Systematic Review and Meta-Analysis

Neonatology

Neonatology 2019;115:116–126
DOI: 10.1159/000492859

Received: July 24, 2018
Accepted after revision: August 12, 2018
Published online: November 8, 2018

Neonatal Glycaemia and Neurodevelopmental Outcomes: A Systematic Review and Meta-Analysis

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Keywords
Hypoglycaemia · Infant · Newborn · Neurodevelopmental disorders · Child development

Abstract
Background: Hypoglycaemia is the most common metabolic problem in neonates but there is no universally accepted threshold for safe blood glucose concentrations due to uncertainty regarding effects on neurodevelopment. ***Objective:*** To systematically assess the association between neonatal hypoglycaemia on neurodevelopment outcomes in childhood and adolescence. ***Methods:*** We searched MEDLINE, EMBASE, CINAHL, and PsycINFO from inception until February 2018. We included studies that reported one or more prespecified outcomes and compared children exposed to neonatal hypoglycaemia with children not exposed. Studies of neonates with congenital malformations, inherited metabolic disorders and congenital hyperinsulinism were excluded. Two authors independently extracted data using a customized form. We used ROBINS-I to assess risk of bias, GRADE for quality of evidence, and REVMAN for meta-analysis (inverse variance, fixed effects). ***Results:*** 1,665 studies were screened, 61 reviewed in full, and 11 included (12 publications). In early childhood, exposure to neonatal hypoglycaemia was not associated with neurodevelopmental impairment (n = 1,657 infants; OR = 1.16, 95% CI = 0.86–1.57) but was associated with visual-motor impairment (n = 508; OR = 3.46, 95% CI = 1.13–10.57) and executive dysfunction (n = 463; OR = 2.50, 95% CI = 1.20–5.22). In mid-childhood, neonatal hypoglycaemia was associated with neurodevelopmental impairment (n = 54; OR = 3.62, 95% CI = 1.05–12.42) and low literacy (n = 1,395; OR = 2.04, 95% CI = 1.20–3.47) and numeracy (n = 1,395; OR = 2.04, 95% CI = 1.21–3.44). No data were available for adolescents. ***Conclusions:*** Neonatal hypoglycaemia may have important long-lasting adverse effects on neurodevelopment that may become apparent at later ages. Carefully designed randomized trials are required to determine the optimal management of neonates at risk of hypoglycaemia with long-term follow-up at least to school age.

Introduction

Neonatal hypoglycaemia is the most common metabolic problem in newborn infants and a readily preventable cause of brain injury in infancy. However, clinical thresholds for diagnosis and treatment of neonatal hypoglycaemia are widely debated, with no universally accepted safe blood glucose concentration for newborns [1, 2]. This uncertainty is largely due to a lack of evidence regarding the effect of low neonatal glucose concentra-

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tions on neurodevelopmental outcomes. Further, recent studies have suggested that higher glucose concentrations after hypoglycaemia may also contribute to brain injury [3], thus adding complexity to this common clinical problem.

Key risk factors for neonatal hypoglycaemia include being born preterm, large for gestational age or high birth weight, small for gestational age or low birth weight, and being an infant of a diabetic mother. Approximately 30% of all neonates are considered at risk, of whom approximately 50% develop hypoglycaemia [4]. The most common definition of neonatal hypoglycaemia is a blood glucose concentration <47 mg/dL (2.6 mmol/L), but lower and higher thresholds have been recommended. For example, the American Academy of Pediatrics advises that intravenous treatment is not needed until glucose concentrations are <25 mg/dL (1.4 mmol/L) within the first 4 h after birth, or <35 mg/dL (2.0 mmol/L) from 4 to 24 h [5]. However, the Pediatric Endocrine Society recommends that in babies at risk of hypoglycaemia, glucose concentrations should be maintained >50 mg/dL (2.8 mmol/L), or >60 mg/dL (3.3 mmol/L) if interventions beyond normal feeds are required [6]. This lack of consensus reflects the paucity of evidence about long-term outcomes after neonatal hypoglycaemia.

In 2006, Boluyt et al. [7] carried out a systematic review of the available studies on prognosis after neonatal hypoglycaemia. The review concluded that the extent of neurodevelopment impairment after neonatal hypoglycaemia in the first week of life was unclear, and thus the authors proposed an optimal study design to establish the relationship between neonatal hypoglycaemia and subsequent neurodevelopment. In 2008, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Workshop on Neonatal Hypoglycaemia also identified major gaps in knowledge about neonatal hypoglycaemia and its clinical implications and prioritized it as a key area for research. Since then, although several review articles on the topic have appeared [8–10], no new systematic review has emerged.

This aim of this systematic review was to assess the association between neonatal hypoglycaemia on neurodevelopment outcomes at early childhood (2–5 years), mid-childhood (6–11 years), and adolescence (12–18 years).

Methods

This systematic review was conducted in accordance with the PRISMA statement, and was registered in PROSPERO (CRD42017073430, http://www.crd.york.ac.uk/PROSPERO/).

Search Strategy

We searched MEDLINE, EMBASE, CINAHL, and PsycINFO databases using the search terms infant, newborn, hypoglycaemia, neurodevelopmental disorders, neurological sequelae, neuroimaging, brain imaging, computed tomography scan, ultrasonography, and magnetic resonance imaging, including spelling variants (online suppl. material for full search strategy; see www.karger.com/doi/10.1159/000492859 for all online suppl. material). The search was restricted to studies involving humans and published in English. There was no limit on the year of publication. The search was last updated on February 12, 2018. We also hand-searched bibliographies of included studies, review papers and conference abstracts to identify additional items. One author conducted the search and initial title and abstract screening. Records identified for full-text screening were reviewed by two authors. Screening and eligibility assessments were performed using COVIDENCE (http://www.covidence.org/). Conflicts were resolved by consensus or after consultation with a third author.

Inclusion Criteria

We included all studies (trials, cohort, and case-control) that reported one or more of the primary or secondary outcomes and compared children or adolescents who were screened and found to be hypoglycaemic to those who were screened but were not hypoglycaemic. Studies were limited to neonates born at ≥32 weeks' gestation and who were screened for hypoglycaemia in the first week after birth. We excluded case series, conference abstracts, and studies that reported outcomes in neonates with congenital malformations, inherited metabolic disorders or congenital hyperinsulinism.

Primary outcomes were neurodevelopmental impairment, visual-motor impairment, and executive dysfunction, as defined by authors. Secondary outcomes were cognitive impairment (as defined by authors), mild cognitive impairment (developmental or intelligence quotient from 2 to 1 standard deviation below the mean), moderate-severe cognitive impairment (developmental/intelligence quotient more than 2 standard deviations below the mean), epilepsy (afebrile seizures or as defined by authors), highest educational level (adolescence), death, measures of general health and health care utilization, emotional-behavioural difficulty, abnormal brain imaging findings, visual impairment, hearing impairment, motor impairment, low literacy and low numeracy (mid-childhood and early adolescence), all as defined by authors.

Data Extraction and Analysis

Data for primary and secondary outcomes were extracted independently by two authors using a customized data form. Conflicts were resolved by consensus or following consultation with a third author.

We planned meta-analysis using the inverse variance, fixed effects method in REVMAN (version 5.3), with the inclusion of adjusted analyses where possible. If there were data for more than one age within an age band, then the most recent data were used. We assessed statistical heterogeneity using the I^2 statistic; values >30% were regarded as evidence of substantial heterogeneity. Forest plots are provided in the online supplementary material. We planned sensitivity analysis of the primary outcomes including only studies at low risk of bias and only those that used accurate methods for measuring glucose concentrations.

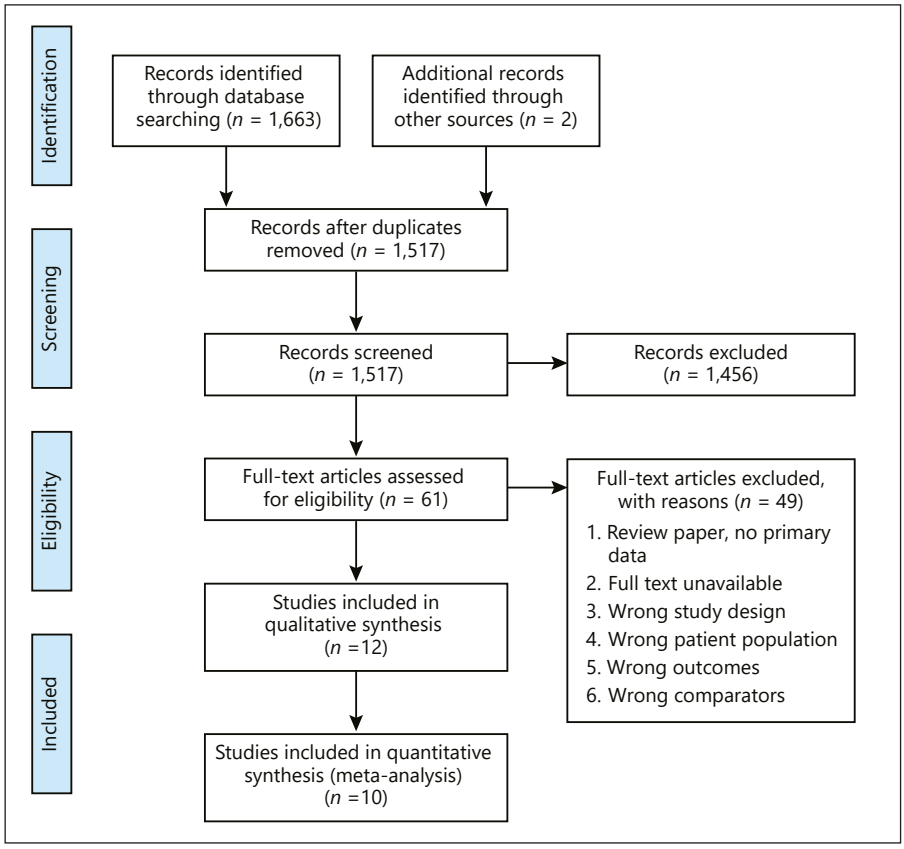

Fig. 1. Flow diagram of study identification and selection.

Quality of Evidence

We assessed the risk of bias for each study using a modified version of the ROBINS-I tool for non-randomized studies of interventions, as previously described [11]. This included assessment of the following domains for bias: recruitment and selection of participants, confounding, ascertainment of exposures, measurement of outcomes, missing data, and reporting of results. Two authors independently performed risk of bias assessments. Conflicts were resolved by consensus or by consultation with a third author.

We evaluated the overall quality of evidence for each research question using the GRADE approach [12]. Seven outcomes were selected for GRADE assessment: neurodevelopmental impairment, cognitive impairment, visual-motor impairment, low language/literacy, low numeracy, epilepsy, and executive dysfunction. Two authors independently assessed the quality of evidence. Conflicts were resolved by consensus or by consultation with a third author.

Results

Search Results

Of 1,665 records identified through databases and hand searching, 148 were duplicates and were removed. Of the remaining 1,517 studies, 1,456 were excluded following title and abstract screening, and a further 49 were excluded following full-text review (Fig. 1). One cohort study reported outcomes separately at 2 and 4.5 years of age [3, 13]. Thus, a total of 11 studies (12 publications), comprising 4,041 infants were included, of which 9 (10 publications) provided data suitable for meta-analysis in early and mid-childhood. No studies reported outcomes in adolescence.

Characteristics of the Selected Studies

All of the included studies were cohort studies; 3 were prospective [13–15], 6 were retrospective [16–21], and for 2 it was unclear whether all data were collected prospectively [22, 23] (Table 1). All studies were conducted in developed countries, including Europe, the USA, Canada, and New Zealand. Four studies were conducted in the 1970s [14, 15, 20, 22], 2 in the 1990s [17, 21], 1 in the 2000s [16] and 4 in the 2010s [13, 18, 19, 23]. In 10 studies the study population comprised infants at risk of hypoglycaemia; 1 study included all the infants born at the hospital. Only 4 studies (5 publications) each had uncertain or low risk of bias in one or more domains, and each adjusted results for potential confounding [3, 13, 18, 19,

Table 1. Characteristics of included studies

First author and date	Study type	Study population	Sample size	Definition of hypoglycaemia	Glucose screening protocol	Test method	Target range for treatment	Treatments	Age at follow-up	Neurodevelopmental tests	Included in meta-analysis	Adjustment for potential confounding
Griffiths [22], 1971	Cohort	Neonates admitted to special care unit	41 exposed, 41 unexposed	<1.11 mmol/L (<20 mg/dL)	Single blood glucose measurement within 24 h of admission; further blood glucose measurement only if hypoglycaemic or if symptomatic	Capillary whole blood; modified Watson method	Not specified	Not specified	4.2 years (mean)	Cognition: Stanford-Binet or Griffiths Behavior: Stott Systemic Interview Motor: Griffiths Locomotor Scale Vision: Stycar	Yes	No
Koivisto [20], 1972	Retrospective cohort	At-risk or symptomatic neonates screened for hypoglycaemia	151 exposed, 56 unexposed	<1.7 mmol/L (<30 mg/dL)	Blood glucose measured 3 times daily for 2–4 days in at-risk and symptomatic infants, and continued for 24 h after euglycaemic or discontinuation of treatment	Capillary whole blood; laboratory-modified Hultman or glucose oxidase method	Not specified	10–20% intravenous glucose; hydrocortisone	1–4 years	Cognitive, language and motor tests not specified Behavioural assessment not specified Ophthalmologic examination	Yes	No
Pildes [15], 1974	Prospective cohort	At-risk or symptomatic neonates screened for hypoglycaemia (mostly preterm or SGA)	39 exposed, 41 unexposed	<1.11 mmol/L (<20 mg/dL)	Daily blood glucose measurement for 1–4 days	Capillary whole blood; laboratory glucose oxidase method	Not specified	Oral dextrose; 10–15% intravenous dextrose; hydrocortisone or ACTH	1–7 years	Cognitive: Cattell Infant Scale, Stanford-Binet or Wechsler Intelligence Scale for Children Social: Vineland Social Maturity Scale Electroencephalogram	Yes	No
Haworth [14], 1976	Prospective cohort	Infants of diabetic mothers	25 exposed, 12 unexposed	≤1.11 mmol/L (≤20 mg/dL) in low birth weight babies (<2.5 kg) and ≤1.65 mmol/L (≤30 mg/dL) in normal weight babies	0.5, 1, 2, 3, 6,12, 24, 48 and 72 h, and more frequently if hypoglycaemic	Capillary whole blood; laboratory Huggett and Nixon method	Not specified	Intravenous glucose, long-acting adrenalin or both	4.5 years (mean)	Yale Developmental Schedule	Yes	No
Stenninger [21], 1998	Retrospective cohort	Infants of diabetic mothers	13 exposed 15 unexposed	<1.5 mmol/L (<27 mg/dL)	Glucose measurements for the first 24 h, frequency not specified	Capillary whole blood; laboratory glucose oxidase method	Not specified	Not specified	7–8 years	Cognitive: Griffiths' Developmental Scales Motor: Movement Assessment Battery for Children Behaviour: questionnaires (not specified) Validated neurological screening test for evaluation of minimal brain dysfunction Electroencephalogram	Yes	No
Duvanel [17], 1999	Retrospective cohort	Preterm (≤34 weeks) and SGA	62 exposed, 23 unexposed	<2.6 mmol/L (47 mg/dL)	Blood glucose measured approximately every 4–5 h for the first 24 h	Dextrostix for screening; if <2 mmol/L confirmed by laboratory venous sample using glucose oxidase or hexokinase method	Not specified	10% intravenous dextrose	6, 12, and 18 months, and 3.5 and 5 years	Cognitive: Griffith's Developmental Scales, McCarthy Scales of Aptitude	No	No
Brand [16], 2005	Retrospective cohort	Term and large for gestational age	60 exposed, 15 unexposed	<2.2 mmol/L (<40 mg/dL)	1, 3, and 5 h after birth and more frequently if hypoglycaemic	Capillary whole blood; laboratory glucose oxidase method	Not specified	Additional feeding or intravenous dextrose	4 years	Cognitive: Denver Developmental Scale, Snijders-Oomen non-verbal intelligence test Behaviour: Dutch version of the Child Behaviour Check List	Yes	No
Kerstjens [23], 2012	Cohort	Moderate preterm (32–35 weeks' gestation)	67 exposed, 765 unexposed	<1.7 mmol/L (<30 mg/dL)	Blood glucose measured several times during the first 24 h	Bedside glucometer; laboratory confirmation if <3.0 mmol/L (54 mg/dL) or <2.5 mmol/L (45 mg/dL), depending on site protocol	Not specified	Not specified	3.5–4 years	Ages and Stages Questionnaire	Yes	Yes

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Table 1 (continued)

First author and date	Study type	Study population	Sample size	Definition of hypoglycaemia	Glucose screening protocol	Test method	Target range for treatment	Treatments	Age at follow-up	Neurodevelopmental tests	Included in meta-analysis	Adjustment for potential confounding
McKinlay 2015 [3]	Prospective cohort	Term and late-preterm neonates born at risk for hypoglycaemia	216 exposed, 188 unexposed	<2.6 mmol/L (<47 mg/dL)	1 h, then before feeds 3–4 h for first 24 h, then 6–8 h for next 24 h and until hypoglycaemia no longer a clinical concern. More frequent if hypoglycaemic or receiving intravenous dextrose	Capillary whole blood; laboratory glucose oxidase method; masked continuous interstitial glucose monitoring	≥2.6 mmol/L (47 mg/dL)	Additional feeding, buccal dextrose gel, intravenous dextrose	2 years	Cognitive: Bayley Scales of Infant Development III. Executive: a battery of four tasks, and Behavior Rating Inventory of Executive Function (Preschool version) Vision: visual screening using four assessment categories and random-dot kinematograms of varying coherence Hearing: audiologic screening	Yes	Yes
Kaiser [19], 2015	Retrospective cohort	All neonates	89 exposed, 1,306 unexposed	<1.94 mmol/L (<35 mg/dL)	Universal newborn glucose screening at 1–3 h after birth; repeated after 1 h if hypoglycaemic	Laboratory glucose oxidase	Not specified	Intravenous dextrose or additional feeding	10 years	Fourth Grade Benchmark Examination (literacy and mathematics)	Yes	Yes
Goode [18], 2016	Retrospective cohort	Preterm and low birth weight	461 exposed/ 282 unexposed	<2.49 mmol/L (<45 mg/dL)	Not specified	Dextrostix or plasma glucose, method not specified	Not specified	Not specified	5, 8, and 18 years	Cognitive: Stanford-Binet, Peabody Picture Vocabulary Test, Wechsler Intelligence Scale for Children, Wechsler Abbreviated Scale of Intelligence. Academic: Woodcock-Johnson Tests of Achievement Behaviour: Child Behaviour Checklist, Youth Report Behaviour Surveillance System	No	Yes
McKinlay [13], 2017	Prospective cohort	Term and moderate to late preterm infants born at risk of hypoglycaemia	280 exposed, 197 unexposed	<2.6 mmol/L (<47 mg/dL)	1 h, then before feeds 3–4 h for first 24 h, then 6–8 h for next 24 h and until hypoglycaemia no longer a clinical concern. More frequent if hypoglycaemic or receiving intravenous dextrose	Capillary whole blood; laboratory glucose oxidase method; masked continuous interstitial glucose monitoring	≥2.6 mmol/L (47 mg/dL)	Additional feeding, buccal dextrose gel, intravenous dextrose	4.5 years	Cognitive: Wechsler Preschool and Primary Scale of Intelligence (version 3) Executive: a battery of five graded tasks, Behaviour Rating Inventory of Executive Function Motor: Movement Assessment Battery for Children (version 2) and Beery Buktenica Developmental Test of Visual Motor Integration (version 6) (BBV-MI-6) Vision: visual screening using six assessment categories, visual processing subscale of BBV-MI-6, random dot kinetograms of varying coherence Auditory processing: auditory subscale of the Phelps Kindergarten Readiness Scale Emotional and behaviour: Strengths and Difficulties Questionnaire, Child Behaviour Checklist	Yes	Yes

SGA, small for gestational age; ACTH, adrenocorticotropin.

Table 2. Risk of bias assessment

Author and date	Domain					
	selection of comparison groups	confounding	ascertainment of exposures	measurement of outcomes	missing data	reporting of results
Griffiths [22], 1971	uncertain	uncertain	high	low	uncertain	low
Koivisto [20], 1972	uncertain	uncertain	high	uncertain	low	uncertain
Pildes [15], 1974	low	high	uncertain	low	high	uncertain
Haworth [14], 1976	uncertain	high	low	low	uncertain	low
Stenninger [21], 1998	uncertain	high	low	low	high	low
Duvanel [17], 1999	uncertain	uncertain	uncertain	uncertain	uncertain	uncertain
Brand [16], 2005	low	uncertain	low	low	high	uncertain
Kerstjens [23], 2012	low	low	uncertain	low	uncertain	low
McKinlay [3], 2015	low	low	low	low	uncertain	uncertain
Kaiser [19], 2015	low	low	low	low	uncertain	low
Goode [18], 2016	low	low	uncertain	low	uncertain	low
McKinlay [13], 2017	low	low	low	low	uncertain	uncertain

Assessed using a modified version of the ROBINS-I tool for non-randomized studies of interventions [11].

23]. No study was at low risk of bias across all domains. Seven studies were small with fewer than 100 participants and had very imprecise estimates of exposure effect.

Early Childhood (2–5 Years)

Primary Outcomes

The risk of neurodevelopmental impairment in early childhood did not differ between those who were and were not exposed to neonatal hypoglycaemia (6 studies, 1,657 infants; 25.8 vs. 16.6%; OR = 1.16, 95% CI = 0.86–1.57; $p = 0.34$; $I^2 = 16\%$) [3, 13–16, 20, 23]. Four out of the 6 studies contributing data to this meta-analysis were at high risk of bias in one or more domains (Table 2). In 2 studies, exposure to neonatal hypoglycaemia was associated with increased risk of visual-motor impairment (508 infants; 4.6 vs. 1.5%; OR = 3.46, 95% CI = 1.13–10.57; $p = 0.03$; $I^2 = 0\%$) [13, 14]. One of these studies was at high risk of bias for confounding but contributed few data to the meta-analysis [14]. In 1 study, there was an association between neonatal hypoglycaemia and executive dysfunction (463 infants; 10.6 vs. 4.7%; OR = 2.50, 95% CI = 1.20–5.22; $p = 0.01$). This study had a low to uncertain risk of bias [13]. There were insufficient data to undertake the planned sensitivity analyses.

Secondary Outcomes

In early childhood, those exposed to neonatal hypoglycaemia compared with those not so exposed had similar rates of any cognitive impairment (3 studies, 746 infants, 15.4 vs. 15.9%; OR = 1.11, 95% CI = 0.73–1.69; $p = 0.63$; $I^2 = 28\%$), mild cognitive impairment (3 studies, 746 infants, 12.8 vs. 13.7%; OR = 0.86, 95% CI = 0.55–1.35; $p = 0.52$; $I^2 = 61\%$) and moderate-severe cognitive impairment (3 studies, 746 infants, 2.6 vs. 2.1%; OR = 1.57, 95% CI = 0.55–4.48; $p = 0.40$, $I^2 = 34\%$) [13, 20, 22]. Two of these 3 studies were at high risk of bias in one or more domains. The risk of epilepsy in early childhood did not differ between those exposed and not exposed to neonatal hypoglycaemia (4 studies, 772 infants, 4.2 vs. 2.1%; OR = 1.93, 95% CI = 0.76–4.85; $p = 0.16$, $I^2 = 0\%$) [13, 14, 20, 22]. Three of these 4 studies were at high risk of bias in one or more domains. The risk of emotional-behavioural difficulty did not differ between those exposed and not exposed to neonatal hypoglycaemia (3 studies, 587 infants, 18.9 vs. 19.0%; OR = 1.00, 95% CI = 0.66–1.53; $p = 0.98$, $I^2 = 0\%$) [13, 14, 22]. One of these studies was at low or uncertain risk of bias while 2 were at high risk of bias in one or more domains. The risk of visual impairment in early childhood did not differ between those exposed or not exposed to neonatal hypoglycaemia (2 studies, 616 infants, 5.0 vs. 1.7%; OR = 2.14, 95% CI = 0.70–6.53; $p = 0.18$, $I^2 = 0\%$) [13, 20]. One of these studies was at high risk of bias in one or more domains and contributed the most data to the meta-analysis [20]. In 1 study, the rate of hearing impairment in early childhood did not differ between those exposed or not exposed to neonatal hypoglycaemia (477 infants, 0 vs. 0.5%; OR = 0.23, 95% CI = 0.01–5.76; $p = 0.37$) [13]. This study had a low to uncertain risk

of bias. The risk of motor impairment in early childhood did not differ between those who were and were not exposed to neonatal hypoglycaemia (4 studies, 777 infants, 17.5 vs. 17.8%; OR = 1.06, 95% CI = 0.70–1.60; $p = 0.79$, $I^2 = 6\%$) [13, 14, 20, 22]. Three out of 4 of these studies were at high risk of bias in one or more domains. One study reported higher rates of low language/literacy in those exposed to neonatal hypoglycaemia compared with those not so exposed but results were imprecise and not statistically significant (37 infants, 16 vs. 0%; OR = 5.23, 95% CI = 0.26–105.50; $p = 0.28$) [14]. This study had an uncertain to high risk of bias. One study reported on rates of cerebral palsy and found no difference between those exposed and not exposed to neonatal hypoglycaemia (401 infants, 0.9 vs. 1.1%; OR = 0.81, 95% CI = 0.11–6.07; $p = 0.84$) [3]. This study was at a low to uncertain risk of bias. None of the included studies reported on abnormal brain imaging, highest education level, death or measures of general health and health care utilization in early childhood.

Quality of Evidence

For the primary outcomes in early childhood, the quality of evidence was either low or very low (Table 3). For the selected secondary outcomes of any cognitive impairment, epilepsy, and low language/literacy, the quality of evidence was also very low (Table 3).

Mid-Childhood (6–11 Years)

Primary Outcomes

In 2 small studies, those exposed to neonatal hypoglycaemia compared with those not so exposed had a higher risk of neurodevelopmental impairment (54 infants, 47.8 vs. 22.6%; OR = 3.62, 95% CI = 1.05–12.42; $p = 0.04$, $I^2 = 0\%$) [15, 21]. Both of these studies were at an uncertain to high risk of bias in one or more domains. None of the included studies reported on visual-motor impairment or executive dysfunction in mid-childhood. There were insufficient data to undertake the planned sensitivity analyses.

Secondary Outcomes

In 1 study, the risk of emotional-behavioural difficulty in mid-childhood was non-significantly increased in those exposed to neonatal hypoglycaemia than those not so exposed (28 infants, 30.8 vs. 6.7%; OR = 6.22, 95% CI = 0.60–64.97; $p = 0.13$) but rates of motor impairment were similar (28 infants, 15.4 vs. 13.3%; OR = 1.18, 95% CI = 0.14–9.83; $p = 0.88$) [21]. This study had an uncertain to high risk of bias in one or more domains. In another study, those exposed to neonatal hypoglycaemia compared with those not so exposed had an increased risk of low language/literacy (1,395 infants, 67.4 vs. 43.0%; OR = 2.04, 95% CI = 1.20–3.47; $p = 0.008$) [19] and low numeracy (1,395 infants, 53.9 vs. 34.0%; OR = 2.04, 95% CI = 1.21–3.44; $p = 0.007$) in mid-childhood [19]. This study had a low to uncertain risk of bias.

None of the included studies reported on any cognitive impairment, mild cognitive impairment, moderate-severe cognitive impairment, epilepsy, abnormal brain imaging, visual impairment, hearing impairment, highest educational level, death, and measures of general health and health care utilization in mid-childhood.

Quality of Evidence

For the primary outcome of neurodevelopmental impairment in mid-childhood the quality of the evidence was very low (Table 3). For the selected secondary outcomes of low language/literacy and low numeracy, the quality of the evidence was low (Table 3).

Adolescence (12–18 Years)

None of the included studies reported on primary or secondary outcomes in adolescence.

Discussion

Neonatal hypoglycaemia is the most common metabolic condition in newborn infants [4] and has been associated with widespread changes in the developing brain [24], yet the impact of neonatal hypoglycaemia on long-term neurodevelopment is widely debated [25]. We undertook this systematic review to determine the relationship between neonatal hypoglycaemia and neurodevelopment throughout childhood. We found low-quality evidence that in early childhood (2–5 years) neonatal hypoglycaemia is associated with specific cognitive deficits, including a two- to threefold increased risk of visual-motor impairment and executive dysfunction. In later childhood (6–11 years), we found low-quality evidence that neonatal hypoglycaemia is associated with a twofold increased risk of literacy and numeracy problems, and very low-quality evidence of an increased risk of general cognitive impairment. No data were available on outcomes in adolescence.

Visual-motor integration is the coordination of visual perception, the ability to extract and organize visual information from the environment, and motor skills, especially fine motor ones [26]. It allows the use of eyes and

Table 3. GRADE summary of quality of evidence for effect of neonatal hypoglycaemia on neurodevelopmental outcomes

Outcome	Exposure effect OR (95% CI)	Participants (studies)	Certainty/ quality of evidence	Comments
Early childhood (2–5 years)				
Neurodevelopmental impairment	1.16 (0.86–1.57)	1,657 (6)	Very low	Initial level low. Downgraded as 4 studies were at high risk of bias in several domains, and only 2 studies adjusted for confounding
Visual-motor impairment	3.46 (1.13–10.57)	508 (2)	Low	Initial level low. Downgraded as results were imprecise. Upgraded 1 level due to large treatment effect
Executive dysfunction	2.50 (1.20–5.22)	463 (1)	Low	Initial level low. Downgraded as there was only a single study. Upgraded 1 level due to large treatment effect
Any cognitive impairment	1.11 (0.73–1.69)	746 (3)	Very low	Initial level low. Downgraded as two studies were at high risk of bias, and only one study adjusted for confounding
Epilepsy	1.93 (0.76–4.85)	772 (4)	Very low	Initial level low. Downgraded as 2 studies were at high risk of bias, results were imprecise, and only 1 study adjusted for confounding
Low language/literacy	5.23 (0.26–105.50)	37 (1)	Very low	Initial level low. Large treatment effect but downgraded as there was only 1 study at high risk of bias with imprecise results
Mid-childhood (6–11 years)				
Neurodevelopmental impairment	3.62 (1.05–12.42)	54 (2)	Very low	Initial level low. Large treatment effect but downgraded as both studies were at high risk of bias with imprecise results
Visual-motor impairment	–	–	–	No data
Executive dysfunction	–	–	–	No data
Any cognitive impairment	–	–	–	No data
Epilepsy	–	–	–	No data
Low language/literacy	2.04 (1.20–3.47)	1,395 (1)	Low	Initial level low. Downgraded as there was only a single study. Upgraded 1 level due to large treatment effect
Low numeracy	2.04 (1.21–3.44)	1,395 (1)	Low	Initial level low. Downgraded as there was only a single study. Upgraded 1 level due to large treatment effect

Evaluated using the GRADE approach [12].

hands in a coordinated and efficient way, enabling, for example, one to perceive and copy shapes, letters, and numbers. Thus, visual-motor integration is important for learning and academic achievement including reading, writing, and mathematics [27, 28].

The development of visual and motor systems is closely related [29], and coordination of visual-motor function is thought to occur within the ventral and dorsal cortical visual streams. The ventral stream supports form processing and object recognition, and includes the occipital primary visual cortex and the inferior temporal lobe. The dorsal stream is responsible for motion perception and visually guided motor function and includes the occipital primary visual cortex, middle temporal lobe, and poste-

rior parietal lobe. In the neonatal period, these cortical areas appear to be particularly susceptible to injury from neuroglycopenia, possibly because of higher metabolic activity [9, 30–32]. This provides a possible pathophysiological basis for the association between neonatal hypoglycaemia and impaired visual-motor integration in early childhood.

Executive function is the collective capacity for problem-solving, planning, attention control, and goal-directed behaviour [33]. Children with impaired executive control have difficulty remembering and carrying out instructions, staying focused, and planning and monitoring progress with a specific task, which can affect not only daily activities but also learning. The prefrontal cortex is responsible for the proper development of executive function, and increased activation of this region is associated with better performance on executive function tasks, as well as academic outcomes [34, 35]. The development of the prefrontal cortex and executive capacity is continuous from childhood through adolescence and into early adulthood [36, 37], and any abnormality in this region can result in executive function difficulties. Although neonatal hypoglycaemia has traditionally been associated with posterior brain injury, recent studies have suggested that its effects on the brain may be more widespread and include the frontal cortex [24, 38], potentially interfering with the normal development of executive capacity.

Demands on visual-motor and executive function increase with age, but we could not determine whether the changes seen in early childhood after neonatal hypoglycaemia persist or worsen over time due to the lack of longer-term outcome data. However, the finding of a twofold increased risk of literacy and numeracy problems in mid-childhood suggests a trajectory of worsening function in skills that are important for learning [39, 40]. The fact that neonatal hypoglycaemia was associated with general cognitive impairment in mid-childhood but not in early childhood supports this hypothesis. Importantly, this systematic review shows that tests of general development in infancy are unlikely to adequately assess the effects of neonatal hypoglycaemia on brain development. Thus, intervention studies will require longer-term end points, at least into mid-childhood, including specific tests of visual-motor and executive function.

It is more than a decade since Boluyt et al. [7] conducted the first systematic review of neurodevelopmental outcomes after neonatal hypoglycaemia. They concluded that there were insufficient data to quantify the effect of neonatal hypoglycaemia on neurodevelopment and provided recommendations about an optimal study design. Our systematic review identified 3 subsequent studies, but only 1 that followed these recommendations [3, 13], including prospective cohort design, nested randomized trial of treatment, gold standard glucose measurements, standardized neurodevelopmental assessment and sufficient sample size [7]. This is somewhat surprising given the recognition of neonatal hypoglycaemia as a priority research area and calls from the National Institute of Child Health and Human Development for further high-quality studies [1].

There are several differences between our systematic review and that of Boluyt et al. [7]. We excluded case series because without contemporaneous controls it is not possible to account for confounding, especially relating to the reasons that babies were considered at risk of hypoglycaemia and socio-economic factors. We also excluded studies that assessed outcomes at less than 2 years of age, due to the limited predictive value of very early developmental assessment [41], and studies that primarily included infants with congenital hyperinsulinism. We assessed not only the methodological quality of individual studies, but also the overall strength of the evidence for key outcomes using the GRADE approach.

Even with optimal study design, several challenges remain in determining the effect of neonatal hypoglycaemia on later neurodevelopment. As with any cohort study, the possibility of residual confounding cannot be excluded. Although neuroglycopenia can cause irreversible brain injury, other mechanisms may underlie associations between episodes of hypoglycaemia and neurodevelopmental impairment. For example, genetic polymorphisms of ATP-dependent potassium channels could affect both pancreatic β-cells and neuronal function [42].

In addition, the relationship between the severity, frequency, and duration of neonatal hypoglycaemic episodes and cerebral energy supply and utilization remains unclear [43], and thus the best measure of exposure for use in analyses is uncertain [25]. This is complicated by different approaches to screening, diagnosis, and treatment of hypoglycaemia, making characterization of the degree of exposure challenging. Further, masked continuous interstitial glucose monitoring has shown that the burden of hypoglycaemia in the early newborn period may be substantially greater than is detected by serial glucose measurements, even with frequent screening [3]. These undetected and thus untreated episodes may have an important influence on long-term outcomes [13]. However, there are few data on the effect of different approaches to treatment on glucose concentrations after hypoglycaemia [44].

Limitations

A key limitation of this systematic review is that only a limited number of studies were identified that met the inclusion criteria, leading to imprecise estimates of effect, and that data were not available for all prespecified outcomes at each epoch. There are several possible reasons for this including the difficulty of recruiting large cohorts around the time of birth, and the cost and complexity of long-term neurodevelopmental follow-up throughout childhood. Of note, only 3 of the included studies contributed data beyond 5 years of age [18, 21, 23]. Another limitation is the lack of adjustment for potential confounding factors, with only half of the included studies attempting to control for this potential source of bias. Finally, the description of hypoglycaemic management and treatment targets was generally poor. This may be important, as there is emerging evidence both in animals and humans that glucose reperfusion injury may exacerbate oxidative stress associated with hypoglycaemia if the correction is too rapid or too high, even within the normal glucose range [3, 45, 46].

Recommendations for Research

Studies are needed to determine the efficacy and cost-effectiveness of different strategies for improving long-term outcomes in neonates born at risk of hypoglycaemia. Future studies should involve large prospective cohorts with nested randomized trials of different approaches to treatment, or large randomized trials of different approaches to prevention or screening and diagnosis of hypoglycaemia in neonates considered at risk. All studies require the use of gold standard glucose assay methods [25, 47] and long-term follow-up at least to school age, with attention to visual-motor and executive function, and educational achievement. Consideration should be given to the use of masked continuous glucose monitoring to aid in the interpretation of study results, although retrospective point-to-point recalibration against all laboratory blood glucose values is important for accurate interstitial measurements in babies [48].

Conclusion

This systematic review found that neonatal hypoglycaemia is associated with a two- to threefold increased risk of specific cognitive deficits in early childhood (2–5 years), including visual-motor impairment and executive dysfunction, and general cognitive impairment and literacy and numeracy problems in later childhood (6–11 years). Although the overall quality of evidence was low to very low, this review nevertheless suggests that neonatal hypoglycaemia may have important long-lasting adverse effects on neurodevelopment. Carefully designed intervention trials are needed to determine the optimal management of neonates at risk of hypoglycaemia to improve long-term outcomes.

Disclosure Statement

The authors have no conflicts of interest to declare.

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