Long-term outcomes following Hypoxic Ischemic Encephalopathy

Systematic Review: The long-term school and psychosocial outcomes of hypoxic ischemic encephalopathy

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Empirical Study: Long-term neuropsychological and behavioural outcomes of mild and moderate hypoxic ischemic encephalopathy

Thesis submitted by

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Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

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List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	Analysis of variance
ASEBA	Achenbach System of Empirically Based Assessment
BPVS-III	British Picture Vocabulary Scale – 3rd Edition
BRIEF-II	Behaviour Rating Inventory of Executive Functioning – 2nd Edition
CBCL	Children Behaviour Checklist
CMS	Children's Memory Scale
CP	Cerebral palsy
DKEFS	Delis Kaplan Executive Functioning Systems
EEG	Electroencephalogram
FES	Family Environment Scale
HIE	Hypoxic ischemic encephalopathy
INFANT	Irish Centre for Foetal and Neonatal Translational Research
IQ	Intellectual Quotient
M	Mean
Mdn	Median
NE	Neonatal encephalopathy
NEPSY-II	Neuropsychological Assessment Tool – 2nd Edition

NICU	Neonatal intensive care unit
RCFT	Rey Complex Figure Test
SD	Standard Deviation
SDQ	Strengths and Difficulties Questionnaire
TH	Therapeutic hypothermia
WIAT-III	Wechsler Individual Achievement Test – 3rd Edition
WISC-V	Wechsler Intelligence Scale for Children – 5th Edition

Chapter 1

Introduction

1.1 Hypoxic Ischemic Encephalopathy

Hypoxic ischemic encephalopathy (HIE) is a brain injury characterised by a lack of oxygen (hypoxia) and blood (ischemia) to the brain during the prenatal, intrapartum or postnatal period. HIE falls under the broader umbrella term neonatal encephalopathy (NE) which describes any clinical encephalopathy in the hours and days immediately following birth. It is estimated HIE accounts for up to 80% of all NE and is recognised as a major public health issue that afflicts millions of new-borns worldwide (1, 2). The terms HIE and NE are often used interchangeably in the literature due to the difficulty in differentiating causation in retrospective studies. Estimates of prevalence show that HIE occurs in approximately 1 to 6 of every 1000 live full-term births (3), and up to 26 per 1000 live births in underdeveloped countries (4). Despite increased understanding of neonatal pathologies in recent decades, HIE remains a leading cause of infant mortality and chronic neurodevelopmental morbidities (5). Approximately 20% of infants die during the new-born period, and of those who survive about 25% develop disabilities (6). Sequalae include intellectual disability, cerebral palsy (CP), cognitive impairment, seizures, language delay, and motor problems (7). Long-term prospective studies following children across all developmental domains are uncommon.

1.2 Clinical Presentation and Diagnostic Criteria

HIE presents clinically in the first hours and days of the life of a full-term new-born, usually in the form of unconsciousness, respiratory difficulties, depressed tone, and seizures. However, no single clinical sign characterises HIE. Instead, a collection of clinical signs and symptoms are considered to ascertain type and severity of deficit. Accordingly, Sarnat and Sarnat (8) developed a classification system that is used and widely accepted in the medical community. It categorises neurological symptoms and electroencephalogram (EEG) readings into three

types of severity: mild (Grade I), moderate (Grade II), and severe (Grade III). Table 1.1 reports the list of clinical features associated with each grade of HIE.

Table 1.1 Clinical features of the three grades of HIE

	Grade I (Mild)	Grade II (Moderate)	Grade III (Severe)
Level of consciousness	Hyperalert	Lethargic	Stuporous
Muscle Tone	Normal	Mild hypotonia	Flaccid
Suck	Weak	Weak or absent	Absent
Tonic neck	Slight	Strong	Absent
Heart Rate	Tachycardia	Bradycardia	Variable
Seizures	None	Common	Uncommon
EEG	Normal	Low voltage pattern	Periodic Pattern
Duration	Less than 24 hours	2 to 14 days	Hours to weeks

Source: Sarnat et al. (1976) (8)

The pathogenesis of HIE is conceptualised as an evolving process. The timing of the brain injury associated with HIE can affect the presentation of clinical symptoms and the progression of the encephalopathy. While the majority of insults take place during the perinatal period, they can also occur during the antenatal period. A severe antenatal event can recover to present as a mild HIE case at birth. Likewise, a HIE presentation presenting as mild grading at 6 hours post-birth can evolve into moderate and severe gradings after 24 hours. Unfortunately, clinicians are not yet able to accurately identify, before the onset of labour, which new-borns are likely to suffer HIE at birth. Moreover, the accurate identification of HIE grading at birth by neurological examination can be mediated by factors such as when the insult occurred, maternal sedation, and maternal analgesia.

1.3 Current Treatment

Despite advances in medical care and obstetric screening aimed at preventing HIE, incidence rates have not declined (9). Indeed, much neonatal research continues to focus on minimising the extent of injury resulting from HIE. Therapeutic hypothermia (TH) has been shown to reduce the risk of death and disability in new-borns with moderate and severe HIE (10, 11). A number of research trials have confirmed its efficacy and safety (12, 13). TH refers to the cooling of the brain within the first 6 hours of birth and is the only validated treatment for HIE (14). However, TH does not provide protection to all cases with only 1 in 6 new-borns benefiting from the treatment (6). Furthermore, there is a lack of knowledge about whether TH in the first hours of life impacts long-term HIE outcomes. Other therapeutic strategies involve ventilation, seizure monitoring, and neurological consultation.

Clinical trials of TH tended to exclude infants with mild HIE as research focused on treatments for children who were at higher risk of long-term disability following HIE. Consequently, mild HIE has been understudied and not monitored for long-term impairments.

1.4 Outcomes

While there has been a substantial body of research investigating the outcomes of children with HIE, the emphasis has been on the early childhood period and outcomes related to mortality and severe motor disability. Traditionally, the effects of HIE were viewed in a black or white manner, where children either developed normally or became severely impaired. More recently, studies have begun to include a broader assessment of neuropsychological and behavioural functioning beyond infancy following HIE (15, 16). Research suggests long-term outcomes of children with HIE is dependent on the severity of grading, with risk of adverse effects increasing with grade. Adverse outcome and disability are invariably always present for children with a history of severe HIE.

It was widely accepted that those with mild HIE had a favourable prognosis (8, 17). However, there is recent evidence to suggest the long-term outcomes of children with mild HIE is less favourable than predicted. Studies have indicated learning difficulties are present in school age children following mild HIE (16). A recent review found that by 5 years 35% of children with mild HIE experienced difficulties in at least one neurodevelopmental area (18). As a result, the authors recommended detailed long-term follow-up of children with a history of mild HIE to detect previously unrecognised disability.

Children with a history of moderate HIE appear to exhibit a more heterogeneous range of outcomes. For example, research suggests rates of cognitive impairment can range from 20-50% (19), regardless of motor function. As such, providing reliable prognoses of infants with moderate HIE is difficult. Deficits can be subtle and not become evident, or cannot be assessed, until later years making it likely that impairments are underdiagnosed. As a result, there is a growing consensus that children with moderate HIE also require longer-term follow-up into school going years and adolescence on neuropsychological, behavioural, and educational evaluation (20).

1.5 Rationale for Thesis

The majority of HIE outcome studies assess children in infancy or early childhood and focus on outcomes such as mortality, CP, and global intellectual disability. Less is known about discrete, subtle neuropsychological and psychosocial sequalae into later childhood and beyond, and school attainment. Understanding the wider spectrum of long-term developmental effects of HIE is important as it enables professionals to identify children requiring intervention and support. Long-term adverse outcomes following mild and moderate HIE, even though subtle, are likely to have clinical and wider societal implications such as high medical expenses, additional educational costs, and multifaceted impacts on families (21). Knowing the extent of

outcomes following HIE may encourage obstetricians, neonatal paediatricians, and researchers to develop new interventions that protect infants from HIE at birth. Furthermore, despite accounting for the majority of HIE cases, children with a history of mild HIE have been scarcely studied due to a common consensus that it was a benign condition. However, as mentioned above there has been emerging evidence to challenge this view with research indicating difficulties increase for children with mild HIE as they mature to school age and beyond. While the long-term outcomes of children with moderate HIE has received more attention, there remains variance in the extent of their difficulties. Accordingly, this body of research takes particular interest in the neuropsychological, behavioural, psychosocial, and school outcomes of school age children and adolescents with a history of mild-moderate HIE.

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Chapter Two

Systematic Review

Title: **The long-term school and psychosocial outcomes of neonatal hypoxic ischemic encephalopathy: a systematic review**

Prepared in accordance with submission guidelines of *Developmental Medicine & Child Neurology*

(See Supplementary Chapter 3 for Author Guidelines[1])

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The long-term school and psychosocial outcomes of hypoxic ischemic encephalopathy: A systematic review

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ABSTRACT

Aim: To determine the long-term school and psychosocial outcomes in survivors of mild and moderate hypoxic ischemic encephalopathy (HIE) without cerebral palsy (CP).

Methods: A systematic review was conducted on five databases (Medline, PsycINFO, Embase, PubMed, and Cochrane Trials Database). All prospective and retrospective studies (randomised controlled trials, observational and case-controlled cohort in design), with a clear definition of HIE, where mild and moderate grade of HIE was explicitly stated, and that reported long-term school and psychosocial data were included.

Results: Seven articles met the inclusion criteria (n = 405). Results indicated adverse school outcomes (e.g. attendance at special school, academic delay, and lower scores on standardised school performance tests) were associated with both mild and moderate HIE without CP, although impact was greatest for the moderate HIE cohorts. Similar associations were found for psychosocial outcomes (e.g. anxiety, social withdrawal, and inattention).

Interpretation: Children of school-age with moderate HIE in infancy are at increased risk of adverse school outcomes as noted above, with some evidence of slightly elevated risk for mild HIE cases. These findings highlight the need for monitoring of children with HIE beyond infancy to identify academic needs and maximise their opportunities.

KEYWORDS: Hypoxic ischemic encephalopathy; long-term; school; psychosocial; outcomes

2.1 Introduction

Hypoxic ischemic encephalopathy (HIE) is a brain injury characterised by a lack of oxygen (hypoxia) and blood (ischemia) to the brain during the prenatal, intrapartum or postnatal period (1). Infant survivors of HIE have a high risk of neurological impairment including epilepsy, cerebral palsy (CP), intellectual disability, and cognitive deficits (2). HIE is classified into different levels of severity based on the grading system developed by Sarnat and Sarnat (3). Their system categorises HIE into mild (Grade I), moderate (Grade II), and severe (Grade III) according to level of consciousness, reflexes, heart rate, presence of seizures, autonomic functions, and EEG. Risk of long-term disability increases with grade.

Traditionally, long-term outcomes for mild HIE infants were considered more favourably to the moderate and severe grades, with little to no adverse consequences (3). As a result, few prospective studies included children with mild HIE, and outcome data is lacking (4). However, there is growing evidence that mild HIE does in fact lead to adverse outcomes. Barnett et al. (5) found children with mild HIE with normal outcome at 2 years, had neurological dysfunction and motor-perceptual difficulties at early school age. Other research indicated difficulties exist in mild HIE cohorts even in the absence of major disability (6). Difficulties may become evident once a child reaches school age as the injured brain fails to develop optimally across time and as cognitive demands increase, but few studies present outcome data beyond the first years of life.

Long-term research for all HIE grades has generally focused on cognitive and neurodevelopmental outcomes (7, 8, 9). Few studies have focused on school and psychosocial outcomes and much of the literature focuses on development prior to school going age. Given cognitive and neurodevelopmental deficits do not always translate to functional impairments

in behaviour and school functioning, there is a need to establish whether or not school progress and psychosocial adjustment are compromised in children with mild and moderate HIE.

Research evaluating school outcomes in children following HIE has demonstrated difficulties in reading and comprehension, with survivors more likely to require additional educational support (10). Robertson et al. (11) highlighted that spelling, reading and mathematics were impaired in 5-year-old survivors of moderate HIE, without other disability, compared to peers. Reduced school readiness was associated with increased behavioural problems in emotional regulation and irritability. Lee-Kelland et al. (12) reported children with moderate and severe HIE required greater special educational needs. They recommended continued educational assessment during school years to monitor the needs of children with HIE. Another study, using parental observations, found that children with signs consistent with moderate to severe HIE at birth were at an increased risk of needing extra school resources, and having reduced academic performance in reading and mathematics compared to healthy controls (13). However, the evidence for school difficulties associated with moderate HIE was weak when excluding children with co-morbid CP (10). Many studies have failed to include mild HIE cases or focus specifically on mild and moderate cohorts.

There is increasing recognition that chronic illnesses in general, and neurological conditions in particular, in early childhood are associated with psychosocial difficulties across development (14, 15). The monitoring of long-term psychosocial outcomes following HIE is, however, lacking in the literature. Previously, consistent associations were found between severe HIE (usually involving CP) and behavioural difficulties, while the extent of psychosocial dysfunction for mild and moderate HIE cohorts has been less clear (16). Adolescents aged 15-19 with moderate HIE without CP are said to have social and peer functioning difficulties that interfere with daily living compared to siblings (17). Moster et al. (13) found parents identified greater behavioural problems related to anxiety, aggression and

passivity in children with HIE compared to control, with more pronounced problems associated with severe HIE. Following mild HIE, teachers reported children aged 9-10 exhibited increased problematic behaviours compared to control (18). The authors reported children with mild HIE performed in between controls and a moderate HIE cohort. However, further follow up was recommended as the control group was much younger. In contrast, in a Canadian sample aged 8 years, children with mild HIE were found to have similar school performance scores to those of their peers (11). Therefore, there is some, but equivocal, emerging evidence that adverse psychosocial outcomes may also be associated with mild and moderate HIE, thus a review of potential problems is considered important.

Currently, no systematic review has evaluated the school and psychosocial outcomes of children following mild to moderate neonatal HIE. Existing reviews evaluated cognitive and neurodevelopmental outcomes (4, 19). Generally, outcome studies evaluated infants of pre-school age and focused on outcomes such as death, CP, and global cognitive impairment. There is evidence HIE sequalae continue into later childhood and adolescence. This review sought to determine whether survivors of mild and moderate HIE without CP are at an increased risk of adverse school and psychosocial outcomes.

2.2 Methods

Methods were specified in advance and prospectively registered on PROSPERO (CRD42020143238). The review was conducted in accordance with Prisma guidelines for the reporting of systematic reviews (20).

2.2.1 Inclusion Criteria

The types of studies considered for the review included all prospective and retrospective studies which were randomised-controlled trials, observational studies or case-controlled studies. Studies were included if they were based in the English language only. Studies were included

if they reported outcomes for children of school age with mild or moderate HIE without CP. Studies were only included if they provided sufficient evidence that HIE was present as per Sarnat grading (3) and/or other markers indicative of encephalopathy such as low Apgar scores at birth, need for resuscitation and seizures. Studies were excluded if they had an unclear definition of HIE, or if participants were not of school going age, and or if they did not differentiate the results of HIE survivors with and without CP.

2.2.2 Outcome Measures

Outcomes were categorised into school-related and psychosocial outcomes. School outcomes were defined as standardised school assessment scores (e.g. *Metropolitan Readiness Test*), teacher reported attainment scores (e.g. expected national curriculum scores), and whether participants were in receipt of special educational support or not. Psychosocial outcomes were defined as self-parental-teacher reported outcomes on emotional, behavioural, social functioning, and quality of life measures.

2.2.3 Search Strategy

A scoping review was run to identify key reference papers, to establish the likelihood of sufficient articles being available to answer the research question, and to help in establishing the final search terms (see section 3.2 in Supplementary Chapter 3). Iterative searches of key words were conducted through Google to identify common terms in the research area. Preliminary search terms were then refined by consultation with a university librarian and subject matter experts (CMC and DM). Once finalised, a systematic search was conducted through the databases Medline, Embase, PsycINFO, PubMed, and Cochrane Trials Database, with the last search conducted on 1st November 2019. No date restriction was applied. The following search terms were used: (hypoxic isch* encephalopathy OR neonatal encephalopathy

OR neonatal hypoxia) and (education OR behavio* OR attainment OR academic OR psych* OR adjustment).

A search of the grey literature was completed by using key terms in web search engines such as Google Scholar. This search was supplemented by scanning the reference lists of the final review papers for any articles that met inclusion criteria.

Systematic search results in each of the databases were extracted to the reference manager Zotero. Duplications were removed. Studies were identified for the final review in a phased process involving two of the authors independently (SH and CMC) (Figure 2.1). Firstly, articles were selected or excluded through review of title and abstract by the first author S.H. Secondly, those that were selected were reviewed in full text to determine if they met inclusion criteria. At this stage, the first author (SH) reviewed all articles and the second author (CMC) did a random independent check of 25% of the articles. There was full agreement on articles chosen to be included or excluded. Lastly, the articles for the final review were identified.

2.2.4 Quality assessment

Each study in the final review were independently quality assessed by the first and second authors (SH and CMC) using the *Newcastle-Ottawa Scale* (21) (See Appendix A Supplementary Chapter 3). This assessment tool was developed to facilitate quality assessment of non-randomised as well as randomised studies and has been previously used in HIE research (21). The scale consists of 9 quality appraisal questions where a point is allocated if the criterion is met. Minor discrepancies in scoring were resolved through discussion until a common consensus was agreed. Articles with a total score ≥ 7 were deemed 'good' quality while articles < 7 were deemed 'adequate' quality. Articles rated adequate quality shared similar characteristics e.g. lack of a control group. A total of seven studies, published between 1989

and 2018, were included in the review. Five studies were rated ‘good’ quality and two studies were rated ‘adequate’ quality (Table 2.1).

2.2.5 Data Collection and Synthesis

Study characteristics, grade of HIE, participant demographics such as age and gender, the number of participants with mild and moderate HIE without CP, control group characteristics, outcome measures, and results were extracted from the review studies based on a form previously used in HIE research (4) (see Table 2.2). Results of data extraction were discussed between authors and consensus was agreed. A narrative synthesis of findings was completed. Mean, standard deviations, and effect sizes were reported where possible.

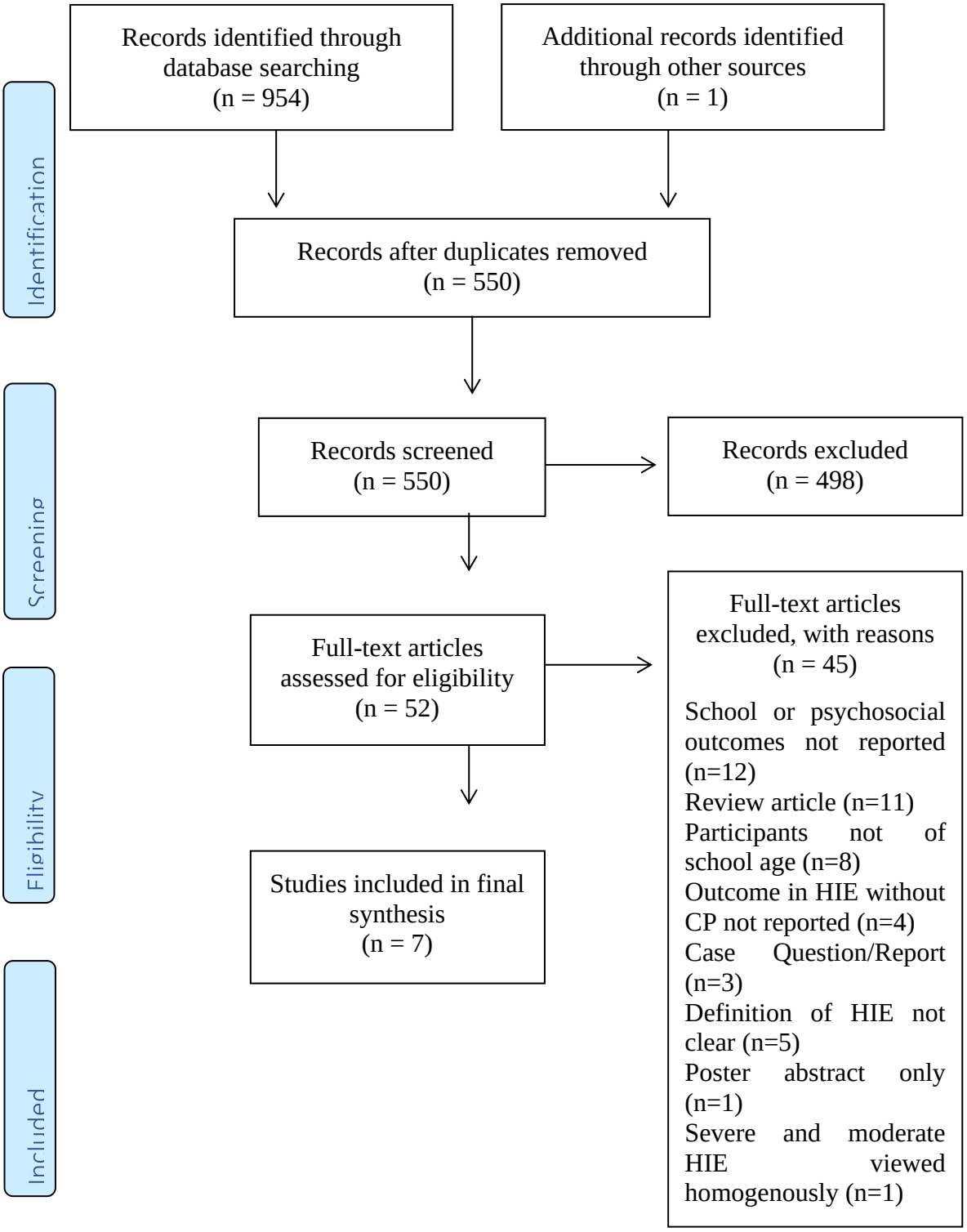

Figure 2.1 Prisma Flow Chart demonstrating systematic search process

Table 2.1 Quality Assessment of Review Articles using the Newcastle-Ottawa Scale

Study, Year	Adequate case definition	Representativeness of cases/cohorts	Selection of controls/non-exposed	Definition of controls/absence of disease prior to study	Comparability of cases/cohorts and controls	Assessment of outcome/ascertainment of exposure	Long enough follow up period/same method of ascertainment	Non-response rate/cases lost to follow up
Hayes et al. 2018* (23)	✓	✓	X	✓	X X	✓	✓	✓
Lindstrom et al. 2006** (17)	✓	✓	✓	✓	✓ X	✓	✓	✓
Marlow et al. 2005** (24)	✓	✓	✓	✓	✓ ✓	✓	X	X
Robertson et al. 1989** (11)	✓	✓	✓	✓	✓ ✓	✓	✓	X
Robertson et al. 1992** (25)	✓	✓	✓	✓	✓ ✓	✓	✓	✓
Van Kooij et al. 2010** (26)	✓	✓	✓	✓	✓ ✓	X	✓	X
Van Schie et al. 2015* (27)	✓	✓	X	✓	X X	✓	✓	✓

Note. ✓ indicates criterion was met, X indicates criterion was absent, ** indicates 'Good' quality, * indicates 'Adequate' quality

2.3 Results

Seven papers were identified for inclusion in the review. Of the seven studies, five studies reported school outcomes for moderate HIE cohorts, and three studies reported school outcomes for mild HIE cohorts. For psychosocial outcomes, four studies reported moderate HIE outcomes and two studies reported mild HIE outcomes. Four studies were case-controlled (11, 24, 25, 26) and three were cohort in design (17, 23, 27). The seven studies reported outcomes for 143 mild and 262 moderate HIE participants without CP. Studies included participants with mild or moderate HIE from 4 to 19 years of age, with a mean age of 8 and median of 7 years across all studies. Five studies used control groups, four with community non-HIE participants, and one with non-HIE sibling participants.

Five of the seven studies reported school outcomes. The type of school outcomes reported included standardised academic attainment tests (*McCracken Standard Reading Inventory* (28); *Edmonton Spelling Abilities Test* (29); *Keymath Diagnostic Arithmetic Test* (30); *Metropolitan Readiness Test* (31)), teacher reported attainment levels, need for additional educational support, and attendance at special school. Four of the seven studies reported psychosocial outcomes. Outcome measures evaluated emotional and behavioural difficulties through the *Strengths and Difficulties Questionnaire* (*SDQ*) Parent and Teacher Form (32) and the *Child Behaviour Checklist* (*CBCL*) (33). Also, level of social interaction, hyperactivity, inattention, and executive functioning were measured through the *Connors rating scale* (34), the *ADHD rating scale IV* (35), the *Asperger's Screening Questionnaire* (36), and the *BRIEF-II* (37) respectively.

Table 2.2 Characteristics of the Review Studies

Study/Year	Participant Characteristics	Control Details	Outcome Measures	Results
Hayes et al. 2018	> 36 weeks gestation, Sarnat classifications used, 4 – 8 years, mean 5.66 years; *n* = 66, 49 mild HIE and 17 moderate HIE	n/a	• *CBCL* • *BRIEF-II* (Parents & Teacher)	<u>Psychosocial</u> • Moderate HIE were significantly more likely than mild HIE to have difficulties with anxiety (22% v 5%)*, sleep problems (28% v 7%)*, withdrawn behaviour (28% v 5%)*, aggressive behaviour (22% v 0%)**, externalising problems (22% v 0%)** and total problems (28% v 5%)* on the *CBCL*. • Parents (14%) and teachers (20%) reported higher number than expected of children with mild and moderate HIE scored within the clinical range on total problems on the *BRIEF-II*. Behavioural regulation index – parents (16%), teachers (25%), Metacognition Index – parents (14%), teachers (23%). No significant differences found between mild and moderate HIE.
Lindstrom et al. 2006	Full term, 15 - 19 years, mean age 16; *n* = 28 moderate HIE	*n* = 15 siblings, mean age 14	• *Connors* 10 item scale • *ADHD rating scale IV* • *Asperger Screening Questionnaire* • Need for Special Education	<u>Psychosocial</u> • Moderate HIE scored significantly higher on the *Conner's scale***, the Inattention subscale of the *ADHD Rating Scale IV***, and on the *Asperger Screening Questionnaire*** compared to siblings.

				<u>School</u> • 18% (5/28) moderate HIE required special educational support compared to 0% (0/15) siblings
Marlow et al. 2005	>35 weeks gestation, 6-9 years, mean age = 7; *n* = 32 moderate HIE	*n* = 49, children from same classroom, matched for sex, age, ethnicity and language. 6-8 years	• *SDQ* (parents and teacher) • School performance test in English[a] and Maths[a]	<u>Psychosocial</u> • *SDQ* (parents) – No significant differences between moderate HIE and control on all *SDQ* subscales. • *SDQ* (teachers) - No significant differences between moderate HIE and control on all *SDQ* subscales. <u>School</u> • A significant proportion of the moderate HIE group achieved lower scores in spelling***** and reading***** compared to control. No other differences were observed. • Moderate HIE (24%, 7/26) have greater unmet educational needs than control (7%, 3/42)*****
Robertson et al. 1989	Sarnat classifications used, 8 years; *n* = 122, 56 mild HIE, 66 moderate HIE	*n* = 155, community sample, randomly selected, 8 years (+ or -) 4 months	• Standardised school performance tests in Reading[b], Spelling[c] and Arithmetic[d]	<u>School</u> • Moderate HIE scored significantly lower in reading******, spelling****** and arithmetic****** than control • No significant differences between mild HIE and control. • Moderate HIE scored significantly lower than mild HIE in Reading****** and Spelling******

Robertson et al. 1992	>36 weeks gestation, Sarnat classifications used, mean 5.5 years; *n* = 71 moderate HIE	*n* = 71, community sample, matched for gender, age, school attendance, language, parental status	• Standardised school performance test[e]	<u>School</u> • Moderate HIE (*M* = 3.8, *SD* = 1.6) scored significantly lower than control (*M* = 4.5, *SD* = 1.5)**, *d* = 0.42 • 44% of moderate HIE scored > 1*SD* below the mean norm on school performance[e].
Van Kooij et al. 2010	Full term, Sarnat classifications used, 9 – 10 years; *n* = 69, 32 mild HIE and 37 moderate HIE	*n* = 52, community sample, matched for age and sex	• Attending special school or not	<u>School</u> • Attending special school: mild (9%), moderate (22%), control (0%)
van Schie et al. 2015	Full term, Sarnat classifications used, 6-8 years, mean age = 7; *n* = 17, 6 mild HIE, 11 moderate HIE	n/a	• *CBCL* (parents) • *TACQOL* (parents) • Delay in school progress	<u>Psychosocial</u> • *CBCL* - Parents reported mild (0%, 0/6) & moderate (9%, 1/11) HIE did not have higher behavioural difficulties compared to norms. • *TACQOL* – there were no significant differences between means on all scales, between HIE (mild and moderate reported homogenously) group and the Dutch reference sample. <u>School</u> • Delay in School progress: Mild (17%, 1/6), Moderate (18%, 2/11)

ADHD: Attention Deficit Hyperactivity Disorder; SDQ: Strengths and Difficulties Questionnaire (32); CBCL: Child Behaviour Checklist (33); TACQOL: TNO-AZL Questionnaires for Children's Health-Related Quality of Life (38); BRIEF-II: Behaviour Rating Inventory of Executive Functioning – 2nd Edition (37); [a]teacher assessed UK national curriculum attainment levels; [b]McCracken Standard Reading Inventory (28); [c]Edmonton Spelling Abilities Test (29); [d]Keymath Diagnostic Arithmetic Test (30); [e]Metropolitan Readiness Test (31); * = $p < 0.05$, ** = $p < 0.01$, *M* = mean, *SD* = standard deviation, *d* = effect size.

2.3.1 School Outcomes

2.3.1.1 School attainment scores

Three of five studies, all rated as 'good' methodological quality, reported outcomes on standardised scales (11, 25) and teacher assessed national curriculum attainment scores (24). Marlow et al. (24) compared teacher-reported levels of attainment in national curriculum targets in English and Mathematics. The moderate HIE group scored significantly lower on reading and spelling compared to non-HIE peers despite similar levels of general cognitive abilities across both groups. Teachers identified children with moderate HIE as having greater unmet educational needs than controls. Similarly, Robertson et al. (11) assessed the school performance of children in the areas of reading, spelling and arithmetic in comparison to a community control group. Children with moderate HIE significantly underachieved in all academic areas compared to controls. This was in the context of general cognitive ability in the moderate HIE group being significantly below that of their mild HIE and non-HIE peers. There were no significant differences in school attainment between the mild HIE group and the control group. Comparing outcomes between HIE grade, the moderate group attained much lower scores in reading and spelling. Furthermore, Robertson and Grace (25) again found children with moderate HIE achieved significantly lower on school attainment tests compared to non-HIE peers, with a medium effect size.

2.3.1.2 Need for special school and school delay

Three of the five studies evaluating school outcomes reported need for special school or school delay. Van Kooij et al. (26) measured the frequency of children with both mild and moderate HIE, who attended special school compared to community controls. While all healthy peers attended mainstream schools, 9% mild and 22% moderate HIE attended special school. Similarly, Lindstrom et al. (17) found 18% of children with moderate HIE required special

education compared to none of the controls. This study looked only at moderate HIE gradings in adolescence and used siblings as the comparison group. Finally, Van Schie et al. (27) indicated the frequency of school delay in HIE cohorts was 17% in mild grading and 18% in moderate. They reported 17% of the mild HIE group and 18% of the moderate HIE group experienced school delay.

2.3.2 Psychosocial Outcomes

Three out of the four studies (17, 23, 24) indicated adverse psychosocial outcomes for children with moderate HIE, and one out of two (23) studies suggested some adverse outcomes for the mild HIE group.

2.3.2.1 Emotional and behavioural adjustment

Marlow et al. (24) and van Schie et al. (27) found parents or teachers reported similar emotional and behavioural adjustment between children with moderate or mild HIE and their peers. Scores were in line with the normative population, suggesting few problems existed in their school and social environments. However, Marlow et al. (24) noted that while differences failed to reach statistical significance, moderate HIE cases were consistently lower performers than their non-HIE classmates. In contrast, Hayes et al. (23) reported children with moderate HIE were more likely to experience problems related to anxiety, aggression, social withdrawal, and sleep disturbance than mild HIE cases. Furthermore, Hayes et al. (23) found executive functioning deficits in a higher percentage of children with mild HIE than would be expected in the normative population. Similarly, Lindstrom et al. (17) found problems in executive functioning-related behaviours for adolescents with moderate HIE. They observed a higher degree of perceived inattention and impaired social skills in the HIE cases. Semi-structured interviews with mothers, assessing social functioning and general health, also found moderate

HIE cases experienced short-term memory difficulties which impacted their daily life (64%), problems with time perception (50%) and difficulties with orientation (28%).

2.4 Discussion

We have highlighted across seven observational studies the outcomes for 405 children with mild and moderate HIE without CP. This systematic review highlights the lack of research in the long-term school and psychosocial outcomes of school going children with HIE. The key findings of importance were: (i) in five out of five studies where this was assessed, there was an increased prevalence of adverse school outcomes in moderate HIE cohorts, with increased prevalence of attendance at special school, academic delay, and lower scores on standardised attainment tests compared to mild HIE and non-HIE peers. In two out of three studies examining mild HIE school outcomes, there was a slightly elevated risk of school delay or attending special school, with 8-17% prevalence rates in mild HIE cases compared to 0% in controls; (ii) in three out of four studies, children with moderate HIE were more likely to experience emotional and behavioural problems compared to mild HIE cohorts or non-HIE peers. Problems reported related to anxiety, aggression, sleep disturbances, social interactions, social withdrawal, and inattention. Of the two studies which examined emotional and behavioural outcomes for children with mild HIE without CP, there was little evidence of maladjustment.

There was evidence that school difficulties and psychosocial problems exist across the different developmental stages of childhood in the moderate HIE group, with the review reporting findings from the ages 4 to 19. For the four studies evaluating mild HIE outcomes, the age of participants did not extend beyond 10 years. However, latent difficulties may not manifest until later years as children mature. Indeed, van Handel et al. (18) indicated social problems and mood disturbances began emerging in children with a history of mild and

moderate encephalopathy at the age of 10. There is evidence that the gap between children with mild HIE and non-HIE peers widens over time. Conway et al. (4) described that the prospect of disabilities appears less severe initially due to limitations in accurately measuring outcomes at a young age. They reported that the proportion of children with mild HIE with adverse outcomes increased with age. Therefore, the level of unrecognised disability and deficit in these children may be much greater than what our review suggests.

Our review indicated that there may be an association between HIE severity and adverse outcomes. In three out of four studies which assessed both mild and moderate gradings, there was a significantly increased risk of impairment in the moderate group compared to the mild. This supports previous research examining HIE outcomes where it is widely accepted that higher levels of impairment are more evident on the severe and moderate end of the HIE spectrum and less so on the mild end (39). However, we acknowledge that, in clinical terms, the distinction between HIE categories can be subtle, and HIE grades can be viewed along a continuous spectrum of severity. In particular, those with moderate HIE constitute a much more heterogenous group, which likely lowers the predictive value in outcomes for this population.

This review is the first to systematically bring together those studies which have robustly examined school and psychosocial outcomes in children with both mild and moderate HIE across childhood. This is an important focus in order to explore whether functional outcomes emerge along with the neurodevelopmental problems previously identified. Problems with interpretation remain. There are only a small number of studies to date to evaluate this evidence. Moreover, studies included were not designed to solely evaluate the school and psychosocial outcomes of mild and moderate HIE groups without CP. Instead, these outcomes of interest were reported as part of a wider assessment of long-term outcomes for HIE. As such, all but one study (25) did not report means and standard deviations on outcome

measures, limiting our ability to discern clinically significant scores between HIE groups and controls, as well as calculating effect sizes.

Whilst the review encompasses both parent and teacher informants, no studies reported data from the young people themselves. However, there is well-established research that suggests children may be better reporters of their own psychopathology than their parents (40). Moreover, there may be a measurement confound depending on the scales used. For example, Hayes et al. (23), rated as 'adequate' methodological quality, and Marlow et al. (24), rated as 'good' methodological quality, found conflicting results for emotional and behavioural outcomes among moderate HIE cohorts. Hayes et al. (23) reported the moderate HIE group experienced significant problems in relation to emotional well-being through the *CBCL*, while Marlow et al. (24) reported emotional well-being to be equivalent to general population norms through the *SDQ*. Thus, future research using similar evaluation methods is preferable. In addition, reporting of difficulties in self-report measures can differ substantially between responders. In Hayes et al. (23), parents and teachers noted different rates of behavioural difficulties, suggesting a detection bias.

None of the seven studies included in this review reported participants who received therapeutic hypothermia, a standard care treatment for children with moderate HIE. Given that the majority of studies are from the era where cooling was not a recognised treatment option, the results for children with moderate HIE may not be representative of current day cohorts.

Of the studies included for review, most had small sample sizes, therefore may have lacked statistical power. For example, van Schie et al. (27) explicitly conceded that, due to small sample size, further research on psychosocial outcomes was necessary before definitive conclusions could be made. The methodological quality of their study was rated as 'adequate'

due to a lack of a control group. Given the risk of bias in some studies and the heterogeneity of outcome measures, a meta-analysis was not considered.

Our findings have important wider educational and societal implications for HIE cohorts. They indicate that there is a higher prevalence of subtle impairment in school attainment for children with HIE, particularly in moderate HIE groups. Careful educational assessment may be required to optimise learning opportunities for individuals and prevent additional educational costs and academic delay. Reduced school attainment could impact future occupational opportunities and psychological well-being.

2.4.1 Conclusion

To our knowledge, this is the first systematic review which examines the long-term school and psychosocial outcomes of children with mild and moderate HIE without CP. This review has highlighted that children with moderate HIE without CP are at greater risk of adverse school outcomes compared to their non-HIE peers, while there is some evidence of slightly elevated risk for mild HIE cases. Consequently, these findings support the call for more extended follow-ups of children with mild and moderate HIE without CP into school age. The majority of long-term studies have focused on cognitive and neurodevelopmental outcomes as primary outcomes (6, 41). Instead, research evaluating long-term school outcomes in children posits cognitive ability is not necessarily the best predictor of school attainment (42). It is already recognised that children with mild HIE are under-studied and under-represented in HIE research (4). The rate of deficits is less than that of moderate HIE. However, the incidence of mild HIE is greater than other HIE grades, meaning its level of disease burden and long-term impact on quality of life can be equated to that of moderate HIE. The small number of studies included for review further highlights the need for future research on the long-term school, psychological, and social outcomes of children following HIE during infancy.

Conflict of Interest

The authors declare no conflicts of interest.

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Chapter 3

Systematic Review Supplementary Information

3.1 Systematic Review

A systematic review is a transparent process of identifying, evaluating and synthesising all literature pertaining to a well-defined research question (1). A systematic review synthesises information in an organised manner and adheres to a predefined search strategy. Accordingly, studies that do and do not support the research question are identified and interpreted thus reducing bias. The rationale for conducting such a review relate to the need to summarise the existing empirical evidence in the area of research, the need to identify any gaps in the current literature for further research, and to provide a background that will guide new areas of research. The major advantage of reviews is that if they report consistent findings they can provide more definitive evidence of outcomes or phenomena. In contrast, if findings are inconsistent across studies, it guides further research into why there is such variation. In this way, a systematic review was considered necessary to establish the prevailing evidence for long-term school and psychosocial outcomes in children with HIE.

3.2 Conducting a Scoping Review

According to Grant and Booth (2, p. 95), a scoping review is "preliminary assessment of potential size and scope of available research literature" and which "aims to identify the nature and extent of research evidence". They noted that scoping reviews are best served when there is a body of literature that has not been comprehensively reviewed. There was a common consensus among the authors that long-term school and psychosocial outcomes in children with HIE is a scarcely researched area. Therefore, it was anticipated few studies meeting inclusion criteria may exist. However, it was still deemed important to collate what research did exist, and synthesise this evidence to summarise what the long-term school and psychosocial outcomes are for children with mild and moderate HIE without CP. Consequently, a scoping

review was run prior to conducting the systematic review in order to establish the likelihood of there being sufficient articles to complete the review.

The scoping review was conducted through the databases Medline and PsycINFO. Medline is a widely used and recognised bibliographic database that contains peer-reviewed articles in life sciences and biomedical information. PsycINFO is one of the largest databases in the world which contains peer-reviewed literature in behavioural science, psychology and mental health. These databases were chosen as their disciplinary focus related to the research topic of school and psychosocial outcomes of HIE.

The aspects of the review were developed into two concepts: (i) the condition (i.e. HIE) and (ii) outcomes (i.e. educational and psychosocial). To help devise the search terms a recent previous systematic review in the area examining neurodevelopmental outcome and mortality was consulted (3). Additionally, iterative searches of key words were conducted through google scholar to identify common terms used in the research area. As psychosocial, and not social alone, was a primary outcome, it was anticipated the search term psycho* would capture all relevant search results in this area. Outcomes related to emotional adjustment were anticipated to be sufficiently captured using the terms psycho*, adjust*, and behaviour*. Once the search terms were established, the below electronic search terms were entered in PsycINFO and Medline databases to perform the scoping review.

TI (hypoxic ischemic encephalopathy OR neonatal hypoxia OR neonatal encephalopathy) OR AB (hypoxic ischemic encephalopathy OR neonatal hypoxia OR neonatal encephalopathy) NOT TI (rats or mice) NOT AB (rats OR mice)

AND

TI (education* OR behaviour* OR school OR attainment OR academic OR psycho* OR

adjust*) OR AB (education* OR behaviour* OR school OR attainment OR academic OR psycho* OR adjust*)

After entering the search terms through Medline, 141 results were returned. Results were reviewed by title and abstract and 68 were catalogued as possibly relevant to the research question. After entering the above search terms through PsycINFO, 27 results were returned. Results were reviewed by title and abstract and 13 articles were catalogued as possibly relevant to the research questions. During cataloguing articles, it was recognised educational and psychosocial outcomes may not be explicitly noted in the Title or Abstract and instead could be secondary outcomes in the main body of the text. Therefore, articles were catalogued for further analysis where they referenced non-specific outcomes of HIE. The search limiter "NO rats or mice" was included as initial search results included many studies that included rats and mice only which was not relevant to the aims of this review.

The scoping review provided enough output to suggest a comprehensive systematic review of the literature was feasible. It was decided the databases used in the review would be broadened. Previous systematic reviews in the area of NE and HIE helped inform this process, as well as consultation with a subject matter expert. The following electronic databases were chosen for final review: 1. Medline, 2. PsycINFO, 3. Embase, 4. PubMed, 5. Cochrane Trials Database.

3.3 Systematic Review versus Meta-analysis

It can be a common misconception that a systematic review and a meta-analysis are the same. While a systematic review answers a defined research question by collating and summarising all empirical studies within prescribed eligibility criteria, a meta-analysis refers to the additional use of statistical methods to summarise the results of the studies. The rationale for a

meta-analysis is that, by pooling the samples of the all individual studies, the overall sample size is increased, thereby improving the statistical power of the analysis.

As referenced in section 2.4 in Chapter 2, a meta-analysis was not considered for the current review as there were too few studies, heterogeneity in outcome measures, and limited amount of statistical data.

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Appendix A - Quality Assessment Tool

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self-reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self-report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self-report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self-report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Appendix B – Developmental Medicine and Child Neurology (Author Guidelines)

Author Guidelines

Developmental Medicine & Child Neurology

Updated October 2019

All papers should be submitted online at **http://mc.manuscriptcentral.com/dmcn**. Please email the editorial office with any queries about the process (**dmcn@editorialoffice.co.uk**).

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Clinical practice guidelines	Unstructured, 150 words	1 to 5 points	3000	30	4	No
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Articles should comprise an introductory section (but not headed 'Introduction'), followed by 'Method' (with optional subheadings, such as 'Participants' (rather than 'Subjects') and 'Statistical analysis'), 'Results', and 'Discussion' sections. The Discussion section should include the limitations of the study. Subheadings should otherwise be kept to a minimum.

Authors are encouraged to submit video material supporting their papers, where appropriate, for publication in the Journal.

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We publish three types of review. Please refer to the 'Reporting guidelines' section for reporting guidelines and protocol registration.

1. **Systematic review**: a type of research synthesis of quantitative evidence that uses pre-defined, explicit, systematic methods selected to minimize bias and provide reliable findings on which to make decisions. A systematic review answers a precise, pre-stated question based on the PICO/PICOT (Population, Intervention, Comparator, Outcome [and Treatment]) elements. Quality assessment of the evidence both within the review and across the included studies is essential in order to analyse the risks of bias and gauge the degree of confidence that can be had in its conclusions.

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Journal Article
Abrams RA, Tsai AM, Watson B, Jamali A, Lieber RL. Skeletal muscle recovery after tenotomy and 7-day delayed muscle length restoration. *Muscle Nerve* 2003; **23**: 707–14.

Auvin S, Joriot-Chekaf S, Cuvellier JC, Vallée C. Familial alternating hemiplegia of childhood or channelopathy? [letter]. *Dev Med Child Neurol* 2004; **46**: 500.

Journal Article, online only
High PC; the Committee on Early Childhood, Adoption, and Dependent Care and Council on School Health. School readiness. *Pediatrics* 2008; **121**: e1008–15.

Journal Article, e-pub/online early
Forsyth R, Basu AP. The change we want to see: the promotion of recovery after acquired brain injury. *Dev Med Child Neurol* 2014 Sep 8. doi: 10.1111/dmcn.12575. [Epub ahead of print].

Book, whole
Mesibov GB, Kunce L, Schopler E. Asperger syndrome or high functioning autism? Current issues in autism. New York: Plenum Press, 1998.

Book, chapter
Finnegan LP, Kaltenbach K. Neonatal abstinence syndrome. In: Hoekelman RA, Nelson NM, editors. Primary pediatric care. 2nd edition. St. Louis: Mosby Yearbook, Inc., 1992: 1367–78.

For references to online sources, supply the author names, full title, and full URL including the date on which the site was accessed.

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Chapter 4

Empirical Study

Title: **Long-term neuropsychological and behavioural outcomes of mild and moderate hypoxic ischemic encephalopathy**

Prepared in accordance with submission guidelines of *Brain Injury*

(See Supplementary Chapter 5 for instruction for authors[1])

Word Count: 4,101 (excluding abstract, tables, figures, and references)

[1]Tables and Figures are usually included at the end of text or in separate files for journal submission, however they have been inserted in text for ease of examination.

Long-term neuropsychological and behavioural outcome of mild and moderate hypoxic ischemic encephalopathy

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ABSTRACT

Objective: Follow-up study of infants with mild-moderate hypoxic ischemic encephalopathy (HIE) into later childhood is sparse. The current controlled study sought to explore the neuropsychological and behavioural outcomes of adolescents with mild and moderate HIE.

Methods: Adolescents with a history of mild-moderate HIE (*n* = 23), their siblings (*n* = 13), and healthy peers (*n* = 14) underwent neuropsychological assessment across key cognitive domains of functioning. Behavioural adjustment, school, and social competencies were also measured through both parental and youth report questionnaires.

Results: No differences in neuropsychological and behavioural outcomes were observed between mild and moderate HIE cohorts. Adolescents with mild-moderate HIE at birth had significantly lower scores on tests of attention/executive functioning, verbal reasoning and sensory-motor ability compared to healthy peers, with moderate to large effect sizes. In terms of behavioural adjustment, parents reported elevated levels of peer problems only in the HIE group compared to both siblings and healthy controls.

Conclusions: The data indicated some evidence for neuropsychological deficits and behavioural difficulties in adolescents with mild-moderate HIE compared to healthy peers and siblings. This combination of deficits can result in distinct problems such as school attainment and there was evidence of such in this cohort. The absence of differences on some measures when compared to sibling controls -v- other healthy controls is discussed.

KEYWORDS: Hypoxic ischemic encephalopathy; long-term; neuropsychological; cognitive; behavioural; outcome

4.1 Introduction

Neonatal hypoxic ischemic encephalopathy (HIE) is a brain injury following a lack of oxygen (hypoxia) and blood (ischemia) to the brain during the prenatal, intrapartum or postnatal period (1). It is one of the leading causes of infant mortality globally, with survivors at an increased risk of disability and major neurological sequalae (2). In Ireland, HIE is estimated to affect between 1.5 and 3 per 1000 term births (3). Following HIE, approximately 20% of infants die in the neonatal period and 24-40% develop permanent neurodevelopmental abnormalities (2, 4, 5). Neurodevelopmental sequalae include cerebral palsy (CP), intellectual disability, cognitive impairment, epilepsy, and motor deficits (6, 7). Long-term studies have reported impairments continue to emerge during school going years. Specifically, educational delay, reduced working memory and attention, and lower IQ are associated with HIE (8, 9, 10).

The severity of HIE is classified into three groupings: mild (Grade 1), moderate (Grade 2), and severe (Grade 3) (11). These classifications are based on electroencephalographic (EEG) readings, neurological examination, and clinical features such as foetal heart rate, seizures, level of consciousness, and tone. The severity of HIE is strongly correlated with the incidence of neurological sequalae and death, with moderate and severe gradings associated with greater disability and mortality (12, 13).

Research has documented the neuropsychological outcomes of children with moderate and severe HIE during early school years. Memory and executive functioning were found to be impaired in children of 7 years age relative to their classmates (14). While outcomes for children with severe grading have been consistently negative, outcomes are more heterogeneous for children with moderate HIE. A review of cognitive functioning among the moderate HIE cohort found children scored lower than age matched peers in learning and memory, although still within the normal range (15). Memory deficits were reported in the

verbal domain with visual memory seemingly intact. However, outcome studies included in the review did not go beyond the age of 9 and some lacked control groups. Behavioural adjustment for moderate HIE has received little attention so far. The few studies completed have indicated increased hyperactivity in children with moderate HIE, but not in children with mild HIE (14, 16). Furthermore, children with moderate HIE were shown to exhibit more problem behaviours. Van Handel et al. (17) reported a moderate HIE cohort showed increased problematic behaviours compared to peers, including social problems, depressed/anxious behaviours, and attention problems.

The outcomes for mild HIE has historically been considered to be similar to that of non-HIE children (18, 19, 20). Consequently, few prospective studies have included mild HIE cohorts, instead focusing on moderate and severe grades. However, there is emerging evidence that mild grade infants may also experience learning and neuropsychological difficulties at school age (21). A recent systematic review of mild HIE outcomes reported 22% of children had an abnormal outcome at 18 months, where abnormal was defined as death, CP, developmental delay, or intellectual impairment (22). By 5 years, 35% were having difficulties in one or more developmental areas. Behavioural outcome for mild HIE has received even less attention than cognitive outcomes in the literature. One study which did examine behavioural outcome in mild HIE suggested behavioural problems at school age were milder but not absent (17), as opposed to the traditional view that negative effects were limited to moderate and severe HIE groups.

The deficit gap between healthy controls and children with HIE appears to widen with age. In the absence of motor deficits, children aged between 9 and 10 with mild HIE were found to be at an increased risk of cognitive impairment (21). There is evidence that risk of disability and impairment increases with age (22), indicating later developmental effects. One of the few studies which followed HIE outcomes into adolescence reported 70% of teenagers

with a moderate grading had learning and behavioural problems which interfered with their daily functioning (23). Thus, the degree of future neuropsychological deficits and behavioural difficulties may be greater than predicted.

The comparison groups in previous HIE studies have performed better than expected on standardised tests (14, 24), scoring > 1 standard deviation above normative means. Such healthy controls may be 'healthier' than children chosen from the normal population. This may be due to socioeconomic factors or local population differences. The current study sought to use an additional sibling comparison group to limit the effects of such an anomaly.

This study sought to explore the long-term neuropsychological and behavioural outcomes of an Irish sample of adolescents with mild-moderate HIE compared to siblings and healthy controls.

4.2 Methods

The study was a further follow-up of a prospective study which assessed the neurodevelopmental outcomes of children with a history of HIE from infancy to childhood. Previous outcomes have been reported elsewhere (24, 25) or remain unpublished. The comparison of previous outcomes with outcomes from the current study was beyond the scope of this paper. Ethical approval was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC).

4.2.1 Initial and Current Recruitment

The original baseline study recruited children with HIE between May 2003 and December 2005 from a maternity hospital in Ireland with approximately 6000 deliveries per annum (25). Children were recruited if they met two of the following criteria: (i) initial capillary or arterial pH < 7.1, (ii) Apgar score < 5 at 5 min, (iii) initial arterial or capillary lactate > 7 mmol/L, or (iv) abnormal neurology and/or clinical seizures. Participants were excluded if they

had co-existing congenital anomalies, or significant co-morbidity. Parents of children meeting criteria were approached and written consent was obtained typically 6 hours after birth. Neurological assessment, continuous EEG monitoring up to 72 hours, and HIE Sarnat grading was performed. In total, 65 infants with HIE were recruited and 53 remained after dropouts and exclusionary factors. In the succeeding years, participants completed standardised developmental assessments at 6, 12 and 24 months (25), and at 5 years of age (24).

For the current study, families were contacted by telephone and invited to participate in a longer-term follow up of neuropsychological and behavioural outcome during adolescence. Families who wished to participate were sent written information outlining the purpose of the study. Parents or guardians and adolescents completed informed consent and assent forms prior to scheduling an assessment appointment. Control group children were recruited from the same control sample as in the previous study. Participants were healthy term infants with normal neurologic features and born between October 2005 and August 2007. Exclusion criteria were birth weight < 2.5 kg, maternal diabetes or epilepsy, congenital defects, or admission to neonatal unit for special or intensive care. A sibling comparison group of nearest aged siblings was also included for the present study. This was an important feature of the study and was included for the reasons noted above. Siblings were recruited if they met the following conditions; (i) aged between 6 and 16, (ii) no neurodevelopmental diagnoses, and (iii) no adverse neonatal conditions.

In total, 53 participants were recruited to the study: 25 children with neonatal HIE, 14 siblings and 14 controls. Of the original HIE sample, 10 families did not consent to participate in the current study, 7 were uncontactable, and 5 failed to attend assessment appointment or cancelled. Of the remaining 25 children, 2 were excluded due to having a severe HIE diagnosis. When the representativeness of HIE participants for the current study was assessed, there were no statistically significant differences found between responders and non-responders from

baseline data obtained at birth (see Table 4.1). In the sibling group, 16 children were recruited and 3 removed due to exclusionary factors. Of the 30 children comprising the control comparison group at baseline, 16 were lost at follow-up. The healthy controls did not differ to the original control group in terms of gender (p = .65), age (p = .58), and socio-economic status (p = .70).

Table 4.1 Clinical characteristics of HIE responders and non-responders from baseline study

Variable	Responders (n = 23)	Non-responders (n = 30)	*P*
HIE			.28[1]
Mild *n*	11 (48%)	19 (63%)	
Moderate *n*	12 (52%)	11 (37%)	
Gender			.27[1]
Male *n*	14 (61%)	13(43%)	
Female *n*	9 (39%)	17 (57%)	
Gestational Age in weeks mean (SD)	40 (1.37)	39.9 (1.5)	.85[2]
Birth Weight in grams mean (SD)	3452 (557)	3285 (630)	.32[2]
EEG[a]			.83[1]
Normal *n*	20 (91%)	25 (93%)	
Abnormal *n*	2 (9%)	2 (7%)	
Deprivation Index[b]			.47[1]
Affluent *n*	3 (13%)	3 (13%)	
Average *n*	19 (83%)	17 (71%)	
Disadvantaged *n*	1 (4%)	4 (17%)	

[1]Fisher's Exact Test, [2]Independent samples *t*-test, [a]Normal = EEG Grade 1 to 2, Abnormal = EEG Grade 3^{+}; [b]Pobal HP Deprivation Index scores for Small Areas (26).

There was a significant difference between study groups on age. For all other demographic characteristics, no statistically significant differences were found (Table 4.2). Although not reaching statistical significance, there was a higher prevalence of families living in affluent areas in the control group. Similarly, with respect to HIE grading, no differences on

clinical or demographic characteristics were observed between mild and moderate HIE participants (Table 5.4 in Supplementary Chapter 5).

Table 4.2 Demographic Characteristics of HIE, Sibling and Control groups

Demographic Variable	HIE (N=23)	Sibling (N=13)	Control (N=14)	*P*
Mean years (*SD*)	14.45 (1.03)	12.5 (2.31)	11.85 (0.96)	< **.001**[1]
Gender (*n*)				.19[2]
Male	14 (61%)	4 (30%)	5 (36%)	
Female	9 (39%)	9 (70%)	9 (64%)	
Family composition (*n*)				.44[2]
Two parents at home	22 (96%)	13 (100%)	12 (86%)	
Lone parent	1 (4%)	0	2 (14%)	
Maternal employment (*n*)				.80[2]
Employed	19 (81%)	10 (79%)	12 (86%)	
Not employed	4 (19%)	3 (21%)	2 (14%)	
Paternal employment (*n*)				n/a
Employed	23 (100%)	13 (100%)	14 (100%)	
Not Employed	0	0	0	
Deprivation index score[a] (*n*)				.20[2]
Affluent	3 (13%)	2 (15%)	6 (43%)	
Average	19 (83%)	10 (77%)	7 (50%)	
Disadvantaged	1 (4%)	1 (8%)	1 (7%)	

[1]One-way analysis of variance (ANOVA); [2]Fisher's Exact Test; [a]Pobal HP Deprivation Index scores for Small Areas (26).

4.2.2 Outcomes

Assessment during adolescence was assessed by a trainee clinical psychologist (SH) and two psychology graduates (JW and EC) trained to undertake the current neuropsychological assessment battery. Training and assessment fidelity were assured by two senior clinical neuropsychologists (CMC and LF).

Neuropsychological outcomes were assessed in the cognitive domains of attention/executive functioning, verbal reasoning, non-verbal reasoning, visual and verbal memory, sensory-motor ability, language, and speed of information processing. Two senior neuropsychologists (CMC and LF) chose the neuropsychological assessments, and categorised subtests into cognitive domains for the purposes of the study. Table 4.3 outlines each subtest and the related cognitive construct measured. Standardised scores for each subtest were calculated. The *WIAT-III* and *BPVS-III* scores are standardised with a mean (standard deviation (SD)) of 100 (15). The *RCFT – Copy Test* provided a raw score and percentile ranks. All other subtest scores were standardised with a mean (SD) of 10 (3).

Behavioural outcomes were measured through the *Behaviour Rating Inventory of Executive Function – 2nd Edition* (*BRIEF-II*) (34), the *Strengths and Difficulties Questionnaire* (*SDQ*) (35) and the competency subscales of the *Child Behaviour Checklist List* (*CBCL*) and *Youth Self-Report* (*YSR*) (36). See Supplementary Chapter 5 for further description of all outcome measures. Assessments and questionnaires were completed at the research centre or at the participant's home.

A bespoke parental questionnaire was designed to capture demographic information, neurodevelopmental diagnoses, and attendance at early intervention services (see Appendix J Supplementary Chapter 5).

4.2.3 Statistical Analysis

Statistical analysis was completed by using IBM SPSS Statistics 26.0 for MS Windows. Analyses explored differences between HIE and comparison groups on neuropsychological and behavioural outcomes. Between groups differences on demographic and clinical data for HIE and comparison groups, and for mild and moderate HIE comparison, were explored using analysis of variance (ANOVA) and independent sample *t*-tests for continuous variables, and

Fisher's exact test for categorical variables. Our primary research question related to the HIE group in comparison to each of the control groups separately (rather than in evaluating differences across all three groups per se). Thus, independent t-tests, with Benjamini-Hochberg (37) corrections applied to tests within each cognitive domain, were utilised, consistent with previous such research with HIE neuropsychological outcomes (14). Outliers (> 3 standard SD from subgroup means) were removed from the dataset (n = 5 outliers removed). Equivalent non-parametric tests were performed on outcome data not assuming normal distribution. All p-values were two-tailed with statistical significance cut-off set at < 0.05. Effect sizes for between-group differences were calculated using partial eta squared.

Table 4.3 Neuropsychological Subtests and Descriptions

Neuropsychological Outcome	Subtest Description
Verbal Reasoning	
Similarities[a]	Measures ability to think logically, verbal concept formation, and verbal abstract reasoning.
Non-verbal reasoning	
Matrix Reasoning[a]	Measures abstract reasoning, spatial perception, and visual processing.
Speed of Information Processing	
Symbol Search[a]	Measures visual perception, fine-motor speed and accuracy, and recognition.
Coding[a]	Measures visual-motor and fine-motor dexterity and speed.
Attention/Executive Functioning	
Letter Fluency[b]	Measures the ability to generate words within specific initial letter categories.
Digit Span[a]	Measures attention and short-term auditory memory.
Visual Scanning[c]	Measures attentional ability to rapidly locate objects on a page.
Number Sequencing[c]	Measures numerical processing and mental sequencing.
Letter Sequencing[c]	Measures letter processing and mental sequencing.
Switching[c]	Measures complex mental processes of cognitive flexibility, multi-tasking, and divided attention.
Motor[c]	Measures visuomotor speed.
Rey Complex Figure Copy[d]	Measures attentional and planning abilities.
Visual Memory	
Memory for faces Immediate[b]	Measures encoding of facial features, face discrimination, and recognition.
Memory for faces Delay[b]	Measures delayed retrieval of facial recognition.
Verbal Memory	
List Learning Immediate[e]	Measures verbal learning and memory, and the role of interference in recall for verbal items.
List Learning Delay[e]	Measures delayed recall of verbal items.
Sensory Motor	
Finger Tap Sequencing[b]	Measures finger dexterity and motor speed.
Language	
Speeded Naming[b]	Measures quick semantic access to and production of names of letters.
Spelling[f]	Measures written spelling of letter sounds and single words.
Reading[f]	Measures speed and accuracy of word recognition.
Receptive Vocabulary[g]	Measures oral language and receptive vocabulary.

[a]*Wechsler Intelligence Scale for Children – 5th Edition* (*WISC-V*) (27); [b]*Neuropsychological Assessment Tool – 2nd Edition* (*NEPSY-II*) (28); [c]*Delis-Kaplan Executive Function System Trail Making tests* (*DKEFS*) (29); [d]*Rey Complex Figure Test - Copy test* (*RCFT*) (30); [e]*Children's Memory Scale* (*CMS*) (31); [f]*Wechsler Individual Achievement Test – 3rd Edition* (*WIAT-III*) (32); [g]*British Picture Vocabulary Scale – 3rd Edition* (*BPVS-III*) (33)

4.3 Results

4.3.1 Neuropsychological Outcome

Cognitive assessment was available for 23 children with HIE (11 mild, 12 moderate), 13 siblings and 14 control children. The mean and standard deviation scores on each neuropsychological subtest for mild and moderate HIE grades are displayed in Table 4.4. There were no statistically significant differences in all cognitive domains across mild and moderate HIE grades, nor was there a pattern evident for the moderate group to perform more poorly than the mild group (see Figure 4.1). Instead, both subgroups tended to score below reference group norms. Consequently, mild and moderate HIE participants were grouped into one homogenous group for continued analysis.

Table 4.4 Mean neuropsychological scores for mild and moderate HIE groups

Neuropsychological Outcome	Mild (*n* = 11)	Moderate (*n* = 12)	*P*
Verbal Reasoning			
Similarities[a] (SD)	8.27 (2.49)	9.42 (3.06)	.34
Non-verbal Reasoning			
Matrix Reasoning[a]	8 (3.49)	8.58 (2.94)	.69
Speed of Information Processing			
Symbol Search[a]	8.55 (2.16)	9.42 (3.37)	.47
Coding[a]	8.55 (4.06)	10.27 (3.96)	.16[1]
Attention/Executive Functioning			
Letter Fluency[b]	10.27 (2.33)	8.92 (3.87)	.32
Digit Span[a]	9.91 (3.86)	9.92 (2.78)	.99
Visual Scanning[c]	9.10 (2.92)	8.50 (3.63)	.68
Number Sequencing[c]	9.20 (4.21)	10 (1.71)	.92[1]
Letter Sequencing[c]	7.50 (4.17)	8 (3.52)	.76
Switching[c]	8.20 (3.33)	8.91 (3.05)	.62
Motor[c]	7.80 (3.71)	7.91 (3.24)	.94[1]
Rey Complex Figure Copy[d]	33.35 (2.78)	31.18 (4.74)	.24[1]
Verbal Memory			
List Learning Immediate[e]	9.27 (3.41)	11.08 (4.4)	.29
List Learning Delay[e]	9.55 (4.16)	11.92 (3.42)	.10[1]
Visual Memory			

Memory for faces Immediate[b]	8.55 (3.21)	10.17 (2.37)	.18
Memory for faces Delay[b]	8.45 (3.91)	9.42 (3.97)	.57
Sensory Motor			
Finger Tap Sequencing[b]	9.64 (2.30)	10.42 (3.61)	.32[1]
Language			
Speeded Naming[b]	8 (2.65)	9.58 (3.66)	.23
Spelling[f]	87.64 (11.19)	98.58 (15.95)	.07
Reading[f]	87.55 (11.93)	98.17 (12.46)	.06[1]
Receptive Vocabulary[g]	95.60 (10.20)	94.33 (9.37)	.77

[1]Non-parametric Mann Whitney test; [a]WISC-V; [b]NEPSY-II; [c]DKEFS; [d]RCFT; [e]CMS; [f]WIAT-III; [g]BPVS-III

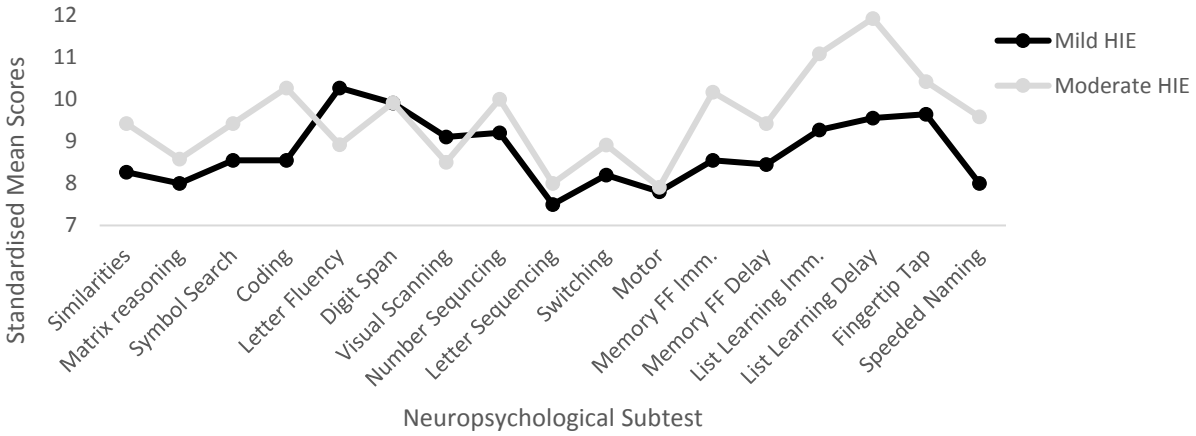

*Figure 4.1 Pattern of scores for mild and moderate HIE participants across neuropsychological subtests**

*Spelling, Reading, Vocabulary subtests excluded due to different standardisation of scores

Looking at comparisons between the mild-moderate HIE study group and the two different control groups, a pattern was evident. Figure 4.2 captured this pattern in suggesting that across neuropsychological subtests the HIE group tended to do worse than the healthy control group (on 19/21 tests). On specific tests of verbal reasoning (*Similarities*), attention/executive functioning (*Visual Scanning* and *Letter Sequencing*), sensory-motor skills (*Fingertip Tapping*) and language and literacy (*Speeded Naming, Reading* and *Spelling*), these differences reached statistical significance with moderate-large effect sizes (see Table 4.5).

However, after Benjamini-Hochberg corrections were applied, using a false discovery rate of .05, results did not reach statistical significance for the language subtests. Looking at the percentage of each group whose scores fell more than a standard deviation below the normative mean a similar pattern emerges (see Table 4.6). Often a quarter to a third of the HIE group reached clinical caseness in comparison to generally much lower rates in the healthy control group (below 10% caseness on most of the tests).

However, when the siblings were referenced as a control group, these differences disappeared. Figure 4.2 suggests the HIE performed more poorly than siblings on only 13 / 21 tests and differences did not reach statistical significance. As summarised in Table 4.5 and Table 4.6, this is because, within the sibling group, scores were generally below clinical means and the percentage of the sibling sample who fell one or more standard deviations below these norms was almost as high as in the HIE group.

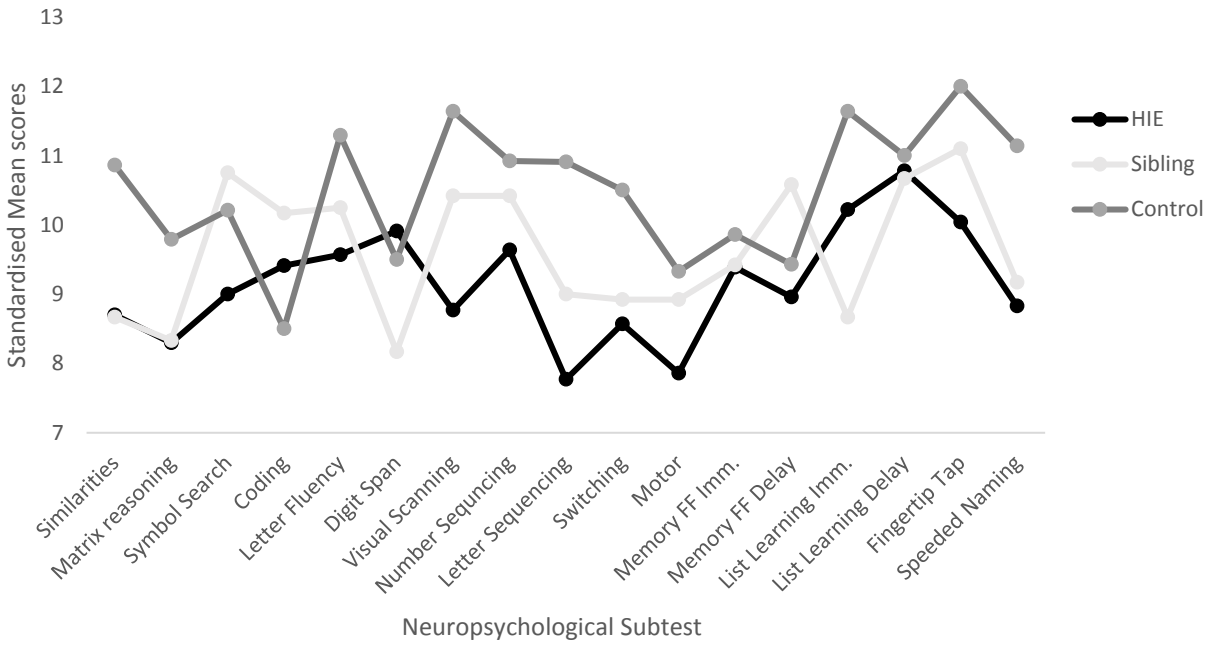

*Figure 4.2 Pattern of scores across neuropsychological subtests**

* Spelling, Reading, Vocabulary subtests excluded due to different standardisation of scores

Table 4.5 Mean neuropsychological scores for HIE, Sibling and Control groups

Neuropsychological Outcome	HIE (1)	Sibling (2)	*P* (1-2)	η_p^2	Control (3)	*P* (1-3)	η_p^2
Verbal Reasoning							
Similarities[a] (SD)	8.7 (2.80)	8.67 (2.02)	.83	.001	10.86 (2.38)	**.03**	.122
Non-verbal reasoning							
Matrix Reasoning[a]	8.3 (3.15)	8.33 (2.39)	.98	.000	9.79 (3.07)	.17	.053
Speed of Information Processing							
Symbol Search[a]	9 (2.83)	10.75 (3.38)	.08	.092	10.21 (2.16)	.18	.051
Coding[a]	9.41 (3.99)	10.17 (3.38)	.58	.010	8.5 (2.18)	.30	.018
Attention/Executive Functioning							
Letter Fluency[b]	9.57 (3.23)	10.25 (2.80)	.54	.012	11.29 (2.05)	.08	.083
Digit Span[a]	9.91 (3.26)	8.17 (2.04)	.19[1]	.079	9.50 (2.35)	.90[1]	.005
Visual Scanning[c]	8.77 (3.27)	10.42 (2.07)	.20[1]	.072	11.64 (1.80)	**.004**[1]	.190
Number Sequencing[c]	9.64 (3.05)	10.42 (2.81)	.61[1]	.016	10.92 (1.93)	.25[1]	.051
Letter Sequencing[c]	7.77 (3.74)	9 (3.28)	.35	.028	10.91 (1.76)	**.003**	.182
Switching[c]	8.57 (3.12)	8.92 (2.61)	.75	.003	10.50 (2.11)	.07	.104
Motor[c]	7.86 (3.38)	8.92 (1.51)	.75[1]	.033	9.33 (2.35)	.36[1]	.054
Rey Complex Figure Copy[d]	32.21 (3.99)	26.50 (9.15)	.09[1]	.168	31.19 (6.55)	.67[1]	.011
Visual Memory							
Memory for faces Immediate[b]	9.39 (2.86)	9.42 (2.54)	.89[1]	.000	9.86 (3.46)	.39[1]	.006
Memory for faces Delay[b]	8.96 (3.88)	10.58 (2.87)	.28[1]	.047	9.43 (3.84)	.65[1]	.004
Verbal Memory							
List Learning Immediate[e]	10.22 (3.98)	8.67 (2.71)	.24	.042	11.64 (2.79)	.25	.038
List Learning Delay[e]	10.78 (3.90)	10.67 (2.74)	.47[1]	.000	11.00 (2.18)	.74[1]	.001
Sensory Motor							
Finger Tap Sequencing[b]	10.04 (3.01)	11.10 (2.08)	.39[1]	.032	12.00 (1.96)	**.04**[1]	.118
Language							
Speeded Naming[b]	8.83 (3.24)	9.17 (1.47)	.69[1]	.004	11.14 (2.98)	**.04**[1]	.119
Spelling[f]	93.35 (14.68)	92.42 (13.81)	.86	.001	103 (9.82)	**.04**	.116
Reading[f]	93.09 (13.10)	93.92 (17.79)	.88	.001	102.64 (11.24)	**.03**	.128
Receptive Vocabulary[g]	94.91 (9.54)	87.91 (11.36)	**.03**[1]	.101	100.86 (1.56)	.10[1]	.077

Independent Sample t-tests used unless otherwise stated; *p*-values in bold indicate statistical significance; η_p^2 = partial eta squared, effect size range 0.01 small, 0.06 medium, 0.14 large; [1]Mann-Whitney U test; [a]WISC-V; [b]NEPSY-II; [c]DKEFS; [d]RCFT; [e]CMS; [f]WIAT-III; [g]BPVS-III

Table 4.6 Participants scoring ≤ 1 SD on neuropsychological outcomes norms

Neuropsychological Outcome	HIE	Sibling	Control
Verbal Reasoning			
Similarities[a]	39%	42%	7%
Non-verbal Reasoning			
Matrix Reasoning[a]	35%	50%	21%
Speed of Information Processing			
Symbol Search[a]	43%	8%	7%
Coding[a]	36%	33%	36%
Attention/Executive Functioning			
Letter Fluency[b]	26%	25%	0%
Digit Span[a]	26%	33%	29%
Visual Scanning[c]	27%	8%	9%
Number Sequencing[c]	14%	25%	8%
Letter Sequencing[c]	45%	33%	0%
Switching[c]	29%	33%	8%
Motor[c]	33%	17%	17%
Rey Complex Figure Copy[d]	39%	42%	23%
Verbal Memory			
List Learning Immediate[e]	26%	25%	0%
List Learning Delay[e]	22%	17%	7%
Visual Memory			
Memory for faces Immediate[b]	35%	17%	14%
Memory for faces Delay[b]	30%	17%	36%
Sensory-Motor			
Finger Tap Sequencing[b]	8%	0%	0%
Language			
Speeded Naming[b]	30%	17%	14%
Spelling[f]	26%	33%	8%
Reading[f]	17%	25%	7%
Receptive Vocabulary[g]	9%	36%	7%

P-values in bold indicate statistical significance difference; [a]WISC-V; [b]NEPSY-II; [c]DKEFS; [d]RCFT; [e]CMS; [f]WIAT-III; [g]BPVS-III

4.3.2 Behavioural and School outcomes

The SDQ (parent and youth informants) was used to examine behavioural adjustment across groups. Looking at data from parent respondents (Table 4.7) results suggested poorer scores

on all subscales in the HIE group in comparison to both the healthy control group and the sibling control group. These differences reached statistical significance for the *Total Score* and the *Peer Problems* score in particular. These differences yielded a moderate effect size in comparison to siblings and a large effect size in comparisons to controls. On the youth respondent questionnaire, there were no statistically significant differences between groups on total scores or subscale scores, although the pattern was the same and there was a medium effect size difference on the *Peer Problems* subscale. Table 5.5 in Supplementary Chapter 5 outlines percentage clinical caseness for this data.

There were significant group differences on the *CBCL* competency scales between the HIE group and control group. Parents reported children with HIE were significantly more likely to have overall behavioural difficulties, problems at school, reduced activities and fewer social interactions, with large effect sizes observed for each competency (see Table 4.8). In contrast, similar mean scores were reported for children with HIE and siblings. Moreover, children with HIE were significantly more likely to score ≤ 1 *SD* below the normative mean compared to healthy peers on overall behavioural competencies and social competency (Table 5.7 in Supplementary Chapter 5). The same effects were not observed between HIE and sibling comparisons.

Within the *CBCL* competency scales, specific prevalence rates were noted for children who required special educational interventions (repetition of a grade, classroom assistance, or remedial help). This data yielded a higher percentage for children with HIE (38%) compared to siblings (18%) and healthy controls (0%), with a significant difference observed between HIE and the control group ($p = .01$, Fisher's Exact Test). More detailed school outcomes of participants were assessed and reported elsewhere (38).

Table 4.7 Mean scores on the SDQ for HIE, Sibling and Control groups

	HIE (1)	Sibling (2)	*P* (1-2)	η_p^2	Control (3)	*P* (1-3)	η_p^2
Parent							
Total Score (SD)	10.43 (7.15)	6.75 (5.33)	.13	.069	5.21 (2.89)	**.004**	.161
Subscales							
Emotional Problems	3.17 (2.71)	2.25 (2.30)	.41[1]	.030	1.86 (1.96)	.13	.067
Conduct Problems	1.26 (1.63)	1.17 (1.70	.66[1]	.001	0.64 (1.50)	.07	.037
Hyperactivity	3.83 (3.13)	2.50 (2.02)	.29[1]	.051	2.36 (1.82)	.22	.068
Peer Problems	2.17 (2.10)	0.83 (1.19)	**.04[1]**	.111	0.36 (0.63)	**.001**	.219
Prosocial	7.48 (2.78)	9.08 (1.44)	**.03**	.095	8.71 (1.82)	.15	.059
Youth							
Total Score	10.80 (6.49)	8.00 (5.97)	.23	.047	7.50 (5.02)	.12	.074
Subscales							
Emotional Problems	3.10 (2.53)	2.25 (2.09)	.41[1]	.031	1.79 (1.42)	.13	.088
Conduct Problems	1.90 (1.94)	1.92 (2.43)	.76[1]	.000	1.14 (1.10)	.33	.051
Hyperactivity	3.85 (3.03)	3.08 (2.11)	.45	.019	3.71 (2.84)	.90	.001
Peer Problems	1.95 (1.88)	0.75 (1.22)	.06[1]	.115	0.86 (1.03)	.09	.109
Prosocial	8.35 (2.13)	8.75 (1.82)	.48[1]	.010	8.14 (2.28)	.94	.002

[1]Mann-Whitney *U* test; *p*-values in bold indicate statistical significance; η_p^2 = partial eta squared

Table 4.8 Mean scores on the CBCL and YSR for HIE, Sibling and Control groups

	HIE (1)	Sibling (2)	*P* (1-2)	η_p^2	Control (3)	*P* (1-3)	η_p^2
Parent							
Total (SD)	41.56 (10.8)	46 (7.5)	.44[1]	.050	57.92 (8.7)	**<.001**	.406
Activities	42 (9.2)	42.45 (5)	.86	.001	53.92 (10.4)	**.003[1]**	.279
Social	43.71 (13.7)	50.91 (7.8)	.12	.083	55.57 (6.5)	**.005**	.225
School	45.63 (8.8)	48 (7.3)	.49[1]	.020	52.23 (3.1)	**.006**[1]	.181
Youth							
Total	48.06 (8.5)	45.20 (9.2)	.42	.026	50.64 (14.9)	.55	.013
Activities	45.29 (9.3)	42.91 (7.2)	.48	.020	48.36 (12.5)	.55[1]	.021
Social	51.12 (4.2)	51.70 (10.3)	.87	.002	51.93 (8.6)	.75	.004

[1]Non-parametric Mann Whitney test; *p*-values in bold indicate statistical significance. η_p^2 = partial eta squared; Data was missing from *CBCL* for nine children (5 HIE, 2 siblings, 2 control). Data was missing from the youth questionnaire for nine children (6 HIE, 3 siblings).

Within the *BRIEF-III* parental report, the HIE group obtained higher total problem scores than siblings and controls. However, these differences did not reach statistically significance on any subscale (Table 5.8 in Supplementary Chapter 5).

4.4 Discussion

We have presented data for a cohort of mild-moderate HIE survivors into adolescence. Few studies have followed up moderate HIE, and no other studies were identified which evaluated long-term outcomes of mild HIE cohorts into later childhood. Other strengths of the current study included the inclusion of a sibling control group, in addition to the more typical healthy peer control group, and the use of both parent and child informants. A number of findings were evident.

Firstly, we found no significant differences in adolescence between the survivors of mild -v- moderate HIE. As summarised in Table 4.5, both groups generally fell below normative means for the neuropsychological scales, and the mild group certainly did not perform any better than the moderate HIE group. This pattern of outcome opposes the common view that adverse effects of HIE are limited to moderate and severe gradings. The number of children affected by mild HIE is greatest (39), suggesting a level of disease burden exists which can impact the quality of life for these children and families.

Secondly, findings suggested some evidence for neuropsychological deficits in adolescents with mild-moderate HIE compared to healthy peers when considering statistical significance, effect sizes, and pattern of scores. This is supported by the extent of reported school difficulties children with HIE experienced, such as repeated grades and need for educational assistance, compared to comparison groups.

Poorer scores were observed in the cognitive domains of attention and executive functioning, verbal reasoning, language, and sensory-motor ability, with executive functioning differences reaching statistical significance with large effect sizes. Moreover, a higher percentage of children with HIE scored significantly below the normative means across neuropsychological subtests compared to healthy controls.

In previous research, Robertson et al. (20) found evidence of no cognitive deficits in mild HIE cohorts with a mean age of 8 years. However, the authors did not include measures of attention, executive functioning, memory, or verbal reasoning. A more recent study by Hayes et al. (40) showed evidence of cognitive and behavioural difficulties in children with mild HIE and moderate with a mean age of 5 years. They found reduced performance in attention/executive functioning and language subtests, with a graded effect observed between mild and moderate cohorts. Similar to the current study, the authors observed mean neuropsychological scores for the HIE group as a whole fell within the normal range. Mañeru et al. (41) demonstrated that children with moderate HIE performed poorer than controls on measures of memory, perceptual motor ability, and executive functioning, despite scoring in the average range for IQ. This suggests children and adolescents with a history of HIE who score within the normal range for general intelligence, may still exhibit discrete, subtle neuropsychological deficits. Thus, when compared to a healthy control group (as evident in the other studies noted above), there is evidence of persistent neuropsychological sequalae.

Thirdly, this research has also been original in utilising a sibling control group as well as healthy peers. Unexpectedly, the siblings also demonstrated below-average performances in comparison to healthy controls (See Table 5.5 in Supplementary Chapter 5) and the differences between the HIE and the sibling comparison group did not reach statistical significance. Both groups generally scored below normative means. A number of interpretations are possible. It may be the case that when the more stringent sibling control group is included, evidence for long-term deficits in the mild-moderate HIE group disappears. Although possible, the relatively poorer performance of both groups may suggest that sibling profiles are obscuring, rather than illuminating, outcomes for the HIE group and that instead we should question why this sibling sub-sample performed poorly.

This may suggest a possible genetic underlay which renders children susceptible to both compromised neuropsychological functioning and HIE. This would still mean that HIE was not the *only* factor in understanding these longer-term outcomes. Alternatively, family factors such as maternal education (which we did not unfortunately record in this study) or socioeconomic status may be relevant. As noted above in Table 4.2, although differences were not statistically significant, there was a greater preponderance of "affluence" in the control group compared to the HIE and sibling groups. HIE may also more generally impact on subsequent family functioning. Indeed, research has shown siblings of children with early life illness are more likely to experience psychological maladjustment such as depression and anxiety (42, 43). A time of increased family stress and reduced parental self-efficacy can mediate parents' ability to provide home learning opportunities (44). The age of siblings in relation to their family member with HIE must be considered. Birth order has been shown to affect the level of vulnerabilities identified in siblings of children with neurodevelopmental conditions, with younger siblings performing lower than expected on cognitive and behavioural outcomes (45). We did include a measure of family functioning not reported in this paper (the *Family Environment Scale* (46)). Table 5.9 (Supplementary Chapter 5) however suggested no group differences with respect to family cohesion. Reasons for poorer sibling performance must remain speculative at this stage.

Finally, based on parental reports, adolescents with HIE showed higher levels of overall problematic behaviours and reduced competencies at home and school, compared to healthy peers. Specific problems included peer problems, reduced activities, and school difficulties. Significant peer problems in the HIE group compared to control had also been recorded at 5-year follow-up (47) indicating social difficulties have remained, and possibly increased, within a 10-year period. This finding supports previous research showing children of school age with mild or moderate HIE experience higher levels of social problems compared to non-HIE peers

(17). It again challenges the view that mild HIE cohorts have no long-term adverse outcomes and adds to the growing evidence that difficulties may increase as children with HIE mature to school age and adolescence (22). This time specific problem with respect to peer relationships was also confirmed in comparison to siblings (see Table 4.7 above) which suggest this is a distinct area of maladjustment.

It should be noted, however, that these emotional, behavioural, and social problems were not evident when we looked at youth self-reports. Such discrepancies between parental and youth report on behavioural adjustment has been evident in the literature more generally (48, 49) and is especially associated with family dysfunction and poor developmental outcome (48). As with the neuropsychological outcomes, behavioural measures did not yield significant differences between mild and moderate HIE subgroups.

Findings must be considered with respect to some study limitations. Primarily, relatively small study numbers reduced power to detect statistically significant differences and we have referenced effect sizes to partially compensate for this. Recruitment of children with HIE can be difficult, and sample sizes are comparable to the only other study known to authors which prospectively followed children with HIE into adolescence (23). Secondly, it may be that families who participated in the study were more likely to have concerns about their other children than the non-responders, and this may be why this particular sibling group performed so poorly. Thirdly, the groups were not matched for age with the control group being significantly younger and mostly attending primary school. While the standardisation of outcome measures controlled for this discrepancy, it may be that behavioural difficulties related to social competencies and peer problems are more likely to manifest in later adolescence and secondary school. Fourthly, while assessment was standardised, researchers were not blinded to the neonatal data of the HIE and control group.

Finally, the study was based on the outcomes of children with HIE who were born approximately 14 years ago and prior to the introduction of therapeutic hypothermia as a treatment. Studies have since shown therapeutic hypothermia can reduce the long-term risk of disability and cognitive impairment in moderate HIE cohorts (50, 51). As a result, the long-term outcomes of children with HIE who received hypothermia treatment may differ to the outcomes presented in this study.

Our findings have wider clinical implications. They indicated the presence of neuropsychological and psychosocial sequalae in adolescence for children with mild and moderate HIE. The continued assessment of children with a history of HIE is important to help professionals to identify children requiring intervention and support. Long-term adverse outcomes following mild and moderate HIE, even though subtle, are likely to have broader implications such as high medical expenses, additional educational costs, and emotional distress for affected individuals and families.

4.4.1 Conclusion

The study showed some evidence that neuropsychological ability and behavioural adjustment are reduced during adolescence for children with mild-moderate HIE compared with a healthy comparison group. These relatively small deficits that were observed in specific cognitive domains can interact with subtle behavioural maladjustments to result in distinct problems, such as school difficulties. No differences in neuropsychological ability or behavioural adjustment were evident between mild and moderate HIE grades. In general, children with HIE and siblings scored similarly across outcomes. The findings support the need for more research into the long-term outcomes of mild-moderate HIE cohorts and the identification of siblings as an at-risk group. It is suggested future research continues to monitor mild-moderate HIE cohorts into adolescence. Transitionary periods, such as progressing from primary to secondary

education, can bring greater challenges in terms of cognition and psychosocial adjustment, therefore making it more likely for subtle adverse sequalae to emerge. Additionally, research into the development of new interventions that protect infants from HIE at birth are necessary.

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Declaration of Interest

The authors declare no conflicts of interest.

4.5 References

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Chapter Five

Empirical Study Supplementary Information

5.1 Additional Methodological Detail

Included in this section is additional methodological information to supplement the main study paper in Chapter 4. An overview of study design, the procedure, and descriptions of outcome measures are provided.

5.2 Study Design

The study used a prospective case-controlled design where it tracked two groups (HIE and control) from exposure to outcome. The sibling group was an additional study group recruited for the purposes of the current study and was not part of the original research. It was initially anticipated that the research would include outcome comparisons between the current study and the 5-year follow up. Unfortunately, we encountered difficulty obtaining the data necessary for comparison and it became too great a time-challenge to incorporate such analysis in the current study. It is envisioned that outcome comparisons at the two different time points will be completed in the near future and a manuscript prepared for publication.

A case-controlled study enables the researcher to compare outcome of a group exposed to a factor like a certain disease or condition to another group not exposed to the factor. A prospective design allows outcomes to be assessed directly over time and confounding variables to be considered.

Some advantages of this design include its effectiveness in investigating multiple outcomes that may occur from a single condition (e.g. HIE), its ability to reduce survivor bias, and how it allows the calculation of incidence rates. Disadvantages include the selection bias inherent to prospective case-controlled designs, the high participant attrition rates for longer-follow-ups, and the cost and time required.

5.3 Participants

As noted in Chapter 4, the healthy control group were significantly younger than the HIE and sibling groups. This was a legacy from the original baseline study when participants were first recruited to the prospective research study. Participants with a diagnosis of HIE were recruited between 2003 and 2005. The control group was recruited between 2005 and 2007. This methodology legacy meant age was a significant covariate for the current study.

5.4 Procedure

After ethical approval was granted by CREC, the authors were provided with the contact information of eligible families who had participated in the original prospective study. Parent(s) and/or guardian(s) of eligible children were contacted by telephone to explain the purpose of the research and asked if they wished for their son/daughter to participate in this longer-term follow-up. For families where telephone information was unavailable, a letter explaining the purpose of the study was posted to the relevant address asking them to contact the authors if they wished to participate. Those who agreed to participate were sent information packs containing information sheets, consent/assent forms, and outcome questionnaires. Families were invited to complete questionnaires at home. Following this, participants were invited to attend the INFANT centre where neuropsychological assessment was completed. At the assessment appointment, the purpose of the study was re-explained to families and questions were invited. Once families indicated they wished to proceed, the assessment began. Participants who had not completed questionnaires were asked to do so at appointment. The duration of assessment was approximately 90 minutes. There were few expected risks from participating in the study. A protocol was in place for participants who became distressed during assessment. They would be reminded that their participation is voluntary and that they are free to withdraw without consequence to their care. They would be offered a debriefing

session and could avail of emotional support through the INFANT centre. A protocol was in place if new clinical needs were identified during assessment. A referral to the consultant paediatrician at INFANT would be recommended to families. Once neuropsychological assessment was completed, families were provided with a summary report of findings, framed in terms of strengths and weaknesses. Families were informed that the information contained in the report could not be used for medico-legal, clinical, or educational purposes. Data was stored according to GDPR and Data Protection Law.

5.5 Outcome Measures

Below are descriptions of each of the neuropsychological and behavioural outcome measures administered. A selection of subtests from each assessment was chosen by two senior neuropsychologists for the purposes of the current study.

Neuropsychological

5.5.1 Wechsler Intelligence Scale for Children – 5th Edition (WISC-V)

The *WISC-V* is an individually administered assessment for comprehensively evaluating the cognitive ability of children aged 6 years to 16 years, 11 months. The *WISC-V* consists of ten primary and six secondary subtests. See Table 5.1 for a list of all subtests. The primary and secondary subtests produce a scaled score with a mean of 10 and a standard deviation (*SD*) of 3. The subtest scores range from 1 to 19, with scores between 8 and 12 considered average. The subtests make up primary index scales which represent cognitive functioning in five domains: *Verbal Comprehension*, *Visual Spatial*, *Fluid Reasoning*, *Working Memory*, and *Processing Speed*. The assessment produces a Full-Scale IQ (*FSIQ*) which represents and individual's overall general ability. The *FSIQ* is comprised of 7 core subtests (Table 5.1). Subtests which may be substituted with secondary subtests are in italics.

Table 5.1 Subtests which comprise the WISC-V

Full Scale IQ (FSIQ)

Verbal Comprehension	Visual Spatial	Fluid Reasoning	Working Memory	Processing Speed
Similarities	Block Design	Matrix Reasoning	Digit Span	Coding
Vocabulary	*Visual Puzzles*	Figure Weights	*Picture Span*	*Symbol Search*
Information		*Picture Concepts*	*Letter-Number Sequencing*	*Cancellation*
Comprehension		*Arithmetic*		

5.5.2 Neuropsychological Assessment Tool – 2nd Edition (NEPSY-II)

The *NEPSY-II* is a clinical instrument that comprehensively assesses the cognitive ability of children between the ages of 3 and 16. The *NEPSY-II* assesses cognition in 6 domains: Attention and Executive Functioning, Language, Memory and Learning, Sensorimotor, Social Perception, and Visuospatial Processing. Subtests are administered which produce scaled scores. The assessment can be tailored to the child's individual needs as only subtests relevant to the clinical question need to be administered. The assessment is often used in making accurate diagnoses and intervention planning. See Table 5.2 for a breakdown of all subtests.

Table 5.2 Subtests which comprise the NEPSY-II

Domain	Subtest	Age Range
Attention and Executive Functioning	• Animal Sorting	7 to 16
	• Auditory Attention and Response Set	5 to 16
	• Clocks	7 to 16
	• Design Fluency	5 to 12
	• Inhibition	5 to 16
	• Statue	3 to 6
Language	• Body Part Naming and Identification	3 to 4
	• Comprehension of Instructions	3 to 16
	• Oromotor Sequences	3 to 12
	• Phonological Processing	3 to 16

	• Repetition of Nonsense Words • Speeded Naming • Word Generation	5 to 12 3 to 16 3 to 16
Memory and Learning	• List Memory (Immediate and Delayed) • Memory for Designs (Immediate and Delayed) • Memory for Faces (Immediate and Delayed) • Memory for Names (Immediate and Delayed) • Narrative Memory • Sentence Repetition • Word List Interference	7 to 12 3 to 16 5 to 16 5 to 16 3 to 16 3 to 6 7 to 16
Sensorimotor	• Fingertip Tapping • Imitating Hand Positions • Manual Motor Sequences • Visuomotor Precision	5 to 16 3 to 12 3 to 12 3 to 12
Social Perception	• Affect Recognition • Theory of Mind	3 to 16 3 to 16
Visuospatial Processing	• Arrows • Block Construction • Design Copying • Geometric Puzzles • Picture Puzzles • Route Finding	5 to 16 3 to 16 3 to 16 3 to 16 7 to 16 5 to 12

5.5.3 Picture Vocabulary Scale – 3rd Edition (BPVS-III)

The *BPVS-III* is a clinical instrument which assesses receptive vocabulary in children aged between 3 and 16. The test is administered on a one-to-one level. For each question, the instructor displays 4 pictures. The instructor then says a word and the child is asked to respond by selecting the picture that best represents the word's meaning. Accordingly, the test helps identify potential delay in vocabulary formation. The assessment produces a standardised score with a mean of 100 and *SD* of 15. Standard scores between 85 and 115 are considered within the 'normal' range. As no reading is required, the test is suitable for non-readers and children with specific learning difficulties.

5.5.4 Children's Memory Scale (CMS)

The *CMS* is an individually administered clinical instrument that comprehensively assesses learning and memory in children aged between 5 and 16. It consists of 9 subtests that evaluate learning and memory ability in 3 domains: Verbal, Visual, and Attention/Working memory. The *CMS* is widely used to identify difficulties in learning and memory, impaired recall strategies, and underlying processing disorders. The memory dimensions assessed include immediate and delayed recall, and recognition. Standardised scale scores are derived from subtests, with a mean of 100 and *SD* of 15.

5.5.5 Wechsler Individual Achievement Test – 3rd Edition (WIAT-III)

The *WIAT-III* is an individually administered clinical instrument which assesses the academic achievement of children and adults aged 4 to 85. The test allows for a comprehensive assessment of academic skills or a particular area of need depending on the clinical question. The test is comprised of 4 primary index scales: Reading, Mathematics, Writing, and Oral Language. These scales are made up of 9 primary subtests and 6 secondary subtests (See Table 5.3). The assessment produces standardised scores with a mean of 100 and a *SD* of 15. The majority of individuals (68%) obtain scores between 85-115. The test is used to identify academic strengths and weaknesses and to inform intervention planning.

Table 5.3 Subtests which comprise the WIAT-III

Domain	Subtests	Age Range
Reading	• Listening Comprehension • Early Reading Skills • Reading Comprehension • Pseudoword Decoding	4 to 17+ 4 to 8 6 to 17+ 6 to 17+
Mathematics	• Maths Problem Solving • Numeracy • Maths Fluency – Addition • Maths Fluency – Subtraction	4 to 17+ 5 to 17+ 6 to 17+ 6 to 17+

	• Maths Fluency – Multiplication	8 to 17+
Written Language	• Spelling • Essay Composition • Alphabet Writing Fluency • Sentence Composition	5 to 17+ 8 to 17+ 4 to 8 6 to 17+
Oral Language	• Oral Reading Fluency • Oral Expression • Word Reading	6 to 17+ 4 to 17+ 6 to 17+

5.5.6 Delis-Kaplan Executive Function System (DKEFS) - Trail Making Test

The *DKEFS* trail making test forms part of a wider clinical instrument for assessing executive dysfunction. The trail making test is comprised of 5 conditions: Visual Scanning, Number Sequencing, Letter Sequencing, Motor, and Number-Letter Switching. Poor performance in the switching condition is indicative of deficits in cognitive flexibility or an impairment in one of the skills required to complete the switching task (i.e. visual scanning, motor speed, number sequencing, or letter sequencing) (1). The test produces a standardised score for each condition with a mean of 10 and *SD* of 3.

5.5.7 Rey Complex Figure Test (RCFT) - Copy Test

The *RCFT* is a standardised clinical instrument which measures visuospatial ability and visuospatial memory through drawing of the Rey Complex figure. It is normed for individuals aged 6 to 89. The test evaluates cognitive ability in 5 domains: visuospatial recall memory, visuospatial recognition memory, response bias, processing speed, and visuospatial constructional ability. The scoring of the drawings is based a 36-point scoring system and the same scoring criteria is applied to all tests (i.e., Copy trial, Immediate Recall trial, and Delayed Recall trial). The scoring units are scored based on accuracy and placement criteria.

Behavioural

5.5.8 Behaviour Rating Inventory of Executive Function – 2nd Edition (BRIEF-II)

The *BRIEF-II* is a standardised questionnaire used to measure behavioural aspects of executive functioning. It has a high internal consistency and clinical validity. Standardised scores (M = 50, SD = 10) account for age and gender, with higher scores indicating less executive dysfunction. For the purposes of the current research, the parental version was administered. Overall, the questionnaire derives three indexes; Cognitive Regulation, Emotional Regulation, and Behavioural Regulation. These three indexes are composed of 8 empirically and theoretically subscales: Shift, Inhibit, Initiate, Emotional Control, Working Memory, Plan/Organize, Organisation of Materials, and Monitor.

5.5.9 Family Environment Scale (FES)

The *FES* is a measure of family social environments. It highlights interpersonal relationships among family members and the structure and attitudes of the family. Test-retest reliability and clinical validity have been shown for the measure. The measure is administered to parents who answer with true or false on 45 items. The *FES* consists of five subscales: Cohesion, Conflict, Independence, Expressiveness, and Active Recreation.

5.5.10 Strength and Difficulties Questionnaire - SDQ

The *SDQ* is a brief behavioural screening questionnaire measuring adjustment in peer relationships, emotions, and behaviours. The measure was designed to be applicable for children between 3 and 16 years. A youth, parent, and teacher version exist. The *SDQ* is a 25-item measure with three response categories from zero to two (not true, somewhat true, and certainly true). Of the 25 items, 15 are negatively phrased and 10 are positively phrased. Both a child's strengths and difficulties are well represented in five dimensions: conduct, emotional, peer relationships, hyperactivity, and prosocial. This screening tool measures emotional symptoms,

conduct problems, hyperactivity–inattention, peer interaction difficulties, and prosocial behaviour. An overall score is derived from summing the first four subscales, where a high score indicates increased difficulties. The prosocial subscale provides information on protective factors that exist for the child and a low score is less favourable. Research has shown moderate to strong internal consistency, and good external validity (2).

5.5.11 Child Behaviour Checklist (CBCL) Competency Scales

The competency scales of the *CBCL* and *YSR* are a part of the overall Achenbach System of Empirically Based Assessment (ASEBA) (3). The questionnaire is used to evaluate the emotional and behavioural adjustment of children aged 1 to 18 years. Research has indicated satisfactory test–retest reliability, internal consistency, and clinical validity. The present study focused on the three competency scales Activities, Social, and School, and the Total competency score. A higher score is indicative of greater competency.

5.6 Additional Analyses

Steps taken to prepare the data prior to analyses are detailed alongside normality tests and quality assurance procedures. Rationale for test selection is provided. Additional analyses not presented in the main paper are discussed below.

5.6.1 Data Cleaning

Prior to performing tests of normality and completing analyses, the data was reviewed for outliers. An outlier was defined as a standardised score on an outcome measure which was more than 3 *SD* above or below the mean. Steam-and-Leaf plots were reviewed on SPSS 26.0. Identified outliers were subsequently removed from the dataset. This action controlled for Type I error i.e. finding a false positive result.

5.6.2 Normality Checks

Given the use of parametric statistical tests in the study, the data for each outcome measure was assessed for normal distribution. Both skewness and kurtosis values and Shapiro-Wilk test results were reviewed. Skewness and kurtosis values between -2 and 2 indicated less variation in the data, fewer extreme scores, and greater normal distribution. The Shapiro-Wilk test is considered a normality test with high sensitivity and is more appropriate for small samples. Non-significant scores, > .05, are considered normally distributed.

Data that was deemed normally distributed was analysed using parametric tests. When completing Independent Sample *t*-tests, the assumption of homogeneity of variance was assessed. This assumption is that variance and distribution of scores on a continuous variable between independent groups are equal. Levine's Test of Equality of Variances is used to test this assumption, where a *p*-value of $\leq .05$ is considered a violation. For data that violated this assumption, the alternative *t*-test *p*-value, when equal variance was not assumed, was used.

5.6.3 Quality Assurance Procedures

Quality assurance procedures were completed to ensure the integrity of the data. Procedures included the authors cross-checking the accurate transfer of data from outcome measures to SPSS 26.0. Furthermore, two authors individually checked the data and performed statistical tests before meeting as a pair to review results. Differences and anomalies were noted and prompted authors to go through their workings. Each statistical test was performed more than once to check findings were consistent. Subsequent corrections to the data were applied where appropriate.

5.6.4 Independent sample *t*-tests versus ANOVA

As referred to in the main paper (see section 4.2.3, p. 73), independent sample *t*-tests were chosen over ANOVA analysis for HIE between group comparisons, given the study's lack of

an a priori position. Additionally, an ANOVA would have brought the error variance related to the sibling and control group into the statistical procedure.

5.6.5 Multiple Comparisons

To control for the problem of multiple comparisons on specific cognitive domains on the neuropsychological assessment, the Benjamini-Hochberg (4) correction was applied. This method was chosen over the Bonferroni correction method as it is less stringent and, over many subtests, it is less likely to produce false negatives (5). The Benjamini-Hochberg method ranks *p*-values from lowest to highest and treats each *p*-value according to their rank, whereas the Bonferroni treats each *p*-value equally. When performing a large number of statistical tests, the risk of falsely rejecting the null hypothesis increases. This is because a significant *p*-value of < .05 can occur by chance. For the current study, corrections were applied per cognitive domain rather than taking all 21 subtests. This was because not all subtests measured the same constructs from a neuropsychological perspective. Given the study's exploratory approach to outcomes the neuropsychological assessment did not have a single outcome point but rather multiple outcomes of different cognitive domains to detect where deficits may lie. Therefore, multiple outcomes required multiple corrections. The study adopted an exploratory approach to outcomes rather than a hypothesis-testing approach as the study was not sufficiently powered and the long-term outcomes for children with a history of HIE are relatively unknown. Furthermore, taking all subtests as one overall cognitive variable, when calculating Benjamini-Hochberg corrections in a low powered study, would increase the risk of Type II error i.e. falsely accepting the null hypothesis.

5.6.6 Additional Findings

Below are tables that were referenced but not included in the main text of the study. Commentary of analyses is provided.

Both mild and moderate HIE subgroups were similar in clinical and demographic characteristics assessed at baseline (See Table 5.4).

Table 5.4 Clinical and Demographic characteristics of mild and moderate HIE groups

Demographic Variable	Mild HIE (*n* = 11)	Moderate HIE (*n* = 12)	*P*
Mean years (*SD*)	14.69 (1.17)	14.24 (0.87)	0.31[1]
Gender (*n*)	11	12	0.80[2]
Male	7 (64%)	7 (58%)	
Female	4 (36%)	5 (42%)	
EEG (*n*)	10	12	0.28[2]
Grade 1	7 (70%)	5 (42%)	
Grade 2	3 (39%)	5 (42%)	
Grade 3	0	2 (16%)	
NICU (*n*)	11	11	
Mean days (SD)	4.73 (2.5)	6.64 (3.49)	0.08[1]
Family Deprivation Index[a] (*n*)	11	12	0.61[2]
Affluent	1 (9%)	2 (17%)	
Average	10 (91%)	9 (75%)	
Disadvantaged	0	1 (8%)	

[1]Independent Sample *t*-test; [2]Fisher's Exact Test; [a]Pobal HP Deprivation Index scores for Small Areas (37); SD = standard deviation; EEG = electroencephalography; NICU = neonatal intensive care unit.

As referenced in the main paper (see section 4.4, p. 84), comparisons between the siblings and healthy controls indicated a certain pattern was evident. Table 5.5 showed the sibling group tended to score lower across neuropsychological subtests than the control group. After corrections, these differences reached significant differences on the specific cognitive domains of verbal reasoning (*Similarities*), memory (*List Learning Immediate*), and language (*Receptive Vocabulary*), with large effect sizes.

Table 5.5 Mean neuropsychological scores Sibling -v- Control group

Neuropsychological Outcome	Sibling	Control	*P*	η_p^2
Verbal Reasoning				
Similarities[a] (SD)	8.67 (2.02)	10.86 (2.38)	**0.02**	.208
Non-verbal reasoning				

Matrix Reasoning[a]	8.33 (2.39)	9.79 (3.07)	0.20	.069
Speed of Information Processing				
Symbol Search[a]	10.75 (3.38)	10.21 (2.16)	0.55	.015
Coding[a]	10.17 (3.38)	8.5 (2.18)	0.14	.088
Attention/Executive Functioning				
Letter Fluency[b]	10.25 (2.80)	11.29 (2.05)	0.29	.047
Digit Span[a]	8.17 (2.04)	9.50 (2.35)	0.16[1]	.089
Visual Scanning[c]	10.42 (2.07)	11.64 (1.80)	0.16[1]	.097
Number Sequencing[c]	10.42 (2.81)	10.92 (1.93)	0.72[1]	.012
Letter Sequencing[c]	9 (3.28)	10.91 (1.76)	0.10	.123
Switching[c]	8.92 (2.61)	10.50 (2.11)	0.11	.108
Motor[c]	8.92 (1.51)	9.33 (2.35)	0.59[1]	.012
Rey Complex Figure Copy[d]	26.50 (9.15)	31.19 (6.55)	0.24[1]	.092
Visual Memory				
Memory for faces Immediate[b]	9.42 (2.54)	9.86 (3.46)	0.47[1]	.006
Memory for faces Delay[b]	10.58 (2.87)	9.43 (3.84)	0.58[1]	.029
Verbal Memory				
List Learning Immediate[e]	8.67 (2.71)	11.64 (2.79)	**0.01**	.239
List Learning Delay[e]	10.67 (2.74)	11.00 (2.18)	0.48[1]	.005
Sensory Motor				
Finger Tap Sequencing[b]	11.10 (2.08)	12.00 (1.96)	0.34[1]	.050
Language				
Speeded Naming[b]	9.17 (1.47)	11.14 (2.98)	0.06[1]	.153
Spelling[f]	92.42 (13.81)	103 (9.82)	**0.04**	.177
Reading[f]	93.92 (17.79)	102.64 (11.24)	0.14	.088
Receptive Vocabulary[g]	87.91 (11.36)	100.86 (1.56)	**0.01**[1]	.254

Independent Sample t-tests used unless otherwise stated; *p*-values in bold indicate statistical significance; [1]Mann-Whitney U test; [a]WISC-V; [b]NEPSY-II; [c]DKEFS; [d]RCFT; [e]CMS; [f]WIAT-III; [g]BPVS-II

Table 5.6 and Table 5.7 outline the percentage of participants who scored within clinical caseness according to the *SDQ* and *CBCL/YSR* respectively. Within the *SDQ* subscales, a pattern emerged where often a quarter to a third of the HIE group reached clinical caseness in comparison to generally lower rates in the healthy control group (below 15% caseness on the majority of subtests). Similarly, much lower rates of clinical caseness were observed in siblings (below 10% on most subtests). Data from the competency scales of the CBCL/YSR indicated those with mild-moderate HIE generally had higher rates of difficulties in overall competencies, social difficulties, and school difficulties compared to healthy controls. Similar effects were not observed between HIE and sibling comparisons.

Table 5.6 Percentage of scores within the Clinical Range on the SDQ

	HIE (1)	Sibling (2)	Control (3)
Parent			
Total Score	26%	18%	0%
Subscales			
Emotional Problems	39%	42%	14%
Conduct Problems	22%	25%	14%
Hyperactivity	26%	8%	0%
Peer Problems	30%	8%	0%
Prosocial	43%	8%	21%
Youth			
Total Score	25%	8%	14%
Subscales			
Emotional Problems	30%	8%	7%
Conduct Problems	15%	18%	0%
Hyperactivity	35%	9%	21%
Peer Problems	35%	9%	0%
Prosocial	10%	8%	29%

Clinical Range indicates scores outside of 80% of the normative population; Data was missing from parental questionnaire for one child (sibling). Data was missing from the youth questionnaire for four children (3 HIE, 1 sibling).

Table 5.7 Percentage scores ≤ 1 SD below normative mean on the CBCL and YSR

	HIE (1)	Sibling (2)	Control (3)
Parent			
Total	44%	36%	0%
Activities	45%	36%	15%
Social	26%	9%	0%
School	21%	18%	0%
Youth			
Total	12%	30%	29%
Activities	24%	36%	43%
Social	0%	20%	7%

[1]Fisher's Exact test; *p*-values in bold indicate statistical significance. Data was missing from *CBCL* for nine children (5 HIE, 2 siblings, 2 control). Data was missing from the youth questionnaire for nine children (6 HIE, 3 siblings).

Subgroup comparisons between mild and moderate HIE on the *SDQ* yielded no statistically significant differences across all subscales (See Table 5.8).

Table 5.8 Comparison on the SDQ between Mild and Moderate HIE

	Mild	Moderate	*P*	η_p^2
Parent				
Total Score (SD)	9.09	11.67	.40	.034
Subscales				
Emotional Problems	2.45	3.83	.23	.068
Conduct Problems	0.82	1.67	.47[1]	.071
Hyperactivity	3.45	4.17	.60	.014
Peer Problems	2.36	2.00	.93[1]	.008
Prosocial	6.45	8.42	.20[1]	.130
Youth				
Total Score	7.63	12.92	.07	.168
Subscales				
Emotional Problems	2.25	3.67	.23	.079
Conduct Problems	1.00	2.50	.10[1]	.150
Hyperactivity	3.00	4.42	.32	.055
Peer Problems	1.38	2.33	.18[1]	.066
Prosocial	7.88	8.67	.69[1]	.035

[1]Mann-Whitney *U* test; Data missing for three children on the Youth form (3 mild).

As referenced in the Results section in the main paper, Table 5.9 demonstrates a higher pattern of scores for the mild-moderate HIE group indicating greater executive functioning-related problems, although differences did not reach statistical significance for any subscale.

Table 5.9 Mean scores on the BRIEF-II

Scale/Subscale	HIE		Sibling		Control		*p*
	M	*SD*	*M*	*SD*	*M*	*SD*	
Total Score	52.60	14.17	49	8.58	45.69	5.77	0.62[1]
Behavioural Reg. Index	50.60	12.59	47	7.76	44.43	8.02	0.36[1]
Emotional Reg. Index	54.05	15.35	48.25	8.71	45.93	5.26	0.43[1]
Cognitive Reg. Index	51.35	12.70	47.42	12.58	46.23	5.59	0.70[1]
Inhibit	50.15	12.51	46.75	7.45	44.21	6.35	0.37[1]
Self-Monitor	51.45	13.08	48.42	7.62	45.07	8.81	0.16[1]
Shift	52.65	13.59	47.42	8.17	48.29	6.65	0.57[1]
Emotional Control	56.75	15.66	51.25	11.14	45.21	5.55	0.07[1]
Initiate	51.55	10.69	50.25	9.27	46.36	6.64	0.28
Working Memory	50.90	12.68	47.67	7.88	46.71	6.63	0.85[1]
Plan	52.20	13.73	47.33	7.43	44.86	5.59	0.42[1]
Task Monitor	51.75	11.01	50.58	8.51	46.86	6.32	0.31

Organisation	50.90	13.31	51.25	8.40	47.23	7.00	0.55[1]

[1]Non-parametric Kruskal Wallis test; Reg. = regulation.

Table 5.10 outlines a measure of family functioning as assessed through the *FES*. There were no statistically significant group differences on all subscales. The pattern of scores suggested parents of healthy controls had a tendency to rate their family environment more positively than HIE/sibling families.

Table 5.10 Group Comparisons on the Family Environment Scale

Scale/Subscale	HIE/Sibling	Control	*P*[1]
	Mdn	*Mdn*	
Cohesion	7.62	8.18	.38
Conflict	3	1.86	.53
Independence	6.06	6.88	.30
Expressiveness	5.88	6.88	.18
Active Recreation	6	6.13	.74

[1]Non-parametric Mann-Whitney *U* test

5.7 My Role in the Research

Upon joining this research study, I completed a literature review to identify gaps in the literature regarding outcomes for HIE cohorts. I was required to amend and re-submit an application for ethical approval to CREC to include my name on the research, as well as additional outcome measures e.g. SDQ, CBCL. I contacted a high proportion of families from the 5-year follow up study to invite them to participate in the current study. I helped co-ordinate the planning of assessment dates and times, while organising test kits and clinical rooms in the hospital. I completed approximately 20 of the neuropsychological assessments with participants. I scored up each assessment I completed. I provided a brief summary report of neuropsychological findings to families. I created an SPSS file to store all outcome variables.

I entered all data points from the assessments I carried out into SPSS. I completed quality assurance checks on all other data points entered on the SPSS file to verify accuracy. I independently ran all statistical analyses and then cross-checked results with my supervisor (CMC). Finally, I prepared the manuscript for this study.

5.8 References

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Appendix C – Ethical approval for Empirical Study

COISTE EITICE UM THAIGHDE CLINICIÚIL

Clinical Research Ethics Committee of the Cork Teaching Hospitals

Tel: +353-21-4901901
Email: crec@ucc.ie

University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

Our Ref: ECM 3 (ssss) 06/11/18 & 4 (hhh) 05/02/08

6th November 2018

Professor Geraldine Boylan
Secior Lecturer
School of Medicine
Brookfield Health Sciences Complex
University College Cork
College Road
Cork

Re: Ability of early continuous EEG to predict long term neurological outcome at 4.5 years in infants following neonatal hypoxic ischaemic encephalopathy.

Dear Professor Boylan

The Chairman approved the following:

- Cover Letter dated 16th October 2018 (received 16th October 2018)
- Amendment Application Form signed 16th October 2018
- Consent Form Version 3.0 dated 16th October 2018
- Study Assent Form Version 3.0 dated 16th October 2018
- Control Consent Form Version 2.0 dated 16th October 2018
- Control Assent Form Version 2.0 dated 16th October 2018
- Sibling Control Assent Form Version 2.0 dated 16th October 2018
- Study Protocol Version 5.0 dated 16th October 2018.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Appendix D - Parent/Guardian Invitation Letter

Dear Parents/Guardians,

Your Child was enrolled in an important research study shortly after birth and also took part in a follow-up neurodevelopmental research study as a young child. We are now looking at the longer-term development of all the children enrolled in this study. As part of our ongoing research it is important that we find out now how your child is doing, several years on and we would appreciate your help. We wish to invite you to take part in this longer-term follow-up study.

If you wish to take part in this study you will be asked to enclosed read the Information Leaflets and if happy to do so for you to sign the Consent Form and for your child to sign the Assent form. Also enclosed is a pack with a number of questionnaires. The study will involve you attending the INFANT Discovery Centre for an Interview with our research psychologists and these questionnaires being completed.

- You, as a parent or guardian, will be asked to complete four questionnaires.
- Your child will be asked to complete a single questionnaire
- You will be required to ask one of your child's teachers to complete a single questionnaire and return this to us in a stamped and addressed envelope.

Both of the child and teacher questionnaires will ask similar things to the parent/guardian questionnaire but from their different points of view. The length of each questionnaire will vary, but none should take longer than 30 minutes to complete. The team will go through these questionnaires with you during your visit to the INFANT centre. We will also conduct neuropsychological assessments with your child during this visit. We will also examine information collected about your child's medical history and previous assessments by the study team.

We also wish to recruit a sibling control group to this important neurodevelopmental follow-up study. This will allow us to study family and environment factors that influence outcome following HIE. If this is relevant to your family we would invite you to consider consenting any sibling to also complete the neurodevelopmental assessments by asking them to read and, if happy to participate, complete the separate Sibling Control assent form and an additional set of questionnaires.

We would be extremely grateful if you would consider continuing in the study and delighted if you would fill out the attached forms and return it to us in the envelope provided. Being part of the study is completely voluntary. You or your child can withdraw from the study at any stage. Not being part of the study will not affect any part of the medical care of you or your child.

(Name, Titles, Email Addresses for all Primary Researchers)

Appendix E - Participant Invitation Letter

Dear Participant,

We are inviting you to participate in a long-term neurodevelopmental follow-up research study. As part of our ongoing research it is important that we find out how children who have had a difficult time at birth are doing several years on. We also need to look at children who did not have issues at birth so that we can see if there are any differences. We would appreciate your help with this research.

If you wish to take part in this study you will be asked to read the enclosed Information Leaflets and if happy to do so for you to sign the Assent Form and for your parent or guardian to sign the Consent form. Also enclosed is a pack with a number of questionnaires. The study will involve you attending the INFANT Discovery Centre for an Interview with our research psychologists and these questionnaires being completed.

In signing these forms, you allow us to access and study your medical data that was collected shortly after your birth. You also agree to your teacher and parent or guardian filling in questionnaires in relation to you and allow us to study this information.

Your parent or guardian will be asked to complete three questionnaires. These will ask about your behaviour, activities and life at home and school as well as your development to date. You will be asked to complete a single questionnaire, and your teacher will be asked to complete a single questionnaire and to return this to us directly. Both of these will ask about similar topics to your parent or guardians' questionnaire but will allow us to have you and your teacher's points of view. Your questionnaire should take no longer than 30 minutes to complete. Additionally, we will invite you to the Infant Centre, at a time and date that suits you, to complete an assessment of your strengths and weaknesses. The assessment should take no longer than 120 minutes to complete with a break included.

We would be extremely grateful if you would consider continuing in the study and delighted if you would fill out the attached forms and return it to us in the envelope provided. Being part of the study is completely voluntary. You can withdraw from the study at any stage. Not being part of the study will not affect any part of your medical care

Thank you for considering this invitation and in anticipation of your interest in the study. If you have any questions regarding the study please contact the following Investigators

(Name, Titles, Email Addresses for all Primary Researchers)

Appendix F - Parent/Guardian Information Sheet

Dear Parent/Guardian,

Your child was previously enrolled in an important research study shortly after their birth, and again as a child, which examined developmental outcomes following neonatal encephalopathy. We are now looking at the development and adjustment of this group of children, as teenagers. The research carried out with your help has resulted in important improvements in the knowledge that is available to doctors about children following neonatal encephalopathy. We are inviting you and your child to take part in research to examine how you child is doing now as a teenager. This research is being conducted in conjunction with The Irish Centre for Fetal and Neonatal Translational Research (INFANT) and the School of Applied Psychology, University College Cork.

What would you and your child have to do?
If you and your child wish to take part in this study, then we will ask you to sign the attached consent forms confirming that you are happy to take part. The signed consent forms can be returned via the enclosed stamp addressed envelope.

We have also enclosed a pack with a number of questionnaires. The study will involve you attending the INFANT Discovery centre for an interview with our research psychologists and completing these questionnaires. You, as a parent or guardian, will be asked to complete four questionnaires.

Additionally, your child will be asked to complete a single questionnaire, your child's teacher will be asked to complete a single questionnaire and return this to us in a stamped and addressed envelope. Both of these questionnaires will ask similar things to the parent/guardian questionnaire but from their different points of view. The length of each questionnaire will vary, but none should take longer than 30 minutes to complete. **The team will go through these questionnaires with you during your visit to the INFANT centre. Additionally, your child(s) will be invited to participate in a series of neuropsychological assessments at the INFANT Centre. We will also examine information collected about your child's medical history and previous assessments by the study team**.

Do we have to take part?
No. Taking part in the research is completely voluntary and it is up to you and your child if you wish to be part of the study. You also have the right to withdraw from the research without reason, any time before your information is anonymised and summarised.

What are the benefits / risks of taking part?
The benefits of taking part in the study are to help us understand the outcomes for adolescents who experienced neonatal encephalopathy. We hope this understanding will lead to improvements in psychological and medical care for other children and adolescents. There are no known or expected risks from participating in this study for you or your child. However, if participating does raise any issues for you, you may discuss this with those involved in the research via the contact details included or arrange a visit with Leanna Fogarty or Professor Deirdre Murray.

What happens to the information from the study?
All the information you return on the questionnaires will be treated in confidence and will be anonymised. The only exception to this confidentiality is if you give us information which suggests you

or your child is at risk of harm. In such unusual cases we would have to act to reduce this risk. Your personal information would be stored securely at the INFANT centre. An anonymised database (where participants are assigned numbers and there is no identifiable information) will also be stored on the researchers' password protected computers at UCC. All information management will adhere to the Data Protection Act 1998 (amended 2003). The final report will be written up and submitted (a) as part of the researchers' master's/doctoral theses and (b)for publication. No personally identifiable information will be presented in either paper –the research write-up will report the group results only. You may also request a brief summary of the findings once complete and it will be available on the INFANT website.

What to do next?

If you would like to discuss any aspect of this study before making a decision, you may contact any of the main researchers at the e-mail addresses below and they will get back to you. Otherwise, if you are happy for you and your child to take part in this research study, please fill in and sign the enclosed consent form and questionnaires. Please bring these forms and your child's assent and questionnaire form to the arranged meeting to the INFANT Centre. If your child assents to taking part, please give your child's teacher the relevant teacher questionnaire ask them and return to us in the stamped addressed envelope enclosed at their earliest convenience.

Thank you for considering this invitation and in anticipation of your interest in the study.

(Name, Titles, Email Addresses for all Primary Researchers)

Appendix G - Participant Information Sheet

Dear Participant,

As a baby, you were part of an important research study shortly after your birth, and again as a child, which examined childhood development following Neonatal Encephalopathy (NE). NE is a condition where, for many reasons a baby may not cry immediately at birth and may need help to breathe, or resuscitation. They may need to be admitted to the special care baby unit and they may need close observation for a few days. Occasionally these babies can have seizures or may need support for their breathing or feeding. The NE study has given doctors and nurses caring for these children important information which we can now use to explain to parents what is happening and how this might affect their babies in the longer term. It is important that we also see how the children of the study are doing now that they are in their teenage years. We are inviting you to take part in research. This research is being conducted in conjunction with The Irish Centre for Fetal and Neonatal Translational Research (INFANT) and the School of Applied Psychology, University College Cork.

What is informed "assent"?
This information sheet will help you to understand what will happen during the study. Then, you can decide if you want to take part. If you want to take part in the study, you will write your name on the assent form at the end of this information sheet. This is called "informed assent" and means that you have been told all about the study, that you understand what will happen, and that you want to take part. We will explain the study to your parent(s)/guardian(s) and they will decide whether they want you to take part. They will be given a separate "informed consent form" sheet to sign if they want you to take part. Both you and your parent(s)/guardian(s) must agree that you want to take part in the study. If this information sheet contains words or information that you do not understand, please ask your parent(s)/guardian(s) to explain them or else ask the study staff when you visit.

What would you have to do if you take part?
If you wish to take part in this study, then both you and your parent(s)/ or guardian(s) should complete the enclosed consent and assent forms. In signing these forms, you allow us to access and study your medical data that was collected in the previous studies. You also agree to your teacher and parent(s) or guardian(s) filling in questionnaires in relation to you and allow us to study this information. After you and your parent(s) or guardian(s) sign these forms, they will be sent back to us. You will also find enclosed a pack, addressed to your parent or guardian, which includes a number of questionnaires. Your parent(s) or guardian(s) will be asked to complete four questionnaires. These will ask about your behaviour, activities and life at home and school as well as your development to date. You will be asked to complete a single questionnaire, and your teacher will be asked to complete a single questionnaire and to return this to us directly. Both of these will ask about similar topics to your parent(s) or guardian(s) questionnaire but will allow us to have you and your teacher's points of view. Your questionnaire should take no longer than 30 minutes to complete. Additionally, we will invite you to the INFANT Centre, at a time and date that suits you and your parent(s)/guardian(s), to complete an assessment of your strengths and weaknesses. The assessment should take no longer than 120 minutes to complete with a break included.

Do we have to take part?
No. Taking part in the research is completely voluntary and it is up to you and your parents or guardians if you wish to be part of the study. You do not have to take part if you do not want to. You also have the right to withdraw from the research without reason, any time before your information is anonymised and summarised.

What are the good things/ bad things about taking part?

The good things about taking part in the study are to help us understand the outcomes for teenagers who experienced NE. We hope this understanding will lead to better care for future children and adolescents who have a similar experience to you at birth. There are no expected bad things from taking part in this study for you. However, if participating does raise any issues for you, you may discuss this with your parent(s) or guardian(s) who may contact those involved in the research, or you and your parent(s) or guardian(s) can arrange a visit with Leanna Fogarty or Professor Deirdre Murray.

What happens to the information from the study?
All the information you return on the questionnaires will be treated in confidence and will be anonymised. The only exception to this confidentiality is if the information we receive suggests you are at risk of harm; in which case we would have to act to reduce this risk. Your personal information would be stored safely at the INFANT centre and an anonymised version will be stored on the researcher's password protected computers at UCC. The final report will be written up and submitted (a) as part of researchers' master's/doctoral theses and (b) for publication. No personally identifiable information will be presented in either paper – rather the research write-up will report on the group results only. Your parent(s) or guardian(s) may also request a brief summary of the findings once complete and it will be available on the INFANT website once published.

What to do next?
If you would like to discuss any aspect of this study before making a decision, you may contact any of the main researchers at the e-mail addresses below and they will get back to you. Otherwise, if you are happy to take part in this research study, please fill in and sign the assent form. This along with your parent(s) or guardian(s) consent form will be returned to us and we would then ask you to complete the study questionnaires. Thank you for considering this invitation and in anticipation of your interest in the study.

(Name, Titles, Email Addresses for all Primary Researchers)

Appendix H - Parent/Guardian Consent Form

Parent/Guardian CONSENT FORM

Title of Project:

Name of Principal Investigators:

Please circle YES or NO

1. I confirm I have read and understand the information sheet for the above study. **YES NO**

2. I confirm that I have read through the information sheet with my child and I am happy that he/she understands the information given. **YES NO**

3. I agree to participate and for my child to participate in the study. . I understand that our participation is voluntary and that we are free to withdraw at any time, without giving a reason. **YES NO**

4. I consent to information being obtained and analysed from my child's teacher in relation to my child. **YES NO**

5. I consent to medical / previous data being extracted from my child's research files, and for this information to be used as part of the research. **YES NO**

6. I give permission for the information collected about my child to be stored for possible future research unrelated to this study without my further consent being required but subject to approval by a Research Ethics Committee. **YES NO**

…… ……..

Name of Parent/Guardian Date

(Please Print)

Participant ID Number: (Researcher Use only)

……

Signature

Appendix I - Participant Assent Form

Adolescent ASSENT FORM

Title of Project:

Name of Principal Investigator:

This Assent form must be used in conjunction with the appropriate parent/legal guardian consent form. On its own, it does not provide informed consent for a minor to take part in the study.

Please circle YES or NO

1. I read through the information sheet with my parent/guardian and I understand the information given for this study. **YES NO**

2. I would like to take part in the study and I understand that I don't have to if I don't want to. **YES NO**

3. I agree to information being obtained about me from my parents or guardian. **YES NO**

4. I agree to information being obtained about me from my teacher. **YES NO**

5. I agree to the researcher accessing my previous INFANT files and for medical/previous data to be included in this study. **YES NO**

…… ……..

Name of Participant Date
(Please Print)

Participant ID Number: (Researcher Use only)

……

Signature

Appendix J - Health Questionnaire

Have teachers/public health nurse expressed any concern about your child's development?

YES ☐ NO ☐

If YES please specify:

Has your child been assessed by any of the following?

Psychologist? Clinical/Educational	YES	☐	NO	☐	UNKNOWN
Speech and Language therapist	YES	☐	NO	☐	UNKNOWN
Psychotherapist	YES	☐	NO	☐	UNKNOWN
Occupational Therapist	YES	☐	NO	☐	UNKNOWN

Has your child been diagnosed with any of the following?

Language delay	YES	☐	NO	☐	UNKNOWN
Hyperactivity/Attention Deficit Disorder	YES	☐	NO	☐	UNKNOWN
Hearing Difficulties	YES	☐	NO	☐	UNKNOWN
Visual Difficulties	YES	☐	NO	☐	UNKNOWN
Autistic Spectrum Disorder (Including Asperger's syndrome)	YES	☐	NO	☐	UNKNOWN

OTHER please specify:

	Participant ID Number:

Appendix K - Template of Neuropsychological Report

INFANT Address

Neuropsychology Report

PRIVATE & CONFIDENTIAL

This information is purely for research purposes

Name:	
Address:	
D.O.B:	
D.O.A:	Chronological Age:

Dear XXX,

Thank you and XXX for participating in research conducted by INFANT and the School of Applied Psychology, University College Cork (UCC). As you know this study aims to understand how children who experienced a Hypoxic Ischemic Encephalopathy (HIE) at birth are now doing as they enter their teenage years compared to children who did not experience HIE at birth. As you are aware, part of the study involved a neuropsychological assessment, which was completed with XXX on the XX/XX/XXXX. The results of this assessment are interpreted below. It is advised that the assessment does **not** provide a comprehensive description and evaluation of intellectual ability and is not to be used for clinical, educational or medico-legal purposes.

Results of assessment

XXX's cognitive development was assessed using a tailored neurodevelopmental assessment which included some subtests from the Wechsler Intelligence Scale for Children 5th Edition (WISC-V), NEPSY-II, Rey Complex Figure Test, Wechsler Individual Achievement Test 3rd Edition (WIAT-III), Children's Memory Scale (CMS), Delis-Kaplan Executive Function System (D-KEFS), and British Picture Vocabulary Scale 3rd Edition (BPVS-III). This assessment provided measures in the domains of Speed of Information Processing, Working Memory, Language, Verbal and Non-Verbal reasoning, and Spelling and Reading, giving us an individual profile of her strengths.

Speed of Information Processing: *Assessed speed and accuracy in identifying simple visual information.* It was estimated that XXX's scores in this area were **above/within/below** expected developmental age.

Working Memory and Learning: *Measured ability to register, store, recall, and recognise visual and auditory information.* It was estimated that XXX's scores in this area were **above/within/below** expected developmental age.

Verbal/Non-verbal Reasoning: *Assessed ability in accessing and applying existing word knowledge, and in abstract thinking.* It was estimated that XXX's scores in this area were **above/within/below** expected developmental age.

Language: *Measured receptive language skills, ability to produce words within specific categories.* It was estimated that XXX's scores in this area were **above/within/below** expected developmental age.

Executive Functioning: *Assessed ability to sustain attention, plan, organise and switch between tasks.* It was estimated that XXX's scores in this area were **above/within/below** expected developmental age.

Sensorimotor: *Assessed ability in fine motor and visuomotor co-ordination, using a pencil with speed and precision.* It was estimated that XXX's scores in this area were **above/within/below** expected developmental age.

Spelling and Reading: *Assessed written spelling of single words and measured speed and accuracy of word recognition.* It was estimated that XXX's scores in this area were **above/within/below** expected developmental age.

Summary:

XXX's overall profile suggests relative strengths in (*cognitive domain*) and (*cognitive domain*). He/she is doing very well for his/her age which reflects much care and dedication from family and teachers who have provided a rich learning environment for his/her. There is nothing in this report that suggests further action needs to be taken at this time.

If you have any questions or queries in relation to any aspects of this report, please contact the INFANT research centre on XXX XXXXX.

On behalf of the research team at INFANT and UCC, we would like to thank you for your participation.

Yours sincerely

_____ _____

Author 1 **Author 2**

_____

Author 3

Appendix L – Brain Injury (Author Instructions)

About the Journal

Brain Injury is an international, peer-reviewed journal publishing high-quality, original research. Please see the journal's Aims & Scope for information about its focus and peer-review policy.

Please note that this journal only publishes manuscripts in English.

Brain Injury accepts the following types of article: original research, letters to the editor.

Brain Injury is committed to improving and maintaining the consistency and quality of manuscripts submitted and published. Authors are strongly encouraged to review and comply with the reporting guidelines relevant to their submission. Reviewers have been instructed to evaluate submissions on the basis of their conformity to the guidelines. More information on guidelines for different study types: case reports (www.care-statement.org), diagnostic accuracy (www.stard-statement.org), observational studies (http://strobe-statement.org), randomized controlled trial (www.consort-statement.org), systematic reviews, meta-analyses (www.prisma-statement.org).

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Preparing Your Paper

All authors submitting to medicine, biomedicine, health sciences, and allied and public health journals should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (ICMJE).

Structure

Your paper should be compiled in the following order: title page; abstract; keywords; main text introduction, materials and methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

Word Limits

Please include a word count for your paper.

A typical paper for this journal should be no more than 5000 words.

Style Guidelines

Please refer to these quick style guidelines when preparing your paper, rather than any published articles or a sample copy.

Please use American spelling style consistently throughout your manuscript.

Please use double quotation marks, except where “a quotation is ‘within’ a quotation”. Please note that long quotations should be indented without quotation marks.

Brain Injury accepts the following types of submissions: original research and Letters to the Editor. Letters to the Editor will be considered for publication subject to editor approval and provided that they either relate to content previously published in the Journal or address any

item that is felt to be of interest to the readership. Letters relating to articles previously published in the Journal should be received no more than three months after publication of the original work. Pending editor approval, letters may be submitted to the author of the original paper in order that a reply be published simultaneously. Letters to the Editor can be signed by a maximum of three authors, should be between 750 and 1,250 words, may contain one table/figure and may cite a maximum of five references. All Letters should be submitted via ScholarOne Manuscripts and should contain a Declaration of Interest statement. Some journals set a maximum length for submissions. Though Brain Injury does not have a specific limit, we prefer that manuscripts not exceed 5,000 words excluding abstract, references, tables, and figure legends. If articles are greater than 5,000 words, authors may be asked to shorten their manuscript. Your paper should be compiled in the following order: title page; abstract; keywords; main text; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

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Checklist: What to Include

1. **Author details.** Please ensure everyone meeting the International Committee of Medical Journal Editors (ICMJE) requirements for authorship is included as an author of your paper. All authors of a manuscript should include their full name and affiliation on the cover page of the manuscript. Where available, please also include ORCiDs and social media handles (Facebook, Twitter or LinkedIn). One author will need to be identified as the corresponding author, with their email address normally displayed in the article PDF (depending on the journal) and the online article. Authors' affiliations are the affiliations where the research was conducted. If any of the named co-authors moves affiliation during the peer-review process, the new affiliation can be given as a footnote. Please note that no changes to affiliation can be made after your paper is accepted. Read more on authorship.
2. Should contain a structured abstract of 200 words. For papers reporting original research, state the primary objective and any hypothesis tested; describe the research design and your reasons for adopting that methodology; state the methods and procedures employed, including where appropriate tools, hardware, software, the selection and number of study areas/subjects, and the central experimental interventions; state the main outcomes and results, including relevant data; and state the conclusions that might be drawn from these data and results, including their implications for further research or application/practice. For review essays,

state the primary objective of the review; the reasoning behind your literature selection; and the way you critically analyse the literature; state the main outcomes and results of your review; and state the conclusions that might be drawn, including their implications for further research or application/practice.

3. You can opt to include a **video abstract** with your article. Find out how these can help your work reach a wider audience, and what to think about when filming.
4. Between 3 and 5 **keywords**. Read making your article more discoverable, including information on choosing a title and search engine optimization.
5. **Funding details.** Please supply all details required by your funding and grant-awarding bodies as follows:

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   This work was supported by the [Funding Agency] under Grant [number xxxx].

   For multiple agency grants

   This work was supported by the [Funding Agency #1] under Grant [number xxxx]; [Funding Agency #2] under Grant [number xxxx]; and [Funding Agency #3] under Grant [number xxxx].
6. **Disclosure statement.** This is to acknowledge any financial interest or benefit that has arisen from the direct applications of your research. Further guidance on what is a conflict of interest and how to disclose it.
7. **Biographical note.** Please supply a short biographical note for each author. This could be adapted from your departmental website or academic networking profile and should be relatively brief (e.g., no more than 200 words).
8. **Data availability statement.** If there is a data set associated with the paper, please provide information about where the data supporting the results or analyses presented in the paper can

be found. Where applicable, this should include the hyperlink, DOI or other persistent identifier associated with the data set(s). Templates are also available to support authors.

9. **Data deposition.** If you choose to share or make the data underlying the study open, please deposit your data in a recognized data repository prior to or at the time of submission. You will be asked to provide the DOI, pre-reserved DOI, or other persistent identifier for the data set.
10. **Supplemental online material.** Supplemental material can be a video, dataset, fileset, sound file or anything which supports (and is pertinent to) your paper. We publish supplemental material online via Figshare. Find out more about supplemental material and how to submit it with your article.
11. **Figures.** Figures should be high quality (1200 dpi for line art, 600 dpi for grayscale and 300 dpi for color, at the correct size). Figures should be supplied in one of our preferred file formats: EPS, PDF, PS, JPEG, TIFF, or Microsoft Word (DOC or DOCX) files are acceptable for figures that have been drawn in Word. For information relating to other file types, please consult our Submission of electronic artwork document.
12. **Tables.** Tables should present new information rather than duplicating what is in the text. Readers should be able to interpret the table without reference to the text. Please supply editable files.
13. **Equations.** If you are submitting your manuscript as a Word document, please ensure that equations are editable. More information about mathematical symbols and equations.
14. **Units.** Please use SI units (non-italicized).