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.

PROSPERO registration number CRD42020193016.

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.

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]

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

Continued

Table 1 Continued

Study ID; country; study design; sample size	Gestation/BW (in weeks and grams)	Hyperglycaemia definition: age when hyperglycaemia was detected; incidence
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%
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: 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

Table 2 Newcastle–Ottawa scale for cohort studies

	Selection				Comparability	Outcome			
Study ID	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	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.

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.

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.

Table 3 Newcastle–Ottawa scale for cohort studies

	Selection				Comparability	Exposure			
Study ID	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.

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, non-parametric 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%: 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).

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]	.	.	.	.	.	.	↑	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Continued

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]	.	.	.	.	.	.	.	.	↑	.	.	.	.	.	.	.	.	.	.	.	.	.
Vannadil 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.

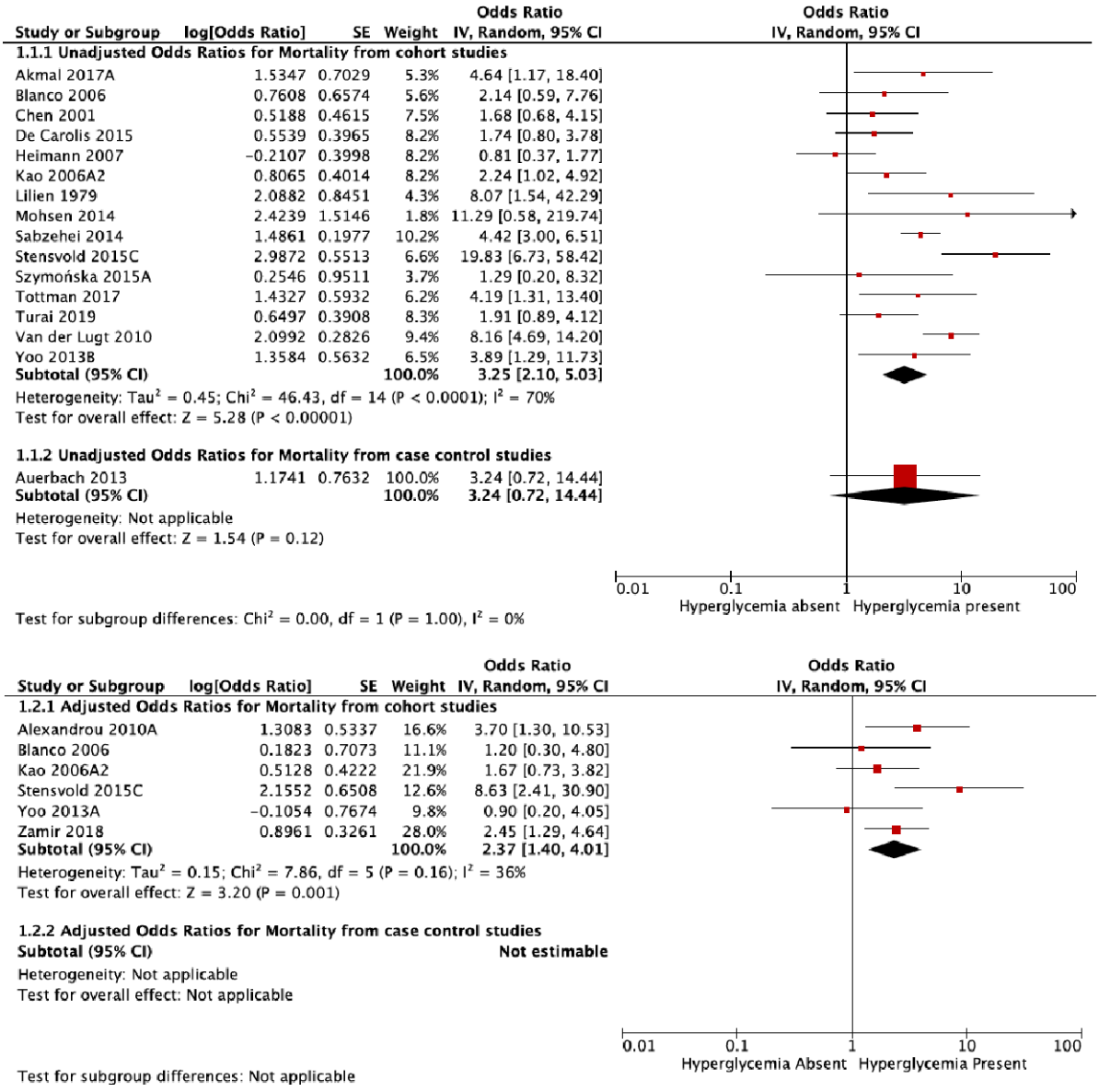

Figure 1 Forest plot showing the association between hyperglycaemic and mortality. IV, inverse variance.

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 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

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

Outcome	Reference of studies included	Total number of studies included	Pooled OR (95% CI)	I^2 (%)	P value
Cohort studies					
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.

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).

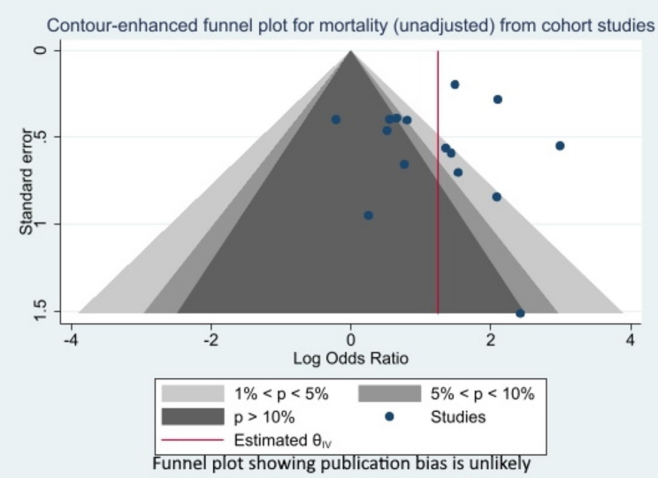

Figure 2 Funnel plot of studies reporting mortality (unadjusted).

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.

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 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.

Contributors CPR and SCR conceptualised and designed the study, data collection instruments, drafted the initial manuscript, carried out the initial analyses, and reviewed and revised the manuscript. MS, SM and CPR collected data, reviewed and revised the manuscript. SP coordinated and supervised data collection, and critically reviewed the manuscript.

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of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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e Table 1: Study Outcomes

Study ID	Results	Covariates adjusted for	Author's conclusion
Villamizar 2020	HG for ≥5 days was negatively associated with fat mass and fat free mass z scores at discharge, and fat free mass z score at 4 months' PMA. Hyperglycaemia for ≥5 days was negatively associated with cognition, language, and motor scores on the BSDI-III at 12months. Associations with body composition and BSID-III were diminished when models included first week nutrition yet remained unchanged when illness severity was included.	Gender, GA, CRIB score	HG is associated with decreased lean mass at 4 months' PMA and poorer neurodevelopmental outcome at 12 months' PMA.
Vannadil 2019	Group with higher maximum glucose (Mean 10.15 ± 0.89 mmol/L vs mean 8.71 ± 0.59		A high average blood glucose level in neonates during the

	mmol/L) had a higher incidence of ROP. p=0.179.		first week of life is an indicator for developing ROP at a later date
Bochkova 2019	9 babies from the insulin group and 7 from the no insulin group developed grade II and III IVH.		In preterm infants with VLBW, HG can be considered a transitional state. The appointment of insulin inappropriate
Jagla 2019	Univariate analysis revealed that HG was not associated with mortality before term-equivalent age (p=0.664). Higher GV was associated with grade 3 or 4 IVH (CV p=0.025; MAGE p=0.032) and ROP requiring treatment (SD p=0.019; CV p=0.026; MAGE=0.029). However, logistic regression models did not show a significant association between GV and grade 3 or 4 IVH (MAGE OR 1.31; 95% CI 0.16-10.67) or ROP requiring treatment (MAGE OR 1.74; 95% CI 0.57-5.32).	GA, O2 exposure	Logistic regression model did not show any association between glucose variability and severe IVH or ROP. No association was found between HG and IVH or PVL or mortality.
Zamir 2019	HG and its duration during postnatal weeks 1–4 were associated primarily with higher diastolic BP z-scores at 6.5 years of age. Duration of hyperglycaemia >14 mmol/L was significantly positively associated with both SBP and DBP z-scores. Each additional day with hyperglycaemia >14mmol/L was associated with an increase of ~0.05 SD in both SBP and DBP (P=0.047 and 0.014, respectively).		HG and its duration during postnatal weeks 1–4 were associated primarily with higher diastolic BP z-scores.
Goldner Perez 2019	No deaths either in HG or NG group. Incidence of NEC and PDA was more in HG group compared to NG group and is statistically significant (p= 0.039 and 0.001 respectively), whereas the incidence of CLD and IVH was not statistically significant. Moderate HG in the first week (p=0.002) and month (p=0.026) of life was associated with motor deficits. Composite BSID score was significantly lower (1SD) in infants with HG greater than 10mmol/L in the first week of life (p=0.02), but not in the first month.		HG had minimal effect on neurodevelopment. Moderate HG in the 1st week of life is associated with motor and language deficits, including after adjusting for GA and BW.
Turai 2019	No significant difference in terms of mortality (p=0.093). The GA and BW of the hyperglycaemic infants were significantly lower (p<0.001). The incidence of severe ROP and CLD was significantly higher in HG group (p= 0.012 and 0.002). Among survivors (n = 155), HG was a risk factor for severe retinopathy (p<0.001) in logistic regression analysis. Out of 17 patients with high creatinine 10 had HG.	GA, BW	HG is common in preterm infants. Monitoring of these infants for ROP, kidney dysfunction, and hypertension is recommended.
Zamir 2018	Higher 28-day mortality by a multiplicative factor of 2.45, adjusted for GA and BW (Beta 0.897; *P* = .006). HG for 2 consecutive days-multiplicative factor of 2.55, adjusted GA and BW (B 0.935; *P* = .005). No differences were noted with regards to sex, NEC, IVH grades 3-4 or number of confirmed sepsis events between HG and NG group.	GA, BW	HG during the first 28 days is associated with increased mortality. Insulin treatment during this period was associated with lower mortality.
Slidsborg	After adjustment for known risk factors,	GA, SGA,	An independent association

2018	hyperglycaemic index remained a statistically independent risk factor for development of treatment demanding ROP (OR: 1.022; 95%CI 1.002 to 1.042; p 0.031)	Gender	was found between HG events and treatment demanding ROP, when adjusted for known risk factors.
Naseh 2017	Days with glucose >8.3 mmol/l correlated independently with reduced white matter volume (p = 0.045). When BW was included in the analysis, days with glucose >8.3 mmol/l reached borderline significance (p = 0.068). In the 45 infants with follow up, only days with glucose >8.3 mmol/l was independently associated with a lower motor index on BSID-III.		Prolonged duration of high blood glucose >8.3 mmol/l during the first week of life is associated with reduced white matter volume and may also be associated with poorer motor performance at 2.5 years
Tottman 2017	Death in NG group 6/287 (2%) vs HG group 6/73 (8%) before discharge. Infants in the NG category had shorter neonatal stays and were less likely to have severe ROP, NEC, LOS, or CLD. HG and unstable infants were less likely to survive without neonatal morbidity and less likely to survive without neurodevelopmental impairment at 2 years of age. Higher mean blood glucose concentration was seen in the HG and unstable groups, and was associated with worse neonatal and 2-year outcomes. No associations between measures of neonatal glycemia and neonatal or 2-year outcomes remained after correction for gestation, birth weight z-score, and socioeconomic status.	GA, BW, ethnicity, CRIB II score Socioeconomic quantile, type of assessment at 2 years	In very preterm infants, measures of neonatal glycemia are markers of GA and intrauterine growth, and are not independent predictors of neonatal illness or outcomes at 2 years of age
Akmal 2017	Mortality- HG- 18 out of 40 neonates, NG-3 out of 20 neonates, p= 0.022. Mild/moderate HG vs Severe HG 7 /20 neonates vs 11 /20 neonates, P=0.2. There was statistically significant relation between HG and LOS and IVH. (p = 0.001, 0.003 respectively). There was statistically significant relation between severity of HG and infection in 1st week and IVH (p = 0.025 & 0.05 respectively). A significant negative correlation was found with GA and BW (p = 0.019, 0.002 respectively).		There was a statistically significant relation between HG and complications (LOS, IVH, death).
Kim 2017	In glycaemic characteristics, HG duration, average and maximum glucose level for 3 weeks after birth showed statistical significance in relation to ROP. But, in a multivariate analysis glycaemic characteristic were not. In comparisons based on ROP severity, HG duration, average blood glucose level of 3rd week after birth, and insulin use showed significant difference, but they were not independent factors.		Glycaemic characteristics were statistically significantly associated with ROP, but they were not independent factors associated with ROP development.
Reyes 2017	HG was significantly associated with ROP with a p value of 0.031.		HG is an important risk factor for ROP.
Bermick 2016	IVH developed more frequently in infants with HG (P = 0.006, odds ratio (OR) 2.3, 95% confidence interval (CI) 1.3 to 4.1), in infants with hypernatremia (P = 0.018, OR 2.0, 95% CI 1.2 to 3.5) and in infants with hypernatremia plus HG (P = 0.001, OR 3.2, 95% CI 1.6 to 6.4). Multivariate regression analysis confirmed the independent association of		HG increases the risk of IVH in hypernatremic preterm infants

	higher risk of IVH with the presence of hypernatremia plus HG (P = 0.015, OR 2.6, 95% CI 1.2 to 5.5) but not with hypernatremia or HG alone.		
Lee 2016	HG alone was not associated with severe ROP (OR=0.88 (95% CI 0.66-1.17)).	GA, SGA status, year of discharge, sex, APGAR score at 5 minutes, need for mechanical ventilation, O2 supplementation, steroid use, insulin use, bacteraemia	HG alone was not associated with severe ROP in ELBW infants.
Manzoni 2016	After controlling for all variables significantly associated with infections (i.e., LF exposure, birth weight, gestational age), occurrence of at least one episode of early HG spell retained a significant and independent association with the occurrence of infections only by Gram-positives (OR: 5.45; 95% CI: 1.92–15.42; $p < 0.001$) and fungal agents (OR: 3.37; 95% CI: 1.01–11.97; $p = 0.04$), but not by gram negatives. The day of onset of infections occurred significantly earlier in HG infants compared with NG: 13.9 versus 20.1 mean days ($p = 0.03$), regardless of the pathogen.	Lactoferrin exposure, BW, GA	Early HG spells are significantly predictive of development of LOS by gram-positives and fungal microorganisms in preterm infants
Scheurer 2016	Inpatient days, IVH and ROP was significantly higher in HG group compared to NG group. (p= <0.0001, 0.004 and 0.0001 respectively). Infants with >5 days of HG were lighter (5345 vs 6455 g, P≤ 0.001), shorter (57.9 vs 60.9 cm, P≤ 0.01), had smaller occipital-frontal head circumference (39.4 vs 42.0 cm, P≤ 0.05) and were leaner (percent body fat 15.0 vs 23.8, P ≤0.01) at 4 months CA		HG is associated with decreased body size and lower adiposity at 4 months CA independent of nutritional deficit, insulin use and illness. These changes may influence long-term growth and cognitive development.
De Carolis 2015	Mortality in NG group 18/79 (22.7) vs HG group 18/53 (33.9). Any IVH rate was higher in HG group and Hypo & HG group respect to NG Group (p=0.002) as well as IVH grade3. The rate of both any ROP and ROP ≥ stage 2 in survived neonates was higher in HG group respect to N-Group (p=0.008 and p=0.002, respectively)		All forms of IVH, ROP and sepsis was higher in the HG group.
Nicolaeva 2015	There were no significant differences in the blood glucose levels between children with and without ROP, and also between children with spontaneously regressing ROP and progressive ROP (p>0.05).		The blood glucose level is not related to the development of ROP nor with its progression or regression.
Stensvold 2015	After the introduction of early enhanced TPN, the prevalence of mortality was higher (10.9% [14 of 129] vs 24.3% [52 of 214], P = .003). Multivariate analysis- Severe HG is an independent risk factor for death (OR, 4.68; 95%CI, 1.82-12.03).	Early enhanced parenteral nutrition, GA, CRIB score, any vasopressor use	In the multivariable analysis early, severe HG is a strong predictor of death

Szymońska 2015	The tendency to increased mortality by the 28th day of life (p=0.09 for X^2 test) was observed. Moreover, a significant positive association with the severity of HG (p=0.02 for Cochran–Armitage test) was revealed. A higher incidence of IVH (p=0.09) in groups with mild and moderate/severe HG was noted. Other outcomes like CLD, PVL, NEC, ROP and hospital stay did not significantly differ between the groups.		A significantly higher mortality rate on the 28th day of life noted.
Cardona 2014	Rate of ROP increased with hyperglycaemia at 1 week and 1 month (p=0.003 and p=0.05, respectively). As the hours of HG increased, so did the probability of increase in the stage of ROP (p= 0.003). There was a trend for increase in ROP with HG >10mmol/L when corrected for BW and GA (p=0.1)		A significantly higher incidence of ROP were seen with HG in the 1st week and month of life.
Ahmadpour-Kacho 2014	The severity of ROP showed no significant differences between the2 groups (P = 0.35). The logistic regression for GA and BW showed a significant correlation between HG and ROP (P = 0.0001).	GA, BW	HG is an important risk factor for ROP that can be prevented along with other risk factors by accurate supervision
Mohsen 2014	Mortality- NG vs HG 0 vs 4 (13%), p 0.031. There were more cases of ROP in the HG group compared with the NG group (45% vs 15%, P = 0.007). Patients who developed ROP had significantly higher maximum and average glucose concentrations when compared with non-ROP patients. In a logistic regression model including all significant variables, average blood glucose in the first week of life was the factor independently associated with ROP with an OR of: 1.77 (95% confidence interval: 1.08 to 2.86), p = 0.024.CLD and IVH was not significantly different between 2 groups.		Elevated average blood glucose concentrations in the first week of life is independently associated with the development of ROP
Sabzehei 2014	91 out of 179 in HG group and 73 out of 385 in the NG group expired. (OR-4.2, 95% CI- 3-6.5, p<0.001). Higher incidence of IVH>Gr2 (OR-2.88, 95%CI-1.28-6.49, p=0.01), hospital stay>28 days in survivors (OR-3.56, 95%CI- 2.02-6.25, p=<0.001) and more ≥stage 2 ROP (OR-2.05, 95%CI-1.11-3.78, p=0.02)		HG is associated with IVH, ROP in survived neonates, prolonged hospitalization and risk of mortality. These findings underscore the need for prompt diagnosis and appropriate management.
Auerbach 2013	Increase in HG duration was most prominently increasing the adjusted OR for severe IVH (OR = 10.33, 95% CI = 10.0-10.6, P = .033). 35 out of 154 neonates with HG compared to 2 out of 24 neonates with NG died.	Semi-quantitative severity index score based on death , days of ventilation, BPD, need for dopamine treatment, and day of enteral feeds commencement	Longer duration of HG in the first 96 hours of life was most strongly associated with severe IVH in preterm infants
Mohamed 2013	HG days (mean) 2.3 ± 3.2 (No ROP group) vs 7.1 ± 6.6(ROP group) p= < 0.0001. Multiple	GA, sepsis, IVH, PDA,	HG is associated with the development of ROP in

	regression analysis for any ROP = HG days – Beta coefficient= 0.07, OR (95%CI) = 1.073 (1.004, 1.146), p value=0.04. Multiple regression analysis for stage 3 ROP= HG days- Beta coefficient= 0.0003, OR (95% CI) = 1.000 (0.938, 1.066), p = 0.99	ventilation days, neonatal steroids	premature infants
Ramel 2013	Controlling for BW, HG was a statistically significant predictor of ROP >stage 2, z=2.39, P=0.02. HG was also a significant predictor of number of episodes of sepsis, z=5.90, P=0.001. HG was not a significant predictor of IVH, z=0.64, P=0.53. By 24 months, infants with 5+ days of HG were predicted to be 2 kg lighter and 5cm shorter than infants with 0 days of HG. Statistically significant for prediction of Bayley scale scores at 12 months (initial status), but not significant for prediction of Bayley scale score at 24 months. (All infants were followed to 1-year CA and 62 (78%) were followed to 2 years CA)		Neonatal HG was associated with poor physical growth until at least 2 years CA in this cohort of VLBW preterm infants.
van der Merwe 2013	Though HG is a significant risk factor for development of ROP in univariate analysis(p=0.0267), in multiple regression analysis it was not found to be significantly associated with ROP		HG is not a risk factor for ROP
Yoo 2013	Discharge mortality: N=4/38(10.5%), P= 11/101 (10.9%), T= 38/121 (31.4%) Adjusted odds ratio- P to N odds ratio (95% CI) = 0.9 (0.2-4.8), p value- 0.89, T to N odds ratio (95% CI) = 0.8 (0.1-5.2), p= 0.84. In multivariate analysis adjusted for GA, BW, RDS, and ventilator support/major surgery/antibiotic use in 14 days, there was no significant differences in CLD, severe IVH, PVL, NEC and ROP requiring treatment between groups. Growth rate was highest in group P and lowest in group T. Although the birth weight of P was significantly smaller than N, P infants gained weight faster than N infants. Long term development found no significant difference between group N and P in terms of cerebral palsy, hearing loss or developmental delay in Bayley scale.	GA, BW, RDS, Ventilator support/ major surgery/ any antibiotics use in the first 14 days	Permissive HG up to < 16.66 mmol/L without insulin treatment during the first 14 days of life is not associated with osmotic diuresis or increased mortality or morbidities, suggesting that it is not detrimental in ELBW infants.
Bozdag 2012	Multivariate analysis for ROP- duration of HG (days; OR 3.26; 95% CI 1.09–9.80; p= 0.035) was significantly associated with ROP.	BW, Gram positive sepsis, IVH (grade 3 or more), RDS and days on CPAP, Oxygen	Duration of HG may contribute to the development of ROP
Kaempf 2011	Higher cumulative mean glucose, more episodes of HG, and more insulin exposure were associated with an increased incidence and severity of ROP. Ordinal logistic regression identified higher glucose as predictors for severity of ROP.		After adjusting for important risk factors, HG and especially Insulin use in premature infants may increase the risk of ROP.
Chavez-Valdez	The frequency of levels of blood sugar >8.3mmol/L was equal among neonates those		High overall glycaemic status is associated with the

2011	who had ROP and those who did not. Multivariate regression confirmed 30 days' time weighted glucose level of ≥6.5mmol/L (OR 9.4 to 10) was significantly associated with development of ROP. (p=<0.05)		development of severe ROP.
Van der Lugt 2010	27 out of 66 infants with HG died during admission versus 62/793 infants without HG. A multivariable regression analysis - A significant increase in mortality in the exposed cohort (p = 0.001). Sepsis was more prominent in infants with HG and a BW of >1,000 gram (p = 0.002) and/or GA of 29-32 weeks (p = 0.009) than in infants without HG. Growth at 2 years of age was similar, but neurological and behavioural development was more frequently abnormal among those with neonatal HG (p = 0.036and 0.021 respectively).		Mortality was higher in VLBW infants with HG treated with insulin during the neonatal period. At 2 years of age survivors showed normal growth, but a higher incidence of neurological and behavioural problems.
Alexandrou 2010	The proportion with HG was significantly greater among infants who subsequently died (10 [53%] of 19 infants), compared with survivors (20 [21%] of 94 infants; *P*= 0.03). Multiple regression- For mortality in the first 24 hours-1.3 ± 0.54 (B±SE), 6.0 (Wald $X^{2)}$, p-0.01, OR (95%CI) - 3.7 (1.3-10.6). Multivariate logistic regression analysis revealed that hyperglycaemia during the first 24 hours of life remained a risk factor for WM reduction= 1.1 ± 0.58 (B±SE), 4.1 (Wald $X^{2)}$ p- 0.04, OR (95%CI) - 3.1 (1.0-9.2). No statistically significant association between HG and IVH was found after adjusting gender and CRIB scores, (OR: 1.7 [95% CI: 0.58 –5.01]; *P* = .33).	GA, gender, CRIB score	HG on the first day of life was associated with increased mortality rates and brain damage, as reflected by WM reduction at term age
Heimann 2007	11 infants out of 82 in Gr1, 9 out of 125 in Gr II and 10 out of 45 in Gr III died. A significant increase in mortality (P-0.0001) with increasing median blood glucose level and repeated (≥4) incidents of blood glucose levels ≥8.3mmol/ and in infants with low GA (<27 weeks).Neonates who developed IVH, sepsis or ROP did not have an increased number of elevated blood glucose levels		Premature infants with low gestational age (<27 weeks), elevated median blood glucose levels and/or repeatedly elevated blood glucose levels have a significantly increased mortality.
Blanco 2006; USA	3 out of 19 in euglycemic group and 43 out of 150 in hyperglycaemic group died. The adjusted OR (95%CI) for death before discharge was 1.2(0.3-4.2). Threshold ROP did not reach statistical significance, although laser treatment was required in 15 of 66 patients with ROP in the hyperglycaemic group and in none of the three patients with ROP in the euglycemic group (P = 0.21). Adjusted OR (95%CI) for ROP was 4.6(1.1-18.9). Hyperglycaemia was not found to be associated incidence of CLD or IVH (Adjusted OR (95%)-1.8(0.4-7.4) and 2.3 (0.4-11.3). OR (95%CI) for length of hospital stay of >90 days was 2.5(0.6-11).	GA, BW, Postnatal steroid use	Hyperglycaemia was associated with increased incidence of ROP.
Ertl 2006	ROP occurred more frequently in HG infants.	GA, BW,	The logistic regression model

	Logistic regression model for ROP: HG OR (CI) - 3.15(1.12-8.84), p value- <0.05.	APGAR score, CRIB score	revealed that HG may influence ROP development in VLBW
Hays 2006	Early adverse outcomes (death or the occurrence of grade 3 or 4 IVH before day 10 of life) were associated with the average highest daily blood glucose concentration. (OR1.012). The length of hospital stay was associated with the time ratio for blood glucose concentrations of ≥8.3mmol/L through interaction with birth weight and the average highest daily percentage of inspired oxygen.		High blood glucose concentrations increase the risk of early death and grade 3 or 4 IVH and the length of hospital stay among survivors without IVH, which suggests that prevention and treatment of HG may improve the outcomes ELBW infants.
Kao 2006	Multivariate analysis (Mortality)- Severe HG (≥10mmol/L) but not mild to moderate HG (6.66-9.9mmol/L) was significantly associated with mortality when assessed after 7 days of life (OR (95%CI)- 30.4(3.37-274)). Multivariate analysis- HG ((≥10mmol/L) was not significantly associated with late onset sepsis when assessed after 3 or 7 days of life. (OR -0.92 and 0.56 respectively). Persistent severe HG was associated with the development of Stage II/III NEC, after adjusting for age and male gender (OR: 9.49, 95% CI: 1.52 to 59.3). There was no correlation between mean glucose category and number of days of mechanical ventilation or length of stay in the hospital on univariate or multivariate analyses	GA	Severe HG in the first few days after birth is associated with increased odds of death and sepsis in ELBW infants.
Manzoni 2006	HG occurred significantly more often in group A (21/45, 46.6%) than in group B neonates (11/46, 23.9%) (OR 1.95, 95% CI 1.235-4.432, p =0.008)		HG is significantly more frequent in neonates who subsequently develop fungal rather than bacterial late-onset sepsis, with a typical 3-d interval.
Sutija 2004	Proportion of neonates in whom HG could not be controlled was higher in the ROP group (36.8% vs 0.5%; p<0.0001)		HG presents a major risk for ROP in VLBW neonates
Garg 2003	The patients in the ROP group had higher glucose maximums (p = 0.017), averages (p = 0.043) and medians (p = 0.048) for the first month of life. On more days than controls, ROP patients had at least one glucose value exceeding 8.3mmol/L (ROP 8.4 days, controls 5.3 days, p = 0.028). A simple logistic regression analysis suggested an increased risk for the development of ROP for each 0.55mmol/L increase of mean serum glucose (OR 1.96; 95% CI 1.13 to 3.42). In a multiple regression model: An increased ROP risk for each 0.55mmol/L increase of mean serum glucose (OR 2.7; 95% CI 1.044 to 8.62)	BW, Vitamin E and FiO2	The glucose levels in the first month of life are associated with development of ROP.
Chen 2001	10 of 39 HG infants died compared to 15 of the 88 infants in the NG group. (25% vs. 17%, p<0.05). Persistent periventricular hyperechogenicity (> 2 weeks), cystic PVL and parenchymal lesions were more common in HG infants (33% vs. 11%, p<0.05)		The neonatal mortality rate was higher in the HG group. HG in VLBW neonates was associated with abnormal brain ultrasound.
Lilien 1979	11 out of 14 infants in the HG group and 5 out of 16 in the NG group died.		There was no difference in mortality between stressed HG

	9 out of 14 infants in the HG group and 2 out of 16 in the NG group had brain haemorrhage.		and stressed NG infants; stress, rather than HG, was related to mortality.

GA: Gestational age, BW: Birth weight, PMA: Post menstrual age, CA: Corrected age, VLBW: Very low birth weight infant, ELBW: Extremely low birth weight infant, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NA: Not available, RDS: Respiratory distress syndrome, IVH: Intra ventricular haemorrhage, NEC: Necrotising enterocolitis, CLD: Chronic lung disease, LOS: Late onset sepsis, ROP: Retinopathy of prematurity, PVL: Periventricular leucomalacia, GV: Glycaemic variability, CV: Coefficient of variation, MAGE: Mean amplitude glucose excursion, OR: Odds ratio, CI: Confidence interval, SD: Standard deviation, IQR- Inter quartile range, SEM: Standard error of mean, LF: Lactoferrin, TPN: Total parenteral nutrition, WM: White matter, BSID: Bayley scale of infant development, DA: Developmental assessment, SGA: Small for gestational age, FiO2: Fraction of inspired oxygen, CRIB: Clinical risk index for babies, NG: Normoglycaemia, HG: Hyperglycaemia, RC: Retrospective cohort study, PC: Prospective cohort study, CC: Case control study.

e Table 2: Sensitivity analysis after including multiple results from the same study

Outcome		**Number of studies in the meta-analysis**	**OR (95% CI)**	**P value**	**I^2 in %**
Cohort studies					
Mortality	Unadjusted	23	3.37 (2.27-5.00)	<0.00001	69
	Adjusted	12	2.41 (1.39-4.17)	0.002	57
IVH (Undefined)	Unadjusted	13	2.81 (1.85-4.28)	<0.00001	47
	Adjusted	3	2.20 (1.12-4.32)	0.02	0
IVH (Severe)	Unadjusted	11	1.98 (1.36-2.89)	0.0004	28
	Adjusted	2	1.07 (0.36-3.17)	0.90	0
ROP (Any)	Unadjusted	8	1.66 (1.06-2.61)	0.03	41
	Adjusted	2	3.7 (1.55-8.84)	0.003	0
ROP (Severe)	Unadjusted	12	3.32 (1.84-5.99)	<0.0001	65
	Adjusted	4	1.74 (0.67-4.54)	0.26	86
LOS	Unadjusted	14	1.63 (1.03-2.57)	0.04	70
	Adjusted	6	1.09 (0.59-1.99)	0.79	58
NEC (Undefined)	Unadjusted	5	1.25 (0.73-2.15)	0.42	0
	Adjusted	No study available			
NEC (Severe)	Unadjusted	8	1.43 (0.63-3.22)	0.39	46
	Adjusted	4	1.34 (0.34-5.21)	0.67	54
CLD	Unadjusted	10	2.46 (1.92-3.15)	<0.00001	0
	Adjusted	4	1.37 (0.85-2.21)	0.19	0
PVL	Unadjusted	6	0.77 (0.37-1.60)	0.48	0
	Adjusted	2	0.56 (0.27-1.18)	0.13	0
Disability	Unadjusted	4	1.99 (1.24-3.19)	0.004	16
	Adjusted	1	1.27 (0.56-2.86)	0.57	NA (1 study only)
Case control studies					
Mortality	Unadjusted	1	3.24 (0.72-14.44)	0.12	NA (1 study only)
	Adjusted	No study available			
IVH (Undefined)	Unadjusted	3	2.06 (1.34-3.18)	0.001	0
	Adjusted	No study available			
IVH (Severe)	Unadjusted	2	2.58 (1.48-4.48)	0.0008	0
	Adjusted	1	10.33 (10-10.67)	<0.00001	NA (1 study only)
ROP (Any)	Unadjusted	3	6.49 (1.97-21.39)	0.002	82
	Adjusted	3	1.26 (0.79-2.00)	0.33	52
ROP (Severe)	Unadjusted	3	2.15 (1.98-2.34)	<0.00001	0
	Adjusted	4	1.01 (0.96-1.07)	0.67	42
LOS	Unadjusted	No study available			
	Adjusted	No study available			
NEC (Undefined)	Unadjusted	No study available			
	Adjusted	No study available			

NEC (Severe)	Unadjusted	No study available			
	Adjusted	No study available			
CLD	Unadjusted	1	3.07 (0.87-10.81)	0.08	NA (1 study only)
	Adjusted	No study available			
PVL	Unadjusted	No study available			
	Adjusted	No study available			
Disability	Unadjusted	No study available			
	Adjusted	No study available			

CLD: Chronic Lung Disease, LOS: Late onset sepsis, IVH: Intraventricular haemorrhage, ROP: Retinopathy of prematurity, NEC: Necrotising enterocolitis, PVL: Periventricular leukomalacia, NA: Not applicable, OR: Odds ratio, CI: Confidence interval, I^2: Heterogeneity

e table 3: Grade of evidence for association of neonatal hyperglycaemia with adverse outcome

Certainty assessment							**Effect**	
No of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pooled OR (95% CI)**	**Certainty**
Unadjusted Odds Ratios for Mortality from Cohort Studies								
15	observational studies	not serious	serious [a]	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	**3.25** (2.10 to 5.03)	⊕⊕◯◯ LOW
Unadjusted Odds Ratios for Mortality from Case Control studies								
1	observational studies	not serious	serious [b]	not serious	very serious [c]	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**3.24** (0.72 to 14.44)	⊕◯◯◯ VERY LOW
Adjusted Odds Ratios for Mortality from Cohort studies								
6	observational studies	not serious	serious [e]	not serious	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [d]	**2.37** (1.40 to 4.01)	⊕◯◯◯ VERY LOW

Adjusted Odds Ratios for Mortality from Case Control studies								
0	observational studies							
Unadjusted Odds Ratios for "Any IVH" from Cohort studies								
10	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**2.30** (1.55 to 3.40)	⊕⊕◯◯ LOW
Unadjusted Odds Ratios for "Any IVH" from Case Control studies								
1	observational studies	not serious	serious [b]	not serious	not serious	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**2.30** (1.30 to 4.07)	⊕◯◯◯ VERY LOW
Adjusted Odd Ratios for "Any IVH" from Cohort studies								
2	observational studies	not serious	not serious	not serious	serious [c]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [d]	**2.60** (1.09 to 6.20)	⊕◯◯◯ VERY LOW
Adjusted Odds Ratios for "Any IVH" from Case Control studies								
0	observational studies							
Unadjusted Odds Ratios for "Severe IVH" from Cohort studies								
9	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**1.85** (1.37 to 2.51)	⊕⊕◯◯ LOW
Unadjusted Odds Ratios for "Severe IVH" from Case Control studies								
2	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected	**2.58** (1.48 to	⊕⊕◯◯

						all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	4.48)	LOW
Adjusted Odds Ratios for "Severe IVH" from Cohort studies								
1	observational studies	not serious	serious [b]	not serious	serious [c]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [d]	**0.8** (0.2 to 3.2)	⊕◯◯◯ VERY LOW
Adjusted Odds Ratios for "Severe IVH" from Case Control studies								
1	observational studies	not serious	serious [b]	not serious	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [d]	**10.33** (10.00 to 10.67)	⊕◯◯◯ VERY LOW
Unadjusted Odds Ratios for "Any stage ROP" from Cohort studies								
7	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**1.78** (1.12 to 2.83)	⊕⊕◯◯ LOW
Unadjusted Odds Ratios for "Any stage ROP" from Case Control studies								
3	observational studies	not serious	very serious [a]	not serious	serious [c]	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**6.49** (1.97 to 21.39)	⊕◯◯◯ VERY LOW
Adjusted Odds Ratios for "Any stage ROP" from Cohort studies								
2	observational studies	not seriou	not serious	not serious	serious [c]	publication bias strongly	**3.70** (1.55	⊕◯◯

		s				suspected all plausible residual confounding would reduce the demonstrated effect [d]	to 8.84)	◯ VERY LOW
Adjusted Odds Ratios for "Any stage ROP" from Case Control studies								
3	observational studies	not serious	serious [e]	not serious	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [d]	**1.26** (0.79 to 2.00)	⊕◯◯◯ VERY LOW
Unadjusted Odds Ratios for "Severe ROP" from Cohort studies								
9	observational studies	not serious	serious [e]	not serious	not serious	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**3.42** (1.82 to 6.40)	⊕◯◯◯ VERY LOW
Unadjusted Odds Ratios for "Severe ROP" from Case Control studies								
3	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**2.15** (1.98 to 2.34)	⊕⊕◯◯ LOW
Adjusted Odds Ratios for "Severe ROP" from Cohort studies								
3	observational studies	not serious	very serious [a]	not serious	serious [c]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [d]	**1.97** (0.56 to 6.93)	⊕◯◯◯ VERY LOW
Adjusted Odds Ratios for " Severe ROP" from Case Control studies								
4	observational studies	not serious	serious [e]	not serious	not serious	publication bias strongly suspected	**1.01** (0.96 to	⊕◯◯◯

						all plausible residual confounding would reduce the demonstrated effect [d]	1.07)	VERY LOW
Unadjusted Odds Ratios for "Late onset sepsis" from Cohort studies								
9	observational studies	not serious	serious [e]	not serious	not serious	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**1.97** (1.18 to 3.28)	⊕◯◯◯ VERY LOW
Unadjusted Odds Ratios for "Late onset sepsis" from Case Control studies								
0	observational studies							
Adjusted Odds Ratios for "Late onset sepsis" from Cohort studies								
3	observational studies	not serious	very serious [a]	not serious	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [d]	**1.38** (0.41 to 4.72)	⊕◯◯◯ VERY LOW
Adjusted Odds Ratios for "Late onset sepsis" from Case Control studies								
0	observational studies							
Unadjusted Odds Ratios for "Undefined NEC" from Cohort studies								
4	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**1.29** (0.72 to 2.30)	⊕⊕◯◯ LOW
Unadjusted Odds Ratios for "Undefined NEC" from Case Control studies								
0	observational studies							
Adjusted Odds Ratios for "Undefined NEC" from Cohort studies								
0	observational studies							
Adjusted Odds Ratios for "Undefined NEC" from Case Control studies								
0	observational studies							

Unadjusted Odds Ratios for "Severe NEC" from Cohort studies								
6	observational studies	not serious	serious [e]	not serious	not serious	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**1.91** (0.74 to 4.89)	⊕◯◯◯ VERY LOW
Unadjusted Odds Ratios for "Severe NEC" from Case Control studies								
0	observational studies							
Adjusted Odds Ratios for "Severe NEC" from Cohort studies								
3	observational studies	not serious	serious [e]	not serious	serious [c]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [d]	**1.78** (0.29 to 10.78)	⊕◯◯◯ VERY LOW
Adjusted Odds Ratios for "Severe NEC" from Case Control studies								
0	observational studies							
Unadjusted Odds Ratios for CLD from Cohort studies								
8	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**2.55** (1.96 to 3.30)	⊕⊕◯◯ LOW
Unadjusted Odds Ratios for CLD from Case Control studies								
1	observational studies	not serious	very serious [b]	not serious	serious [c]	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**3.07** (0.87 to 10.81)	⊕◯◯◯ VERY LOW
Adjusted Odds Ratios for CLD from Cohort studies								
3	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected	**1.42** (0.85 to	⊕⊕◯◯

						all plausible residual confounding would reduce the demonstrated effect [d]	2.37)	LOW
Adjusted Odds Ratios for CLD from Case Control studies								
0	observational studies							
Unadjusted Odds Ratios for PVL from Cohort studies								
4	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**1.01** (0.40 to 2.56)	⊕⊕◯◯ LOW
Unadjusted Odds Ratios for PVL from Case Control studies								
0	observational studies							
Adjusted Odds Ratios for PVL from Cohort studies								
1	observational studies	not serious	very serious [b]	not serious	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [d]	**0.50** (0.20 to 1.25)	⊕◯◯◯ VERY LOW
Adjusted Odds Ratios for PVL from Case Control studies								
0	observational studies							
Unadjusted Odds Ratios for Disability from Cohort studies								
3	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would suggest spurious effect, while no effect was observed [d]	**2.35** (1.47 to 3.73)	⊕⊕◯◯ LOW
Unadjusted Odds Ratios for Disability from Case Control studies								
0	observational studies							
Adjusted Odds Ratios for Disability from Cohort studies								
1	observational studies	not serious	very serious [b]	not serious	not serious	publication bias strongly	**1.27** (0.56	⊕◯◯◯

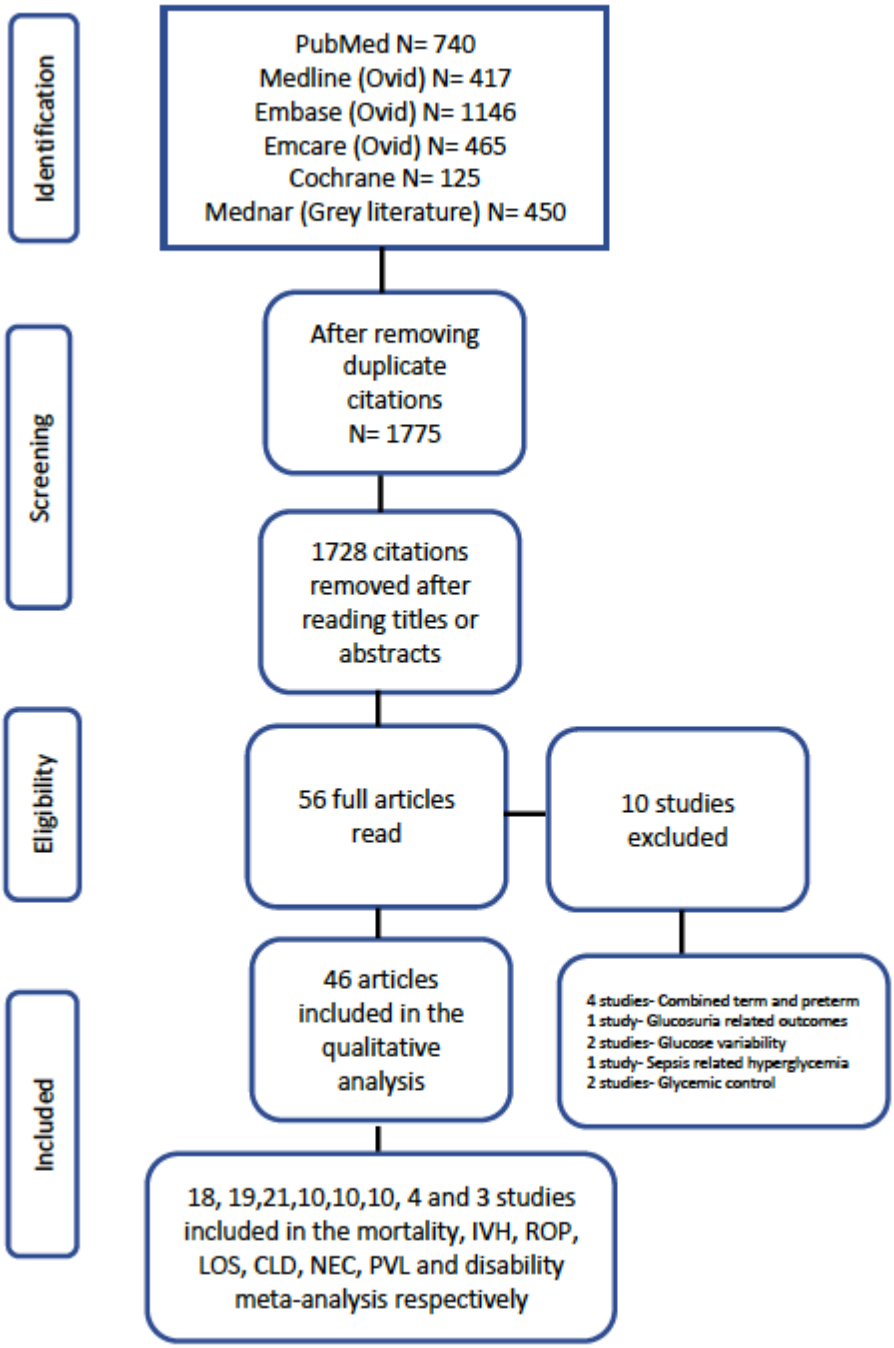
		s				suspected all plausible residual confounding would reduce the demonstrated effect [d]	to 2.86)	VERY LOW
Adjusted Odds Ratios for Disability from Case Control studies								
0	observational studies							

CI: Confidence interval; OR: Odds ratio; IVH: Intraventricular Hemorrhage; ROP: Retinopathy of Prematurity; NEC: Necrotising Enterocolitis; CLD: Chronic Lung Disease; PVL: Periventricular Leukomalacia

Explanations

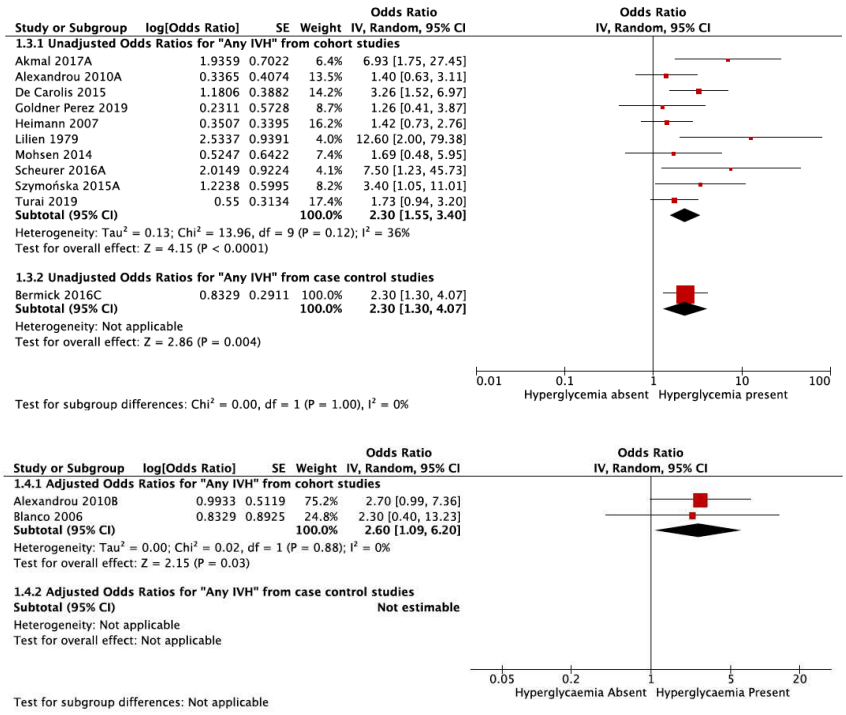
a. High statistical heterogeneity
b. Only 1 study available
c. Wide Confidence intervals
d. Publication Bias could not be assessed since less than 10 studies
e. Moderate statistical heterogeneity

E Figure 1:



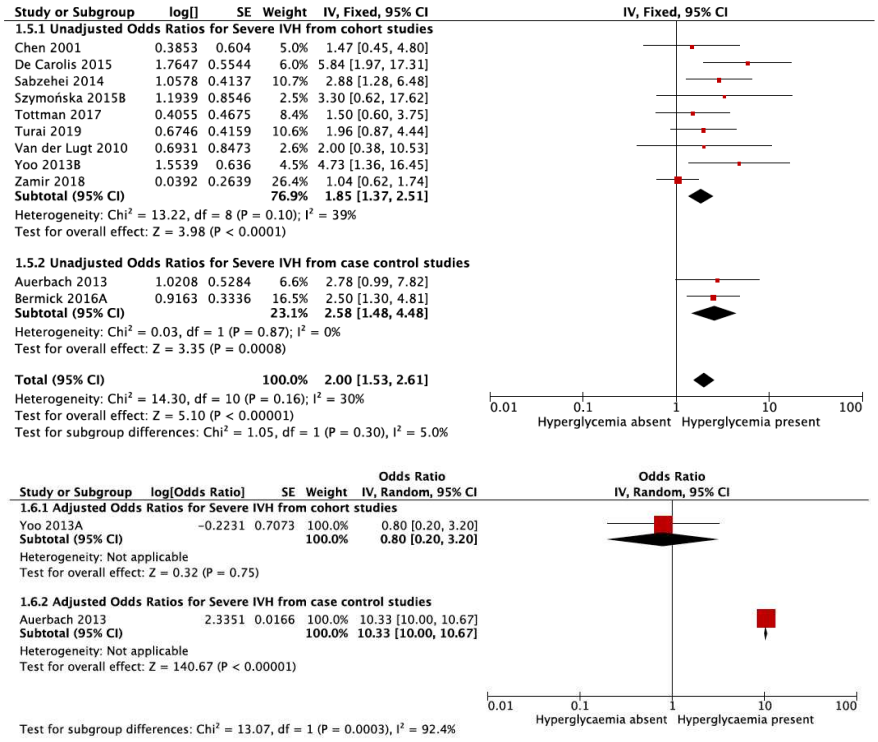
e Figure 1: Flow chart for study selection (IVH- Intraventricular hemorrhage, ROP- Retinopathy of prematurity, LOS- Late inset sepsis, CLD- Chronic lung disease, NEC- Necrotizing enterocolitis, PVL- Periventricular leukomalacia)

e Figure 2:



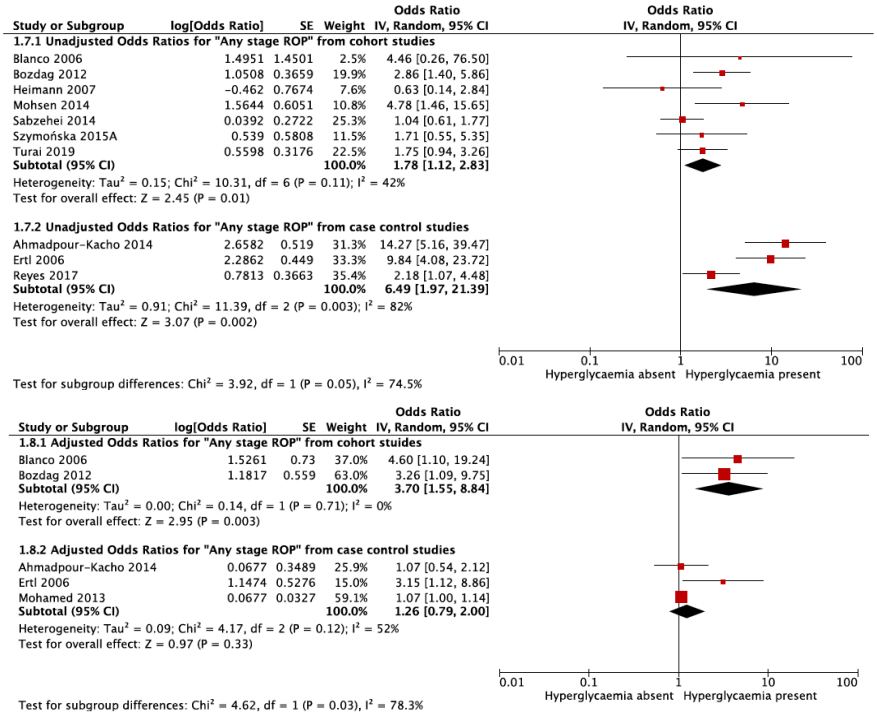
Forest plot showing the association between hyperglycemia and any grade intraventricular hemorrhage. (SE- Standard error, CI- Confidence interval, IV- Inverse variance)

e Figure 3:



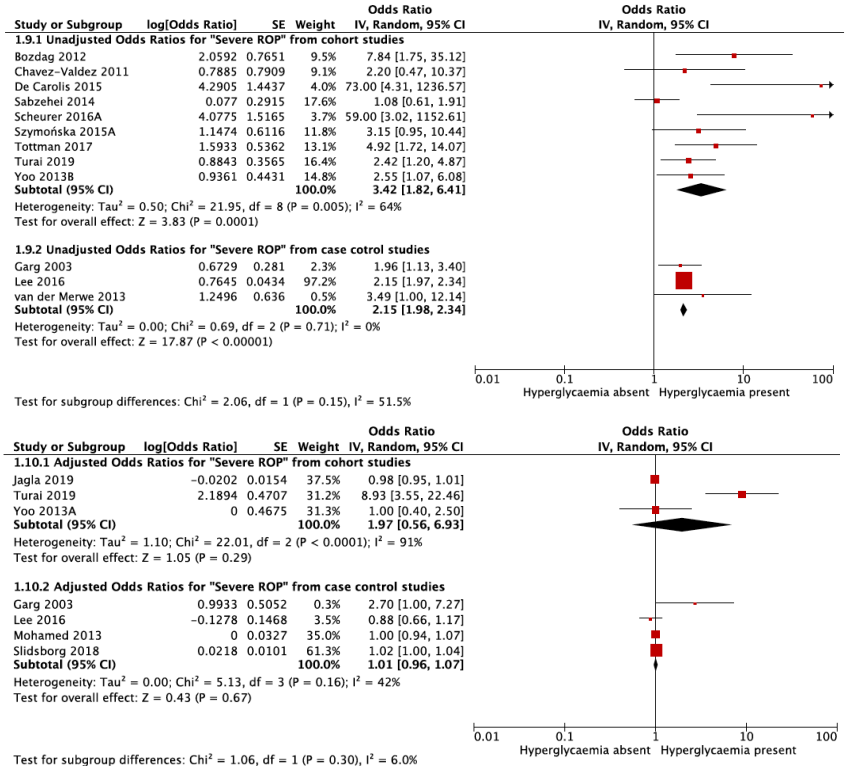
Forest plot showing the association between hyperglycaemia and severe intraventricular haemorrhage (SE- Standard error, CI- Confidence interval, IV- Inverse variance)

e Figure 4:



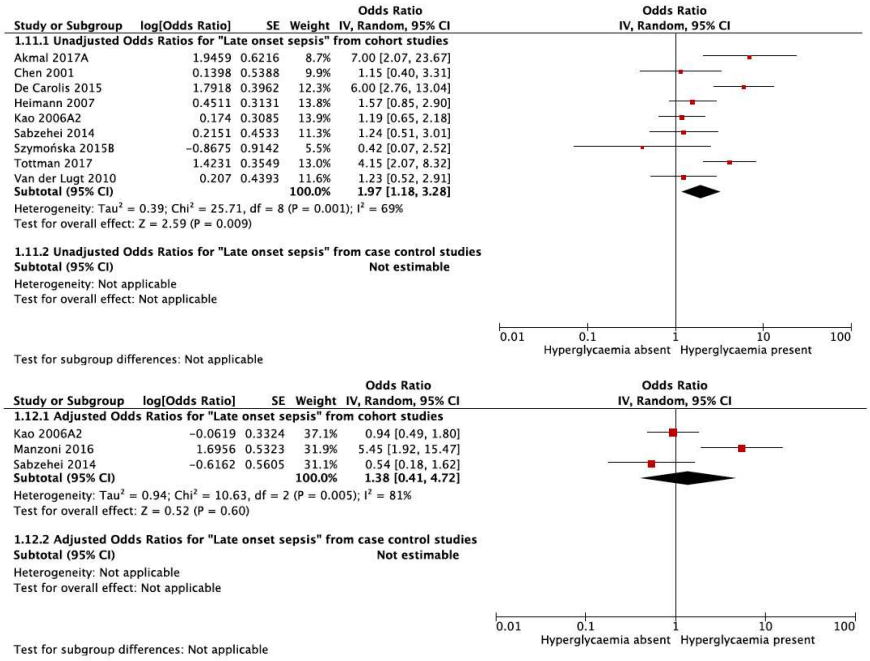
Forest plot showing the association between hyperglycemia and any stage retinopathy of prematurity. (SE- Standard error, CI- Confidence interval, IV- Inverse variance)

e Figure 5:



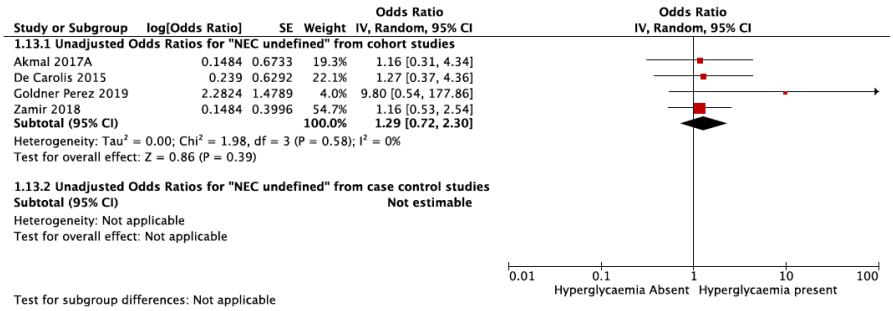
Forest plot showing the association between hyperglycemia and severe retinopathy of prematurity. (SE- Standard error, CI- Confidence interval, IV- Inverse variance)

e Figure 6:



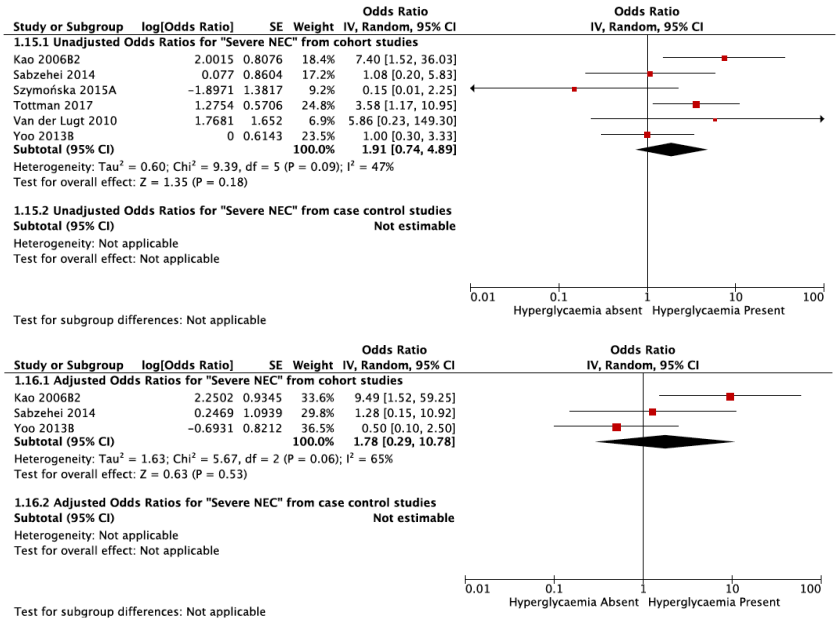
Forest plot showing the association between hyperglycemia and late onset sepsis. (SE- Standard error, CI- Confidence interval, IV- Inverse variance)

e Figure 7:



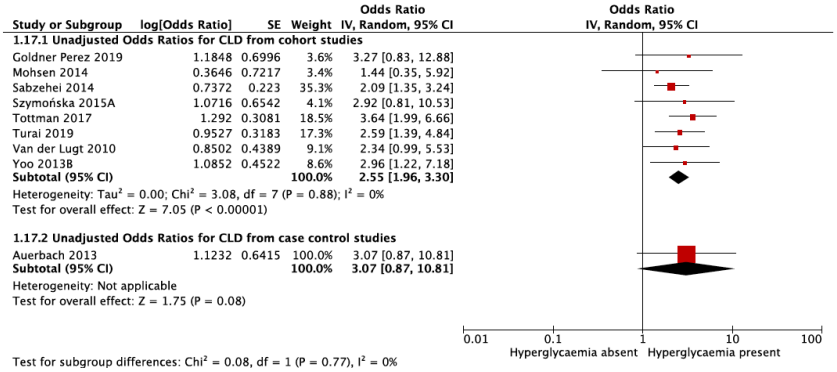
Forest plot showing the association between hyperglycemia and undefined necrotizing enterocolitis. (SE- Standard error, CI- Confidence interval, IV- Inverse variance)

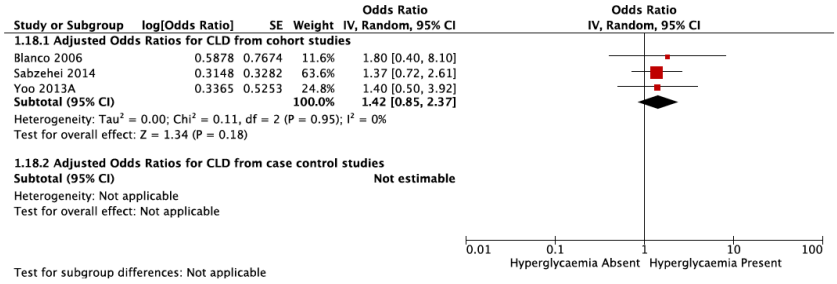
e Figure 8:



Forest plot showing the association between hyperglycemia and severe necrotizing enterocolitis. (SE- Standard error, CI- Confidence interval, IV- Inverse variance)

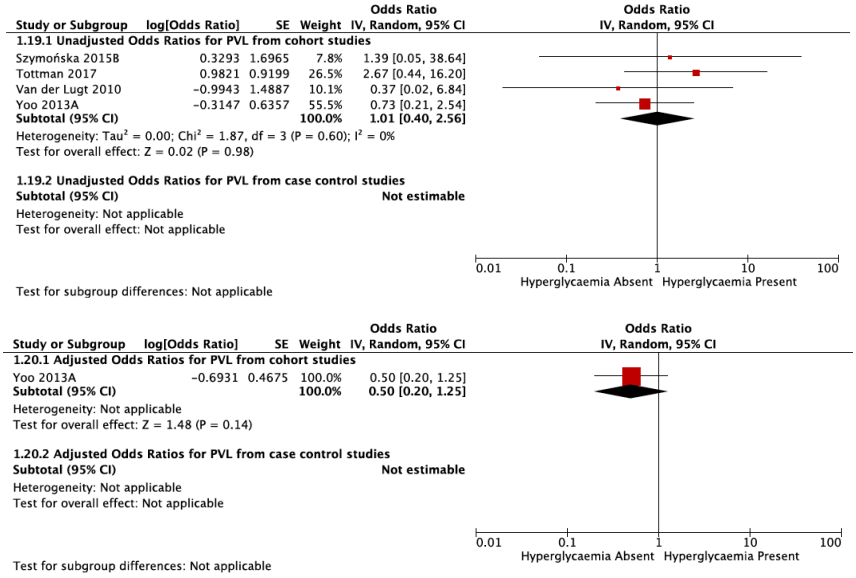
e figure 9:





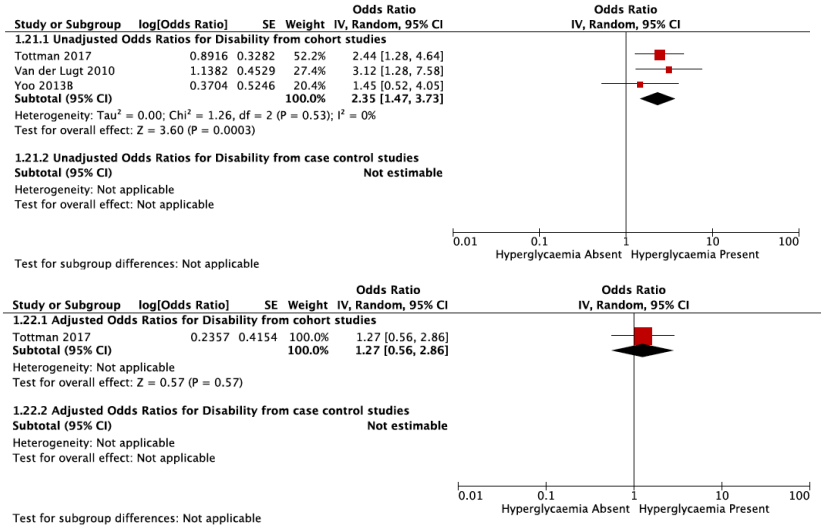
Forest plot showing the association between hyperglycemia and chronic lung disease. (SE- Standard error, CI- Confidence interval, IV- Inverse variance)

e Figure 10:



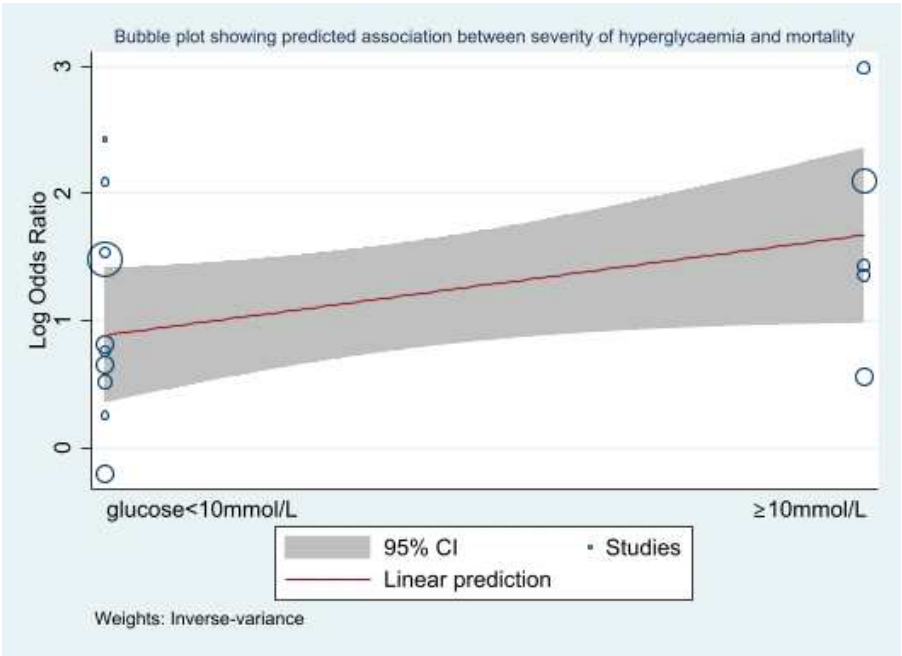
Forest plot showing the association between hyperglycemia and periventricular leucomalacia. (SE- Standard error, CI- Confidence interval, IV- Inverse variance)

\e Figure 11:



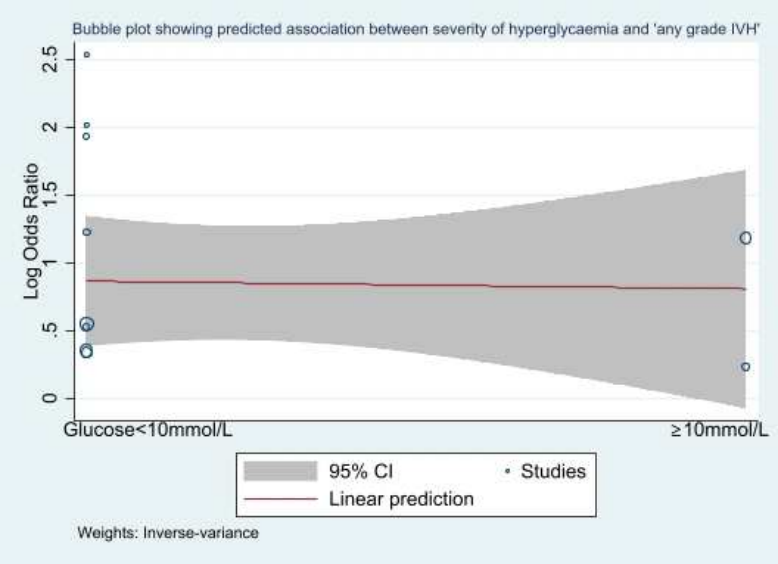
Forest plot showing the association between hyperglycemia and disability. (SE- Standard error, CI- Confidence interval, IV- Inverse variance)

e Figure 12:



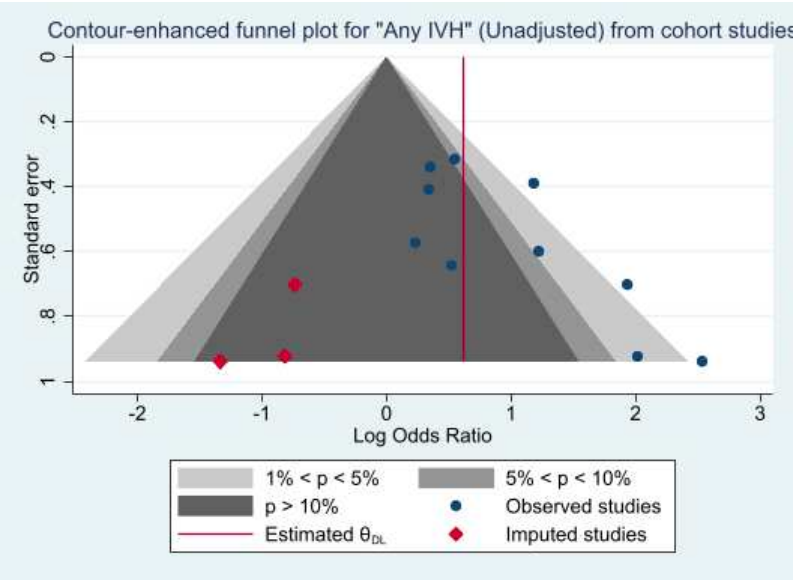
Bubble plot showing relationship between blood glucose level and unadjusted mortality

e Figure 13



Bubble plot showing relationship between blood glucose level and unadjusted any grade intraventricular hemorrhage

e Figure 14:



Funnel plot shows presence of publication bias probably due to 3 missing studies.