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Systematic Review: Long-term cognitive and behavioural outcomes of neonatal hypoxic-ischaemic encephalopathy in children without cerebral palsy

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Systematic Review: Long-term cognitive and behavioural outcomes of neonatal hypoxic-ischaemic encephalopathy in children without cerebral palsy

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Short title: Outcomes in neonatal encephalopathy without cerebral palsy

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ABSTRACT

Aim: To evaluate long-term cognitive and behavioural outcomes of children with neonatal hypoxic-ischaemic encephalopathy in the absence of cerebral palsy.

Methods: A systematic search was performed on five databases (EMBASE, Medline, PubMed, Web of Science, PsycInfo). Randomised-controlled trials, non-randomised controlled trials, or observational studies, published between 1990--2017, that reported long-term (age ≥ 4 years) cognitive and/or behavioural outcomes of neonatal hypoxic-ischaemic encephalopathy without cerebral palsy were included.

Results: Seven articles met the inclusion criteria (n=352 total participants, n=53 treated with therapeutic hypothermia). Studies reporting cognitive outcome demonstrate impairment of general cognitive abilities in 25--63% of participants with hypoxic-ischaemic encephalopathy without cerebral palsy. Specific cognitive difficulties were reported in two studies for attention, executive functioning, memory function, and language. Results regarding behavioural outcome possibly indicate a higher risk of difficulties.

Conclusion: A substantial proportion of children with neonatal HIE who survive without cerebral palsy are at increased risk of general and/or specific cognitive impairments. Behavioural problems may be more common, but evidence is limited. Results highlight the importance of comprehensive long-term follow-up to identity difficulties and enable intervention to optimise educational achievement and behavioural adjustment.

Keywords: neonatal hypoxic-ischaemic encephalopathy, long-term outcome, cognitive outcome, behavioural outcome

Key Notes: Outcome studies in neonatal hypoxic-ischaemic encephalopathy (HIE) often focus on death, cerebral palsy and cognitive impairment, but the extent of cognitive deficits following HIE in children without cerebral palsy is not well described. This systematic review suggests that, following HIE, up to 60% of children without cerebral palsy have cognitive impairments, and are at risk of behavioural problems. Long-term follow-up of children with HIE is important irrespective of neuromotor impairment.

Neonatal hypoxic-ischaemic encephalopathy (HIE) occurs at an estimated incidence of 1.3 to 1.9 per 1000 live births in high and middle income countries(1, 2) and 8.5 per 1000 live births in low income countries(2). It is associated with a high risk of brain injury and long-term neurological and neurodevelopmental impairments including cerebral palsy (CP), cognitive impairment, behavioural difficulties, visual or hearing impairment, and epilepsy(3). While neonatal encephalopathy (NE) is a clinical description of disturbed neurological function in the neonatal period that does not require an association with aetiology(4), the term HIE should be reserved for such cases of NE where there is evidence of perinatal asphyxia (PA) and/or hypoxic-ischaemic brain injury. Current criteria for a diagnosis of HIE are usually based on those used in the large randomised controlled trials (RCT) of therapeutic hypothermia (TH)(5, 6), which include clinical and biochemical markers of perinatal asphyxia, as well as signs of encephalopathy and/or seizures.

Outcome of children who suffered from neonatal HIE is dependent on the severity of encephalopathy(3). The most frequently used grading of HIE is based on the scoring system of Sarnat and Sarnat, which differentiates between mild, moderate and severe encephalopathy(7). It is widely accepted that those children who suffer from severe HIE are at significantly increased risk of mortality and neurodevelopmental sequlae, whereas those with mild HIE have a better prognosis. Newborns with moderate HIE have a variable outcome, making prediction more difficult(3, 8). In recent years TH has become the standard of care in tertiary neonatal centres for newborns with HIE(9, 10), following large RCTs that have shown TH to reduce mortality and severe neurodisability at toddler age (11-14), with evidence that the benefits in cognitive outcome continue to school-age (14-16). Rates of children with no disabilities post TH for HIE are described between 41--68%, whereas 22--35% if children will have moderate or severe disabilities (14, 15).

Most outcome studies in HIE assess children in infancy and early childhood and focus on outcomes such as death, CP and severe global cognitive impairment. There is

some indication that cognitive deficits also occur in children with a history of HIE who do not present with CP (17-19). Understanding the full spectrum of neurodevelopmental outcome, including in those children without CP, is important as it allows professionals to identify children requiring early intervention and ongoing follow-up. We aimed to systematically review and evaluate the current evidence for long-term cognitive and behavioural outcomes in children with neonatal HIE who survive without CP.

Patients and Methods

Study Design: The review protocol was prospectively registered on PROSPERO (CRD42015027808, original registration date 11/11/15). The protocol as updated as the research question became more refined, and to make it clear that focus was specifically on children with HIE who survived without CP. It was also amended to be clear that the review would exclude studies that did not report outcomes specifically for these children (PROSPERO record updated retrospectively 22/02/19). Studies were considered if they were RCTs, non-randomised control trials (NRCT), or observational studies. Only studies in humans and studies published in English, between 1990 and 2017, were included.

Inclusion Criteria: Studies were included if the participants were aged between 4 and 19 years and had been born at ≥35 weeks gestational age. Only studies that used standardised psychometric tests and questionnaires to assess cognition and behaviour were included. Studies that did not report results in children without CP separately were excluded. As there is some disparity in the literature between the definitions of HIE and the term is often used simultaneously with NE and birth/perinatal asphyxia(1), all four terms were added in the search. To be included, studies had to specifically state they were investigating outcomes in infants with HIE. However, studies were only included where the inclusion and exclusion criteria were considered sufficient to suggest hypoxia-ischaemia as the cause of

encephalopathy in the majority of patients. Accepted definitions of HIE were those which included a marker of PA (such as metabolic acidosis within the first hour after birth, low Apgar scores at 5 minutes or beyond, history of an acute perinatal event and the need for prolonged resuscitation or ventilation) together with signs of encephalopathy and/or seizures, or meeting the criteria laid out by Sarnat for HIE grading. It is important to point out that there is a considerable variability in the definition of and use of the terms HIE/NE/PA across the studies. For consistency throughout this review, the term HIE has been used, replacing NE where it occurs.

Outcome measures: Outcome measures were general or specific cognitive abilities and/or behavioural outcome, assessed by any form of standardised psychometric test or questionnaire. General cognitive abilities are commonly assessed by IQ tests, such as the Wechsler Scales, or "general cognitive ability" using the British Ability Scale. Specific cognitive abilities are cognitive abilities in more specific domains, such as Executive Function and memory. Cognitive and behavioural impairment were both defined as the presence of significant differences to typically developing children in test/questionnaire scores (Case-control studies) or as score more than 1 SD below the population norm (cohort studies).

Literature searching strategy: A systematic search was carried out using the search strategy detailed in table 1. The electronic databases MEDLINE, EMBASE, PubMed, Web of Science and PsycInfo were used, with the last search carried out on 02/12/2018. Reference searching was performed on articles that were selected for review. Searches were undertaken by two reviewers (MS and AG) using the same search terms and both reviewers assessed studies for eligibility independently. Neither reviewer was blinded to the study's authors or institutions.

Study selection: Selection was carried out independently by two authors (MS and AG) on the basis of titles and abstracts, with the full text obtained where necessary. Any disagreement that could not be resolved by discussion between the two reviewers was adjudicated by a third (MJ). Conference abstracts were not included due to increased risk of bias secondary to incomplete data.

Data collection process: Data regarding study characteristics, patient demographics and outcome measures were extracted using a specifically designed spreadsheet.

Risk of bias assessment: The quality of RCT and NRCT was assessed using the Cochrane risk of bias tool(20). Observational studies were assessed using the Newcastle-Ottawa scale(21). Both reviewers performed the risk of bias assessment independently and resolved any disagreement by consensus.

Synthesis of results: Meta-analysis for outcome measures with sufficient homogeneity was planned. Heterogeneity was checked using the I^2 statistic, which reports the percentage of variation attributable to heterogeneity. For continuous outcomes, the weighted mean difference was calculated using the inverse variance method. When the I^2 statistic was greater than 50%, a random effects model was used. For binary outcome data, the Peto method was used to calculate a pooled odds ratio. Where available data were not sufficiently homogeneous to allow this a narrative synthesis comparing study results was performed.

Results

Study selection and characteristics

The review process is demonstrated in figure 1. Seven papers, published between 2001 and 2017, were included for review: All were observational studies following up infants with HIE, with 5 cohort studies (including one which followed up a cohort of patients from a

RCT) and 2 case control studies that included a control group of matched controls drawn from a normal population for comparison of outcomes. In addition, one cohort study used siblings of cases for behavioural outcomes. Characteristics of the studies are summarised in table 2. More detailed information on the study eligibility criteria of each included study, and fulfilment of HIE criteria can be found in Appendix S1. One study followed up children from an RCT who received TH as an intervention for the treatment of HIE compared to intensive care with normothermia.

Quality assessment

Assessments of quality and risk of bias in the studies are summarised in table 3. The potential risk of bias in studies was taken into consideration during data interpretation.

Primary outcomes

The results of primary outcomes were split into cognitive and behavioural outcomes. Results of the included studies are shown in table 2.

General and specific cognitive abilities

Cognitive outcome was reported in 6 studies. The most commonly used tests were the Wechsler Scales; the Wechsler Pre-School and Primary Scale of Intelligence (WPSSI) and Wechsler Intelligence Scale for Children (WISC), dependent on the age of participants. These were used in four of the six included studies. Full-scale IQ (FSIQ) was reported in 4 studies; one study estimated FSIQ based on a limited number of subtests. Two studies used the Developmental Neuropsychological Assessment (NEPSY) to assess executive function, including memory function (22, 23). One of these studies also used the British Ability Scale (BAS) as another measure of general cognitive abilities(22), while the other also used the Behavior Rating Inventory of Executive Function (BRIEF) as another measure of executive function(23). Of note, on the Wechsler Scales the mean FSIQ in a normative population is 100 with a standard deviation (SD) of 15. Therefore the proportion of scores in a normative

population below 2SD is 2.27%, and 13.59% between 1 and 2 SD, meaning that a proportion of 15.86% of children in the general population would score a FSIQ below 85. Similarly, standard scores are also obtained for the cluster scores used in the BAS, with a mean score of 100 and a standard deviation of 15 points to either side.

Case-control studies

Two case-control studies reporting cognitive outcomes were included. Van Kooij et al(24) compared FSIQ scores using the WISC-III in 62 children aged 9--10 years with mild to moderate HIE (defined in Appendix S1) without CP and 52 sex and age matched controls. Marlow et al(22) used the BAS-II to assess general cognitive abilities and the NEPSY for attention, executive functioning and memory in seven-year old children with a history of moderate to severe HIE (see Appendix S1) but without motor disability and matched those children attending mainstream school to classmates. The results of both of these studies for FSIQ are illustrated as forest plots in figure 2. However, due to the reporting differences between mild, moderate and severe cases of HIE, it was only possible to perform a meta-analysis for the effects of moderate HIE on FSIQ (also shown in figure 2). It can be seen that whilst Marlow et al demonstrate a clear effect of severe HIE on IQ compared to controls (mean IQ difference 11.3; 95%CI 4.1--18.5), and Van Kooij et al show a clear impact of mild HIE on IQ compared to controls (mean IQ difference 10; 95%CI 4.2--15.9), the meta-analysis of both studies shows no significant effects for moderate HIE on IQ compared to controls (mean IQ difference 9; 95%CI 5.9--24.2). However, it is important to note that there are differences in the definitions of moderate and severe HIE used by the two studies. In addition, looking at the individual results it can be seen that in the study by Van Kooij et al a significant difference was found between the moderate HIE group and the controls, and that this difference was more marked than that seen between mild HIE and controls. Furthermore, Marlow et al found poorer scores on neuropsychological assessments in children with a history of HIE, particularly in those with a history of severe HIE. Significant

differences ($p < 0.001$) between the severe HIE group attending mainstream school and classmates were found on the BAS for general cognitive ability and three of the subscales (Special non-verbal composite, Non-verbal reasoning score, Spatial scale score), as well as in the NEPSY for attention and executive function, language, memory and learning, narrative memory and orientation. In contrast, significantly lower scores in the moderate HIE group were only found in the language, narrative memory and sentence repetition domain on the NEPSY.

Cohort studies

Three cohort studies reporting FSIQ using the Wechsler Scales were included in the review; verbal and performance IQ scores were not separately reported. Lindstrom et al(25) studied a population-based cohort of 28 children with a history of HIE without CP out of which 11 underwent standardised IQ testing as part of a separate study in connection with neuroimaging. Four of the 11 children (36%) had a FSIQ ≤70 and 3 out of the 11 participants (27%) had IQ scores 71--84. Overall, results indicated higher rates of lower IQ scores in this group of children compared to population norms, with a greater proportion of children presenting with FSIQ scores of less than 85 (i.e. >1 SD of population mean). However, the group that underwent testing was small, representing less than half of the total cohort, with a further drop-out rate of 23%. In contrast to these results, Barnett et al(26) reported opposing evidence for cognitive outcome in 34 five to six year old children with a history of HIE without CP, with the majority (94%) of participants having FSIQ scores of ≥ 80. Pappas et al performed a secondary analysis from data of the large NICHD RCT on whole-body hypothermia(6, 27), demonstrating relatively high rates of low FSIQ scores in all 86 children with HIE without CP. In those children who underwent therapeutic hypothermia, 43% had an FSIQ <84 while 36% of the normothermia group had an FSIQ <85, though this study was not powered to detect differences between treatment arms in children without CP. Hayes et al reported the cognitive outcomes of 68 children with HIE but no evidence of CP, using

the NEPSY-2 and BRIEF assessments(23). While the cohort had normal mean NEPSY-2 scores, a greater than expected proportion of scores fell into the impaired range. Children with moderate HIE performed more poorly than those with mild HIE, particularly with regard to attention and executive function. A greater proportion of children also fell into the clinical (impaired) range on the BRIEF.

Behavioural outcomes

Behavioural outcomes were reported in four studies. Two studies used the parental version of the Child Behavior Checklist (CBCL), one study used the parental version of the Strength and Difficulties Questionnaire (SDQ), and one study used the Connors 10-item scale, ADHD Rating Scale IV, as well as the Asperger Syndrome Screening Questionnaire.

Case-control studies

One case-control study reported behavioural outcome. Marlow et al's(22) results of the parent reported SDQ demonstrate an increase in behavioural problems in the severe HIE group without CP in comparison to the moderate HIE group without CP and typically developing controls, with a significant difference seen in the overall behavioural scores ($p=0.02$) and hyperactivity subscale scores ($p<0.01$) between these two groups. Teacher scores revealed more problematic behaviour than parental responses, with significant differences in the moderate NE group compared to the normal comparison groups in the total behavioural scores ($p<0.01$), emotional problems ($p=0.01$), hyperactivity ($p<0.01$), pro-social behaviour ($p=0.02$), and impact on everyday functioning ($p<0.01$). Pervasive behaviour disorders, which were identified as overall abnormal behaviour scores on both parent and teacher questionnaire, were found in 23% in the severe HIE group compared with 8% in the moderate HIE and 2% in the comparison group.

Cohort studies

Three cohort studies reporting on behavioural outcome were included. Lindstrom et al(25) performed parent interviews with a group of 28 children with a history of HIE but without

CP, including parental questionnaires assessing the risk of ADHD (Connors 10-item scale and ADHD Rating Scale IV). Results were compared to a group of 15 siblings, demonstrating significant differences between the HIE group and the comparison sibling group on both the Connors scale ($p<0.003$) and the Inattention subscale of the ADHD Rating Scale IV ($p<0.006$), indicating a higher risk for perceived attention problems in the group of children with HIE. The authors found significantly higher scores on the Asperger Syndrome Screening Questionnaire in the HIE group ($p<0.003$) suggesting a higher risk for social communication and interaction difficulties. In contrast to these results, van Schie et al(28) found no difference in the rate of behavioural problems between their cohort of infants with HIE without CP and a Dutch reference sample using the CBCL. Hayes et al also assessed behaviour in their cohort study of children with HIE in the absence of CP, using the CBCL(23). They found internalising problems in 27.8% of children following moderate HIE and in 7.3% of children following mild HIE. Compared to children with mild HIE, those with moderate HIE were significantly more likely to have anxiety, somatic complaints, withdrawn behaviour, sleep problems, and externalising problems such as aggressive behaviour.

Discussion

To our knowledge, this is the first systematic review on long-term behavioural and cognitive outcomes in children with HIE without CP. Overall, this review suggests an increased risk of general and/or specific cognitive impairments in this group of children. In contrast, the evidence for behavioural difficulties is less clear.

Cognitive outcome

All included studies reporting on cognitive outcome reported a higher proportion of cognitive impairments at school-age in children with a history of HIE, with the exception of

Barnett et al(26). However, the low incidence of severe brain injury on neuroimaging may have accounted for the observed higher IQ scores in Barnett et al's study. Even though Van Kooij(24) reported mean FSIQ in the normal range, many studies found a higher than expected proportion of children scoring below 1 SD in standardised IQ tests(24, 25, 27), suggesting that children with HIE without cerebral palsy are at increased risk of cognitive impairment and/ learning disability.

Marlow at el(22) reported specific cognitive difficulties in the areas of attention, executive functioning, memory and language, particularly in the severe HIE group without CP. Hayes et al also found a greater than expected proportion scores in the impaired range in tests of executive function, with the moderate HIE group without CP differing significantly from the mild HIE group without CP(23). The lack of literature on specific cognitive difficulties in children with HIE without CP suggest that more research is needed to identify such difficulties in these children. In addition to standardised cognitive testing or psychometric questionnaires, Lindstrom et al(25) reported parent interview data. Taking into account all available information from standardised assessments as well as non-standardised interview data, more than 70% of the children in the study were found to have executive function difficulties that interfered with their daily functioning. It is furthermore noteworthy that, similar to Marlow et al's results(22), other studies have also suggested specific difficulties in language related domains in children with HIE (29-32) and associations between Verbal IQ and a pattern of watershed brain injury on neuroimaging (33, 34).

The increased risk of general and/or specific cognitive impairments in children with HIE without CP is supported by reports of increased rates of special educational needs as an indirect measure of cognitive difficulties. Marlow et al(22) reported significantly lower attainment levels for reading and spelling in the moderate HIE group without CP and these differences in attainment levels were even more pronounced in the severe HIE group

without CP. Children with severe HIE without CP were also significantly more often reported to have academic special needs and educational statements and individual learning plans. Van Kooij et al(24) reported that even in the HIE group without CP, 9.3% of children with mild HIE and 21.6% of children with moderate HIE attended special education, while all of the control participants attended main stream school. Other studies in this review found similar results(23, 25, 27), in addition to studies that did not meet inclusion criteria for this review(30, 35).

Behavioural outcome

Given the small number of studies included, their heterogeneity and limitations it is overall difficult to draw a conclusion as to the risk of HIE on adverse behavioural outcome in children without CP, although results indicate that children with HIE without CP may be at increased risk for behavioural problems. Only four studies that report on behavioural difficulties in children without cerebral palsy were included. Based on the findings from Marlow et al(22), Hayes et al(23) and Lindstrom et al(25), it appears that behavioural problems may occur more readily in children with HIE without CP compared to a comparison group, particularly if HIE is graded more severe than mild. These include symptoms of inattention and hyperactivity, as well as increased difficulties with pro-social behaviour and making friends. However, it is important to note that Lindstrom et al(25) used a comparison group of siblings that was unmatched in terms of sex and age. Interestingly, teacher reports in Marlow et al's study(22) generated more significant results than the parent reports, which is an example of detection bias. This is important to note for any future trials that use parental assessment of behaviour. In contrast, Van Schie et al(28) found no difference in the rate of behavioural problems between the study's cohort of infants with HIE without CP and a Dutch reference sample using the CBCL. However, the study sample cohort was small and 32% of children were lost to follow-up. Moreover, the study included no cases of severe HIE which is likely to have skewed the results. Other

studies not included in the review also report different results with regards to behavioural outcome(36-38).

The association between Autism Spectrum Disorders and HIE is even more uncertain. Lindstrom et al(25) report significant differences on the Asperger Syndrome Questionnaire as compared to the sibling group, however there is very little other literature to support an increased rate of Autism Spectrum Disorders in children with HIE. The only study investigating this association is by Badawi et al(39), who reported a significantly higher incidence of Autism Spectrum Disorders in infants with HIE. However, the authors did not exclude aetiologies of HIE other than PA and included all patients irrespective of neuromotor outcome.

Association of severity of HIE with outcome

As described above, several of the studies included in this review suggest that the risk of later cognitive impairment is related to the severity of the neonatal clinical presentation, as previously described by other reviews(3, 40). Marlow et al(22) found greater levels of neurodevelopmental and behavioural impairment in children with severe HIE without CP compared to other groups, whilst both Hayes et al(23) and Van Kooij et al(24) found greater impairment in children with moderate HIE without CP compared to those with mild or no HIE. While it is widely accepted that the difference in outcome becomes more evident on the severe spectrum of clinical presentation, this is less clear for children with mild as opposed to moderate HIE[2,7]. Van Kooij et al(24) described the mild HIE group without CP scoring intermediately between the control subjects and children with moderate HIE without CP, demonstrating that even children with mild HIE are at increased risk for impairment of cognitive abilities. This finding is supported by Murray et al(41), who found significantly lower IQ scores and Children's Memory Scale subtest scores in five-year old children with mild HIE as compared to a comparison group, and no significant differences between the mild and moderate HIE group in any of the WPSSI-III measures. In

contrast, some other studies not included in this review have found no significant increase in cognitive impairment in school-aged children with a history of mild HIE(29, 30). Overall, results of this systematic review suggest that the risk of cognitive and/or behavioural impairments is related to severity of HIE, though the impact of mild HIE remains inconclusive.

Limitations

There are substantial differences in eligibility criteria resulting in varying definitions of HIE and PA, resulting in a heterogeneous study population for this review. Furthermore, there is heterogeneity in study design and outcome measures, limiting the potential for meta-analysis and presenting challenges when it was carried out. Different behavioural outcome measures were used in included studies, and although most studies reporting on cognitive outcome used the Wechsler Intelligence tests, results of these were reported differently, e.g. by recording mean IQ scores, differences of IQ scores to controls, and/or proportions of abnormal IQ scores, making meta-analysis challenging. Most studies focus on general cognitive abilities only and reports on specific cognitive abilities are sparse. Many of the studies also had small sample sizes and so may lack statistical power. Moreover, we are aware that the age range of 4-19 years is wide and that there are limitations to pooling all of these ages as maturational changes across this age range may occur, in particular, for specific cognitive functions. Finally, the majority of studies included and cited in this review are from the pre-cooling era. As TH is now standard of care for children with moderate to severe HIE, the results from most included studies do not necessarily represent the current patient cohort.

Conclusion

This systematic review provides evidence for an increased risk of cognitive impairments in school-aged children with a history of HIE without CP. It appears that a significant proportion of these children have some degree of cognitive difficulties, including executive

function and language-related difficulties, with a significant proportion requiring additional support in school. Impaired cognitive outcome remains a concern even in those children treated with TH; however, evidence in this group of children without neuromotor impairment is currently sparse. Although the evidence is limited and more research is needed, the results also indicate that there may be an increased risk for behavioural problems, such as attention problems and hyperactivity, which again, will be relevant for school success.

The results of this review highlight the importance of standardised comprehensive and long-term follow-up beyond toddler age even in those children with a history of HIE who do not develop significant neuromotor difficulties. Cognitive difficulties may be subtle but nevertheless relevant for academic progress and may remain undetected at an early age and only emerge with increasing cognitive demands within the school setting. Knowledge about possible cognitive difficulties in these children leads to better understanding and likely earlier intervention to optimise opportunities for the individual children. The small number of studies included in this review following the systematic search demonstrates the need for future research with focus on assessment of specific cognitive and behavioural functions in school-aged children with HIE without neuromotor impairment, particularly in those children that have received TH as this is now standard of care for most children with moderate or severe HIE.

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Abbreviations

ADHD - Attention Deficit Hyperactivity Disorder; BAS - British Ability Scale; BRIEF - Behavior Rating Inventory of Executive Function; CBCL - Child Behavior Checklist; CP – Cerebral Palsy; FSIQ - Full-scale Intelligence Quotient; HIE – Hypoxic Ischaemic Encephalopathy; IQ - Intelligence Quotient; NE – Neonatal Encephalopathy; NEPSY - Developmental Neuropsychological Assessment; NRCT – Non-Randomised Controlled Trial PA – Perinatal Asphyxia; RCT – Randomised Controlled Trial; SD – Standard Deviation; SDQ - Strength and Difficulties Questionnaire (SDQ); TH – Therapeutic Hypothermia; WISC - Wechsler Intelligence Scale for Children (WISC); WPPSI - Wechsler Pre-School and Primary Scale of Intelligence.

Conflict of interest

None to declare

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	Search terms
1	Neonatal encephalopathy.mp.
2	Perinatal Asphyxia.mp.
3	Birth Asphyxia.mp.
4	Hypoxic isch* encephalopathy.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5	1 or 2 or 3 or 4
6	outcome.mp.
7	behavio*.mp.
8	cogniti*.mp.
9	neurodevelopment*.mp.
10	Long-term.mp.
11	School-age*.mp.
12	childhood.mp.
13	7 or 8 or 9 or 10 or 11 or 12
14	5 and 6 and 13
15	limit 14 to (english language and humans and yr = "1990 -Current")

Table 1: Search terms and strategy used for electronic searches[1]

[1] *Performed by using OvidSp (Wolters Kluwer Health; http://www.ovid.com); .mp.,multipurpose search across the subject headings*

Author, year	Study type	Primary outcome	Age	Cohort details	N	Sex (boys/N)	Characteristics controls	Measures	Results	Conclusion	Comments
Barnett 2002	Obs, cohort (p)	Cog	5.5--6.5y	≥38 weeks gestation, born 05/91--01/96	63 eligible for inclusion, 53 participated, 34 without CP	19/34	NA	WPPSI-R	31/34 Full scale IQ > 80 2/34 Full scale IQ < 80 1/34 not able to test due to cooperation	No conclusion in paper with regards to cognitive outcome	Study mainly focuses on motor difficulties and their association with cognitive impairments
Hayes 2017	Obs, cohort (r+p)	Cog + Beh	Mean 5y8m, range 3y8m--8y10m)	≥ 36 weeks gestation, admitted with HIE in the first 48 h after birth from 01/2001--07/2005 (retrospective data collection) and 07/2005--12/2008 (prospective)	237 eligible for inclusion, 68 participated without CP n = 47 with HIE Grade I, n = 21 with HIE Grade II		NA	Cog: NEPSY II (58/68), BRIEF (40/68) Beh: CBCL (66/68)	Cog: Normal mean scores for NEPSY subtests but greater than expected proportion of scores > 1 SD below the mean in 16/24 subtests, grade 2 cases differed significantly compared to grade 1 cases in attention and executive function, language (speeded naming) and memory and learning (narrative memory). Greater proportion than expected scored within clinical range in all areas of the BRIEF. Beh: 11.8% children had total score in clinical range, 27.8% of children with grade 2 HIE and 7.3% of children with grade 1 HIE had internalising problems	Infants with HIE are at risk of problems with higher cognitive functioning, particularly in the areas of attention, memory and behaviour	IQ not assessed but there is ongoing evaluation. Exclusion of non-hypoxic aetiology, however no definition of hypoxic-ischaemia given and no definition of clinical signs of NE.
Lindstrom 2006	Obs, cohort (r)	Cog + Beh	Mean 16y1m, SD 1y4m, range 15y--19y1m	Term born Swedish birth cohort, born 1985	54 identified, 43 participated, 28 without CP	18/28	N =15 siblings for comparison of behaviour outcome Mean age 14y2m (SD 2y), range 10y11m--17y5m; age significantly younger ($p < 0.01$) 5/15 boys	Cog (11/28): WISC-III Beh (28/28 + comparison sibling group): Parental questionnaires via telephone interview consisting of Connors 10-item scale, ADHD Rating Scale IV, Asperger Syndrome Screening Questionnaire	Cog: 4/11 with IQ ≤ 70; 3/11 with IQ 71-85 Beh: Significant differences to comparison siblings on the Connors scale ($p < 0.003$), the Inattention subscale of the ADHD Rating Scale IV ($p < 0.006$) and the Asperger Syndrome Screening Questionnaires ($p < 0.003$)	A considerable proportion of teenagers with moderate NE without CP present with cognitive deficits	IQ testing only in group in conjunction with neuroimaging. Draws indirect conclusions from special educational support onto IQ without standardised testing. Small non age and sex matched control group at significantly different age.
Marlow 2005	Obs, case-control (r)	Cog + Beh	7y2m (6y6m--9y)	GA ≥ 35 weeks, identified from the Trent Neonatal Survey database of babies with defined neonatal conditions, born 04/1992--04/1994	120 identified, 65 participated, 50 without CP n = 32 with moderate NE; n = 18 with severe NE	31/50	N = 49 Children attending main-stream school were compared to a child from same school, matched for sex, ethnic group, first language and age (within 3 months), randomly selected from 3 children identified by the head teacher. Median age 7y1m (range 6y4m--8y)	Cog BAS-II; NEPSY Beh SDQ (parental and teacher)	Cog *Moderate NE:* No significant difference for general cognitive ability or subscale scores on BAS, significantly lower scores on language, sensorimotor, narrative memory and sentence repetition domain on NEPSY. *Severe NE*: Significantly lower scores compared to control group in general cognitive ability on BAS and domains of NEPSY (Attention and executive function, language, visuospatial, memory and learning, memory for names, narrative memory, orientation and everyday memory impairment). Beh *Mod NE*: no significant difference compared to control group. *Severe NE*: Significantly higher overall behavioural scores and hyperactivity compared with either other groups.	Children with NE have poorer scores on cognitive, neuropsychological, educational and behavioural assessments than classmates; these are particularly evident in children with severe NE.	Exclusion of non-hypoxic aetiology, however no definition of hypoxic-ischaemia given.
Pappas 2015	Obs, cohort (p)	Cog	6--7y	≥ 36 weeks gestation, born 07/2000--05/2003 Secondary analysis of RCT on whole-body hypothermia	140 survivors, 110 participated, 86 without CP n = 53 hypothermia participants n = 33 normo-thermia participants	61/110	NA	WPPSI-III; WISC-IV	51/86 (59%) of children without CP with IQ > 84; 27/86 (31%) with IQ 70--84; 8/86 (9%) with IQ of < 70. Rates were similar among the subgroup of infants treated with hypothermia or normothermia	Cognitive impairment remains a concern for all children with NE; early intervention and school-age assessments recommended regardless of motor impairment	Behaviour reported but not separate for those children without CP NEPSY reported but not separate for those children without CP
Van Kooij 2010	Obs, case-control (r)	Cog	9--10y	Full-term infants, born 1993--1997 and admitted to local NICU	118 survivors; 80 with mild/ moderate NE participated Some results given for children without CP (n = 69)	NK	52, matched for sex and age Exclusion criteria: perinatal complications, assisted instrumental delivery, birth weight < 10th centile, referral to a paediatrician or admission to a hospital in the first month of life	WISC-III (79/80) IQ estimated with subtests (Similarities, Vocabulary, Block Patterns, and Object Assembly)	Control children had significantly higher mean estimate IQ scores compared with the group of children with mild or moderate NE without CP ($p = 0.019$ and $p < 0.001$ respectively). An increased proportion of children without CP scored below 2 SD (7.2%) and between 1 and 2 SD (17.4%) of the normative population.	Children with mild and moderate NE are at increasing risk for cognitive deficits even in the absence of functional motor deficits.	Other causes of NE cannot clearly be excluded, no specific mention of exclusion of children with other disorders such as genetic or metabolic that might have also suffered from HIE. IQ scores estimated.
Van Schie 2015	Obs, cohort (p)	Beh	Mean 7y6m (range 6y4m--8y2m)	Term neonates, born 08/1999--07/2002	35 in initial cohort, 25 participated,17 without CP	19/25	NA	CBCL (parents)	4/17 children had total score in subclinical (n = 3) or clinical (n = 1) range; proportion not much higher than in Dutch reference sample	More research needed on behavioural and cognitive effects of HIE	No definition of clinical signs of NE

Table 2: Characteristics of reviewed studies; Obs: Observational, p: prospective, r: retrospective, RCT: randomised controlled trial, Cog: Cognitive, Beh: Behaviour, CP: cerebral palsy, HIE: Hypoxic-ischaemic encephalopathy, NE: Neonatal encephalopathy, NA: Not applicable, WPPSI: Wechsler Pre-School and Primary Scale of Intelligence, WPPSI-R: Wechsler Pre-School and Primary Scale of Intelligence-Revised, WISC: Wechsler Intelligence Scale for Children, ADHD: Attention Deficit Hyperactivity Disorder, BAS: British Ability Scale, NEPSY: Developmental Neuropsychological Assessment, SDQ: Strength and Difficulties Questionnaire, BRIEF: Behavior Rating Inventory of Executive Function, CBCL: Child Behavior Checklist, IQ: Intelligence Quotient

Study, year	Adequacy of case definition[1]	Representativeness of the cases[2]	Selection of controls[3]	Definition of controls[4]	Comparability of cases and controls on the basis of design or analysis[5]	Ascertainment of exposure[6]	Same method of ascertainment for cases and controls[7]	Non-response rate[8]
Barnett, 2002	+	+	NA	NA	NA	+	NA	+
Hayes, 2017	+	+	NA	NA	-	+	NA	-
Lindstrom, 2006	+	+	NA	NA	+ (family)	+	NA	-
Marlow, 2005	+	+	+	+	++ (age, sex)	-	+	-
Pappas, 2015	+	+	NA	NA	NA	+	NA	+
Van Kooij 2010	+	+	-	+	++ (age, sex)	-	+	-
Van Schie, 2015	+	+	NA	NA	NA	+	NA	-

Table 3: Quality assessment of observational studies using Newcastle Ottawa Scale.

1. Yes with independent validation (+), Yes, eg record linkage or based on self report or no description (-)

2. Consecutive or obviously representative (+), potential for selection bias or not stated (-)

3. Community controls (+), hospital controls or no description (-)

4. No history of disease (+), no description of source (-)

5. Controls for age or any additional factor (+), Does not control for any factor (-)

6. Secure record or structured interview where blind to case/control status (+), interview not blinded or self report or medical record only or no description (-)

7. Yes (+), No (-)

8. Same rate for both groups (+), Non respondents described or rate different and no designation (-)

Figure Legends

Figure 1: Flow diagram of review process

Figure 2: IQ compared to controls in mild, moderate and severe HIE without CP

Systematic Review: Long-term cognitive and behavioural outcomes of neonatal hypoxic-ischaemic encephalopathy in children without cerebral palsy

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Short title: Outcomes in neonatal encephalopathy without cerebral palsy

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ABSTRACT

Aim: To evaluate long-term cognitive and behavioural outcomes of children with neonatal hypoxic-ischaemic encephalopathy in the absence of cerebral palsy.

Methods: A systematic search was performed on five databases (EMBASE, Medline, PubMed, Web of Science, PsycInfo). Randomised-controlled trials, non-randomised controlled trials, or observational studies, published between 1990--2017, that reported long-term (age ≥ 4 years) cognitive and/or behavioural outcomes of neonatal hypoxic-ischaemic encephalopathy without cerebral palsy were included.

Results: Seven articles met the inclusion criteria (n=352 total participants, n=53 treated with therapeutic hypothermia). Studies reporting cognitive outcome demonstrate impairment of general cognitive abilities in 25--63% of participants with hypoxic-ischaemic encephalopathy without cerebral palsy~~, including 40% who were treated with therapeutic hypothermia~~. Specific cognitive difficulties were reported in two studies for attention, executive functioning, memory function, and language. Results regarding behavioural outcome possibly indicate a higher risk of difficulties.

Conclusion: A substantial proportion of children with neonatal HIE who survive without cerebral palsy are at increased risk of general and/or specific cognitive impairments~~, irrespective of hypothermia treatment~~. Behavioural problems may be more common, but evidence is limited. Results highlight the importance of comprehensive long-term follow-up to identity difficulties and enable intervention to optimise educational achievement and behavioural adjustment.

Keywords: neonatal hypoxic-ischaemic encephalopathy, long-term outcome, cognitive outcome, behavioural outcome

Key Notes: Outcome studies in neonatal hypoxic-ischaemic encephalopathy (HIE) often focus on death, cerebral palsy and cognitive impairment, but the extent of cognitive deficits following HIE in children without cerebral palsy is not well described. This systematic review suggests that, fFollowing ~~neonatal hypoxic-ischaemic encephalopathy (~~HIE~~)~~, up to 60% of children without cerebral palsy have cognitive impairments, and are at ~~.~~ ~~These include general and specific cognitive difficulties~~risk of ~~.~~ Bbehavioural problems ~~in HIE may be more common although evidence is limited~~. Long-term follow-up of children with HIE is important irrespective of neuromotor impairment.

Neonatal hypoxic-ischaemic encephalopathy (HIE) occurs at an estimated incidence of 1.3 to 1.9 per 1000 live births in high and middle income countries(1, 2) and 8.5 per 1000 live births in low income countries(2). It is associated with a high risk of brain injury and long-term neurological and neurodevelopmental impairments including cerebral palsy (CP), cognitive impairment, behavioural difficulties, visual or hearing impairment, and epilepsy(3). While neonatal encephalopathy (NE) is a clinical description of disturbed neurological function in the neonatal period that does not require an association with aetiology(4), the term HIE should be reserved for such cases of NE where there is evidence of perinatal asphyxia (PA) and/or hypoxic-ischaemic brain injury. Current criteria for a diagnosis of HIE are usually based on those used in the large randomised controlled trials (RCT) of therapeutic hypothermia (TH)(5, 6), which include clinical and biochemical markers of perinatal asphyxia, as well as signs of encephalopathy and/or seizures.

Outcome of children who suffered from neonatal HIE is dependent on the severity of encephalopathy(3). The most frequently used grading of HIE is based on the scoring system of Sarnat and Sarnat, which differentiates between mild, moderate and severe encephalopathy(7). It is widely accepted that those children who suffer from severe HIE are at significantly increased risk of mortality and neurodevelopmental sequlae, whereas those with mild HIE have a better prognosis. Newborns with moderate HIE have a variable outcome, making prediction more difficult(3, 8). In recent years TH has become the standard of care in tertiary neonatal centres for newborns with HIE(9, 10), following large RCTs that have shown TH to reduce mortality and severe neurodisability at toddler age (11-14), with evidence that the benefits in cognitive outcome continue to school-age (14-16). Rates of children with no disabilities post TH for HIE are described between 41--68%, whereas 22--35% if children will have moderate or severe disabilities (14, 15).

Most outcome studies in HIE assess children in infancy and early childhood and focus on outcomes such as death, CP and severe global cognitive impairment. There is

some indication that cognitive deficits also occur in children with a history of HIE who do not present with CP (17-19). Understanding the full spectrum of neurodevelopmental outcome, including in those children without CP, is important as it allows professionals to identify children requiring early intervention and ongoing follow-up. We aimed to systematically review and evaluate the current evidence for long-term cognitive and behavioural outcomes in children with neonatal HIE who survive without CP.

Patients and Methods

Study Design: The review protocol was prospectively registered on PROSPPSERO (CRD42015027808, original registration date 11/11/15). The protocol as updated as the research question became more refined, and to make it clear that focus was specifically on children with HIE who survived without CP. It was also amended to be clear that the review would exclude studies that did not report outcomes specifically for these children (PROSPERO record updated retrospectively 22/02/19). Studies were considered if they were RCTs, non-randomised control trials (NRCT), or observational studies. Only studies in humans and studies published in English, between 1990 and 2017, were included.

Inclusion Criteria: Studies were included if the participants were aged between 4 and 19 years and had been born at ≥35 weeks gestational age. Only studies that used standardised psychometric tests and questionnaires to assess cognition and behaviour were included. Studies that did not report results in children without CP separately were excluded. As there is some disparity in the literature between the definitions of HIE and the term is often used simultaneously with NE and birth/perinatal asphyxia(1), all four terms were added in the search. To be included, studies had to specifically state they were investigating outcomes in infants with HIE. However, studies were only included where the inclusion and exclusion criteria were considered sufficient to suggest hypoxia-ischaemia as the cause of

encephalopathy in the majority of patients. Accepted definitions of HIE were those which included a marker of PA (such as metabolic acidosis within the first hour after birth, low Apgar scores at 5 minutes or beyond, history of an acute perinatal event and the need for prolonged resuscitation or ventilation) together with signs of encephalopathy and/or seizures, or meeting the criteria laid out by Sarnat for HIE grading. It is important to point out that there is a considerable variability in the definition of and use of the terms HIE/NE/PA across the studies. For consistency throughout this review, the term HIE has been used, replacing NE where it occurs.

Outcome measures: Outcome measures were general or specific cognitive abilities and/or behavioural outcome, assessed by any form of standardised psychometric test or questionnaire. General cognitive abilities are commonly assessed by IQ tests, such as the Wechsler Scales, or "general cognitive ability" using the British Ability Scale. Specific cognitive abilities are cognitive abilities in more specific domains, such as Executive Function and memory. Cognitive and behavioural impairment were both defined as the presence of significant differences to typically developing children in test/questionnaire scores (Case-control studies) or as score more than 1 SD below the population norm (cohort studies).

Literature searching strategy: A systematic search was carried out using the search strategy detailed in table 1. The electronic databases MEDLINE, EMBASE, PubMed, Web of Science and PsycInfo were used, with the last search carried out on 02/12/2018. Reference searching was performed on articles that were selected for review. Searches were undertaken by two reviewers (MS and AG) using the same search terms and both reviewers assessed studies for eligibility independently. Neither reviewer was blinded to the study's authors or institutions.

Study selection: Selection was carried out independently by two authors (MS and AG) on the basis of titles and abstracts, with the full text obtained where necessary. Any disagreement that could not be ~~was~~ resolved by discussion between the two reviewers was adjudicated by a third ~~party~~ (MJ)~~consensus~~. Conference abstracts were not included due to increased risk of bias secondary to incomplete data.

Data collection process: Data regarding study characteristics, patient demographics and outcome measures were extracted using a specifically designed spreadsheet.

Risk of bias assessment: The quality of RCT and NRCT was assessed using the Cochrane risk of bias tool(20). Observational studies were assessed using the Newcastle-Ottawa scale(21). Both reviewers performed the risk of bias assessment independently and resolved any disagreement by consensus.

Synthesis of results: Meta-analysis for outcome measures with sufficient homogeneity was planned. Heterogeneity was checked using the I^2 statistic, which reports the percentage of variation attributable to heterogeneity. For continuous outcomes, the weighted mean difference was calculated using the inverse variance method. When the I^2 statistic was greater than 50%, a random effects model was used. For binary outcome data, the Peto method was used to calculate a pooled odds ratio. Where available data were not sufficiently homogeneous to allow this a narrative synthesis comparing study results was performed.

Results

Study selection and characteristics

The review process is demonstrated in figure 1. Seven papers, published between 2001 and 2017, were included for review: All were observational studies following up infants with HIE, with 5 cohort studies (including one which followed up a cohort of patients from a

RCT) and 2 case control studies that included a control group of matched controls drawn from a normal population for comparison of outcomes. In addition, one cohort study used siblings of cases for behavioural outcomes. Characteristics of the studies are summarised in table 2. More detailed information on the study eligibility criteria of each included study, and fulfilment of HIE criteria can be found in Appendix S1. One study followed up children from an RCT who received TH as an intervention for the treatment of HIE compared to intensive care with normothermia.

Quality assessment

Assessments of quality and risk of bias in the studies are summarised in table 3. The potential risk of bias in studies was taken into consideration during data interpretation.

Primary outcomes

The results of primary outcomes were split into cognitive and behavioural outcomes. Results of the included studies are shown in table 2.

General and specific cognitive abilities

Cognitive outcome was reported in 6 studies. The most commonly used tests were the Wechsler Scales; the Wechsler Pre-School and Primary Scale of Intelligence (WPSSI) and Wechsler Intelligence Scale for Children (WISC), dependent on the age of participants. These were used in four of the six included studies. Full-scale IQ (FSIQ) was reported in 4 studies; one study estimated FSIQ based on a limited number of subtests. Two studies used the Developmental Neuropsychological Assessment (NEPSY) to assess executive function, including memory function (22, 23). One of these studies also used the British Ability Scale (BAS) as another measure of general cognitive abilities(22), while the other also used the Behavior Rating Inventory of Executive Function (BRIEF) as another measure of executive function(23). Of note, on the Wechsler Scales the mean FSIQ in a normative population is 100 with a standard deviation (SD) of 15. Therefore the proportion of scores in a normative

population below 2SD is 2.27%, and 13.59% between 1 and 2 SD, meaning that a proportion of 15.86% of children in the general population would score a FSIQ below 85. Similarly, standard scores are also obtained for the cluster scores used in the BAS, with a mean score of 100 and a standard deviation of 15 points to either side.

Case-control studies

Two case-control studies reporting cognitive outcomes were included. Van Kooij et al(24) compared FSIQ scores using the WISC-III in 62 children aged 9--10 years with mild to moderate HI~~N~~E (defined in Appendix S1) without CP and 52 sex and age matched controls. Marlow et al(22) used the BAS-II to assess general cognitive abilities and the NEPSY for attention, executive functioning and memory in seven-year old children with a history of moderate to severe HI~~N~~E (see Appendix S1) but without motor disability and matched those children attending mainstream school to classmates. The results of both of these studies for FSIQ are illustrated as forest plots in figure 2. However, due to the reporting differences between mild, moderate and severe cases of HIE, it was only possible to perform a meta-analysis for the effects of moderate HIE on FSIQ (also shown in figure 2). It can be seen that whilst Marlow et al demonstrate a clear effect of severe HIE on IQ compared to controls (mean IQ difference 11.3; 95%CI 4.1--18.5), and Van Kooij et al show a clear impact of mild HIE on IQ compared to controls (mean IQ difference 10; 95%CI 4.2--15.9), the meta-analysis of both studies shows no significant effects for moderate HIE on IQ compared to controls (mean IQ difference 9; 95%CI 5.9--24.2). However, it is important to note that there are differences in the definitions of moderate and severe HIE used by the two studies. In addition, looking at the individual results it can be seen that in the study by Van Kooij et al~~l~~ a significant difference was found ~~found a significant difference~~ between~~in~~ the moderate HIE group ~~compared~~ and the ~~to~~ controls, and that this difference was more marked ~~when compared to the~~than that seen between mild HIE and controls. Furthermore, Marlow et al found poorer scores on neuropsychological assessments in children with a

history of HIE, particularly in those with a history of severe HIE. Significant differences ($p < 0.001$) between the severe HIE group attending mainstream school and classmates were found on the BAS for general cognitive ability and three of the subscales (Special non-verbal composite, Non-verbal reasoning score, Spatial scale score), as well as in the NEPSY for attention and executive function, language, memory and learning, narrative memory and orientation. In contrast, significantly lower scores in the moderate HIE group were only found in the language, narrative memory and sentence repetition domain on the NEPSY.

Cohort studies

Three cohort studies reporting FSIQ using the Wechsler Scales were included in the review; verbal and performance IQ scores were not separately reported. Lindstrom et al(25) studied a population-based cohort of 28 children with a history of HIE without CP out of which 11 underwent standardised IQ testing as part of a separate study in connection with neuroimaging. Four of the 11 children (36%) had a FSIQ ≤70 and 3 out of the 11 participants (27%) had IQ scores 71--84. Overall, results indicated higher rates of lower IQ scores in this group of children compared to population norms, with a greater proportion of children presenting with FSIQ scores of less than 85 (i.e. >1 SD of population mean). However, the group that underwent testing was small, representing less than half of the total cohort, with a further drop-out rate of 23%. In contrast to these results, Barnett et al(26) reported opposing evidence for cognitive outcome in 34 five to six year old children with a history of HIE without CP, with the majority (94%) of participants having FSIQ scores of ≥ 80. Pappas et al performed a secondary analysis from data of the large NICHD RCT on whole-body hypothermia(6, 27), demonstrating relatively high rates of low FSIQ scores in all 86 children with HIE without CP. In those children who underwent therapeutic hypothermia, 43% had an FSIQ <84 while 36% of the normothermia group had an FSIQ <845, though this study was not powered to detect differences between treatment arms in children without

CP.Pappas et al performed a secondary analysis from data of the large NICHD RCT on whole-body hypothermia(6, 27), demonstrating relatively high rates of low FSIQ scores in all 86 children with HIE without CP. In those children who underwent therapeutic hypothermia, 43% had a FSIQ <84, while 36% of the normothermia group had a FSIQ<84, though this study was not powered to detect differences between treatment arms in children without CP., irrespective of treatment (FSIQ score <84 in 40% and <70 in 9%, respectively). Hayes et al reported the cognitive outcomes of 68 children with HIE but no evidence of CP, using the NEPSY-2 and BRIEF assessments(23). While the cohort had normal mean NEPSY-2 scores, a greater than expected proportion of scores fell into the impaired range. Children with moderate HIE performed more poorly than those with mild HIE, particularly with regard to attention and executive function. A greater proportion of children also fell into the clinical (impaired) range on the BRIEF.

Behavioural outcomes

Behavioural outcomes were reported in four studies. Two studies used the parental version of the Child Behavior Checklist (CBCL), one study used the parental version of the Strength and Difficulties Questionnaire (SDQ), and one study used the Connors 10-item scale, ADHD Rating Scale IV, as well as the Asperger Syndrome Screening Questionnaire.

Case-control studies

One case-control study reported behavioural outcome. Marlow et al's(22) results of the parent reported SDQ demonstrate an increase in behavioural problems in the severe HINE group without CP in comparison to the moderate NHIE group without CP and typically developing controls, with . Sa significant differences were seen in the overall behavioural scores (p=0.002) and hyperactivity/inattention subscale scores (p<0.001) between these two groups, while differences between moderate NE and comparisons remained statistically insignificant. Teacher scores revealed more problematic behaviour than parental responses, with significant differences in the moderate NE group compared to the

~~to~~ normal ~~the~~ comparison groups in the total behavioural scores (p<0.0~~0~~1), emotional problems (p=0.01), hyperactivity~~/inattention~~ (p<~~=~~0.~~0~~01), pro-social behaviour (p=0.02), and impact on everyday functioning (p<~~=~~0.~~0~~01). Pervasive behaviour disorders, which were identified as overall abnormal behaviour scores on both parent and teacher questionnaire, were found in 23% in the severe HI~~N~~E group compared with 8% in the moderate HI~~N~~E and 2% in the comparison group.

Cohort studies

Three cohort studies reporting on behavioural outcome were included. Lindstrom et al(25) performed parent interviews with a group of 28 children with a history of HI~~N~~E but without CP, including parental questionnaires assessing the risk of ADHD (Connors 10-item scale and ADHD Rating Scale IV). Results were compared to a group of 15 siblings, demonstrating significant differences between the HI~~N~~E group and the comparison sibling group on both the Connors scale (p<0.003) and the Inattention subscale of the ADHD Rating Scale IV (p<0.006), indicating a higher risk for perceived attention problems ~~and ADHD~~ in the group of children with HI~~N~~E. The authors found significantly higher scores on the Asperger Syndrome Screening Questionnaire in the HI~~N~~E group (p<0.003) suggesting a higher risk for social communication and interaction difficulties. In contrast to these results, van Schie et al(28) found no difference in the rate of behavioural problems between their cohort of infants with HIE without CP and a Dutch reference sample using the CBCL. Hayes et al also assessed behaviour in their cohort study of children with HIE in the absence of CP, using the CBCL(23). They found internalising problems in 27.8% of children following moderate HIE and in 7.3% of children following mild HIE. Compared to children with mild HIE, those with moderate HIE were significantly more likely to have anxiety, somatic complaints, withdrawn behaviour, sleep problems, and externalising problems such as aggressive behaviour.

Discussion

To our knowledge, this is the first systematic review on long-term behavioural and cognitive outcomes in children with HIE without CP. Overall, this review suggests an increased risk of general and/or specific cognitive impairments in this group of children. In contrast, the evidence for behavioural difficulties is less clear. ~~Of note, most school-age follow-up studies have been conducted prior to the introduction of TH; thus data on long-term cognitive or behavioural outcomes in children with a history of TH for neonatal HIE without neuromotor impairments remain sparse.~~

Cognitive outcome

All included studies reporting on cognitive outcome reported a higher proportion of cognitive impairments at school-age in children with a history of HIE, with the exception of Barnett et al(26). However, the low incidence of severe brain injury on neuroimaging may have accounted for the observed higher IQ scores in Barnett et al's study. Even though Van Kooij(24) reported mean FSIQ in the normal range, many studies found a higher than expected proportion of children scoring below 1 SD in standardised IQ tests(24, 25, 27), suggesting that children with HIE without cerebral palsy are at increased risk of cognitive impairment and/ learning disability.

Marlow at el(22) reported specific cognitive difficulties in the areas of attention, executive functioning, memory and language, particularly in the severe HI~~N~~E group without CP. Hayes et al also found a greater than expected proportion scores in the impaired range in tests of executive function, with the moderate HI~~N~~E group without CP differing significantly from the mild HI~~N~~E group without CP(23). The lack of literature on specific cognitive difficulties in children with HIE without CP suggest that more research is needed to identify such difficulties in these children. In addition to standardised cognitive testing or psychometric questionnaires, Lindstrom et al(25) reported parent interview data. Taking

into account all available information from standardised assessments as well as non-standardised interview data, more than 70% of the children in the study were found to have executive function difficulties that interfered with their daily functioning. It is furthermore noteworthy that, similar to Marlow et al's results(22), other studies have also suggested specific difficulties in language related domains in children with HIE (29-32) and associations between Verbal IQ and a pattern of watershed brain injury on neuroimaging (33, 34).

The increased risk of general and/or specific cognitive impairments in children with HIE without CP is supported by reports of increased rates of special educational needs as an indirect measure of cognitive difficulties. Marlow et al(22) reported significantly lower attainment levels for reading and spelling in the moderate HI~~N~~E group without CP and these differences in attainment levels were even more pronounced in the severe HI~~N~~E group without CP. Children with severe HI~~N~~E without CP were also significantly more often reported to have academic special needs and educational statements and individual learning plans. Van Kooij et al(24) reported that even in the HI~~N~~E group without CP, 9.3% of children with mild HI~~N~~E and 21.6% of children with moderate HI~~N~~E attended special education, while all of the control participants attended main stream school. Other studies in this review found similar results(23, 25, 27), in addition to studies that did not meet inclusion criteria for this review(30, 35).

Behavioural outcome

Given the small number of studies included, their heterogeneity and limitations it is overall difficult to draw a conclusion as to the risk of HIE on adverse behavioural outcome in children without CP, although results indicate that children with HIE without CP may be at increased risk for behavioural problems. Only four studies that report on behavioural difficulties in children without cerebral palsy were included. Based on the findings from Marlow et al(22), Hayes et al(23) and Lindstrom et al(25), it appears that behavioural

problems may occur more readily in children with HIE without CP compared to a comparison group, particularly if HIE is graded more severe than mild. These include symptoms of inattention and hyperactivity, as well as increased difficulties with pro-social behaviour and making friends. However, it is important to note that Lindstrom et al(25) used a comparison group of siblings that was unmatched in terms of sex and age. Interestingly, teacher reports in Marlow et al's study(22) generated more significant results than the parent reports, which is an example of detection bias. This is important to note for any future trials that use parental assessment of behaviour. In contrast, Van Schie et al(28) found no difference in the rate of behavioural problems between the study's cohort of infants with HIE without CP and a Dutch reference sample using the CBCL. However, the study sample cohort was small and 32% of children were lost to follow-up. Moreover, the study included no cases of severe HIE which is likely to have skewed the results. Other studies not included in the review also report different results with regards to behavioural outcome(36-38).

The association between Autism Spectrum Disorders and ~~NE/~~HIE is even more uncertain. Lindstrom et al(25) report significant differences on the Asperger Syndrome Questionnaire as compared to the sibling group, however there is very little other literature to support an increased rate of Autism Spectrum Disorders in children with HIE. The only study investigating this association is by Badawi et al(39), who reported a significantly higher incidence of Autism Spectrum Disorders in infants with HI~~N~~E. However, the authors did not exclude aetiologies of HI~~N~~E other than PA and included all patients irrespective of neuromotor outcome.

Association of severity of HIE with outcome

As described above, several of the studies included in this review suggest that the risk of later cognitive impairment is related to the severity of the neonatal clinical presentation, as previously described by other reviews(3, 40). Marlow et al(22) found greater levels of

neurodevelopmental and behavioural impairment in children with severe HI~~N~~E without CP compared to other groups, whilst both Hayes et al(23) and Van Kooij et al(24) found greater impairment in children with moderate HIE without CP compared to those with mild or no HIE. While it is widely accepted that the difference in outcome becomes more evident on the severe spectrum of clinical presentation, this is less clear for children with mild as opposed to moderate HIE[2,7]. Van Kooij et al(24) described the mild HI~~N~~E group without CP scoring intermediately between the control subjects and children with moderate HI~~N~~E without CP, ~~which would suggest~~demonstrating that even children with mild HI~~N~~E are at increased risk for impairment of cognitive abilities. This finding is supported by Murray et al(41), who found significantly lower IQ scores and Children's Memory Scale subtest scores in five-year old children with mild HIE as compared to a comparison group, and no significant differences between the mild and moderate HIE group in any of the WPSSI-III measures. In contrast, some other studies not included in this review have found no significant increase in cognitive impairment in school-aged children with a history of mild HI~~N~~E(29, 30). Overall, results of this systematic review suggest that the risk of cognitive and/or behavioural impairments is related to severity of HIE, though the impact of mild HIE remains inconclusive.

Limitations

There are substantial differences in eligibility criteria resulting in varying definitions of HI~~N~~E and PA, resulting in a heterogeneous study population for this review. Furthermore, there is heterogeneity in study design and outcome measures, limiting the potential for meta-analysis and presenting challenges when it was carried out. Different behavioural outcome measures were used in included studies, and although most studies reporting on cognitive outcome used the Wechsler Intelligence tests, results of these were reported differently, e.g. by recording mean IQ scores, differences of IQ scores to controls, and/or proportions of abnormal IQ scores, making meta-analysis challenging. Most studies focus on general

cognitive abilities only and reports on specific cognitive abilities are sparse. Many of the studies also had small sample sizes and so may lack statistical power. Moreover, we are aware that the age range of 4-19 years is wide and that there are limitations to pooling all of these ages as maturational changes across this age range may occur, in particular, for specific cognitive functions. Finally, the majority of studies included and cited in this review are from the pre-cooling era. As TH is now standard of care for children with moderate to severe HIE, the results from most included studies do not necessarily represent the current patient cohort.

Conclusion

This systematic review provides evidence for an increased risk of cognitive impairments in school-aged children with a history of HIE without CP. It appears that a significant proportion of these children have some degree of cognitive difficulties, including executive function and language-related difficulties, with a significant proportion requiring additional support in school. Impaired cognitive outcome remains a concern even in those children treated with TH; however, evidence in this group of children without neuromotor impairment is currently sparse. Although the evidence is limited and more research is needed, the results also indicate that there may be an increased risk for behavioural problems, such as attention problems and hyperactivity, which again, will be relevant for school success.

The results of this review highlight the importance of standardised comprehensive and long-term follow-up beyond toddler age even in those children with a history of HIE who do not develop significant neuromotor difficulties. Cognitive difficulties may be subtle but nevertheless relevant for academic progress and may remain undetected at an early age and only emerge with increasing cognitive demands within the school setting. Knowledge about possible cognitive difficulties in these children leads to better understanding and likely earlier intervention to optimise opportunities for the individual

children. The small number of studies included in this review following the systematic search demonstrates the need for future research with focus on assessment of specific cognitive and behavioural functions in school-aged children with HIE without neuromotor impairment, particularly in those children that have received TH as this is now standard of care for most children with moderate or severe HIE.

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Abbreviations

ADHD - Attention Deficit Hyperactivity Disorder; BAS - British Ability Scale; BRIEF - Behavior Rating Inventory of Executive Function; CBCL - Child Behavior Checklist; CP – Cerebral Palsy; FSIQ - Full-scale Intelligence Quotient; HIE – Hypoxic Ischaemic Encephalopathy; IQ - Intelligence Quotient; NE – Neonatal Encephalopathy; NEPSY - Developmental Neuropsychological Assessment; NRCT – Non-Randomised Controlled Trial PA – Perinatal Asphyxia; RCT – Randomised Controlled Trial; SD – Standard Deviation; SDQ - Strength and Difficulties Questionnaire (SDQ); TH – Therapeutic Hypothermia; WISC - Wechsler Intelligence Scale for Children (WISC); WPPSI - Wechsler Pre-School and Primary Scale of Intelligence.

Conflict of interest

None to declare

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	Search terms
1	Neonatal encephalopathy.mp.
2	Perinatal Asphyxia.mp.
3	Birth Asphyxia.mp.
4	Hypoxic isch* encephalopathy.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5	1 or 2 or 3 or 4
6	outcome.mp.
7	behavio*.mp.
8	cogniti*.mp.
9	neurodevelopment*.mp.
10	Long-term.mp.
11	School-age*.mp.
12	childhood.mp.
13	7 or 8 or 9 or 10 or 11 or 12
14	5 and 6 and 13
15	limit 14 to (english language and humans and yr = "1990 -Current")

Table 1: Search terms and strategy used for electronic searches[1]

[1] *Performed by using OvidSp (Wolters Kluwer Health; http://www.ovid.com); .mp.,multipurpose search across the subject headings*

Author, year	Study type	Primary outcome	Age	Cohort details	N	Sex (boys/N)	Characteristics controls	Measures	Results	Conclusion	Comments
Barnett 2002	Obs, cohort (p)	Cog	5.5--6.5y	≥38 weeks gestation, born 05/91--01/96	63 eligible for inclusion, 53 participated, 34 without CP	19/34	NA	WPPSI-R	31/34 Full scale IQ > 80 2/34 Full scale IQ < 80 1/34 not able to test due to cooperation	No conclusion in paper with regards to cognitive outcome	Study mainly focuses on motor difficulties and their association with cognitive impairments
Hayes 2017	Obs, cohort (r+p)	Cog + Beh	Mean 5y8m, range 3y8m--8y10m)	≥ 36 weeks gestation, admitted with HIE in the first 48 h after birth from 01/2001--07/2005 (retrospective data collection) and 07/2005--12/2008 (prospective)	237 eligible for inclusion, 68 participated without CP n = 47 with HIE Grade I, n = 21 with HIE Grade II		NA	Cog: NEPSY II (58/68), BRIEF (40/68) Beh: CBCL (66/68)	Cog: Normal mean scores for NEPSY subtests but greater than expected proportion of scores > 1 SD below the mean in 16/24 subtests, grade 2 cases differed significantly compared to grade 1 cases in attention and executive function, language (speeded naming) and memory and learning (narrative memory). Greater proportion than expected scored within clinical range in all areas of the BRIEF. Beh: 11.8% children had total score in clinical range, 27.8% of children with grade 2 HIE and 7.3% of children with grade 1 HIE had internalising problems	Infants with HIE are at risk of problems with higher cognitive functioning, particularly in the areas of attention, memory and behaviour	IQ not assessed but there is ongoing evaluation. Exclusion of non-hypoxic aetiology, however no definition of hypoxic-ischaemia given and no definition of clinical signs of NE.
Lindstrom 2006	Obs, cohort (r)	Cog + Beh	Mean 16y1m, SD 1y4m, range 15y--19y1m	Term born Swedish birth cohort, born 1985	54 identified, 43 participated, 28 without CP	18/28	N =15 siblings for comparison of behaviour outcome Mean age 14y2m (SD 2y), range 10y11m--17y5m; age significantly younger ($p < 0.01$) 5/15 boys	Cog (11/28): WISC-III Beh (28/28 + comparison sibling group): Parental questionnaires via telephone interview consisting of Connors 10-item scale, ADHD Rating Scale IV, Asperger Syndrome Screening Questionnaire	Cog: 4/11 with IQ ≤ 70; 3/11 with IQ 71-85 Beh: Significant differences to comparison siblings on the Connors scale ($p < 0.003$), the Inattention subscale of the ADHD Rating Scale IV ($p < 0.006$) and the Asperger Syndrome Screening Questionnaires ($p < 0.003$)	A considerable proportion of teenagers with moderate NE without CP present with cognitive deficits	IQ testing only in group in conjunction with neuroimaging. Draws indirect conclusions from special educational support onto IQ without standardised testing. Small non age and sex matched control group at significantly different age.
Marlow 2005	Obs, case-control (r)	Cog + Beh	7y2m (6y6m--9y)	GA ≥ 35 weeks, identified from the Trent Neonatal Survey database of babies with defined neonatal conditions, born 04/1992--04/1994	120 identified, 65 participated, 50 without CP n = 32 with moderate NE; n = 18 with severe NE	31/50	N = 49 Children attending main-stream school were compared to a child from same school, matched for sex, ethnic group, first language and age (within 3 months), randomly selected from 3 children identified by the head teacher. Median age 7y1m (range 6y4m--8y)	Cog BAS-II; NEPSY Beh SDQ (parental and teacher)	Cog *Moderate NE:* No significant difference for general cognitive ability or subscale scores on BAS, significantly lower scores on language, sensorimotor, narrative memory and sentence repetition domain on NEPSY. *Severe NE*: Significantly lower scores compared to control group in general cognitive ability on BAS and domains of NEPSY (Attention and executive function, language, visuospatial, memory and learning, memory for names, narrative memory, orientation and everyday memory impairment). Beh *Mod NE*: no significant difference compared to control group. *Severe NE*: Significantly higher overall behavioural scores and hyperactivity compared with either other groups.	Children with NE have poorer scores on cognitive, neuropsychological, educational and behavioural assessments than classmates; these are particularly evident in children with severe NE.	Exclusion of non-hypoxic aetiology, however no definition of hypoxic-ischaemia given.
Pappas 2015	Obs, cohort (p)	Cog	6--7y	≥ 36 weeks gestation, born 07/2000--05/2003 Secondary analysis of RCT on whole-body hypothermia	140 survivors, 110 participated, 86 without CP n = 53 hypothermia participants n = 33 normo-thermia participants	61/110	NA	WPPSI-III; WISC-IV	51/86 (59%) of children without CP with IQ > 84; 27/86 (31%) with IQ 70--84; 8/86 (9%) with IQ of < 70. Rates were similar among the subgroup of infants treated with hypothermia or normothermia	Cognitive impairment remains a concern for all children with NE; early intervention and school-age assessments recommended regardless of motor impairment	Behaviour reported but not separate for those children without CP NEPSY reported but not separate for those children without CP
Van Kooij 2010	Obs, case-control (r)	Cog	9--10y	Full-term infants, born 1993--1997 and admitted to local NICU	118 survivors; 80 with mild/ moderate NE participated Some results given for children without CP (n = 69)	NK	52, matched for sex and age Exclusion criteria: perinatal complications, assisted instrumental delivery, birth weight < 10th centile, referral to a paediatrician or admission to a hospital in the first month of life	WISC-III (79/80) IQ estimated with subtests (Similarities, Vocabulary, Block Patterns, and Object Assembly)	Control children had significantly higher mean estimate IQ scores compared with the group of children with mild or moderate NE without CP ($p = 0.019$ and $p < 0.001$ respectively). An increased proportion of children without CP scored below 2 SD (7.2%) and between 1 and 2 SD (17.4%) of the normative population.	Children with mild and moderate NE are at increasing risk for cognitive deficits even in the absence of functional motor deficits.	Other causes of NE cannot clearly be excluded, no specific mention of exclusion of children with other disorders such as genetic or metabolic that might have also suffered from HIE. IQ scores estimated.
Van Schie 2015	Obs, cohort (p)	Beh	Mean 7y6m (range 6y4m--8y2m)	Term neonates, born 08/1999--07/2002	35 in initial cohort, 25 participated,17 without CP	19/25	NA	CBCL (parents)	4/17 children had total score in subclinical (n = 3) or clinical (n = 1) range; proportion not much higher than in Dutch reference sample	More research needed on behavioural and cognitive effects of HIE	No definition of clinical signs of NE

Table 2: Characteristics of reviewed studies; Obs: Observational, p: prospective, r: retrospective, RCT: randomised controlled trial, Cog: Cognitive, Beh: Behaviour, CP: cerebral palsy, HIE: Hypoxic-ischaemic encephalopathy, NE: Neonatal encephalopathy, NA: Not applicable, WPPSI: Wechsler Pre-School and Primary Scale of Intelligence, WPPSI-R: Wechsler Pre-School and Primary Scale of Intelligence-Revised, WISC: Wechsler Intelligence Scale for Children, ADHD: Attention Deficit Hyperactivity Disorder, BAS: British Ability Scale, NEPSY: Developmental Neuropsychological Assessment, SDQ: Strength and Difficulties Questionnaire, BRIEF: Behavior Rating Inventory of Executive Function, CBCL: Child Behavior Checklist, IQ: Intelligence Quotient

Study, year	Adequacy of case definition[1]	Representativeness of the cases[2]	Selection of controls[3]	Definition of controls[4]	Comparability of cases and controls on the basis of design or analysis[5]	Ascertainment of exposure[6]	Same method of ascertainment for cases and controls[7]	Non-response rate[8]
Barnett, 2002	+	+	NA	NA	NA	+	NA	+
Hayes, 2017	+	+	NA	NA	-	+	NA	-
Lindstrom, 2001~~1~~6	+	+	NA	NA	+ (family)~~NA~~	+	NA	-
Marlow, 2005	+	+	+	+	++ (age, sex)	-	+	-
Pappas, 2015	+	+	NA	NA	NA	+	NA	+
Van Kooij 2010	+	+	-	+	++ (age, sex)	-	+	-
Van Schie, 2015	+	+	NA	NA	NA	+	NA	-

Table 3: Quality assessment of observational studies using Newcastle Ottawa Scale.

1. Yes with independent validation (+), Yes, eg record linkage or based on self report or no description (-)

2. Consecutive or obviously representative (+), potential for selection bias or not stated (-)

3. Community controls (+), hospital controls or no description (-)

4. No history of disease (+), no description of source (-)

5. Controls for age or any additional factor (+), Does not control for any factor (-)

6. Secure record or structured interview where blind to case/control status (+), interview not blinded or self report or medical record only or no description (-)

7. Yes (+), No (-)

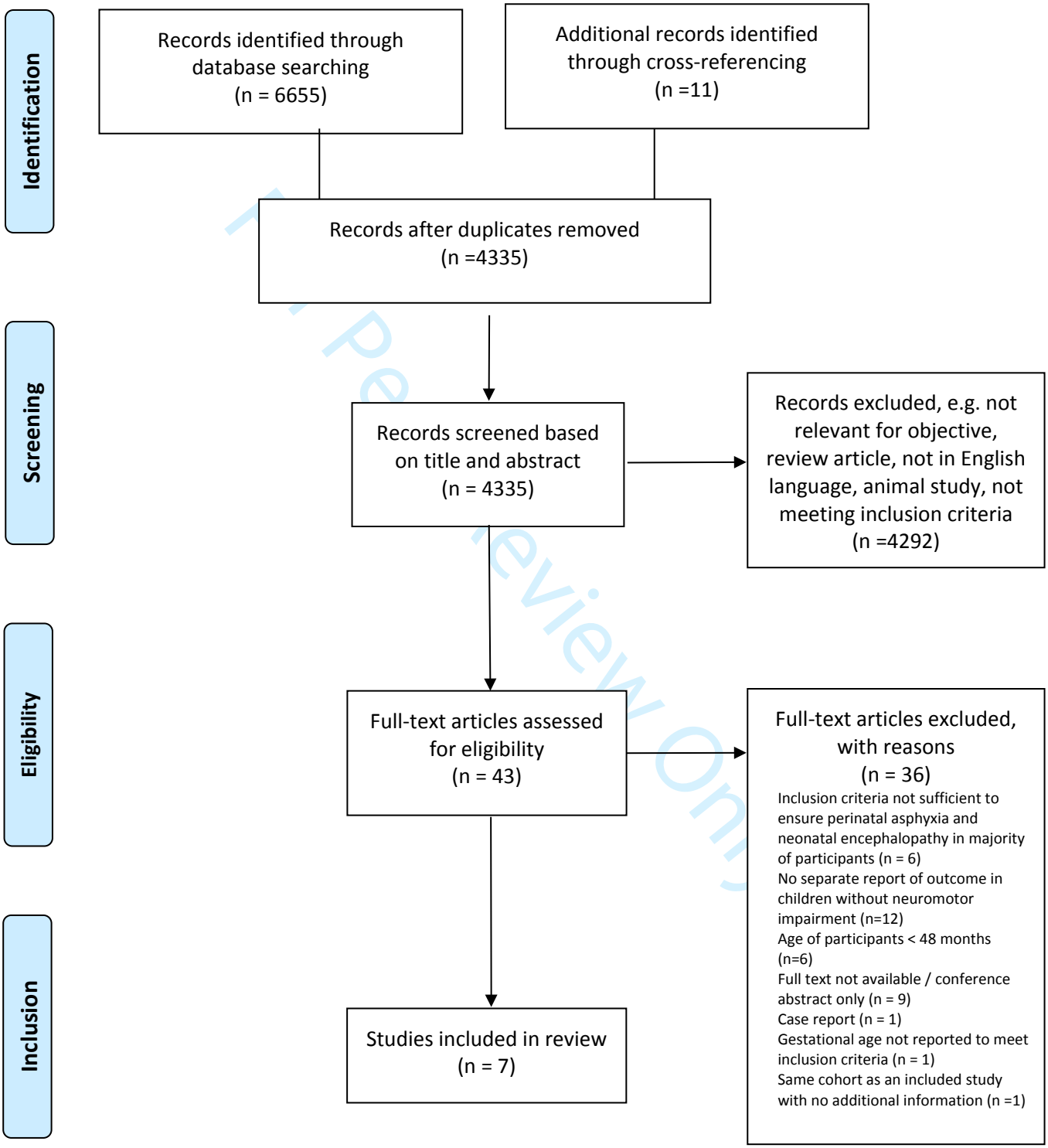
8. Same rate for both groups (+), Non respondents described or rate different and no designation (-)

Figure Legends

Figure 1: Flow diagram of review process

Figure 2: IQ compared to controls in mild, moderate and severe HIE without CP

Figure 1: Flow diagram of review process



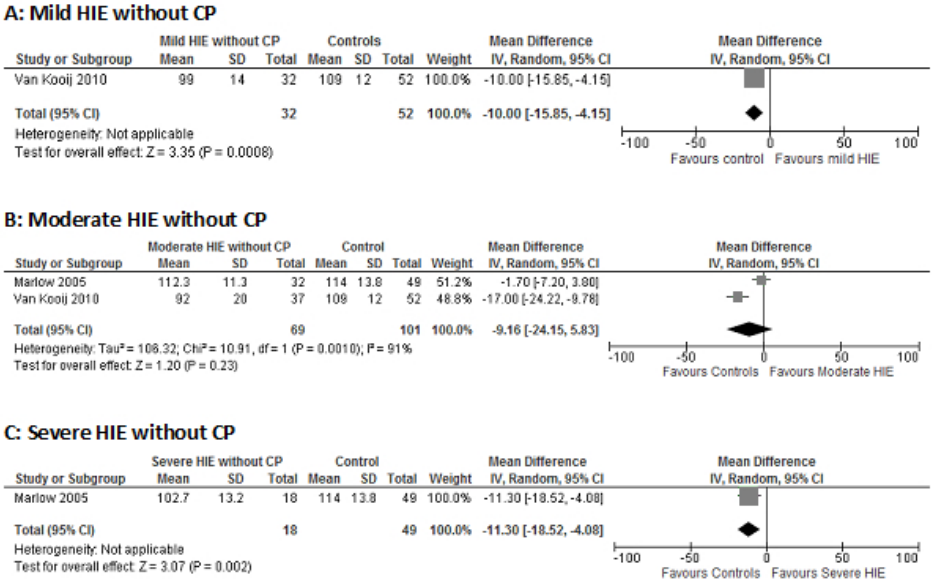


Figure 2: IQ compared to controls in mild, moderate and severe HIE without CP

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53x37mm (300 x 300 DPI)

Study, year	Inclusion criteria	Exclusion criteria	Fulfilment of HIE criteria	Comment
Barnett, 2002	Apgar scores < 5 at 1 minute and clinical signs of NE in the first 48 hours after delivery (convulsions and/or signs of neurological abnormalities such as abnormal tone, poor feeding, and altered level of consciousness) Severity of NE graded according to Sarnat in first week after birth	Genetic or metabolic conditions, other neonatal complications such as septicaemia or neonatal meningitis, dysmorphic features, other clinical or brain MRI findings suggesting major congenital malformations	No	Apgar score not felt to be sufficient to meet criteria of PA; however, other causes of NE excluded and Sarnat staging used to assess severity of NE suggesting presence of NE
Hayes, 2017	HIE defined by the presence of encephalopathy with onset from birth and evidence of intrapartum or late antepartum brain hypoxia and ischemia. Biochemical evidence of multi organ injury (raised liver transaminases, creatinine, lactate dehydrogenase and creatinine phosphokinase) was used to support the diagnosis Severity of HIE graded according to Sarnat	Newborns with any primary cause for encephalopathy other than hypoxia-ischaemia.	No	No inclusion criteria defined with regards to PA
Lindstrom, 2006	Apgar score < 7 at 5 minutes and signs of moderate or severe encephalopathy on review of records Severity of NE according to Sarnat	Major malformations (with and without chromosomal aberrations), severe perinatal infections, opioid-induced depression	No	Apgar score not felt to be sufficient to meet criteria for PA; however, some other causes of NE excluded and Sarnat staging used to assess severity of NE suggesting presence of NE
Marlow, 2005	Recorded as having "neonatal seizures" or "encephalopathy" Severity of NE graded as follows: Moderate NE -presenting in first week with either seizures alone, or any two of the following lasting longer than 24 hours: abnormal consciousness, difficulty maintaining respiration (of presumed central origin), abnormal tone and reflexes Severe NE - one of the following: ventilation for more than 24 hours; two or more anticonvulsant treatment required, comatose or stuporous	Congenital neurological abnormality, postnatal cause for encephalopathy, non-hypoxic aetiology of NE, seizures without any other evidence of encephalopathy	No	No inclusion criteria defined with regards to PA; however, non-hypoxic aetiology and postnatal causes of NE excluded
Pappas, 2015	pH ≤ 7.0 or base deficit ≥ -16 mmol/l in a sample of umbilical-cord blood or any blood during the first hour after birth * and presence of seizures or encephalopathy Encephalopathy defined as presence of one or more signs in at least three of the following categories: reduced level of consciousness, decreased level of spontaneous activity, abnormal posture, decreased tone, decreased primitive reflexes (suck, Moro), autonomic changes such as pupil, heart rate and respiration changes Severity of NE determined by number of moderate or severe signs: Moderate NE – lethargic, decreased spontaneous activity, distal flexion or complete extension, general or focal hypotonia, weak suck or incomplete Moro, constricted pupils or bradycardia or periodic breathing Severe NE – stupor or coma, no spontaneous activity, decerebrate posture, flaccid tone, absent suck or Moro, deviated, dilateted, or nonreactive pupils or variable heart rate or apnoe * If a pH was between 7.01 and 7.15, a base deficit was between 10 and 15.9 mmol/l, or a blood gas was not available in the interval, additional criteria were required, including an acute perinatal event (e.g. late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, haemorrhage, or cardiorespiratory arrest) and either a 10-minute Apgar score of ≤ 5 or assisted ventilation initiated at birth and continued for at least 10 minutes.	Inability to enrol by six hours of age, major congenital abnormalities, severe growth restriction (birth weight ≤ 1800g), refusal of consent by a parent of attending neonatologist, moribund infants for whom no further aggressive treatment was planned	Yes	
Van Kooij, 2010	Admission to neonatal unit with NE and presence of at least three of the following criteria: (1) late decelerations on fetal monitoring or meconium staining; (2) delayed onset of respiration; (3) arterial cord blood pH less than 7.1; (4) Apgar score < 7 at 5 minutes; ; and (5) multiorgan failure Severity of NE graded according to Sarnat in first week after birth	Hypotonia without other signs of HIE	Yes	Criteria considered close to HIE criteria as per RCT trials; however, no information on exclusion of other causes of NE and congenital abnormalities
Van Schie, 2015	Clinical signs of NE and at least one of the following criteria: signs of intra-uterine asphyxia (late decelerations or meconium-stained amniotic fluid), umbilical cord pH < 7.10; respirator insufficiency at birth in need of mechanical ventilation; APGAR score < 5 at 5 minutes Severity of NE graded according to Sarnat	Dysmorphic syndromes, malformations, evidence of intra-uterine or perinatal infections, intracranial haemorrhage, surgical intervention in the neonatal period	Yes	Criteria considered close to HIE criteria as per RCT trials; some other causes of NE excluded

Appendix S1: Eligibility criteria of reviewed studies and fulfilment of HIE criteria based on inclusion and exclusion criteria of each study; NE: Neonatal encephalopathy; CP: cerebral palsy; PA: perinatal asphyxia

Response to reviewers

Associate Editor' Comments to the Author:
I agree with the reviewer that it would be valuable to contact Dennis Azzopardi to get his data from the TOBY study

We do understand this comment but feel we cannot do this- see comment below in response to reviewer 1.

Referee 1:
In the rebuttal they make the following statement: 'We did contact the authors of all included studies.' It is not clear to me whether they contacted the PI of the Coolcap trial and the Toby trial. As these are two very large trials, I would strongly recommend that they would do this, as this would certainly increase the value of this paper very much. I have been asked for data several times in the past myself and do not agree that they say this unusual.

I have checked with the co-authors responsible for the searches and data collection (MS, AG), and they confirm they did indeed contact the authors of the included studies. As per the comment of the other reviewer, they did in fact also contact the authors of the Coolcap trial (Prof R Guillet). This was early on in the review process before we had refined and finalised our protocol to be clear that we would exclude studies that did not specifically report outcomes for children who had survived HIE without CP. It was as a result of this early work that we refined and finalised our protocol (there was no data on outcomes of HIE survivors without CP for CoolCap), as it would clearly not be possible to contact the authors of any study on HIE over the past few decades on the chance they had data specifically for HIE children without CP. According to the final iteration of our protocol, clearly, in retrospect, we should in fact not have contacted Prof Guillet as the Coolcap study was ineligible (however this was done early in the process as part of our testing of the includable papers and available data). As per our previous response, we did not contact the authors of the TOBY trial as it did not meet the inclusion criteria. We could not have selectively chosen the bigger trials and not contacted the authors of all excluded trials at that point, as this would have not been appropriate or in accordance with accepted systematic review practice.

Methods, please correct the word PROSPERO Page 9, line 3 is not correct: In figure 3 of the paper by van Kooij 2010, it is shown that both the mild HIE group AND the moderate HIE group are doing significantly worse than the controls. They do say it themselves in a correct way in the discussion on page 15. Line 8, line 15, why use the word 'suggest' when it is shown to be significant in figure 3?

We thank the reviewer for picking this up. The spelling error on page 9 has now been correct and the phrase relating to the Van Kooij paper in the discussion, has now been amended from 'which would suggest' to 'demonstrating' to make a firmer pint (page 16 line 9)

Referee 2:
Systematic Review: Long-term cognitive and behavioural outcomes of neonatal hypoxic-ischaemic encephalopathy in children without cerebral palsy

I appreciate the effort of authors for their revision. There are few more queries which needs addressing.
Comments:

1. Abstract: "including 40% who were treated with therapeutic hypothermia". How did the authors arrive at this 40%. Total children without CP in this review is 352, cooled children 53: 15%.

We agree with the reviewer that this is confusing, so have removed it from the abstract.

2. "at increased risk of general and/or specific cognitive impairments, irrespective of hypothermia treatment." Please see the comment below

Again, the comment relating to hypothermia had been removed as this is not clear from the data.

3. Patients and Methods:
Study design: "The review protocol was registered on PROPSERO (CRD42015027808)." In line with research ethics, the authors should leave the word prospectively with the year when it was registered. Please add the date of amendment and the details of amendment. Although this protocol violation is cited as an oversight, it is important to be published.

This has been done (page 6)

4. Inclusion criteria:
"However, only studies where hypoxia-ischaemia was considered as the cause of encephalopathy in the majority of patients were included."

How did the authors define that hypoxia-ischaemia was the cause of encephalopathy? Additionally, in Appendix S1, what is the HIE criteria?

To be included, studies had to specifically state they were investigating outcomes in infants with HIE. However, studies were only included where the inclusion and exclusion criteria were considered sufficient to suggest hypoxia-ischaemia as the cause of encephalopathy in the majority of patients. Accepted definitions of HIE were those which included a marker of perinatal asphyxia (such as metabolic acidosis within the first hour after birth, low Apgar scores at 5 minutes or beyond, history of an acute perinatal event and the need for prolonged resuscitation or ventilation) together with signs of encephalopathy and/or seizures, or meeting the criteria laid out by Sarnat for HIE grading. These were the criteria used in the studies and in table S1. Some text has been added on pages 5 and 6 to make this clearer.

5. Study selection: Who was involved in the third party consensus? How many disagreements occurred? How was it resolved?

Dr Johnson was involved in the third party consensus. There were none that required his involvement, as all queries were resolved by discussion between Drs Schreglmann and Ground. The text on page 7 has been amended to make this clearer.

6. Results:
Study selection and characteristics:
Why is the detail of sibling controls for the cohort study not reflected in Table 3?

This is a good point. Table 3 has been amended to reflect this. Lindstrom 2006 now has a '+' for comparability of controls, as these children were from the same family. They were significantly younger than the cases however, and no statistical adjustment was made for differences in age and gender.

7. Page 9: “In addition, looking at the individual results it can be seen that Van Kooij et al found a significant difference in the moderate HIE group compared to controls, and that this difference was more marked when compared to the that seen between mild HIE and controls.”
Please rephrase this sentence. Currently it is not clear.

This has been amended so that it now says: “In addition, looking at the individual results it can be seen that in the study by Van Kooij et al a significant difference was found between the moderate HIE group and the controls, and that this difference was more marked than that seen between mild HIE and controls.”

8. Page 10: “Pappas et al performed a secondary analysis from data of the large NICHD RCT on whole-body hypothermia(6, 27), demonstrating relatively high rates of low FSIQ scores in all 86 children with HIE without CP, irrespective of treatment (FSIQ score <84 in 40% and <70 in 9%, respectively).”

This is misleading and incorrect. The proportions in the cooled and non-cooled arm should be given. Was this study powered (cooled n= 53, non-cooled n=33) to detect the difference in proportion of children with IQ< 85 between hypothermia and normothermia? If one does post hoc power analysis to detect a significant difference at an alpha of 0.05, the study will have only around 10% power. The way the data is presented here is cooling vs non-cooling. I think what the authors are indicating is comparing the proportion of cooled children with IQ < 85 to the expected proportion in the population using the test norm. Please change this in the results and abstract.

This is a very good point which we agree with. The text has been amended to read: “Pappas et al performed a secondary analysis from data of the large NICHD RCT on whole-body hypothermia(6, 27), demonstrating relatively high rates of low FSIQ scores in all 86 children with HIE without CP. In those children who underwent therapeutic hypothermia, 43% had an FSIQ <84, while 36% of the normothermia group had an FSIQ <85, though this study was not powered to detect differences between treatment arms in children without CP.” The comment relating to cooling has been removed from the abstract (see above)

9. Page 10: “Significant differences were seen in the overall behavioural scores (p=0.002) and hyperactivity/inattention subscale scores (p<0.001).
Please clarify here between which groups?

The differences were seen between the moderate HIE group and normal comparators. The sentence has been rephrased to make this clearer (page 12).

10. Page 10: while differences between moderate NE and comparisons remained statistically insignificant.”
Moderate NE and what comparisons?

We agree that this sentence is confusing and is not adding to the picture, so it has been removed.

11. “revealed more problematic behaviour than parental responses, with significant differences to the comparison groups in the total behavioural scores (p<0.001), emotional problems (p=0.01), hyperactivity/inattention (p≤0.001), pro-social behaviour (p=0.02), and impact on everyday functioning (p≤0.001).”

Please clarify: “with significant differences to the comparison groups” what comparisons are these ? and in which groups of children severe or moderate?

This has again been amended to make this clearer (page 12)

12. "Results were compared to a group of 15 siblings, demonstrating significant differences between the NE group and the comparison sibling group on both the Connors scale ($p<0.003$) and the Inattention subscale of the ADHD Rating Scale IV ($p<0.006$), indicating a higher risk for attention problems and ADHD in the group of children with NE."

Does Lindstrom et al really present data showing that children with encephalopathy have a higher risk of

ADHD. ADHD is not diagnosed based only on parental questionnaire. This is incorrect.

This is a fair point, as this is not evidence of cause and effect here, especially given the use of parental questionnaires and interviews. We have therefore amend end of the sentence so it now reads: "…..demonstrating significant differences between the NE group and the comparison sibling group on both the Connors scale (p<0.003) and the Inattention subscale of the ADHD Rating Scale IV (p<0.006), indicating a higher risk for perceived attention problems in the group of children with NE."

13. Page 12: Discussion: ". Of note, most school-age follow-up studies have been conducted prior to the introduction of TH; thus data on long-term cognitive or behavioural outcomes in children with a history of TH for neonatal HIE without neuromotor impairments remain sparse."

This conclusion needs amending. Although school-age follow up studies were conducted in children who underwent cooling, due to the inclusion criteria of this systematic review that stipulated the data should have been published, this study was unable to report the cognitive outcomes on children cooled for NE and did not develop CP.

The comment at the start of the discussion on page 13 relating to long term outcomes in TH has been removed as it was not needed at this opening point of the discussion, and we agree with the reviewer's view that this is not correct given the limitations of this review.

In relation to this, in the acknowledgement authors mention: "We would like to thank Professor Guillet and colleagues for providing us with their study data; unfortunately the findings could not be included in the systematic review as we were not able to obtain cognitive results in the absence of neuromotor impairment." I assume this refers to reference 16. If it is, then this unfortunately is inconsistent with the author's response for not contacting the TOBY investigators. While the "CoolCap" and "TOBY" trial school age follow up did not satisfy the inclusion criteria of this paper (i.e neither paper published the outcomes separately for children without CP), I am not sure how the authors can justify contacting one set of investigators and not others. The author's response to the previous comments did not address this. Please can this be adequately addressed.

This is a fair point which requires further explanation. Please see response to reviewer 1 above

14. Through out the manuscript, the term NE and HIE is used interchangeably. For example in page 14, "more readily in children with HIE without CP": These studies did not fulfil the authors criteria for HIE (appendix S1), then why do they use the term HIE here? Furthermore, if four of the included studies did not fulfil the HIE criteria, then should the data on children with NE and children with HIE not be synthesized separately? Why were they combined?

This is a good point. We have now stated on page 6 that "It is important to point out that there is a considerable variability in the definition of and use of the terms HIE/NE/PA across the studies. For consistency throughout this review, the term HIE has been used, replacing NE where it occurs"

15. Fig 1: Eligibility: how did the authors get 41 papers after screening? 4335-4182= 153. There should be 153 articles. Furthermore excluded full text articles add up to 36 and not 34. This will leave only 5 articles for review.

This is an error where the flow diagram had not been fully updated at each iteration and repeat of the searches. It has been amended so that so the number are now correct and add up.

Editorial Office's Comments to Author:
Please note that Key Notes for Acta Paediatrica should total no more than 70 words and authors are encouraged to use this word count as fully as possible. They should comprise three, single sentence bullet points that summarise: 1) why the study was needed 2) what it found and 3) further findings or the implications for clinical practice or further research. Please amend your current Key Notes to 3 sentences instead of 4.

This has been done