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Incidence and outcomes of intrapartum-related neonatal encephalopathy in low-income and middle-income countries: a systematic review and meta-analysis

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ABSTRACT

Aim To examine the incidence of intrapartum-related neonatal encephalopathy, and neonatal mortality and neurodevelopmental outcomes associated with it in low-income and middle-income countries.

Methods Reports were included when neonatal encephalopathy diagnosed clinically within 24 hours of birth in term or near-term infants born after intrapartum hypoxia-ischaemia defined as any of the following: (1) pH≤7.1 or base excess ≤−12 or lactate ≥6, (2) Apgar score ≤5 at 5 or 10 min, (3) continuing resuscitation at 5 or 10 min or (4) no cry from baby at 5 or 10 min. Peer-reviewed articles were searched from Ovid MEDLINE, Cochrane, Web of Science and WHO Global Index Medicus with date limits 1 November 2009 to 17 November 2021. Risk of bias was assessed using modified Newcastle Ottawa Scale. Inverse variance of heterogenicity was used for meta-analyses.

Results There were 53 reports from 51 studies presenting data on 4181 children with intrapartum-related neonatal encephalopathy included in the review. Only five studies had data on incidence, which ranged from 1.5 to 20.3 per 1000 live births. Neonatal mortality was examined in 45 studies and in total 636 of the 3307 (19.2%) infants died. Combined outcome of death or moderate to severe neurodevelopmental disability was reported in 19 studies and occurred in 712 out of 1595 children (44.6%) with follow-up 1 to 3.5 years.

Conclusion Though there has been progress in some regions, incidence, case mortality and morbidity in intrapartum-related neonatal encephalopathy has been static in the last 10 years.

PROSPERO registration number CRD42020177928.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Intrapartum-related neonatal encephalopathy is one of the leading causes of newborn death and disability in low-income and middle-income countries.

WHAT THIS STUDY ADDS

⇒ Although mortality and morbidity associated with intrapartum-related neonatal encephalopathy have been at large static in over the last 10 years, some hospitals in middle-income countries report outcomes similar to high-income settings.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given the scarcity of population-based data, more research on the epidemiology of intrapartum-related neonatal encephalopathy is needed to inform policy makers on progress at national and subnational levels, especially focusing on the poorest children.

BACKGROUND

Neonatal encephalopathy (NE) is a syndrome of disturbed neurological function presenting during the first days of life.[1] Hallmarks of NE include decreased level of consciousness or seizures, difficulty with initiating and maintaining respiration, and altered tone and reflexes.[1] Intrapartum-related hypoxia-ischaemia is the most common cause of NE and one of the top three causes of neonatal death globally.[2] Nearly half of the survivors of intrapartum-related NE risk neurodevelopmental disability including cerebral palsy (CP), intellectual impairment, deafness and blindness.[2 3] These risks are related to the severity of encephalopathy commonly graded as mild, moderate or severe, or grade I, II, III, respectively, based on early neurological examination.[4] Intrapartum-related NE is a term primarily used in reference to term and near-term infants.[1]

The most recent systematic review and meta-analysis from 2013[3] estimated 1.15 million cases of intrapartum-related NE globally per year resulting in 287 000 neonatal deaths and 233 000 moderate or severe disabilities: 96% occurred in low-income and middle-income countries (LMICs).[3] Given global increase in facility deliveries[5] and improved neonatal resuscitation[6] during the decade that has elapsed since, the situation has likely

changed. Without data, though, the task of the policymakers becomes near impossible. Reducing the burden of intrapartum-related NE is one of the key factors for achieving the Every Newborn Action Plan.[7] We, therefore, conducted a systematic review of intrapartum-related NE in LMICs with the objective of quantifying the following parameters: (1) incidence, (2) neonatal mortality and (3) neurodevelopmental outcomes at follow-up of ≥1 year.

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020[8] guidelines were followed and the study protocol was registered beforehand in PROSPERO database (CRD42020177928).

Eligibility criteria

Types of reports

All article types (observational and trial based) providing information on incidence, neonatal mortality or childhood neurodevelopmental outcomes of NE in humans were considered for inclusion. Qualitative studies, reviews, protocols, conference abstracts, editorials and opinion pieces were excluded.

Additional study characteristics

Only data from LMICs classified by World Bank country and lending groups at the median year of data collection were considered.[9] Only reports published after 1 November 2009 were included as this was the last date searched by Lee *et al* in their previous review[3] and as changes in peripartum care reduce the relevance of older studies.[5 6] No language restrictions were applied.

Types of study participants

Neonatal encephalopathy

NE was defined clinically as disturbed neurological function diagnosed using criteria proposed by Sarnat and Sarnat or another validated scale within 24 hours of birth.[4] A cut-off of 24 hours was selected to ensure early onset of symptoms commensurate with a hypoxic-ischaemic origin while acknowledging that the symptoms evolve over the first week of life.[4] Due to limited availability in LMICs, electroencephalographic confirmation and neuroimaging were not mandated.

Relation to intrapartum events

Evidence of intrapartum hypoxia-ischaemia was required for inclusion to distinguish from other similar clinical phenotypes.[10] Any of the following parameters was accepted for inclusion[1 11]:

- Abnormal umbilical cord blood or neonatal blood sample within 1 hour of birth (pH ≤7.1 or base excess ≤ −12 or lactate ≥6).[11]
- Apgar score ≤5 at 5 or 10 min.[11]
- Ongoing neonatal resuscitation at 5 or 10 min.[11]
- No cry from baby at 5 or 10 min.

Studies where stated hypoxia-ischaemia criteria were not fully concordant, but sentinel data were provided were discussed and decided case by case.

Gestational age

Gestational age limit was set to ≥35+0 weeks defined by last menstrual period, first trimester ultrasound, fundal height or Ballard score.[1 11] Lack of data on gestational age or mixing term and preterm infants <35 weeks of gestation in the report led to exclusion of the study to avoid contamination by non-hypoxic-ischaemic preterm brain injury.[12]

Additional exclusion criteria

Studies reporting NE due to other specified causes, such as hyperbilirubinaemia, and those where the whole cohort had some specific risk factor such as maternal hypertension rendering the sample non-representative of the normal population were excluded.

Types of outcomes

Reports were included if they included data on one or more of the outcomes below regardless of the original study purpose.

Inclusion criteria for objective 1

Main outcome was incidence of intrapartum-related NE in a birth cohort of a defined size regardless of the denominator used.

Inclusion criteria for objective 2

Main outcome was incidence of mortality in children with intrapartum-related NE either during the neonatal period (first 28 days of life) or until discharge from hospital.

Inclusion criteria for objective 3

Main outcome was incidence of death or moderate to severe disability at follow-up of 1–17 years defined similar to a previous systematic review[11] as any grade of CP, intellectual impairment (IQ≥2 SD below mean), blindness (vision<6/60 in both eyes), or developmental delay using a validated instrument.[13] In difference to Jacobs *et al*,[11] any form of deafness was considered and in studies using Bayley Scales of Infant and Toddler Development version II (BSID-II) cut-off of < −2 SD or <70 was used to define moderate to severe disability whereas in BSID-III, < −1 SD or <85 was used for the same as these have been found to be equivalent.[14]

Secondary outcomes were CP, developmental delay assessed with any validated developmental assessment tool,[13] blindness, deafness, epilepsy and neuropsychiatric disorders. Reports without developmental assessment were excluded.

Information sources and search strategy

The following databases were interrogated with the help of a librarian at Uppsala University, Sweden: Ovid MEDLINE, Cochrane, Web of Science and WHO Global

Index Medicus. Search terms related to neonate AND encephalopathy AND LMIC using the Cochrane EPOC LMIC filter version 3 were combined, and the complete searches are presented in online supplemental table 1. This search strategy had not been previously validated. A search was performed for dates 1 November 2009 to 10 June 2020 and this was later updated on 18 November 2021.

Personal records and reference lists of related reviews were hand searched for further publications.[11 15–29]

Study selection

Records identified were exported to Zotero reference management software (V.5.0.96.3, Roy Rosenzweig Center for History and New Media, Virginia, USA) for removal of duplicates and then transferred to Rayyan (Rayyan Systems, Cambridge, Massachusetts, USA) for blinded screening of title and abstract by two independent reviewers (AJK and SW). Screening questions based on inclusion and exclusion criteria were developed and piloted a priori (online supplemental figure 1). Disagreements were discussed between the two reviewers. Google Translate was used for translation of abstracts when necessary. Full-text articles of records included in the first stage were retrieved and, when not found, the first authors were contacted via email or, when email was not available, via ResearchGate (ResearchGate, Germany) to request access. If no answer was received within 1 month, the article was excluded.

Full-text screening was done similarly using a prepiloted flow chart (online supplemental figure 2) with results independently recorded on Excel sheets (V.2108, Microsoft, USA). Results were compared and disagreements solved with an arbitrator (NB). Kappa score was calculated to quantify the level of agreement between the reviewers. Reasons for study exclusion in full-text screening stage were recorded in online supplemental table 2). No contact was made with authors to request missing, ambiguous or unprocessed data. If several reports using data from the same study patients were identified, only the report with most complete data was included. Reviewers were not blinded to report authors, institutions or journals. Articles written in languages not understood by the review team were translated into English by people fluent in the language.

Data collection process and data items

Study data were extracted by single reviewer (AJK) on an Excel sheet. Unclear cases were discussed with a second reviewer (NB).

The following background data were recorded: first author and publication year; country/ies; World Bank country income group (low, lower middle or upper middle)[9] and national neonatal mortality rate (NMR, low<5/1000, mid 5–15/1000 and high >15/1000 live births)[30] at median year of data collection; whether a population or hospital-based study; level of hospital; study design; case definition of NE; definition of intrapartum hypoxia-ischaemia; gestational age; exclusion criteria; number of cases classified as mild, moderate and severe NE; sex; type of intervention provided during neonatal period.

In terms of denominator (objective 1), we accepted both term live births and all births during the study period. Numerators for objective 2 were: number of deaths, duration of follow-up and attrition rate and for objective 3: the number of deaths; length of follow-up; attrition rate; definition(s) of abnormal neurodevelopmental outcome(s) and number of children with abnormal outcome(s). Neurodevelopmental outcomes were subcategorised by type when possible.

All outcome data were disaggregated by the severity of intrapartum-related NE when possible.[4] Data on intervention and control arms in trials were collected separately. One report could contribute data to several objectives.

Risk of bias in individual studies

Risk of bias was assessed by discussion between two reviewers (AJK and SW) using the Newcastle Ottawa Scale for cohort studies.[31] The original tool was modified by removing questions related to comparability of cohorts. The modified version had two questions related to selection of the cohort and three related to outcome assessment with each question awarded maximum one star (table 1, online supplemental table 3).

Synthesis of results

We expected substantial clinical and methodological heterogenicity between the included studies whereby narrative synthesis was prioritised. This included describing the methodological characteristics of each study, their settings and individual strengths and limitations.[32 33] Particular attention was paid to comparison of study findings between different geographical and economic contexts.

The three objectives of the review guided grouping of the reports into tables and figures. Forest plots of the prevalence of main outcomes with point estimate and 95% CIs calculated by Freeman-Tukey double arcsine transformation were presented.[34] Inverse variance of heterogenicity model was chosen for meta-analyses as it is suitable for pooling data from heterogeneous studies of varying sizes.[35] All analyses were made by using MetaXL V.5.3 (EpiGear International, Sunrise Beach, Queensland, Australia) add-in in Excel. For objective 1, a population-based rather than hospital-based incidence was mandated for meta-analysis due to wide context related variability. For objectives 2 and 3, data were separated by neonatal intervention status and duration of follow-up.

Subgroup analyses by grade of intrapartum-related NE were planned a priori. However, as limited data were available, we combined grades II and III together. Statistical heterogenicity was analysed with I^2 analysis and >50% considered a sign of high heterogenicity in which case further subgroup analyses post hoc were considered. Sensitivity analysis of stepwise removal of each study

Table 1 Overview of the included reports disaggregated by type(s) of outcome(s) reported

Author, reference, year	Country	Study type	Intervention	Cases	NOS
Incidence					Max 2+3
Yang, 2019[48]	China	Cohort	Unclear	262	2+0
Incidence and neonatal mortality					Max 2+3/2+3
Horn, 2013[47]	South Africa	Retrospective observational	Unclear	110 *	2+1/1+1
Moshiro, 2019[39]	Tanzania	Prospective observational	NT	146	0+1/0+2
Niaz, 2021[50]	Pakistan	Prospective observational	Unclear	122†	1+1/0+2
Incidence, neonatal mortality and developmental outcome					Max 2+3/2+3+3
Lally, 2014[38]	India	Prospective observational	TH in 31%	54	0+2/0+2+2
Neonatal mortality					Max 2+3
Aly, 2015[72]	Egypt	RCT	TH+Melatonin Vs. TH	30	0+3
Bharadwaj, 2012[73]	India	RCT	TH vs NT	130	0+2
Biselele, 2013[37]	Congo DR	Prospective observational	NT	44	0+2
Biselele, 2020[74]	Congo Dr	Pilot/case-series	2-Iminobiotin	7	0+2
Biselele, 2018[45]	Congo Dr	Prospective observational	NT	57	1+2
Biselele, 2014[57]	Congo Dr	Prospective observational	NT	19	0+1
Bozkurt, 2021[75]	Turkey	Retrospective observational	TH	166	0+1
El Shimi, 2014[51]	Egypt	RCT	EPO vs TH vs NT	30	0+2
Enweronu-Laryea, 2019[54]	Ghana	Cohort	Passive TH	13	1+1
Hassanein, 2017[55]	Egypt	Case-Control	Unclear	20	0+1
Horn, 2010[52]	South Africa	Case Series	TH	5	0+2
Horn, 2012[76]	South Africa	Case Series	TH	14	0+2
Kinoshita, 2021[77]	Brazil	Retrospective observational	TH (FGP)	71	0+1
Martínez-Hernández, 2020[78]	Mexico	Before-After Study	EPO+TH (WBC vs SHC)	12	0+1
Oliveira, 2018[79]	India	Prospective observational	TH	82	0+2
Surmeli Onay, 2021[80]	Turkey	Before-After Study	TH vs TH+Aminophylline	34	0+0
Prashantha, 2019[81]	India	Before-After Study	TH (PCM vs FGP)	62	0+1
Shabeer,‡§ 2017[82]	India	Before-After Study	TH (PCM vs FGP)	68	0+1
Shrestha, 2020[83]	Nepal	Prospective observational	NT	20¶	0+1
Tanigasalam, 2016[56]	India	RCT	TH (FGP) vs NT	120	0+2
Thomas,** 2018[84]	India	Prospective observational	TH (PCM)	103	0+1
Umran, 2016[40]	Iraq	Case- Control	NT	29	0+1
Variane, 2017[85]	Brazil	Prospective observational	TH	17	0+0
Yang and Li, 2020[86]	China	RCT	TH (48 hours) vs TH (72 hours) vs NT	92	0+2
Neonatal mortality and developmental outcome					MAX 2+3+3
Aker,‡ 2021[87]	India	RCT	TH (PCM) vs NT	49	0+3+3
Catherine,**†† 2021[88]	India	RCT	TH (PCM) vs NT	158	0+1+3
Catherine,**†† 2020[89]	India	RCT	TH (PCM) vs NT	158	0+1+3
Celik,‡‡ 2015[53]	Turkey	RCT	TH SHC vs WBC	7	0+2+3
Celik,‡‡ 2016[90]	Turkey	RCT	TH SHC vs WBC	29	0+2+3
Das, 2017[91]	India	RCT	TH (FGP) vs NT	60	0+3+3
Gucuyener, 2012[60]	Turkey	Case Series	TH	10	0+3+2

Continued

Table 1 Continued

Author, reference, year	Country	Study type	Intervention	Cases	NOS
Jia, 2018[41]	China	Non-random trial	TH early vs TH late vs NT	152	0+2+2
Khuwuthyakorn, 2021[92]	Thailand	Observational	TH	23	0+1+3
Malla, 2017[59]	India	RCT	EPO vs NT	100	1+3+3
Maoulainine, 2017[49]	Morocco	Non-random comparison	TH 50%, NT 50%	38	1+1+1
Perez, 2018[93]	Brazil	Cohort	TH (LFU)	53	0+1+3
Procianoy, 2020[94]	Brazil	Prospective observational	TH	72	0+2+3
Sun, 2012[44]	China	RCT	TH vs NT	51	1+3+3
Thayyil, 2021[46]	3 Countries	RCT	TH vs NT	408	1+1+2
Valera, 2015[95]	Argentina	Observational	TH	27	0+3+3
Zhou,§ 2010[42]	China	RCT	TH vs NT	194	1+1+2
Zhu, 2009[96]	China	RCT	EPO vs NT	167	1+2+2
Zou,§ 2019[43]	China	RCT	TH vs NT	99	1+2+3
Developmental outcome					MAX 2+3
Ballot, 2020[58]	South Africa	Cohort	TH in 58%	99	0+2
Charki, 2020[97]	India	Non-Random Comparison	TH vs NT	210	0+1
Koshy,§ 2011[98]	India	Prospective observational	TH	20	0+2
Mbatha, 2021[99]	South Africa	Retrospective observational	TH in 73%	155	0+2
Weng, 2021[100]	China	Before-After	TH vs NT	61	0+3

NOS = Newcastle-Ottawa Scale of bias evaluation consisting of two questions related to selection of cohort and three questions related to reporting of outcome (see online supplemental table 3).
*Included several definitions of hypoxia-ischaemia and NE. N=110 = widest definition available.
†Recruited 45 children with gestational age 34+0…36+6 that were excluded from the neonatal mortality analysis.
‡Potential partial overlap between Shabeer *et al*[82] and Aker *et al*[87].
§Koshy 2011 presents follow-up data for some of the children that were potentially included by Shabeer *et al*[82].
¶Recruited 84 children with Apgar <7 at 5 min. Out of those, 20 fulfilled the inclusion criteria of pH<7.05 and only those were included.
**Potential partial overlap between Thomas *et al*[84] and Catherine *et al*[89] and Catherine *et al*[88]
††Same patients in both reports by Catherine, but different outcomes are reported.
‡‡Mostly same patients in both reports by Celik. Only cases with grade I were included from Çelik *et al*[53] as the outcomes of grade II–III cases were reported in Celik *et al*[90] that includes five additional children.
EPO, erythropoietin; FGP, frozen gel packs; LFU, laminar flow unit; NT, standard care with normothermia; PCM, phase-changing material; RCT, randomized-controlled trial; SHC, selective head cooling; TH, therapeutic hypothermia; WBC, whole body cooling.

were done for all estimates to see if any single study was inflicting disproportionate effect on the results.

Risk of bias across studies

A funnel plot of studies included for the forest plots was examined as an indication of potential publication bias.[36]

Patient and public involvement

No patients were involved in the design and conduct of this study.

RESULTS

Study selection

The final search produced 1750 records and after removing 417 duplicates and 11 reports published prior to November 2009, 1322 unique reports remained (figure 1). All articles included an abstract in English. There were 121 cases of conflicts between the reviewers during title and abstract screening, which were solved by discussion. The 269 reports identified were sought for retrieval and complemented by 104 reports found from other sources.

Screening of full text resulted in 53 reports from 51 studies being included in the review. There were 35 cases of conflict between the reviewers, which were solved by arbitration (88.2% agreement, Cohen's kappa=0.55, moderate agreement). Translation into English was done for 13 reports (8 from Chinese, 2 from Turkish and 1 from Russian). Reasons for excluding reports in the full-text screening stage are presented in online supplemental table 2.

Study characteristics

Characteristics of the included reports are presented in table 1. The studies included 4181 children with intrapartum-related NE. When looking at only those nine

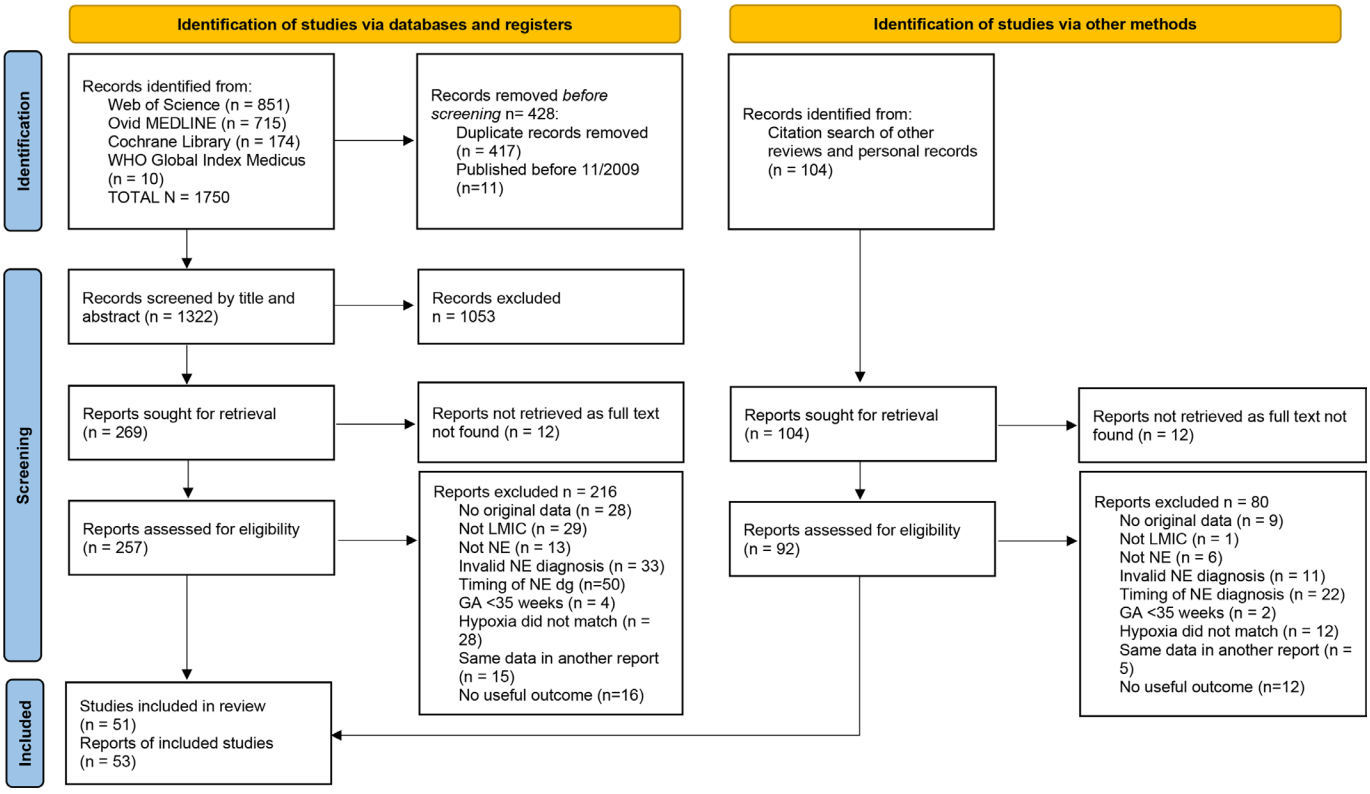

Figure 1 PRISMA 2020 flow chart of study inclusion, from Page *et al*.[8] PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. GA, gestational age; LMIC, low- and middle-income country; NE, neonatal encephalopathy.

studies[37–45] that recruited and reported all NE grades indiscriminately, the distribution of severity was 334/858 (38.9%) mild, 292/858 (34.0%) moderate and 232/858 (27.0%) severe NE. Sex of the newborn was reported in 38 studies and pooled prevalence of male sex was 63% (95% CI 58% to 69%, I^2=80%) (online supplemental figure 3).

The studies included data from 18 countries with 14 reports from Africa, 6 from Americas, 34 from Asia and none from Oceania or Europe with Turkey classified as part of Asia. Low-income countries were presented in 5 reports, lower-middle in 23 reports and upper-middle-income countries in 25 reports. National NMR was low in 1, medium in 24 and high in 27 reports at the time of data collection. One study presented data from both from a low NMR setting (Sri Lanka) and high mortality settings (Bangladesh and India)[46] (online supplemental table 4).

The vast majority (45/51) of studies were conducted in either university or tertiary hospitals and only two studies from China and South Africa, respectively, claimed to be population-based.[47 48] Inclusion criteria used in the individual studies varied widely and are presented in online supplemental table 4. Therapeutic hypothermia was routinely used in 21 and trialled in 18 of the 53 reports.

Bias evaluation of the included studies

Results of the risk of bias evaluation are presented in table 1 and online supplemental table 3. No report achieved full scores. Major shortcomings were identified in the representativeness of the data with only three papers scoring a star in this question.[47–49] Reports about neonatal mortality and developmental outcomes had better scores for case ascertainment than those where incidence of intrapartum-related NE was examined. About half of the reports had issues with incomplete follow-up, which might further bias the results.

No obvious asymmetry implying publication bias was observed in the funnel plots presented in online supplemental figures 4 and 5, but the results were scattered due to high heterogenicity.

Results of individual studies and syntheses

Studies reporting incidence

Data on incidence of intrapartum-related NE are presented in table 2. Incidence of all grade NE ranged from 20.3/1000 live births[50] to 1.5/1000 term live births[48] depending on study setting and location (median 4.7/1000 live births, five studies). Only two population-based studies were included whereby no meta-analysis was conducted.[47 48] One was examining different definitions of intrapartum-related NE in Cape Town, South Africa, and in this paper the incidence of any grade NE ranged from 2.3 to 4.3 per 1000 live births.[47] The second presented data from 27 hospitals in China with incidence of any grade of NE 1.5 per 1000 live births.[48]

Table 2 Studies reporting incidence of intrapartum-related neonatal encephalopathy

Author (ref)	Country	Definition of denominator	Reported incidence		Incidence/1000
Horn, 2013[47]	South Africa	All live births (incl. home births)	All grades	N/A	2.3…4.3/1000
			Grade I	N/A	0.4…1.3/1000
			Grades II–III	N/A	1.5…3.7/1000
Lally, 2014[38]	India	All births in the hospital	All grades	54/11 532	4.7/1000
Moshiro, 2019[39]	Tanzania	All live births in the hospital	All grades	146/10 320	14.1/1000
			Grade I	113/10 320	10.9/1000
			Grade II	16/10 320	1.6/1000
			Grade III	17/10 320	1.6/1000
			Grades II–III	33/10 320	3.2/1000
Niaz, 2021[50]	Pakistan	All births in the hospital	All grades	122/5986	20.3/1000
			Grade I	61/5986	10.2/1000
			Grade II	42/5986	7.0/1000
			Grade III	19/5986	32./1000
			Grades II–III	61/5986	10.2/1000
Yang, 2019[48]	China	Term live births in the 27 hospitals	All grades	262/175 223	1.5/1000

N/A, Not Available.

The hospital-based studies on incidence came from India,[38] Pakistan[50] and Tanzania[39] all of which had high national NMR at the time of data collection.

Studies reporting neonatal mortality

Neonatal mortality associated with intrapartum-related NE was reported in 45 studies (online supplemental table 5). In total, 636 of the 3307 (19.2%) included neonates died. Mortality ranged from 19/30 (63.3%) in a small Egyptian trial comparing conventional care with therapeutic hypothermia and erythropoietin[51] to 0/5 in a case series of therapeutic hypothermia in South Africa[52] and 1/51 (2.0%) in a cooling trial in a tertiary centre in China.[44]

There were limited data available for neonatal mortality disaggregated by severity of NE. Only 10 reports included data on mortality associated with grade I intrapartum-related NE.[37–40 44 45 53–56] In total, 22/236 (9.3%) mild NE cases died. Four reports included at least one death in patients with mild NE.[39 40 45 57]

Figure 2 presents neonatal mortality in infants with grade II and III intrapartum-related NE. Data were split by intervention status during neonatal period. Pooled mortality in the conventional care group was 35.7% (95% CI 14% to 41%, I^2=80%, 17 studies) and in the intervention group 15.8% (95% CI% 11 to 22%, I^2=90%, 33 studies).

Results of the post hoc subgroup analyses of neonatal mortality by national NMR and World Bank country income group were heterogenous (online supplemental figure 6). Sensitivity analysis with stepwise removal of studies only changed the pooled point estimates by few percentage points.

Studies reporting neurodevelopmental outcome

Neurodevelopmental follow-up of at least 1 year was conducted in 23 studies (online supplemental table 6). No studies continued follow-up beyond 3.5 years precluding inference on neuropsychiatric conditions. A combined outcome of death or moderate to severe neurodevelopmental disability was reported in 19 studies with 1595 children with any grade of NE of whom 712 (44.6%) had adverse outcome.

Only three studies provided data on outcomes of children with mild NE.[42 53 58] None of the seven children treated with normothermia in Turkey had death or moderate to severe disability at 12 months' age.[53] In a therapeutic hypothermia trial in China, 6 out of 19 cooled and 7 out of 15 normothermic infants had moderate intellectual disability (Gesell Child Development Age Scale 70–84) at 18 months' age while none died or had severe disability.[42] A cohort study from South Africa reported that 1 out of 14 infants with mild NE developed CP at follow-up of mean 14.3 months.[58]

Figure 3 shows the combined outcome of death or moderate to severe developmental disability in children with grade II or III intrapartum-related NE from 16 studies where these data could be extracted. All these studies were either intervention trials or used therapeutic hypothermia as part of routine care and the results are split by intervention status and duration of follow-up. Children in conventional care group had somewhat higher incidence of the combined outcome than those in the intervention group at 1–2 years' follow-up (52% (95% CI 44% to 66%, I^2=61%, 7 studies) vs 40% (95% CI 29% to 52%, I^2=84%, 13 studies)). Only three studies had follow-up longer than two or more years. No single study had overwhelming impact in the results in a sensitivity analysis.

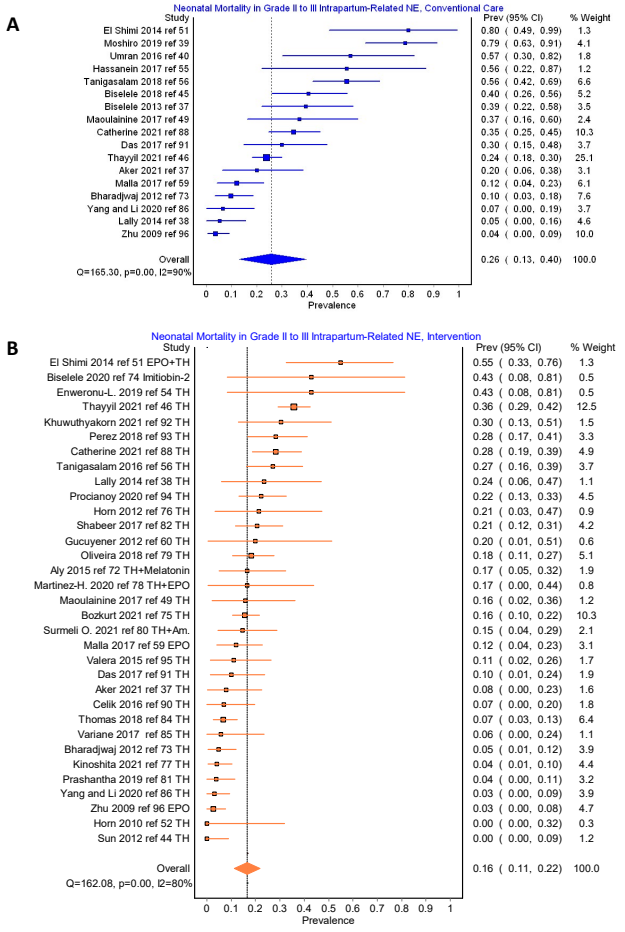

Figure 2 Prevalence of neonatal mortality in children with grades II–III intrapartum-related neonatal encephalopathy (NE) in (A) conventional care group, (B) intervention group. Prevalence of 1.0 = 100% mortality. Am, aminophylline; EPO, erythropoietin; TH, therapeutic hypothermia.

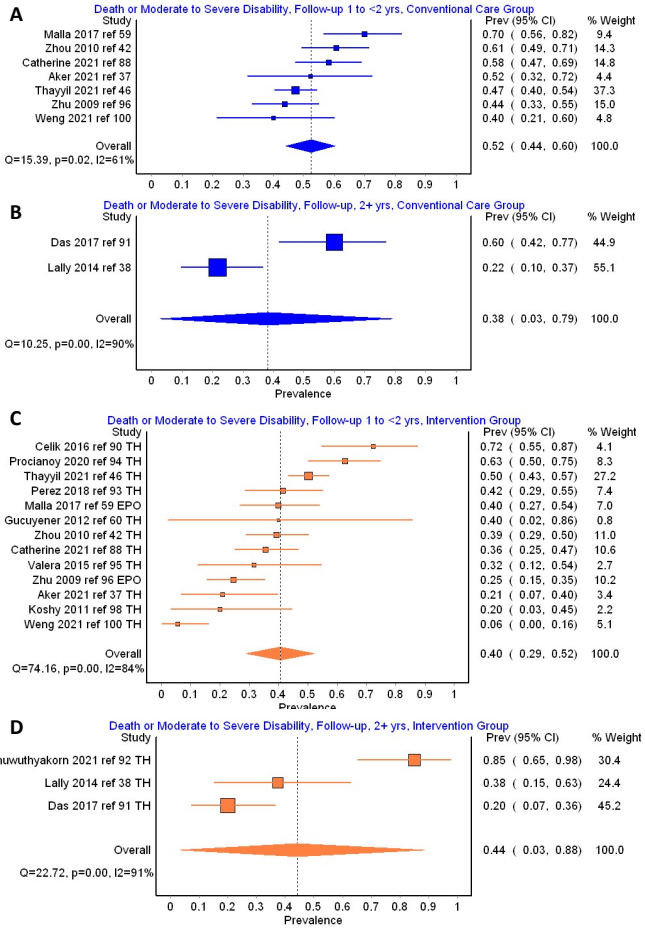

Figure 3 Prevalence of death or moderate to severe neurodevelopmental disability associated with grades II–III intrapartum-related neonatal encephalopathy in (A) conventional care group with follow-up 1 to <2 years, (B) conventional care group with follow-up ≥2 years, (c) intervention group with follow-up 1 to <2 years, (D) intervention group with follow-up ≥2 years. Prevalence of 1.0=100% adverse outcome. EPO, erythropoietin; TH, therapeutic hypothermia.

CP in survivors was evaluated in 11 reports (914 children, mean incidence 16.7%, online supplemental table 6 and online supplemental figure 7). In infants surviving grades II–III intrapartum-related NE, incidence of CP ranged from 29/84 (34.5%) at mean age of 19 months in a trial of erythropoietin in India[59] to 3/38 (7.9%) at mean age of 3.4 years in another Indian cohort where one-third of the children were treated with hypothermia.[38] In one Turkish case series, none of the three children surviving therapeutic hypothermia treatment had CP by the age of 12 months.[60]

DISCUSSION

This systematic review identified 53 reports from 51 studies reinforcing the scale of intrapartum-related NE in terms of burden of disease, death and disability in LMICs.

Estimates of NE incidence ranged from 1.5 to 20.3/1000 births comparable to 2013 review by Lee *et al*.[3] A study from China reported low NE incidence at 1.5/1000 term live births[48] resembling levels seen in high-income countries with low NMR.[3 61] Low incidence combined with excellent outcomes reported in other studies included in the review is in line with recent Global Burden of Disease data indicating that the burden of NE in China is rapidly decreasing[62] with the rider that assessment bias cannot be ruled out in the register based incidence study.

NE-related neonatal mortality and adverse neurodevelopmental outcome were associated with all grades of intrapartum-related NE. There was scarcity of data on grade I NE, but the result shows that in LMIC settings, even mild NE carries a risk of neonatal mortality in addition to early disability reported previously from high-income settings.[63] We do not have the data to speculate about later childhood neuropsychiatric issues and future studies should extend their follow-up to include also these outcomes.[64]

Studies reporting data on combined grades II–III intrapartum-related NE produced the most comparable estimates of neonatal mortality and neurodevelopmental outcomes. Similar to Lee *et al*,[3] the highest mortality was

seen in studies from high national NMR settings when no neuroprotective interventions during the newborn period were provided (pooled mortality 32% (95% CI 16% to 49% vs 28% (95% CI 19% to 37%) reported by Lee *et al*[3]).

The combined outcome of death or moderate to severe neurodevelopmental disability occurred on average at similar rate as in the original cooling trials, where its pooled incidence was 31.7% in the intervention arm and 61.4% in the control group.[11] Overall, our review showed better outcomes in studies where infants received therapeutic hypothermia or other neuroprotective interventions during neonatal period, but the pooled results in figures are not comparable as different studies were included in each group. This area is currently highly controversial in the light of the HELIX multicentre trial where cooling was predictive of a significantly neonatal higher mortality,[46] the interpretation of which is causing difficulty for institutions and policy makers. Several meta-analyses with conflicting results have been recently published on efficacy of therapeutic hypothermia in LMICs.[16 65 66]

Though we cannot extrapolate from the data exactly which single interventions will have the greatest impact on neonatal and childhood neurodevelopmental outcomes, it is likely, that a combined approach including improved antenatal care, adolescent health, family planning and access to hospital delivery centres rather than a silo-driven policy will be required to reduce the disease burden.[7]

Strengths

Our review has several strengths, including up-to-date data, PRISMA adherence, clear a priori assessment processes and a wide geographical spread of studies.

Limitations

NE is a challenging diagnosis and only a minority of papers reported standardisation of the criteria. We cannot be sure that all the infants fulfilling the inclusion criteria were true cases of intrapartum-related NE but tried to minimise this by only including studies where intrapartum hypoxia-ischaemia could be presumed with a high degree of certainty. Indirectly, this led to exclusion of studies from lower levels of care with limited access to physicians trained in NE assessment. Remaining heterogenicity in inclusion criteria of individual studies partly explains the wide differences in the reported outcomes.

Only two of the included studies were population-denominator based and the substantial heterogenicity in outcomes is likely to reflect both true variance between populations and methodological differences. The meta-analysis results should, therefore, be interpreted with caution. The preponderance of intervention studies from tertiary level referral hospitals from middle-income countries is likely to have further limited generalisability, but on the other hand use of therapeutic hypothermia is already widespread in such settings.[67–70]

Further limitation on interpretation of the forest plots is that the Freeman Tukey back-transformation is prone to producing misleading results when sample sizes vary greatly, but we did not observe such issue in our data.[71]

Lastly, although we conducted a systemic search of databases, 12 of the 53 included articles were identified from other sources indicating that the search terms used were not optimal and potential articles might have been missed. The Cochrane EPOC LMIC filter has not been validated and NE has no MeSH term whereby terms related to hypoxia-ischaemia were used instead. Chinese language databases and grey literature were not searched.

CONCLUSION

Though there has been progress in some regions, the incidence, neonatal mortality and morbidity of intrapartum-related NE has in most LMICs been static in the 10 years since the last review.

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