9±8.3, n=2 (10%) No IVH =30 weeks' gestation n=20:44, 3±7.8, n=1 (4%) IVH =30 weeks' gestation n=20:49, 1, n=5, (21%) No IVH =30 weeks' gestation =29, 2±9.1, n=5, (21%) No IVH =30 weeks' gestation =32, 2±9.1, n=5, (21%) No IVH =30 weeks' gestation =32, 2±9.1, n=5, (21%) No IVH =30 weeks' gestation =32, 2±9.1, n=5, (21%) No IVH =30 weeks' gestation =32, 2±9.1, n=5, (21%) No IVH =30 weeks' gestation =32, 2±9.1, n=5, (21%) No IVH =30 weeks' gestation =32, 2±9.1, n=5, (21%) No IVH =30 weeks' gestation =32, 2±9.1, n=5, (21%) No IVH =30 weeks' gestation =32, 2±9.1, n=5, (21%) No IVH =30 weeks' gestation =32, 2±9.1, n=5, (21%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%) No IVH =30 weeks' gestation =45, 1±5, n=1, (15%)					
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No IVH < 30weeks' gestation: 43.7 ±7.5, n=0 (0%) TRF teachers score: mean T score ±SD, n in subclinical range (%)					IVH: 46.8 ±9.4, n=2 (8%)
TRF teachers score: mean T score ±SD, n in subclinical range (%)					
					500 Estation 3.7 ±1.3, ii v (070)
Total scale IVH n=25: 54.7 ±8.7, n=6 (24%)					
IVH <30 weeks' gestation n=19: 53.9 \pm 9.0, n=4 (21%)					IVH <30 weeks' gestation n=19: 53.9 ±9.0, n=4 (21%)
No IVH $<$ 30 weeks' gestation n=22: 50.9 \pm 9.8, n=4 (18%)					
Internalising problem scale					Internalising problem scale
Internating products See 1 [VH: 53.2 ± 10.8, 4 (16%)					
IVH <30 weeks' gestation: 52.2 ±11.7, n=3 (16%)					IVH <30 weeks' gestation: 52.2 ±11.7, n=3 (16%)
No IVH <30 weeks¹ gestation: 52.4 ±11.4, n=7 (32%)					No IVH <30 weeks' gestation: 52.4 ±11.4, n=7 (32%)
Externalizing problem scale					Externalizing problem scale
IVH: 54.3 ±6.7, 3 (12%)					IVH: 54.3 ±6.7, 3 (12%)
IVH <30 weeks' gestation: 54.1 ±7.0, n=2 (11%) No IVH <30 weeks' gestation: 49.7 ±7.7, n=2 (9%)					IVH <30 weeks' gestation: 54.1 ±7.0, n=2 (11%)
No IVH <50 weeks gestation: 49.7 ±7.7, n=2 (9%)					140 1411 >30 weeks gestation. 49.7 ±7.7, n=2 (9%)
N=13 (41%) had repeated a school class, had educational help and/or attended					
special education					special education

Campbell 2021 ^{to} USA Prospective cohort study Prospective cohort study Prospective cohort study Exposure I'H without WHI (n=124) WM without IVH (n=30) I'H and WMI (n=63) Comparator (n=641) Umatched No I'VH or WMI Ascertainment/ definition WItrasound imaging reviewed by two independent binder radiologists WMI: parenchymal echolucency or modrate to severe ventriculomegaly on a late scan	Outcomes Neurocognitive development (composite) Cognitive Cerebral palsy Behavioural/ mental health Epilepsy Quality of life Measurement/ assessment Differential Ability Scale II NEPSY II Neurological exam GMFCS Parental questionnaire Social Communication Questionnaire Child Symptom Inventory 4 Peds QoL 4 Follow up 10 years 74% follow-up	Neurodevelopmental burden No impairments IVH and WMI n=24, 38% WMI n=12, 60% No IVH or WMI n=36, 69% No IVH or WMI n=36, 69% No cognitive impairment; I or more of cerebral palsy, ASD, or epilepsy IVH and WMI n=4, 6% WMI n=4, 13% WMI n=4, 13% WMI n=4, 13% WMI n=5, 13% WMI n=5, 13% WMI n=8, 13% WMI n=1, 28% WMI n=1, 28%



6	Chou 2020 ⁷⁴ Taiwan Retrospective cohort study	Population Preterms infants <37 weeks' gestation (n=21,474) Infants born small for gestational age (n=2206) Born 2000-2010 Exposure Preterm with cerebral haemorrhage SGA with cerebral haemorrhage Comparator (n=94,720) Matched 1:4 on gender, urbanisation of residential area and parental occupation No cerebral haemorrhage Ascertainment/ definition National children's medical record database ICD 9 codes	Outcome	Epilepsy Preterm with cerebral haemorrhage HR 42.4 95%CI (29.8, 60.3) aHR 42.5 95 %CI (29.6, 60.5) SGA with cerebral haemorrhage HR 39.3 95%CI (5.51, 274.5) aHR 38.7 95%CI (5.43, 275.5)
7	Davidovitch 2020 ³⁵ Israel Retrospective cohort study	Population (n=4963) VLBW infants ≤1500g Born 1999-2012 Exposure IVH grade 3-4 (n=256) PVL (n=200) Post-haemorrhagic hydrocephalus (n=152) Comparator Unmatched No IVH grade 3-4 (n=4600) No PVL (n=3813) No post-haemorrhagic hydrocephalus (n=4810) Ascertainment/ definition Israel national very low birthweight infant database linked to electronic medical records. Ultrasound diagnosis Papile classification	Outcome ASD Assessment/ measurement Physical, neurological, and developmental assessment (by a qualified healthcare professional) Independent psychological assessment Follow-up 8-15 years (median 11.6) Only those linked to electronic medical records included	ASD IVH n=10, 3.9% No IVH n=103, 2.2% p=0.085 PVL n=5, 2.5% No PVL n=88, 2.3% p=0.86 Post-haemorrhagic hydrocephalus n=7, 4.6% No post-haemorrhagic hydrocephalus n=106, 2.2% p=0.051 IVH, PVL, post-haemorrhagic hydrocephalus or ROP n=27,23.9% No brain injury n=571, 11.8% p<0.0001 aOR 1.62 95% CI (0.96–2.73)
8*	Doyle 2000 ⁷⁵ Australia Prospective Cohort	Population	Outcomes Survival Cerebral palsy Measurement/assessment Clinical assessment by blinded paediatricians Functional assessment Follow-up Syears 93% follow-up for 1980s epoch 94% follow-up for 1992 epoch	Cerebral Palsy Grade of IVH 1980s epoch No IVH n=5, 5% IVH grade 3 n=2, 29% IVH grade 4 n=0 1992s epoch No IVH n=4, 4% IVH grade 3 n=3, 33% IVH grade 4 n=1, 100%

Population Gestation 24-28 weeks Born 2005-2009 Moderate to severe disability (composite) Now thite matter injury, n=8, 9% Mild white matter injury, n=8, 15% Severe white matter injury, n=1, 182% Pool of the matter injury, n=1, 182% P	
USA Retrospective cohort Retrospective cohort Exposure MRI Mild WMI (n=223) Moderate WMI (n=51) Severe WMI (n=15) Any cerebellar lesion (n=57) Significant cerebellar lesion (n=39) Early cranial ultrasound No IVH 3-4 or cPVL (n=321) Iate cranial ultrasound No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=394) Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) Minimal or no disability Cerebral palsy No Mild white matter injury, n=8, 15% Severe white matter injury, n=14, 82% p>-0.0001 Moderate white matter injury, n=14, 82% p>-0.0001 Moderate or severe white matter injury acor severe white matter injury acor 1.1 95% CI (0.42, 2.92) Moderate or severe white matter injury, n=88, 12/4 Moderate white matter injury, n=14, 82% p>-0.0001 Moderate or severe white matter injury, n=8, 15% Severe white matter injury acor 1.1 95% CI (0.42, 2.92) Moderate white matter injury, n=47, 55% Mild white matter injury, n=88, 224% Moderate white matter injury, n=88, 224% Moderate white matter injury, n=15, 28% Severe white matter injury, n=0, 0% p>-0.0001 Follow-up 6 -6 7 years 8 3.3% follow-up of survivors Follow-up • 6-7 years • 8 3.3% follow-up of survivors Follow-up • 6-7 years • 7 Cognitive impairment (FSIQ mean (SD)) No white matter injury, 82 (17) Severe white matter injury, 92 (16.8) Moderate white matter injury, 92 (16.8) Moderate white matter injury, 92 (17.96) p>-0.0001 Cognitive impairment FSIQ <70	
Retrospective cohort Exposure MRI MId WMI (n=223) Moderate WMI (n=51) Severe WMI (n=15) Any cerebellar lesion (n=57) Significant cerebellar lesion (n=39) Early cranial ultrasound No IVH 3-4 or cPVL (n=32) I Late cranial ultrasound No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) Late cranial ultrasound No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) Minimal or no disability Cognitive Neasurement/ assessment Neasurement/ assessment New ISC IV Neurological exam Mid white matter injury, n=27, 12% Moderate white matter injury, n=14, 82% Poon (n=4) No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=354) Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) Minimal or no disability No white matter injury, n=47, 55% Mid white matter injury, n=8, 224% Moderate white matter injury, n=47, 55% Mid white matter injury, n=14, 82% Poon (n=4) No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=354) Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=354) Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=354) Poon (n=4) Severe white matter injury, n=27, 12% Moderate white matter injury, n=14, 82% Moderate or severe white matter injury, n=47, 55% Mild white matter injury, n=47, 55% Mild white matter injury, n=8, 224% Moderate white matter injury, n=0, 0% Poon (n=4) Severe white matter injury, n=0, 0% No white matter injury, n=0, 0% Severe white matter injury, n=0, 0% No white matter injury, n=0, 0% Severe white matter injury, n=0, 0% Severe white matter injury, n=0, 0% Severe white matter injury, n=0	
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• Moderate WMI (n=51) • Severe WMI (n=15) • Any cerebellar lesion (n=57) • Significant cerebellar lesion (n=39) Early cranial ultrasound • No IVH 3-4 or cPVL (n=341) • IVH 3-4 or cPVL (n=32) Late cranial ultrasound • No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=354) • Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) Moderate or severe white matter injury aoR 1.1 95% CI (0.42, 2.92) Minimal or no disability No white matter injury, n=88, 224% Moderate white matter injury, n=15, 28% Severe white matter injury, n=15, 28% Severe white matter injury, n=0,0% p<0.0001 Cognitive impairment (FSIQ mean (SD)) No white matter injury, 84 (17) Severe white matter injury, 82.7 (19.6) p<0.0001 Cognitive impairment FSIQ <70	
• Severe WMI (n=15) • Any cerebellar lesion (n=57) • Significant cerebellar lesion (n=39) Early cranial ultrasound • No IVH 3-4 or cPVL (n=341) • IVH 3-4 or cPVL (n=32) Late cranial ultrasound • No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=354) • Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) Moderate vasessment • WISC IV • Neurological exam • GMFCS • Clinical examination • Parental report Follow-up • 6-7 years • 6-7 years • 6-7 years • 6-7 years • 83.3% follow-up of survivors Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=354) • Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) Cognitive impairment (FSIQ mean (SD)) No white matter injury, 84 (17) Severe white matter injury, 82.7 (19.6) p<0.0001 Cognitive impairment FSIQ <70	
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• No IVH 3-4 or cPVL (n=341) • IVH 3-4 or cPVL (n=32) Late cranial ultrasound • No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=354) • Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) • No IVH 3-4 or cPVL (n=341) • 6-7 years • 83.3% follow-up of survivors • Cognitive impairment (FSIQ mean (SD)) No white matter injury, 90.1 (15.5) Mild white matter injury, 85.9 (16.8) Moderate white matter injury, 85.9 (16.8) Moderate white matter injury, 62.7 (19.6) p<0.0001 Cognitive impairment FSIQ <70	
• IVH 3-4 or cPVL (n=32) Late cranial ultrasound • No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) • Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) Follow-up • 6-7 years • 83.3% follow-up of survivors Sollow-up of survivors Follow-up • 6-7 years • 83.3% follow-up of survivors Mild white matter injury, 85.9 (16.8) Moderate white matter injury, 84 (17) Severe white matter injury, 62.7 (19.6) p<0.0001 Cognitive impairment (FSIQ mean (SD)) No white matter injury, 85.9 (16.8) Moderate white matter injury, 62.7 (19.6) p<0.0001 Cognitive impairment (FSIQ mean (SD)) No white matter injury, 85.9 (16.8) Moderate white matter injury, 62.7 (19.6) p<0.0001	
Late cranial ultrasound No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) • 6-7 years • 6-7 years • 83.3% follow-up of survivors Say follow-up of survivors • 6-7 years • 83.3% follow-up of survivors • 83.3% follow-up of survivors Mild white matter injury, 90.1 (15.5) Mild white matter injury, 84. (17) Severe white matter injury, 62.7 (19.6) p<0.0001 Cognitive impairment (FSIQ mean (SD)) No white matter injury, 90.1 (15.5) Moderate white matter injury, 84. (17) Severe white matter injury, 62.7 (19.6) p<0.0001	
• 83.3% follow-up of survivors No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=354) • Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) • 83.3% follow-up of survivors No white matter injury, 90.1 (15.5) Mild white matter injury, 84 (17) Severe white matter injury, 62.7 (19.6) p<0.0001 Cognitive impairment FSIQ <70	
moderate to severe ventricular enlargement or shunt (n=354) Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) Moderate white matter injury, 84 (17) Severe white matter injury, 62.7 (19.6) p<0.0001 Cognitive impairment FSIQ <70	
enlargement or shunt (n=5)4) Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) Cognitive impairment FSIQ <70	
to severe ventricular enlargement or shunt (n=19) Cognitive impairment FSIQ <70	
shunt (n=19) Cognitive impairment FSIQ <70	
Mild white matter injury, n=25, 11% Moderate white matter injury, n=6, 12%	
No white matter injury on MRI Severe white matter injury, n=9, 60%	
(n=84) No cerebellar lesion on MRI (n=316)	
No IVH 3-4 or cPVL (n=32) Moderate or severe white matter injury	
Normal early cranial ultrasound aOR 1.14 95% CI (0.39, 3.26)	
(n=227)	
No porencephalic cyst, cPVL	
enlargement or shunt (n=19) Mild white matter injury, n=100, 45%	
Normal late cranial ultrasound (n=284) Normal late cranial ultrasound (n=284) Moderate white matter injury, n=29, 57% Severe white matter injury, n=13, 87%	
Severe white matter injury, n=13, 87% p<0.0001	
Ascertainment/ definition	
NICHD neonatal research network (NEURO study and SUPPORT No cognitive impairment FSIQ ≥85 No white matter injury, n=57, 68%	
(NEURO study and SUPPORT No white matter injury, n=57, 68% Cohort) No white matter injury, n=123, 55%	
Two masked central imaging readers Moderate white matter injury, n=22, 43%	
NiCHD neonatal research network (NEURO study and SUPPORT cohort) Two masked central imaging readers for all cranial ultrasounds and one for MRI No cognitive impairment FSIQ ≥85 No white matter injury, n=57, 68% Mild white matter injury, n=123, 55% Moderate white matter injury, n=22, 43% Severe white matter injury, n=2, 13% p<0.0001	
All had cranial ultrasound and MRI	
(at 35-42 weeks) Any cerebral palsy	
Unilateral and bilateral cranial No white matter injury, n=2, 2% Mild white matter injury, n=6, 3%	
Moderate white matter injury, n=4, 7%	
Severe white matter injury, n=10, 59%	
p<0.0001	
Cerebral palsy with GMFCS ≥2	
No white matter injury, n=0, 0% Mild white matter injury, n=1, 0%	
Moderate white matter injury, n=1, 2%	
Severe white matter injury, n=4, 24%	
p<0.0001	
Cerebellar lesions	
Moderate to severe disability No cerebellar lesion, n=37, 12%	
Any cerebellar lesion, n=20, 33% p<0.0001	
Significant cerebellar lesion, n=15, 36%	
Significant cerebellar lesions	
aOR 2.71 95% CI (1.09, 6.71)	
Minimal or no disability	
No cerebellar lesion, n=135, 42%	
Any cerebellar lesion n=15, 25% p<0.0001 Significant cerebellar lesion, n=15, 36%	
Cognitive impairment (FSIQ mean (SD)) No cerebellar lesion, 87 (16.5)	
Any cerebellar lesion 78.4 (20) p=0.001	
Significant cerebellar lesion 76.8 (20.4)	
Cognitive impairment FSIO <70	
No cerebellar lesion, n=32, 10%	
Any cerebellar lesion, n=15, 26% p=0.001 Significant cerebellar lesion, n=10, 26%	
Significant defeodral resion, n=10, 20%	
Significant cerebellar lesions aOR 1.96 95% CI (0.72, 5.36)	
Committing immunity ECIO 405	
Cognitive impairment FSIQ <85 No cerebellar lesion, n=136, 43%	
Any cerebellar lesion, n=33, 58% p=0.038	
Significant cerebellar lesion, n=22, 56%	
No cognitive impairment FSIQ ≥85	
No cerebellar lesion, n=180, 57%	
Any cerebellar lesion, n=24, 42% P=0.038 Significant cerebellar lesion, n=17, 44%	
Any cerebral palsy	

No cerebellar lesion, n=13, 4% Any cerebellar lesion, n=9, 15% p=0.001 Significant cerebellar lesion, n=9, 21%

Cerebral palsy with GMFCS ≥2 No cerebellar lesion, n=3, 1% Any cerebellar lesion, n=3, 5% p=0.19 Significant cerebellar lesion, n=3, 7%

A. No IV, Early cranial ultrasound abnormalities No IVH 3-4 or cPVL, n=43, 12% IVH 3-4 or cPVL, n=14, 42% p<0.0001 Normal scan, n=35, 12%

aOR 0.61 95% CI (0.14, 2.59)

Minimal or no disability No IVH 3-4 or cPVL, n=143, 41% IVH 3-4 or cPVL, n=7, 21% p<0.0001 Normal scan, n=120, 43%

Cognitive impairment, FSIQ mean (SD) No IVH 3-4 or cPVL, 86.4 (17) IVH 3-4 or cPVL, 77.9 (19.1) p=0.008 Normal scan, 86 (16.7)

Cognitive impairment FSIQ <70 No IVH 3-4 or cPVL, n=38, 11% IVH 3-4 or cPVL, n=9, 28% p=0.006 Normal scan, n=31, 11% aOR 0.42 95% CI (0.07, 2.33)

Cognitive impairment FSIQ <85 No IVH 3-4 or cPVL, n=149, 44% IVH 3-4 or cPVL, n=20, 63% p=0.041 Normal scan, n=123, 44%

No cognitive impairment FSIQ ≥85 No IVH 3-4 or cPVL, n=192, 56% IVH 3-4 or cPVL, n=12, 38% p=0.041 Normal scan, n=154, 56%

Any cerebral palsy No IVH 3-4 or cPVL, n=149, 44% IVH 3-4 or cPVL, n=20, 63% p=0.041 Normal scan, n=123, 44%

Cerebral palsy with GMFCS \geq 2 No IVH 3-4 or cPVL, n=3, 1% IVH 3-4 or cPVL, n=3, 9% p<0.0001 Normal scan, n=2, 1%

<u>Late cranial ultrasound abnormalities</u> Moderate to severe disability

No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=40, 11% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=17, 77% p<0.0001

Normal scan, n=27, 10% aOR 27.85 95% CI (6.03, 128.68)

Minimal or no disability

No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=149, 42%

Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=1, 5% P<0.0001 Normal scan, n=117, 43%

Cognitive impairment (FSIO mean (SD))

No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, 86.7 (16.7) Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, 65.9 (18.7) P<0.0001

Normal scan, 87 (16.1)

Cognitive impairment FSIQ <70

No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt. n=36, 10% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=11, 58% p<0.0001

Normal scan, n=24, 9% aOR 20.05 95% CI (3.63, 110.84)

Cognitive impairment FSIQ <85 No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=153, 43%

Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=16, 84% p<0.0001 Normal scan, n=118, 43%

No cognitive impairment FSIQ ≥85

No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=201, 57% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=3, 16% p<0.0001

Normal scan, n=156, 57%

Any cerebral palsy No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=10, 3%

Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt

10	Hirovonen, 2017 ²⁸ Finland Retrospective cohort	Population Gestation >22 weeks Birth weight >500g Born 1991-2008 Exposure (n=557) Intracranial haemorrhage Comparison (n=708,977) No intracranial haemorrhage ICD code Ascertainment/ definition Finnish national register ICD codes	Outcomes Cognitive Measurement/ assessment ICD 9 and 10 codes BSID 1993 Finnish WISC Follow-up 7 years 98% follow-up	n=12, 50% p<0.0001 Normal scan, n=6, 2% Cerebral palsy with GMFCS ≥2 No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=2, 1% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=4, 17% p<0.0001 Normal scan, n=1, 0% Any intellectual disability after intracranial haemorrhage (HR (95%CI); p-value) Very preterm infants 2.92 (1.58–5.41); p= 0.001 Moderately preterm 5.59 (1.57–19.9); p= 0.008 Late preterm 4.58 (1.36–15.4); p= 0.014 Term 2.94 (1.08-8); p=0.035

11	Hollebrandse	Population	Outcomes	Cognitive
*	202125	 Gestation <28 weeks Born 1991-1992, 1997, 2005 	Cognitive Motor	IQ score <-2 SD IVH grade 4 n=5, 42% p=0.08 (X ² trend)
	Australia	• Bolli 1991-1992, 1997, 2003	Cerebral palsy	IVH grade 3 n=5, 22%
		Exposure	Cereoral pansy	No IVH n=41, 12%
	Retrospective	IVH grade 1 n=80	Assessment/ measurement	BHI 2 4: OB 2 (9.050/ CI (1.21.5.04) ::=0.01
	cohort	• IVH grade 2 n=53	 WISC III (1991-1992 cohort) WISC IV (1997 cohort) 	IVH 3-4: OR 2.68 95% CI (1.21, 5.94) p=0.01
		 IVH grade 3 n=23 IVH grade 4 n=12 	WISC IV (1997 cohort) Differential Abilities Scale 2 nd edition	Impaired executive function
		1 vii giade 4 ii–12	(2005 cohort)	Global executive composite ≥65
		Comparator	 WRAT III (1991-92; 1997 cohorts) 	IVH grade 4 n=2, 18% p=0.78 (X ² trend)
		Unmatched	WRAT IV (2005 cohort)	IVH grade 3 n=4, 18% No IVH n=49, 16%
		Preterm infants without IVH n=331	Behaviour rating inventory of executive functioning (parent-completed)	
		Ascertainment/ definition	Movement ABC 1st edition (1991-1992)	IVH 3-4: OR 1.17 95% CI (0.46, 2.97) p=0.75
		Ultrasound diagnosis	and 1997 cohorts)	Behavioural regulation index ≥65
		Worst grade of IVH	Movement ABC 2 nd edition (2005)	IVH grade 4 n=2, 18% p=0.21 (X ² trend)
		Papile classification	cohort) • GMFCS (1997 and 2005 cohort)	IVH grade 3 n=6, 27%
			Blinded assessment	No IVH n=46, 15%
				IVH 3-4: OR 1.76 95% CI (0.75, 4.11) p=0.2
			Follow-up	
			8 yearsFollow-up 85-91.4%	Metacognition index ≥65
			- 1000w-up 65-71.470	IVH grade 4 n=3, 27% p=0.1 (X ² trend) IVH grade 3 n=5, 23%
				No IVH n=48, 16%
				IVH 3-4: OR 1.73 95% CI (0.74, 4.06) p=0.21
				Impaired academic skills (any academic skill <-2SD)
				IVH grade 4 n=7, 64% p<0.001 (X ² trend)
				IVH grade 3 n=5, 24%
				No IVH n=50, 16%
			X	IVH 3-4: OR 2.91 95% CI (1.35, 6.27) p=0.006
		· ·		Impaired reading <-2SD
				IVH grade 4 n=6, 55% p=0.002 (X ² trend)
				IVH grade 3 n=4, 19% No IVH n=21, 10%
				IVH 3-4: OR 3.62 95% CI (1.59, 8.24) p=0.002
				Impaired spelling <- 2 SD
				IVH grade 4 n=5, 45% p=0.011 (X ² trend)
				IVH grade 3 n=3, 14%
				No IVH n=21, 7%
				IVH 3-4: OR 4.48 95% CI (1.8, 11.2) p=0.001
				Impaired arithmetic < -2 SD
				IVH grade 4 n=5, 45% p=0.09 (X ² trend) IVH grade 3 n=4, 19%
				No IVH n=38, 12%
				IVH 3-4: OR 2.79 95% CI (1.2, 6.48) p=0.017
				Motor and cerebral palsy
				Any motor dysfunction (cerebral palsy or MABC <5th centile)
				IVH grade 4 n=11, 92% p<0.001 (X ² trend) IVH grade 3 n=10, 43%
				No IVH grade 3 n=10, 43% No IVH n=81, 24%
				IVH 3-4: OR 4.45 95% CI (2.18, 9.08) p<0.001
				Cerebral palsy IVH grade 4 n=9, 75% p<0.001(X ² trend)
				IVH grade 3 n=6, 26%
				No IVH n=26, 8%
				IVH 3-4: OR 8.8 95% CI (4.03, 19.2) p<0.001
				MABC <5th percentile (for the 2005 cohort)
				IVH grade 4 n=11, 92% p<0.001 (X2 trend)
				IVH grade 3 n=9, 45% No IVH n=79, 26%
				NO IVII II-/9, 2070
				IVH 3-4: OR 4.7 95% CI (2.21, 9.97) p<0.001
		1	I.	

12	Hreinsdottir 2018 ⁵⁴ Sweden Prospective cohort study	Population Born 2004-2007 Gestation <32 years Exposure (n=9) IVH grade 3-4 and/ or PVL Comparator (n=99) Unmatched No IVH grade 3-4 or PVL Ascertainment/ definition Ultrasound imaging performed by paediatric radiologist Papile classification for IVH PVL defined by size, laterality and as cystic of diffuse	Outcomes Visual impairment Assessment/ measurement Linear visual acuity (Lea Hyvarinen chart) Cover test Refraction Follow-up 6.5 years 78% follow-up	Vision Subnormal visual acuity IVH 3-4 and or PVL OR 1.11 95% CI (0.25, 4.83) p=0.891 Contrast sensitivity IVH 3-4 and or PVL OR 1.87 95% CI (0.43, 8.17) p=0.403 Refractive error IVH 3-4 and or PVL OR 2.5 95% CI (0.55, 11.41) p=0.237 Manifest strabismus IVH 3-4 and or PVL OR 4 95% CI (0.65, 24.55) p=0.134 Composite score 1: Visual acuity with both eyes of less than 0.3, significant refractive error in the better eye and manifest strabismus IVH 3-4 and or PVL OR 3.63 95% CI (0.65, 37.48) p=0.121 Composite score 2: Visual acuity in worse eye of less than 0.3, significant refractive error in worse eye according and manifest strabismus IVH 3-4 and or PVL OR 5.67 95% CI (1.34, 24.07) p=0.019 aOR 10.4 95% CI (1.34, 24.07) p=0.019 aOR 10.4 95% CI (1.34, 24.07) p=0.019 aOR 10.4 95% CI (1.734) p=0.032 Composite score 3: Visual acuity with both eyes of less than 0.5, significant refractive error in the better eye, manifest strabismus, negative stereopsis and contrast sensitivity less than 0.4 IVH 3-4 and or PVL OR 7.6 95% CI (1.7, 34) p=0.008 aOR 18.19 95% CI (2.15, 154.05) p=0.008 Composite score 4: Visual acuity with both eyes of 0.8 or less, significant refractive error in the better eye, manifest strabismus, negative stereopsis and CS less than 0.5 IVH 3-4 and or PVL OR 7.6 95% CI (1.7, 34) p=0.008 aOR 18.19 95% CI (2.15, 154.05) p=0.008 Composite score 4: Visual acuity with both eyes of 0.8 or less, significant refractive error in the better eye, manifest strabismus, negative stereopsis and CS less than 0.5 IVH 3-4 and or PVL OR 4.63 95% CI (0.9, 23.85) p=0.067 a6.23 95% CI (1.15, 33.83) p=0.034
13	Jansen 2020 ²⁹ Netherlands Prospective cohort study	Population Gestation <32 weeks Admitted 2006-2007 Exposure Mild WMI (n=18) Severe WMI (n=14) Severe WMI (n=8) Mild cerebellar injury (n=11) Moderate cerebellar injury (n=6) Comparator Unmatched No WMI (n=46) No cerebellar injury (n=65) Ascertainment/ definition Ultrasound imaging and term MRI Imaging reviewed by two blinded experienced investigators (neonatologists)	Outcomes Cognitive Assessment/ measurement National standardised achievement tests Follow-up 9-10 years 77% follow-up	Cognitive Reading comprehension Moderate-severe WMI vs. no injury B 0.241 p=0.483 Moderate-severe cerebellar injury vs. no injury B 0.799 p=0.325 Spelling Moderate-severe WMI vs. no injury B 1.076 p=0.075 Moderate-severe cerebellar injury vs. no injury B 1.293 p= 0.115 Mathematics Moderate-severe WMI vs. no injury B 1.856 p=0.003 Moderate-severe cerebellar injury vs. no injury B 1.504 p=0.088
14	Kaur 2020 ³⁸ Canada Retrospective cohort study	Population Preterm and term infants Born 2006-2016 Exposure IVH grade 1 (n=811) IVH grade 2 (n=186) IVH grade 3-4 (n=194) Preterm haemorrhage (n=1139) Comparator Ummatched No IVH (n=793, 062) Preterm no haemorrhage (n=50, 185) Ascertainment/ definition ICD 10 codes (based on ultrasound or MRI imaging) Papile classification	Outcome Reason for hospitalisation Assessment/ measurement ICD 10 codes Follow-up 12 years Completeness of follow-up not specified	Incidence of hospitalisation for: Cerebral palsy, n, incident rate per 1,000 person years (95%CI) IVH n=57, 6.8 (5.3, 8.8) No haemorrhage n=432, 0.1 (0.1, 0.1) Hazard ratio: 4.78 95% CI (3.21, 7.13) IVH grade 3-4 n=24 HR 14.78 95% CI (8.72-25.06) Ophthalmologic, n, incident rate per 1,000 person years (95%CI) IVH n=91 11.1 (9, 13.6) No haemorrhage n=6773, 1.2 (1.2, 1.3) HR 3.01 95% CI (2.32, 3.89) IVH grade 3-4 n=32 HR 7.87 95% CI (5.31-11.67) Otologic n, incident rate per 1,000 person years (95%CI) IVH n=328, 46.7 (41.9, 52) No haemorrhage n=102,153 22.1 (22, 22.2) HR 1.19 95% CI (1.06, 1.34) IVH grade 3-4 n=202 HR 1.07 95% CI (0.79-1.46)

Second Composition Population Composition Composit					
Comparison Continued Authorition Comparison (page 2015) Compari	15	Kiechl-	Population	Outcomes	Delayed numerical skills
2013	1 1				
Austina				205	
Autoration Propositive color Internated homorology gate 1-d (not-) Internated homorology gate 1-d (not-) Internated homorology gate 1-d (not-) Propositive color Internated homorology gate 1-d (not-) Propositive color (not-) Propositive color (not-) Propositive color		2013	Bom 2003-2000	Massurament/assassment	uote 1.00 /2/v e1 (1.20, 12./2) p 0.00/
Prospective Color		Austria	Evnosuro		Intracranial haemorrhage grade 3-4 n=3 11 10%
Projective color	1 1	. rustitu			
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Comparator Follow-up Sujects Comen Nonverhal Intelligence Tat TED/MATH TED/M					intraparenchymai echodense resions n=0
Fig.		conort			
Intraparechymal echnolense lesions (m ¹) Comparature				 Snijders-Oomen Nonverbal Intelligence 	
Comparative			• PVL (n=2)	Test	
Comparative			Intraparenchymal echodense lesions	TEDI-MATH	
Comparator					
Comparator			,	Follow-up	
16 Kebermass- Solved			Comparator		
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Outcomes Projective classification Projective cohort Proje			Cimiatened	72.276 IOHOW-up	
Outcomes Projective classification Projective cohort Proje			Assertainment/definition		
16 Kickermans Population Castaline 22 weeks Population Castaline 22 weeks Population Populati					
Determinate Comparation Control					
Schedof 2012*	—				
Austria Kapoure Cerebral palay C	16				Outcomes at 5.5 years
Austria Exposure			Gestation <32 weeks	 Neurosensory impairment (composite) 	
Austria Prospective clobert Prospectiv		2012^{26}	 Admitted to NICU 1994-2005 	Motor	
Austria Prospective cubort Proposective cubort Proposectiv				Cerebral palsy	KABC <70
Prospective cobort Propective cobort Pro	1 1	Austria	Exposure		No IVH, 7.6%
Prospective colort Color Follow-up	1 1				
Comparator (n-320)		Prospective			
Not	1 1			- Hearing	
No. Comparator (n=328) C				Maasuramant/assassmant	KABC mean (SD)
Comparation (n=320)			• IVII grade 4 (II=12)		
Turkey Populatin (r=09)			G (v. 220)		
No. Will. Section	1 1				
Ascertainment/ definition Ultrasound diagnosis Most severe scan used September S	1 1				6-300 i, 00.5 (10.0) p 110t significant
Accertainment/ definition			No IVH	VMI	VMI mean (SD)
Follow-up -				Clinical assessment	
Follow-up Foll			Ascertainment/ definition		
Martine: Case control			Ultrasound diagnosis	Follow-up	
Papile classification					IVH grade 4, 76 (26.8) p=0.04
17					
17			T upile classification		
TVH grade 4, 90.9% p-0.01 Visual impairment No IVH, 2.7% IVH grade 3, 45.5%, p=0.03 IVH grade 4, 90.9% p-0.01 Visual impairment No IVH, 2.7% IVH grade 3, 45.5%, p=0.03 IVH grade 3, 45.5%, p=0.03 IVH grade 3, 45.5%, p=0.03 IVH grade 4, 90.9% p-0.01 Acoustic impairment No IVH, 2.7% IVH grade 4, 90.9% p-0.01 Acoustic impairment No IVH, 2.7% IVH grade 4, 90.9% p-0.01 Acoustic impairment No IVH, 2.7% IVH grade 4, 90.9% p-0.01 Acoustic impairment No IVH, 2.7% IVH grade 4, 90.9% p-0.01 Acoustic impairment No IVH, grade 4, 90.9% p-0.01 Acoustic impairment No IVH, grade 4, 90.9% p-0.03 IVH grade 4, 90.9% p-0.01 Acoustic impairment No IVH, grade 4, 90.9% p-0.03 IVH grade 4, 90.9% p-0.03				(loss to follow-up not specified)	
17					
No IVH, 7.5% No IVH, 7.5% IVH grade 3, 45.5%, p=0.03 IVH grade 4, 90.9% p=0.01					IVH grade 4, 90.9% p<0.01
No IVH, 7.5% IVH grade 3, 45.5%, p=0.03 IVH grade 4, 90.9% p=0.01					
17					Visual impairment
17					
IVH grade 4, 90.9% p<0.01 Acoustic impairment No IVH, 22% IVH grade 3, 0% p= not significant IVH grade 4, 0% p= not significant IVH grade 3, 0% p= not significant IVH grade 4, 0% p= not significant IVH (p=7.46, 7%) No IVH (p=7.46, 7%) No IVH (p=7.5; 33.3%) No IVH (p=7.6, 7%) No IVH (p=7.5; 33.3%) P=0.381 P					
17					
No IVH, 2.2% No IVH, 2.2% IVH grade 3, 0% p= not significant IVH grade 4, 0%					1111 grade 4, 50.570 p 10.01
No IVH, 2.2% No IVH, 2.2% IVH grade 3, 0% p= not significant IVH grade 4, 0%					Acoustic impairment
17					
TVH grade 4, 0% p= not significant	1 1				
Turkey Retrospective cohort Exposure (cohort No IVH (n=75) No IVH (n=75)					
Turkey					ivri grade 4, 0% p= not significant
Turkey	\vdash				
Turkey Birthweight < 1500g Born 2001 Measurement/ assessment WISC-R WISC	17	Koc 2016 ³⁰			
Retrospective cohort	1 1		Gestation <32 weeks	Cognitive	
Retrospective cohort		Turkey	Birthweight <1500g		No IVH (n= 25; 33.3%)
Retrospective cohort Exposure IVH grade 1-2 (n= 7) IVH grade 3-4 (n= 8) Comparator No IVH (n=75) Ascertainment/ definition Neonatal unit database and medical records Population Gestation <34 weeks Birthweight <1500g Born 1990-2005 Exposure (n=103) IVH Comparator (n=315) No IVH Ascertainment/ definition Follow-up Sensorineural hearing loss Maximezer Cruz 200851 Case control Case control Comparator (n=315) No IVH Ascertainment/ definition Follow-up Sensorineural hearing loss Sensorineural hearing loss Measurement/ assessment Barainstem auditory evoked potentials Transient auditory evoked potentials Transient auditory evoked otoacoustic emissions Behavioural hearing evaluation For Efed audiometry Tympanometry Pure Tone Audiometry Pure Tone Audiometry Pure Tone Audiometry Pure Tone Audiometry WISC-R Sor >852 IVH grade (n=8, 13.8%) No IVH Grade (n=8, 13.8%) Policy (n=10, 14, 14, 14, 14, 14, 14, 14, 14, 14, 14				Measurement/ assessment	
Exposure Follow-up Follow-up No IVH (n=5); 84.2%		Retrospective			
IVH grade 1-2 (n= 7) IVH grade 3-4 (n= 8) Comparator No IVH (n=75) Ascertainment/ definition Neonatal unit database and medical records Population Gruz 2008 ⁵¹ Cruz 2008 ⁵¹ Case control Exposure (n=103) IVH Comparator (n=315) No IVH Ascertainment/ definition Sensorineural hearing loss Mexico Case control Exposure (n=103) No IVH Ascertainment/ definition Sensorineural hearing evaluation Free field audiometry No IVH Ascertainment/ definition Sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=32; 11.8%) Multivariate logistic regression of risk factors for sensorineural hearing loss IVH: aOR 7.1 95% CI (4.34, 11.6) p<0.000					
IVH grade 1-2 (n= 7) IVH grade 3-4 (n= 8) Comparator No IVH (n=75) Ascertainment/ definition Neonatal unit database and medical records Population Gruz 2008 ⁵¹ Cruz 2008 ⁵¹ Case control Exposure (n=103) IVH Comparator (n=315) No IVH Ascertainment/ definition Sensorineural hearing loss Mexico Case control Exposure (n=103) No IVH Ascertainment/ definition Sensorineural hearing evaluation Free field audiometry No IVH Ascertainment/ definition Sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=32; 11.8%) Multivariate logistic regression of risk factors for sensorineural hearing loss IVH: aOR 7.1 95% CI (4.34, 11.6) p<0.000			Exposure	Follow-up	No IVH (n= 50; 84.2%)
TVH grade 3-4 (n= 8) 100% follow-up p=0.381	1 1				
Response of the control Comparator	1 1				p=0.381
Comparator No IVH (n=75) Ascertainment/ definition Neonatal unit database and medical records Martinez- Cruz 2008 ⁵¹ Mexico Case control Case control Case control Comparator (n=315) No IVH Ascertainment/ definition Comparator (n=315) No IVH Ascertainment/ definition Comparator (n=315) No IVH Ascertainment/ definition Comparator (n=315) No IVH No I			1 VII grade 3-4 (II- 8)	- 100/0 Ionow-up	
No IVH (n=75) Ascertainment/ definition Neonatal unit database and medical records Neonatal unit databa			Commonator		
Ascertainment/ definition Neonatal unit database and medical records Martinez- Cruz 2008 ⁵¹ Mexico Case control Case control Case control Comparator (n=315) No IVH Ascertainment/ definition Outcomes Sensorineural hearing loss Sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=32; 11.8%) Multivariate logistic regression of risk factors for sensorineural hearing loss IVH Sensorineural hearing loss (n=32; 11.8%) Multivariate logistic regression of risk factors for sensorineural hearing los IVH: aOR 7.1 95% CI (4.34, 11.6) p<0.000					
Neonatal unit database and medical records Neonatal unit database and medical records			• No IVH (n=75)		
Neonatal unit database and medical records Neonatal unit database and medical records	1 1				
Restrict Population Outcomes Sensorineural hearing loss No sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=32; 11.8%)					
Martinez- Cruz 2008 ⁵¹			 Neonatal unit database and medical 		
Cruz 2008 ⁵¹ Mexico Mexico Case control Case control Case control Comparator (n=315) No IVH Ascertainment/ definition Sensorineural hearing loss Sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=32; 11.8%) Measurement/ assessment Brainstem auditory evoked potentials Transient auditory evoked otoacoustic emissions Behavioural hearing evaluation Free field audiometry Tympanometry Pure Tone Audiometry Sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=32; 11.8%) Multivariate logistic regression of risk factors for sensorineural hearing loss IVH: aOR 7.1 95% CI (4.34, 11.6) p<0.000	1 1		records		
Cruz 2008 ⁵¹ Mexico Mexico Case control Case control Case control Comparator (n=315) No IVH Ascertainment/ definition Sensorineural hearing loss Sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=32; 11.8%) Measurement/ assessment Brainstem auditory evoked potentials Transient auditory evoked otoacoustic emissions Behavioural hearing evaluation Free field audiometry Tympanometry Pure Tone Audiometry Sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=32; 11.8%) Multivariate logistic regression of risk factors for sensorineural hearing loss IVH: aOR 7.1 95% CI (4.34, 11.6) p<0.000					
Cruz 2008 ⁵¹ Mexico Mexico Case control Case control Case control Comparator (n=315) No IVH Ascertainment/ definition Sensorineural hearing loss Sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=32; 11.8%) Measurement/ assessment Brainstem auditory evoked potentials Transient auditory evoked otoacoustic emissions Behavioural hearing evaluation Free field audiometry Tympanometry Pure Tone Audiometry Sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=32; 11.8%) Multivariate logistic regression of risk factors for sensorineural hearing loss IVH: aOR 7.1 95% CI (4.34, 11.6) p<0.000	18	Martinez-	Population	Outcomes	IVH
Mexico Case control Exposure (n=103) IVH Comparator (n=315) No IVH Ascertainment/ definition Measurement/ assessment Brainstem auditory evoked potentials Transient auditory evoked otoacoustic emissions Behavioural hearing evaluation Free field audiometry Pure Tone Audiometry No sensorineural hearing loss (n=32; 11.8%) Multivariate logistic regression of risk factors for sensorineural hearing loss IVH: aOR 7.1 95% CI (4.34, 11.6) p<0.000		Cruz 200851			
Mexico Case control Exposure (n=103) IVH Comparator (n=315) No IVH Ascertainment/ definition Measurement/ assessment Brainstem auditory evoked potentials Transient auditory evoked otoacoustic emissions Behavioural hearing evaluation Free field audiometry Pure Tone Audiometry Multivariate logistic regression of risk factors for sensorineural hearing los IVH: aOR 7.1 95% CI (4.34, 11.6) p<0.000					
Case control Exposure (n=103) IVH Comparator (n=315) No IVH Ascertainment/ definition Brainstem auditory evoked potentials Transient auditory evoked otoacoustic emissions Behavioural hearing evaluation Free field audiometry Tympanometry Pure Tone Audiometry Multivariate logistic regression of risk factors for sensorineural hearing los IVH: aOR 7.1 95% CI (4.34, 11.6) p<0.000		Mexico		Measurement/assessment	, , , , , , , , , , , , , , , , , , , ,
Case control Exposure (n=103) IVH Comparator (n=315) No IVH Ascertainment/ definition Transient auditory evoked otoacoustic emissions Behavioural hearing evaluation Free field audiometry Tympanometry Pure Tone Audiometry			. Doin 1770 2003		Multivariate logistic regression of risk factors for sensorineural hearing loss
Omparator (n=315) No IVH Ascertainment/ definition emissions Behavioural hearing evaluation Free field audiometry Tympanometry Pure Tone Audiometry		Case control	Evnosuro (n=102)		
Comparator (n=315) No IVH Ascertainment/ definition Behavioural hearing evaluation Free field audiometry Tympanometry Pure Tone Audiometry	1 1	Cuse condu			111. WOR 7.1 7570 CI (7.57, 11.0) p \0.000
Comparator (n=315) No IVH Ascertainment/ definition Free field audiometry Tympanometry Pure Tone Audiometry			• IVH		
No IVH Ascertainment/ definition Tympanometry Pure Tone Audiometry					
No IVH Ascertainment/ definition Tympanometry Pure Tone Audiometry					
Ascertainment/ definition • Pure Tone Audiometry			Comparator (n=315)	Free neid audiometry	
Ascertainment/ definition					
				Tympanometry	
- modern records Fullow-up			No IVH	Tympanometry	
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1			No IVH Ascertainment/ definition	Tympanometry Pure Tone Audiometry	
			No IVH Ascertainment/ definition Medical records	Tympanometry Pure Tone Audiometry Follow-up	
Papile classification. 100% follow-up (case control)			No IVH Ascertainment/ definition Medical records Ultrasound diagnosis.	Tympanometry Pure Tone Audiometry Follow-up Mean age 7.8±3.7 years	

220	Neubauer 2008 ¹⁸ Germany Prospective cohort Piris Borregas	Population Birthweight <1000g Born 1993-1998 Exposure IVH grade 1-2 (n=26) IVH grade 3-4, PVL (n=18) Comparator Ummatched No IVH or PVL (n=91) Ascertainment/ definition	Outcomes Neurodevelopmental impairment (composite) Measurement/assessment Modified Touwen test K-ABC Snijders-Oomen Non-Verbal Intelligence Test Hamburg-Wechsler Intelligence Test	Logistic regression for major impairment vs. normal development or minor impairment at school age Grade 3-4 IVH or PVL Normal (n=4, 22%) Minor (n=2, 11%) Major (n=12, 67%) Risk of impairment: OR 2.46 95% CI (0.52–11.7)
20	Germany Prospective cohort	Born 1993-1998 Exposure IVH grade 1-2 (n=26) IVH grade 3-4, PVL (n=18) Comparator Unmatched No IVH or PVL (n=91)	(composite) Measurement/assessment Modified Touwen test K-ABC Snijders-Oomen Non-Verbal Intelligence Test	Grade 3-4 IVH or PVL Normal (n=4, 22%) Minor (n=2, 11%) Major (n=12, 67%)
20	Prospective cohort	Exposure IVH grade 1-2 (n=26) IVH grade 3-4, PVL (n=18) Comparator Unmatched No IVH or PVL (n=91)	Measurement/assessment Modified Touwen test K-ABC Snijders-Oomen Non-Verbal Intelligence Test	Normal (n=4, 22%) Minor (n=2, 11%) Major (n=12, 67%)
20	cohort	IVH grade 1-2 (n=26) IVH grade 3-4, PVL (n=18) Comparator Unmatched No IVH or PVL (n=91)	Modified Touwen test K-ABC Snijders-Oomen Non-Verbal Intelligence Test	Minor (n=2, 11%) Major (n=12, 67%)
20	cohort	IVH grade 3-4, PVL (n=18) Comparator Unmatched No IVH or PVL (n=91)	K-ABC Snijders-Oomen Non-Verbal Intelligence Test	Major (n=12, 67%)
20		Comparator Unmatched No IVH or PVL (n=91)	Snijders-Oomen Non-Verbal Intelligence Test	
	Diris Parragas	Unmatched No IVH or PVL (n=91)	Intelligence Test	rust of imparation. Of 2.10 9570 of (0.52 11.7)
	Diris Parragas	Unmatched No IVH or PVL (n=91)		
	Diric Porroges	Ì , í		
	Diric Porroges	A	for Children	
	Biris Barragas		Follow-up	
	Diric Dorrages	Ultrasound diagnosis	• 10 years	
	Diric Dorrogos	Papile classification	• 79% follow-up	
		Population (n=1001)	Outcomes	Poor neurodevelopmental outcome
	201919	Birthweight 500-1250g	Neurodevelopment (composite)	Severe brain injury, n=46, 32%
	Spain	• Born 1991-2008	Cognitive	No severe brain injury, n=208, 24% OR 1.41 95% CI (0.94, 2.10) p=0.09
	Spani	Exposure	Motor Hearing impairment	Independent OR 2.02 95% CI (1.22, 3.31) p=0.18
	Retrospective	Severe brain injury (IVH grade 3-4,	Visual impairment	
	cohort study	ventriculomegaly III, PVL or	· · · · · · · · · · · · · · · · · · ·	Severe brain injury (birthweight 500-1000g)
		intraparenchymal echodense lesion	Assessment/ measurement	Independent OR 2.02 95% CI (1.22, 3.31)
		grade 3 or greater)	• GMFCS	
		Comparator	Follow-up	
		Unmatched	• 7 years	
		Ascertainment/ definition		
		Neonatal database Ultrasound diagnosis		
		Papile classification		
21	Pittet 201931	Population	Outcomes	Cognitive (K-ABC – MPC score < 1SD)
	Cit11	Gestation <30 weeks	Cognitive	IVH 3-4 or PVL
	Switzerland	Born 2006	Cerebral palsy Visual impairment	OR 2.9 95% CI (1, 8.2) p=0.04 aOR 2.3 95% CI (0.7, 7.7) p=0.15
	Prospective	Exposure	Hearing impairment	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	cohort study	IVH grade 3-4 or cPVL (n=22)	Tearing impairment	
			Assessment/ measurement	Use of early intervention/ therapy service IVH 3-4 or cPVL aOR 2.7 95% CI (1.3, 5.7)
		Comparator	Kaufman ABC	1VH 3-4 01 CF VL aOK 2.7 93% CI (1.3, 3.7)
		Unmatched No IVH grade 3-4 or cPVL (n=213)	Neurological exam GMFCS	
		Tro TVII glade 5 4 of Cl VE (ii 215)	GWIFCS	
		Ascertainment/ definition	Follow-up	
		Swiss neonatal network follow-up	• 5.5 – 6 years	
		group	81% follow-up	

22 20,50%
No. Fig. 10. Sept. 10. Sep

				Grade 3 IVH 96.8 (11.9) Grade 4 IVH 73.5 (20.0)
				ANOVA F4,250 = 4.0; p = 0.003 Arithmetic No IVH 88.3 (14.3) Grade 1 IVH 93.6 (14.9) Grade 2 IVH 92.6 (10.6) Grade 3 IVH 89.1 (10.1) Grade 4 IVH 65.5 (14.5) ANOVA F4,248 = 4.5; p = 0.002
				Cognitive test scores (compared to normal birthweight controls) IQ score <1 SD from the mean (n, %) No IVH n=64 (35.6%) Grade 1 IVH n=18 (38.3%) Grade 2 IVH n=9 (36%) Grade 3 IVH n=7 (58.3%) Grade 4 IVH n=6(100%) X² linear trend=6.8; P=0.009
				Wide range achievements test score <1 SD from the mean, n (%) Low reading No IVH n=42 (24.4%) Grade 1 IVH n=6 (13.3%) Grade 2 IVH n=5 (20.8%) Grade 3 IVH n=2 (18.2%) Grade 4 IVH n=3 (75%) X² linear trend=0.1; p=0.77
				Low spelling No IVH n=33 (19.2%) Grade 1 IVH n=6 (13.6%) Grade 2 IVH n=2 (8.3%) Grade 3 IVH n=3 (27.3%) Grade 4 IVH n=3 (75%) X² linear trend=0.7; p=0.39
				Low arithmetic No IVH n=47 (27.6%) Grade 1 IVH n=9 (20.5%) Grade 2 IVH n=2 (8.3%) Grade 3 IVH n=3 (27.3%) Grade 4 IVH n=4 (100%) X* linear trend=0.1; p=0.79
23	Tymofiyeva 2018 ³⁹ USA Prospective cohort	Population (n=24)	Outcome Cognitive Behaviour Assessment/ measurement Test of variables of attention Conners comprehensive behaviour rating scales CBCL Assessment undertaken by a blinded psychologist Parental questionnaire Follow-up	Attention (abnormal) Mild WMI n=3, 75% Moderate WMI n=0, 0% No WMI n=8, 57% p=0.05
		Unmatched No WMI (n=14) No IVH (n=19) Ascertainment/ definition MRI imaging reviewed by a blinded paediatric neuroradiologist Used own classification of white matter injury Papile classification	10-14 years Completeness not specified	

24 Van de Bor 2004 ²¹ Netherlands Prospective cohort	Population Gestation < 32 weeks Birthweight < 1500 g Born 1983 Exposure IVH grade 1-2 (n=45) IVH grade 3-4 (n=17) Comparator (n=216) Unmatched No IVH Ascertainment/ definition Ultrasound diagnosis Papile classification	Outcomes Disability (composite) Cognitive Neurological status (motor) Speech and language Behaviour Hearing Vision Measurement/assessment Questionnaires (completed by parents at 9 years; adolescents at 14 years) Home visit and neurodevelopmental assessment by paediatrician unaware of medical history WHO classification of impairment, disability, and handicap Follow-up S, 9 and 14 years 91.5% follow-up of survivors at 14 years	Disability at 5 years No IVH n=49 (23%) IVH grade 3-4 n=5 (31.3%) Cognitive disability No IVH n=18 (8.3%) IVH grade 3-4 n=1 (5.9%) p=not significant Motor disability No IVH n=8 (3.7%) IVH grade 3-4 n=3 (17.6%) p=0.00 Speech/language disability No IVH n=34 (15.7%) IVH grade 3-4 n=1 (5.9%) p= not significant Visual disability No IVH n=1 (0.5%) IVH grade 3-4 n=0 p= not significant Hearing disability No IVH n=5 (2.3%) IVH grade 3-4 n=0 p= not significant Hearing disability No IVH n=5 (2.3%) IVH grade 3-4 n=0 p= not significant School performance at 5 years Special education No IVH n=17 (8.7%) IVH grade 3-4 n=3 (20%) p=0.02 School performance at 9 years Slow learner No IVH n=57 (29.5%) IVH grade 3-4 n=4 (26.7%) Special education No IVH n=29 (15%) IVH grade 3-4 n=4 (26.7%) p=0.04 School performance at 14 years Slow learner No IVH n=93 (44.1) IVH grade 3-4 n=4 (23.5%) Special education No IVH n=93 (44.1) IVH grade 3-4 n=6 (35.3%) p=0.00 Need for special education at 14 years IVH (all grades) OR 2.56 95%CI (1.17-4.86) aOR 2.33 95%CI (1.17-4.86) aOR 2.33 95%CI (1.15, 4.75) IVH grade 3-4 aOR 3.99 95%CI (1.36, 11.69)

25 Van Den Hout 2000 ³² Netherlands Prospective cohort	Population Mean gestation 28-30 weeks Born 1989-1991 Exposure IVH (n=17) PVL (n=12) Comparator (n=17) Normal cranial ultrasound Ascertainment/ definition Ultrasound diagnosis Modified Levene and DeVries classification for IVH DeVries classification for PVL	Outcomes	Total intelligence quotient, mean (SD) IVH 92.4 (16.3) PVL 79.6 (20.5) No brain injury 102.8 (14.4) IQ < 85 IVH n=6, 50.96 No brain injury n=2, 11.8% Performance age in years, mean (SD) IVH 5.22 (1.16) PVL 4.37 (1.19) No brain injury 6.22 (0.89) Visual grating acuity in c/deg, mean (SD) IVH 37.4 (13.5) PVL 33.5 (15.9) No brain injury 47.1 (13.5) Visual grating acuity <25c/deg (%) IVH (11.8) PVL (33.3) No brain injury (0) Impairment on each of the eight 1.94 tasks Visual matching % (n) IVH 0 (17) PVL 0 (12) No brain injury 5.9 (17) Unconventional Object Views % (n) IVH 29.4 (17) PVL 41.7 (12) No brain injury 17.6 (17) De Vos task % (n) IVH 29.4 (17) PVL 4.1.7 (12) No brain injury 11.8 (17) Line Drawings Occluded by Noise% (n) IVH 6.3 (16) PVL 3.3 (15) PVL 3.5 (8) No brain injury 0 (17) Line Drawings Occluded by Noise% (n) IVH 13.3 (15) PVL 25.0 (8) No brain injury 5.9 (17) Developmental test of visual motor integration % (n) IVH 9.1 (16) PVL 0.7 (17) No brain injury 1.6 (17) Constructing block designs % (n) IVH 30.8 (13) PVL 80.0 (3) IVH 1.4.71 (17.81) PVL 3.20 (14.4) No brain injury 31.3 (16) Mean percentage of L94 tasks on which child is impaired (mean, SD; %) IVH 1.4.71 (17.81) IVH 3.9 (17) PVL 3.9 (17.9) PVL 3.9

26 Vollm * 2003 ² UK Prospc cohord	Gestation <33 we Born 1983-1988 Exposure IVH (n=159) Ventricular dilata IVH, PV flare, ve (n=164) Hydrocephalus (n Haemorrhagic pan (HPI) (n=61) PVL n=26 Comparator (n=348) Unmatched Normal scan Ascertainment/ definitie	(composite) Visual impairme Hearing impairm Hearing impairm Structured neuro Pure-tone audiog Vision test (Snel Henderson-Stott Beery test of VN WISC-R for chil WISC-III for chi Follow-up 8 years 91.7% follow-up on greviewed by two	nent nent logic examination gram llen chart) t TOMI dI ldren born 1983-1986 ildren born 1987-1988	Neurodevelopmental status Group A (<28 weeks) All impairments (n,%) GMH/IVH (5, 18%) Ventricular dilatation (4, 50%) GMH/IVH, flare, ventricular dilatation (19, 51%) Hydrocephalus (7, 78%) HPI (15, 100%) No brain injury (12, 32%) Disabling impairments (n, %) GMH/IVH (1, 4%) Ventricular dilatation (0, 0%) GMH/IVH, flare, ventricular dilatation (9, 24%) Hydrocephalus (7, 78%) HPI (14, 93%) GPVL (3, 75%) No brain injury (3, 8%) Group B (28-32 weeks) All impairments (n, %) GMH/IVH (16, 29%) Ventricular dilatation (5, 31%) GMH/IVH, flare, ventricular dilatation (30, 43%) Hydrocephalus (7, 54%) HPI (5, 83%) cPVL (9, 75%) No brain injury (67, 29%) Disabling impairments (n, %) GMH/IVH, (5, 5%) Ventricular dilatation (1, 6%) GMH/IVH, flare, ventricular dilatation (16, 23%) Hydrocephalus (6, 46%) HPI (3, 50%) Ventricular dilatation (1, 6%) GMH/IVH, flare, ventricular dilatation (16, 23%) Hydrocephalus (6, 46%) HPI (3, 50%) No brain injury (14, 6%)	

17 11	lua ou	Donulation	Outcomes	TOMI amon coops mean (CD)
Volli 2006		Population Gestation <33 weeks	Outcomes Motor	TOMI error score, mean (SD) Normal scan 2.78 (2.1)
2000	oa	Born 1985-1991	Cognitive	Normal Scan 2.76 (2.1)
UK			Cerebral palsy	All left-sided lesions 4.3 (3.5)
Prosi	spective	Bilateral brain lesions (n=201)	Visual	Left-sided non-parenchymal lesions 4.5 (3.8) Left-sided parenchymal lesions 3.7 (2.1)
coho		Right-sided brain lesion (n=41)		
		Left-sided brain lesion (n=57)	Measurement/ assessment	All right-sided lesions 3.5 (2.9) Right-sided non-parenchymal lesions 2.7 (1.8)
		Brain lesion types	Neurological examination (modified Amiel-Tison assessment)	Right-sided parenchymal lesions 4.9 (3.8)
		Non-parenchymal:	TOMI	
		Uncomplicated IVH	WISC-R	All bilateral lesions 4.5 (4.3) Bilateral non-parenchymal lesions 4.1 (3.7)
		Parenchymal: Haemorrhagic parenchymal infarction	Test of VMI	Bilateral parenchymal lesions 4.1 (3.7) Bilateral parenchymal lesions 4.9 (4.7)
		(HPI)	Follow-up	ANOVA for a serial lesion on the section of 0001
		• cPVL	8 years	ANOVA for parenchymal lesions only p <0.0001 ANOVA including parenchymal and non-parenchymal lesions p <0.0001
		PV flare	80% follow-up	ANOVA excluding parenchymal lesions, p <0.0001
		Comparator (n=369)		VMI centile, mean (SD)
		Unmatched		Normal scan 59.2 (30.0)
		Normal ultrasound		
		Ascertainment/ definition		All left-sided lesions 40.3 (30.1) Left-sided non-parenchymal lesions 46.8 (31.0)
		Ultrasound imaging reviewed by two		Left-sided parenchymal lesions 21 (22)
		experienced observers Modified Stewart classification		All right-sided lesions 60.2 (31.9)
				Right-sided non-parenchymal lesions 64.2 (30.2)
				Right-sided parenchymal lesions 54 (35)
				All bilateral lesions 46.0 (33.5)
				Bilateral non-parenchymal lesions 55.1 (32.1)
				Bilateral parenchymal lesions 38 (32)
				ANOVA for parenchymal lesions only p <0.0001
				ANOVA including parenchymal and non-parenchymal lesions p <0.0001
				ANOVA excluding parenchymal lesions reported as both p <0.0001 and p=0.98 Ω(potential error in the manuscript table)
				22(potential error in the manuscript table)
				Cerebral palsy, n (%) Normal scan 2 (0.7%)
				Normal Scan 2 (0.776)
				All left-sided lesions 4 (9%)
				Left-sided non-parenchymal lesions 2 (6%) Left-sided parenchymal lesions 2 (16%)
				All right-sided lesions 2 (6%) Right-sided non-parenchymal lesions 1 (4%)
				Right-sided non-parenchymal lesions 1 (4%) Right-sided parenchymal lesions 1 (8%)
				All bilateral lesions 37 (21%) Bilateral non-parenchymal lesions 8 (10%)
				Bilateral parenchymal lesions 29 (31%)
				Chi-square for parenchymal and non-parenchymal lesions, p <0.0001
				Chi-square excluding parenchymal lesions, p <0.0001
				Chi-square for parenchymal lesions only, p <0.0001
				ANOVA parenchymal lesions only, p <0.0001
				TA 1.10 (CD)
				Full scale IQ, mean (SD)
				Normal scan 101 (16)
				All left-sided lesions 93 (17)
				Left-sided non-parenchymal lesions 98 (15)
				Left-sided parenchymal lesions 80 (15)
				All right-sided lesions 102 (17)
				Right-sided non-parenchymal lesions 104 (15)
				Right-sided parenchymal lesions 100 (19)
1			I.	
				All bilateral lesions 91 (21)
				Bilateral non-parenchymal lesions 96(19)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001.
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137.
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001.
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19) All left-sided lesions 98 (20)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19) All left-sided lesions 98 (20) Left-sided non-parenchymal lesions 102 (20) Left-sided parenchymal lesions 85 (18)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19) All left-sided lesions 98 (20) Left-sided non-parenchymal lesions 102 (20)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19) All left-sided lesions 98 (20) Left-sided non-parenchymal lesions 102 (20) Left-sided parenchymal lesions 85 (18) All right-sided lesions 107 (18)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19) All left-sided lesions 98 (20) Left-sided non-parenchymal lesions 102 (20) Left-sided parenchymal lesions 85 (18) All right-sided lesions 107 (18) Right-sided non-parenchymal lesions 108 (16) Right-sided parenchymal lesions 107 (22)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19) All left-sided lesions 98 (20) Left-sided non-parenchymal lesions 102 (20) Left-sided parenchymal lesions 85 (18) All right-sided lesions 107 (18) Right-sided non-parenchymal lesions 108 (16)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19) All left-sided lesions 98 (20) Left-sided non-parenchymal lesions 102 (20) Left-sided parenchymal lesions 85 (18) All right-sided lesions 107 (18) Right-sided non-parenchymal lesions 108 (16) Right-sided parenchymal lesions 107 (22) All bilateral lesions 96 (23)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19) All left-sided lesions 98 (20) Left-sided non-parenchymal lesions 102 (20) Left-sided parenchymal lesions 85 (18) All right-sided lesions 107 (18) Right-sided non-parenchymal lesions 108 (16) Right-sided parenchymal lesions 107 (22) All bilateral lesions 96 (23) Bilateral non-parenchymal lesions 100 (20) Bilateral parenchymal lesions 91 (25)
				Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19) All left-sided lesions 98 (20) Left-sided non-parenchymal lesions 102 (20) Left-sided parenchymal lesions 85 (18) All right-sided lesions 107 (18) Right-sided non-parenchymal lesions 108 (16) Right-sided parenchymal lesions 107 (22) All bilateral lesions 96 (23) Bilateral non-parenchymal lesions 100 (20)

28 *	Vollmer 2006b ³³ UK Prospective cohort	Population Gestation <33 weeks Born 1979-1991 Exposure (n=66) Ventricular dilatation and IVH Comparator (n=616) Unmatched Normal cranial ultrasound Ascertainment/ definition Ultrasound imaging reviewed by two experienced observers In-house classification used	Outcomes Neurological impairment with or without disability (composite) Cognitive Motor Vision Measurement/ assessment Structured neurological exam TOMI Test of VMI WISC Follow-up 8 years 81% follow-up	Performance IQ, mean (SD) Normal scan 96 (15) All left-sided lesions 86 (16) Left-sided non-parenchymal lesions 90 (15) Left-sided parenchymal lesions 76 (15) All right-sided lesions 95 (16) Right-sided non-parenchymal lesions 98 (13) Right-sided non-parenchymal lesions 98 (13) Right-sided parenchymal lesions 92 (19) All bilateral lesions 85 (22) Bilateral non-parenchymal lesions 91 (20) Bilateral parenchymal lesions 80 (21) ANOVA for parenchymal lesions 80 (21) ANOVA including parenchymal and non-parenchymal lesions, p <0.0001 ANOVA excluding parenchymal lesions, p =0.59 Disabling motor impairment, n (%) Ventricular dilatation and IVH n=10 (16%) Normal ultrasound n=10 (2%) Cognitive Full scale IQ, mean (SD) Ventricular dilatation and IVH 96 (23) Normal ultrasound 101 (17) Verbal IQ, mean (SD) Ventricular dilatation and IVH 97 (15) Normal ultrasound 91 (21) Motor and vision VMI centile, mean (SD) Ventricular dilatation and IVH 37 (33) Normal ultrasound 52 (31)
			9	Normal ultrasound 52 (31) TOMI, mean (SD) Ventricular dilatation and IVH 5.98 (4.2) Normal ultrasound 3.26 (2.5)

	hitaker 11 ³⁶	Population • Birthweight <2000g	Mental health conditions	Logistic regression assessing odds of current and lifetime mental health conditions after brain injury
US	SA	 'Non-disabled' survivors Born 1984-1987	Measurement/ assessment	Current ADHD- inattentive type IVH
	ospective hort	Exposure	Parent report version of the Diagnostic Interview Schedule for Children–IV WASI	OR 0.97 95% CI (0.21-4.47) aOR 1.01 95% CI (0.19-5.44)
Con		IVH (n=69) Parenchymal lesions and/or ventricular enlargement (n=21)	Follow-up 16 years	Parenchymal lesions and/or ventricular enlargement OR 7.645 95% CI (2.20-24.48)
		Comparison (n=368) Unmatched	• 72.9% follow-up	aOR 6.83° 95% CI (1.26-36.91)
		Normal cranial ultrasound Ascertainment/ definition Ultrasound imaging reviewed by		Lifetime ADHD – inattentive type IVH OR 0.83 95% CI (0.34-2.04) aOR 0.64 95% CI (0.24-1.74)
		 Ultrasound imaging reviewed by three blinded radiologists independently, disagreements resolved through consensus and inter- observer reliability checked. 		Parenchymal lesions and/or ventricular enlargement OR 2.71 95% CI (0.94-7.82) aOR 1.13 95% CI (0.31-4.10)
		Paneth classification		Current major depression IVH OR 2.66 95% CI (1.04-6.78) aOR 2.23 95% CI (0.80-6.24)
				Lifetime major depression
				IVH OR 2.76 95% CI (1.19-6.38) aOR 2.59 95% CI (1.02-6.58)
				Current tic disorders IVH
			5	OR 1.63 95% CI (0.44-6.07) aOR 1.89 95% CI (0.42-8.57)
				Parenchymal lesions and/or ventricular enlargement OR 8.42 95% CI (2.40-29.62) aOR 9.77 95% CI (1.69-56.47)
				Lifetime tic disorders IVH
				OR 0.95 95% CI (0.27-3.34) aOR 0.85 95% CI (0.21-3.51)
				Parenchymal lesions and/or ventricular enlargement OR 5.07 95% CI (1.53-16.82) aOR 5.02 95% CI (1.05-23.92)
			0,	Current obsessive-compulsive disorder IVH OR 9.52 95% CI (3.02-30.06) aOR 11.85 95% CI (3.22-43.62)
				Parenchymal lesions and/or ventricular enlargement OR 7.64 95% CI (1.39-41.98) aOR 15.32 95% CI (1.82-128.74)
				Lifetime obsessive compulsive disorder IVH
				OR 9.52 95% CI (3.05-30.06) aOR 11.85 95% CI (3.22-43.62)
				Parenchymal lesions and/or ventricular enlargement OR 7.64 95% CI (1.39-41.98) aOR 15.32 95% CI (1.82-128.74)
				Current diagnoses additionally controlled for full score IQ and motor function
				ADHD inattentive type IVH
				OR 0.86 95% CI (0.18-3.99) aOR 0.99 95% CI (0.21-4.62)
				Parenchymal lesions and/or ventricular enlargement OR 5.04 95% CI (1.36-18.65) aOR 5.43 95% CI (1.32-22.40)
				Major depression IVH OR 0.43 95% CI (0.16-1.11) aOR 0.40 95% CI (0.15-1.05)
				Tic disorders IVH OR 1.54 95% CI (0.41-5.78) aOR 1.45 95% CI (0.38-5.48)
				Parenchymal lesions and/or ventricular enlargement OR 7.01 95% CI (1.88-28.14) aOR 4.38 95% CI (1.05-18.23)
				Obsessive compulsive disorder IVH OR 8.68 95% CI (2.72-27.69) aOR 10.91 95% CI (3.13-37.99)
				Parenchymal lesions and/or ventricular enlargement OR 4.78 95% CI (0.83-28.10) aOR 3.58 95% CI (0.50-25.94)

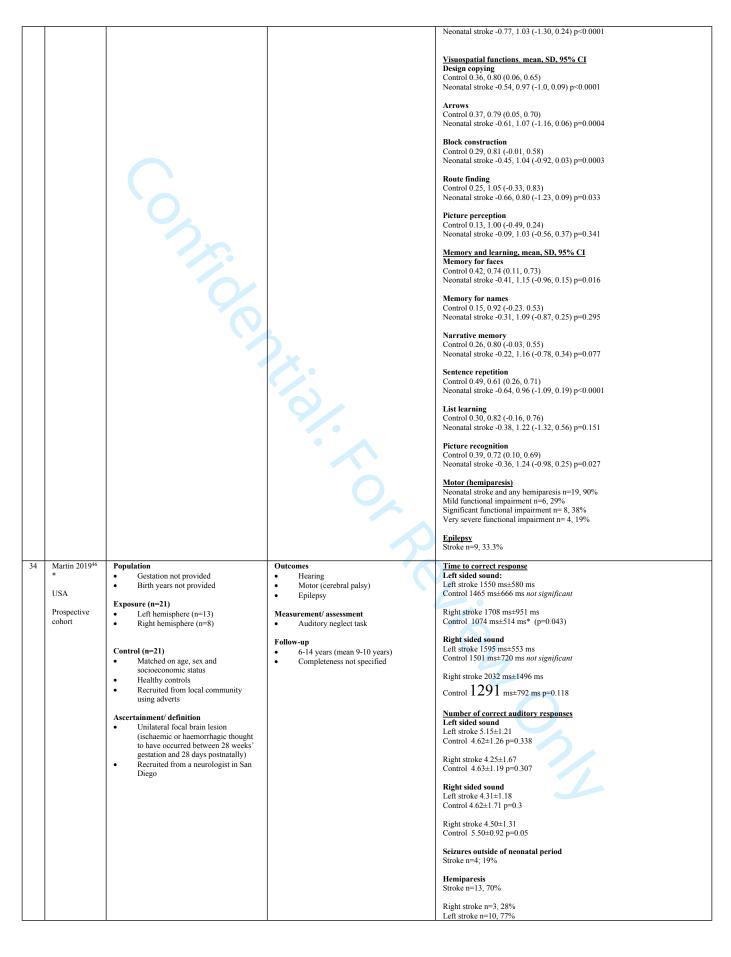
Dullamyne Population S week Barn Pol 2001	erinatal stroke			
	Ballantyne * 2007 47 USA Prospective	Mean gestation 38.5 weeks Born 1991-2001 Exposure (n=28) Left lesions (n=17) Right lesions (n=11) Comparator (n=57) Unmatched Healthy controls with normal medical and developmental histories Recruited from the community Ascertainment/ definition Single unilateral lesions the result of perinatal strokes occurring between 28 weeks' gestation and 28 days after birth; infarct or haemorrhage Identified through medical history and neuroimaging Severity rated on a 5-point scale adapted from the Vargha-Khadem	Speech and language Assessment/ measurement CELF-R Wechsler Intelligence Scales (WPPSI-R, WISC-R, or WISC-III) PPVT-Revised Expressive One-Word Picture Vocabulary Test-Revised or Upper-Extension Total Language Standard Scores Follow-up 6-9 years	CELF-R Receptive, mean (SD) All strokes: 82.54 (17.12) p<.0001 Left stroke: 83.18 (16.66) p<.0001 Right stroke: 81.55 (18.59) p=0.001 Control: 106.37 (12.51) CELF-R Expressive mean (SD) All strokes: 73.57 (16.79) p<.0001 Left stroke: 73.06 (14.88) p<.0001 Right stroke: 74.82 (20.11) p=0.001 Control: 101.02 (13.63) CELF-R Total mean (SD) All strokes: 76.93 (17.31) p<.0001 Left stroke: 76.94 (15.39) p<.0001 Right stroke: 76.94 (15.39) p<.0001 Right stroke: 76.94 (15.39) p<.0001 Right stroke: 76.90 (20.74) p=0.001
		adapted from the Vargha-Khadem classification		

31	Ballantyne 2008 ⁴⁰ *	Population • 32- 40 weeks' gestation	Outcomes Cognitive (academic skills)	Hemiparesis Stroke n=18,62%
	USA	Birth years not reported	Speech and language Motor	Visual field deficit Stroke n=7, 26%
	Prospective cohort	Left hemisphere (n=20) Right hemisphere (n=9)	Vision Epilepsy	Seizures
31	2008 ⁴⁰ * USA Prospective	32- 40 weeks' gestation Birth years not reported Exposure (n=29) Left hemisphere (n=20) Right hemisphere (n=9) Control (n=38) Healthy controls (normal neurodevelopment) Recruited through a university and community adverts Ascertainment/ definition Unilateral ischaemic perinatal stroke confirmed through clinical history and neuroimaging Lesion location and severity reviewed by blinded neuroradiologist Severity rated on a 5-point scale adapted from the Vargha-Khadem classification	Cognitive (academic skills) Speech and language Motor Cerebral palsy Vision	Stroke n=18,62% Visual field deficit Stroke n=7, 26%
				Arithmetic (WRAT -R) Time point 1 (mean age 7-8 years) Stroke 91.5 (10.2) Control 111.9 (11.2) Time point 2 (mean age 10 – 12 years)
				Stroke 94.2 (18.7)
				Between group affect (stroke vs. control) p<0.0001
				Speech and language Receptive language score Time point 1 (mean age 7-8 years) Stroke 84.2 (10.9) Control 109.1 (12.2)
				Time point 2 (mean age 10 – 12 years) Stroke 82.3 (20.1) Control 111.4 (13.7)
				Between group affect (stroke vs. control) p<0.0001 Time effect not significant
				Expressive language score Time point 1 (mean age 7-8 years) Stroke 72.5 (12) Control 101 (17.5)
				Time point 2 (mean age 10 – 12 years) Stroke 78.4 (16)

Onlidential: For Review Only Control 105.8 (11.9) Between group affect (stroke vs. control) p<0.0001

22	Cold 201441	Donulation	Outcomes	Constitution
32	Gold 2014 ⁴¹	Population Gestation not provided	Outcomes Cognitive (IQ and memory)	Cognitive Memory
	USA	Birth years not provided	Motor	Stories immediate recall
	Prospective	F	Cerebral palsy	Controls, mean (SE)13.5 (0.7)
	cohort	Exposure (n=27) Right-sided stroke (n=12)	Measurement/ assessment	Stroke, mean (SE) 8.4 (0.8) p<0.001
		Left-sided stroke (n=15)	WISC-III	Stroke and seizures, mean (SE)7 (0.8)
			Dots and Stories subtests of the	Stroke and no seizures, mean (SE) 10.1 (1.4) p=0.06
		Comparator (n=19) Matched for age at follow up, sex,	Children's Memory Scales	Right lesion, mean (SE) 7.8 (1.1)
		socioeconomic group and maternal	Follow-up	Left lesion, mean (SE) 8.9 (1.2) p=0.51
		education	• 6-16 years	Delayed recall
		Healthy controls Recruited through local advertising	100% follow-up	Controls, mean (SE) 13.9 (0.8)
		• Recruited through local advertising		Stroke, mean (SE) 7.9 (0.8) p<0.001
		Ascertainment/ definition		Stroke and seizures, mean (SE) 6.2 (0.9)
		Single, unilateral brain lesion in an arterial vascular distribution, either		Stroke and no seizures, mean (SE) 10 (1.2) p=0.02
		identified in the neonatal period with		Dight logical moon (SE) 7.2 (1.1)
		neuroimaging, or identified later in		Right lesion, mean (SE) 7.3 (1.1) Left lesion, mean (SE) 8.3 (1.2) p=0.56
		infancy after presentation with a hemiparesis and imaging		. , , , , ,
		documentation of an old unilateral		Delayed recognition Controls, mean (SE) 11.5 (0.5)
		infarct (presumed perinatal stroke) Recruited from paediatric neurology		Stroke, mean (SE) 8 (0.8) p=0.001
		clinics		G(1 1 1 1 (11)
		Severity graded 1-5 using Trauner/ Vargha-Khaldem classification		Stroke and seizures, mean (SE) 7.1 (1.1) Stroke and no seizures, mean (SE) 9.2 (0.9) p=0.17
				Right lesion, mean (SE) 8.3 (1.4)
				Left lesion, mean (SE) 7.9 (0.9) p=0.8
				Dots learning
				Controls, mean (SE) 10.9 (0.5) Stroke, mean (SE) 8.9 (0.8) p=0.05
			C.	Stroke and seizures, mean (SE) 7.6 (1.1) Stroke and no seizures, mean (SE) 10.6 (0.8) p=0.05
				Right lesion, mean (SE) 9.3 (1.4) Left lesion, mean (SE) 8.7 (0.9) p=0.71
				Total
				Controls, mean (SE) 11.8 (0.5) Stroke, mean (SE) 9 (0.7) p=0.003
			•	
				Stroke and seizures, mean (SE) 7.8 (0.9) Stroke and no seizures, mean (SE) 10.6 (0.9) p=0.04
				Right lesion, mean (SE) 9.2 (0.7) Left lesion, mean (SE) 10.2 (0.7) p=0.62
				Delayed recall
				Controls, mean (SE) 12.6 (0.4) Stroke, mean (SE) 10 (0.5) p<0.001
			2	Stroke and seizures, mean (SE) 8.8 (0.5) Stroke and no seizures, mean (SE) 11.4 (0.8) p=0.009
			1	Right lesion, mean (SE) 9.7 (0.7)
				Left lesion, mean (SE) 10.2 (0.7) p=0.62
				WISC-III IQ, mean (SD)
				Right stroke, 85.0 (6)
				Left stroke, 91 (6) p=0.49
				IQ scores
				Controls 117 (2.7)
				All stroke patients 88 (4.0) p<0.001 No seizures 100 (6.4)
				Seizures 78 (3.7)
				Motor (hominavosis)
				Motor (hemiparesis) Stroke patients n=16; 59%
				Control n=0; p=0.05

33 Kolk 2011 ⁴² Estonia Retrospective cohort	Population Gestation not provided Born 1995-2006 Exposed (n=21) Neonatal stroke Control (n=31) Matched on age and sex Healthy children Recruited locally Ascertainment/ definition Estonian stroke registry Arterial ischaemic stroke or haemorrhagic	Outcomes Cognitive Neuropsychological Motor Cerebral palsy Speech and language Epilepsy Measurement/ assessment NEPSY Kaufman ABC Paediatric Stroke Outcome Measure Follow-up 4-10 years 100% follow-up	Neuromotor impairment (Paediatric Stroke Outcome Measure) Neonatal stroke
			Control 0.30, 0.53 (0.08, 0.52) Neonatal stroke -0.40, 1.23 (-1.03, 0.24) p=0.026 Verbal fluency: semantic Control 0.43, 0.81 (0.13, 0.73) Neonatal stroke -0.60, 0.95 (-1.04, 0.15) p<0.0001 Verbal fluency: phonemic Control 0.40, 0.93 (-0.12, 0.92)
			Oromotor sequences Control 0.31, 0.64 (0.07, 0.54)
			Sensorimotor functions, mean, SD, 95% CI Finger tapping Control 0.49, 0.33 (0.35, 0.62) Neonatal stroke -0.53, 1.27 (-1.16, 0.10) p=0.0007 Imitating hand positions
			Control 0.57, 0.68 (0.32-0.82) Neonatal stroke -0.72, 0.92 (-1.14, 0.30) p<0.0001 Visuomotor precision: time Control 0.13, 0.83 (-0.17, 0.43) Neonatal stroke -0.24, 0.97 (-0.69, 0.20) p=0.145
			Visuomotor precision: mistakes Control 0.45, 0.50 (0.27, 0.64) Neonatal stroke -0.42, 1.05 (-0.90, 0.05) p=0.0002 Manual motor sequences
			Control 0.50, 0.62 (0.27, 0.73) Neonatal stroke -0.92, 0.95 (-1.43, 0.41) p<0.0001 Finger discrimination Control 0.53, 0.57 (0.29, 0.77)



35	Northam 2018 ⁴³ UK Prospective cohort	Population Gestation not provided Born 1991-2001 Exposure (n=30) Perinatal stroke Control (n=40) Matched on age, sex and maternal education Term infants Ascertainment/ definition Arterial or ischaemic stroke confirmed by MRI in the neonatal period	Outcomes Cognitive Speech and language Motor (cerebral palsy) Measurement/ assessment WASI CELF Comprehensive Test of Phonological Processing Follow-up 6-18 years (mean 12.4 and 13.5) 100% follow up	Cognitive Full scale IQ mean (SD) Stroke 99 (14) Control 112 (16) p<0.0001 Mainstream education Stroke n=28, 93% Receiving additional education support Stroke n=12, 40% Speech and language Expressive language score, mean (SD) Stroke 95 (17) Control 108 (13) p=0.001 Receptive language score, mean (SD) Stroke 91 (16) Control 104 (14) p < 0.0001 Motor (hemiparesis) Stroke n=9, 3%
36	Tillema 2008 ⁴⁴ USA Retrospective cohort	Population Gestation not provided Birth years not provided Exposure (n=10) Left perinatal stroke Control (n=10) Matched on age, sex, and handedness Healthy Randomly drawn from a large database of children recruited for a different study of language development in healthy children Ascertainment/ definition Middle cerebral artery ischaemic stroke	Outcomes Cognitive Epilepsy Measurement/ assessment WISC-III Language activation tasks – Verb generation task whilst in an fMRI Follow-up G-16 years 100% follow up	Focal epilepsy Stroke, n=6, 60% Cognitive, mean (SD) Stroke VIQ 84 (13.4) Control VIQ 108 (14.2) p=0.002 Stroke FSIQ 80 (14.1) Control FSIQ 108 (11.7) p=0.001
37	Trauner 2001 ⁴⁵ USA Retrospective cohort	Population Gestation not reported Birth years not reported Exposure (n=39) Left perinatal stroke (n=25) Right perinatal stroke (n=14) Control (n=54) Matched on age and socioeconomic status Normal neurodevelopmental history Identified from clinics, community adverts, schools Ascertainment/ definition Pre or perinatal onset unilateral brain damage (focal lesion) from cerebral infarction or intraparenchymal haemorrhage Identified through from clinical referrals. All confirmed by neuroimaging. Severity rated on 5-point scale adapted from Vargha-Khadem et al.	Outcomes Behavioural Cognitive Epilepsy Measurement/ assessment Achenbach CBCL WPPSI-R (4-5 years) WISC-R (6-16 years) Follow-up 4-18 years 100% follow up	Cognitive Full scale IQ mean (SD) Stroke 93.4 (22) Control 116.2 (13) p<0.0001 Left stroke 90.1 (22) Right stroke 97.4 (22) – no significant difference Seizures (outside of the neonatal period) Stroke n=17, 50% (missing data for 5 subjects)
38	Bedford 2001 ⁴⁸ England & Wales Prospective cohort	Population All gestational ages included Born 1985-1987 Exposure (n=274) Neonatal meningitis Comparison (n=1391) Matched on age and sex Recruited through GP Ascertainment/ definition Identified through clinician reporting	Outcomes Neuromotor disability (composite) Cognitive Hearing Vision Behaviour Seizure disorder Assessment/ measurement Parental questionnaire GP questionnaire McIntyre et al. classification of disability severity Follow-up Syears St-94% follow-up	Neuromotor disability Meningitis, n=45, 16% No meningitis, n=2, 0.1% Severe disability Meningitis, n=20, 7% No meningitis, n=1, 0.1% Moderate disability Meningitis, n=50, 18% No meningitis, n=50, 18% No meningitis, n=20, 1% Mild disorder Meningitis, n=66, 24% No meningitis, n=275, 20% No disability Meningitis, n=138, 50% No meningitis, n=138, 50% No meningitis, n=1095, 79%

39	Horváth- Puhó 2021 ⁴⁹ Denmark and Netherlands Retrospective matched cohort study	Population Gestation not specified Born 1997-2017 Exposure GBS meningitis (Denmark) (n=168) GBS meningitis (Netherlands) (n=198) Comparison Randomly selected Matched 1:10 on sex, birth year and month, and gestation No GBS (Denmark) (n=13,689) No GBS (Netherlands) (n=4,983) Ascertainment/ definition Invasive Group B Streptococcal disease by 89 days of age (most were neonatal – hence inclusion) ICD 10 codes (Denmark) CSF culture positive on national laboratory register (Netherlands)	Outcomes Neurodevelopmental impairment (composite) Cognitive Motor Behavioural, mental and social disorders Hearing impairment Visual impairment ICD 10 codes Follow-up Denmark 5 years, 7 years, 10 years, 15 years Netherlands 5 years, 7 years, 10 years and 11 years 95% follow-up	Any neurodevelopmental impairment RR (95%CI) 5 years Denmark GBS meningitis 7-80 (4-42-13-77) Netherlands GBS meningitis 5-30 (2-57-10-89) 7 years Denmark GBS meningitis 4-69 (2-78-7-89) Netherlands GBS meningitis 3-71 (1-05-6-72) 10 years Denmark GBS meningitis 3-47 (2-19-5-50) Netherlands GBS meningitis 2-81 (1-69-4-68) 11 years Netherlands GBS meningitis 2-99 (1-83-4-88) 15 years Denmark GBS meningitis 3-15 (1-82-5-46) Moderate to severe neurodevelopmental impairment RR (95%CI) 5 years Denmark GBS meningitis 5-13 (2-24-11-79) 7 years Denmark GBS meningitis 5-27 (2-80-9-92) Netherlands GBS meningitis 15-88 (2-15-6-99) Netherlands GBS meningitis 3-88 (2-15-6-99) Netherlands GBS meningitis 3-05 (1-62-5-73)
40	Martinez- Cruz 2008 ⁵¹ Mexico Retrospective case control	Population Gestation < 34 weeks Birthweight < 1500g Born 1990-2005 Exposure (n=22) Neonatal meningitis Comparator (n=374) No meningitis Ascertainment/ definition Meningitis not defined	Outcomes • Sensorineural hearing loss Assessment/ measurement • Brainstem Auditory Evoked Potentials • Transient Auditory Evoked Otoacoustic Emissions • Tympanometry • Free Field Audiometry • Pure tone audiometry • Behavioural hearing evaluation Follow-up • 7-11 years • 100% follow-up	Sity data
			100/a tonow-up	

En Wa	tevens 103 ³⁰ ngland & /ales rospective short study	Population Term born infants Born 1985-1987 Exposure (n=111) Meningitis Comparison (n=162) Matched on hospital of birth, birthweight and sex Hospital control (n=113) GP control (n=49) Ascertainment/ definition CSF positive culture	Outcomes Disability and functional impairment (composite) Cognitive Motor Vision Hearing Assessment/ measurement MISC-III Movement ABC Blinded examination Hearing screening Sonksen-Silver acuity system Follow-up 9-10 years 67% follow-up of meningitis group	Cognitive IQ, mean (95% CI) Meningitis, 88.8 (85, 92) Hospital control, 99.4 (97, 102) GP control, 99.6 (95, 103) Motor mABC score, mean (95% CI) Meningitis 7.1 (5.9, 8.5) Hospital controls 5.0 (4.3, 5.8) GP controls 4.0 (2.9, 5.4) Sever disability/functional impairment Meningitis, n=12, 10.8% Hospital control, n=0, 0% GP control, n=0, 0% Moderate disability/functional impairment Meningitis, n=10, 9% Hospital control, n=2, 1.8% GP control, n=0, 0% Mild disability/functional impairment Meningitis, n=10, 17.1% Hospital control, n=13, 11.5% GP control, n=8, 16% No disability or functional impairment Meningitis, n=70, 63.1% Hospital control, n=98, 86.7% GP control, n=41, 84% Hearing loss (unilateral or bilateral sensorineural hearing loss or requiring hearing aids) Meningitis, n=4, 3,6% Hospital control, n=0, 0% GP control, n=0, 0% GP control, n=0, 0% Visual impairment (bilateral) Meningitis, n=18, 17% (6 unassessed because of their disability) Hospital control, n=21, 18.5% GP control, n=4, 8% Visual impairment (unilateral) Meningitis, n= 10, 9.9% (6 unassessed because of their disability) Meningitis, n=10, 9.9% (6 unassessed because of their disability) Meningitis, n=10, 9.9% (6 unassessed because of their disability) Meningitis, n=10, 9.9% (6 unassessed because of their disability) Meningitis, n=10, 9.9% (6 unassessed because of their disability) Meningitis, n=10, 9.9% (6 unassessed because of their disability)
Hypoxic-i	-ischaemic encep	phalopathy		Hospital control, n=8, 7% GP control, n=2, 4% Seizures outside of the neonatal period Meningitis, n=6, 5.4% Hospital control, n=2, 1.8% GP control, n=0, 0%
Tu:	383 Koc 1316 ³⁰ urkey etrospective ohort	Population Gestation < 32 weeks Birthweight < 1500g Born 2001 Exposure (n=9) Perinatal asphyxia Comparator (n=81) No asphyxia Ascertainment/ definition Perinatal asphyxia diagnosed on: fetal pH, Apgar score, and neonatal cerebral and multiorgan dysfunction	Outcomes Cognitive Assessment/ measurement WISC-R Performed by blinded psychologist Follow-up 5-8 years 100% follow-up	Cognitive WISC-R IQ Score (combined verbal and performance scores) <85 Perinatal asphyxia n=8, 89% No asphyxia n=24, 30% p=0.001

			_	
43	Lee-Kelland	Population	Outcomes	Cognitive
	201952*	 Gestation ≥ 36 weeks 	Cognitive	Full scale IQ, mean (SD)
		Born 2008-2010	Motor	HIE 91 (10.37)
	United		 Speech and language 	No HIE 105 (13.41)
	Kingdom	Exposure (n=29)	Behaviour	Mean difference -13.62 95% CI (-20.53 to -6.71) p<0.001
	Retrospective	Moderate-severe HIE without		Perceptual reasoning, mean (SD)
	cohort study	subsequent cerebral palsy	Assessment/ measurement	HIE 89 (11.15)
	conort study	Comparator (n=20)	WISC IV (blinded)	No HIE 103 (12.49)
		Matched on age, sex and social class	Movement ABC 2	Mean difference -13.9 95% CI (-20.78 to -7.09) p<0.001
		Born without HIE	Strengths and difficulties questionnaire	,
		Bom without THE	Follow-up	Working memory, mean (SD)
		Ascertainment/ definition	• 6-8 years	HIE 94 (13.76)
		Received therapeutic hypothermia	61% follow-up	No HIE 102 (13.82)
		based on TOBY trial criteria	o 176 lonow-up	Mean difference -8.2 95% CI (-16.29 to -0.17) p=0.04
				D (OD)
				Processing speed, mean (SD) HIE 96 (13.76)
				No HIE 107 (17.59)
				Mean difference -11.6 95% CI (-20.69 to -2.47) p=0.01
				Mean difference 11.0 /5/0 C1 (20.0 / to 2.47) p 0.01
				Additional classroom support
				HIE n=10, 34%
				No HIE n=1, 5%
				OR: 10.0, 95%CI 1.16 to 86.0
				Special educational needs
				HIE n=1, 3.4% No HIE n=0, 0%
				NO FILE II-0, 0%
				Motor
				MABC-2 score, mean (SD)
				HIE 7.9 (3.26)
				No HIE 10.2 (2.86)
				Mean difference -2.12 95% CI (-3.93 to -0.30) p=0.02
				Speech and language
				Verbal comprehension, mean SD) HIE 94 (8.79)
				No HIE 103 (10.09)
				Mean difference -8.8 95% CI (-14.25 to -3.34) p=0.002
				Mean difference 0.0 7570 CT (14.25 to 5.54) p 0.002
				Behaviour
				Total difficulties, median (IQR)
				HIE 12 (6.5–13.5)
				No HIE 6 (2.25–10) P=0.005
				Emotional problems, median (IQR)
				HIE 2 (1–4.5)
				No HIE 0.5 (0–2.75) P=0.03
				(* =) : *****
				Hyperactivity, median (IQR)
				HIE 2 (1–3)
				No HIE 1 (0-2) P=0.06
				G I (II (III (III (III)
				Conduct problems, median (IQR) HIE 4 (2.5-6.5)
				No HIE 3 (1–5) p=0.06
				Peer problems, median (IQR)
				HIE 0 (0–2.5)
			•	No HIE 0 (0–1) p=3.56 Ω (potential error in manuscript table)
				Prosocial, median (IQR)
				HIE 9 (7.5–10)
				No HIE 9 (8.25–10) p=0.13
				Impact score, median (IQR)
				HIE 0 (0–2.5)
				No HIE 0 (0–2.0) p=0.31
				. (-10) F

Tonks 2019 ⁵³ * United Kingdom Prospective cohort study	Population Gestation ≥36 weeks English as primary language Exposure (n=29) Moderate-severe HIE without subsequent cerebral palsy Comparator (n=20) Matched on age, sex and social class Recruited from schools in the area Born without HIE Ascertainment/ definition Received therapeutic hypothermia based on TOBY trial criteria	Outcomes Cognitive Neuropsychological Assessment/ measurement Conner's continuous performance test NEPSY-II block construction test NEPSY-II arrows' test Follow-up 6-8 years 77% follow-up	Attention Hit response time HIE 84.1 percentile mean rank 27; Proportion performing below 2 SD 32% Comparator 67.3 percentile mean rank 17.89; p = .024 Proportion performing below 2 SD 11% Hit response time standard error HIE standard error mean rank 26.8 Proportion performing below 2 SD 18% Comparator standard error mean rank 18.2; p = 0.032 Proportion performing below 2 SD 11% Hit response time by block HIE Mean 49.1, SD 23.9 Comparator Mean 61.9, SD 18.4; p = 0.047 Visual discrimination HIE Below 1 SD 10% Comparator Below 1 SD 5% HIE vs comparator scores, p = 0.049 Visuo-spatial mental rotation task HIE Below 1 SD 17%
		3	Comparator Below 1 SD 5% HIE vs comparator scores, p = 0.034

Supplement 5: Risk of bias table

overlapping data; Clinical Evaluation of Language Fundamentals (CELF); Cystic Periventricular leukomalacia (cPVL); Intelligence Quotient (IQ); Intraventricular haemorrhage (IVH); Mental Developmental Index (MDI); Neonatal Intensive Care Unit (NICU); Psychomotor Development Index (PDI); Periventricular leukomalacia (PVL); Spontaneous Intestinal Perforation (SIP); Wechsler Intelligence Scale for Children (WISC); White Matter Injury (WMI);

Preterm brain injury: cohort studies

	Selecti	on (*cati	efactory	No =not	Compa	rability	Exposure	/ Outcor	ne	Subtotal as	recement		Total score:	Additional comments
		ctorily do		NO -not		factory; ot ctorily	(*satisfacto	tory; No	=not	Subtotal as	Subtotal assessment			Additional comments
	1	2	3	4	1a	1b	1	2	3	Selection (0- 1=Poor; 2=Fair; 3+ Good)	Comparabil ity (0=poor; 1=fair; 2+=good)	Exposure / outcome (0=poor; 1=fair; 2+=good)	moderate risk of bias 7-9 low risk of bias	
Adant 2019	No	*	*	* (excluded those with congenital anomalies)	*	*	No	*	No	Good	Good	Fair	6	Population not representative as focus of study was spontaneous intestinal perforation. Infants without IVH didn't have brain injury excluded per se (but didn't have IVH 3-4 on imaging). Matched on gender, gestational age, date of birth. Multiples matched to sibling without SIP. Excluded those with necrotising enterocolitis, mechanical obstruction or congenital anomalies. Adjusted for gender, gestation, birthweight, SIP and IVH. Independent outcome assessment but not blinded; telephone survey of parents. High numbers lost to follow-up. Table 3 contains errors with respect to outcomes (MDI and PDI mislabelled as motor and cognitive respectively).

Beaino 2010	*	*	No	* (cerebral palsy could not be present at birth)	*	*	*	*	*	Good	Good	Good	8	3% of infants did not have a cranial ultrasound, a further 11% had only one cranial ultrasound during neonatal period - therefore ascertainment of exposure may be compromised Model A adjusted for:
Brouwer	No	No	*	* (given the types	No	No	No	*	*	Fair	Poor	Good	4	and no significant differences with respect to ultrasound brain injury findings between groups Study of a select group i.e. those with IVH
2012	INU	NU		of outcomes assessed)	NU	NO	NO		C	T dii	1001	Good		requiring neurosurgical intervention. No description of setting, how patients were enrolled, how many were excluded No description of how control group was derived, or what era they were from. Only some infants (those <30weeks) were matched on gestation, birthweight, sex to controls. Different intelligence tests used at followup. >80% completion rate of Child Behaviour Checklist and teacher report form by parents and teachers

Campbell 2021	*	*	*	* (given the types of outcomes assessed)	*	*	*	*	No	Good	Good	Good	8	Males and those born at 23-24 weeks gestation were overrepresented in the IVH WMI group. Adjusted for gestation, birthweight Z score, sex, maternal education, bronchopulmonary dysplasia, sepsis, necrotising enterocolitis (Bell stage 2-3) and severe retinopathy of prematurity.
Cheong 2018#	*	*	*	No (visual or hearing impairment could be congenital)	*	*	*	*	*	Good	Good	Good	8	Adjusted for era of birth, antenatal corticosteroid exposure, inborn status, gestation, sex, multiple birth, birthweight Z score, surfactant use, IVH grade 3 or 4 (in cPVL), cPVL (in IVH grade 3-4), bronchopulmonary dysplasia, postnatal corticosteroid use, necrotising enterocolitis (stage 2 or worse), surgery in the newborn period, and retinopathy of prematurity (stage 3 or worse).
Chou 2020	*	*	*	* (given the types of outcomes assessed)	No	*	*	*	No	Good	Fair	Good	7	Matched and adjusted for, urbanisation and parental occupation.
											Ch	Ch	¹ O	No information about missing data or completeness of follow-up

Davidovite h 2020	*	*	*	* (given the types of outcomes assessed)	No	*	*	*	No	Good	Fair	Good	7	Only low birthweight infants included (therefore birthweight partially accounted for). Unmatched. No information about excluding brain injury from comparators e.g. comparing those with IVH grade 3-4 to those without could include those with IVH 1-2; both groups could also include infants with other types of brain injury. Missing data not presented or accounted for. Adjusted the composite brain injury group (which included retinopathy of prematurity in its definition) for gestation, maternal diabetes, small for gestational age, year of birth, bronchopulmonary dysplasia, and receipt of postnatal steroids.
Doyle 2000 #	*	*	*	* (given the types of outcomes assessed)	No	No	*	*	*	Good	Poor	Good	7	IVH and no IVH groups not matched for gestation or birthweight, no adjustment for these variables appears to have been done. Relatively old cohort (most did not receive surfactant), comparator group only includes infants born in the 1980s. Not
Hintz 2018	*	*	*	* (given the types of outcomes assessed)	*	*	*	*	*	Good	Good	Good	9	representative due to time-period of care. Assessed interobserver reliability of central imaging readers. Unmatched Adjusted for gestation, race, sex, multiple gestation, maternal education, sepsis, bronchopulmonary dysplasia, postnatal steroids, surgery for patent ductus arteriosus, necrotising enterocolitis, retinopathy of prematurity. Only 83% follow-up of survivors but those lost to follow-up are accounted for.

Hirovonen 2017	*	*	*	* (given the types of outcomes assessed)	*	*	*	*	*	Good	Good	Good	9	Excluded infants who died at <1 year of age, infants with major congenital anomalies, and those with missing data.
														Characteristics of those with brain injury not presented.
			-(No breakdown by severity of brain injury because that level of detail was not available in the database.
				1//0	<u> </u>	つさ		/.						No matching but there is stratification by gestation and adjustment for: maternal characteristics, pregnancy characteristics, delivery characteristics, sex, gestation, birthweight, Apgar score at 1-minute, umbilical artery pH, resuscitation provided, NICU admission, receipt of phototherapy, ventilator requirement, antibiotic receipt, respiratory distress syndrome, sepsis, seizures, hyperbilirubinaemia.
Hollebrand se 2021#	*	*	*	* (given the types of outcomes assessed)	*	*	*	*	*	Good	Good	Good	9	Gestation similar across all groups and other baseline perinatal characteristics similar across groups. Preterm brain injury and no brain injury group not matched. Unclear if IVH and no IVH group had other brain injuries excluded or may have had more than one injury type (e.g. PVL). Impact of epoch/ era of birth explored and adjusted for.
Hreinsdotti r 2018	*	*	*	No (visual impairment could have been congenital)	*	*	*	*	No	Good	Good	Good	7	Unsure if comparator group in logistic regression includes those with IVH 1-2. Adjusted for gestation, birthweight, retinopathy of prematurity, sex, cognitive score, cerebral palsy.

Jansen 2020	*	*	*	* (given the types of outcomes assessed)	No	No	*	*	No	Good	Poor	Good	6	Excluded infants with congenital abnormalities, metabolic disorders or neonatal meningitis.
Kaur 2020	*	*	*	No (visual or hearing impairment could be congenital)	No	*	*	*	No	Good	Fair	Good	6	Unmatched. Compared infants with IVH to all infant without haemorrhage (of all gestations). Adjusted for maternal age, pregnancy complications, infant sex, neonatal comorbidity, birthweight, socioeconomic deprivation, and year of birth.
Kiechl- Kohlendorf er 2013	*	*	*	* (given the types of outcomes assessed)	*	٠ //	*	No	No	Good	Good	Fair	7	Low numbers of infants included. Outcomes assessed at 1 year - likely not long enough for robust assessment of neurodevelopmental outcomes; <85% follow-up and no detailed description of those lost to follow up - though authors do state that there were no significant differences between those followed up and those lost to follow up.
Klebermass -Schrehof 2012	*	*	*	No (could have had congenital blindness)	*	No	*	*	No	Good	Fair	Good	6	Adjusted for gestation. Significant difference between groups for key neonatal comorbidities such as ROP, RDS, CLD and characteristics such as antenatal steroid exposure. No clear description of number lost to follow-up, though mentions that follow-up rate at 5.5 years was 54-61%.
Koc 2016	*	*	No	* (given the types of outcomes assessed)	No	No	*	*	No	Good	Poor	Good	5	Small numbers included. No breakdown of characteristics of those with brain injury. No description of IVH grading used or schedule of ultrasound exams; no description of criteria for establishing perinatal asphyxia, number lost to follow-up not stated.

Neubauer 2008	*	n/a	*	No (deafness or blindness could have been congenital)	*	*	*	*	*	Fair	Good	Fair	7	Neurodevelopmental assessors not blinded; follow-up rate <85% but paper does give description of those lost to follow-up
Piris Borregas 2019	*	*	*	* (excluded infants with congenital malformations)	No	No	*	*	No	Good	Poor	Good	6	Only those followed up to 7 years included. Excluded infants who died before 36 weeks corrected age, with major malformations, or those with missing data. Unclear if independent odds ratio includes adjustment for covariates. Unclear if those without 'severe brain injury' had other types of brain injury.
Pittet 2019	*	*	*	* (excluded infants with congenital malformations)	No	*	*0/	*	*	Good	Fair	Good	8	Excluded infants with congenital malformations affecting neurodevelopment and infants from centres without 5 years of follow-up cognitive testing. Unclear if other types of brain injury excluded from comparator group. Adjusted for gender and socioeconomic status. No significant difference in cognitive outcome between extreme preterms and those 28-30 weeks' gestation. Gestation not adjusted for.
Sherlock 2005#	*	*	*	No (deafness or blindness could have been congenital)	No	No	*	*	*	Good	Poor	Good	6	Comparability of IVH vs. no IVH cohorts not clear - not enough information to determine if groups were comparable with respect to gestational age or birthweight

Tymofiyev a 2018	*	*	*	* (given the types of outcomes assessed)	No	No	*	*	No	Good	Poor	Good	6	Excluded infants with congenital malformations/ syndromes, congenital infections, or those who were too unstable for MR imaging. The last exclusion criteria in particular could limit generalisability quite considerably. Unclear about the validity of grouping the attention scores across different assessment tools together into a dichotomous variable for attention.
Van De Bor 2004	*	*	*	* (excluded those with major congenital malformations)	*	*	No	No	*	Good	Good	Fair	7	IVH vs. no IVH cohorts comparable with respect to gestation; some differences in gender composition but paper states this was controlled for in the analysis. Primary outcome entirely self-reported. Outcomes reported at 14 years. Adjusted for gestational age, birth weight, small for gestational age, sex, ethnicity, duration of assisted ventilation, maximum serum total bilirubin concentration and maternal education.
Van Den Hout 2000	* (exce pt for HIE expo sure grou p)	*	*	* (excluded those with congenital anomalies)	No	No	*	*	*	Good	Poor	Good	7	Low numbers and relatively old cohort. Relative gender imbalance in IVH group compared to those with normal scans or PVL. IVH group also 1.4 weeks more premature than 'normal scan' group.
Vollmer 2003#	*	*	*	No (deafness or blindness could have been congenital)	*	No	*	*	*	Good	Fair	Good	7	Note change in version of Weschler scale during follow-up period. Authors state no difference in mean IQ after change. Baseline characteristics of groups with and without brain injury not given; no indication of matching or adjustment for factors other than gestation.

Vollmer 2006a#	*	*	*	No (deafness or blindness could have been congenital)	*	*	*	*	*	Good	Good	Good	8	Note gender imbalance in cohort as a whole (M>F), but male: female ratio in each group appears similar. No matching or adjustment for covariates. <85% follow-up but clear description of those lost and appears no significant differences.
Vollmer 2006b#	*	*	*	No (deafness or blindness could have been congenital)	No	No	*	*	No	Good	Poor	Good	5	Marked gender imbalance in ventricular dilatation group. Lower birthweight and gestation in groups with abnormal cranial ultrasound. No indication of matching or adjustment. <85% follow-up and the limited description of those lost to follow-up indicates that these babies were of lower birthweight and gestation.
Whitaker 2011	*	*	*	* (given the types of outcomes assessed)	*	*	(No)	*	*	Good	Good	Good	8	Severely disabled survivors (n=33) were excluded. Half had later ultrasounds (just before discharge). No breakdown of the characteristics of the exposed and comparator groups – unable to assess how comparable they are. Adjusted for: maternal social risk, sex, gestation, fetal growth ratio, multiplicity, maternal smoking status, maternal alcohol status, labour onset, presentation at birth, base excess on first postnatal blood gas, thyroid status, hypocapnia, hypoxia, systolic hypotension, prolonged ventilation. Primary outcome assessment reliant on parental report, albeit via structured interview with some evidence for validity. Interviewers were blinded to the child's history. Parents were blinded to the study hypothesis.

				Phric	Ye									Less than 85% follow-up (psychiatric interviews in 51% of survivors) however clear descriptions of groups with and without psychiatric evaluation given in table 2 and little apparent difference between groups.
Preterm bra	in injury	: case-co	ntrol stu	idies		17	· /°							
	Case defin ition	Repr esent ative ness of cases	Selection of controls	4 Definition of controls	1a	16	Ascerta inment of exposu re	Sam e meth od of ascer tain ment for cases and contr ols	Non-respo nse rate	(0- 1=Poor; 2=Fair; 3+ Good)	y (0=poor; 1=fair; 2+=good)	(0=poor; 1=fair; 2+=good)	Total score: 0-3 high risk of bias; 4-6 moderate risk of bias 7-9 low risk of bias	Additional comments
Martinez- Cruz 2008 (IVH)	*	*	*	*	*	No	*	*	No	Good	Fair	Good	7	Appears to be case-control design hence star ratings are as per case control rating sheet. Controls not well matched for birth weight. No description of whether full information on exposures could be obtained for all cases/controls e.g. missing records etc.

	Select satisfa	ion (*sati ctorily do	sfactory; one; n/a)	No =not	(*satis	ctorily	Exposure (*satisfacte satisfacte	ctory; No	=not	Subtotal as:	sessment		Total score: 0-3 high risk of bias; 4-6 moderate risk of bias	Additional comments
	1	2	3	4	1a	1b	1	2	3	Selection (0- 1=Poor; 2=Fair; 3+ Good)	Comparabil ity (0=poor; 1=fair; 2+=good)	Exposure / outcome (0=poor; 1=fair; 2+=good)	7-9 low risk of bias	
Ballantyne 2007	No	No	*	*	No	77	No	*	No	Fair	Fair	Fair	4	No description of derivation of exposed cohort - whether single institute or multicentre, whether same community as non-exposed group or not. Predominance of right-handed children amongst controls otherwise similar baseline characteristics. Note male preponderance in exposed group and female preponderance in non-exposed No matching or adjustment for confounders. No description of who performed outcome assessment, whether blinded and independent.
Ballantyne 2008	*	*	*	No	No	*	*	*	No	Good	Fair	Good	6	Excluded children with brain lesions from other causes e.g. head trauma, tumours Gestational age of exposed cohort ranged from 32 to 40 weeks. No statement as to whether control group were matched on this. Note preponderance of males in stroke group and females in control group. In study 1, significant numbers of participants did not complete the planned developmental assessments - across exposed and control groups, completeness ranged from 50% for WISC-R to 69% for CELF-R.

Gold 2014	No	No	*	*	No	*	*	*	*	Fair	Fair	Good	6	No description of how subjects were selected or recruited from neurology clinics. Nonexposed group selected from a different source. No description of gestational age of subjects or of controlling for this. Matched for age at follow up, sex, socioeconomic group and maternal education.
				JA FIG	Y 0	ク _*								Excluded infants with bilateral lesions, a history of hypoxic ischemic encephalopathy, central nervous system infection, in-utero drug exposure, significant closed head injury, or any other condition that might have caused brain damage other than from the stroke.
Kolk 2011	*	*	*	*	No	*	*	*	No	Good	Fair	Good	7	No description of gestational age of subjects or of controlling for this. Difficult to ascertain completeness of follow-up from paper. Adjusted for age of outcome assessment.
Martin 2019	*	*	*	*	No	*	*	*	*	Good	Fair	Good	8	Excluded infants with bilateral lesions, hearing impairment, or a history of a problem that may have caused more global brain damage (e.g. meningitis, closed head injury, hypoxic-ischemic encephalopathy). Matched on age, sex and socioeconomic status
Northam 2018	*	No	*	*	*	*	*	*	*	Good	Good	Good	8	No description of source of unexposed cohort. Matched on age, sex, and maternal education.
Tillema 2008	*	*	*	*	No	*	*	*	No	Good	Fair	Good	7	Exposed and comparator groups not matched for gestation, but were matched for age, sex and handedness. 17 subjects included initially but 7 of these excluded for various reasons meaning that neurodevelopmental outcome data/Weschler scores only presented for 10 of 17.

Trauner 2013	*	*	*		No	No	No	*	No	Good	Poor	Fair	5	Excluded infants if bilateral or multifocal lesions identified, history of meningitis, or history of antenatal drug exposure Matched on age and socioeconomic status No baseline characteristics given to establish comparability of exposed and comparator cohorts. Likely comparable with regards to gestation based on stated inclusion criteria. Main outcome measure based on parental questionnaire - no direct linguistic assessments done, however may not have been feasible/appropriate in such a young cohort. No information on response rate/loss to follow-up. IQ used as covariate IQ combined across the age range and
														assessed with two different tools. This assumes IQ is fixed which may not be true.
Central nervo	ous infect	tions: col	nort studio	es						<i>/- ,</i>				
			isfactory; one; n/a)	No =not	Compa (*satist No =no satisfac done; r	factory; ot ctorily	Exposure (*satisfac satisfacto	ctory; No	=not	Subtotal as:	sessment	; e ₄	Total score: 0-3 high risk of bias; 4-6 moderate risk of bias 7-9 low risk of bias	Additional comments
	1	2	3	4	1a	1b	1	2	3	Selection (0- 1=Poor; 2=Fair; 3+ Good)	Comparabil ity (0=poor; 1=fair; 2+=good)	Exposure / outcome (0=poor; 1=fair; 2+=good)		

Bedford 2001#	*	*	*	No	*	*	No	*	*	Good	Good	Good	7	Matched on sex and age.
200111														Study focuses on meningitis in infancy but also presents outcomes after neonatal meningitis.
				Phric	Y_									Did not exclude children with other comorbidities e.g. congenital conditions associated with neurodevelopmental impairment. Exposed cases derived from same cohort as Stevens 2003. Outcome assessment based on parent or GP report with no formal neurodevelopmental assessment.
Horváth- Puhó 2021	*	*	*	No	*	*	*	*	*	Good	Good	Good	8	Invasive Group B Streptococcal infection diagnosed in the first 89 days (however most of these were neonatal, particularly in the first week of life (45%) hence inclusion.
							9/	•						Matched 1:10 on sex, birth year and month, and gestation. Neurodevelopmental impairment defined differently in each cohort. Missing data accounted for and its impact explored.
Stevens 2003#	(*)	(*)	*	No	*	*	*	*	No	Good	Good	Good	7	Exposed cohort based on recall of consultant paediatricians filling out monthly returns thus may be biased towards more severe or otherwise memorable cases. Some in comparator group selected from a different hospital than exposed cohort.
														Matched on hospital of birth, birth weight and sex.
														Results stratified by birthweight
		1				1								Significant rate of loss to follow-up.

	Case defin ition	Repr esent ative ness of cases	Selection of controls	4 Definition of controls	1a	1b	Ascerta inment of exposu re	Sam e meth od of ascer tain ment for cases and contr ols	Non-respo nse rate	(0- 1=Poor; 2=Fair; 3+ Good)	y (0=poor; 1=fair; 2+=good)	(0=poor; 1=fair; 2+=good)	Total score: 0-3 high risk of bias; 4-6 moderate risk of bias 7-9 low risk of bias	Additional comments
Martinez- Cruz 2008	*	*	* ppathy: c	* ohort studies	No	No	*	*	No	Good	Poor	Good	6	Excluded those with history of parental consanguinity or TORCH infections. Number of those with and without meningitis who may have had other types of brain injuries not specified – unable to assess overlap/ impact of meningitis alone. Odds ratio presented for meningitis does not appear to be crude so potential adjustment for confounding factors but no description of this in the methods section. No description of proportion of missing data.
		on (*sati	sfactory; one; n/a)	No =not		ctorily	Exposure (*satisfacto	ctory; No	=not	Subtotal as:	Comparabil	Exposure	Selection (*satisfacto ry; No =not satisfactoril y done; n/a)	Additional comments
										(0- 1=Poor; 2=Fair; 3+ Good)	ity (0=poor; 1=fair; 2+=good)	outcome (0=poor; 1=fair; 2+=good)	0-3 high risk of bias; 4-6 moderate risk of bias 7-9 low risk of bias	

Koc 2016	No	*	*		No	No	*	*	No	Fair	Poor	Good	5	Representativeness not clear as no description given of babies who did not complete follow-up at the study institution. No apparent adjustment for gestation or other covariates. Pre-therapeutic hypothermia era. Small number, no breakdown of characteristics or other neurodevelopmental outcomes by brain injury Number of those with and without birth asphyxia who had other types of brain
Lee- Kelland 2019	No	*	*	*	*	*	*	No	No	Good	Good	Good	6	injuries e.g. IVH not specified. Excluded those who underwent therapeutic hypothermia outside of the standard criteria, infants with metabolic disorders and non-English speaking infants. Matched on age, sex and social class.
Tonks 2019	*	No	*	*	No	*	*	*	No	Good	Fair	Good	6	Included cases had no diagnoses other than encephalopathy. Excluded infants with neurological issues other than encephalopathy. Matched on age, sex and socioeconomic status.
											Per	101	ν _C	age, sex and socioeconomic status.

Supplement 6: Overview of key findings for school-age outcomes of infants with perinatal brain injury compared to those without brain injury (*Does not include studies where infants with IVH grade 3-4 cannot be separated from those with WMI or those with IVH 1-2)

(# Does not include studies using hearing or visual outcomes only as part of their composite outcome)

Adjusted Odds Ratio (aOR); Attention Deficit Hyperactivity Disorder (ADHD); Autism Spectrum Disorder (ASD); Confidence Interval (CI); cystic periventricular leukomalacia (cPVL); Group B Streptococcus (GBS); Hypoxic-Ischaemic Encephalopathy (HIE); Hazard Ratio (HR); Intelligence Quotient (IQ); Interquartile range (IQR); Intraventricular Hagmorrhage (IVH); Odds Ratio (OR); Periventricular Leukomalacia (PVL); Visual Motor Integration (VMI); White Matter Injury (WMI)

riacinorniage (eukomalacia (PVL); Visual						
	NDI	Cognitive	Motor	Speech and language	Behavioural	Hearing#	Vision#	Other	
VH grade 3-	6 studies(15, 17-21)	9 studies(15, 20, 21, 24-26, 30, 70)	6 studies(20, 23-26, 33)	3 studies(20, 21, 25)	3 studies(15, 24, 35)	3 studies(21, 26, 38)	5 studies(15, 21, 26, 33, 38)		
• •			Not comparable	Not comparable	Not comparable	, , , , , , , , , , , , , , , , , , ,			
	2 comparable studies in	Not comparable	All reported increased risk of	Van de Bor 2004: no	Brouwer 2012: no	Not comparable	Not comparable		
	meta-	Consistently highlighted	motor impairment	significant difference in	association with any	Outcome too rare	Outcome to rare for		
	analysis(17,	lower cognitive scores	The state of the s	language scores	behavioural domains	for inferential	inferential analysis		
	20)		Cerebral palsy		assessed (internalising,	analysis	in most studies.		
		Brouwer 2012: significantly	2 comparable studies	Sherlock 2005: downward	externalising and sleep				
	Meta-analysis (2 studies):	lower performance IQ but preserved verbal IQ. Lower	OR 8.13 (95%CI: 4.64, 14.22)	trend in language scores from no brain injury to	problems)	Kaur 2020: increased risk of	Adant 2019: no increased risk of		
	(2 studies): Increased risk	IQ for those with IVH grade	P=0%.	each grade of IVH but not	Adant 2019: no	hospitalisation for	visual impairment		
	of	4 requiring neurosurgery	1 0/0.	statistically significant	increased risk of	otologic reasons	(needing glasses)		
	moderate -	(91+/-10 vs. 98+/-15) but		p=0.12	attention deficits,	HR	aOR 0.47 (95%CI:		
	severe	little difference for those			conduct issues or ASD	7.87 (95%CI:	0.13, 1.69)		
	neurodevelop	with grade 3 IVH requiring		Hollebrandse 2021:	aOR 1.24 (95%CI: 0.32,	5.31, 11.67)	771.1		
	mental impairment	neurosurgery (96+/-15 vs. 98+/-15).		Increased risk of impaired reading OR 3.62 (95%CI:	4.8).		Klebermass- Schrehof 2012:		
	OR 3.69	96+7-13).		1.59, 8.24), and spelling	Davidovich 2020: no		increased prevalence		
	(95%CI: 1.7,	Hollebrandse 2021:		OR 4.48 (95%CI: 1.8,	increased risk of ASD		of visual impairment		
	$7.98) I^2 = 0\%$	increased risk of cognitive		11.2)	(n=10, 3.9% vs. n=103,		(needing glasses or		
		impairment OR 2.68			2.2% p=0.085)		blindness) after IVH		
	Van de Bor 2004:	(95%CI: 1.21, 5.94). Increased risk of academic					grade 3 (45.4%) and IVH grade 4		
	increased	impairment across all					(90.9%) vs.		
	prevalence of	academic domains:					comparators (7.5%).		
	disability	reading OR 3.62 (95%CI:							
	31% vs. 16%	1.59, 8.24);					Kaur 2020:		
		spelling OR 4.48 (95%CI:				/) /.	increased risk of hospitalisation for		
		1.8, 11.2); arithmetic OR 2.79)95%CI:					ophthalmic reasons		
		1.2, 6.48)					HR 7.87 (95%CI:		
		1.2, 0.10)					5.31, 11.67).		
		Sherlock 2005: significantly							
		lower IQ scores after IVH					Klebermass-		
		grade 4 vs. IVH 1-3 and no					Schrehof 2012: significantly lower		
		brain injury, also seen for several domains: freedom					VMI scores		
		from distractibility,							

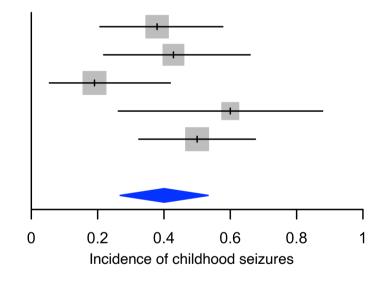
	processing speed, reading, spelling and arithmetic. No difference in executive function. Van de Bor 2004: increased special education needs at 5, 9 and 14 years aOR 3.99 (95%CI: 1.36, 11.69).					(67.5 ± 14 vs. 76 ± 26.8; p=0.04)	
WMI* 3 studies(16 17, 22) Not comparable Campbell 2021: living with no impairment was less common wi WMI (n=12 40%) vs. controls (n=487, 769 Cheong 20 increased ri of survival with major disability af cPVL aOR 9·17 (95%6 3·57, 23·53 Vollmer 2003: Disabling impairment were more common af cPVL a<28 weeks' gestation (n 75% <28 weeks) vs. controls (n=	Not comparable Van den Hout 2000: 50% with PVL had IQ scores <85 vs. 11.8% without injury and a lower performance age 4.3 years vs. 6.2 years Campbell 2021: increased risk of moderate-severe cognitive impairment aOR 5.07 (95%CI: 2.13, 12.02) Jansen 2020: WMI predictive of poorer performance on standardised mathematics tests (B 1.856 p=0.003), but not performance on spelling (B 1.076 p=0.075) or reading tests (B 0.241 p=0.483)	Cerebral palsy 1 study(16) Campbell 2020: increased risk of cerebral palsy aOR 18.63 (95%CI: 7.37, 47.06)	1 study(29) Jansen 2020: No association between WMI and spelling (B 1.076 p=0.075) or reading performance (B 0.241 p=0.483)	4 studies(16, 35, 36, 71) Not comparable Conflicting results Campbell 2021: No increased risk of: ADHD (n=3, 10% vs. n=97, 15%); anxiety (n=3, 10% vs. n=98, 15%); depression (n=7, 23% vs. n=100, 16%); or ASD aOR 0.74 (95%CI: 0.09, 5.88) Davidovich 2020: No increased risk of ASD after PVL (n=5, 2.5% vs. n=88, 2.3% p=0.86) Whitaker 2011: increased risk of ADHD aOR 6.83 (95%CI: 1.26-36.91); major depression aOR 2.59 (95%CI: 1.02-6.58); tic disorders aOR 9.77 (95%CI: 1.69-56.47); obsessive compulsive disorders aOR 15.32 (95%CI: 1.82-128.74)	0 studies	1 study(32)	

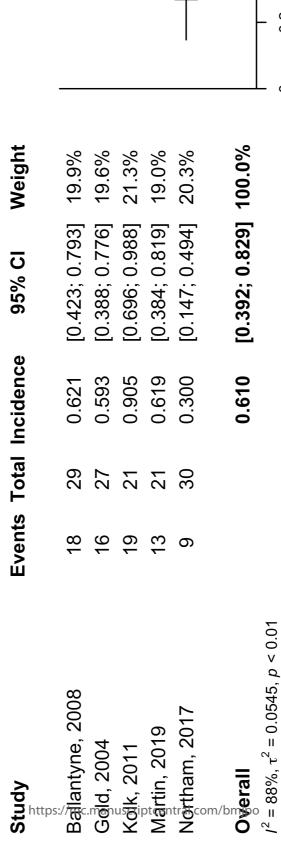
	8%) and at over 28 weeks' gestation (n=6,50% vs. n=14,6%)							
Stroke	0 studies	6 studies(39, 41, 42, 44-46) 5 comparable studies in meta-analysis (39, 41, 44-46) Meta-analysis (5 studies): significant mean difference in full scale IQ: -24.2 (95%CI: -30.73, -17.67) I²=80% Trauner 2001 and Gold 2014: no significant difference in full scale IQ scores in left vs. right-sided strokes Ballantyne 2008: significantly lower performance IQ (p=0.002) and verbal IQ (p<0.0001). Lower mean scores for reading (p<0.0001) and arithmetic (p<0.0001) and arithmetic (p<0.0001) ar 7-8 years persisting to 10-12 years Tillema 2008: reduced verbal IQ scores (mean 84 SD 13.4) vs. (mean 108 SD 14.2 P=0.002) Kolk 2011: poorer attention (across 4 of the 7 assessment sub-domains), visuo-spacial function (across 4 of the 5 sub-domains), and memory and learning (across 4 of the 6 sub-domains), but normal executive function scores. Those with left-sided strokes	5 studies(39, 41-44) Combined hemiparesis incidence: 61% (95%CI: 39.2, 82.9 F=88%) Kolk 2011: moderate to severe neuromotor impairment in 62% n=13) and significantly lower scores on 5/6 sensorimotor domains of the NEPSY	5 studies(39, 40, 42, 44, 45) 3 comparable studies in meta-analysis Meta-analysis (3 studies): lower receptive language scores-20.88 (95%CI: -36.66, -5.11) I²=88% and lower expressive language scores -20.25 (95%CI: -34.36, -6.13) I²=87% Ballantyne 2007 and Ballantyne 2008: deficits in receptive language scores at 7-8 years persist at 10-12 years but expressive language scores improved (p=0.012) particularly for children with right-sided strokes (p=0.034) Kolk 2011: significantly lower scores for 8/9 NEPSY domains including phonologic processing, comprehension of instructions, correct speeded naming, repetition of nonsense words, verbal fluency (semantic and phonetic), oromotor sequences, and sentence comprehension	1 study(46)	Martin 2019: left-sided strokes predispose children to contralateral auditory neglect and right-sided strokes predispose children to bilateral auditory neglect	Ballantyne 2008: visual field defects are common (n=7, 26%) after perinatal stroke	Seizures 8 studies(39, 42, 43, 45, 46) 5 comparable studies(39, 42, 43, 45, 46) Combined incidence of seizures: 40.1% (95%CI: 26.8, 53.3) I²=56%

		had poorer						
		neuropsychological scores.						
		N 41 2010						
		Northam 2018: most						
		children are in mainstream						
		education (n=28, 93%) but						
		many require additional						
		support (n=12, 40%)						
Meningitis	3 studies(47-	1 study(49)	1 study(49)	0 studies	0 studies	2 studies(49, 72)	1 study(49)	
	49)							
	Not	Stevens 2003: significantly	Stevens 2003: significantly			Martinez Cruz	Stevens 2003:	
	comparable	lower mean cognitive scores	higher motor impairment scores			2008: increased	Bilateral visual	
		(mean 88.8 (95%CI: 85, 92)	(mean 7.1 (95%CI: 5.9, 8.5) vs.			odds of neonatal	impairment was	
	All reported	vs. mean 99.4 (95%CI: 97,	mean 5 (95%CI: 4.3, 5.8))			meningitis	common after	
	increased risk	102))				amongst preterm	neonatal meningitis	
	of					infants with	(n=18, 17%)	
	neurodevelop		/ / * •			sensorineural		
	mental					hearing loss OR		
	impairment					4.37 (95%CI: 1.7,		
			` () / .			10.9		
	Bedford		7/0 /					
	2011:		· · · / ·			Stevens 2003:		
	increased					3.6% (n=4) had		
	prevalence of					hearing loss		
	neuromotor			Jh.		compared to none		
	disability					in the control		
	(n=45, 16%					group.		
	vs. n=2, 0.1%)							
				10,				
	Stevens 2003:							
	Risk of severe							
	disability seen							
	in Bedford							
	2011 at 5							
	years of age							
	persisted until							
	9-10 years							
	(n=12, 10.8%		mean 5 (95%CI: 4.3, 5.8))					
	vs. n=0, 0%)							
	Howath							
	Horvath- Puho 2021:							
	increased risk							
	of any							
	neurodevelop							
	mental							
	impairment after GBS							
	alter GBS	1		<u> </u>			1	

with HIE significantly more likely to have below average IQ scores (n=8, 89% vs. n=24, 30% p=0.001) Lee-Kelland 2020 and Tonks 2019: report lower full scale IQ scores after moderate to severe HIE (mean difference -13.62 (95%CI: -20.53, -6.71)) and poorer perceptual reasoning, working memory and processing speed. Children with previous HIE more likely to receive additional classroom support OR 10	HIE	meningitis in the Netherlands RR 5.30 (95%CI: 2.57, 10.89) and Denmark RR 7.80 (95%CI: 4.42, 13.77) at 5 years of age persisting to 11 years in the Netherlands RR 2.99 (95%CI: 1.83, 4.88) and 15 years in Denmark RR 3.15 (95%CI: 1.82, 5,46) 0 studies	3 studies(30, 50, 51) (two of the same population) Not comparable Koc 2016: preterm infants	2 studies(50, 51) (of the same population) Lee-Kelland 2020 and Tonks 2019: significantly lower motor scores (mean difference –2.12	2 studies(50, 51) (of the same population) Lee-Kelland 2020 and Tonks 2019: significantly lower verbal	2 studies(50, 51) (of the same population) Lee-Kelland 2020 and Tonks 2019: higher behavioural difficulty	0 studies	0 studies	
(95%CI: 1.16, 86) Kernicterus 0 studies	Kernicterus		with HIE significantly more likely to have below average IQ scores (n=8, 89% vs. n=24, 30% p=0.001) Lee-Kelland 2020 and Tonks 2019: report lower full scale IQ scores after moderate to severe HIE (mean difference –13.62 (95%CI: –20.53, –6.71)) and poorer perceptual reasoning, working memory and processing speed. Children with previous HIE more likely to receive additional	(95%CI: -3.93, -0.30)) after moderate-severe HIE (for	comprehension scores (mean difference –8.8 (95%CI: –14.25, –3.34)) after moderate-severe HIE.	scores (median score 12 IQR (6.5, 13.5 vs. median score 6 IQR	クケ		

13 14 Study	Events	Total	Incidence	95% CI	Weight
15 16					
¹⁷ Ballantyne, 2008	11	29	0.379	[0.207; 0.577]	22.2%
18 19 Kolk , 2011	9	21	0.429	[0.218; 0.660]	19.0%
²⁰ ₂₁ Martin, 2019	4	21	0.190	[0.054; 0.419]	23.1%
²² Tilema, 2008	6	10	0.600	[0.262; 0.878]	12.5%
²³ ²⁴ Trauner, 2001	17	34	0.500	[0.324; 0.676]	23.1%
25 26					
²⁷ ₂₈ Overall			0.401	[0.268; 0.533]	100.0%
$\frac{^{29}}{^{30}}I^2 = 56\%, \tau^2 = 0.0124, \rho = 0.06$. , .	





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0.8

9.0

0.4

0.2

Incidence of hemiplegia

0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 5														
6		Perina	atal str	oke	C	ontrol			Mean Difference		Me	an Differer	ıce	
7 _	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, F	Random, 95	5% CI	
8	Ballantyne 2008	82.3	20.1	29	111.4		38		-29.10 [-37.61, -20.59]		-	-		
9	Northam 2017	91	16	30	104	14	40	51.0%	-13.00 [-20.18, -5.82]			-		
0	T-4-1 (050/ OI)						70	400.00/	00 00 1 00 00 5 441		_			
1	Total (95% CI)	440.45	21.12	59	4 (5	0.005		100.0%	-20.88 [-36.66, -5.11]				1	
2	Heterogeneity: Tau ² =	113.45; (/D = 0 /	3.02, dt	= 1 (P =	0.005); 1² = 8	88%		-100	-50	Ó	50	100
3	Test for overall effect: 2	Z = 2.59	(P = 0.0	009)										
4 5														
5 6														
7														
/ 0														
9														
0														
1														
2														
3														
4														
5														
6														
7														
8														

0 1 2 3 4 5 5 7 3 9 0 1 2 3 4 5														
7	Study or Subgroup	Perinat Mean		oke Total		ontrol on		Weight	Mean Difference IV, Random, 95% CI			an Differer Random, 95		
3	Ballantyne 2008	78.4	16	29	105.8		38		-27.40 [-34.34, -20.46]		-		,,,, 01	
)	Northam 2017	95	17	30	108	13	40	49.7%	-13.00 [-20.30, -5.70]					
)	Total (95% CI)			59			78	100 0%	-20.25 [-34.36, -6.13]		4			
	Heterogeneity: Tau ² = 9	90.47; Chi	i² = 7.8		1 (P = 0	0.005)			_0.20 [0-4.00, -0.10]	100				
<u> </u>	Test for overall effect: 2				`	,				-100	-50	0	50	100
, 1 1 5 5 7 3 9 1 1 5 5 1 5 1 5 1 5 1 5 1 5 1 5 1 5 1														
7 3														

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School-age outcomes of children after perinatal brain injury: a systematic review and meta-analysis

Philippa Rees¹ MPhil MBBCh, Caitriona Callan² MB BChir, Karan R Chadda³ MB BChir, Meriel Vaal MRes MBChB¹, James Diviney⁴ MB BChir, Shahad Sabti⁵ MBBS, Fergus Harnden⁶ MBChB, Julian Gardiner¹PhD, Cheryl Battersby⁷ PhD, Chris Gale⁷ PhD, Alastair Sutcliffe¹ PhD

Affiliations:

- 1. Population Policy and Practice, Great Ormond Street UCL Institute of Child Health, London, UK.
- 2. Nuffield Department of Primary Care Health Sciences, University of Oxford.
- 3. Department of Paediatrics, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.
- 4. Paediatric Intensive Care Unit, Great Ormond Street Hospital, London, UK
- 5. Kings College London, UK.
- 6. Chelsea and Westminster Hospital NHS Foundation Trust, London, UK.
- 7. Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London, London, UK.

Address correspondence to: Dr Philippa Rees, Population Policy Practice, UCL Institute of Child Health, 1st Floor 30 Guilford Street, London, WC1N 1EH, p.rees@ucl.ac.uk

School-age outcomes of children after perinatal brain injury: a systematic review and meta-analysis

Background

Over 3,000 children suffer a perinatal brain injury in England every year according to national surveillance. The childhood outcomes of infants with perinatal brain injury are however unknown.

Methods

A systematic review and meta-analyses were undertaken of studies published between 2000-September 2021 exploring school-aged neurodevelopmental outcomes of children after perinatal brain injury compared to those without perinatal brain injury. The primary outcome was neurodevelopmental impairment which included cognitive, motor, speech and language, behavioural, hearing, or visual impairment after 5 years of age.

Results

This review included 42 studies. Preterm infants with intraventricular haemorrhage (IVH) grade 3-4 were found to have a three-fold greater risk of moderate-severe neurodevelopmental impairment at school age OR 3.69 (95%CI: 1.7, 7.98). Infants with perinatal stroke had an increased incidence of hemiplegia 61% (95%CI: 39.2, 82.9) and an increased risk of cognitive impairment (difference in full scale IQ -24.2 (95%CI: -30.73, -17.67) . Perinatal stroke was also associated with poorer academic performance; and lower mean receptive -20.88 (95%CI: -36.66, -5.11) and expressive language scores -20.25 (95%CI: -34.36, -6.13) on the CELF assessment. Studies reported an increased risk of persisting neurodevelopmental impairment at school age after neonatal meningitis. Cognitive impairment and special educational needs were highlighted after moderate-severe HIE. However, there were limited comparative studies providing school-aged outcome data across neurodevelopmental domains and few provided adjusted data. Findings were further limited by the heterogeneity of studies.

Conclusions

Longitudinal population studies exploring childhood outcomes after perinatal brain injury are urgently needed to better enable clinicians to prepare affected families, and to facilitate targeted developmental support to help affected children reach their full potential.

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What is already known on this topic

Thousands of children suffer a brain injury around the time of birth every year in England. Many of these injuries are associated with neurodevelopmental impairment at two years of age. However, two-year outcomes are not necessarily representative of later childhood outcomes and function, which are a priority for parents.

What this study adds

This review provides an overview of existing evidence of childhood outcomes after perinatal brain injury. It indicates that there is some evidence of on-going impairment throughout childhood for different types of perinatal brain injury but that there are considerable gaps in knowledge.

How this study might affect research, practice or policy

research, p.
i for detailed highmes after perinatal bran. This review shows the need for detailed high-quality longitudinal population studies exploring childhood outcomes after perinatal brain injury

School-age outcomes of children after perinatal brain injury: a systematic review and meta-analysis

Perinatal brain injuries can have wide-ranging deleterious consequences for children, families and broader society.(1-4) Over 3,000 infants experience perinatal brain injury in England annually¹ and the Department of Health and Social Care (DHSC) has committed to halving the rate of perinatal brain injuries by 2030 as part of the national maternity ambition.(5) To monitor progress towards this goal, a standardised definition of perinatal brain injury was developed.(6) The degree to which this definition captures and represents true perinatal brain injuries is unclear and requires us to look beyond the neonatal period.(6)

Focusing on the childhood outcomes of infants with perinatal brain injury provides a fuller understanding of the population captured by the DHSC definition. Despite their importance to families, school-age outcomes following neonatal care have been an overlooked research priority. Neonatal studies typically focus on two-year composite outcomes which may mask the true neurodevelopmental burden of injuries, and are known to be poorly predictive of future functioning.(7-10) As such, our understanding of childhood developmental trajectories after brain injuries – and whether any sequelae are fixed, stable or amenable to interventions – is limited. We therefore undertook a systematic review to explore school-age neurodevelopmental outcomes following perinatal brain injury.

METHODS

Study selection

The review was conducted as per the pre-registered protocol (CRD 42021278572) and the PRISMA statement.(11) We included observational comparative studies exploring neurodevelopmental outcomes of children over five years of age after perinatal brain injury, published between 2000-September 2021 (Table 1). The DHSC definition of perinatal brain injuries used includes intraventricular haemorrhage, preterm white matter injuries, stroke, central nervous system infection, hypoxic ischaemic encephalopathy, and kernicterus diagnosed during the neonatal period.(6, 12) We did not include seizures in isolation. For inclusion, studies were required to have a non-brain injured comparator group. The primary outcome was neurodevelopmental impairment; secondary outcomes included motor, cognitive, speech and language, behavioural and neuropsychological, visual and hearing outcomes and seizures.

A search strategy incorporating 99 key terms and mesh headings was developed in Medline Ovid, adapted and run across 10 databases. Snowballing techniques were used to augment search sensitivity (Supplement 1 & 2). All titles were screened independently by two reviewers. The full-texts of all potentially relevant titles were retrieved, reviewed and their risk of bias assessed by two trained reviewers independently (PR, CC, MV, JD, SS). Disagreements were arbitrated by a third reviewer.

Data extraction and synthesis

Studies were stratified by brain injury type, sub-stratified by age of outcome assessment and outcome type, and summarised in a narrative synthesis. Where sufficient suitable data were available from contextually and clinically comparable studies, data were pooled in random

effects meta-analyses using RevMan 5.4. Continuous data were pooled using the inverse variance method; dichotomous data were pooled using the Mantel-Haenszel method; and analysis data from studies which did not provide raw data were pooled with dichotomous data from other studies using the generic inverse variance method.(13) Where studies provided insufficient comparative data for a particular outcome, the combined incidence figures for that outcome within the brain injured population was calculated across studies using the Fisher exact test for binomial data.(14) Statistical heterogeneity was assessed using the I² statistic and substantial heterogeneity (>85%) was explored further in sub-group analyses.

Quality assessment

The Newcastle Ottawa Tool was used to assess risk of bias across three domains: population selection, the comparability of the 'brain injured' and 'non brain injured' comparator groups, and outcome assessment.(15) Studies were classed as poor, fair, or good for each domain and given an overall risk of bias classification.

Patient and Public Involvement

Patients or the public were not involved in the design or conduct of this review. However the review's findings will be used to shape the larger CHERuB study in partnership with our parent advisory panel.

RESULTS

Searches identified 14,210 records and 42 studies were included (Figure 1). Studies focused on intraventricular haemorrhage (n=27), white matter injury (WMI) amongst preterm infants (n=15), perinatal stroke (n=8), neonatal meningitis (n=4), and HIE (n=3); these were not mutually exclusive (Supplement 3). Most studies were undertaken in the USA (n=10), the UK (n=8), the Netherlands (n=5) or Australia (n=4). These were prospective (n=27) or retrospective cohort studies (n=14). Included studies were deemed to be moderate (n=17) or low risk of bias (n=27) (Supplement 4).

Preterm injuries

The 29 studies exploring outcomes after IVH or WMI mostly included infants born <32 weeks' gestation (n=22) after the year 2000 (n=18) (Supplement 3). Most studies confirmed injury on ultrasound or MRI imaging (n=22) these were reviewed by radiologists (n=6), neonatologists (n=3) or both (n=1); 14 studies used the Papile classification; only 2 studies stratified results by laterality.

Nine studies explored neurodevelopmental impairment at 5-14 years of age after preterm brain injury including IVH (n=9) and WMI (n=6).(16-24) Two comparable studies highlighted a considerably increased pooled crude risk of moderate-severe neurodevelopmental impairment after IVH grade 3-4 at 8 years of age OR 3.69 (95%CI: 1.7, 7.98; 2 studies) $I^2 = 0\%$ (Figure 2, Table 2).(18, 21)

Six studies explored motor outcomes after IVH grade 3-4: they consistently highlighted an increased risk of motor impairment at 5-12 years of age.(21, 24-28) Additionally, two

comparable studies reported an 8-fold increased crude risk of cerebral palsy after IVH grade 3-4 OR 8.13 (95%CI: 4.64, 14.22; 2 studies; 1,557 subjects) *I*²=0% (Figure 3).

Cognitive outcomes at school-age after preterm brain injuries were reported by 16 studies using 25 different cognitive assessment tools - limiting the potential for meta-analysis (Supplement 3).(16, 17, 21, 22, 24-35) Educational outcomes were reported by 5 studies.(21, 22, 26, 30, 35)

Studies consistently reported lower cognitive scores at school-age following IVH grade 3-4. (16, 21, 22, 25-27, 31, 35) Hollebrandse 2021 reported an increased risk of cognitive impairment at 8 years of age OR 2.68 (95%CI: 1.21, 5.94).(26) Van de Bor 2000 and Hollebrandse 2021 reported that the cognitive impact of IVH grade 3-4 affected educational needs.(22, 26) Van de Bor 2000 reported increased special educational needs at 5, 9 and 14 years: the adjusted risk at 14 years of age was marked, aOR 3.99 (95%CI: 1.36, 11.69).(22) Studies reported no significant differences in language scores after IVH grade 3-4.(21, 22) However, an association with reading OR 3.62 (95%CI: 1.59, 8.24), spelling OR 4.48 (95%CI: 1.8, 11.2), and arithmetic OR 2.79 (95%CI: 1.2, 6.48) impairment was demonstrated.(26) Most studies highlighted cognitive effects after WMI.(17, 30, 33, 35)

Studies exploring behavioural outcomes after IVH 3-4 did not find any associations with attention deficits, conduct issues or autism spectrum disorder (Table 2).(16, 25, 36)

However, there was conflicting evidence around the mental health effects of WMI.(17, 37)

Studies exploring hearing impairment after IVH and/or WMI were small or not comparable. 10 studies explored visual impairment after IVH or WMI, 4 provided meaningful outcome data.(16, 21-23, 27, 28, 33, 34, 38, 39) An increased prevalence of visual impairment after IVH grade 3-4 (45.4% and 90.9%) compared to controls (7.5%) was reported in addition to significantly lower visual motor integration scores.(27)

Perinatal stroke

Eight comparative studies explored school-age outcomes after perinatal stroke, these included 177 children with perinatal stroke (100 left-sided and 54 right-sided – not all studies specified laterality) and 232 comparator children (Supplement 3).(40-47) Infants' gestation age was largely unspecified. Five studies presented a combined incidence of childhood seizures after perinatal stroke of 40.1% (95%CI: 26.8-53.3%; 5 studies; 115 subjects) I^2 =56% (Supplement 5).(40, 43, 44, 46, 47) The combined incidence of hemiparesis after perinatal stroke was 61% (95%CI: 39.2, 82.9 I^2 =88%). There was considerable heterogeneity across studies, and likely detection bias (Supplement 6).(40, 42-45)

Five studies identified a significant combined mean difference in full scale IQ scores at 7-13 years of age after perinatal stroke: -24.2 (95%CI: -30.73, -17.67; 5 studies; 296 subjects) I^2 =80% (Figure 4).(40, 42, 45-47) There was heterogeneity across studies in terms of assessment timing, assessment tools, and combining those with left and right-sided strokes.

Differences in stroke laterality partially explained the heterogeneity. The combined mean difference in full scale IQ following left-sided strokes was -26.01 (95%CI: -29.1, -22.93; 2 studies; 113 subjects) I^2 =0%; compared to -26.7 (95%CI: -39.38. -14.02; 2 studies; 99

subjects) I^2 =76% for right-sided strokes. No significant differences in cognitive outcomes were found by laterality.(40, 42, 45-47)

Kolk 2011 reported significantly lower scores across all NEPSY domains other than executive function after perinatal stroke, including attention, visuo-spacial function, memory, and learning.(43)

Two studies presented educational outcomes after perinatal stroke. Although Northam 2018 found that most children with perinatal stroke were in mainstream education (n=28, 93%), they also highlighted that additional educational support was often required (n=12, 40%). This was in keeping with Ballantyne 2008 reporting lower mean scores for reading (85 (16.1) vs. 113 (13.3); p<0.0001), spelling (82.5 (18.2) vs. 106.2 (15.9) p=0.001) and arithmetic (91.5 (10.2) vs. 111.9 (11.2) p<0.0001) after perinatal stroke compared to controls at 7-8 years of age, persisting on re-assessment at 10-12 years.

Kolk 2011 reported significantly lower scores compared to controls across most NEPSY language domains following perinatal stroke. (43) Significantly lower receptive and expressive mean language scores on the CELF assessment were also reported across studies: -20.88 (95%CI: -36.66, -5.11; 2 studies; 137 subjects) I^2 =88% and -20.25 (95%CI: -34.36, -6.13; 2 studies; 137 subjects) I^2 =87% respectively (Supplement 7, 8). (40, 45) Statistical heterogeneity may have been as a result of studies combining left and right-sided strokes and the varying age of outcome assessment. Studies highlighted that deficits in receptive language scores present at 7-8 years persisted at 10-12 years but that expressive language scores improved (p=0.012). (40, 41)

Meningitis

Studies consistently reported an increased risk of neurodevelopmental impairment after neonatal meningitis (Table 2).(48-50) An increased likelihood of neuromotor disability at 5 years of age (n=45/274, 16%) compared to controls (n=2/1391, 0.1%) was reported (Supplement 3).(48) On re-assessment of the same population at 9-10 years, this increased risk of severe disability persisted (n=12, 10.8% compared to n=0, 0%).(50) An increased risk of any neurodevelopmental impairment at 5 years after neonatal *Group-B Streptococcal* meningitis was also reported in the Netherlands, RR 5.30 (95%CI: 2·57-10·89), and in Denmark, RR 7.80 (95%CI: 4·42-13·77).(49) This increased risk persisted on subsequent assessment: at 11 years of age in the Netherlands, RR 2.99 (95%CI: 1.83, 4.88) and at 15 years of age in Denmark RR, 3.15 (95%CI: 1.82, 5,46).(49)

Hypoxic-ischaemic encephalopathy

Two comparative studies (of the same cohort) explored outcomes of term-born infants with moderate-severe HIE, but without cerebral palsy, at school age (Supplement 3).(51, 52) They highlighted significantly lower full scale IQ scores after HIE (mean difference –13.62 (95%CI: –20.53 to –6.71)).(51) This difference in cognition was also seen for perceptual reasoning, working memory, and processing speed. Children with HIE were also more likely than controls to receive additional classroom support: OR 10 (95%CI: 1.16, 86) although the confidence interval for this risk estimate was wide.(51) Children with HIE (without cerebral palsy) also had significantly lower motor scores (mean difference –2.12 (95%CI: –3.93, –0.30)) and verbal comprehension scores (mean difference –8.8 (95%CI: –14.25, –3.34)).(51) They were also noted to have higher behavioural difficulty scores especially for emotional problems.(51)

DISCUSSION

This review brings together the existing evidence on the later childhood outcomes of infants with perinatal brain injury. Although 42 studies are included, small study populations, limited data on injury severity and laterality, and the heterogeneity of outcome measures limited the potential power of results. However, studies demonstrate a three-fold higher risk of moderate-severe neurodevelopmental impairment at school age following IVH grade 3-4. Studies consistently report cognitive impairment after IVH grade 3-4 but suggest that speech and language is relatively preserved. A higher risk of hemiplegia, cognitive impairment and poorer academic performance after perinatal stroke is reported in addition to poorer receptive and expressive language scores. Studies report a higher risk of persisting neurodevelopmental impairment after neonatal meningitis – however few studies address this question. Few comparative studies explore school-age outcomes after HIE.

In following our a priori protocol only comparative studies were included. This was with a view to enabling inferential analyses and adjustment for key confounders such as gestation. Unfortunately due to this strict inclusion criterion many pertinent non-comparative studies were excluded.

Heterogeneity in terms of outcomes assessed, outcome assessment tools, and timing of outcome assessment limited the comparability of studies and the potential for meta-analyses. Several meta-analyses included low numbers of studies, reducing the reliability of the I² statistic.(53) This review was also limited by the size of available studies and how studies presented data for extraction. Few studies presented adjusted data or explored childhood trajectories after perinatal brain injury.

Previous reviews were limited by a lack of comparable studies, heterogeneity, the inclusion of much older cohorts, or by including non-comparative studies.(4, 54-56) Whilst this review was also limited by studies' heterogeneity and the quality of available data, new and important findings - for example the risk of neurodevelopmental impairment - at school age after IVH 3-4 were identified. Our finding of a higher risk of cerebral palsy after IVH and motor impairments after preterm brain injuries is echoed by previous studies.(54, 55, 57)

Lynch 2001 highlighted that 60% of infants have neurological sequelae that emerge over time following perinatal stroke. This was in-keeping with our findings of a higher risk of hemiparesis, cognitive impairment, and speech and language impairment. (58) Several non-comparative population-based studies also mirror these findings. (59-62)

Although previous reviews highlight an increased risk of various neurodevelopmental impairments after neonatal meningitis in early childhood – we are unaware of any focusing on school-age outcomes after neonatal meningitis.(4, 63)

The review's findings of potential on-going impairments across cognitive, speech and language, and behavioural domains - in addition to a need for increased school support – after HIE are mirrored by other studies.(64-68) Shankaran 2012 and Azzopardi 2014 highlight ongoing neurodevelopmental sequelae at school age amongst children who received therapeutic hypothermia for moderate-severe HIE.(64, 65, 67)

Implications

Considerable gaps in the evidence are highlighted, particularly around the risk of specific outcomes following different types of injury, the precision around risk estimates, the impact

of different factors (such as injury laterality), and the developmental trajectories of these children. This information is key to prepare families for the future, inform enhanced developmental surveillance, and enable targeted multidisciplinary support to help affected children to reach their full potential. As such, this review highlights a pressing need for high-quality, comparative studies which use the 'Core Outcomes In Neonatology' to explore long-term outcomes after perinatal brain injury and permit future meta-analyses.(10) Additionally, to meet the DHSC ambition to reduce perinatal brain injury, real-time longitudinal population data, extending beyond the neonatal period to childhood, are necessary as the current definition is limited to 'indicators' of injury from the neonatal period. This could be achieved through linkage of existing population datasets within the UK.

CONCLUSION

This review provides an overview of existing evidence of the impact of perinatal brain throughout childhood. Studies' heterogeneity significantly limited the potential for evidence synthesis.

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Contributors' statement

Dr Rees conceptualised and designed the review, reviewed and appraised studies, undertook data extraction and synthesis, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Callan conceptualized and designed the review, designed and oversaw the search strategy, reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Chadda reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Vaal reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Diviney reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Sabti reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Harnden reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Gardiner was the lead statistician for the review, he advised on and oversaw the data analysis, and reviewed and revised the manuscript.

Dr Battersby oversaw and supervised the review and critically revised the manuscript for important intellectual content.

Professor Gale oversaw and supervised the review and critically revised the manuscript for important intellectual content.

Professor Sutcliffe oversaw and supervised the review and critically revised the manuscript for important intellectual content.

All authors approve the final manuscript as submitted and agree to be accountable for all aspects of the work.

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manuscript and the standard supplemental file 5 and 6. **Additional Contributions:** The authors would like to thank Dr Roxanna Short for creating the figures in supplemental file 5 and 6.

- Figure 1: PRISMA flow diagram
- Figure 2: Crude risk of neurodevelopmental impairment at 8 years of age after IVH grade 3-4
- Figure 3: Crude risk of cerebral palsy after IVH grade 3-4
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 aroke Figure 4: Pooled mean difference in IQ scores at 7-13 years between those with and without

perinatal stroke

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Inclusion Criteria	Exclusion Criteria
Peer-reviewed observational studies (cohort, case-	Non-comparative studies; opinions; commentaries;
control, cross-sectional)	reviews; case-reports; lab studies
Studies in all languages	Studies where the population includes adults and children and the data for children cannot be extracted
Studies published after 2000	Studies focused on children with IVH grade 1-2, neonatal seizures, hypoglycaemic brain injury, or neonatal abstinence syndrome
Children with a diagnosis of brain injury occurring at or around the time of birth (including during the neonatal period) as defined by the DHSC (including those with any white matter injury but not including those with isolated seizures)	Studies which include infants with brain injuries diagnosed during the neonatal and infancy period where most were diagnosed outside of the neonatal period
Studies including infants with moderate to severe HIE born in the post therapeutic hypothermia era (i.e. where infants received therapeutic hypothermia)	Studies including infants with moderate-severe HIE born during the pre-therapeutic hypothermia era or in low- or middle-income countries that do not offer therapeutic hypothermia
Studies focused on school-aged neurodevelopmental	Studies of infants with mild HIE

Primary outcome(s):

including:

Neurodevelopmental impairment, as defined by authors (including direct testing, clinical record review, and parental interview/ survey)

outcomes (of children between 5-18 years of age)

Secondary outcome(s):

- 1. Any cognitive impairment, as defined by authors (direct testing)
- 2. Mild cognitive impairment (intelligence or developmental quotient 1-2 standard deviations below the mean)
- 3. Moderate-severe cognitive impairment (intelligence or developmental quotient more than 2 standard deviations below the mean)
- 4 Executive dysfunction, as defined by authors (direct testing)
- 5. Low numeracy, as defined by authors (by direct testing or educational achievement tests)
- 6. Low literacy, as defined by authors (by direct testing or educational achievement tests)
- 7. Special educational needs as defined by authors (school or parental report)
- 8. Motor impairment, as defined by authors (including direct testing, clinical record review, and reporting)
- 9. Visual-motor impairment, as defined by authors (on direct testing)

- 10. Emotional-behavioural difficulty, as defined by authors (including direct testing, clinical record review, and parental reporting
- 11. Speech and language impairment, as defined by authors (on direct testing)
- 12. Visual impairment, as defined by authors (including direct testing, clinical record review, and parental reporting)
- 13. Hearing impairment, as defined by authors (including direct testing, clinical record review, and parental reporting)
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 and wn. 14. Epilepsy/seizures, as defined by authors (including medical history taking, clinical record review and parental reporting

Studies reporting outcomes for children diagnosed with

Studies where comparable outcome data from those with and without perinatal brain injury cannot be extracted

Table 2: Overview of key findings for school-age outcomes of infants with perinatal brain injury compared to those without brain injury (*Does not include studies where infants with IVH grade 3-4 cannot be separated from those with WMI or those with IVH 1-2) (# Does not include studies using hearing or visual outcomes only as part of their composite outcome)

Adjusted Odds Ratio (aOR); Attention Deficit Hyperactivity Disorder (ADHD); Autism Spectrum Disorder (ASD); Confidence Interval (CI); cystic periventricular leukomalacia (cPVL); Group B Streptococcus (GBS); Hypoxic-Ischaemic Encephalopathy (HIE); Hazard Ratio (HR); Intelligence Quotient (IQ); Interquartile range (IQR); Intraventricular Haemorrhage (IVH); Odds Ratio (OR); Periventricular Leukomalacia (PVL); Visual Motor Integration (VMI); White Matter Injury (WMI)

	NDI	Cognitive	Motor	Speech and language	Behavioural	Hearing#	Vision#	Other
VH grade 3-	6 studies(15, 17-21)	9 studies(15, 20, 21, 24-26, 30, 70)	6 studies(20, 23-26, 33)	3 studies(20, 21, 25)	3 studies(15, 24, 35)	3 studies(21, 26, 38)	5 studies(15, 21, 26, 33, 38)	
		y 11 40	Not comparable	Not comparable	Not comparable	N	N	
	2 comparable studies in	Not comparable	All reported increased risk of	Van de Bor 2004: no	Brouwer 2012: no	Not comparable	Not comparable	
	meta-	Consistently highlighted	motor impairment	significant difference in	association with any	Outcome too rare	Outcome to rare for	
	analysis(17,	lower cognitive scores		language scores	behavioural domains	for inferential	inferential analysis	
	20)	_	Cerebral palsy		assessed (internalising,	analysis	in most studies.	
		Brouwer 2012: significantly	3 comparable studies	Sherlock 2005: downward	externalising and sleep	Y 2020		
	Meta-analysis (2 studies):	lower performance IQ but preserved verbal IQ. Lower	OR 8.67 (95%CI: 5.27, 14.28)	trend in language scores from no brain injury to	problems)	Kaur 2020: increased risk of	Adant 2019: no increased risk of	
	Increased risk	IO for those with IVH grade	P=0%.	each grade of IVH but not	Adant 2019: no	hospitalisation for	visual impairment	
	of	4 requiring neurosurgery		statistically significant	increased risk of	otologic reasons	(needing glasses)	
	moderate -	(91+/-10 vs. 98+/-15) but		p=0.12	attention deficits,	HR	aOR 0.47 (95%CI:	
	severe	little difference for those			conduct issues or ASD	7.87 (95%CI:	0.13, 1.69)	
	neurodevelop mental	with grade 3 IVH requiring neurosurgery (96+/-15 vs.		Hollebrandse 2021: Increased risk of impaired	aOR 1.24 (95%CI: 0.32,	5.31, 11.67)	Klebermass-	
	impairment	98+/-15).		reading OR 3.62 (95%CI:	4.8).		Schrehof 2012:	
	OR 3.15	30.7 13).		1.59, 8.24), and spelling	Davidovich 2020: no		increased prevalence	
	(95%CI: 1.67,	Hollebrandse 2021:		OR 4.48 (95%CI: 1.8,	increased risk of ASD		of visual impairment	
	$5.92) I^2 = 0\%$	increased risk of cognitive		11.2)	(n=10, 3.9% vs. n=103,		(needing glasses or	
	V d- D	impairment OR 2.68			2.2% p=0.085)		blindness) after IVH	
	Van de Bor 2004:	(95%CI: 1.21, 5.94). Increased risk of academic					grade 3 (45.4%) and IVH grade 4	
	increased	impairment across all					(90.9%) vs.	
	prevalence of	academic domains:					comparators (7.5%).	
	disability	reading OR 3.62 (95%CI:					Kaur 2020:	
	31% vs. 16%	1.59, 8.24);				///	increased risk of	
		spelling OR 4.48 (95%CI: 1.8, 11.2);					hospitalisation for	
		arithmetic OR 2.79)95%CI:					ophthalmic reasons	
		1.2, 6.48)					HR 7.87 (95%CI:	
							5.31, 11.67).	
		Sherlock 2005: significantly					Klebermass-	
		lower IQ scores after IVH grade 4 vs. IVH 1-3 and no					Schrehof 2012:	
		brain injury, also seen for					significantly lower	

	several domains: freedom from distractibility, processing speed, reading, spelling and arithmetic. No difference in executive function. Van de Bor 2004: increased special education needs at 5, 9 and 14 years aOR 3.99 (95%CI: 1.36, 11.69).					VMI scores (67.5 ± 14 vs. 76 ± 26.8; p=0.04)	
WMI* 3 studies(16, 17, 22) Not comparable Campbell 2021: living with no impairment was less common with WMI (n=12, 40%) vs. controls (n=487, 76%) Cheong 2018: increased risk of survival with major disability after cPVL aOR 9·17 (95%CI: 3·57, 23·53) Vollmer 2003: Disabling impairments were more common after cPVL at<28 weeks' gestation (n=3, 75% <28	mathematics tests (B 1.856 p=0.003), but not performance on spelling (B 1.076 p=0.075) or reading tests (B 0.241 p=0.483)	Cerebral palsy 1 study(16) Campbell 2020: increased risk of cerebral palsy aOR 18.63 (95%CI: 7.37, 47.06)	Jansen 2020: No association between WMI and spelling (B 1.076 p=0.075) or reading performance (B 0.241 p=0.483)	4 studies(16, 35, 36, 71) Not comparable Conflicting results Campbell 2021: No increased risk of: ADHD (n=3, 10% vs. n=97, 15%); anxiety (n=3, 10% vs. n=98, 15%); depression (n=7, 23% vs. n=100, 16%); or ASD aOR 0.74 (95%CI: 0.09, 5.88) Davidovich 2020: No increased risk of ASD after PVL (n=5, 2.5% vs. n=88, 2.3% p=0.86) Whitaker 2011: increased risk of ADHD aOR 6.83 (95%CI: 1.26-36.91); major depression aOR 2.59 (95%CI: 1.02-6.58); tic disorders aOR 9.77 (95%CI: 1.69-56.47); obsessive compulsive disorders aOR 15.32 (95%CI: 1.82-128.74)	0 studies	1 study(32)	

	weeks) vs. controls (n=3, 8%) and at over 28 weeks' gestation (n=6,50% vs. n=14, 6%)							
Stroke	0 studies	6 studies(39, 41, 42, 44-46) 5 comparable studies in meta-analysis (39, 41, 44-46) Meta-analysis (5 studies): significant mean difference in full scale IQ: -24.2 (95%CI: -30.73, -17.67) P=80% Trauner 2001 and Gold 2014: no significant difference in full scale IQ scores in left vs. right-sided strokes Ballantyne 2008: significantly lower performance IQ (p=0.002) and verbal IQ (p<0.0001). Lower mean scores for reading (p<0.0001), spelling (p=0.001) and arithmetic (p<0.0001) at 7-8 years persisting to 10-12 years	5 studies(39, 41-44) Combined hemiparesis incidence: 61% (95%CI: 39.2, 82.9 <i>P</i> =88%) Kolk 2011: moderate to severe neuromotor impairment in 62% n=13) and significantly lower scores on 5/6 sensorimotor domains of the NEPSY	5 studies(39, 40, 42, 44, 45) 3 comparable studies in meta-analysis Meta-analysis (3 studies): lower receptive language scores-20.88 (95%CI: - 36.66, -5.11) I²=88% and lower expressive language scores -20.25 (95%CI: -34.36, -6.13) I²=87% Ballantyne 2007 and Ballantyne 2008: deficits in receptive language scores at 7-8 years persist at 10-12 years but expressive language scores improved (p=0.012) particularly for children with right-sided strokes (p=0.034)	1 study(46)	1 study(43) Martin 2019: left-sided strokes predispose children to contralateral auditory neglect and right-sided strokes predispose children to bilateral auditory neglect	l study(39) Ballantyne 2008: visual field defects are common (n=7, 26%) after perinatal stroke	Seizures 8 studies(39 42, 43, 45, 46) 5 comparabl studies(39 42, 43, 45, 46) Combined incidence of seizures 40.1% (95%CI: 26.8, 53.3) <i>P</i> =56%
		Tillema 2008: reduced verbal IQ scores (mean 84 SD 13.4) vs. (mean 108 SD 14.2 P=0.002) Kolk 2011: poorer attention (across 4 of the 7 assessment sub-domains), visuo-spacial function (across 4 of the 5 sub-domains), and memory and learning (across 4 of the 6 sub-domains), but normal executive function scores.		Kolk 2011: significantly lower scores for 8/9 NEPSY domains including phonologic processing, comprehension of instructions, correct speeded naming, repetition of nonsense words, verbal fluency (semantic and phonetic), oromotor sequences, and sentence comprehension		クケ		

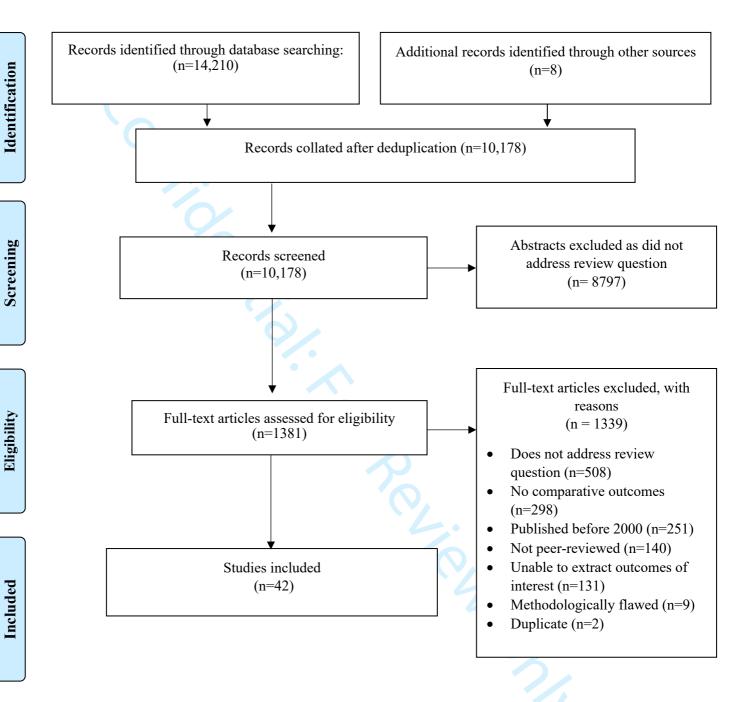
		Those with left-sided strokes had poorer neuropsychological scores. Northam 2018: most children are in mainstream education (n=28, 93%) but many require additional support (n=12, 40%)						
Meningitis	3 studies(47-49) Not comparable All reported increased risk of neurodevelop mental impairment Bedford 2011: increased prevalence of neuromotor disability (n=45, 16% vs. n=2, 0.1%) Stevens 2003: Risk of severe disability seen in Bedford 2011 at 5 years of age persisted until 9-10 years (n=12, 10.8% vs. n=0, 0%) Horvath- Puho 2021: increased risk of any neurodevelop mental impairment	Stevens 2003: significantly lower mean cognitive scores (mean 88.8 (95%CI: 85, 92) vs. mean 99.4 (95%CI: 97, 102))	1 study(49) Stevens 2003: significantly higher motor impairment scores (mean 7.1 (95%CI: 5.9, 8.5) vs. mean 5 (95%CI: 4.3, 5.8))	0 studies	0 studies	Martinez Cruz 2008: increased odds of neonatal meningitis amongst preterm infants with sensorineural hearing loss OR 4.37 (95%CI: 1.7, 10.9 Stevens 2003: 3.6% (n=4) had hearing loss compared to none in the control group.	Stevens 2003: Bilateral visual impairment was common after neonatal meningitis (n=18, 17%)	

THE	meningitis in the Netherlands RR 5.30 (95%CI: 2·57, 10·89) and Denmark RR 7.80 (95%CI: 4·42, 13·77) at 5 years of age persisting to 11 years in the Netherlands RR 2.99 (95%CI: 1.83, 4.88) and 15 years in Denmark RR 3.15 (95%CI: 1.82, 5,46)	3 ctudies (30, 50, 51) (two of	2 studies/50, 51) (of the same	2 studies(50, 51) (of the	2 studies(50, 51) (of the	0 studies	0 studies	
HIE	0 studies	3 studies(30, 50, 51) (two of the same population) Not comparable Koc 2016: preterm infants with HIE significantly more likely to have below average IQ scores (n=8, 89% vs. n=24, 30% p=0.001) Lee-Kelland 2020 and Tonks 2019: report lower full scale IQ scores after moderate to severe HIE (mean difference –13.62 (95%CI: –20.53, –6.71)) and poorer perceptual reasoning, working memory and processing speed. Children with previous HIE more likely to receive additional classroom support OR 10 (95%CI: 1.16, 86)	2 studies(50, 51) (of the same population) Lee-Kelland 2020 and Tonks 2019: significantly lower motor scores (mean difference -2.12 (95%CI: -3.93, -0.30)) after moderate-severe HIE (for children without cerebral palsy)	2 studies(50, 51) (of the same population) Lee-Kelland 2020 and Tonks 2019: significantly lower verbal comprehension scores (mean difference –8.8 (95%CI: –14.25, –3.34)) after moderate-severe HIE.	2 studies(50, 51) (of the same population) Lee-Kelland 2020 and Tonks 2019: higher behavioural difficulty scores (median score 12 IQR (6.5, 13.5 vs. median score 6 IQR (2.25, 10) p=0.005)	U studies	U studies	
Kernicterus				0 studies				

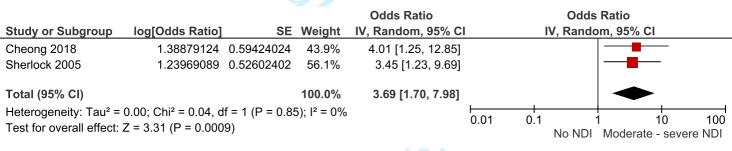




PRISMA 2009 Flow Diagram







0 1 2 3 4 5 6 7 8 9 0 1 2 3 4									
5		IVH grade	3-4	No IV	Н		Odds Ratio	Odds Ratio	
б -	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
/	Beaino 2010	9	38	46	1153	48.5%	7.47 [3.34, 16.69]	_	
8 9	Hollebrandse 2021	15	35	26	331	51.5%	8.80 [4.03, 19.19]	-	
0	Total (95% CI)		73		1484	100.0%	8.13 [4.64, 14.22]	•	
1	Total events	24		72					
2	Heterogeneity: Tau ² =		0.08, d	f = 1 (P =	: 0.77);	$I^2 = 0\%$			400
3 4	Test for overall effect: 2				,			0.01 0.1 1 10 No cerebral palsy Cerebral palsy	100
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7									
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9									
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2									
3									
4									
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6									
7									
8									
9									

0 1 2 3 4 5 6 7 8 9 0 1 2 3 4															
5			atal str			strok			Mean Difference				Differen		
5 -	Study or Subgroup	Mean			Mean			Weight	IV, Random, 95% C	l		IV, Ran	dom, 95	% CI	
7	Ballayntyne 2008	94.7	20.4	29	123	15	38	18.2%	-28.30 [-37.12, -19.48]			_			
8	Gold 2014	88	4	27	117	2.7	19	26.6%	-29.00 [-30.94, -27.06]				_		
9	Northam 2017	99	14	30	112	16	40	20.7%	-13.00 [-20.05, -5.95]						
n	Tilema 2008	80	14.1	10		11.7	10		-28.00 [-39.36, -16.64]						
1	Trauner 2001	93.4	22	39	116.2	13	54	19.7%	-22.80 [-30.53, -15.07]						
l n	Total (95% CI)			135			161	100.00/	-24.20 [-30.73, -17.67]						
2		40 0E. C	hi2 – 20		- 4 (D -	- 0 000			-24.20 [-30.73, -17.67]	1					
5 4	Heterogeneity: Tau ² = Test for overall effect:				– 4 (P –	- 0.000	лэ), r- –	00%		-100	-50		Ó	50	100
5															
6															
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8															
9															

Supplement 1: databases searched

Cochrane Central Register of Controlled Trials

EBSCO-CINAHL (Cumulative Index to Nursing and Allied Health Literature)

Google Scholar

Ovid-EMBASE

Ovid-MEDLINE

Ovid-MEDLINE E-pub ahead of print

Ovid-MEDLINE In-Process and Other Non-Indexed Citations

PubMed

Scopus

1 Index Expande. Web of Knowledge (Science Citation Index Expanded and Conference Proceedings Citation Index Science)

Supplement 2: Medline Ovid Search Strategy

- 1. exp CHILD/
- 2. exp Child, Preschool/
- 3. exp ADOLESCENT/
- 4. exp INFANT/ or exp INFANT, NEWBORN/
- 5. (child* or toddler* or baby or infant* or adolescent*).mp.
- 6. 1 or 2 or 3 or 4 or 5
- 7. exp Educational Status/
- 8. exp Child Development/
- 9. exp Learning Disorders/
- 10. exp Educational Measurement/
- 11. exp SCHOOLS/
- 12. exp Academic Performance/
- 13. school performance.mp.
- 14. exp COGNITION/
- 15. exp LEARNING/
- 16. exp SPATIAL LEARNING/
- 17. exp VERBAL LEARNING/
- 18. exp SOCIAL LEARNING/
- 19. exp Intelligence Tests/
- 20. exp INTELLIGENCE/
- 21. exp Intellectual Disability/
- 22. exp Neurodevelopmental Disorders/
- 23. neurodevelopm*.mp.
- 24. (nervous system dys* or CNS dys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 25. (nervous system abnorm* or CNS abnorm*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 26. (nervous system malform* or CNS malform*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 27. (nervous system dis* or CNS dis*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 28. (mental health condi* or mental health dis*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 29. mental health outcome.mp.
- 30. behaviour* abnorm*.mp.
- 31. cognitive impairment.mp. or exp Cognitive Dysfunction/
- 32. visual impairment.mp. or exp Vision Disorders/
- 33. visual develop*.mp.
- 34. (visual dis* or visual dys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

- 35. (nystagmus or strabismus).mp.
- 36. (visual acuity or refractive error*).mp.
- 37. hearing impairment.mp. or exp Hearing Loss/
- 38. exp Deafness/
- 39. exp DEAF-BLIND DISORDERS/
- 40. exp Hearing Loss, Sensorineural/
- 41. exp Movement Disorders/
- 42. exp Cerebral Palsy/
- 43. motor impairment.mp.
- 44. (seizure* or convulsi*).mp.
- 45. exp EPILEPSY/ or epilepsy.mp.
- 46. exp Executive Function/
- 47. visual-motor impairment.mp.
- 48. numeracy.mp.
- 49. literacy.mp. or exp LITERACY/
- 50. jaundice.mp.
- 51. exp Language Development Disorders/ or exp Child Language/ or language impairment.mp. or exp Reading/ or exp Dyslexia/ or reading impairment.mp.
- 52. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
- 53. 49 or 50 or 51
- 54. 52 or 53
- 55. exp JAUNDICE, NEONATAL/
- 56. exp JAUNDICE/
- 57. exp Hyperbilirubinemia, Neonatal/
- 58. exp Hyperbilirubinemia/
- 59. hyperbilirubin*.mp.
- 60. exp Hyperbilirubinemia, Hereditary/
- 61. bilirubin encephalopathy.mp.
- 62. bilirubin-induced neuro*.mp.
- 63. exchange transfusion.mp.
- 64. exp ASPHYXIA NEONATORUM/
- 65. (exp ASPHYXIA/ or asphyxia.mp.) and neonat*.mp.
- 66. exp Hypoxia-Ischemia, Brain/ and neonat*.mp.
- 67. perinatal asphyxia.mp.
- 68. birth asphyxia.mp.
- 69. (hypoxic-ischemic encephalopathy or hypoxic-ischaemic encephalopathy).mp.
- 70. neonatal encephalopathy.mp.
- 71. (exp Cerebral Hemorrhage/ or exp Intracranial Hemorrhages/ or exp Brain Ischemia/ or intracranial haemorrhage.mp. or exp Subarachnoid Hemorrhage/ or exp Stroke/) and neonat*.mp.
- 72. perinatal stroke.mp.
- 73. (central nervous system infection.mp. or exp Central Nervous System Infections/) and neonat*.mp.
- 74. (exp Meningoencephalitis/ or meningo-encephalitis.mp.) and neonat*.mp.
- 75. (MENINGITIS/ or meningitis.mp.) and neonat*.mp.

- 76. exp MENINGITIS, VIRAL/ and neonat*.mp.
- 77. (meningoencephalitis and neonat*).mp.
- 78. (encephalitis.mp. or exp ENCEPHALITIS, VIRAL/ or exp INFECTIOUS ENCEPHALITIS/ or exp ENCEPHALITIS/) and neonat*.mp.
- 79. kernicterus.mp. or exp KERNICTERUS/
- 80. preterm white matter disease.mp.
- 81. (periventricular leukomalacia.mp. or exp Leukomalacia, Periventricular/) and neonat*.mp.
- 82. (therapeutic hypothermia.mp. or exp Hypothermia, Induced/) and neonat*.mp.
- 83. ((subdural haemorrhage or subdural hemorrhage) and neonat*).mp.
- 84. (exp Hematoma, Subdural/ or subdural haemorrhage.mp. or exp Craniocerebral Trauma/) and neonat*.mp.
- 85. (intraventricular haemorrhage and neonat*).mp.
- 86. (tentorial tear and neonat*).mp.
- 87. (parenchymal haemorrhage and neonat*).mp.
- 88. (ventriculoperitoneal shunt.mp. or exp Cerebrospinal Fluid Shunts/ or exp Ventriculoperitoneal Shunt/) and neonat*.mp.
- 89. ((ventricular drain or Rickham reservoir or CSF shunt) and neonat*).mp.
- 90. neonatal stroke.mp.
- 91. (cerebrovascular accident and neonat*).mp.
- 92. neonatal cerebral ischaemia.mp.
- 93. (exp Intracranial Thrombosis/ or cerebral venous thrombosis.mp.) and neonat*.mp.
- 94. (seizure.mp. or exp Seizures/) and neonat*.mp.
- 95. 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94
- 96. exp Cohort Studies/
- 97. exp Retrospective Studies/
- 98. (cohort* or (case\$ and control\$)).tw.
- 99. exp Cross-Sectional Studies/
- 100. exp Randomized Controlled Trial/
- 101. 96 or 97 or 98 or 99 or 100
- 102. exp "REVIEW"/
- 103. exp Case Reports/
- 104. Animals/
- 105. animal stud*.mp.
- 106. 102 or 103 or 104 or 105
- 107. 6 and 52 and 95 and 101
- 108. 107 not 106

Supplement 3: included studies of school-aged outcomes after perinatal brain injury

* overlapping study data; Ω potential error in manuscript; Adjusted Odds Ratio (aOR); Autism spectrum Disorder (ASD); Attention Deficit Hyperactivity Disorder (ADHD); Bayley Scale of Infant Development (BSID); Child Behaviour Checklist (CBCL); Clinical Evaluation of Language Fundamentals (CELF); Cystic Periventricular leukomalacia (cPVL); Gross Motor Function Classification System, (GMFCS); Haemorrhagic parenchymal infarction (HPI); Hazard Ratio (HR); International Classification of Disease (ICD); Intraventricular haemorrhage (IVH); Intelligence Quotient (IQ); Kaufman Assessment Battery for Children (K-ABC); Mental Developmental Index (MDI); Peabody Picture Vocabulary Test (PPVT); Periventricular (PV); Periventricular leukomalacia (PVL); National Institute of Child Health and Human Development (NICHD); Neonatal Intensive Care Unit (NICU); Psychomotor Development Index (PDI); Retinopathy of Prematurity (ROP); Small for Gestational Age (SGA); Spontaneous Intestinal Perforation (SIP); Standard Deviation (SD); Standard Error (SE); Test of Motor Impairment (TOMI); Very low birthweight (VLBW); Visuomotor integration (VMI); Wechsler Abbreviated Scale of Intelligence (WASI); Wechsler Intelligence Scale for Children (WISC); Wechsler Preschool & Primary Scale of Intelligence (WPSI); White Matter Injury (WMI); Wide Range Achievement Test (WRAT)

Author Year	Population Exposures	Outcomes	Main result(s)
Country Study type	Comparator Ascertainment/ definition		
Adant 2019 ⁹ Belgium Retrospective cohort	Population • Gestation ≤32 weeks with and without spontaneous intestinal perforation (SIP) • Born 1994-2014 Exposure (n=19) • IVH grade 3-4 Comparator (n=44) • Matched on gender, gestational age, date of birth (multiples matched to sibling without SIP) • No IVH Ascertainment/ definition • Clinical record review	Outcomes Functional disability (composite) Cognitive Motor Visual Behavioural/ mental health Wellbeing Quality of life Physical health Measurement/ assessment BSID II Telephone survey (parents) PedsQL IQ testing Follow-up 67% follow-up at 7-11 months 41% follow-up at 18-22 months 49% follow-up at 4-10 years 86% follow-up telephone survey	Outcomes of those with SIP compared to controls without SIP – by IVH subgroup Disability aOR 8.79 95%CI (1.72, 44.86) Multiple disabilities aOR 5.97 95%CI (1.61, 22.15) Cognitive Regular education system (not a special educational needs school) aOR 8.73 95%CI (2.1, 36.72) Visual outcomes (wearing glasses) aOR 0.474 95%CI (0.13, 1.69) Behavioural/ mental health disorder (including attention problems, conduct problems and autism spectrum disorders) aOR 1.24 95%CI (0.32, 4.8) PedsQL low quality of life score aOR 0.87 95%CI (0.77, 0.99) PedsQL low physical health score
Beaino 2010 ⁶⁸	Gestation <33 weeks	Outcomes • Cerebral palsy	aOR 0.82 95%CI (0.66, 1.01) Cerebral palsy Grade 3 IVH
France Prospective cohort	Born 1997 Exposure IVH grade 1 (n=173) IVH grade 2 (n=117) IVH grade 3 (n=32) Intraparenchymal haemorrhage (IPH) (n=6) Persistent echodensities or ventricular dilatation (n=241) cPVL (n=66) Comparator (n=1153) Unmatched	Measurement/assessment Standardised questionnaires completed by physicians Follow-up 5 years 77% follow-up	OR 3.75 95%CI (2.41–5.85) Grade 3 IVH or echodensities of ventricular dilatation Model A aOR 3.25 95%CI (2.02–5.22) Model B aOR 3.40 95%CI (2.07–5.60) Model C aOR 3.31 95%CI (2.00–5.48) cPVL OR 33.41 95%CI (19.25–57.96) Cystic PVL or IPH Model A aOR 29.66 95%CI (16.71–52.62) Model B aOR 28.41 95%CI (15.65–51.59) Model C n/a
Brouwer	No IVH Ascertainment/ definition Ultrasound imaging undertaken and reviewed by neonatologists or radiographers Population	Outcomes	Cerebral palsy
Netherlands Prospective cohort	Gestation <32 weeks Born 1999-2004 Exposure (n=32) Post-haemorrhagic ventricular dilatation after IVH grade 3-4 requiring neurosurgical intervention No PVL Comparator (n=23) Matched on gestation, birthweight, and sex No IVH Ascertainment/ definition Ultrasound diagnosis Papile classification	Motor Cerebral palsy Cognitive Behavioural Measurement/ assessment Movement ABC GMFCS WPPSI (3 rd edition Dutch version) Revisie Amsterdamse Kinder Intelligentietest Snijders Oomen Nonverbal Intelligence Test 2.5-7 – Revised CBCL Teacher Report Form Follow-up 4-8 years (median 5.7) 97% follow-up	IVH grade 3 n=0 IVH grade 4 n=8, 53%; all unilateral spastic cerebral palsy GMFCS level 1, n=5 GMFCS level 2, n=2 GMFCS level 3, n=1 Movement ABC motor score (for those without cerebral palsy) Score \(\sigma \) 5 (definite motor problems) IVH grade 3 n=6, 26% IVH grade 4 h=3, 13% No IVH n=0 Score p 5-15 (borderline motor function) IVH grade 3 (n=6; 26%) IVH grade 4 (n=0; 0%) No IVH (n=5; 29.4%) Score p> 15 IVH grade 3 n=6, 26% IVH grade 4 n=0, 0%
			No IVH n=12, 70.6% Cognition Wechsler intelligence test (mean ±SD) Verbal scale IVH n=23, 97±13 IVH <30weeks' gestation n=16, 94±13 No IVH n=24, 96±13; Performance scale IVH, n=23, 94±16; IVH <30weeks' gestation n=16, 93±15 No IVH n=24, 103±14;

US Pro	impbell 121 10 SA ospective hort study	Population (n=858) Gestation 23-27 weeks Born 2002-2004 Exposure IVH without WMI (n=124) WMI without IVH (n=30) IVH and WMI (n=63) Comparator (n=641) No IVH or WMI Ascertainment/ definition Ultrasound imaging reviewed by two independent blinded radiologists WMI parenchymal echolucency or moderate to severe ventriculomegaly on a late scan	Outcomes Neurocognitive development (composite) Cognitive Ceptral palsy Behavioural/ mental health Epilepsy Quality of life Measurement/ assessment NEPSY II Neurological exam GMFCS Parental questionnaire Social Communication Questionnaire Child Symptom Inventory 4 Peds QoL 4 Follow up 10 years 74% follow-up	IVH n=23, 87=22; IVH =30weeks' gestation n=16, 85±24 No IVH n=24, 93±14 Intelligence quotrient (n; mean +t/SD) IVH grade 3 n=17; IQ 96±15; IQ=85 n=13 (76.5%) IVH IV n=15; IQ 91±10; IQ=85 n=9 (64.3%) IVH <30 weeks' gestation n=23; IQ 92±17; IQ=85 n=15 (65.2%) IVH <30 weeks' gestation n=23; IQ 92±17; IQ=85 n=17 (74%) IVH =73.10 98±15, IQ=85 n=17 (74%) IVH =73.10 98±15, IQ=85 n=17 (74%) IVH =73.10 98±15, IQ=85 n=17 (74%) IVH =73.10 weeks' gestation =22: 44.3 ±7.8, n=1 (4%) IVH =73.00 weeks' gestation =23: 44.3 ±7.8, n=1 (4%) IVH =30 weeks' gestation =23: 44.3 ±7.8, n=1 (4%) Internalising problem scale IVH: 49.2 ±8.9, n=5 (19%) IVH =30 weeks' gestation: 28.2 ±8.4, n=3 (15%) IVH =30 weeks' gestation: 49.2 ±9.1, n=5 (21%) IVH =30 weeks' gestation: 49.2 ±9.1, n=5 (21%) IVH =30 weeks' gestation: 43.7 ±7.5, n=0 (0%) IVH =30 weeks' gestation: 43.7 ±7.5, n=0 (0%) IVH =30 weeks' gestation: 43.7 ±7.5, n=0 (18%) IVH =30 weeks' gestation: 52.9 ±9.8, n=4 (18%) IVH =30 weeks' gestation: 52.4 ±11.4, n=7 (32%) IVH =30 weeks' gestation:
				Low cognitive function IVH and WMI n=18. 30% WMI n=10, 34%

WMI n=7, 24% IVH n=24, 20% No IVH or WMI n=93, 15% Severe cognitive impairment IVH and WMI n=18, 30% WMI n=7, 24% IVH n=7, 6% No IVH or WMI n=35, 6% Nonverbal IO IVH vs. No IVH or WMI Crude mean difference -3 95%CI (-6.6, 0.6) Full scale IQ IVH vs No IVH or WMI Crude mean difference -2.2 95%CI (-5.7, 1.4) Cerebral palsy IVH and WMI n=32, 51% n=32, 51% OR 16.85 95% CI (9.29, 30.55) aOR 13.43 95% CI (7, 25.78) n=14, 47% OR 14.28 95% CI (6.48, 41.48) aOR 18.63 95% CI (7.37, 47.06) IVH n=9, 7% OR 1.28 95% CI (0.6, 2.72) aOR 1.19 95% CI (0.54, 2.61) No IVH or WMI n=37,6%Reference category GMFCS>0 IVH and WMI n=16, 25% WMI n=10, 33% IVH n=4, 3% No IVH or WMI n=13, 2% Epilepsy IVH and WMI n=12, 19% OR 5.44 95 % CI (2.72, 10.86) aOR 4.89 95% CI (2.31, 10.35) **WMI** n=8, 27%; OR 6.92 95% CI (2.86, 16.75) aOR 7.56 95% CI (2.85, 20.06) n= 11, 9%; OR 1.85 95% CI (0.91, 3.78) aOR 1.5 95% CI (0.68, 3.3) No IVH or WMI Reference category Neuropsychiatric/ behavioural outcomes ASD IVH and WMI n=4, 6% OR 0.97 95% CI (0.34, 2.79) aOR 0.58 95% CI (0.19, 1.77) OR 1.02 95% CI (0.23, 4.42) aOR 0.74 95% CI (0.09, 5.88) IVH n=11, 9% n=11, 9% OR 1.39 95% CI (0.69, 2.78) aOR 1.24 95% CI (0.59, 2.6) No IVH or WMI n=42, 7% Reference category Social responsiveness scale (over 65 among children with IQ >85 excluding those with ASD) IVH and WMI n=5, 8% WMI n=4, 13% IVH n=14, 11% No IVH or WMI n=62, 10% ADHD IVH and WMI n=13, 24% WMI n=3, 10% IVH n=31, 25% OR 1.6 95% CI (1.1, 2.5) No IVH or WMI n=97, 15%

	ı			A system (second seconds)
				Anxiety (parent-reported) IVH and WMI n=6, 10% WMI n=3, 10% IVH n=10, 8% No IVH or WMI n=98, 15%
				Anxiety (teacher-reported) IVH and WMI n=12, 19% WMI n=3, 10% IVH n=14, 11% No IVH or WMI n=88, 14%
				Depression (parent-reported) IVH and WMI n=7, 11% WMI n=7, 23% IVH n=14, 11% No IVH or WMI n=100, 16%
		,0		Depression (teacher-reported) IVH and WMI n=20, 32% WMI n=7 23% IVH n=18, 15% No IVH or WMI n=96, 15%
				Poor quality of life (<70) IVH and WMI n=31, 49% WMI n=12, 40% IVH n=41, 25% No IVH or WMI n=131, 20%
5	Cheong 2018 ¹¹ Australia	Population ■ Gestation 22-27 weeks ■ Born 1991-1992; 1997-1998; 2005-2006	Survival with major disability (composite) Survival without major disability	Survival with major disability IVH grade 3-4 OR 2-98 95% CI (1:34, 6:63) p=0.01 aOR 2-61 95%CI (1:11-6:15) p=0.028
	Three prospective cohort studies	Exposure • IVH grade 3-4 (n=100) • cPVL (n=38)	(composite) Cognitive Cerebral palsy Visual impairment (acuity less than 6/60 in better eye)	1997 and 2005 cohort only: OR 4·01 95% CI (1·25, 12·84) p=0.02 cPVL
		Comparator Unmatched No IVH grade 3-4 (n=446) No cPVL (n=508)	Hearing impairment (requiring hearing aid or cochlear amplification) Assessment/ measurement GMFCS WISC III	OR 8·11 95% CI (3·24, 20·30) p<0.001 aOR 9·17 95% CI (3·57–23·53) p<0·0001 1997 and 2005 cohort only OR 17·0 95% CI (4·19, 69·02) p<0·001
		Ascertainment/ definition Not specified	WISC IV Differential Abilities Scales 2 nd edition Follow-up 8 years 91% follow-up of survivors	
6	Chou 2020 ⁶⁹	Population • Preterms infants <37 weeks' gestation	91% follow-up of survivors Outcome Epilepsy	Epilepsy Preterm with cerebral haemorrhage
	Taiwan Retrospective cohort study	(n=21,474) • Infants born small for gestational age (n=2206) • Born 2000-2010	Assessment/ measurement • ICD 9 Follow-up	HR 42.4 95%CI (29.8, 60.3) aHR 42.5 95 %CI (29.6, 60.5) SGA with cerebral haemorrhage HR 39.3 95%CI (5.51, 274.5)
		Exposure Preterm with cerebral haemorrhage GA with cerebral haemorrhage	2-12 years (mean 9 years) Completeness of follow-up not specified	aHR 38.7 95%CI (5.43, 275.5)
		Comparator (n=94,720) Matched 1:4 on gender, urbanisation of residential area and parental occupation No cerebral haemorrhage		
		Ascertainment/ definition National children's medical record database ICD 9 codes		12
7	Davidovitch 2020 ²⁹ Israel	Population (n=4963) ■ VLBW infants ≤1500g ■ Born 1999-2012	Outcome • ASD Assessment/ measurement	ASD IVH n=10, 3.9% No IVH n=103, 2.2% p=0.085
	Retrospective cohort study	Exposure • IVH grade 3-4 (n=256) • PVL (n=200)	Physical, neurological, and developmental assessment (by a qualified healthcare professional)	PVL n=5, 2.5% No PVL n=88, 2.3% p=0.86
		Post-haemorrhagic hydrocephalus (n=152) Comparator.	Independent psychological assessment Follow-up 8-15 years (median 11.6)	Post-haemorrhagic hydrocephalus n=7, 4.6% No post-haemorrhagic hydrocephalus n=106, 2.2% p=0.051 IVH, PVL, post-haemorrhagic hydrocephalus or ROP n=27,23.9%
		Comparator Unmatched No IVH grade 3-4 (n=4600) No PVL (n=3813) No post-haemorrhagic hydrocephalus (n=4810)	8- 15 years (median 11.6) Only those linked to electronic medical records included	No brain injury n=571, 11.8% p<0.0001 aOR 1.62 95% CI (0.96–2.73)
		Ascertainment/ definition Israel national very low birthweight infant database linked to electronic medical records. Ultrasound diagnosis Papile classification		
8	Doyle 2000 ⁷⁰	Population	Outcomes	<u>Cerebral Palsy</u>
	Australia	 Birthweight 500–1499 g Born 1980-1981; 1992 	Survival Cerebral palsy	Grade of IVH

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USA Bernogecive very control of the property	Cohort	1980s epoch IVH grade 1 (n=18) IVH grade 2 (n=9) IVH grade 3 (n=7) IVH grade 4 (n=4) 1992 epoch IVH grade 1 (n=23) IVH grade 2 (n=10) IVH grade 3 (n=9) IVH grade 4 (n=1) Comparator Unmatched No intracranial haemorrhage (n=223) 1980s epoch (n=113) Ascertainment/ definition Ultrasound imaging Post-mortem examination	Clinical assessment by blinded paediatricians Functional assessment Follow-up 5 years 93% follow-up for 1980s epoch	No IVH n=5, 5% IVH grade 3 n=2, 29% IVH grade 4 n=0 1992s epoch No IVH n=4, 4% IVH grade 3 n=3, 33%
	USA Retrospective	Gestation 24-28 weeks Born 2005-2009 Exposure MRI Mild WMI (n=223) Moderate WMI (n=51) Severe WMI (n=15) Any cerebellar lesion (n=57) Significant cerebellar lesion (n=39) Early cranial ultrasound No IVH 3-4 or cPVL (n=341) IVH 3-4 or cPVL (n=32) Late cranial ultrasound No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=354) Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) Comparator No white matter injury on MRI (n=84) No cerebellar lesion on MRI (n=316) No IVH 3-4 or cPVL (n=32) Normal early cranial ultrasound (n=227) No porencephalic cyst, cPVL moderate to severe ventricular enlargement or shunt (n=19) Normal late cranial ultrasound (n=224) Ascertainment/ definition NICHD neonatal research network (NEURO study and SUPPORT cohort) Two masked central imaging readers for all cranial ultrasounds and one for MRI All had cranial ultrasound and MRI (at 35-42 weeks) Unilateral and bilateral cranial	Moderate to severe disability (composite) Minimal or no disability Corebral palsy Hearing Vision Measurement/ assessment WISC IV Neurological exam GMFCS Clinical examination Parental report Follow-up 6-7 years	No white matter injury, n=8, 9% Mild white matter injury, n=8, 15% Severe white matter injury, n=14, 82% p=0.0001 Moderate or severe white matter injury aOR 1.1 95% CI (0.42, 2.92) Minimal or no disabiliy No white matter injury, n=8, 224% Midd white matter injury, n=8, 224% Moderate white matter injury, n=8, 224% Moderate white matter injury, n=0, 0% p=0.0001 Cognitive impairment (FSIQ mean (SD)) No white matter injury, 85.9 (16.8) Moderate white matter injury, 86.9 (16.8) Moderate white matter injury, 87.9 (16.8) Moderate white matter injury, 62.7 (19.6) p=0.0001 Cognitive impairment FSIQ <70 No white matter injury, n=7, 8% Mild white matter injury, n=9, 60% p=0.0001 Cognitive impairment FSIQ <8% Moderate white matter injury, n=9, 60% p=0.0001 Moderate or severe white matter injury aOR 1.14 95% CI (0.39, 3.26) Cognitive impairment FSIQ <85 No white matter injury, n=10, 45% Mild white matter injury, n=27, 32% Mild white matter injury, n=10, 45% Moderate white matter injury, n=13, 87% p=0.0001 No cognitive impairment FSIQ ≥85 No white matter injury, n=123, 55% Moderate white matter injury, n=123, 55% Moderate white matter injury, n=22, 43% Severe white matter injury, n=22, 43% Severe white matter injury, n=2, 13% Moderate white matter injury, n=2, 34% Moderate white matter injury, n=2, 44% p=0.0001 Any cerebral palsy No white matter injury, n=2, 9% Moderate white matter injury, n=1, 9% Moderate white matte

No cerebellar lesion, n=135, 42% Any cerebellar lesion n=15, 25% p<0.0001 Significant cerebellar lesion, n=15, 36%

Cognitive impairment (FSIQ mean (SD))

No cerebellar lesion, 87 (16.5) Any cerebellar lesion 78.4 (20) p=0.001 Significant cerebellar lesion 76.8 (20.4)

Cognitive impairment FSIQ <70

No cerebellar lesion, n=32, 10% Any cerebellar lesion, n=15, 26% p=0.001 Significant cerebellar lesion, n=10, 26%

Significant cerebellar lesions aOR 1.96 95% CI (0.72, 5.36)

Cognitive impairment FSIQ <85

No cerebellar lesion, n=136, 43% Any cerebellar lesion, n=33, 58% p=0.038 Significant cerebellar lesion, n=22, 56%

No cognitive impairment FSIQ ≥85

No cerebellar lesion, n=180, 57% Any cerebellar lesion, n=24, 42% P=0.038 Significant cerebellar lesion, n=17, 44%

Any cerebral palsy

No cerebellar lesion, n=13, 4% Any cerebellar lesion, n=9, 15% p=0.001 Significant cerebellar lesion, n=9, 21%

Cerebral palsy with GMFCS ≥2

No cerebellar lesion, n=3, 1% Any cerebellar lesion, n=3, 5% p=0.19 Significant cerebellar lesion, n=3, 7%

Early cranial ultrasound abnormalities Moderate to severe disability No IVH 3-4 or cPVL, n=43, 12% IVH 3-4 or cPVL, n=14, 42% p<0.0001 Normal scan, n=35, 12% aOR 0.61 95% CI (0.14, 2.59)

Minimal or no disabilityNo IVH 3-4 or cPVL, n=143, 41%
IVH 3-4 or cPVL, n=7, 21% p<0.0001 Normal scan, n=120, 43%

Cognitive impairment, FSIQ mean (SD) No IVH 3-4 or cPVL, 86.4 (17) IVH 3-4 or cPVL, 77.9 (19.1) p=0.008Normal scan, 86 (16.7)

Cognitive impairment FSIQ <70

No IVH 3-4 or cPVL, n=38, 11% IVH 3-4 or cPVL, n=9, 28% p=0.006 Normal scan, n=31, 11% aOR 0.42 95% CI (0.07, 2.33)

Cognitive impairment FSIQ <85 No IVH 3-4 or cPVL, n=149, 44%

IVH 3-4 or cPVL, n=20, 63% p=0.041 Normal scan, n=123, 44%

No cognitive impairment FSIQ ≥85 No IVH 3-4 or cPVL, n=192, 56% IVH 3-4 or cPVL, n=12, 38% p=0.041 Normal scan, n=154, 56%

Any cerebral palsy

No IVH 3-4 or cPVL, n=149, 44% IVH 3-4 or cPVL, n=20, 63% p=0.041 Normal scan, n=123, 44%

Cerebral palsy with GMFCS ≥2 No IVH 3-4 or cPVL, n=3, 1% IVH 3-4 or cPVL, n=3, 9% p<0.0001 Normal scan, n=2, 1%

Late cranial ultrasound abnormalities Moderate to severe disability

No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=40, 11%

Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=17, 77% p<0.0001 Normal scan, n=27, 10%

aOR 27.85 95% CI (6.03, 128.68)

Minimal or no disability

No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=149, 42%

Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=1, 5% P<0.0001

Normal scan, n=117, 43%

Cognitive impairment (FSIQ mean (SD))

No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, 86.7 (16.7)

Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, 65.9 (18.7) P<0.0001

				Normal scan, 87 (16.1)
				Cognitive impairment FSIQ <70 No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=36, 10% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=11, 58% p<0.0001 Normal scan, n=24, 9% aOR 20.05 95% CI (3.63, 110.84)
				Cognitive impairment FSIQ <85 No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=153, 43% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=16, 84% p<0.0001 Normal scan, n=118, 43%
		0		No cognitive impairment FSIQ ≥85 No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=201, 57% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=3, 16% p<0.0001 Normal scan, n=156, 57%
		ONEIDE		Any cerebral palsy No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=10, 3% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=12, 50% p<0.0001 Normal scan, n=6, 2%
				Cerebral palsy with GMFCS ≥2 No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=2, 1% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=4, 17% p<0.0001 Normal scan, n=1, 0%
10	Hirovonen, 2017 ²² Finland	Population Gestation >22 weeks Birth weight >500g Born 1991-2008	Outcomes	Any intellectual disability after intracranial haemorrhage (HR (95%CI); p-value) Very preterm infants 2.92 (1.58–5.41); p= 0.001 Moderately preterm 5.59 (1.57–19.9); p= 0.008
	Retrospective cohort	Exposure (n=557) Intracranial haemorrhage	ICD 9 and 10 codes BSID 1993 Finnish WISC	Late preterm 4.58 (1.36–15.4); p= 0.014 Term 2.94 (1.08-8); p=0.035
		Comparison (n=708,977) No intracranial haemorrhage	Follow-up • 7 years	
		ICD code Ascertainment/ definition	• 98% follow-up	
		Finnish national register ICD codes		
	Hollebrandse 2021 ¹⁹ Australia Retrospective cohort	Population Gestation <28 weeks Born 1991-1992, 1997, 2005 Exposure IVH grade 1 n=80 IVH grade 2 n=53 IVH grade 3 n=23 IVH grade 4 n=12 Comparator Unmatched Preterm infants without IVH n=331 Ascertainment/ definition Ultrasound diagnosis Worst grade of IVH Papile classification	Outcomes Cognitive Motor Cerebral palsy Assessment/ measurement WISC III (1991-1992 cohort) WISC IV (1997 cohort) WISC IV (1997 cohort) WISC IV (1997 cohort) WRAT III (1991-92; 1997 cohorts) WRAT IV (2005 cohort) Behaviour rating inventory of executive functioning (parent-completed) Movement ABC 1st edition (1991-1992 and 1997 cohorts) Movement ABC 2nd edition (2005 cohort) GMFCS (1997 and 2005 cohort) Blinded assessment Follow-up Syears Follow-up 85-91.4%	Cognitive IQ score <-2 SD IVH grade 4 n=5, 42% p=0.08 (X² trend) IVH grade 3 n=5, 22% No IVH n=41, 12% IVH 3-4: OR 2.68 95% CI (1.21, 5.94) p=0.01 Impaired executive function Global executive composite ≥65 IVH grade 4 n=2, 18% p=0.78 (X² trend) IVH grade 3 n=4, 18% No IVH n=49, 16% IVH 3-4: OR 1.17 95% CI (0.46, 2.97) p=0.75 Behavioural regulation index ≥65 IVH grade 4 n=2, 18% p=0.21 (X² trend) IVH grade 3 n=6, 27% No IVH n=46, 15% IVH 3-4: OR 1.76 95% CI (0.75, 4.11) p=0.2 Metacognition index ≥65 IVH grade 4 n=3, 27% p=0.1 (X² trend) IVH grade 3 n=5, 23% No IVH n=48, 16% IVH 3-4: OR 1.73 95% CI (0.74, 4.06) p=0.21 Impaired academic skills (any academic skill <-2SD) IVH grade 4 n=7, 64% p<0.001 (X² trend) IVH grade 3 n=5, 24% No IVH n=50, 16% IVH 3-4: OR 2.91 95% CI (1.35, 6.27) p=0.006 Impaired reading <-2SD
				IVH grade 4 n=6, 55% p=0.002 (X ² trend) IVH grade 3 n=4, 19% No IVH n=21, 10%
				IVH 3-4: OR 3.62 95% CI (1.59, 8.24) p=0.002

12	Hreinsdottir 2018 ⁴⁸ Sweden Prospective cohort study	Population Born 2004-2007 Gestation <32 years Exposure (n=9) IVH grade 3-4 and/ or PVL Comparator (n=99) Unmatched No IVH grade 3-4 or PVL Ascertainment/ definition Ultrasound imaging performed by paediatric radiologist Papile classification for IVH PVL defined by size, laterality and as cystic of diffuse	Outcomes • Visual impairment Assessment/ measurement • Linear visual acuity (Lea Hyvarinen chart) • Cover test • Refraction Follow-up • 6.5 years • 78% follow-up	No IVH n=21, 7% IVH 3-4: OR 4.48 95% CI (1.8, 11.2) p=0.001 Impaired arithmetic <-2 SD IVH grade 4 n=5, 43% p=0.09 (X² trend) IVH grade 3 n=4, 19% No IVH n=38, 12% IVH 3-4: OR 2.79 95% CI (1.2, 6.48) p=0.017 Motor and cerebral palsy Any motor dysfunction (cerebral palsy or MABC <5th centile) IVH grade 4 n=11, 92% p=0.001 (X² trend) IVH grade 4 n=11, 92% p=0.001 (X² trend) IVH grade 3 n=10, 43% No IVH n=81, 24% IVH 3-4: OR 4.45 95% CI (2.18, 9.08) p<0.001 Cerebral palsy IVH grade 3 n=6, 26% No IVH grade 3 n=6, 26% No IVH grade 4 n=9, 75% p<0.001(X² trend) IVH grade 3 n=6, 26% No IVH n=66, 8% IVH 3-4: OR 8.8 95% CI (4.03, 19.2) p<0.001 MABC <5th percentile (for the 2005 cohort) IVH grade 4 n=11, 92% p<0.001 (X² trend) IVH grade 4 n=17, 92% p<0.001 (X² trend) IVH grade 3 n=9, 43% No IVH n=79, 26% IVH 3-4: OR 4.7 95% CI (2.21, 9.97) p<0.001 Vision Subnormal visual acuity IVH 3-4 and or PVL OR 1.11 95% CI (0.25, 4.83) p=0.891 Contrast sensitivity IVH 3-4 and or PVL OR 2.5 95% CI (0.55, 11.41) p=0.237 Manifest strabismus IVH 3-4 and or PVL OR 2.5 95% CI (0.65, 24.55) p=0.134 Composite score 1: Visual acuity with both eyes of less than 0.3, significant refractive error in the better eye and manifest strabismus IVH 3-4 and or PVL OR 3.63 95% CI (0.65, 24.55) p=0.134 Composite score 2: Visual acuity in worse eye of less than 0.3, significant refractive error in worse eye according and manifest strabismus IVH 3-4 and or PVL OR 5.67 95% CI (1.34, 24.07) p=0.019 a0R 10.4 95% CI (1.23, 88) p=0.032 Composite score 3: Visual acuity with both eyes of less than 0.5, significant refractive error in worse eye according and manifest strabismus IVH 3-4 and or PVL OR 7.6 95% CI (1.53, 15.40) p=0.08 aOR 18.19 95% CI (1.53, 154.05) p=0.008 aOR 18.19 95% CI (1.53, 154.05) p=0.008 aOR 18.19 95% CI (1.51, 154.05) p=0.008 aOR 18.19 95% CI (1.51, 154.05) p=0.008
13	Jansen 2020 ²³ Netherlands Prospective cohort study	Population Gestation <32 weeks Admitted 2006-2007 Exposure Mild WMI (n=18) Moderate WMI (n=14) Severe WMI (n=8) Mild cerebellar injury (n=11) Moderate cerebellar injury (n=4) Severe cerebellar injury (n=6)	Outcomes Cognitive Assessment/ measurement National standardised achievement tests Follow-up 9-10 years 77% follow-up	IVH 3-4 and or PVL OR 7.6 95% CI (1.7, 34) p=0.008
		Comparator Unmatched No WMI (n=46) No cerebellar injury (n=65) Ascertainment/ definition Ultrasound imaging and term MRI Imaging reviewed by two blinded experienced investigators (neonatologists or radiologists)		Moderate-severe cerebellar injury vs. no injury B 1.293 p= 0.115 Mathematics Moderate-severe WMI vs. no injury B 1.856 p=0.003 Moderate-severe cerebellar injury vs. no injury B 1.504 p=0.088

15	Kaur 2020 ³² Canada Retrospective cohort study Kiechl-Kohlendorfer 2013 ²⁸	Population Preterm and term infants Born 2006-2016 Exposure IVH grade 1 (n=811) IVH grade 2 (n=186) IVH grade 3-4 (n=194) Preterm haemorrhage (n=1139) Comparator Unmatched No IVH (n=793, 062) Preterm no haemorrhage (n=50, 185) Ascertainment/ definition ICD 10 codes (based on ultrasound or MRI imaging) Papile classification Population Gestation <32 weeks Born 2003-2006	Outcome Reason for hospitalisation Assessment/ measurement ICD 10 codes Follow-up 12 years Completeness of follow-up not specified Outcomes Cognitive Measurement/assessment	Incidence of hospitalisation for: Cerebral palsy, n, incident rate per 1,000 person years (95%CI) IVH n=57, 6.8 (5.3, 8.8) No haemorrhage n=432, 0.1 (0.1, 0.1) Hazard ratio: 4.78 95% CI (3.21, 7.13) IVH grade 3-4 n=24 HR 14.78 95% CI (8.72-25.06) Ophthalmologic, n, incident rate per 1,000 person years (95%CI) IVH n=91 11.1 (9, 13.6) No haemorrhage n=6773, 1.2 (1.2, 1.3) HR 3.01 95% CI (2.32, 3.89) IVH grade 3-4 n=32 HR 7.87 95% CI (5.31-11.67) Otologic n, incident rate per 1,000 person years (95%CI) IVH n=328, 46.7 (41.9, 52) No haemorrhage n=102,153 22.1 (22, 22.2) HR 1.19 95% CI (1.06, 1.34) IVH grade 3-4 n=202 HR 1.07 95% CI (0.79-1.46) Delayed numerical skills Intracranial haemorrhage (all grades) n=11, 40,7% aOR 4.66 95% CI (1.56, 13.93) p=0.007
16	Austria Prospective cohort Klebermass-Schrehof 2012 ²⁰	Exposure Intracranial haemorrhage (all grades) (n=24) Intracranial haemorrhage grade 3-4 (n=4) PVL (n=2) Intraparenchymal echodense lesions (n=2) Comparator Ummatched Ascertainment/ definition Ultrasound imaging Papile classification Population Gestation <32 weeks Admitted to NICU 1994-2005	Physical examination Hannover-Wechsler Intelligence Test for preschool children, third edition WPPSI Snijders-Oomen Nonverbal Intelligence Test TEDI-MATH Follow-up 5 years 72.2% follow-up Outcomes Neurosensory impairment (composite) Motor Cerebral palsy	Intracranial haemorrhage grade 3-4 n=3, 11.1% PVL n=2, 7.4% Intraparenchymal echodense lesions n=0 Outcomes at 5.5 years Group 1: infants born < 28 weeks' gestation KABC <70
	Austria Prospective cohort	Exposure IVH grade 1 (n=37) IVH grade 2 (n=84) IVH grade 3 (n=18) IVH grade 4 (n=12) Comparator (n=320) Unmatched No IVH Ascertainment/ definition Ultrasound diagnosis Most severe scan used Papile classification	Language Visual Hearing Measurement/assessment BSID II (MDI, PDI) K-ABC Beery-Buktenica Developmental Test of VMI Clinical assessment Follow-up S years (1, 2, and 3.5 years) Only those with follow-up included (loss to follow-up not specified)	No IVH, 7.6% IVH grade 3, 33.3% IVH grade 4, 50% KABC mean (SD) No IVH, 91.5 (15.1) IVH grade 3, 88.6 (11.1) p=not significant IVH grade 4, 88.5 (10.6) p= not significant VMI mean (SD) No IVH, 92.7 (20) IVH grade 3, 67.5 (14) p=0.04 IVH grade 3, 67.5 (14) p=0.04 Cerebral palsy No IVH, 14.3% IVH grade 3, 63.6% p<0.01 IVH grade 4, 90.9% p<0.01 Visual impairment No IVH, 7.5% IVH grade 3, 45.5%, p=0.03 IVH grade 4, 90.9% p<0.01 Acoustic impairment No IVH, 2.2% IVH grade 3, 0% p= not significant IVH grade 4, 0% p= not significant IVH grade 4, 0% p= not significant
17	Koc 2016 ²⁴ Turkey Retrospective cohort	Population (n=90) Gestation <32 weeks Birthweight <1500g Born 2001 Exposure IVH grade 1-2 (n= 7) IVH grade 3-4 (n= 8) Comparator No IVH (n=75) Ascertainment/ definition Neonatal unit database and medical records	Outcomes Cognitive Measurement/ assessment WISC-R Follow-up 5.9-7.9 years 100% follow-up	WISC-R score <85 IVH (n=7; 46.7%) No IVH (n= 25; 33.3%) WISC-R score >85 IVH grade (n=8; 13.8%) No IVH (n= 50; 84.2%) p=0.381
18	Martinez- Cruz 2008 ⁴⁵ Mexico Case control	Population Gestation <34 weeks Birthweight <1500g Born 1990-2005 Exposure (n=103) IVH	Outcomes Sensorineural hearing loss Measurement/ assessment Brainstem auditory evoked potentials Transient auditory evoked otoacoustic emissions Behavioural hearing evaluation	IVH Sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=32; 11.8%) Multivariate logistic regression of risk factors for sensorineural hearing loss IVH: aOR 7.1 95% CI (4.34, 11.6) p<0.000

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Polysolation Population P					
2019 2019					
Spain	20	Piris Borregas			Poor neurodevelopmental outcome
Spain Retroposition Secretarisation Secr			Birthweight 500-1250g		Severe brain injury, n=46, 32%
Retrospective Color study		Sania.	• Born 1991-2008		
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Swiss neonatal network follow-up group S. 5. 5 - 6 years			• No IVH grade 3-4 or cPVL (n=213)	• GMFCS	
Swiss neonatal network follow-up group S. 5. 5 - 6 years			Ascertainment/ definition	Follow-up	
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Extremely low birth weight or very preterm infants without IVH (n=180) Ascertainment/ definition ■ Enrolled in Victorian Collaborative Study ■ Ultrasound diagnosis (at least one scan by a certified sonographer) ■ Worst grade of IVH on either side used ■ Papile classification - Tower of London - Rey Complex Figure - WRAT Follow-up - Mean 8.7 years - 92.3% follow-up Moderate to severe cerebral palsy No IVH (n=4, 2.2%) Grade 1 IVH (n=0, 0%) Grade 2 IVH (n=1, 8.3%) Grade 4 IVH (n=5, 83.3%) Az' linear trend = 40.8; p <0.0001 Major neurosensory disability No IVH (n=2, 15.6%) Grade 2 IVH (n=5, 10.6%) Grade 2 IVH (n=1, 8.3%) Grade 4 IVH (n=6, 100%) A' linear trend = 51.7; p <0.0001 Moderate to severe cerebral palsy No IVH (n=4, 2.2%) Grade 1 IVH (n=0, 0%) Grade 2 IVH (n=1, 8.3%) Grade 4 IVH (n=5, 83.3%) Grade 4 IVH (n=5, 83.3%) Grade 4 IVH (n=5, 10.6%) Grade 2 IVH (n=1, 8.3%) Grade 4 IVH (n=6, 100%) A' linear trend = 51.7; p <0.0001					
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					Verbal comprehension index mean (SD)
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Grade 2 IVH 99.6 (12.8)					
Grade 3 IVH 93.1 (15.4)					

Grade 4 IVH 74.3 (12.7) ANOVA F4,251 = 1.8; p = 0.12Perceptual organisation index mean (SD) No IVH 98.5 (16.3) A Spel Nr Grade 1 IVH 98.2 (15.7) Grade 2 IVH 96.9 (14.8) Grade 3 IVH 91.6 (12.7) Grade 4 IVH 71.7 (11.1) ANOVA F4,249 = 2.5; p = 0.042Freedom from distractibility index mean (SD) No IVH 92.3 (114.9) Grade 1 IVH 95.5 (15.0) Grade 2 IVH 97.7 (12.8) Grade 3 IVH 94.9 (17.4) Grade 4 IVH 71.0 (3.5) ANOVA F4,250 = 2.8; p = 0.026Processing speed index mean (SD) No IVH 99.5 (15.8) Grade 1 IVH 99.1 (16.6) Grade 2 IVH 99.3 (13.0) Grade 3 IVH 94.9 (19.3) Grade 4 IVH 71.0 (9.5) ANOVA F4,245 = 2.7; p = 0.033Tower of London (executive function) raw score mean (SD) Grade 1 IVH 71.5 (12.4) Grade 2 IVH 71.1 (20.4) Grade 3 IVH 66.5 (8.3) Grade 4 IVH 54.3 (22.0) ANOVA F4,244 = 1.8; p = 0.13 Rey complex figure (executive function) raw score mean (SD) No IVH 22.5 (7.5) Grade 1 IVH 23.1 (7.4) Grade 2 IVH 24 2 (5.8) Grade 3 IVH 19.3 (8.3) Grade 4 IVH 11.2 (9.8) ANOVA F4,242 = 2.6; p = 0.037 Wide range achievements test score mean (SD) Reading No IVH 95.2 (15.7) Grade 1 IVH 102.7 (15.4) Grade 2 IVH 99.0 (14.2) Grade 3 IVH 98.1 (11.9) Grade 4 IVH 70.5g (20.9) ANOVA F4,251 = 5.1; p = 0.001 Spelling No IVH 93.6 (12.4) Grade 1 IVH 97.8 (12.3) Grade 2 IVH 95.9 (10.8) Grade 3 IVH 96.8 (11.9) Grade 4 IVH 73.5 (20.0) ANOVA F4,250 = 4.0; p = 0.003Arithmetic No IVH 88.3 (14.3) Grade 1 IVH 93.6 (14.9) Grade 3 IVH 89.1 (10.1) Grade 4 IVH 65.5 (14.5) ANOVA F4,248 = 4.5; p = 0.002Cognitive test scores (compared to normal birthweight controls) IQ score <1 SD from the mean (n, %) No IVH n=64 (35.6%) Grade 1 IVH n=18 (38.3%) Grade 2 IVH n=9 (36%) Grade 3 IVH n=7 (58.3%) Grade 4 IVH n=6(100%) X2 linear trend=6.8; P=0.009 Wide range achievements test score <1 SD from the mean, n (%) Low reading No IVH n=42 (24.4%) Grade 1 IVH n=6 (13.3%) Grade 2 IVH n=5 (20.8%) Grade 3 IVH n=2 (18.2%) Grade 4 IVH n=3 (75%) X^2 linear trend=0.1; p=0.77 Low spelling No IVH n=33 (19.2%) Grade 1 IVH n=6 (13.6%) Grade 2 IVH n=2 (8.3%) Grade 3 IVH n=3 (27.3%) Grade 4 IVH n=3 (75%) X^2 linear trend=0.7; p=0.39 Low arithmetic No IVH n=47 (27.6%) Grade 1 IVH n=9 (20.5%) Grade 2 IVH n=2 (8.3%) Grade 3 IVH n=3 (27.3%) Grade 4 IVH n=4 (100%) X^2 linear trend=0.1; p=0.79

23	Tymofiyeva	Population (n=24)	Outcome	Attention (abnormal)
23	Tymofiyeva 2018 ³³ USA Prospective cohort	Population (n=24)	Outcome	Attention (abnormal) Mild WMI n=3, 75% Moderate WMI n=0, 0% No WMI n=8, 57% p=0.05
24	Van de Bor 2004 ¹⁵ Netherlands Prospective cohort	Population Gestation < 32 weeks Birthweight < 1500 g Born 1983 Exposure IVH grade 1-2 (n=45) IVH grade 3-4 (n=17) Comparator (n=216) Unmatched No IVH Ascertainment/ definition Ultrasound diagnosis Papile classification	Outcomes Disability (composite) Cognitive Neurological status (motor) Speech and language Behaviour Hearing Vision Measurement/assessment Questionnaires (completed by parents at 9 years; adolescents at 14 years) Home visit and neurodevelopmental assessment by paediatrician unaware of medical history WHO classification of impairment, disability, and handicap Follow-up 5, 9 and 14 years 91.5% follow-up of survivors at 14 years	Disability at 5 years No IVH n=49 (23%) IVH grade 3-4 n=5 (31.3%) Cognitive disability No IVH n=18 (8.3%) IVH grade 3-4 n=1 (5.9%) p=not significant Motor disability No IVH n=8 (3.7%) IVH grade 3-4 n=3 (17.6%) p=0.00 Speech/language disability No IVH n=34 (15.7%) IVH grade 3-4 n=1 (5.9%) p= not significant Visual disability No IVH n=10 (0.5%) IVH grade 3-4 n=0 p= not significant Hearing disability No IVH n=5 (2.3%) IVH grade 3-4 n=0 p= not significant School performance at 5 years Special education No IVH n=17 (8.7%) IVH grade 3-4 n=3 (20%) p=0.02 School performance at 9 years Slow learner No IVH n=57 (29.5%) IVH grade 3-4 n=4 (26.7%) Special education No IVH n=29 (15%) IVH grade 3-4 n=4 (26.7%) p=0.04 School performance at 14 years Slow learner No IVH n=93 (44.1) IVH grade 3-4 n=4 (23.5%) Special education No IVH n=93 (44.1) IVH grade 3-4 n=6 (35.3%) p=0.00 Need for special education at 14 years IVH (all grades) OR 2.36 95%CI (1.17-4.86) aOR 2.33 95%CI (1.17-4.86) aOR 2.33 95%CI (1.15, 4.75) IVH grade 3-4 OR 3.99 95%CI (1.36, 11.69)
25	Van Den Hout 2000 ²⁶ Netherlands Prospective cohort	Population Mean gestation 28-30 weeks Born 1989-1991 Exposure IVH (n=17) PVL (n=12) Comparator (n=17) Preterm Normal cranial ultrasound Ascertainment/ definition Ultrasound diagnosis Modified Levene and DeVries classification for IVH DeVries classification for PVL	Outcomes Cognitive Visual acuity Measurement/ assessment L94 visual-perceptual ability test Grating acuity cards McCarthy scales of children's abilities Wechsler preschool and primary scale of intelligence Snijders-Oomen non-verbal intelligence test Leiden Diagnostic test Follow-up Mean 5.3 years 88% follow-up	Total intelligence quotient, mean (SD) IVH 92.4 (16.3) PVL 79.6 (20.5) No brain injury 102.8 (14.4) IQ <85 IVH n=6, 35.3% PVL n=6, 50% No brain injury n=2, 11.8% Performance age in years, mean (SD) IVH 5.22 (1.16) PVL 4.37 (1.19) No brain injury 6.22 (0.89) Visual grating acuity in c/deg, mean (SD) IVH 37.4 (13.5) PVL 33.5 (15.9)

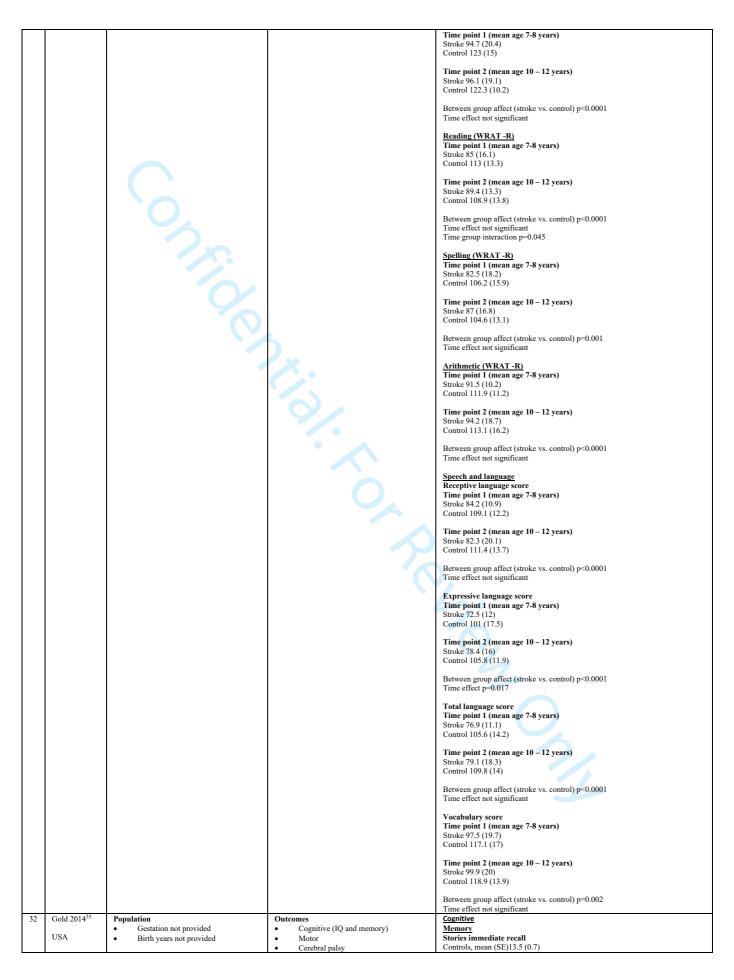
	ı			T
				No brain injury 47.1 (13.5)
				Visual grating acuity <25c/deg (%) IVH (11.8) PVL (33.3) No brain injury (0)
				No oram injury (0)
				Impairment on each of the eight L94 tasks Visual matching % (n) IVH 0 (17) PVL 0 (12) No brain injury 5.9 (17)
				Unconventional Object Views % (n) IVH 29.4 (17) PVL 41.7 (12) No brain injury 17.6 (17)
		,0		De Vos task % (n) IVH 29.4 (17) PVL 41.7 (12) No brain injury 11.8 (17)
				Line Drawings Occluded by Noise% (n) IVH 6.3 (16) PVL 36.4 (11) No brain injury 0 (17)
				Line Drawings Occluded by Noise% (n) IVH 13.3 (15) PVL 25.0 (8) No brain injury 5.9 (17)
			<u> </u>	Developmental test of visual motor integration % (n) IVH 0 (16) PVL 0 (7) No brain injury 0 (17)
			0	Matching block designs % (n) IVH 5.9 (17) PVL 20.0 (10) No brain injury 17.6 (17)
				Constructing block designs% (n) IVH 30.8 (13) PVL 80.0 (5) No brain injury 31.3 (16)
			0,	Mean percentage of L94 tasks on which child is impaired (mean, SD; %) IVH 14.71 (17.81) PVL 32.04 (24.64) No brain injury 11.13 (9.79)
26 *	Vollmer 2003 ¹⁶ UK Prospective cohort	Population Gestation <33 weeks Born 1983-1988 Exposure IVH (n=159) Ventricular dilatation (n=32) IVH, PV flare, ventricular dilatation (n=164) Hydrocephalus (n=36) Haemorrhagic parenchymal infarction (HPI) (n=61) CPVL n=26 Comparator (n=348) Unmatched Normal scan	Outcomes Neurodevelopmental impairment (composite) Visual impairment Hearing impairment Measurement/ assessment Structured neurologic examination Pure-tone audiogram Vision test (Snellen chart) Henderson-Stott TOMI Beery test of VMI WISC-R for children born 1983-1986 WISC-III for children born 1987-1988 Follow-up 8 years 91.7% follow-up	Neurodevelopmental status Group A (~28 weeks) All impairments (n,%) GMH/IVH (5, 18%) Ventricular dilatation (4, 50%) GMH/IVH, flare, ventricular dilatation (19, 51%) Hydrocephalus (7, 78%) HPI (15, 100%) CPVL (4, 100%) No brain injury (12, 32%) Disabling impairments (n, %) GMH/IVH (1, 4%) Ventricular dilatation (0, 0%) GMH/IVH, flare, ventricular dilatation (9, 24%) Hydrocephalus (7, 78%) HPI (14, 93%) cPVL (3, 75%) No brain injury (3, 8%)
		Ascertainment/ definition Ultrasound imaging reviewed by two experienced observers In-house classification used		Group B (28-32 weeks) All impairments (n, %) GMH/IVH (16, 29%) Ventricular dilatation (5, 31%) GMH/IVH, flare, ventricular dilatation (30, 43%) Hydrocephalus (7, 54%) HPI (5, 83%) ePVL (9, 75%) No brain injury (67, 29%)
				Disabling impairments (n, %) GMH/IVH (5, 5%) Ventricular dilatation (1, 6%) GMH/IVH, flare, ventricular dilatation (16, 23%) Hydrocephalus (6, 46%) HPI (3, 50%) cPVL (6, 50%) No brain injury (14, 6%)
27 *	Vollmer 2006a ²¹	Population • Gestation <33 weeks	Outcomes Motor	TOMI error score, mean (SD) Normal scan 2.78 (2.1)
	UK Prospective	Born 1985-1991 Exposure Bilateral brain lesions (n=201)	Cognitive Cerebral palsy Visual	All left-sided lesions 4.3 (3.5) Left-sided non-parenchymal lesions 4.5 (3.8) Left-sided parenchymal lesions 3.7 (2.1)
	cohort	Right-sided brain lesion (n=41)		

Left-sided brain lesion (n=57) All right-sided lesions 3.5 (2.9) Measurement/ assessment Neurological examination (modified Amiel-Tison assessment) Right-sided non-parenchymal lesions 2.7 (1.8) Right-sided parenchymal lesions 4.9 (3.8) Brain lesion types Non-parenchymal:

• Uncomplicated IVH TOMI All bilateral lesions 4.5 (4.3) WISC-R Parenchymal: Bilateral non-parenchymal lesions 4.1 (3.7) Bilateral parenchymal lesions 4.9 (4.7) Test of VMI Haemorrhagic parenchymal infarction v-up ANOVA for parenchymal lesions only p <0.0001 cPVL 8 years 80% follow-up ANOVA including parenchymal and non-parenchymal lesions p $<\!0.0001$ ANOVA excluding parenchymal lesions, p $<\!0.0001$ PV flare Comparator (n=369) VMI centile, mean (SD) Normal scan 59.2 (30.0) Unmatched Normal ultrasound All left-sided lesions 40.3 (30.1) Ascertainment/ definition Left-sided non-parenchymal lesions 46.8 (31.0) Left-sided parenchymal lesions 21 (22) Ultrasound imaging reviewed by two experienced observers Modified Stewart classification All right-sided lesions 60.2 (31.9) Right-sided non-parenchymal lesions 64.2 (30.2) Right-sided parenchymal lesions 54 (35) All bilateral lesions 46.0 (33.5) Bilateral non-parenchymal lesions 55.1 (32.1) Bilateral parenchymal lesions 38 (32) ANOVA for parenchymal lesions only p $<\!0.0001$ ANOVA including parenchymal and non-parenchymal lesions p $<\!0.0001$ ANOVA excluding parenchymal lesions reported as both p <0.0001 and p=0.98 Ω (potential error in the manuscript table) Cerebral palsy, n (%) Normal scan 2 (0.7%) All left-sided lesions 4 (9%) Left-sided non-parenchymal lesions 2 (6%) Left-sided parenchymal lesions 2 (16%) All right-sided lesions 2 (6%) Right-sided non-parenchymal lesions 1 (4%) Right-sided parenchymal lesions 1 (8%) All bilateral lesions 37 (21%) Bilateral non-parenchymal lesions 8 (10%) Bilateral parenchymal lesions 29 (31%) Chi-square for parenchymal and non-parenchymal lesions, p $<\!0.0001$ $\label{eq:chi-square} Chi-square excluding parenchymal lesions, p < 0.0001 \\ Chi-square for parenchymal lesions only, p < 0.0001 \\ ANOVA parenchymal lesions only, p < 0.0001 \\$ Full scale IQ, mean (SD) Normal scan 101 (16) All left-sided lesions 93 (17) Left-sided non-parenchymal lesions 98 (15) Left-sided parenchymal lesions 80 (15) All right-sided lesions 102 (17) Right-sided non-parenchymal lesions 104 (15) Right-sided parenchymal lesions 100 (19) All bilateral lesions 91 (21) Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19) All left-sided lesions 98 (20) Left-sided non-parenchymal lesions 102 (20) Left-sided parenchymal lesions 85 (18) All right-sided lesions 107 (18) Right-sided non-parenchymal lesions 108 (16) Right-sided parenchymal lesions 107 (22) All bilateral lesions 96 (23) Bilateral non-parenchymal lesions 100 (20) Bilateral parenchymal lesions 91 (25) ANOVA for parenchymal lesions only, p <0.0001 ANOVA including parenchymal and non-parenchymal lesions, p $<\!0.0001$ ANOVA excluding parenchymal lesions, p $=\!0.38$ Performance IQ, mean (SD) Normal scan 96 (15) All left-sided lesions 86 (16) Left-sided non-parenchymal lesions 90 (15) Left-sided parenchymal lesions 76 (15)

28 Vollmer * 2006b ²⁷ UK Prospective cohort	Population Gestation <33 weeks Born 1979-1991 Exposure (n=66) Ventricular dilatation and IVH Comparator (n=616) Unmatched Normal cranial ultrasound Ascertainment/ definition Ultrasound imaging reviewed by two experienced observers In-house classification used	Outcomes Neurological impairment with or without disability (composite) Cognitive Motor Vision Measurement/ assessment Structured neurological exam TOMI Test of VMI WISC Follow-up 8 years 181% follow-up	All right-sided lesions 95 (16) Right-sided non-parenchymal lesions 98 (13) Right-sided parenchymal lesions 92 (19) All bilateral lesions 85 (22) Bilateral non-parenchymal lesions 91 (20) Bilateral parenchymal lesions 80 (21) ANOVA for parenchymal lesions sonly, p <0.0001 ANOVA including parenchymal lesions, p =0.59 Disabling motor impairment, n (%) Ventricular dilatation and IVH n=10 (16%) Normal ultrasound n=10 (2%) Cognitive Full scale IQ, mean (SD) Ventricular dilatation and IVH 96 (23) Normal ultrasound 101 (17) Verbal IQ, mean (SD) Ventricular dilatation and IVH 101 (22) Normal ultrasound 104 (19) Performance IQ mean (SD) Ventricular dilatation and IVH 97 (15) Normal ultrasound 91 (21) Motor and vision VMI centile, mean (SD) Ventricular dilatation and IVH 37 (33) Normal ultrasound 52 (31) TOMI, mean (SD) Ventricular dilatation and IVH 5.98 (4.2) Normal ultrasound 3.26 (2.5)
29 Whitaker 2011 ³⁰ USA Prospective cohort	Population Birthweight <2000g Von-disabled' survivors Born 1984-1987 Exposure Vivi (n=69) Parenchymal lesions and/or ventricular enlargement (n=21) Comparison (n=368) Unmatched Normal cranial ultrasound Ascertainment/ definition Ultrasound imaging reviewed by three blinded radiologists independently, disagreements resolved through consensus and interobserver reliability checked. Paneth classification	Mental health conditions Measurement/ assessment Parent report version of the Diagnostic Interview Schedule for Children—IV WASI Follow-up 16 years 72.9% follow-up	Logistic regression assessing odds of current and lifetime mental health conditions after brain injury

				Parenchymal lesions and/or ventricular enlargement OR 7.64 95% CI (1.39-41.98) aOR 15.32 95% CI (1.82-128.74)
				Current diagnoses additionally controlled for full score IQ and motor function
				ADHD inattentive type IVH OR 0.86 95% CI (0.18-3.99) aOR 0.99 95% CI (0.21-4.62)
				Parenchymal lesions and/or ventricular enlargement OR 5.04 95% CI (1.36-18.65) aOR 5.43 95% CI (1.32-22.40)
				Major depression IVH OR 0.43 95% CI (0.16-1.11) aOR 0.40 95% CI (0.15-1.05)
				Tic disorders IVH OR 1.54 95% CI (0.41-5.78) aOR 1.45 95% CI (0.38-5.48)
				Parenchymal lesions and/or ventricular enlargement OR 7.01 95% CI (1.88-28.14) aOR 4.38 95% CI (1.05-18.23)
		0		Obsessive compulsive disorder IVH OR 8.68 95% CI (2.72-27.69) aOR 10.91 95% CI (3.13-37.99)
			۲.	Parenchymal lesions and/or ventricular enlargement OR 4.78 95% CI (0.83-28.10) aOR 3.58 95% CI (0.50-25.94)
Peri	natal stroke			
30	Ballantyne * 2007 41 USA Prospective cohort	Population	Outcomes Speech and language Assessment/ measurement CELF-R Wechsler Intelligence Scales (WPPSI-R, WISC-R, or WISC-III) PPVT-Revised	Speech and language
		Comparator (n=57) Ummatched Healthy controls with normal medical and developmental histories Recruited from the community	Expressive One-Word Picture Vocabulary Test–Revised or Upper– Extension Total Language Standard Scores	All strokes: 73.75 (16.79) p<.0001 Left stroke: 73.06 (14.88) p<.0001 Right stroke: 74.82 (20.11) p=0.001 Control: 101.02 (13.63)
		Ascertainment/ definition Single unilateral lesions the result of perinatal strokes occurring between 28 weeks' gestation and 28 days after birth; infarct or haemorrhage Identified through medical history and neuroimaging Severity rated on a 5-point scale adapted from the Vargha-Khadem classification	Follow-up 6-9 years 100% follow-up	All strokes: 76.93 (17.31) p<.0001 Left stroke: 76.94 (15.39) p<.0001 Right stroke: 76.91 (20.74) p=0.001 Control: 104.00 (12.58)
31	Ballantyne 2008 ³⁴ *	Population	Outcomes	Hemiparesis Stroke n=18,62%
	USA Prospective cohort	Exposure (n=29) Left hemisphere (n=20) Right hemisphere (n=9)	Motor Cerebral palsy Vision Epilepsy	Visual field deficit Stroke n=7, 26% Seizures Stroke n=11, 38%
		Control (n=38) Healthy controls (normal neurodevelopment) Recruited through a university and community adverts Ascertainment/ definition Unilateral ischaemic perinatal stroke confirmed through clinical history and neuroimaging Lesion location and severity reviewed by blinded neuroradiologist Severity rated on a 5-point scale adapted from the Vargha-Khadem classification	Measurement/ assessment WISC- Revised WRAT- Revised CELF- Revised PPVT-Revised WPSI/WPPSI- Revised WISC-III Follow-up 7-12 years 100% follow up	Cognitive, mean (SD) Verbal IO (WISC-R) Time point 1 (mean age 7-8 years) Stroke 96.6 (20.5) Control 126.1 (16) Time point 2 (mean age 10 – 12 years) Stroke 98.7 (20) Control 123.6 (13.1) Between group affect (stroke vs. control) p<0.0001 Time effect not significant Performance IO (WISC-R) Time point 1 (mean age 7-8 years) Stroke 92.8 (19.9) Control 115.2 (13.8) Time point 2 (mean age 10 – 12 years) Stroke 93.5 (20)
				Control 116 (10.5) Between group affect (stroke vs. control) p=0.002 Time effect not significant Full scale IQ (WISC-R)



Prospective cohort	Exposure (n=27) • Right-sided stroke (n=12)	Measurement/ assessment	Stroke, mean (SE) 8.4 (0.8) p<0.001
	Left-sided stroke (n=15) Comparator (n=19)	WISC-III Dots and Stories subtests of the Children's Memory Scales	Stroke and seizures, mean (SE)7 (0.8) Stroke and no seizures, mean (SE) 10.1 (1.4) p=0.06
	 Matched for age at follow up, sex, socioeconomic group and maternal 	Follow-up	Right lesion, mean (SE) 7.8 (1.1) Left lesion, mean (SE) 8.9 (1.2) p=0.51
	education Healthy controls Recruited through local advertising	• 6-16 years • 100% follow-up	Delayed recall Controls, mean (SE) 13.9 (0.8) Stroke, mean (SE) 7.9 (0.8) p<0.001
	Single, unilateral brain lesion in an arterial vascular distribution, either		Stroke and seizures, mean (SE) 6.2 (0.9) Stroke and no seizures, mean (SE) 10 (1.2) p=0.02
	identified in the neonatal period with neuroimaging, or identified later in infancy after presentation with a		Right lesion, mean (SE) 7.3 (1.1) Left lesion, mean (SE) 8.3 (1.2) p=0.56
	hemiparesis and imaging documentation of an old unilateral infarct (presumed perinatal stroke) Recruited from paediatric neurology		Delayed recognition Controls, mean (SE) 11.5 (0.5) Stroke, mean (SE) 8 (0.8) p=0.001
	clinics Severity graded 1-5 using Trauner/ Vargha-Khaldem classification		Stroke and seizures, mean (SE) 7.1 (1.1) Stroke and no seizures, mean (SE) 9.2 (0.9) p=0.17
			Right lesion, mean (SE) 8.3 (1.4) Left lesion, mean (SE) 7.9 (0.9) p=0.8
	0		Dots learning Controls, mean (SE) 10.9 (0.5) Stroke, mean (SE) 8.9 (0.8) p=0.05
			Stroke and seizures, mean (SE) 7.6 (1.1) Stroke and no seizures, mean (SE) 10.6 (0.8) p=0.05
		X	Right lesion, mean (SE) 9.3 (1.4) Left lesion, mean (SE) 8.7 (0.9) p=0.71
		8	Total Controls, mean (SE) 11.8 (0.5) Stroke, mean (SE) 9 (0.7) p=0.003
			Stroke and seizures, mean (SE) 7.8 (0.9) Stroke and no seizures, mean (SE) 10.6 (0.9) p=0.04
		•	Right lesion, mean (SE) 9.2 (0.7) Left lesion, mean (SE) 10.2 (0.7) p=0.62
			Delayed recall Controls, mean (SE) 12.6 (0.4) Stroke, mean (SE) 10 (0.5) p<0.001
			Stroke and seizures, mean (SE) 8.8 (0.5) Stroke and no seizures, mean (SE) 11.4 (0.8) p=0.009
			Right lesion, mean (SE) 9.7 (0.7) Left lesion, mean (SE) 10.2 (0.7) p=0.62
			WISC- III IQ, mean (SD) Right stroke, 85.0 (6) Left stroke, 91 (6) p=0.49
		(IQ scores Controls 117 (2.7) All stroke patients 88 (4.0) p<0.001 No seizures 100 (6.4) Seizures 78 (3.7)
			Motor (hemiparesis) Stroke patients n=16; 59% Control n=0; p=0.05
33 Kolk 2011 ³⁶ Estonia Retrospective cohort	Population Gestation not provided Born 1995-2006 Exposed (n=21) Neonatal stroke	Outcomes	Neuromotor impairment (Paediatric Stroke Outcome Measure) Neonatal stroke Severe n=4, 19% Moderate n=9, 43% Good n=6, 28.6% Normal n=2, 9.5%
	Control (n=31) • Matched on age and sex • Healthy children	Measurement/ assessment NEPSY	Cognitive/ neuropsychological
	Recruited locally Ascertainment/ definition	Kaufman ABC Paediatric Stroke Outcome Measure	Attention and executive function, mean, SD, 95% CI Tower Control 0.22, 0.64 (-0.05, 0.48)
	Estonian stroke registry Arterial ischaemic stroke or haemorrhagic	Follow-up • 4-10 years • 100% follow-up	Neonatal stroke -0.34, 1.34 (-1.03, 0.35) p=0.142 Auditory attention Control 0.27, 0.72 (-0.03, 0.57) Neonatal stroke -0.38, 1.10 (-1.04, 0.28) p=0.009
			Visual attention: time Control 0.37, 0.81, (0.07, 0.67) Neonatal stroke -0.40, 0.93 (-0.82, 0.03) p=0.004
			Visual attention: correct Control 0.48, 0.50 (0.30, 0.67) Neonatal stroke -0.54, 0.97 (0.98, 0.1) p<0.0001
1	1		1

Control 0.26, 0.77 (-0.03, 0.54) Neonatal stroke -0.23, 1.09, (-0.73, 0.28) p=0.086 Design fluence Control 0.18, 1.04 (-0.25, 0.61) i. Co. N. Neonatal stroke -0.36, 0.70 (-0.78, 0.06) p=0.06 Knock and tap Control 0.31, 0.50 (0.10, 0.51) Neonatal stroke -0.44, 1.52, (-1.32, 0.43) p==0.03 Language, mean, SD, 95% CI Phonological processing Control 0.24, 0.80 (-0.05, 0.54) Neonatal stroke -0.38, 0.99 (-0.83, 0.08) p=0.001 Comprehension of instructions Control 0.43, 0.70 (0.18, 0.69) Neonatal stroke -0.59 1.06 (-1.07, 0.11) p<0.0001 Speeded naming: time Control 0.24, 0.70 (-0.05, 0.52) Neonatal stroke -0.14, 1.03 (-0.73, 0.46) p=0.188 **Speeded naming: correct** Control 0.42, 0.41 (0.25, 0.59) Neonatal stroke -0.45, 1.41 (-1.26, 0.37) p=0.008 **Repetition of nonsense words**Control 0.30, 0.53 (0.08, 0.52)
Neonatal stroke -0.40, 1.23 (-1.03, 0.24) p=0.026 Verbal fluency: semantic Control 0.43, 0.81 (0.13, 0.73) Neonatal stroke -0.60, 0.95 (-1.04, 0.15) p<0.0001 Verbal fluency: phonemic Control 0.40, 0.93 (-0.12, 0.92) Neonatal stroke -0.67, 0.90 (-1.42, 0.08) p=0.008 Oromotor sequences Control 0.31, 0.64 (0.07, 0.54) Neonatal stroke -0.52, 1.25 (-1.15, 0.10) Sentence comprehension Control 0.19, 0.78 (-0.09, 0.48) Neonatal stroke -0.35, 1.09 (-0.91, 0.21) p=0.027 Sensorimotor functions, mean, SD, 95% CI Finger tapping Control 0.49, 0.33 (0.35, 0.62) Neonatal stroke -0.53, 1.27 (-1.16, 0.10) p=0.0007 Imitating hand positions Control 0.57, 0.68 (0.32-0.82) Neonatal stroke -0.72, 0.92 (-1.14, 0.30) p<0.0001 Visuomotor precision: time Control 0.13, 0.83 (-0.17, 0.43) Neonatal stroke -0.24, 0.97 (-0.69, 0.20) p=0.145 Visuomotor precision: mistakes Control 0.45, 0.50 (0.27, 0.64) Neonatal stroke -0.42, 1.05 (-0.90, 0.05) p=0.0002 **Manual motor sequences** Control 0.50, 0.62 (0.27, 0.73) Neonatal stroke -0.92, 0.95 (-1.43, 0.41) p<0.0001 Control 0.53, 0.57 (0.29, 0.77) Neonatal stroke -0.77, 1.03 (-1.30, 0.24) p<0.0001 Visuospatial functions, mean, SD, 95% CI Design copying Control 0.36, 0.80 (0.06, 0.65) Neonatal stroke -0.54, 0.97 (-1.0, 0.09) p<0.0001 Control 0.37, 0.79 (0.05, 0.70) Neonatal stroke -0.61, 1.07 (-1.16, 0.06) p=0.0004 **Block construction** Control 0.29, 0.81 (-0.01, 0.58) Neonatal stroke -0.45, 1.04 (-0.92, 0.03) p=0.0003 Route finding Control 0.25, 1.05 (-0.33, 0.83)

Neonatal stroke -0.66, 0.80 (-1.23, 0.09) p=0.033

Neonatal stroke -0.09, 1.03 (-0.56, 0.37) p=0.341

Neonatal stroke -0.41, 1.15 (-0.96, 0.15) p=0.016

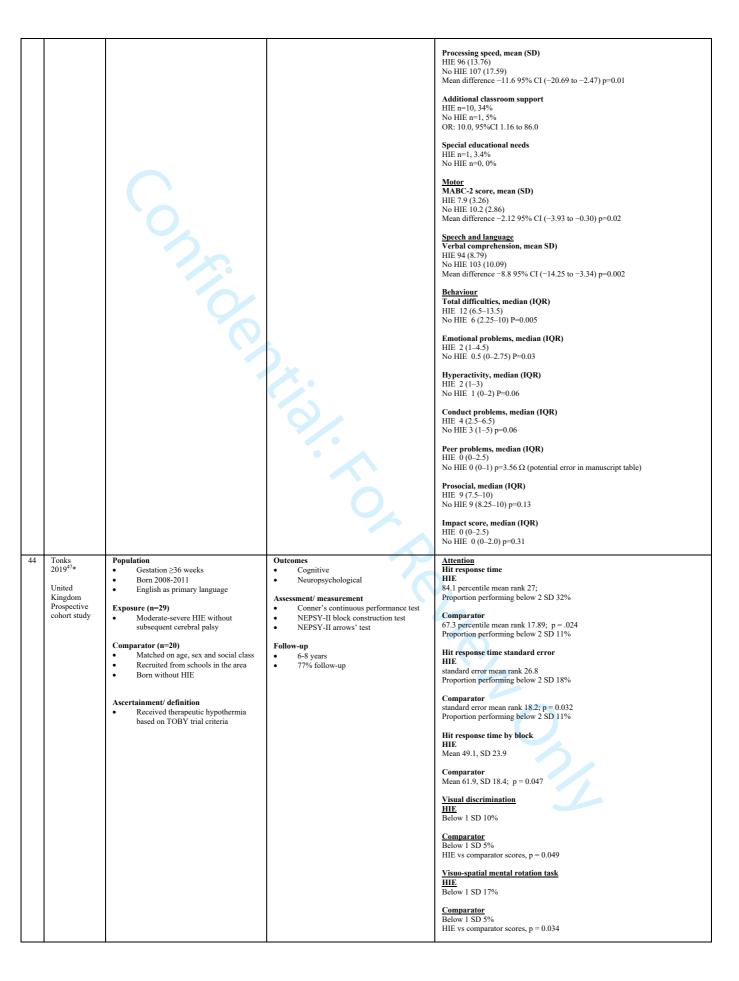
Memory and learning, mean, SD, 95% CI Memory for faces Control 0.42, 0.74 (0.11, 0.73)

Picture perception Control 0.13, 1.00 (-0.49, 0.24)

Memory for names Control 0.15, 0.92 (-0.23, 0.53) Neonatal stroke -0.31, 1.09 (-0.87, 0.25) p=0.295 Narrative memory Control 0.26, 0.80 (-0.03, 0.55) Neonatal stroke -0.22, 1.16 (-0.78, 0.34) p=0.077 Sentence repetition Control 0.49, 0.61 (0.26, 0.71) Neonatal stroke -0.64, 0.96 (-1.09, 0.19) p<0.0001 List learning Control 0.30, 0.82 (-0.16, 0.76) Neonatal stroke -0.38, 1.22 (-1.32, 0.56) p=0.151 Picture recognition Control 0.39, 0.72 (0.10, 0.69) Neonatal stroke -0.36, 1.24 (-0.98, 0.25) p=0.027 Motor (hemiparesis) Neonatal stroke and any hemiparesis n=19, 90% Mild functional impairment n=6, 29% Significant functional impairment n=6, 29% Significant functional impairment n=6, 38% Very severe functional impairment n= 4, 19% Epilepsy Stroke n=9, 33.3%
Martin 2019 Population
Northam Population
Motor (hemiparesis) Stroke n=9, 3%

37	Trauner 2001 ³⁹ USA Retrospective cohort	Matched on age, sex, and handedness Healthy Randomly drawn from a large database of children recruited for a different study of language development in healthy children Ascertainment/ definition Middle cerebral artery ischaemic stroke Population Gestation not reported Birth years not reported Exposure (n=39) Left perinatal stroke (n=25) Right perinatal stroke (n=14) Control (n=54) Matched on age and socioeconomic status Normal neurodevelopmental history Identified from clinics, community adverts, schools Ascertainment/ definition Pre or perinatal onset unilateral brain damage (focal lesion) from cerebral infarction or intraparenchymal haemorrhage	Follow-up	Stroke FSIQ 80 (14.1) Control FSIQ 108 (11.7) p=0.001 Cognitive Full scale IQ mean (SD) Stroke 93.4 (22) Control 116.2 (13) p<0.0001 Left stroke 90.1 (22) Right stroke 97.4 (22) — no significant difference Seizures (outside of the neonatal period) Stroke n=17, 50% (missing data for 5 subjects)
Centr	ral nervous systen	Identified through from clinical referrals. All confirmed by neuroimaging. Severity rated on 5-point scale adapted from Vargha-Khadem et al.)×.	
38	Bedford	Population	Outcomes	Neuromotor disability
	2001 ⁴² England & Wales Prospective cohort	All gestational ages included Born 1985-1987 Exposure (n=274) Neonatal meningitis Comparison (n=1391) Matched on age and sex Recruited through GP Ascertainment/ definition Identified through clinician reporting	Neuromotor disability (composite) Cognitive Hearing Vision Behaviour Seizure disorder Assessment/ measurement Parental questionnaire GP questionnaire McIntyre et al. classification of disability severity Follow-up S years S5-94% follow-up	Meningitis, n=45, 16% No meningitis, n=2, 0.1% Severe disability Meningitis, n=20, 7% No meningitis, n=10, 11% Moderate disability Meningitis, n=50, 18% No meningitis, n=20, 1% Mild disorder Meningitis, n=66, 24% No meningitis, n=275, 20% No disability Meningitis, n=138, 50%
39	Horváth- Puhó 2021 ⁴³ Denmark and Netherlands Retrospective matched cohort study	Population Gestation not specified Born 1997-2017 Exposure GBS meningitis (Denmark) (n=168) GBS meningitis (Netherlands) (n=198) Comparison Randomly selected Matched 1:10 on sex, birth year and month, and gestation No GBS (Denmark) (n=13,689) No GBS (Netherlands) (n=4,983) Ascertainment/ definition Invasive Group B Streptococcal disease by 89 days of age (most were neonatal — hence inclusion) ICD 10 codes (Denmark) CSF culture positive on national laboratory register (Netherlands)	Outcomes Neurodevelopmental impairment (composite) Cognitive Motor Behavioural, mental and social disorders Hearing impairment Visual impairment ICD 10 codes Follow-up Denmark 5 years, 7 years, 10 years, 15 years Netherlands 5 years, 7 years, 10 years and 11 years Signal of the property of the prope	No meningitis, n=1095, 79% Any neurodevelopmental impairment RR (95%CI) 5 vears Denmark GBS meningitis 7·80 (4·42-13·77) Netherlands GBS meningitis 5·30 (2·57-10·89) 7 vears Denmark GBS meningitis 4·69 (2·78-7·89) Netherlands GBS meningitis 3·71 (1·05-6·72) 10 vears Denmark GBS meningitis 3·47 (2·19–5·50) Netherlands GBS meningitis 2·81 (1·69-4·68) 11 vears Netherlands GBS meningitis 2·99 (1·83-4·88) 15 vears Denmark GBS meningitis 3·15 (1·82–5·46) Moderate to severe neurodevelopmental impairment RR (95%CI) 5 vears Denmark GBS meningitis 8·49 (4·28-16·86) Netherlands GBS meningitis 5·13 (2·24-11·79) 7 vears Denmark GBS meningitis 5·27 (2·80-9·92) Netherlands GBS meningitis 3·88 (2·15-6·99) Netherlands GBS meningitis 3·38 (1·77-6·33) 11 vears Netherlands GBS meningitis 3·34 (1·77-6·33)
40	Martinez- Cruz 2008 ⁴⁵	Population Gestation < 34 weeks Birthweight <1500g	Outcomes • Sensorineural hearing loss	Meningitis Sensorineural hearing loss: n=15; 10.3% No Sensorineural hearing loss: n=7; 2.6%

	Movies	Dama 1000 2005	Assassment/ massurement	Odds of provious populated manifestic if several translations to
41	Mexico Retrospective case control Stevens 2003 ⁴⁴ England & Wales Prospective cohort study	Born 1990-2005 Exposure (n=22) Neonatal meningitis Comparator (n=374) No meningitis Ascertainment/ definition Meningitis not defined Population Term born infants Born 1985-1987 Exposure (n=111) Meningitis Comparison (n=162) Matched on hospital of birth, birthweight and sex Hospital control (n=113) GP control (n=49) Ascertainment/ definition CSF positive culture	Assessment/ measurement Brainstem Auditory Evoked Potentials Transient Auditory Evoked Otoacoustic Emissions Tympanometry Free Field Audiometry Pure tone audiometry Behavioural hearing evaluation Follow-up T-11 years Diosability and functional impairment (composite) Cognitive Motor Wision Hearing Assessment/ measurement WISC-III Movement ABC Blinded examination Hearing screening Sonksen-Silver acuity system Follow-up 9-10 years 67% follow-up of meningitis group	Odds of previous neonatal meningitis if sensorineural hearing loss OR 4.368, 95% CI (1.7, 10.9) p= 0.002 Cognitive IQ, mean (95% CI) Meningitis, 88.8 (85, 92) Hospital control, 99.4 (97, 102) GP control, 99.6 (95, 103) Motor mABC score, mean (95% CI) Meningitis 7.1 (5.9, 8.5) Hospital control 5, 9.4 (3, 5.8) GP controls 4.0 (2.9, 5.4) Severe disability/ functional impairment Meningitis, n=12, 10.8% Hospital control, n=0, 0% GP control, n=0, 0% GP control, n=0, 0% Moderate disability/ functional impairment Meningitis, n=19, 17.1% Hospital control, n=2, 1.8% GP control, n=0, 0% Mild disability/ functional impairment Meningitis, n=19, 17.1% Hospital control, n=3, 11.5% GP control, n=8, 16% No disability or functional impairment Meningitis, n=70, 63.1% Hospital control, n=98, 86.7% GP control, n=98, 86.7% GP control, n=941, 84%
				Hospital control, n=98, 86.7%
				Visual impairment (unilateral) Meningitis, n= 10, 9.9% (6 unassessed because of their disability) Hospital control, n=8, 7% GP control, n=2, 4% Seizures outside of the neonatal period Meningitis, n=6, 5.4% Hospital control, n=2, 1.8% GP control, n=0, 0%
Нурс	oxic-ischaemic enc	ephalopathy		
42	3383 Koc 2016 ²⁴ Turkey Retrospective cohort	Population Gestation < 32 weeks Birthweight < 1500g Porn 2001 Exposure (n=9) Perinatal asphyxia Comparator (n=81) No asphyxia Ascertainment/ definition Perinatal asphyxia diagnosed on: fetal pH, Apgar score, and neonatal cerebral and multiorgan dysfunction	Outcomes Cognitive Assessment/ measurement WISC-R Performed by blinded psychologist Follow-up 5-8 years 100% follow-up	Cognitive WISC-R IQ Score (combined verbal and performance scores) <85 Perinatal asphyxia n=8, 89% No asphyxia n=24, 30% p=0.001
43	Lee-Kelland 2019 ⁴⁶ * United Kingdom Retrospective cohort study	Population • Gestation ≥ 36 weeks • Born 2008-2010 Exposure (n=29) • Moderate-severe HIE without subsequent cerebral palsy Comparator (n=20) • Matched on age, sex and social class • Born without HIE Ascertainment/ definition • Received therapeutic hypothermia based on TOBY trial criteria	Outcomes Cognitive Motor Speech and language Behaviour Assessment/ measurement WISC IV (blinded) Movement ABC 2 Strengths and difficulties questionnaire Follow-up 6-8 years 61% follow-up	Cognitive Full scale IQ, mean (SD) HIE 91 (10.37) No HIE 105 (13.41) Mean difference –13.62 95% CI (-20.53 to –6.71) p<0.001 Perceptual reasoning, mean (SD) HIE 89 (11.15) No HIE 103 (12.49) Mean difference –13.9 95% CI (-20.78 to –7.09) p<0.001 Working memory, mean (SD) HIE 94 (13.76) No HIE 102 (13.82) Mean difference –8.2 95% CI (-16.29 to –0.17) p=0.04



Supplement 4: Risk of bias table

overlapping data; Clinical Evaluation of Language Fundamentals (CELF); Cystic Periventricular leukomalacia (cPVL); Intelligence Quotient (IQ); Intraventricular haemorrhage (IVH); Mental Developmental Index (MDI); Neonatal Intensive Care Unit (NICU); Psychomotor Development Index (PDI); Periventricular leukomalacia (PVL); Spontaneous Intestinal Perforation (SIP); Wechsler Intelligence Scale for Children (WISC); White Matter Injury (WMI);

Preterm brain injury: cohort studies

		Selection (*satisfactory; No =not satisfactorily done; n/a) Comparability (*satisfactory; No =not satisfactorily done; n/a) Exposure/ Outcome (*satisfactory; No =not satisfactorily done; n/a) Subtotal assessment					Total score: 0-3 high risk of bias; 4-6 moderate Additional comments							
	1	2	3	4	1a	1b		2	3	Selection (0- 1=Poor; 2=Fair; 3+ Good)	Comparabil ity (0=poor; 1=fair; 2+=good)	Exposure / outcome (0=poor; 1=fair; 2+=good)	risk of bias 7-9 low risk of bias	
Adant 2019	No	*	*	* (excluded those with congenital anomalies)	*	*	No	*	No	Good	Good	Fair	6	Population not representative as focus of study was spontaneous intestinal perforation. Infants without IVH didn't have brain injury excluded per se (but didn't have IVH 3-4 on imaging). Matched on gender, gestational age, date of birth. Multiples matched to sibling without SIP. Excluded those with necrotising enterocolitis, mechanical obstruction or congenital anomalies. Adjusted for gender, gestation, birthweight, SIP and IVH. Independent outcome assessment but not blinded; telephone survey of parents. High numbers lost to follow-up. Table 3 contains errors with respect to outcomes (MDI and PDI mislabelled as motor and cognitive respectively).

Brouwer 2012 No No * * (given the types of outcomes assessed) **Tair** **Tair** **Poor** **Good** **Good** **Tair** **Poor** **Tair** **Poor** **Good** **Tair** **Poor* **Good** **Tair** **Tair** **Poor* **Good** **Tair** **Tair** **Poor* **Good** **Tair** **Tai	Beaino 2010#	*	*	No	* (cerebral palsy could not be present at birth)	Xe.	* ク ₂	*	*	*	Good	Good	Good	8	3% of infants did not have a cranial ultrasound, a further 11% had only one cranial ultrasound during neonatal period - therefore ascertainment of exposure may be compromised Model A adjusted for:
Total by parcits and cachers		No	No	*	of outcomes	No	No	No	*	· C	Fair	Poor	Good	4	clear description of those lost to follow-up and no significant differences with respect to ultrasound brain injury findings between groups Study of a select group i.e. those with IVH requiring neurosurgical intervention. No description of setting, how patients were enrolled, how many were excluded No description of how control group was derived, or what era they were from. Only some infants (those <30weeks) were matched on gestation, birthweight, sex to controls. Different intelligence tests used at follow-

Campbell 2021	*	*	*	* (given the types of outcomes assessed)	*	*	*	*	No	Good	Good	Good	8	Males and those born at 23-24 weeks gestation were overrepresented in the IVH WMI group. Adjusted for gestation, birthweight Z score, sex, maternal education, bronchopulmonary dysplasia, sepsis, necrotising enterocolitis (Bell stage 2-3) and severe retinopathy of prematurity.
Cheong 2018	*	*	*	No (visual or hearing impairment could be congenital)	*	*	*	*	*	Good	Good	Good	8	Adjusted for era of birth, antenatal corticosteroid exposure, inborn status, gestation, sex, multiple birth, birthweight Z score, surfactant use, IVH grade 3 or 4 (in cPVL), cPVL (in IVH grade 3-4), bronchopulmonary dysplasia, postnatal corticosteroid use, necrotising enterocolitis (stage 2 or worse), surgery in the newborn period, and retinopathy of prematurity (stage 3 or worse).
Chou 2020	*	*	*	* (given the types of outcomes assessed)	No	*	*	*	No	Good	Fair	Good	7	Matched and adjusted for, urbanisation and parental occupation. No information about missing data or completeness of follow-up
											'C/	101	ν _C	No information about missing data or completeness of follow-up

Davidovite h 2020	*	*	*	* (given the types of outcomes assessed)	No	*	*	*	No	Good	Fair	Good	7	Only low birthweight infants included (therefore birthweight partially accounted for). Unmatched. No information about excluding brain injury from comparators e.g. comparing those with IVH grade 3-4 to those without could include those with IVH 1-2; both groups could also include infants with other types of brain injury. Missing data not presented or accounted for. Adjusted the composite brain injury group (which included retinopathy of prematurity in its definition) for gestation, maternal diabetes, small for gestational age, year of birth, bronchopulmonary dysplasia, and receipt of postnatal steroids.
Doyle 2000 #	*	*	*	* (given the types of outcomes assessed)	No	No	*	*	*	Good	Poor	Good	7	IVH and no IVH groups not matched for gestation or birthweight, no adjustment for these variables appears to have been done. Relatively old cohort (most did not receive surfactant), comparator group only includes infants born in the 1980s. Not representative due to time-period of care.
Hintz 2018	*	*	*	* (given the types of outcomes assessed)	*	*	*	*	*	Good	Good	Good	9	Assessed interobserver reliability of central imaging readers. Unmatched Adjusted for gestation, race, sex, multiple gestation, maternal education, sepsis, bronchopulmonary dysplasia, postnatal steroids, surgery for patent ductus arteriosus, necrotising enterocolitis, retinopathy of prematurity. Only 83% follow-up of survivors but those lost to follow-up are accounted for.

Hirovonen 2017	*	*	*	* (given the types of outcomes assessed)		*	*	*	*	Good	Good	Good	9	Excluded infants who died at <1 year of age, infants with major congenital anomalies, and those with missing data. Characteristics of those with brain injury not presented. No breakdown by severity of brain injury because that level of detail was not available in the database. No matching but there is stratification by gestation and adjustment for: maternal characteristics, pregnancy characteristics, delivery characteristics, sex, gestation, birthweight, Apgar score at 1-minute, umbilical artery pH, resuscitation provided, NICU admission, receipt of phototherapy, ventilator requirement, antibiotic receipt, respiratory distress syndrome, sepsis, seizures, hyperbilirubinaemia.
Hollebrand se 2021	*	*	*	* (given the types of outcomes assessed)	*	*	*	*	*	Good	Good	Good	9	Gestation similar across all groups and other baseline perinatal characteristics similar across groups. Preterm brain injury and no brain injury group not matched. Unclear if IVH and no IVH group had other brain injuries excluded or may have had more than one injury type (e.g. PVL). Impact of epoch/ era of birth explored and adjusted for.
Hreinsdotti r 2018	*	*	*	No (visual impairment could have been congenital)	*	*	*	*	No	Good	Good	Good	7	Unsure if comparator group in logistic regression includes those with IVH 1-2. Adjusted for gestation, birthweight, retinopathy of prematurity, sex, cognitive score, cerebral palsy.

Jansen 2020	*	*	*	* (given the types of outcomes assessed)	No	No	*	*	No	Good	Poor	Good	6	Excluded infants with congenital abnormalities, metabolic disorders or neonatal meningitis.
Kaur 2020	*	*	*	No (visual or hearing impairment could be congenital)	No	No	*	*	No	Good	Poor	Good	5	Unmatched. Compared IVH with all infant without haemorrhage (of all gestations).
Kiechl- Kohlendorf er 2013	*	*	*	* (given the types of outcomes assessed)	*	*	*	No	No	Good	Good	Fair	7	Low numbers of infants included. Outcomes assessed at 1 year - likely not long enough for robust assessment of neurodevelopmental outcomes; <85% follow-up and no detailed description of those lost to follow up - though authors do state that there were no significant differences between those followed up and those lost to follow up.
Klebermass -Schrehof 2012	*	*	*	No (could have had congenital blindness)	*	*	*	*	No	Good	Good	Good	7	Adjusted for gestation. No clear description of number lost to follow-up, though mentions that follow-up rate at 5.5 years was 54-61%.
Koc 2016	*	*	No	* (given the types of outcomes assessed)	No	No	*	*	No	Good	Poor	Good	5	Small numbers included. No breakdown of characteristics of those with brain injury. No description of IVH grading used or schedule of ultrasound exams; no description of criteria for establishing perinatal asphyxia, number lost to follow-up not stated.
														7/1
Neubauer 2008	*	n/a	*	No (deafness or blindness could have been congenital)	*	*	*	*	*	Fair	Good	Fair	7	Neurodevelopmental assessors not blinded; follow-up rate <85% but paper does give description of those lost to follow-up

Piris Borregas 2019	*	*	*	* (excluded infants with congenital malformations)	No	No	*	*	No	Good	Poor	Good	6	Only those followed up to 7 years included. Excluded infants who died before 36 weeks corrected age, with major malformations, or those with missing data. Unclear if independent odds ratio includes adjustment for covariates. Unclear if those without 'severe brain injury' had other types of brain injury.
Pittet 2019	*	*	*	* (excluded infants with congenital malformations)	No	* //	*	*	*	Good	Fair	Good	8	Excluded infants with congenital malformations affecting neurodevelopment and infants from centres without 5 years of follow-up cognitive testing. Unclear if other types of brain injury excluded from comparator group. Adjusted for gender and socioeconomic status. No significant difference in cognitive outcome between extreme preterms and those 28-30 weeks' gestation. Gestation not adjusted for.
Sherlock 2005#	*	*	*	No (deafness or blindness could have been congenital)	No	No	*	*	*	Good	Poor	Good	6	Comparability of IVH vs. no IVH cohorts not clear - not enough information to determine if groups were comparable with respect to gestational age or birthweight
Tymofiyev a 2018	*	*	*	* (given the types of outcomes assessed)	No	No	*	*	No	Good	Poor	Good	6	Excluded infants with congenital malformations/ syndromes, congenital infections, or those who were too unstable for MR imaging. The last exclusion criteria in particular could limit generalisability quite considerably. Unclear about the validity of grouping the attention scores across different assessment tools together into a dichotomous variable for attention.

Van De Bor 2004	*	*	*	* (excluded those with major congenital malformations)	*	*	No	No	*	Good	Good	Fair	7	IVH vs. no IVH cohorts comparable with respect to gestation; some differences in gender composition but paper states this was controlled for in the analysis. Primary outcome entirely self-reported. Outcomes reported at 14 years.
Van Den Hout 2000	* (exce pt for HIE expo sure grou p)	*	*	* (excluded those with congenital anomalies)	No	No	*	*	*	Good	Poor	Good	7	Low numbers and relatively old cohort. Relative gender imbalance in IVH group compared to those with normal scans or PVL. IVH group also 1.4 weeks more premature than 'normal scan' group.
Vollmer 2003#	*	*	*	No (deafness or blindness could have been congenital)	*	No	*	*	*	Good	Fair	Good	7	Note change in version of Weschler scale during follow-up period. Authors state no difference in mean IQ after change. Baseline characteristics of groups with and without brain injury not given; no indication of matching or adjustment for factors other than gestation.
Vollmer 2006a#	*	*	*	No (deafness or blindness could have been congenital)	*	*	*	*	*	Good	Good	Good	8	Note gender imbalance in cohort as a whole (M>F), but male: female ratio in each group appears similar. No matching or adjustment for covariates. <85% follow-up but clear description of those lost and appears no significant differences.
Vollmer 2006b#	*	*	*	No (deafness or blindness could have been congenital)	No	No	*	*	No	Good	Poor	Good	5	Marked gender imbalance in ventricular dilatation group. Lower birthweight and gestation in groups with abnormal cranial ultrasound. No indication of matching or adjustment. <85% follow-up and the limited description of those lost to follow-up indicates that these babies were of lower birthweight and gestation.

Whitaker 2011	*	*	*	* (given the types of outcomes	*	*	(No)	*	*	Good	Good	Good	8	Severely disabled survivors (n=33) were excluded.
				assessed)										Half had later ultrasounds (just before discharge).
				06										No breakdown of the characteristics of the exposed and comparator groups – unable to assess how comparable they are.
				1) Fig	Y e	クォ								Adjusted for: maternal social risk, sex, gestation, fetal growth ratio, multiplicity, maternal smoking status, maternal alcohol status, labour onset, presentation at birth, base excess on first postnatal blood gas, thyroid status, hypocapnia, hypoxia, systolic hypotension, prolonged ventilation.
						• •	9/	/.						Primary outcome assessment reliant on parental report, albeit via structured interview with some evidence for validity. Interviewers were blinded to the child's history. Parents were blinded to the study hypothesis.
														Less than 85% follow-up (psychiatric interviews in 51% of survivors) however clear descriptions of groups with and without psychiatric evaluation given in table 2 and little apparent difference between groups.
Preterm bra	in injury	: case-co	ontrol stu	ıdies										
	Case defin ition	Repr esent ative ness of cases	3 Selection of controls	4 Definition of controls	1a	1b	Ascerta inment of exposu re	Sam e meth od of ascer tain ment for cases and contr ols	3 Non- respo nse rate	(0- 1=Poor; 2=Fair; 3+ Good)	y (0=poor; 1=fair; 2+=good)	(0=poor; 1=fair; 2+=good)	Total score: 0-3 high risk of bias; 4-6 moderate risk of bias 7-9 low risk of bias	Additional comments

Martinez- Cruz 2008 (IVH)	*	*	*	*	*	No	*	*	No	Good	Fair	Good	7	Appears to be case-control design hence star ratings are as per case control rating sheet. Controls not well matched for birth weight. No description of whether full information on exposures could be obtained for all cases/controls e.g. missing records etc.
Perinatal stro	Selecti		sfactory;	No =not	Compa (*satis: No =no satisfac done; r	ctorily	Exposure (*satisfacto	tory; No	=not	Subtotal as	sessment		Total score: 0-3 high risk of bias; 4-6 moderate risk of bias	Additional comments
	1	2	3	4	1a	1b	6)	2	3	Selection (0- 1=Poor; 2=Fair; 3+ Good)	Comparabil ity (0=poor; 1=fair; 2+=good)	Exposure / outcome (0=poor; 1=fair; 2+=good)	7-9 low risk of bias	
Ballantyne 2007	No	No	*	*	No	*	No	*	No	Fair	Fair	Fair	4	No description of derivation of exposed cohort - whether single institute or multicentre, whether same community as non-exposed group or not. Predominance of right-handed children amongst controls otherwise similar baseline characteristics. Note male preponderance in exposed group and female preponderance in non-exposed No matching or adjustment for confounders. No description of who performed outcome assessment, whether blinded and independent.
Ballantyne 2008	*	*	*	No	No	*	*	*	No	Good	Fair	Good	6	Excluded children with brain lesions from other causes e.g. head trauma, tumours

				つから										Gestational age of exposed cohort ranged from 32 to 40 weeks. No statement as to whether control group were matched on this. Note preponderance of males in stroke group and females in control group. In study 1, significant numbers of participants did not complete the planned developmental assessments - across exposed and control groups, completeness ranged from 50% for WISC-R to 69% for CELF-R.
Gold 2014	No	No	*	*	No	*	*	*	*	Fair	Fair	Good	6	No description of how subjects were selected or recruited from neurology clinics. Nonexposed group selected from a different source. No description of gestational age of subjects or of controlling for this. Matched for age at follow up, sex, socioeconomic group and maternal education.
									C					Excluded infants with bilateral lesions, a history of hypoxic ischemic encephalopathy, central nervous system infection, in-utero drug exposure, significant closed head injury, or any other condition that might have caused brain damage other than from the stroke.
Kolk 2011	*	*	*	*	No	*	*	*	No	Good	Fair	Good	7	No description of gestational age of subjects or of controlling for this. Difficult to ascertain completeness of follow-up from paper. Adjusted for age of outcome assessment.
Martin 2019	*	*	*	*	No	*	*	*	*	Good	Fair	Good	8	Excluded infants with bilateral lesions, hearing impairment, or a history of a problem that may have caused more global brain damage (e.g. meningitis, closed head injury, hypoxic-ischemic encephalopathy). Matched on age, sex and socioeconomic status

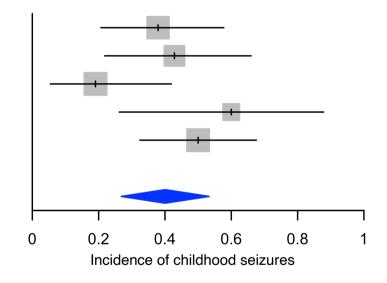
Northam 2018	*	No	*	*	*	*	*	*	*	Good	Good	Good	8	No description of source of unexposed cohort. Matched on age, sex, and maternal education.
Tillema 2008	*	*	*	*)///:-	No	*	*	*	No	Good	Fair	Good	7	Exposed and comparator groups not matched for gestation, but were matched for age, sex and handedness. 17 subjects included initially but 7 of these excluded for various reasons meaning that neurodevelopmental outcome data/Weschler scores only presented for 10 of 17.
Trauner 2013	*	*	*	*	No	No	No	*	No	Good	Poor	Fair	5	Excluded infants if bilateral or multifocal lesions identified, history of meningitis, or history of antenatal drug exposure Matched on age and socioeconomic status No baseline characteristics given to establish comparability of exposed and comparator cohorts. Likely comparable with regards to gestation based on stated inclusion criteria. Main outcome measure based on parental questionnaire - no direct linguistic assessments done, however may not have been feasible/appropriate in such a young cohort. No information on response rate/loss to follow-up. IQ used as covariate IQ combined across the age range and assessed with two different tools. This assumes IQ is fixed which may not be true.

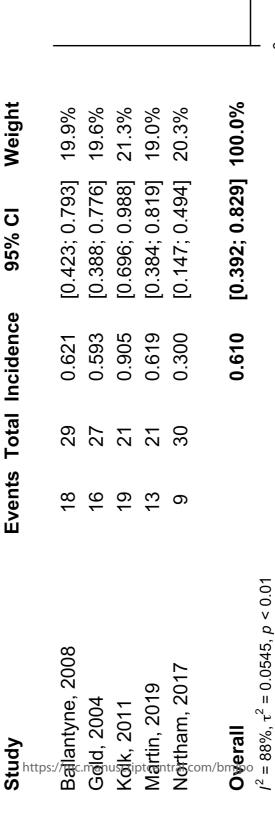
		on (*satis		No =not		ctorily	Exposure (*satisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactorsatisfactors	tory; No	=not	Subtotal ass	sessment		Total score: 0-3 high risk of bias; 4-6 moderate risk of bias 7-9 low risk of bias	Additional comments
	1	2	3	4	la	1b	1	2	3	Selection (0- 1=Poor; 2=Fair; 3+ Good)	Comparabil ity (0=poor; 1=fair; 2+=good)	Exposure / outcome (0=poor; 1=fair; 2+=good)		
Bedford 2001#	*	*	*	No	*	*	No	*	*	Good	Good	Good	7	Matched on sex and age. Study focuses on meningitis in infancy but also presents outcomes after neonatal meningitis. Did not exclude children with other comorbidities e.g. congenital conditions associated with neurodevelopmental impairment. Exposed cases derived from same cohort as Stevens 2003. Outcome assessment based on parent or GP report with no formal neurodevelopmental assessment.
Horváth- Puhó 2021	*	*	*	No	*	*	*	*	*	Good	Good	Good	8	Invasive Group B Streptococcal infection diagnosed in the first 89 days (however most of these were neonatal, particularly in the first week of life (45%) hence inclusion. Matched 1:10 on sex, birth year and month, and gestation. Neurodevelopmental impairment defined differently in each cohort. Missing data accounted for and its impact explored.

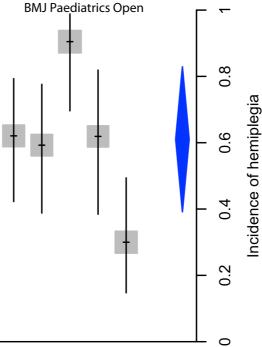
Stevens 2003#	(*)	(*)	* ions: case	No se control studies	*	*	*	*	No	Good	Good	Good	7	Exposed cohort based on recall of consultant paediatricians filling out monthly returns thus may be biased towards more severe or otherwise memorable cases. Some in comparator group selected from a different hospital than exposed cohort. Matched on hospital of birth, birth weight and sex. Results stratified by birthweight Significant rate of loss to follow-up.
	Case defin ition	Repr esent ative ness of cases	3 Selection of controls	4 Definition of controls	la	16	Ascerta inment of exposu re	Sam e meth od of ascer tain ment for cases and contr ols	3 Non- respo nse rate	(0- 1=Poor; 2=Fair; 3+ Good)	y (0=poor; 1=fair; 2+=good)	(0=poor; 1=fair; 2+=good)	Total score: 0-3 high risk of bias; 4-6 moderate risk of bias 7-9 low risk of bias	Additional comments
Martinez- Cruz 2008	*	*	*	*	No	No	*	*	No	Good	Poor	Good	6	Excluded those with history of parental consanguinity or TORCH infections. Number of those with and without meningitis who may have had other types of brain injuries not specified – unable to assess overlap/ impact of meningitis alone. Odds ratio presented for meningitis does not appear to be crude so potential adjustment for confounding factors but no description of this in the methods section. No description of proportion of missing data.

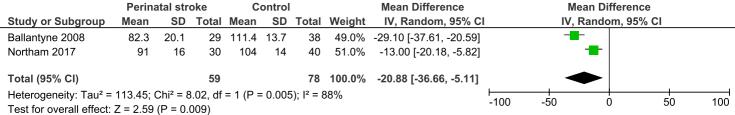
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Koc 2016	No	*	*	*	No	No	*	*	No	Fair	Poor	Good	5	Representativeness not clear as no description given of babies who did not complete follow-up at the study institution. No apparent adjustment for gestation or other covariates. Pre-therapeutic hypothermia era. Small number, no breakdown of characteristics or other neurodevelopmental outcomes by brain injury Number of those with and without birth asphyxia who had other types of brain injuries e.g. IVH not specified.
Lee- Kelland 2019	No	*	*	*	*	*	*	No	No	Good	Good	Good	6	Excluded those who underwent therapeutic hypothermia outside of the standard criteria, infants with metabolic disorders and non-English speaking infants. Matched on age, sex and social class.
Tonks 2019	*	No	*	*	No	*	*	*	No	Good	Fair	Good	6	Included cases had no diagnoses other than encephalopathy. Excluded infants with neurological issues other than encephalopathy. Matched on age, sex and socioeconomic status.

13 14 Study	Events	Total	Incidence	95% CI	Weight
15 16					
¹⁷ Ballantyne, 2008	11	29	0.379	[0.207; 0.577]	22.2%
18 19 Kolk , 2011	9	21	0.429	[0.218; 0.660]	19.0%
²⁰ ₂₁ Martin, 2019	4	21	0.190	[0.054; 0.419]	23.1%
²² Tilema, 2008	6	10	0.600	[0.262; 0.878]	12.5%
²³ ²⁴ Trauner, 2001	17	34	0.500	[0.324; 0.676]	23.1%
25 26					
²⁷ ₂₈ Overall			0.401	[0.268; 0.533]	100.0%
$\frac{^{29}}{^{30}}I^2 = 56\%, \tau^2 = 0.0124, \rho = 0.06$				- · · · •	









0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6		Perinata	al stro	aka.		ontrol			Mean Difference		M	ean Differer	nce.	
7	Study or Subgroup	Mean			Mean		Total	Weight	IV, Random, 95% CI			Random, 95		
8 -	Ballantyne 2008	78.4	16	29			38		-27.40 [-34.34, -20.46]			F		
9	Northam 2017	95	17	30	108	13	40	49.7%	-13.00 [-20.30, -5.70]			-		
U 1	Total (95% CI)			59			78	100.0%	-20.25 [-34.36, -6.13]		<			
1 2 3	Heterogeneity: Tau ² = 9 Test for overall effect: 2			5, df =	1 (P =	0.005);				-100	-50	0		100
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School-age outcomes of children after perinatal brain injury: a systematic review and meta-analysis

Philippa Rees¹ MPhil MBBCh, Caitriona Callan² MB BChir, Karan R Chadda³ MB BChir, Meriel Vaal MRes MBChB¹, James Diviney⁴ MB BChir, Shahad Sabti⁵ MBBS, Fergus Harnden⁶ MBChB, Julian Gardiner¹PhD, Cheryl Battersby⁷ PhD, Chris Gale⁷ PhD, Alastair Sutcliffe¹ PhD

Affiliations:

- 1. Population Policy and Practice, Great Ormond Street UCL Institute of Child Health, London, UK.
- 2. Nuffield Department of Primary Care Health Sciences, University of Oxford.
- 3. Department of Paediatrics, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.
- 4. Paediatric Intensive Care Unit, Great Ormond Street Hospital, London, UK
- 5. Kings College London, UK.
- 6. Chelsea and Westminster Hospital NHS Foundation Trust, London, UK.
- 7. Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London, London, UK.

Address correspondence to: Dr Philippa Rees, Population Policy Practice, UCL Institute of Child Health, 1st Floor 30 Guilford Street, London, WC1N 1EH, p.rees@ucl.ac.uk

School-age outcomes of children after perinatal brain injury: a systematic review and meta-analysis

Background

Over 3,000 children suffer a perinatal brain injury in England every year according to national surveillance. The childhood outcomes of infants with perinatal brain injury are however unknown.

Methods

A systematic review and meta-analyses were undertaken of studies published between 2000-September 2021 exploring school-aged neurodevelopmental outcomes of children after perinatal brain injury compared to those without perinatal brain injury. The primary outcome was neurodevelopmental impairment which included cognitive, motor, speech and language, behavioural, hearing, or visual impairment after 5 years of age.

Results

This review included 42 studies. Preterm infants with intraventricular haemorrhage (IVH) grade 3-4 were found to have a three-fold greater risk of moderate-severe neurodevelopmental impairment at school age OR 3.69 (95%CI: 1.7, 7.98) compared to preterm infants without IVH. Infants with perinatal stroke had an increased incidence of hemiplegia 61% (95%CI: 39.2, 82.9) and an increased risk of cognitive impairment (difference in full scale IQ -24.2 (95%CI: -30.73, -17.67) . Perinatal stroke was also associated with poorer academic performance; and lower mean receptive -20.88 (95%CI: -36.66, -5.11) and expressive language scores -20.25 (95%CI: -34.36, -6.13) on the CELF assessment. Studies reported an increased risk of persisting neurodevelopmental impairment at school age after neonatal meningitis. Cognitive impairment and special educational needs were highlighted after moderate-severe HIE. However, there were limited comparative studies providing school-aged outcome data across neurodevelopmental domains and few provided adjusted data. Findings were further limited by the heterogeneity of studies.

Conclusions

Longitudinal population studies exploring childhood outcomes after perinatal brain injury are urgently needed to better enable clinicians to prepare affected families, and to facilitate targeted developmental support to help affected children reach their full potential.

School-age outcomes of children after perinatal brain injury: a systematic review and meta-analysis

What is already known on this topic

Thousands of children suffer a brain injury around the time of birth every year. Many of these injuries are associated with neurodevelopmental impairment at two years of age. However, two-year outcomes are not necessarily representative of later childhood outcomes and function, which are a priority for parents.

What this study adds

This review provides an overview of existing evidence of childhood outcomes after perinatal brain injury. It indicates that there is some evidence of on-going impairment throughout childhood for different types of perinatal brain injury but that there are considerable gaps in knowledge.

How this study might affect research, practice or policy

t research, p. for detailed high-s, nes after perinatal bran. This review shows the need for detailed high-quality longitudinal population studies exploring childhood outcomes after perinatal brain injury

School-age outcomes of children after perinatal brain injury: a systematic review and meta-analysis

Perinatal brain injuries can have wide-ranging deleterious consequences for children, families and broader society.(1-4) Over 3,000 infants experience perinatal brain injury in England annually¹ and the Department of Health and Social Care (DHSC) has committed to halving the rate of perinatal brain injuries by 2030 as part of the national maternity ambition.(5) To monitor progress towards this goal, a standardised definition of perinatal brain injury was developed.(6) The degree to which this definition captures and represents true perinatal brain injuries is unclear and requires us to look beyond the neonatal period.(6)

Focusing on the childhood outcomes of infants with perinatal brain injury provides a fuller understanding of the population captured by the DHSC definition. Despite their importance to families, school-age outcomes following neonatal care have been an overlooked research priority. Neonatal studies typically focus on two-year composite outcomes which may mask the true neurodevelopmental burden of injuries, and are known to be poorly predictive of future functioning.(7-10) As such, our understanding of childhood developmental trajectories after brain injuries – and whether any sequelae are fixed, stable or amenable to interventions – is limited. We therefore undertook a systematic review to explore school-age neurodevelopmental outcomes following perinatal brain injury.

METHODS

Study selection

The review was conducted as per the pre-registered protocol (CRD 42021278572) and the PRISMA statement.(11) We included observational comparative studies exploring neurodevelopmental outcomes of children over five years of age after perinatal brain injury, published between 2000-September 2021 (Table 1). The DHSC definition of perinatal brain injuries used includes intraventricular haemorrhage, preterm white matter injuries, stroke, central nervous system infection, hypoxic ischaemic encephalopathy, and kernicterus diagnosed during the neonatal period.(6, 12) We did not include seizures in isolation. For inclusion, studies were required to have a non-brain injured comparator group. The primary outcome was neurodevelopmental impairment; secondary outcomes included motor, cognitive, speech and language, behavioural and neuropsychological, visual and hearing outcomes and seizures.

A search strategy incorporating 99 key terms and mesh headings was developed in Medline Ovid, adapted and run across 10 databases. Snowballing techniques were used to augment search sensitivity (Supplement 1 & 2). All titles were screened independently by two reviewers. The full-texts of all potentially relevant titles were retrieved, reviewed and their risk of bias assessed by two trained reviewers independently (PR, CC, MV, JD, SS). Disagreements were arbitrated by a third reviewer.

Data extraction and synthesis

Studies were stratified by brain injury type, sub-stratified by age of outcome assessment and outcome type, and summarised in a narrative synthesis. Where sufficient suitable data were available from contextually and clinically comparable studies, data were pooled in random

effects meta-analyses using RevMan 5.4. Continuous data were pooled using the inverse variance method; dichotomous data were pooled using the Mantel-Haenszel method; and analysis data from studies which did not provide raw data were pooled with dichotomous data from other studies using the generic inverse variance method.(13) Where studies provided insufficient comparative data for a particular outcome, the combined incidence figures for that outcome within the brain injured population was calculated across studies using the Fisher exact test for binomial data.(14) Statistical heterogeneity was assessed using the I² statistic and substantial heterogeneity (>85%) was explored further in sub-group analyses.

Quality assessment

The Newcastle Ottawa Tool was used to assess risk of bias across three domains: population selection, the comparability of the 'brain injured' and 'non brain injured' comparator groups, and outcome assessment.(15) Studies were classed as poor, fair, or good for each domain and given an overall risk of bias classification.

Patient and Public Involvement

Patients or the public were not involved in the design or conduct of this review. However the review's findings will be used to shape the larger CHERuB study in partnership with our parent advisory panel.

RESULTS

Searches identified 14,210 records and 42 studies were included (Figure 1). Studies focused on intraventricular haemorrhage (n=27), white matter injury (WMI) amongst preterm infants (n=15), perinatal stroke (n=8), neonatal meningitis (n=4), and HIE (n=3); these were not mutually exclusive (Supplement 3). Most studies were undertaken in the USA (n=10), the UK (n=8), the Netherlands (n=5) or Australia (n=4). These were prospective (n=27) or retrospective cohort studies (n=14). Included studies were deemed to be moderate (n=17) or low risk of bias (n=27) (Supplement 4).

Preterm injuries

The 29 studies exploring outcomes after IVH or WMI mostly included infants born <32 weeks' gestation (n=22) after the year 2000 (n=18) (Supplement 3). Most studies confirmed injury on ultrasound or MRI imaging (n=22) these were reviewed by radiologists (n=6), neonatologists (n=3) or both (n=1); 14 studies used the Papile classification; only 2 studies stratified results by laterality.

Nine studies explored neurodevelopmental impairment at 5-14 years of age after preterm brain injury including IVH (n=9) and WMI (n=6).(16-24) Two comparable studies highlighted a considerably increased pooled crude risk of moderate-severe neurodevelopmental impairment after IVH grade 3-4 at 8 years of age OR 3.69 (95%CI: 1.7, 7.98; 2 studies) $I^2 = 0\%$ (Figure 2, Table 2).(18, 21)

Six studies explored motor outcomes after IVH grade 3-4: they consistently highlighted an increased risk of motor impairment at 5-12 years of age.(21, 24-28) Additionally, two

comparable studies reported an 8-fold increased crude risk of cerebral palsy after IVH grade 3-4 OR 8.13 (95%CI: 4.64, 14.22; 2 studies; 1,557 subjects) *I*²=0% (Figure 3).

Cognitive outcomes at school-age after preterm brain injuries were reported by 16 studies using 25 different cognitive assessment tools - limiting the potential for meta-analysis (Supplement 3).(16, 17, 21, 22, 24-35) Educational outcomes were reported by 5 studies.(21, 22, 26, 30, 35)

Studies consistently reported lower cognitive scores at school-age following IVH grade 3-4. (16, 21, 22, 25-27, 31, 35) Hollebrandse 2021 reported an increased risk of cognitive impairment at 8 years of age OR 2.68 (95%CI: 1.21, 5.94).(26) Van de Bor 2000 and Hollebrandse 2021 reported that the cognitive impact of IVH grade 3-4 affected educational needs.(22, 26) Van de Bor 2000 reported increased special educational needs at 5, 9 and 14 years: the adjusted risk at 14 years of age was marked, aOR 3.99 (95%CI: 1.36, 11.69).(22) Studies reported no significant differences in language scores after IVH grade 3-4.(21, 22) However, an association with reading OR 3.62 (95%CI: 1.59, 8.24), spelling OR 4.48 (95%CI: 1.8, 11.2), and arithmetic OR 2.79 (95%CI: 1.2, 6.48) impairment was demonstrated.(26) Most studies highlighted cognitive effects after WMI.(17, 30, 33, 35)

Studies exploring behavioural outcomes after IVH 3-4 did not find any associations with attention deficits, conduct issues or autism spectrum disorder (Table 2).(16, 25, 36)

However, there was conflicting evidence around the mental health effects of WMI.(17, 37)

Studies exploring hearing impairment after IVH and/or WMI were small or not comparable. 10 studies explored visual impairment after IVH or WMI, 4 provided meaningful outcome data.(16, 21-23, 27, 28, 33, 34, 38, 39) An increased prevalence of visual impairment after IVH grade 3-4 (45.4% and 90.9%) compared to controls (7.5%) was reported in addition to significantly lower visual motor integration scores.(27)

Perinatal stroke

Eight comparative studies explored school-age outcomes after perinatal stroke, these included 177 children with perinatal stroke (100 left-sided and 54 right-sided – not all studies specified laterality) and 232 comparator children (Supplement 3).(40-47) Infants' gestation age was largely unspecified. Five studies presented a combined incidence of childhood seizures after perinatal stroke of 40.1% (95%CI: 26.8-53.3%; 5 studies; 115 subjects) I^2 =56% (Supplement 5).(40, 43, 44, 46, 47) The combined incidence of hemiparesis after perinatal stroke was 61% (95%CI: 39.2, 82.9 I^2 =88%). There was considerable heterogeneity across studies, and likely detection bias (Supplement 6).(40, 42-45)

Five studies identified a significant combined mean difference in full scale IQ scores at 7-13 years of age after perinatal stroke: -24.2 (95%CI: -30.73, -17.67; 5 studies; 296 subjects) I^2 =80% (Figure 4).(40, 42, 45-47) There was heterogeneity across studies in terms of assessment timing, assessment tools, and combining those with left and right-sided strokes.

Differences in stroke laterality partially explained the heterogeneity. The combined mean difference in full scale IQ following left-sided strokes was -26.01 (95%CI: -29.1, -22.93; 2 studies; 113 subjects) I^2 =0%; compared to -26.7 (95%CI: -39.38. -14.02; 2 studies; 99

subjects) I^2 =76% for right-sided strokes. No significant differences in cognitive outcomes were found by laterality.(40, 42, 45-47)

Kolk 2011 reported significantly lower scores across all NEPSY domains other than executive function after perinatal stroke, including attention, visuo-spacial function, memory, and learning.(43)

Two studies presented educational outcomes after perinatal stroke. Although Northam 2018 found that most children with perinatal stroke were in mainstream education (n=28, 93%), they also highlighted that additional educational support was often required (n=12, 40%). This was in keeping with Ballantyne 2008 reporting lower mean scores for reading (85 (16.1) vs. 113 (13.3); p<0.0001), spelling (82.5 (18.2) vs. 106.2 (15.9) p=0.001) and arithmetic (91.5 (10.2) vs. 111.9 (11.2) p<0.0001) after perinatal stroke compared to controls at 7-8 years of age, persisting on re-assessment at 10-12 years.

Kolk 2011 reported significantly lower scores compared to controls across most NEPSY language domains following perinatal stroke. (43) Significantly lower receptive and expressive mean language scores on the CELF assessment were also reported across studies: -20.88 (95%CI: -36.66, -5.11; 2 studies; 137 subjects) I^2 =88% and -20.25 (95%CI: -34.36, -6.13; 2 studies; 137 subjects) I^2 =87% respectively (Supplement 7, 8). (40, 45) Statistical heterogeneity may have been as a result of studies combining left and right-sided strokes and the varying age of outcome assessment. Studies highlighted that deficits in receptive language scores present at 7-8 years persisted at 10-12 years but that expressive language scores improved (p=0.012). (40, 41)

Meningitis

Studies consistently reported an increased risk of neurodevelopmental impairment after neonatal meningitis (Table 2).(48-50) An increased likelihood of neuromotor disability at 5 years of age (n=45/274, 16%) compared to controls (n=2/1391, 0.1%) was reported (Supplement 3).(48) On re-assessment of the same population at 9-10 years, this increased risk of severe disability persisted (n=12, 10.8% compared to n=0, 0%).(50) An increased risk of any neurodevelopmental impairment at 5 years after neonatal *Group-B Streptococcal* meningitis was also reported in the Netherlands, RR 5.30 (95%CI: 2·57-10·89), and in Denmark, RR 7.80 (95%CI: 4·42-13·77).(49) This increased risk persisted on subsequent assessment: at 11 years of age in the Netherlands, RR 2.99 (95%CI: 1.83, 4.88) and at 15 years of age in Denmark RR, 3.15 (95%CI: 1.82, 5,46).(49)

Hypoxic-ischaemic encephalopathy

Two comparative studies (of the same cohort) explored outcomes of term-born infants with moderate-severe HIE, but without cerebral palsy, at school age (Supplement 3).(51, 52) They highlighted significantly lower full scale IQ scores after HIE (mean difference –13.62 (95%CI: –20.53 to –6.71)).(51) This difference in cognition was also seen for perceptual reasoning, working memory, and processing speed. Children with HIE were also more likely than controls to receive additional classroom support: OR 10 (95%CI: 1.16, 86) although the confidence interval for this risk estimate was wide.(51) Children with HIE (without cerebral palsy) also had significantly lower motor scores (mean difference –2.12 (95%CI: –3.93, –0.30)) and verbal comprehension scores (mean difference –8.8 (95%CI: –14.25, –3.34)).(51) They were also noted to have higher behavioural difficulty scores especially for emotional problems.(51)

DISCUSSION

This review brings together the existing evidence on the later childhood outcomes of infants with perinatal brain injury. Although 42 studies are included, small study populations, limited data on injury severity and laterality, and the heterogeneity of outcome measures limited the potential power of results. However, studies demonstrate a three-fold higher risk of moderate-severe neurodevelopmental impairment at school age following IVH grade 3-4. Studies consistently report cognitive impairment after IVH grade 3-4 but suggest that speech and language is relatively preserved. A higher risk of hemiplegia, cognitive impairment and poorer academic performance after perinatal stroke is reported in addition to poorer receptive and expressive language scores. Studies report a higher risk of persisting neurodevelopmental impairment after neonatal meningitis – however few studies address this question. Few comparative studies explore school-age outcomes after HIE.

In following our a priori protocol only comparative studies were included. This was with a view to enabling inferential analyses and adjustment for key confounders such as gestation. Unfortunately due to this strict inclusion criterion many pertinent non-comparative studies were excluded. Additionally our searches were conducted in September 2021, more recent studies would therefore have been missed.

Heterogeneity in terms of outcomes assessed, outcome assessment tools, and timing of outcome assessment limited the comparability of studies and the potential for meta-analyses. Several meta-analyses included low numbers of studies, reducing the reliability of the I² statistic.(53) This review was also limited by the size of available studies and how studies presented data for extraction. Few studies presented adjusted data or explored childhood trajectories after perinatal brain injury.

Previous reviews were limited by a lack of comparable studies, heterogeneity, the inclusion of much older cohorts, or by including non-comparative studies.(4, 54-56) Whilst this review was also limited by studies' heterogeneity and the quality of available data, new and important findings - for example the risk of neurodevelopmental impairment - at school age after IVH 3-4 were identified. Our finding of a higher risk of cerebral palsy after IVH and motor impairments after preterm brain injuries is echoed by previous studies.(54, 55, 57)

Lynch 2001 highlighted that 60% of infants have neurological sequelae that emerge over time following perinatal stroke. This was in-keeping with our findings of a higher risk of hemiparesis, cognitive impairment, and speech and language impairment. (58) Several non-comparative population-based studies also mirror these findings. (59-62)

Although previous reviews highlight an increased risk of various neurodevelopmental impairments after neonatal meningitis in early childhood – we are unaware of any focusing on school-age outcomes after neonatal meningitis.(4, 63)

The review's findings of potential on-going impairments across cognitive, speech and language, and behavioural domains - in addition to a need for increased school support – after HIE are mirrored by other studies.(64-68) Shankaran 2012 and Azzopardi 2014 highlight ongoing neurodevelopmental sequelae at school age amongst children who received therapeutic hypothermia for moderate-severe HIE.(64, 65, 67)

Implications

Considerable gaps in the evidence are highlighted, particularly around the risk of specific outcomes following different types of injury, the precision around risk estimates, the impact of different factors (such as injury laterality), and the developmental trajectories of these children. This information is key to prepare families for the future, inform enhanced developmental surveillance, and enable targeted multidisciplinary support to help affected children to reach their full potential. As such, this review highlights a pressing need for high-quality, comparative studies which use the 'Core Outcomes In Neonatology' to explore long-term outcomes after perinatal brain injury and permit future meta-analyses.(10) Additionally, to meet the DHSC ambition to reduce perinatal brain injury, real-time longitudinal population data, extending beyond the neonatal period to childhood, are necessary as the current definition is limited to 'indicators' of injury from the neonatal period. This could be achieved through linkage of existing population datasets within the UK.

CONCLUSION

This review provides an overview of existing evidence of the impact of perinatal brain throughout childhood. Studies' heterogeneity significantly limited the potential for evidence synthesis.

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Contributors' statement

Dr Rees conceptualised and designed the review, reviewed and appraised studies, undertook data extraction and synthesis, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Callan conceptualized and designed the review, designed and oversaw the search strategy, reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Chadda reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Vaal reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Diviney reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Sabti reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Harnden reviewed and appraised studies, undertook data extraction, and reviewed and revised the manuscript.

Dr Gardiner was the lead statistician for the review, he advised on and oversaw the data analysis, and reviewed and revised the manuscript.

Dr Battersby oversaw and supervised the review and critically revised the manuscript for important intellectual content.

Professor Gale oversaw and supervised the review and critically revised the manuscript for important intellectual content.

Professor Sutcliffe oversaw and supervised the review and critically revised the manuscript for important intellectual content.

All authors approve the final manuscript as submitted and agree to be accountable for all aspects of the work.

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- Figure 1: PRISMA flow diagram
- Figure 2: Crude risk of neurodevelopmental impairment at 8 years of age after IVH grade 3-4
- Figure 3: Crude risk of cerebral palsy after IVH grade 3-4
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 ed mean difference in IQ score.

 aroke Figure 4: Pooled mean difference in IQ scores at 7-13 years between those with and without

perinatal stroke

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Inclusion Criteria	Exclusion Criteria
Peer-reviewed observational studies (cohort, case-	Non-comparative studies; opinions; commentaries;
control, cross-sectional)	reviews; case-reports; lab studies
Studies in all languages	Studies where the population includes adults and children and the data for children cannot be extracted
Studies published after 2000	Studies focused on children with IVH grade 1-2, neonatal seizures, hypoglycaemic brain injury, or neonatal abstinence syndrome
Children with a diagnosis of brain injury occurring at or around the time of birth (including during the neonatal period) as defined by the DHSC (including those with any white matter injury but not including those with isolated seizures)	Studies which include infants with brain injuries diagnosed during the neonatal and infancy period where most were diagnosed outside of the neonatal period
Studies including infants with moderate to severe HIE born in the post therapeutic hypothermia era (i.e. where infants received therapeutic hypothermia)	Studies including infants with moderate-severe HIE born during the pre-therapeutic hypothermia era or in low- or middle-income countries that do not offer therapeutic hypothermia
Studies focused on school-aged neurodevelopmental	Studies of infants with mild HIE

Primary outcome(s):

including:

Neurodevelopmental impairment, as defined by authors (including direct testing, clinical record review, and parental interview/ survey)

outcomes (of children between 5-18 years of age)

Secondary outcome(s):

- 1. Any cognitive impairment, as defined by authors (direct testing)
- 2. Mild cognitive impairment (intelligence or developmental quotient 1-2 standard deviations below the mean)
- 3. Moderate-severe cognitive impairment (intelligence or developmental quotient more than 2 standard deviations below the mean)
- 4 Executive dysfunction, as defined by authors (direct testing)
- 5. Low numeracy, as defined by authors (by direct testing or educational achievement tests)
- 6. Low literacy, as defined by authors (by direct testing or educational achievement tests)
- 7. Special educational needs as defined by authors (school or parental report)
- 8. Motor impairment, as defined by authors (including direct testing, clinical record review, and reporting)
- 9. Visual-motor impairment, as defined by authors (on direct testing)

- 10. Emotional-behavioural difficulty, as defined by authors (including direct testing, clinical record review, and parental reporting
- 11. Speech and language impairment, as defined by authors (on direct testing)
- 12. Visual impairment, as defined by authors (including direct testing, clinical record review, and parental reporting)
- 13. Hearing impairment, as defined by authors (including direct testing, clinical record review, and parental reporting)
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 and wn. 14. Epilepsy/seizures, as defined by authors (including medical history taking, clinical record review and parental reporting

Studies reporting outcomes for children diagnosed with

Studies where comparable outcome data from those with and without perinatal brain injury cannot be extracted

Table 2: Overview of key findings for school-age outcomes of infants with perinatal brain injury compared to those without brain injury (*Does not include studies where infants with IVH grade 3-4 cannot be separated from those with WMI or those with IVH 1-2) (# Does not include studies using hearing or visual outcomes only as part of their composite outcome)

Adjusted Odds Ratio (aOR); Attention Deficit Hyperactivity Disorder (ADHD); Autism Spectrum Disorder (ASD); Confidence Interval (CI); cystic periventricular leukomalacia (cPVL); Group B Streptococcus (GBS); Hypoxic-Ischaemic Encephalopathy (HIE); Hazard Ratio (HR); Intelligence Quotient (IQ); Interquartile range (IQR); Intraventricular Haemorrhage (IVH); Odds Ratio (OR); Periventricular Leukomalacia (PVL); Visual Motor Integration (VMI); White Matter Injury (WMI)

	NDI	Cognitive	Motor	Speech and language	Behavioural	Hearing#	Vision#	Other
VH grade 3-	6 studies(15, 17-21)	9 studies(15, 20, 21, 24-26, 30, 70)	6 studies(20, 23-26, 33)	3 studies(20, 21, 25)	3 studies(15, 24, 35)	3 studies(21, 26, 38)	5 studies(15, 21, 26, 33, 38)	
		y 11	Not comparable	Not comparable	Not comparable	N	N	
	2 comparable studies in	Not comparable	All reported increased risk of	Van de Bor 2004: no	Brouwer 2012: no	Not comparable	Not comparable	
	meta-	Consistently highlighted	motor impairment	significant difference in	association with any	Outcome too rare	Outcome to rare for	
	analysis(17,	lower cognitive scores		language scores	behavioural domains	for inferential	inferential analysis	
	20)	_	Cerebral palsy		assessed (internalising,	analysis	in most studies.	
		Brouwer 2012: significantly	3 comparable studies	Sherlock 2005: downward	externalising and sleep	Y 2020		
	Meta-analysis (2 studies):	lower performance IQ but preserved verbal IQ. Lower	OR 8.67 (95%CI: 5.27, 14.28)	trend in language scores from no brain injury to	problems)	Kaur 2020: increased risk of	Adant 2019: no increased risk of	
	Increased risk	IO for those with IVH grade	P=0%.	each grade of IVH but not	Adant 2019: no	hospitalisation for	visual impairment	
	of	4 requiring neurosurgery		statistically significant	increased risk of	otologic reasons	(needing glasses)	
	moderate -	(91+/-10 vs. 98+/-15) but		p=0.12	attention deficits,	HR	aOR 0.47 (95%CI:	
	severe	little difference for those			conduct issues or ASD	7.87 (95%CI:	0.13, 1.69)	
	neurodevelop mental	with grade 3 IVH requiring neurosurgery (96+/-15 vs.		Hollebrandse 2021: Increased risk of impaired	aOR 1.24 (95%CI: 0.32,	5.31, 11.67)	Klebermass-	
	impairment	98+/-15).		reading OR 3.62 (95%CI:	4.8).		Schrehof 2012:	
	OR 3.15	30.7 13).		1.59, 8.24), and spelling	Davidovich 2020: no		increased prevalence	
	(95%CI: 1.67,	Hollebrandse 2021:		OR 4.48 (95%CI: 1.8,	increased risk of ASD		of visual impairment	
	$5.92) I^2 = 0\%$	increased risk of cognitive		11.2)	(n=10, 3.9% vs. n=103,		(needing glasses or	
	V d- D	impairment OR 2.68			2.2% p=0.085)		blindness) after IVH	
	Van de Bor 2004:	(95%CI: 1.21, 5.94). Increased risk of academic					grade 3 (45.4%) and IVH grade 4	
	increased	impairment across all					(90.9%) vs.	
	prevalence of	academic domains:					comparators (7.5%).	
	disability	reading OR 3.62 (95%CI:					Kaur 2020:	
	31% vs. 16%	1.59, 8.24);					increased risk of	
		spelling OR 4.48 (95%CI: 1.8, 11.2);					hospitalisation for	
		arithmetic OR 2.79)95%CI:					ophthalmic reasons	
		1.2, 6.48)					HR 7.87 (95%CI:	
							5.31, 11.67).	
		Sherlock 2005: significantly					Klebermass-	
		lower IQ scores after IVH					Schrehof 2012:	
		grade 4 vs. IVH 1-3 and no brain injury, also seen for					significantly lower	

	several domains: freedom from distractibility, processing speed, reading, spelling and arithmetic. No difference in executive function. Van de Bor 2004: increased special education needs at 5, 9 and 14 years aOR 3.99 (95%CI: 1.36, 11.69).					VMI scores (67.5 ± 14 vs. 76 ± 26.8; p=0.04)	
WMI* 3 studies(16, 17, 22) Not comparable Campbell 2021: living with no impairment was less common with WMI (n=12, 40%) vs. controls (n=487, 76%) Cheong 2018: increased risk of survival with major disability after cPVL aOR 9·17 (95%CI: 3·57, 23·53) Vollmer 2003: Disabling impairments were more common after cPVL at<28 weeks' gestation (n=3, 75% <28	mathematics tests (B 1.856 p=0.003), but not performance on spelling (B 1.076 p=0.075) or reading tests (B 0.241 p=0.483)	Cerebral palsv 1 study(16) Campbell 2020: increased risk of cerebral palsy aOR 18.63 (95%CI: 7.37, 47.06)	Jansen 2020: No association between WMI and spelling (B 1.076 p=0.075) or reading performance (B 0.241 p=0.483)	4 studies(16, 35, 36, 71) Not comparable Conflicting results Campbell 2021: No increased risk of: ADHD (n=3, 10% vs. n=97, 15%); anxiety (n=3, 10% vs. n=98, 15%); depression (n=7, 23% vs. n=100, 16%); or ASD aOR 0.74 (95%CI: 0.09, 5.88) Davidovich 2020: No increased risk of ASD after PVL (n=5, 2.5% vs. n=88, 2.3% p=0.86) Whitaker 2011: increased risk of ADHD aOR 6.83 (95%CI: 1.26-36.91); major depression aOR 2.59 (95%CI: 1.02-6.58); tic disorders aOR 9.77 (95%CI: 1.69-56.47); obsessive compulsive disorders aOR 15.32 (95%CI: 1.82-128.74)	0 studies	1 study(32)	

	weeks) vs. controls (n=3, 8%) and at over 28 weeks' gestation (n=6,50% vs. n=14, 6%)							
Stroke	0 studies	6 studies(39, 41, 42, 44-46) 5 comparable studies in meta-analysis (39, 41, 44-46) Meta-analysis (5 studies): significant mean difference in full scale IQ: -24.2 (95%CI: -30.73, -17.67) P=80% Trauner 2001 and Gold 2014: no significant difference in full scale IQ scores in left vs. right-sided strokes Ballantyne 2008: significantly lower performance IQ (p=0.002) and verbal IQ (p<0.0001). Lower mean scores for reading (p<0.0001) and arithmetic (p<0.0001) and arithmetic (p<0.0001) at 7-8 years persisting to 10-12 years	5 studies(39, 41-44) Combined hemiparesis incidence: 61% (95%CI: 39.2, 82.9 <i>P</i> =88%) Kolk 2011: moderate to severe neuromotor impairment in 62% n=13) and significantly lower scores on 5/6 sensorimotor domains of the NEPSY	5 studies(39, 40, 42, 44, 45) 3 comparable studies in meta-analysis Meta-analysis (3 studies): lower receptive language scores-20.88 (95%CI: - 36.66, -5.11) I²=88% and lower expressive language scores -20.25 (95%CI: -34.36, -6.13) I²=87% Ballantyne 2007 and Ballantyne 2008: deficits in receptive language scores at 7-8 years persist at 10-12 years but expressive language scores improved (p=0.012) particularly for children with right-sided strokes (p=0.034)	1 study(46)	1 study(43) Martin 2019: left-sided strokes predispose children to contralateral auditory neglect and right-sided strokes predispose children to bilateral auditory neglect	l study(39) Ballantyne 2008: visual field defects are common (n=7, 26%) after perinatal stroke	Seizures 8 studies(39 42, 43, 45 46) 5 comparab studies(39 42, 43, 45 46) Combined incidence of seizure: 40.1% (95%CI: 26.8, 53.3 I^2 =56%
		Tillema 2008: reduced verbal IQ scores (mean 84 SD 13.4) vs. (mean 108 SD 14.2 P=0.002) Kolk 2011: poorer attention (across 4 of the 7 assessment sub-domains), visuo-spacial function (across 4 of the 5 sub-domains), and memory and learning (across 4 of the 6 sub-domains), but normal executive function scores.		Kolk 2011: significantly lower scores for 8/9 NEPSY domains including phonologic processing, comprehension of instructions, correct speeded naming, repetition of nonsense words, verbal fluency (semantic and phonetic), oromotor sequences, and sentence comprehension		クケ		

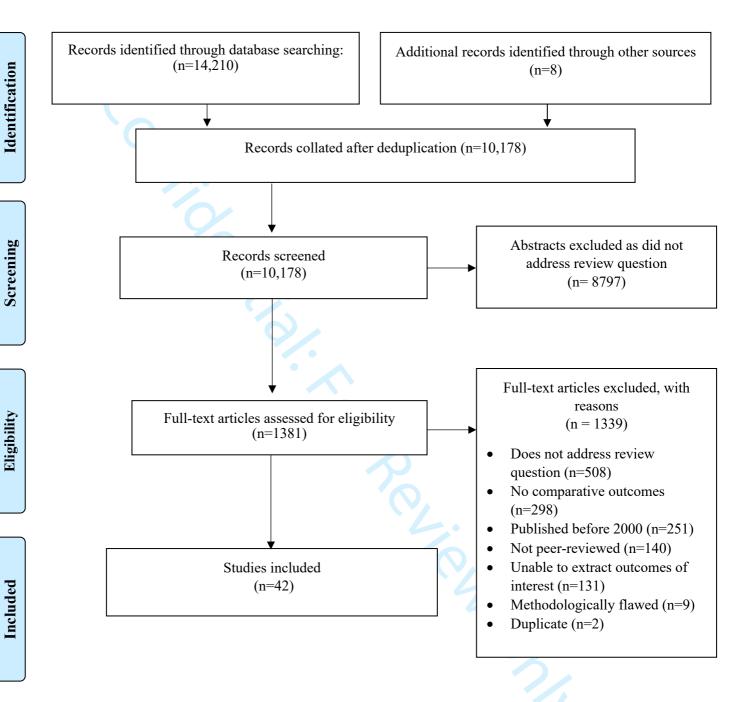
		Those with left-sided strokes had poorer neuropsychological scores. Northam 2018: most children are in mainstream education (n=28, 93%) but many require additional support (n=12, 40%)						
Meningitis	3 studies(47-49) Not comparable All reported increased risk of neurodevelop mental impairment Bedford 2011: increased prevalence of neuromotor disability (n=45, 16% vs. n=2, 0.1%) Stevens 2003: Risk of severe disability seen in Bedford 2011 at 5 years of age persisted until 9-10 years (n=12, 10.8% vs. n=0, 0%) Horvath- Puho 2021: increased risk of any neurodevelop mental impairment	Stevens 2003: significantly lower mean cognitive scores (mean 88.8 (95%CI: 85, 92) vs. mean 99.4 (95%CI: 97, 102))	1 study(49) Stevens 2003: significantly higher motor impairment scores (mean 7.1 (95%CI: 5.9, 8.5) vs. mean 5 (95%CI: 4.3, 5.8))	0 studies	0 studies	Martinez Cruz 2008: increased odds of neonatal meningitis amongst preterm infants with sensorineural hearing loss OR 4.37 (95%CI: 1.7, 10.9 Stevens 2003: 3.6% (n=4) had hearing loss compared to none in the control group.	Stevens 2003: Bilateral visual impairment was common after neonatal meningitis (n=18, 17%)	

THE	meningitis in the Netherlands RR 5.30 (95%CI: 2·57, 10·89) and Denmark RR 7.80 (95%CI: 4·42, 13·77) at 5 years of age persisting to 11 years in the Netherlands RR 2.99 (95%CI: 1.83, 4.88) and 15 years in Denmark RR 3.15 (95%CI: 1.82, 5,46)	3 ctudies (30, 50, 51) (two of	2 studies/50, 51) (of the same	2 studies(50, 51) (of the	2 studies(50, 51) (of the	0 studies	0 studies	
HIE	0 studies	3 studies(30, 50, 51) (two of the same population) Not comparable Koc 2016: preterm infants with HIE significantly more likely to have below average IQ scores (n=8, 89% vs. n=24, 30% p=0.001) Lee-Kelland 2020 and Tonks 2019: report lower full scale IQ scores after moderate to severe HIE (mean difference –13.62 (95%CI: –20.53, –6.71)) and poorer perceptual reasoning, working memory and processing speed. Children with previous HIE more likely to receive additional classroom support OR 10 (95%CI: 1.16, 86)	2 studies(50, 51) (of the same population) Lee-Kelland 2020 and Tonks 2019: significantly lower motor scores (mean difference -2.12 (95%CI: -3.93, -0.30)) after moderate-severe HIE (for children without cerebral palsy)	2 studies(50, 51) (of the same population) Lee-Kelland 2020 and Tonks 2019: significantly lower verbal comprehension scores (mean difference –8.8 (95%CI: –14.25, –3.34)) after moderate-severe HIE.	2 studies(50, 51) (of the same population) Lee-Kelland 2020 and Tonks 2019: higher behavioural difficulty scores (median score 12 IQR (6.5, 13.5 vs. median score 6 IQR (2.25, 10) p=0.005)	U studies	U studies	
Kernicterus				0 studies				

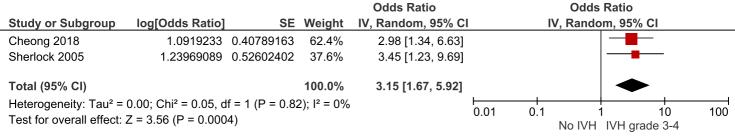




PRISMA 2009 Flow Diagram







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6	Study or Subgroup	Events		Events		Weight	M-H, Random, 95% CI			lom, 95% CI	
7	Beaino 2010	9	38	46	1153	38.5%	7.47 [3.34, 16.69]		,		
.8	Hollebrandse 2021	15	35	26	331	40.9%	8.80 [4.03, 19.19]				
9	Sherlock 2005	8	18	12	179	20.6%	11.13 [3.71, 33.41]				-
0	5.1.5.1.5.1.X 2 .5.5	· ·				_0.070					
1	Total (95% CI)		91		1663	100.0%	8.67 [5.27, 14.28]			•	
2	Total events	32		84							
3	Heterogeneity: Tau ² =		= 0.33, d		0.85);	$I^2 = 0\%$		0.01 0	 	<u> </u>	
4	Test for overall effect: 2				,,			0.01 0		i 10 IVH grade 3-4	100
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5			atal str			strok			Mean Difference	_			Differen		
5 -	Study or Subgroup	Mean			Mean			Weight	IV, Random, 95% C	l		IV, Ran	dom, 95	% CI	
7	Ballayntyne 2008	94.7	20.4	29	123	15	38	18.2%	-28.30 [-37.12, -19.48]						
8	Gold 2014	88	4	27	117	2.7	19	26.6%	-29.00 [-30.94, -27.06]			•			
9	Northam 2017	99	14	30	112	16	40	20.7%	-13.00 [-20.05, -5.95]				-		
<u></u>	Tilema 2008	80	14.1	10		11.7	10		-28.00 [-39.36, -16.64]						
1	Trauner 2001	93.4	22	39	116.2	13	54	19.7%	-22.80 [-30.53, -15.07]						
I	T (1 (050/ O1)			405			404	400.00/	04 00 1 00 70 47 071						
2	Total (95% CI)			135					-24.20 [-30.73, -17.67]	1					
3	Heterogeneity: Tau ² =				= 4 (P =	0.000)5); l² =	80%		-100	-50		0	50	100
4	Test for overall effect:	Z = 7.26	(P < 0.0)	00001)											
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Supplement 1: databases searched

Cochrane Central Register of Controlled Trials

EBSCO-CINAHL (Cumulative Index to Nursing and Allied Health Literature)

Google Scholar

Ovid-EMBASE

Ovid-MEDLINE

Ovid-MEDLINE E-pub ahead of print

Ovid-MEDLINE In-Process and Other Non-Indexed Citations

PubMed

Scopus

1 Index Expande. Web of Knowledge (Science Citation Index Expanded and Conference Proceedings Citation Index Science)

Supplement 2: Medline Ovid Search Strategy

- 1. exp CHILD/
- 2. exp Child, Preschool/
- 3. exp ADOLESCENT/
- 4. exp INFANT/ or exp INFANT, NEWBORN/
- 5. (child* or toddler* or baby or infant* or adolescent*).mp.
- 6. 1 or 2 or 3 or 4 or 5
- 7. exp Educational Status/
- 8. exp Child Development/
- 9. exp Learning Disorders/
- 10. exp Educational Measurement/
- 11. exp SCHOOLS/
- 12. exp Academic Performance/
- 13. school performance.mp.
- 14. exp COGNITION/
- 15. exp LEARNING/
- 16. exp SPATIAL LEARNING/
- 17. exp VERBAL LEARNING/
- 18. exp SOCIAL LEARNING/
- 19. exp Intelligence Tests/
- 20. exp INTELLIGENCE/
- 21. exp Intellectual Disability/
- 22. exp Neurodevelopmental Disorders/
- 23. neurodevelopm*.mp.
- 24. (nervous system dys* or CNS dys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 25. (nervous system abnorm* or CNS abnorm*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 26. (nervous system malform* or CNS malform*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 27. (nervous system dis* or CNS dis*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 28. (mental health condi* or mental health dis*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 29. mental health outcome.mp.
- 30. behaviour* abnorm*.mp.
- 31. cognitive impairment.mp. or exp Cognitive Dysfunction/
- 32. visual impairment.mp. or exp Vision Disorders/
- 33. visual develop*.mp.
- 34. (visual dis* or visual dys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

- 35. (nystagmus or strabismus).mp.
- 36. (visual acuity or refractive error*).mp.
- 37. hearing impairment.mp. or exp Hearing Loss/
- 38. exp Deafness/
- 39. exp DEAF-BLIND DISORDERS/
- 40. exp Hearing Loss, Sensorineural/
- 41. exp Movement Disorders/
- 42. exp Cerebral Palsy/
- 43. motor impairment.mp.
- 44. (seizure* or convulsi*).mp.
- 45. exp EPILEPSY/ or epilepsy.mp.
- 46. exp Executive Function/
- 47. visual-motor impairment.mp.
- 48. numeracy.mp.
- 49. literacy.mp. or exp LITERACY/
- 50. jaundice.mp.
- 51. exp Language Development Disorders/ or exp Child Language/ or language impairment.mp. or exp Reading/ or exp Dyslexia/ or reading impairment.mp.
- 52. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
- 53. 49 or 50 or 51
- 54. 52 or 53
- 55. exp JAUNDICE, NEONATAL/
- 56. exp JAUNDICE/
- 57. exp Hyperbilirubinemia, Neonatal/
- 58. exp Hyperbilirubinemia/
- 59. hyperbilirubin*.mp.
- 60. exp Hyperbilirubinemia, Hereditary/
- 61. bilirubin encephalopathy.mp.
- 62. bilirubin-induced neuro*.mp.
- 63. exchange transfusion.mp.
- 64. exp ASPHYXIA NEONATORUM/
- 65. (exp ASPHYXIA/ or asphyxia.mp.) and neonat*.mp.
- 66. exp Hypoxia-Ischemia, Brain/ and neonat*.mp.
- 67. perinatal asphyxia.mp.
- 68. birth asphyxia.mp.
- 69. (hypoxic-ischemic encephalopathy or hypoxic-ischaemic encephalopathy).mp.
- 70. neonatal encephalopathy.mp.
- 71. (exp Cerebral Hemorrhage/ or exp Intracranial Hemorrhages/ or exp Brain Ischemia/ or intracranial haemorrhage.mp. or exp Subarachnoid Hemorrhage/ or exp Stroke/) and neonat*.mp.
- 72. perinatal stroke.mp.
- 73. (central nervous system infection.mp. or exp Central Nervous System Infections/) and neonat*.mp.
- 74. (exp Meningoencephalitis/ or meningo-encephalitis.mp.) and neonat*.mp.
- 75. (MENINGITIS/ or meningitis.mp.) and neonat*.mp.

- 76. exp MENINGITIS, VIRAL/ and neonat*.mp.
- 77. (meningoencephalitis and neonat*).mp.
- 78. (encephalitis.mp. or exp ENCEPHALITIS, VIRAL/ or exp INFECTIOUS ENCEPHALITIS/ or exp ENCEPHALITIS/) and neonat*.mp.
- 79. kernicterus.mp. or exp KERNICTERUS/
- 80. preterm white matter disease.mp.
- 81. (periventricular leukomalacia.mp. or exp Leukomalacia, Periventricular/) and neonat*.mp.
- 82. (therapeutic hypothermia.mp. or exp Hypothermia, Induced/) and neonat*.mp.
- 83. ((subdural haemorrhage or subdural hemorrhage) and neonat*).mp.
- 84. (exp Hematoma, Subdural/ or subdural haemorrhage.mp. or exp Craniocerebral Trauma/) and neonat*.mp.
- 85. (intraventricular haemorrhage and neonat*).mp.
- 86. (tentorial tear and neonat*).mp.
- 87. (parenchymal haemorrhage and neonat*).mp.
- 88. (ventriculoperitoneal shunt.mp. or exp Cerebrospinal Fluid Shunts/ or exp Ventriculoperitoneal Shunt/) and neonat*.mp.
- 89. ((ventricular drain or Rickham reservoir or CSF shunt) and neonat*).mp.
- 90. neonatal stroke.mp.
- 91. (cerebrovascular accident and neonat*).mp.
- 92. neonatal cerebral ischaemia.mp.
- 93. (exp Intracranial Thrombosis/ or cerebral venous thrombosis.mp.) and neonat*.mp.
- 94. (seizure.mp. or exp Seizures/) and neonat*.mp.
- 95. 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94
- 96. exp Cohort Studies/
- 97. exp Retrospective Studies/
- 98. (cohort* or (case\$ and control\$)).tw.
- 99. exp Cross-Sectional Studies/
- 100. exp Randomized Controlled Trial/
- 101. 96 or 97 or 98 or 99 or 100
- 102. exp "REVIEW"/
- 103. exp Case Reports/
- 104. Animals/
- 105. animal stud*.mp.
- 106. 102 or 103 or 104 or 105
- 107. 6 and 52 and 95 and 101
- 108. 107 not 106

Supplement 3: included studies of school-aged outcomes after perinatal brain injury

* overlapping study data; Ω potential error in manuscript; Adjusted Odds Ratio (aOR); Autism spectrum Disorder (ASD); Attention Deficit Hyperactivity Disorder (ADHD); Bayley Scale of Infant Development (BSID); Child Behaviour Checklist (CBCL); Clinical Evaluation of Language Fundamentals (CELF); Cystic Periventricular leukomalacia (cPVL); Gross Motor Function Classification System, (GMFCS); Haemorrhagic parenchymal infarction (HPI); Hazard Ratio (HR); International Classification of Disease (ICD); Intraventricular haemorrhage (IVH); Intelligence Quotient (IQ); Kaufman Assessment Battery for Children (K-ABC); Mental Developmental Index (MDI); Peabody Picture Vocabulary Test (PPVT); Periventricular (PV); Periventricular leukomalacia (PVL); National Institute of Child Health and Human Development (NICHD); Neonatal Intensive Care Unit (NICU); Psychomotor Development Index (PDI); Retinopathy of Prematurity (ROP); Small for Gestational Age (SGA); Spontaneous Intestinal Perforation (SIP); Standard Deviation (SD); Standard Error (SE); Test of Motor Impairment (TOMI); Very low birthweight (VLBW); Visuomotor integration (VMI); Wechsler Abbreviated Scale of Intelligence (WASI); Wechsler Intelligence Scale for Children (WISC); Wechsler Preschool & Primary Scale of Intelligence (WPSI); White Matter Injury (WMI); Wide Range Achievement Test (WRAT)

Author Year	Population Exposures	Outcomes	Main result(s)
Country Study type	Comparator Ascertainment/ definition		
Adant 2019 ⁹ Belgium Retrospective cohort	Population • Gestation ≤32 weeks with and without spontaneous intestinal perforation (SIP) • Born 1994-2014 Exposure (n=19) • IVH grade 3-4 Comparator (n=44) • Matched on gender, gestational age, date of birth (multiples matched to sibling without SIP) • No IVH Ascertainment/ definition • Clinical record review	Outcomes Functional disability (composite) Cognitive Motor Visual Behavioural/ mental health Wellbeing Quality of life Physical health Measurement/ assessment BSID II Telephone survey (parents) PedsQL IQ testing Follow-up 67% follow-up at 7-11 months 41% follow-up at 18-22 months 49% follow-up at 4-10 years 86% follow-up telephone survey	Outcomes of those with SIP compared to controls without SIP – by IVH subgroup Disability aOR 8.79 95%CI (1.72, 44.86) Multiple disabilities aOR 5.97 95%CI (1.61, 22.15) Cognitive Regular education system (not a special educational needs school) aOR 8.73 95%CI (2.1, 36.72) Visual outcomes (wearing glasses) aOR 0.474 95%CI (0.13, 1.69) Behavioural/ mental health disorder (including attention problems, conduct problems and autism spectrum disorders) aOR 1.24 95%CI (0.32, 4.8) PedsQL low quality of life score aOR 0.87 95%CI (0.77, 0.99) PedsQL low physical health score
Beaino 2010 ⁶⁸	Gestation <33 weeks	Outcomes • Cerebral palsy	aOR 0.82 95%CI (0.66, 1.01) Cerebral palsy Grade 3 IVH
France Prospective cohort	Born 1997 Exposure IVH grade 1 (n=173) IVH grade 2 (n=117) IVH grade 3 (n=32) Intraparenchymal haemorrhage (IPH) (n=6) Persistent echodensities or ventricular dilatation (n=241) cPVL (n=66) Comparator (n=1153) Unmatched	Measurement/assessment Standardised questionnaires completed by physicians Follow-up 5 years 77% follow-up	OR 3.75 95%CI (2.41–5.85) Grade 3 IVH or echodensities of ventricular dilatation Model A aOR 3.25 95%CI (2.02–5.22) Model B aOR 3.40 95%CI (2.07–5.60) Model C aOR 3.31 95%CI (2.00–5.48) cPVL OR 33.41 95%CI (19.25–57.96) Cystic PVL or IPH Model A aOR 29.66 95%CI (16.71–52.62) Model B aOR 28.41 95%CI (15.65–51.59) Model C n/a
Brouwer	No IVH Ascertainment/ definition Ultrasound imaging undertaken and reviewed by neonatologists or radiographers Population	Outcomes	Cerebral palsy
Netherlands Prospective cohort	Gestation <32 weeks Born 1999-2004 Exposure (n=32) Post-haemorrhagic ventricular dilatation after IVH grade 3-4 requiring neurosurgical intervention No PVL Comparator (n=23) Matched on gestation, birthweight, and sex No IVH Ascertainment/ definition Ultrasound diagnosis Papile classification	Motor Cerebral palsy Cognitive Behavioural Measurement/ assessment Movement ABC GMFCS WPPSI (3rd edition Dutch version) Revisie Amsterdamse Kinder Intelligentietest Snijders Oomen Nonverbal Intelligence Test 2.5-7 - Revised CBCL Teacher Report Form Follow-up 4-8 years (median 5.7) 97% follow-up	IVH grade 3 n=0 IVH grade 4 n=8, 53%; all unilateral spastic cerebral palsy GMFCS level 1, n=5 GMFCS level 2, n=2 GMFCS level 3, n=1 Movement ABC motor score (for those without cerebral palsy) Score \(\sigma \) 5 (definite motor problems) IVH grade 3 n=6, 26% IVH grade 4 h=3, 13% No IVH n=0 Score p 5-15 (borderline motor function) IVH grade 3 (n=6; 26%) IVH grade 4 (n=0; 0%) No IVH (n=5; 29.4%) Score p> 15 IVH grade 3 n=6, 26% IVH grade 4 n=0, 0%
			No IVH n=12, 70.6% Cognition Wechsler intelligence test (mean ±SD) Verbal scale IVH n=23, 97±13 IVH <30weeks' gestation n=16, 94±13 No IVH n=24, 96±13; Performance scale IVH, n=23, 94±16; IVH <30weeks' gestation n=16, 93±15 No IVH n=24, 103±14;

US Pro	impbell 121 10 SA ospective hort study	Population (n=858) Gestation 23-27 weeks Born 2002-2004 Exposure IVH without WMI (n=124) WMI without IVH (n=30) IVH and WMI (n=63) Comparator (n=641) No IVH or WMI Ascertainment/ definition Ultrasound imaging reviewed by two independent blinded radiologists WMI parenchymal echolucency or moderate to severe ventriculomegaly on a late scan	Outcomes Neurocognitive development (composite) Cognitive Ceptral palsy Behavioural/ mental health Epilepsy Quality of life Measurement/ assessment NEPSY II Neurological exam GMFCS Parental questionnaire Social Communication Questionnaire Child Symptom Inventory 4 Peds QoL 4 Follow up 10 years 74% follow-up	IVH n=23, 87=22; IVH =30weeks' gestation n=16, 85±24 No IVH n=24, 93±14 Intelligence quotrient (n; mean +t/SD) IVH grade 3 n=17; IQ 96±15; IQ=85 n=13 (76.5%) IVH IV n=15; IQ 91±10; IQ=85 n=9 (64.3%) IVH <30 weeks' gestation n=23; IQ 92±17; IQ=85 n=15 (65.2%) IVH <30 weeks' gestation n=23; IQ 92±17; IQ=85 n=17 (74%) IVH =73.10 98±15, IQ=85 n=17 (74%) IVH =73.10 98±15, IQ=85 n=17 (74%) IVH =73.10 98±15, IQ=85 n=17 (74%) IVH =73.10 weeks' gestation =22: 44.3 ±7.8, n=1 (4%) IVH =73.00 weeks' gestation =23: 44.3 ±7.8, n=1 (4%) IVH =30 weeks' gestation =23: 44.3 ±7.8, n=1 (4%) Internalising problem scale IVH: 49.2 ±8.9, n=5 (19%) IVH =30 weeks' gestation: 28.2 ±8.4, n=3 (15%) IVH =30 weeks' gestation: 49.2 ±9.1, n=5 (21%) IVH =30 weeks' gestation: 49.2 ±9.1, n=5 (21%) IVH =30 weeks' gestation: 43.7 ±7.5, n=0 (0%) IVH =30 weeks' gestation: 43.7 ±7.5, n=0 (0%) IVH =30 weeks' gestation: 43.7 ±7.5, n=0 (18%) IVH =30 weeks' gestation: 52.9 ±9.8, n=4 (18%) IVH =30 weeks' gestation: 52.4 ±11.4, n=7 (32%) IVH =30 weeks' gestation:
				Low cognitive function IVH and WMI n=18. 30% WMI n=10, 34%

WMI n=7, 24% IVH n=24, 20% No IVH or WMI n=93, 15% Severe cognitive impairment IVH and WMI n=18, 30% WMI n=7, 24% IVH n=7, 6% No IVH or WMI n=35, 6% Nonverbal IO IVH vs. No IVH or WMI Crude mean difference -3 95%CI (-6.6, 0.6) Full scale IQ IVH vs No IVH or WMI Crude mean difference -2.2 95%CI (-5.7, 1.4) Cerebral palsy IVH and WMI n=32, 51% n=32, 51% OR 16.85 95% CI (9.29, 30.55) aOR 13.43 95% CI (7, 25.78) n=14, 47% OR 14.28 95% CI (6.48, 41.48) aOR 18.63 95% CI (7.37, 47.06) IVH n=9, 7% OR 1.28 95% CI (0.6, 2.72) aOR 1.19 95% CI (0.54, 2.61) No IVH or WMI n=37,6%Reference category GMFCS>0 IVH and WMI n=16, 25% WMI n=10, 33% IVH n=4, 3% No IVH or WMI n=13, 2% Epilepsy IVH and WMI n=12, 19% OR 5.44 95 % CI (2.72, 10.86) aOR 4.89 95% CI (2.31, 10.35) **WMI** n=8, 27%; OR 6.92 95% CI (2.86, 16.75) aOR 7.56 95% CI (2.85, 20.06) n= 11, 9%; OR 1.85 95% CI (0.91, 3.78) aOR 1.5 95% CI (0.68, 3.3) No IVH or WMI Reference category Neuropsychiatric/ behavioural outcomes ASD IVH and WMI n=4, 6% OR 0.97 95% CI (0.34, 2.79) aOR 0.58 95% CI (0.19, 1.77) OR 1.02 95% CI (0.23, 4.42) aOR 0.74 95% CI (0.09, 5.88) IVH n=11, 9% n=11, 9% OR 1.39 95% CI (0.69, 2.78) aOR 1.24 95% CI (0.59, 2.6) No IVH or WMI n=42, 7% Reference category Social responsiveness scale (over 65 among children with IQ >85 excluding those with ASD) IVH and WMI n=5, 8% WMI n=4, 13% IVH n=14, 11% No IVH or WMI n=62, 10% ADHD IVH and WMI n=13, 24% WMI n=3, 10% IVH n=31, 25% OR 1.6 95% CI (1.1, 2.5) No IVH or WMI n=97, 15%

	ı			A system (second seconds)
				Anxiety (parent-reported) IVH and WMI n=6, 10% WMI n=3, 10% IVH n=10, 8% No IVH or WMI n=98, 15%
				Anxiety (teacher-reported) IVH and WMI n=12, 19% WMI n=3, 10% IVH n=14, 11% No IVH or WMI n=88, 14%
				Depression (parent-reported) IVH and WMI n=7, 11% WMI n=7, 23% IVH n=14, 11% No IVH or WMI n=100, 16%
		,0		Depression (teacher-reported) IVH and WMI n=20, 32% WMI n=7 23% IVH n=18, 15% No IVH or WMI n=96, 15%
				Poor quality of life (<70) IVH and WMI n=31, 49% WMI n=12, 40% IVH n=41, 25% No IVH or WMI n=131, 20%
5	Cheong 2018 ¹¹ Australia	Population ■ Gestation 22-27 weeks ■ Born 1991-1992; 1997-1998; 2005-2006	Survival with major disability (composite) Survival without major disability	Survival with major disability IVH grade 3-4 OR 2-98 95% CI (1:34, 6:63) p=0.01 aOR 2-61 95%CI (1:11-6:15) p=0.028
	Three prospective cohort studies	Exposure • IVH grade 3-4 (n=100) • cPVL (n=38)	(composite) Cognitive Cerebral palsy Visual impairment (acuity less than 6/60 in better eye)	1997 and 2005 cohort only: OR 4·01 95% CI (1·25, 12·84) p=0.02 cPVL
		Comparator Unmatched No IVH grade 3-4 (n=446) No cPVL (n=508)	Hearing impairment (requiring hearing aid or cochlear amplification) Assessment/ measurement GMFCS WISC III	OR 8·11 95% CI (3·24, 20·30) p<0.001 aOR 9·17 95% CI (3·57–23·53) p<0·0001 1997 and 2005 cohort only OR 17·0 95% CI (4·19, 69·02) p<0·001
		Ascertainment/ definition Not specified	WISC IV Differential Abilities Scales 2 nd edition Follow-up 8 years 91% follow-up of survivors	
6	Chou 2020 ⁶⁹	Population • Preterms infants <37 weeks' gestation	91% follow-up of survivors Outcome Epilepsy	Epilepsy Preterm with cerebral haemorrhage
	Taiwan Retrospective cohort study	(n=21,474) • Infants born small for gestational age (n=2206) • Born 2000-2010	Assessment/ measurement • ICD 9 Follow-up	HR 42.4 95%CI (29.8, 60.3) aHR 42.5 95 %CI (29.6, 60.5) SGA with cerebral haemorrhage HR 39.3 95%CI (5.51, 274.5)
		Exposure Preterm with cerebral haemorrhage GA with cerebral haemorrhage	2-12 years (mean 9 years) Completeness of follow-up not specified	aHR 38.7 95%CI (5.43, 275.5)
		Comparator (n=94,720) Matched 1:4 on gender, urbanisation of residential area and parental occupation No cerebral haemorrhage		
		Ascertainment/ definition National children's medical record database ICD 9 codes		12
7	Davidovitch 2020 ²⁹ Israel	Population (n=4963) ■ VLBW infants ≤1500g ■ Born 1999-2012	Outcome • ASD Assessment/ measurement	ASD IVH n=10, 3.9% No IVH n=103, 2.2% p=0.085
	Retrospective cohort study	Exposure • IVH grade 3-4 (n=256) • PVL (n=200)	Physical, neurological, and developmental assessment (by a qualified healthcare professional)	PVL n=5, 2.5% No PVL n=88, 2.3% p=0.86
		Post-haemorrhagic hydrocephalus (n=152) Comparator.	Independent psychological assessment Follow-up 8-15 years (median 11.6)	Post-haemorrhagic hydrocephalus n=7, 4.6% No post-haemorrhagic hydrocephalus n=106, 2.2% p=0.051 IVH, PVL, post-haemorrhagic hydrocephalus or ROP n=27,23.9%
		Comparator Unmatched No IVH grade 3-4 (n=4600) No PVL (n=3813) No post-haemorrhagic hydrocephalus (n=4810)	8- 15 years (median 11.6) Only those linked to electronic medical records included	No brain injury n=571, 11.8% p<0.0001 aOR 1.62 95% CI (0.96–2.73)
		Ascertainment/ definition Israel national very low birthweight infant database linked to electronic medical records. Ultrasound diagnosis Papile classification		
8	Doyle 2000 ⁷⁰	Population	Outcomes	<u>Cerebral Palsy</u>
	Australia	 Birthweight 500–1499 g Born 1980-1981; 1992 	Survival Cerebral palsy	Grade of IVH

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USA Bernogecive very control of the property	Cohort	1980s epoch IVH grade 1 (n=18) IVH grade 2 (n=9) IVH grade 3 (n=7) IVH grade 4 (n=4) 1992 epoch IVH grade 1 (n=23) IVH grade 2 (n=10) IVH grade 3 (n=9) IVH grade 4 (n=1) Comparator Unmatched No intracranial haemorrhage (n=223) 1980s epoch (n=113) Ascertainment/ definition Ultrasound imaging Post-mortem examination	Clinical assessment by blinded paediatricians Functional assessment Follow-up 5 years 93% follow-up for 1980s epoch	No IVH n=5, 5% IVH grade 3 n=2, 29% IVH grade 4 n=0 1992s epoch No IVH n=4, 4% IVH grade 3 n=3, 33%
	USA Retrospective	Gestation 24-28 weeks Born 2005-2009 Exposure MRI Mild WMI (n=223) Moderate WMI (n=51) Severe WMI (n=15) Any cerebellar lesion (n=57) Significant cerebellar lesion (n=39) Early cranial ultrasound No IVH 3-4 or cPVL (n=341) IVH 3-4 or cPVL (n=32) Late cranial ultrasound No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=354) Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt (n=19) Comparator No white matter injury on MRI (n=84) No cerebellar lesion on MRI (n=316) No IVH 3-4 or cPVL (n=32) Normal early cranial ultrasound (n=227) No porencephalic cyst, cPVL moderate to severe ventricular enlargement or shunt (n=19) Normal late cranial ultrasound (n=224) Ascertainment/ definition NICHD neonatal research network (NEURO study and SUPPORT cohort) Two masked central imaging readers for all cranial ultrasounds and one for MRI All had cranial ultrasound and MRI (at 35-42 weeks) Unilateral and bilateral cranial	Moderate to severe disability (composite) Minimal or no disability Corebral palsy Hearing Vision Measurement/ assessment WISC IV Neurological exam GMFCS Clinical examination Parental report Follow-up 6-7 years	No white matter injury, n=8, 9% Mild white matter injury, n=8, 15% Severe white matter injury, n=14, 82% p=0.0001 Moderate or severe white matter injury aOR 1.1 95% CI (0.42, 2.92) Minimal or no disabiliy No white matter injury, n=8, 224% Midd white matter injury, n=8, 224% Moderate white matter injury, n=8, 224% Moderate white matter injury, n=0, 0% p=0.0001 Cognitive impairment (FSIQ mean (SD)) No white matter injury, 85.9 (16.8) Moderate white matter injury, 86.9 (16.8) Moderate white matter injury, 87.9 (16.8) Moderate white matter injury, 62.7 (19.6) p=0.0001 Cognitive impairment FSIQ <70 No white matter injury, n=7, 8% Mild white matter injury, n=9, 60% p=0.0001 Cognitive impairment FSIQ <8% Moderate white matter injury, n=9, 60% p=0.0001 Moderate or severe white matter injury aOR 1.14 95% CI (0.39, 3.26) Cognitive impairment FSIQ <85 No white matter injury, n=10, 45% Mild white matter injury, n=27, 32% Mild white matter injury, n=10, 45% Moderate white matter injury, n=13, 87% p=0.0001 No cognitive impairment FSIQ ≥85 No white matter injury, n=123, 55% Moderate white matter injury, n=123, 55% Moderate white matter injury, n=22, 43% Severe white matter injury, n=22, 43% Severe white matter injury, n=2, 13% Moderate white matter injury, n=2, 34% Moderate white matter injury, n=2, 44% p=0.0001 Any cerebral palsy No white matter injury, n=2, 9% Moderate white matter injury, n=1, 9% Moderate white matte

No cerebellar lesion, n=135, 42% Any cerebellar lesion n=15, 25% p<0.0001 Significant cerebellar lesion, n=15, 36%

Cognitive impairment (FSIQ mean (SD))

No cerebellar lesion, 87 (16.5) Any cerebellar lesion 78.4 (20) p=0.001 Significant cerebellar lesion 76.8 (20.4)

Cognitive impairment FSIQ <70

No cerebellar lesion, n=32, 10% Any cerebellar lesion, n=15, 26% p=0.001 Significant cerebellar lesion, n=10, 26%

Significant cerebellar lesions aOR 1.96 95% CI (0.72, 5.36)

Cognitive impairment FSIQ <85

No cerebellar lesion, n=136, 43% Any cerebellar lesion, n=33, 58% p=0.038 Significant cerebellar lesion, n=22, 56%

No cognitive impairment FSIQ ≥85

No cerebellar lesion, n=180, 57% Any cerebellar lesion, n=24, 42% P=0.038 Significant cerebellar lesion, n=17, 44%

Any cerebral palsy

No cerebellar lesion, n=13, 4% Any cerebellar lesion, n=9, 15% p=0.001 Significant cerebellar lesion, n=9, 21%

Cerebral palsy with GMFCS ≥2

No cerebellar lesion, n=3, 1% Any cerebellar lesion, n=3, 5% p=0.19 Significant cerebellar lesion, n=3, 7%

Early cranial ultrasound abnormalities Moderate to severe disability No IVH 3-4 or cPVL, n=43, 12% IVH 3-4 or cPVL, n=14, 42% p<0.0001 Normal scan, n=35, 12% aOR 0.61 95% CI (0.14, 2.59)

Minimal or no disabilityNo IVH 3-4 or cPVL, n=143, 41%
IVH 3-4 or cPVL, n=7, 21% p<0.0001 Normal scan, n=120, 43%

Cognitive impairment, FSIQ mean (SD) No IVH 3-4 or cPVL, 86.4 (17) IVH 3-4 or cPVL, 77.9 (19.1) p=0.008Normal scan, 86 (16.7)

Cognitive impairment FSIQ <70

No IVH 3-4 or cPVL, n=38, 11% IVH 3-4 or cPVL, n=9, 28% p=0.006 Normal scan, n=31, 11% aOR 0.42 95% CI (0.07, 2.33)

Cognitive impairment FSIQ <85 No IVH 3-4 or cPVL, n=149, 44%

IVH 3-4 or cPVL, n=20, 63% p=0.041 Normal scan, n=123, 44%

No cognitive impairment FSIQ ≥85 No IVH 3-4 or cPVL, n=192, 56% IVH 3-4 or cPVL, n=12, 38% p=0.041 Normal scan, n=154, 56%

Any cerebral palsy

No IVH 3-4 or cPVL, n=149, 44% IVH 3-4 or cPVL, n=20, 63% p=0.041 Normal scan, n=123, 44%

Cerebral palsy with GMFCS ≥2 No IVH 3-4 or cPVL, n=3, 1% IVH 3-4 or cPVL, n=3, 9% p<0.0001 Normal scan, n=2, 1%

Late cranial ultrasound abnormalities Moderate to severe disability

No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=40, 11%

Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=17, 77% p<0.0001 Normal scan, n=27, 10%

aOR 27.85 95% CI (6.03, 128.68)

Minimal or no disability

No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=149, 42%

Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=1, 5% P<0.0001

Normal scan, n=117, 43%

Cognitive impairment (FSIQ mean (SD))

No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, 86.7 (16.7)

Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, 65.9 (18.7) P<0.0001

				Normal scan, 87 (16.1)
				Cognitive impairment FSIQ <70 No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=36, 10% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=11, 58% p<0.0001 Normal scan, n=24, 9% aOR 20.05 95% CI (3.63, 110.84)
				Cognitive impairment FSIQ <85 No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=153, 43% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=16, 84% p<0.0001 Normal scan, n=118, 43%
		0		No cognitive impairment FSIQ ≥85 No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=201, 57% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=3, 16% p<0.0001 Normal scan, n=156, 57%
		ONSIDE		Any cerebral palsy No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=10, 3% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=12, 50% p<0.0001 Normal scan, n=6, 2%
) _× .	Cerebral palsy with GMFCS ≥2 No porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=2, 1% Porencephalic cyst, cPVL, moderate to severe ventricular enlargement or shunt, n=4, 17% p<0.0001 Normal scan, n=1, 0%
10	Hirovonen, 2017 ²² Finland	Population ■ Gestation >22 weeks ■ Birth weight >500g ■ Born 1991-2008	Outcomes Cognitive Measurement/assessment	Any intellectual disability after intracranial haemorrhage (HR (95%CI); p-value) Very preterm infants 2.92 (1.58–5.41); p= 0.001 Moderately preterm 5.59 (1.57–19.9); p= 0.008
	Retrospective cohort	Exposure (n=557) Intracranial haemorrhage	ICD 9 and 10 codesBSID 1993Finnish WISC	Late preterm 4.58 (1.36–15.4); p= 0.014 Term 2.94 (1.08-8); p=0.035
		Comparison (n=708,977) No intracranial haemorrhage	Follow-up • 7 years	
		ICD code	• 98% follow-up	
		Ascertainment/ definition Finnish national register ICD codes		
11	Hollebrandse 2021 ¹⁹ Australia Retrospective cohort	Population ■ Gestation <28 weeks ■ Born 1991-1992, 1997, 2005 Exposure ■ IVH grade 1 n=80 ■ IVH grade 2 n=53 ■ IVH grade 3 n=23 ■ IVH grade 4 n=12 Comparator	Outcomes Cognitive Motor Cerebral palsy Assessment/ measurement WISC III (1991-1992 cohort) WISC IV (1997 cohort) Differential Abilities Scale 2 nd edition (2005 cohort) WRAT III (1991-92; 1997 cohorts)	Cognitive IQ score <2 SD IVH grade 4 n=5, 42% p=0.08 (X² trend) IVH grade 3 n=5, 22% No IVH n=41, 12% IVH 3-4: OR 2.68 95% CI (1.21, 5.94) p=0.01 Impaired executive function Global executive composite ≥65 IVH grade 4 n=2, 18% p=0.78 (X² trend)
		Unmatched Preterm infants without IVH n=331	WRAT IV (2005 cohort) Behaviour rating inventory of executive functioning (parent-completed)	IVH grade 3 n=4, 18% No IVH n=49, 16% IVH 3-4: OR 1.17 95% CI (0.46, 2.97) p=0.75
		Ascertainment/ definition Ultrasound diagnosis Worst grade of IVH Papile classification	Movement ABC 1st edition (1991-1992 and 1997 cohorts) Movement ABC 2nd edition (2005 cohort) GMFCS (1997 and 2005 cohort)	Behavioural regulation index ≥65 IVH grade 4 n=2, 18% p=0.21 (X² trend) IVH grade 3 n=6, 27%
			Blinded assessment	No IVH n=46, 15% IVH 3-4: OR 1.76 95% CI (0.75, 4.11) p=0.2
			Follow-up 8 years Follow-up 85-91.4%	Metacognition index ≥65 IVH grade 4 n=3, 27% p=0.1 (X² trend) IVH grade 3 n=5, 23% No IVH n=48, 16%
				IVH 3-4: OR 1.73 95% CI (0.74, 4.06) p=0.21
				Impaired academic skills (any academic skill <-2SD) IVH grade 4 n=7, 64% p<0.001 (X ² trend) IVH grade 3 n=5, 24% No IVH n=50, 16%
				IVH 3-4: OR 2.91 95% CI (1.35, 6.27) p=0.006
				Impaired reading <-2SD IVH grade 4 n=6, 55% p=0.002 (X ² trend) IVH grade 3 n=4, 19% No IVH n=21, 10%
				IVH 3-4: OR 3.62 95% CI (1.59, 8.24) p=0.002
				Impaired spelling <- 2 SD IVH grade 4 n=5, 45% p=0.011 (X ² trend) IVH grade 3 n=3, 14%

12	Hreinsdottir 2018 ⁴⁸ Sweden Prospective cohort study	Population Born 2004-2007 Gestation <32 years Exposure (n=9) IVH grade 3-4 and/ or PVL Comparator (n=99) Unmatched No IVH grade 3-4 or PVL Ascertainment/ definition Ultrasound imaging performed by paediatric radiologist Papile classification for IVH PVL defined by size, laterality and as cystic of diffuse	Outcomes • Visual impairment Assessment/ measurement • Linear visual acuity (Lea Hyvarinen chart) • Cover test • Refraction Follow-up • 6.5 years • 78% follow-up	No IVH n=21, 7% IVH 3-4: OR 4.48 95% CI (1.8, 11.2) p=0.001 Impaired arithmetic <-2 SD IVH grade 4 n=5, 43% p=0.09 (X² trend) IVH grade 3 n=4, 19% No IVH n=38, 12% IVH 3-4: OR 2.79 95% CI (1.2, 6.48) p=0.017 Motor and cerebral palsy Any motor dysfunction (cerebral palsy or MABC <5th centile) IVH grade 4 n=11, 92% p=0.001 (X² trend) IVH grade 4 n=11, 92% p=0.001 (X² trend) IVH grade 3 n=10, 43% No IVH n=81, 24% IVH 3-4: OR 4.45 95% CI (2.18, 9.08) p<0.001 Cerebral palsy IVH grade 3 n=6, 26% No IVH grade 3 n=6, 26% No IVH grade 4 n=9, 75% p<0.001(X² trend) IVH grade 4 n=1, 92% p<0.001 (X² trend) IVH grade 4 n=11, 92% p<0.001 (X² trend) IVH grade 4 n=11, 92% p<0.001 (X² trend) IVH grade 4 n=11, 92% p<0.001 (X² trend) IVH grade 4 n=17, 92% p<0.001 (X² trend) IVH 3-4: OR 4.7 95% CI (2.21, 9.97) p<0.001 Vision Subnormal visual acuity IVH 3-4 and or PVL OR 1.19 5% CI (0.25, 4.83) p=0.891 Contrast sensitivity IVH 3-4 and or PVL OR 2.5 95% CI (0.65, 24.55) p=0.134 Composite score 1: Visual acuity with both eyes of less than 0.3, significant refractive error in the better eye and manifest strabismus IVH 3-4 and or PVL OR 3.63 95% CI (0.65, 24.55) p=0.134 Composite score 2: Visual acuity with both eyes of less than 0.3, significant refractive error in worse eye according and manifest strabismus IVH 3-4 and or PVL OR 5.67 95% CI (1.34, 24.07) p=0.019 aOR 10.4 95% CI (1.23, 88) p=0.032 Composite score 3: Visual acuity with both eyes of less than 0.5, significant refractive error in worse eye according and manifest strabismus, negative stereopsis and contrast sensitivity less than 0.4 IVH 3-4 and or PVL OR 7.6 95% CI (1.53, 154.05) p=0.008 aOR 18.19 95% CI (1.54, 154.05) p=0.008
13	Jansen 2020 ²³ Netherlands Prospective cohort study	Population Gestation <32 weeks Admitted 2006-2007 Exposure Mild WMI (n=18) Moderate WMI (n=14) Severe WMI (n=8) Mild cerebellar injury (n=11) Moderate cerebellar injury (n=4) Severe cerebellar injury (n=6)	Outcomes Cognitive Assessment/ measurement National standardised achievement tests Follow-up 9-10 years 77% follow-up	IVH 3-4 and or PVL OR 7.6 95% CI (1.7, 34) p=0.008
		Comparator Unmatched No WMI (n=46) No cerebellar injury (n=65) Ascertainment/ definition Ultrasound imaging and term MRI Imaging reviewed by two blinded experienced investigators (neonatologists or radiologists)		Moderate-severe cerebellar injury vs. no injury B 1.293 p= 0.115 Mathematics Moderate-severe WMI vs. no injury B 1.856 p=0.003 Moderate-severe cerebellar injury vs. no injury B 1.504 p=0.088

15	Kaur 2020 ³² Canada Retrospective cohort study Kiechl- Kohlendorfer 2013 ²⁸	Population Preterm and term infants Proterm and term infants Protection (10,000) Exposure VIVH grade 1 (n=811) VIVH grade 2 (n=186) VIVH grade 3-4 (n=194) Preterm haemorrhage (n=1139) Comparator Unmatched No IVH (n=793, 062) Preterm no haemorrhage (n=50, 185) Ascertainment/ definition ICD 10 codes (based on ultrasound or MRI imaging) Papile classification Population Gestation <32 weeks Born 2003-2006	Outcome Reason for hospitalisation Assessment/ measurement ICD 10 codes Follow-up 12 years Completeness of follow-up not specified Outcomes Cognitive Measurement/assessment	Incidence of hospitalisation for: Cerebral palsy, n, incident rate per 1,000 person years (95%CI) IVH n=57, 6.8 (5.3, 8.8) No haemorrhage n=432, 0.1 (0.1, 0.1) Hazard ratio: 4.78 95% CI (3.21, 7.13) IVH grade 3-4 n=24 HR 14.78 95% CI (8.72-25.06) Ophthalmologic, n, incident rate per 1,000 person years (95%CI) IVH n=91 11.1 (9, 13.6) No haemorrhage n=6773, 1.2 (1.2, 1.3) HR 3.01 95% CI (2.32, 3.89) IVH grade 3-4 n=32 HR 7.87 95% CI (5.31-11.67) Otologic n, incident rate per 1,000 person years (95%CI) IVH n=328, 46.7 (41.9, 52) No haemorrhage n=102,153 22.1 (22, 22.2) HR 1.19 95% CI (1.06, 1.34) IVH grade 3-4 n=202 HR 1.07 95% CI (0.79-1.46) Delayed numerical skills Intracranial haemorrhage (all grades) n=11, 40,7% aOR 4.66 95% CI (1.56, 13.93) p=0.007
16	Austria Prospective cohort Klebermass-Schrehof 2012 ²⁰	Exposure Intracranial haemorrhage (all grades) (n=24) Intracranial haemorrhage grade 3-4 (n=4) PVL (n=2) Intraparenchymal echodense lesions (n=2) Comparator Unmatched Ascertainment/ definition Ultrasound imaging Papile classification Population Gestation <32 weeks Admitted to NICU 1994-2005	Physical examination Hannover-Wechsler Intelligence Test for preschool children, third edition WPPSI Snijders-Oomen Nonverbal Intelligence Test TEDI-MATH Follow-up 5 years 72.2% follow-up Outcomes Neurosensory impairment (composite) Motor	Intracranial haemorrhage grade 3-4 n=3, 11.1% PVL n=2, 7.4% Intraparenchymal echodense lesions n=0 Outcomes at 5.5 years Group 1: infants born < 28 weeks' gestation KABC <70
	Austria Prospective cohort	Exposure IVH grade 1 (n=37) IVH grade 2 (n=84) IVH grade 3 (n=18) IVH grade 4 (n=12) Comparator (n=320) Ummatched No IVH Ascertainment/ definition Ultrasound diagnosis Most severe scan used Papile classification	Cerebral palsy Language Visual Hearing Measurement/assessment BSID II (MDI, PDI) K-ABC Beery-Buktenica Developmental Test of VMI Clinical assessment Follow-up Syears (1,2, and 3.5 years) Only those with follow-up included (loss to follow-up not specified)	No IVH, 7.6% IVH grade 3, 33.3% IVH grade 4, 50% KABC mean (SD) No IVH, 91.5 (15.1) IVH grade 3, 88.6 (11.1) p=not significant IVH grade 4, 88.5 (10.6) p= not significant VMI mean (SD) No IVH, 92.7 (20) IVH grade 3, 67.5 (14) p=0.04 IVH grade 4, 76 (26.8) p=0.04 Cerebral palsy No IVH, 14.3% IVH grade 3, 63.6% p<0.01 IVH grade 4, 90.9% p<0.01 Visual impairment No IVH, 7.5% IVH grade 3, 45.5%, p=0.03 IVH grade 4, 90.9% p<0.01 Acoustic impairment No IVH, 2.2% IVH grade 3, 0% p= not significant IVH grade 4, 0% p= not significant IVH grade 4, 0% p= not significant
17	Koc 2016 ²⁴ Turkey Retrospective cohort	Population (n=90) Gestation <32 weeks Birthweight <1500g Born 2001 Exposure IVH grade 1-2 (n= 7) IVH grade 3-4 (n= 8) Comparator No IVH (n=75) Ascertainment/ definition Neonatal unit database and medical records	Outcomes Cognitive Measurement/ assessment WISC-R Follow-up 5.9-7.9 years 100% follow-up	WISC-R score <85 IVH (n=7; 46.7%) No IVH (n= 25; 33.3%) WISC-R score >85 IVH grade (n=8; 13.8%) No IVH (n= 50; 84.2%) p=0.381
18	Martinez- Cruz 2008 ⁴⁵ Mexico Case control	Population Gestation <34 weeks Birthweight <1500g Born 1990-2005 Exposure (n=103) IVH	Outcomes Sensorineural hearing loss Measurement/ assessment Brainstem auditory evoked potentials Transient auditory evoked otoacoustic emissions Behavioural hearing evaluation	IVH Sensorineural hearing loss (n=71; 48.6%) No sensorineural hearing loss (n=32; 11.8%) Multivariate logistic regression of risk factors for sensorineural hearing loss IVH: aOR 7.1 95% CI (4.34, 11.6) p<0.000

		Commonaton (m. 215)	F 6-11 P	T
		Comparator (n=315) No IVH	Free field audiometry Tympanometry	
			Pure Tone Audiometry	
		Ascertainment/ definition	•	
		Medical records Ultrasound diagnosis.	Follow-up	
		 Ultrasound diagnosis. Papile classification. 	 Mean age 7.8±3.7 years 100% follow-up (case control) 	
19	Neubauer	Population	Outcomes	Logistic regression for major impairment vs. normal development or minor
	200812	Birthweight <1000g	Neurodevelopmental impairment	impairment at school age
	Germany	• Born 1993-1998	(composite)	Grade 3-4 IVH or PVL
	Germany	Exposure	Measurement/assessment	Normal (n=4, 22%)
	Prospective	• IVH grade 1-2 (n=26)	Modified Touwen test	Minor (n=2, 11%)
	cohort	• IVH grade 3-4, PVL (n=18)	K-ABC Sniiders-Oomen Non-Verbal	Major (n=12, 67%) Risk of impairment: OR 2.46 95% CI (0.52–11.7)
		Comparator	Snijders-Oomen Non-Verbal Intelligence Test	Nisk of impairment of 2110 year of (0.02 1117)
		Unmatched	Hamburg-Wechsler Intelligence Test	
		No IVH or PVL (n=91)	for Children	
		Ascertainment/ definition	Follow-up	
		Ultrasound diagnosis	10 years	
		Papile classification	• 79% follow-up	
20	Piris Borregas 2019 ¹³	Population (n=1001) Birthweight 500-1250g	Outcomes Neurodevelopment (composite)	Poor neurodevelopmental outcome Severe brain injury, n=46, 32%
	2019	Born 1991-2008	Cognitive	No severe brain injury, n=40, 32%
	Spain		Motor	OR 1.41 95% CI (0.94, 2.10) p=0.09
	Retrospective	Exposure	Hearing impairment	Independent OR 2.02 95% CI (1.22, 3.31) p=0.18
	cohort study	 Severe brain injury (IVH grade 3-4, ventriculomegaly III, PVL or 	Visual impairment	Severe brain injury (birthweight 500-1000g)
		intraparenchymal echodense lesion	Assessment/ measurement	Independent OR 2.02 95% CI (1.22, 3.31)
		grade 3 or greater)	GMFCS	
		Comparator	Follow-up	
		Unmatched	• 7 years	
			,,	
		Ascertainment/ definition Neonatal database		
		Ultrasound diagnosis		
		Papile classification		
21	Pittet 2019 ²⁵	Population	Outcomes	Cognitive (K-ABC – MPC score < 1SD)
	Switzerland	Gestation <30 weeksBorn 2006	Cognitive Cerebral palsy	IVH 3-4 or PVL OR 2.9 95% CI (1, 8.2) p=0.04
		. Dom 2000	Visual impairment	aOR 2.3 95% CI (0.7, 7.7) p=0.15
	Prospective	Exposure	Hearing impairment	
	cohort study	• IVH grade 3-4 or cPVL (n=22)	Assessment/ measurement	Use of early intervention/ therapy service
		Comparator	Kaufman ABC	IVH 3-4 or cPVL aOR 2.7 95% CI (1.3, 5.7)
		Unmatched	Neurological exam	
		• No IVH grade 3-4 or cPVL (n=213)	• GMFCS	
		Ascertainment/ definition	Follow-up	
		 Swiss neonatal network follow-up 	• 5.5 – 6 years	
2.5	Cl. 1 '	group	81% follow-up	
22	Sherlock 2005 ¹⁴	Population • Gestation <28 weeks	Outcomes • Disability (composite)	Abnormal movement No IVH (n=39, 22.5%)
		Birthweight <1000g	Neurosensory disability (composite)	Grade 1 IVH (n=11, 25%)
	Australia	 Survivors born 1991-1992 	Cognitive	Grade 2 IVH (n=6, 30%)
	Prospective	Exposure	Motor Graph and analysis	Grade 3 IVH (n=3, 27.3%) Grade 4 IVH (n=4, 100%)
	cohort	IVH Grade 1 (n=47)	Cerebral palsy Speech and language	X^2 linear trend = 5.3; P = 0.021
		• IVH Grade 2 (n= 25)	Visual impairment	Carabral paley
		• IVH Grade 3 (n= 12)	Hearing impairment	Cerebral palsy No IVH (n=12, 6.7%)
		• IVH Grade 4 (n= 6)	Measurement/assessment	Grade 1 IVH (n=3, 6.4%)
		Comparator	Medical assessment	Grade 2 IVH (n=6, 24%)
		 Matched on sex, mother's country of 	Movement ABC	Grade 3 IVH (n=2, 16.7%) Grade 4 IVH (n=6, 100%)
		birth, and health insurance status Extremely low birth weight or very	WISC-III To the state of the state	X^2 linear trend = 31.7; p <0.0001
		preterm infants without IVH (n=180)	Tower of London Rey Complex Figure	Madavata ta assara assahual nalari
		1	WRAT	Moderate to severe cerebral palsy No IVH (n=4, 2.2%)
		Ascertainment/ definition Enrolled in Victorian Collaborative		Grade 1 IVH (n=0, 0%)
		Enrolled in Victorian Collaborative Study	Follow-up Mean 8.7 years	Grade 2 IVH (n=4, 15%) Grade 3 IVH (n=1, 8.3%)
		 Ultrasound diagnosis (at least one 	Mean 8.7 years92.3% follow-up	Grade 3 IVH (n=1, 8.3%) Grade 4 IVH (n=5, 83.3%)
		scan by a certified sonographer)	, up	X^2 linear trend = 40.8; p < 0.0001
		 Worst grade of IVH on either side used 		Major paurosansary disability
		Papile classification		Major neurosensory disability No IVH (n=28, 15.6%)
		-		Grade 1 IVH (n=5, 10.6%)
				Grade 2 IVH (n=5, 20%)
				Grade 3 IVH (n=1, 8.3%) Grade 4 IVH (n=6, 100%)
				X^2 linear trend = 6.9; p = 0.009
				IO seems mean (SD)
				IQ score mean (SD) No IVH 0.71 (1.25)
				Grade 1 IVH 0.76 (1.32)
			1	Grade 2 IVH 0.71 (1.12)
				Grade 3 IVH 1.21 (1.13)
				Grade 3 IVH 1.21 (1.13) Grade 4 IVH 3.28 (0.88) ANOVA F4,265 = 6.7; p<0.0001
				Grade 3 IVH 1.21 (1.13) Grade 4 IVH 3.28 (0.88) ANOVA F4,265 = 6.7; p<0.0001 Verbal comprehension index mean (SD)
				Grade 3 IVH 1.21 (1.13) Grade 4 IVH 3.28 (0.88) ANOVA F4,265 = 6.7; p<0.0001
				Grade 3 IVH 1.21 (1.13) Grade 4 IVH 3.28 (0.88) ANOVA F4,265 = 6.7; p<0.0001 Verbal comprehension index mean (SD) No IVH 96.6 (16.2)

Grade 4 IVH 74.3 (12.7) ANOVA F4,251 = 1.8; p = 0.12Perceptual organisation index mean (SD) No IVH 98.5 (16.3) A Spel Nr Grade 1 IVH 98.2 (15.7) Grade 2 IVH 96.9 (14.8) Grade 3 IVH 91.6 (12.7) Grade 4 IVH 71.7 (11.1) ANOVA F4,249 = 2.5; p = 0.042Freedom from distractibility index mean (SD) No IVH 92.3 (114.9) Grade 1 IVH 95.5 (15.0) Grade 2 IVH 97.7 (12.8) Grade 3 IVH 94.9 (17.4) Grade 4 IVH 71.0 (3.5) ANOVA F4,250 = 2.8; p = 0.026Processing speed index mean (SD) No IVH 99.5 (15.8) Grade 1 IVH 99.1 (16.6) Grade 2 IVH 99.3 (13.0) Grade 3 IVH 94.9 (19.3) Grade 4 IVH 71.0 (9.5) ANOVA F4,245 = 2.7; p = 0.033Tower of London (executive function) raw score mean (SD) Grade 1 IVH 71.5 (12.4) Grade 2 IVH 71.1 (20.4) Grade 3 IVH 66.5 (8.3) Grade 4 IVH 54.3 (22.0) ANOVA F4,244 = 1.8; p = 0.13 Rey complex figure (executive function) raw score mean (SD) No IVH 22.5 (7.5) Grade 1 IVH 23.1 (7.4) Grade 2 IVH 24 2 (5.8) Grade 3 IVH 19.3 (8.3) Grade 4 IVH 11.2 (9.8) ANOVA F4,242 = 2.6; p = 0.037 Wide range achievements test score mean (SD) Reading No IVH 95.2 (15.7) Grade 1 IVH 102.7 (15.4) Grade 2 IVH 99.0 (14.2) Grade 3 IVH 98.1 (11.9) Grade 4 IVH 70.5g (20.9) ANOVA F4,251 = 5.1; p = 0.001 Spelling No IVH 93.6 (12.4) Grade 1 IVH 97.8 (12.3) Grade 2 IVH 95.9 (10.8) Grade 3 IVH 96.8 (11.9) Grade 4 IVH 73.5 (20.0) ANOVA F4,250 = 4.0; p = 0.003Arithmetic No IVH 88.3 (14.3) Grade 1 IVH 93.6 (14.9) Grade 3 IVH 89.1 (10.1) Grade 4 IVH 65.5 (14.5) ANOVA F4,248 = 4.5; p = 0.002Cognitive test scores (compared to normal birthweight controls) IQ score <1 SD from the mean (n, %) No IVH n=64 (35.6%) Grade 1 IVH n=18 (38.3%) Grade 2 IVH n=9 (36%) Grade 3 IVH n=7 (58.3%) Grade 4 IVH n=6(100%) X2 linear trend=6.8; P=0.009 Wide range achievements test score <1 SD from the mean, n (%) Low reading No IVH n=42 (24.4%) Grade 1 IVH n=6 (13.3%) Grade 2 IVH n=5 (20.8%) Grade 3 IVH n=2 (18.2%) Grade 4 IVH n=3 (75%) X^2 linear trend=0.1; p=0.77 Low spelling No IVH n=33 (19.2%) Grade 1 IVH n=6 (13.6%) Grade 2 IVH n=2 (8.3%) Grade 3 IVH n=3 (27.3%) Grade 4 IVH n=3 (75%) X^2 linear trend=0.7; p=0.39 Low arithmetic No IVH n=47 (27.6%) Grade 1 IVH n=9 (20.5%) Grade 2 IVH n=2 (8.3%) Grade 3 IVH n=3 (27.3%) Grade 4 IVH n=4 (100%) X^2 linear trend=0.1; p=0.79

23	Tymofiveva	Population (n=24)	Outcome	Attention (abnormal)
24	Tymofiyeva 2018 ³³ USA Prospective cohort Van de Bor 2004 ¹⁵ Netherlands Prospective cohort	Population (n=24) Gestation < 33 weeks Exposure Mild WMI (n=4) Moderate WMI (n=5) Severe WMI (n=1) IVH grade 1 (n=5) IVH grade 2 (n=0) IVH grade 3 (n=0) IVH grade 4 (n=0) Comparator Unmatched No WMI (n=14) No IVH (n=19) Ascertainment/ definition MR1 imaging reviewed by a blinded paediatric neuroradiologist Used own classification of white matter injury Papile classification Population Gestation < 32 weeks Birthweight < 1500 g Born 1983 Exposure IVH grade 1-2 (n=45) IVH grade 3-4 (n=17) Comparator (n=216) Unmatched No IVH Ascertainment/ definition Ultrasound diagnosis Papile classification	Outcome Cognitive Behaviour Assessment/ measurement Test of variables of attention Conners comprehensive behaviour rating scales CBCL Assessment undertaken by a blinded psychologist Parental questionnaire Follow-up 10-14 years Completeness not specified Outcomes Disability (composite) Cognitive Neurological status (motor) Speech and language Behaviour Hearing Vision Measurement/assessment Questionnaires (completed by parents at 9 years; adolescents at 14 years) Home visit and neurodevelopmental assessment by paediatrician unaware of medical history WHO classification of impairment, disability, and handicap Follow-up 5, 9 and 14 years 91.5% follow-up of survivors at 14 years	Mild WMI n=3, 75% Moderate WMI n=0, 0% No WMI n=8, 57% p=0.05 Disability at 5 vears No IVH n=49 (23%) IVH grade 3-4 n=5 (31.3%) Cognitive disability No IVH n=18 (8.3%) IVH grade 3-4 n=1 (5.9%) p=not significant Motor disability No IVH n=8 (3.7%) IVH grade 3-4 n=1 (5.9%) p= not significant Motor disability No IVH n=8 (3.7%) IVH grade 3-4 n=1 (5.9%) p= not significant Vival disability No IVH n=8 (3.7%) IVH grade 3-4 n=1 (5.9%) p= not significant Vival disability No IVH n=9 41 (15.7%) IVH grade 3-4 n=0 p= not significant Hearing disability No IVH n=10.5%) IVH grade 3-4 n=0 p= not significant Hearing disability No IVH n=6 (2.3%) IVH grade 3-4 n=0 p= not significant Hearing disability No IVH n=7 (2.3%) IVH grade 3-4 n=0 p= not significant School performance at 5 vears Special education No IVH n=7 (2.9.5%) IVH grade 3-4 n=0 p= not significant School performance at 9 vears Slow learner No IVH n=75 (29.5%) IVH grade 3-4 n=4 (26.7%) Special education No IVH n=29 (15%) IVH grade 3-4 n=4 (26.7%) Special education No IVH n=92 (42.1) IVH grade 3-4 n=4 (26.5%) Special education No IVH n=26 (12%) IVH grade 3-4 n=6 (35.3%) p=0.00 Need for special education at 14 years IVH (all grades) OR 2.56 95%CI (1.17.4.86) OR 2.36 95%CI (1.17.4.86)
25	Van Den Hout 2000 ²⁶ Netherlands	Population • Mean gestation 28-30 weeks • Born 1989-1991	Outcomes Cognitive Visual acuity	aOR 3.99 95%CI (1.36, 11.69) Total intelligence quotient, mean (SD) IVH 92.4 (16.3) PVL 79.6 (20.5) No brain injury 102.8 (14.4)
	Prospective cohort	Exposure IVH (n=17) PVL (n=12) Comparator (n=17) Preterm Normal cranial ultrasound Ascertainment/ definition Ultrasound diagnosis Modified Levene and DeVries classification for IVH DeVries classification for PVL	Measurement/ assessment L94 visual-perceptual ability test Grating acuity cards McCarthy scales of children's abilities Wechsler preschool and primary scale of intelligence Snijders-Oomen non-verbal intelligence test Leiden Diagnostic test Follow-up Mean 5.3 years 88% follow-up	IQ <85 IVH n=6, 35.3% PVL n=6, 50% No brain injury n=2, 11.8% Performance age in years, mean (SD) IVH 5.22 (1.16) PVL 4.37 (1.19) No brain injury 6.22 (0.89) Visual grating acuity in c/deg, mean (SD) IVH 37.4 (13.5) PVL 33.5 (15.9)

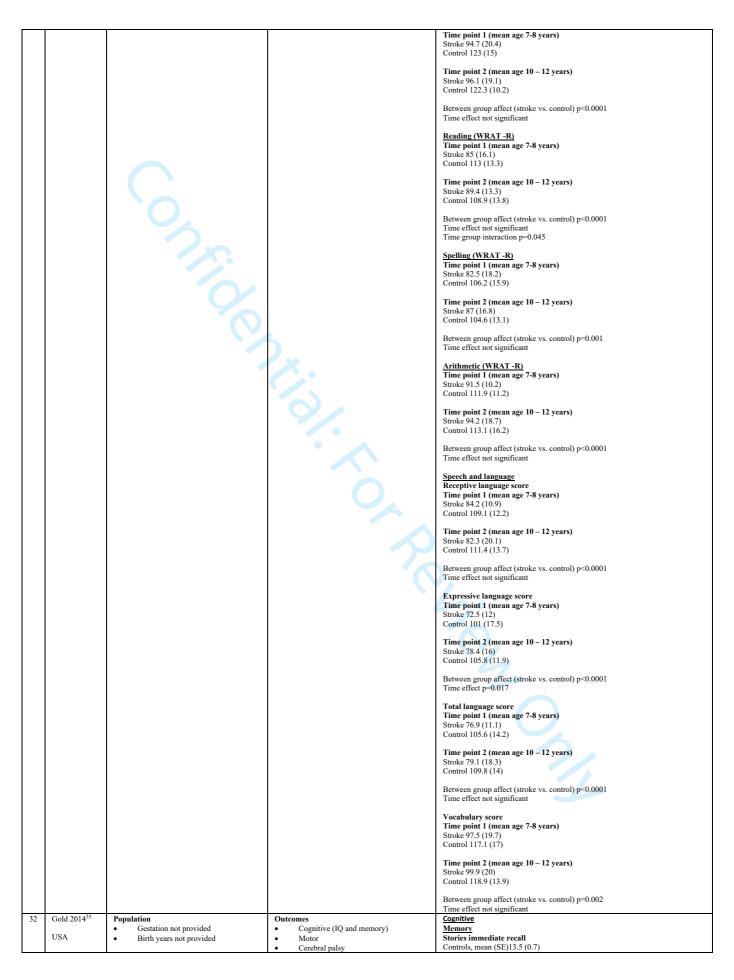
	ı			T
				No brain injury 47.1 (13.5)
				Visual grating acuity <25c/deg (%) IVH (11.8) PVL (33.3) No brain injury (0)
				No oram injury (0)
				Impairment on each of the eight L94 tasks Visual matching % (n) IVH 0 (17) PVL 0 (12) No brain injury 5.9 (17)
				Unconventional Object Views % (n) IVH 29.4 (17) PVL 41.7 (12) No brain injury 17.6 (17)
		,0		De Vos task % (n) IVH 29.4 (17) PVL 41.7 (12) No brain injury 11.8 (17)
				Line Drawings Occluded by Noise% (n) IVH 6.3 (16) PVL 36.4 (11) No brain injury 0 (17)
				Line Drawings Occluded by Noise% (n) IVH 13.3 (15) PVL 25.0 (8) No brain injury 5.9 (17)
			<u> </u>	Developmental test of visual motor integration % (n) IVH 0 (16) PVL 0 (7) No brain injury 0 (17)
			0	Matching block designs % (n) IVH 5.9 (17) PVL 20.0 (10) No brain injury 17.6 (17)
				Constructing block designs% (n) IVH 30.8 (13) PVL 80.0 (5) No brain injury 31.3 (16)
			0,	Mean percentage of L94 tasks on which child is impaired (mean, SD; %) IVH 14.71 (17.81) PVL 32.04 (24.64) No brain injury 11.13 (9.79)
26 *	Vollmer 2003 ¹⁶ UK Prospective cohort	Population Gestation <33 weeks Born 1983-1988 Exposure IVH (n=159) Ventricular dilatation (n=32) IVH, PV flare, ventricular dilatation (n=164) Hydrocephalus (n=36) Haemorrhagic parenchymal infarction (HPI) (n=61) CPVL n=26 Comparator (n=348) Unmatched Normal scan	Outcomes Neurodevelopmental impairment (composite) Visual impairment Hearing impairment Measurement/ assessment Structured neurologic examination Pure-tone audiogram Vision test (Snellen chart) Henderson-Stott TOMI Beery test of VMI WISC-R for children born 1983-1986 WISC-III for children born 1987-1988 Follow-up 8 years 91.7% follow-up	Neurodevelopmental status Group A (~28 weeks) All impairments (n,%) GMH/IVH (5, 18%) Ventricular dilatation (4, 50%) GMH/IVH, flare, ventricular dilatation (19, 51%) Hydrocephalus (7, 78%) HPI (15, 100%) CPVL (4, 100%) No brain injury (12, 32%) Disabling impairments (n, %) GMH/IVH (1, 4%) Ventricular dilatation (0, 0%) GMH/IVH, flare, ventricular dilatation (9, 24%) Hydrocephalus (7, 78%) HPI (14, 93%) cPVL (3, 75%) No brain injury (3, 8%)
		Ascertainment/ definition Ultrasound imaging reviewed by two experienced observers In-house classification used		Group B (28-32 weeks) All impairments (n, %) GMH/IVH (16, 29%) Ventricular dilatation (5, 31%) GMH/IVH, flare, ventricular dilatation (30, 43%) Hydrocephalus (7, 54%) HPI (5, 83%) ePVL (9, 75%) No brain injury (67, 29%)
				Disabling impairments (n, %) GMH/IVH (5, 5%) Ventricular dilatation (1, 6%) GMH/IVH, flare, ventricular dilatation (16, 23%) Hydrocephalus (6, 46%) HPI (3, 50%) cPVL (6, 50%) No brain injury (14, 6%)
27 *	Vollmer 2006a ²¹	Population • Gestation <33 weeks	Outcomes Motor	TOMI error score, mean (SD) Normal scan 2.78 (2.1)
	UK Prospective	Born 1985-1991 Exposure Bilateral brain lesions (n=201)	Cognitive Cerebral palsy Visual	All left-sided lesions 4.3 (3.5) Left-sided non-parenchymal lesions 4.5 (3.8) Left-sided parenchymal lesions 3.7 (2.1)
	cohort	Right-sided brain lesion (n=41)		

Left-sided brain lesion (n=57) All right-sided lesions 3.5 (2.9) Measurement/ assessment Neurological examination (modified Amiel-Tison assessment) Right-sided non-parenchymal lesions 2.7 (1.8) Right-sided parenchymal lesions 4.9 (3.8) Brain lesion types Non-parenchymal:

• Uncomplicated IVH TOMI All bilateral lesions 4.5 (4.3) WISC-R Parenchymal: Bilateral non-parenchymal lesions 4.1 (3.7) Bilateral parenchymal lesions 4.9 (4.7) Test of VMI Haemorrhagic parenchymal infarction v-up ANOVA for parenchymal lesions only p <0.0001 cPVL 8 years 80% follow-up ANOVA including parenchymal and non-parenchymal lesions p $<\!0.0001$ ANOVA excluding parenchymal lesions, p $<\!0.0001$ PV flare Comparator (n=369) VMI centile, mean (SD) Normal scan 59.2 (30.0) Unmatched Normal ultrasound All left-sided lesions 40.3 (30.1) Ascertainment/ definition Left-sided non-parenchymal lesions 46.8 (31.0) Left-sided parenchymal lesions 21 (22) Ultrasound imaging reviewed by two experienced observers Modified Stewart classification All right-sided lesions 60.2 (31.9) Right-sided non-parenchymal lesions 64.2 (30.2) Right-sided parenchymal lesions 54 (35) All bilateral lesions 46.0 (33.5) Bilateral non-parenchymal lesions 55.1 (32.1) Bilateral parenchymal lesions 38 (32) ANOVA for parenchymal lesions only p $<\!0.0001$ ANOVA including parenchymal and non-parenchymal lesions p $<\!0.0001$ ANOVA excluding parenchymal lesions reported as both p <0.0001 and p=0.98 Ω (potential error in the manuscript table) Cerebral palsy, n (%) Normal scan 2 (0.7%) All left-sided lesions 4 (9%) Left-sided non-parenchymal lesions 2 (6%) Left-sided parenchymal lesions 2 (16%) All right-sided lesions 2 (6%) Right-sided non-parenchymal lesions 1 (4%) Right-sided parenchymal lesions 1 (8%) All bilateral lesions 37 (21%) Bilateral non-parenchymal lesions 8 (10%) Bilateral parenchymal lesions 29 (31%) Chi-square for parenchymal and non-parenchymal lesions, p $<\!0.0001$ $\label{eq:chi-square} Chi-square excluding parenchymal lesions, p < 0.0001 \\ Chi-square for parenchymal lesions only, p < 0.0001 \\ ANOVA parenchymal lesions only, p < 0.0001 \\$ Full scale IQ, mean (SD) Normal scan 101 (16) All left-sided lesions 93 (17) Left-sided non-parenchymal lesions 98 (15) Left-sided parenchymal lesions 80 (15) All right-sided lesions 102 (17) Right-sided non-parenchymal lesions 104 (15) Right-sided parenchymal lesions 100 (19) All bilateral lesions 91 (21) Bilateral non-parenchymal lesions 96(19) Bilateral parenchymal lesions 86 (22) ANOVA for parenchymal lesions only, p <0.0001. ANOVA including parenchymal and non-parenchymal lesions, p <0.0001. ANOVA excluding parenchymal lesions, p =0.137. Verbal IQ, mean (SD) Normal scan 103 (19) All left-sided lesions 98 (20) Left-sided non-parenchymal lesions 102 (20) Left-sided parenchymal lesions 85 (18) All right-sided lesions 107 (18) Right-sided non-parenchymal lesions 108 (16) Right-sided parenchymal lesions 107 (22) All bilateral lesions 96 (23) Bilateral non-parenchymal lesions 100 (20) Bilateral parenchymal lesions 91 (25) ANOVA for parenchymal lesions only, p <0.0001 ANOVA including parenchymal and non-parenchymal lesions, p $<\!0.0001$ ANOVA excluding parenchymal lesions, p $=\!0.38$ Performance IQ, mean (SD) Normal scan 96 (15) All left-sided lesions 86 (16) Left-sided non-parenchymal lesions 90 (15) Left-sided parenchymal lesions 76 (15)

28 Vollmer * 2006b ²⁷ UK Prospective cohort	Population Gestation <33 weeks Born 1979-1991 Exposure (n=66) Ventricular dilatation and IVH Comparator (n=616) Unmatched Normal cranial ultrasound Ascertainment/ definition Ultrasound imaging reviewed by two experienced observers In-house classification used	Outcomes Neurological impairment with or without disability (composite) Cognitive Motor Vision Measurement/ assessment Structured neurological exam TOMI Test of VMI WISC Follow-up 8 years 181% follow-up	All right-sided lesions 95 (16) Right-sided non-parenchymal lesions 98 (13) Right-sided parenchymal lesions 92 (19) All bilateral lesions 85 (22) Bilateral non-parenchymal lesions 91 (20) Bilateral parenchymal lesions 80 (21) ANOVA for parenchymal lesions sonly, p <0.0001 ANOVA including parenchymal lesions, p =0.59 Disabling motor impairment, n (%) Ventricular dilatation and IVH n=10 (16%) Normal ultrasound n=10 (2%) Cognitive Full scale IQ, mean (SD) Ventricular dilatation and IVH 96 (23) Normal ultrasound 101 (17) Verbal IQ, mean (SD) Ventricular dilatation and IVH 101 (22) Normal ultrasound 104 (19) Performance IQ mean (SD) Ventricular dilatation and IVH 97 (15) Normal ultrasound 91 (21) Motor and vision VMI centile, mean (SD) Ventricular dilatation and IVH 37 (33) Normal ultrasound 52 (31) TOMI, mean (SD) Ventricular dilatation and IVH 5.98 (4.2) Normal ultrasound 3.26 (2.5)
29 Whitaker 2011 ³⁰ USA Prospective cohort	Population Birthweight <2000g Von-disabled' survivors Born 1984-1987 Exposure Vivi (n=69) Parenchymal lesions and/or ventricular enlargement (n=21) Comparison (n=368) Unmatched Normal cranial ultrasound Ascertainment/ definition Ultrasound imaging reviewed by three blinded radiologists independently, disagreements resolved through consensus and interobserver reliability checked. Paneth classification	Mental health conditions Measurement/ assessment Parent report version of the Diagnostic Interview Schedule for Children—IV WASI Follow-up 16 years 72.9% follow-up	Logistic regression assessing odds of current and lifetime mental health conditions after brain injury

				Parenchymal lesions and/or ventricular enlargement OR 7.64 95% CI (1.39-41.98) aOR 15.32 95% CI (1.82-128.74)
				Current diagnoses additionally controlled for full score IQ and motor function
				ADHD inattentive type IVH OR 0.86 95% CI (0.18-3.99) aOR 0.99 95% CI (0.21-4.62)
				Parenchymal lesions and/or ventricular enlargement OR 5.04 95% CI (1.36-18.65) aOR 5.43 95% CI (1.32-22.40)
				Major depression IVH OR 0.43 95% CI (0.16-1.11) aOR 0.40 95% CI (0.15-1.05)
				Tic disorders IVH OR 1.54 95% CI (0.41-5.78) aOR 1.45 95% CI (0.38-5.48)
				Parenchymal lesions and/or ventricular enlargement OR 7.01 95% CI (1.88-28.14) aOR 4.38 95% CI (1.05-18.23)
		0		Obsessive compulsive disorder IVH OR 8.68 95% CI (2.72-27.69) aOR 10.91 95% CI (3.13-37.99)
			۲.	Parenchymal lesions and/or ventricular enlargement OR 4.78 95% CI (0.83-28.10) aOR 3.58 95% CI (0.50-25.94)
Peri	natal stroke			
30	Ballantyne * 2007 41 USA Prospective cohort	Population	Outcomes Speech and language Assessment/ measurement CELF-R Wechsler Intelligence Scales (WPPSI-R, WISC-R, or WISC-III) PPVT-Revised	Speech and language
		Comparator (n=57) Unmatched Healthy controls with normal medical and developmental histories Recruited from the community	Expressive One-Word Picture Vocabulary Test–Revised or Upper– Extension Total Language Standard Scores	All strokes: 73.75 (16.79) p<.0001 Left stroke: 73.06 (14.88) p<.0001 Right stroke: 74.82 (20.11) p=0.001 Control: 101.02 (13.63)
		Ascertainment/ definition Single unilateral lesions the result of perinatal strokes occurring between 28 weeks' gestation and 28 days after birth; infarct or haemorrhage Identified through medical history and neuroimaging Severity rated on a 5-point scale adapted from the Vargha-Khadem classification	Follow-up 6-9 years 100% follow-up	All strokes: 76.93 (17.31) p<.0001 Left stroke: 76.94 (15.39) p<.0001 Right stroke: 76.91 (20.74) p=0.001 Control: 104.00 (12.58)
31	Ballantyne 2008 ³⁴ *	Population	Outcomes	Hemiparesis Stroke n=18,62%
	USA Prospective cohort	Exposure (n=29) Left hemisphere (n=20) Right hemisphere (n=9)	Motor Cerebral palsy Vision Epilepsy	Visual field deficit Stroke n=7, 26% Seizures Stroke n=11, 38%
		Control (n=38) Healthy controls (normal neurodevelopment) Recruited through a university and community adverts Ascertainment/ definition Unilateral ischaemic perinatal stroke confirmed through clinical history and neuroimaging Lesion location and severity reviewed by blinded neuroradiologist Severity rated on a 5-point scale adapted from the Vargha-Khadem classification	Measurement/ assessment WISC- Revised WRAT- Revised CELF- Revised PPVT-Revised WPPSI/WPPSI- Revised WISC-III Follow-up 7-12 years 100% follow up	Cognitive, mean (SD) Verbal IO (WISC-R) Time point 1 (mean age 7-8 years) Stroke 96.6 (20.5) Control 126.1 (16) Time point 2 (mean age 10 – 12 years) Stroke 98.7 (20) Control 123.6 (13.1) Between group affect (stroke vs. control) p<0.0001 Time effect not significant Performance IO (WISC-R) Time point 1 (mean age 7-8 years) Stroke 92.8 (19.9) Control 115.2 (13.8) Time point 2 (mean age 10 – 12 years) Stroke 93.5 (20)
				Control 116 (10.5) Between group affect (stroke vs. control) p=0.002 Time effect not significant Full scale IQ (WISC-R)



Prospective cohort Right-sided stroke (n=12) Left-sided stroke (n=15) Comparator (n=19) Matched for age at follow up, sex, socioeconomic group and maternal education Measurement/ assessment WISC-III Dots and Stories subtests of the Children's Memory Scales Follow-up Follow-up 6-16 years Stroke, mean (SE) 8.4 (0.8) p<0.001 Stroke and seizures, mean (SE) 10.1 (1.4) p=0.06 Stroke and seizures, mean (SE) 10.1 (1.4) p=0.06 Right lesion, mean (SE) 7.8 (1.1) Left lesion, mean (SE) 8.9 (1.2) p=0.51	
Left-sided stroke (n=15) Comparator (n=19) Matched for age at follow up, sex, socioeconomic group and maternal Pollow-up WISC-III Dots and Stories subtests of the Children's Memory Scales Right lesion, mean (SE) 7.8 (1.1) Left lesion, mean (SE) 8.9 (1.2) p=0.51	
• Matched for age at follow up, sex, socioeconomic group and maternal Follow-up Right lesion, mean (SE) 7.8 (1.1) Left lesion, mean (SE) 8.9 (1.2) p=0.51	
education • 6-16 years	
 Healthy controls Recruited through local advertising 100% follow-up Delayed recall Controls, mean (SE) 13.9 (0.8) Stroke, mean (SE) 7.9 (0.8) p<0.001 	
Ascertainment/ definition Single, unilateral brain lesion in an arterial vascular distribution, either Stroke and seizures, mean (SE) 6.2 (0.9) Stroke and no seizures, mean (SE) 10 (1.2) p=0.02	
identified in the neonatal period with neuroimaging, or identified later in infancy after presentation with a Right lesion, mean (SE) 7.3 (1.1) Left lesion, mean (SE) 8.3 (1.2) p=0.56	
hemiparesis and imaging documentation of an old unilateral infarct (presumed perinatal stroke) Recruited from paediatric neurology Recruited from paediatric neurology	
clinics Severity graded 1-5 using Trauner/ Vargha-Khaldem classification Stroke and seizures, mean (SE) 7.1 (1.1) Stroke and no seizures, mean (SE) 9.2 (0.9) p=0.17	
Right lesion, mean (SE) 8.3 (1.4) Left lesion, mean (SE) 7.9 (0.9) p=0.8	
Dots learning Controls, mean (SE) 10.9 (0.5) Stroke, mean (SE) 8.9 (0.8) p=0.05	
Stroke and seizures, mean (SE) 7.6 (1.1) Stroke and no seizures, mean (SE) 10.6 (0.8) p=0.05	
Right lesion, mean (SE) 9.3 (1.4) Left lesion, mean (SE) 8.7 (0.9) p=0.71	
Total Controls, mean (SE) 11.8 (0.5) Stroke, mean (SE) 9 (0.7) p=0.003	
Stroke and seizures, mean (SE) 7.8 (0.9) Stroke and no seizures, mean (SE) 10.6 (0.9) p=0.04	
Right lesion, mean (SE) 9.2 (0.7) Left lesion, mean (SE) 10.2 (0.7) p=0.62	
Delayed recall Controls, mean (SE) 12.6 (0.4) Stroke, mean (SE) 10 (0.5) p<0.001	
Stroke and seizures, mean (SE) 8.8 (0.5) Stroke and no seizures, mean (SE) 11.4 (0.8) p=0.009	
Right lesion, mean (SE) 9.7 (0.7) Left lesion, mean (SE) 10.2 (0.7) p=0.62	
WISC- III IQ, mean (SD) Right stroke, 85.0 (6) Left stroke, 91 (6) p=0.49	
IQ scores Controls 117 (2.7) All stroke patients 88 (4.0) p<0.001 No seizures 100 (6.4) Seizures 78 (3.7)	
Motor (hemiparesis) Stroke patients n=16; 59% Control n=0; p=0.05	
Solution Separation Separation Separation Separation not provided Severe n=4, 19% Separation Separation Severe n=4, 19% Severe n=9, 43% Separation Sep	ne Measure)
Matched on age and sex Healthy children Messurement/ assessment NEPSY Messurement/ assessment NEPSY Attack on age and sex NEPSY	7
Ascertainment/ definition • Rautman ABC • Paediatric Stroke Outcome Measure Tower Control 0.22, 0.64 (-0.05, 0.48)	<u></u>
• Estonian stroke registry • Arterial ischaemic stroke or haemorrhagic • I00% follow-up • 4-10 years • 100% follow-up • Arterial ischaemic stroke or haemorrhagic • 100% follow-up • A-10 years • 100% follow-up • A-10 years • 100% follow-up • Auditory attention Control 0.27, 0.72 (-0.03, 0.57) Neonatal stroke -0.38, 1.10 (-1.04, 0.28) p=0.009	
Visual attention: time Control 0.37, 0.81, (0.07, 0.67) Neonatal stroke -0.40, 0.93 (-0.82, 0.03) p=0.004	
Visual attention: correct Control 0.48, 0.50 (0.30, 0.67) Neonatal stroke -0.54, 0.97 (0.98, 0.1) p<0.0001	
Statue	

Control 0.26, 0.77 (-0.03, 0.54) Neonatal stroke -0.23, 1.09, (-0.73, 0.28) p=0.086 Design fluence Control 0.18, 1.04 (-0.25, 0.61) i. Co. N. Neonatal stroke -0.36, 0.70 (-0.78, 0.06) p=0.06 Knock and tap Control 0.31, 0.50 (0.10, 0.51) Neonatal stroke -0.44, 1.52, (-1.32, 0.43) p==0.03 Language, mean, SD, 95% CI Phonological processing Control 0.24, 0.80 (-0.05, 0.54) Neonatal stroke -0.38, 0.99 (-0.83, 0.08) p=0.001 Comprehension of instructions Control 0.43, 0.70 (0.18, 0.69) Neonatal stroke -0.59 1.06 (-1.07, 0.11) p<0.0001 Speeded naming: time Control 0.24, 0.70 (-0.05, 0.52) Neonatal stroke -0.14, 1.03 (-0.73, 0.46) p=0.188 **Speeded naming: correct** Control 0.42, 0.41 (0.25, 0.59) Neonatal stroke -0.45, 1.41 (-1.26, 0.37) p=0.008 **Repetition of nonsense words**Control 0.30, 0.53 (0.08, 0.52)
Neonatal stroke -0.40, 1.23 (-1.03, 0.24) p=0.026 Verbal fluency: semantic Control 0.43, 0.81 (0.13, 0.73) Neonatal stroke -0.60, 0.95 (-1.04, 0.15) p<0.0001 Verbal fluency: phonemic Control 0.40, 0.93 (-0.12, 0.92) Neonatal stroke -0.67, 0.90 (-1.42, 0.08) p=0.008 Oromotor sequences Control 0.31, 0.64 (0.07, 0.54) Neonatal stroke -0.52, 1.25 (-1.15, 0.10) Sentence comprehension Control 0.19, 0.78 (-0.09, 0.48) Neonatal stroke -0.35, 1.09 (-0.91, 0.21) p=0.027 Sensorimotor functions, mean, SD, 95% CI Finger tapping Control 0.49, 0.33 (0.35, 0.62) Neonatal stroke -0.53, 1.27 (-1.16, 0.10) p=0.0007 Imitating hand positions Control 0.57, 0.68 (0.32-0.82) Neonatal stroke -0.72, 0.92 (-1.14, 0.30) p<0.0001 Visuomotor precision: time Control 0.13, 0.83 (-0.17, 0.43) Neonatal stroke -0.24, 0.97 (-0.69, 0.20) p=0.145 Visuomotor precision: mistakes Control 0.45, 0.50 (0.27, 0.64) Neonatal stroke -0.42, 1.05 (-0.90, 0.05) p=0.0002 **Manual motor sequences** Control 0.50, 0.62 (0.27, 0.73) Neonatal stroke -0.92, 0.95 (-1.43, 0.41) p<0.0001 Control 0.53, 0.57 (0.29, 0.77) Neonatal stroke -0.77, 1.03 (-1.30, 0.24) p<0.0001 Visuospatial functions, mean, SD, 95% CI Design copying Control 0.36, 0.80 (0.06, 0.65) Neonatal stroke -0.54, 0.97 (-1.0, 0.09) p<0.0001 Control 0.37, 0.79 (0.05, 0.70) Neonatal stroke -0.61, 1.07 (-1.16, 0.06) p=0.0004 **Block construction** Control 0.29, 0.81 (-0.01, 0.58) Neonatal stroke -0.45, 1.04 (-0.92, 0.03) p=0.0003 Route finding Control 0.25, 1.05 (-0.33, 0.83)

Neonatal stroke -0.66, 0.80 (-1.23, 0.09) p=0.033

Neonatal stroke -0.09, 1.03 (-0.56, 0.37) p=0.341

Neonatal stroke -0.41, 1.15 (-0.96, 0.15) p=0.016

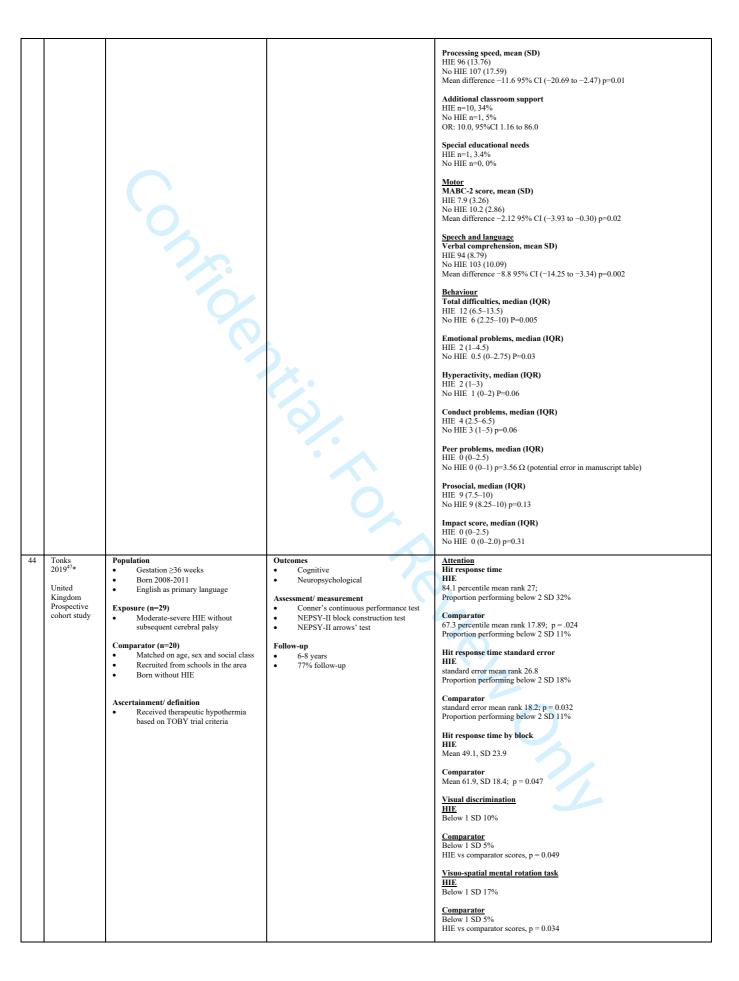
Memory and learning, mean, SD, 95% CI Memory for faces Control 0.42, 0.74 (0.11, 0.73)

Picture perception Control 0.13, 1.00 (-0.49, 0.24)

Memory for names Control 0.15, 0.92 (-0.23, 0.53) Neonatal stroke -0.31, 1.09 (-0.87, 0.25) p=0.295 Narrative memory Control 0.26, 0.80 (-0.03, 0.55) Neonatal stroke -0.22, 1.16 (-0.78, 0.34) p=0.077 Sentence repetition Control 0.49, 0.61 (0.26, 0.71) Neonatal stroke -0.64, 0.96 (-1.09, 0.19) p<0.0001 List learning Control 0.30, 0.82 (-0.16, 0.76) Neonatal stroke -0.38, 1.22 (-1.32, 0.56) p=0.151 Picture recognition Control 0.39, 0.72 (0.10, 0.69) Neonatal stroke -0.36, 1.24 (-0.98, 0.25) p=0.027 Motor (hemiparesis) Neonatal stroke and any hemiparesis n=19, 90% Mild functional impairment n=6, 29% Significant functional impairment n=6, 29% Significant functional impairment n=6, 38% Very severe functional impairment n= 4, 19% Epilepsy Stroke n=9, 33.3%
Martin 2019 Population
Northam Population
Motor (hemiparesis) Stroke n=9, 3%

37	Trauner 2001 ³⁹ USA Retrospective cohort	Matched on age, sex, and handedness Healthy Randomly drawn from a large database of children recruited for a different study of language development in healthy children Ascertainment/ definition Middle cerebral artery ischaemic stroke Population Gestation not reported Birth years not reported Exposure (n=39) Left perinatal stroke (n=25) Right perinatal stroke (n=14) Control (n=54) Matched on age and socioeconomic status Normal neurodevelopmental history Identified from clinics, community adverts, schools Ascertainment/ definition Pre or perinatal onset unilateral brain damage (focal lesion) from cerebral infarction or intraparenchymal haemorrhage	Follow-up	Stroke FSIQ 80 (14.1) Control FSIQ 108 (11.7) p=0.001 Cognitive Full scale IQ mean (SD) Stroke 93.4 (22) Control 116.2 (13) p<0.0001 Left stroke 90.1 (22) Right stroke 97.4 (22) — no significant difference Seizures (outside of the neonatal period) Stroke n=17, 50% (missing data for 5 subjects)
Centr	ral nervous systen	Identified through from clinical referrals. All confirmed by neuroimaging. Severity rated on 5-point scale adapted from Vargha-Khadem et al.)×.	
38	Bedford	Population	Outcomes	Neuromotor disability
	2001 ⁴² England & Wales Prospective cohort	All gestational ages included Born 1985-1987 Exposure (n=274) Neonatal meningitis Comparison (n=1391) Matched on age and sex Recruited through GP Ascertainment/ definition Identified through clinician reporting	Neuromotor disability (composite) Cognitive Hearing Vision Behaviour Seizure disorder Assessment/ measurement Parental questionnaire GP questionnaire McIntyre et al. classification of disability severity Follow-up S years S5-94% follow-up	Meningitis, n=45, 16% No meningitis, n=2, 0.1% Severe disability Meningitis, n=20, 7% No meningitis, n=10, 11% Moderate disability Meningitis, n=50, 18% No meningitis, n=20, 1% Mild disorder Meningitis, n=66, 24% No meningitis, n=275, 20% No disability Meningitis, n=138, 50%
39	Horváth- Puhó 2021 ⁴³ Denmark and Netherlands Retrospective matched cohort study	Population Gestation not specified Born 1997-2017 Exposure GBS meningitis (Denmark) (n=168) GBS meningitis (Netherlands) (n=198) Comparison Randomly selected Matched 1:10 on sex, birth year and month, and gestation No GBS (Denmark) (n=13,689) No GBS (Netherlands) (n=4,983) Ascertainment/ definition Invasive Group B Streptococcal disease by 89 days of age (most were neonatal — hence inclusion) ICD 10 codes (Denmark) CSF culture positive on national laboratory register (Netherlands)	Outcomes Neurodevelopmental impairment (composite) Cognitive Motor Behavioural, mental and social disorders Hearing impairment Visual impairment ICD 10 codes Follow-up Denmark 5 years, 7 years, 10 years, 15 years Netherlands 5 years, 7 years, 10 years and 11 years Signal of the property of the prope	No meningitis, n=1095, 79% Any neurodevelopmental impairment RR (95%CI) 5 vears Denmark GBS meningitis 7·80 (4·42-13·77) Netherlands GBS meningitis 5·30 (2·57-10·89) 7 vears Denmark GBS meningitis 4·69 (2·78-7·89) Netherlands GBS meningitis 3·71 (1·05-6·72) 10 vears Denmark GBS meningitis 3·47 (2·19–5·50) Netherlands GBS meningitis 2·81 (1·69-4·68) 11 vears Netherlands GBS meningitis 2·99 (1·83-4·88) 15 vears Denmark GBS meningitis 3·15 (1·82–5·46) Moderate to severe neurodevelopmental impairment RR (95%CI) 5 vears Denmark GBS meningitis 8·49 (4·28-16·86) Netherlands GBS meningitis 5·13 (2·24-11·79) 7 vears Denmark GBS meningitis 5·27 (2·80-9·92) Netherlands GBS meningitis 3·88 (2·15-6·99) Netherlands GBS meningitis 3·38 (1·77-6·33) 11 vears Netherlands GBS meningitis 3·34 (1·77-6·33)
40	Martinez- Cruz 2008 ⁴⁵	Population Gestation < 34 weeks Birthweight <1500g	Outcomes • Sensorineural hearing loss	Meningitis Sensorineural hearing loss: n=15; 10.3% No Sensorineural hearing loss: n=7; 2.6%

	Movies	Dama 1000 2005	Assassment/ massurement	Odds of provious populated manifestic if several translations to
41	Mexico Retrospective case control Stevens 2003 ⁴⁴ England & Wales Prospective cohort study	Born 1990-2005 Exposure (n=22) Neonatal meningitis Comparator (n=374) No meningitis Ascertainment/ definition Meningitis not defined Population Term born infants Born 1985-1987 Exposure (n=111) Meningitis Comparison (n=162) Matched on hospital of birth, birthweight and sex Hospital control (n=113) GP control (n=49) Ascertainment/ definition CSF positive culture	Assessment/ measurement Brainstem Auditory Evoked Potentials Transient Auditory Evoked Otoacoustic Emissions Tympanometry Free Field Audiometry Pure tone audiometry Behavioural hearing evaluation Follow-up T-11 years Diosability and functional impairment (composite) Cognitive Motor Wision Hearing Assessment/ measurement WISC-III Movement ABC Blinded examination Hearing screening Sonksen-Silver acuity system Follow-up 9-10 years 67% follow-up of meningitis group	Odds of previous neonatal meningitis if sensorineural hearing loss OR 4.368, 95% CI (1.7, 10.9) p= 0.002 Cognitive IQ, mean (95% CI) Meningitis, 88.8 (85, 92) Hospital control, 99.4 (97, 102) GP control, 99.6 (95, 103) Motor mABC score, mean (95% CI) Meningitis 7.1 (5.9, 8.5) Hospital control 5, 9.4 (4.3, 5.8) GP controls 4.0 (2.9, 5.4) Severe disability/ functional impairment Meningitis, n=12, 10.8% Hospital control, n=0, 0% GP control, n=0, 0% GP control, n=0, 0% Moderate disability/ functional impairment Meningitis, n=19, 17.1% Hospital control, n=2, 1.8% GP control, n=0, 0% Mild disability/ functional impairment Meningitis, n=19, 17.1% Hospital control, n=3, 11.5% GP control, n=8, 16% No disability or functional impairment Meningitis, n=70, 63.1% Hospital control, n=98, 86.7% GP control, n=98, 86.7% GP control, n=941, 84%
				Hospital control, n=98, 86.7%
				Visual impairment (unilateral) Meningitis, n= 10, 9.9% (6 unassessed because of their disability) Hospital control, n=8, 7% GP control, n=2, 4% Seizures outside of the neonatal period Meningitis, n=6, 5.4% Hospital control, n=2, 1.8% GP control, n=0, 0%
Нурс	oxic-ischaemic enc	ephalopathy		
42	3383 Koc 2016 ²⁴ Turkey Retrospective cohort	Population Gestation < 32 weeks Birthweight < 1500g Porn 2001 Exposure (n=9) Perinatal asphyxia Comparator (n=81) No asphyxia Ascertainment/ definition Perinatal asphyxia diagnosed on: fetal pH, Apgar score, and neonatal cerebral and multiorgan dysfunction	Outcomes Cognitive Assessment/ measurement WISC-R Performed by blinded psychologist Follow-up 5-8 years 100% follow-up	Cognitive WISC-R IQ Score (combined verbal and performance scores) <85 Perinatal asphyxia n=8, 89% No asphyxia n=24, 30% p=0.001
43	Lee-Kelland 2019 ⁴⁶ * United Kingdom Retrospective cohort study	Population • Gestation ≥ 36 weeks • Born 2008-2010 Exposure (n=29) • Moderate-severe HIE without subsequent cerebral palsy Comparator (n=20) • Matched on age, sex and social class • Born without HIE Ascertainment/ definition • Received therapeutic hypothermia based on TOBY trial criteria	Outcomes Cognitive Motor Speech and language Behaviour Assessment/ measurement WISC IV (blinded) Movement ABC 2 Strengths and difficulties questionnaire Follow-up 6-8 years 61% follow-up	Cognitive Full scale IQ, mean (SD) HIE 91 (10.37) No HIE 105 (13.41) Mean difference –13.62 95% CI (-20.53 to –6.71) p<0.001 Perceptual reasoning, mean (SD) HIE 89 (11.15) No HIE 103 (12.49) Mean difference –13.9 95% CI (-20.78 to –7.09) p<0.001 Working memory, mean (SD) HIE 94 (13.76) No HIE 102 (13.82) Mean difference –8.2 95% CI (-16.29 to –0.17) p=0.04



Supplement 4: Risk of bias table

overlapping data; Clinical Evaluation of Language Fundamentals (CELF); Cystic Periventricular leukomalacia (cPVL); Intelligence Quotient (IQ); Intraventricular haemorrhage (IVH); Mental Developmental Index (MDI); Neonatal Intensive Care Unit (NICU); Psychomotor Development Index (PDI); Periventricular leukomalacia (PVL); Spontaneous Intestinal Perforation (SIP); Wechsler Intelligence Scale for Children (WISC); White Matter Injury (WMI);

Preterm brain injury: cohort studies

		on (*satis		No =not		ctorily	Exposure (*satisfactor	ctory; No	=not	Subtotal as	sessment		Total score: 0-3 high risk of bias; 4-6 moderate	Additional comments
	1	2	3	4	1a	1b		2	3	Selection (0- 1=Poor; 2=Fair; 3+ Good)	Comparabil ity (0=poor; 1=fair; 2+=good)	Exposure / outcome (0=poor; 1=fair; 2+=good)	risk of bias 7-9 low risk of bias	
Adant 2019	No	*	*	* (excluded those with congenital anomalies)	*	*	No	*	No	Good	Good	Fair	6	Population not representative as focus of study was spontaneous intestinal perforation. Infants without IVH didn't have brain injury excluded per se (but didn't have IVH 3-4 on imaging). Matched on gender, gestational age, date of birth. Multiples matched to sibling without SIP. Excluded those with necrotising enterocolitis, mechanical obstruction or congenital anomalies. Adjusted for gender, gestation, birthweight, SIP and IVH. Independent outcome assessment but not blinded; telephone survey of parents. High numbers lost to follow-up. Table 3 contains errors with respect to outcomes (MDI and PDI mislabelled as motor and cognitive respectively).

Brouwer 2012 No No * * (given the types of outcomes assessed) **Tair** **Tair** **Poor** **Good** **Good** **Tair** **Poor** **Tair** **Poor** **Good** **Tair** **Poor* **Good** **Tair** **Poor* **Tair** **Poor* **Good** **Tair** **Poor* **Good** **Tair** **Poor* **Tair** **Poor* **Tair** **Poor* **Tair** **Poor* **Tair** **Poor* **Tair** **Poor* **Tair** **Tair** **Poor* **Tair** **T	Beaino 2010#	*	*	No	* (cerebral palsy could not be present at birth)	Xe.	* ク ₂	*	*	*	Good	Good	Good	8	3% of infants did not have a cranial ultrasound, a further 11% had only one cranial ultrasound during neonatal period - therefore ascertainment of exposure may be compromised Model A adjusted for:
Total by parcits and cachers		No	No	*	of outcomes	No	No	No	*	· C	Fair	Poor	Good	4	clear description of those lost to follow-up and no significant differences with respect to ultrasound brain injury findings between groups Study of a select group i.e. those with IVH requiring neurosurgical intervention. No description of setting, how patients were enrolled, how many were excluded No description of how control group was derived, or what era they were from. Only some infants (those <30weeks) were matched on gestation, birthweight, sex to controls. Different intelligence tests used at follow-

Campbell 2021	*	*	*	* (given the types of outcomes assessed)	*	*	*	*	No	Good	Good	Good	8	Males and those born at 23-24 weeks gestation were overrepresented in the IVH WMI group. Adjusted for gestation, birthweight Z score, sex, maternal education, bronchopulmonary dysplasia, sepsis, necrotising enterocolitis (Bell stage 2-3) and severe retinopathy of prematurity.
Cheong 2018	*	*	*	No (visual or hearing impairment could be congenital)	*	*	*	*	*	Good	Good	Good	8	Adjusted for era of birth, antenatal corticosteroid exposure, inborn status, gestation, sex, multiple birth, birthweight Z score, surfactant use, IVH grade 3 or 4 (in cPVL), cPVL (in IVH grade 3-4), bronchopulmonary dysplasia, postnatal corticosteroid use, necrotising enterocolitis (stage 2 or worse), surgery in the newborn period, and retinopathy of prematurity (stage 3 or worse).
Chou 2020	*	*	*	* (given the types of outcomes assessed)	No	*	*	*	No	Good	Fair	Good	7	Matched and adjusted for, urbanisation and parental occupation. No information about missing data or completeness of follow-up
											'C/	101	ν _C	No information about missing data or completeness of follow-up

Davidovite h 2020	*	*	*	* (given the types of outcomes assessed)	No	* ^/	*	*	No	Good	Fair	Good	7	Only low birthweight infants included (therefore birthweight partially accounted for). Unmatched. No information about excluding brain injury from comparators e.g. comparing those with IVH grade 3-4 to those without could include those with IVH 1-2; both groups could also include infants with other types of brain injury. Missing data not presented or accounted for. Adjusted the composite brain injury group (which included retinopathy of prematurity in its definition) for gestation, maternal diabetes, small for gestational age, year of birth, bronchopulmonary dysplasia, and receipt of postnatal steroids.
Doyle 2000 #	*	*	*	* (given the types of outcomes assessed)	No	No	*	*	*	Good	Poor	Good	7	IVH and no IVH groups not matched for gestation or birthweight, no adjustment for these variables appears to have been done. Relatively old cohort (most did not receive surfactant), comparator group only includes infants born in the 1980s. Not
Hintz 2018	*	*	*	* (given the types of outcomes assessed)	*	*	*	*	*	Good	Good	Good	9	representative due to time-period of care. Assessed interobserver reliability of central imaging readers. Unmatched Adjusted for gestation, race, sex, multiple gestation, maternal education, sepsis, bronchopulmonary dysplasia, postnatal steroids, surgery for patent ductus arteriosus, necrotising enterocolitis, retinopathy of prematurity. Only 83% follow-up of survivors but those lost to follow-up are accounted for.

Hirovonen 2017	*	*	*	* (given the types of outcomes assessed)	*	* つ な	*	*	*	Good	Good	Good	9	Excluded infants who died at <1 year of age, infants with major congenital anomalies, and those with missing data. Characteristics of those with brain injury not presented. No breakdown by severity of brain injury because that level of detail was not available in the database. No matching but there is stratification by gestation and adjustment for: maternal characteristics, pregnancy characteristics, delivery characteristics, sex, gestation, birthweight, Apgar score at 1-minute, umbilical artery pH, resuscitation provided, NICU admission, receipt of phototherapy, ventilator requirement, antibiotic receipt, respiratory distress syndrome, sepsis, seizures, hyperbilirubinaemia.
Hollebrand se 2021	*	*	*	* (given the types of outcomes assessed)	*	*	*	*	*	Good	Good	Good	9	Gestation similar across all groups and other baseline perinatal characteristics similar across groups. Preterm brain injury and no brain injury group not matched. Unclear if IVH and no IVH group had other brain injuries excluded or may have had more than one injury type (e.g. PVL). Impact of epoch/ era of birth explored and adjusted for.
Hreinsdotti r 2018	*	*	*	No (visual impairment could have been congenital)	*	*	*	*	No	Good	Good	Good	7	Unsure if comparator group in logistic regression includes those with IVH 1-2. Adjusted for gestation, birthweight, retinopathy of prematurity, sex, cognitive score, cerebral palsy.

Jansen 2020	*	*	*	* (given the types of outcomes assessed)	No	No	*	*	No	Good	Poor	Good	6	Excluded infants with congenital abnormalities, metabolic disorders or neonatal meningitis.
Kaur 2020	*	*	*	No (visual or hearing impairment could be congenital)	No	No	*	*	No	Good	Poor	Good	5	Unmatched. Compared IVH with all infant without haemorrhage (of all gestations).
Kiechl- Kohlendorf er 2013	*	*	*	* (given the types of outcomes assessed)	*	*	*	No	No	Good	Good	Fair	7	Low numbers of infants included. Outcomes assessed at 1 year - likely not long enough for robust assessment of neurodevelopmental outcomes; <85% follow-up and no detailed description of those lost to follow up - though authors do state that there were no significant differences between those followed up and those lost to follow up.
Klebermass -Schrehof 2012	*	*	*	No (could have had congenital blindness)	*	*	*	*	No	Good	Good	Good	7	Adjusted for gestation. No clear description of number lost to follow-up, though mentions that follow-up rate at 5.5 years was 54-61%.
Koc 2016	*	*	No	* (given the types of outcomes assessed)	No	No	*	*	No	Good	Poor	Good	5	Small numbers included. No breakdown of characteristics of those with brain injury. No description of IVH grading used or schedule of ultrasound exams; no description of criteria for establishing perinatal asphyxia, number lost to follow-up not stated.
														7/1
Neubauer 2008	*	n/a	*	No (deafness or blindness could have been congenital)	*	*	*	*	*	Fair	Good	Fair	7	Neurodevelopmental assessors not blinded; follow-up rate <85% but paper does give description of those lost to follow-up

Piris Borregas 2019	*	*	*	* (excluded infants with congenital malformations)	No	No	*	*	No	Good	Poor	Good	6	Only those followed up to 7 years included. Excluded infants who died before 36 weeks corrected age, with major malformations, or those with missing data. Unclear if independent odds ratio includes adjustment for covariates. Unclear if those without 'severe brain injury' had other types of brain injury.
Pittet 2019	*	*	*	* (excluded infants with congenital malformations)	No	* //	*	*	*	Good	Fair	Good	8	Excluded infants with congenital malformations affecting neurodevelopment and infants from centres without 5 years of follow-up cognitive testing. Unclear if other types of brain injury excluded from comparator group. Adjusted for gender and socioeconomic status. No significant difference in cognitive outcome between extreme preterms and those 28-30 weeks' gestation. Gestation not adjusted for.
Sherlock 2005#	*	*	*	No (deafness or blindness could have been congenital)	No	No	*	*	*	Good	Poor	Good	6	Comparability of IVH vs. no IVH cohorts not clear - not enough information to determine if groups were comparable with respect to gestational age or birthweight
Tymofiyev a 2018	*	*	*	* (given the types of outcomes assessed)	No	No	*	*	No	Good	Poor	Good	6	Excluded infants with congenital malformations/ syndromes, congenital infections, or those who were too unstable for MR imaging. The last exclusion criteria in particular could limit generalisability quite considerably. Unclear about the validity of grouping the attention scores across different assessment tools together into a dichotomous variable for attention.

Van De Bor 2004	*	*	*	* (excluded those with major congenital malformations)	*	*	No	No	*	Good	Good	Fair	7	IVH vs. no IVH cohorts comparable with respect to gestation; some differences in gender composition but paper states this was controlled for in the analysis. Primary outcome entirely self-reported. Outcomes reported at 14 years.
Van Den Hout 2000	* (exce pt for HIE expo sure grou p)	*	*	* (excluded those with congenital anomalies)	No	No	*	*	*	Good	Poor	Good	7	Low numbers and relatively old cohort. Relative gender imbalance in IVH group compared to those with normal scans or PVL. IVH group also 1.4 weeks more premature than 'normal scan' group.
Vollmer 2003#	*	*	*	No (deafness or blindness could have been congenital)	*	No	*	*	*	Good	Fair	Good	7	Note change in version of Weschler scale during follow-up period. Authors state no difference in mean IQ after change. Baseline characteristics of groups with and without brain injury not given; no indication of matching or adjustment for factors other than gestation.
Vollmer 2006a#	*	*	*	No (deafness or blindness could have been congenital)	*	*	*	*	*	Good	Good	Good	8	Note gender imbalance in cohort as a whole (M>F), but male: female ratio in each group appears similar. No matching or adjustment for covariates. <85% follow-up but clear description of those lost and appears no significant differences.
Vollmer 2006b#	*	*	*	No (deafness or blindness could have been congenital)	No	No	*	*	No	Good	Poor	Good	5	Marked gender imbalance in ventricular dilatation group. Lower birthweight and gestation in groups with abnormal cranial ultrasound. No indication of matching or adjustment. <85% follow-up and the limited description of those lost to follow-up indicates that these babies were of lower birthweight and gestation.

Whitaker 2011	*	*	*	* (given the types of outcomes	*	*	(No)	*	*	Good	Good	Good	8	Severely disabled survivors (n=33) were excluded.
				assessed)										Half had later ultrasounds (just before discharge).
				06										No breakdown of the characteristics of the exposed and comparator groups – unable to assess how comparable they are.
					Y e	クォ								Adjusted for: maternal social risk, sex, gestation, fetal growth ratio, multiplicity, maternal smoking status, maternal alcohol status, labour onset, presentation at birth, base excess on first postnatal blood gas, thyroid status, hypocapnia, hypoxia, systolic hypotension, prolonged ventilation.
						• •	9/	/.						Primary outcome assessment reliant on parental report, albeit via structured interview with some evidence for validity. Interviewers were blinded to the child's history. Parents were blinded to the study hypothesis.
														Less than 85% follow-up (psychiatric interviews in 51% of survivors) however clear descriptions of groups with and without psychiatric evaluation given in table 2 and little apparent difference between groups.
Preterm bra	in injury	: case-co	ontrol stu	adies										
	Case defin ition	Repr esent ative ness of cases	3 Selection of controls	4 Definition of controls	1a	1b	Ascerta inment of exposu re	Sam e meth od of ascer tain ment for cases and contr ols	3 Non- respo nse rate	(0- 1=Poor; 2=Fair; 3+ Good)	y (0=poor; 1=fair; 2+=good)	(0=poor; 1=fair; 2+=good)	Total score: 0-3 high risk of bias; 4-6 moderate risk of bias 7-9 low risk of bias	Additional comments

Martinez- Cruz 2008 (IVH)	*	*	*	*	*	No	*	*	No	Good	Fair	Good	7	Appears to be case-control design hence star ratings are as per case control rating sheet. Controls not well matched for birth weight. No description of whether full information on exposures could be obtained for all cases/controls e.g. missing records etc.
Perinatal stro	Selecti		sfactory;	No =not	Compa (*satis: No =no satisfac done; r	ctorily	Exposure (*satisfacto	tory; No	=not	Subtotal as	sessment		Total score: 0-3 high risk of bias; 4-6 moderate risk of bias	Additional comments
	1	2	3	4	1a	1b	0/	2	3	Selection (0- 1=Poor; 2=Fair; 3+ Good)	Comparabil ity (0=poor; 1=fair; 2+=good)	Exposure / outcome (0=poor; 1=fair; 2+=good)	7-9 low risk of bias	
Ballantyne 2007	No	No	*	*	No	*	No	*	No	Fair	Fair	Fair	4	No description of derivation of exposed cohort - whether single institute or multicentre, whether same community as non-exposed group or not. Predominance of right-handed children amongst controls otherwise similar baseline characteristics. Note male preponderance in exposed group and female preponderance in non-exposed No matching or adjustment for confounders. No description of who performed outcome assessment, whether blinded and independent.
Ballantyne 2008	*	*	*	No	No	*	*	*	No	Good	Fair	Good	6	Excluded children with brain lesions from other causes e.g. head trauma, tumours

				つりゃ										Gestational age of exposed cohort ranged from 32 to 40 weeks. No statement as to whether control group were matched on this. Note preponderance of males in stroke group and females in control group. In study 1, significant numbers of participants did not complete the planned developmental assessments - across exposed and control groups, completeness ranged from 50% for WISC-R to 69% for CELF-R.
Gold 2014	No	No	*	*	No	*	*	*	*	Fair	Fair	Good	6	No description of how subjects were selected or recruited from neurology clinics. Nonexposed group selected from a different source. No description of gestational age of subjects or of controlling for this. Matched for age at follow up, sex, socioeconomic group and maternal education.
									C					Excluded infants with bilateral lesions, a history of hypoxic ischemic encephalopathy, central nervous system infection, in-utero drug exposure, significant closed head injury, or any other condition that might have caused brain damage other than from the stroke.
Kolk 2011	*	*	*	*	No	*	*	*	No	Good	Fair	Good	7	No description of gestational age of subjects or of controlling for this. Difficult to ascertain completeness of follow-up from paper. Adjusted for age of outcome assessment.
Martin 2019	*	*	*	*	No	*	*	*	*	Good	Fair	Good	8	Excluded infants with bilateral lesions, hearing impairment, or a history of a problem that may have caused more global brain damage (e.g. meningitis, closed head injury, hypoxic-ischemic encephalopathy). Matched on age, sex and socioeconomic status

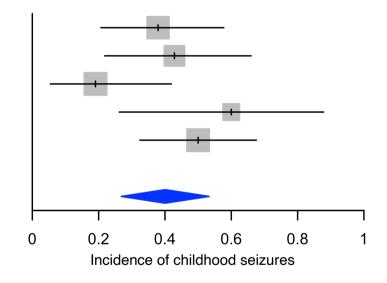
Northam 2018	*	No	*	*	*	*	*	*	*	Good	Good	Good	8	No description of source of unexposed cohort. Matched on age, sex, and maternal education.
Tillema 2008	*	*	*	*)///:-	No	*	*	*	No	Good	Fair	Good	7	Exposed and comparator groups not matched for gestation, but were matched for age, sex and handedness. 17 subjects included initially but 7 of these excluded for various reasons meaning that neurodevelopmental outcome data/Weschler scores only presented for 10 of 17.
Trauner 2013	*	*	*	*	No	No	No	*	No	Good	Poor	Fair	5	Excluded infants if bilateral or multifocal lesions identified, history of meningitis, or history of antenatal drug exposure Matched on age and socioeconomic status No baseline characteristics given to establish comparability of exposed and comparator cohorts. Likely comparable with regards to gestation based on stated inclusion criteria. Main outcome measure based on parental questionnaire - no direct linguistic assessments done, however may not have been feasible/appropriate in such a young cohort. No information on response rate/loss to follow-up. IQ used as covariate IQ combined across the age range and assessed with two different tools. This assumes IQ is fixed which may not be true.

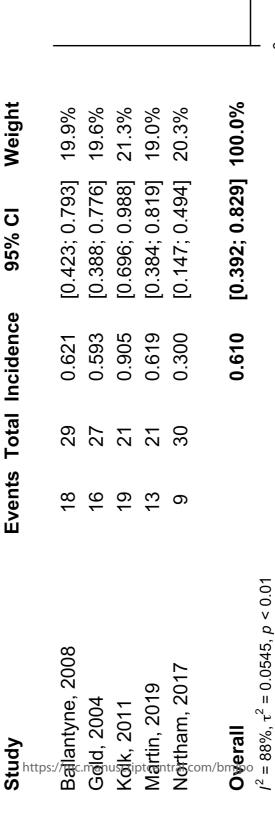
		on (*satis		No =not	(*satist No =no satisfac	emparability satisfactory; to =not satisfactorily one; n/a) Exposure/ Outcome (*satisfactory; No =not satisfactorily done; n/a)				Subtotal ass	sessment		Total score: 0-3 high risk of bias; 4-6 moderate risk of bias 7-9 low risk of bias	Additional comments
	1	2	3	4	la	1b	1	2 3		Selection (0- 1=Poor; 2=Fair; 3+ Good)	Comparabil ity (0=poor; 1=fair; 2+=good)	Exposure / outcome (0=poor; 1=fair; 2+=good)		
Bedford 2001#	*	*	*	No	*	*	No	*	*	Good	Good	Good	7	Matched on sex and age. Study focuses on meningitis in infancy but also presents outcomes after neonatal meningitis. Did not exclude children with other comorbidities e.g. congenital conditions associated with neurodevelopmental impairment. Exposed cases derived from same cohort as Stevens 2003. Outcome assessment based on parent or GP report with no formal neurodevelopmental assessment.
Horváth- Puhó 2021	* * * No			No	*	*	*	*	*	Good	Good	Good	8	Invasive Group B Streptococcal infection diagnosed in the first 89 days (however most of these were neonatal, particularly in the first week of life (45%) hence inclusion. Matched 1:10 on sex, birth year and month, and gestation. Neurodevelopmental impairment defined differently in each cohort. Missing data accounted for and its impact explored.

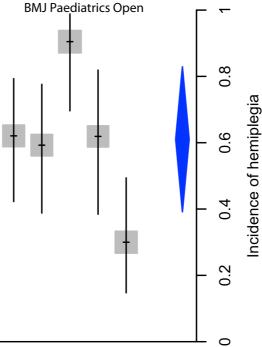
Stevens 2003#	(*)	(*)	* ions: case	No se control studies	*	*	*	*	No	Good	Good	Good	7	Exposed cohort based on recall of consultant paediatricians filling out monthly returns thus may be biased towards more severe or otherwise memorable cases. Some in comparator group selected from a different hospital than exposed cohort. Matched on hospital of birth, birth weight and sex. Results stratified by birthweight Significant rate of loss to follow-up.
	Case defin ition	Repr esent ative ness of cases	3 Selection of controls	4 Definition of controls	la	16	Ascerta inment of exposu re	Sam e meth od of ascer tain ment for cases and contr ols	3 Non- respo nse rate	(0- 1=Poor; 2=Fair; 3+ Good)	y (0=poor; 1=fair; 2+=good)	(0=poor; 1=fair; 2+=good)	Total score: 0-3 high risk of bias; 4-6 moderate risk of bias 7-9 low risk of bias	Additional comments
Martinez- Cruz 2008	*	*	*	*	No	No	*	*	No	Good	Poor	Good	6	Excluded those with history of parental consanguinity or TORCH infections. Number of those with and without meningitis who may have had other types of brain injuries not specified – unable to assess overlap/ impact of meningitis alone. Odds ratio presented for meningitis does not appear to be crude so potential adjustment for confounding factors but no description of this in the methods section. No description of proportion of missing data.

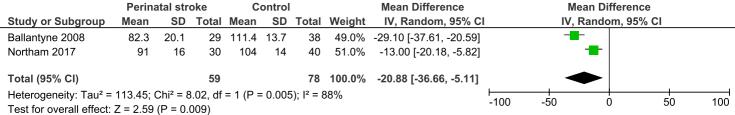
			isfactory; one; n/a)	No =not		ctorily	Exposure/ Outcome (*satisfactory; No =not satisfactorily done; n/a)			Subtotal assessment			Selection (*satisfacto ry; No =not satisfactoril y done; n/a)	Additional comments
	1	2	3		la	16	1	2	3	Selection (0- 1=Poor; 2=Fair; 3+ Good)	Comparabil ity (0=poor; 1=fair; 2+=good)	Exposure / outcome (0=poor; 1=fair; 2+=good)	Total score: 0-3 high risk of bias; 4-6 moderate risk of bias 7-9 low risk of bias	
Koc 2016	No	*	*	*	No	No	*	*	No	Fair	Poor	Good	5	Representativeness not clear as no description given of babies who did not complete follow-up at the study institution. No apparent adjustment for gestation or other covariates. Pre-therapeutic hypothermia era. Small number, no breakdown of characteristics or other neurodevelopmental outcomes by brain injury Number of those with and without birth asphyxia who had other types of brain injuries e.g. IVH not specified.
Lee- Kelland 2019	No	*	*	*	*	*	*	No	No	Good	Good	Good	6	Excluded those who underwent therapeutic hypothermia outside of the standard criteria, infants with metabolic disorders and non-English speaking infants. Matched on age, sex and social class.
Tonks 2019	*	No	*	*	No	*	*	*	No	Good	Fair	Good	6	Included cases had no diagnoses other than encephalopathy. Excluded infants with neurological issues other than encephalopathy. Matched on age, sex and socioeconomic status.

13 14 Study	Events	Total	Incidence	95% CI	Weight
15 16					
¹⁷ Ballantyne, 2008	11	29	0.379	[0.207; 0.577]	22.2%
18 19 Kolk , 2011	9	21	0.429	[0.218; 0.660]	19.0%
²⁰ ₂₁ Martin, 2019	4	21	0.190	[0.054; 0.419]	23.1%
²² Tilema, 2008	6	10	0.600	[0.262; 0.878]	12.5%
²³ ²⁴ Trauner, 2001	17	34	0.500	[0.324; 0.676]	23.1%
25 26					
²⁷ ₂₈ Overall			0.401	[0.268; 0.533]	100.0%
$\frac{29}{30}I^2 = 56\%, \tau^2 = 0.0124, \rho = 0.06$				- · · · •	









0 1 2 3 4 5 6 7 3 9 0 1 2 3 4 5															
5	06	Perinat				ontrol		14/-1-1-4	Mean Difference				ifference		
, -	Study or Subgroup	Mean 78.4	16		Mean 105.8			Weight	IV, Random, 95% CI -27.40 [-34.34, -20.46]			, Rando	om, 95%	UI .	
))	Ballantyne 2008 Northam 2017	78.4 95	16 17	30	105.8	11.9	38 40	50.3% 49.7%	-27.40 [-34.34, -20.46] -13.00 [-20.30, -5.70]						
) 	Total (95% CI) Heterogeneity: Tau ² =			59			78	100.0%		——		•			
<u>?</u> 3	Test for overall effect: 2				1 (1-1	J.003)	, I ⁻ – 6 <i>1</i>	70		-100	-50	(Ó	50	100
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