Socioemotional and Psychological Outcomes of Hypoxic-Ischemic Encephalopathy: A Systematic Review

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BACKGROUND AND OBJECTIVES: Therapeutic hypothermia has reduced the risk of death or major disability following perinatal hypoxic-ischemic encephalopathy (HIE); however, many children who experience perinatal HIE still go on to develop personal and behavioral challenges, which can be difficult for caregivers and a public health burden for society. Our objective with this review is to systematically identify and synthesize studies that evaluate associations between perinatal HIE and socioemotional or psychological outcomes.

METHODS: We screened all search-returned journal articles from Cochrane Library, Embase, Medline, PsycINFO, Scopus, and Web of Science from data inception through February 1, 2023. Keywords related to HIE (eg, neonatal encephalopathy, neonatal brain injury) and outcomes (eg, social, emotion, behavioral, and psychological deficits throughout infancy, childhood, and adolescence) were searched with a predefined search string. We included all observational human studies reporting socioemotional or psychological sequelae of term HIE. Study data were recorded on standardized sheets, and the Newcastle-Ottawa Scale was adapted to assess study quality.

RESULTS: We included 43 studies documenting 3244 HIE participants and 2132 comparison participants. We found statistically significant associations between HIE and social and emotional, behavioral, and psychological deficits throughout infancy, childhood, and adolescence (19 studies). The authors of the included studies also report nonsignificant findings (11 studies) and outcomes without statistical comparison (25 studies).

CONCLUSIONS: Perinatal HIE may be a risk factor for a range of socioemotional and psychological challenges in the short- and long-term. Routine screening, early intervention, and follow-up support may be particularly beneficial to this population.

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Neonatal encephalopathy (NE) is disturbed neurologic function in term infants characterized by difficulty initiating and maintaining respiration, depression of tone and reflexes, subnormal levels of alertness, and often seizures. The most common cause of NE is lack of oxygen and blood flow to the brain during the perinatal period, usually referred to as hypoxic-ischemic encephalopathy (HIE), which can lead to life-long morbidities or death. The overall incidence of NE is estimated at 3 per 1000 live births and is even higher in low- and middle-income countries.

Neonates with suspected HIE are classified according to the Sarnat staging system as stage I (mild), stage II (moderate), or stage III (severe). A modified version of this system is used to identify infants that may benefit from therapeutic hypothermia (TH) after birth, which has been shown to reduce the risk of death or major disabilities following moderate or severe HIE; however, improvement of holistic outcomes has been modest. Understanding the burden of HIE is important to support the development of targeted interventions and to ensure that those with HIE receive appropriate follow-up care.

Studies of disability after HIE have focused on motor or cognitive deficits. However, rodent models associate HIE with social, emotional, and psychological dysregulation, including hyperactive, antisocial, anxiety-like, and aggressive behaviors. In parallel, the authors of a growing body of research have reported disrupted psycho-socio-emotional development after human HIE throughout infancy, childhood, and adulthood. In this systematic review, we aimed to synthesize studies that reveal associations between HIE and social, emotional, or psychological functioning.

**METHODS**

We followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses and preregistered this review via PROSPERO, an international database of prospectively registered systematic reviews (ID: CRD42021267939). Keywords related to HIE or NE and relevant outcomes were searched with a predefined search string (Supplemental Fig 2). We searched for studies referring either to HIE or to NE after hypoxic ischemia, as many authors use these terms interchangeably. Relevant outcome measures were (1) responses to social, emotional, or psychological stimuli, (2) scores on standardized social, emotional, or psychological assessments, (3) scores on social, emotional, or psychological questionnaires, (4) referral to psychology, psychiatry, or other mental health services, and (5) symptoms or diagnosis related to social, emotional, or psychological functioning.

We retrieved records from Cochrane Library, Embase, Medline, PsycINFO, Scopus, and Web of Science (Supplemental Fig 3) from data inception through July 22, 2021 (original search), August 18, 2022 (first rerun search), and February 1, 2023 (second rerun search). With Rayyan, duplicates were manually removed, and titles and abstracts were blindly screened by 2 of 3 authors (GHK, HP, SN) until a consensus was reached. Reports were excluded if they were written in a non-English language, not a journal article, not reporting measures for the correct population or cohort, or not reporting measures relevant to the review. We included observational human studies reporting social, emotional, or psychological sequelae of term HIE/NE (Supplemental Fig 4) and screened included studies’ reference lists.

Study data were recorded on standardized data collection sheets. Because of the heterogeneity of studies, a meta-analysis could not be performed. The quality of studies was critically appraised with adapted versions of the Newcastle-Ottawa Scale by 2 of 4 authors (HP, SN, HW, TA), with discrepancies resolved by a third author (GHK; Supplemental Figs 5–7).

**RESULTS**

**Study Selection and Critical Appraisal**

Of 3340 distinct records screened, 3103 were excluded, and 237 were retrieved and assessed for eligibility. We include 43 studies, published between 1998 and 2022, documenting 3244 participants with HIE/NE and 2132 non-HIE/NE comparison participants (Table 1). Of these, 22 are cohort studies (8 prospective, 14 retrospective), 20 are case series studies (13 prospective, 5 retrospective, 2 mixed), and 1 is a case-control study (retrospective). The studies are predominantly based in Europe (25/43) or North America (7/43), with few in Asia (5/43), Australia (3/43), or mixed regions (1/43). Of the 43 included studies, 21 administered TH after birth to eligible infants with HIE/NE, 6 were rated as low-quality, 32 were rated as medium-quality, and 5 were rated as high-quality (Tables 2–4). Studies reported a wide range of relevant outcome measures, which we categorized into social and emotional outcomes, behavioral outcomes, and psychological and psychiatric outcomes.

**Social and Emotional Outcomes**

The authors of 21 studies reported social, personal-social, socioemotional, emotional, or related outcomes, documenting participants from birth to 12 years of age (Fig 1). Of these studies, 6 reported significant associations between deficits and presence and severity of HIE (2/6 administered TH; 3/6 were rated as low-quality; and 3/6 were rated as medium-quality or high-quality), 4 reported nonsignificant differences (2/4 administered TH; 1/4 was rated as low-quality; and 3/4 were rated as medium-quality), and 12 reported HIE outcome scores or ranges without statistical comparison (Fig 1).
<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>Design</th>
<th>Location</th>
<th>Relevant Measures</th>
<th>Population and Sample Size</th>
<th>Relevant Results</th>
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<tbody>
<tr>
<td>Robertson and Finer&lt;sup&gt;15&lt;/sup&gt; (1998)</td>
<td>Psychosocial follow-up of mild/moderate NE due to birth asphyxia with- out disability</td>
<td>Prospective cohort study</td>
<td>Alberta, Canada</td>
<td>DRSH, caregiver-reported behavior problems (see article Table 6 for subscales)</td>
<td>Nondisabled mild/moderate NE groups (without hypothermia) and non-NE tertiary-care survivor comparison group at 5.5 y</td>
<td>M ± SD of overall DRSH, scored from 6 to 98, with higher score indicating more behavior problems (see article Table 6 for subscale results): mild NE group: 19.4 ± 3.4, moderate NE group: 20.8 ± 4.4, comparison group 19.1 ± 3.1 (significant differences, $P &lt; .05$)</td>
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<td>Dixon, Badawi, Kurinczuk, et al&lt;sup&gt;62&lt;/sup&gt; (2006)</td>
<td>Neurodevelopmental follow-up of moderate/severe NE</td>
<td>Retrospective cohort study (population-based)</td>
<td>Western Australia</td>
<td>GMDS: personal-social DQ</td>
<td>Moderate/severe NE group (without hypothermia) and non-NE comparison group at 1 y</td>
<td>M of GMDS personal-social DQ (normative M ± SD = 100 ± 13, higher score = increasing ability): NE group: 104.8, comparison group: 111.5; non-cerebral palsy NE group: 107.1, non-cerebral palsy comparison group: 111.5 (significant difference, $P &lt; .001$); non-cerebral palsy, no other medical conditions NE group: 108.0, non-cerebral palsy, no other medical conditions comparison group: 111.5 (significant difference, $P &lt; .01$)</td>
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<td>Moster, Lie and Markestad&lt;sup&gt;63&lt;/sup&gt; (2002)</td>
<td>Neurodevelopmental follow-up of 5-minute Apgar score and symptoms of NE</td>
<td>Retrospective cohort study (population-based)</td>
<td>Norway</td>
<td>YCS (with additional questionnaire): caregiver-reported behavior problems (see article Table 5 for subscales)</td>
<td>Groups with varying 5-minute Apgar scores (without hypothermia) at 8–13 y</td>
<td>YCS behavior problems (see article Table 5 for subscale results): problems with tractability, aggressivity, passivity, and anxiety increased with the presence of symptoms of NE ($P &lt; .005$) Compared with group with Apgar score range 7–10 without symptoms of NE, group with Apgar score range 7–10 with symptoms of NE was 6.6 times more likely to have an ADHD-related diagnosis (see article Table 2 for full ADHD-related diagnosis results) and 22 times more likely to have experienced referral to a psychologist (see article Table 2 for full psychologist referral results)</td>
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<td>Barnett, Guzzetta, Mercuri, et al&lt;sup&gt;28&lt;/sup&gt; (2004)</td>
<td>Examination of predictive value of early developmental testing for identifying school-age impairment after NE</td>
<td>Prospective case series study</td>
<td>London, United Kingdom</td>
<td>GMDS: personal-social DQ</td>
<td>NE group (without hypothermia) at 1 y and/or 2 y: 1 y (n = 58), 2 y (n = 45)</td>
<td>M ± SD of GMDS personal-social DQ, (normative M ± SD = 100 ± 13, higher score = increasing ability): 1 y: 102.73 ± 14.00 (5 in NE group ≥1 SD below M; 2 y: 106.87 ± 13.87 (3 in NE group ≥1 SD below M)</td>
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<td>Marlow, Rose, Rands, et al&lt;sup&gt;7&lt;/sup&gt; (2005)</td>
<td>Neurodevelopmental follow-up of moderate/severe NE without motor disability</td>
<td>Retrospective cohort study</td>
<td>Former Trent region, United Kingdom</td>
<td>SDQ: caregiver-reported behavior problems (see article Table 4 for subscales)</td>
<td>Nondisabled moderate/severe NE group (without hypothermia) and matched non-NE classmate comparison group at 7 y</td>
<td>SDQ (see article Table 4 for subscale results and children in the normal, borderline clinical, and clinical total score ranges): Caregiver-reported behavior problems total difficulties: fewer “normal” range children in severe NE group than in moderate NE ($P = .05$) or comparison ($P = .02$) groups Teacher-reported behavior problems</td>
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TABLE 1 Study Characteristics

- M: Mean
- SD: Standard Deviation
- GMDS: Gesell Developmental Scales
- SDQ: Strengths and Difficulties Questionnaire
<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>Badawi, Dixon, Felix, et al. (2006); draws from same cohort as Dixon, Badawi, Kurniawati, et al. (2002)</td>
<td>Evaluation of association between moderate/severe NE and ASD</td>
<td>Retrospective cohort study</td>
<td>Western Australia</td>
<td>Likelihood of diagnosis of ASD</td>
<td>(n = 16), teacher-reported SDQ (n = 19) comparison group (n = 49); completed caregiver-reported SDQ (n = 48), teacher-reported SDQ (n = 44)</td>
<td>Moderate/severe NE group (without hypothermia) and non-NE comparison group at 5 y NE group (n = 28) Comparison group (n = 56) NE group was 5.9 (95% CI: 2.0-16.9) times more likely to be diagnosed with ASD than comparison group, NE group: 12/259 ASD comparison group: 5/563 ASD</td>
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<td>Lindstrom, Lagerroos, Gilberg, et al. (2006)</td>
<td>Neurodevelopmental follow-up of moderate NE without cerebral palsy</td>
<td>Retrospective cohort study</td>
<td>Sweden</td>
<td>Asperger Syndrome Screening Questionnaire: caregiver-reported: ASD-related traits</td>
<td>Non-cerebral palsy moderate NE group (without hypothermia) and non-NE sibling comparison group NE group (n = 29), age range: 15-19 y Comparison group (n = 15), age range: 10-17 y</td>
<td>ASD-related traits rating: significant difference between NE and comparison groups, with more traits in NE group, P &lt; .003 ADHD-related traits rating: significant difference between NE and comparison groups for inattention (but not hyperactivity/impulsivity) subscale, with more inattention in NE group, P &lt; .006</td>
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<td>Al-Macki, Miller, Hall, et al. (2009)</td>
<td>Neurodevelopmental follow-up of moderate/severe NE due to birth asphyxia</td>
<td>Retrospective case series study</td>
<td>Montreal, Quebec, Canada</td>
<td>DSM-IV classification of ASD or ADHD</td>
<td>Non-cerebral palsy moderate/severe NE group without hypothermia at 2-16 y (n = 17)</td>
<td>BSIM-IV classification: 1/17 ASD, 5/17 ADHD</td>
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<td>van Handel, Swaab, de Vries, et al. (2010)</td>
<td>Behavioral and psychiatric follow-up of mild/moderate NE due to birth asphyxia</td>
<td>Retrospective cohort study</td>
<td>Utrecht, Netherlands</td>
<td>CBQ: caregiver-reported social problems (see article Table 1 for subscales)</td>
<td>NE group (without hypothermia and matched non-NE peer comparison group at 9-10 y NE group (n = 81): mild NE group (n = 34), completed TRF (n = 33), completed CBCL (n = 33), completed CSBQ (n = 33), completed DISC-IV (n = 31); moderate NE group (n = 47), completed TRF (n = 47), completed CBCL (n = 47), completed CSBQ (n = 46), completed DISC-IV (n = 47) Comparison group (n = 53); completed TRF (n = 45), completed CBCL (n = 53), completed CSBQ (n = 53), completed DISC-IV (n = 53)</td>
<td>M ± SD of CBQ total social problems (higher score = more problems) (see article Tables 2-3 for full results): mild NE group: 51.4 ± 11.7, moderate NE group: 54.6 ± 8.1, comparison group: 54.7 ± 6.4 (significant differences, P = .003) M ± SD of TRF and CBCL (normative M ± SD = 50 ± 10, higher score = more problems) (see article Tables 1-2 for subscale results): TRF behavior problems: mild NE group: 54.2 ± 7.0, moderate NE group: 52.7 ± 6.7, comparison group: 47.0 ± 7.0 (no significant differences, P = .03) DISC-IV DSM-IV classification (see article Table 3 for diagnosis incidence): no differences between mild NE, moderate NE, and comparison groups</td>
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<td>Martinez-Biarge, Bregant, Wusthoff, et al. (2012)</td>
<td>Evaluation of association between white matter (WM) injury (normal basal ganglia/thalamus) on</td>
<td>Retrospective case series study</td>
<td>London, United Kingdom</td>
<td>GMDS: social DQ Presence of behavior problems (including inattention, hyperactivity, anxiety, autistic type behavior, and aggression)</td>
<td>HIE group (without hypothermia) at 1.1-4 y Normal/mild WM injury (n = 28): behavioral data (n = 28), completed GMDS (n = 22) Moderate WM injury (n = 34)</td>
<td>M ± SD of GMDS social DQ (normative M ± SD = 100 ± 13, higher score = increasing ability): normal/mild WM injury: 114.3 ± 15.3, moderate WM injury: 108.5 ± 129, severe WM injury: 96.1 ± 23.7 (significant differences, P = .003)</td>
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<td>Shankaran, Pappas, McDonald, et al. (2012); draws from same cohort as Pappas, Shankaran, McDonald, et al. (2015)</td>
<td>Neurodevelopmental follow-up of therapeutic hypothermia and normothermia groups from NICHD trial (Shankaran, Laptook, Ehrenkranz, et al.)</td>
<td>Prospective cohort study (follow-up of randomized controlled trial)</td>
<td>Centers throughout United States</td>
<td>Questionnaire of child’s caregiver-reported self-esteem (“child’s satisfaction with his/her life”) and emotional impact (“worry caused by child’s emotional well-being or behavior”)</td>
<td>Moderate/severe HIE group at 6-7 y Hypothermia group (n = 78): completed self-esteem question (n = 67) emotional impact question (n = 67) Normothermia group (n = 52): completed self-esteem question (n = 48), emotional impact question (n = 50)</td>
<td>Self-esteem: hypothermia group 49/65 very, 11/65 somewhat, 5/65 neutral; normothermia group 53/66 very, 11/66 somewhat, 0/66 neutral Emotional impact: hypothermia group 33/87 none, 13/67 a little, 8/67 some, 4/67 quite a bit, 9/67 a lot; normothermia group 17/50 none, 10/50 a little, 8/50 some, 7/50 quite a bit, 8/50 a lot</td>
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<td>Tusor, Wysotthof, Sne, et al. (2012)</td>
<td>Evaluation of association between diffusion tensor imaging and HIE neurodevelopmental outcomes</td>
<td>Prospective case series study</td>
<td>London, United Kingdom</td>
<td>GMDS, revised personal-social Q</td>
<td>HIE group (with hypothermia) at 1-2 y (n = 52): cerebral palsy (n = 2)</td>
<td>M ± SD of GMDS personal-social Q (normative M ± SD = 100 ± 13, higher score = increasing ability): 100 ± 24, residuals of personal-social scores significantly correlated with white matter fractional anisotropy values from diffusion tensor imaging (R² = 0.326)</td>
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<td>Azopardi, Strom, Marlow, et al. (2014); draws from same cohort as Campbell, Eddama, Azopardi, et al. (2018)</td>
<td>Neurodevelopmental follow-up of therapeutic hypothermia and normothermia groups from TOBY trial (Azopardi, Brocklehurst, Edwards, et al.)</td>
<td>Prospective cohort study (follow-up of randomized controlled trial)</td>
<td>Centers throughout United Kingdom</td>
<td>ADHD Rating Scale-IV, caregiver-reported ADHD-related traits ADHD Rating Scale-IV, teacher-reported ADHD-related traits</td>
<td>Moderate/severe HIE group at 6-7 y Hypothermia group (n = 98): completed caregiver-reported ADHD Rating Scale-IV (n = 88), completed teacher-reported ADHD Rating Scale-IV (n = 84), teacher-naive ADHD Rating Scale-IV (n = 83) Normothermia group (n = 96): completed caregiver-reported ADHD Rating Scale-IV (n = 58) completed teacher-reported ADHD Rating Scale-IV (n = 56)</td>
<td>Moderate/severe HIE group at 6-7 y Hypothermia group (n = 98): completed caregiver-reported ADHD Rating Scale-IV (n = 88), completed teacher-reported ADHD Rating Scale-IV (n = 84), teacher-naive ADHD Rating Scale-IV (n = 83) Normothermia group (n = 96): completed caregiver-reported ADHD Rating Scale-IV (n = 58) completed teacher-reported ADHD Rating Scale-IV (n = 56)</td>
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<td>Zubcevic, Heljin, Spahovic, et al. (2014); draws from same cohort as Zubovec, Heljin, Catbusic, et al. (2015)</td>
<td>Neurodevelopmental follow-up of moderate/severe HIE</td>
<td>Prospective case series study</td>
<td>Sarajevo, Bosnia, and Herzegovina</td>
<td>ASQ: caregiver-reported personal-social skills/development</td>
<td>Moderate/severe HIE group (with hypothermia) at 4-56 mo (n = 28), completed ASQ-3 (n = 19)</td>
<td>ASQ-3 personal-social skills/development range: 15/19 normal, 5/19 abnormal, 1/19 needs retesting</td>
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<td>Pappas, Shankaran, McDonald, et al. (2015); draws from same cohort as Shankaran, Pappas, McDonald, et al. (2012)</td>
<td>Neurodevelopmental follow-up of therapeutic hypothermia and normothermia groups from NICHD trial (Shankaran, Laptook, Ehrenkranz, et al.)</td>
<td>Prospective cohort study (follow-up of randomized controlled trial)</td>
<td>Centers throughout United States</td>
<td>BSID Behavior Rating Scale Presence of behavior problems (&lt;10th percentile) or questionable problems (11th-25th percentile); presence of behavior problems from caregiver-reported CBCL or school services (see article Suppl. Table 8 for details)</td>
<td>Moderate/severe HIE group at 18-22 mo and/or 6-7 y Hypothermia group (n = 63): completed BSID-2 at 18-22 mo (n = 52), completed CBCL at 6-7 y (n = 60) Normothermia group (n = 47): completed BSID-2 at 18-22 mo (n = 38), completed CBCL at 6-7 y (n = 47)</td>
<td>BSID 2 behavior problems at 18-22 mo (see article Suppl. Table 8 for details): hypothermia group: 11/52 with behavior problems, 8/32 with “questionable problems”; normothermia group: 12/38 with behavior problems, 5/38 with “questionable problems” CBCL or social services presence of behavior problems at 6-7 y (see article Suppl. Table 8 for details): hypothermia group: 4/90 with behavior problems; normothermia group: 4/47 with behavior problems</td>
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<td>van Schie, Schijns, Becher, et al (2015)</td>
<td>Evaluation of association between pattern of injury on neonatal MRI and mild/moderate HIE neurodevelopmental or health-related quality of life</td>
<td>Prospective case series study</td>
<td>Amsterdam, Netherlands</td>
<td>TACQOL: caregiver-reported health-related quality of life</td>
<td>Mild/moderate HIE group (without hypothermia) at 6-8 y (n = 25) Mild HIE (n = 6), moderate HIE (n = 19)</td>
<td>TACQOL health-related quality of life, non-cerebral palsy HIE group: no differences between HIE group and reference sample on any of the seven subscales (Ps &gt; 0.05)</td>
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<td>CBCL: caregiver-reported behavior problems (see article Table 2 for subscales)</td>
<td>Non-cerebral palsy (n = 17), cerebral palsy (n = 9)</td>
<td>Diagnoses of HIE group (without hypothermia) at 6-8 y (n = 25) Non-cerebral palsy (n = 17), cerebral palsy (n = 9) MRI normal (n = 10), abnormal basal ganglia (n = 2), abnormal cortex (n = 4), abnormal basal ganglia and cortex (n = 9)</td>
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<tr>
<td>Zubcevic, Heljic, Catibusic, et al (2015)</td>
<td>Neurodevelopmental follow-up of moderate/severe HIE</td>
<td>Prospective case study</td>
<td>Sarajevo, Bosnia, and Herzegovina</td>
<td>ASQ: caregiver-reported personal-social skills/development</td>
<td>Moderate/severe HIE group (with hypothermia) at 5-6, 12-18, and/or 24-36 mo (n = 19) Completed ASQ-3 at 3-6 mo (n = 19) 12-18 mo (n = 17), 24-36 mo (n = 14)</td>
<td>ASQ-3 personal-social skills/development: range, 3-6 mo: 13/19 normal, 3/19 abnormal, 2/19 others MRI normal (n = 10), abnormal (n = 2), abnormal basal ganglia (n = 3), abnormal cortex (n = 9) Diagnoses of HIE group (without hypothermia) at 3-6 mo; 12-18 mo; 24-36 mo (n = 19) 12-18 mo: 11/17 normal, 3/17 abnormal, 5/17 needs retesting, range, 24-36 mo: 8/14 normal, 3/14 abnormal, 3/14 needs retesting</td>
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<td>Hayes, Ryan, McGarvey, et al (2016)</td>
<td>Evaluation of association between pattern of injury on neonatal MRI and HIE neurodevelopmental outcomes</td>
<td>Mixed prospective/retrospective case series study</td>
<td>Dublin, Ireland</td>
<td>Diagnosis of ASD</td>
<td>HE group (without hypothermia; n = 237) at childhood age; underwent MRI (n = 89) “Normal” (n = 38), assessment data (n = 21); “basal ganglia/thalamus” (n = 13), assessment data (n = 10); “watershed” (n = 9), assessment data (n = 4); “mixed” (n = 14), assessment data (n = 8), “other” (n = 14), assessment data (n = 14)</td>
<td>Observed pattern of injury on MRI and reported diagnosis of ASD: 0/21 of “normal” MRI pattern diagnosed with ASD, 0/10 of “basal ganglia/thalamus” MRI pattern diagnosed with ASD, 0/4 of “watershed” MRI pattern diagnosed with ASD, 0/3 of “mixed” MRI pattern diagnosed with ASD, 0/2 of “other” MRI pattern diagnosed with ASD</td>
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<td>Murray O’Connor, Ryan, et al (2016)</td>
<td>Evaluation of association between neonatal EEG grade and HIE neurodevelopmental outcomes</td>
<td>Prospective case series study</td>
<td>Cork, Ireland</td>
<td>Diagnosis of ASD or ADHD</td>
<td>HE group (without hypothermia) at 5 y (n = 7); mild HIE (n = 22), moderate HIE (n = 19), severe HIE (n = 6); neonatal EEG recorded at 6 and/or 24 h (n = 47)</td>
<td>Diagnosis of ASD or ADHD: 1/47 diagnosed with ASD (mild HIE, no EEG at 6 h, mild EEG impairment at 24 h); 2/47 diagnosed with ADHD (1 with mild HIE and mild EEG impairment at 6 and 24 h, 1 with moderate HIE and moderate EEG impairment at 6 and 24 h)</td>
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<td>Wang Xu, Wang, et al (2016)</td>
<td>Evaluation of potential biomarker for ASD diagnosis</td>
<td>Retrospective case-control study</td>
<td>Wuhan, China</td>
<td>Incidence of HIE in case and control groups with/without ASD diagnosis</td>
<td>ASD case group and matched non-ASD control group at 28-45 mo Case group (n = 116): mild-to-moderate ASD (n = 91), severe ASD (n = 25) Control group (n = 116)</td>
<td>Incidence of ASD across groups with/without ASD diagnosis: 72/116 HIE in ASD case group; 8/116 HIE in non-ASD control group (significant difference, P &lt; 0.001)</td>
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<td>Adhikari and Rao (2017)</td>
<td>Neurodevelopmental follow-up of moderate HIE</td>
<td>Prospective case series study</td>
<td>Pokhara, Nepal</td>
<td>DDS1: personal-social milestones</td>
<td>Moderate HIE group (without hypothermia) at 5 mo (n = 26), at 6 mo (n = 32), at 9 mo (n = 30), at 12 mo (n = 35), at 18 mo (n = 32), at 24 mo (n = 32)</td>
<td>DDS1:2 personal-social milestones, categorized as “with social delay” or “without social delay”: 3/36 with social delay at 3 mo, 3/32 with social delay at 6 mo, 1/30 with social delay at 9 mo, 15/35 with social delay at 12 mo, 2/25 with social delay at 20 mo, 8/32 with social delay at 24 mo (significant difference, P = 0.011)</td>
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</table>
| O’Connor Ryan, Boylan, et al (2017) | Evaluation of association between early neurodevelopmental | Prospective case series study | Cork, Ireland | Diagnosis of ASD or ADHD Referral to additional | HE group (without hypothermia) at 5 y; mild HIE (n = 22), moderate HIE (n = 19), severe HIE (n = 9) | Diagnosis of ASD or ADHD: 1/47 diagnosed with ASD (mild HIE), 2/47 diagnosed with ADHD (1 with mild
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<td>Murray, O’Connor, Ryan, et al. (2016) and Halpin, McCusker, Fogarty, et al. (2022)</td>
<td>Assessment and HE neurodevelopmental outcomes</td>
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<td>Services (mental health, psychology)</td>
<td>HE, 1 with moderate HE</td>
<td>Additional services referral: 1/47 referred to child/adolescent mental health service (mild HE), 6/47 referred to psychology (4 with mild HE, 2 with moderate HE)</td>
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<td>Tan, Minutillo, McMichael, et al. (2017)</td>
<td>Evaluation of association between hypoglycemia and HE neurodevelopmental outcomes</td>
<td>Retrospective cohort study (population-based)</td>
<td>Western Australia</td>
<td>SSID: caregiver-reported socioemotional development</td>
<td>HE group (with hypothermia), with or without episodes of neonatal hypoglycemia, at 2 y Group with episodes of hypoglycemia* (n = 38): mild HE (n = 6), moderate HE (n = 23), severe HE (n = 9) Comparison group, without hypoglycemia (n = 84): mild HE (n = 24), moderate HE (n = 40), severe HE (n = 20) Hypoglycemia: blood glucose level &lt;2.6 mmol/L</td>
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<td>Campbell, Eddama, Azopardi, et al. (2018); draws from same cohort as Azopardi, Strohm, Mariow, et al. (2014)</td>
<td>Health-related quality of life follow-up of therapeutic hypothermia and normothermia groups from TOBY trial (Azopardi, Brocklehurst, Edwards, et al.)</td>
<td>Prospective cohort study (follow-up of randomized controlled trial)</td>
<td>United Kingdom</td>
<td>HUI3: caregiver-reported emotion attribute (“happy and interested in life”)</td>
<td>Moderate/severe HE group at 6-7 y Hypothermia group (n = 98): excluded for missing/unavailable (n = 23), missing HUI3 (n = 1) Normothermia group (n = 86): excluded for missing/unavailable (n = 16) HUI3 emotion attribute, scored from levels 1 to 6, with higher level indicating more severe impairment: hypothermia group: 65/74 Level 1, 11/74 Level 2, normothermia group: 50/70 Level 1, 18/70 Level 2/3, 0/70 Level 3, 1/70 Level 4, 2/70 Level 5 (no significant trend, P &gt; .05)</td>
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<td>Chalak, Nguyen, Prempunpong, et al. (2018)</td>
<td>Neurodevelopmental follow-up of mild HE</td>
<td>Prospective case series study</td>
<td>Canada (x1), United States (x3), United Kingdom (x1), Thailand (x1)</td>
<td>Diagnosis of ASD</td>
<td>Mild HE group (without hypothermia) at 18-22 mo (n = 63): completed neurodevelopmental assessment (n = 43)</td>
<td>2/43 infants with ASD diagnosis at 18-22 mo (diagnosis confirmed by developmental health care specialist at beyond 36 mo of age)</td>
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<td>Hayes, Doherty, Grehan, et al. (2018); draws from same cohort as Hayes, Ryan, McSurvey, et al. (2016)</td>
<td>Neurodevelopmental follow-up of HE without cerebral palsy</td>
<td>Mixed prospective/retrospective case series study</td>
<td>Dublin, Ireland</td>
<td>BSI:VTD: caregiver-reported developmental “other” clinical problems/behavior regulation index BRIEF: caregiver-reported behavior regulation index CBCL: caregiver-reported behavior problems, “other” clinical problems, and sleep problems (see article Table 3 for subscales)</td>
<td>Non-cerebral palsy HE group (without hypothermia) at &lt;3.5 and/or ≥3.5 y Mild HE group (n = 12) at &lt;3.5 y (n = 65): completed BSI:VTD-3 (n = 65) at ≥3.5 y (n = 49), completed BRIEF (n = 27), completed CBCL (n = 49) Moderate HE group (n = 33) at &lt;3.5 y (n = 12): completed BSI:VTD-3 (n = 12) at ≥3.5 y (n = 21), completed BRIEF (n = 13), completed CBCL (n = 17) Severe HE group (n = 11) at ≥3.5 y (n = 1): completed BSI:VTD-3</td>
<td>BSI:VTD-3 socioemotional development scaled scores (normative M ± SD = 10 ± 3, higher score = increasing ability): non-cerebral palsy HE group: 47/66 scaled score &lt;4, 12/76 scaled score 5-7, 25/76 scaled score 8-10, 35/76 scaled score ≥11 BRIEF index: caregiver-reported behavior regulation range (n = 38): 26/36 normal, 6/38 borderline clinical, 6/38 clinical; teacher-reported behavior regulation range (n = 38): 11/32 normal, 13/32 borderline clinical, 8/32 clinical CBCL behavior problems, “other” clinical problems and sleep problems (see article Table 3 for subscale results); more behavior problems, anxiety disorder, ADHD, oppositional defiant, and sleep problems in moderate HE group than in mild HE group (P &lt; 0.05)</td>
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<td>Study</td>
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<td>Population and Sample Size</td>
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<td>Kauranen and Saalhede (2020)</td>
<td>Evaluation of the association between severity of HIE and ASD symptoms</td>
<td>Retrospective case series study</td>
<td>M-CHAT, ages 1.5-5 y: caregiver-reported behavior</td>
<td>Presence of first signs of ASD-related traits, higher score indicating more ASD-related symptoms</td>
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<td>Lee-Kelland, Jary, Tonks, Cainelli, Vedovelli (2021)</td>
<td>Neuropsychological development in children born after hypothermia-related HIE</td>
<td>Retrospective cohort study</td>
<td>Median (IQR) of NEPSY-2 subtests:</td>
<td>Greater difficulties in theory of mind and social skills in HIE compared to non-HIE controls</td>
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<td>Danguscan, E Shaheed, Somers, et al (2021)</td>
<td>Evaluation of the association between severity of HIE and ASD symptoms</td>
<td>Retrospective case series study</td>
<td>M-CHAT, ages 1.5-5 y: caregiver-reported behavior</td>
<td>Presence of first signs of ASD-related traits, higher score indicating more ASD-related symptoms</td>
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<td>Edmonds, Cianfaglione, Cornforth, et al56 (2021), draws from same cohort as Edmonds, Helps, Hart, et al56 (2020) and Edmonds, Cianfaglione, Cornforth, et al56 (2021)</td>
<td>Neurodevelopmental follow-up of moderate/severe HIE without cerebral palsy</td>
<td>Retrospective cohort study</td>
<td>Southampton, United Kingdom</td>
<td>BRIEF: caregiver-reported behavior regulation index</td>
<td>Non-cerebral palsy moderate/severe HIE group (with hypothermia) and matched non-HIE comparison group at 5-7 y</td>
<td>Median (IQR) of BRIEF index (normative ± S.D) of DuPaul “Home” (caregiver-reported) ADHD rating, inattention subscale, scored from 0-27, with higher score indicating more severe symptoms: HIE group 5.18 ± 4.39, comparison group 3.27 ± 2.88 (no significant difference, P &gt; 0.05)</td>
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<td>Erdi-Krausz, Rocha, Brown, et al51 (2021), draws from same cohort as Edmonds, Helps, Hart, et al51 (2020) and Edmonds, Cianfaglione, Cornforth, et al51 (2021)</td>
<td>Neurodevelopmental follow-up of moderate/severe HIE without cerebral palsy</td>
<td>Retrospective cohort study</td>
<td>Southampton, United Kingdom</td>
<td>DuPaul ADHD Rating Scale: “Home” version (caregiver-reported) ADHD-related traits inattention subscale</td>
<td>Non-cerebral palsy moderate/severe HIE group (with hypothermia) and matched non-HIE comparison group at 5 y</td>
<td>$M \pm SD$ of DuPaul “Home” (caregiver-reported) ADHD rating, inattention subscale, scored from 0-27, with higher score indicating more severe symptoms: HIE group $5.18 \pm 4.39$, comparison group $3.27 \pm 2.88$ (no significant difference, P &gt; 0.05)</td>
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<td>Jenkins, Moss, Brown, et al51 (2021)</td>
<td>Clinical trial of administration of N-acetylcysteine and calcitriol (vitamin D) during therapeutic hypothermia for moderate/severe HIE and neurodevelopmental follow-up</td>
<td>Prospective case series study</td>
<td>Charleston, South Carolina, United States</td>
<td>M-CHAT: caregiver-reported ASD-related traits</td>
<td>Moderate/severe HIE group (with hypothermia) at 2-4 y ($n = 30$); completed M-CHAT ($n = 22$); moderate HIE ($n = 9$), severe HIE ($n = 13$)</td>
<td>$M \pm SD$ of M-CHAT, scored from 0 to 20, with higher score indicating presence of more ASD-related traits: moderate HIE group $0.4 \pm 0.3$, severe HIE group $0.14 \pm 0.4$ (“no evidence of autism”)</td>
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<td>Lee, Gano, Rogers, et al51 (2021), draws from same cohort as Robb, Yonks, Spencer, et al51 (2022)</td>
<td>Neurodevelopmental follow-up of HIE with watershed injury</td>
<td>Prospective case series study</td>
<td>San Francisco, United States</td>
<td>Clinical neurologic diagnosis</td>
<td>HIE group (without hypothermia) with watershed injury at 10-16 y ($n = 23$), excluded for no neurodevelopmental testing ($n = 6$), excluded for severely impaired development ($n = 1$)</td>
<td>1/16 diagnosed with ADHD</td>
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<tr>
<td>Liu, Geng, Cui, et al51 (2021)</td>
<td>Evaluation of effect of mild HIE on ability to differentiate emotional prosodies</td>
<td>Prospective cohort study</td>
<td>Beijing, China</td>
<td>fNIRS monitoring of changes in oxyhemoglobin and deoxyhemoglobin in response to emotional prosodies (vocal stimuli: happy, fearful, angry, neutral)</td>
<td>Mild HIE group (without hypothermia) and non-HIE comparison group in neonatal stage (within first 24 h of life) and at 3 y</td>
<td>Significant difference between mild HIE and comparison groups in neonatal fNIRS change in oxyhemoglobin in the middle frontal gyrus in response to emotional prosodies ($P &lt; 0.01$)</td>
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<tr>
<td>Zareen, Allen, Kelly, et al51 (2021)</td>
<td>Sleep disorder clinical symptom and health-related quality of life</td>
<td>Retrospective cohort study</td>
<td>Dublin, Ireland</td>
<td>PedsQL: caregiver-reported health-related quality of life (see article Tables 2-3 for subscales)</td>
<td>NE group and age-matched non-NE group at 4-8 y and comparison group ($n = 20$), $M \pm SD$ of ASQ: personal-social skills/development rating, scored from 0-60, with higher score indicating increasing ability: HIE group $49.5 \pm 3.2$, comparison group ($n = 20$), $50.5 \pm 4.5$ (no significant difference, P &gt; 0.05)</td>
<td>PedsQL: health-related quality of life (see article Tables 2-3 for subscale results): overall NE group and mild NE group both showed lower total</td>
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<tr>
<td>Study</td>
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<td>K-SADS-PL and additional questionnaire (see article Table 1 for subscale results)</td>
<td>Retrospective cohort study</td>
<td>Padova, Italy</td>
<td>Moderate/severe HE group (n = 17)</td>
<td>NE group: 5/19 ADHD, 2/19 separation anxiety, 3/19 depressive mood; comparison group: 1/17 ADHD, 1/17 separation anxiety, 0/17 depressive mood</td>
<td>Clinical problems (see article Table 3 for subscale results)</td>
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<td>chinese culture child and adolescent depression self-report scale (CC-ADS) and additional questionnaire (see article Table 1 for subscale results)</td>
<td>Retrospective cohort study</td>
<td>Padova, Italy</td>
<td>Moderate/severe HE group (n = 17)</td>
<td>NE group: 5/19 ADHD, 2/19 separation anxiety, 3/19 depressive mood; comparison group: 1/17 ADHD, 1/17 separation anxiety, 0/17 depressive mood</td>
<td>Clinical problems (see article Table 3 for subscale results)</td>
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<tr>
<td>Evaluation ofassociation between autonomic function variability, social skills, and psychopathological milestones in children at risk for developing ADHD (see article Table 1 for subscale results)</td>
<td>Retrospective cohort study</td>
<td>Padova, Italy</td>
<td>Moderate/severe HE group (n = 17)</td>
<td>NE group: 5/19 ADHD, 2/19 separation anxiety, 3/19 depressive mood; comparison group: 1/17 ADHD, 1/17 separation anxiety, 0/17 depressive mood</td>
<td>Clinical problems (see article Table 3 for subscale results)</td>
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<tr>
<td>Effect of cerebral palsy on quality of life and mental health outcomes in children at risk for developing ADHD (see article Table 1 for subscale results)</td>
<td>Retrospective cohort study</td>
<td>Padova, Italy</td>
<td>Moderate/severe HE group (n = 17)</td>
<td>NE group: 5/19 ADHD, 2/19 separation anxiety, 3/19 depressive mood; comparison group: 1/17 ADHD, 1/17 separation anxiety, 0/17 depressive mood</td>
<td>Clinical problems (see article Table 3 for subscale results)</td>
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<tr>
<td>Halpin, McCusker, Fogarty, et al (2016)</td>
<td>Neurodevelopmental follow-up of mild/moderate HIE</td>
<td>Prospective cohort study</td>
<td>Cork, Ireland</td>
<td>SDQ: caregiver-reported behavior problems (see article Table 6 for subscales)</td>
<td>Mild/moderate HIE without hypothermia and non-HIE sibling and peer comparison groups at adolescent age</td>
<td>SDQ total difficulties (see article Table 6 for subscale results) Caregiver-reported behavior problems: higher total difficulties in HIE group than in peer comparison group (P = 0.04) but not sibling comparison group (P &gt; 0.05) Self-reported behavior problems: no difference in total difficulties between HIE group and peer or sibling comparison groups (P &gt; 0.05)</td>
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<tr>
<td>McConkey, Ryan, O'Connor, et al (2017)</td>
<td>Communication skills follow-up of moderate/severe HIE without cerebral palsy</td>
<td>Retrospective cohort study</td>
<td>Bristol, United Kingdom</td>
<td>CCC: caregiver-reported ASD-related traits</td>
<td>Non-cerebral palsy moderate/severe HIE group (with hypothermia) and matched non-HIE comparison group at 6-8 y HIE group (n = 48) Comparison group (n = 42)</td>
<td>M ± SD of CCC ASD-related traits (normative M ± SD = 10 ± 3, with higher score indicating better performance): Social relations subscale: HIE group: 9.1 ± 3.63, comparison group: 9.7 ± 2.99 Differences: HIE group: 8.7 ± 2.40, comparison group: 10.0 ± 2.63 No difference in overall traits (P &gt; 0.05)</td>
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<tr>
<td>Whelan, Corcoran, et al (2022)</td>
<td>Neurodevelopmental follow-up of HIE</td>
<td>Retrospective case series study</td>
<td>Stockholm, Sweden</td>
<td>FT: caregiver-reported social skills and behavior problems FT: caregiver-reported behavior problems Diagnosis of ASD or ADHD (including ADD)</td>
<td>HE group (with hypothermia) at 6-8 and 10-12 y; completed FT: 6-8 y (n = 44), 10-12 y (n = 45); diagnosis outcome known: mild HIE (n = 2), moderate HIE (n = 45), severe HIE (n = 11)</td>
<td>FT number (percentage) of children in HIE group scoring &gt;90th percentile, indicating obvious difficulties: Social skills: age 6-8 y: 4/44 (9.1%), age 10-12 y: 8/45 (17.8%); behavior problems: age 6-8 y: 3/44 (6.8%); age 10-12 y: 8/45 (17.8%); no differences between HIE group and normative sample (P &lt; 0.05) Diagnosis of ASD or ADHD (incl. ADD): 2/58 with confirmed diagnosis of ASD (both moderate HIE, 4/58 with confirmed diagnosis of ADHD/ADD (3 moderate HIE, 1 severe HIE), 7/58 with suspected diagnosis of ADHD/ADD (0 moderate HIE, 1 mild HIE)</td>
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</table>

ADD, attention deficit disorder; ASQ, Ages and Stages Questionnaire; BRIEF, Behavior Rating Inventory of Executive Function; BSID, Bayley Scales of Infant Development; BSITD, Bayley Scales of Infant/Toddler Development; CBCL, Child Behavior Checklist; CCG, Children’s Communication Checklist; CI, confidence interval; CRS, Conners Rating Scales; CSBQ, Children’s Social Behavior Questionnaire; CSHQ, Child Sleep Habit Questionnaire; DDST, Denver Developmental Screening Tool; DISC, Diagnostic Interview Schedule for Children; DQ, developmental quotient; DRSH, Davids Rating Scales for Hyperkinesis; FT, Five-to-Fifteen; GDS, Gesell Developmental Schedule; GMDS, Grifths Mental Development Scales; HUI, Health Utilities Index; IQR, interquartile range; K-SADS-PL, Kiddie Schedule of Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime version; M, mean; MCHAT, Modified Checklist for Autism in Toddlers; NEPSY, Developmental Neuropsychological Assessment; PedsQOL, Pediatric Quality of Life Inventory; PRESS, Preschool Symptom Self-Report; Q-CHAT, Quantitative Checklist for Autism in Toddlers; SDQ, Strengths and Difficulties Questionnaire; TACQOL, Netherlands Organisation for Applied Scientific Research Academic Medical Centre Child Quality Of Life Questionnaire; TRF, teacher’s report form; YCIS, Yale Children’s Inventory Scales.
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<th>Selection of the nonexposed cohort</th>
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<th>Comparability of cohorts in study analysis</th>
<th>Assessment of outcome(s) of interest</th>
<th>Was follow-up long enough?</th>
<th>Adequacy of follow-up or nonresponse rate</th>
<th>Total (quality rating)</th>
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<td>Marlow, Rose, Rands and Draper54 (2005)</td>
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<td>Lee-Kelland, Jary, Tonks, Cowan, Thoresen and Chakkarapani60 (2020)</td>
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<td>Cainelli, Vedovelli, Mastronardi, Gregori, Suppiej and Bisiacchi57 (2021)</td>
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The authors of 15 studies reported social (including personal-social) findings. At 1 year, personal-social scores were lower in NE groups than in comparison groups and lower in a moderate HIE group than in a mild HIE group. Personal-social scores at 1 to 2 years in HIE/NE groups and social scores at 1 to 4 years in an HIE group were predominantly normal. The proportions of delay in personal-social milestones up to 2 years in a moderate HIE group were reported. In moderate and severe HIE groups, personal-social scores at 2 years were predominantly normal, with a reported range of scores up to 3 years, and there was no difference in scores at 3 years between a mild HIE group and a comparison group. Personal-social scores at 3 to 6 years were lower in a moderate and severe HIE group than in a comparison group. In moderate and severe HIE and comparison groups at 6 to 9 years, a range of social skills were reported, and social skills did not differ between groups; social skills at 6 to 10 years in an HIE group also did not differ from a normative sample. At 9 to 10 years, groups with mild NE and moderate NE had more social problems than a comparison group.

The authors of 7 studies reported emotional (including socioemotional and quality of life) findings. Within the first 24 hours of life, a mild HIE group and a comparison group reported different patterns of hemodynamic brain responses in the middle frontal gyrus in response to happy, fearful, angry, and neutral emotional prosodies. At 2 years, socioemotional scores in an HIE group were predominantly normal. A range of socioemotional scores at <3.5 years in an HIE group were reported. At 4 to 6 years, an NE group and a mild NE subgroup both had lower health-related quality of life scores than a comparison group; the NE group had lower scores in the emotional and social functioning subdomains than the comparison group (with no differences between mild NE and comparison groups or moderate and severe and mild NE groups). A moderate and severe NE subgroup had lower health-related quality of life scores than a mild NE subgroup. A range of “self-esteem” and “emotional impact” scores, as well as “emotion” scores at 6 to 7 years in moderate and severe HIE groups were reported, and no difference was found between a mild and moderate HIE group and a reference sample on any health-related quality of life subscales at 6 to 8 years.

**Behavioral Outcomes**

The authors of 16 studies reported behavior-related outcomes, documenting participants from 1 year to adolescent age (Fig 1). Of these studies, 10 reported significant associations between deficits and the presence and severity of HIE (3/10 administered TH, 2/10 were rated as low-quality, and 8/10 were rated as medium or high-quality).
4 reported nonsignificant differences (2/4 administered TH;45,51 0/4 were rated as low-quality and were rated as 4/4 as medium;40,51 or high-quality38,45), and 6 reported HIE outcome scores or ranges without statistical comparison (Fig 1).29,36,40,44,49,50

The authors of 3 studies reported behavior problems on the Strengths and Difficulties Questionnaire. There were more problems at 6 to 8 years in a moderate and severe HIE group than in a comparison group,46 fewer “normal”-range children at 7 years in a severe NE group than in moderate NE or comparison groups (caregiver-reported and teacher-reported),47 and more problems at adolescent age in a mild and moderate HIE group than in a peer (but not a sibling) comparison group (no difference in self-reported problems).48 These studies also report subscale differences between groups.46–48

The authors of 8 studies reported behavior problems on the Child Behavior Checklist.31,35,36,38,40,44,49,50 Reported HIE group scores of problems related to internalizing and externalizing at ≥1.5 years fell below the normative mean but without a statistically significant difference.49 There were more problems at 2 years in a moderate and severe HIE subgroup with minor neurologic signs than in a subgroup without minor neurologic signs31 and at ≥3.5 years in a moderate HIE group than in a mild HIE group.40 The proportions of problems at 6 to 7 years in a moderate and severe HIE group were reported,50 and problems at 6 to 8 years in a mild and moderate HIE group were “not much higher” than in a Dutch reference sample.44 The proportions of problems at 6 to 9 years in a moderate and severe HIE group and a comparison group were reported,50 and there were no differences at 9 to 10 years between mild NE, moderate NE, and comparison groups.38 The authors of 4 studies also reported subscale differences between groups.31,35,38,40

The authors of 8 studies reported additional behavior-related findings.29,38,40,45,50–53 Proportions of behavior problems at 1 to 4 years in an HIE group29 and 18 to 22 months in a moderate and severe HIE group50 and a range of behavior regulation problems at ≥3.5 years in a mild and moderate HIE group40 were reported. There were more behavior regulation problems (teacher-reported, but not caregiver-reported) at 5 to 7 years in a moderate and severe HIE group than in a comparison group.51 Overall behavior problems and subscales differed between groups with mild and moderate NE and comparison groups at 5.5 years52 and 9 to 10 years (teacher-reported, not caregiver-reported).38 Behavior problems at 6 to 8 and 10 to 12 years in an HIE group did not differ from a normative sample.45 Problems of tractability, aggressivity, passivity, and anxiety at 8 to 13 years increased with the presence of symptoms of NE.53

Psychological and Psychiatric Outcomes

The authors of 22 studies reported additional psychological or psychiatric symptomatology or diagnoses or referral to related services, documenting participants from 1.5 to 19 years of age (Fig 1).31,35–38,40,41,44,45,53–57 Of these studies, 10 reported significant associations between deficits and the presence and severity of HIE (4/10 administered TH;31,35,37,41 3/10 were rated as low-quality,35,40,41 and 7/10 were rated as medium-quality;31,37,53,60,62–64 5 reported nonsignificant differences (4/5 administered TH;31,35,64,67 1/5 were rated as low-quality;35,40 and 4/5 were rated as medium-31,64,67 or high-quality38), and 11 reported HIE outcome scores or ranges without statistical comparison (Fig 1).36,45,54–59,61,66

The authors of 8 studies reported rates of psychiatric diagnosis in HIE/NE groups.36,38,45,54–59 The incidence of diagnoses of autism spectrum disorder (ASD) at 18 to 22 months,54 Diagnostic and Statistical Manual of Mental Disorders (DSM)-V classifications at 18 to 36 months after a positive score on an ASD checklist,55 ASD and attention deficit hyperactivity disorder (ADHD) at 2 to 16 years,56 ASD and ADHD at 5 years,57 psychiatric problems at 6 to 9 years,36 ASD and ADHD or attention deficit disorder at 6 to 10 to 12 years,45 clinical neurologic problems at 10 to 16 years,58 and ASD at childhood age59 were reported for HIE/NE groups. No differences in DSM-IV classifications at 9 to 10 years between mild NE, moderate NE, and comparison groups were reported.38

The authors of 6 studies reported additional ASD findings.31,35,50–63 In a moderate and severe NE group, 18.2% scored positively on an ASD checklist (general rate 4.4%-9.4%) at 18 to 36 months.55 No difference in ASD-related traits at 2 years was reported between a moderate and severe HIE group31 and a normative sample.68 There was a higher incidence of HIE in an ASD case group than in a non-ASD control group at 28 to 45 months,68 and a low level of ASD-related traits at 2 to 4 years in a moderate and severe HIE group.61 A moderate and severe NE group was 5.9 times more likely to be diagnosed with ASD than a comparison group at 5 years,52 and there were more ASD-related traits in a moderate NE group than in a comparison group at 10 to 19 years.63 ASD-related traits at 6 to 8 years did not differ between a moderate and severe HIE group and a comparison group.67

The authors of 4 studies reported additional ADHD findings.33,63–65 At 5 years, a moderate and severe HIE group showed more ADHD-related inattention (teacher-reported, but not caregiver-reported) than a comparison group.64 Scores of ADHD-related traits at 6 to 7 years in a moderate and severe HIE group were reported.65 A group with Apgar scores ranging from 7 to 10 with symptoms of NE was 6.6 times more likely to have an ADHD-related diagnosis at 8 to 13 years than a group with Apgar scores.
ranging from 7 to 10 without symptoms of NE, and there were more ADHD-related traits (inattention, but not hyperactivity/impulsivity) at 10 to 19 years in a moderate NE group than in a comparison group.

The authors of 7 studies reported additional clinical findings. According to the Child Behavior Checklist, there were more clinical and sleep problems at 2 years in a moderate and severe HIE subgroup with minor neurologic signs than in a subgroup without minor neurologic signs, no differences in clinical or sleep problems at 3 to 6 years between a moderate and severe HIE group and a comparison group, and more anxiety disorder, ADHD, oppositional defiance, and sleep problems at ≥3.5 years in a moderate HIE group than in a mild HIE group. At 3 to 6 years, a moderate and severe HIE group showed more depression symptoms than a comparison group. At 4 to 6 years, an NE group showed higher bedtime resistance and sleep anxiety than a comparison group, and a moderate and severe NE group showed higher sleep onset delay than a mild NE group (with no other subscale differences). A range of rates of referral to mental health or psychology services at 5 years in an HIE group were reported, and there was a higher incidence of psychopathology at 6 to 9 years in a moderate and severe HIE than in a comparison group. A group with Apgar scores ranging from 7 to 10 with symptoms of NE was 2.2 times more likely to be referred to services by a psychologist at 813 years than a group with Apgar scores ranging from 7 to 10 without symptoms of NE.

DISCUSSION

Impact

Systematic reviews of outcomes after perinatal hypoxic-ischemic encephalopathy (HIE) have focused on motor, cognitive, and visual deficits. We present a comprehensive systematic review of social, emotional, psychological, and related outcomes after perinatal HIE. Significant associations between the presence or severity of HIE and these deficits were reported in 19 of 43 included studies, with age ranges of study populations spanning from birth to 19 years (Fig 1). Significant associations persisted in studies in which researchers administered the Social and Behavioral Skills checklist, and across studies that were rated as low-quality or medium-/high-quality. We included studies referring either to HIE or NE, as many authors use these interchangeably, and we preserved each article’s chosen terminology in our narrative. Because of the heterogeneity of studies, we were unable to conduct a meta-analysis.

Decreased health-related quality of life and personal-social quotient and increased bedtime resistance and sleep anxiety were reported in groups with NE. The likelihood of behavior problems (tractability, aggressivity, passivity, anxiety), ADHD-related diagnosis, or referral to psychological services increased with the presence of symptoms of NE. In addition, there was a higher incidence of HIE in children with ASD. Mild HIE was associated with lower health-related quality of life and abnormal hemodynamic brain responses to emotional prosodies, and mild NE was associated with social and thought problems. Behavior problems were reported in mild or moderate HIE (peer problems, less prosocial) and mild or moderate NE (worse attention span, variability, irritability, explosiveness). Moderate NE was associated with social and attention problems and anxious or depressed behavior, and a moderate and severe NE group was 5.9 times more likely to be diagnosed with ASD. Additionally, compared with mild HIE/NE, moderate HIE was associated with lower personal-social ability, and moderate or severe NE was associated with lower health-related quality of life and increased sleep onset delay.

Some significant differences persisted even when studies excluded children with other disabilities. After excluding children with cerebral palsy, moderate or severe HIE was associated with lower personal-social skills and development, behavior problems, anxious or depressed and aggressive behavior, behavior regulation problems, ADHD-related inattention, depression symptoms, and a higher incidence of psychopathology. In addition, moderate NE was associated with ASD-related traits and ADHD-related traits. After excluding children with cerebral palsy, a moderate HIE group showed more behavior problems (externalizing, withdrawn or depressed, aggressive) and elevated levels of anxiety disorder, ADHD, oppositional defiance, and sleep problems compared with a mild HIE group, and a moderate and severe HIE subgroup with minor neurologic signs showed more behavior problems (internalizing, anxious or depressed), clinical problems, and sleep problems than a subgroup without minor neurologic signs. After excluding children with disabilities, NE was associated with a lower personal-social developmental quotient and more behavior problems (hyperactivity, emotional problems, less prosocial) than groups without NE, and a severe NE group showed more behavior problems (hyperactivity, emotional problems, peer problems) compared with a moderate NE group.

Understanding how treatments or markers of injury relate to outcomes is critical for improving prognostic ability and identifying children in need of early intervention. The authors of 8 included studies explored the associations between social, emotional, and psychological outcomes of HIE/NE and other clinical characteristics. Personal-social developmental quotient and behavior problems worsened in HIE subgroups with normal or mild, 41

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FIGURE 1
Outcome measures and statistical significance of association with HIE. Each reported measure is represented by a bar spanning the study population age range; a black border indicates administration of therapeutic hypothermia. Studies are designated by citation number. Bar color indicates statistically significant associations between deficits and the presence and severity of HIE (green), nonsignificant findings (magenta), or no statistical comparison reported (grey).
HIE/NE was associated with significant deficits in personal-social and socioemotional functioning and behavioral functioning. Associations with ASD and ADHD were also reported. One potential mechanism of increased ASD risk after HIE is dysregulation of the mammalian target of rapamycin signaling cascade, which is associated with Fragile X syndrome (the most common inherited cause of intellectual disability, with concomitant ASD in 30% of cases) and has been observed in hypoxic-ischemic injury of premature infants compared with age-matched control subjects. Similar to the present findings, increased ADHD risk has also been reported for children exposed to in utero hypoxic-ischemic conditions who did not necessarily develop encephalopathy, although risk factors for ADHD are less well understood. Importantly, although the authors of the included studies reported associations between HIE/NE and outcomes, we cannot determine if HIE/NE is the direct cause of these outcomes or if they are caused by another factor also related to encephalopathy. For example, caregiver mental status may be affected by a baby with HIE/NE, in turn impacting the child’s socioemotional development. Also, because children with HIE/NE often receive more comprehensive neurodevelopmental follow-up than other children, problems may be more readily identifiable.

In this systematic review, more deficits were reported at older ages than at younger ages (Fig 1), implying that children who experienced perinatal HIE/NE would benefit from long-term longitudinal follow-up. Increased reports of difficulties at older ages may be because these challenges naturally arise later or because there is a lack of accessible, robust screening tools at younger ages. Researchers should continue to develop and validate standardized evaluations of social, emotional, and psychological functioning in infancy and early childhood to assist in the early identification of at-risk individuals. A variety of standardized early screening tools and assessments are used worldwide, although there is a clear lack of international standardization. Popular choices include the Ages and Stages Questionnaire or ASQ (0- to 6-year-olds), the Bayley Scales of Infant (and Toddler) Development or BSI(T)D (1- to 42-month-olds), the (Brief) Infant-Toddler Social Emotional Assessment or (B)ITSEA (12- to 36-month-olds), the Child Behavior Checklist or CBCL11/2-5 (1.5- to 5-year-olds), the Modified Checklist for Autism in Toddlers or M-CHAT (16- to 30-month-olds), and the Strengths and Difficulties Questionnaire or SDQ (from 4 years old).

This systematic review revealed that children who experience HIE/NE, even children who experience mild or moderate HIE/NE and those who do not go on to develop cerebral palsy or other disabilities, may be at an increased risk of social, emotional, or psychological dysregulation. The purpose of this review was to synthesize outcomes rather than evaluate their mechanisms or early biomarkers. Future work should further research the relationship between markers of injury (eg, structural and functional brain imaging) and long-term social, emotional, and psychological outcomes, as well as the efficacy of early interventions in this population. When possible, the authors of future studies should adjust for IQ in these comparisons to delineate social, emotional, and psychological outcomes from cognitive outcomes, which can be interrelated. Additionally, the authors of future work should explore the relationships between initial injury, socioeconomic and cultural context of the caregiver(s), and outcomes to help identify and target infants most at risk.

Limitations

Limitations include the exclusion of non-English-language reports and non-journal articles (eg, posters or conference abstracts). Another limitation is our inability to conduct a meta-analysis because of heterogeneity in study design (measurements, timing of assessments) and clinical characteristics (classification of HIE or NE, administration of TH). Because the sample sizes of many included cohorts were relatively small, the studies may have been underpowered to detect potential significant associations and differences; however, there is also a bias toward reporting significant findings, which may underestimate nonsignificant findings. Studies were predominantly based in Europe and North America with few from Asia and Australia and none from South America or Africa. Finally, 6 of the 43 included studies had low-quality ratings.

Conclusions

This systematic review revealed a clear burden of social, emotional, and psychological sequelae after perinatal HIE, which persisted across varying age ranges,
administration of TH, severity of injury, and when excluding children with significant disabilities. Behavioral challenges such as these are often the most difficult for caregivers and pose a major public health problem for society. To identify children at risk and minimize long-term comorbidities, clinicians should implement early and longitudinal screening and intervention, and researchers should standardize study design and focus on identifying possible mediators of outcome.

**ABBREVIATIONS**

ADHD: attention deficit hyperactivity disorder  
ASD: autism spectrum disorder  
DSM: Diagnostic and Statistical Manual of Mental Disorders  
HIE: hypoxic-ischemic encephalopathy  
NE: neonatal encephalopathy  
TH: therapeutic hypothermia

**REFERENCES**


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Supplemental Information

Protocol
The protocol for this systematic review was published on PROSPERO international prospective register of systematic reviews (ID: CRD42021267939) on 16 August 2021 and can be accessed there. The inclusion and exclusion criteria were established a priori. We aimed to include any prospective or retrospective journal article with a human population (including cohort studies, case-control studies, case series studies, and/or follow-ups of randomized controlled trials) that reports relevant outcomes of hypoxic-ischemic encephalopathy (HIE) or neonatal encephalopathy (NE) at term; hypoxia/asphyxia without symptoms of encephalopathy was not sufficient. Relevant outcome measures were: (1) responses to social, emotional, or psychological stimuli, (2) scores on standardized social, emotional, or psychological assessments, (3) scores on child-report, caregiver-report, or teacher-report social, emotional, or psychological functioning.

Search Strategy
We conducted record searches of titles, abstracts, and keywords across six databases (Cochrane Library, Embase via Ovid, MEDLINE via Ovid, PsycINFO, Scopus, and Web of Science), unrestricted by date, using the below Boolean logic search string. Synonymous search terms were grouped together with the Boolean “OR,” while search terms regarding the diagnosis of HIE/NE were separated from search terms regarding social, emotional, and psychological outcomes with the Boolean “AND”.

(hypoxic-ischemic encephalopathy OR hypoxic-ischaemic encephalopathy) OR HIE OR neonatal encephalopathy OR neonatal brain injury OR perinatal brain injury OR neonatal asphyxia OR perinatal asphyxia OR birth asphyxia OR neonatal hypoxia OR perinatal hypoxia OR peripartum hypoxia OR birth hypoxia) AND (social OR emotion* OR socioemotional OR psychosocial OR psychoemotional OR behav* issue* OR behav* problem* OR behav* disorder* OR externalising OR internalising OR self-control OR mental health OR self-esteem OR depression OR depressed OR anxiety OR anxious OR psychologically OR neuropsycholog* OR psychiatr* OR neuropsychiatr* OR attention deficit hyperactivity disorder OR ADHD OR autism OR ASD OR Asperger OR schizophrenia OR bipolar)

The original systematic search, retrieving all records across the six databases from data inception, was conducted on 22 July 2021. The systematic search was re-run on 18 August 2022 and on 1 February 2023 to include all additional articles added to the six databases since the original search.

Screening
We selected studies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Citations of all retrieved searches were collected and uploaded to Rayyan. After manual deletion of duplicate records, the titles and abstracts of the remaining records were blindly screened by two independent reviewers (original search: G.H.K and H.P.; re-run search: G.H.K. and S.N.) until consensus was reached. Records that clearly did not fit inclusion criteria were excluded. The full texts of the remaining reports that may or may not fit inclusion criteria were retrieved, and all were assessed for eligibility through conversations amongst reviewers (G.H.K., H.P., and S.N.). Reports were excluded if published in a language other than English, if in a format besides journal article, if not reporting measures for the presented population or cohort, or if not reporting measures relevant to the review. The reference lists of included studies were screened to find additional studies that fit inclusion criteria.

Data Extraction
We extracted relevant outcome data from each of the included studies in tabular form on standardized data collection sheets (G.H.K.). For each study, we extracted stated purpose, study design (prospective vs. retrospective, cohort vs. case series vs. case-control, and indication if cohort study is population-based or a follow-up of a randomized controlled trial), study location, relevant measures to the present systematic review, population and sample size/demographics, and relevant results to the present systematic review. Due to the heterogeneity of included studies, we were unable to conduct a meta-analysis.

Quality Assessment
The quality of included studies was critically appraised via a star-based ranking system using adapted versions of the Newcastle-Ottawa Scale. The exact flow of quality assessment varied based on observational study subtype. For our purposes, cohort studies were defined as reporting outcomes for both a group with HIE/NE and a comparison group without HIE/NE, including population-based studies and follow-ups of randomized controlled trials; cases series studies were defined as only reporting outcomes for a group with HIE/NE; and case-control studies were defined as reporting presence or absence of a history of HIE/NE for a group with social, emotional, and/or psychological outcome(s) of interest. Two independent reviewers (H.P. and S.N.) blindly assessed the remaining criteria, including selection of the group without HIE/NE, comparability of the groups with and without HIE/NE, and assessment of outcome(s) of interest (cohort studies); selection of the group with HIE/NE, clear reporting of demographic/clinical information, and assessment of outcome(s) of interest (case series studies); or selection of the group with outcome of interest, selection of the group without outcome of interest, and comparability of the groups with and without outcome of interest (case-control studies). All quality assessments were independently reviewed by a third reviewer (G.H.K.) to check ratings and resolve disagreements. Studies with overall ratings of 1/9 to 3/9 stars were classified as low quality, studies with overall ratings of 4/9 to 6/9 stars were classified as medium quality, and studies with overall ratings of 7/9 to 9/9 stars were classified as high quality.

SUPPLEMENTAL FIGURE 2
Detailed methods.
Eligibility Screening

Inclusion criteria defined:

Studies included in review (n = 43):
- From systematic search (n = 38)
- From screening reference lists of included studies (n = 5)

Reports excluded (n = 199):
- Non-English language (n = 27)
- Not journal article (n = 56)
- Incorrect population or cohort (n = 74)
- Measures not relevant to review (n = 42)

SUPPLEMENTAL FIGURE 4
PRISMA diagram of study selection.
### Exposure (maximum: ★★★)

**Representativeness of the exposed cohort (maximum: ★★★)**
- a. cohort representative of exposure (HIE/NE) in the community (e.g., exclusion of infants with abnormal neonatal characteristics; no exclusion for cerebral palsy or other deficits) (★★)
- b. cohort somewhat representative of exposure in the community
- c. cohort not representative of exposure in the community

**Ascertainment of exposure (maximum: ★★★)**
- a. by direct rigorous diagnosis (HIE/NE or severity of HIE/NE, e.g., by Sarnat & Sarnat) (★★)
- b. by reference to primary source, e.g., medical records, with rigorous diagnosis (★)
- c. by self-report only
- d. other, or no description

### Selection (maximum: ★★★)

1. **Selection of the non-exposed cohort (maximum: ★★★)**
   - a. non-exposed cohort (group without HIE/NE or other comparison group) drawn from the same community as exposed cohort (★★)
   - b. non-exposed cohort drawn from a different community as exposed cohort, or potentially biased subset of the same community, e.g., hospitalized individuals
   - c. no description

2. **Prospective or retrospective design (maximum: ★★★)**
   - a. prospective cohort study (with respect to recruitment of group with HIE/NE) (★★)
   - b. retrospective cohort study (with respect to recruitment of group with HIE/NE)

### Comparability (maximum: ★★★)

1. **Comparability of cohorts in study design (maximum: ★★★)**
   - a. cohorts are matched by an important factor, e.g., by age (★★)
   - b. cohorts are not matched

2. **Comparability of cohorts in study analysis (maximum: ★★★)**
   - a. at least one confounder is adjusted for in analysis (of outcome of interest) (★★)
   - b. confounders are not adjusted for in analysis

### Outcome (maximum: ★★★)

1. **Assessment of outcome(s) of interest (maximum: ★★★)**
   - a. by reference to primary source, e.g., medical records (★★)
   - b. by blind, standardized assessment or interview (★★)
   - c. by self-report only (e.g., caregiver- or teacher-report)
   - d. other, or no description

2. **Was follow-up long enough for outcome(s) of interest to occur? (maximum: ★★★)**
   - a. yes (★★)
   - b. no

3. **Adequacy of follow-up or non-response rate (maximum: ★★★)**
   - a. (prospective) follow-up rate from initial enrollment high (≥70%), or those lost described (★★)
   - b. (retrospective) response rate high (≥70%), or non-respondents described (★★)
   - c. above conditions not fulfilled, or no description

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**SUPPLEMENTAL FIGURE 5**
Adapted Newcastle-Ottawa Scale for cohort studies.
### Exposure (maximum: ★ ★)

1. **Representativeness of the cases** (maximum: ★)
   - a. cohort representative of cases (HIE/NE) in the community (e.g., exclusion of infants with abnormal neonatal characteristics; no exclusion for cerebral palsy or other deficits) (★)
   - b. cohort somewhat representative of cases in the community
   - c. cohort not representative of cases in the community

2. **Identification of the cases** (maximum: ★)
   - a. by direct rigorous diagnosis (of HIE/NE or severity of HIE/NE, e.g., by Sarnat & Sarnat) (★)
   - b. by reference to primary source, e.g., medical records, with rigorous diagnosis (★)
   - c. by self-report only
   - d. other, or no description

### Selection (maximum: ★ ★)

1. **Inclusion of the cases** (maximum: ★)
   - a. all eligible cases (of HIE/NE) over a defined period of time or geographic area, or an appropriate (e.g., random) sample of those, were included (★)
   - b. potential for selection biases
   - c. unclear, or no description

2. **Prospective or retrospective design** (maximum: ★)
   - a. prospective case series study (★)
   - b. retrospective case series study

### Case Information (maximum: ★ ★)

1. **Clear reporting of demographics of the cases** (maximum: ★)
   - a. demographics (e.g., gestational age, birthweight, or sex) comprehensively reported (★)
   - b. demographics not comprehensively reported

2. **Clear reporting of clinical information of the cases** (maximum: ★)
   - a. clinical information (e.g., HIE/NE severity, cooling, comorbidities) comprehensively reported (★)
   - b. clinical information not comprehensively reported

### Outcome (maximum: ★ ★ ★)

1. **Assessment of outcome(s) of interest** (maximum: ★)
   - a. by blind, standardized assessment or interview (★)
   - b. by reference to primary source, e.g., medical records (★)
   - c. by self-report only (e.g., caregiver- or teacher-report)
   - d. other, or no description

2. **Was follow-up long enough for outcome(s) of interest to occur?** (maximum: ★)
   - a. yes (★)
   - b. no

3. **Adequacy of follow-up or non-response rate** (maximum: ★)
   - a. (prospective) follow-up rate from initial enrollment high (≥70%), or those lost described (★)
   - b. (retrospective) response rate high (≥70%), or non-respondents described (★)
   - c. above conditions not fulfilled, or no description
Exposure (maximum: ★)
1. Ascertainment of exposure (maximum: ★)
   a. by reference to primary source, e.g., medical records, with rigorous diagnosis of HIE/NE or severity of HIE/NE, e.g., by Sarnat & Sarnat (★★)
   b. by self-report only (e.g., caregiver-report via questionnaire)
   c. other, or no description
2. Same method of ascertainment of exposure for cases and controls (maximum: ★)
   a. yes (★★)
   b. no, or no description

Cases (maximum: ★★★)
1. Selection of the cases (group with outcome of interest) (maximum: ★★★)
   a. by independent validation or blind, standardized assessment or interview (★★★★)
   b. by reference to primary source, e.g., medical records (★★★★)
   c. by self-report only
   d. no description of selection of cases
2. Inclusion of the cases (group with outcome of interest) (maximum: ★★★)
   a. all eligible cases with the outcome of interest over a defined period of time or geographic area, or an appropriate (e.g., random) sample of those, were included (★★★★)
   b. potential for selection biases
   c. unclear, or no description

Controls (maximum: ★★★)
1. Selection of the controls (group without outcome of interest) (maximum: ★★★)
   a. controls drawn from the same community as cases (★★★★)
   b. controls drawn from a different community as cases, or potentially biased subset of the same community, e.g., hospitalized individuals
   c. no description of selection of controls
2. Definition of the controls (group without outcome of interest) (maximum: ★★★)
   a. no history of outcome of interest (★★★★)
   b. potential undetected history of outcome of interest
   c. no description of history of outcome of interest

Comparability (maximum: ★★★★★)
1. Comparability of cases and controls in study design (maximum: ★★★★★)
   a. cases and controls are matched by an important factor, e.g., by age (★★★★★★)
   b. cases and controls are not matched
2. Comparability of cases and controls in study analysis (maximum: ★★★★★)
   a. at least one confounder is adjusted for in analysis, e.g., in calculation of odds ratio (★★★★★★)
   b. confounders are not adjusted for in analysis
3. Non-response rate (maximum: ★★★★★)
   a. non-response rate for cases and controls similar, or non-respondents described (★★★★★★)
   b. non-response rate for cases and controls dissimilar, or no description of non-respondents

SUPPLEMENTAL FIGURE 7
Adapted Newcastle-Ottawa Scale for case-control studies.