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

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abstract

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*, behav* problem, psycholog*, psychiatr*) 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 and psychiatric 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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Ms Kromm conceptualized the systematic review, designed the search strategy, conducted the search, screened records for inclusion, extracted study data, resolved discrepancies in critical appraisal of included study quality, drafted the initial manuscript, and critically reviewed and revised the manuscript; Ms Patankar and Mr Nagalotimath contributed to the design of the systematic review, screened records for inclusion, and critically appraised the quality of included studies; Dr Wong and Prof Austin conceptualized the systematic review, critically appraised the quality of included studies, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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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.[1] 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.[2] The overall incidence of NE is estimated at 3 per 1000 live births and is even higher in low- and middle-income countries.[3]

Neonates with suspected HIE are classified according to the Sarnat staging system as stage I (mild), stage II (moderate), or stage III (severe).[4] 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.[5] Understanding the burden of HIE is important to support the development of targeted interventions[6] and to ensure that those with HIE receive appropriate follow-up care.

Studies of disability after HIE have focused on motor or cognitive deficits.[7–16] However, rodent models associate HIE with social, emotional, and psychological dysregulation, including hyperactive, antisocial, anxiety-like, and aggressive behaviors.[17–20] 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).[21] 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.[2] 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).[22] 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.[23] 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).[24]

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).[25–45] Of these studies, 6 reported significant associations between deficits and presence and severity of HIE (2/6 administered TH;[35,41] 3/6 were rated as low-quality;[34,35,41] and 3/6 were rated as medium-[25,26] or high-quality[38]), 4 reported nonsignificant differences (2/4 administered TH;[37,45] 1/4 was rated as low-quality;[34] and 3/4 were rated as medium-quality[37,44,45]), and 12 reported HIE outcome scores or ranges without statistical comparison (Fig 1).[27–33,36,39,40,42,43]

TABLE 1 Study Characteristics

Study	Purpose	Design	Location	Relevant Measures	Population and Sample Size	Relevant Results
Robertson and Finer[52] (1998)	Psychoeducational follow-up of mild/moderate NE due to birth asphyxia without disability	Prospective cohort study	Alberta, Canada	DRSH: caregiver-reported **behavior problems** *(see article Table 6 for subscales)*	Nondisabled mild/moderate NE groups (without hypothermia) and non-NE tertiary-care survivor comparison group at 5.5 y Mild NE group ($n = 56$), moderate NE group ($n = 71$), comparison group ($n = 71$)	$M \pm$ SD of overall DRSH, scored from 6 to 36, 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, $P < .05$)
Dixon, Badawi, Kurinczuk, et al[25] (2002); *draws from same cohort as Badawi, Dixon, Felix, et al[62] (2006)*	Neurodevelopmental follow-up of moderate/severe NE	Retrospective cohort study (population-based)	Western Australia	GMDS: **personal-social** DQ	Moderate/severe NE group (without hypothermia) and non-NE comparison group at 1 y NE group ($n = 190$): non-cerebral palsy ($n = 169$), non-cerebral palsy, no other medical conditions ($n = 151$) Comparison group ($n = 443$): non-cerebral palsy ($n = 443$), non-cerebral palsy, no other medical conditions ($n = 439$)	M of GMDS **personal-social** DQ (normative $M \pm$ SD $= 100 \pm 13$, 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, $P < .001$); non-cerebral palsy, no other medical conditions NE group: 108.0, non-cerebral palsy, no other medical conditions comparison group: 111.5 (significant difference, $P < .01$)
Moster, Lie and Markestad[53] (2002)	Neurodevelopmental follow-up of 5-minute Apgar score and symptoms of NE	Retrospective cohort study (population-based)	Norway	YCIS (with additional questionnaire): caregiver-reported **behavior problems** *(see article Table 5 for subscales)* Likelihood of **ADHD**-related diagnosis Likelihood of **referral** to services by a psychologist	Groups with varying 5-minute Apgar scores (without hypothermia) at 8–13 y Apgar score 0–3 group ($n = 155$): symptoms of NE* ($n = 77$), no symptoms of NE ($n = 78$) Apgar score 4–6 group ($n = 274$): symptoms of NE ($n = 122$), no symptoms of NE ($n = 152$) Apgar score 7–10 group ($n = 298$): symptoms of NE ($n = 40$), no symptoms of NE ($n = 258$) **Symptoms of NE: seizures, feeding difficulties, and/or ventilator treatment in first week*	YCIS **behavior problems** *(see article Table 5 for subscale results)*: problems with tractability, aggressivity, passivity, and anxiety increased with the presence of symptoms of NE (Ps < 0.05) 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 2.2 times more likely to have experienced **referral** to a psychologist *(see article Table 3 for full psychologist referral results)*
Barnett, Guzzetta, Mercuri, et al[28] (2004)	Examination of predictive value of early developmental testing for identifying school-age impairment after NE	Prospective case series study	London, United Kingdom	GMDS: **personal-social** DQ	NE group (without hypothermia) at 1 y and/or 2 y; 1 y ($n = 59$), 2 y ($n = 45$)	$M \pm$ SD of GMDS **personal-social** DQ, (normative $M \pm$ SD $= 100 \pm 13$, higher score = increasing ability): 1 y: 102.73 ± 14.00 (5 in NE group ≥1 SD below M); 2 y: 106.67 ± 13.87 (3 in NE group ≥1 SD below M)
Marlow, Rose, Rands, et al[47] (2005)	Neurodevelopmental follow-up of moderate/severe NE without motor disability	Retrospective cohort study	Former Trent region, United Kingdom	SDQ: caregiver-reported **behavior problems** *(see article Table 4 for subscales)* SDQ: teacher-reported **behavior problems** *(see article Table 4 for subscales)*	Nondisabled moderate/severe NE group (without hypothermia) and matched non-NE classmate comparison group at 7 y NE group ($n = 50$): moderate NE group ($n = 32$), completed caregiver-reported SDQ ($n = 31$), teacher-reported SDQ ($n = 26$); severe NE group ($n = 18$), completed caregiver-reported SDQ	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 ($P = .08$) or comparison ($P = .02$) groups Teacher-reported **behavior problems**

TABLE 1 Continued

Study	Purpose	Design	Location	Relevant Measures	Population and Sample Size	Relevant Results
					(n = 16), teacher-reported SDQ (n = 15) Comparison group (n = 49): completed caregiver-reported SDQ (n = 46), teacher-reported SDQ (n = 44)	total difficulties: fewer "normal" range children in severe NE group than in moderate NE (P = .01) or comparison (P < .01) groups
Badawi, Dixon, Felix, et al[62] (2006); *draws from same cohort as Dixon, Badawi, Kurinczuk, et al[25] (2002)*	Evaluation of association between moderate/severe NE and ASD	Retrospective cohort study (population-based)	Western Australia	Likelihood of diagnosis of **ASD**	Moderate/severe NE group (without hypothermia) and non-NE comparison group at 5 y NE group (n = 239) Comparison group (n = 563)	NE group was 5.9 (95% CI: 2.0-16.9) times more likely to be diagnosed with **ASD** than comparison group; NE group: 12/239 ASD, comparison group: 5/563 ASD
Lindstrom, Lagerroos, Gillberg, et al[63] (2006)	Neurodevelopmental follow-up of moderate NE without cerebral palsy	Retrospective cohort study (population-based)	Sweden	Asperger Syndrome Screening Questionnaire: caregiver-reported **ASD**-related traits ADHD Rating Scale-IV: caregiver-reported **ADHD**-related traits	Non-cerebral palsy moderate NE group (without hypothermia) and non-NE sibling comparison group NE group (n = 28), age range: 15-19 y Comparison group (n = 15), age range: 10-17 y	**ASD**-related traits rating: significant difference between NE and comparison groups, with more traits in NE group, P <.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 < .006
Al-Macki, Miller, Hall, et al[58] (2009)	Neurodevelopmental follow-up of moderate/severe NE due to birth asphyxia	Retrospective case series study	Montreal, Quebec, Canada	**DSM-IV classification** of ASD or ADHD	Non-cerebral palsy moderate/severe NE group (without hypothermia) at 2-16 y (n = 17)	**DSM-IV classification**: 1/17 ASD, 3/17 ADHD
van Handel, Swaab, de Vries, et al[38] (2010)	Behavioral and psychiatric follow-up of mild/moderate NE due to birth asphyxia	Retrospective cohort study	Utrecht, Netherlands	CSBQ: caregiver-reported **social problems** TRF: teacher-reported **behavior problems** *(see article Table 1 for subscales)* CBCL: caregiver-reported **behavior problems** *(see article Table 2 for subscales)* DISC: caregiver interview to obtain **DSM-IV classification**	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 = 30); 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 = 46), completed CBCL (n = 53), completed CSBQ (n = 53), completed DISC-IV (n = 53)	M ± SD of CSBQ total **social problems** (higher score = more problems) *(see article Tables 2-3 for full results)*: mild NE group: 15.2 ± 13.4, moderate NE group: 19.2 ± 17.9, comparison group: 9.2 ± 9.1 (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: 51.4 ± 11.7, moderate NE group: 54.6 ± 8.1, comparison group: 46.7 ± 7.6 (significant differences, P < .001); CBCL **behavior problems**: mild NE group: 52.2 ± 12.0, moderate NE group: 52.3 ± 12.2, comparison group: 47.0 ± 11.7 (no significant differences, P = .05) DISC-IV **DSM-IV classification** *(see article Table 3 for diagnosis incidence)*: no differences between mild NE, moderate NE, and comparison groups
Martinez-Biarge, Bregant, Wusthoff, et al[29] (2012)	Evaluation of association between white matter (WM) injury (normal basal ganglia/ thalami) on	Retrospective case series study	London, United Kingdom	GMDS: **social** DQ Presence of **behavior problems** *(including inattention, hyperactivity, anxiety, autistic type behavior, and aggression)*	HIE group (without hypothermia) at 1-4 y Normal/mild WM injury (n = 28): behavioral data (n = 28), completed GMDS (n = 22) Moderate WM injury (n = 34):	M ± SD of GMDS **social** DQ (normative M ± SD = 100 ± 13, higher score = increasing ability): normal/mild WM injury: 114.3 ± 13.3, moderate WM injury: 108.5 ± 12.9, severe WM injury: 96.1 ± 23.7 (significant

TABLE 1 Continued

Study	Purpose	Design	Location	Relevant Measures	Population and Sample Size	Relevant Results
	neonatal MRI and HIE neurodevelopmental outcomes			based on direct clinical observation and corroborated by caregiver report	behavioral data ($n = 34$), completed GMDS ($n = 28$) Severe WM injury ($n = 22$): behavioral data ($n = 19$), completed GMDS ($n = 21$)	differences, $P = .02$) Presence of **behavior problems**: normal/mild WM injury: 1/28, moderate WM injury: 10/34, severe WM injury: 13/19 (significant differences, $P < .001$)
Shankaran, Pappas, McDonald, et al[42] (2012); *draws from same cohort as Pappas, Shankaran, McDonald, et al[50] (2015)*	Neurodevelopmental follow-up of therapeutic hypothermia and normothermia groups from NICHD trial *(Shankaran, Laptook, Ehrenkranz, et al[81])*	Prospective cohort study (follow-up of randomized controlled trial)	Centers throughout United States	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")	Moderate/severe HIE group at 6-7 y Hypothermia group ($n = 70$): completed self-esteem question ($n = 65$), emotional impact question ($n = 67$) Normothermia group ($n = 52$): completed self-esteem question ($n = 46$), emotional impact question ($n = 50$)	**Self-esteem**: hypothermia group: 49/65 very, 11/65 somewhat, 5/65 neutral; normothermia group: 35/46 very, 11/46 somewhat, 0/46 neutral **Emotional impact**: hypothermia group: 33/67 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
Tusor, Wusthoff, Smee, et al[27] (2012)	Evaluation of association between diffusion tensor imaging and HIE neurodevelopmental outcomes	Prospective case series study	London, United Kingdom	GMDS, revised: **personal-social** DQ	HIE group (with hypothermia) at 1-2 y ($n = 32$); cerebral palsy ($n = 2$)	$M \pm$ SD of GMDS **personal-social** DQ (normative $M \pm$ SD $= 100 \pm 13$, higher score = increasing ability): 100 ± 24; residuals of personal-social scores significantly correlated with white matter fractional anisotropy values from diffusion tensor imaging ($R^2 = 0.326$)
Azzopardi, Strohm, Marlow, et al[65] (2014); *draws from same cohort as Campbell, Eddama, Azzopardi, et al[43] (2018)*	Neurodevelopmental follow-up of therapeutic hypothermia and normothermia groups from TOBY trial *(Azzopardi, Brocklehurst, Edwards, et al[82])*	Prospective cohort study (follow-up of randomized controlled trial)	Centers throughout United Kingdom	ADHD Rating Scale-IV: caregiver-reported **ADHD**-related traits ADHD Rating Scale-IV: teacher-reported **ADHD**-related traits	Moderate/severe HIE group at 6-7 y Hypothermia group ($n = 98$): completed caregiver-reported ADHD Rating Scale-IV ($n = 68$), completed teacher-reported ADHD Rating Scale-IV ($n = 63$) Normothermia group ($n = 86$): completed caregiver-reported ADHD Rating Scale-IV ($n = 56$), completed teacher-reported ADHD Rating Scale-IV ($n = 56$)	$M \pm$ SD of ADHD Rating Scale-IV, scored from 0-54, with higher score indicating more severe symptoms: Caregiver-reported **ADHD** rating: hypothermia group: 10.1 ± 11.5, normothermia group: 12.6 ± 11.4 (no significant difference, $P > .05$) Teacher-reported **ADHD** rating: hypothermia group: 9.8 ± 11.1, normothermia group: 11.3 ± 10.0 (no significant difference, $P > .05$)
Zubcevic, Heljic, Spahovic, et al[32] (2014); *draws from same cohort as Zubcevic, Heljic, Catibusic, et al[53] (2015)*	Neurodevelopmental follow-up of moderate/severe HIE	Prospective case series study	Sarajevo, Bosnia, and Herzegovina	ASQ: caregiver-reported **personal-social** skills/development	Moderate/severe HIE group (with hypothermia) at 4-36 mo ($n = 25$); completed ASQ-3 ($n = 19$)	ASQ-3 **personal-social** skills/development range: 13/19 normal, 5/19 abnormal, 1/19 needs retesting
Pappas, Shankaran, McDonald, et al[50] (2015); *draws from same cohort as Shankaran, Pappas, McDonald, et al[42] (2012)*	Neurodevelopmental follow-up of therapeutic hypothermia and normothermia groups from NICHD trial *(Shankaran, Laptook, Ehrenkranz, et al[81])*	Prospective cohort study (follow-up of randomized controlled trial)	Centers throughout United States	BSID Behavior Rating Scale Presence of **behavior problems** ($\leq$10th percentile) or questionable problems (11th-25th percentile); presence of **behavior problems** from caregiver-reported CBCL or school services *(see article Suppl. Table 8 for details)*	Moderate/severe HIE group at 18-22 mo and/or 6-7 y Hypothermia group ($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$)	BSID-2 **behavior problems** at 18-22 mo *(see article Suppl. Table 8 for details)*: hypothermia group: 11/52 with behavior problems, 8/52 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: 4/60 with behavior problems; normothermia group: 4/47 with behavior problems

TABLE 1 Continued

Study	Purpose	Design	Location	Relevant Measures	Population and Sample Size	Relevant Results
van Schie, Schijns, Becher, et al[44] (2015)	Evaluation of association between pattern of injury on neonatal MRI and mild/moderate HIE neurodevelopmental or health-related quality of life outcomes	Prospective case series study	Amsterdam, Netherlands	TACQOL: caregiver-reported **health-related quality of life** CBCL: caregiver-reported **behavior problems** *(see article Table 2 for subscales)*	Mild/moderate HIE group (without hypothermia) at 6-8 y ($n = 25$) Mild HIE ($n = 6$), moderate HIE ($n = 19$) Non-cerebral palsy ($n = 17$), cerebral palsy ($n = 8$) MRI normal ($n = 10$), abnormal basal ganglia ($n = 2$), abnormal cortex ($n = 4$), abnormal basal ganglia and cortex ($n = 9$)	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 ($Ps > 0.05$) CBCL **behavior problems**, non-cerebral palsy HIE group range: 13/17 normal, 3/17 borderline clinical, 1/17 clinical; percent of children with behavior problems (24%) "not much higher" than Dutch reference sample (20%)
Zubcevic, Heljic, Catibusic, et al[33] (2015); *draws from same cohort as Zubcevic, Heljic, Spahovic, et al[32] (2014)*	Neurodevelopmental follow-up of moderate/severe HIE	Prospective case series study	Sarajevo, Bosnia, and Herzegovina	ASQ: caregiver-reported **personal-social** skills/ development	Moderate/severe HIE group (with hypothermia) at 3-6, 12-18, and/or 24-36 mo ($n = 25$) Completed ASQ-3 at 3-6 mo ($n = 19$), 12-18 mo ($n = 17$), 24-36 mo ($n = 14$)	ASQ-3 **personal-social** skills/ development: range, 3-6 mo: 13/19 normal, 3/19 abnormal, 3/19 needs retesting; range, 12-18 mo: 11/17 normal, 3/17 abnormal, 3/17 needs retesting; range, 24-36 mo: 8/14 normal, 3/14 abnormal, 3/14 needs retesting
Hayes, Ryan, McGarvey, et al[59] (2016); *draws from same cohort as Hayes, Doherty, Grehan, et al[40] (2018)*	Evaluation of association between pattern of injury on neonatal MRI and HIE neurodevelopmental outcomes	Mixed prospective/ retrospective case series study	Dublin, Ireland	Diagnosis of **ASD**	HIE group (without hypothermia; $n = 237$) at childhood age; underwent MRI ($n = 88$) "Normal" ($n = 38$), assessment data ($n = 21$); "basal ganglia/thalami" ($n = 13$), assessment data ($n = 10$); "watershed" ($n = 9$), assessment data ($n = 4$); "mixed" ($n = 14$), assessment data ($n = 8$); "other" ($n = 14$), assessment data ($n = 14$)	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/thalami" MRI pattern diagnosed with ASD, 0/4 of "watershed" MRI pattern diagnosed with ASD, 0/8 of "mixed" MRI pattern diagnosed with ASD, 2/14 of "other" MRI pattern diagnosed with ASD
Murray, O'Connor, Ryan, et al[57] (2016); *draws from same cohort as O'Connor, Ryan, Boylan, et al[66] (2017) and Halpin, McCusker, Fogarty, et al[48] (2022)*	Evaluation of association between neonatal EEG grade and HIE neurodevelopmental outcomes	Prospective case series study	Cork, Ireland	Diagnosis of **ASD** or **ADHD**	HIE 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 ($n = 47$)	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)
Wang, Xu, Wang, et al[60] (2016)	Evaluation of potential biomarker for ASD diagnosis	Retrospective case-control study	Wuhan, China	Incidence of HIE in case and control groups with/ without **ASD** diagnosis	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 ($n = 116$)	Incidence of HIE across groups with/ without **ASD** diagnosis: 72/116 HIE in ASD case group; 8/116 HIE in non-ASD control group (significant difference, $P < .0001$)
Adhikari and Rao[30] (2017)	Neurodevelopmental follow-up of moderate HIE	Prospective case series study	Pokhara, Nepal	DDST: **personal-social** milestones	Moderate HIE group (without hypothermia) at 3 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 ($n = 32$)	DDST-2 **personal-social** milestones, categorized as "with social delay" or "without social delay": 3/26 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, 2/32 with social delay at 18 mo, 8/32 with social delay at 24 mo (significant differences, $P = .001$)
O'Connor, Ryan, Boylan, et al[66] (2017); *draws from same cohort as*	Evaluation of association between early neurodevelopmental	Prospective case series study	Cork, Ireland	Diagnosis of **ASD** or **ADHD** **Referral** to additional	HIE group (without hypothermia) at 5 y; mild HIE ($n = 22$), moderate HIE ($n = 19$), severe HIE ($n = 6$)	Diagnosis of **ASD** or **ADHD**: 1/47 diagnosed with ASD (mild HIE), 2/47 diagnosed with ADHD (1 with mild

TABLE 1 Continued

Study	Purpose	Design	Location	Relevant Measures	Population and Sample Size	Relevant Results
Murray, O'Connor, Ryan, et al[57] (2016) and Halpin, McCusker, Fogarty, et al[48] (2022)	assessment and HIE neurodevelopmental outcomes			services (mental health, psychology)		HIE, 1 with moderate HIE) Additional services **referral**: 1/47 referred to child/adolescent mental health service (mild HIE), 6/47 referred to psychology (4 with mild HIE, 2 with moderate HIE)
Tan, Minutillo, McMichael, et al[39] (2017)	Evaluation of association between hypoglycemia and HIE neurodevelopmental outcomes	Retrospective cohort study (population-based)	Western Australia	BSID: caregiver-reported **socioemotional** development	HIE group (with hypothermia), with or without episodes of neonatal hypoglycemia, at 2 y Group with episodes of hypoglycemia* ($n = 38$): mild HIE ($n = 6$), moderate HIE ($n = 23$), severe HIE ($n = 9$) Comparison group, without hypoglycemia ($n = 84$): mild HIE ($n = 24$), moderate HIE ($n = 40$), severe HIE ($n = 20$) * *Hypoglycemia: blood glucose level <2.6 mmol/L*	*M* ± SD of BSID-3 **socioemotional** development scaled scores (normative *M* ± SD = 100 ± 15, higher score = increasing ability), grouped by hypoglycemia episodes: Group with ≥1 episode: 99 ± 22 (no significant difference, $P > .05$)* Subgroup with ≥2 episodes: 93 ± 25 (no significant difference, $P > .05$)* Subgroup with ≥3 episodes: 74 ± 23 (significant difference, $P = .004$);* Comparison group: 99 ± 20 * *Compared with comparison group, with no episodes of hypoglycemia*
Campbell, Eddama, Azzopardi, et al[43] (2018); *draws from same cohort as Azzopardi, Strohm, Marlow, et al[65] (2014)*	Health-related quality of life follow-up of therapeutic hypothermia and normothermia groups from TOBY trial *(Azzopardi, Brocklehurst, Edwards, et al[82])*	Prospective cohort study (follow-up of randomized controlled trial)	Centers throughout United Kingdom	HUI: caregiver-reported **emotion** attribute ("happy and interested in life")	Moderate/severe HIE 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: 63/74 Level 1, 11/74 Level 2; normothermia group: 59/70 Level 1, 6/70 Level 2, 2/70 Level 3, 1/70 Level 4, 2/70 Level 5 (no significant trend, $P > .05$)
Chalak, Nguyen, Prempunpong, et al[54] (2018)	Neurodevelopmental follow-up of mild HIE	Prospective case series study	Canada (×1), United States (×3), United Kingdom (×1), Thailand (×1)	Diagnosis of **ASD**	Mild HIE group (without hypothermia) at 18-22 mo ($n = 63$); completed neurodevelopmental assessment ($n = 43$)	2/43 infants with **ASD** diagnosis at 18-22 mo (diagnosis confirmed by developmental health care specialist at beyond 36 mo of age)
Hayes, Doherty, Grehan, et al[40] (2018); *draws from same cohort as Hayes, Ryan, McGarvey, et al[59] (2016)*	Neurodevelopmental follow-up of HIE without cerebral palsy	Mixed prospective/retrospective case series study	Dublin, Ireland	BSITD: caregiver-reported **socioemotional** development BRIEF: caregiver-reported **behavior regulation** index BRIEF: teacher-reported **behavior regulation** index CBCL: caregiver-reported **behavior problems**, "other" **clinical problems**, and **sleep problems** *(see article Table 3 for subscales)*	Non-cerebral palsy HIE group (without hypothermia) at <3.5 and/or ≥3.5 y Mild HIE group ($n = 112$) at <3.5 y ($n = 65$): completed BSITD-3 ($n = 65$) at ≥3.5 y ($n = 49$), completed BRIEF ($n = 27$), completed CBCL ($n = 49$) Moderate HIE group ($n = 33$) at <3.5 y ($n = 12$): completed BSITD-3 ($n = 12$) at ≥3.5 y ($n = 21$), completed BRIEF ($n = 13$), completed CBCL ($n = 17$) Severe HIE group ($n = 1$) at <3.5 y ($n = 1$): completed BSITD-3 ($n = 1$)	BSITD-3 **socioemotional** development scaled scores (normative *M* ± SD = 10 ± 3, higher score = increasing ability; $n = 76$) range: 4/76 scaled score <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 ($n = 38$): 26/38 normal, 6/38 borderline clinical, 6/38 clinical; teacher-reported **behavior regulation** range ($n = 32$): 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 HIE group than in mild HIE group (*P*s < 0.05)
Edmonds, Helps, Hart, et al[31] (2020); *draws*	Neurodevelopmental follow-up of	Retrospective case series study		ASQ: caregiver-reported **personal-social** skills/	Non-cerebral palsy moderate/severe HIE group (with hypothermia) at	ASQ-3 **personal-social** skills/development: 9/10 normal, 1/10 borderline clinical

TABLE 1 Continued

Study	Purpose	Design	Location	Relevant Measures	Population and Sample Size	Relevant Results
from same cohort as Edmonds, Cianfaglione, Cornforth, et al[57] (2021) and Erdi-Krausz, Rocha, Brown, et al[64] (2021)	moderate/severe HIE without cerebral palsy		Southampton, United Kingdom	development CBCL, ages 1.5-5 y: caregiver-reported **behavior problems**, "other" **clinical problems**, and **sleep problems** *(see article Table 4 for subscales)* Q-CHAT: caregiver-reported **ASD**-related traits	2 y (n = 94); completed ASQ-3 (n = 10), completed CBCL (n = 74), completed Q-CHAT (n = 71); minor neurologic signs, excluding cerebral palsy (n = 13); normal neurology (n = 81)	CBCL **behavior problems**, "other" **clinical problems**, and **sleep problems** *(see article Table 4 for subscale results)*: more behavior problems (P = .04), clinical problems (P = .01), and sleep problems (P = .04) in group with (n = 10) than in group without (n = 64) minor neurologic signs M ± SD of Q-CHAT, scored from 0-100, with higher score indicating more **ASD**-related traits: 28.0 ± 9.4; no difference from normative sample M ± SD (26.7 ± 7.8), P > .05 (Allison, Baron-Cohen, Wheelwright, et al[68])
Karabulut and Sahbudak[55] (2020)	Evaluation of association between moderate/severe NE and ASD	Retrospective case series study	Izmir, Turkey	M-CHAT: caregiver-reported **ASD**-related traits, completed with help of health professionals **DSM-V classification** by child/adolescent psychiatrist	Non-neurologic deficit moderate/severe NE group (with hypothermia) at 18-36 mo (n = 37); completed M-CHAT (n = 33)	M-CHAT indication of negative (low) or positive (high) risk of **ASD** diagnosis, with general population positivity rate reported as 4.4% to 9.4% (Karabulut and Sahbudak[55]): 27/33 (81.8%) negative M-CHAT, 6/33 (18.2%) positive M-CHAT **DSM-V classification** (n = 4): diagnosed with ASD (n = 1), diagnosed with ADHD (n = 1), no diagnosis (n = 2)
Lee-Kelland, Jary, Tonks, et al[46] (2020)	Neurodevelopmental follow-up of moderate/severe HIE without cerebral palsy	Retrospective cohort study	Bristol, United Kingdom	SDQ: caregiver-reported **behavior problems** *(see article Table 2 for subscales)*	Non-cerebral palsy moderate/severe HIE group (with hypothermia) and matched non-HIE comparison group at 6-8 y HIE group (n = 29): moderate HIE (n = 26), severe HIE (n = 3) Comparison group (n = 20)	SDQ **behavior problems** total difficulties *(see article Table 2 for subscale results)*: higher total difficulties in HIE group than in comparison group (P = .005)
Cainelli, Vedovelli, Mastretta, et al[37] (2021)	Neurodevelopmental follow-up of moderate/severe HIE	Prospective cohort study	Centers throughout Italy	NEPSY: **social skills** *(subscales: affect recognition, theory of mind A, theory of mind B)* Presence of **psychopathology** from caregiver-reported CBCL or CRS, revised *(subscales: opposition, inattention, hyperactivity, anxiety, shyness, perfectionism, social problems, psychosomatic issues)*	Moderate/severe HIE group (with hypothermia) and non-HIE peer comparison group at 6-9 y HIE group (n = 40): completed psychopathology assessment(s) (n = 36) Comparison group (n = 33): completed psychopathology assessment(s) (n = 25)	Median (IQR) of NEPSY-2 **social skills**: Affect recognition: HIE group: 9.5 (7.0 to 11.8), comparison group: 10.10 (9.0 to 11.0) (no significant difference, P > .05) Theory of mind A: HIE group: 0.21 (-0.77 to 0.94), comparison group: 0.07 (-0.82 to 0.68) (no significant difference, P > .05) Theory of mind B: HIE group: -0.04 (-0.77 to 0.34), comparison group: 0.12 (-0.36 to 0.49) (no significant difference, P > .05) Presence of **psychopathology** from CBCL or CRS-R: HIE group: 12/36 present, comparison group: 3/25 present (significant difference, P = .04)
Danguecan, El Shahed, Somerset, et al[49] (2021)	Evaluation of association between social factors or presence of injury on neonatal MRI and HIE neurodevelopmental outcomes	Retrospective case series study	Toronto, Ontario, Canada	CBCL, ages 1.5-5 y: caregiver-reported **behavior problems** *(subscales: internalizing, externalizing)*	HIE group at ≥6 mo (n = 54); received hypothermia (n = 47); completed CBCL (n = 25) MRI normal group (n = 32) MRI injury group (n = 22): mild MRI injury (n = 6), moderate MRI injury (n = 7), severe MRI injury (n = 9)	M ± SD of CBCL **behavior problems** related to internalizing or externalizing (normative M ± SD = 50 ± 10, higher score = more problems): internalizing: 44 ± 8 (MRI normal group: 42 ± 8, MRI injury group: 48 ± 6), externalizing: 43 ± 8 (MRI normal group: 42 ± 7, MRI injury group: 45 ± 11) (no significant differences between MRI groups, Ps > 0.05)

TABLE 1 Continued

Study	Purpose	Design	Location	Relevant Measures	Population and Sample Size	Relevant Results
Edmonds, Cianfaglione, Cornforth, et al[51] (2021); *draws from same cohort as Edmonds, Helps, Hart, et al[31] (2020) and Erdi-Krausz, Rocha, Brown, et al[64] (2021)*	Neurodevelopmental follow-up of moderate/severe HIE without cerebral palsy	Retrospective cohort study	Southampton, United Kingdom	BRIEF: caregiver-reported **behavior regulation** index BRIEF: teacher-reported **behavior regulation** index	Non-cerebral palsy moderate/severe HIE group (with hypothermia) and matched non-HIE comparison group at 5-7 y HIE group (n = 31): completed caregiver-reported BRIEF (n = 30), teacher-reported BRIEF (n = 28) Comparison group (n = 49): completed caregiver-reported BRIEF (n = 15), teacher-reported BRIEF (n = 20)	Median (IQR) of BRIEF index (normative $M \pm SD = 50 \pm 10$, higher score = more problems) *(see article Table 3 for additional subscale results)*: Caregiver-reported **behavior regulation**: HIE group: 49.00 (23.00), comparison group: 46.00 (13.00; no significant difference, $P > .05$); Teacher-reported **behavior regulation**: HIE group: 48.50 (11.75), comparison group: 44.00 (7.25; (significant difference, $P = .036$)
Erdi-Krausz, Rocha, Brown, et al[64] (2021); *draws from same cohort as Edmonds, Helps, Hart, et al[31] (2020) and Edmonds, Cianfaglione, Cornforth, et al[51] (2021)*	Neurodevelopmental follow-up of moderate/severe HIE without cerebral palsy	Retrospective cohort study	Southampton, United Kingdom	DuPaul ADHD Rating Scale: "Home" version (caregiver-reported) **ADHD**-related traits inattention subscale DuPaul ADHD Rating Scale: "School" version (teacher-reported) **ADHD**-related traits, inattention subscale	Non-cerebral palsy moderate/severe HIE group (with hypothermia) and matched non-HIE comparison group at 5 y HIE group (n = 27) Comparison group (n = 20)	$M \pm SD$ of DuPaul "Home" (caregiver-reported) **ADHD** rating, inattention subscale, scored from 0-27, with higher score indicating more severe symptoms: HIE group: 5.18 ± 4.99, comparison group: 3.27 ± 2.68 (no significant difference, $P > .05$) $M \pm SD$ of DuPaul "School" (teacher-reported) **ADHD** rating, inattention subscale, scored from 0-27, with higher score indicating more severe symptoms: HIE group: 6.37 ± 7.11, comparison group: 3.05 ± 4.90 (significant difference, $P = .032$)
Jenkins, Moss, Brown, et al[61] (2021)	Clinical trial of administration of N-acetylcysteine and calcitriol (vitamin D) during therapeutic hypothermia for moderate/severe HIE and neurodevelopmental follow-up	Prospective case series study	Charleston, South Carolina, United States	M-CHAT: caregiver-reported **ASD**-related traits	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)	$M \pm SD$ of M-CHAT, scored from 0 to 20, with higher score indicating presence of more **ASD**-related traits: moderate HIE group: 0.4 ± 0.5, severe HIE group: 0.14 ± 0.4 ("no evidence of autism")
Lee, Gano, Rogers, et al[58] (2021); *draws from same cohort as Robb, Tonks, Spencer, et al[67] (2022)*	Neurodevelopmental follow-up of HIE with watershed injury	Prospective case series study	San Francisco, United States	**Clinical neurologic diagnosis**	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)	1/16 diagnosed with **ADHD**
Liu, Geng, Cui, et al[34] (2021)	Evaluation of effect of mild HIE on ability to differentiate emotional prosodies	Prospective cohort study	Beijing, China	fNIRS monitoring of changes in oxyhemoglobin and deoxyhemoglobin in **response to emotional prosodies** (vocal stimuli: happy, fearful, angry, neutral) ASQ: **personal-social** skills/development	Mild HIE group (without hypothermia) and non-HIE comparison group in neonatal stage (within first 24 h of life) and at 3 y HIE group in neonatal stage (n = 37), at 3 y (n = 29) Comparison group in neonatal stage (n = 20), at 3 y (n = 20)	Significant difference between mild HIE and comparison groups in neonatal fNIRS change in oxyhemoglobin in the middle frontal gyrus in **response to emotional prosodies** ($P = .001$) $M \pm SD$ of ASQ **personal-social** skills/development rating (3 y), scored from 0-60, with higher score indicating increasing ability: HIE group (n = 29): 49.5 ± 3.2, comparison group (n = 20): 50.5 ± 4.3 (no significant difference, $P >$ .05)
Zareen, Allen, Kelly, et al[41] (2021)	Sleep disorder clinical symptom and health-related quality of life	Retrospective cohort study	Dublin, Ireland	PedsQOL: caregiver-reported **health-related quality of life** *(see article Tables 2-3 for subscales)*	NE group and age-matched non-NE comparison group at 4-6 y NE group (n = 45): mild NE group (n = 15), moderate/severe NE	PedsQOL **health-related quality of life** *(see article Tables 2-3 for subscale results)*: overall NE group and mild NE group both showed lower total

TABLE 1 Continued

Study	Purpose	Design	Location	Relevant Measures	Population and Sample Size	Relevant Results
	follow-up of NE due to birth asphyxia			CSHQ: caregiver-reported **sleep disorder clinical symptoms** *(see article Table 1 for subscales)*	group (n = 30), received hypothermia (n = 24) Comparison group (n = 55)	quality of life than comparison group (Ps < 0.05); moderate/severe NE group showed lower total quality of life than mild NE group (P = .007) CSHQ **sleep disorder clinical symptoms** *(see article Table 1 for subscale results)*: NE group showed more bedtime resistance (P = .028) and sleep anxiety (P = .01) than comparison group; moderate/severe NE group showed more sleep onset delay (P = .04) than mild NE group
Zhang, Hu, Dong, et al[26] (2021)	Evaluation of association between neonatal EEG and mild/moderate HIE neurodevelopmental outcomes	Prospective case series study	Changzhou, China	GDS: **personal-social** ability based on observation	Mild/moderate HIE group (without hypothermia) at 1 y Mild HIE group (n = 20) Moderate HIE group (n = 15)	M ± SD of GDS **personal-social** ability (normative M ± SD = 100 ± 13, higher score = increasing ability): mild HIE group: 103.95 ± 9.21, moderate HIE group: 97.27 ± 8.96 (significant difference, P = .039)
Alvarez-Garcia, Cuellar-Flores, Sierra-Garcia, et al[35] (2022)	Mood disorder follow-up of moderate/severe HIE	Retrospective cohort study	Madrid, Spain	ASQ: caregiver-reported **personal-social** skills/development CBCL, ages 1.5-5 y: caregiver-reported **behavior problems**, "other" **clinical problems**, and **sleep problems** *(see article Table 3 for subscales)* PRESS: child-reported (self-reported) **depression symptoms**	Non-cerebral palsy moderate/severe HIE group (with hypothermia) and non-HIE comparison group at 3-6 y HIE group (n = 14) Comparison group (n = 15)	Median (95% CI) of ASQ **personal-social** skills/development rating, scored from 0-60, with higher score indicating increasing ability: HIE group: 50 (44.9-53.6), comparison group: 60 (51.9-60.7) (significant difference, P = .002) CBCL **behavior problems**, "other" **clinical problems**, and **sleep problems** *(see article Table 3 for subscale results)*: higher scores on anxious/depressed and aggressive behavior subscales of behavior problems (Ps <0.05), but not for clinical problems or sleep problems (Ps >0.05), in HIE group than comparison group PRESS child-reported (self-reported) **depression symptoms**: more symptoms in HIE group than comparison group (P = .01)
Cainelli, Vedovelli, Bottigliengo, et al[36] (2022)	Evaluation of association between autonomic function (heart rate variability), social skills, and psychopathological functioning in at-risk children	Retrospective cohort study	Padova, Italy	NEPSY: **social skills** *(see article Table 1 for subscales)* CBCL: caregiver-reported **behavior problems** *(see article Table 1 for internalizing and externalizing subscales)* K-SADS-PL (with additional questionnaire): caregiver-reported **psychiatric diagnosis** *(see article Table 1 for subscales)*	Moderate/severe HIE group (with hypothermia) and non-HIE comparison group at 6-9 y HIE group (n = 19) Comparison group (n = 17)	NEPSY-2 **social skills** *(see article Table 1 for subscale results)*: Affect recognition: HIE group range: 3/19 borderline clinical, 4/19 clinical; comparison group range: 4/17 borderline clinical, 0/17 clinical Total theory of mind: HIE group range: 3/19 borderline clinical, 1/19 clinical; comparison group range: 2/17 borderline clinical, 1/17 clinical CBCL presence of **behavior problems** *(see article Table 1 for subscale results related to internalizing or externalizing)*: HIE group: 6/19, comparison group: 2/17 K-SADS-PL and additional questionnaire presence of **psychiatric diagnosis** *(see article Table 1 for subscale results)*: HIE group: 5/19 ADHD, 2/19 separation anxiety, 3/19 depressive mood; comparison group: 1/17 ADHD

TABLE 1 Continued

Study	Purpose	Design	Location	Relevant Measures	Population and Sample Size	Relevant Results
Halpin, McCusker, Fogarty, et al[48] (2022); *draws from same cohort as Murray, O'Connor, Ryan, et al[57] (2016) and O'Connor, Ryan, Boylan, et al[66] (2017)*	Neurodevelopmental follow-up of mild/moderate HIE	Prospective cohort study	Cork, Ireland	SDQ: caregiver-reported **behavior problems** *(see article Table 6 for subscales)* SDQ: child-reported (self-reported) **behavior problems** *(see article Table 6 for subscales)*	Mild/moderate HIE (without hypothermia) and nearest-age non-HIE sibling and peer comparison groups at adolescent age HIE group ($n = 23$) Sibling comparison group ($n = 13$) Peer comparison group ($n = 14$)	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 ($P = .004$) but not sibling comparison group ($P > .05$) Self-reported **behavior problems**: no difference in total difficulties between HIE group and peer or sibling comparison groups ($Ps > 0.05$)
Robb, Tonks, Spencer, et al[67] (2022); *draws from same cohort as Lee, Gano, Rogers, et al[58] (2021)*	Communication skills follow-up of moderate/severe HIE without cerebral palsy	Retrospective cohort study	Bristol, United Kingdom	CCC: caregiver-reported **ASD**-related traits	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 ($n = 42$)	$M \pm$ SD of CCC **ASD**-related traits (normative $M \pm SD = 10 \pm 3$, with higher score indicating better performance): "Social relations" subscale: HIE group: 9.1 ± 3.55, comparison group: 9.7 ± 2.99 "Interests" subscale: HIE group: 8.7 ± 2.40, comparison group: 10.0 ± 2.63 No difference in overall traits ($P > .05$)
Robertsson Grossmann, Eriksson Westblad, Blennow, et al[45] (2022)	Neurodevelopmental follow-up of HIE	Retrospective case series study	Stockholm, Sweden	FTF: caregiver-reported **social skills** and **behavior problems** FTF: caregiver-reported **behavior problems** Diagnosis of **ASD** or **ADHD** (including ADD)	HIE group (with hypothermia) at 6-8 and 10-12 y; completed FTF: 6-8 y ($n = 44$), 10-12 y ($n = 45$); diagnosis outcome known: mild HIE ($n = 2$), moderate HIE ($n = 45$), severe HIE ($n = 11$)	FTF number (percentage) of children in HIE group scoring >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 ($Ps < 0.05$) 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 (6 moderate HIE, 1 mild HIE)

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; CCC, 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; FTF, Five-to-Fifteen; GDS, Gesell Developmental Schedule; GMDS, Griffiths 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; M-CHAT, 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.

TABLE 2 Critical Appraisal of Cohort Studies

Study	Exposure		Selection		Comparability		Outcome			Total (quality rating)
	Representativeness of the exposed cohort	Ascertainment of exposure	Selection of the nonexposed cohort	Prospective or retrospective design	Comparability of cohorts in study design	Comparability of cohorts in study analysis	Assessment of outcome(s) of interest	Was follow-up long enough?	Adequacy of follow-up or nonresponse rate	
Robertson and Finer[52] (1998)		⋆		⋆				⋆	⋆	4/9 (medium)
Dixon, Badawi, Kurinczuk, et al[25] (2002)		⋆	⋆		⋆		⋆		⋆	5/9 (medium)
Moster, Lie and Markestad[53] (2002)	⋆		⋆		⋆	⋆		⋆	⋆	6/9 (medium)
Marlow, Rose, Rands and Draper[47] (2005)		⋆	⋆		⋆			⋆		4/9 (medium)
Badawi, Dixon, Felix, et al[62] (2006)		⋆	⋆		⋆			⋆	⋆	5/9 (medium)
Lindstrom, Lagerroos, Gillberg and Fernell[63] (2006)		⋆	⋆					⋆	⋆	4/9 (medium)
van Handel, Swaab, de Vries and Jongmans[38] (2010)	⋆	⋆	⋆		⋆	⋆		⋆	⋆	7/9 (high)
Shankaran, Pappas, McDonald, et al[42] (2012)	⋆	⋆	⋆	⋆				⋆		5/9 (medium)
Azzopardi, Strohm, Marlow, et al[65] (2014)	⋆	⋆	⋆	⋆				⋆		5/9 (medium)
Pappas, Shankaran, McDonald, et al[50] (2015)	⋆	⋆	⋆	⋆		⋆	⋆			6/9 (medium)
Tan, Minutillo, McMichael and Rao[39] (2017)	⋆	⋆	⋆						⋆	4/9 (medium)
Campbell, Eddama, Azzopardi, Edwards, Strohm and Rivero-Arias[43] (2018)	⋆	⋆	⋆	⋆				⋆		5/9 (medium)
Lee-Kelland, Jary, Tonks, Cowan, Thoresen and Chakkarapani[46] (2020)			⋆		⋆			⋆	⋆	4/9 (medium)
Cainelli, Vedovelli, Mastretta, Gregori, Suppiej and Bisiacchi[37] (2021)	⋆			⋆			⋆	⋆	⋆	5/9 (medium)
Edmonds, Cianfaglione, Cornforth and Vollmer[51] (2021)		⋆	⋆		⋆			⋆		4/9 (medium)
Erdi-Krausz, Rocha, Brown, et al[64] (2021)		⋆	⋆		⋆			⋆		4/9 (medium)
Liu, Geng, Cui, et al[34] (2021)		⋆		⋆					⋆	3/9 (low)
Zareen, Allen, Kelly, McDonald, Sweetman and Molloy[41] (2021)		⋆			⋆				⋆	3/9 (low)
Alvarez-Garcia, Cuellar-Flores, Sierra-Garcia and Martinez-Orgado[35] (2022)		⋆	⋆		⋆					3/9 (low)
Cainelli, Vedovelli, Bottigliengo, Boschiero and Suppiej[36] (2022)		⋆	⋆			⋆		⋆		4/9 (medium)
Halpin, McCusker, Fogarty, et al[48] (2022)	⋆	⋆	⋆					⋆		4/9 (medium)
Robb, Tonks, Spencer, et al[67] (2022)		⋆	⋆		⋆			⋆	⋆	5/9 (medium)

TABLE 3 Critical Appraisal of Case Series Studies

Study	Exposure		Selection		Case Information		Outcome			Total (quality rating)
	Representativeness of the cases	Identification of the cases	Inclusion of the cases	Prospective or retrospective design	Clear reporting of demographics of the cases	Clear reporting of clinical information of the cases	Assessment of outcome(s) of interest	Was follow-up long enough?	Adequacy of follow-up or nonresponse rate	
Barnett, Guzzetta, Mercuri, et al[28] (2004)	⋆	⋆	⋆	⋆					⋆	5/9 (medium)
Al-Macki, Miller, Hall and Shevell[56] (2009)		⋆			⋆	⋆				3/9 (low)
Martinez-Biarge, Bregant, Wusthoff, et al[29] (2012)	⋆	⋆	⋆		⋆	⋆			⋆	6/9 (medium)
Tusor, Wusthoff, Smee, et al[27] (2012)		⋆		⋆	⋆	⋆			⋆	5/9 (medium)
Zubcevic, Heljic, Spahovic, Kalkan, Terzic and Sadikovic[32] (2014)		⋆		⋆	⋆	⋆			⋆	5/9 (medium)
van Schie, Schijns, Becher, Barkhof, van Weissenbruch and Vermeulen[44] (2015)		⋆		⋆	⋆	⋆		⋆	⋆	6/9 (medium)
Zubcevic, Heljic, Catibusic, Uzicanin, Sadikovic and Krdzalic[33] (2015)		⋆		⋆	⋆	⋆			⋆	5/9 (medium)
Hayes, Ryan, McGarvey, et al[59] (2016)		⋆	⋆			⋆			⋆	4/9 (medium)
Murray, O'Connor, Ryan, Korotchikova and Boylan[57] (2016)	⋆	⋆		⋆	⋆	⋆		⋆	⋆	7/9 (high)
Adhikari and Rao[30] (2017)	⋆	⋆	⋆	⋆	⋆	⋆				6/9 (medium)
O'Connor, Ryan, Boylan and Murray[66] (2017)	⋆	⋆		⋆	⋆	⋆		⋆	⋆	7/9 (high)
Chalak, Nguyen, Prempunpong, et al[54] (2018)	⋆	⋆		⋆	⋆	⋆			⋆	6/9 (medium)
Hayes, Doherty, Grehan, et al[40] (2018)		⋆	⋆			⋆				3/9 (low)
Edmonds, Helps, Hart, et al[31] (2020)		⋆	⋆		⋆	⋆			⋆	5/9 (medium)
Karabulut and Sahbudak[55] (2020)		⋆	⋆		⋆	⋆				4/9 (medium)
Danguecan, El Shahed, Somerset, Fan, Ly and Williams[49] (2021)	⋆				⋆	⋆				3/9 (low)
Jenkins, Moss, Brown, et al[61] (2021)		⋆	⋆	⋆	⋆	⋆			⋆	6/9 (medium)
Lee, Gano, Rogers, et al[58] (2021)	⋆	⋆	⋆	⋆	⋆	⋆		⋆		7/9 (high)
Zhang, Hu, Dong and Feng[26] (2021)		⋆		⋆	⋆				⋆	4/9 (medium)
Robertsson Grossmann, Eriksson Westblad, Blennow and Lindstrom[45] (2022)	⋆	⋆	⋆		⋆	⋆		⋆	⋆	7/9 (high)

TABLE 4 Critical Appraisal of Case-Control Studies

Study	Exposure		Cases		Controls		Comparability			Total (quality rating)
	Ascertainment of exposure	Same method of ascertainment of exposure for cases and controls	Selection of the cases	Inclusion of the cases	Selection of the controls	Definition of the controls	Comparability of cases and controls in study design	Comparability of cases and controls in study analysis	Nonresponse rate	
Wang, Xu, Wang, et al[60] (2016)		*	*		*		*			4/9 (medium)

The authors of 15 studies reported social (including personal-social) findings.[25–38,45] At 1 year, personal-social scores were lower in NE groups than in comparison groups[25] and lower in a moderate HIE group than in a mild HIE group.[26] Personal-social scores at 1 to 2 years in HIE/NE groups[27,28] and social scores at 1 to 4 years in an HIE group[29] were predominantly normal. The proportions of delay in personal-social milestones up to 2 years in a moderate HIE group were reported.[30] In moderate and severe HIE groups, personal-social scores at 2 years were predominantly normal,[31] with a reported range of scores up to 3 years,[32,33] and there was no difference in scores at 3 years between a mild HIE group and a comparison group.[34] Personal-social scores at 3 to 6 years were lower in a moderate and severe HIE group than in a comparison group.[35] In moderate and severe HIE and comparison groups at 6 to 9 years, a range of social skills were reported,[36] and social skills did not differ between groups;[37] social skills at 6 to 8 and 10 to 12 years in an HIE group also did not differ from a normative sample.[45] At 9 to 10 years, groups with mild NE and moderate NE had more social problems than a comparison group.[38]

The authors of 7 studies reported emotional (including socioemotional and quality of life) findings.[34,39–44] 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.[34] At 2 years, socioemotional scores in an HIE group were predominantly normal.[39] A range of socioemotional scores at <3.5 years in an HIE group[40] 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.[41] A range of "self-esteem" and "emotional impact" scores,[42] as well as "emotion" scores[43] 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.[44]

Behavioral Outcomes

The authors of 16 studies reported behavior-related outcomes, documenting participants from 1 year to adolescent age (Fig 1).[29,31,35,36,38,40,44–53] Of these studies, 10 reported significant associations between deficits and the presence and severity of HIE (3/10 administered TH;[31,35,46] 2/10 were rated as low-quality;[35,40] and 8/10 were rated as medium-[31,46–48,51–53] or high-quality[38]),

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-[48,51] or high-quality[38,45]), 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 signs[31] 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,[36] 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 group[29] and 18 to 22 months in a moderate and severe HIE group[50] and a range of behavior regulation problems at ≥3.5 years in a mild and moderate HIE group[40] 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 years[52] 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).[31,35–38,40,41,45,53–67] 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] and 4/5 were rated as medium-[31,64,67] or high-quality[38]), and 11 reported HIE outcome scores or ranges without statistical comparison (Fig 1).[36,45,54–59,61,65,66]

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 8 and 10 to 12 years,[45] clinical neurologic problems at 10 to 16 years,[58] and ASD at childhood age[59] 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.[31,55,60–63] 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 group[31] 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[60] 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,[62] 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.[53,63–65] 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,[53] 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.[63]

The authors of 7 studies reported additional clinical findings.[31,35,37,40,41,53,66] 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,[31] no differences in clinical or sleep problems at 3 to 6 years between a moderate and severe HIE group and a comparison group,[35] 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.[40] At 3 to 6 years, a moderate and severe HIE group showed more depression symptoms than a comparison group.[35] 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).[41] A range of rates of referral to mental health or psychology services at 5 years in an HIE group were reported,[66] and there was a higher incidence of psychopathology at 6 to 9 years in a moderate and severe HIE than in a comparison group.[37] 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.[53]

DISCUSSION

Impact

Systematic reviews of outcomes after perinatal hypoxic-ischemic encephalopathy (HIE) have focused on motor, cognitive, and visual deficits.[10,69,70] 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).[25,26,31,34,35,37,38,40,41,46–48,51–53,60,62–64] Significant associations persisted in studies in which researchers administered TH[31,35,37,41,46] and across studies that were rated as low-[34,35,40,41] or medium-/high-quality.[25,26,31,37,38,46–48,51–53,60,62–64] We included studies referring either to HIE or NE, as many authors use these interchangeably,[2] 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[41] and personal-social quotient[25] and increased bedtime resistance and sleep anxiety[41] 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.[53] In addition, there was a higher incidence of HIE in children with ASD.[60] Mild HIE was associated with lower health-related quality of life[41] and abnormal hemodynamic brain responses to emotional prosodies,[34] and mild NE was associated with social and thought problems.[38] Behavior problems were reported in mild or moderate HIE (peer problems, less prosocial)[48] and mild or moderate NE (worse attention span, variability, irritability, explosiveness).[52] Moderate NE was associated with social and attention problems and anxious or depressed behavior,[38] and a moderate and severe NE group was 5.9 times more likely to be diagnosed with ASD.[62] Additionally, compared with mild HIE/NE, moderate HIE was associated with lower personal-social ability,[26] and moderate or severe NE was associated with lower health-related quality of life and increased sleep onset delay.[41]

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,[35] behavior problems,[46] anxious or depressed and aggressive behavior,[35] behavior regulation problems,[51] ADHD-related inattention,[64] depression symptoms,[35] and a higher incidence of psychopathology.[37] In addition, moderate NE was associated with ASD-related traits[63] and ADHD-related traits.[63] 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,[40] 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.[31] After excluding children with disabilities, NE was associated with a lower personal-social developmental quotient[25] and more behavior problems (hyperactivity, emotional problems, less prosocial)[47] than groups without NE, and a severe NE group showed more behavior problems (hyperactivity, emotional problems, peer problems) compared with a moderate NE group.[47]

Understanding how treatments or markers of injury relate to outcomes is critical for improving prognostic ability and identifying children in need of early intervention.[71] The authors of 8 included studies explored the associations between social, emotional, and psychological outcomes of HIE/NE and other clinical characteristics.[27,29,39,42,43,49,50,65] Personal-social developmental quotient and behavior problems worsened in HIE subgroups with normal or mild,

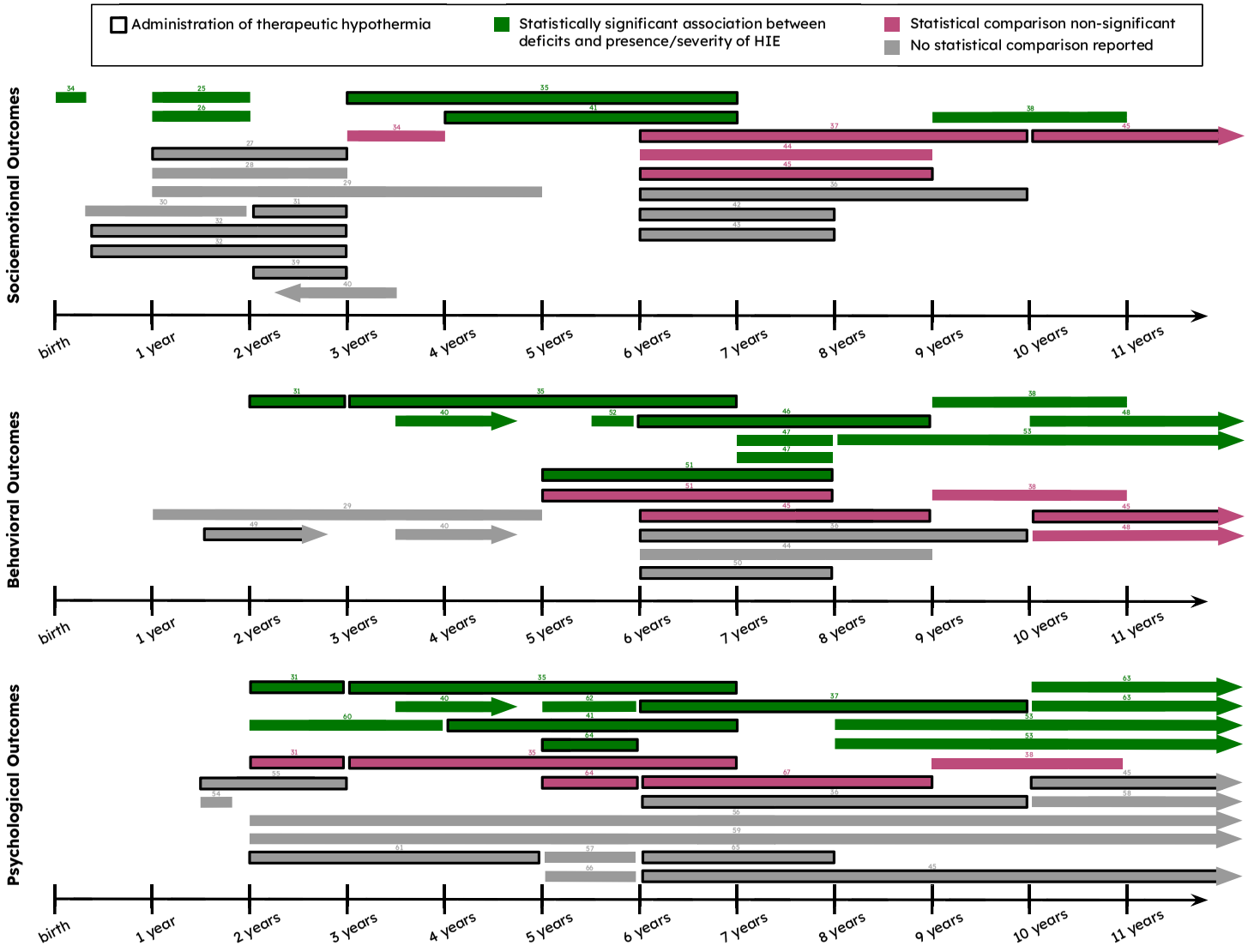

FIGURE 1

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).

moderate, and severe white matter injury, respectively,[29] and residuals of personal-social developmental quotient scores in an HIE group correlated with white matter fractional anisotropy values.[27] Socioemotional development scores were also lower in an HIE group with ≥3 episodes of hypoglycemia than in an HIE group with no episodes of hypoglycemia.[39] However, no differences in internalizing or externalizing between HIE groups with normal or abnormal neonatal MRI[49] or in emotional wellbeing, behavior problems, or ADHD-related traits between moderate and severe HIE groups who did or did not receive TH after birth, were reported.[42,43,50,65] No included studies assessed early intervention.

HIE/NE was associated with significant deficits in personal-social and socioemotional functioning[25,26,34,35,38,41] and behavioral functioning.[31,35,38,40,46–48,51–53] These deficits may be a result of injury to or abnormal organization of areas in the brain that coordinate socioemotional processing and behavior, as has been observed in human HIE[72,73] and rodent models.[74,75] Associations with ASD[60,62,63] and ADHD[53,63,64] 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 prematurity as compared with age-matched controls.[76] 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.[77,78] 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 psychoemotional development.[79] 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,[80] 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

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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 questionnaires, (4) referral to psychology, psychiatry, or other mental health services, and (5) presence of symptoms or diagnosis related to 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** "peripartum brain injury" **OR** "neonatal asphyxia" **OR** "perinatal asphyxia" **OR** "peripartum 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* difficult*" **OR** "behav* disorder*" **OR** externalising **OR** externalizing **OR** internalising **OR** internalizing **OR** "self-control" **OR** "mental health" **OR** "self-esteem" **OR** depression **OR** depressed **OR** anxiety **OR** anxious **OR** psycholog* **OR** neuropsycholog* **OR** psychiatr* **OR** neuropsychiatr* **OR** "attention deficit hyperactivity disorder" **OR** ADHD **OR** autis* **OR** ASD **OR** Asperger* **OR** schizo* **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.[21] 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 correct 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

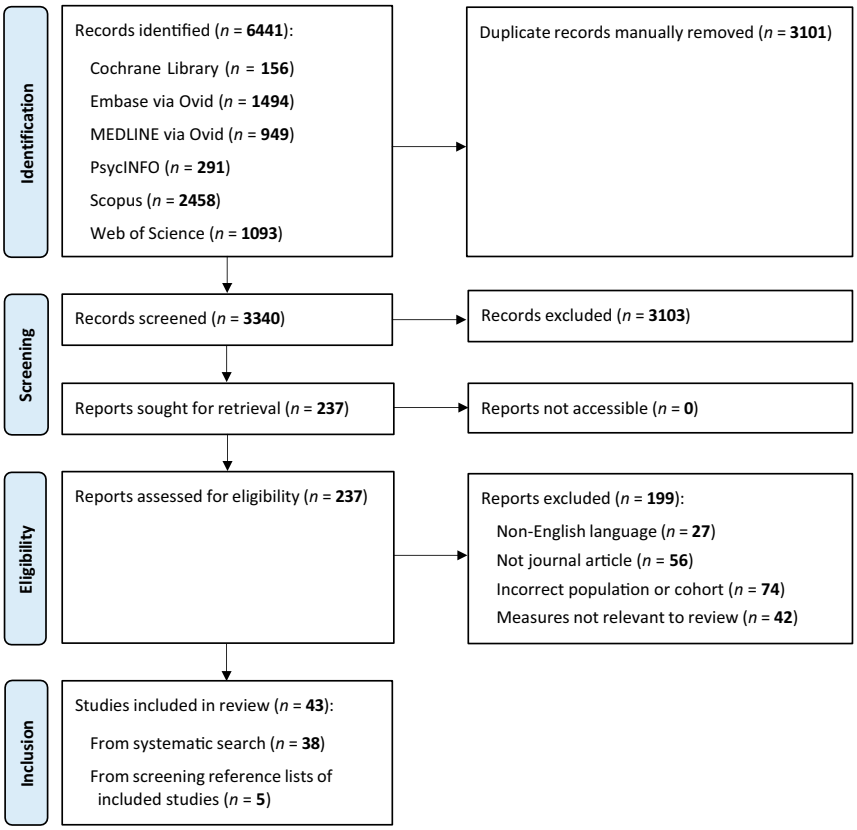
The quality of included studies was critically appraised via a star-based ranking system using adapted versions of the Newcastle-Ottawa Scale.[24] The exact flow of quality assessment varied based on observational study subtype. For our purposes, *cohort studies* were defined as reporting outcomes for 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. Additionally, we defined *prospective cohort studies* as recruiting the group with HIE/NE prospectively (e.g., at birth) and *retrospective cohort studies* as recruiting the group with HIE/NE retrospectively (e.g., at childhood age), regardless of timing of recruitment of the comparison group.

Two independent reviewers who are consultant neonatologists (H.W. and T.A.) blindly assessed the representativeness and identification of the group with HIE/NE (cohort and case series studies) or the identification of the presence or absence of a history of HIE/NE (case-control studies). 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.

Cochrane Library	("hypoxic-ischemic encephalopathy" OR "hypoxic-ischaemic encephalopathy" OR HIE OR "neonatal encephalopathy" OR "neonatal brain injury" OR "perinatal brain injury" OR "peripartum brain injury" OR "neonatal asphyxia" OR "perinatal asphyxia" OR "peripartum asphyxia" OR "birth asphyxia" OR "neonatal hypoxia" OR "perinatal hypoxia" OR "peripartum hypoxia" OR "birth hypoxia"):ti,ab,kw AND (social* OR emotion* OR socioemotional OR psychosocial OR psychoemotional OR "behav* issue*" OR "behav* problem*" OR "behav* difficult*" OR "behav* disorder*" OR externalising OR externalizing OR internalising OR internalizing OR "self-control" OR "mental health" OR "self-esteem" OR depression OR depressed OR anxiety OR anxious OR psycholog* OR neuropsycholog* OR psychiatr* OR neuropsychiatr* OR "attention deficit hyperactivity disorder" OR ADHD OR autis* OR ASD OR Asperger* OR schizo* OR bipolar):ti,ab,kw
Embase via Ovid	("hypoxic-ischemic encephalopathy" OR "hypoxic-ischaemic encephalopathy" OR HIE OR "neonatal encephalopathy" OR "neonatal brain injury" OR "perinatal brain injury" OR "peripartum brain injury" OR "neonatal asphyxia" OR "perinatal asphyxia" OR "peripartum asphyxia" OR "birth asphyxia" OR "neonatal hypoxia" OR "perinatal hypoxia" OR "peripartum hypoxia" OR "birth hypoxia") .ti,ab,kw. AND (social* OR emotion* OR socioemotional OR psychosocial OR psychoemotional OR "behav* issue*" OR "behav* problem*" OR "behav* difficult*" OR "behav* disorder*" OR externalising OR externalizing OR internalising OR internalizing OR "self-control" OR "mental health" OR "self esteem" OR depression OR depressed OR anxiety OR anxious OR psycholog* OR neuropsycholog* OR psychiatr* OR neuropsychiatr* OR "attention deficit hyperactivity disorder" OR ADHD OR autis* OR ASD OR Asperger* OR schizo* OR bipolar) .ti,ab,kw.
MEDLINE via Ovid	("hypoxic-ischemic encephalopathy" OR "hypoxic-ischaemic encephalopathy" OR HIE OR "neonatal encephalopathy" OR "neonatal brain injury" OR "perinatal brain injury" OR "peripartum brain injury" OR "neonatal asphyxia" OR "perinatal asphyxia" OR "peripartum asphyxia" OR "birth asphyxia" OR "neonatal hypoxia" OR "perinatal hypoxia" OR "peripartum hypoxia" OR "birth hypoxia") .ti,ab,kw. AND (social* OR emotion* OR socioemotional OR psychosocial OR psychoemotional OR "behav* issue*" OR "behav* problem*" OR "behav* difficult*" OR "behav* disorder*" OR externalising OR externalizing OR internalising OR internalizing OR "self-control" OR "mental health" OR "self-esteem" OR depression OR depressed OR anxiety OR anxious OR psycholog* OR neuropsycholog* OR psychiatr* OR neuropsychiatr* OR "attention deficit hyperactivity disorder" OR ADHD OR autis* OR ASD OR Asperger* OR schizo* OR bipolar) .ti,ab,kw.
PsycINFO	((TI ("hypoxic-ischemic encephalopathy" OR "hypoxic-ischaemic encephalopathy" OR HIE OR "neonatal encephalopathy" OR "neonatal brain injury" OR "perinatal brain injury" OR "peripartum brain injury" OR "neonatal asphyxia" OR "perinatal asphyxia" OR "peripartum asphyxia" OR "birth asphyxia" OR "neonatal hypoxia" OR "perinatal hypoxia" OR "peripartum hypoxia" OR "birth hypoxia")) OR (AB ("hypoxic-ischemic encephalopathy" OR "hypoxic-ischaemic encephalopathy" OR HIE OR "neonatal encephalopathy" OR "neonatal brain injury" OR "perinatal brain injury" OR "peripartum brain injury" OR "neonatal asphyxia" OR "perinatal asphyxia" OR "peripartum asphyxia" OR "birth asphyxia" OR "neonatal hypoxia" OR "perinatal hypoxia" OR "peripartum hypoxia" OR "birth hypoxia")) OR (KW ("hypoxic-ischemic encephalopathy" OR "hypoxic-ischaemic encephalopathy" OR HIE OR "neonatal encephalopathy" OR "neonatal brain injury" OR "perinatal brain injury" OR "peripartum brain injury" OR "neonatal asphyxia" OR "perinatal asphyxia" OR "peripartum asphyxia" OR "birth asphyxia" OR "neonatal hypoxia" OR "perinatal hypoxia" OR "peripartum hypoxia" OR "birth hypoxia"))) AND ((TI (social* OR emotion* OR socioemotional OR psychosocial OR psychoemotional OR "behav* issue*" OR "behav* problem*" OR "behav* difficult*" OR "behav* disorder*" OR externalising OR externalizing OR internalising OR internalizing OR "self-control" OR "mental health" OR "self-esteem" OR depression OR depressed OR anxiety OR anxious OR psycholog* OR neuropsycholog* OR psychiatr* OR neuropsychiatr* OR "attention deficit hyperactivity disorder" OR ADHD OR autis* OR ASD OR Asperger* OR schizo* OR bipolar)) OR (AB (social* OR emotion* OR socioemotional OR psychosocial OR psychoemotional OR "behav* issue*" OR "behav* problem*" OR "behav* difficult*" OR "behav* disorder*" OR externalising OR externalizing OR internalising OR internalizing OR "self-control" OR "mental health" OR "self-esteem" OR depression OR depressed OR anxiety OR anxious OR psycholog* OR neuropsycholog* OR psychiatr* OR neuropsychiatr* OR "attention deficit hyperactivity disorder" OR ADHD OR autis* OR ASD OR Asperger* OR schizo* OR bipolar)) OR (KW (social* OR emotion* OR socioemotional OR psychosocial OR psychoemotional OR "behav* issue*" OR "behav* problem*" OR "behav* difficult*" OR "behav* disorder*" OR externalising OR externalizing OR internalising OR internalizing OR "self-control" OR "mental health" OR "self-esteem" OR depression OR depressed OR anxiety OR anxious OR psycholog* OR neuropsycholog* OR psychiatr* OR neuropsychiatr* OR "attention deficit hyperactivity disorder" OR ADHD OR autis* OR ASD OR Asperger* OR schizo* OR bipolar)))
Scopus	(TITLE-ABS-KEY("hypoxic-ischemic encephalopathy" OR "hypoxic-ischaemic encephalopathy" OR HIE OR "neonatal encephalopathy" OR "neonatal brain injury" OR "perinatal brain injury" OR "peripartum brain injury" OR "neonatal asphyxia" OR "perinatal asphyxia" OR "peripartum asphyxia" OR "birth asphyxia" OR "neonatal hypoxia" OR "perinatal hypoxia" OR "peripartum hypoxia" OR "birth hypoxia")) AND TITLE-ABS-KEY(social* OR emotion* OR socioemotional OR psychosocial OR psychoemotional OR "behav* issue*" OR "behav* problem*" OR "behav* difficult*" OR "behav* disorder*" OR externalising OR externalizing OR internalising OR internalizing OR "self-control" OR "mental health" OR "self-esteem" OR depression OR depressed OR anxiety OR anxious OR psycholog* OR neuropsycholog* OR psychiatr* OR neuropsychiatr* OR "attention deficit hyperactivity disorder" OR ADHD OR autis* OR ASD OR Asperger* OR schizo* OR bipolar)
Web of Science	((TI=("hypoxic-ischemic encephalopathy" OR "hypoxic-ischaemic encephalopathy" OR HIE OR "neonatal encephalopathy" OR "neonatal brain injury" OR "perinatal brain injury" OR "peripartum brain injury" OR "neonatal asphyxia" OR "perinatal asphyxia" OR "peripartum asphyxia" OR "birth asphyxia" OR "neonatal hypoxia" OR "perinatal hypoxia" OR "peripartum hypoxia" OR "birth hypoxia")) OR (AB=("hypoxic-ischemic encephalopathy" OR "hypoxic-ischaemic encephalopathy" OR HIE OR "neonatal encephalopathy" OR "neonatal brain injury" OR "perinatal brain injury" OR "peripartum brain injury" OR "neonatal asphyxia" OR "perinatal asphyxia" OR "peripartum asphyxia" OR "birth asphyxia" OR "neonatal hypoxia" OR "perinatal hypoxia" OR "peripartum hypoxia" OR "birth hypoxia")) OR (KP=("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 "peripartum asphyxia" OR "birth asphyxia" OR "neonatal hypoxia" OR "perinatal hypoxia" OR "peripartum hypoxia" OR "birth hypoxia"))) AND ((TI=(social* OR emotion* OR socioemotional OR psychosocial OR psychoemotional OR "behav* issue*" OR "behav* problem*" OR "behav* difficult*" OR "behav* disorder*" OR externalising OR externalizing OR internalising OR internalizing OR "self-control" OR "mental health" OR "self-esteem" OR depression OR depressed OR anxiety OR anxious OR psycholog* OR neuropsycholog* OR psychiatr* OR neuropsychiatr* OR "attention deficit hyperactivity disorder" OR ADHD OR autis* OR ASD OR Asperger* OR schizo* OR bipolar)) OR (AB=(social* OR emotion* OR socioemotional OR psychosocial OR psychoemotional OR "behav* issue*" OR "behav* problem*" OR "behav* difficult*" OR "behav* disorder*" OR externalising OR externalizing OR internalising OR internalizing OR "self-control" OR "mental health" OR "self-esteem" OR depression OR depressed OR anxiety OR anxious OR psycholog* OR neuropsycholog* OR psychiatr* OR neuropsychiatr* OR "attention deficit hyperactivity disorder" OR ADHD OR autis* OR ASD OR Asperger* OR schizo* OR bipolar)) OR (KP=(social* OR emotion* OR socioemotional OR psychosocial OR psychoemotional OR "behav* issue*" OR "behav* problem*" OR "behav* difficult*" OR "behav* disorder*" OR externalising OR externalizing OR internalising OR internalizing OR "self-control" OR "mental health" OR "self-esteem" OR depression OR depressed OR anxiety OR anxious OR psycholog* OR neuropsycholog* OR psychiatr* OR neuropsychiatr* OR "attention deficit hyperactivity disorder" OR ADHD OR autis* OR ASD OR Asperger* OR schizo* OR bipolar)))

SUPPLEMENTAL FIGURE 3
Detailed search strategy.



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

2. *Ascertainment of exposure* (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. *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

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

SUPPLEMENTAL FIGURE 6

Adapted Newcastle-Ottawa Scale for case series studies.

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.