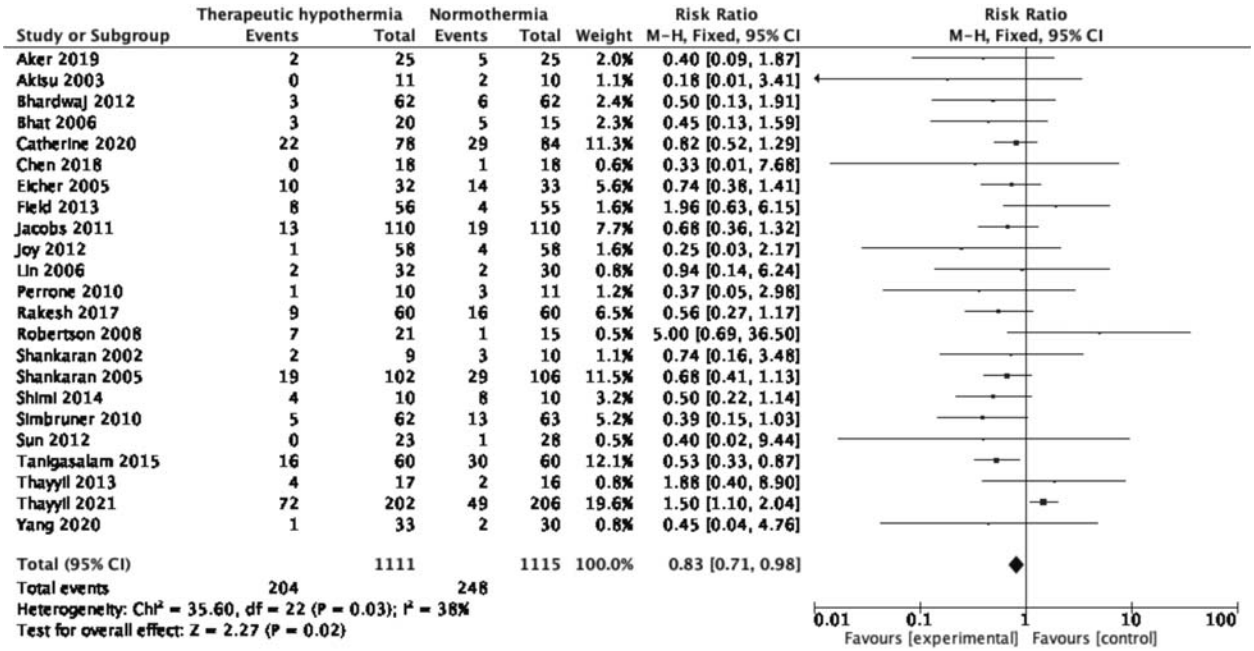
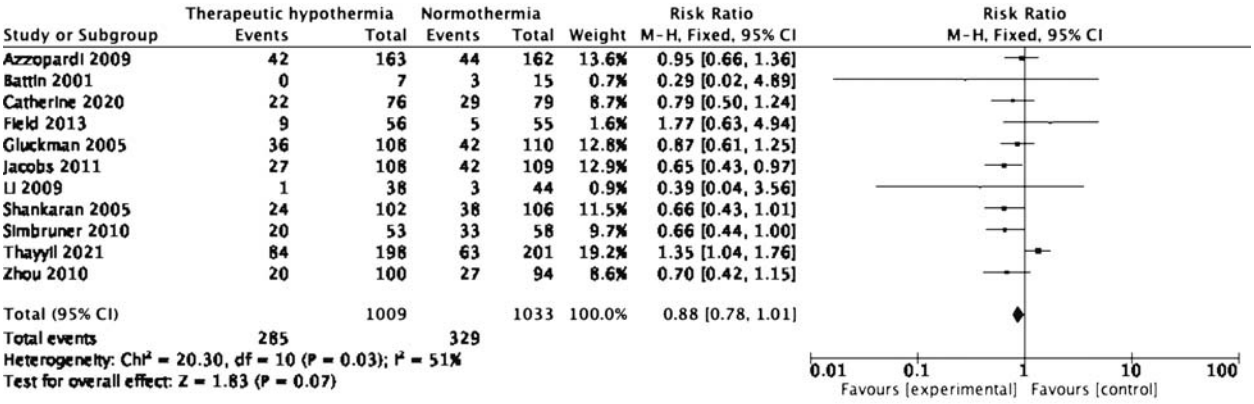
Up-to-date Systematic Review and Meta-analysis of Therapeutic Hypothermia for Neonatal Encephalopathy: Is the Crown Losing Its Sheen?

The extensive critical appraisal [1,2] of the recently published HELIX trial [3] prompts this brief communication. Therapeutic hypothermia (TH) holds the crown as the most effective intervention for neonatal hypoxic encephalopathy (HIE) [4]. The Cochrane review of 2013 had reported that TH reduces mortality [5], and this has been reiterated by another recent systematic review [6]. However, the latter has several methodological errors, including duplication of data from some trials, combining short-term and long-term mortality, as well as errors in data analysis [6]. In contrast to the findings of these, a systematic review, including trials exclusively from developing countries, did not find any benefit of TH on neonatal mortality [7]. More alarming, the HELIX trial [3],

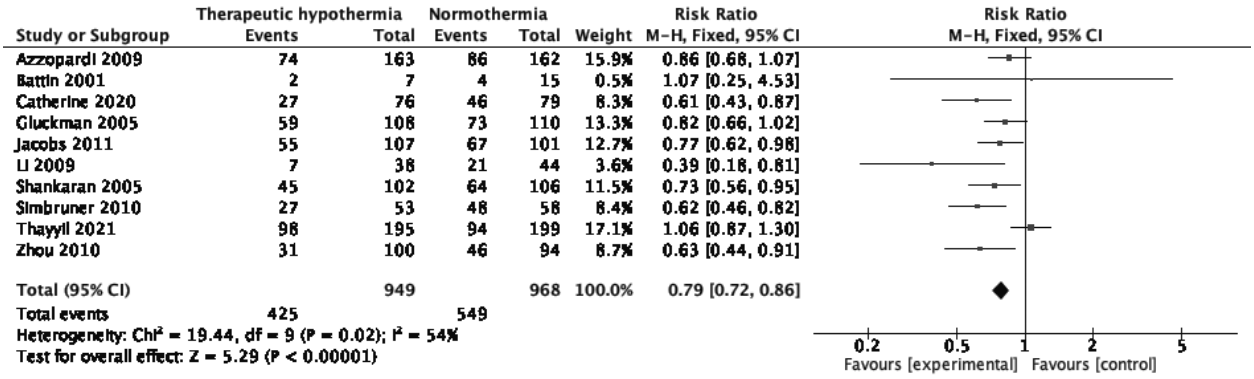


Panel A: Therapeutic hypothermia vs Normothermia for neonatal encephalopathy: Mortality before discharge

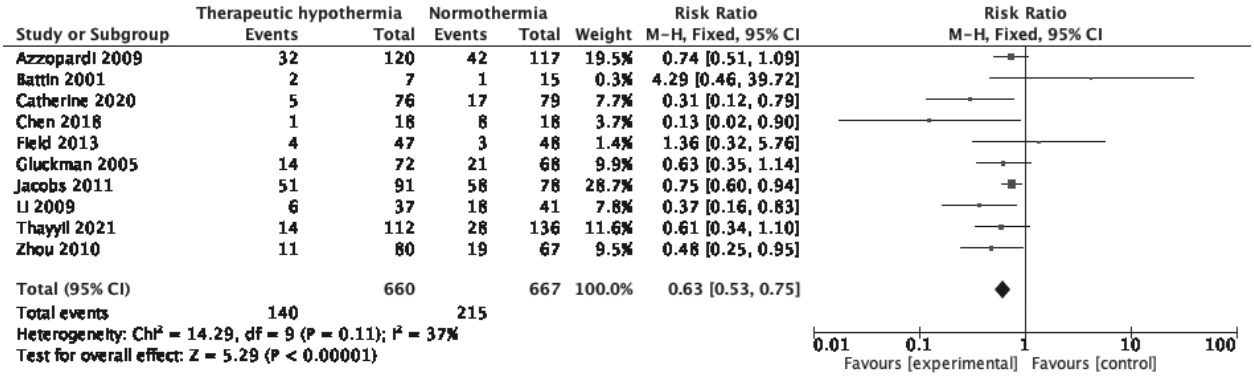


Panel B: Therapeutic hypothermia vs Normothermia for neonatal encephalopathy: Mortality at 18-24 months of age

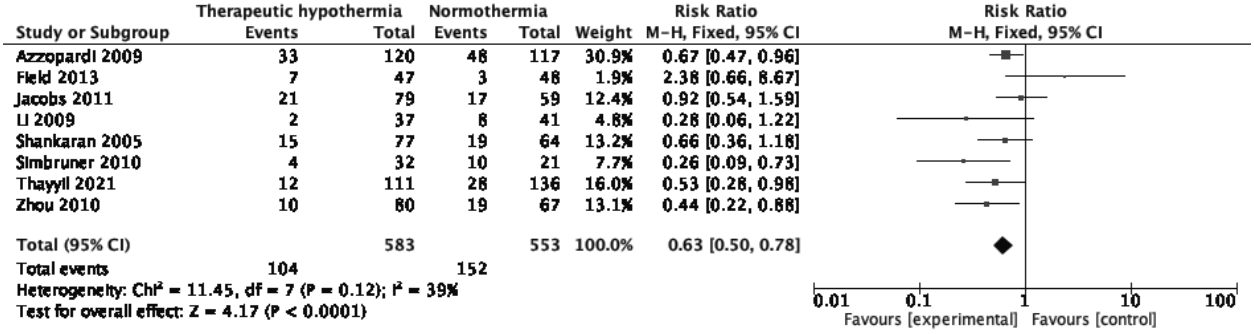
Fig. 1 Meta-analyses of therapeutic hypothermia vs normothermia for neonatal hypoxic encephalopathy, for short-term and long-term outcomes.



Panel C: Therapeutic hypothermia vs Normothermia for neonatal encephalopathy: Mortality or disability at 18-24 months of age



Panel D: Therapeutic hypothermia vs Normothermia for neonatal encephalopathy: Disability at 18-24 months of age



Panel E: Therapeutic hypothermia vs Normothermia for neonatal encephalopathy: Cerebral palsy at 18-24 months of age

reported increased short-term and long-term mortality, in low and middle income country settings. Such divergent results necessitate an up-to-date systematic review to evaluate the effect of therapeutic hypothermia (inter-vention) versus normothermia (comparison) in neonatal hypoxic encephalopathy (population), on mortality and neuro-development (outcomes).

We searched multiple databases without language or date restrictions, published up to 30 September, 2021. We included randomized controlled trials (RCT) comparing therapeutic hypothermia (defined as whole-body or selective head cooling, to temperature <34.5 °C for 48-72 hours) initiated within 6 hours of birth, versus no hypothermia, in neonates with hypoxic encephalopathy (defined by Apgar scoring and/or cord blood analysis, and supportive clinical findings), and reporting any of the following outcomes: mortality before discharge, mortality at 18-24 months, mortality or neurologic disability at 18-24 months, disability at 18-24 months, and cerebral palsy at 18-24 months.

We identified 36345 citations, of which 149 citations were

short-listed, and 32 publications (reporting 29 trials), were included. Using Cochrane Risk of Bias (RoB) 2 tool [8], two authors independently categorized, 11, 8, and 10 RCT as having high, moderate, and low RoB. Meta-analysis using Cochrane Review Manager [9] (fixed effect model) [10] revealed pooled relative risks (95% CI) as follows (**Fig. 1**): Mortality before discharge: 0.83 (0.71, 0.98), 23 trials, 2221 participants, I^2 38%; mortality at 18-24 months: 0.88 (0.78, 1.01), 11 trials, 2042 participants, I^2 51%; mortality or neurologic disability at 18-24 months: 0.79 (0.72, 0.86), 10 trials, 1914 participants, I^2 54%; neurologic disability at 18-24 months: 0.63 (0.53, 0.75), 10 trials, 1327 participants, I^2 37%; and, cerebral palsy at 18-24 months: 0.63 (0.50, 0.78), 8 trials, 1136 participants, I^2 39%. These data suggested statistically significant benefit for all outcomes except mortality at 18-24 months of age.

Subgroup analysis by study setting (developed versus developing countries) showed marked differences in mortality before discharge: RR 0.68 (95% CI 0.51, 0.92), 8 trials, 790 participants, I^2 0% versus RR 0.91 (95%CI 0.75, 1.10), 15 trials, 1431 participants, I^2 49%; and mortality at 18-24 month: RR 0.79 (0.66, 0.93), 7 trials, 1212 participants, I^2 7%, versus RR 1.05 (0.86, 1.29), 4 trials, 830 participants, I^2 65%. Other outcomes showed benefit of TH in both developed and developing countries, the magnitude of effect being greater in developing countries for disability and cerebral palsy.

The respective risk ratios (95% CI) for trials with low versus moderate/high RoB were as follows: Mortality before discharge: 1.04 (0.84, 1.29), 7 trials, 1186 partici-pants, I^2 62%, versus 0.63 (0.49, 0.80), 16 trials, 1035 participants, I^2 0%; mortality at 18-24 months: 0.97 (0.82, 1.15), 5 trials, 1011 participants, I^2 60%, versus 0.78 (0.64, 0.96), 6 trials, 1031 participants, I^2 7%; mortality or neurologic disability at 18-24 months: 0.86 (0.76, 0.97), 5 trials, 997 participants, I^2 55%, versus 0.71 (0.62, 0.81), 5 trials, 920 participants, I^2 40%; neurologic disability at 18-24 months: 0.66 (0.54, 0.82), 5 trials, 734 participants, I^2 40%, versus 0.58 (0.43, 0.78), 5 trials, 593 participants, I^2 41%; and, cerebral palsy at 18-24 months: 0.70 (0.46, 1.05), 2 trials, 385 participants, I^2 44%, versus 0.60 (0.46, 0.78), 6 trials, 751 participants, I^2 45%.

These data confirm that some of the benefits of TH reported in trials and systematic reviews are biased by studies with moderate/high RoB. TH reduces neurologic disability and cerebral palsy in later infancy in diverse settings. However, the expected benefit on short-term and long-term mortality is uncertain, especially in developing country settings. A systematic review with several additional outcomes is in progress (PROSPERO 2021 CRD42021279682). Meanwhile, these findings will help physicians, families, and policymakers, to make evidence-informed choices and decisions about therapeutic hypothermia for neonatal encephalopathy.

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