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ORIGINAL ARTICLE

Long-term neurodevelopmental outcome in preterm infants with intraventricular haemorrhage

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Background: Intraventricular haemorrhage (IVH) is one of the key risks for long-term neurodevelopmental issues. There remains controversy over the impact low-grade IVH has on the long-term outcome of premature infants. This study describes the long-term neurodevelopmental impact of Grade I and II IVH in former preterm infants in the early school years.

Methods: This is a retrospective cohort analysis from one tertiary neonatal intensive care unit (NICU) in Australia including all infants born at <30 weeks' gestation and admitted to the NICU between 2006 and 2013 with complete ultrasound reports and follow-up results. Results of standardised tests for neurodevelopmental outcomes at 5 and 8 years were compared between infants who suffered mild IVH and infants who had normal head ultrasounds.

Results: During the study period, 491 infants <30 weeks gestation were admitted; 275 patients had full follow-up data available. We found no significant difference in examined outcomes at 5- and 8-year follow-up.

Conclusion: Mild IVH does not affect cognitive, motor and academic outcomes at school age.

Key words: intraventricular haemorrhage; long-term outcome; neurodevelopmental outcome; premature infant.

What is already known on this topic

1 Intraventricular haemorrhage (IVH) is one of the main conditions that contributes to poorer long-term developmental outcomes in premature infants.
2 Recent literature showed that mild IVH was associated with higher odds of death or moderate–severe neurodevelopmental impairment at 18–24 months.
3 Over the past decade, there have been major advances in neuroprotective measures for infants born prematurely.

What this paper adds

1 We found no significant difference in neurodevelopmental outcomes in preterm infants who suffered a mild IVH compared to infants without intraventricular haemorrhage (IVH) at school age.
2 We saw an overall improvement in results over time for the patients who were affected by mild IVH.
3 Ongoing research is required to determine meaningful measurements to predict developmental outcomes.

Over the last two decades, survival of infants born before 30 weeks' gestation has dramatically improved. Australia and New Zealand Neonatal Network data have shown an improvement in survival at 26 weeks from 80% in 2000 to 92.1% in 2018.[1] Despite the improvements in survival, the proportion of children with developmental impairments remains high.[2] One of the main conditions that contributes to poorer long-term developmental outcomes in premature infants is intraventricular haemorrhage (IVH). The incidence of all grades of IVH in the extremely preterm population has been described between 31 and 36%, while the incidence of severe IVH varies between 10 and 17%.[3,4] Previous studies have shown that any IVH can severely impact long-term neurodevelopmental outcomes. The severity of these adverse effects increases incrementally with the severity of IVH grade.[5]

The predicted damage from an IVH can be explained through two possible pathophysiological pathways. First, IVH originates within the germinal matrix and therefore leads to local destruction of glial precursor cells migrating to cortical layers.[6] These immature cells form a critical part in post-natal myelination. Disruption of myelination could lead to motor impairment. Studies have found reduced grey matter volume following mild IVH in premature infants at term which could be a result of this loss of cortical organisation and growth.[7] Second, the clinical associations of preterm birth that led to IVH, such as hypotension, poor cerebral perfusion, hypoxia and acidosis, can potentially affect the white matter

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adversely.[8] Argyropoulo et al. found in a series of near-term MRIs in very low birthweight infants that suffered a low-grade IVH 'cortical underdevelopment, functional impairment and microstructural immaturity of major white matter tracts'.[9] From studies evaluating periventricular leukomalacia, we know that white matter damage is highly predictive of motor and cognitive deficits.[10] Taking into consideration that even low-grade IVH affects grey matter directly and potentially white matter indirectly, deficits in motor and cognitive abilities can be expected.[11]

Historically, low-grade IVH has been reported not to have an impact on short-term outcomes once data was adjusted for gestational age, birthweight, gender and ethnic background.[12] Contrary to these findings, a recent meta-analysis showed that mild IVH was associated with higher odds of death or moderate–severe neurodevelopmental impairment at 18–24 months compared with no IVH.[13] Many of these studies, however, only include follow-up data at relatively young ages. Assessing NICU graduates below 2 years of age with the Bayley Scales of Infant and Toddler development has been shown to have only limited predictive value for later development.[14]

Limited data exist on these patients once they reach school age and beyond. The few papers that do report on outcomes beyond the first 3 years almost exclusively analyse preterm infants born in the 1980s and 1990s before the introduction of routine antenatal steroid or Magnesium sulphate administration and advanced neonatal practices.[15] Those measures have dramatically increased survival and decreased the risk of cerebral palsy.

Up-to-date, long-term developmental outcomes in infants with IVH would be valuable to effectively counsel families.[16] Furthermore, children with predicted adverse neurodevelopmental outcomes benefit greatly from early intervention.[17]

The aim of this study is to describe the long-term neurodevelopmental impact of Grade I and II IVH in former preterm infants in the early school years.

Methods

This is a retrospective cohort analysis of prospectively collected data from one tertiary NICU in New South Wales, Australia. The study population included all infants born at <30 weeks' gestation admitted between 1 January 2006 and 31 December 2013. Infants with major congenital malformations, those who died or had incomplete ultrasound or follow-up data were excluded.

To increase statistical power and in view of the relatively small number of patients affected by IVH in our cohort, a case–control design was chosen. One affected patient was matched with two unaffected patients for the following demographic parameters: gender, gestational age, antenatal steroid coverage, outborn status and IUGR incidence. We chose these characteristics as they have been described as the most impactful perinatal parameters for survival and IVH risk.[18]

At Royal Prince Alfred (RPA) NICU, cranial ultrasound is the standard screening test to detect IVH for all preterm infants born before 31 weeks' gestation on day 7 and day 28 of life. The Papile classification was used to grade the severity of IVH on ultrasound.[19] The ultrasound pictures were assessed by the same radiologist throughout the examined period. All results were double-checked for accuracy prior to grouping patients based on their worst ultrasound result.

Clinical data for this study was sourced from the prospectively collected Neonatal Intensive Care Units' (NICUS) Data Collection, an ongoing regional audit of live-born neonates admitted to tertiary NICUs in New South Wales and the Australian Capital Territory.

The follow-up data were accessed through a dedicated prospectively collected database.

All preterm infants with a gestation <30 weeks were examined in the developmental follow-up clinic. They were assessed by a developmental paediatrician and a clinical psychologist.

Main outcome measures

At 5 years of age, cognitive development was assessed using the Wechsler Preschool and Primary Scales of Intelligence (WPPSI).[20] This assessment tool gives an overall estimate of cognitive functioning (Full Scale Intelligence Quotient – FSIQ) and examines specific domains of development known to underpin learning in early school years. FSIQ results were grouped as follows: FSIQ > 109 above average, FSIQ 90–109 average, FSIQ 75–89 concern range and FSIQ < 75 mild intellectual deficit.

Similarly, at 8 years of age, the Wechsler Intelligence Scale for Children[21] was administered. Like the WPPSI, it gives an overall estimate of cognitive ability (FSIQ) and examines major domains. In addition, at 8 years, we report the Bruininks-Oseretsky Test of Motor Proficiency (BOT)[22] or the Movement Assessment Battery for Children (MABC)[23] as well as measurements for reading, spelling and maths. A diagnosis of Developmental Coordination Disorder (DCD) is made when the motor assessment score is below the 15th percentile (<5th percentile classed as severe DCD). Timing of assessment was established using chronological age, and not corrected for prematurity.

Statistical analysis

All *P* values were two-sided. Statistical significance was assumed when *P* levels were <0.05 and the significance level was not changed as only a small number of comparisons were performed. Parametric testing was used after normal distribution of the outcome measures was confirmed. Two-sided *t*-tests were used to evaluate differences in outcomes between the pairs. Differences in categorical data were assessed using Chi-square tests.

The full data set can be made available on request.

Results

Study population

During the study period, 491 infants <30 weeks' gestation were admitted to RPA NICU. Fourteen infants died before head ultrasound screening, 27 received their initial neonatal intensive care in another NICU or were transferred to a different unit prior to the first ultrasound. The study population therefore comprised of 450 infants, of whom 69 (15%) were diagnosed with IVH, 46 (10%) Grade I IVH, 17 (4%) Grade II IVH, 3 (0.6%) Grade III, 3 (0.6%) Grade IV IVH and 6 with PVL (1.2%). Forty-seven patients died in the first few weeks of life. Figure 1 explains the inclusion process and the lost to follow-up proportion including IVH incidence in the lost to follow up patients. 275 patients were eligible with full follow-up data available.

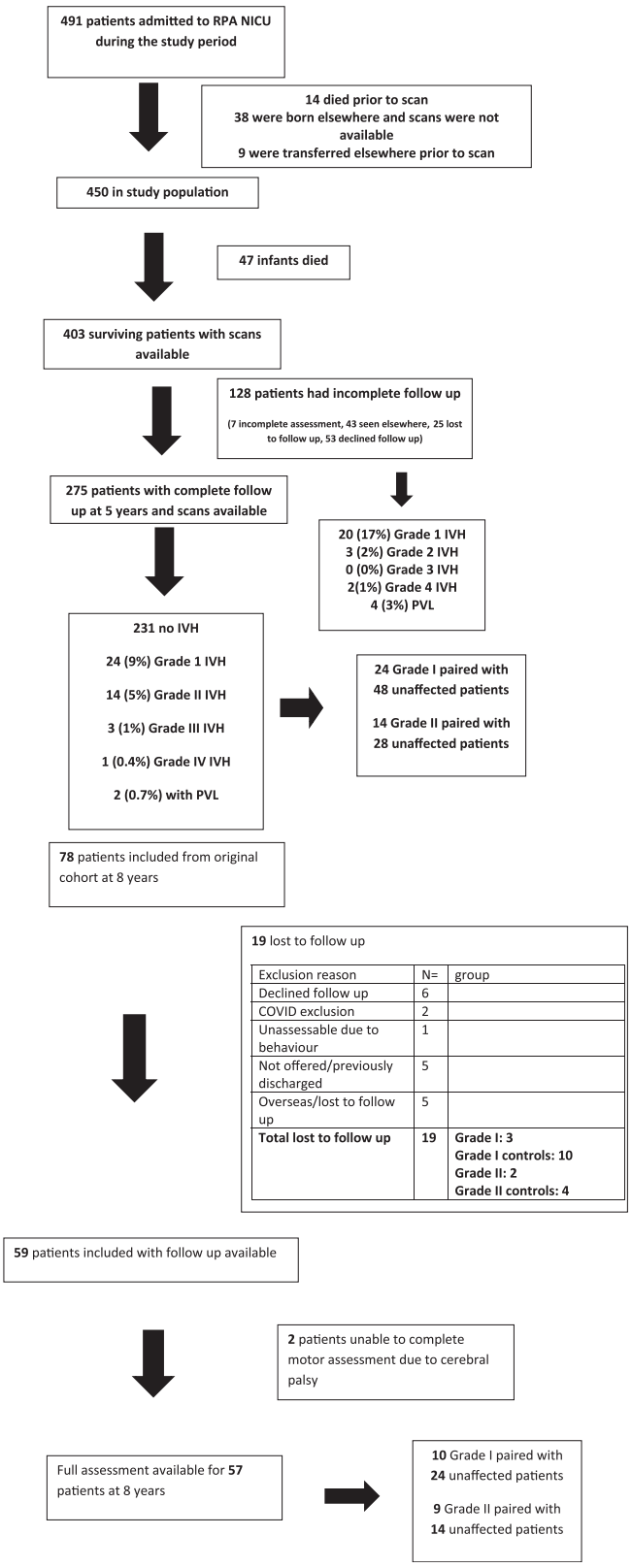

Fig. 1 Flowchart of included cases and incidence of IVH in study population. IVH, intraventricular haemorrhage.

As mentioned above, a case–control design was chosen, 24 patients with a Grade I IVH (23 unilateral Grade I, 1 bilateral Grade I) were matched with 48 unaffected patients, 14 patients with Grade II IVH (13 unilateral Grade II, 1 bilateral Grade II) were matched with 28 unaffected patients.

The number of infants with a Grade III, Grade IV and PVL was so small that statistical analysis was not meaningful.

In total, 78 patients were old enough for the 8-year follow-up assessment at the time of data analysis. 19 patients were lost to follow-up for the 8-year assessment. Two patients did not receive the motor assessment due to cerebral palsy and only completed the other elements. Both patients were in the control groups. The remaining 59 patients received a full assessment, consisting of WISC, spelling, maths and reading assessment and motor assessment.

Demographics

The demographic data of the included patients are described in Table 1. The significant differences between the matched pairs were lower 1- and 5-min Apgar scores, and higher post-natal steroids use in patients with Grade I IVH and significantly more hours on mechanical ventilation for patients with Grade II IVH at 5 years.

Assessment results

At 5 years, the WPPSI results showed no statistically significant differences in outcome between the matched groups (see Table 2). There was no significant difference in the number of children in the intellectual impairment or concern range between the IVH patients and their controls at 5 years (see Fig. 2).

The WISC results at 8 years showed a significant difference in patients who were classed as 'concern range' who had a Grade I IVH compared to their matched controls. Overall, there was a similar percentage of patients with and without IVH who scored results in the average and above average range. Patients at 8 years of age with low-grade IVH scored higher in almost all measured academic domains with significantly better results in mathematics for the patients with Grade I IVH (see Table 3).

The results for the motor assessment at 8 years showed that 40% of the children who were affected by any grade IVH showed below average motor abilities, compared to 55% in their respective controls. These results did not reach statistical significance.

Trajectory of FSIQ over time

We examined the change in FSIQ outcomes for each patient between the two examinations (at 5 and 8 years). Over time we found a decrease in patients who had suffered a mild IVH and scored an FSIQ result in the mild intellectual disability range. This trend could not be seen in the matched controls. Figure 2 shows the trends over time. The patients lost to follow-up between the 5-year assessment and the 8-year assessment were predominantly patients with no IVH (14 out of 19). Their WPPSI results at 5 years were mostly in the average and above average range (89–113). The patients that were lost to follow-up that were affected by IVH were two infants with a Grade I, both had below average results at the 5-year assessment and three infants with a Grade II, all of whom achieved average to above average results (89–108) at 5.

Table 1 Demographic and clinical data for patients assessed at 5 years

Group	IVH Grade I	Matched Controls I	*P*	IVH Grade II	Matched controls II	*P*
n	24	48		14	28	
Gender (female)	9 (38%)	15 (31%)	0.6	6 (43%)	12 (43%)	1
Birthweight (mean ± SD)	966 (±268)	941 (±281)	0.7	1025 (±306)	1036 (±265)	0.9
GA (median)	27	26.7	0.8	27	27	1
IUGR† incidence	3 (13%)	6 (13%)	0.9	2 (14%)	2 (7%)	0.5
Apgars (median)						
1 min	4.5	5.6	0.03*	5	6	0.6
5 min	7	7.5	0.02*	8	8	0.9
Steroid cover:			0.89			0.78
Complete ‡	11 (50%)	25 (57%)		8 (53%)	16 (53%)	
<24 h	6 (27%)	10 (22%)		5 (33%)	9 (30%)	
>7 days	1 (5%)	3 (7%)		2 (13)	4 (13%)	
None	4 (18%)	6 (14%)		0	1 (3%)	
Outborn	5 (21%)	8 (17%)	0.6	0	0	
Singleton	21 (88%)	37 (77%)	0.2	12 (85%)	24 (85%)	0.9
CLD	3 (13%)	11 (23%)	0.3	3 (21%)	3 (10%)	0.4
Chorio amnionitis	11 (46%)	19 (40%)	0.9	7 (50%)	13 (46%)	0.7
$MgSO_4$ cover (any)	10 (42%)	11 (23%)	0.1	5 (36%)	14 (50%)	0.4
Maternal age (mean ± SD)	32 (±5)	33 (±7)	0.4	29 (±4)	30 (±7)	0.5
Hrs mech vent (mean ± SD)	41 (±163)	43 (±134)	0.9	52.5 (±321)	19 (±63)	0.046*
Postnatal steroids	9 (38%)	8 (17%)	0.01*	3 (21%)	7 (25%)	0.9

cGA, corrected gestational age; CLD, chronic lung disease (oxygen at 36 weeks cGA); GA, gestational age; Hrs mech vent, hours of mechanical ventilation; IUGR, intrauterine growth restriction; IVH, intraventricular haemorrhage; $MgSO_4$, magnesium sulphate.
‡ Complete steroid cover defined as two doses of Betamethasone 24 h apart prior to delivery.
† IUGR defined as <10th birthweight percentile.
* Statistical significance.

Table 2 WPPSI results at 5 years of age for IVH and control groups

Group (*n*)	Grade I (24)	controls I (48)	*P*	Grade II (14)	Controls II (28)	*P*
FSIQ (mean composite score ± standard deviation)	84.8 (±11.1)	88.9 (±12.2)	0.24	91.4 (±10.9)	89.5 (±11.3)	0.62
PIQ or VS4 (mean composite score ± standard deviation)	91.7 (±12.2)	96.2 (±12.7)	0.27	97.6 (±11.8)	95.7 (±14.5)	0.69
VIQ or VC4 (mean composite score ± standard deviation)	82.7 (±12.3)	90.2 (±11.2)	0.07	94.8 (±9.9)	91.4 (±10.6)	0.4
CP (total number)	0	3	0.22	0	1	0.48

CP, cerebral palsy; FSIQ, Full Scale Intelligence Quotient WPPSI, IVH, intraventricular haemorrhage; PIQ, performance IQ; VC4, verbal comprehension WPPSI 4; VIQ, verbal IQ; VS4, visual spatial WPPSI 4.

Discussion

Despite the theoretical and previously described impact an IVH and the resulting injury should have on the long-term neurodevelopmental outcome of the patient,[8] our study found no difference in outcomes at 5 or 8 years. Overall, there was no difference in patients with average intellect and those below average between the Grade I and Grade II and their non-IVH control groups. These findings are remarkable, especially considering that our affected patients not only suffered an IVH but also differed from their controls in other clinical features that have been described to adversely affect neurodevelopmental outcomes, most importantly lower 1- and 5-min Apgar scores and higher use of post-natal steroids.[24] We found significantly better results in the academic assessment of mathematics in patients who suffered a Grade I IVH compared to their controls. This finding might have occurred by chance or could be the result of early intervention as discussed further below. Furthermore, two patients in the Grade I IVH group were lost to follow-up in between assessments, both had scored below average FSIQ results at 5 years. Failing to obtain their eight-year assessment results could affect the comparison.

We found that throughout all groups, there was an improvement of IQ results from 5- to 8-year assessment. Interestingly, only the group of patients who had suffered an IVH showed a significant decrease in patients with FSIQ results in the intellectual disability range over time.

These results offer reassurance for parents and clinicians of affected infants. They also highlight the importance of ongoing research to determine meaningful measurements to predict developmental outcomes more precisely and help identify patients who would benefit from early intervention the most.

The timing of the assessments at 5 and 8 years covers an important time in a child's development as they start school. The improvement in assessment results could reflect successes of early intervention for patients at risk and more rigorous preparation for school as well as continued brain maturation and recovery. There is existing literature supporting an improvement in neurodevelopmental outcomes over time in preterm infants[25]; with some suggesting a major role of early intervention.[17]

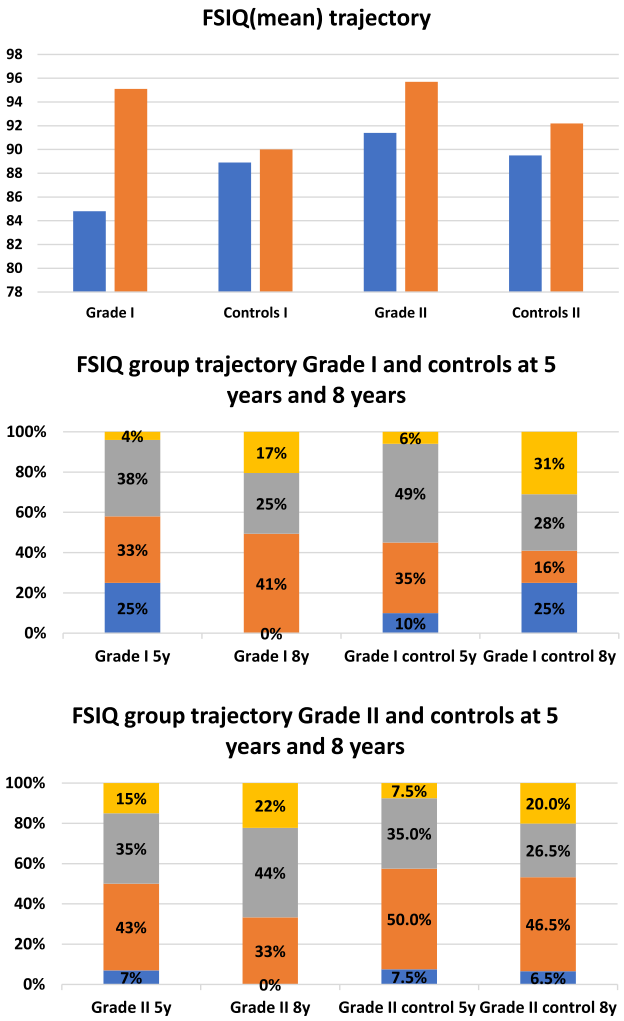

Fig. 2 FSIQ trajectories from 5 to 8 years. FSIQ, Full Scale Intelligence quotient. (■) FSIQ at 5, (■) FSIQ at 8, (■) mild disability, (■) concern range, (■) average, and (■) above average.

Despite multiple studies and a recent meta-analysis finding worse neurodevelopmental outcome at 18–24 months,[5,12,13] studies evaluating the impact on long-term outcome are congruent with our findings. Sherlock et al. in their study from the early 2000s found that at 8 years, the 'children with grades one and two IVH performed similarly on cognitive measures to children with no IVH'. Likewise, Ann Wy et al. found no difference in neurodevelopmental outcome of premature infants with low-grade IVH at 3, 8 and 18 years compared to infants without IVH.[26] Hollebrandse et al. evaluated extreme preterm infants at school age and found low-grade IVH had no effect on intellectual ability, executive function, academic skills or overall motor function.[27] The most recent study from Campbell et al. showed significant impact of white matter damage on cognitive and motor outcomes but no impact of any grade IVH, highlighting the importance of ongoing developmental assessment of all preterm infants at risk and encouraging cautious optimism when counselling.

The strength of our study is a complete record of trajectories over time. The developmental assessments were performed by the same team at 5 and 8 years and the reporting of the head ultrasound findings was completed by the same radiologist, eliminating inter-observer differences in ultrasound and developmental examination findings.

Our study has some limitations. The small number of patients with IVH and inevitable loss to follow-up means the results have to be interpreted with caution. The proportion of patients who were affected by a Grade I IVH in the lost to follow-up population was higher than in the examined population (17% vs. 9%) potentially skewing the results. However, the patients affected by a Grade 2 were overrepresented in the included population (5% in the included patients vs. 2% in the lost to follow-up patients).

To increase statistical accuracy, we facilitated matched paired analysis. However, given that this study was a retrospective analysis, some significant differences between the pairs persisted. This study was performed at a single centre potentially leading to further bias. In addition, specifics on early intervention or potential tutoring following discharge were not available, omitting an important confounding factor. Larger cohorts and a prospective

Table 3 WISC results at 8 years of age for IVH and control groups

Group (*n*)	Grade I (10)	Controls I (24)	*P*	Grade II (9)	Controls II (14)	*P*
FSIQ (mean composite score ± standard deviation)	95.1 (±12.8)	90 (±14.7)	0.51	95.7 (±12.6)	92.2 (±12.1)	0.59
Verbal IQ (mean composite score ± standard deviation)	92.9 (±8.1)	87.9 (±13.7)	0.55	95.1 (±6.3)	91.4 (±8.4)	0.53
Nonverbal IQ (mean composite score ± standard deviation)	87.5 (±8.1)	89.9 (±13.2)	0.59	94.9 (±14.3)	87.9 (±11.7)	0.35
Reading (mean composite score ± standard deviation)	93.5 (±16.9)	84.2 (±17.4)	0.61	97.8 (±10.8)	95.2 (±18.5)	0.88
Maths (mean composite score ± standard deviation)	100.6 (±10.8)	89.2 (±11.2)	0.04*	98.8 (±13)	84.9 (±11.4)	0.05
Spelling (mean composite score ± standard deviation)	102.8 (±8.7)	97.1 (±9.9)	0.28	97.9 (±6.3)	100.4 (±13.6)	0.57

FSIQ, Full Scale Intelligence Quotient; IVH, intraventricular haemorrhage; WISC, Wechsler Intelligence Scale for Children.
* Statistical significance.

study design including cohesive inclusion criteria and confounding factors are required to further validate the results.

In summary, the impact of mild IVH in very preterm infants on neurodevelopmental outcome has been described as significant in studies that examined children within the first 2 years of life.[2] However, our study suggests that that difference does not persist at 5 and 8 years of age. Our findings add to a growing body of evidence suggesting low-grade IVH is less predictive for long-term outcome than many other demographic and early clinical outcome parameters.

Future research should focus on alternative prediction tools and cranial imaging methods to identify patients at risk more precisely. Once at-risk patients can be identified research should provide a more detailed answer to the role of early intervention.

Conclusion

There is no difference in neurodevelopmental outcomes at five and eight years on formal developmental testing in extremely preterm infants with mild IVH (grade I and II) compared to infants with no IVH.

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Ethics Statement

The study was approved by the Sydney Local Health district ethics committee (X19-0262 and 2019/ETH12060). This study was performed in accordance with the Declaration of Helsinki.

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