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Risk factors for neonatal hypoglycemia: a meta-analysis

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Abstract

Objective This Study aims to investigate the risk factors of hypoglycemia in neonates through meta-analysis.

Method PubMed, Embase, Cochrane library, and Web of science databases were searched for case-control studies on risk factors for neonatal hypoglycemia. The search was done up to 1st October 2023 and Stata 15.0 was used for data analysis.

Results A total of 12 published studies were included, including 991 neonates in the hypoglycemic group and 4388 neonates in the non-hypoglycemic group. Meta-analysis results suggested caesarean section [OR = 1.90 95%CI (1.23, 2.92)], small gestational age[OR = 2.88, 95%CI (1.59, 5.20)], gestational diabetes [OR = 1.65, 95%CI (1.11, 2.46)], gestational hypertension[OR = 2,79, 95%CI (1.78, 4.35)] and respiratory distress syndrome[OR = 5.33, 95%CI (2.22, 12.84)] were risk factors for neonatal hypoglycemia.

Conclusion Based on the current study, we found that caesarean section, small gestational age, gestational diabetes, gestational hypertension, respiratory distress syndrome are risk factors for neonatal hypoglycemia.

PROSPERO registration number CRD42023472974.

Keywords Neonatal, Hypoglycemia, Risk factors, Meta-analysis

Introduction

In the realm of neonatal health, neonatal hypoglycemia has emerged as a prevalent metabolic ailment affecting newborns [1]. Evidently, neonatal hypoglycemia has been designated as a substantial peril, attributing to an array of adverse neurodevelopmental outcomes, including learning disabilities, attention deficit, developmental delay, hyperactivity, epilepsy, and autism, particularly in neonates with blood glucose levels measuring below 2.6 mmol/L, irrespective of gestational age, weight [2–4]. The incidence of this condition spans from 5 to 15% among typical neonates, surging to as high as 50% among those born with notable risk factors [5, 6]. The neonatal phase encapsulates the critical transition from in utero reliance on the maternal system to autonomous metabolic regulation upon birth [7]. The constancy of blood glucose levels hinges upon factors encompassing glucose utilization, hepatic and renal glycogen catabolism, activation of gluconeogenic metabolic pathways, and the provisioning of exogenous glucose. Thus, insufficiency in glycogen reserves, heightened consumption, limited gluconeogenic capacity, and inadequate external glucose supply can collectively precipitate hypoglycemia. Crucially, glucose constitutes the primary energy source for cerebral metabolism, rendering the brain susceptible to

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harm when glucose availability wanes [8, 9]. The risk of hypoglycemic brain injury is further intertwined with the duration of hypoglycemia and the amplitude of glycemic fluctuations. Given the dynamic growth and development of the neonatal brain, diminished blood glucose levels entail a heightened vulnerability, amplifying the odds of neurological impairment [10].

Detecting neonatal hypoglycemia presents a formidable challenge, as its clinical manifestations are notably non-specific, encompassing symptoms such as lethargy, altered gaze, irritability, seizures, feeding difficulties, respiratory distress, cyanosis [11, 12]. The American Academy of Pediatrics underscores the identification of risk factors as the linchpin in averting severe neurological consequences. Recent investigations into risk factors associated with neonatal hypoglycemia have, however, yielded disparate results, fostering an element of controversy [13]. Hence, the primary objective of this investigation is to undertake a thorough meta-analysis of preexisting research concerning the risk factors correlated with neonatal hypoglycemia. The overarching goal of this endeavor is to pinpoint the risk factors contributing to neonatal hypoglycemia and to establish a foundation for early preventive measures.

Method

This study was registered in the PROSPERO International Prospective Register of Systematic Reviews (Registration number: CRD42023472974), and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

Literature retrieval

The databases PubMed, Embase, Cochrane library, and Web of science were searched for case-control studies on risk factors for hypoglycemia in newborn infants, the search time was from the start of each database establishment until October 1, 2023. The search was performed using subject terms plus free words: infant, newborn, hypoglycemia, risk factors, and the specific search strategy is described in Supplementary Material 1.

Criteria for inclusion and exclusion

Inclusion criteria: Case-control study of neonates (including gestational age < 37 weeks) who met the diagnostic criteria for hypoglycemia [15]. The primary outcome indicators were unifactorial and multifactorial risk factor analyses, without qualifying unifactorial analyses versus multifactorial factor analyses, but when both unifactorial and multifactorial results were included in the same paper, multifactorial results were preferred and multifactorial adjusted risk values were extracted, or if only unifactorial analyses were available, unifactorial results were extracted.

Exclusion criteria: conference abstracts, protocols, letters, repetitive publications, systematic reviews, inaccessibility of full text, inaccessibility of available data, animal experiments.

Data extraction

Two independent reviewers independently screened the literature to extract the data, read the title and abstract of the literature, as well as the full text, and directly screen the literature that is easy to judge; For the literature that can be included with objections, consult relevant experts for opinions, and screen by directly downloading and reading the full text. In the screening process, the inclusion and exclusion criteria are strictly followed, the corresponding indicators in the study are extracted, and the extracted data are cross-checked to ensure the consistency of the extracted data. The main contents of data extraction include: first author, year of publication, country, sample size, sex, gestational age.

Risk of bias

The Newcastle-Ottawa Scale (NOS) [16] was used to evaluate the case-control study, including selection of study population (4 points), comparability between groups (2 points), exposure factors or outcome measures (3 points). The total score of the scale is 9 points, ≤4 is classified as low quality, 5–6 is classified as medium quality, and ≥7 is classified as high quality. If the two researchers have differences in the evaluation process, they will discuss the decision or ask the third party to decide.

Statistical analysis

Stata15.0 was used for statistical analysis of the data. Our univariate analyses for comparing baseline values in the case and non-case groups. Multivariate analyses were performed by combining the OR, RR or HR and 95% confidence intervals for each article. The risk value of each study was not distinguished by OR, RR or HR, but was described by OR value. The aggregate OR value and 95% confidence interval were calculated. According to the results of heterogeneity test (Q-test method) and I^2 statistic [17], the corresponding model was selected to calculate the combined OR value. If $I^2 > 50\%$, the random effects model was used; if $I^2 \leq 50\%$, the fixed effects model was used. With $I^2 > 50\%$ [18], Sensitivity analysis was performed by eliminating literature one by one for indicators with large heterogeneity, and publication bias was analyzed by the Egger test, with the test level $\alpha = 0.05$. $P < 0.05$ was statistically significant [19].

Result

Literature search results

The search of PubMed, Embase, Cochrane library, and Web of science databases initially yielded 1964 documents, 1384 documents were obtained by removing duplicates, 17 articles were obtained by reading the titles and abstracts for initial screening, and 12 articles [20–31] were finally included by reading the full text, and the specific flowchart of the search is shown in Fig. 1.

Characteristics of included documents

Twelve articles [20–31] were included, four [22, 23, 25, 30] from China, two [20, 31] from Indonesia, one [28] from Japan, one [29] from Australia, one from [27] India, and one [24] from the Netherlands. There were 991 in the hypoglycemic group and 4388 in the non-hypoglycemic group, and the specific literature characteristics are tabulated in Table 1.

Twelve articles were included using the NOS quality assessment, with one [21] scoring 6, a medium quality study. The rest scored 7–8, with overall high quality of the included studies. Specific quality ratings are shown in Table 2.

Univariate meta-analysis

Caesarean section

Caesarean section was mentioned in 9 articles [20–27, 30], and the test of heterogeneity (I^2=82.2%,P=0.001) was analyzed using a random effects model, and the results of the analysis suggested that caesarean section was a risk factor for hypoglycemia in neonates, and the difference was statistically significant [OR=1.90 95%CI (1.23, 2.92)], Fig. 2; Table 3.

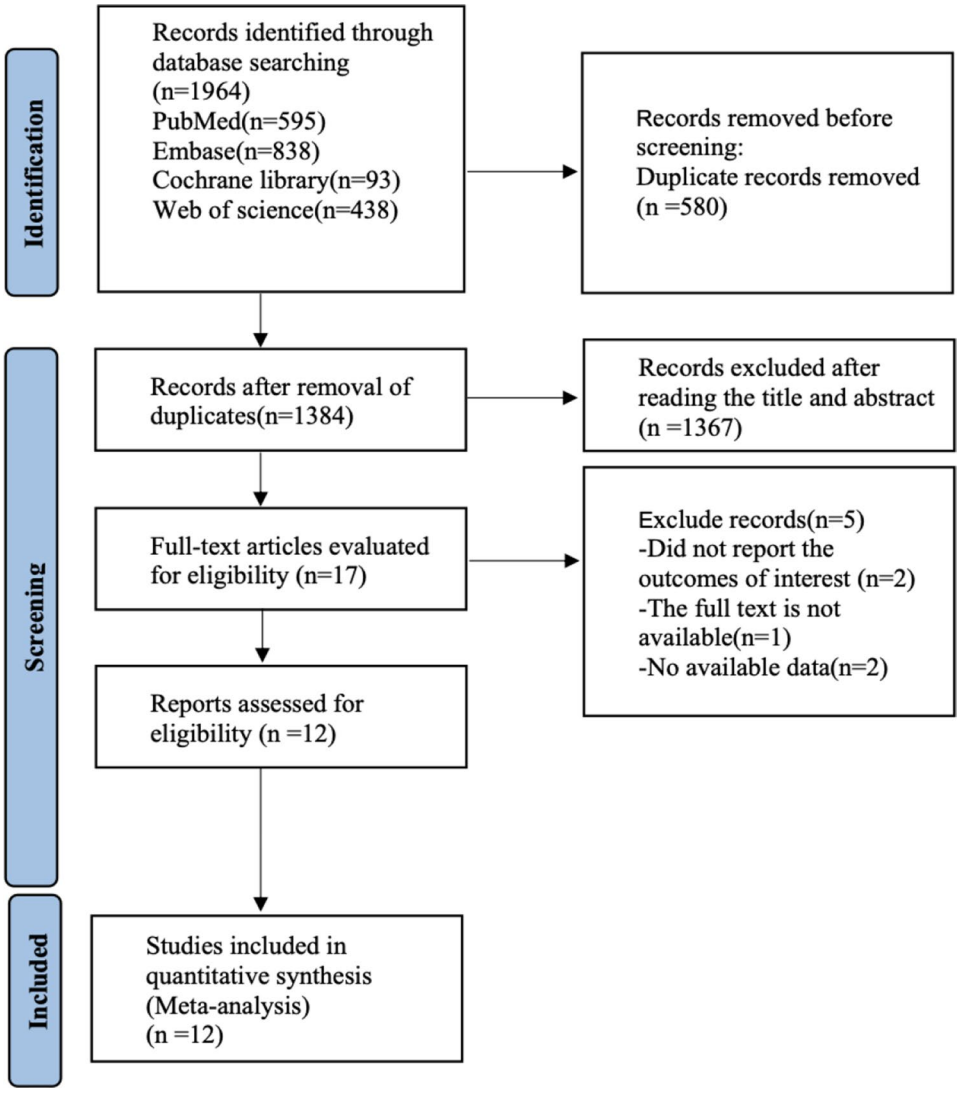

Fig. 1 Flow chart of literature search

Table 1 Literature characteristics table

Study	Country	Sample size		Gender(M/F)	Gestational age (week)
		H	NH		
Angelika	Indonesia	26	65	46/45	< 37
Butorac	Croatia	92	296	205/183	33
Cao	China	104	776	456/424	< 37
chen	China	148	296	207/237	< 37
Koolen	Netherlands	137	557	386/328	29.3
Li	China	19	210	-	35
Mitchell	Canada	59	116	89/27	28.2
Sasidharan	India	128	476	-	-
Shimokawa	Japan	99	504	-	37
Thevarajah	Australia	60	707	-	30–40
Yuan	China	86	172	135/123	30
Yunarto	Indonesia	123	123	107/139	-

Small gestational age

Small gestational age was mentioned in 8 articles [21, 23–27, 30, 31], and the test of heterogeneity (I^2=82%,*P*=0.001) was analyzed using a random effects model, and the results of the analysis suggested that small gestational age was a risk factor for hypoglycemia in neonates, and the difference was statistically significant [OR=2.88, 95%CI (1.59, 5.20)], Fig. 3; Table 3.

Gestational diabetes

Gestational diabetes was mentioned in 9 articles [21, 23–30], and the test of heterogeneity (I^2=62.8%,*P*=0.006) was analyzed using a random effects model, and the results of the analysis suggested that gestational diabetes was a risk factor for hypoglycemia in neonates, and the difference was statistically significant [OR=1.65, 95%CI (1.11, 2.46)], Fig. 4; Table 3.

Gestational hypertension

Gestational hypertension was mentioned in 7 articles [21, 24–27, 29, 30], and the test of heterogeneity (I^2=67%,*P*=0.006) was analyzed using a random effects model, and the results of the analysis suggested that gestational hypertension was a risk factor for hypoglycemia in neonates, and the difference was statistically significant [OR=2,79, 95%CI (1.78, 4.35)], Fig. 5; Table 3.

Respiratory distress syndrome

Respiratory distress syndrome was mentioned in 5 articles [21, 25, 27, 29, 30], and the test of heterogeneity (I^2=84.3%,*P*=0.001) was analyzed using a random effects model, and the results of the analysis suggested that respiratory distress syndrome was a risk factor for hypoglycemia in neonates, and the difference was statistically significant [OR=5.33, 95%CI (2.22, 12.84)], Fig. 6; Table 3.

Other factor meta-analysis

Gender, Large gestational age, Necrotizing enterocolitis, Mechanical ventilation, and Twins were not statistically significant in relation to neonatal hypoglycemia, as shown in Table 3.

Multivariate meta-analysis

Multivariate analysis showed that Gestational hypertension was a risk factor for neonatal hypoglycemia, and the difference was statistically significant [OR=1.91, 95%CI (1.35, 2.71)] Fig. 7; Table 4. There was no significant difference between Gestational age deficiency (gestational age less than 37 weeks) and neonatal hypoglycemia [OR=1.32, 95%CI (0.92, 1.90)].

Table 2 NOS score

Study	Is the case definition adequate?	Representativeness of the cases	Definition of Controls	Comparability of cases and controls based on the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non response	Total scores
Angelika [20]	*	*	*	**	*	*	*	8
Butorac [21]	*	*	*	*	*	*	-	6
Cao [22]	*	*	*	*	*	*	*	7
Chen [23]	*	*	*	**	*	*	*	8
Koolen [24]	*	*	*	*	*	*	*	7
Li [25]	*	*	*	*	*	*	*	7
Mitchell [26]	*	*	*	**	*	*	*	8
Sasidharan [27]	*	*	*	**	*	*	*	8
Shimokawa [28]	*	*	*	**	*	*	*	8
Thevarajah [29]	*	*	*	**	*	*	*	8
Yuan [30]	*	*	*	**	*	*	*	8
Yunarto [31]	*	*	*	*	*	*	-	6

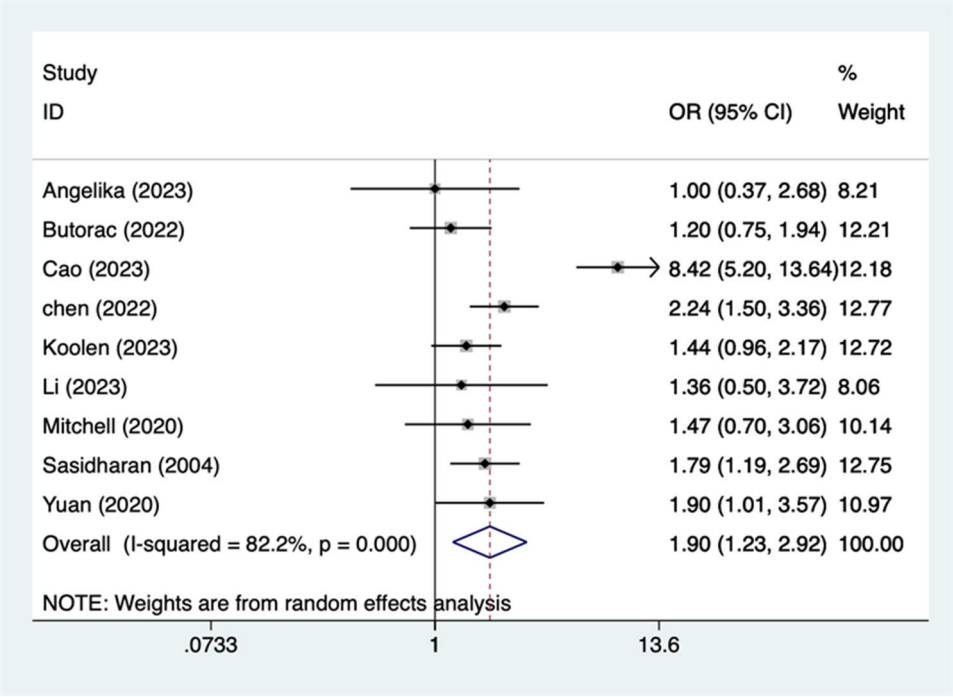

Fig. 2 Forest plot of caesarean section

Table 3 Univariate meta-analysis

Risk factors	No of study	heterogeneity		OR (95%CI)	*P*	Egger
		I^2(%)	*P*			
Male	8	0	0.475	0.97 (0.82, 1.15)	0.710	0.51
Female	8	0	0.475	1.03 (0.87, 1.22)	0.710	0.544
Caesarean section	9	82.2	0.001	1.90 (1.23, 2.92)	0.004	0.627
Small gestational age	8	82.0	0.001	2.88 (1.59, 5.20)	0.001	0.003
Large gestational age	5	0	0.971	1.03 (0.71, 1.50)	0.876	0.662
Gestational diabetes	9	62.8	0.006	1.65 (1.11, 2.46)	0.014	0.339
Gestational hypertension	7	67.0	0.006	2.79 (1.78, 4.35)	0.0001	0.226
Necrotizing enterocolitis	2	0	0.5	0.94 (0.44, 2.03)	0.877	-
Mechanical ventilation	2	50.2	0.156	0.63 (0.35, 1.15)	0.136	-
Respiratory distress syndrome	5	84.3	0.0001	5.33 (2.22, 12.84)	0.0001	0.806
Twins	3	97.1	0.001	4.63 (0.53, 40.44)	0.166	0.561

Publication bias

Small gestational age ($P<0.05$) was found to have publication bias in the univariate meta-analysis by egger's test for each risk factor. No publication bias was detected in any of the other univariate, multivariate meta-analyses Tables 3 and 4.

Discussion

The current study represents the inaugural meta-analysis dedicated to the exploration of risk factors associated with neonatal hypoglycemia. Through univariate and multivariate analyses, we have ascertained that neonatal hypoglycemia is significantly linked to several factors, including cesarean section, small gestational age, gestational diabetes, gestational hypertension, and neonatal respiratory distress syndrome.

In the context of gestational diabetes, maternal hyperglycemia impels the fetus to undergo enhanced glucose uptake, consequently stimulating fetal pancreatic β-cell proliferation and elevating insulin levels, ultimately culminating in fetal hyperinsulinemia [32, 33]. Following delivery, the fetus experiences an abrupt cessation in the maternal glucose supply, yet insulin levels remain elevated. The neonate's limited capacity for glucose isomerism in the early postnatal period exacerbates the situation, thereby instigating neonatal hypoglycemia. Research indicates that neonatal hypoglycemia can affect as much as 30–50% of offspring born to mothers with gestational diabetes [34]. Gestational hypertension

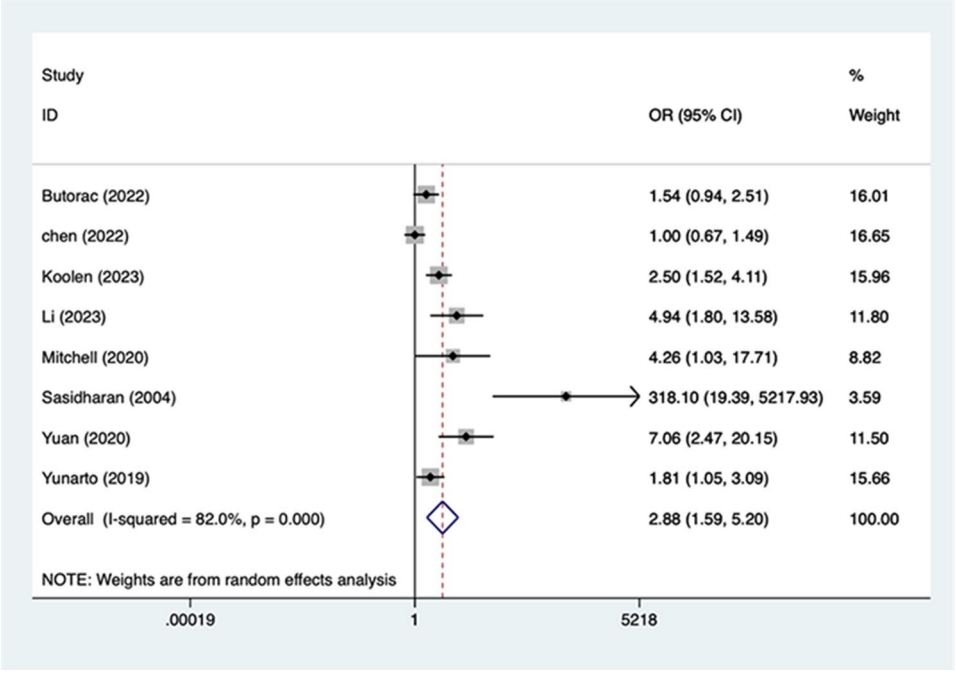

Fig. 3 Forest plot of small gestational age

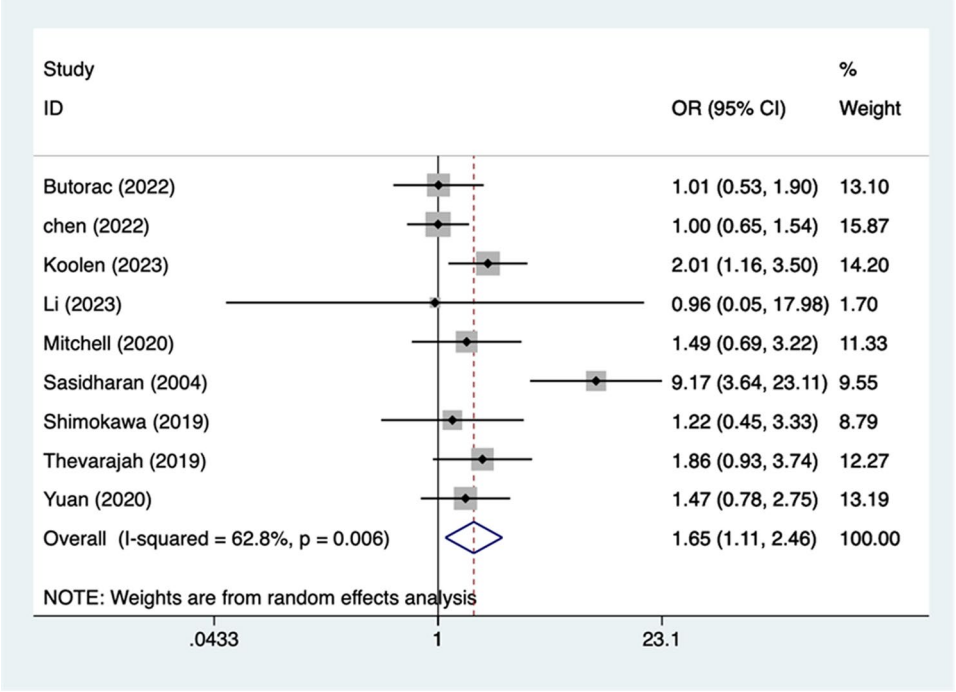

Fig. 4 Forest plot of gestational diabetes

during pregnancy leads to reduced placental blood perfusion, impacting the oxygen and blood supply to the fetus, thus hindering fetal development in utero [35], Concurrently, ischemia and hypoxia diminish glycogen synthase activity, impairing fetal glycogen synthesis and substantially elevating the risk of hypoglycemia in neonates [36, 37]. Cesarean section procedures, often involving preoperative fasting, lead to a marked decline in maternal blood glucose levels, consequently diminishing the glucose supply to the fetus and raising the risk of neonatal hypoglycemia [38, 39], This suggests a need for healthcare practitioners to carefully manage the timing of food

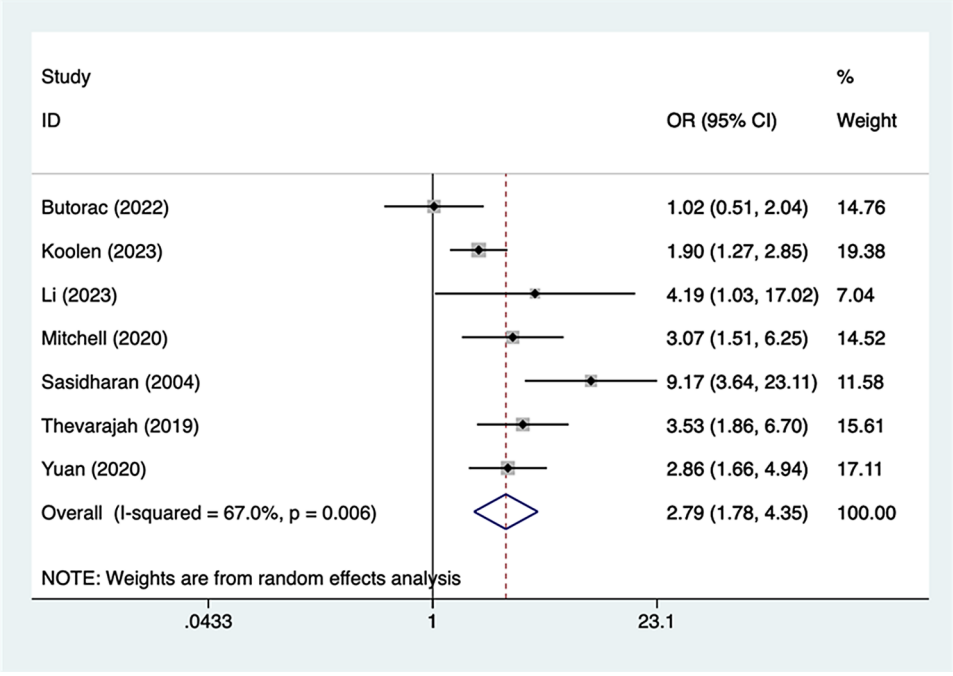

Fig. 5 Forest plot of gestational hypertension

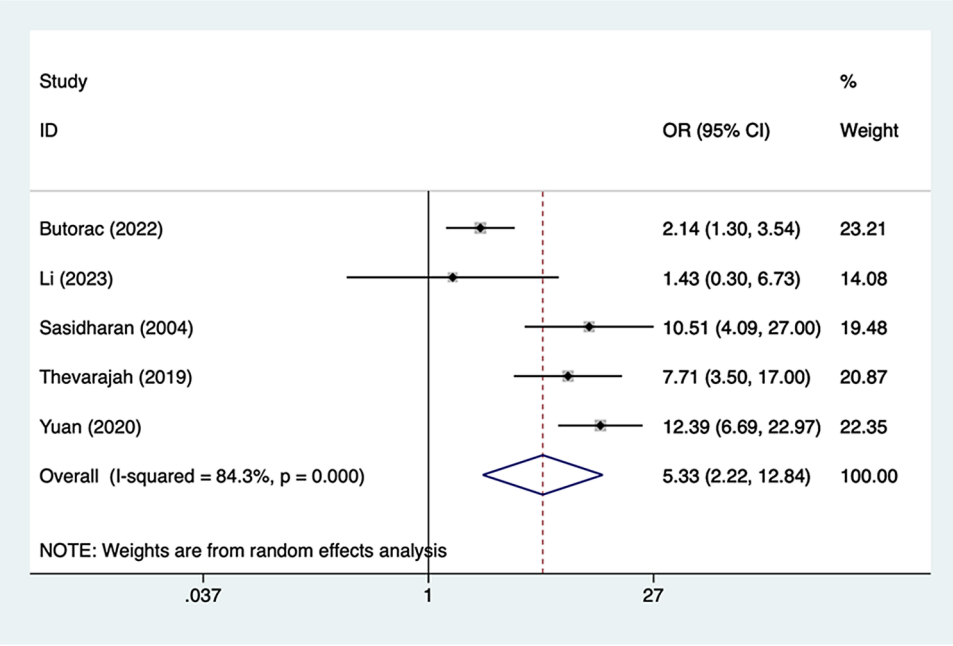

Fig. 6 Forest plot for respiratory distress syndrome

and fluid intake for expectant mothers undergoing cesarean sections and consider preoperative glucose infusion, all the while intensifying the monitoring of fetal hypoxia to prevent neonatal hypoglycemia.

The stability of neonatal blood glucose levels is contingent on both maternal blood glucose and inherent regulatory mechanisms. Fetal glycogen storage begins in the second trimester of pregnancy, with adipose tissue differentiation commencing around 26 weeks of gestational age. As a result, preterm infants and those born prior to their gestational age may suffer from hypoglycemia due to inadequate glycogen and fat reserves, along with underdeveloped glycogen catabolism and isomerism processes [40], Given that most low-birth-weight neonates fall into these categories, it is advisable for healthcare professionals to encourage early breastfeeding

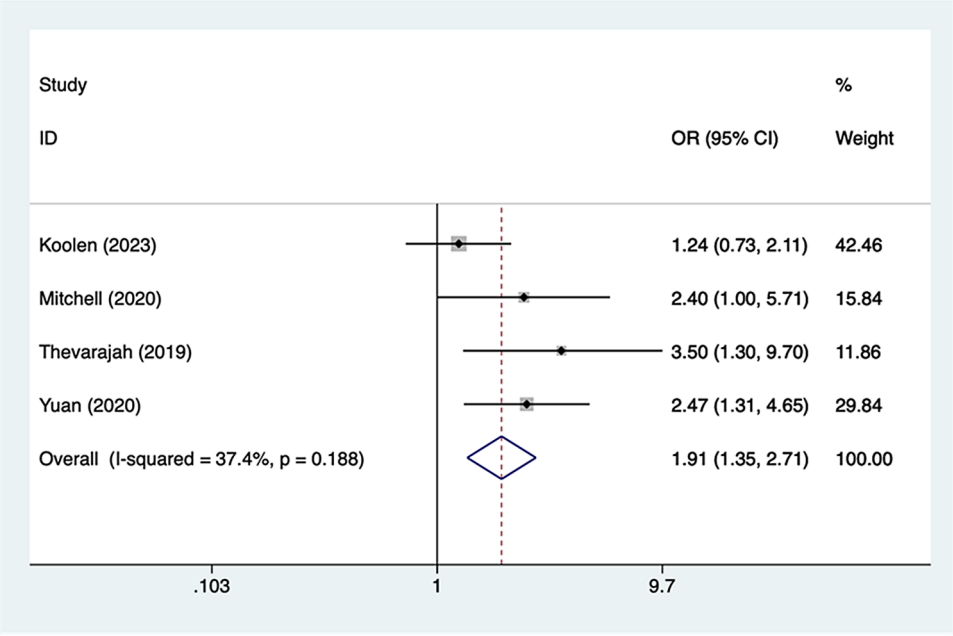

Fig. 7 Forest plot for multivariate analysis of gestational hypertension

Table 4 Multivariate meta-analysis

Risk factors	No of study	Heterogeneity		OR (95%CI)	*P*	Egger
		I^2 (%)	*P*			
Gestational age	7	92.0	0.001	1.32 (0.92, 1.90)	0.131	0.494
Gestational hypertension	4	37.4	0.188	1.91 (1.35, 2.71)	0.001	0.172

initiation and proactive glucose supplementation, with shorter intervals between feeds yielding better results [41]. Neonatal respiratory distress syndrome (NRDS) is characterized by a delay in establishing regular respiration within 1 min of birth, often due to hypoxia. Hypoxia prompts anaerobic metabolism, diminishing glucose utilization, depleting glycogen stores, and ultimately precipitating neonatal hypoglycemia [42]. Some studies [43, 44] suggest that asphyxia is a prominent risk factor for neonatal hypoglycemia, emphasizing the importance of monitoring blood glucose in asphyxiated neonates in addition to tracking blood oxygen levels.

However, it's crucial to acknowledge several limitations in this study. The small number of studies included, and a high degree of inter-study inconsistency may influence the robustness of our conclusions. Additionally, heterogeneity exists in the diagnostic criteria for neonatal hypoglycemia among the selected studies. Furthermore, the scarcity of common indicators for multifactorial analyses necessitates additional high-quality research and data to strengthen and refine our findings in the future.

Conclusion

Based on the current study, we found that caesarean section, small gestational age, gestational diabetes, gestational hypertension, respiratory distress syndrome are risk factors for neonatal hypoglycemia, and healthcare professionals should consider both maternal and neonatal factors when developing interventions. Therefore, it is recommended that healthcare professionals should consider both maternal and neonatal factors when developing relevant interventions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01700-7.

Supplementary Material 1

Supplementary Material 2

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None.

Author contributions
Design of the work—XJ and DW. Article retrieval and data collection—JS and JN. Article selection—JS, JN and FH. Data analysis, code writing and mapping—DW and XZ. Supervision conducted and responsibility for the entire study—XJ. Drafting the manuscript and revising it—all authors.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
All analyses were based on previously published studies; thus, no ethical approval is required.

Consent for publication
Not required.

Competing interests
The authors declare no competing interests.

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