Early Human Development 218 (2026) 106536

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Glucose abnormalities in infants with birth asphyxia are associated with later neurological diagnoses

Niina Viitaharju [a,*], Vilhelmiina Parikka [a,b,c,d], Eliisa Löyttyniemi [e], Bishwesvar Singh [e], Kjell Helenius [a,b]

[a] Department of Clinical Medicine, University of Turku, 20521, Turku, Finland
[b] Department of Pediatrics and Adolescent Medicine, Turku University Hospital, 20521, Turku, Finland
[c] MediCity Research Laboratories, University of Turku, 20520, Turku, Finland
[d] InFLAMES Research Flagship Center, University of Turku, 20520, Turku, Finland
[e] Department of Biostatistics, University of Turku and Turku University Hospital, 20520, Turku, Finland

ARTICLE INFO

Keywords:
Birth asphyxia
Hypoglycemia
Hyperglycemia
Neurodevelopmental disorders
Epilepsy
Cerebral Palsy
Hearing disorders

ABSTRACT

Objective: To investigate the association between early glycemic profile and neurological outcome in neonates with birth asphyxia.

Study design: Retrospective single-center study on infants born ≥36 weeks gestational age with an ICD-10 diagnosis of birth asphyxia and/or hypoxic-ischemic encephalopathy, using early (<72 h) glucose values and clinical follow-up data extracted from medical records. Outcomes: death or any ICD-10 diagnoses indicating neurodevelopmental disorders (NDD; psychiatric, epileptical, paralytical, visual or hearing disorders) and individual diagnostic classes. Estimates were adjusted for infant sex, delivery mode and therapeutic hypothermia.

Results: Among 272 neonates, 44 infants received therapeutic hypothermia and 228 infants did not. In multivariate analyses of all infants, the association was significant between glucose <2.6 mmol/l and hearing disorders (aOR = 6.7, 95%CI 1.2–37.3). Glucose >8.3 mmol/l was significantly associated with cerebral palsy (OR = 4.5, 95%Cl 1.2–16.4) and hearing disorders (OR = 6.1, 95%Cl 1.2–29.7). In univariate analyses of the 228 infants who did not receive therapeutic hypothermia, both hypoglycemia and hyperglycemia were associated with cerebral palsy: glucose <2.6 mmol/l: OR 5.63 (1.1–29.7) and >8.3 mmol/l OR 8.83 (1.88–41.47); epilepsy: glucose <1.6 mmol/l: OR 12.2 (1.6–91.9) and >8.3 mmol/l 19.4 (2.0–192.6); and hearing disorders: glucose<1.6 mmol/l OR 8.1 (1.3–51.7) and >8.3 mmol/l OR 9.7 (1.6–60.2).

Conclusions: This study suggests that the glycemic profile in neonates with birth asphyxia during the first 72 h is associated with neurodevelopmental disorders. Further research is needed to verify these findings and investigate if neurological outcome could be improved by rigorous glycemic control.

1. Introduction

Birth asphyxia is one of the most severe complications during birth and a major cause of neonatal mortality [1]. It has been reported to be the third most common cause of neonatal death after preterm birth and severe infections [2]. Birth asphyxia can lead to hypoxic-ischemic encephalopathy (HIE) caused by insufficient blood flow and oxygen delivery to the brain during or shortly after birth, manifesting as various neurological symptoms [3]. The incidence of HIE is 1.5–2.5 per 1000 live births in developed countries [4]. HIE can lead to death or severe disabilities such as cognitive disability, epilepsy and cerebral palsy. Therapeutic hypothermia is the only evidence-based treatment in clinical use for infants with HIE [5], and reduces mortality and the risk of severe neurological impairment in infants with moderate or severe HIE [4]. Despite this treatment, there is a considerable burden of disability in survivors, and early recognition of the most severely affected individuals remains a clinical challenge.

Early dysglycemia is a common finding after birth asphyxia, occurring in approximately 42–63% of infants with moderate to severe HIE [6–8]. Several studies have found an association between hypoglycemia and unfavorable MRI findings or neurological outcomes in HIE

* Corresponding author.
E-mail addresses: nimarv@utu.fi (N. Viitaharju), vilpar@utu.fi (V. Parikka), eliisa.loyttyniemi@utu.fi (E. Löyttyniemi), bishwesvar.p.singh@utu.fi (B. Singh), kkhele@utu.fi (K. Helenius).

https://doi.org/10.1016/j.earlhumdev.2026.106536
Received 12 December 2025; Received in revised form 4 February 2026; Accepted 7 March 2026
Available online 17 March 2026

Abbreviations

HIE	Hypoxic-ischemic encephalopathy
ICD-10	International Classification of Diseases, 10th Revision
MRI	magnetic resonance imaging
NDD	Neurodevelopmental disorder

[6,7,9,10]. In particular, recurrent hypoglycemia or prolonged duration of hypoglycemia within the first 12–72 h has been associated with adverse outcomes [11–13]. The results related to hyperglycemia are more conflicting. According to some previous studies, hyperglycemia does not increase the risk of brain injury in MRI [10,13], and has been suggested to be associated with a more favorable response to therapeutic hypothermia [9].

In a recent study using continuous glucose monitoring, episodes of hyperglycemia were found to last significantly longer than episodes of hypoglycemia [12]. Another study revealed that periods of hyperglycemia, but not hypoglycemia, were temporally associated with worse aEEG background scores and electrographic seizures [14]. Hyperglycemia has also been linked to abnormalities in evoked potentials [15], worse MRI findings [16,17], adverse outcomes at 18–24 months [6,12,18], and death [7,18]. The mechanisms underlying early glucose disturbances are not fully understood, and further studies are needed to determine whether these abnormalities primarily serve as markers of more severe brain injury or if the prognosis could be altered through glycemic control.

Previous studies on the association between glucose levels and neurological outcome have mainly focused on infants diagnosed with moderate or severe HIE. Additionally, there is a paucity of data beyond the 18–24-month follow-up period. Although previous research has demonstrated some associations between glucose levels and adverse neurodevelopmental outcomes, the potential real-world impact of such impairments in the long term remains largely unclear. Therefore, we aimed to describe the potential association between early glucose abnormalities and long-term neurological outcome in infants diagnosed with birth asphyxia, focusing also on infants who did not fulfil clinical criteria for therapeutic hypothermia.

2. Methods

2.1. Study population

This was a retrospective study of infants born at ≥36 gestational weeks and admitted for neonatal care due to birth asphyxia (ICD-10 category P21, defined as cardiorespiratory compromise related to asphyxia accompanied with Apgar score <8 at 1 min of age and/or umbilical artery pH <7.05) and/or hypoxic-ischemic encephalopathy (ICD-10 subcategory P91.0, defined according to Sarnat staging) within Turku University Central Hospital catchment area between Jan 1, 2010 and Jun 1, 2022. Infants with severe congenital anomalies, genetic conditions or congenital viral infections were excluded. Participant data were extracted from electronic medical records, excluding infants with missing laboratory values or follow-up data (depending on municipality, some children in our region are by default followed up after discharge at a non-affiliated pediatric subspecialty center, for whom follow-up data are not available in our database). Medical records were evaluated for any erroneous inclusion diagnoses, and infants not meeting the inclusion criteria (such as infants needing short-term ventilation due to maternal general anesthesia) were excluded.

Due to the retrospective design of the study, Sarnat scores could not be reliably verified in all cases due to partly incomplete reporting of the individual Sarnat criteria; therefore, receipt of therapeutic hypothermia was used as a proxy. In our unit, therapeutic hypothermia has been routine care for moderate and severe HIE (Sarnat stage 2 and 3) since 2010. Therapeutic hypothermia is not used for mild HIE (Sarnat stage 1). The protocol is strictly adhered to and has remained the same throughout the study period.

2.2. Glucose

We collected all glucose values recorded within the first 72 h of life during routine neonatal care from medical records, and compared infants based on their highest and lowest glucose values. Glucose values <2.6 mmol/l (approximately 47 mg/dl) were considered hypoglycemic and values >8.3 mmol/l (150 mg/dl) were considered hyperglycemic. We also performed the analyses using different glucose thresholds that have been used in other similar studies (<2.2 mmol/l, 40 mg/dl; <1.6 mmol/l, 29 mg/dl; and >10.0 mmol/l, 180 mg/dl). Blood glucose is usually measured either as part of capillary or arterial blood gas sampling (ABL Radiometer, Brønshøj, Denmark) or through point of care glucose testing (HemoCue, Ängelholm, Sweden).

2.3. Outcome

The primary outcome was defined as any occurrence of death or ICD-10 diagnoses indicating neurodevelopmental disorders (NDD): F70-98 (psychiatric disorders), G40-41 (epileptic disorders), G80-83 (cerebral palsy and other paralytic syndromes), H47-49 and H53-54 (visual disorders) or H90-91 (hearing disorders). Diagnostic classes were also analyzed individually. All diagnoses were made within pediatric specialized health care in our tertiary university hospital, involving specialists such as pediatricians, pediatric neurologists, ophthalmologists, otorhinolaryngologists, audiologists and pediatric psychiatrists.

2.4. Statistical methods

Categorical variables are summarized using counts and percentages. Continuous variables are summarized with mean and standard deviation (SD), or median and interquartile range (IQR), as appropriate, based on their distribution. For specified time periods (0-1 h, 1-6 h, 6-24 h, 24-72 h) minimum, maximum and mean glucose values, and the number of infants having glucose values below or above predefined thresholds are summarized using median with interquartile range (IQR). Some infants did not have glucose measurements in every time interval and therefore the number of infants in each time interval varies.

Univariate logistic regression was performed to study the association between dysglycemia (defined as at least one glucose measurement outside the predefined thresholds) and the selected outcomes; this analysis was performed also separately on those infants who did not receive therapeutic hypothermia. After the univariate approach, a multivariate logistic regression model was applied to the whole cohort, adjusting for therapeutic hypothermia, infant sex, and mode of delivery (vaginal or C-section). Infant sex and mode of delivery were included in the model due to their potential effect on the studied outcomes. All results are presented as odds ratios (OR) or adjusted odds ratios (aOR) together with 95% confidence intervals (95%CI).

Due to non-standardized follow-up time, age at diagnosis for selected glucose thresholds and outcomes was presented using Kaplan-Meier plots where the end of follow-up as well as time of death was used as censored times (competing risk model) in log-rank test. A two-tailed p-value of <0.05 was considered statistically significant. Data analyses were generated using SAS software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

3. Results

We identified a total of 304 infants, of which 32 infants were excluded according to exclusion criteria, leaving 272 eligible infants. Table 1 shows detailed background information on the study

Table 1
Distribution of background variables among 272 infants with the diagnosis of birth asphyxia (ICD-10 category P21) and/or hypoxic-ischemic encephalopathy (ICD-10 subcategory P91.0)[1].

	Total (*n* = 272)	Therapeutic hypothermia (*n* = 44)	No therapeutic hypothermia (*n* = 228)
Gestational age, weeks	40 (39, 41)	40 (36, 42)	40 (36, 42)
Birth weight, grams	3579 (539)	3655 (527)	3564 (542)
Sex			
Male	156 (57.4%)	26 (59.1%)	130 (57.0%)
Female	116 (42.6%)	18 (40.9%)	98 (43.0%)
Multiple gestation	4 (1.5%)	1 (2.3%)	3 (1.3%)
Apgar scores			
1 min (*n* = 270)	3 (2, 4)	2 (0, 3)	3 (2, 4)
5 min (*n* = 267)	6 (4, 6)	3 (1, 4)	6 (4, 7)
10 min (*n* = 100)	7 (5, 8)	4 (3, 5)	7 (6, 8)
Umbilical arterial pH (*n* = 244)	7.07 (0.14)	7.06 (0.16)	7.07 (0.13)
Umbilical vein pH (*n* = 224)	7.19 (0.15)	7.18 (0.17)	7.19 (0.14)
Mode of delivery			
Vaginal delivery	174 (64.0%)	27 (61.4%)	147 (64.5%)
Cesarean section	98 (36.0%)	17 (38.6%)	81 (35.5%)
Delivery room management			
Mask ventilation	209 (76.8%)	40 (90.9%)	169 (74.1%)
Intubation	48 (17.6%)	28 (63.6%)	20 (8.8%)
Chest compression	22 (8.1%)	15 (34.1%)	7 (3.1%)
Adrenaline	9 (3.3%)	9 (20.5%)	0 (0.0%)
Other resuscitation medications	2 (0.7%)	2 (4.5%)	0 (0.0%)
IV fluid bolus	41 (15.1%)	19 (43.2%)	22 (9.6%)
Blood/Red blood cell transfusion	2 (0.7%)	1 (2.3%)	1 (0.4%)
Time to first spontaneous breath (min) (*n* = 249)	11.7 (10.6)	21.6 (11.4)	9.8 (9.3)
Time to spontaneous circulation (min) (*n* = 253)	3.2 (3.9)	7.4 (7.1)	2.3 (2.0)
Clinical care			
Mechanical ventilation	74 (27.2%)	39 (88.6%)	35 (15.4%)
Medications			
Sedative	90 (33.1%)	40 (90.9%)	50 (21.9%)
Inotropic	36 (13.2%)	12 (27.3%)	24 (10.5%)
Anticonvulsant	30 (11.0%)	19 (43.2%)	11 (4.8%)
Age at hospital discharge, days	6 (4, 8)	12 (8, 17)	6 (4, 7)

[1] Values are presented as n (%), mean (SD) or median (IQR), as appropriate, unless otherwise stated.

population. Median Apgar scores were 3 at 1 min and 6 at 5 min, and the mean umbilical arterial pH was 7.07 (SD 0.14). 209 (76.8%) infants required ventilation after birth and 48 (17.6%) needed intubation. 228 (83.8%) infants did not receive therapeutic hypothermia, and 44 (16.2%) infants did. The median age at hospital discharge was 6 (IQR 4–8) days.

3.1. Glucose values at different time points

All 272 infants had at least one (median 7, range 1 to 26) recorded glucose value within the first 72 h of life (data not shown). The median number of glucose measurements outside the normal range (2,6–8,3 mmol/l) was 2 (range 1–12) per infant. The frequency of hypoglycemia was highest between 1 and 6 h of life (*n* = 48 out of 240, 20.0%). Between 24 and 72 h of life, 25 out of 239 (10.5%) infants had hypoglycemia. The frequency of hyperglycemia was also highest between 1 and 6 h of life (*n* = 40 out of 240, 16.7%). Between 24 and 72 h of life, 9 out of 239 (3.8%) infants had hyperglycemia. The total number of infants with at least one glucose below the threshold were 23 (8,5%), 55 (20,2%) and 90 (33,1%) for thresholds <1,6 mmol/l, <2,2 mmol/l and <2,6 mmol/l, respectively. The total number of infants with at least one glucose measurement above the hyperglycemic thresholds were 59 (21,7%) and 33 (12,1%) for thresholds >8,3 mmol/l and >10,0 mmol/l, respectively.

3.2. Neurological outcomes

The median age at the last follow-up record was 11.44 years (range 2.39–14.81). The annual incidence of birth asphyxia and/or HIE in our hospital catchment area decreased from approximately 40 during the first three years of the study period to approximately 12 during the last full three years (data not shown), which explains the high median follow-up age. In the whole cohort, 52 out of 272 (19.1%) infants were diagnosed with at least one of the studied diagnoses. Of these, 9 (3.3%) were diagnosed with epileptic disorders, 13 (4.8%) with cerebral palsy, 9 (3.3%) with hearing disorders, 12 (4.4%) with visual disorders and 38 (14.0%) with psychiatric disorders. Five infants (1.8%) died, all had received therapeutic hypothermia, and all died during the first two weeks of life.

Among the 228 infants who did not receive therapeutic hypothermia, diagnoses were distributed as follows: epileptic disorders 4 (1.8%); cerebral palsy 7 (3.1%); hearing disorders 5 (2.2%); visual disorders 7 (3.1%); psychiatric disorders 28 (12.3%).

3.3. Hypoglycemia and neurological outcome

Infants with hypoglycemic values had a higher risk of being diagnosed with neurodevelopmental disorders (Fig. 1 forest plot, Supplementary Fig. 1a-b, Supplementary Table 1). In univariate analyses, there was a statistically significant association between glucose <1.6 mmol/l and NDD or death, NDD, cerebral palsy, epilepsy, hearing disorders and visual disorders. In the multivariate analyses the association remained significant for NDD and hearing disorders. The timing of diagnoses (NDD or death, cerebral palsy, epilepsy and hearing disorders) is shown in a Kaplan-Meier plot comparing infants with glucose <1.6 mmol/l to those with glucose >1.6 mmol/l (Fig. 2a-d).

In univariate analyses, there was a statistically significant association between glucose <2.2 mmol/l and NDD and hearing disorders. Glucose <2.6 mmol/l was associated with hearing disorders. In the multivariate analyses the associations between hypoglycemia and hearing disorders remained significant for glucose <2.6 mmol/l.

Among the 228 infants who did not receive therapeutic hypothermia, univariate analyses showed a statistically significant association between glucose <1.6 mmol/l and NDD or death, cerebral palsy, epileptic disorders and hearing disorders; between glucose <2.2 mmol/l and NDD or death; between glucose <2.6 mmol/l and cerebral palsy (Table 2.).

3.4. Hyperglycemia and neurological outcome

In univariate analyses glucose >10 mmol/l was statistically significantly associated with NDD or death, NDD, cerebral palsy and hearing disorders. (Fig. 3 forest plot, Supplementary Table 2). In the multivariate analyses the association remained statistically significant for NDD or death and hearing disorders.

In univariate analyses glucose >8.3 mmol/l was statistically significantly associated with NDD or death, NDD, cerebral palsy, epilepsy,

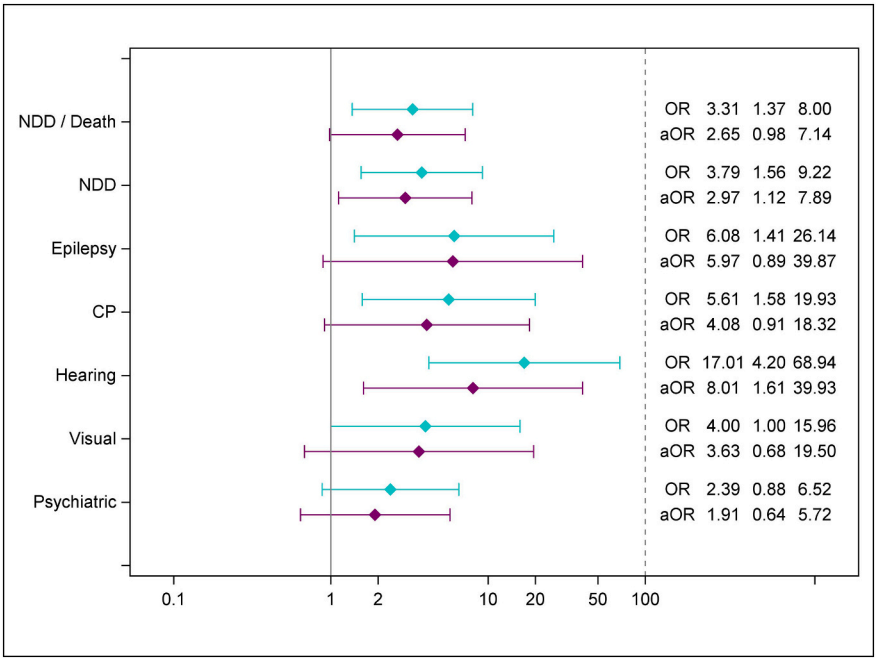

Fig. 1. Forest plot of the unadjusted (OR) and adjusted (aOR) estimates of associations between severe hypoglycemia (<1.6 mmol/l) and neurodevelopmental disorders.

hearing disorders and psychiatric disorders (Supplementary Fig. 2). In the multivariate analyses the association remained statistically significant for cerebral palsy and hearing disorders. The timing of diagnoses (NDD or death, cerebral palsy, epilepsy and hearing disorders) is shown in a Kaplan-Meier plot comparing infants with hyperglycemia (glucose >8,3 mmol/l) to those without hyperglycemia (Fig. 4a-d).

Among the 228 infants who did not receive therapeutic hypothermia, univariate analyses showed a statistically significant association between glucose >10.0 mmol/l and cerebral palsy and hearing disorders; between glucose >8.3 mmol/l and cerebral palsy, epileptic disorders and hearing disorders (Table 2.).

4. Discussion

This study found a statistically significant association between the primary outcome of death or neurodevelopmental disorders and severe hypo- and hyperglycemia, but no significant associations with other predefined levels of dysglycemia. However, when analyzing diagnosis groups individually, our results suggest associations with the most severe forms of dysglycemia, which were especially pronounced relating to hearing disorders. Interestingly, hearing disorders emerged in severely dysglycemic infants even in the absence of therapeutic hypothermia, suggesting that disease severity may not be the only factor affecting the auditory system in these infants.

Although adverse outcomes were quite rare in this study, the rates of neurodevelopmental diagnoses were higher compared to previously reported national rates, also among infants who did not qualify for therapeutic hypothermia. A Finnish register-based study project evaluated the incidence of neurodevelopmental disorders among preterm and term infants using ICD-10 codes in national registers and found that in term infants from 2002 to 2008, the incidence of epilepsy was 0.4%, CP 0.1%, hearing loss 0.23% and visual disturbances 0.55% [19–21].

Previous studies have emphasized the high prevalence and clinical significance of early dysglycemia in infants with HIE [6,9,25]. Retrospective analysis of large clinical trials, such as CoolCap [6], HEAL [7], and LyTONEPAL [8] have reported abnormal glucose values in 43–63% of study infants with moderate-to-severe HIE. In a recent single-center study, dysglycemia was most prevalent in the first 24 h of therapeutic hypothermia, with hyperglycemia occurring more frequently than hypoglycemia [13]. Our study supports this finding, as hyperglycemia in our data was observed mainly during the first 24 h. However, hypoglycemia still occurred up to 72 h of age in our study, suggesting that continuous glucose monitoring extended to 72 h could be beneficial.

Post hoc analysis of the CoolCap trial with 234 HIE infants showed that both hypo- and hyperglycemia during the first 12 h were associated with death or severe disability (abnormal Gross Motor Function Classification System score, low score in Bayley scales or bilateral cortical visual impairment) at 18 months of age [6,13]. Another post hoc analysis of 491 infants using Bayley Scales and Gross Motor Function Classification System for the assessment reported that hypoglycemic neonates had an increased risk of death and neurodevelopmental impairment at 22 to 36 months [7]. Similarly, some other studies have shown an association between early hypoglycemia and adverse neurodevelopmental outcome [12]. In contrast, studies on the association between hyperglycemia in asphyxic infants and neurological outcome has yielded variable results. One study using continuous glucose monitoring found no associations between hyperglycemia and unfavorable outcome [13]. One multi center post hoc analysis found a reduced risk of unfavorable outcome with hyperglycemia in HIE infants who were treated with hypothermia [9]. On the other hand, recent studies have linked early hyperglycemia to abnormalities in evoked potentials [15], worse MRI findings [16,17], adverse outcomes at 18–24 months [6,12] and death [7]. Our data focusing on long term outcomes and demonstrating an association between early hyperglycemia and unfavorable neurological outcome is in line with some of these previously reported early-phase findings.

Our retrospective study with a median follow-up of 11 years, using ICD-10 diagnostic codes for neurodevelopmental disorders assigned by pediatric specialists, revealed an interesting association between hearing impairment and hypo- and hyperglycemic values during the first 72 h. This association was pronounced in the subgroup with severe hyperglycemia (>10 mmol/l). This may further highlight the vulnerability of the auditory system to glucose imbalances. Of note, no similar association was found for visual disorders. To date, previous studies focusing on early clinical findings or neurodevelopmental assessments at 18–24 months of age have not actively investigated or reported the association

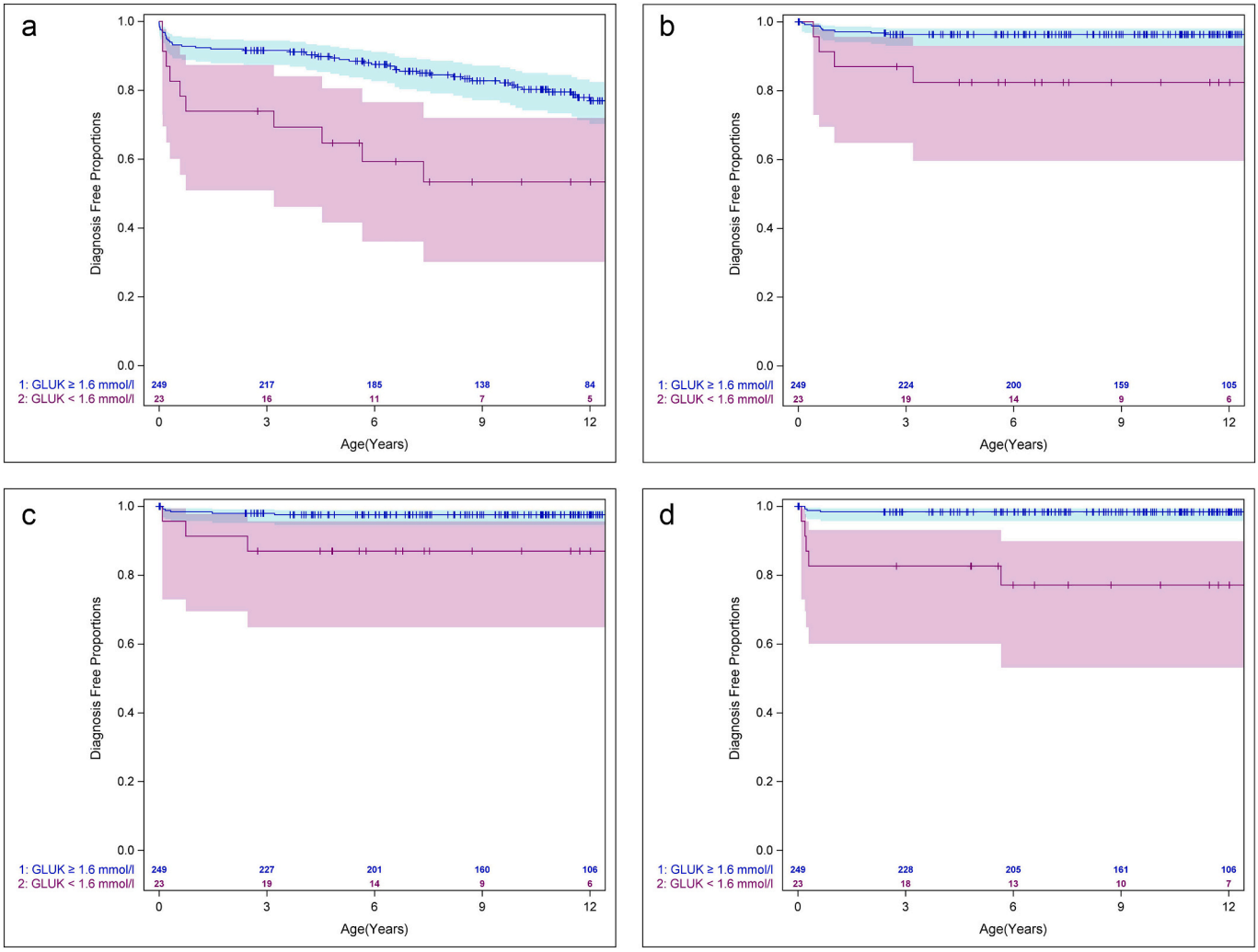

Fig. 2. Incidence over time of diagnoses of neurodevelopmental disorders (a. NDD or death, b. cerebral palsy, c. epilepsy, d. hearing disorders) comparing infants with severe hypoglycemia (glucose <1.6 mmol/l) to those without severe hypoglycemia.

Table 2
Univariate associations between dysglycemia and adverse neurodevelopmental outcome in infants with birth asphyxia and no or mild hypoxic-ischemic encephalopathy (therapeutic hypothermia criteria not fulfilled, n = 228).

	<1.6	<2.2	<2.6	>8.3	>10
NDD or death OR (95% CI)	3.35 (1.22–9.17)	2.28 (1.04–4.98)	1.70 (0.83–3.47)	1.76 (0.73–4.27)	2.68 (0.76–9.39)
Cerebral palsy OR (95% CI)	9.61 (1.98–46.70)	3.29 (0.71–15.28)	5.63 (1.07–29.72)	8.83 (1.88–41.47)	8.44 (1.46–48.97)
Epileptic disorders OR (95% CI)	12.18 (1.61–91.92)	4.33 (0.59–31.65)	6.60 (0.68–64.57)	19.40 (1.95–192.62)	6.46 (0.62–67.20)
Hearing disorders OR (95% CI)	8.08 (1.26–51.70)	2.87 (0.47–17.74)	3.28 (0.54–20.06)	9.65 (1.55–60.17)	35.67 (5.28–240.73)
Visual disorders OR (95% CI)	1.88 (0.21–16.48)	0.69 (0.08–5.88)	0.35 (0.04–2.92)	0.98 (0.12–8.45)	NA
Psychiatric disorders	2.06 (0.63–6.70)	2.23 (0.93–5.35)	1.71 (0.76–3.83)	2.23 (0.86–5.77)	2.55 (0.65–10.04)

between abnormal glucose levels and hearing impairment. However, an increased risk of hearing loss has previously been described in a retrospective analysis focusing on risk factors for hearing impairment [22]. In that study, abnormal initial blood glucose levels (either <2.7 mmol/l or >10 mmol/l) were identified as a risk factor for the development of hearing loss in infants treated with therapeutic hypothermia for HIE in a univariate model. Another recent study examining the relationship between the first postnatal blood glucose values and outcomes beyond 12 months of age reported a correlation between hyperglycemia and hearing impairment [16]. Interestingly, hearing impairment was significantly more common in infants with hyperglycemia but not in those with hypoglycemia. In contrast, a retrospective cohort study assessing the association between hypoglycemia and neurodevelopmental outcomes at 24 months found that deafness was more frequent in infants who experienced three or more episodes of hypoglycemia compared to those with no recorded hypoglycemic episodes [11].

Although our findings suggest a relationship between the degree of

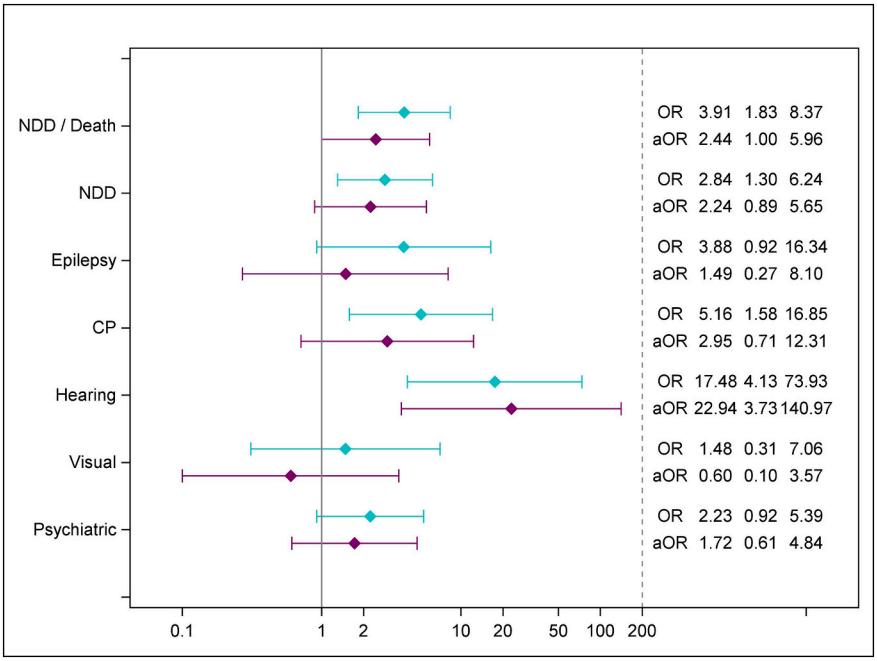

Fig. 3. Forest plot of the unadjusted (OR) and adjusted (aOR) estimates of associations between hyperglycemia (>10 mmol/l) and neurodevelopmental disorders.

glucose abnormality and the risk of a future diagnosis of hearing disorders, the causal nature of this association remains uncertain. In a study by Lee et al., hyperglycemia, in addition to hearing impairment, was correlated with clinical staging and parenchymal brain lesions on MRI [16]. In our cohort, however, hearing impairment was not limited to infants receiving therapeutic hypothermia (as proxy for moderate-severe HIE), but six out of ten infants who developed hearing defects had not received therapeutic hypothermia. The mechanisms underlying the adverse effects of hypo- and hyperglycemia remain elusive. Recently, particular attention has been given to the role of hyperglycemia and its pathophysiological mechanisms, which have been actively studied and debated. It has been proposed that hyperglycemia is associated with prolonged or intermittent hypoxia and may result from elevated stress hormones, increased insulin resistance, and decreased glucose uptake by the depressed tissue [16,26]. Additionally, hyperglycemia has been shown to induce increased cellular oxidative stress. A prospective cohort study using continuous glucose monitoring has further highlighted the significance of hyperglycemia, demonstrating that episodes of hyperglycemia were temporally associated with abnormal findings and greater seizure frequency on aEEG monitoring [14]. Similar associations between hyperglycemia and EEG findings have been reported in a recent study which found associations between hyperglycemic episodes and worse visual EEG background scores and 11 computational EEG measures out of 22 measures investigated in the study [23].

Recent studies have suggested that continuous glucose monitoring can be used to promptly detect dysglycemia and thereby facilitate better management of glucose levels [18,24]. Our analyses were performed retrospectively but we captured all recorded glucose values during the first 72 h, and used specific clinical diagnoses as outcomes, which might be more clinically relevant in estimating the prognostic value of dysglycemia and planning follow-up of asphyxia survivors. Using specific diagnosis classes and extending the follow-up period beyond the typical 18 months may elaborate the view on neurodevelopmental outcomes. Previous studies have primarily focused on infants with moderate/severe HIE. Our study provides useful new information by including also infants with birth asphyxia without a given HIE diagnosis, which is clinically relevant because most infants with birth asphyxia do not develop moderate/severe HIE and are largely overlooked in clinical research. Using this approach, we found an association between early hypoglycemia and epilepsy, as well as between early hyperglycemia and cerebral palsy. Both hypo-and hyperglycemia during the first 72 h were also associated with hearing disorders.

We acknowledge several limitations in our study. Data were collected from patient records retrospectively, and some infants were excluded because of missing information due to follow-up at a non-affiliated subspecialty center. Additionally, the follow-up time was not standardized, leading to variation in the number of patients at risk at different ages, as illustrated in the Kaplan-Meier plots, and potentially biasing the findings towards more severe outcomes as more severely affected infants might have more frequent follow-up visits. However, the median follow-up time of 11 years can be regarded as a strength. Our data indicated that most of the infants were diagnosed before the age of 2 years, except for children with psychiatric diagnoses. Therefore, it is reasonable to assume that the follow-up was sufficient to capture important neurological and sensory disorders, though it may not have been adequately powered to detect all long-term psychiatric morbidities, which often present closer to school age. Another limitation was the lack of access to the results of structured neurodevelopmental assessments. Using tests such as the Bayley scales is a gold standard in neonatal research, but issues such as hearing disorders might not necessarily be captured at 18 months of age. By using specific diagnostic domains assigned in specialized health care as outcome, we were able to pinpoint the strong association between hyperglycemia and hearing disorders. Sensorineural hearing loss can be caused also by factors such as ototoxic drugs, which were not available with desired precision in our data.

An additional limitation was that we did not use continuous glucose monitoring. In our dataset, infants had variable amounts of recorded glucose values, as laboratory testing was performed based on clinical indications. Sick infants typically undergo frequent laboratory testing, and less sick infants might have undetected episodes of dysglycemia due to few glucose measurements. Including a uniform glucose measurement protocol, continuous glucose monitoring and hence data on the duration of hypo- and hyperglycemic episodes could have increased the value of our study. Initially, we aimed to compare infants with varying degrees of hypo- and hyperglycemia to normoglycemic infants, but the number of infants with neurodevelopmental diagnoses was too small to enable

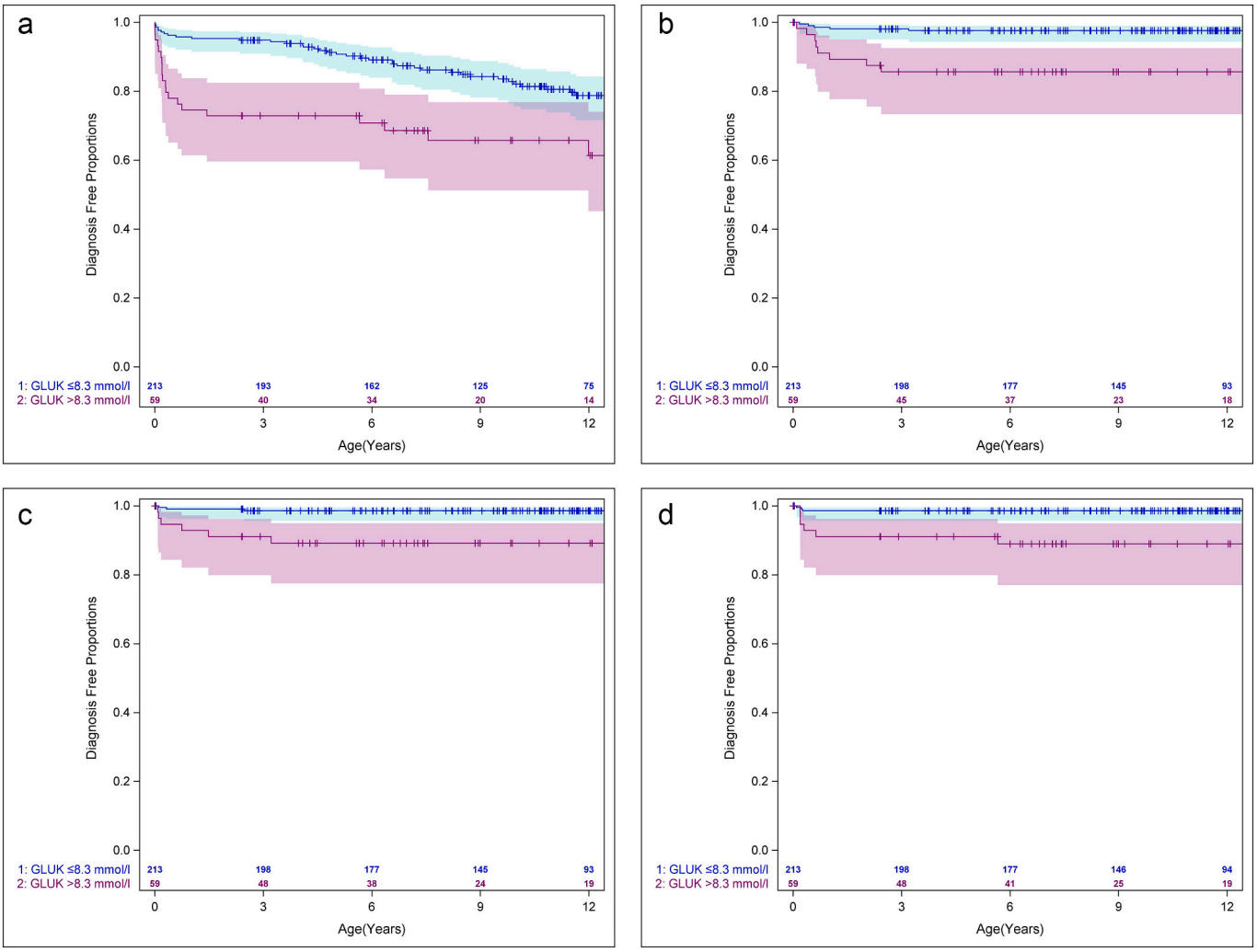

Fig. 4. a-d. Incidence over time of diagnoses of neurodevelopmental disorders (a. NDD or death, b. cerebral palsy, c. epilepsy, d. hearing disorders) comparing infants with hyperglycemia (glucose >8.3 mmol/l) to those without hyperglycemia.

meaningful analyses with sufficient granularity to identify e.g. associations with hearing disorders ($n = 9$). Using all infants with e.g., glucose values above 1,6 mmol/l as comparison group will introduce a bias, as this group includes both normoglycemic and mildly-moderately hypoglycemic infants but based on the existing knowledge on the effects of hypoglycemia on neurodevelopment, the true effects of severe hypoglycemia would most likely be underestimated, not overestimated using this analytic model. In addition, several infants displayed both hypo- and hyperglycemic values, which further complicates the analytic approach. In addition to the above-mentioned limitations, the relatively small numbers of infants with neurodevelopmental diagnoses in our population lead to unstable estimates for some outcomes as shown by the wide confidence intervals. Evaluating infants who with reasonable certainty had mild or no HIE separately is a novel approach, but as outcomes were even more scarce in this population, the estimates were unstable and are to be regarded as descriptive and hypothesis generating. Nevertheless, the suggested association between hyperglycemia and hearing disorders warrants further attention in future studies.

5. Conclusions

Both hypo- and hyperglycemia were associated with later neurological diagnoses, with notable associations between hyperglycemia and hearing disorders. A similar association was noted among infants who did not qualify for therapeutic hypothermia, warranting larger, prospective and sufficiently powered studies accounting for potential confounders on this subgroup of asphyxic neonates. No causal inferences can be drawn from our data due to the non-interventional, non-randomized design. Also, it should be noted that the analyses were performed on a relatively small population, especially among infants who received hypothermia, and thus the results should be interpreted with caution. Nevertheless, maintaining normoglycemia during the first vulnerable hours of life in infants with birth asphyxia is a promising and reachable clinical goal with the theoretical potential to diminish morbidity. Based on our findings, future studies might benefit from including glycemic control interventions and detailed long-term follow-up, with special focus on sensory impairment.

CRediT authorship contribution statement

Niina Viitaharju: Writing – original draft, Visualization, Funding acquisition, Data curation, Conceptualization. **Vilhelmiina Parikka:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Eliisa Löyttyniemi:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Bishwesvar Singh:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Kjell Helenius:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

This research was supported by Foundation of Turku University Central Hospital, Foundation for Pediatric Research, Finland (Grant numbers 240099, 240413, 210225 and 240032), The South-Western Finnish Foundation of Neonatal Research and State research grant (Hospital district of Southwest Finland, 13255 and 30013). The funding sources had no role in the study design, collection, analysis and interpretation of data, writing of the report and decision to submit the article for publication. Authors have no other conflicts of interest relating to the work under submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2026.106536.

References

[1] D. Mota-Rojas, D. Villanueva-García, A. Solimano, R. Muns, D. Ibarra-Ríos, A. Mota-Reyes, Pathophysiology of perinatal asphyxia in humans and animal models, Biomedicines 10 (2) (Feb. 2022) 347, https://doi.org/10.3390/BIOMEDICINES10020347.

[2] J.E. Lawn, S. Cousens, J. Zupan, 4 Million neonatal deaths: when? Where? Why? Lancet 365 (9462) (Mar. 2005) 891–900, https://doi.org/10.1016/S0140-6736(05)71048-5.

[3] H.B. Sarnat, M.S. Sarnat, Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study, Arch. Neurol. 33 (10) (1976) 696–705, https://doi.org/10.1001/ARCHNEUR.1976.00500100030012.

[4] K.A. Allen, D.H. Brandon, Hypoxic ischemic encephalopathy: pathophysiology and experimental treatments, Newborn Infant Nurs Rev 11 (3) (Sep. 2011) 125, https://doi.org/10.1053/J.NAINR.2011.07.004.

[5] S.E. Jacobs, M. Berg, R. Hunt, W.O. Tarnow-Mordi, T.E. Inder, P.G. Davis, Cooling for newborns with hypoxic ischaemic encephalopathy, Cochrane Database Syst. Rev. 2013 (1) (Jan. 2013), https://doi.org/10.1002/14651858.CD003311.PUB3/MEDIA/CDSR/CD003311/IMAGE_N/NCD003311-CMP-001-24.PNG.

[6] S.K. Basu, J.R. Kaiser, D. Guffey, C.G. Minard, R. Guillet, A.J. Gunn, Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study, Arch. Dis. Child. Fetal Neonatal Ed. 101 (2) (Mar. 2016) F149–F155, https://doi.org/10.1136/ARCHDISCHILD-2015-308733.

[7] U. Mietzsch, et al., Early glycemic state and outcomes of neonates with hypoxic-ischemic encephalopathy, Pediatrics 152 (4) (Oct. 2023) e2022060965, https://doi.org/10.1542/PEDS.2022-060965.

[8] I. Guellec, et al., Glycemia and neonatal encephalopathy: outcomes in the LyTONEPAL (long-term outcome of neonatal hypoxic EncePhALopathy in the era of neuroprotective treatment with hypothermia) cohort, J. Pediatr. 257 (Jun. 2023), https://doi.org/10.1016/J.JPEDS.2023.02.003.

[9] S.K. Basu, et al., Hyperglycaemia in infants with hypoxic-ischaemic encephalopathy is associated with improved outcomes after therapeutic hypothermia: a post hoc analysis of the CoolCap Study, Arch. Dis. Child. Fetal Neonatal Ed. 102 (4) (Jul. 2017) F299–F306, https://doi.org/10.1136/ARCHDISCHILD-2016-311385.

[10] C.E.J. Parmentier, et al., Hypoglycemia in infants with hypoxic-ischemic encephalopathy is associated with additional brain injury and worse neurodevelopmental outcome, J. Pediatr. 245 (Jun. 2022) 30–38, e1, https://doi.org/10.1016/J.JPEDS.2022.01.051.

[11] J.K.G. Tan, C. Minutillo, J. McMichael, S. Rao, Impact of hypoglycaemia on neurodevelopmental outcomes in hypoxic ischaemic encephalopathy: a retrospective cohort study, BMJ Paediatr. Open 1 (1) (Dec. 2017), https://doi.org/10.1136/BMJPO-2017-000175.

[12] P. Montaldo, et al., Continuous glucose monitoring profile during therapeutic hypothermia in encephalopathic infants with unfavorable outcome, Pediatr. Res. 88 (2) (Aug. 2020) 218–224, https://doi.org/10.1038/S41390-020-0827-4.

[13] J. Wang, et al., Association between continuous glucose profile during therapeutic hypothermia and unfavorable outcome in neonates with hypoxic-ischemic encephalopathy209 23-32, Early Hum. Dev. 187 (Dec. 2023) 105878, https://doi.org/10.1016/J.EARLHUMDEV.2023.105878.

[14] E.F. Pinchefsky, et al., Hyperglycemia and glucose variability are associated with worse brain function and seizures in neonatal encephalopathy: a prospective cohort study, J. Pediatr. 209 (Jun. 2019) 23–32, https://doi.org/10.1016/J.JPEDS.2019.02.027.

[15] D. Kamino, et al., Abnormalities in evoked potentials associated with abnormal glycemia and brain injury in neonatal hypoxic-ischemic encephalopathy, Clin. Neurophysiol. 132 (1) (Jan. 2021) 307–313, https://doi.org/10.1016/J.CLINPH.2020.09.024.

[16] I.C. Lee, J.J. Yang, Y.M. Liou, Early blood glucose level post-admission correlates with the outcomes and oxidative stress in neonatal hypoxic-ischemic encephalopathy, Antioxidants (Basel) 11 (1) (Jan. 2021), https://doi.org/10.3390/ANTIOX11010039.

[17] E.W.Y. Tam, et al., Hyperglycemia associated with acute brain injury in neonatal encephalopathy, Neuroimage Clin. 32 (Jan. 2021), https://doi.org/10.1016/J.NICL.2021.102835.

[18] D. Kamino, et al., Severity and duration of dysglycemia and brain injury among patients with neonatal encephalopathy, EClinicalMedicine 58 (Apr. 2023), https://doi.org/10.1016/J.ECLINM.2023.101914.

[19] M. Hirvonen, et al., Visual and hearing impairments after preterm birth, Pediatrics 142 (2) (Aug. 2018), https://doi.org/10.1542/PEDS.2017-3888.

[20] M. Hirvonen, et al., Cerebral palsy among children born moderately and late preterm, Pediatrics 134 (6) (Dec. 2014) e1584–e1593, https://doi.org/10.1542/PEDS.2014-0945.

[21] M. Hirvonen, et al., The incidence and risk factors of epilepsy in children born preterm: a nationwide register study, Epilepsy Res. 138 (Dec. 2017) 32–38, https://doi.org/10.1016/J.EPLEPSYRES.2017.10.005.

[22] M.P. Fitzgerald, A. Reynolds, C.M. Garvey, G. Norman, M.D. King, B.C. Hayes, Hearing impairment and hypoxia ischaemic encephalopathy: Incidence and associated factors, Eur. J. Paediatr. Neurol. 23 (1) (Jan. 2019) 81–86, https://doi.org/10.1016/J.EJPN.2018.10.002.

[23] J. Parokaran Varghese, et al., Neurophysiological changes associated with dysglycemia in term neonates with neonatal encephalopathy, Clin. Neurophysiol. 179 (Nov. 2025), https://doi.org/10.1016/J.CLINPH.2025.2111002.

[24] M.S. Kalogeropoulou, L. Thomson, K. Beardsall, Continuous glucose monitoring during therapeutic hypothermia for hypoxic ischaemic encephalopathy: a feasibility study, Arch. Dis. Child. Fetal Neonatal Ed. 108 (3) (May 2023) F309–F315, https://doi.org/10.1136/ARCHDISCHILD-2022-324593.

[25] M. Lagacé, E.W.Y. Tam, Neonatal dysglycemia: a review of dysglycemia in relation to brain health and neurodevelopmental outcomes, Pediatr. Res. 96 (6) (Nov. 2024) 1429–1437, https://doi.org/10.1038/S41390-024-03411-0.

[26] S. Asif, et al., Hypoglycemia and hyperglycemia in neonatal encephalopathy: a narrative review, Medicine 103 (36) (Sep. 2024) e39488, https://doi.org/10.1097/MD.0000000000039488.