From Kidneys to the Brain: A Systematic Review and Meta-Analysis of Neurodevelopmental Outcomes in Neonates with Acute Kidney Injury

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Acute Kidney Injury Disrupts Kidney Brain Axis

Ischemic Reperfusion

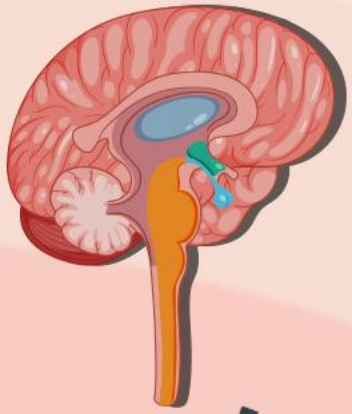
Elevated osmolality (hypernatremia)

Uremic toxin

generation of ROS

inflammation-related brain injury

Neurotoxicity

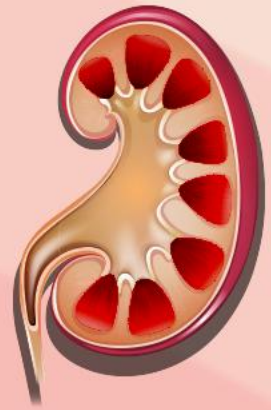


AKI

Cognitive

Motor

Language



30%

Neonates in NICU develop acute kidney injury

1 : 10

Mortality rate Non-AKI vs AKI

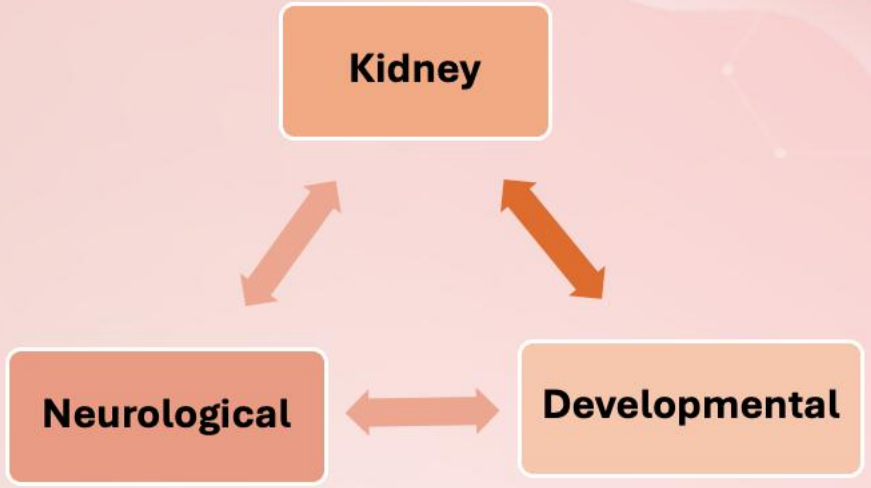
(Faucher *et al.*, 2023; Wang *et al.*, 2025; Assem *et al.*, 2018; Jetton *et al.*, *2017*)

It's a Global Problem

<10%

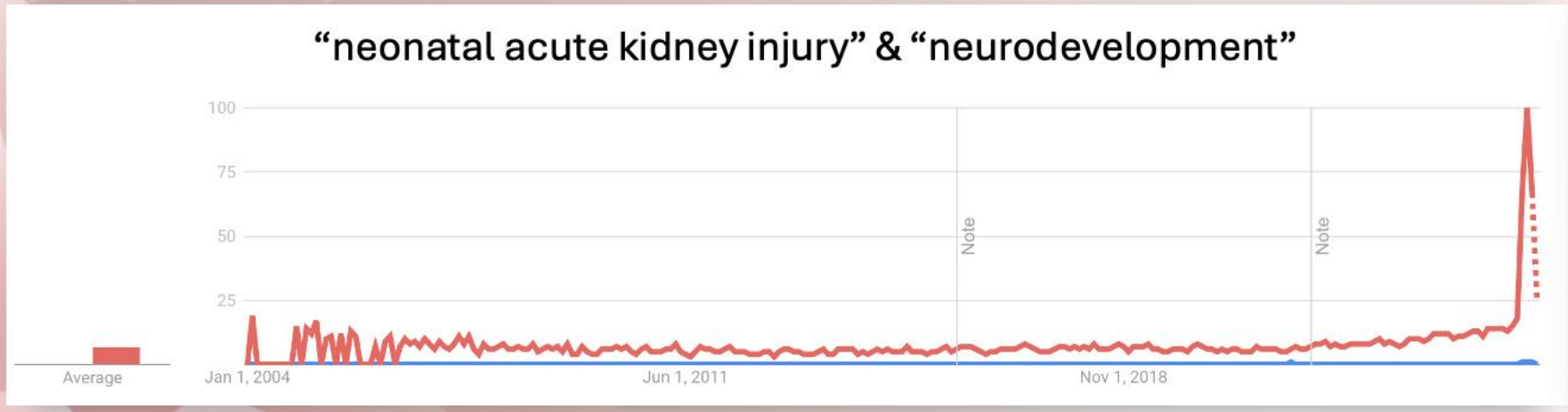
Studies in low-middle country followed AKI long-term outcomes

(Selby *et al.*, 2025)



Often seen as a transient renal problem, not as a multisystemic insult

Google Trends 2004 - Present



Objectives of the Study

1. To evaluate the association between **birth weight** and the risk of neonatal acute kidney injury (AKI).
2. To compare **head circumference (HC)** growth trajectories between neonates with and without AKI as an early **neurodevelopmental** marker.
3. To assess neurodevelopmental and structural outcomes using **Bayley Scales** of Infant and Toddler development and **brain MRI** findings in infants with AKI.
4. To determine the incidence of hard clinical endpoints, including **cerebral palsy (CP)** and **neurodevelopmental impairment (NDI),** among survivors of neonatal AKI.

Method

Keywords dan MeSH Terms

Neonates	Neonate* OR Neonatal OR Newborn* OR **Infant***
	AND
Acute Kidney Injury	AKI OR ARF OR "Acute Kidney Injury*" OR "Acute Renal Injury*" OR "Acute Kidney Failure*" OR " "Acute Renal Failure" OR "Acute Renal Insufficiency*" OR "Acute Kidney Insufficiency*" OR "Kidney Injury*" OR "Renal Injury*" OR "Renal Dysfunction" OR "Kidney disfunction" OR "Acute Kidney Disease*" OR "Acute Renal Disease*"

Analysis

Meta-analysis was performed using a bivariate **random-effects model (REML)** in R Studio and heterogeneity was assessed using I^2.

Inclusion Criterias

1. **Clinical** studies involving neonates or infants with acute kidney injury (AKI).
2. Studies reporting **head circumference (HC), Bayley Scales of Infant Development, neurodevelopmental impairment (NDI), cerebral palsy, or brain MRI** outcomes in neonates with AKI.

Exclusion Criterias

1. **Comorbid** patients
2. Studies with **insufficient data**, (including lack of: quantitative outcome measurements & follow-up data)
3. **Review articles or non-clinical** studies.

PRISMA FLOWCHART

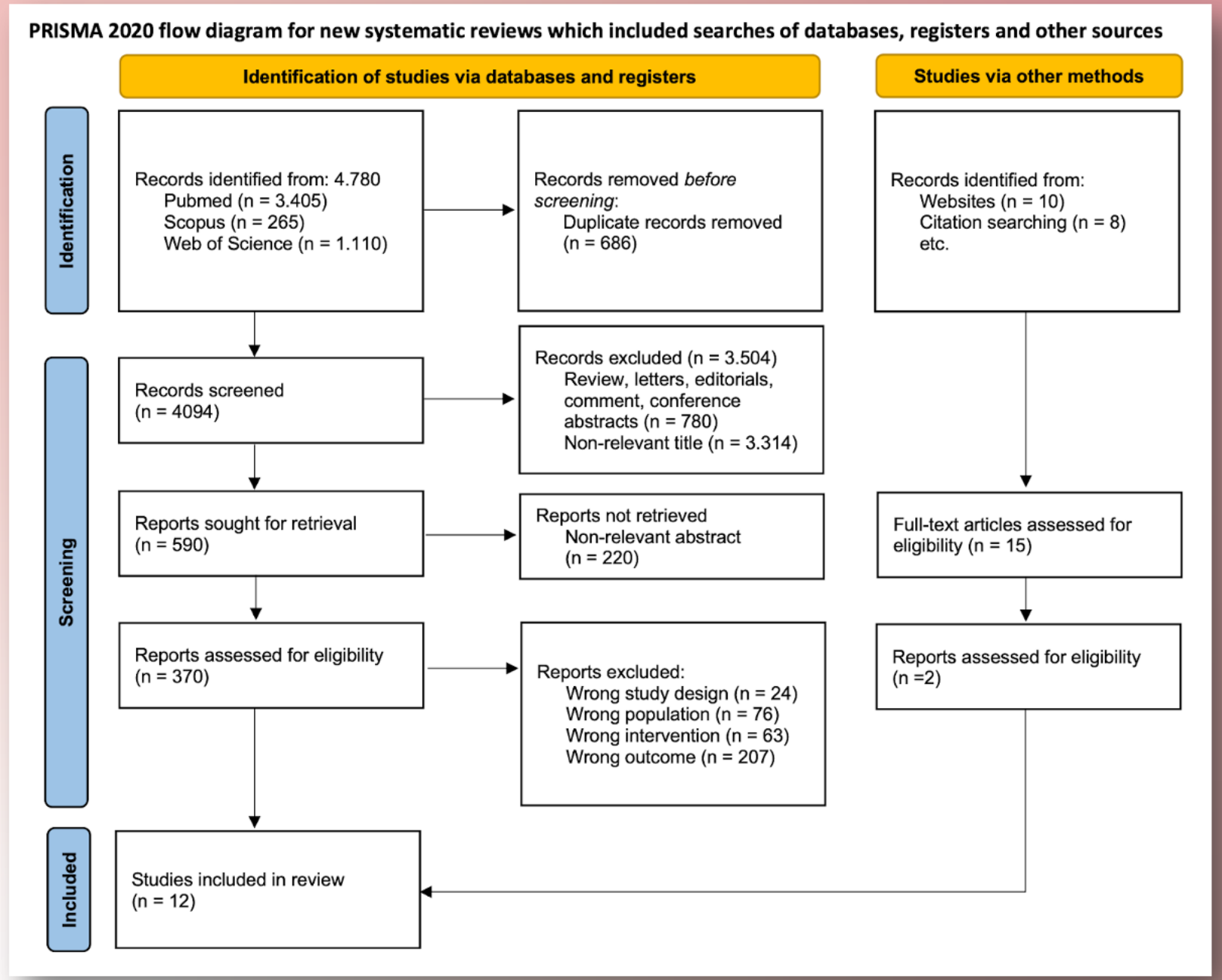
PubMed
3,405 studies

Scopus
265 studies

Clarivate Web of Science™
1,110 studies

Cochrane Library
268 studies

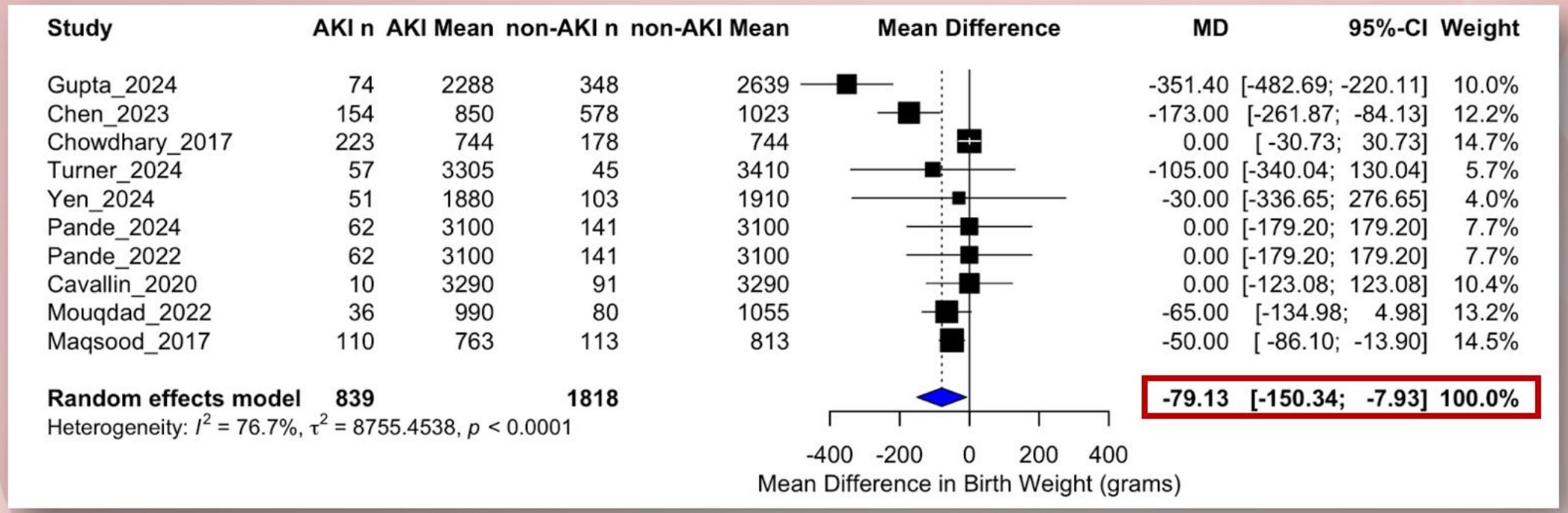
5.048 studies
→ **12 included studies**
(2.602 neonates)



Characteristic of Included Studies

No.	Title_Year	Country	Study Design	n patient			AKI Diagnosis	AKI Etiology	Follow Up Duration
				AKI	Non-AKI	Total			
1	**Gupta_2024**	India	cross-sectional	74	348	422	Modified KDIGO	**metabolic imbalance** (dyselectrolytemia, hypoglycemia), **hypoxic-ischemic changes** (birth asphyxia), hemorrhage, meningitis, and hyperbilirubinemia	at admission
2	**Chen_2023**	Taiwan	longitudinal follow-up cohort retrospective	154	578	732	Modified KDIGO	**hypotension, sepsis**	6, 12, 24 months
3	**Chowdhary_2017**	USA	retrospective cohort	223	178	401	Modified KDIGO	**kidney immaturity**, critical illness, olyguria	9 months
4	**Turner_2024**	USA	multicenter prospective cohort	12	45	57	Modified KDIGO	**hypoxic-ischemic encephalopathy** (HIE)	at admission
5	**Yen_2024**	Taiwan	retrospective case control	51	103	154	Modified KDIGO	perinatal **asphyia**, brain insult, non-congenital urologic anomalies, bronchopulmonary dysplasia	6, 12, 24 months
6	**Pande_2024**	USA	observational retrospective cohort	62	141	203	Modified KDIGO	**congenital heart disease surgery**	20 months
7	**Pande_2022**	USA	single-center retrospective cohort	62	141	203	Modified KDIGO	**congenital heart disease surgery**	20 months
8	**Gallo_2021**	Belanda	retrospective cohort	42	0	42	NIDDK	perinatal **asphyxia**, CAKUT, congenital heart diseae, sepsis, PDA, CAKUT, perinatal asphyxia, hypothermia, nefrotoxic drugs	24 months
9	**Sarkar_2014**	USA	observational retrospective cohort	34	54	88	Modified KDIGO	perinatal **asphyxia**	7-10 days
10	**Cavallin_2020**	India	observational prospective cohort	10	91	101	Modified KDIGO	**hypoxic-ischemic encephalopathy (HIE)**	12, 24 months
11	**Mouqdad_2022**	Saudi Arabia	retrospective cohort	36	80	116	Modified KDIGO	**Prematurity, sepsis,** IVH, NEC, hemodinamic problem	-
12	**Maqsood_2017**	USA	retrospective case control	110	113	222	Modified KDIGO	**Sepsis, asphyxia**	at admission

1 Forrest Plot: Mean Birth Weight with & without AKI



AKI had a significantly lower mean birth weight compared to those without AKI
Mean different: −79.13 grams (−150.34 to −7.93; p < 0.05)

2 Forrest Plot: Mean Differences in Head Circumference (HC)

Follow Up

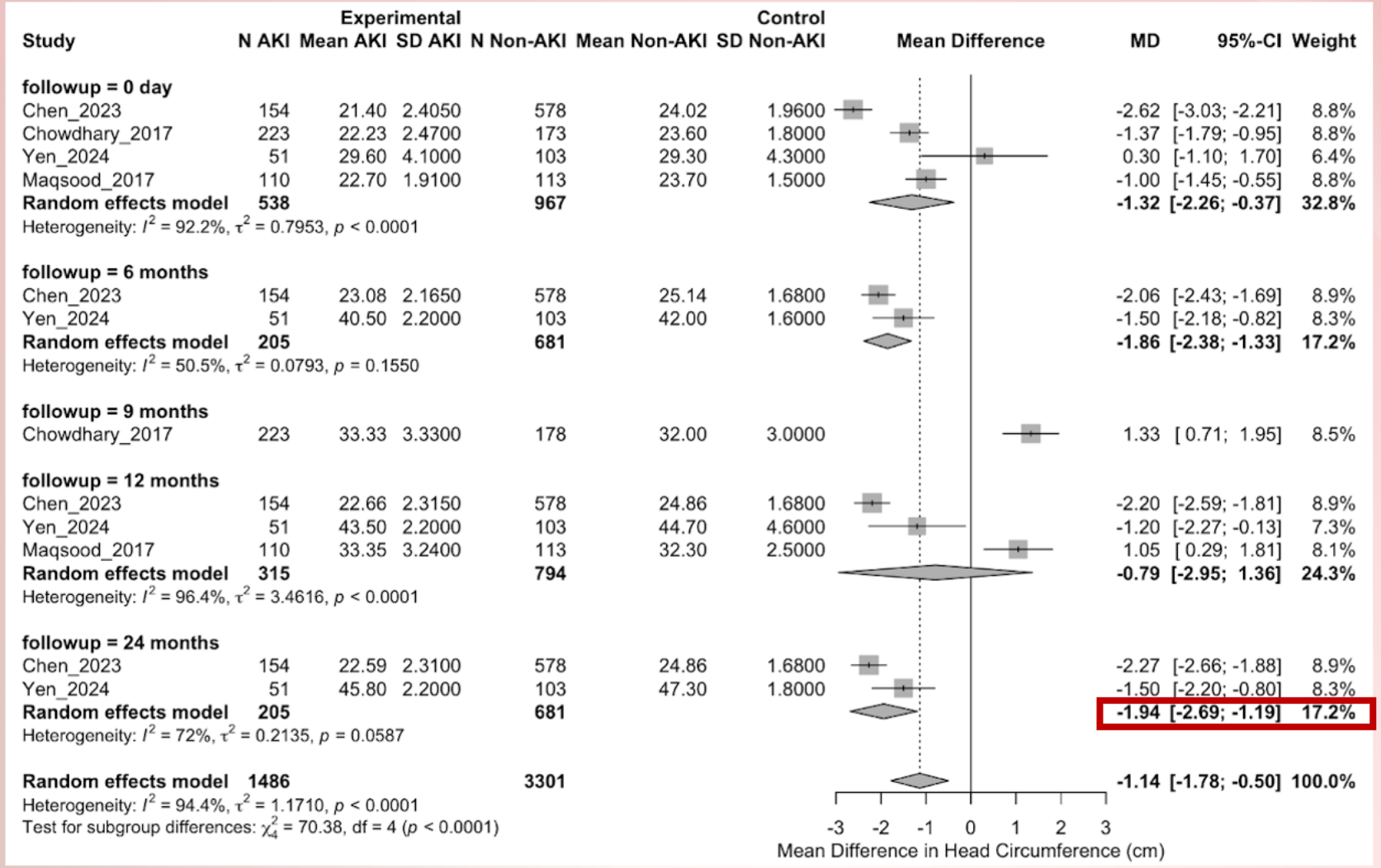
Baseline

6 months

9 months

12 months

24 months



Neonates with AKI consistently exhibited smaller head circumferences compared to non-AKI, beginning from birth (MD = −1.32 cm) up to 24 months of age (MD = −1.94 cm, p < 0.0001).

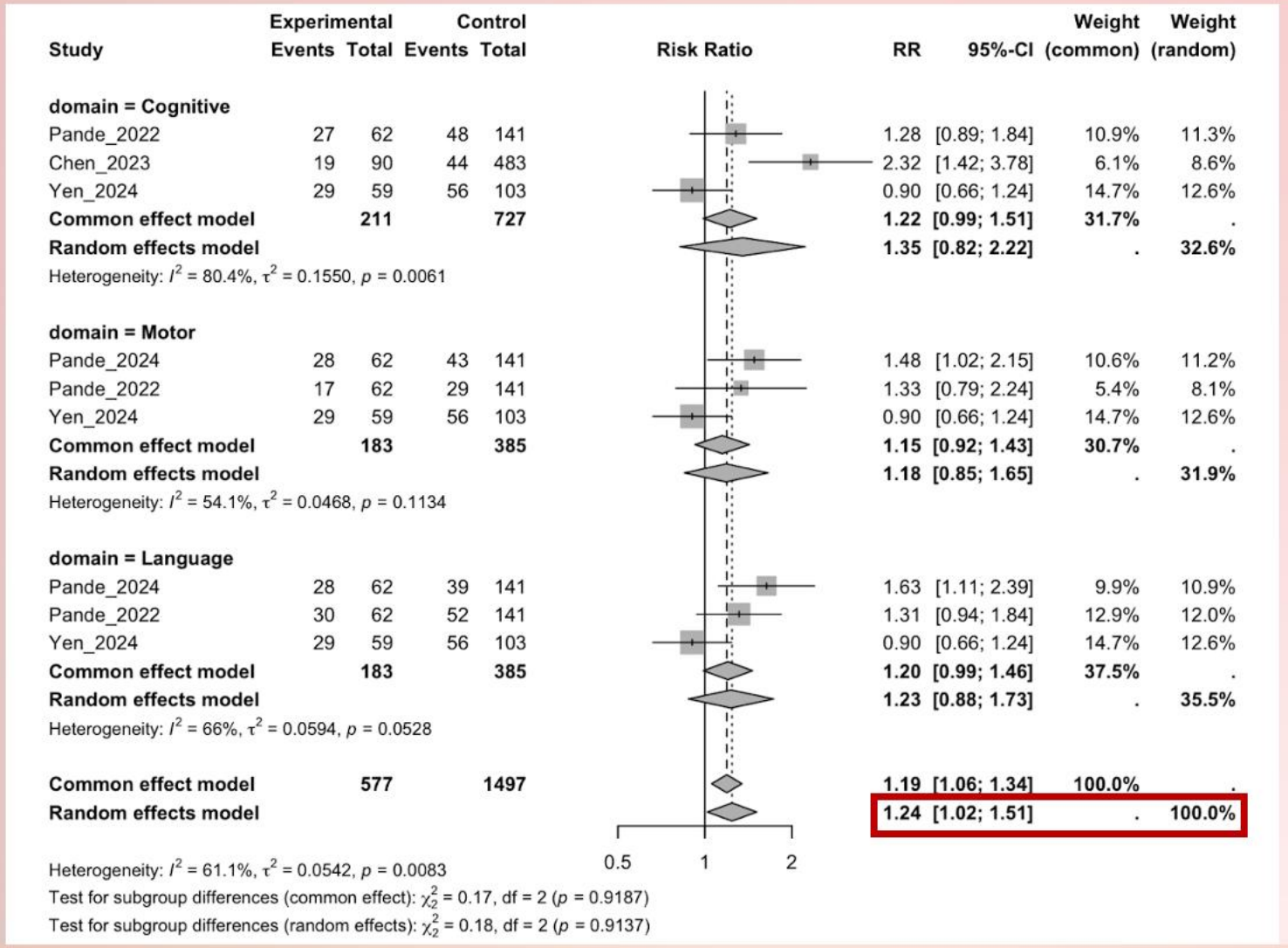
3 Forrest Plot: Bayley Scales Infant Development

3 Domains

Cognitive

Motor

Languange



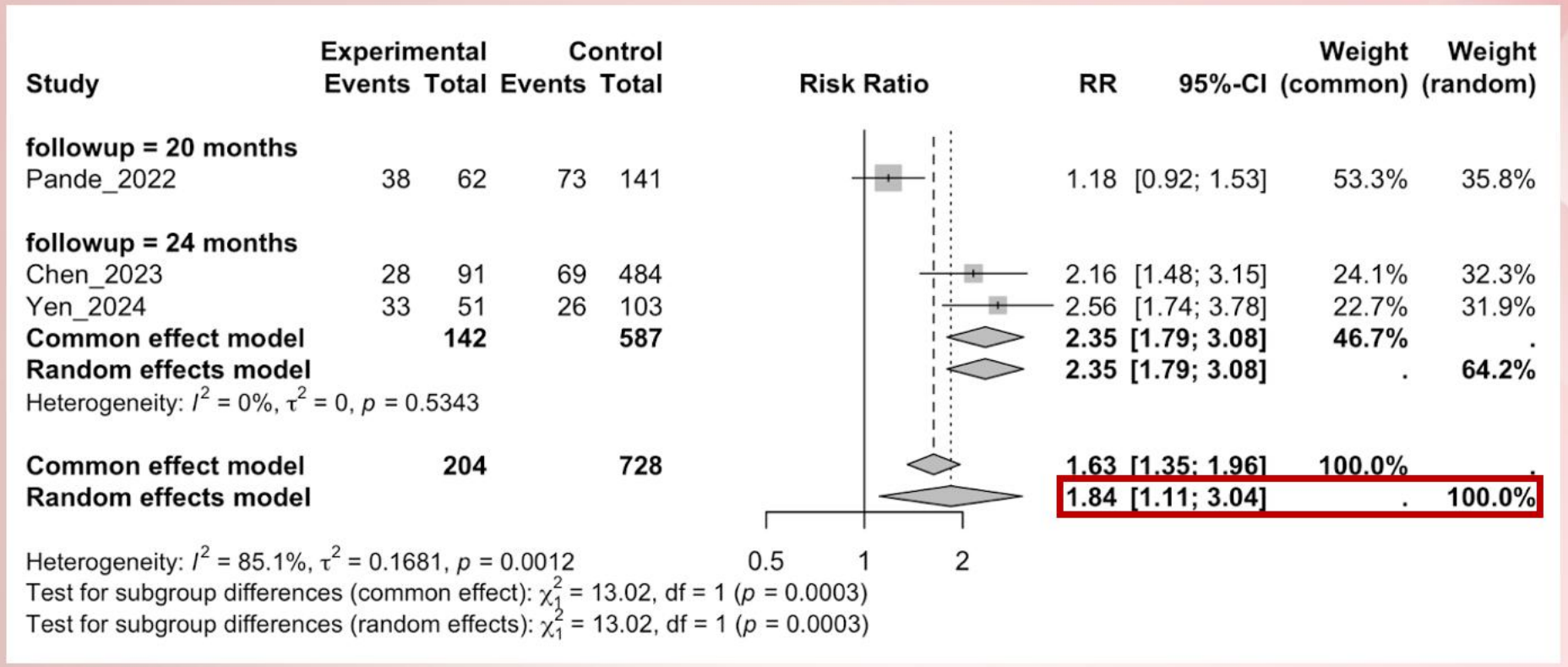
Neonates with AKI showed a significantly higher risk of developmental delay compared to those without AKI (Relative Risk [RR] = 1.24; 95% CI: 1.02–1.51)

4 Forrest Plot: Neurodevelopmental Impairment (NDI)

Follow Up

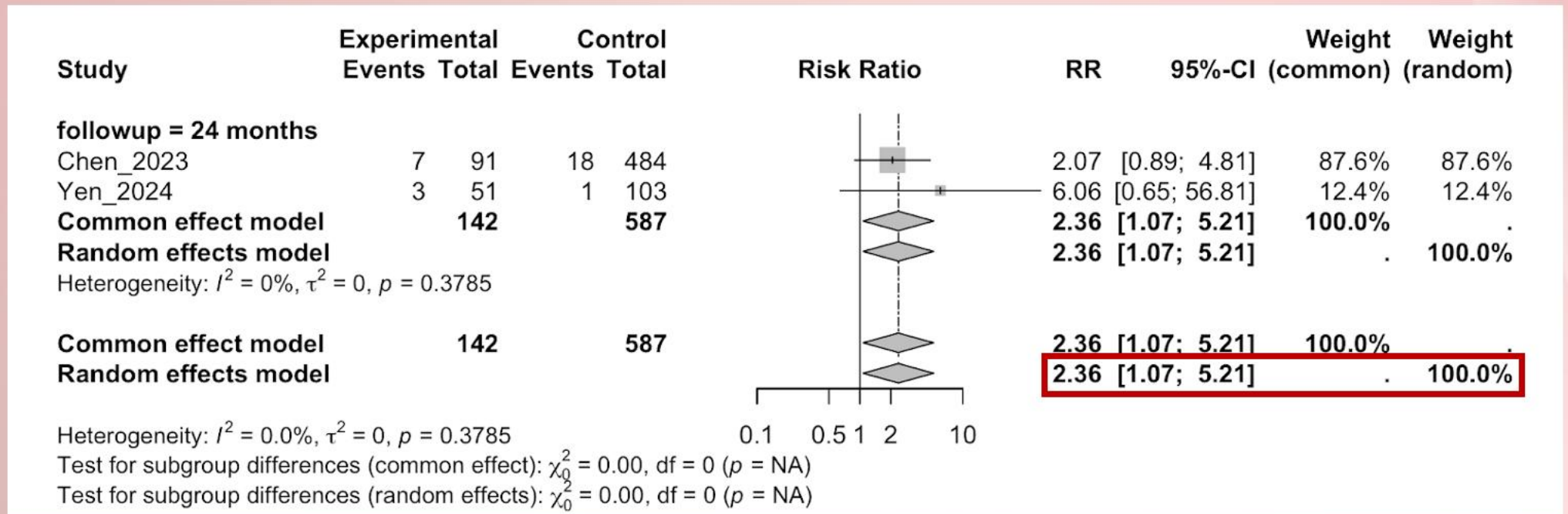
20 months

24 months



NDI was significantly more prevalent in neonates with AKI compared to non-AKI (RR = 1.84; 95% CI: 1.11–3.04)

5 Forrest Plot: Cerebral Palsy Incidence

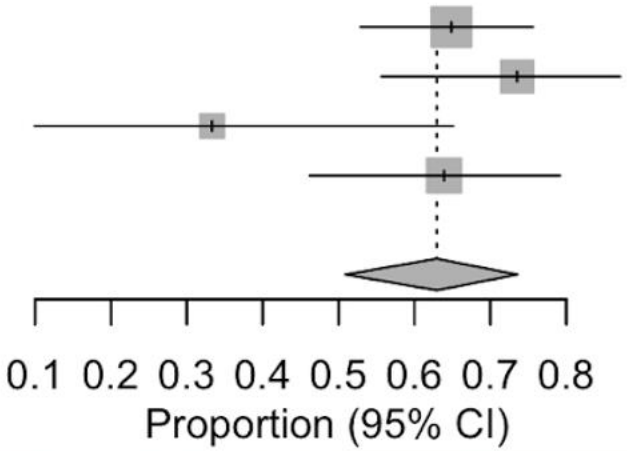


Cerebral palsy was more than twice as likely to occur in neonates with AKI compared with those without AKI (RR = 2.36; 95% CI: 1.07–5.21)

6 Forrest Plot: Abnormal Brain MRI Findings

Study	MRI Abnormal	Total AKI	Proportion	95%-CI	Weight
Gupta_2024	48	74	0.65	[0.53; 0.76]	36.3%
Sarkar_2013	25	34	0.74	[0.56; 0.87]	23.8%
Turner_2024	4	12	0.33	[0.10; 0.65]	13.0%
Mouqdad_2022	23	36	0.64	[0.46; 0.79]	26.9%
Random effects model			**0.63**	**[0.51; 0.74]**	**100.0%**

Heterogeneity: I^2 = 46.7%, τ^2 = 0.1159, p = 0.1309



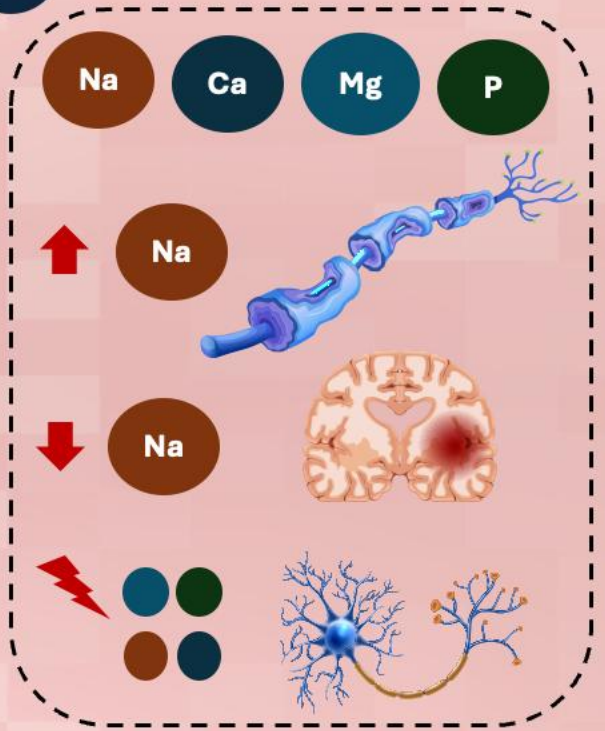
More than half of neonates with AKI exhibit detectable structural brain abnormalities on MRI

Pooled propotion: *63% (95% CI: 51%–74%, I^2 = 46.7%)*

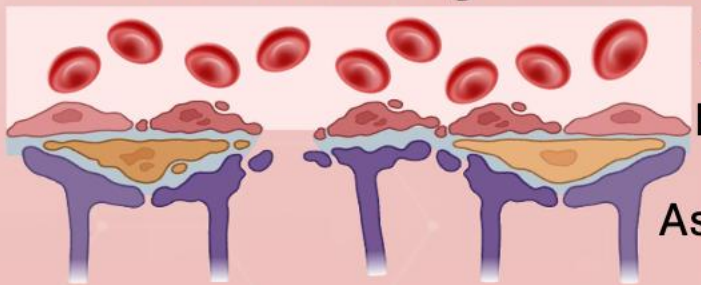
KIDNEY BRAIN AXIS

1 Ischemic Reperfusion Injury → ROS → NF-κB → TNF-α, Il-6, IL-1, IFN-γ

3 Metabolic Disbalance



Vascular damage → BBB disruption



Brain

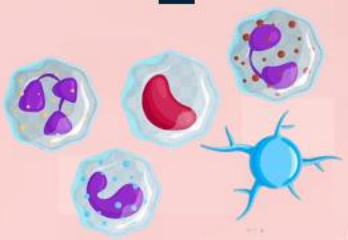
2 Uremic Toxin

guanidine

creatinine

indoxyl sulfate

ROS



(Yan *et al.*, 2024; Watanabe *et al.*, 2021; He *et al.*, 2025)

THE EFFECTS

1 Functional

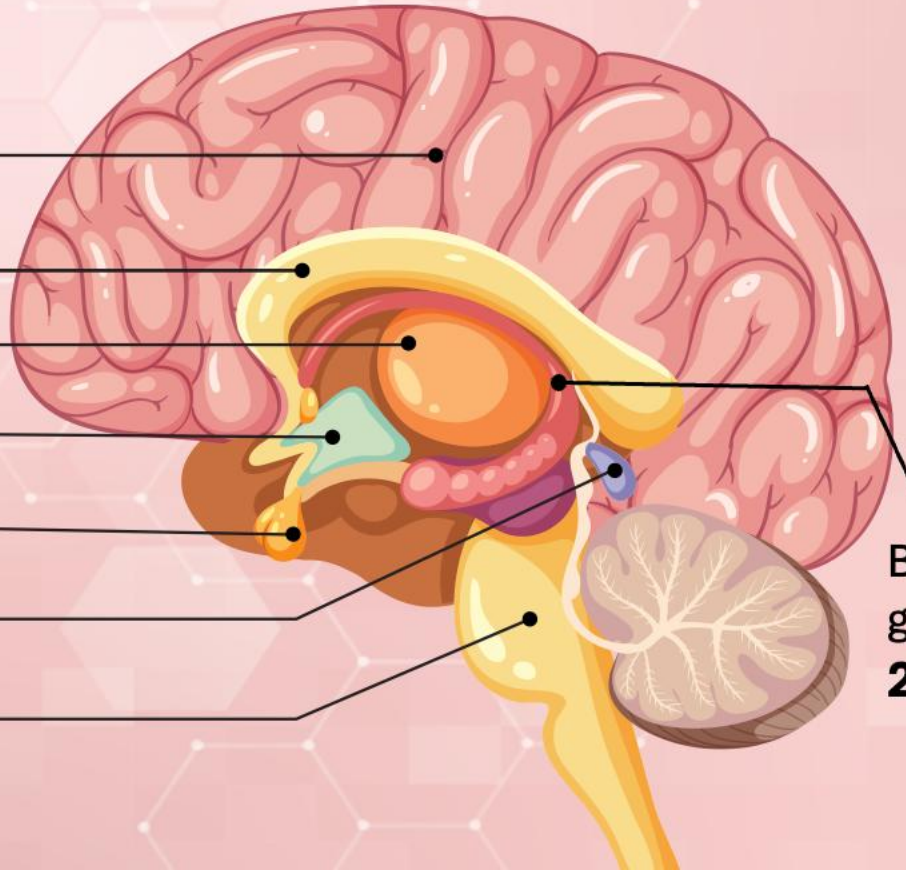
Bayley Scales:
Cognitive
Memory
Language

2 Structural

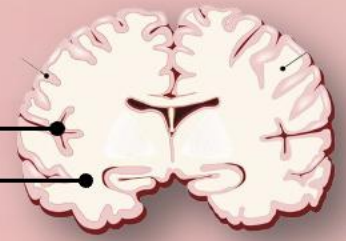
Head Circumference
Abnormal MRI

3 Neurodevelopment

Cerebral Palsy (CP)
Neurodevelopmental impairment (NDI)



Affected Brain Tissue



Grey Matter: 82.34%[1]
White Matter: 31.08%[1]

Seizure Event

Mix ← asphyxia ← HIE ← CHD
83.3%[1] 54%[2] 30%[3] 6.4%[4]

Encephalopathic Event

Lethargy = 78.4%[1]
Irritability: 35.1%[1]
Both: 66.7%[1]

[1]Gupta *et al.*, 2024; [2]Sarkar *et al.*, 2013; [3]Turner *et al.*, 2024; [4]Pande *et al.*, 2022

WHAT SHOULD WE DO?

1 Early Neurodevelopmental Screening

0 - 2 Weeks	1– 3 Months	32 & 40 Weeks	3, 6, 12, 24 Months
• Tone, reflexes • Early head circumference	General movements	Structural monitoring	• Gross & fine motor • Cognitive
Tool: Hammersmith Neonatal Neurological Examination (HNNE)	Tool: general movement assessment (GMA)	32 weeks: EEG 40 weeks: MRI otak	tools: Bayley or Age and Stages Questionnaires (ASQ)

Nephrologists & Pediatricians are the first doctors to notice AKI & recommend these steps

2 Optimal Supportive Care

3 Integrated Multidisciplinary

Nephrologist
Pediatrician
Neurologist
Nutritionists

Conclusion

1. Neonates with AKI had significantly **lower birth weights** (MD −79 gram), indicating that **growth-restricted** and **physiologically immature** infants are at greater risk of developing AKI.
2. Across 0–24 months, infants with AKI consistently demonstrated **smaller head circumference**, with the largest deficit at 24 months (MD −1.94 cm), reflecting sustained impairment in **early brain growth.**
3. AKI was associated with higher risks of **cognitive, language, and motor** delays (overall RR 1.24), and infants showed brain MRI abnormalities involving **gray matter, white matter, deep nuclei, cerebellum, and myelination pathways**.
4. By 20–24 months, AKI survivors had significantly higher incidences of **neurodevelopmental impairment** (RR 1.84) and **cerebral palsy** (RR 2.36), underscoring AKI as a major determinant of long-term neurologic morbidity.

Recommendation

1. Long-term, prospective, multicenter cohorts across diverse populations
2. Integration of kidney–brain biomarkers (including NGAL, cystatin C, troponin, and inflammatory or metabolic markers)
3. Advanced neuroimaging and mechanistic studies (high-resolution MRI, diffusion metrics, and perfusion imaging)

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References

Al-Mouqdad, M.M., Jamjoom, D.Z., Abdalgader, A.T., Ameen, W.S., Khalil, T.M., Asfour, Y.S., Al-Anazi, M.R. and Asfour, S.S., 2022. Association between acute kidney injury and brain injury on term-equivalent age brain magnetic resonance imaging in very preterm infants. *Pediatric Nephrology*, *37*(12), pp.3235-3242.

Assem, M., Lando, M., Grissi, M., Kamel, S., Massy, Z.A., Chillon, J.M. and Hénaut, L., 2018. The impact of uremic toxins on cerebrovascular and cognitive disorders. *Toxins*, *10*(7), p.303.

Cavallin, F., Rubin, G., Vidal, E., Cainelli, E., Bonadies, L., Suppiej, A. and Trevisanuto, D., 2020. Prognostic role of acute kidney injury on long-term outcome in infants with hypoxic-ischemic encephalopathy. *Pediatric Nephrology*, *35*(3), pp.477-483.

Chen, C.C., Chu, C.H., Lin, Y.C. and Huang, C.C., 2023. Neurodevelopment after neonatal acute kidney injury in very preterm-birth children. *Kidney International Reports*, *8*(9), pp.1784-1791.

Chowdhary, V., Vajpeyajula, R., Jain, M., Maqsood, S., Raina, R., Kumar, D. and Mhanna, M.J., 2018. Comparison of different definitions of acute kidney injury in extremely low birth weight infants. *Clinical and Experimental Nephrology*, *22*(1), pp.117-125.

Faucher, Q., van der Made, T.K., De Lange, E. and Masereeuw, R., 2023. Blood-brain barrier perturbations by uremic toxins: Key contributors in chronic kidney disease-induced neurological disorders?. *European Journal of Pharmaceutical Sciences*, *187*, p.106462.

Gallo, D., de Bijl-Marcus, K.A., Alderliesten, T., Lilien, M. and Groenendaal, F., 2021. Early acute kidney injury in preterm and term neonates: incidence, outcome, and associated clinical features. *Neonatology*, *118*(2), pp.174-179.

Gupta, P., Meena, A.K., Parakh, E., Wander, A., Rathore, B., Jangid, H. and Parakh, M., 2024. Neurological Manifestation of Neonatal Acute Kidney Injury: Focusing on the Clinico-Radiological Profile. *Cureus*, *16*(9).

He, Y., Xie, K., Yang, K., Wang, N. and Zhang, L., 2025. Unraveling the Interplay Between Metabolism and Neurodevelopment in Health and Disease. *CNS Neuroscience & Therapeutics*, *31*(5), p.e70427.

Jetton, J.G., Boohaker, L.J., Sethi, S.K., Wazir, S., Rohatgi, S., Soranno, D.E., Chishti, A.S., Woroniecki, R., Mammen, C., Swanson, J.R. and Sridhar, S., 2017. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. *The lancet child & adolescent health*, *1*(3), pp.184-194.

References

Maqsood, S., Fung, N., Chowdhary, V., Raina, R. and Mhanna, M.J., 2017. Outcome of extremely low birth weight infants with a history of neonatal acute kidney injury. *Pediatric Nephrology*, *32*(6), pp.1035-1043.

Pande, C.K., Akcan-Arikan, A., Monteiro, S., Guffey, D., Serrano, F., Afonso, N., Puri, K., Achuff, B.J., Shekerdemian, L. and Noll, L., 2024. Recurrent acute kidney injury is associated with delayed language development in infants with Congenital Heart Disease. *Cardiology in the Young*, *34*(11), pp.2377-2381.

Pande, C.K., Noll, L., Afonso, N., Serrano, F., Monteiro, S., Guffey, D., Puri, K., Achuff, B.J., Akcan-Arikan, A. and Shekerdemian, L., 2022. Neurodevelopmental outcomes in infants with cardiac surgery associated acute kidney injury. *The Annals of Thoracic Surgery*, *114*(6), pp.2347-2354.

Sarkar, S., Askenazi, D.J., Jordan, B.K., Bhagat, I., Bapuraj, J.R., Dechert, R.E. and Selewski, D.T., 2014. Relationship between acute kidney injury and brain MRI findings in asphyxiated newborns after therapeutic hypothermia. *Pediatric research*, *75*(3), pp.431-435.

Selby, N.M. and Bobot, M., 2025. From acute to chronic: the long-term consequences of AKI in South and Southeast Asia. *Intensive Care Medicine*, pp.1-3.

Turner, M.J., Rumpel, J.A., Spray, B.J., Stence, N., Neuberger, I., Frymoyer, A., Chock, V.Y., Courtney, S. and Gist, K., 2024. Urine biomarkers of acute kidney injury and association with brain MRI abnormalities in neonatal hypoxic-ischemic encephalopathy. *Journal of Perinatology*, *44*(8), pp.1203-1207.

Wang, J., Gao, S., Cui, Y., Liu, X.Z., Chen, X.X., Hang, C.H. and Li, W., 2025. Remote Organ Damage Induced by Stroke: Molecular Mechanisms and Comprehensive Interventions. *Antioxidants & Redox Signaling*, *42*(16-18), pp.885-904.

Watanabe, K., Sato, E., Mishima, E., Watanabe, M., Abe, T., Takahashi, N. and Nakayama, M., 2021. Effect of uremic toxins on hippocampal cell damage: analysis in vitro and in rat model of chronic kidney disease. *Heliyon*, *7*(2).

Yan, Q., Liu, M., Xie, Y., Lin, Y., Fu, P., Pu, Y. and Wang, B., 2024. Kidney-brain axis in the pathogenesis of cognitive impairment. *Neurobiology of disease*, *200*, p.106626.

Yen, C.W., Chiang, M.C., Chu, S.M., Wang, H.C., Wu, L.C., Yen, P.C. and Yu, M.C., 2024. Sustained acute kidney injury as an independent risk factor for neurodevelopmental and growth outcomes in a single NICU center. *BMC pediatrics*, *24*(1), p.233.

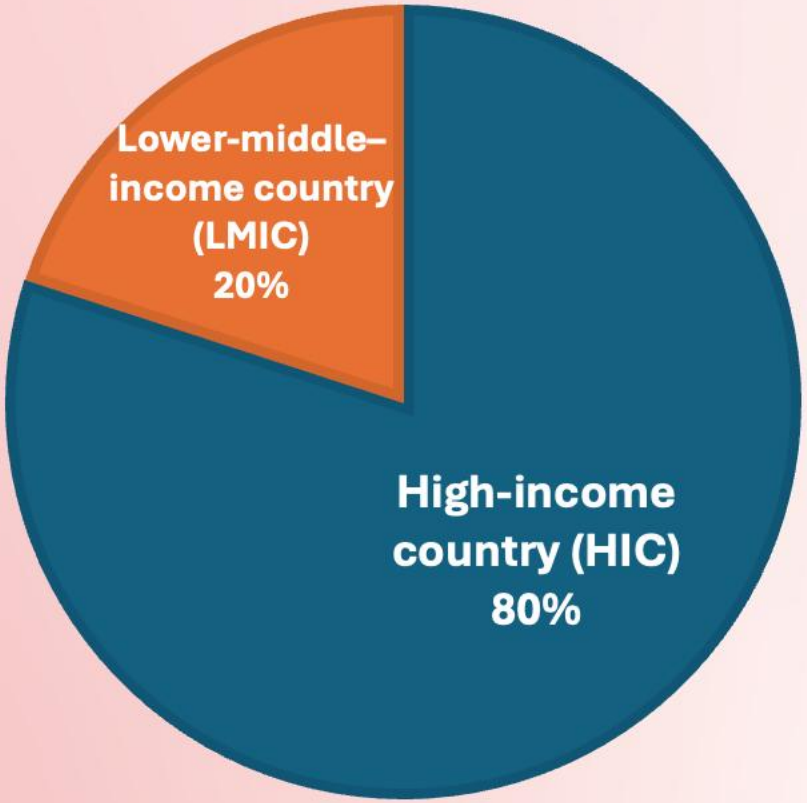
This is the crucial moments that we don't want any mother to feel the heartbreak of watching her child fall behind.

THANK YOU

No. 2025 1184

Characteristic of Included Studies

COUNTRY INCOME LEVEL



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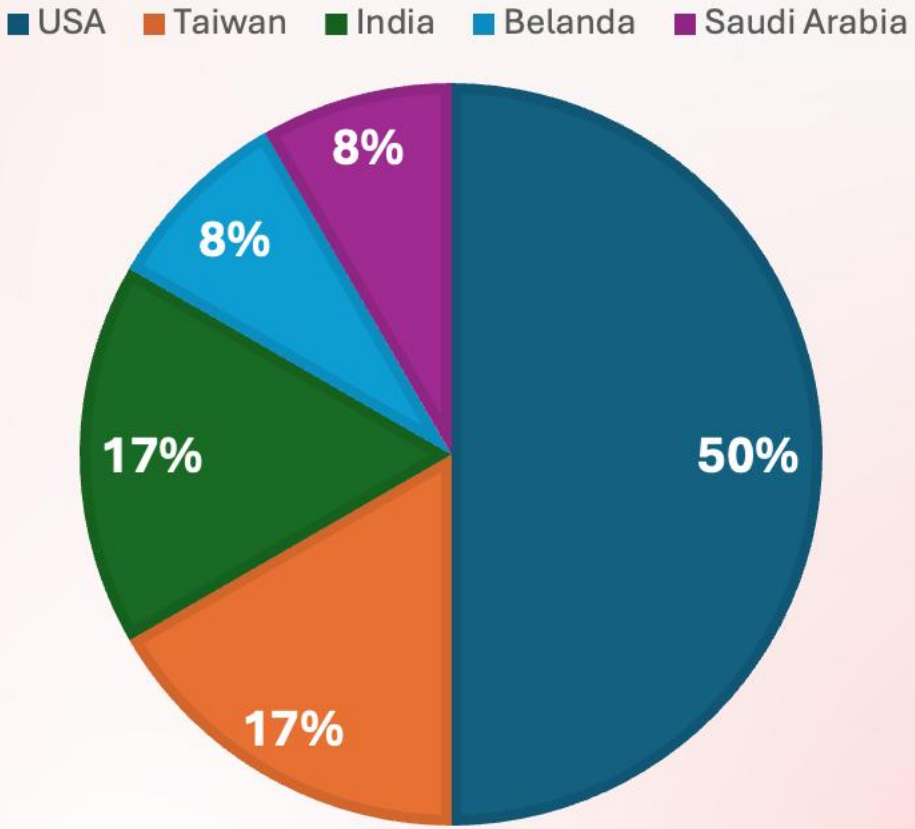

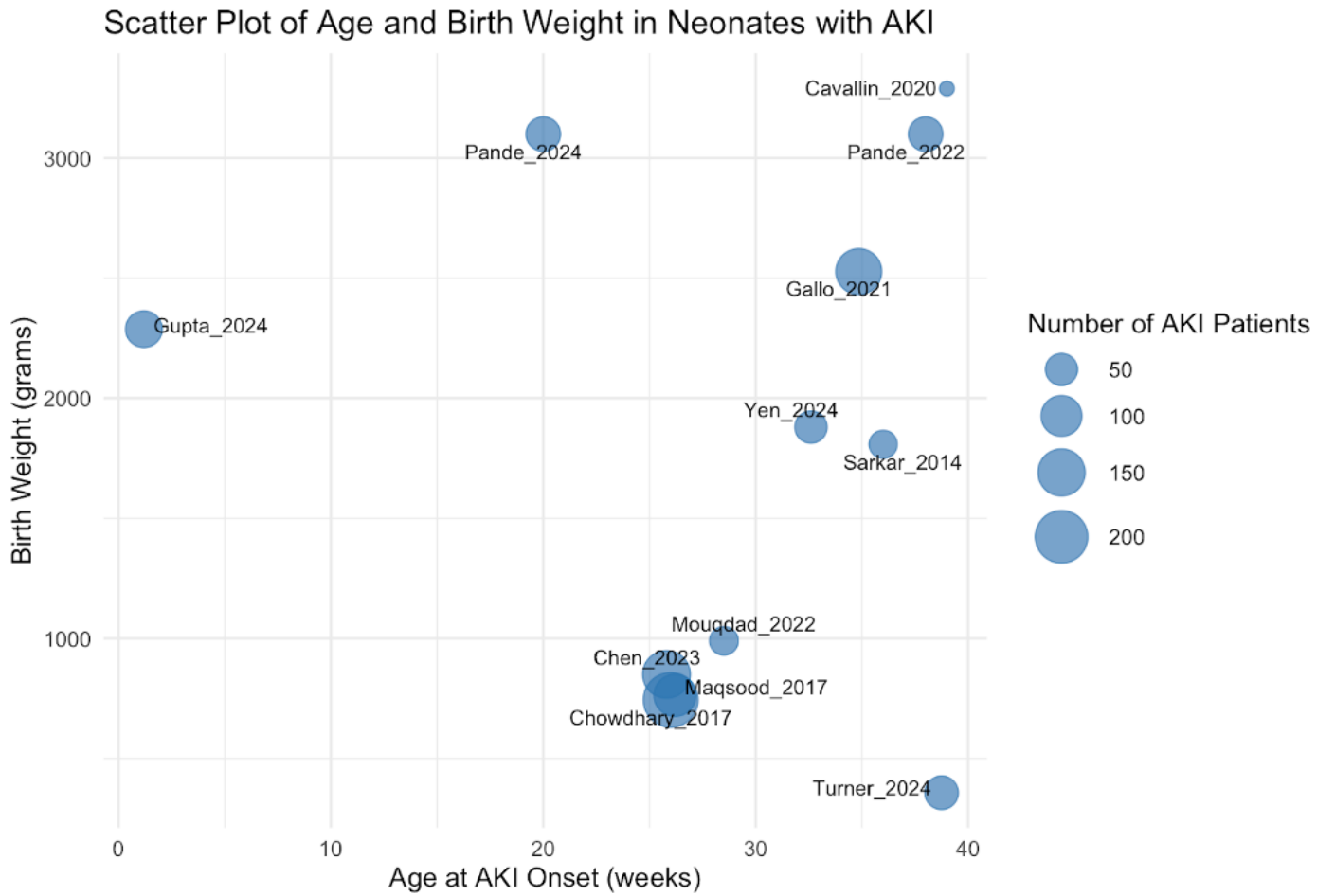

Figure 3. Scatter plot of the relationship between age at onset of AKI and birth weight in neonates.
Each dot represents a single study, with the size of the bubble reflecting the number of neonates with AKI reported in that study.

Table 2 Indications for neonatal brain MRI.

Condition	Indications	Optimal timing of imaging	Special sequences (in addition to basic protocol [Table 1])
Acute encephalopathy (other than HIE) or seizures of unknown etiology	All patients	As soon as possible	MRS in all cases
Hypoxic-ischemic encephalopathy	All patients treated with TH Neonates with mild HIE with an atypical presentation or abnormal CUS findings	Optimal: 4—7 days post birth Valid: 4—14 days post birth Early (2—4 days) if redirection of care is considered	Consider MRS, voxel-based mapping of BGT T2-axial: 2 mm-thick slices needed for visualization of mammillary bodies
Neonatal ischemic stroke	Clinical presentation (clonic seizure or apnea) Suggestive sonographic findings (increased echogenicity corresponding to a vascular territory)	Within a week of onset	Cerebral and cervical non-contrast MR angiography (3D-TOF) to assess for carotid artery dissection, occlusion or stenosis of large or medium vessels or vascular anomalies SWI allows detection of clots
Cerebral venous thrombosis	Clinical presentation Suggestive sonographic findings	Within a week of onset	SWI allows visualization of congested small cerebral veins and isolated congestion or thrombosis of deep medullary veins and superficial cerebral veins Phase-contrast MR venography (if CVST is suspected)
Cerebral venous sinus thrombosis	Clinical presentation Suggestive sonographic findings (especially intraventricular hemorrhage, thalamic hemorrhage or white matter involvement)	As soon as possible after suspecting the condition if treatment with anticoagulants is considered. No anticoagulation: 5—7 days later to assess progression and delineate associated parenchymal lesions. If anticoagulation: consider monitoring to discontinue treatment at 6 weeks and, if thrombus persists, at 12 weeks	SWI allows visualization of intraluminal clot; significant asymmetries in vascular perfusion Venogram: assessment of venous flow
Meningoencephalitis	Abnormal or suggestive findings on CUS Complicated course	Depending on clinical and sonographic features If viral infection is suspected: first week (repeating 2—3 weeks later if initial results were abnormal)	

Table 2 (*Continued*)

Condition	Indications	Optimal timing of imaging	Special sequences (in addition to basic protocol [Table 1])
Congenital heart disease	Neurologic manifestations Abnormal or suggestive findings in CUS. Consider after extracorporeal surgery	As soon as the patient's condition allows	
Congenital cytomegalovirus infection	Infection acquired during the first trimester of pregnancy Symptomatic infection (including neonates with isolated CNS infection) Neonates with abnormal CUS findings (lenticulostriate vasculopathy, ventriculomegaly, intraventricular septations, subependymal, periventricular or temporal cysts, abnormal white matter echogenicity, corpus callosum dysgenesis)	Urgent if there are doubts whether or not to start treatment As soon as possible in all other cases	SWI and GRE: make it easier to visualize calcifications
Neurometabolic disease	In every case	As soon as possible after it is suspected	MRS: single-voxel spectroscopy with a short TE can detect metabolites at low concentrations. Place the voxel in acute lesions with restricted restriction and in the BGT and, optionally, the parietal WM or mid-parietal gray matter. Avoid areas with chronic lesions secondary necrosis, hemorrhage or calcifications.
Hypoglycemia	Neurologic dysfunction (encephalopathy, seizures) Sonographic findings suggestive of injury	Within 2 weeks	
Hyperbilirubinemia	Acute neurologic manifestations Consider on a case-to-case basis if persistent severe hyperbilirubinemia requiring exchange transfusion or abnormal evoked potentials	At term-equivalent age Repeat at around 6—9 months in case of normal or uncertain neonatal MRI and abnormal psychomotor development	
Suspected CNS structural anomaly	Neurologic manifestations, craniofacial features Suggestive sonographic findings	Whenever possible Consider repeating later if there is uncertainty, especially in case of suspected cortical development abnormalities or in preterm infants.	Consider including non-contrast enhanced MR angiography of the brain

Table 3 Magnetic resonance imaging findings in HIE and correlation with neurodevelopmental outcomes.

Sequences	Anatomical region	Assessment	Prognostic correlation
Conventional and diffusion MRI Qualitative and systematic assessment of the following structures	Basal ganglia and thalamus	Assess for potential injury and its extension	The presence and severity of injury is associated with the risk and severity of motor impairment
	Posterior limb of internal capsule	Assess for appropriate myelination for gestational age.	Abnormal myelination is a highly sensitive risk factor for motor impairment
	Brainstem	Assess involvement and extent of injury	Increases the severity of motor problems and is associated with an increased mortality
	White matter and cortex	Assess for abnormalities in signal intensity, whether they are focal or diffuse, and their extent	White matter injury increases the risk of visual, cognitive and behavioral problems. When it is very extensive, it is associated with mild CP.
	Mammillary bodies	Assess whether there is an increase in signal intensity in the axial or coronal T2-weighted images (requires 2 mm slice thickness).	Injury in the mammillary bodies increases the risk of learning and memory problems in school-aged children, even when the rest of the structures appear normal in the MRI
Spectroscopy Single voxel Short TE (35 ms)	Basal ganglia-thalamus	Lactate-threonine/NAA levels correlate to neurodevelopmental outcomes at age 2 years	Values equal to or greater than 0.39 for lactate/NAA have been found to offer: - Sen 100% and Spe 97% for predicting motor impairment - Sen 90% and Spe 97% for predicting cognitive impairment - Sen 81% and Spe 97% for predicting language disorder

Abbreviations: CP, cerebral palsy; HIE, hypoxic-ischemic encephalopathy; MR, magnetic resonance; NAA, N-acetyl-aspartate; Sen, sensitivity; Spe, specificity; TE, time to echo.