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Scoping review of evidence for managing postnatal hypoglycaemia

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ABSTRACT

Objectives To identify what is known empirically about the screening, treatment and harm of exposure to neonatal hypoglycaemia.

Design Scoping review that applied a preregistered protocol based on established frameworks.

Data sources Medline and Embase, up to 12 May 2020.

Study selection Comparative and case-series studies, as well as guidelines, published in English or French, on the topic of immediate inpatient postnatal glucose screening in newborns.

Data gathering Article selection and characterisation were performed in duplicate using predefined data extraction forms specific to primary studies and guidelines.

Results 12 guidelines and 74 primary studies were included. A neurodevelopmental outcome was primary in 32 studies: 30 observational studies followed up posthypoglycaemic, and the 2 intervention studies included 1 randomised controlled trial (RCT) about treatment thresholds. Three other RCTs assessed dextrose gel (two) and oral sucrose (one). 12 of 30 studies that evaluated non-neurodevelopmental primary outcomes were intervention studies. Only one cohort study compared outcomes in screened vs unscreened newborns. The guidelines did not arrive at a consensus definition of postnatal hypoglycaemic, and addressed potential harms of screening more often than primary studies.

Conclusions The primary literature that informs hypoglycaemia screening is a series of studies that relate neurodevelopmental outcomes to postnatal hypoglycaemia. Further research is needed to better define an optimal threshold for hypoglycaemia that warrants intervention, based on long-term neurodevelopmental outcomes and a better delineation of potential screening harms.

INTRODUCTION

Hypoglycaemia screening in at-risk babies is a well-accepted practice in the third of babies with risk factors;[1–5] however, screening approaches vary in the context of ongoing controversy around diagnosis and treatment.[6] Screening for postnatal hypoglycaemia aims to avoid acute and long-term hypoglycaemia complications such as seizures and neurodevelopmental delay;[7] however, recognition that screening is not entirely benign[8] means asymptomatic, low-risk babies are not

Strengths and limitations of this study

► Broad literature search.
► Transparent and systematic application of established methodological frameworks.
► As a scoping study, did not consider study results or assess the quality of the evidence, so does not provide synthesised answers to inform clinical decision making.
► The analysis considered only primary study outcomes as opposed to all study outcomes.
► Language restrictions may have missed a small number of studies.

screened. Ongoing debate around the justification for newborn screening in general cites concerns around costs, the nature of subsequent treatment and consent.[9] There is no consensus regarding the threshold for hypoglycaemia risk that warrants screening, nor the hypoglycaemia threshold that requires intervention. Ideally, both values would be informed by a balance of demonstrated benefits and harms.

A recent systematic review on neonatal hypoglycaemia (NH) and neurodevelopment found that NH was associated with impairment that becomes fully apparent after school age is reached.[10] However, the latest broad NH-evidence review is more than a decade old.[11]

This scoping review provides an updated description of the literature on NH harms, and NH screening and treatment. The objectives of this scoping review are to better understand the basis in evidence for different approaches to managing NH, and guide future NH research. The scoping-review approach allowed for a characterisation of the relevant supporting evidence, as well as gaps in the literature. Guideline review provided an overview of different approaches to managing NH, which further contextualised this evidence summary.

METHODS

The scoping literature review used established methodological frameworks.[12 13 14]

Patient and public involvement

Patients and the public were not involved in this study's design, conduct or dissemination plans.

Search strategy

The peer-reviewed search strategy[15] searched MEDLINE and Embase via the Ovid platform on 12 May 2020. The main search concept was NH, along with search filters for systematic reviews, guidelines, clinical trials and observational studies, built on established filters from the Canadian Agency for Drugs and Technologies in Health.[16] Based on findings from preliminary searches for systematic reviews and guidelines, the final search limited systematic reviews from 2005 to present, but applied no other date limits. The search was limited to English or French language publications, and omitted conference abstracts. Reference lists of systematic reviews and guidelines were reviewed manually to identify potentially relevant articles.

Study selection

Three reviewers (AM, LM and JH) independently screened study titles and abstracts in duplicate. Disagreements around eligibility could be resolved by the third reviewer: and if needed, by a fourth (MS).

Included studies involved human newborn glucose screening in the perinatal hospital setting, with onset of hypoglycaemia at less than 48 hours of life. Potential interventions and exposures included hypoglycaemia, screening for hypoglycaemia, and treatment for hypoglycaemia. Eligible outcomes were related to either health (eg, seizures) or resource use (eg, length of stay).

All comparative study designs were included: that is, RCTs, cohorts, case–controls, pre–post and interrupted time-series studies. Since we anticipated a limited amount of research on NH with non-neurodevelopmental outcomes, case studies with greater than five subjects and non-neurodevelopmental outcomes were included. Thus, case series (where no exposure-based comparison was possible) with both a neurodevelopmental and a non-neurodevelopmental outcome were included; however, only primary study outcomes were considered. All other case series' were excluded. Primary outcomes were as specified in the study reports: based on the data extractors' impressions when unspecified.

We envisioned four main categories of primary comparative studies:

1. Developmental outcomes of hypoglycaemia.
2. Non-developmental hypoglycaemia-related outcomes.
3. Outcomes of hypoglycaemic treatment versus no treatment.
4. Outcomes of hypoglycaemic screening (routine screening for NH based on predefined risk categories).

We also included national and international guidelines, programmes of care, treatment protocols, policy
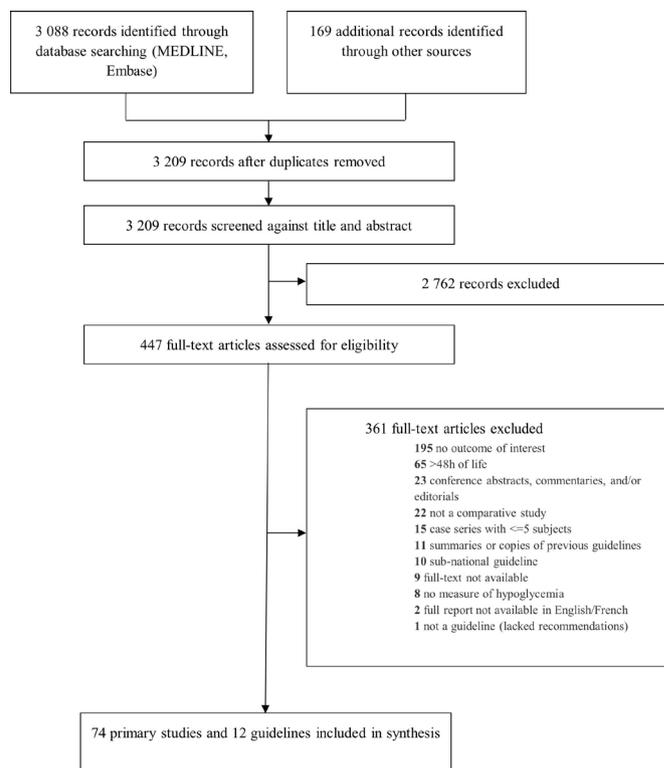

Figure 1 Screening and selection process.

statements and position statements that addressed NH. We excluded those lacking treatment recommendations and excluded summaries or copies of previous guidelines.[17] We excluded conference abstracts, commentaries, editorials and articles not available in English or French.

Data management software

Endnote tracked references and excluded duplicate articles. Covidence tracked article inclusions and exclusions.[18] We entered extracted data into Google sheets, using preset categories as much as possible.

Data extraction

Predefined data extraction forms specific to primary studies and guidelines were edited and used after pilot extraction. As is the norm for scoping reviews, we did not evaluate the risk of bias in the study findings, though we did employ the AGREE-II question about guidelines' use of systematic methods to search for evidence.[19] The three data collectors met regularly and reviewed their work on a 5% sample at each new step. Content analysis was used to analyse the data and identify emergent themes.

RESULTS
Primary studies

We included 74 primary studies (figure 1 and online supplemental table 1), primarily from the Organisation for Economic Co-operation and Development countries ('OECD'; 80% of studies). Their median publication date was 2012 (mean 2005; range 1965–2020). Three-quarters were controlled observational studies (table 1).

Table 1 Characteristics of primary studies

Total primary studies	n=74
Sample size: median, mean	
Study group (n=71)	58.5, 529.0
Control group (n=42)	70.0, 2579.9
Design (n=74)	
Cohort, prospective	47%
Cohort, retrospective	30%
Case series	9%
RCT	5%
Pre–post	5%
Case–control	3%
Funding source (n=31)	
Non-profit	68%
Industry	32%
Premature (n=43)	37%
Gestational age, mean weeks (n=45)	36.9
Birth weight: mean (n=45)	2773.8 g
Basis of hypoglycaemia diagnosis (n=71)	
Glucose value alone	86%
Glucose value and clinical signs	14%
Testing method (n=42)	
Laboratory	50%
Bedside	33%
Continuous glucose monitoring	7%
Laboratory and bedside	7%
Laboratory and continuous glucose monitoring	2%
Sample (n=13)	
Capillary	85%
Venous	15%
Both	0%
Sample assayed (n=11)	
Plasma	55%
Whole blood	45%
Screening Indication (n=75)*	
Infant of diabetic mother	37%
Small for gestational age	33%
Large for gestational age	28%
Premature birth	33%
Other (n=52)	
No reason for screening provided	69%
Symptomatic hypoglycaemia	21%
'High-risk infants'	13%
Blanket screening policy (all newborns)	12%
Asphyxia	10%
Sepsis	10%
Seizures	10%
Hypoxic ischaemic	10%

Continued

Table 1 Continued

Encephalopathy	8%
Poor feeding	8%
Respiratory distress	8%
Low Apgar score	6%

*Some studies counted in multiple categories.
RCT, randomised controlled trial.

Babies were typically early term (online supplemental figure 1) and studies' subjects on average were 56% male (n=60). In 86%, hypoglycaemia diagnoses were based on glucose levels alone. The most common hypoglycaemia threshold was 2.6 mmol/L (mean 2.22 mmol/L, median 2.4 mmol/L, n=67). Blood glucose was measured in the lab in 50% of reporting studies, at the bedside in 33.3%, both in the lab and at bedside in 7% and from continuous glucose monitors in 7%. Few studies reported whether sampling was capillary or venous; whole blood or plasma.

Neurodevelopmental studies

The 32 studies with a primary neurodevelopmental outcome were published between 1965 and 2020 (median 2010, mean 2002). Of these, 2 were interventional (1 randomised) and 30 observational (table 2). The mean sample size was 320; the total was 10 253. Study hypoglycaemia thresholds ranged from 1.11 to 2.8 mmol/L (mean 2.19, median 2.3, mode 2.6). Hypoglycaemia diagnosis was also based on symptoms in 4 of 32 reporting studies (with a mean publication date of 1984, and a mean hypoglycaemic threshold of 1.7 mmol/L).

Although three of the studies screened all newborns for hypoglycaemia, 19 of the studies screened newborns specifically for at least one of the most common indications: prematurity, small for gestational age (GA), large for GA or maternal diabetes. The other studies focused on babies who were compromised or potentially symptomatic.

The Bayley Scales of Infant Development III, Griffiths Scale of Mental Development, and Wechsler Intelligence Scale for Children were used most frequently (online supplemental table 2). Studies also addressed specific domains such as vision. Follow-up duration averaged 5.5 years, but spanned a range of 20 years; 12% of studies addressed the first year of life, 59% early childhood (2–5 years), 21% mid-childhood (6–11 years) and 3% early adulthood (18 years or older).

The two studies of treatment included a randomised controlled trial (RCT) of dextrose-gel treatment thresholds and psychomotor development at 18 months, and a prospective cohort study that related maternal glucose therapy in labour to neurobehaviour at 1–2 hours of age. Twenty-seven comparative exposure studies and three case series investigated neurodevelopmental outcomes with postnatal hypoglycaemia. One investigated glucose variation in the first 24 hours in hypoxic-ischaemic encephalopathy and neurodevelopment.

Table 2 Characteristics of primarily neurodevelopmental and non-neurodevelopmental studies

Primary studies: neurodevelopmental		Primary studies: non-neurodevelopmental	
Total	N=32	Total	N=30
Design		Design	
Cohort, prospective	56%	Cohort, retrospective	40%
Cohort, retrospective	25%	Cohort, prospective	33%
Case series	9%	Pre–post	13%
Case–control	6%	RCT	10%
RCT	3%	Case series	3%
Indications for screening	(n=32)*	Exposures and study design	(n=17)
Premature	40%	Hypoglycaemic neonates	47%
Small for gestational age	34%	Other exposures	53%
Large for gestational age	34%	Neonatal seizures	18%
Infant of diabetic mother	28%	Infants of diabetic mothers	6% each
Others:		Hypoglycaemia risk criteria	
Hypoxic ischaemic injury	6%	Hypoglycaemia and acidemia	
Symptomatic hypoglycaemia	6%	Blood glucose fluctuation	
At risk for neonatal encephalopathy	3%	Hypoxic-ischaemic encephalopathy	
Neonatal asphyxia†	3%	Screening for asymptomatic hypoglycaemia	
Neonatal convulsions	3%		
Other conditions (eg, poor feeding, respiratory distress, sepsis, intrauterine growth retardation, pregnancy-induced hypertension)	16%		
Screen all newborns	9%		
Outcomes	(n=32)*	Outcomes	(n=30)*
Neurodevelopmental impairment	75%	Admission rate	27%
Literacy and test scores		Seizures	17%
Establishment of neurodevelopmental	9%	Brain injury	13%
diagnoses‡	9%	Early frequent breastfeeding to prevent hypoglycaemia	13%
Executive dysfunction	6%	Breastfeeding rate	10%
Visual impairment	6%	Cost of treatment	7%
	9%	Mortality	3% each
	6%	Complications of continuous glucose monitoring	
	6%	Cardiothoracic abnormality	
		Inborn error of metabolism	
		Growth parameter abnormality	
		Intravenous dextrose treatment	
		Dextrose gel treatment	
		Intravenous bolus treatment	
		Hypoglycaemic relapse	
		Interventions and study designs	(n=12)*
		40% dextrose gel§	50%
		Altered breastfeeding	33%
		Intravenous Infusion	25%
		Toolkit creation§	8%
		Skin to skin	8%
		Oral sucrose	8%

*Some studies counted in multiple categories.
†Defined as two or more of: initial capillary or arterial pH <7.1, Apgar score <5 at 5 min, initial capillary or arterial lactate >7 mmol/L, abnormal neurology or clinical seizures.
‡For example, cerebral palsy, autism, mental retardation.
§One study had an unspecified intervention threshold.
RCT, randomised controlled trial.

Non-neurodevelopmental studies

Studies with a primary non-neurodevelopmental outcome were published between 1975 and 2020 (median 2016, mean 2011; 73% OECD). Thirty studies evaluated the relationship between NH and non-neurodevelopmental primary outcomes; 11 evaluated the relationship as a secondary outcome. Their mean sample sizes were 973 and 276 for the treatment and control groups. Study hypoglycaemic thresholds ranged from 1.6 to 2.6 mmol/L (mean 2.34, median 2.4, mode 2.6); one study adjusted the threshold for birth weight. Twenty-one studies were cohort studies, and four were RCTs (table 2).

Aside from the case-series study, 17 studies explored exposures and 12 assessed different interventions (table 2). The following significant outcomes were measured only in observational studies: mortality, brain injury, inborn errors of metabolisms, and growth parameter abnormalities. Among the 17 exposure studies, outcomes included admission rates, brain injury, seizures, mortality and diagnosed inborn error of metabolism. One study of continuous glucose monitoring considered the parental perspective on such monitoring.

Six of the intervention studies were on carbohydrate gels: one oral sucrose; three intravenous infusions; four breastfeeding interventions; one toolkit creation and one skin to skin. The interventions that were assessed with RCTs were dextrose gels (two), oral sucrose (one) and altered intravenous infusion (one), with outcomes that included admission rates, treatment cost and intravenous treatment.

The follow-up duration for the non-neurodevelopmental studies was detailed in eight studies, and ranged from 7 days to 21 years. Interestingly, neonates with suspected brain injury outcomes were followed for the shortest duration: 7 days in two studies, 2 years in another and 5 years in the last study. In contrast, the follow-up duration for seizures outcomes was 1 year in one study, 2 years in one study and 21 years in another study.

Both neurodevelopmental and non-neurodevelopmental outcomes

Eight cohort studies and three case series studies focused equally on neurodevelopmental and non-neurodevelopmental outcomes. Their themes were outcomes of NH (n=7); glucose profiles with therapeutic hypothermia for hypoxic-ischaemic encephalopathy (n=1); NH-related events such as seizures (n=2); a central nervous system/ocular outcomes (n=1); and differentiation between symptomatic and asymptomatic hypoglycaemic (n=2).

Hypoglycaemia screening versus no screening

One cohort compared breastfeeding and formula supplementation in the first week in women with and without insulin-dependent diabetes mellitus (IDDM). Infants of women with IDDM had been placed separately in the neonatal unit after birth for observation of hypoglycaemia, though the method of screening was not described.

Table 3 Guideline overview

Total no of guidelines	n=12
Guideline types (n=12)	
Sponsored national	50%
Unsponsored international	33%
Sponsored international	17%
Definition of hypoglycaemia (n=12)	
Yes	75%
Unclear	17%
No	8%
Whom to screen	
Infant of diabetic mother	75%
Premature	75%
Small for gestational age	66%
Large for gestational age	58%
Intrapartum asphyxia, sepsis, Rhesus disease	8% each
Perinatal hypoxia-ischaemia, congenital heart disease, infection, hypothermia, intrauterine growth retardation, maternal risk factors	
Not specified	8%
Recommended glucose assays (n=9)	
Screen with point-of-care meter;* confirm with laboratory†	56%
Point-of-care glucose metre is sufficient*	22%
Laboratory† is preferred but point-of-care* an option for rapid results	11%
Laboratory† should be used for diagnosis	11%
Acute harms of hypoglycaemia (n=5)	
Seizures	80%
Visual loss, apnoea, cyanosis, coma	40% each
Hearing loss, brain injury, lethargy, irritability, hypotonia, poor suck, tachypnoea, bradycardia, hypothermia	20% each
Long-term neurodevelopmental harms (n=7)	
Cognitive dysfunction	57%
Motor dysfunction	43%
Visual dysfunction	29%
Seizures, unspecified neurodevelopmental harms	14% each
Screening harms (n=7)	
Pain and discomfort	43%
Breast feeding	43%
Cost	14%

*Laboratory methods include: glucose oxidase, hexokinase or dehydrogenase methods.
†For example, glucostix reagent strips, handheld reflectance colorimeter and electrode methods.

Guidelines

The 12 included guidelines were published between 1997 and 2018 (median 2009: table 3). Seventeen per cent clearly defined a systematic literature search. None specified a funding source.

Most guidelines (75%) clearly defined NH. One stated that NH cannot be described by a single value, and another defined hypoglycaemia as a range of values at which the onset of abnormal symptoms arise (online supplemental table 3). Twenty-five per cent of guidelines (n=3) based the diagnosis of hypoglycaemia on clinical manifestations, while 42% (n=5) based the severity of hypoglycaemia on clinical manifestations. The most common quantitative thresholds for hypoglycaemic were <2.2 mmol/L (n=3) and <2.6 mmol/L (n=2).

The most common reasons for asymptomatic hypoglycaemia screening were maternal diabetes, prematurity, small for GA and large for GA (table 3). Of the 50% of guidelines that defined large-for-GA and small-for-GA (n=6), all but one defined small for GA as birth weight below the 10th percentile and large for GA as birth weight above the 90th. Five of the nine guidelines that commented on choice of assay methods suggested screening immediately with a point-of-care glucose metre and confirming results by a laboratory method; the others disagreed (table 3).

More guidelines explicitly considered potential harms of hypoglycaemia than potential harms of screening. Five of 12 guidelines (42%) characterised acute harms of hypoglycaemia including seizures, apnoea, cyanosis, lethargy, irritability, hypotonia, poor sucking, tachypnoea, bradycardia, hypothermia, visual and hearing loss. Seven guidelines (58%) described neurodevelopmental harms associated with hypoglycaemia, including seizures and worsening visual, motor and cognitive function. Seven guidelines (58%) cited parental concerns about hypoglycaemia screening: most commonly neonatal pain and discomfort, breastfeeding difficulty, and cost. No concerns about parents were mentioned, aside from their need for education.

DISCUSSION
Screening-related studies
The primary literature that informs hypoglycaemia screening is a series of studies that relate neurodevelopmental outcomes (especially at preschool ages) to postnatal hypoglycaemia observed at a wide variety of quantitative thresholds. Most studies are of routinely screened babies, though many address more compromised neonates. Although many observational studies described the association between hypoglycaemia and neurodevelopment, only one RCT evaluated different treatment thresholds in terms of their neurodevelopmental outcome.[20]

Other hypoglycaemia-related outcomes included admissions, seizures, and breastfeeding. One study compared (breastfeeding) outcomes of babies who were screened to those who were not screened: but confounded by maternal diabetes, and with a co-intervention of rooming in.[21]

Intervention-related studies
Aside from the above-mentioned studies, only one other intervention study included neurodevelopment as an outcome, although neurodevelopment justifies intervention: rather, the outcomes of intervention studies generally were intended effects of treatment such as admissions, costs and breast feeding. The RCTs assessed dextrose gels (two), oral sucrose (one) and different glucose-level thresholds of intervention (1); other studied interventions included altered breastfeeding and emphasis on skin to skin.

Guidelines
Limitations with this evidence complicate the establishment of normative hypoglycaemia thresholds, which varied significantly among guidelines. Guidelines often distinguished symptomatic and asymptomatic hypoglycaemia, but few primary studies did, which limits the epidemiological support for this nuance. Guidelines did not arrive at a consensus definition of postnatal hypoglycaemia. Guidelines mostly agree on screening infants of diabetic mothers and premature babies, though fewer would screen babies at the extremes of birth weight centiles. Guidelines' most commonly cited concerns were long-term neurodevelopmental harm, and acute hypoglycaemia complications. Most guidelines did not discuss potential harms of screening, although implicit in screening only 'at-risk babies' is that although hypoglycaemic occurs in 'normal' babies,[22 23] screening likely harms more than it helps at some threshold of low risk.

Gaps
Other gaps emerged from this review. Only one cohort study directly compared outcomes in screened versus unscreened newborns, and did not consider neurodevelopmental outcomes. Many observational studies described the association between hypoglycaemia and neurodevelopment, but only one RCT evaluated different treatment thresholds in terms of their neurodevelopmental outcome at 18 months of age; ideally, such a study would be replicated, and extended to school age to better understand the developmental effects of different thresholds for intervention.[11]

More guidelines addressed potential harms of screening than primary studies, with listed concerns including neonatal pain, breastfeeding difficulty and cost. Further potential complications of screening include lowered maternal confidence in her ability to care for her baby, and maternal anxiety in general.[8] No study considered the parental perspective on 'routine' glucose monitoring.

Markers of increased pain were associated with decreased brain cortical thickness, and poorer early-childhood cognitive and internalising behaviour scores in premature babies.[24] Maternal–infant separation[24] and maternal anxiety[25] also appear to have negative effects, possibly causing altered neurodevelopment and cognitive outcomes[24] and generally less effective parenting behaviours.[25] Breastfeeding failure increases certain newborn and maternal health risks.[26] From a risk–benefit perspective, it would be informative to conduct research

that considers potential harms of screening as well as benefits.

Future research

It still[11 27 28] would be informative for future research to better define an optimal threshold for hypoglycaemia that warrants screening and intervention, based on long-term neurodevelopmental outcomes: informed also by a better definition of potential harms of screening. The threshold can be defined in terms of the level of the low glucose, the timing of the low glucose, and the persistence of the low level.[20] A clearer threshold could inform our interpretation of descriptive studies of glucose levels in the context of different risk factors, to inform which risk factors together warrant screening. As literature on oxygenation in prematurity moved towards assessing target oxygen levels,[29] the NH literature should describe empirical testing of different glucose targets based on the hypotheses generated from the many observational studies about harms associated with hypoglycaemia: such intervention studies should consider neurodevelopmental outcomes as well as intended ancillary treatment benefits. Also worthy of study would be a comparison of outcomes of screened and unscreened newborns who are potentially at risk, to define the optimal selection of 'at-risk' newborns to screen. Assay and treatment protocols should be described for context: for example, whereas 'gold-standard' glucose assay methods[11] may optimise hypoglycaemia management, quicker point-of-care testing could represent routine clinical practice. To optimise the care approach to the whole family, future research should consider the parents' perspective.

Strengths and limitations

The primary strength of this study was its broad literature search. This review's subsection on neurodevelopmental outcomes and hypoglycaemia included 32 studies and more than 10 000 babies, whereas the 2019 systematic review included 11 studies and 4041 infants.[11] This evidence summary was transparent and systematic in identifying the types of evidence in the field of NH.[30] However, as a scoping study, this review did not consider study results or assess the quality of the evidence, so it does not provide synthesised answers to inform clinical decision making.[30] Our analysis also considered only primary study outcomes as opposed to all study outcomes. Finally, language restrictions may have missed a few studies.

CONCLUSION

The lack of consensus among guidelines on NH screening and treatment reflects the nature of the background literature. The primary literature that informs hypoglycaemia screening is a series of studies that relate neurodevelopmental outcomes to postnatal hypoglycaemia. However, NH-intervention-study outcomes generally were intended effects of treatment such as cost and breastfeeding: there is much less literature on NH treatment from the neurodevelopmental perspective, which justifies NH treatment. Also, guidelines addressed potential harms of screening more often than primary studies. Thus, given the type of evidence that exists on the management of NH, clinicians can anticipate ongoing controversy and uncertainty around NH screening and treatment. The above-proposed research could inform an evidence-based targeting of hypoglycaemia screening and treatment to babies in whom the risk justifies intervention, for this common newborn problem.

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