Supplementary Material

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1. Search strategies

De-novo reviews

1.1. Fluid restriction

- Search strategy for Medline (adapted to Embase, Cochrane CENTRAL and CINAHL)
- *Search date: September 14, 2022*

Search Number	Search Terms
Search Set 1	**Population Terms**
1	((exp Infant, Newborn/) AND (Asphyxia Neonatorum/ OR exp Hypoxia/ OR Hypoxia-ischemia, Brain/))
2	((birth* OR bab* OR infant OR neonat*) AND (asphyx* OR hypox* OR encephalopathy OR hypoxic-ischemic encephalopathy)).mp
Search Set 2	**Intervention Terms**
3	Fluid therapy/
4	(fluid management or fluid restriction).mp
	Joint Terms
5	1 or 2
6	3 or 4
7	5 and 6

1.2. Anti-seizure medications

- Search strategy for Medline (adapted to Embase, Cochrane CENTRAL and CINAHL)
- *Original Search date: September 14, 2022*
- *Updated search date: October 28, 2022*

Search Number	Search Terms
Search Set 1	**Population Terms**
1	(exp Infant, Newborn/ AND (Asphyxia Neonatorum/ OR exp Hypoxia/ OR Hypoxia-ischemia, Brain/))

2	((birth* OR bab* OR infant OR neonat*) AND (asphyx* OR hypox* OR encephalopathy OR hypoxic-ischemic encephalopathy)).mp
Search Set 2	**Intervention Terms**
3	exp Anticonvulsants/
4	(anti-epileptic therapy or anti epileptic therapy or anti-seizure medication* or anti seizure medication* or anticonvuls*).mp
	Joint Terms
5	1 or 2
6	3 or 4
7	5 and 6

Updated reviews

1.3. Allopurinol

- Search strategy with keywords for MEDLINE (adapted to EMBASE, CENTRAL, CINAHL and Google Scholar), from original review [1]
- Custom date range: April 2012 to September 28, 2023

Search Number	Search Terms
Search Set 1	**Population Terms**
1	[Infant, Newborn OR Asphyxia Neonatorum/ OR Hypoxia, Brain/ OR Brain Ischemia/ OR infant OR neonat*]
Search Set 2	**Intervention Terms**
3	[Allopurinol/ OR Free Radical Scavengers/ OR Free Radicals/ OR Antioxidants/]
Search Set 3	**Study design Terms**
4	randomized controlled trial.pt. / OR controlled clinical trial.pt./ OR randomized.ti,ab.
	Joint Terms
5	1 and 3
6	1 and 3 and 4

As-is reviews – secondary analysis of LMIC trials

1.4. Therapeutic hypothermia

- Search strategy, refer [2]
- Search date: inception to October 31, 2021
- Databases: Medline, Embase, Cochrane Library, LIVIVO, Web of Science, Scopus, and CINAHL

1.5. Erythropoietin

- Search strategy, refer [3]
- Search date: January 1999 to 1 June 2020
- Databases: PubMed, Embase, and Web of Science

1.6. Magnesium sulfate

- Search strategy, refer [4]
- Search date: inception to November 2022
- Databases: PubMed, EMBASE (Through OVID), EMCARE (through OVID), MEDLINE (through OVID) and the Cochrane Library.

1.7. Melatonin

- Search strategy, refer [5]
- Search date: inception to May 31, 2020
- Databases: Medline, Embase, CINAHL, LILACS and CENTRAL, Google search

1.8. Early intervention to improve developmental outcomes in asphyxiated babies

- Search strategy, refer [6]
- Search date: inception to 15 November 2021
- Databases: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, Health Technology Assessment Database and the Database of Abstracts of Reviews of Effects.

2. Eligibility criteria

Suppl. Table 2: Detailed eligibility criteria per topic

Participants	Study Design	Setting	Intervention	Comparator	Outcomes
Term or preterm neonates following intrapartum asphyxia with encephalopathy. Newborns without encephalopathy will be excluded.	RCTs and quasi-randomized trials only. Other study designs will be excluded.	Studies from LMIC only settings, as defined by the World Bank, given that all other eligibility criteria have been met. However, should we find limited eligible studies conducted in LMICs, we will leverage findings from high income setting.	**Fluid restriction:** restriction of maintenance fluids to any volume	The intervention will be compared with no fluid restriction or a differing amount of fluid restriction (i.e., higher versus lower fluid intakes). The newborn may be receiving other supportive care interventions (e.g., therapeutic hypothermia, continuous positive air pressure, blood pressure management, glucose management).	**Primary outcomes:** Composite outcome of mortality and severe neurodevelopmental disability, neonatal mortality, infant mortality, severe neurodevelopmental disability (i.e., cerebral palsy). **Secondary outcomes:** Seizure activity diagnosed clinically or through EEG, electrolyte disturbances such as: hyponatremia defined as a serum sodium concentration of < 130 mEq/L. hypernatremia defined as a serum sodium concentration of > 150 mEq/L. SIADH defined as hyponatremia and hypoosmolality with urine spot sodium > 30 mEq/l., renal function abnormalities such as AKI, based on the Acute Kidney Injury Network classification, urine output
			ASMs: any ASM given to a newborn with HIE following asphyxia.	The intervention will be compared with any other ASM for treatment of seizures, supportive care, or a control. Supportive or routine care has been defined as: • Therapeutic hypothermia • Respiratory and ventilator management (i.e., intubation) • Cardiovascular support (i.e., antihypotensive or antihypertensive therapeutics) • Glucose management • Feeding strategies	**Primary outcomes:** Proportion of infants who achieved control of seizures diagnosed clinically at bedside or through EEG, defined as per the ACNS definition: seizure based on EEG as "a sudden, abnormal EEG event, defined by a repetitive and evolving pattern with a minimum 2 KV peak-to-peak voltage and duration of at least 10 seconds" or as per the updated ILAE classification: "an electrographic event with a pattern characterized by sudden, repetitive, evolving stereotyped waveforms with a beginning and end. The duration is not defined but has to be sufficient to demonstrate evolution in frequency and morphology of the discharges and needs to be long enough to allow recognition of onset, evolution, and resolution of an abnormal discharge", death at any point, neurodevelopmental disabilities

					such as: cerebral palsy, developmental delay, intellectual impairment, blindness, defined as bilateral blindness caused by damage to the central nervous system, deafness, defined as greater than 40 dB hearing reduction. **Secondary outcomes:** Age in h at first seizure, seizure cessation rate or h taken to seizure cessation, normal or abnormal EEG, normal or abnormal MRI, normal or abnormal neurologic outcome as defined by trialists based on validated tools, hospitalization in days, adverse effects from the ASM, incidence of thrombocytopenia, deranged kidney function, deranged liver function, hypotension, nitric oxide levels lipid peroxidation (i.e., Malondialdehyde) and antioxidant enzymes (i.e., Superoxide dismutase and Glutathione peroxidase) levels, blood levels of vitamins A and E, electrolyte values (mean of capillary blood glucose levels, serum bilirubin, calcium, sodium, or potassium), hyperoxia and hypoxia
Newborn infants (> 34 weeks' gestation) with HIE defined as clinical evidence of cardiorespiratory or neurological depression (Apgar score < 7 at five minutes and beyond after birth) and/or evidence of severe metabolic acidosis in intrapartum foetal, umbilical arterial cord, or very early neonatal blood samples (pH < 7 or base deficit > 12 mmol/L), and/or clinical or electro-encephalographic (multichannel or amplitude integrated) evidence of NE	RCT	LMIC only	**Allopurinol:** administered within 6 h of delivery. A minimum or maximum dose or duration of treatment was not pre-specified. Allopurinol could have been given in conjunction with another intervention provided both treatment and control groups received the intervention.	Placebo or no drug	**Primary outcomes** Death during infancy, death or severe neurodevelopmental disability in survivors assessed aged ≥12 months of age, defined as any one or combination of the following: non-ambulant cerebral palsy, severe developmental delay assessed using validated tools, auditory and visual impairment (each component analysed individually as well as part of the composite outcome), cognitive and educational outcomes in survivors aged > 5 years old (intelligence quotient and/or indices of educational achievement measured using a validated assessment tool including school examination results). **Secondary outcomes** Seizures in the neonatal period, either apparent clinically or detected by electro-encephalographic recordings, time to achieve full oral feeding independent of enteral tube

					feeding (days after birth), and/or incidence of continued enteral tube feeding at four weeks after birth, cortical, white matter, or basal ganglia abnormalities on brain imaging (magnetic resonance, computed tomography, or ultrasound), potential adverse effects of allopurinol (skin rashes, hypersensitivity reactions) that necessitates discontinuation of therapy.
Newborn infants with a gestational age ≥35 weeks, having evidence of perinatal asphyxia and encephalopathy. Perinatal asphyxia was defined by one or more of the following: a) Apgar score ≤5 at 5 minutes of life; b) need for ongoing resuscitation or respiratory support at 10 minutes; or c) cord blood/arterial blood pH<7.1, or base deficit ≥12 within one h of birth. Evidence of encephalopathy was based on Sarnat staging system or any other recognized staging/classification system	RCT	LMIC only	**Therapeutic hypothermia:** WB or SH cooling by any device/equipment, initiated within 6 h of birth, with documented reduction in core temperature (to ≤34°C in case of WB cooling) or middle ear temperature (to ≤34°C in case of SH cooling)	Normothermia, or no therapeutic cooling, or no intervention	**Primary outcomes:** Mortality, neurological impairment or disability (defined by any standard criteria), the composite outcome of mortality or disability, and cerebral palsy. These were assessed at four time points after randomization: a) Neonatal, i.e., from randomization to discharge or death during the initial hospitalization; b) Infancy, i.e., at the age of 18-24 months, c) Childhood, i.e., at the age of 5-10 years, and d) Long-term, i.e., beyond the age of 10 years. For this analysis, the primary outcome was listed as "mortality or neurological disability" at ≥18 months of age **Secondary outcomes**: seizures, aEEG abnormalities, MRI findings suggesting neuronal damage during the initial hospitalization, duration of hospitalization, and quality of life.
Neonates born at ≥36 weeks gestation with asphyxia. Asphyxia was considered if at least one of the following criteria was met: (i) Apgar score ≤5 at 5 min, (ii) cord or arterial blood pH ≤ 7.0, (iii) base deficit >12 mmol/L within the first hour after birth, or (iv) ongoing resuscitation or mechanical ventilation at 5 min of life. NE was defined using a detailed neurological examination	RCTs as well as all nonrandomized and case-control studies	LMIC only	**Erythropoietin:** parenteral (intravenous or subcutaneous) or one of its analogues was administered within one week of postnatal life	placebo or usual care	**Primary outcome:** composite measure of mortality or neuro-disability at 18 months of age or later. **Secondary outcomes:** mortality, cerebral palsy, brain injury on conventional magnetic resonance imaging, moderate-to-severe cognitive impairment, and any adverse outcomes as a result of erythropoietin administration. Adverse outcomes included: persistent hypotension, grade IV intraventricular haemorrhage on ultrasound, pulmonary haemorrhage, persistent pulmonary hypertension, systematic hypertension, major venous or arterial

performed prior to enrolment which was assessed against objective criteria					thrombosis, prolonged blood coagulation, polycythemia, culture-proven sepsis, necrotising enterocolitis, cardiac arrhythmia requiring therapy, severe thrombocytopenia (platelet count <25,000 per mL), persistent metabolic acidosis lasting over 12 h after birth, renal failure (anuria > 48 h with azotemia), pneumonia, subcutaneous fat necrosis, and neurological examination at discharge
Infants with a gestation >/=35 weeks with HIE	RCTs	LMIC only	**$MgSO_4$:** either as the sole neuroprotective therapy or as an adjunct to TH were included.	Control (No MgSO4)	**Primary outcome**: death or moderate to severe neurodevelopmental disability at ≥18 months of age. (neurodevelopmental disability was defined as the presence of ≥1 of the following: blindness, sensorineural deafness, cerebral palsy, and major neurosensory disability based on validated tools such as Griffiths Scales of Child Development and Bayley Scales of Infant and Toddler Development.) **Secondary outcomes:** mortality before hospital discharge, neurodevelopmental outcomes at >/=18 months, a composite outcome of mortality or abnormal neurological examination at discharge, and hypotension during $MgSO_4$ therapy. Short-term surrogate outcomes before discharge were abnormal neurological examination, poor suck feeds, abnormal EEG and abnormal neuroimaging findings. The following findings on EEG were considered abnormal: burst suppression pattern, low voltage, electrocerebral inactivity, discontinuous pattern, and electrographic seizures. We also accepted individual study authors' definition of abnormal EEG. The following findings on conventional MRI sequences or diffusion restriction sequences were considered as abnormal: watershed infarctions, punctate white matter injury, brainstem injury, global injury pattern, central/basal ganglia-thalamus injury pattern or cerebellar injury. Even though CT scan and

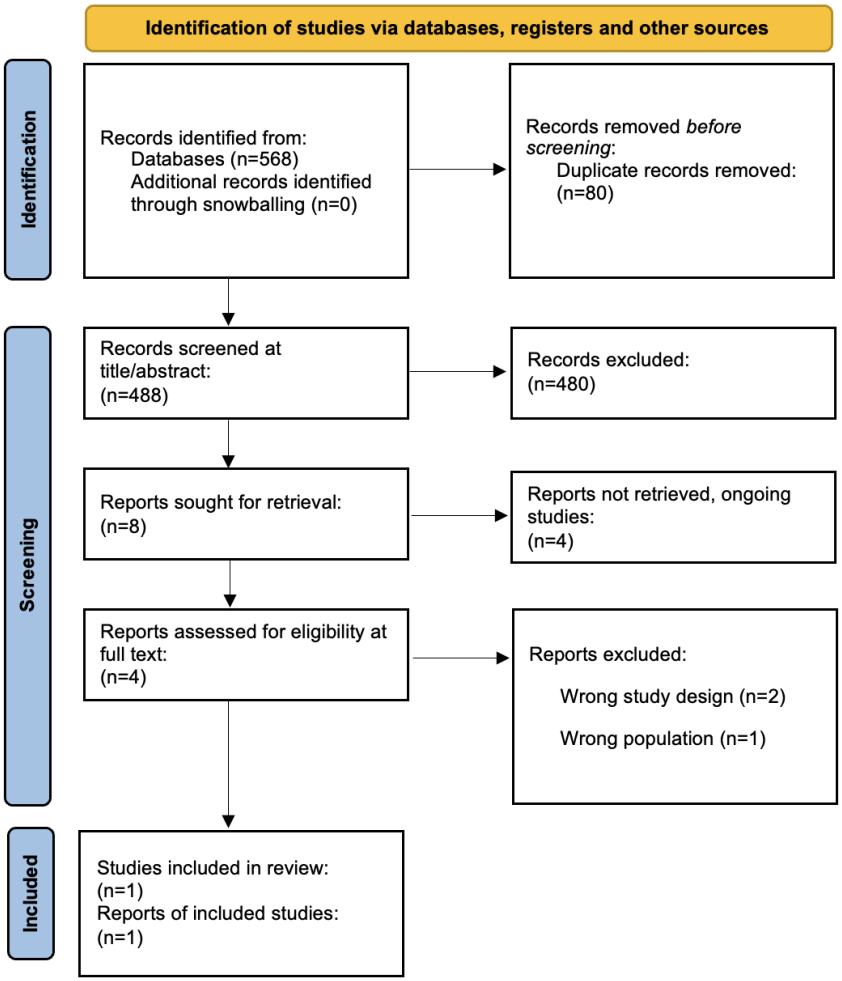
					ultrasound examination have a very low sensitivity to diagnose hypoxic-ischemic injury to the brain, they are commonly performed in low-resource settings and information was collected from studies that report these outcomes.
Neonates (term or late preterm infants) fulfilling criteria for perinatal asphyxia or Neonate with NE due to perinatal asphyxia which is as follows: (i) profound metabolic or mixed acidaemia (pH < 7.00) in an umbilical artery blood sample, if obtained, (ii) persistence of an Apgar score of </=3 for longer than 5 min, (iii) neonatal neurologic sequelae (e.g., seizures, coma, hypotonia), and (iv) multiple organ involvement (e.g., kidney, lungs, liver, heart, intestines)	RCT	LMIC only	**Melatonin:** regardless of dose, duration, and route of administration) as sole therapy or as an adjuvant to therapeutic hypothermia or along with erythropoietin or magnesium sulfate, or a combination of two or more of the therapies which are established for the treatment of perinatal asphyxia	Control - Placebo, TH only	**Primary outcome:** NDI as any form of change assessed at 18-24 months (by any standardized, validated tool like BSID, Griffith, etc.), death before discharge (due to any cause) (early or late neonatal death), cerebral palsy or unilateral deafness or unilateral blindness diagnosed on or before 24 months of age (as defined by the authors), neurodevelopment delay: as one or more of the following i) BSID III score in any domain (e.g.cognitive/motor/language/social/adaptive score > 1SD or >2 SD below the normative mean or ii) BSID II MDI and/or PDI scores >1 SD or>2 SD below the normative mean; iii) non-ambulant cerebral palsy (GMFCS level 3e5); iv) blindness bilateral v) sensorineural deafness requiring amplification. **Secondary outcomes:** Any other clinically important outcome was reported by authors (not pre-specified), MRI and EEG finding at follow up, persistent seizures disorder, biomarkers of brain injury such as S100eB.
Infants under 1 month of age with birth asphyxia history	individual, cluster and quasi-RCTs	LMIC only	The **HCP-ECD interventions** had to be delivered by primary-level. HCPs (e.g., generalist nurses, health visitors, midwives, child health nurses, general practitioners, primary care doctors, community health workers). The interventions could commence in the hospital but had to include community-based post-	no HCP-ECD interventions', that is, any other care, standard care that did not include ECD or no care.	**Primary outcome**: cognitive development in children at 0–36 months of follow-up. **Secondary outcomes**: (1) speech, language, fine motor, gross motor, social, emotional, behavior, executive functioning, and adaptive functioning; and (2) maternal mental health. Studies were included in the systematic review regardless of the type of outcomes. However, only standardized measures, for example, the Bayley Scales of Infant and Toddler Development or the Griffiths Mental Development Scales for

			discharge follow-up. Interventions were required to be face to face in nature, for example, delivered through home visiting, mobile health team visits, clinic visits, child health checks or group programmes		cognitive development, were used in the meta-analyses

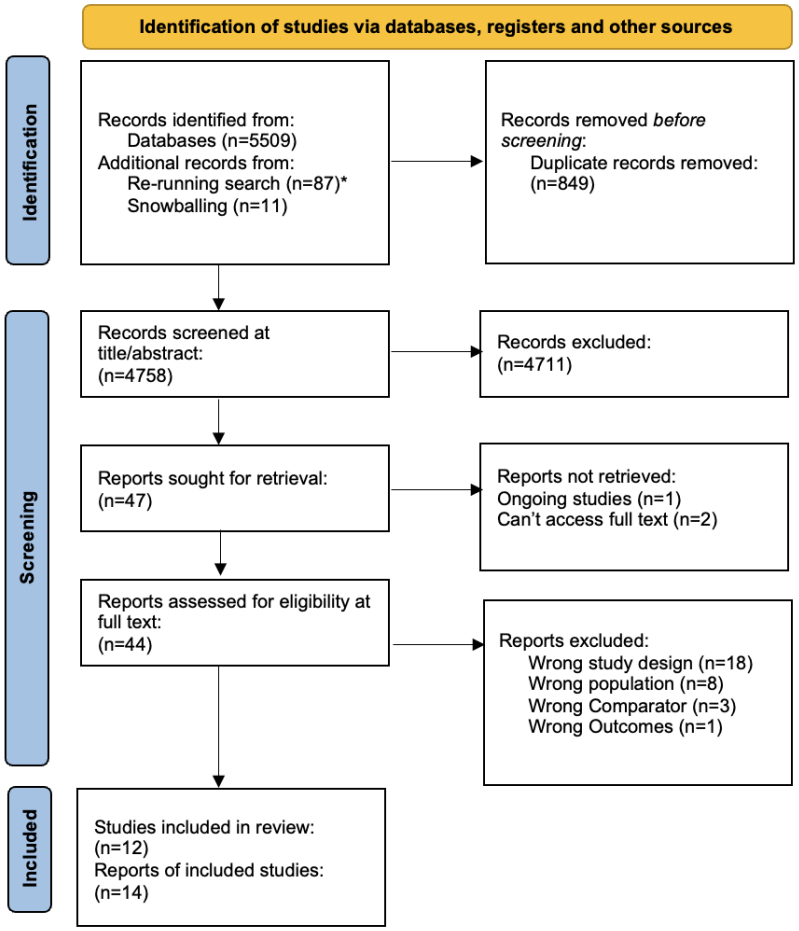
Note - ACNS: American clinical neurophysiology society, AKI: acute kidney injury, ASM: anti-seizure medication, BSID MDI: Bayley scale of infant development mental development index, PDI: psychomotor development index, CT: computed tomography, dB: decibel, ECD: early childhood development, EEG: electroencephalograph, GMFCS: gross motor function classification system, h: hours, HCP: healthcare provider, HIE: hypoxic ischemic encephalopathy, ILAE: international league against epilepsy, IV: intravenous, KV: kilo-volt, LMIC: low and middle-income country, mEq/L: molar equivalents per litre, $MgSO_4$: magnesium sulfate, min: minutes, mL: millilitre, MRI: magnetic resonance imaging, NDI: neurodevelopmental impairment, NE: neonatal encephalopathy, RCT: randomized controlled trials, SD: standard deviation, SH: selective head, SIADH: syndrome of inappropriate antidiuretic hormone release, WB: whole-body

3. PRISMA flow diagrams

Suppl. Figure 3.1. Fluid restriction



Suppl. Figure 3.2. Anti-seizure medications

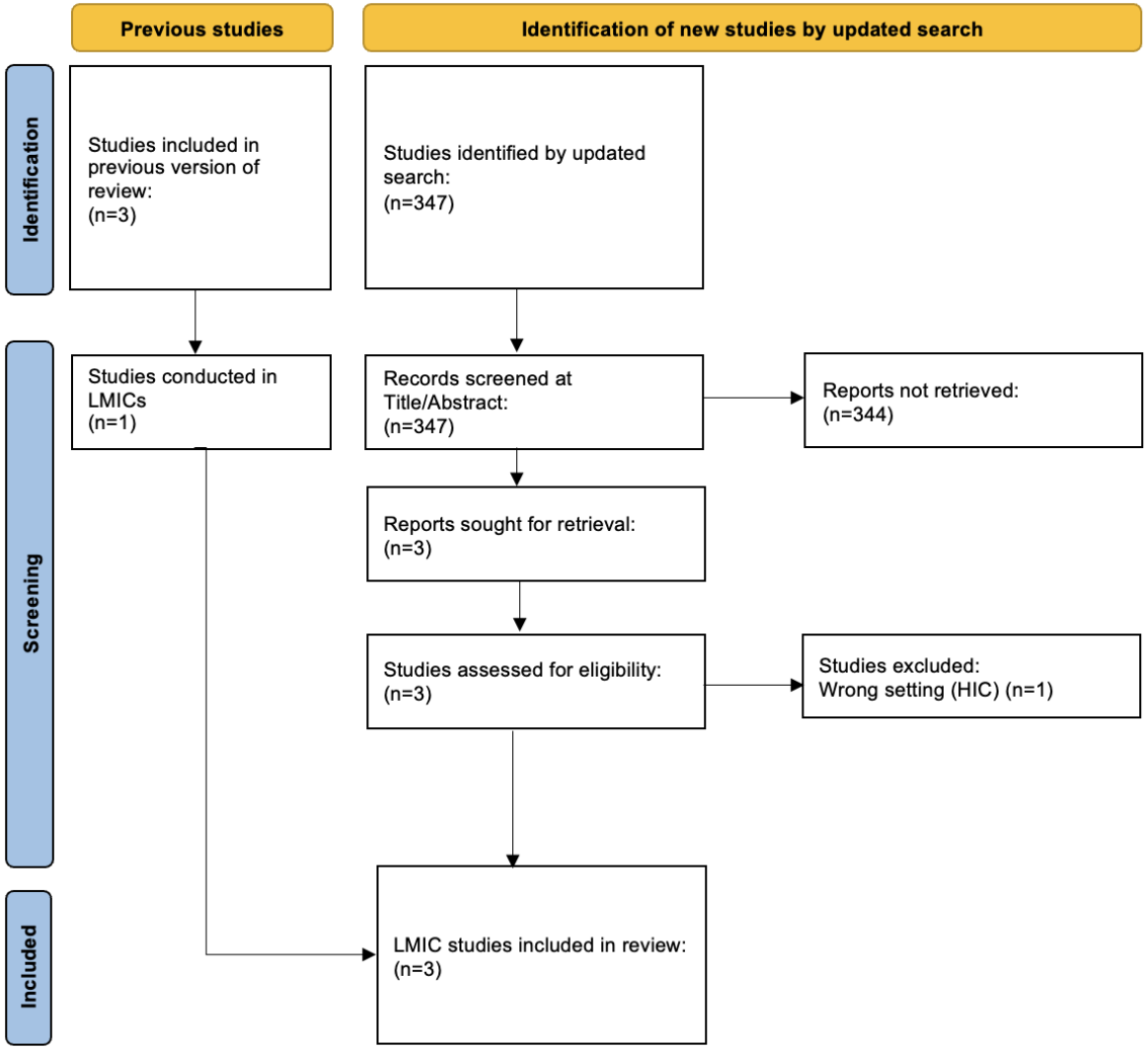


**Term 'anti-seizure medications' was added to search strategy and all searches were re-run (Oct 28, 2022); Original search date: Sep 14, 2022*

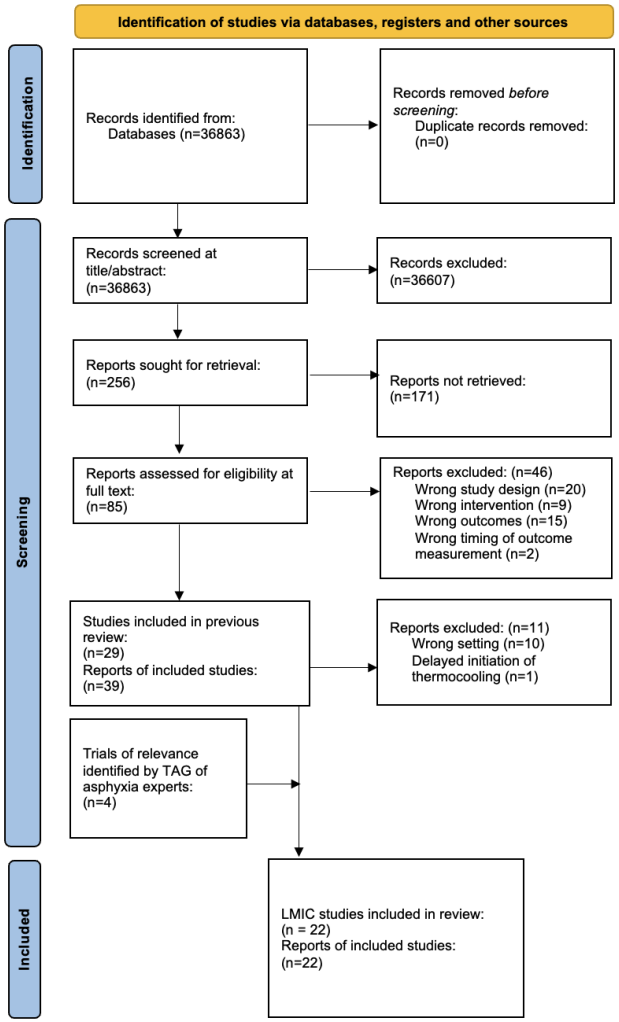
Note:

- Wrong study design (n=18) includes 8 reviews which were collated at full text to search reference lists using the snowball method.

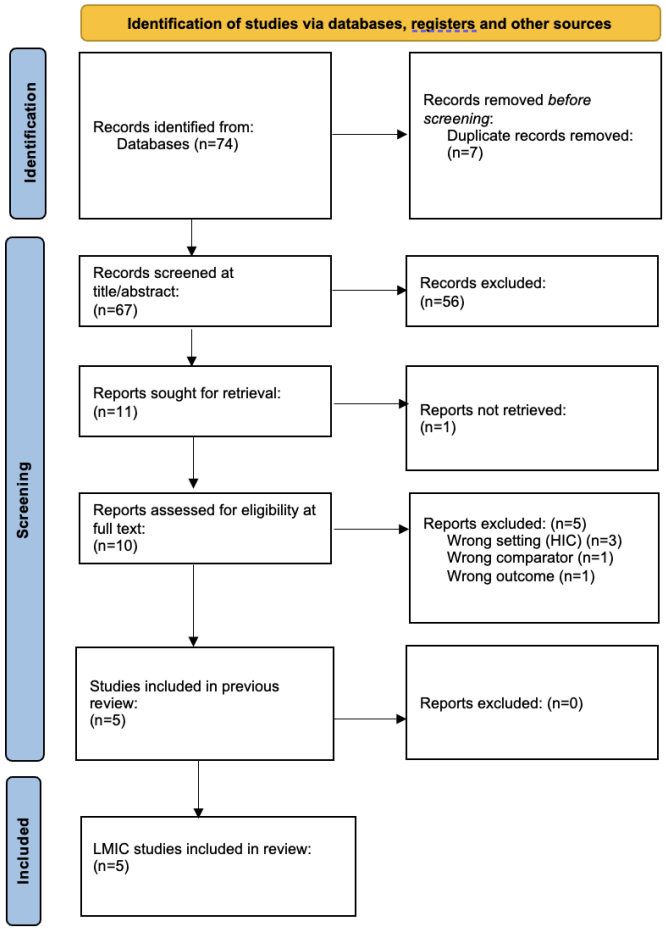
Suppl. Figure 3.3. Allopurinol



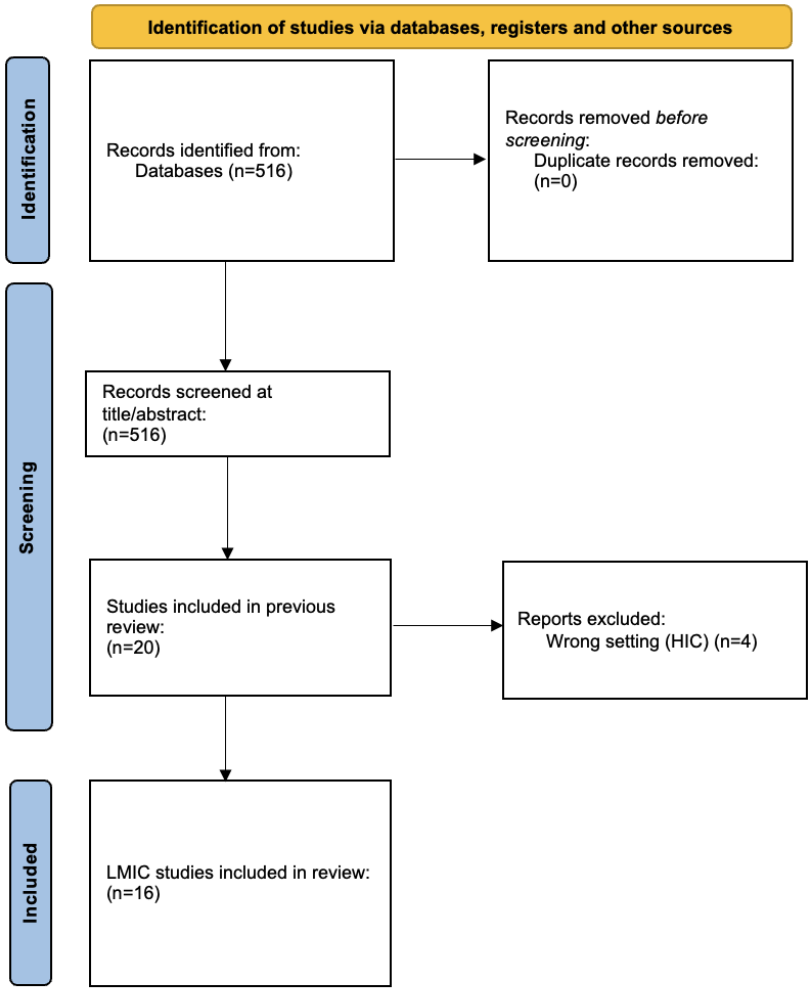
Suppl. Figure 3.4. Therapeutic hypothermia



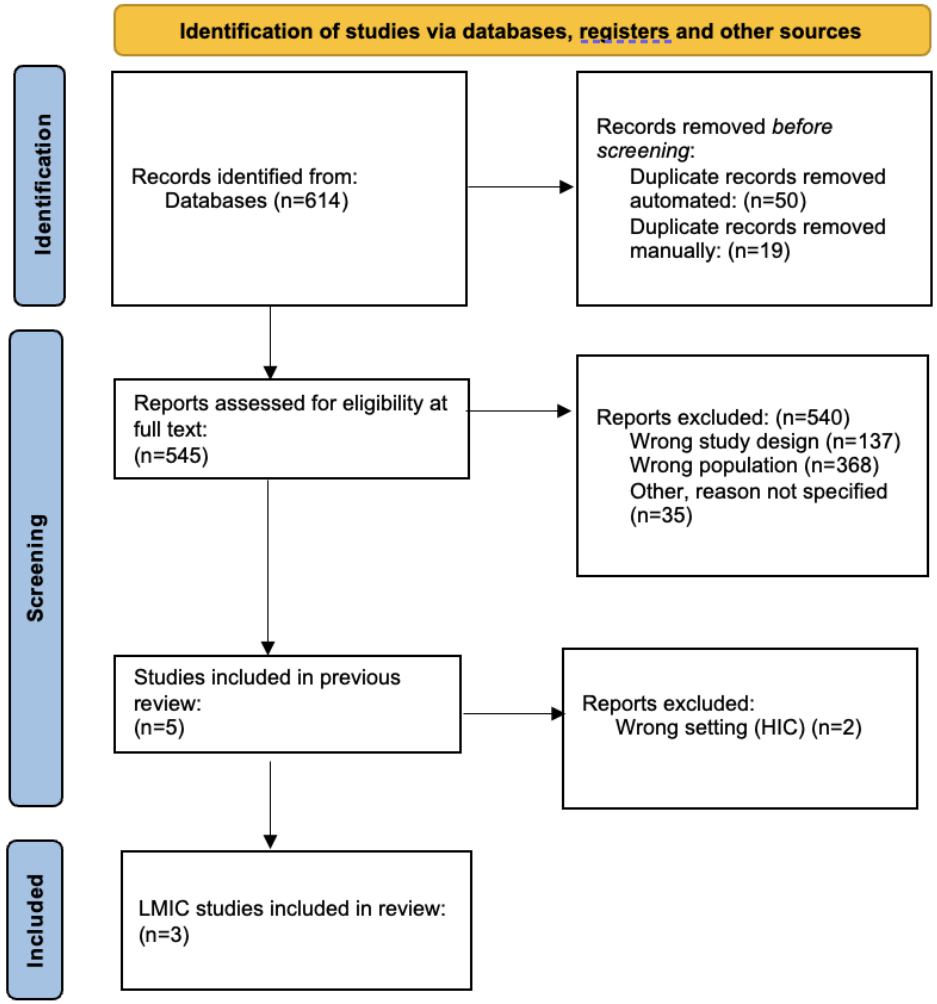
Suppl. Figure 3.5. Erythropoietin



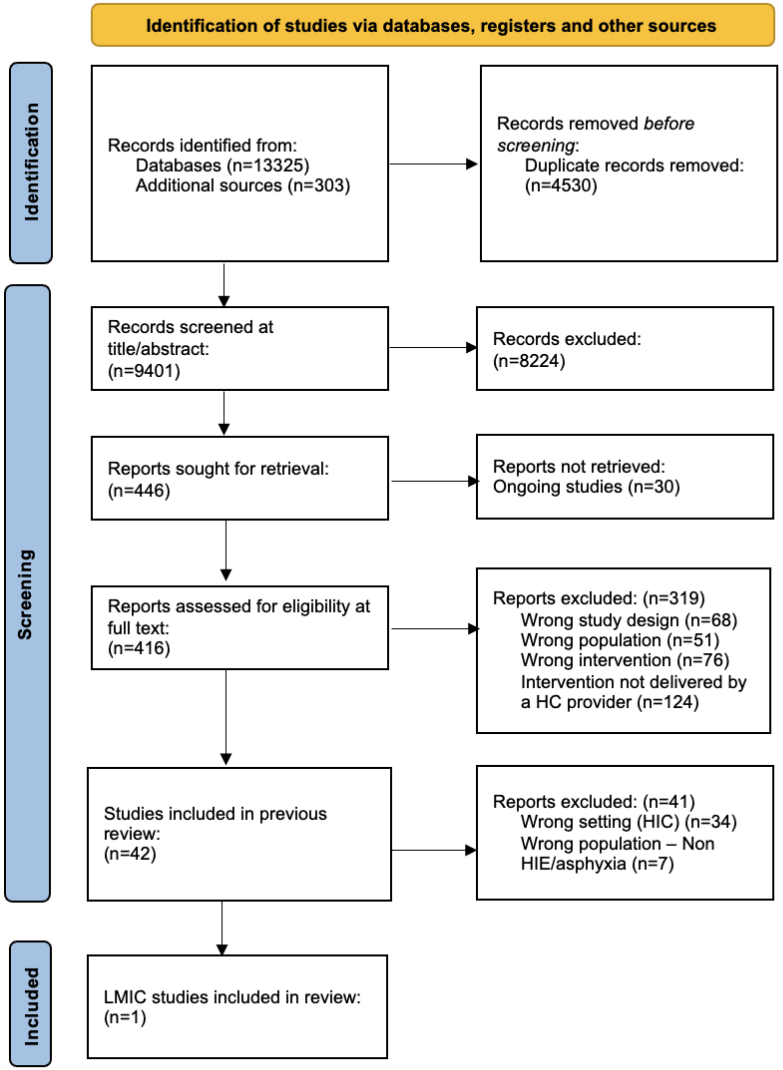
Suppl. Figure 3.6. Magnesium sulfate



Suppl. Figure 3.7. Melatonin



Suppl. Figure 3.8. Early intervention to improve developmental outcomes in asphyxiated babies



4. Excluded studies

Suppl. Table 4: List of Excluded studies

Study ID	**Reason for exclusion**
Fluid restriction (n=3 studies)	
Fedorova 1982	Wrong study design – review
Sikka 2013	Wrong study design – poster
Lorenz 1982	Wrong population – no assessment of HIE
Antiseizure medications (n= 30 studies)	
Berube 2020	Wrong comparator - ASMs used for indications other than neonatal seizures, such as sedation and anaesthesia
Falsaperla 2017	Wrong study design – observational
Falsaperla 2019	Wrong population – All patients were affected by acute symptomatic seizures (ASS) and particularly stroke, CNS infection, and hypoxic-ischemic encephalopathy, no disaggregated results
Filippi 2010	Wrong study design – safety study of prophylactic topiramate
Filippi 2012	Wrong study design – protocol
Gowda 2019	Wrong population - 40% in LEV group and 48% in PHENO group had HIE as etiology of seizures; no disaggregated results
Gyandeep 2023	Wrong population – In neonates with Apgar score < 7 at 5 min, pH of umbilical cord blood or initial ABG within 1 h of age < 7 and base excess > − 16 and those who developed seizure within 48 h of life (could not be explained by other causes) were considered as hypoxic ischemic encephalopathy (HIE) cases, subset of population. No disaggregated results.
Hannan 2020	Wrong study design – commentary on Nunez-Ramiro 2019
Khoshdel 2016	Wrong study design – case control study
Liu 2020	Wrong outcome – No outcomes of seizure incidence/control
Natarajan 2018	Wrong study design - secondary analysis
Painter 1999	Wrong population – Asphyxia, hemorrhage or infarction as primary cause of seizure in subset of population, no assessment of HIE, no disaggregated results
Pathak, 2013	Wrong population – 79% of infants had moderate-severe HIE
Pervez 2018	Wrong population – No assessment of HIE

Prakash 2019	Wrong population – 54.7% in LEV group and 52.6% in PHENO group had HIE as etiology of seizure; no disaggregated results
Rao, 2018	Wrong study design – retrospective
Ruth 1988	Wrong population - Randomized premature, very low birth weight infants to receive phenobarbital or placebo following birth; perinatal asphyxia was not an eligibility criterion
Sarkar 2012	Wrong study design – retrospective
Shany 2007	Wrong study design – retrospective chart review
Srinivasakumar 2015	Wrong comparator – both groups received the same ASM (phenobarbital), treatment of clinical seizures only vs treatment of electrographic and clinical seizures
VandenBroek 2015	Wrong study design – observational study
Van Rooij, 2010	Wrong comparator – both groups received the same ASM (phenobarbital), treatment of clinical seizures only vs treatment of electrographic and clinical seizures
Evans 2000	Wrong study design – review
Evans 2001	Wrong study design – review
Young 2016	Wrong study design – review
Hooper 2021	Wrong study design – review
McGuire 2007	Wrong study design – review
Spiers 2015	Wrong study design – review
Evans 2007	Wrong study design – review
Sharma 2022	Wrong study design – review
Vargas-Origel 2004	Can't access full text
Vela 1987	Can't access full text
Therapeutic hypothermia (n=1 study)	
Li 2009	Wrong population – Therapeutic hypothermia was delayed past 6-hours in some of the infants
Allopurinol (n=3 studies)	
Kaandorp 2012	Wrong setting – HIC
Benders 2006	Wrong setting – HIC
Van Bel 1998	Wrong setting – HIC
Magnesium sulfate (n=3 studies)	
Gulczynska 2018	Wrong setting – HIC

Ichiba 2002	Wrong setting – HIC
Groenendaal 2002	Wrong setting – HIC
Melatonin (n=2 studies)	
Calero AJ 2020	Wrong setting – HIC
Fulia 2001	Wrong setting – HIC
Early intervention to improve developmental outcomes (n=8 studies)	
Ara 2019	Wrong population – Birth asphyxia was not an eligibility criteria
Fatori 2019	Wrong population – Birth asphyxia was not an eligibility criteria
Yousafzai 2014	Wrong population – Birth asphyxia was not an eligibility criteria
Rotheram-Borus 2014	Wrong population – Birth asphyxia was not an eligibility criteria
Wallander 2010-RCT 2	Wrong population - Infants without birth asphyxia who did not require any resuscitation
Cooper 2009	Wrong population – Birth asphyxia was not an eligibility criteria
Gardner 2003	Wrong population – Birth asphyxia was not an eligibility criteria
Cremer 1977	Wrong population – Birth asphyxia was not an eligibility criteria

5. Included studies

Suppl. Table 5: Characteristics of included studies per topic

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
Fluid Restriction (n=1 study)					
Tanigasalam, 2018 [7]	RCT	Single center: tertiary care academic institute in South India	80 term infants with ≥36 weeks' gestation and moderate to severe encephalopathy based on modified Sarnat criteria also undergoing whole-body cooling using phase change material	Restricted fluids [40 to 80 ml/kg] (n=40) vs normal fluids [60 to 120 ml/kg] (n=40) in first 4 days of life	Primary outcomes: Composite outcome of death or major neurodevelopmental disability at 6 months, mortality, major neurodevelopmental disability (DASII <70) Secondary outcomes: hypoglycemia, shock, seizures (clinically diagnosed), hyponatremia, SIADH, AKI, NEC
Prophylactic anti-seizure medications to prevent seizures (n=8 studies)					
Goldberg, 1986 [8]	RCT	Single center: tertiary care academic institute in USA	32 infants with ≥37 weeks' gestation and who have sustained severe perinatal asphyxia. In addition, they must have had, as a result of the asphyxial episode, neurologic signs of HIE during the first h of life and required mechanical ventilation.	IV thiopental (30mg/kg) at an initial dose of 15 mg/kg given over 30 min, and a total of 30 mg/kg within 2 h of initiating therapy, maintained at 5mg/kg for an additional hour then weaned slowly over 20 h vs conventional therapy (fluid restriction, mechanical ventilation if necessary and phenobarbital and diphenylhydantoin	Primary outcomes: Death, neurologic and developmental outcomes.

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
				therapy for seizure activity)	
Hall, 1998 [9]	RCT	Single center: tertiary care NICU of hospital in Kansas City, USA	40 out born infants term or post-term gestation transferred to the NICU within the first day of life who had a history of severe birth asphyxia manifest by (1) an initial arterial pH equal to or less than 7.0 with a BD equal to or greater than 15 mEq/L; (2) an Apgar score equal to or less than 3 at 5 minutes of age; or (3) failure to initiate spontaneous respirations by 10 min of age. Infants were excluded from study entry if they had any condition that was abnormal unrelated to asphyxia.	IV phenobarbital (40mg/kg) given over 60 min as soon as possible after admission vs control (received phenobarbital only with the occurrence of clinical seizures)	Primary outcomes: Death, severe neurologic impairment, moderate neurologic impairment, age at first seizure (h).
Singh 2004, Singh 2005 [10, 11]	RCT	Single center: tertiary care NICU of hospital in central India	45 babies with GA ≥34 weeks were eligible for inclusion if in the settings of low Apgar score (<6 at 1 min of age) and evidence of fetal distress (fetal bradycardia and/or meconium-stained amniotic fluid and/or cord arterial blood pH ≤7.15), they developed features of encephalopathy: alterations	IV phenobarbital (20mg/kg) given over 20 min within first 6 h of life with monitoring of respiration, heartbeat and blood pressure vs control (no ASM)	Primary outcomes: Seizures, mortality at discharge, neurologically abnormal at discharge, neurologically abnormal at 3 months. Secondary outcomes: MDA, SOD, GPx, vitamin A, vitamin E, age at first seizure (h).

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
			of tone, deep tendon reflexes, primitive reflexes and sensorium (Sarnat and Sarnat) within the first six h of life		
Gathwala, 2011 [12]	RCT	Single center: tertiary care teaching institution in India	72 full term inborn babies with severe birth asphyxia who met the selection criteria (umbilical vein cord blood pH<7 and Apgar score<6 at 5 minutes).	IV phenobarbital (40mg/kg) given over 60 min within the first 2 h of life under continuous monitoring for heart rate, oxygen saturation, respiration and mean arterial pressure vs Control (no ASM)	Primary outcomes: Death, seizures - median time to become passive. Secondary outcomes: MDA, SOD, GPx,
Avasiloaiei, 2013 [13]	RCT	Single center: tertiary care NICU of OBGYN hospital in Romania	67 term neonates with severe perinatal asphyxia (defined as having 3 of 4 criteria (umbilical artery blood pH < 7.0 with or without BD</=12 mEq/L, Apgar <3 at > 5 minutes of life, neonatal neurologic sequelae (i.e. seizures, coma, hypotonia) or multiple organ involvement (i.e. kidney, lungs, liver, heart, intestines) without major congenital malformations or hemolytic disease due to Rhesus incompatibility.	IV phenobarbital (40 mg/ kg) as a single dose given in the first 4 h after birth plus supportive treatment vs SC erythropoietin (1000 IU/kg) once a day for the first 3 days plus supportive treatment vs supportive treatment only (oxygen, volume expanders, inotropes, diuretics, antibiotics)	Death or disability at 18 months using BSID-II
Velaphi, 2013 [14]	RCT	Single center: tertiary care	94 infants with GA of ≥34 weeks and/or weight ≥2 000	IV phenobarbital (40mg/kg) as a single dose	Primary: Death, seizures, HIE II and III at discharge,

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
		Academic hospital in Johannesburg, South Africa (public govt. facility)	g were eligible for the study if they had a BD of ≥16 mmol/l on measurement of ABG within 1 h of delivery and an Apgar score of <7 at 5 minutes, or required resuscitation for more than 5 minutes.	given over a period of 1 h started within 6 h after birth vs placebo (normal saline given at 1ml/kg) infused over a period of 1 h within the first 6 h after birth	worsening of HIE (HIE I to II or III).
Filippi 2018, Filippi 2014 [15]	RCT	Multicenter: 3 tertiary care NICUs in Italy	44 neonates with (1) gestational age >36 weeks and birth weight 1800 g with at least 1 of the following: a) Apgar score of 5 at 10 minutes; b) persisting need for resuscitation 10 minutes after birth; c) acidosis within 60 minutes of birth; (2) moderate to severe encephalopathy; (3) moderately or severely abnormal aEEG.	Whole body cooling + Topiramate (Topomax®; Janssen-Cilag, Cologno Monzese, Milan, Italy) given by orogastric tube as enteric-coated granules mixed with water at the dosage of 10mg/kg/day starting from the beginning of hypothermia once a day for the first three days of life alongside cooling therapy vs whole body cooling only	Mortality and severe neurodevelopmental disability, epilepsy, hearing, loss, blindness, cerebral palsy, mechanical ventilation, oxygen supplementation
Nuñez-Ramiro, 2019 [16]	RCT	Multi center: tertiary care NICUs in Spain	110 newborn infants with perinatal asphyxia evolving to HIE and requiring cooling therapy.	Topiramate (Topomax®; Janssen-Cilag, Cologno Monzese, Milan, Italy) given by nasogastric tube at an initial dose of 1 mL/kg (5 mg/kg) and a maintenance dose of 0.6 mL/kg/day (3 mg/kg/day) vs placebo (sterile water for injection)	Primary outcomes: Seizures, Moderate encephalopathy, Severe encephalopathy, Mortality. Secondary outcomes: Abnormal MRI.

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
Anti-seizure medications for treatment of seizures (n=4 studies)					
Boylan, 2004 [17]	Open label RCT	Multicenter: 2 tertiary care NICUs in United Kingdom	22 neonates at high risk of developing seizures because of birth depression or cord blood acidosis, had abnormal movements suggesting seizures, or had meningitis	Second-line therapy with midazolam (n=3) vs lidocaine (n=5) or clonazepam (n=3) in neonates with electrical seizures persisting after 40mg/kg phenobarbital. 11 infants had seizures responding to first line ASM	Seizure control: Complete absence of seizure activity on EEG or a reduction of more than 80% of pre-treatment burden, neurodevelopmental assessment at 1 year
Perveen, 2016 [18]	Open label RCT	Single center: tertiary care government hospital in north India	60 babies of >2 kg admitted in NICU within 48 h of birth with neonatal seizures due to perinatal asphyxia with clinical features of HIE	60 mg/kg/day IV levetiracetam (n=30) vs 20mg/kg/day IV phenobarbitone (n=30) on 12-h dosing schedule	Seizure control: baby was seizures free 24 hrs after last seizures, seizure control after cross-over, electrical seizures after control of clinical seizure, time taken to control seizures, abnormal liver function, abnormal kidney function and neurological examination till 6 months
Sharpe, 2020 [19]	Blinded, controlled, phase IIb efficacy, dose-escalation, and safety study	Multicenter: tertiary care hospitals in USA & New Zealand	106 term neonates at risk for developing seizures or suspected of having seizures[1]	40 mg/kg/day IV levetiracetam (Mylan) ™ (n=64) vs 20mg/kg/day IV phenobarbitone (Westward or Martindale brand) (n=42) on 8-hr dosing schedule	Seizure control: rate of achieving and maintaining electrographic seizure freedom for 24 h, death during study, neonatal death after study, adverse events – hypotension, respiratory abnormality, sedation, heart

[1] 57 of 106 (54%) patients had HIE as the underlying cause of their seizures (35 in levetiracetam group and 22 in phenobarbital group). 42 patients underwent therapeutic hypothermia. Subgroup analysis of seizure cessation at 24 hours was done by study authors in patients with HIE treated with hypothermia.

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
					rate abnormality, poor feeding, infection, vasopressor support
Susnerwala, 2022 [20]	Open-label, active control, pragmatic RCT	Single center: level IIIB NICU of a tertiary care center in India	82 inborn term neonates with asphyxia (WHO 1997) and clinical seizures in the first 48 h of life[2]	20 mg/kg/day IV levetiracetam (n=44) vs 20mg/kg/day IV phenobarbitone (n=38) on 12-h dosing schedule	Seizure control (clinical) after primary drug, Seizures controlled after adding drug from other group, abnormal neurologic examination (assessed by Amiel Tison examination) at discharge, thrombocytopenia, deranged renal function, deranged liver function
Allopurinol (n=3 studies)					
Gunes, 2007 [21]	RCT	Single center: tertiary care NICU in Turkey	60 asphyxiated infants with severity assessed according to Sarnat scoring	IV allopurinol (Apurin) 40mg/kg/day within the first 2 h after birth and continued for 3 days (n=30) vs control (n=30)	Death or severe neurodevelopmental disability in survivors, severe quadriplegia in survivors
Midan, 2015 [22]	RCT	Single centre: tertiary care NICU of Menoufyia university hospital, Egypt	50 newborns with gestational age≥36 weeks and birth weight≥1,800 g with moderate degree of asphyxia as per metabolic, neurologic and EEG criteria	Oral allopurinol 40mg/kg/day within the first 4 h after birth through a nasogastric tube and continued for three days after birth vs conventional treatment	Death in the 1st year, cerebral palsy
Amin 2017 [23]	RCT	Single center: tertiary care teaching hospital in	62 neonates with GA> 36 wk determined by maternal dates and Ballard score,	Oral allopurinol 40mg/kg/day, divided 12h through a nasogastric tube	Mortality

[2] 70 of the 82 (85%) patients had HIE 2 as per Modified Sarnat staging (38 in the levetiracetam group and 32 in phenobarbital group). 11 of the 82 patients (14%) had severe HIE (HIE 3). We assume the 1 remaining infant had mild HIE (HIE 1)

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
		Bahawalpur, Pakistan	admission within 6 h after birth and suffering from stage-2 HIE defined as neonate having respiratory distress (respiratory rate > 60 breath per minute), lethargy (sluggishness, inactivity), flexion posture (folding of arms and legs), hyperactive tendon reflexes (exaggerated response while performing tendon reflex or clonus), multifocal seizures and poor moro reflex	along with available symptomatic treatment was given to allopurinol group whereas conventional treatment group was offered only the available symptomatic treatment.	
Therapeutic hypothermia (n=22 studies)					
Akisu, 2003 [24]	RCT	Single center: tertiary care NICU of University hospital in Turkey	28 infants (21 asphyxiated infants with 5 min Apgar score<6; cord blood or arterial pH 7.1 or BD>10 mmol/l; encephalopathy (stupor, hypotonia, abnormal neonatal reflexes)	Selective head cooling using cooling caps (n=11) vs control (n=10)	Seizure, death before discharge
Bhat, 2006 [25]	RCT	Single center: tertiary care medical institute in Srinagar, India	35 neonates with severe perinatal asphyxia	Whole body cooling (n=20) vs control (n=15)	Mortality before discharge, Abnormal neurological examination at discharge
Lin, 2006 [26]	RCT	Single center: tertiary care Children's Hospital of Medical College in China	62 infants with GA≥37 wk.; Apgar score at 5 min <6 with postnatal ABG pH<7.1 or BD>15 mEq/l; signs of postpartum encephalopathy	Selective head cooling using cooling caps (n=32) vs Control (n=30)	Mortality before discharge

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
			(decreased muscle tone, lethargy, coma, or seizures within 6h after birth)		
Robertson, 2008 [27]	RCT	Single center: tertiary care referral hospital in Kampala, Uganda	36 infants with GA≥37 wk., need for resuscitation, and/or Apgar score<6 at 5 min plus abnormal neurological assessment (>5 on Thompson score) from 30 min to 3h after birth	Whole body cooling using cooling mattress (n=21) vs control (n=15)	Seizure, abnormal neurological exam on day 17, death, length of hospital stay
Zhou, 2010 [28]	RCT	Multicenter: 12 children's hospitals or children's and women's health care centers in China	194 infants with age <6 h, GA 37 wk., BW 2500 g, with clinical evidence of perinatal hypoxia-ischemia or diagnosis of encephalopathy. Apgar score≤3 at 1 min and ≤5 at 5 min; cord blood pH<7.0 or BD≤16 mmol/l; and need for resuscitation or ventilation at 5 min of age	Selective head cooling using a semi-conductor-controlled water circulation cooling device (n=138) vs control (n=118)	Death, severe disability, DQ, CP
Bharadwaj, 2012 [29]	RCT	Single center: tertiary care neonatal unit in south India	107 term infants with HIE	Whole body cooling using gel packs (n=65) vs control (n=65)	Neurological abnormality (assessed by Amiel Tison examination) at discharge, mortality at discharge, death or development delay at 6 months, developmental delay (assessed by Baroda screening test developmental score) at 6 months
Sun, 2012 [30]	RCT	Single center: tertiary care NICU of Children's	51 term neonates admitted to the NICU within 6 h of birth with clinical evidence	Selective head cooling (n=23) vs control (n=28)	Neurodevelopmental abnormality at 12 months

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
		hospital associated with university in Shanghai, China	of exposure to perinatal hypoxia–ischemia or a diagnosis of encephalopathy		
Gane, 2013 [31]	RCT	Single center: tertiary care neonatal unit in south India	115 term neonates with HIE if they had the evidence of encephalopathy (122 were randomized (61 in each group). One discontinued treatment in the TH group and one discharged against medical advice in the control group. During the 12-month follow-up, 3 and 2 lost follow up in the TH and control group, respectively)	Whole body cooling using cloth-covered gel packs (n=57) vs control (n=58)	Death or developmental delay at 12-month follow-up, Death at 12-month follow-up, Developmental delay (assessed by DASII) at 12-month follow-up
Joy, 2013 [32]	RCT	Single center: tertiary care neonatal unit in south India	Term babies with perinatal asphyxia	Whole body cooling using gel packs (n=58) vs control (n=58)	Death at discharge, Neurological deficits (assessed by Amiel-Tison) at discharge
Thayyil, 2013 [33]	RCT	Single center: tertiary care neonatal unit in medical college in India	33 infants with age ≤6 h, NE with Thompsons encephalopathy score >5	Whole body cooling using phase-changing material (n=17) vs control (n=16)	Clinical seizures, neurological abnormality at discharge
El shimi, 2014 [34]	RCT	Single center: tertiary care NICU of University hospital in Egypt	20 infants with pH≤7.0 or BD≥16 mmol/l in cord or any blood during 1st h after birth. If pH 7.01-7.15, BD 10.0-15.9 mmol/l, or BG unavailable, additional criteria viz. acute perinatal event (late or variable	Whole-body cooling using cool packs (n=10) vs control (n=10)	Mortality before discharge

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
			decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest) and either 10 min Apgar score≤5 or assisted ventilation initiated at birth and continued for >10 min		
Tanigasalam, 2015 [35]	RCT	Single center: tertiary care neonatal unit of medical college in south India	120 term neonates with HIE if they had the evidence of encephalopathy	Whole body cooling (n=60) vs control (n=60)	Mortality before discharge
Das, 2017 [36]	RCT	Single center: tertiary care NICU of medical college in Kolkata, India	60 term inborn neonates with perinatal asphyxia, whose cord blood or postnatal (in first hour of life) ABG gas pH < 7.0 or BD > 12.0meq/L with any two of the following: 1. Apgar score ≤5 at 10 minutes 2. Need for positive pressure ventilation for > 1 minute or first cry delayed > 5 minute. 3. Perinatal predisposition for asphyxia and evidence of moderate to severe encephalopathy	Selective head cooling using ice-filled bags (n=30) vs control (n=30)	Combined death and NDD (assessed by using DASII) at 30 months, death at 30 months, NDD at 30 months
Jose, 2017 [37]	RCT	Single center: tertiary care	156 infants with moderate and severe encephalopathy within 6 h after birth after an	Whole body cooling (n=77) vs control group (n=79)	Cerebral palsy at 18 months, cerebral palsy among survivors at 6-8 years,

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
		neonatal unit in south India	acute perinatal event, with acidosis or resuscitation (At the 6 to 8 years' follow-up, data were available for 144 (74 and 70 in the TH and control group)		moderate to severe disability at 18 months, moderate to severe disability at 6-8 years, other scores (ADHD, memory, learning)
Chen, 2018 [38]	RCT	Single center: tertiary care neonatal unit of hospital affiliated with medical college in China	42 infants with moderate to severe HIE	Selective head cooling (n=20) vs supportive care, supplemented by drugs to promote nerve cell growth (n=20)	Mortality before discharge
Liao, 2018 [39]	RCT	Single center: tertiary care medical university hospital in China	48 neonates with gestational age ≥36 weeks and birth weight ≥ 2000g; evidence of fetal distress including history of acute perinatal event; evidence of neonatal distress as shown by at least one of the following: Apgar score ≦ 5 at 10 minutes, pH ≦ 7.0 within 1 h of birth or BD < 16 mEq/L, or need for ventilation for at least 10 min after birth; and eligible infants were then assessed for evidence of moderate or severe encephalopathy by a certified examiner including lethargy, stupor, or coma, with one or more of hypotonia, abnormal	Whole body cooling using cooling mattress (n=24) vs control (n=24)	Mortality before discharge

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
			reflexes (oculomotor or pupillary abnormalities), an absent or weak suck, or clinical evidence of seizures.		
Rakesh, 2018 [40]	RCT	Single center: tertiary care neonatal unit in south India	120 term neonates with perinatal asphyxia	Whole body cooling using phase changing material (n=60) vs control (n=60)	Mortality (time not specified), Mean developmental quotient (assessed by DASII) at 6-month
Sinha, 2018 [41]	RCT	Single center: level 2 NICU of military hospital in India	60 term neonates with umbilical cord or postnatal (in the 1st h of life) ABG pH of <7.0 or BD of more than or equal to 16 along with any two of the following: (1) Apgar score of <5 at 5 min; (2). positive pressure ventilation initiated at birth and continued for at least 10 min; (3) risk factor (anyone) - intrapartum fetal distress, cord prolapse, placental abruption, and uterine rupture/dehiscence.	Whole body cooling (n=30) vs control (n=30)	Neurological abnormality at discharge and at 18 months
Aker, 2020 [42]	RCT	Single center: tertiary care teaching hospital in south India	50 infants with GA≥36 wk., BW>1800 g, age <5 h, perinatal asphyxia (umbilical cord or 1st h pH<7.0 or BD≥12), 5 min Apgar score≤5, or need of PPV≥10 min at birth	Whole body cooling using phase changing material (n=25) vs control (n=25)	Mortality before discharge

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
Yang, 2020 [43]	RCT	Single center: tertiary care – hospital affiliated with medical university in China	92 neonatal patients with age <6 h; GA 37 wk. and BW 2500 g; 1 min Apgar score<3 and 5 min Apgar score <5	Selective head cooling using cooling caps (n=62) vs control (n=30)	Mortality before discharge
Catherine, 2021 [44]	RCT	Single center: tertiary care teaching hospital in south India	162 term babies with moderate or severe encephalopathy according to Sarnat and Sarnat staging were included in the study provided they had a pH </= 7 or BD >/= -12 mEq in cord blood and also satisfied any two of the following criteria: (i) Apgar score at 10 min </=6, (ii) any clinical evidence of fetal distress, (iii) requiring assisted ventilation for at least 10 min soon after delivery, and (iv) any evidence of one or more organ dysfunction.	Whole body cooling using phase changing material (n=84) vs control (n=78)	Neurological abnormality (assessed by DASII) at discharge or 28 days of age, mortality at discharge or 28 days of age, neurological abnormality (assessed using DASII) at 18 months of follow-up, mortality at 18 months of follow-up
Thayyil, 2021 [45]	RCT	Multicenter: tertiary care centres in India, Sri Lanka, Bangladesh	408 infants with GA≥37 wk., BW≥1kg, need for resuscitation at 5 min of age or Apgar score<6 at 5 min of age (for babies born in hospital), or both, or absence of crying by 5 min of age (for babies born at home); and evidence of moderate or severe	Whole body cooling using a servo-controlled device (n=202) vs control (n=206)	Death or moderate or severe disability, mortality before discharge, mortality at 18-22 months, severe disability at 18-22 months, CP at 18-24 months

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
			encephalopathy between 1-6 h of age		
Erythropoietin (n=5 studies)					
Zhu, 2009 [46]	RCT	Single center: China	153 term neonates ≥37–40 weeks and clinical evidence of moderate or severe NE	45 had SC/IV erythropoietin (300 IU/kg) and 28 had SC/IV erythropoietin (500 IU/kg) on alternate days for 2 weeks	Death or disability at 18 months using Bayley Infant Scales of Development II; the presence of cerebral palsy and Mental Development Index < 70
Elmahdy, 2010 [47]	RCT	Single center: tertiary care university hospital in Tanta, Egypt	45 inborn neonates with gestational age between 38-42 weeks, Apgar scores </=3 at 5 min and/or delayed first breath (>5 min after birth), profound metabolic or mixed acidosis and evidence of mild or moderate encephalopathy	HIE erythropoietin group (n=15), HIE control group (n=15), normal healthy group (n=15)	Death or Disability at 6 months using Denver Developmental Screening Test II
Avasiloaiei, 2013 [13]	RCT	Single center: tertiary care NICU of OBGYN hospital in Romania	67 term neonates with severe perinatal asphyxia (defined as having 3 of 4 criteria (umbilical artery blood pH < 7.0 with or without BD >/= 12 mEq/L, Apgar </=3 at > 5 minutes of life, neonatal neurologic sequelae (i.e. seizures, coma, hypotonia) or multiple organ involvement (i.e. kidney, lungs, liver, heart, intestines)) without major	Phenobarbital (40 mg/ kg) as a single dose in the first 4 h after birth vs SC erythropoietin (1000 IU/kg) once a day for the first 3 days vs Routine intensive care or IV	Death or Disability at 18 months using Bayley Infant Scales of Development II

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
			congenital malformations or hemolytic disease due to Rh incompatibility.		
El Shimi, 2013 [34]	RCT	Single center: Egypt	20 term neonates ≥37–40 weeks with perinatal asphyxia	SC erythropoietin (1500 IU/kg) as a single dose	Death or Disability at 3 months using neuromuscular function scale
Malla, 2017 [48]	RCT	Single center: tertiary care NICU of medical institute in Srinagar, India	100 term neonates ≥37–40 weeks, <6 h age and moderate or severe NE	IV erythropoietin (500 IU/kg) on D1,3,5	Death or moderate or severe disability at 19 months using Bayley Infant Scales of Development II
Magnesium Sulfate (n=16 studies)					
Khashaba, 2006 [49]	RCT	Single center: tertiary care university children's hospital in Mansoura, Egypt	47 term neonates with Apgar at 5 min </=3 and/or if they had delayed first breath beyond 10 min after birth.	1 dose of IV $MgSO_4$ 250 mg/kg/ dose, within 24 h of life	CSF aspartate and glutamate levels, mortality, seizures, hypotension
Bhat, 2009 [25]	RCT	Single center: tertiary care NICU of hospital in academic institute in Srinagar, India	40 term neonates with severe perinatal asphyxia, as manifested by 3 of the following 4 criteria: (1) history of fetal distress (late deceleration, loss of beat-to beat variability, fetal bradycardia, or MSL), (2) need for immediate AV for 2 min after delivery, (3) 5-min Apgar <6, or (4) BD of >/=15 mEq/L or pH of </=7 in cord blood or admission arterial blood samples within the first hour after birth.	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h apart,	Neurological status at Discharge

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
Gathwala, 2010 [50]	RCT	Single center: tertiary care neonatal division of teaching hospital in Rohtak, India	40 term neonates with Apgar score of </=3 at 1 min and </=6 at 5 min	3 doses of IV $MgSO_4$ 250 mg/kg/dose on day 1 and 125 mg/kg/dose on day 2 and 3, 24 h apart, within 30 min of life	EEG and CT brain findings, Neurodevelopmental outcome at 6 months of age
Kamalarathnam, 2013 [51]	RCT	Single center: tertiary care maternity and pediatric hospital in Chennai, India	116 term neonates fulfilling two of following 3 criteria: (i) H/O fetal distress (late deceleration, fetal bradycardia, MSL) ii) Need for AV initiated at birth and continued for >2 min after delivery, (iii) Apgar score of 0- 3 at 1 min.	3 doses of IM $MgSO_4$ 250 mg/kg/dose 24 h apart, within 6 h of life	Composite mortality and survival with Abnormal neurological examination at discharge, Time to DBF, length of hospital stays and abnormal CrUSS
Hossain, 2013 [52]	RCT	Single center: tertiary care neonatology department of university hospital in Bangladesh	50 neonates at 36 weeks and perinatal asphyxia with NE stage II and III.	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h apart, within 6 h of life	Suck feeds at discharge and mortality
Rahman, 2015[53]	RCT	Multicentre: tertiary care NICU's in Qatar, Turkey, Saudi Arabia, Egypt, Malaysia, and Abu Dhabi	60 neonates with Apgar <5 at 10 min, continued need for resuscitation including AV at 10 min, Acidosis within 60 min of birth (defined: umbilical cord, arterial or capillary pH <7.00), BD >/=16 in umbilical cord or any blood and (neurological assessment): moderate to severe encephalopathy, consisting of altered state of	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h apart, within 6 h of life adjunct with TH	Mortality and predischarge effects

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
			consciousness (lethargy, stupor, or coma) and 1 of the following = hypotonia, abnormal reflexes including oculomotor or pupillary reflexes, absent or week suck, clinical seizures		
Rashid, 2015 [54]	RCT	Single center: NICU of general hospital in Lahore, Pakistan	100 neonates at 36 weeks and perinatal asphyxia with NE stage II and III.	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h a	Suck feeds at discharge and mortality
Mahmood, 2015 [55]	RCT	Single center: tertiary care department of pediatrics in Rawalpindi, Pakistan	50 term neonates with severe perinatal asphyxia: History of fetal distress, need of AV for >2 min after delivery, 5-min APGAR <6 and BD of >15 mEq/L or pH of <7 in ABG after birth	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h apart,	Suck reflex and CT brain findings at discharge
Savitha, 2015 [56]	RCT	Single center: tertiary care teaching hospital in Mysore, India	120 term neonates with Apgar <7 at 1 min of age	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h apart, within 6 h of life	Seizure control, establishing suck feeds, recovery from abnormal neurology
Sreenivasa, 2017 [57]	RCT	Single center: tertiary care Women and Children's hospital in India	100 neonates appropriate for gestational age, with 1-min Apgar <3 and 5-min Apgar <6	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h apart, within 6 h of life	Seizure control, suck feeds establishment, recovery from abnormal neurology
Firoz, 2020 [58]	RCT	Single center: tertiary care department of pediatrics of teaching hospital in	50 neonates meeting all of the following criteria: (i) profound metabolic or mixed acidemia (pH <7.00) in umbilical artery blood sample, if obtained,	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h apart, within 6 h of life	Seizure control, suck feeds establishment, recovery from abnormal neurology

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
		Faridpur, Bangladesh	(ii)persistence of an Apgar score of 0-3 for longer than 5 min, (iii) neonatal neurological sequelae (eg, seizures, coma, hypotonia), and (iv) multiple organ involvement (eg, kidney, lungs, liver, heart, intestines)		
Siddique, 2021 [59]	RCT	Single center: tertiary care neonatology department of teaching hospital in Lahore, Pakistan	80 term neonates with need for neonatal resuscitation (rather than stabilization) at birth with Apgar scores (</=3 in 1 min and </=7 in 5 min).	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h apart, within 6 h of life	Seizures, suck feeds, neurological status at discharge
Abdel Aziz, 2021 [60]	RCT	Single center: tertiary care NICU of university hospital in Assiut, Egypt	36 neonates fulfilling the physiological and neurological inclusion criteria: Physiologic criteria = 1 of the following: 5 min Apgar </=5; AV at 10 min; arterial, umbilical cord, or capillary pH <7.1 within 60 min or BD >/=16 mmol/L.; manifestations of fetal distress before delivery (as MSL or HR>160/bpm or <100/bpm).	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h apart, within 6 h of life	Seizure burden, number of ASMs at discharge, time to establish suck feeds and brain MRI changes
Iqbal, 2021 [61]	RCT	Single center: tertiary care neonatology department of	62 neonates with inability to initiate or sustain breathing at birth along with clinical features suggestive of	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h apart, within 24 h of life	Short-term neurological status at discharge, developmental status at 6 months of age and CrUSS: No

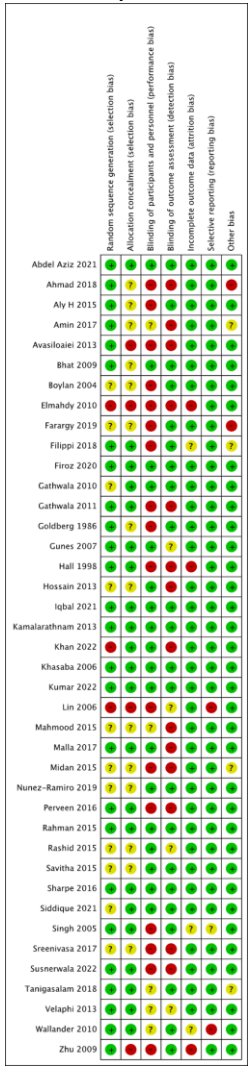
Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
		Children's hospital in Lahore, Pakistan	encephalopathy (neurological depression, depressed respiratory drive, and seizures)		definition in the method section and diffuse or focal echogenicity in the result section
Khan, 2022 [62]	RCT	Single center: tertiary care NICU of medical institute in Islamabad, Pakistan	90 neonates with Apgar <5 at 5 min, umbilical blood pH of <7.0, and moderate NE	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h apart	pH trend, mortality, seizures, renal failure, hypotension
Kumar, 2022 [63]	RCT	Single center: level III NICU of a tertiary care teaching hospital in southern India	134 neonates with UA BG or a postnatal venous BG within 1 h showed a pH of <7 or BD of >/=12 mEq/L, and moderate or severe encephalopathy. If BG was not available, either an Apgar score </=5 at 10 min or AV for >/=10 min after birth, with a history of acute perinatal event (intrapartum fetal distress, uterine rupture, cord prolapse, placental abruption)	3 doses of IV $MgSO_4$ 250 mg/kg/dose 24 h apart, within 6 h of birth adjunct with TH	Composite outcome: mortality and Major NDD at 1 year, seizures, time to attain suck feeds and abnormal neurological status
Melatonin (n=3 studies)					
Aly H, 2015 [64]	RCT	Single center: tertiary care university hospital in Tanta, Egypt	30 inborn term infants with GA 38-42 wk., Apgar score </=3 at 5 min and/or delayed first breath (>5min after birth), profound metabolic or mixed acidosis with serum bicarbonate concentration of >12mmo/l	Melatonin (oral) 10 mg/kg daily for a total of five doses (n=15) Melatonin tablets (1 or 3mg/tablet; Puritan's Pride, Oakdale, NY,	Mortality

Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
			at initial BG analysis and evidence of moderate or severe encephalopathy	USA) were crushed, then dissolved in 5ml of distilled water and administered via an orogastric tube vs whole body cooling with ice packs	
Ahmad, 2018 [65]	RCT	Single center: tertiary care university hospital in Lahore, Pakistan	80 newborns with GA of 34 weeks or higher presenting with symptoms consistent with case definition of HIE admitted to neonatal unit from home or public/private hospital	Melatonin (oral) 10 mg single dose at admission (n=40) vs supportive care (n=40)	Mortality
El Farargy, 2019 [66]	RCT	Single center: tertiary care university hospital in Tanta, Egypt	60 term or late preterm infants with Apgar score </=5 at 5 min, UA acidemia (pH <7.0 and/or BD >/=12 mmol/L) and moderate HIE (Modified Sarnat & Sarnat)	Melatonin + magnesium sulfate (n= 30) vs melatonin (enteral) 10 mg/kg daily for 5 days) (n=30)	Concentration of S100-B, % survived, % died
Early intervention to improve developmental outcomes in asphyxiated babies (n=1 study)					
Wallander 2010 & 2014 [67]	RCT	Multi center: rural communities in India, Pakistan, Zambia	164 Infants with birth asphyxia who were unresponsive to bag and mask ventilation	Home-based, parent implemented intervention based on *Partners for Learning* curriculum; playful interactive learning activities targeting developmentally appropriate competence; covers 23 developmental skill areas; parents trained in bi-weekly home visits vs	BSID-II 36 months score, ASQ-Communication, ASQ-SE at 36 months

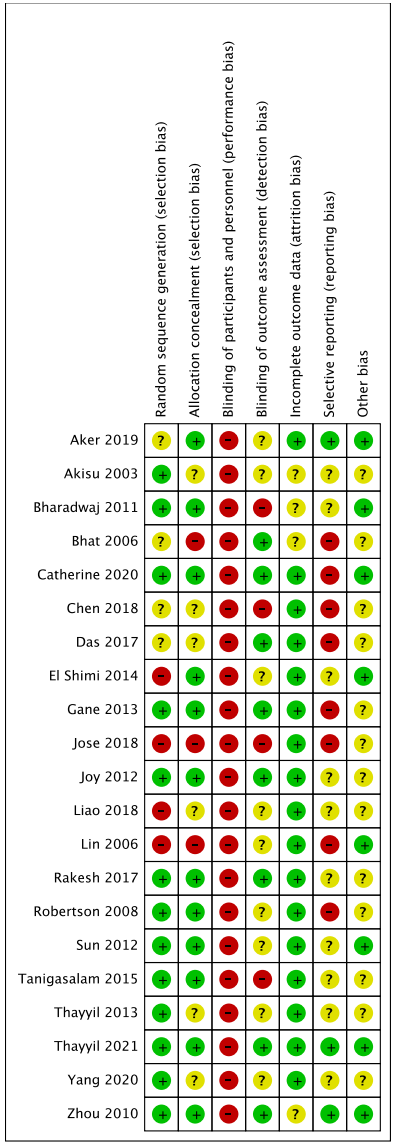
Year, Author	Study design	Setting	Population	Intervention vs Comparator	Outcomes of interest
				usual care (health education during home visits)	

Legend *– ABG: arterial blood gas, ADHD: attention deficit hyperactivity disorder, AKI: acute kidney injury, ASM: antiseizure medication, ASQ-SE: ages and stages questionnaire: social-emotional development screening, ASQ: ages and stages questionnaire, AV: assisted ventilation, BD: base deficit, BG: blood gas, bpm: beats per minute, BSID-II: bayley scales of infant development (II edition), BW: birthweight, CP: cerebral palsy, CrUSS: cranial ultrasound,CSF: cerebrospinal fluid, DASII: developmental assessment for indian infants, DBF: direct breastfeeding, DQ: developmental quotient, EEG: electroencephalogram, GA: gestational age, GPx: glutathione peroxidase, h: hours, H/O: hypothesized/observed, HIE: hypoxic ischemic encephalopathy, HR: heart rate, IU/kg: international units per kilogram body weight, IV: intravenous, MDA: malondialdehyde, mEq/L: molar equivalents per liter, mg: milligram, mg/kg: milligram per kilogram body weight, min: minutes, ml: milliliter, ml/kg: milliliter per kilogram body weight, mmol/l: millimolar per liter, MSL: meconium stained liquor, NDD: neurodevelopmental delay, NE: neonatal encephalopathy, NEC: necrotizing enterocolitis, NICU: neonatal intensive care unit, RCT: randomized controlled trial, S100B: S100 calcium binding protein, SC: subcutaneous, SIADH: syndrome of inappropriate antidiuretic hormone release, SOD: superoxide dismutase, TH: therapeutic hypothermia, UA: umbilical artery, USA: united states of America, WHO: world health organization, wk: week*

6. Quality Assessments for all included studies



Suppl. Figure 6.1: Risk of bias (RoB) summary: review authors' for judgements about each risk of bias item for each included study on fluid restriction, ASMs, pharmacological therapies and early post-natal intervention



Suppl. Figure 6.2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study on therapeutic hypothermia.

7: Effect Estimates and forest plots

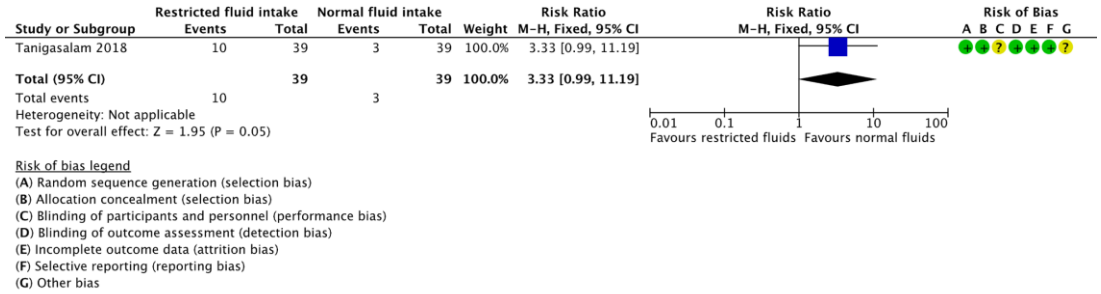
Suppl. Table 7.1: Effect estimates for fluid restriction

Outcome	**No. of studies (No. of participants)**	**Fixed Effect Estimate Risk Ratio (95% CI)**
Comparison 1: Fluid restriction (40-80 ml/kg/day) versus normal fluids (60-120 ml/kg/day) (N=1 study)		
Composite: Death or Major Neurodevelopmental Disability (DASII score<70)	1 (78)	RR=3.33 (0.99, 11.19)
Death at 6 months	1 (78)	RR=2.33 (0.65, 8.37)
Major Neurodevelopmental Disability (DASII score<70)	1 (78)	RR=7.00 (0.37, 131.17)
Hypoglycemia	1 (78)	RR=11.00 (0.63, 192.40)
Shock	1 (78)	RR=1.70 (0.89, 3.23)
Seizures – clinically diagnosed	1 (78)	RR=1.03 (0.96, 1.10)
Hyponatremia	1 (78)	RR=0.77 (0.49, 1.21)
SIADH	1 (78)	RR=1.00 (0.39, 2.58)
AKI	1 (78)	RR=1.88 (0.90, 3.91)
NEC	1 (78)	RR=5.00 (0.61, 40.86)
Legend – AKI: acute kidney injury, DASII: development assessment scale for Indian infants, ml/kg: millilitre per kilogram body weight, NEC: necrotizing enterocolitis, SIADH: syndrome of inappropriate antidiuretic hormone release		

Suppl. Table 7.2: Effect estimate for early intervention to improve developmental outcomes for asphyxiated infants

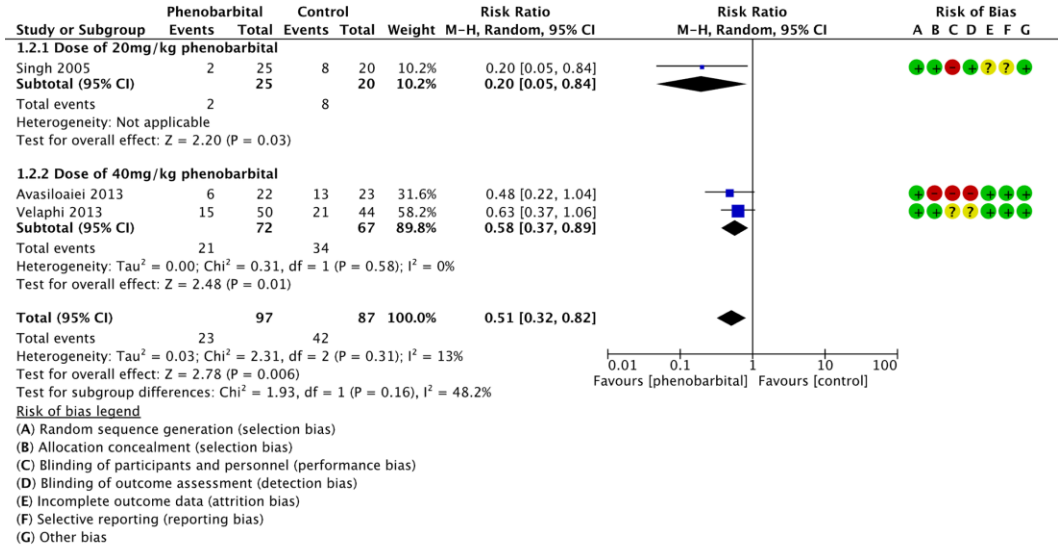
Outcome	**No. of studies (participants)**	**Effect Estimate Mean Difference (95% CI)**	**Heterogeneity (I^2)**	**Test for overall effect (p-value)**
Comparison 1: Early childhood development (ECD) intervention vs. control (N=1 study)				
Cognitive development at 0-36 months of age	1 (123)	**MD=4.60 [0.17, 9.03]**	N/A	Test for overall effect: (p=0.04)

Forest plots:

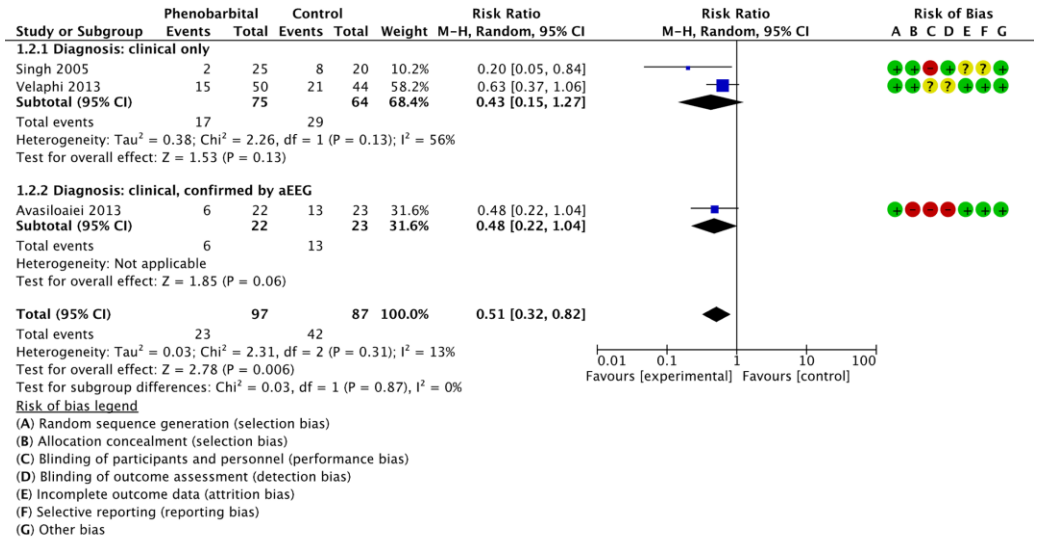


Suppl. Figure 7.1: Forest plot of comparison: 1 Restricted fluid intake (2/3) vs Normal fluid intake, outcome: 1.1 Death or DASII score<70.

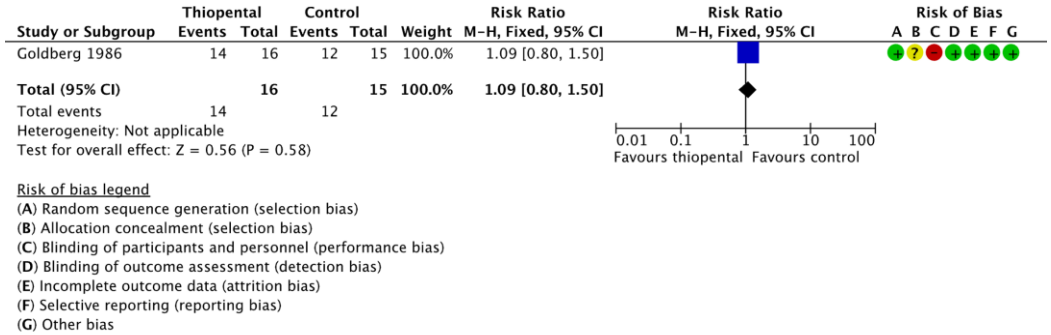
Note: DASII (Developmental Assessment Scale for Indian Infants) is a development assessment tool based on the Bayley Scale or Infant Development (BSID). Developmental delay is defined by DASII as a DQ<70 (Developmental Quotient) in the mental or motor scales. Developmental assessment was done by a trained person who was blinded to the treatment allocation.



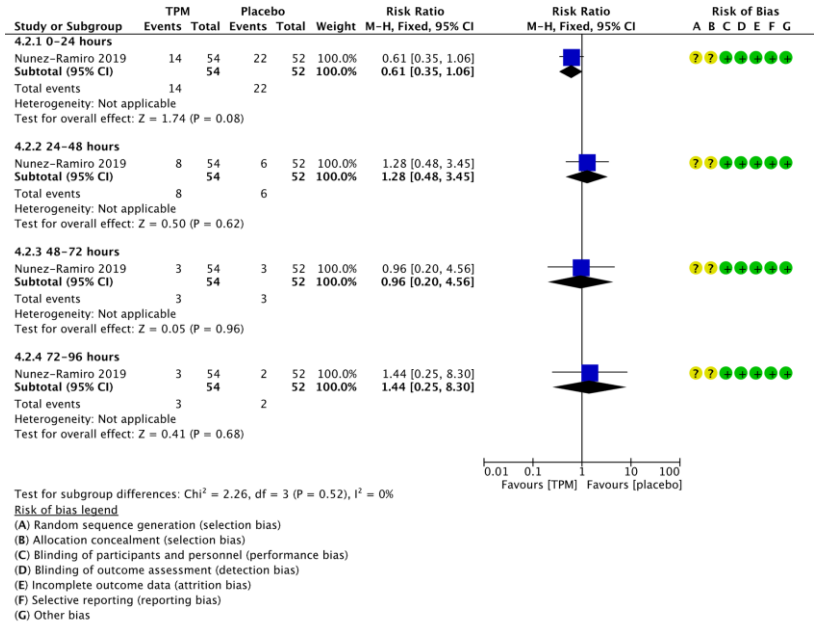
Suppl. Figure 7.2: Forest plot of comparison: 1 Prophylactic phenobarbital vs control, outcome: 1.2 Incidence of probable seizures, subgroup: dosage of ASM



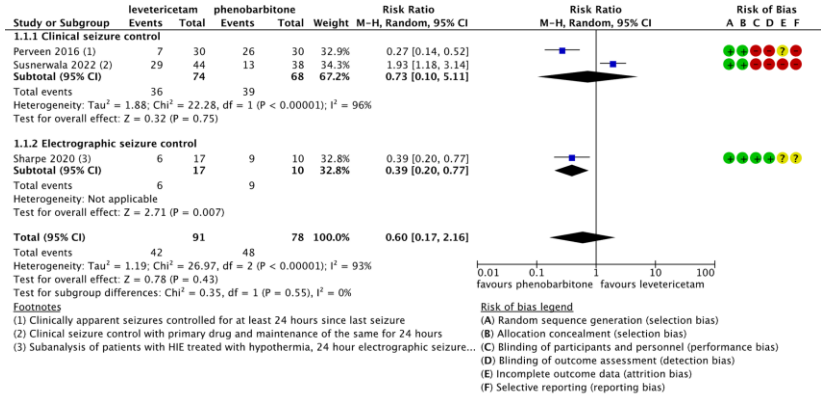
Suppl. Figure 7.3: Forest plot of comparison: 1 Prophylactic phenobarbital vs control, outcome: 1.2 Incidence of probable seizures, subgroup: method of seizure diagnosis



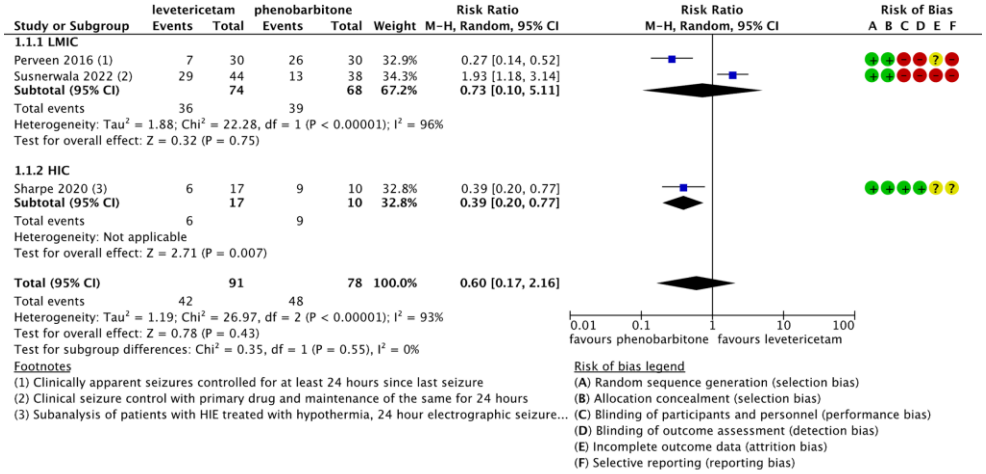
Suppl. Figure 7.4: Forest plot of comparison: 2 Prophylactic thiopental vs control, outcome: 2.2 Incidence of probable seizures



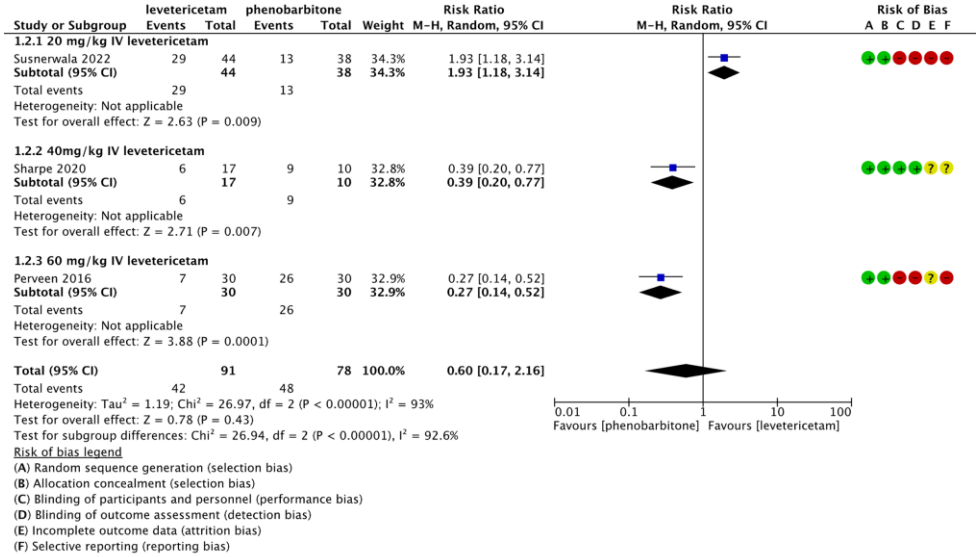
Suppl. Figure 7.5: Forest plot of comparison: 3 Prophylactic topiramate and therapeutic hypothermia vs therapeutic hypothermia only, outcome: 3.1 Incidence of seizures during cEEG monitoring, disaggregated by time point



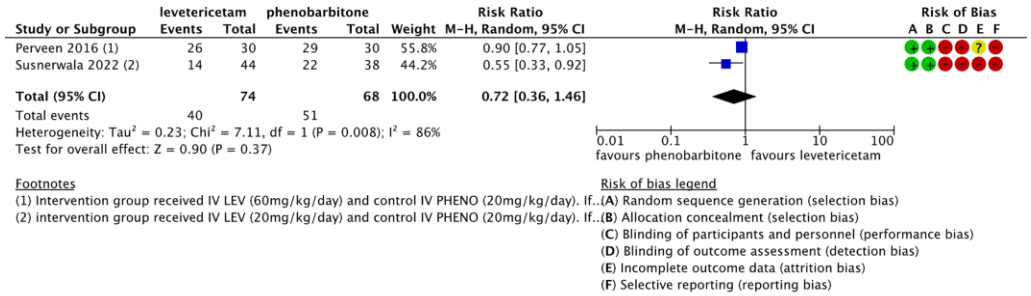
Suppl. Figure 7.6: Forest plot of comparison: 1 levetiracetam vs phenobarbital, outcome: 1.1 Seizure control after primary drug, subgroup by method of seizure diagnosis



Suppl. Figure 7.7: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.1: Seizure control after primary drug, subgroup by income classification



Suppl. Figure 7.8: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.1: Seizure control after primary drug, subgroup by dosage of ASM

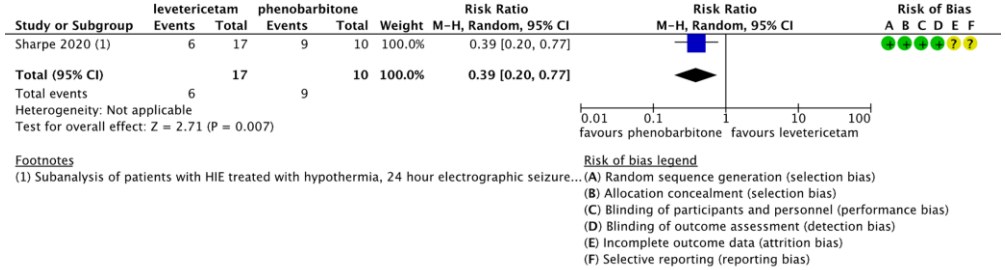


Suppl. Figure 7.9: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.2: seizures controlled after adding drug from other group

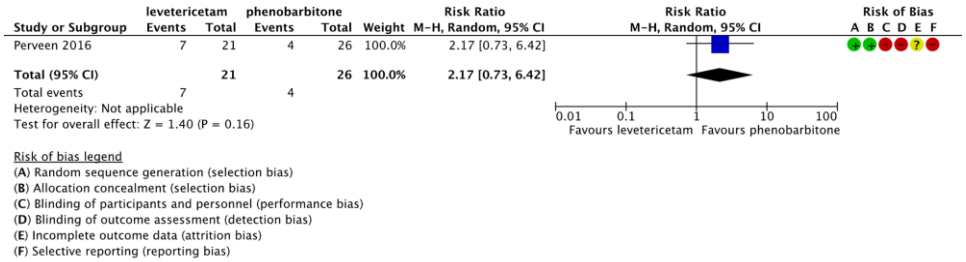
Note:

Perveen 2016: Intervention group received IV LEV (60mg/kg/day) and control IV PHENO (20mg/kg/day). If seizures persisted, they crossed over to other drug. If controlled after cross-over, then they were kept on maintenance dose of both drugs. If seizures persisted despite crossover, the babies were treated as per unit policy. Once the baby was seizure free for 5 days, anticonvulsants were abruptly stopped in the same order as they were started except phenobarbitone. Phenobarbitone was stopped last if neurological examination was normal and EEG demonstrated no electrical seizures.

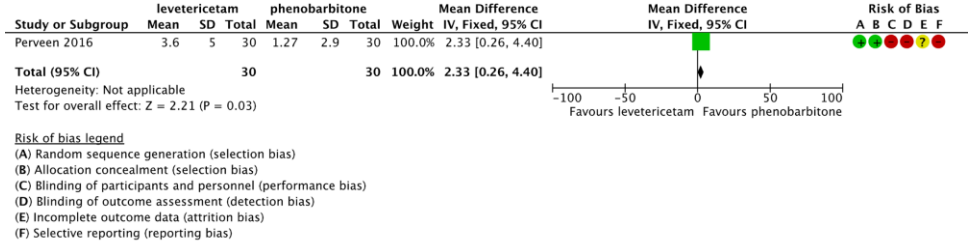
Susnerwala 20222: Intervention group received IV LEV (20mg/kg) and control IV PHENO (20mg/kg). If seizures persisted even after 20 min of the loading dose, the LEV group received injection of phenobarbitone (20mg/kg) followed by maintenance (5 mg/kg/day BD). and IV PHENO group received injection of levetiracetam (20 mg/kg). If seizures continued despite the add-on drug, the infants were treated with phenytoin followed by midazolam infusion according to unit policy. Infants were shifted to the oral formulation of the primary drug after reaching full feeds. The duration of anticonvulsant therapy was based on the examination at discharge and follow-up.



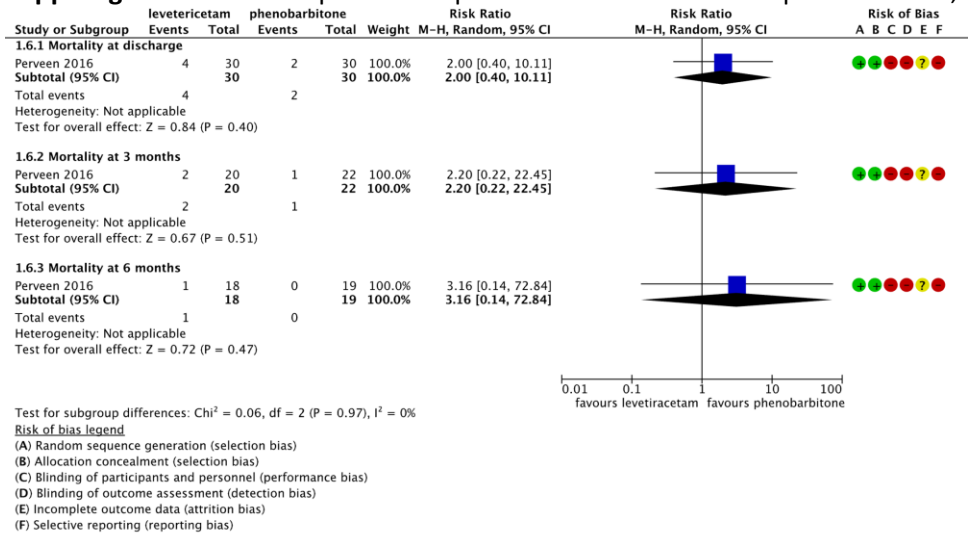
Suppl. Figure 7.10: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.3: 24-hour electrographic seizure cessation rate



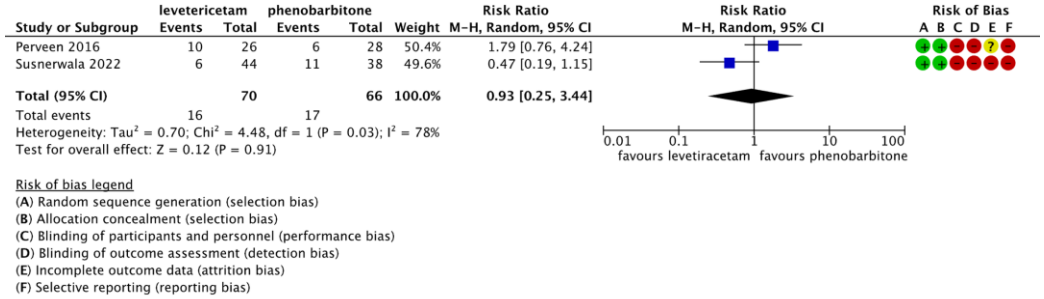
Suppl. Figure 7.11: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.4: electrical seizures after clinical control



Suppl. Figure 7.12: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.5: time of complete control of seizures



Suppl. Figure 7.13:. Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.6: mortality

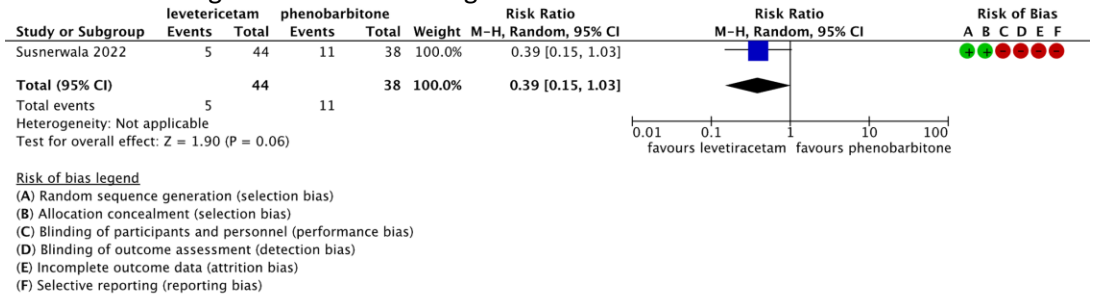


Suppl. Figure 7.14: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.7: abnormal neurological outcome at discharge (Amel Tison method)

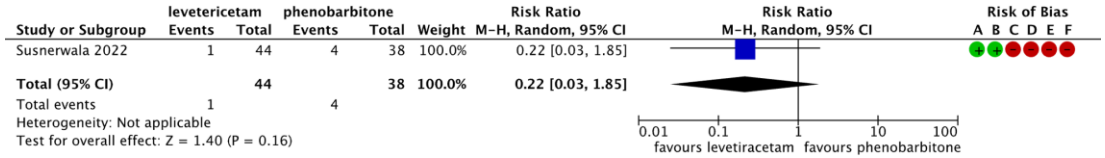
Note:

Perveen 2016: Included examinations of overall activity, response to stimuli, ability to suck and swallow, active and passive tone of neck and trunk muscles and neonatal reflexes (Moro's, traction, and habituation) using Amel Tison method.

Susnerwala 2022: Neurologic examination at discharge included assessing the level of consciousness, neonatal reflexes, and neurological motor examination using Amel Tison Neurologic Assessment at Term.

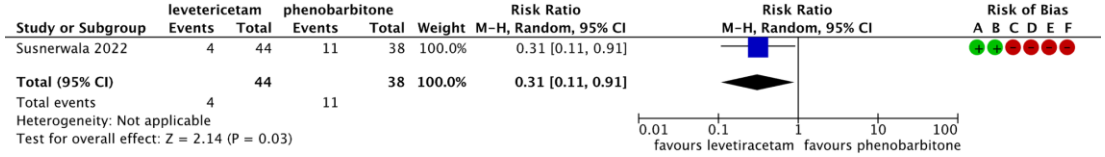


Suppl. Figure 7.15: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.7: abnormal neurological exam at discharge (level of consciousness)



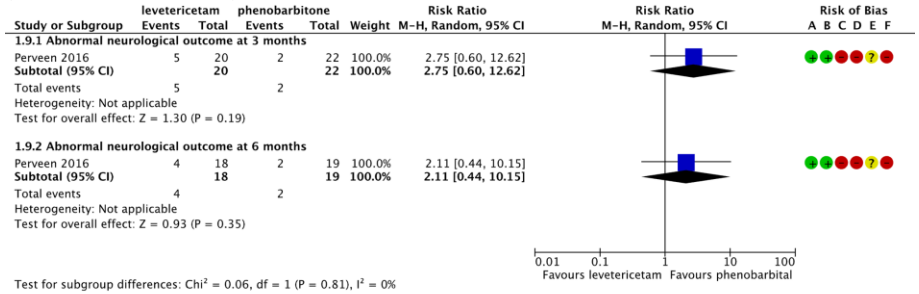
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Suppl. Figure 7.16: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.7: abnormal neurological exam at discharge (neonatal reflexes)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

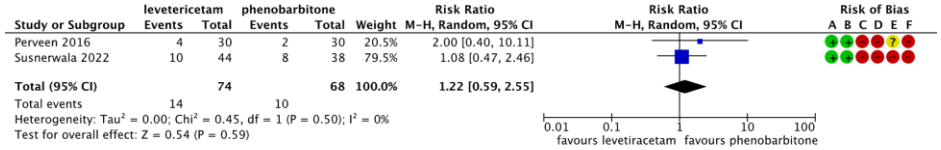
Suppl. Figure 7.17: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.7: abnormal neurological exam at discharge (neuromotor ATNT)



Test for subgroup differences: $Chi^2 = 0.06$, df = 1 (P = 0.81), $I^2 = 0\%$

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Suppl. Figure 7.18: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.8: abnormal neurological exam at follow-up (3 months & 6 months)



Risk of bias legend
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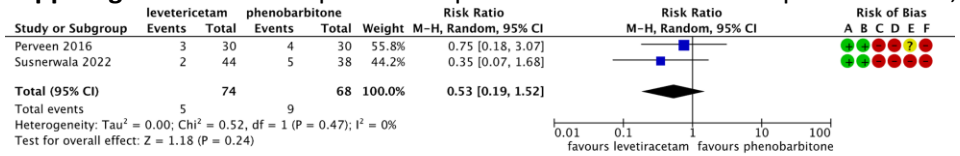
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Suppl. Figure 7.19: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.9: abnormal kidney function



Risk of bias legend
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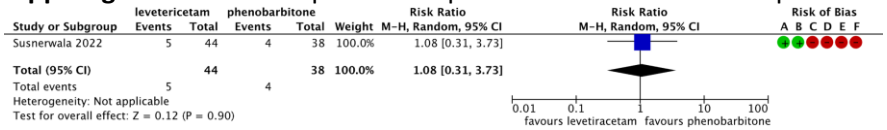
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

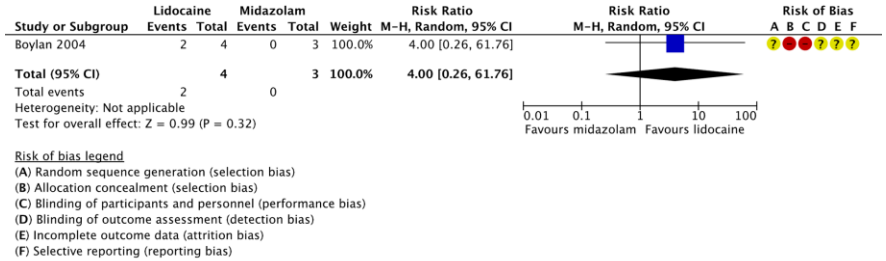
Suppl. Figure 7.20: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.10: abnormal liver function



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Suppl. Figure 7.21: Forest plot of comparison 1: levetiracetam vs phenobarbital, outcome 1.11: thrombocytopenia

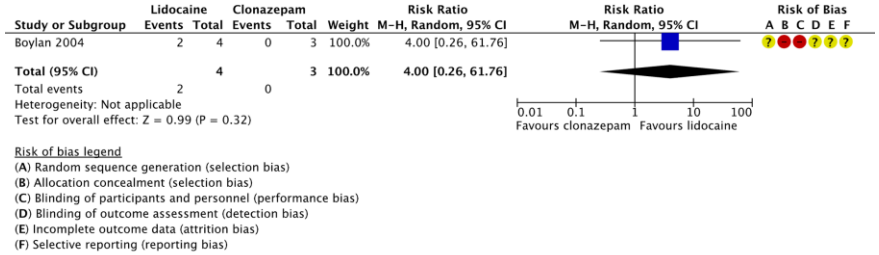
Comparison 2: Lidocaine vs Midazolam as second-line ASM (N=1 study)



Suppl. Figure 7.22: Forest plot of comparison 2: lidocaine vs midazolam, outcome 2.1: seizure control

Note: Seizures were controlled in 3/5 infants in the group that received lidocaine. 1 infant was diagnosed with intracranial hemorrhage, meningitis while the remaining 4 infants were diagnosed with HIE.

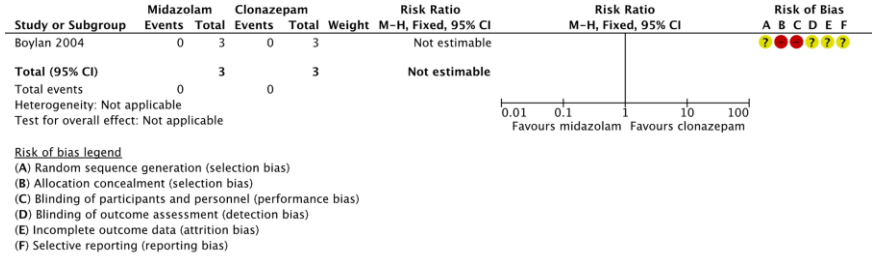
Comparison 3: Lidocaine vs Clonazepam as second-line ASM (N=1 study)



Suppl. Figure 7.23: Forest plot of comparison 3: lidocaine vs clonazepam, outcome 3.1: seizure control

Note: Seizures were controlled in 3/5 infants in the group that received lidocaine. 1 infant was diagnosed with intracranial hemorrhage, meningitis while the remaining 4 infants were diagnosed with HIE.

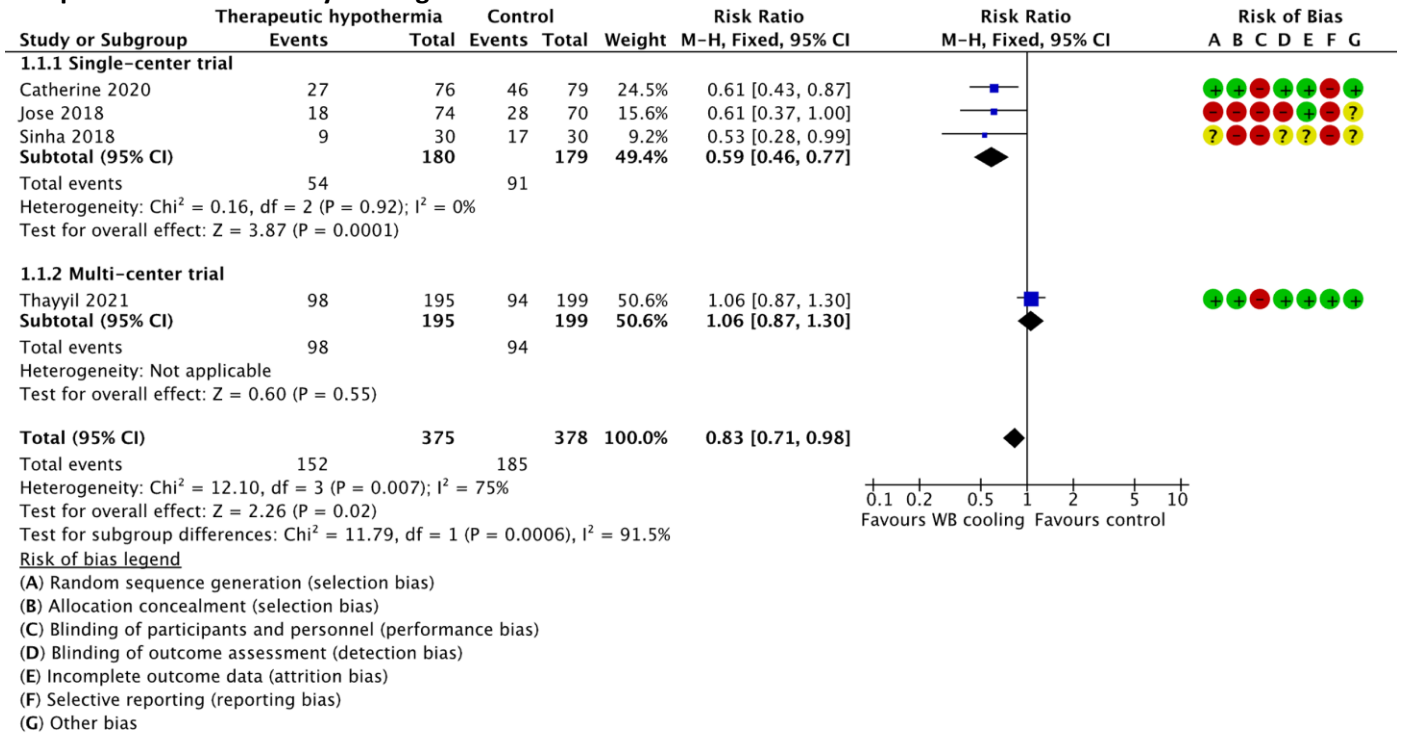
Comparison 4: Midazolam vs Clonazepam as second-line ASM (N=1 study)



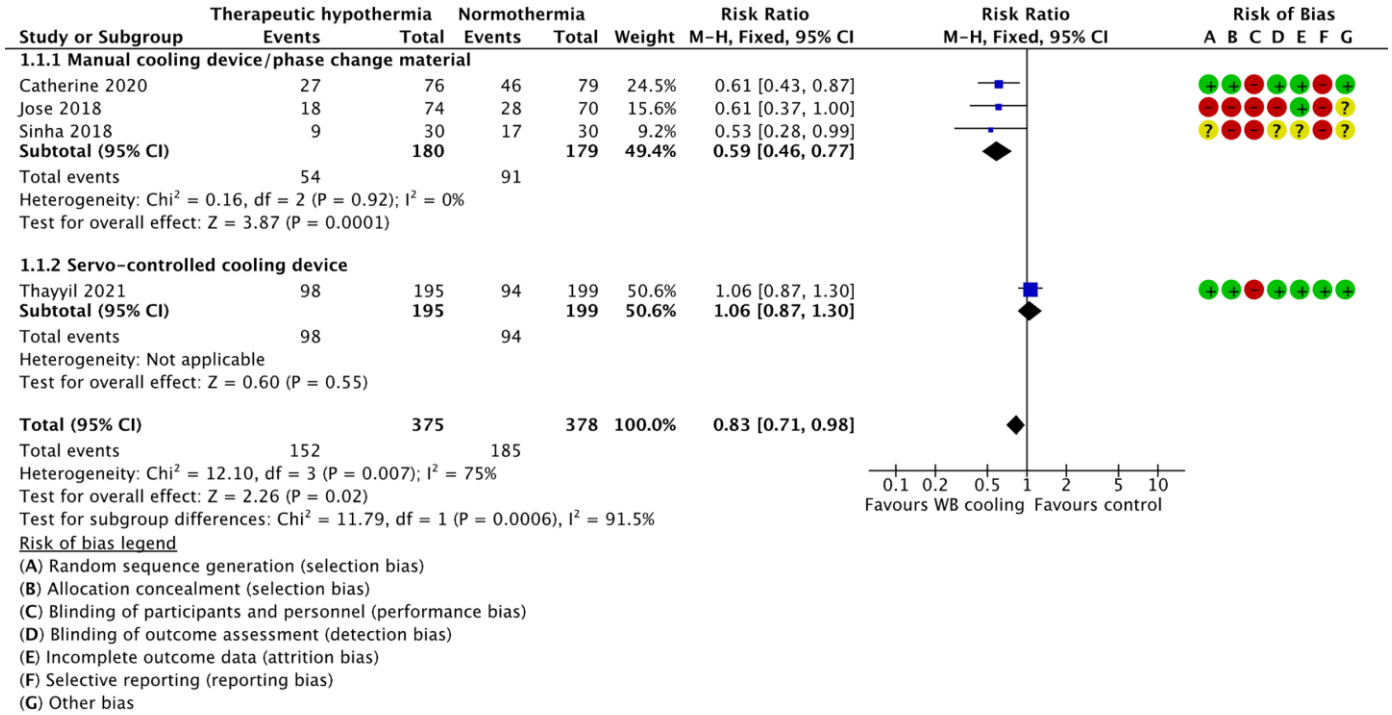
Suppl. Figure 7.24: Forest plot of comparison 4: midazolam vs clonazepam, outcome 4.1: seizure control

Note: Event rate was 0 in both groups hence RR was not estimable. Sample size was small.

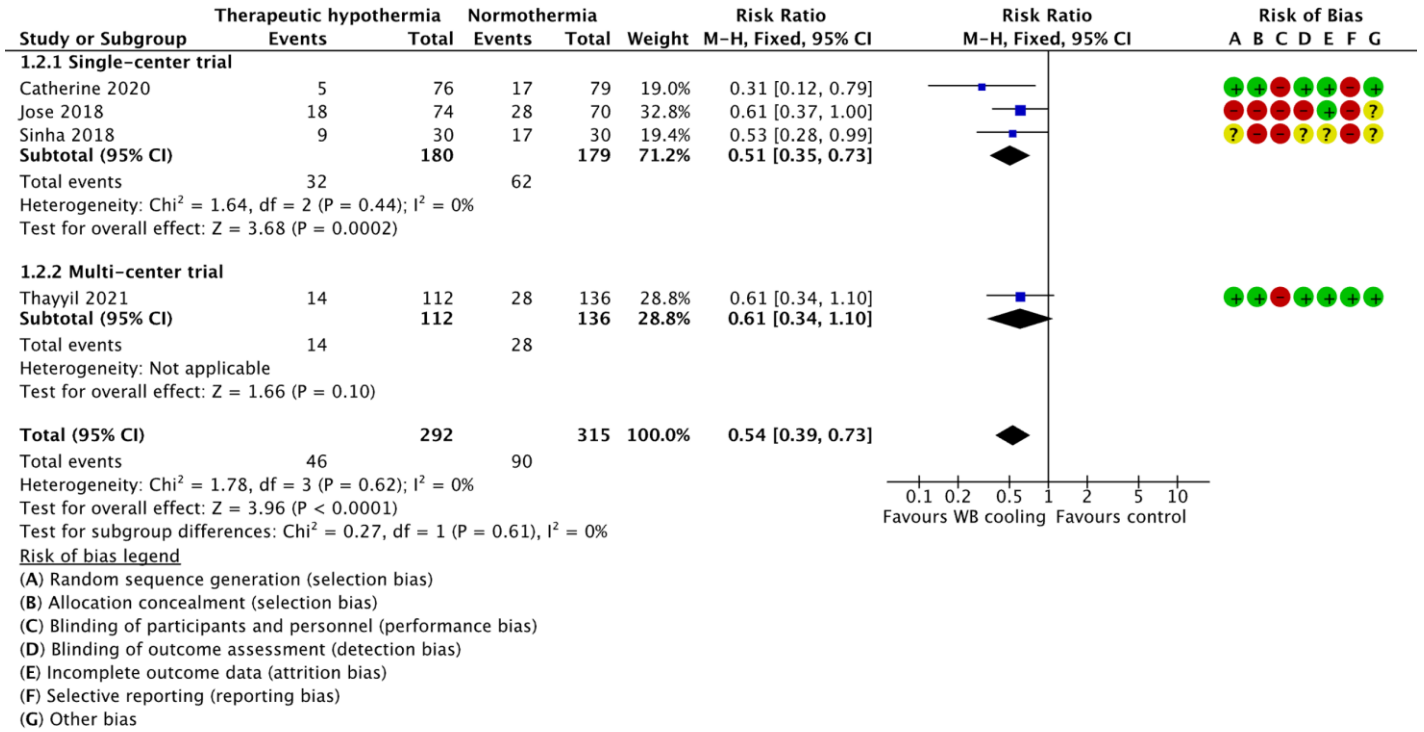
Comparison 1: Whole body cooling vs control



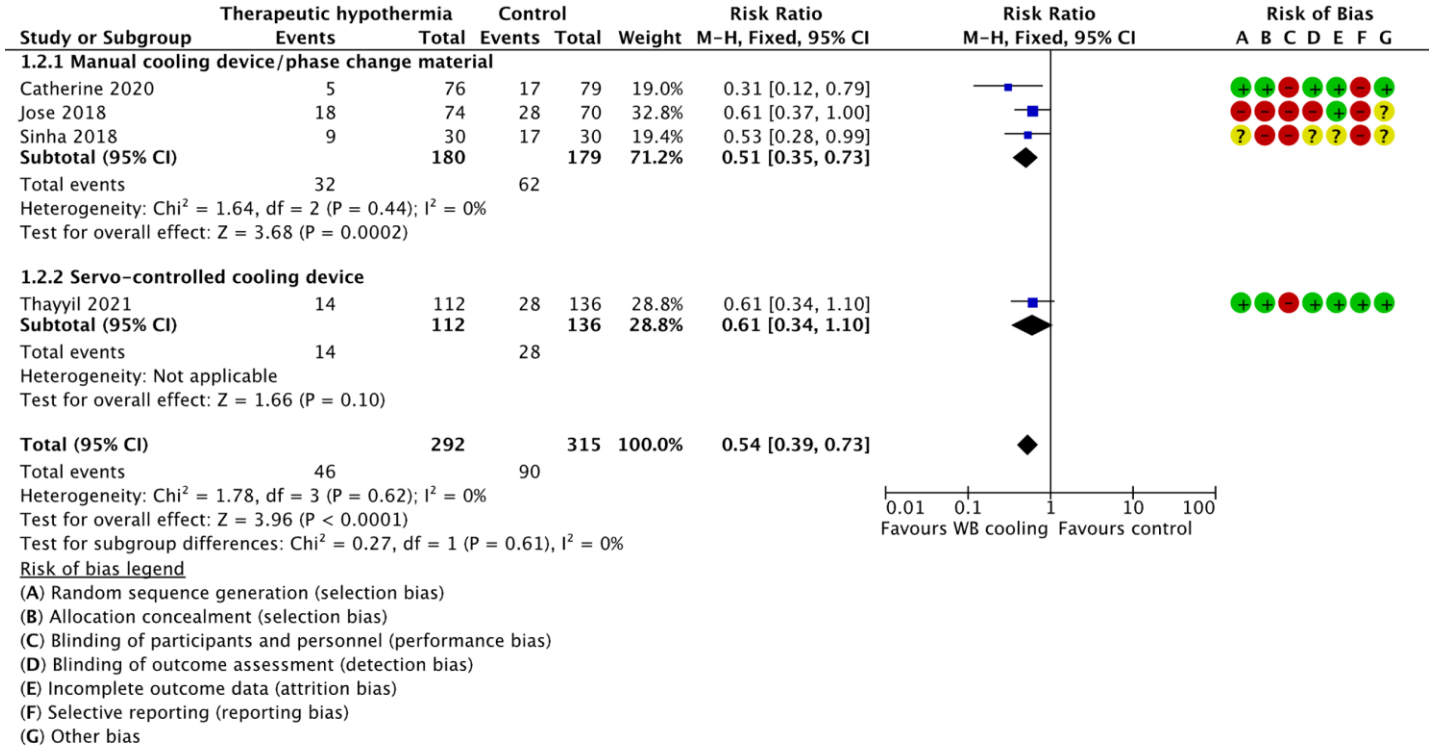
Suppl. Figure 7.25: Forest plot of comparison: 1 Whole body cooling vs normothermia, outcome: 1.1 Death or neurological disabilities at ≥ 18 months, subgroup by trial site



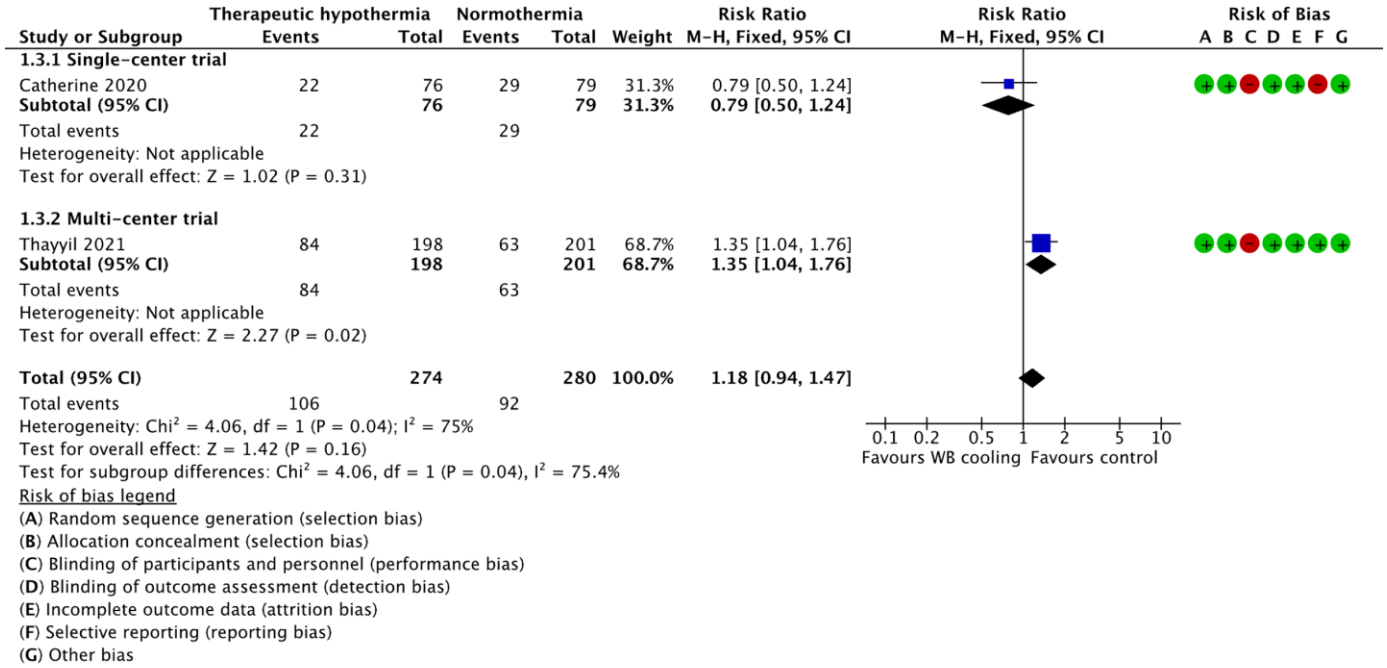
Suppl. Figure 7.26: Forest plot of comparison: 1 Whole body cooling vs normothermia, outcome: 1.1 Death or neurological disabilities at ≥ 18 months, subgroup by type of cooling device



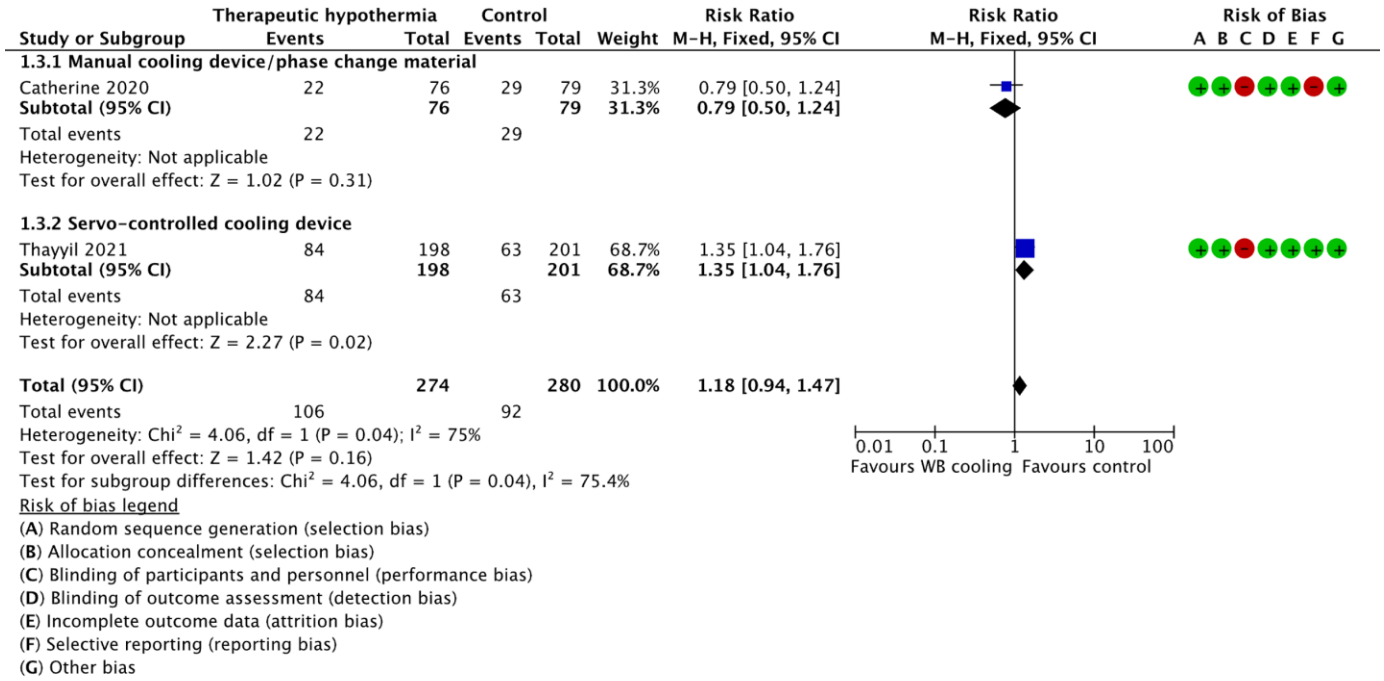
Suppl. Figure 7.27: Forest plot of comparison: 1 Whole body cooling vs normothermia, outcome: 1.2 Neurological disabilities at ≥ 18 months, subgroup by trial site



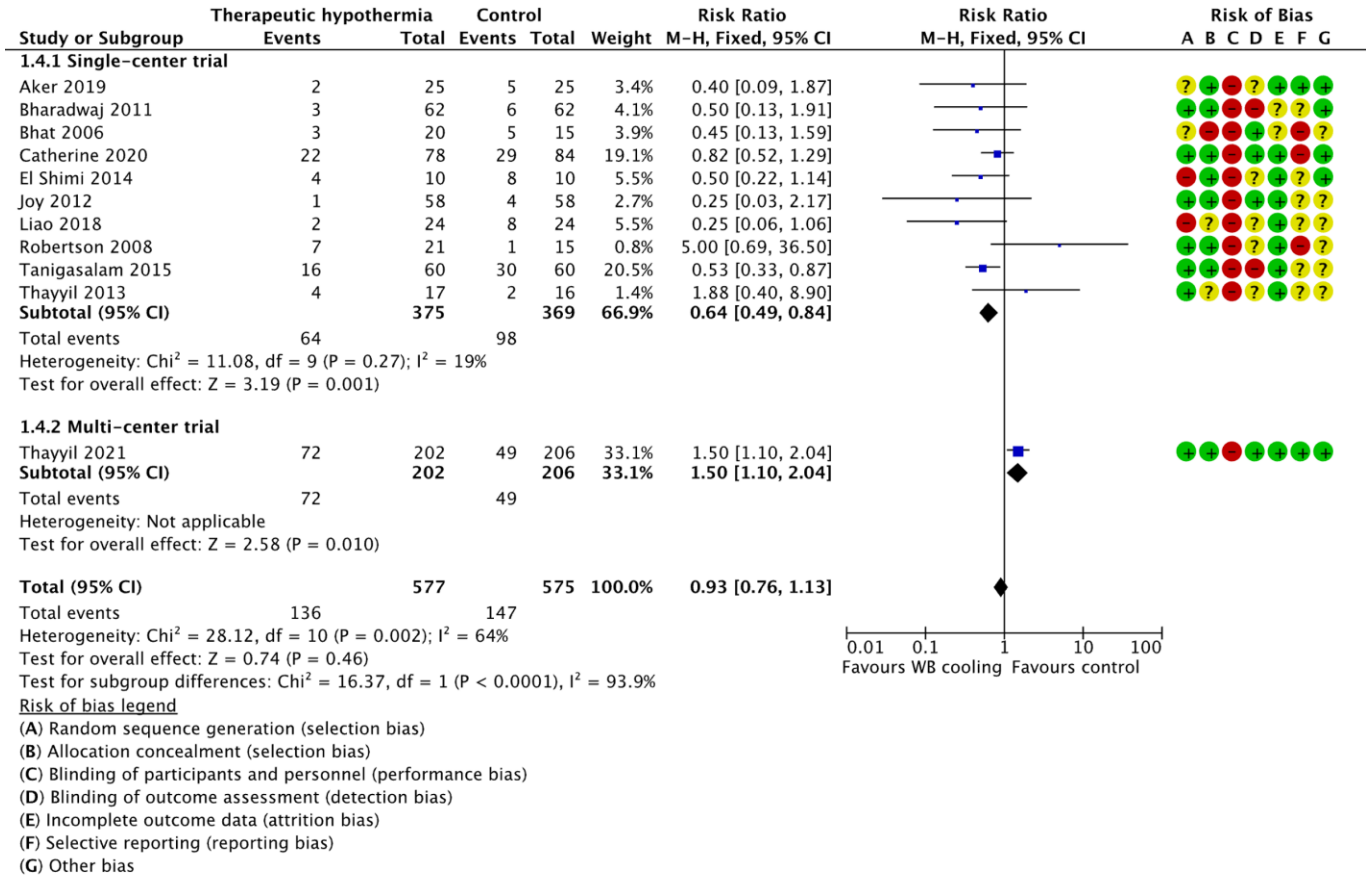
Suppl. Figure 7.28: Forest plot of comparison: 1 Whole body cooling vs normothermia, outcome: 1.2 Neurological disabilities at ≥ 18 months, subgroup by type of cooling device



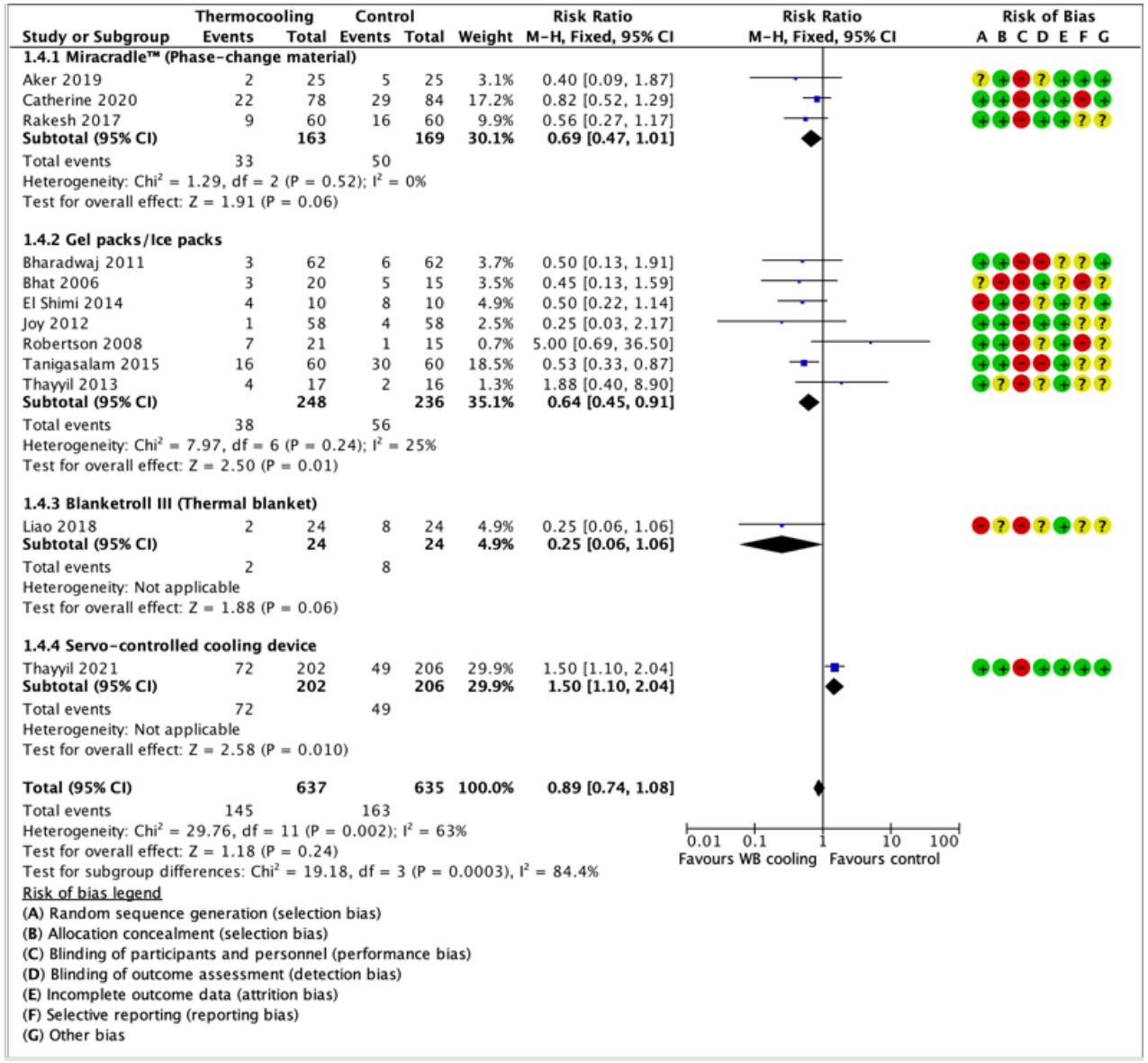
Suppl. Figure 7.29: Forest plot of comparison: 1 Whole body cooling vs normothermia, outcome: 1.3 Mortality at ≥ 18 months, subgroup by trial site



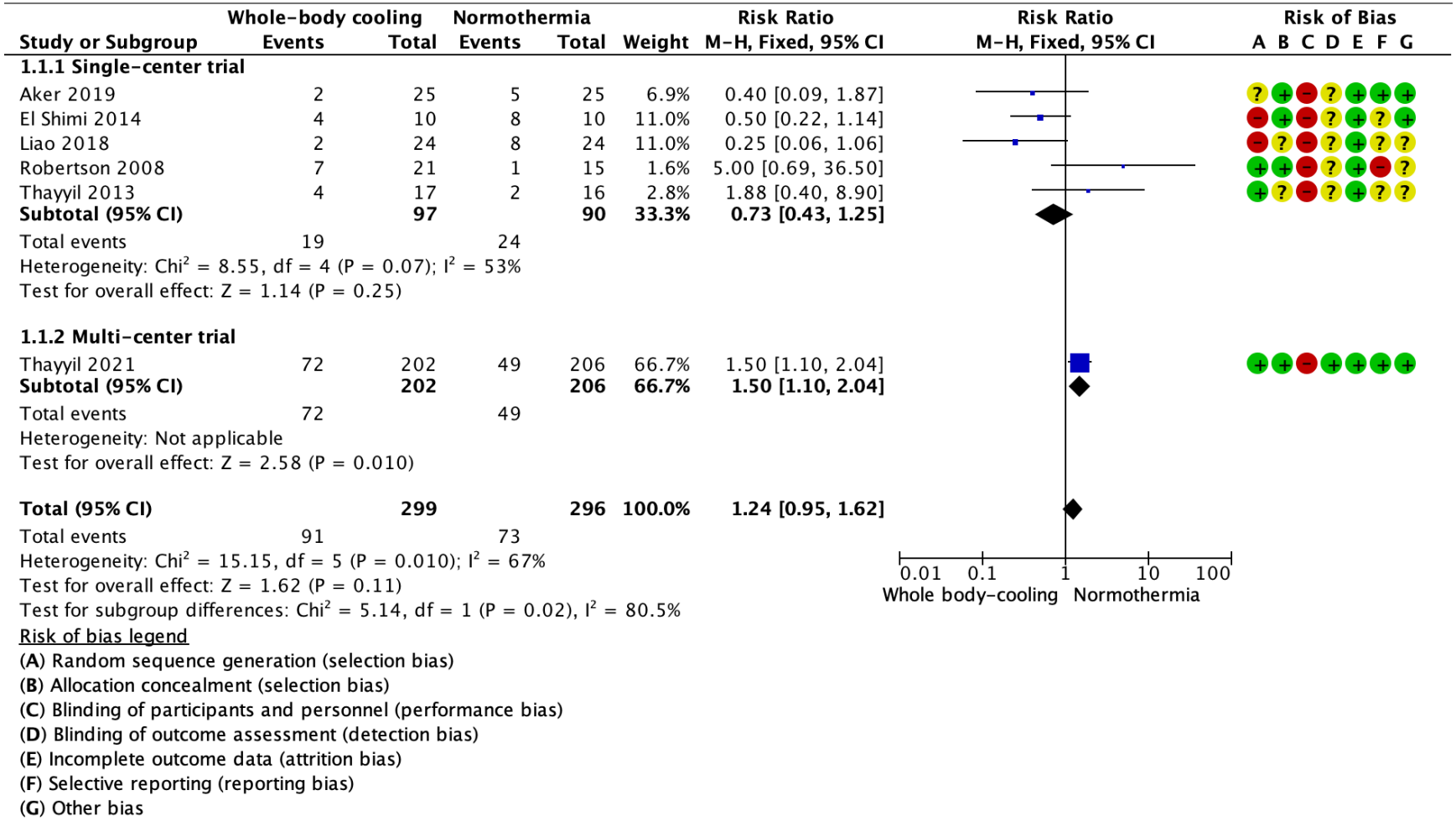
Suppl. Figure 7.30: Forest plot of comparison: 1 Whole body cooling vs normothermia, outcome: 1.3 Mortality at ≥ 18 months, subgroup by type of cooling device



Suppl. Figure 7.31: Forest plot of comparison: 1 Whole body cooling vs normothermia, outcome: 1.4 Neonatal mortality before discharge, subgroup by trial site

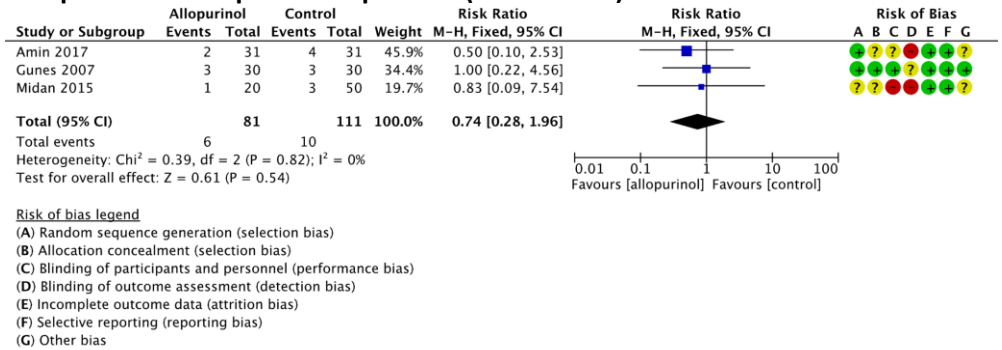


Suppl. Figure 7.32: Forest plot of comparison: 1 Whole body cooling vs normothermia, outcome: 1.4 Neonatal mortality before discharge, subgroup by type of cooling device

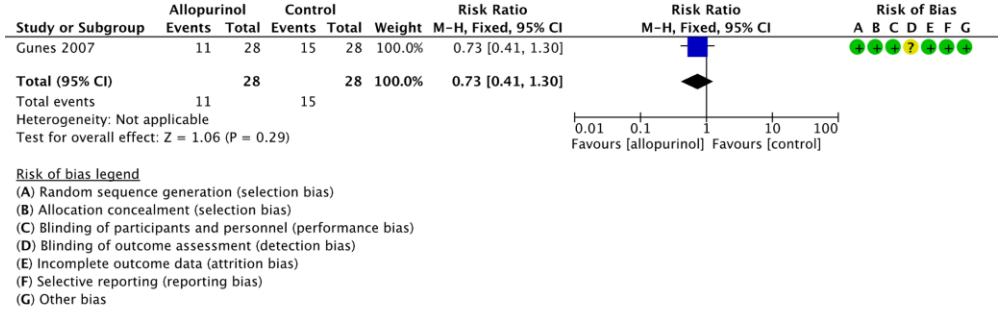


Suppl. Figure 7.33: Forest plot of comparison: 1 Whole body cooling vs normothermia, outcome: 1.4 Neonatal mortality before discharge, sensitivity analysis

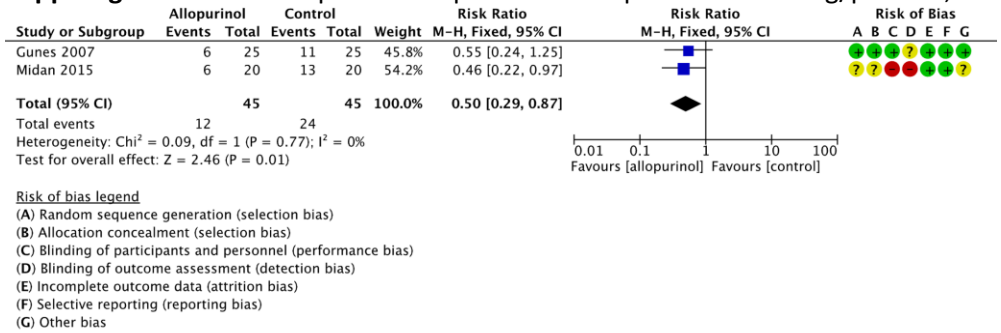
Comparison 1: Allopurinol vs placebo (N=3 studies)



Suppl. Figure 7.34: Forest plot of comparison: 1 Allopurinol vs no drug/placebo, outcome: 1.1 Death during the neonatal period and infancy.

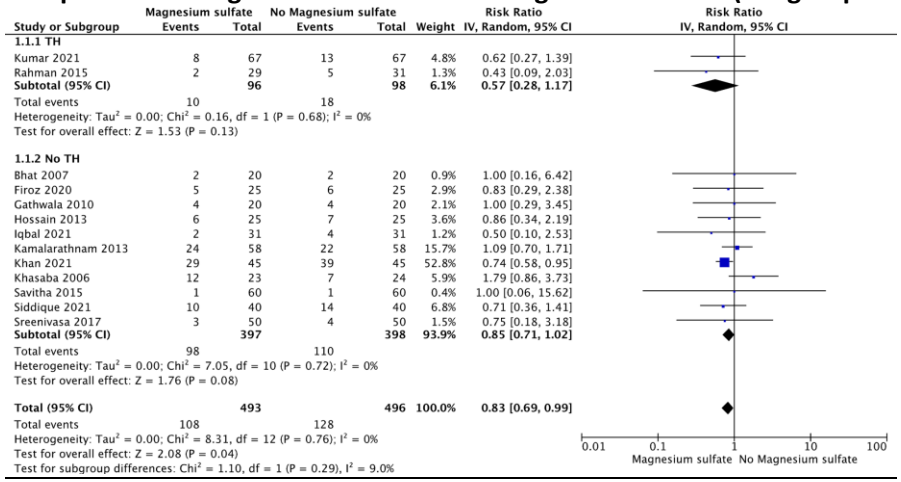


Suppl. Figure 7.35: Forest plot of comparison: 1 Allopurinol vs no drug/placebo, outcome: 1.2 Death or severe neurodevelopmental disability.

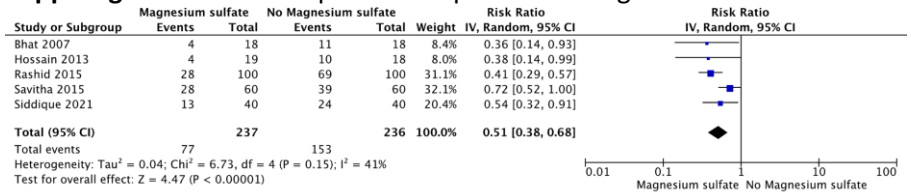


Suppl. Figure 7.36: Forest plot of comparison: 1 Allopurinol vs no drug/placebo, outcome: 1.3 Severe quadriplegia in surviving infants.

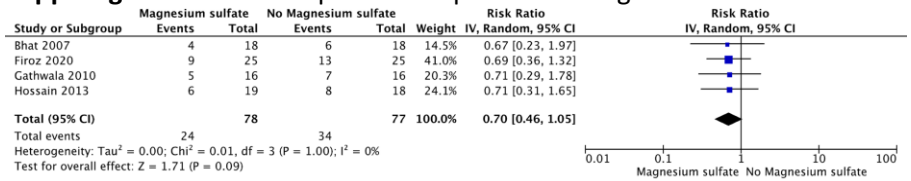
Comparison 2: Magnesium sulfate vs no magnesium sulfate (Subgroup analysis: TH or no TH) (N=17 studies)



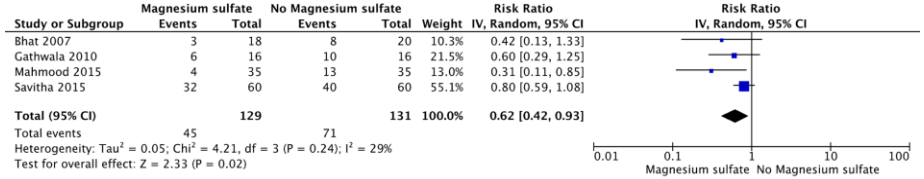
Suppl. Figure 7.37: Forest plot of comparison: 2 Magnesium sulfate vs no magnesium sulfate, outcome: 2.1 Mortality



Suppl. Figure 7.38: Forest plot of comparison: 2 Magnesium sulfate vs no magnesium sulfate, outcome: 2.2 Poor suck feeds at discharge.

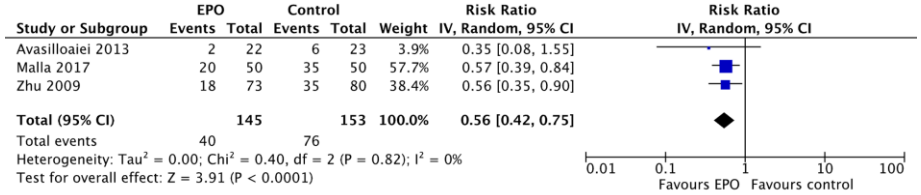


Suppl. Figure 7.39: Forest plot of comparison: 2 Magnesium sulfate vs no magnesium sulfate, outcome: 2.3 Abnormal EEG.

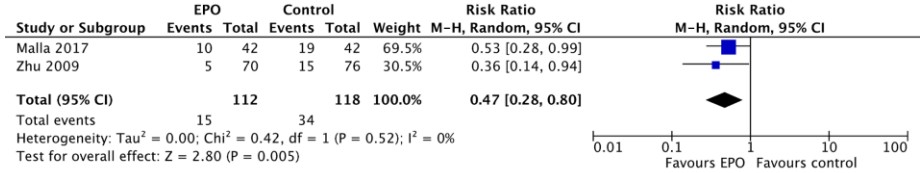


Suppl. Figure 7.40: Forest plot of comparison: 2 Magnesium sulfate vs no magnesium sulfate, outcome: 2.4 Abnormal CT scan of the brain.

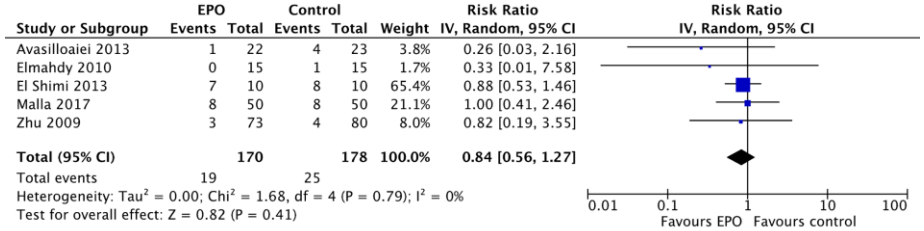
Comparison 3: Erythropoietin vs control (N=5 studies)



Suppl. Figure 7.41: Forest plot of comparison: 3 EPO vs control, outcome: 3.1 Death (neonatal period and at follow-up) or neuro-disability at 18 months of age.

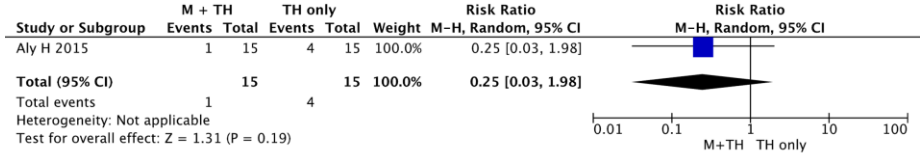


Suppl. Figure 7.42: Forest plot of comparison: 3 EPO vs control, outcome: 3.2 Cerebral palsy.



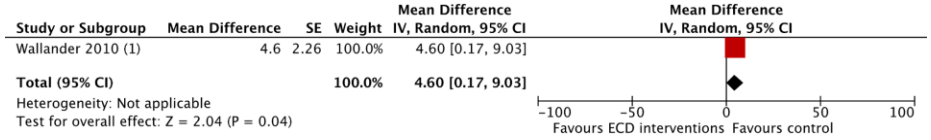
Suppl. Figure 7.43: Forest plot of comparison: 3 EPO vs control, outcome: 3.3 Death (neonatal period and at follow-up) at 3-19 months of age.

Comparison 4: Melatonin with therapeutic hypothermia (M+TH) vs therapeutic hypothermia only (TH) (N=1 study)



Suppl. Figure 7.44: Forest plot of comparison: 4 Melatonin with hypothermia vs hypothermia only, outcome: 4.1 Death in the neonatal period.

Comparison 1: Early childhood development (ECD) intervention vs control



Footnotes
(1) Restricted maximum likelihood estimates and Knapp–Hartung SEs

Suppl. Figure 7.45: Forest plot of comparison: 1 Early childhood development (ECD) intervention vs control outcome: 1.1 Cognitive development at 0-36 months of age

8: Study data and additional analyses

Suppl. Table 8.1: Proportion of outborn neonates in all TH trials

Study ID	Number of outborn neonates	
	Intervention	Control
Aker, 2020 (THIN trial) [75]	12/25 (48%)	8/25 (32%)
Akisu, 2003 [69]	NR	NR
Bharadwaj, 2012 [76]	0/65 (0%)	0/65 (0%)
Bhat, 2006 [77]	NR	NR
Catherine, 2021[78]	0/78 (0%)	0/84 (0%)
Chen, 2018 [72]	NR	NR
Das, 2017 [56]	NR	NR
El shimi, 2014 [79]	NR	NR
Gane, 2013 [54]	0/61 (0%)	0/61 (0%)
Jose, 2017 [80]	35/77 (45%)	32/79 (41%)
Joy, 2013 [81]	0/58 (0%)	0/58 (0%)
Liao, 2018 [53]	NR	NR
Lin, 2006 [70]	NR	NR
Rakesh, 2017 [82]	0/60 (0%)	0/60 (0%)
Robertson, 2008 [21]	0/21 (0%)	0/15 (0%)
Sinha, 2018 [55]	NR	NR
Sun, 2012 [74]	NR	NR
Tanigasalam, 2015 [83]	0/60 (0%)	0/60 (0%)
Thayyil, 2013 [84]	NR	NR
Thayyil, 2021 (HELIX trial)† [25]	140/202 (69%)	145/206 (70%)
Yang, 2020 [73]	NR	NR
Zhou, 2010 [71]	77/100 (77%)	77/94 (82%)

Note – NR: Not reported, †Includes infants born at another hospital and at home. Hospitals referring the infants to the HELIX trial recruiting sites were other tertiary medical college hospitals (65 infants), secondary district hospitals (124 infants), primary care centres (44 infants), private hospitals (40 infants), and unknown (two infants). All home deliveries (10 infants in total) occurred at the site in Dhaka, Bangladesh.

Suppl. Table 8.2: Study data for trials on therapeutic hypothermia (TH)

Study ID	Location	Number of deliveries per year in institution	Number of infants with asphyxia	Type of cooling device (WB/SH) cooling	Target temp, rewarming rate	Death or disability at 18-24 months		Death before discharge		Severe HIE (HIE 3)		Study period
						TH	Control	TH	Control	TH	Control	
Aker 2020 (THIN trial)	Tertiary care teaching hospital in south India	15,000	85	WB: PCM-based cooling device MiraCradle Neonate Cooler, Pluss Advanced Technologies, India	33-33.5°C, 0.2°C–0.5°C/h	NR	NR	2/25 (8%)	1/25 (4%)	NR – Median Thompson score = 9		Sept 2013 to Oct 2015
Akisu 2003	Tertiary care NICU of University hospital in Turkey	Not available	21	SH: cooling caps consisting of cold water (5–10°C)	33.5–33.0°C, 0.5°C/h	NR	NR	0/11 (0%)	2/10 (2%)	3/11 (3%)	3/10 (3%)	Sept 2000 to Dec 2001
Bharadwaj 2012	Tertiary neonatal unit in Puducherry, south India	13,827	160	WB: Cloth-covered gel packs stored at -4°C	33-34 °C, 0.5°C/h	6 mo: 5/62 (8%)	6mo: 18/62 (29%)	3/62 (5%)	6/62 (10%)	7/62 (11%)	8/62 (13%)	Sep 2009 to Apr 2011
Bhat 2006	Tertiary care Kashmir Institute of Medical	Not available	20	WB: Not reported	33.5°C, NR	NR	NR	3/20 (15%)	5/15 (33%)	NR	NR	Not described

Study ID	Location	Number of deliveries per year in institution	Number of infants with asphyxia	Type of cooling device (WB/SH) cooling	Target temp, rewarming rate	Death or disability at 18-24 months		Death before discharge		Severe HIE (HIE 3)		Study period
						TH	Control	TH	Control	TH	Control	
	Science, Srinagar, India											
Catherine 2021	Tertiary neonatal unit in Puducherry, south India	13,827 last year	200	WB: PCM-based cooling device MiraCradle Neonate Cooler, Pluss Advanced Technologies, India	33.5°C, 0.5°C/h	27/76 (36%)	46/79 (58%)	22/78 (28%)	29/84 (35%)	NR	NR	2014 to 2018
Chen 2018	Tertiary care neonatal unit of hospital affiliated with medical college Bengbu, China	Not available	42 children with HIE	SH: medical-specific temperature controller	34.5-35°C, NR	NR	NR	0/	1/	NR	NR	Jan 2015 to June 2017
Das 2017	Tertiary care NICU of the Calcutta	10,000-12,000	60	SH: Ice-filled bags	34-35°C, 0.5°C/h	6/30 (20%)	18/30 (60%)	3/30 (10%)	9/30 (30%)	10/30 (33%)	10/30 (33%)	Jun 2009 to Feb 2014

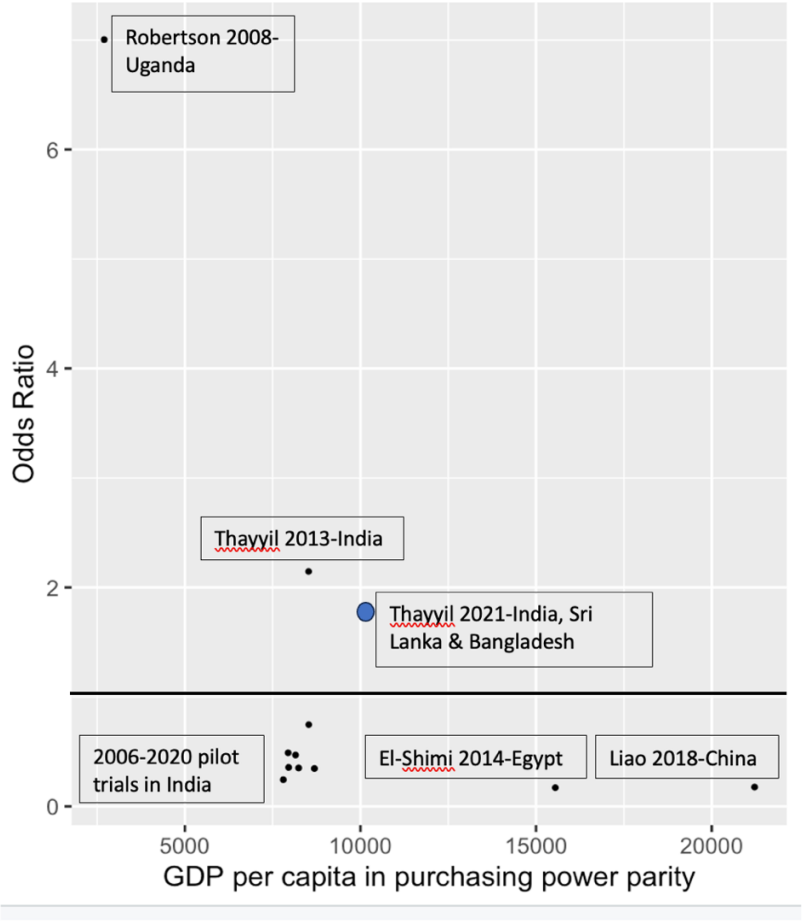
Study ID	Location	Number of deliveries per year in institution	Number of infants with asphyxia	Type of cooling device (WB/SH) cooling	Target temp, rewarming rate	Death or disability at 18-24 months		Death before discharge		Severe HIE (HIE 3)		Study period
						TH	Control	TH	Control	TH	Control	
	National Medical College, Kolkata, India											
El shimi 2014	Tertiary care NICU of University hospital in Egypt	~20,000 in 2011 [43]	30	WB: Cool packs	33-34°C 0.5°C/h	NR	NR	4/10 (40%)	8/10 (80%)	4/10 (40%)	6/10 (60%)	Sept 2007 to Feb 2010
Gane 2013	Tertiary neonatal unit in Puducherry, south India	13,827 last year	187	WB: Gel packs	33-34 C 0.25°C/h	9/53 (17%)	26/50 (52%)	4/47 (9%)	8/58 (14%)	15/60 (25%)	16/60 (27%)	Mar 2011 to Jun 2013
Jose 2017	Tertiary care department of Pediatrics, MES Medical College,Perinthalmanna, Kerala, India	Not available	156	WB: Gel packs	33°C, NR			NR	NR	22/74 (30%)	28/70 (40%)	Nov 2014 to Oct 2016

Study ID	Location	Number of deliveries per year in institution	Number of infants with asphyxia	Type of cooling device (WB/SH) cooling	Target temp, rewarming rate	Death or disability at 18-24 months		Death before discharge		Severe HIE (HIE 3)		Study period
						TH	Control	TH	Control	TH	Control	
Joy 2013	Tertiary neonatal unit in Puducherry, south India	13,827 last year	160	WB: Gel packs	33-34°C 0.5°C/h	22/58 (38%)	42/58 (72%)	1/58 (2%)	4/58 (7%)	9/58 (16%)	7/58 (12%)	Oct 2010 to Jan 2012
Liao, 2018	Tertiary care medical university hospital Guangzhou, China	Not available	48	WB: BLANKETROL III water-blanket medical temperature controller	33.5-34°C, 0.25°C/h	NR	NR	2/24 (8%)	8/24 (33%)	NR	NR	Dec 2015 to Oct 2016
Lin 2006	Tertiary care municipal hospital of medical college in Wenzhou, China	Not available	62	SH: Cooling cap (SDL-V) with circulating cold water at 10°C	34-35°C, spontaneous	NR	NR	2/32 (6%)	2/30 (7%)	7/30 (23%)	6/28 (21%)	July 2000 to June 2003
Rakesh 2017	Tertiary neonatal unit in Puducherry, south India	13,827 last year	150	WB: PCM-based cooling device MiraCradle Neonate Cooler,	33-34°C, NR	NR	NR	9/60 (15%)	16/60 (27%)	18/60 (30%)	14/60 (23%)	Feb 2014 to Jul 2016

Study ID	Location	Number of deliveries per year in institution	Number of infants with asphyxia	Type of cooling device (WB/SH) cooling	Target temp, rewarming rate	Death or disability at 18-24 months		Death before discharge		Severe HIE (HIE 3)		Study period
						TH	Control	TH	Control	TH	Control	
				Pluss Advanced Technologies, India								
Robertson 2008	Special care baby unit in tertiary care referral hospital in Uganda	4957 deliveries in 3-month study period	110	WB: Water bottles	33-34°C, NR	NR	NR	7/21 (33%)	1/15 (7%)	6/21 (29%)	1/15 (7%)	July 2007 to Oct 2007
Sinha 2018	Level 2 NICU of a military hospital in India	1565 in the year of study	65	WB: Icepacks wrapped in towels	33-34°C, 0.2-0.4°C/h	9/30 (30%)	17/30 (57%)	All participants had the outcome of interest at 18 months of age		8/30 (26%)	10/30 (33%)	Oct 2014 to Apr 2016
Sun 2012	Tertiary care NICU of university Children's hospital in Shanghai, China	Not available	51	SH: Henyang YJW608-04B	34.5-35°C, spontaneous	NR	NR	0/23 (0%)	1/28 (4%)	6/23 (26%)	7/28 (25%)	May 2002 to Aug 2006
Tanigasalam 2015	Tertiary neonatal unit in Puducherry	13,827 last year	150	WB: Gel packs	33-34 °C, 0.5°C/h	NR	NR	16/60 (27%)	30/60 (50%)	17/60 (28%)	15/60 (25%)	Oct 2013 to Oct 2015

Study ID	Location	Number of deliveries per year in institution	Number of infants with asphyxia	Type of cooling device (WB/SH) cooling	Target temp, rewarming rate	Death or disability at 18-24 months		Death before discharge		Severe HIE (HIE 3)		Study period
						TH	Control	TH	Control	TH	Control	
	, south India											
Thayyil 2013	Tertiary care neonatal unit in medical college in Kerala, India	16,000-18000 deliveries	33	WB: PCM	33.5°C, 0.2-0.4°C/h	NR	NR	4/17 (24%)	2/16 (13%)	NR – Thompson encephalopathy score > 5 is eligibility criteria for recruitment		Not reported
Thayyil 2021 (HELIX trial)	Tertiary care centres in India, Sri Lanka, Bangladesh	2296	576	WB: Tecotherm Neo	33.5°C 0.5°C/h	98/195 (50%)	94/199 (47%)	73/202 (36%)	49/206 (24%)	41/202 (20%)	39/206 (19%)	Aug 2015 to Feb 2019
Yang, 2020	Tertiary care hospital affiliated with medical university in China	Not available	92	SH: ZJL-2000 II	35-36°C, 0.5°C/h	NR	NR	2/62 (3%)	2/30 (7%)	NR	NR	Jan 2017 to April 2019

Study ID	Location	Number of deliveries per year in institution	Number of infants with asphyxia	Type of cooling device (WB/SH) cooling	Target temp, rewarming rate	Death or disability at 18-24 months		Death before discharge		Severe HIE (HIE 3)		Study period
						TH	Control	TH	Control	TH	Control	
Zhou, 2010	12 children's hospitals or children's and women's health care centers in China	Not available	293, 253 were randomized, 194 infants were assessed for outcomes	SH: Henyang	34.5-35°C, spontaneous	31/100 (31%)	46/94 (50%)	NR	NR	38/100 (38%)	35/94 (37%)	May 2003 to Aug 2005
Legend – NR: Not reported, WB: Whole-body, SH: Selective head												



Suppl. Fig 8.1: Scatter plot of Whole-body cooling trials (n=12)

Legend:

X-axis	Gross Domestic Product (GDP) per capita in purchasing power parity (PPP) of country where trial was conducted (Mean of GDP per capita used for multi-national trials)
Y-axis	Odds ratio (OR) of neonatal mortality before discharge from the hospital in whole body cooling trials (OR not log transformed)

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