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 (WPPSI); White Matter Injury (WMI); Wide Range Achievement Test (WRAT)

	Author Year Country Study type	Population Exposures Comparator Ascertainment/ definition	Outcomes	Main result(s)
1	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** aOR 0.82 95%CI (0.66, 1.01)
2*	Beaino 2010[68] France Prospective cohort	**Population** • Gestation <33 weeks • 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 • No IVH **Ascertainment/ definition** • Ultrasound imaging undertaken and reviewed by neonatologists or radiographers	**Outcomes** • Cerebral palsy **Measurement/assessment** • Standardised questionnaires completed by physicians **Follow-up** • 5 years • 77% follow-up	**Cerebral palsy** **Grade 3 IVH** 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
3	Brouwer 2012[18] Netherlands Prospective cohort	**Population** • 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	**Outcomes** • 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	**Cerebral palsy** 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 <p 5 (definite motor problems)** IVH grade 3 n=6, 26% IVH grade 4 n=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; **Production scale**

				IVH n=23, 87±22; IVH <30weeks' gestation n=16, 85±24 No IVH n=24, 93±14 **<u>Intelligence quotient (n; mean +/-SD)</u>** 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%) No IVH n=23; IQ 98±15, IQ>85 n=17 (74%) **<u>Behavioural outcomes</u>** **CBCL parental score: mean T score ±SD, n in subclinical range (%)** **Total scale** IVH n=26: 48.2 ±8.4, n=3 (12%) IVH <30 weeks' gestation n=20: 46.9 ±8.3, n=2 (10%) No IVH <30 weeks' gestation n=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%) No IVH <30 weeks' gestation: 49.2 ±9.1, n=5 (21%) **Externalizing problem scale** IVH: 46.8 ±9.4, n=2 (8%) IVH <30 weeks' gestation: 45.1 ±9.5, n=1 (15%) No IVH < 30weeks' gestation: 43.7 ±7.5, n=0 (0%) **TRF teachers score: mean T score ±SD, n in subclinical range (%)** **Total scale** IVH n=25: 54.7 ±8.7, n=6 (24%) IVH <30 weeks' gestation n=19: 53.9 ±9.0, n=4 (21%) No IVH <30 weeks' gestation n=22: 50.9 ±9.8, n=4 (18%) **Internalising problem scale** IVH: 53.2 ±10.8, 4 (16%) IVH <30 weeks' gestation: 52.2 ±11.7, n=3 (16%) No IVH <30 weeks' gestation: 52.4 ±11.4, n=7 (32%) **Externalizing problem scale** 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%) N=13 (41%) had repeated a school class, had educational help and/or attended special education
4	Campbell 2021[10] USA Prospective cohort 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)** • Unmatched • 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 • 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	**<u>Neurodevelopmental burden</u>** **No impairments** IVH and WMI n=24, 38% WMI n=12, 40% IVH n= 86, 69% No IVH or WMI n=487, 76% **No cognitive impairment; 1 or more of cerebral palsy, ASD, or epilepsy** IVH and WMI n=4, 6% WMI n=4, 13% IVH n=7, 6% No IVH or WMI n=26, 4% **<u>Cognitive</u>** **Normal cognitive function** IVH and WMI n=8, 13% WMI n=5, 17% IVH n=41, 33% No IVH or WMI n=235, 37% **Cognitive impairment (moderate to severe)** **IVH and WMI** n=35, 56% OR 5.01 95% CI (2.94, 8.54) aOR 4.49 95% CI (2.49, 8.11) **WMI** n=14, 47% OR 3.51 95% CI (1.67, 7.37) aOR 5.07 95% CI (2.13, 12.02) **IVH** n=31, 25% OR 1.34 95% CI (0.85, 2.1) aOR 1.21 95% CI (0.73, 1.98) **No IVH or WMI** n=128. 20% Reference category **Low cognitive function** IVH and WMI n=18. 30% WMI n=10, 34% IVH n=50, 41% No IVH or WMI n=269, 43% **Moderate cognitive impairment** IVH and WMI n=17, 28%

				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 IQ** **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% OR 16.85 95% CI (9.29, 30.55) aOR 13.43 95% CI (7, 25.78) **WMI** 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) **IVH** 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** n=25, 4% 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) **WMI** n=2, 7% OR 1.02 95% CI (0.23, 4.42) aOR 0.74 95% CI (0.09, 5.88) **IVH** 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%

				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% **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 Three prospective cohort studies	**Population** • Gestation 22-27 weeks • Born 1991-1992; 1997-1998; 2005-2006 **Exposure** • IVH grade 3-4 (n=100) • cPVL (n=38) **Comparator** • Unmatched • No IVH grade 3-4 (n=446) • No cPVL (n=508) **Ascertainment/ definition** • Not specified	**Outcomes** • Survival with major disability (composite) • Survival without major disability (composite) • Cognitive • Cerebral palsy • Visual impairment (acuity less than 6/60 in better eye) • Hearing impairment (requiring hearing aid or cochlear amplification) **Assessment/ measurement** • GMFCS • WISC III • WISC IV • Differential Abilities Scales 2nd edition **Follow-up** • 8 years • 91% follow-up of survivors	**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 1997 and 2005 cohort only: OR 4·01 95% CI (1·25, 12·84) p=0.02 **cPVL** 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
6	Chou 2020[69] 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 **Assessment/ measurement** • ICD 9 **Follow-up** • 2-12 years (mean 9 years) • Completeness of follow-up not specified	**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[29] 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[70] Australia	**Population** • Birthweight 500–1499 g • Born 1980-1981; 1992	**Outcomes** • Survival • Cerebral palsy	**Cerebral Palsy** Grade of IVH

	Prospective Cohort	**Exposure** **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=110) • 1992 epoch (n=113) **Ascertainment/ definition** • Ultrasound imaging • Post-mortem examination • Papile classification	**Measurement/assessment** • Clinical assessment by blinded paediatricians • Functional assessment **Follow-up** • 5 years • 93% follow-up for 1980s epoch • 94% follow-up for 1992 epoch	**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%
9	Hintz 2018[17] USA Retrospective cohort	**Population** • Gestation 24-28 weeks • Born 2005-2009 **Exposure** <u>MRI</u> • Mild WMI (n=223) • Moderate WMI (n=51) • Severe WMI (n=15) • Any cerebellar lesion (n=57) • Significant cerebellar lesion (n=39) <u>Early cranial ultrasound</u> • No IVH 3-4 or cPVL (n=341) • IVH 3-4 or cPVL (n=32) <u>Late cranial ultrasound</u> • 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=284) **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 ultrasound lesions combined	**Outcomes** • Moderate to severe disability (composite) • Minimal or no disability • Cognitive • Cerebral palsy • Hearing • Vision **Measurement/ assessment** • WISC IV • Neurological exam • GMFCS • Clinical examination • Parental report **Follow-up** • 6-7 years • 83.3% follow-up of survivors	**<u>White matter injury</u>** **Moderate to severe disability** No white matter injury, n=8, 9% Mild white matter injury, n=27, 12% Moderate 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 disability** No white matter injury, n=47, 55% Mild white matter injury, n=88, 224% Moderate 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, 90.1 (15.5) 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 <70** No white matter injury, n=7, 8% Mild white matter injury, n=25, 11% Moderate white matter injury, n=6, 12% Severe 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=27, 32% Mild white matter injury, n=100, 45% Moderate white matter injury, n=29, 57% Severe white matter injury, n=13, 87% p<0.0001 **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 **Any cerebral palsy** 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 **<u>Cerebellar lesions</u>** **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 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% **<u>Early cranial ultrasound abnormalities</u>** **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 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 ≥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 (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% **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, 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 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	**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 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) • Differential Abilities Scale 2nd edition (2005 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** • 8 years • Follow-up 85-91.4%	**Cognitive** **IQ score <-2 SD** IVH grade 4 n=5, 42% p=0.08 (X^2 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 (X^2 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 (X^2 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 (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% 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 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 (X^2 trend) IVH grade 3 n=9, 45% No IVH n=79, 26% IVH 3-4: OR 4.7 95% CI (2.21, 9.97) p<0.001
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	**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 (0.86, 15.41) p=0.08 aOR 4.95 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 (1.23, 88) 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 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[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) **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)	**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[32] 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** • 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	**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)
15	Kiechl-Kohlendorfer 2013[28] Austria Prospective cohort	**Population** • Gestation <32 weeks • Born 2003-2006 **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	**Outcomes** • Cognitive **Measurement/assessment** • 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	**Delayed numerical skills** Intracranial haemorrhage (all grades) n=11, 40,7% aOR 4.66 95% CI (1.56, 13.93) p=0.007 Intracranial haemorrhage grade 3-4 n=3, 11.1% PVL n=2, 7.4% Intraparenchymal echodense lesions n=0
16	Klebermass-Schrehof 2012[20] Austria Prospective cohort	**Population** • Gestation <32 weeks • Admitted to NICU 1994-2005 **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	**Outcomes** • Neurosensory impairment (composite) • Motor • Cerebral palsy • Language • Visual • Hearing **Measurement/assessment** • BSID II (MDI, PDI) • K-ABC • Beery-Buktenica Developmental Test of VMI • Clinical assessment **Follow-up** • 5 years (1 ,2, and 3.5 years) • Only those with follow-up included (loss to follow-up not specified)	**Outcomes at 5.5 years** **Group 1: infants born < 28 weeks' gestation** **KABC <70** 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
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

		Comparator (n=315) • No IVH **Ascertainment/ definition** • Medical records • Ultrasound diagnosis. • Papile classification.	• Free field audiometry • Tympanometry • Pure Tone Audiometry **Follow-up** • Mean age 7.8±3.7 years • 100% follow-up (case control)	
19	Neubauer 2008[12] Germany Prospective cohort	**Population** • Birthweight <1000g • 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) **Ascertainment/ definition** • Ultrasound diagnosis • Papile classification	**Outcomes** • Neurodevelopmental impairment (composite) **Measurement/assessment** • Modified Touwen test • K-ABC • Snijders-Oomen Non-Verbal Intelligence Test • Hamburg-Wechsler Intelligence Test for Children **Follow-up** • 10 years • 79% follow-up	**<u>Logistic regression for major impairment vs. normal development or minor impairment at school age</u>** **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	Piris Borregas 2019[13] Spain Retrospective cohort study	**Population (n=1001)** • Birthweight 500-1250g • Born 1991-2008 **Exposure** • Severe brain injury (IVH grade 3-4, ventriculomegaly III, PVL or intraparenchymal echodense lesion grade 3 or greater) **Comparator** • Unmatched **Ascertainment/ definition** • Neonatal database • Ultrasound diagnosis • Papile classification	**Outcomes** • Neurodevelopment (composite) • Cognitive • Motor • Hearing impairment • Visual impairment **Assessment/ measurement** • GMFCS **Follow-up** • 7 years	**<u>Poor neurodevelopmental outcome</u>** **Severe brain injury**, n=46, 32% **No severe brain injury**, n=208, 24% OR 1.41 95% CI (0.94, 2.10) p=0.09 Independent OR 2.02 95% CI (1.22, 3.31) p=0.18 **Severe brain injury (birthweight 500-1000g)** Independent OR 2.02 95% CI (1.22, 3.31)
21	Pittet 2019[25] Switzerland Prospective cohort study	**Population** • Gestation <30 weeks • Born 2006 **Exposure** • IVH grade 3-4 or cPVL (n=22) **Comparator** • Unmatched • No IVH grade 3-4 or cPVL (n=213) **Ascertainment/ definition** • Swiss neonatal network follow-up group	**Outcomes** • Cognitive • Cerebral palsy • Visual impairment • Hearing impairment **Assessment/ measurement** • Kaufman ABC • Neurological exam • GMFCS **Follow-up** • 5.5 – 6 years • 81% follow-up	**<u>Cognitive (K-ABC – MPC score < 1SD)</u>** IVH 3-4 or PVL OR 2.9 95% CI (1, 8.2) p=0.04 aOR 2.3 95% CI (0.7, 7.7) p=0.15 **<u>Use of early intervention/ therapy service</u>** IVH 3-4 or cPVL aOR 2.7 95% CI (1.3, 5.7)
22	Sherlock 2005[14] Australia Prospective cohort	**Population** • Gestation <28 weeks • Birthweight <1000g • Survivors born 1991-1992 **Exposure** • IVH Grade 1 (n=47) • IVH Grade 2 (n= 25) • IVH Grade 3 (n= 12) • IVH Grade 4 (n= 6) **Comparator** • Matched on sex, mother's country of birth, and health insurance status • 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	**Outcomes** • Disability (composite) • Neurosensory disability (composite) • Cognitive • Motor • Cerebral palsy • Speech and language • Visual impairment • Hearing impairment **Measurement/assessment** • Medical assessment • Movement ABC • WISC-III • Tower of London • Rey Complex Figure • WRAT **Follow-up** • Mean 8.7 years • 92.3% follow-up	**Abnormal movement** No IVH (n=39, 22.5%) Grade 1 IVH (n=11, 25%) Grade 2 IVH (n=6, 30%) Grade 3 IVH (n=3, 27.3%) Grade 4 IVH (n=4, 100%) X^2 linear trend = 5.3; P = 0.021 **Cerebral palsy** No IVH (n=12, 6.7%) Grade 1 IVH (n=3, 6.4%) Grade 2 IVH (n=6, 24%) Grade 3 IVH (n=2, 16.7%) Grade 4 IVH (n=6, 100%) X^2 linear trend = 31.7; p <0.0001 **Moderate to severe cerebral palsy** No IVH (n=4, 2.2%) Grade 1 IVH (n=0, 0%) Grade 2 IVH (n=4, 15%) Grade 3 IVH (n=1, 8.3%) Grade 4 IVH (n=5, 83.3%) X^2 linear trend = 40.8; p <0.0001 **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 **IQ score mean (SD)** No IVH 0.71 (1.25) Grade 1 IVH 0.76 (1.32) Grade 2 IVH 0.71 (1.12) 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 1 IVH 96.3 (15.7) 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 = 0.12 **Perceptual organisation index mean (SD)** No IVH 98.5 (16.3) 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 = 0.042 **Freedom 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 = 0.026 **Processing 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 = 0.033 **Tower of London (executive function) raw score mean (SD)** No IVH 73.3 (14.4) 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 = 0.003 **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%) X^2 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 2018[33] USA 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** • MRI imaging reviewed by a blinded paediatric neuroradiologist • Used own classification of white matter injury • 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	**<u>Attention (abnormal)</u>** 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	**<u>Disability at 5 years</u>** 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 **<u>School performance at 5 years</u>** **Special education** No IVH n=17 (8.7%) IVH grade 3-4 n=3 (20%) p=0.02 **<u>School performance at 9 years</u>** **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 **<u>School performance at 14 years</u>** **Slow learner** No IVH n=93 (44.1) IVH grade 3-4 n=4 (23.5%) **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) 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[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)

				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 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) **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) **Developmental test of visual motor integration % (n)** IVH 0 (16) PVL 0 (7) No brain injury 0 (17) **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) **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 **Ascertainment/ definition** • Ultrasound imaging reviewed by two experienced observers • In-house classification used	**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	**<u>Neurodevelopmental status</u>** **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%) **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%) cPVL (6, 50%) No brain injury (14, 6%)
27 *	Vollmer 2006a[21] UK Prospective cohort	**Population** • Gestation <33 weeks • Born 1985-1991 **Exposure** • Bilateral brain lesions (n=201) • Right-sided brain lesion (n=41)	**Outcomes** • Motor • Cognitive • Cerebral palsy • Visual	**TOMI error score, mean (SD)** Normal scan 2.78 (2.1) 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)

		• Left-sided brain lesion (n=57) Brain lesion types Non-parenchymal: • Uncomplicated IVH Parenchymal: • Haemorrhagic parenchymal infarction (HPI) • cPVL • PV flare **Comparator (n=369)** • Unmatched • Normal ultrasound **Ascertainment/ definition** • Ultrasound imaging reviewed by two experienced observers • Modified Stewart classification	**Measurement/ assessment** • Neurological examination (modified Amiel-Tison assessment) • TOMI • WISC-R • Test of VMI **Follow-up** • 8 years • 80% follow-up	All right-sided lesions 3.5 (2.9) Right-sided non-parenchymal lesions 2.7 (1.8) Right-sided parenchymal lesions 4.9 (3.8) All bilateral lesions 4.5 (4.3) Bilateral non-parenchymal lesions 4.1 (3.7) Bilateral parenchymal lesions 4.9 (4.7) ANOVA for parenchymal lesions only p <0.0001 ANOVA including parenchymal and non-parenchymal lesions p <0.0001 ANOVA excluding parenchymal lesions, p <0.0001 **VMI centile, mean (SD)** Normal scan 59.2 (30.0) All left-sided lesions 40.3 (30.1) Left-sided non-parenchymal lesions 46.8 (31.0) Left-sided parenchymal lesions 21 (22) 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 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)

				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 only, p <0.0001 ANOVA including parenchymal and non-parenchymal lesions, p <0.0001 ANOVA excluding parenchymal lesions, p =0.59
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 • 81% follow-up	**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 • 'Non-disabled' survivors • Born 1984-1987 **Exposure** • IVH (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 inter-observer reliability checked. • Paneth classification	**Outcomes** • 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** **Current ADHD- inattentive type** **IVH** OR 0.97 95% CI (0.21-4.47) aOR 1.01 95% CI (0.19-5.44) **Parenchymal lesions and/or ventricular enlargement** OR 7.64[b] 95% CI (2.20-24.48) aOR 6.83[c] 95% CI (1.26-36.91) **Lifetime ADHD – inattentive type** **IVH** OR 0.83 95% CI (0.34-2.04) aOR 0.64 95% CI (0.24-1.74) **Parenchymal lesions and/or ventricular enlargement** OR 2.71 95% CI (0.94-7.82) aOR 1.13 95% CI (0.31-4.10) **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** 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) **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) **<u>Current diagnoses additionally controlled for full score IQ and motor function</u>** **<u>ADHD inattentive type</u>** **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) **<u>Major depression</u>** **IVH** OR 0.43 95% CI (0.16-1.11) aOR 0.40 95% CI (0.15-1.05) **<u>Tic disorders</u>** **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) **<u>Obsessive compulsive disorder</u>** **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)
Perinatal stroke				
30	Ballantyne * 2007 [41] USA Prospective cohort	**Population** • 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 classification	**Outcomes** • 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 • 100% follow-up	**<u>Speech and language</u>** **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: 73.75 (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) **CELF-R Total mean (SD)** 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] * USA Prospective cohort	**Population** • 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	**Outcomes** • Cognitive (academic skills) • Speech and language • Motor • Cerebral palsy • Vision • Epilepsy **Measurement/ assessment** • WISC- Revised • WRAT- Revised • CELF- Revised • PPVT-Revised • WPPSI/WPPSI- Revised • WISC-III **Follow-up** • 7-12 years • 100% follow up	**<u>Hemiparesis</u>** Stroke n=18,62% **<u>Visual field deficit</u>** Stroke n=7, 26% **<u>Seizures</u>** Stroke n=11, 38% **<u>Cognitive, mean (SD)</u>** **<u>Verbal IQ (WISC-R)</u>** **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 **<u>Performance IQ (WISC-R)</u>** **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 **<u>Full scale IQ (WISC-R)</u>**

				Time point 1 (mean age 7-8 years) Stroke 94.7 (20.4) Control 123 (15) **Time point 2 (mean age 10 – 12 years)** Stroke 96.1 (19.1) Control 122.3 (10.2) Between group affect (stroke vs. control) p<0.0001 Time effect not significant **Reading (WRAT -R)** **Time point 1 (mean age 7-8 years)** Stroke 85 (16.1) Control 113 (13.3) **Time point 2 (mean age 10 – 12 years)** Stroke 89.4 (13.3) Control 108.9 (13.8) Between group affect (stroke vs. control) p<0.0001 Time effect not significant Time group interaction p=0.045 **Spelling (WRAT -R)** **Time point 1 (mean age 7-8 years)** Stroke 82.5 (18.2) Control 106.2 (15.9) **Time point 2 (mean age 10 – 12 years)** Stroke 87 (16.8) Control 104.6 (13.1) Between group affect (stroke vs. control) p=0.001 Time effect not significant **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) Control 113.1 (16.2) Between group affect (stroke vs. control) p<0.0001 Time effect not significant **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) Control 105.8 (11.9) Between group affect (stroke vs. control) p<0.0001 Time effect p=0.017 **Total language score** **Time point 1 (mean age 7-8 years)** Stroke 76.9 (11.1) Control 105.6 (14.2) **Time point 2 (mean age 10 – 12 years)** Stroke 79.1 (18.3) Control 109.8 (14) Between group affect (stroke vs. control) p<0.0001 Time effect not significant **Vocabulary score** **Time point 1 (mean age 7-8 years)** Stroke 97.5 (19.7) Control 117.1 (17) **Time point 2 (mean age 10 – 12 years)** Stroke 99.9 (20) Control 118.9 (13.9) Between group affect (stroke vs. control) p=0.002 Time effect not significant
32	Gold 2014[35] USA	**Population** • Gestation not provided • Birth years not provided	**Outcomes** • Cognitive (IQ and memory) • Motor • Cerebral palsy	**Cognitive** **Memory** **Stories immediate recall** Controls, mean (SE)13.5 (0.7)

	Prospective cohort	**Exposure (n=27)** • 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 • Healthy controls • Recruited through local advertising **Ascertainment/ definition** • Single, unilateral brain lesion in an arterial vascular distribution, either identified in the neonatal period with neuroimaging, or identified later in infancy after presentation with a hemiparesis and imaging documentation of an old unilateral infarct (presumed perinatal stroke) • Recruited from paediatric neurology clinics • Severity graded 1-5 using Trauner/ Vargha-Khaldem classification	**Measurement/ assessment** • WISC-III • Dots and Stories subtests of the Children's Memory Scales **Follow-up** • 6-16 years • 100% follow-up	Stroke, mean (SE) 8.4 (0.8) p<0.001 Stroke and seizures, mean (SE)7 (0.8) Stroke and no 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 **Delayed recall** Controls, mean (SE) 13.9 (0.8) Stroke, mean (SE) 7.9 (0.8) p<0.001 Stroke and seizures, mean (SE) 6.2 (0.9) Stroke and no seizures, mean (SE) 10 (1.2) p=0.02 Right lesion, mean (SE) 7.3 (1.1) Left lesion, mean (SE) 8.3 (1.2) p=0.56 **Delayed recognition** Controls, mean (SE) 11.5 (0.5) Stroke, mean (SE) 8 (0.8) p=0.001 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) **<u>Motor (hemiparesis)</u>** 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 **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	**<u>Neuromotor impairment (Paediatric Stroke Outcome Measure)</u>** **Neonatal stroke** Severe n=4, 19% Moderate n=9, 43% Good n=6, 28.6% Normal n=2, 9.5% **<u>Cognitive/ neuropsychological</u>** **<u>Attention and executive function, mean, SD, 95% CI</u>** **Tower** Control 0.22, 0.64 (-0.05, 0.48) 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 **Statue**

				Control 0.26, 0.77 (-0.03, 0.54) Neonatal stroke -0.23, 1.09, (-0.73, 0.28) p=0.086 **Design fluency** Control 0.18, 1.04 (-0.25, 0.61) 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 **Finger discrimination** 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 **Arrows** 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 **Picture perception** Control 0.13, 1.00 (-0.49, 0.24) Neonatal stroke -0.09, 1.03 (-0.56, 0.37) p=0.341 **Memory and learning, mean, SD, 95% CI** **Memory for faces** Control 0.42, 0.74 (0.11, 0.73) Neonatal stroke -0.41, 1.15 (-0.96, 0.15) p=0.016

				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= 8, 38% Very severe functional impairment n= 4, 19% **Epilepsy** Stroke n=9, 33.3%
34	Martin 2019[40] * USA Prospective cohort	**Population** • Gestation not provided • Birth years not provided **Exposure (n=21)** • Left hemisphere (n=13) • Right hemisphere (n=8) **Control (n=21)** • Matched on age, sex and socioeconomic status • Healthy controls • Recruited from local community using adverts **Ascertainment/ definition** • Unilateral focal brain lesion (ischaemic or haemorrhagic thought to have occurred between 28 weeks' gestation and 28 days postnatally) • Recruited from a neurologist in San Diego	**Outcomes** • Hearing • Motor (cerebral palsy) • Epilepsy **Measurement/ assessment** • Auditory neglect task **Follow-up** • 6-14 years (mean 9-10 years) • Completeness not specified	**Time to correct response** **Left sided sound:** Left stroke 1550 ms±580 ms Control 1465 ms±666 ms *not significant* Right stroke 1708 ms±951 ms Control 1074 ms±514 ms* (p=0.043) **Right sided sound** Left stroke 1595 ms±553 ms Control 1501 ms±720 ms *not significant* Right stroke 2032 ms±1496 ms Control 1291 ms±792 ms p=0.118 **Number of correct auditory responses** **Left sided sound** Left stroke 5.15±1.21 Control 4.62±1.26 p=0.338 Right stroke 4.25±1.67 Control 4.63±1.19 p=0.307 **Right sided sound** Left stroke 4.31±1.18 Control 4.62±1.71 p=0.3 Right stroke 4.50±1.31 Control 5.50±0.92 p=0.05 **Seizures outside of neonatal period** Stroke n=4; 19% **Hemiparesis** Stroke n=13, 70% Right stroke n=3, 28% Left stroke n=10, 77%
35	Northam 2018[37] 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[38] USA Retrospective cohort	**Population** • Gestation not provided • Birth years not provided **Exposure (n=10)** • Left perinatal stroke **Control (n=10)**	**Outcomes** • Cognitive • Epilepsy **Measurement/ assessment** • WISC-III • Language activation tasks – Verb generation task whilst in an fMRI	**Focal epilepsy** Stroke, n=6, 60% **Cognitive, mean (SD)** Stroke VIQ 84 (13.4) Control VIQ 108 (14.2) p=0.002

		• 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	**Follow-up** • 6-16 years • 100% follow up	Stroke FSIQ 80 (14.1) Control FSIQ 108 (11.7) p=0.001
37	Trauner 2001[39] 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	**<u>Cognitive</u>** **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 **<u>Seizures (outside of the neonatal period)</u>** Stroke n=17, 50% (missing data for 5 subjects)
Central nervous system infections				
38	Bedford 2001[42] 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** • 5 years • 85-94% follow-up	**<u>Neuromotor disability</u>** 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=20, 1% **Mild disorder** Meningitis, n=66, 24% No meningitis, n=275, 20% **No disability** Meningitis, n=138, 50% No meningitis, n=1095, 79%
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 **Assessment/ Measurement** • 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	**<u>Any neurodevelopmental impairment RR (95%CI)</u>** **<u><5 years</u>** Denmark GBS meningitis 7·80 (4·42-13·77) Netherlands GBS meningitis 5·30 (2·57-10·89) **<u><7 years</u>** Denmark GBS meningitis 4·69 (2·78-7·89) Netherlands GBS meningitis 3·71 (1·05-6·72) **<u><10 years</u>** Denmark GBS meningitis 3·47 (2·19–5·50) Netherlands GBS meningitis 2·81 (1·69-4·68) **<u><11 years</u>** Netherlands GBS meningitis 2·99 (1·83-4·88) **<u><15 years</u>** Denmark GBS meningitis 3·15 (1·82–5·46) **<u>Moderate to severe neurodevelopmental impairment RR (95%CI)</u>** **<u><5 years</u>** Denmark GBS meningitis 8·49 (4·28-16·86) Netherlands GBS meningitis 5·13 (2·24-11·79) **<u><7 years</u>** Denmark GBS meningitis 5·27 (2·80-9·92) Netherlands GBS meningitis n/a **<u><10 years</u>** Denmark GBS meningitis 3·88 (2·15–6·99) Netherlands GBS meningitis 3·05 (1·62-5·73) **<u><11 years</u>** Netherlands GBS meningitis 3·34 (1·77-6·33) **<u><15 years</u>** Denmark GBS meningitis 4·52 (2·35–8·67)
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%

	Mexico Retrospective case control	• Born 1990-2005 **Exposure (n=22)** • Neonatal meningitis **Comparator (n=374)** • No meningitis **Ascertainment/ definition** • Meningitis not defined	**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	**Odds of previous neonatal meningitis if sensorineural hearing loss** OR 4.368, 95% CI (1.7, 10.9) p= 0.002
41	Stevens 2003[44] England & Wales Prospective cohort 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** • WISC-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) **Severe 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=19, 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% **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) 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%
Hypoxic-ischaemic encephalopathy				
42	3383 Koc 2016[24] Turkey Retrospective cohort	**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 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

				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 **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% **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 **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 **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
44	Tonks 2019[47]* United Kingdom Prospective cohort study	**Population** • Gestation ≥36 weeks • Born 2008-2011 • 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% **Comparator** Below 1 SD 5% HIE vs comparator scores, p = 0.034