

# INPLASY

## Long-term outcomes of therapeutic hypothermia for moderate-to-severe neonatal hypoxic-ischemic encephalopathy: A systematic review and meta-analysis

INPLASY2025120070

doi: 10.37766/inplasy2025.12.0070

Received: 19 December 2025

Published: 19 December 2025

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### ADMINISTRATIVE INFORMATION

**Support** - This work was supported by grants from the Fujian Provincial Natural Science Foundation Project (No. 2023J011517).

**Review Stage at time of this submission** - Completed but not published.

**Conflicts of interest** - None declared.

**INPLASY registration number:** INPLASY2025120070

**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 December 2025 and was last updated on 19 December 2025.

### INTRODUCTION

**Review question / Objective** To systematically evaluate the long-term outcomes of therapeutic hypothermia for moderate-to-severe neonatal hypoxic-ischemic encephalopathy (HIE) through a comprehensive review and meta-analysis.

**Condition being studied** Neonatal hypoxic-ischemic encephalopathy (HIE) is a critical condition in neonatology, posing a substantial threat to newborns' health worldwide. It occurs when the neonatal brain experiences oxygen and blood flow deprivation during the perinatal period, often due to maternal complications like pre-eclampsia or intrapartum issues such as prolonged labor. The pathophysiology of HIE is intricate. The initial hypoxia-ischemia triggers an energy crisis in brain cells. With energy depletion, ion pumps fail, leading to calcium influx. This activates enzymes that break down cellular components, causing cell

damage. Subsequently, in the secondary energy failure phase, excitatory neurotransmitters like glutamate are released. Excessive glutamate activates NMDA receptors, leading to more calcium influx and the production of reactive oxygen species (ROS). These ROS damage cellular structures, and the activated immune system releases inflammatory cytokines, further exacerbating brain injury. The long-term consequences of HIE are severe. Affected neonates face a high risk of neurological disabilities such as cerebral palsy, intellectual impairment, epilepsy, and learning difficulties. Cerebral palsy impairs movement, while intellectual impairment affects cognitive functions. Epilepsy endangers physical safety and impacts social and emotional well-being. These disabilities burden families and healthcare systems.

Given the gravity of HIE, finding effective treatment strategies is crucial. Over time, multiple approaches have been explored, including pharmacological agents and stem cell therapy.

Therapeutic hypothermia has emerged as a promising option. The principle behind it is that lowering body temperature slows the brain's metabolic rate. This reduces the demand for oxygen and glucose, inhibits the production of ROS and toxic metabolites, and suppresses cell-death pathways and the inflammatory response. Several clinical trials have evaluated therapeutic hypothermia for HIE. Some have reported positive outcomes, indicating a reduced risk of mortality and severe neurological disability. However, many uncertainties persist. There are questions about the best cooling modality (whole-body vs. selective head cooling), the optimal target temperature, the duration of cooling, and the long-term effects. Furthermore, existing studies show heterogeneity in results, which may be due to differences in patient populations, treatment protocols, and outcome assessment methods. A comprehensive systematic review and meta-analysis are thus necessary to synthesize the available evidence. This study aims to conduct such an analysis to provide more definitive answers on the effectiveness and safety of therapeutic hypothermia for moderate-to-severe neonatal HIE, ultimately guiding clinical practice and improving neonates' outcomes.

## METHODS

**Participant or population** Population: Neonates  $\geq 36$  weeks' gestation with moderate-to-severe HIE (defined by Sarnat staging or EEG/amplitude-integrated EEG criteria).

**Intervention** Whole-body or selective head cooling with target temperature  $\leq 35.5^{\circ}\text{C}$  for  $\geq 48$  hours.

**Comparator** Neonates  $\geq 36$  weeks' gestation with moderate-to-severe HIE (defined by Sarnat staging or EEG/amplitude-integrated EEG criteria). Whole-body or selective head cooling with target temperature  $\leq 35.5^{\circ}\text{C}$  for  $\geq 48$  hours.

**Study designs to be included** Randomized controlled trials (RCTs) and prospective cohort studies involving neonates  $\geq 36$  weeks' gestation with moderate-to-severe HIE treated with therapeutic hypothermia were included.

**Eligibility criteria** Inclusion criteria: Population: Neonates  $\geq 36$  weeks' gestation with moderate-to-severe HIE (defined by Sarnat staging or EEG/amplitude-integrated EEG criteria). Intervention: Whole-body or selective head cooling with target temperature  $\leq 35.5^{\circ}\text{C}$  for  $\geq 48$  hours. Outcomes: Mortality and/or severe neurodevelopmental disability (e.g., Bayley-III

score  $< 70$ , cerebral palsy, severe visual/hearing impairment) assessed at  $\geq 12$  months of age.

Study design: Randomized controlled trials (RCTs) or prospective cohort studies.

Exclusion Criteria:

- 1) Studies involving mild HIE, non-cooling interventions (e.g., pharmacotherapy), or overlapping cohorts.
- 2) Animal studies, reviews, case reports, or non-English publications without translatable data.
- 3) Studies with incomplete outcome stratification by HIE severity or cooling protocols.

**Information sources** A systematic search was conducted across PubMed, Embase, and the Cochrane Library

up to December 2023 using Boolean operators to combine keywords: ("therapeutic hypothermia" OR "cooling") AND ("hypoxic-ischemic encephalopathy" OR "HIE") AND ("long-term outcomes" OR "neurodevelopment" OR "mortality" OR "disability")

The search strategy incorporated Medical Subject Headings (MeSH) and Emtree terms, supplemented by free-text variations (e.g., "whole-body cooling," "Bayley Scales," "cerebral palsy"), with language restrictions limited to English. Additional studies were identified through gray literature (e.g., ClinicalTrials.gov, conference abstracts) and backward reference tracking of included articles to mitigate publication bias. All retrieved records were deduplicated using EndNote and imported into Covidence for title/abstract screening and full-text eligibility assessment.

**Main outcome(s)** Mortality and/or severe neurodevelopmental disability (e.g., Bayley-III score  $< 70$ , cerebral palsy, severe visual/hearing impairment) assessed at  $\geq 12$  months of age.

**Quality assessment / Risk of bias analysis** RCTs were evaluated using the Cochrane ROB2 tool; prospective cohorts used ROBINS-I. Key domains included randomization, blinding, incomplete outcome data, and selective reporting. The GRADE framework assessed overall evidence quality, downgrading for risk of bias, inconsistency ( $I^2 > 50\%$ ), indirectness, and imprecision.

**Strategy of data synthesis** All analyses utilized random-effects models (DerSimonian-Laird method) in RevMan 5.4 and R package metafor, with heterogeneity quantified by  $I^2$  statistics ( $I^2 >$

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50% defined as substantial).  $P < 0.10$  indicating potential small-study effects.

**Subgroup analysis** Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for composite endpoint comparisons across subgroups, ensuring methodological consistency and transparency. The subgroup analyses were conducted to investigate sources of heterogeneity.

**Sensitivity analysis** Sensitivity analyses excluded small studies with sample sizes  $< 50$  to evaluate the robustness of pooled estimates. Publication bias was assessed via funnel plot symmetry and Egger's regression test.

**Country(ies) involved** Neonatology Department, Fuzhou Second General Hospital, Fuzhou 350007, Fujian Province, China<sup>2</sup>Neonatology Department, Fuzhou Second General Maternity and Child Health Care Hospital, Fuzhou 350013, Fujian Province, China.

**Keywords** Neonatal hypoxic-ischemic encephalopathy; Therapeutic hypothermia; Long-term outcomes; Moderate; Severe.

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