Outcomes of very preterm infants with neonatal hyperglycaemia: a systematic review and meta-analysis

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ABSTRACT

Objective To explore the association between hyperglycaemia and adverse outcomes in very preterm infants.

Design Systematic review and meta-analysis. Data were pooled separately for adjusted and unadjusted odds ratios (ORs) using random-effects model. Subgroup analysis was conducted based on study design (cohort and case control).

Main outcome measures Association between hyperglycaemia in preterm neonates (<32 weeks or <1500 g) and mortality and morbidities.

Findings Forty-six studies (30 cohort and 16 case control) with data from 34 527 infants were included. Meta-analysis of unadjusted ORs from cohort studies found hyperglycaemia to be significantly associated with mortality, any-grade intraventricular haemorrhage (IVH), severe IVH, any-stage retinopathy of prematurity (ROP), severe ROP, sepsis, chronic lung disease and disability. However, pooling of adjusted ORs found significant associations only for mortality (adjusted OR (CI): 2.37 (1.40 to 4.01); I^2: 36%; 6 studies), 'Any grade IVH' (adjusted OR (CI): 2.60 (1.09 to 6.20); I^2: 0%; 2 studies) and 'Any stage ROP' (adjusted OR (CI): 3.70 (1.55 to 8.84); I^2: 0%; 2 studies). Meta-regression analysis found glucose levels >10 mmol/L to be associated with increased odds of mortality compared with <10 mmol/L. Pooled analysis from case–control studies were similar to cohort studies for most outcomes but limited by small sample size. Longer duration of hyperglycaemia was associated with adverse outcomes. GRADE of evidence was 'Low' or 'Very low'.

Conclusion Hyperglycaemia in very preterm infants is associated with higher odds of mortality, any-grade IVH and any-stage ROP. A limitation was lack of availability of adjusted ORs from many of the included studies.

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INTRODUCTION

Hyperglycaemia is a common finding in very preterm and very low birth weight (VLBW) infants during their stay in neonatal intensive care units. Various thresholds of blood glucose levels (>7, >8.3, 10 and 12 mmol/L) have been used to define neonatal hyperglycaemia.[1–5] A survey found six different definitions of neonatal hyperglycaemia, with majority using a cut-off of 10 mmol/L.[6] The incidence of hyperglycaemia varies from 10% to more than 80% in published studies depending on the definition.[7–10]

What is already known on this topic?

⇒ Neonatal hyperglycaemia is a common finding in very preterm and very low birth weight infants.
⇒ Individual observational studies have explored the associations between hyperglycaemia and adverse outcomes in very preterm infants.

What this study adds?

⇒ This systematic review found that hyperglycaemia is significantly associated with mortality, any-grade intraventricular haemorrhage and any-stage retinopathy of prematurity in very preterm infants.
⇒ Glucose levels >10 mmol/L were associated with increased odds of mortality compared with <10 mmol/L.
⇒ Longer duration of hyperglycaemia was associated with adverse outcomes.

Irrespective of the controversy surrounding its definition, various observational studies have explored the association between hyperglycaemia and adverse outcomes in very preterm infants.[5 11–16] Evidence from animal models suggests that hyperglycaemia is associated with increased mortality and morbidity such as retinal inflammation, intraventricular haemorrhage (IVH), apoptosis and reduced brain weight (especially of the hippocampus).[17–22] A systematic review did not show a significant association (OR 1.08; 95% CI 0.97 to 1.20) between mean glucose levels and retinopathy of prematurity (ROP) in human preterm infants when adjusted ORs were pooled.[23] It also reported that upon pooling of three studies there was a "borderline significant association" between duration of hyperglycaemia and ROP (adjusted OR = 1.08, 95% CI: 1.01–1.15, I^2 = 49%, P = 0.03). Subsequent to that systematic review,[23] many observational studies have evaluated the association of hyperglycaemia with ROP in preterm infants and reported contradictory results in almost equal numbers. Currently, there are no systematic reviews evaluating the association between neonatal hyperglycaemia and other important outcomes such as mortality, sepsis, IVH, periventricular leucomalacia (PVL), chronic lung

Table 1 Characteristics of the included studies

Study ID; country; study design; sample size	Gestation/BW (in weeks and grams)	Hyperglycaemia definition: age when hyperglycaemia was detected; incidence
Villamizar 2020; USA; PC; 97	GA: mean (±SD) 27.8 (±2.4) and BW: mean (±SD) 1059.0 (±300.4)	>8.3 mmol/L; first 7 days; 48.5%
Vannadil 2019; India; PC; 103[9]	GA: mean (±SD) 30.282 (±2.0188) and BW: mean (±SD) 1251 (±313.1432)	NA; first 7 days; NA
Bochkova 2019; Russia; PC; 68[39]	GA: mean (±SD) 29 (±1.1 weeks) and BW: mean (±SD) 1326 (±119.8)	NA; NA; 100%
Jagla 2019; Poland; PC; 74[8]	GA: median (IQR) 28 (26–30) and BW: mean (±SD) 1066 (±267)	>8.33 mmol/L; first 6 days of life; 10.35%
Zamir 2019; Sweden; PC; 171[67]	GA: mean (±SD) 25.4 (±1)	>10 mmol/L for 2 or 3 consecutive days; first 28 days; 46.8%
Goldner Perez 2019; USA; RC; 232[46]	GA: mean (±SD) NG vs HG 29.7±1.7 vs 26.8±2.2, BW: mean (±SD) NG vs HG 1188 (±226) vs 877 (±215) (children who had DA)	Mild >8.3 to 10 mmol/L, moderate >10 to 11.6 mmol/L and severe >11.6 mmol/L; first 7 days; 64.7% who had DA
Turai 2019; Hungary; RC; 188[68]	GA: mean (±SD) 27.1 (±2.2) BW: mean (±SD) 814.9 (±151.9)	>8.5 mmol/L; NA; 32.9%
Zamir 2018; Sweden; RC; 580[5]	GA: mean (±SD) HG vs NG 25.1 (±1.1) vs 25.9 (±0.8), BW: mean (±SD) 725 (±163) vs 852 (±147)	>10 mmol/L; first 28 days; 70%
Slidsborg 2018; Denmark; CC; 310[61]	GA: mean (±SD) ROP vs no ROP 26.57 (±1.8) vs 27.28 (±1.74) and BW: mean (±SD) 848 (±215) vs 998 (±302)	>8.5 mmol/L; first 7 days; NA
Naseh 2017; Sweden; CC; 75[56]	GA mean (±SD): 28.3 (±2.6), BW: mean (±SD) 1178 (±408)	>8.3 mmol/L; first 7 days; 41.3%
Tottman 2017; New Zealand; RC; 443[63]	GA: median NG vs HG 29 vs 26, BW: median 1170 vs 890	≥8.6 mmol/L on ≥2 measures or any blood glucose concentration ≥10.1 mmol/L; first 7 days; 16%
Akmal 2017; Egypt; PC; 60 (A: 8.3–15 mmol/L, B: >15 mmol/L)[11]	GA: mean (±SD) HG 29.8 (±1.8), NG 30.8 (±1.6); BW: mean (±SD) 1258 (±180) vs 1341 (±110)	>8.3 mmol/L (mild >8.3 mmol/L, moderate >10 mmol/L and severe >15 mmol/L); first 7 days; 66.7%
Kim 2017; South Korea; CC; 147[70]	GA: mean (±SD) ROP vs no ROP 27.3 (±1.5) vs 30.5 (±2.7), BW: mean (±SD) 952 (±199) vs 1240 (±219)	>6.9 mmol/L; first 3 weeks; NA
Reyes 2017; Oman; CC; 171[69]	GA: mean (±SD) 30 (±2) BW: mean (±SD) 1200 (±330)	>8 mmol/L; NA; 24%
Bermick 2016; USA; CC; 216 (A: 8.3–11 mmol/L, B: 11.1–13.8 mmol/L, C: >13.9 mmol/L)[15]	GA: mean (±SD) IVH: 25.2 (±1.3), no IVH: 25.9 (±1.5); BW: mean (±SD) IVH: 760 (±137), no IVH: 769 (±162)	>11.1 mmol/L; first 10 days; 51.8%
Lee 2016; USA; CC; 24 548[50]	GA: median (IQR) 26 (25–27) BW: median (IQR) 795 (680–900)	>10 mmol/L; NA; 43% and 26% infants with and without severe ROP, respectively
Manzoni 2016; Italy; RC; 740[53]	NA	>11.1 mmol/L; first 5 days; NA
Scheurer 2016; USA; PC; 53 (A: 1–5 days HG, B: >5 days HG)[60]	GA: mean (±SD) NG 29.3 (±1.3), HG for 1–5 days: 27.2 (±2.0), for >5 days: 24.0 (±1.0); BW: mean (±SD) NG 1217.3 (±170.2), HG for 1–5 days 929.2 (±278.3) and HG for >5 days 681.2 (±143.7)	>8.3 mmol/L; first 14 days; 54.7%
De Carolis 2015; Italy; RC; 166[16]	GA: mean (±SD) NG: 26.8 (±2.0) HG: 26.1 (±2.1), BW: mean (±SD) NG 808 (±136) vs HG 695 (±146)	>13.3 mmol/L any measure or >10 mmol/L in 2 measures; NA; 31.9%
Nicolaeva 2015; Russia; PC; 64[57]	No ROP, spontaneously regressing ROP, ROP regression after LASER treatment—GA: mean (±SD) 28.6 (±1.4), 26.5 (±1.2), 25.4 (±0.7); BW: mean (±SD) 1162 (±322), 905 (±224), 763 (±138)	>8.9 mmol/L; first 3 weeks; NA
Stensvold 2015; Norway; RC; 343 (A: 8.4–10 mmol/L, B: 10.1–12 mmol/L, C: >12 mmol/L)[12]	Period 1 (10% dextrose at birth) vs period 2 (TPN from birth) and GA: mean (±SD) 26.3 (±1.8) vs 26.4 (±2.2), BW: mean (±SD) 765 (±154) vs 736 (±152)	Mild (8.4:10 mmol/L), moderate (10.1:12 mmol/L) or severe (>12 mmol/L); first 7 days; 38% in period 1 vs 71% in period 2
Szymońska 2015; Poland; PC; 63 (A: 8.3–10 mmol/L, B: >10 mmol/L)	GA: mean (±SD) overall population 27.7±2.4, BW: mean (±SD) overall population 1059.4 (±262)	Gr A: <5% of reading time >8.33 mmol/L. Gr B: >5% of reading time >8.3 mmol/L. Gr C: >5% of reading time in >10 mmol/L; first 7 days; >8.33 mmol/L in 84.1%, >10 mmol/L in 34.9%, >15 mmol/L in 4.8%
Cardona 2014; USA; RC; 40[41]	NA	Mild: 8.3:10 mmol/L, moderate: 10.01:11.6 mmol/L, severe: >11.6 mmol/L; first month; 58%
Ahmadpour Kacho 2014; Iran; CC; 155[37]	ROP infant vs control infant GA: mean (±SD) 29.91 (±2.46) vs 30.59 (±1.97) and BW: mean (±SD) 1238.57±344.77 vs 1327.53±293.03	>8.3 mmol/L; until the time baby is fully fed; 24.5% of patients with ROP and 5.9% patients in the control group
Mohsen 2014; Egypt; PC; 65[55]	NG vs HG GA: mean (±SD) 31.2 (±1) vs 30.9 (±1.4) and BW: mean (±SD) 1446 (±193) vs 1318 (±242)	>8.3 mmol/L; first 7 days; 48%
Sabzehei 2014; Iran; RC; 564[59]	BW: mean (±SD) 1179.26 (±258.45) and GA: mean (±SD) 29.68±2.577	>8.3 mmol/L; NA; 31.7%
Auerbach 2013; Israel; CC; 178[14]	GA: mean (±SD) IVH 27.6 (±2.4) vs no IVH 28.4 (±2.2), BW: mean (±SD) IVH 1026 (±385) vs no IVH 1126 (±339)	>6.9 mmol/L; first 96 hours; 86% had 1 and 29% had >4 hyperglycaemic events
Mohamed 2013; USA; CC; 582[54]	No ROP vs ROP group: GA: mean (±SD) 28.1 (±1.8) vs 25.8 (±1.9), BW: mean (±SD) 1080 (±272) vs 831 (±266)	>8.3 mmol/L; NA; NA
Ramel 2013; USA; RC; 80[58]	Overall population: mean (±SD) (range) GA: 27.11 (±2.02) (22.57 to 30.71) BW: 943.62 (±246.16) (510 to 1440)	>8.3 mmol/L; first 14 days; 77%
van der Merwe 2013; South Africa; CC; 356[65]	Overall population GA: mean (±SD) 28.3 (±1.7) and BW: mean 949.3	>8.5 mmol/L; NA; NA
Yoo 2013; Korea; RC; 260 (A: 11.16–16.61 mmol/L, B: >16.66 mmol/L)[66]	NG GA: mean (±SD) 27.2 (±2.3), BW: mean (±SD) 886 (±87), permissive HG group (P): GA: 26.2 (±2.2), BW: 796 (±124), treated HG group (T): GA: 24.4 (±2), BW: 677 (±142)	NG (N): ≤11.11 mmol/L; the permissive HG (without treatment) (P): 11.16–16.61 mmol/L and the treated HG (T): ≥16.66 mmol/L; first 14 days; 15%, 39%, 46% in N, P, T groups, respectively
Bozdag 2012; Turkey; PC; 167[40]	No ROP vs ROP group: GA: mean (±SD) 29.6 (±1.79) vs 28.48 (±1.94) and BW: mean (±SD) 1269.07 (±206.6) vs 1092 (±212.9)	>8.33 mmol/L; NA; 56.28%

Table 1 Continued

Study ID; country; study design; sample size	Gestation/BW (in weeks and grams)	Hyperglycaemia definition: age when hyperglycaemia was detected; incidence
Kaempf 2011; USA; CC; 372[49]	Overall population GA: mean (±SD) 27.6 (±1.4), BW: mean (±SD) 994 (±242)	Mild 8.38 to 10 mmol/L; moderate 10.05 to 11.66 mmol/L; severe >11.66 mmol/L; first 29 days Mild ROP: 37%, 20% and 10%; severe ROP: 45%, 25% and 13% No ROP: 26%, 13% and 6% (order: mild, moderate and severe HG)
Chavez Valdez 2011; USA; RC; 114[42]	Overall population GA: mean (±SD) 26.6 (±2), BW: mean (±SD) 782 (±136)	8.33 mmol/L; first 30 days; 79%
Van der Lugt 2010; Netherlands; RC; 859[64]	Overall population GA: mean (±SD) 29.4 (±2.0), BW: mean (±SD) 1323 (±410)	≥10.0 mmol/L; NA; 8%
Alexandrou 2010; Sweden; PC; 113[7]	Overall population GA: mean (±SD): 25.5 (±1.0), BW: mean (±SD): 796 (±162)	>8.3 mmol/L; first week of life; 81%
Heimann 2007; Germany; RC; 252[48]	GA: mean 27.4 (24 to 35) and BW: mean 952.2 (480 to 1500)	Group I: no glucose levels ≥8.33 mmol/L, group II: 1–3 glucose levels ≥8.33 and group III: 4 or more glucose levels ≥8.3; first week; 49.6% in group II, 17.9% in group III
Blanco 2006; USA; RC; 169[38]	NG GA: mean (±SD) 26.8 (±1.5) and for HG cohort: 25.8 (±2.2). NG BW: mean (±SD) 843 (±120) and for HG 742 (±134)	≥8.3 mmol/L; first 2 weeks; 88%
Ertl 2006; Hungary; CC; 201[44]	GA: mean (±SD) ROP 27 (±1.9), no ROP 30.1 (±2.2). BW: mean (±SD) ROP 971 (±227), no ROP 1237 (±192)	>8.5 mmol/L; NA; 19.4%
Hays 2006; USA; CC; 93[1]	GA: 25.4 (±1.9), BW: mean (±SD) 760 (±158)	>8.33 mmol/L; first 7 days; 32% with a threshold of 13.88 mmol/L and 57% with a threshold of 8.33 mmol/L
Kao 2006; USA; RC; 201 A1: 6.66–9.9 mmol/L for 3 days A2: 6.66–9.9 mmol/L for 7 days B1: >9.9 mmol/L for 3 days B2: >9.9 mmol/L for 7 days[36]	Overall population; GA: mean (±SD) 26.2 (±1.9), BW: mean (±SD) 729 (±127)	Mild: moderate HG (6.66 to 9.9 mmol/L) and severe HG (≥10 mmol/L); first 7 days; 38% severe HG
Manzoni 2006; Italy; CC; 383[52]	Group A: invasive fungal infection: GA (group A): 27.5 (±4), BW: mean (±SD): 985 (±240); group B: LOS (bacterial): GA: 27.7 (±4), BW: mean (±SD) 1044 (±235)	≥12 mmol/L; first month; group A: 46.6%, group B: 23.9%
Sutija 2004; USA; CC; 207[62]	ROP vs no ROP; GA: mean 26.1 vs 27, BW: 781.3 vs 944.3	>6.66 mmol/L; first 28 days; NA
Garg 2003; USA; CC; 47[45]	Overall population; GA: mean 25.0 and BW: 717	>8.3 mmol/L; first 30 days; NA
Chen 2001; Taiwan; RC; 127[43]	HG—GA: mean (±SD) 27.9±5.9, BW: 942±258; NG—GA: mean (±SD) 28.8±4.7, BW 1195±229	>8.3 mmol/L; NA; 31%
Lilien 1979; USA; PC; 30[51]	Stressed group (RDS and mechanically ventilated): mean (±SD) 28.6 (±2.19), BW: 1060 (±56). Control (mild RDS without respiratory support): 29.3 (±3.28) BW: 1120 (±72)	>8 mmol/L plasma glucose and >7 for whole blood glucose; NA; 46.6%

BSID, Bayley Scale of Infant Development; BW, birth weight; CA, corrected age; CC, case–control study; CLD, chronic lung disease; CRIB, Clinical Risk Index for Babies; CV, coefficient of variation; DA, developmental assessment; DBP, diastolic blood pressure; ELBW, extremely low birth weight infant; GA, gestational age; HG, hyperglycaemia; IVH, intraventricular haemorrhage; LF, lactoferrin; LOS, late-onset sepsis; MAGE, mean amplitude glucose excursion; NA, not available; NEC, necrotising enterocolitis; NG, normoglycaemia; PC, prospective cohort study; PMA, post-menstrual age; PVL, periventricular leucomalacia; RC, retrospective cohort study; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SBP, systolic blood pressure; SGA, small for gestational age; TPN, total parenteral nutrition; VLBW, very low birth weight infant; WM, white matter.

disease (CLD), necrotising enterocolitis (NEC) and long-term neurodevelopment. Hence, we conducted a systematic review to evaluate the current evidence in this area.

METHODS

This systematic review was conducted using the COSMOS-E guidance[24] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement[25] and MOOSE guidelines.[26] It was registered on the international prospective register of systematic reviews.

Data sources and searches

Three reviewers independently searched the following electronic bibliographic databases since their inception until August 2020: PubMed, EMBASE (through OVID), EMCARE (through OVID), MEDLINE (through OVID), The Cochrane Library and Google Scholar. The ClinicalTrials.gov website was searched to identify ongoing studies. Grey literature was searched on 'Opengrey' and 'Mednar' (http://mednar.com/mednar/desktop/en/search.html) databases. PubMed was searched using the following broad keywords: (((preterm infant) OR (neonate)) OR (very low birth weight)) AND ((Hyperglycaemia) OR (hyperglycaemia)). PubMed was also searched using the following Mesh terms: (("Infant, Premature"[Mesh] OR "Infant, Extremely Premature"[Mesh]) OR ("Infant, Low Birth Weight"[Mesh] OR "Infant, Extremely Low Birth Weight"[Mesh] OR "Infant, Very Low Birth Weight"[Mesh])) AND ("Hyperglycaemia"[Mesh]). Similar terms were used for searching other databases. There were no restrictions on the search with regards to the publication date or language.

Study selection

The following types of studies were included in the review: (1) cohort and case–control studies that evaluated the association between neonatal hyperglycaemia (present vs absent) and clinical outcomes (present vs absent); (2) randomised controlled trials (RCTs) that provided information on the association between hyperglycaemia and adverse outcomes; (3) studies that evaluated the association between duration of hyperglycaemia and clinical outcomes. Outcomes of interest were (1) mortality before hospital discharge, (2) IVH (any grade), (3) severe IVH (grade III or IV based on Papille's classification),[27] (4) ROP (any stage), (5) severe ROP defined as ≥stage 3 or requiring treatment, (6) CLD (need for respiratory support or oxygen at 36 weeks post-menstrual age), (7) late-onset sepsis (LOS): positive blood culture on a sample collected after 72 hours of birth, (8) PVL, (9) any-stage NEC, (10) NEC ≥stage II (as per modified Bell's classification[28]) and (11) long-term developmental outcomes based on validated tools.

Table 2 Newcastle–Ottawa scale for cohort studies

Study ID	Selection — Representativeness of the exposed cohort	Selection — Selection of the non-exposed cohort	Selection — Ascertainment of exposure	Selection — Demonstration that outcome of interest was not present at start of study	Comparability — Comparability of cohorts on the basis of the design or analysis	Outcome — Assessment of outcome	Outcome — Was follow-up long enough for outcomes to occur?	Outcome — Adequacy of follow-up of cohorts	Total score
Akmal_2017_Egypt	*	*	*	*		*	*	*	7
Alexandrou_2010_Sweden	*	*	*	*	**	*	*	*	9
Blanco_2006_USA	*	*	*	*	**	*	*	*	9
Bochkova_2019_Russia[+]	*			*		*	*	*	5
Bozdag_2012_Turkey	*	*	*	*	**	*	*	*	9
Cardona_2014_USA[+]	*	*	*	*	**	*	*	*	9
Chen_2001_Taiwan	*	*	*	*		*	*	*	7
De Carolis _2015_Italy[+]	*	*	*	*		*	*	*	7
Goldner Perez_ 2019_USA[+]	*		*	*		*	*		5
Heimann_2007_Germany	*	*	*	*		*	*	*	7
Jagla_2019_Poland	*	*	*	*	**	*	*	*	9
Kao_2006_USA	*	*	*	*	**	*	*	*	9
Lilien_1979_USA	*	*	*	*		*	*	*	7
Manzoni_2016_Italy[+]	*	*	*	*	**	*	*	*	9
Mohsen_2014_Egypt	*	*	*	*	**	*	*	*	9
Nicolaeva _2015_Russia	*	*	*	*		*	*	*	7
Ramel_2013_USA	*	*	*	*	**	*	*	*	9
Sabzehei_2014_Iran	*	*	*	*	**	*	*	*	9
Scheurer_2016_USA	*	*	*	*	**	*	*	*	9
Stensvold_2015_Norway	*		*	*	**	*	*	*	8
Szymońska_2015_Poland	*	*	*	*	**	*	*	*	9
Tottman_2017_Newzealand	*	*	*	*	**	*	*		8
Turai_2019_Hungary	*	*	*	*	**	*	*	*	9
Van der Lugt_2010_ Netherlands	*	*	*	*	**	*	*	*	9
Vannadil_2019_India	*			*		*	*	*	5
Villamizar_2020_USA	*	*	*	*	**	*	*	*	9
Yoo_2013_Korea	*	*	*	*	**	*	*	*	9
Zamir_2018_Sweden	*	*	*	*	**	*	*	*	9
Zamir_2019_Sweden	*	*	*	*	**	*	*	*	9
+Abstract only.									

Data extraction and quality assessment

Titles and abstracts identified in the initial broad search were read by two independent reviewers. Full-text articles of the potentially eligible studies were read in detail by two reviewers to confirm their eligibility for inclusion. A standardised form was used to extract data. The incidences of the clinical outcomes of interest in the two groups (hyperglycaemia; no hyperglycaemia) were abstracted. If the authors had provided ORs or risk ratios (adjusted or unadjusted) for those outcomes, they were recorded. Information about the association between duration of hyperglycaemia and clinical outcomes (adjusted and unadjusted ORs) was also collected.

All authors were contacted to provide additional information; seven acknowledged our request, of which two[13 14] provided additional information. Each included article was reviewed by three independent reviewers to assess the methodological quality using the Newcastle–Ottawa scale (NOS).[29]

Data synthesis

Meta-analysis was performed using the Review Manager V.5.4 (Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark) and Stata V.16.0 software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). We separately pooled the reported adjusted and unadjusted ORs from included studies using the inverse-variance method (Cochrane Handbook section 10.3.3). Subgroup analysis was carried out based on study design (cohort and case control). Random-effects model (DerSimonian and Laird) was used for meta-analysis since heterogeneity was expected. If the published manuscripts of the included studies did not have information on ORs, we used the raw numbers to calculate unadjusted ORs using contingency tables prior to pooling. For dichotomous outcomes, the pooled effect size estimates were presented as pooled ORs with 95% CIs. Qualitative synthesis was done for studies where meta-analysis was not possible. Publication bias was assessed using visual inspection of the contour-enhanced funnel plots,[30] Egger's test[31] and Begg's test[32] if ≥10 studies were included for any individual meta-analysis. If these results suggested the possibility of publication bias, nonparametric trim-and-fill analysis was conducted.[33] Statistical heterogeneity was assessed using visual inspection of the forest plots and quantified using the I^2 statistic. The I^2 result was interpreted as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%:

Table 3 Newcastle–Ottawa scale for cohort studies

Study ID	Selection				Comparability	Exposure			
	Is the case definition adequate?	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of design or analysis	Ascertainment of exposure	Same method of ascertainment of cases and controls	Non-response rate	Total score
Ahmadpour-Kacho_2014_Iran	*	*	*	*	**	*	*	*	9
Auerbach_2013_Israel	*	*	*	*	**	*	*	*	9
Bermick_2016_USA	*	*	*	*	**	*	*	*	9
Chavez-Valdez_2011_USA	*	*	*	*	**	*	*	*	9
Ertl_2006_Hungary	*	*	*	*	**	*	*	*	9
Garg_2003_USA	*	*	*	*	**	*	*	*	9
Hays_2006_USA	*	*	*	*	**	*	*	*	9
Kaempf_2011_USA	*	*	*	*	**	*	*	*	9
Kim_2017_Korea	*	*	*	*	**	*	*	*	9
Lee_2016_USA	*	*	*	*	**	*	*	*	9
Manzoni_2006_Italy	*	*	*	*	**	*	*	*	9
Mohamed_2013_USA	*	*	*	*	**	*	*	*	9
Naseh_2017_Sweden[+]	*		*	*			*		4
Reyes_2017_Oman	*	*	*	*	**	*	*	*	9
Slidsborg_2018_Denmark	*	*	*	*	**	*	*	*	9
Sutija_2004_USA[+]	*	*	*	*		*	*	*	7
van der Merwe _2013_South Africa	*	*	*	*	**	*	*	*	9
+Abstract only.									

may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity (Cochrane Handbook).[34] Contingent on availability of adequate data, where necessary, meta-regression was performed[35] to evaluate the association between severity of hyperglycaemia and adverse outcomes after adjusting for the gestational age and birth weight. Some studies had given results for different thresholds of blood glucose levels (eg, 8.3 and 15 mmol/L).[11] Some had given results separately for duration of hyperglycaemia, for example, within the first 72 hours of life and first 1 week of life.[36] In such situations, only the result with least SE was used for pooling. This approach was chosen because if multiple results from the same study were considered as results of separate study while pooling, it would have spuriously exaggerated the sample size. However, a limitation of this approach was the loss of information which was overcome by conducting a sensitivity analysis wherein such multiple results from the same study were considered as results of separate studies while pooling.

RESULTS

Literature search and study selection

A PRISMA flow chart of screening and selection results is shown in online supplemental efigure 1. The initial search identified 1775 articles of which 46 studies were included after application of the selection criteria.[1 5 7–9 11–16 36–70] Out of these studies 18, 19, 21, 10, 10, 10, 4 and 3 studies were included in the meta-analysis for mortality, IVH, ROP, LOS, CLD, NEC, PVL and neurodevelopmental outcomes, respectively. The total sample size was 34 527 and the number of infants in individual studies ranged between 30 and 859, but one large multinational database study had a sample size of 24 548. Among the 46 studies, 16 were case–control studies,[1 14 15 37 44 45 49 50 52 54 56 61 62 65 69 70] 13 were prospective cohort studies[7–9 11 13 39 40 47 51 55 57 60 67] and 17 were retrospective cohort studies[5 12 16 36 38 41–43 46 48 53 58 59 63 64 66 68] (table 1 and online supplemental etable 1). Ten out of 46 included studies

specifically addressed the issue of association between duration of hyperglycaemia and adverse outcomes.[14 40 41 47 54 56 58 60 67 70] The median number of stars in the cohort studies as assessed by NOS was 9 (IQR 7 to 9). The median number of stars in the case–control studies as assessed by NOS was 9 (IQR 9 to 9) (tables 2 and 3).

Overall analysis

Table 4 provides an overview of results of individual studies. Pooling of unadjusted ORs from cohort studies found hyperglycaemia to be significantly associated with mortality, any-grade IVH, severe IVH, any-stage ROP, severe ROP, LOS, CLD and disability. However, pooling of adjusted ORs from cohort studies found significant associations for mortality (figure 1), any-grade IVH and any-stage ROP (online supplemental efigures 2 and 3). Hyperglycaemia was not associated with NEC, severe NEC and PVL, either on adjusted ORs or unadjusted ORs. The detailed results of meta-analysis are given in table 5 and online supplemental efigures 2–11.

Association between duration of hyperglycaemia and adverse outcomes

Ten studies that examined the association between duration of hyperglycaemia and the adverse outcomes reported a significant association.[14 40 41 47 54 56 58 60 67 70] Of them, four studies reported a significant association between duration of hyperglycaemia and ROP,[40 41 54 70] of which the association remained significant on multivariate analysis in two studies.[40 54] One study reported a significant association between duration of hyperglycaemia and severe IVH on both univariate and multivariate analysis.[14] Two studies reported that infants with >5 days of hyperglycaemia were significantly lighter, shorter and had smaller occipital-frontal head circumference at 4 months and 24 months corrected age.[58 60] These findings remained significant after correcting

Table 4 Overview of the results of the included studies

Study ID	Mortality		Any-grade IVH		Severe IVH		Any-stage ROP		Severe ROP		LOS		NEC undefined		Severe NEC		CLD		PVL		Disability/developmental outcome	
	U	A	U	A	U	A	U	A	U	A	U	A	U	A	U	A	U	A	U	A	U	A
Ahmadpour Kacho 2014[37]	.	.	.	.	.	.	↑	↑	.	.	.	.	.	.	.	.	.	.	.	.	.	↑
Akmal 2017A[11]	↑	.	↑	.	.	.	.	.	.	.	↑	.	↕	.	.	.	.	.	.	.	.	.
Akmal 2017B[11]	↑	.	↑	.	.	.	.	.	.	.	↑	.	↕	.	.	.	.	.	.	.	.	.
Alexandrou 2010A[7]	↑	↑	↕	↕	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Alexandrou 2010B[7]	.	.	↕	↕	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Auerbach 2013[14]	.	.	.	.	↑	↑	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Bermick 2016A[15]	.	.	↕	.	↑	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Bermick 2016B[15]	.	.	↕	.	↑	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Bermick 2016C[15]	.	.	↑	↕	↑	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Blanco 2006[38]	↕	↕	.	↕	.	.	↑	↑	↕	.	.	.	.	.	.	.	↕	.	.	.	.	.
Bochkova 2019[39]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Bozdag 2012[40]	.	.	.	.	.	.	↑	↑	↑	.	.	.	.	.	.	.	.	.	.	.	.	.
Cardona 2014[41]	.	.	.	.	.	.	↑	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Chavez Valdez 2011[42]	.	.	.	.	.	.	.	.	↑	↑	.	.	.	.	.	.	.	.	.	.	.	.
Chen 2001[43]	↑	.	↑	.	↑	.	.	.	.	.	↕	.	.	.	.	.	.	.	↑	.	.	.
De Carolis 2015[16]	↕	.	↑	.	↑	.	↑	.	↑	.	↑	.	↕	.	.	.	.	.	.	.	.	.
Ertl 2006[44]	.	.	.	.	.	.	↑	↑	↑	.	.	.	.	.	.	.	.	.	.	.	.	.
Garg 2003[45]	.	.	.	.	.	.	.	.	↑	↑	.	.	.	.	.	.	.	.	.	.	.	.
Goldner Perez 2019[46]	↕	.	↕	.	.	.	.	.	.	.	.	.	.	↑	.	.	↕	.	.	.	↑	↑
Hays 2006[1]	↑	↑	.	.	↑	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Heimann 2007[48]	↑	↑	↕	.	↑	↑	↕	.	↑	.	↕	.	.	.	.	.	.	.	.	.	.	.
Jagla 2019[8]	↕	.	.	.	↕	↕	↑	.	↑	↕	.	.	.	.	.	.	.	.	↕	.	.	.
Kaempf 2011[49]	.	.	.	.	.	.	↑	.	↑	.	.	.	.	.	.	.	.	.	.	.	.	.
Kao 2006A1[36]	↕	↕	.	.	.	.	.	.	.	.	↕	↕	.	.	.	.	.	.	.	.	.	.
Kao 2006A2[36]	↑	↕	.	.	.	.	.	.	.	.	↕	↕	.	.	.	.	.	.	.	.	.	.
Kao 2006B1[36]	↑	↑	.	.	.	.	.	.	.	.	↕	↕	.	.	↑	.	.	.	.	.	.	.
Kao 2006B2[36]	↑	↑	.	.	.	.	.	.	.	.	↕	↕	.	.	↑	↑	.	.	.	.	.	.
Kim 2017[70]	.	.	.	.	.	.	↑	↕	↑	↕	.	.	.	.	.	.	.	.	.	.	.	.
Lee 2016[50]	.	.	.	.	.	.	.	.	↑	↕	.	.	.	.	.	.	.	.	.	.	.	.
Lilian 1979[51]	↑	.	↑	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Manzoni 2006[52]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Manzoni 2016[53]	.	.	.	.	.	.	.	.	.	.	.	↑	.	.	.	.	.	.	.	.	.	.
Mohamed 2013[54]	.	.	.	.	.	.	.	.	↕	↕	.	.	.	.	.	.	.	.	.	.	.	.
Mohsen 2014[55]	↑	↑	↕	.	.	.	↑	↑	↕	.	.	.	.	.	.	.	↕	.	.	.	.	.
Naseh 2017[56]	.	.	.	.	.	.	↑	.	↑	.	.	.	.	.	.	.	.	.	↑	↕	↑	.
Nicolaeva 2015[57]	.	.	.	.	.	.	.	.	↑	.	.	.	.	.	.	.	.	.	.	.	.	.
Ramel 2013[58]	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	↕	.
Reyes 2017[69]	.	.	.	.	.	.	↑	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Table 4 Continued

Study ID	Mortality	Any-grade IVH	Severe IVH	Any-stage ROP	Severe ROP	LOS	NEC undefined	Severe NEC	CLD	PVL	Disability/developmental outcome
Sabzehei 2014[59]	↑	.	↑	↔	↔	↔	.	↔	↑	↔	.
Scheurer 2016A[60]	.	↑	.	↑	.	.	.	.	.	.	.
Scheurer 2016B[60]	.	↑	.	↑	.	.	.	.	.	.	.
Slidsborg 2018[61]	.	.	.	.	↑	.	.	.	.	.	.
Stensvold 2015A[12]	↔	.	.	.	.	.	.	.	.	.	.
Stensvold 2015B[12]	↔	.	.	.	.	.	.	.	.	.	.
Stensvold 2015C[12]	↑	.	.	.	.	.	.	.	.	.	.
Sutija 2004[62]	.	.	.	↑	.	.	.	.	.	.	.
Szymonska 2015A[13]	↔	↑	↔	↔	↔	↔	.	↔	↔	↔	.
Szymonska 2015B[13]	↔	↔	↔	↔	↔	↔	.	↔	↔	↔	.
Tottman 2017[63]	↑	.	↔	.	↑	↑	.	↑	↑	↔	↔
Turai 2019[68]	↔	↔	↔	↔	↑	.	.	.	↑	.	.
Van Der Lugt 2010[64]	↑	.	↔	.	.	↔	.	↔	↔	↔	↑
Van der Merwe 2013[65]	.	.	.	.	↑	.	.	.	.	.	.
Vannadii 2019[9]	.	.	.	↑	.	.	.	.	.	.	.
Villamizar 2020	.	.	.	.	.	.	.	.	.	.	↑
Yoo 2013A[66]	↔	.	↔	.	↔	.	.	↔	↔	.	↔
Yoo 2013B[66]	↔	.	↑	.	↑	.	.	↔	↑	.	↔
Zamir 2018[5]	↑	.	↔	.	.	.	↔	.	.	.	.
Zamir 2019[67]	.	.	.	.	.	.	.	.	.	.	.

Arrows indicate whether there is an association (↑), reported as no significant association (↔). Dot (.) indicates no report.

A, adjusted; CLD, chronic lung disease; IVH, intraventricular haemorrhage; LOS, late-onset sepsis; NEC, necrotising enterocolitis; PVL, periventricular leucomalacia; ROP, retinopathy of prematurity; U, unadjusted.
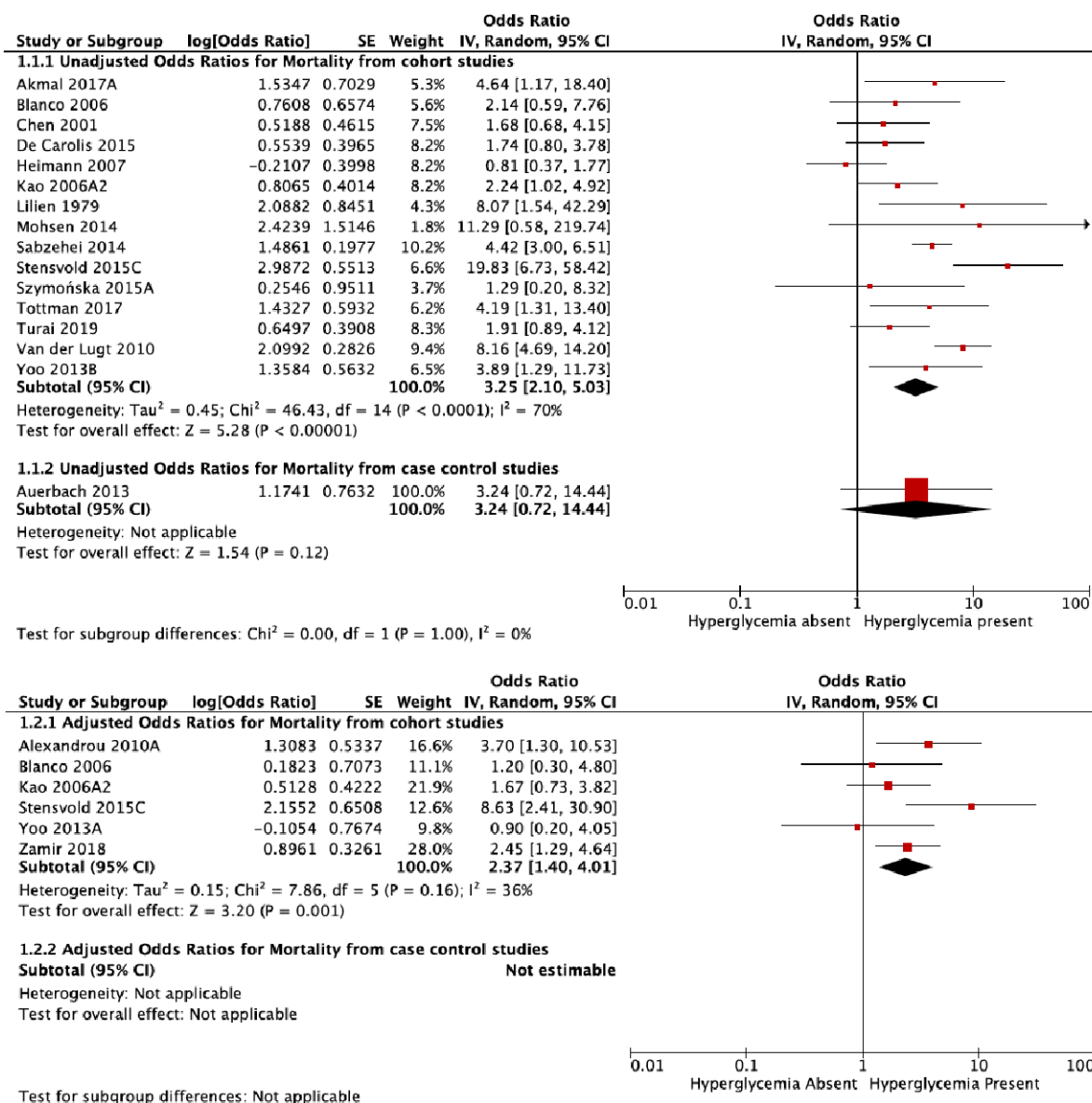
Figure 1 Forest plot showing the association between hyperglycaemic and mortality. IV, inverse variance.

for nutritional and illness factors.[60] Two studies reported that prolonged duration of hyperglycaemia was associated with poorer cognition, language and motor performance at 1–2.5 years and the association remained significant in multivariate analysis.[47 56] We could not pool the aforementioned information in an exclusive meta-analysis since the outcomes of interest were heterogenous.

Sensitivity analysis
Results of the sensitivity analysis were similar to the primary analysis (online supplemental etable 2).

Meta-regression analysis
The meta-regression analysis found that blood glucose levels ≥10 mmol/L were associated with higher odds of mortality compared with <10 mmol/L (regression coefficient 1.0563 (95% CI 0.2193 to 1.8933), p=0.013) (online supplemental efigure 12). On the other hand, there was no association between blood glucose level and the odds of any-grade IVH (regression coefficient −0.2460 (95% CI −1.3729 to 1.3237), p=0.971) (online

supplemental efigure 13). Meta-regression could not be done for the remaining outcomes since there were <10 studies.

Publication bias
Publication bias was assessed only for the outcomes of mortality (unadjusted) and any IVH (unadjusted) since they had ≥10 studies in the meta-analysis. Visual inspection of the contour-enhanced funnel plots and the results of Begg's test or Egger's test suggested publication bias was unlikely for unadjusted mortality (Egger test p=0.59, Begg test p=0.49). The contour-enhanced funnel plot for studies reporting unadjusted mortality is depicted in figure 2. The results of Begg's and Egger's test (p values 0.02 and 0.01) suggested the possibility of funnel plot asymmetry for unadjusted any-grade IVH (online supplemental efigure 14). The results of trim-and-fill analysis that imputed three additional studies continued to show significant association between hyperglycaemia and any-grade IVH (original OR 2.30 (1.55 to 3.40); new OR 1.85 (1.18 to 2.88)). We revisited our literature search after noticing funnel plot asymmetry but did not find any additional studies.

Table 5 Pooled OR (95% CI), heterogeneity (I^2 and p value of the outcomes)

Cohort studies

Outcome	Reference of studies included	Total number of studies included	Pooled OR (95% CI)	I^2 (%)	P value
Mortality (unadjusted)	11–13 16 36 38 43 48 51 55 59 63 64 66 68	15	3.25 (2.10 to 5.03)	70	**<0.00001**
Mortality (adjusted)	5 7 12 36 38 66	6	2.37 (1.40 to 4.01)	36	**0.001**
Any-grade IVH (unadjusted)	7 11 13 16 46 48 51 55 60 68	10	2.30 (1.55 to 3.40)	36	**<0.00001**
Any-grade IVH (adjusted)	7 38	2	2.60 (1.09 to 6.20)	0	**0.03**
Severe IVH (unadjusted)	5 13 16 43 59 63 64 66 68	9	1.85 (1.37 to 2.51)	39	**<0.00001**
Severe IVH (adjusted)	66	1	0.80 (0.20 to 3.20)	NA	0.75
Any-stage ROP (unadjusted)	13 38 40 48 55 59 68	7	1.78 (1.12 to 2.83)	42	**0.01**
Any-stage ROP (adjusted)	38 40	2	3.70 (1.55 to 8.84)	0	**0.003**
Severe ROP (unadjusted)	13 16 40 42 59 60 63 66 68	9	3.42 (1.82 to 6.41)	64	**0.0001**
Severe ROP (adjusted)	8 66 68	3	1.97 (0.56 to 6.93)	91	0.29
LOS (unadjusted)	11 13 16 36 43 48 59 63 64	9	1.97 (1.18 to 3.28)	69	**0.009**
LOS (adjusted)	36 53 59	3	1.38 (0.41 to 4.72)	81	0.60
Undefined NEC (unadjusted)	5 11 16 46	4	1.29 (0.72 to 2.30)	0	0.39
Undefined NEC (adjusted)	No study has reported				
Severe NEC (unadjusted)	13 36 59 63 64 66	6	1.91 (0.74 to 4.89)	47	0.18
Severe NEC (adjusted)	36 59 66	3	1.78 (0.29 to 10.7)	65	0.53
CLD (unadjusted)	13 46 55 59 63 64 66 68	8	2.55 (1.96 to 3.30)	0	**<0.00001**
CLD (adjusted)	38 59 66	3	1.42 (0.85 to 2.37)	0	0.18
PVL (unadjusted)	13 63 64 66	4	1.01 (0.40 to 2.56)	0	0.98
PVL (adjusted)	66	1	0.50 (0.20 to 1.25	NA	0.14
Any disability (unadjusted)	63 64 66	3	2.35 (1.47 to 3.73)	0	**0.003**
Any disability (adjusted)	63	1	1.27 (0.56 to 2.86)	NA	0.57
Case–control studies					
Mortality (unadjusted)	14	1	3.24 (0.72 to 14.44)	NA	0.12
Mortality (adjusted)	No studies available				
Any-grade IVH (unadjusted)	15	1	2.3 (1.3 to 4.07)	NA	**0.004**
Any-grade IVH (adjusted)	No studies available				
Severe IVH (unadjusted)	14 15	2	2.58 (1.48 to 4.48)	0	**0.0008**
Severe IVH (adjusted)	14	1	10.33 (10 to 10.67)	NA	**<0.00001**
Any-stage ROP (unadjusted)	37 44 69	3	6.49 (1.97 to 2139)	82	**0.002**
Any-stage ROP (adjusted)	37 44 54	3	1.26 (0.79 to 2.00)	52	0.33
Severe ROP (unadjusted)	45 50 65	3	2.15 (1.98 to 2.34)	0	**<0.00001**
Severe ROP (adjusted)	45 50 54 61	4	1.01 (0.96 to 1.07)	42	0.67
LOS (unadjusted)	No studies available				
LOS (adjusted)	No studies available				
Undefined NEC (unadjusted)	No studies available				
Undefined NEC (adjusted)	No studies available				
Severe NEC (unadjusted)	No studies available				
Severe NEC (adjusted)	No studies available				
CLD (unadjusted)	14	1	3.07 (0.87 to 10.81)	NA	0.08
CLD (adjusted)	No studies available				
PVL (unadjusted)	No studies available				
PVL (adjusted)	No studies available				
Any disability (unadjusted)	No studies available				
Any disability (adjusted)	No studies available				

CLD, chronic lung disease; IVH, intraventricular haemorrhage; LOS, late-onset sepsis; NA, not applicable; NEC, necrotising enterocolitis; PVL, periventricular leucomalacia; ROP, retinopathy of prematurity.

GRADE evidence

GRADE of evidence was 'Low' or 'Very low' for all outcomes (online supplemental etable 3).

DISCUSSION

This systematic review, which included 46 studies (n=34 527), found that neonatal hyperglycaemia is associated with mortality, any-grade IVH and any-stage ROP based on pooled adjusted ORs in very preterm infants. The evidence was inadequate for other outcomes as very few studies had reported adjusted ORs. While pooled unadjusted ORs suggested a significant association between hyperglycaemia and majority of the adverse outcomes such as severe ROP, late-onset sepsis, CLD and disability, these
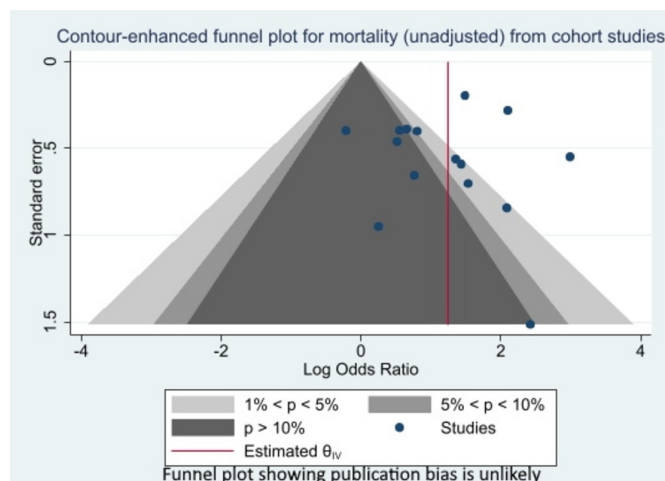
Figure 2 Funnel plot of studies reporting mortality (unadjusted).

results are probably less reliable given that the confounding factors were not adjusted for.

There is a physiological plausibility that the duration and the severity of hyperglycaemia might contribute to mortality and morbidity due to proinflammatory effect, changes in osmolality, fluid shifts, and direct cellular effects in various organs, particularly in the fragile preterm brain.

A recent systematic review involving critically ill adult patients found intensive glucose control significantly reduced the risk of all-cause mortality, length of ICU stay and acquired infections.[71] A meta-analysis of six studies in critically ill children concluded that tight glycaemic control does not reduce mortality but reduces the need for dialysis.[72] Overall, these systematic reviews found tight control group to have higher incidence of hypoglycaemia. A recent observational study including 580 extremely preterm infants concluded that insulin treatment was associated with lower mortality in infants with hyperglycaemia.[5] A RCT of prophylactic infusion therapy in 389 VLBW infants reported that insulin reduces hyperglycaemia but may increase the risk of hypoglycaemia.[73] In a RCT (n=88) of insulin for treatment of hyperglycaemia in preterm infants (<30 weeks), the 'tight glycaemic control with insulin' group showed better weight gain and head growth but reduced linear growth and increased risk of hypoglycaemia.[74] However, nearly 64% of the infants in the control group also had received insulin infusion. At 7 years of follow-up, there was no difference in the incidence of survival without disability, but the tight control group had reduced height, increased height-adjusted lean mass and lower fasting blood glucose concentrations.[75]

The current strategies to treat hyperglycaemia using low glucose infusion rates and insulin therapy are not without problems. Reduced glucose infusion results in poor nutrition delivery which may have consequences for neurodevelopment and growth. On the other hand, insulin therapy can increase the risk of hypoglycaemia, leading to poor outcomes. It is also possible that comorbidities like hypoxia, inflammation, infection or ischaemia causing hyperglycaemia might directly contribute to the morbidity and hence treating hyperglycaemia may not improve outcomes. Strategies such as continuous glucose monitoring to titrate insulin therapy, appropriate insulin therapy to target a liberal glucose level, targeting novel pathophysiological pathways or their combinations need further evaluation.

An important limitation of our review was the lack of data from some studies in a format suitable for pooling, especially for

adjusted ORs. Future observational studies should endeavour to report ORs after adjusting for confounders. Another limitation was the presence of statistical heterogeneity in some outcome measures. We tried to address heterogeneity using three approaches: (1) random-effects model in the meta-analysis; (2) meta-regression wherever there were more than 10 studies in the meta-analysis; (3) analysis of cohort and case–control studies separately. While interpreting the results of our review, it is also important to be aware that association does not always mean cause-and-effect relation. The hyperglycaemia might just be a passenger/marker in another disease process rather than being the causative agent. The strengths of our review include its rigorous methodology, separate pooling of adjusted and unadjusted ORs, sensitivity analyses, meta-regression, the use of contour-enhanced funnel plots, formal statistical tests to assess funnel plot asymmetry and the trim-and-fill analysis. To our knowledge, it is the first systematic review that addresses the association between hyperglycaemia and various adverse outcomes in preterm infants.

CONCLUSIONS
Neonatal hyperglycaemia in preterm infants is associated with higher odds of mortality, any-grade IVH and any-stage ROP. RCTs evaluating the efficacy and safety of strategies to treat hyperglycaemia are needed.

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