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RESEARCH ARTICLE

Outcomes in children after mild neonatal hypoxic ischaemic encephalopathy: A population-based cohort study

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Abstract

Objective: To investigate whether mild neonatal hypoxic ischaemic encephalopathy (HIE) in term born infants is associated with cerebral palsy, epilepsy, mental retardation and death up to 6 years of age.

Design: Population-based cohort study.

Setting: Sweden, 2009–2015.

Population: Live term born infants without congenital malformations or chromosomal abnormalities ($n = 505\,075$).

Methods: Birth and health data were retrieved from Swedish national health and quality registers. Mild HIE was identified by diagnosis in either the Swedish Medical Birth Register or the Swedish Neonatal Quality Register. Cox proportional hazards regression was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs).

Main outcome measures: A composite of the outcomes cerebral palsy, epilepsy, mental retardation and death up to 6 years of age.

Results: Median follow-up time was 3.3 years after birth. Of 414 infants diagnosed with mild HIE, 17 were classified according to the composite outcome and incidence rates were 12.6 and 2.9 per 1000 child-years in infants with and without HIE respectively. Infants with mild HIE was four times as likely to be diagnosed with the composite outcome (HR 4.42, 95% CI 2.75–7.12) compared with infants without HIE. When analysed separately, associations were found with cerebral palsy (HR 21.50, 95% CI 9.59–48.19) and death (HR 19.10, 95% CI 7.90–46.21). HRs remained essentially unchanged after adjustment for covariates.

Conclusions: Mild neonatal HIE was associated with neurological morbidity and mortality in childhood. Challenges include identifying infants who may develop morbidity and how to prevent adverse outcomes.

KEYWORDS
asphyxia, cerebral palsy, epilepsy, mental retardation, neonatal hypoxic ischaemic encephalopathy, neurological outcome

1 | INTRODUCTION

Neonatal hypoxic ischaemic encephalopathy (HIE) is the clinical syndrome of disturbed neonatal brain function caused by perinatal asphyxia in the term or near-term infant. The incidence is 1.3–1.7 per live births in high-income countries.[1] Depending on neurological symptoms and clinical findings in the newborn infant, the condition is graded

as mild, moderate or severe.[2] Moderate and severe HIE are known to be closely associated with significant neurological morbidity, long-term disability and mortality,[3] whereas outcomes after mild HIE have been less characterised.

As mild HIE carries a more favourable prognosis,[4–7] infants with mild HIE are not routinely enrolled in specialised follow-up programmes and are currently not included in therapeutic hypothermia trials for neuroprotection. However, recent studies have questioned this approach, as infants with mild HIE have a higher-than-expected incidence of short-term abnormalities, including abnormal amplitude-integrated electroencephalography (aEEG), brain magnetic resonance imaging (MRI) and neurological examinations at discharge from neonatal care.[8–11] Furthermore, follow-up studies at 2–5 years of age report that children with mild HIE at birth have higher rates of disabilities than controls.[3,12] However, cohort studies on outcome after mild HIE are small, and include up to 60 mild HIE cases,[12,13] with most including fewer than 30 cases. A systematic review from 2018 reported that 22% of 250 infants had abnormal neurological long-term outcomes after mild HIE.[14]

Given that approximately half of all HIE cases are mild,[3,15] the condition might be a contributor to a significant burden of disease. However, outcomes after mild HIE are understudied and population-based studies are lacking. Therefore, the aim of the current study was to investigate the association between mild HIE and severe neurological outcomes and death in a nationwide cohort utilising register-based data.

2 | METHODS

This population-based cohort study included all live, term born (gestational week 37 or later) infants without congenital malformations or chromosomal abnormalities born in Sweden 2009–2015. Data were retrieved from the Swedish Medical Birth Register (MBR) and linked to data from the Swedish Neonatal Quality Register (SNQ), the National Patient Register (NPR), the Cause of Death Register and the Total Population Register. Linkage of registers was possible due to the personal identity numbers allocated to all Swedish residents.

The MBR, founded 1973, contains high-quality validated data on 97–99% of all births in Sweden.[16,17] Data from antenatal, obstetric and neonatal care are collected prospectively by midwives and forwarded to the register through standardised forms. After delivery, diagnoses/procedures of mother and infant are established by physicians, based on the Swedish version of the 10th International Classification of Disease (ICD) codes,[18] and forwarded to the register.

The SNQ, established in 2001, is a validated register that includes detailed information and diagnoses for all infants referred to neonatal care within the first 27 days after birth. Since 1 January 2011, all neonatal care units in Sweden have been affiliated with the register.[19]

The NPR and the Cause of Death Register are both held by the Swedish National Board of Health and Welfare. The NPR includes data on all hospital admissions since 1987 and specialist outpatient care since 2001. Submitted data undergo regular quality controls and under-reporting is low.[20–22] The Cause of Death Register contains information on all deaths in Sweden by ICD codes and is updated yearly.[21] The Total Population Register is held by Statistics Sweden and includes country of birth for all Swedish residents.[23]

From the initial cohort of 710 494 infants, 1030 infants were excluded due to later detected congenital malformations (Figure 1). As the southern region of Sweden did not register data in the SNQ until 1 January 2011, 33 407 infants born in that region during 2009–2010 were excluded. Also excluded were infants with a diagnosis of moderate or severe HIE ($n = 531$) and infants who had received hypothermia treatment without a diagnosis of HIE ($n = 54$). If a woman gave birth to more than one infant during the study period, only one infant was included. If one of these infants had a diagnosis of mild HIE, that infant was included. If no infant had mild HIE, the included infant was selected randomly. The final study cohort included 505 075 live term born infants.

The exposure was mild HIE, diagnosed according to the Sarnat and Sarnat classification,[2] and identified as ICD code P916A, either in the MBR or the SNQ. If an infant had more than one HIE diagnosis, the highest grade of HIE was selected to minimise the risk of including infants with moderate and severe HIE.

Data on maternal, birth and infant characteristics were collected from the MBR. Maternal age, weight and self-reported height were retrieved from the first antenatal visit. Early pregnancy body mass index (BMI) was calculated (kg/m^2) and classified based on the World Health Organization classification: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2) or obesity (BMI ≥30.0 kg/m^2). At the first antenatal visit, the midwives asked questions concerning socio-economic factors, such as daily smoking habits and cohabitation with partner. Smoking habits were also evaluated at 30–32 gestational weeks. Non-smokers were classified as those who did not smoke at the first antenatal visit or at gestational weeks 30–32. Maternal epilepsy was either self-reported at the first antenatal visit or identified based on ICD codes (G40, G41). Intrapartum infection was classified as either fever during labour (ICD-10: O752) or chorioamnionitis (ICD-10: O411). Large for gestational age (LGA) and small for gestational age (SGA) were defined as a birthweight above or below two standard deviations from mean weight for the gestational age and sex according to clinical practice.[24] Multiple births were twins or triplets. Infants treated with therapeutic hypothermia were identified based on a checkbox in the SNQ.

The main outcome was a composite of the diagnoses cerebral palsy (ICD-10: G80–G83), epilepsy (ICD-10: G40, G41), mental retardation (ICD-10: F70–F89) and death during the study period 2009–2015. ICD diagnoses were collected

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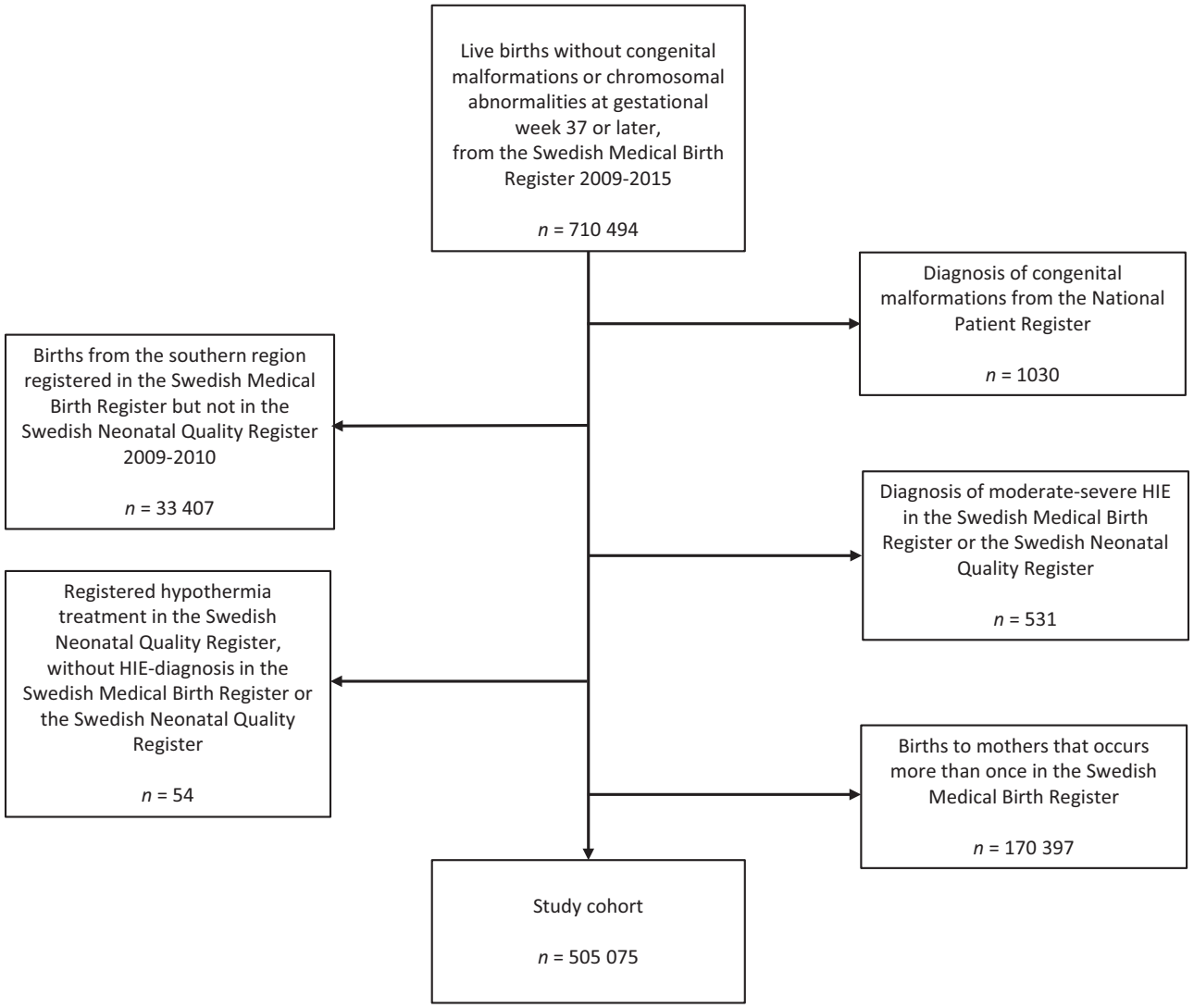

FIGURE 1 Flowchart of the study cohort.

from the NPR and deaths from the Cause of Death Register. Additionally, analyses were conducted on these outcomes separately. Perinatal core outcome sets were not used as they are under development[25] and are not yet available.

IBM SPSS version 28.0 was used for statistical analyses. The chi-square test was used for comparisons between maternal, birth and infant characteristics. A *P*-value <0.05 was considered to indicate statistical significance. Outcomes were captured from birth until the first diagnosis or until the end of the study period (31 December 2015). As the time of follow-up differed, Cox proportional hazard models were used and person-time incidence rates were calculated, in addition to the incidence of the outcomes. To estimate the probability of the outcomes if mild HIE had occurred, compared with if it had not, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Possible confounders were identified using a directed acyclic graph (dagitty.net/m2OPYOk). Hazard ratios were adjusted accordingly for maternal age, maternal BMI, maternal smoking, cohabitation with partner, fever during labour/diagnosis of chorioamnionitis, multiple birth and SGA. The composite outcome and epilepsy were also adjusted for maternal epilepsy to reduce any impact of heredity. Hypothermia treatment was considered but we chose not include the variable in the main regression analysis due to the aim of the study.

3 | RESULTS

In total, 414 infants were diagnosed with mild HIE, corresponding to an incidence of 0.8 per 1000 live-born infants. As a description of the cohort, maternal characteristics are displayed in Table 1. There were no differences in maternal age between mothers who gave birth to infants with or without mild HIE, but primiparity was more common in the mild HIE group ($P<0.01$). Mothers of infants with mild HIE were more often overweight or obese ($P<0.01$), and more often born in a middle- or low-income country ($P=0.02$). Smoking, cohabitation and employment did not differ between the groups. Mothers of infants with mild HIE had a

TABLE 1 Maternal characteristics of the study cohort.

	No HIE *n* = 504 661 *n* (%)	Mild HIE *n* = 414 *n* (%)	*P*-value
Age, years			0.40
≤20	13 048 (2.6)	10 (2.4)	
21–34	372 410 (73.8)	295 (71.3)	
≥35	119 201 (23.6)	109 (26.3)	
Missing	2 (0.0)	0	
Primiparous	229 005 (45.4)	267 (64.5)	<0.01
BMI,[a] kg/m^2			<0.01
<18.5	11 823 (2.3)	2 (0.5)	
18.5–24.9	283 284 (56.1)	195 (47.1)	
25–29.9	119 821 (23.7)	110 (26.6)	
≥30	60 214 (11.9)	75 (18.1)	
Missing	29 519 (5.8)	32 (7.7)	
Country of birth[b]			0.02
Sweden	376 538 (74.6)	296 (71.5)	
High-income country	29 677 (5.9)	21 (5.1)	
Middle-income country	80 417 (15.9)	74 (17.9)	
Low-income country	16 952 (3.4)	21 (5.1)	
Missing	1077 (0.2)	2 (0.5)	
Smokers[c]	30 095 (5.9)	26 (6.3)	0.70
Missing	23 380 (4.6)	25 (6.0)	
Cohabitation with partner	451 459 (89.5)	361 (87.2)	0.90
Missing	19 913 (3.9)	26 (6.3)	
Employment[d]	354 857 (70.3)	300 (72.5)	0.09
Missing	37 072 (7.3)	37 (8.9)	
Epilepsy[e]	2852 (0.6)	2 (0.5)	0.80
Hypertension[f]	21 138 (4.2)	26 (6.3)	0.03
Diabetes mellitus[g]	8236 (1.6)	15 (3.6)	<0.01

HIE, hypoxic ischaemic encephalopathy; *n*, numbers.
[a]Body mass index; calculated from self-reported height and measured weight at first antenatal visit (gestational weeks 8–10).
[b]According to the World Bank Country classification.
[c]At first antenatal visit and/or at gestational weeks 30–32.
[d]Full- or part-time employment.
[e]Self-reported at first antenatal visit and/or a diagnosis of epilepsy in the Swedish Medical Birth Register.
[f]Chronic hypertension, gestational hypertension, pre-eclampsia.
[g]Diabetes mellitus type 1 and 2, gestational diabetes.

higher frequency of hypertensive diseases ($P = 0.03$) and diabetes mellitus ($P < 0.01$).

Table 2 describes birth and infant characteristics and shows that infants with mild HIE were more often born late-term or post-term compared with those without HIE. Intrapartum infection was more common in the mild HIE group (5.8 versus 1.0%, $P < 0.01$), as were obstetric

TABLE 2 Birth and infant characteristics of the study cohort.

	No HIE *n* = 504 661 *n* (%)	Mild HIE *n* = 414 *n* (%)	*P*-value
Gestational age at birth, weeks			<0.01
37–40	372 243 (73.8)	225 (54.3)	
41 (late term)	96 017 (19.0)	128 (30.9)	
≥42 (post-term)	36 401 (7.2)	61 (14.7)	
Intrapartum infection[a]	5086 (1.0)	24 (5.8)	<0.01
Obstetric emergency[b]	3065 (0.6)	76 (18.4)	<0.01
Fetal presentation			<0.01
Occiput anterior	446 970 (88.6)	303 (73.2)	
Occiput posterior	22 620 (4.5)	37 (8.9)	
Breech	13 628 (2.7)	7 (1.7)	
Other	9709 (1.9)	27 (6.5)	
Missing	11 734 (2.3)	40 (9.7)	
Mode of delivery			<0.01
Spontaneous vaginal	378 787 (75.1)	116 (28.0)	
Instrumental[c]	35 687 (7.1)	131 (31.6)	
Caesarean section	83 103 (16.5)	166 (40.1)	
Missing	7084 (1.4)	1 (0.2)	
Multiple birth	4528 (0.9)	6 (1.4)	0.20
Apgar score <7 at 5 minutes	3968 (0.8)	294 (71.0)	<0.01
Missing	2405 (0.5)	7 (1.7)	
Female sex	247 332 (49.0)	179 (43.2)	0.02
LGA[d]	17 054 (3.4)	30 (7.2)	<0.01
SGA[e]	9498 (1.9)	19 (4.6)	<0.01
Therapeutic hypothermia	0	33 (8.0)	<0.01

HIE, hypoxic ischaemic encephalopathy; *n*, numbers.
[a]Chorioamnionitis and/or fever during labour.
[b]Placental abruption, eclampsia, cord prolapse, uterine rupture, shoulder dystocia.
[c]Vacuum extraction or forceps.
[d]Large for gestational age.
[e]Small for gestational age.

emergencies, which occurred in 18.4 versus 0.6% ($P < 0.01$). Instrumental vaginal delivery and caesarean section were also more common in the mild HIE group (both $P < 0.01$). Apgar score below 7 at 5 minutes occurred in 71% of the cases with mild HIE compared with 0.80% of those without HIE ($P < 0.01$). The infants with mild HIE were more often born LGA ($P < 0.01$) or SGA ($P < 0.01$).

Median follow-up time until diagnosis or end of the study was 3.3 years. Of the 414 infants with mild HIE, 17 fulfilled criteria for the composite outcome, indicating neurological morbidity or mortality (Table 3). This corresponded to an incidence of 41 per 1000 live births and an incidence rate of 12.6 per 1000 child-years. The corresponding numbers for infants without HIE were 9.5 per 1000 live births and 2.9 per 1000 child-years. The composite outcome was more than four times as likely to occur in children that had been

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TABLE 3 Infant outcome by hypoxic ischaemic encephalopathy (HIE).

Outcome	No HIE				Mild HIE				HR (95% CI)	
	n = 504 661				*n* = 414					
	n	1/1000	Child-years of follow-up	Rate/1000 child-years	*n*	1/1000	Child-years of follow-up	Rate/1000 child-years	Crude	Adjusted[b]
Composite outcome[a]	4786	9.5	1 678 111	2.9	17	41	1350	12.6	4.42 (2.75–7.12)***	3.85 (2.27–6.50)***
Cerebral palsy	345	0.7	1 685 704	0.2	6	14.5	1360	4.4	21.50 (9.59–48.19)***	13.68 (5.08–36.84)***
Epilepsy	1295	2.6	1 683 558	0.8	5	12.1	1363	3.7	4.78 (1.98–11.49)***	4.32 (1.62–11.53)**
Mental retardation	3129	6.2	1 681 527	1.9	3	7.2	1367	2.2	1.18 (0.38–3.66)	1.23 (0.40–3.81)
Death	324	0.64	1 686 599	0.2	5	12.1	1372	3.7	19.10 (7.90–46.21)***	19.07 (7.84–46.34)***

CI, confidence interval; HR, hazard ratio; *n*, numbers.

[a]Composite outcome of cerebral palsy, epilepsy, mental retardation and death.

[b]Adjusted for maternal age, body mass index, smoking, cohabitation with partner, intrapartum infection, multiple birth, small for gestational age. For the composite outcome and epilepsy, maternal epilepsy was added.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

diagnosed with mild HIE than in children without HIE (HR 4.42, 95% CI 2.75–7.12). Children with mild HIE at birth were also more likely to be diagnosed with cerebral palsy (HR 21.50, 95% CI 9.59–48.19) and epilepsy (HR 4.78, 95% CI 1.98–11.49), but not with mental retardation (HR 1.18, 95% CI 0.38–3.66). Mild HIE at birth also increased the HRs for death (HR 19.10, 95% CI 7.90–46.21). Adjustments for covariates did not significantly change the results.

Of the five infants who died, four died within the first week. Cause of death was infection specific to the perinatal period (P35–39) in two cases and complications of pregnancy, labour and delivery in two (P02-03). The fifth infant died within a month due to cerebrovascular disease (I60–69).

Thirty-three infants (8.0%) with mild HIE were treated with hypothermia, and two of these were diagnosed with the composite outcome. The association between mild HIE and the composite outcome was unaffected when therapeutic hypothermia was included in the regression model (HR 4.20, 95% CI 2.53–6.97; not shown in Table 3).

4 | DISCUSSION

4.1 | Main findings

In this population-based cohort study of term born infants with a median follow-up of about 3 years, infants with mild HIE were four times as likely to develop severe neurological morbidity or mortality as infants without HIE. However, the absolute numbers were low.

4.2 | Strengths and limitations

The size of the cohort and the large number of infants with mild HIE are strengths of our study. To the best of our knowledge, this is currently the largest study on mild neonatal HIE. As both the exposure and the outcomes are rare, the size of the cohort is crucial. The prospectively collected data on exposure from validated, high-quality healthcare registers minimised the risk for selection and information bias. In Sweden, care during pregnancy, labour and puerperium is free of charge and the vast majority of women attend. Child health services are also free of charge and reach all children from infancy to 5 years of age, regardless of socio-economic status.[26] Infants with mild HIE are followed according to the standard child health services programme, the same as infants without HIE, reducing the risk of selection bias. The design of the study also minimises the need for patient contribution and reduces the risk of loss to follow-up.

The study design and the use of ICD diagnoses can be considered both strengths and limitations. The criteria for HIE diagnosis were consistent during the study period. By using the highest grade of HIE in the registers, we increased the certainty of having included true mild HIE cases. However, it is still possible that some infants

with moderate or severe HIE have been misdiagnosed as mild HIE. A limitation is that we cannot validate the HIE diagnoses with regard either to HIE grade or to the role of asphyxia as cause of the encephalopathy. However, a pediatrician or neonatologist set the diagnoses, which makes the diagnoses reliable. The retrospective design constitutes a limitation concerning information on individual data and the severity of the diagnoses. There is also a risk that milder differences in cognition and motor skills, not requiring specialist care during the time of follow-up, have been missed. We also acknowledge the possible impact of confounders that are unknown or unavailable in our dataset.

4.3 | Interpretation

In high-income countries, the incidence of HIE is estimated to 1.5/1000 live births,[1,15] and approximately 40–50% are graded as mild.[3,15] Most studies that report incidence data are hospital-based, and only a few report data from population-based birth registers.[15] Smith et al. investigated trends of incidence over 21 years in a cohort comprising 450 000 births in England. During the last time period (1992–1996), the incidence of mild HIE was 0.8/1000,[27] which is consistent with the incidence reported in this study.

The definition of an abnormal outcome after mild HIE as well as the follow-up time differ between studies and we found no other population-based study that used ICD diagnoses for comparison. Our results indicate an association between mild HIE and abnormal neurological outcome, which is in line with previous studies.[8,12,14,28,29] However, we could not confirm the high proportions of overall abnormal outcomes reported, 22% at ≥18 months follow-up in a systematic review by Conway et al.[14] and 16% (7% severe) at 18–22 months in a study by Chalak et al.[28] In our cohort 4.1% of infants with mild HIE were classified according to the composite outcome, i.e. had an abnormal outcome.

Few studies have investigated the association between mild HIE, cerebral palsy and epilepsy specifically. Chalak et al.[28] reported one case of cerebral palsy (2.3%) 18–22 months after mild HIE in a cohort of 43 infants, whereas Tsuda et al.[30] reported two cases (4.2%) at 3 years' follow-up in a cohort of 48 infants with mild HIE. In the study by Tsuda et al., one of the infants with cerebral palsy also had epilepsy (2%). Although the follow-up time differs, these numbers are in agreement with our findings. Death after mild HIE has rarely been reported, but in a cohort of 60 infants with mild HIE, DuPont et al. reported one death.[13] Although the numbers are small, the association between mild HIE and death found in our study is potentially a new finding. Even though mild HIE was not cause of death, asphyxia may have contributed to the outcome of the causative morbidity.

In contrast to studies that used neurodevelopmental testing, we did not find a significantly increased probability of mental retardation in our cohort. Lower test scores after mild HIE, compared with healthy controls, have been reported at both at 2 and 5 years of age,[3,12] implying developmental delay. The ICD codes used in this study may be less sensitive than a clinical follow-up with a thorough neurological and psychological examination, and we recognise that the rate of disability may be underestimated.

A growing number of studies indicate that infants with mild HIE have an increased risk for short-term neurological abnormalities such as abnormal aEEG, abnormal brain MRI imaging, seizures during the early neonatal period and abnormal neurologic findings at discharge.[8,10,13] These findings may be a first indication of a later adverse outcomes[3,10,31] but their importance in discriminating between infants who could benefit from hypothermia treatment or predicting outcome after mild HIE requires further evaluation.[29] Unfortunately, our study lacked information from aEEG and MRI investigations, which could have contributed important knowledge in this regard.

A small proportion of infants with mild HIE in our study received hypothermia treatment. This illustrates the difficulty in rapidly (within 6 hours) establishing both a correct cause of the presenting symptoms and a correct grading of symptom severity corresponding to the treatment indications for therapeutic hypothermia.[32] Such evaluation will inevitably be more difficult when the presenting symptomatology is milder, and scores (e.g. Apgar) or laboratory findings (e.g. pH, base deficit) are closer to normal. Although a subset of infants diagnosed with mild HIE within 6 hours after birth might benefit from neuroprotective strategies,[10,33] the current clinical HIE categories clearly fall short in selecting infants for such treatment. It is also conceivable that mild encephalopathy may in some cases represent fetal/infant disease that is neither acute nor entirely explained by asphyxia, but rather by other underlying causes of encephalopathy. There is a growing trend to consider hypothermia treatment for mild HIE, although data on both efficacy and safety are lacking.[34] Therefore, the potential role of hypothermia treatment for this population urgently requires further studies.[35]

5 | CONCLUSION

A diagnosis of mild neonatal HIE is associated with cerebral palsy, epilepsy and death during childhood. The numbers are small, but not negligible. Register-based studies cannot establish a causal relation and future studies are needed to reproduce and elaborate on the findings. It remains unclear why an injury that is considered mild may lead to such severe outcomes, and it is important to establish whether the underlying cause is mild HIE, misclassified more severe HIE or other morbidity. Contrary to current routine, infants with HIE who do not fulfil criteria for hypothermia treatment, may benefit from a more thorough evaluation before discharge from neonatal care, as well as from being enrolled in specialist child health services follow-up. How to identify, treat and follow-up the subset of infants with mild HIE that may go on to develop morbidity are challenges and issues for future research.

AUTHOR CONTRIBUTIONS

MJ and AET set up the basis of the study and all co-authors were involved in designing the final version. Collection of data was performed by MJ. AET and SH performed the statistical analysis and all authors contributed to the interpretation of the results. AET and MJ drafted the article. Critical revisions and final approval of the version to be published were made by all authors.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS APPROVAL

The study was approved by the Research and Ethics Committee in Uppsala (No. 2015/156), 6 May 2015. No participant consent was needed, as data were anonymised. No patients or patient associations were involved in designing or conducting the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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