Archives of Gynecology and Obstetrics (2019) 300:503–517
https://doi.org/10.1007/s00404-019-05208-7

REVIEW

Cesarean section and the risk of neonatal respiratory distress syndrome: a meta-analysis

Yan Li[1] · Caixia Zhang[1] · Dongfeng Zhang[1]

Received: 21 March 2019 / Accepted: 30 May 2019 / Published online: 11 June 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Purpose To explore the association between cesarean section (CS) and the risk of neonatal respiratory distress syndrome (RDS).

Methods We searched PubMed, Web of Science, and ClinicalTrials.gov database for studies related to the association between CS and the risk of neonatal RDS up to 25 August 2018. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using a random-effects model (REM).

Results A total of 26 studies from 25 available articles were included in this meta-analysis. For the association between CS and the risk of neonatal RDS, the pooled OR was 1.76 (95% CI 1.48–2.09). The pooled OR of the risk of neonatal RDS was 2.38 (95% CI 1.89–2.99) for elective CS and 1.85 (95% CI 1.34–2.56) for emergency CS.

Conclusion This meta-analysis suggested that CS, elective CS, and emergency CS were associated with an increased risk of neonatal RDS.

Keywords Cesarean section · Epidemiology studies · Meta-analysis · Neonatal respiratory distress syndrome

Introduction

Neonatal respiratory distress syndrome (RDS) is defined as the clinical symptoms of early neonatal respiratory distress with consistent chest radiologic characteristics and requires oxygen supplementation within 24 h of birth to maintain a saturation over 85% [1, 2]. It remains the primary cause of early mortality and morbidity during infancy and childhood, affecting about 1% of newborns [3]. In addition, survivors of RDS appear to be more vulnerable to later lower respiratory tract infections [4]. The potential risk factors of neonatal RDS might include low birthweight, low gestational age, maternal diabetes, maternal age, and multifetal pregnancy [5–7].

Cesarean section (CS) is an operation that gives birth to a baby through an incision in the abdomen and the womb [8], and includes the elective CS or the emergency CS. It is one of the most common surgical procedures worldwide [9], and the CS rates have been increasing continuously. The CS rates rose from just over 20% in 1996–33% in 2011 in the United States [10]. Some studies showed that CS could reduce the neonatal mortality and morbidity from birth trauma (superficial skin laceration and brachial plexus palsy) [11]. However, compared with babies born vaginally, the length of hospital stay for CS was longer, and the rates of hospitalization in intensive care units were higher [12], and CS increases the risks of hypoxic–ischaemic encephalopathy and intracranial hemorrhage [13]. Furthermore, CS increases the risk of respiratory system disease for offspring, such as transient tachypnea and persistent pulmonary hypertension of the newborn [14–16]. However, considering the association between CS and the risk of neonatal RDS, the conclusions of several epidemiological studies have been inconsistent. While CS has been found to significantly increased the risk of neonatal RDS [17–26], other studies [27–29] found no significant association between CS and the risk of neonatal RDS.

Therefore, we conducted this meta-analysis of observational studies to further investigate the associations between CS (not differentiating between elective cesarean section and

✉ Dongfeng Zhang
zhangdf1961@126.com; zhangdf1962@aliyun.com

[1] Department of Epidemiology and Health Statistics, The College of Public Health of Qingdao University, 38 Dengzhou Road, Qingdao 266021, Shandong, People's Republic of China

emergency cesarean section), elective CS and emergency CS and the risk of neonatal RDS, respectively.

Methods

We consulted the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for the reporting of meta-analyses in this analysis [30].

Data sources

We searched PubMed, Web of Science, and ClinicalTrials.gov database up to 10 August 2018 to identify all relevant available studies. Searches were limited to English-language studies in humans and search terms were included as follows: "cesarean delivery" (or "cesarean section" or "delivery mode" or "vaginal delivery") and "respiratory distress syndrome" (or "hyaline membrane disease" or "RDS" or "respiratory distress"). The reference lists of retrieved articles were reviewed to identify additional eligible studies not captured by our databases.

Study selection criteria

The inclusion criteria were as follows: (1) an observational study (cohort or case–control); (2) the exposure group was women experiencing CS (not differentiating between elective CS and emergency CS), elective CS, or emergency CS; (3) the control group was women undergoing vaginal delivery (VD); (4) the outcome of interest was neonatal RDS; and (5) relative risk (RR), odds ratios (OR), or hazard ratios with 95% confidence interval (CI) were provided.

The exclusion criteria were as follows: (1) review articles, experimental study, or meeting abstract; (2) the articles written in other languages instead of English; (3) studies lacking OR and/or 95% CI; (4) unpublished studies; (5) studies not evaluating the association between CS and neonatal RDS; and (6) duplicated data.

Two investigators independently (YL and CZ) searched articles and reviewed all retrieved studies, and discrepancies were discussed and resolved by a third investigator (DZ).

Data extraction and quality assessment

Two investigators (YL and CZ) independently extracted the following data: (1) the first author's name; (2) country or continent, where the study was performed; (3) publication year; (4) study design; (5) exposure; (6) sample size and number of cases; (7) number of fetuses; (8) range of gestational age; (9) OR with 95% CI of the risk of neonatal RDS; and (10) covariates adjusted for.

The study quality was assessed by the Newcastle–Ottawa quality assessment scale (www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Statistical analysis

The study-specific log ORs were weighted by the inverse of their variance to calculate pooled ORs with corresponding 95% CIs of neonatal RDS with CS, elective CS, and emergency CS, respectively. We also evaluated the association between elective CS and the risk of neonatal RDS in newborn delivered at term. I^2 of Higgins and Thompson [31] was used to assess the heterogeneity among studies. We used a random-effects model (REM) as the pooling method in this analysis. Meta-regression analysis was used to explore the potentially important covariates that have significant effects on between-study heterogeneity [32], including the covariates of publication year, sample size, continent, study design (cohort study or case–control study), study quality assessment score, number of fetuses, and adjustment (yes or no) for maternal age, birthweight, and gestational age. We also conducted subgroup analyses by continent, study design (cohort study or case–control study), number of the fetuses, and adjustment for maternal age, birthweight, and gestational age. To evaluate the critical studies that have a significant effect on between-study heterogeneity, a leave-one-out sensitivity analysis was carried out [33]. Influence analysis was used to assess whether a single study has a significant impact on the results. Egger's test [34] and funnel plot were used to assess the small-study effect.

All statistical analyses were performed using StataV.15.0 (Stata Corp, College Station, Texas, USA). All reported probabilities (P values) were two-sided, and $P \leq 0.05$ was considered statistically significant.

Results

Identification of studies and study characteristics

Initially, 1934 articles from PubMed, 1278 articles from the Web of Science, and 62 articles from ClinicalTrials.gov were identified. One additional article was found from reference lists. After reviewing the titles and abstracts, a total of 2631 articles that were not relevant to the associations of CS (not differentiating between elective CS and emergency CS), elective CS, and emergency CS with the risk of neonatal RDS were excluded. We further excluded 49 articles after reviewing the 74 full-text articles. Finally, 25 articles [5, 7, 17–29, 35–44] including 26 studies were eligible for this meta-analysis. The detailed information is shown in Fig. 1.

A total of 26 studies from 25 available articles [5, 7, 17–29, 35–44] with 810,454 participants were included in

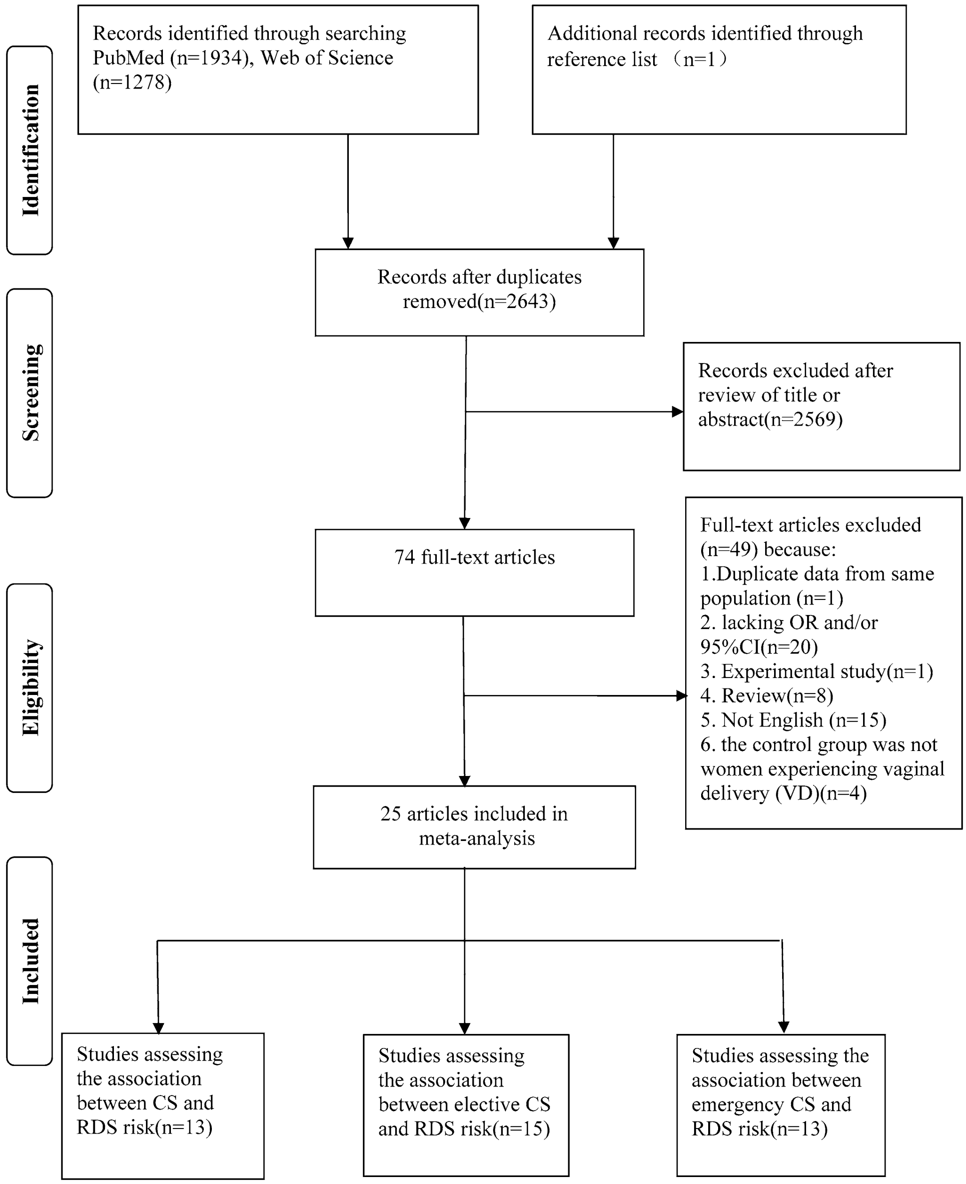

Fig. 1 Flow diagram of literature search (CI, confidence interval; CS, cesarean section; OR, odds ratio; RDS, respiratory distress syndrome)

this meta-analysis. Among the 26 studies, a total of 13 studies [17–29] involving 378,210 participants evaluated the association between CS and the risk of neonatal RDS, 15 studies [5, 7, 17, 19, 22, 35–42, 44] involving 246 347 participants evaluated the association between elective CS and the risk of neonatal RDS, and 13 studies [5, 7, 17, 36–44] involving 185,897 participants evaluated the association between emergency CS and the risk of neonatal RDS. Quality assessment indicated that the Newcastle–Ottawa score of each study was generally good. The detailed characteristics of the included studies are shown in Table 1.

Quantitative synthesis

CS and the risk of neonatal RDS

Among the 13 studies [17–29] assessing the association between CS and the risk of neonatal RDS, 3 studies [24, 28, 29] were conducted in Asia, 9 studies [17–20, 22, 23, 25–27] in North America, and 1 study in Europe [21]. As for study design, there were 10 cohort studies [17–21, 23, 24, 26–28] and 3 case–control studies [17, 22, 29]. The pooled OR of neonatal RDS associated with CS was 1.76 (95% CI

Table 1 Characteristics of studies on the associations between CS, elective CS, and emergency CS and risk of neonatal RDS

Author	Country/Continent (year)	Study type	Exposure	Sample size	No. of fetuses	Range of gestational age (week)	OR (95% CI)	Adjustment for covariates	Score of quality assessment
Sangkomkamhang	Thailand, Malaysia, Indonesia and the Philippines (2011)	Cohort	CS	765	NA	20–36	1.20 (0.8–1.8)	Antenatal corticosteroids, maternal age, parity, GA at birth, maternal complications, and country	7
Beydoun	Lebanon (2003)	Case-control	CS	881	Both	25–36	1.69 (0.85–3.39)	Fetal growth ratio, 1-min Apgar score, maternal age, antenatal steroid administration and pregnancy-related complications	7
Barzilay	Israel (2015)	Cohort	CS	386	Twin	> 24	4.17 (1.37–12.67)	GA, antenatal steroids, chorionicity, maternal age, parity and birthweight	9
Wylie	USA (2008)	Cohort	CS	2466	Single birth	NA	1.23 (0.99–1.51)	Maternal age, birthweight, GA, preterm labor, preeclampsia/eclampsia, abruption, fetal distress, chorioamnionitis, and year of birth (dichotomized)	9
Blue	USA (2015)	Cohort	CS	652	Single birth	$24–30^{+6/7}$	1.79 (1.1–2.9)	GA, birth weight < 10th percentile, hypertensive disorder, and use of oxytocin	8
Hunter	Canada (2018)	Cohort	CS	6218	Twin	$24–32^{+6}$	1.34 (1.15–1.56)	GA, gender, small for GA, SNAP II score > 20, outborn and maternal age	9
Herbst	Sweden (2007)	Cohort	CS	2674	Single birth	25–36	2.1 (1.4–3.2)	Maternal age, parity, year of birth, and gestational age	8
Werner	USA (2013)	Cohort	CS[a]	20231	Single birth	24–34	1.74 (1.61–1.89)	Maternal age, parity, ethnicity, education, insurance, pre-pregnancy weight, GA at delivery, smoking, diabetes and hypertension	8

Table 1 (continued)

Author	Country/Continent (year)	Study type	Exposure	Sample size	No. of fetuses	Range of gestational age (week)	OR (95% CI)	Adjustment for covariates	Score of quality assessment
Werner	USA (2012)	Cohort	CS[b]	2885	Single birth	$25–34^{+6/7}$	1.3 (1.1–1.6)	Maternal age, parity, ethnicity, education, insurance, pre-pregnancy weight, GA at delivery, smoking, diabetes and hypertension	8
Levine	USA (2001)	Cohort	CS	25318	Single birth	≥ 35	3 (1.6–5.3)	NA	7
			Elective CS	22906			1.3 (0.5–3.8)		
Anadkat	USA (2012)	Cohort	CS	286454	Both	34–42	2.64 (2.29–3.05)	Multiplicity of gestation, size for GA, maternal diabetes, preeclampsia/eclampsia, chorioamnionitis and sex, prolonged rupture of membranes, GA race/ethnicity	8
Gerten	USA (2005)	Case-control	CS	28668	Single birth	NA	2.3 (2.1–2.6)	Maternal age and race/ethnicity, diabetes, parity, prenatal care, birth weight, infant sex, and variables associated with fetal distress	8
			Elective CS	28668			2.6 (1.3–2.8)		
White	USA (1985)	Case-control	CS	614	NA	≤ 36	1.63 (1.11–2.39)	GA	7
			Elective CS	406			2.33 (1.23–4.43)		
			Emergency CS	549			1.44 (0.92–2.25)		
Liston	Canada (2008)	Cohort	Elective CS	110434	Single birth	≥ 36	5.39 (3.24–8.98)	Year of delivery, maternal age, parity, smoking, maternal weight at delivery, hypertensive disease, diabetes, previous caesarean delivery, the use of regional anaesthesia, the induction of labor, GA, and large and small for GA, where significant	8
			Emergency CS	116187			2.08 (1.23–3.54)		

Table 1 (continued)

Author	Country/Continent (year)	Study type	Exposure	Sample size	No. of fetuses	Range of gestational age (week)	OR (95% CI)	Adjustment for covariates	Score of quality assessment
Curet	USA (1988)	Cohort	Elective CS	242	Single birth	26–37	3.77 (1.1–12.91)	Race, sex, age of mother, number of prior pregnancies, GA at delivery, tocolytic therapy, premature rupture of the membranes, preeclampsia, diabetes mellitus and chronic hypertension	8
			Emergency CS	258			0.69 (0.19–2.51)		
Luerti	Italy (1993)	Cohort	Elective CS	1108	Both	26–37	1.3 (0.8–2)	Terms for calendar period, study center, sex, weight and, in turn, Apgar score 1st minute, Apgar score 5th minute	7
			Emergency CS	1246			0.5 (0.3–1.1)		
Karlstrom	Sweden (2013)	Case-control	Elective CS	18813	Single birth	NA	2.7 (1.8–3.9)	Age, parity, country of birth, BMI, infertility and length of pregnancy	7
			Emergency CS	13774			2.1 (1.3–3.6)		
Badran	USA (2012)	Cohort	Elective CS	1722	Single birth	> 36	3.19 (0.08–131)	Maternal illness, women pre-pregnancy BMI, labor, baby's gender, and birth weight	7
			Emergency CS	1836			1.16 (0.25–5.45)		
Altman	Sweden (2013)	Case-control	Elective CS	2618	Single birth	30–34	2.57 (1.75–3.77)	Maternal age, parity, BMI, daily smoking in early pregnancy, chronic disease, assisted conception, preeclampsia, preterm rupture of membranes and infant's GA	9
			Emergency CS	4202			2.13 (1.67–2.72)		
Winn	USA (2001)	Cohort	Elective CS[c]	10	Twin	> 24	3.13 (0.11–86.72)	GA and birth weight	8
			Emergency CS[c]	34			2.47 (0.05–122.35)		
			Elective CS[d]	65			0.83 (0.25–5.7)		
			Emergency CS[d]	67			1.42 (0.26–7.82)		

Table 1 (continued)

Author	Country/Continent (year)	Study type	Exposure	Sample size	No. of fetuses	Range of gestational age (week)	OR (95% CI)	Adjustment for covariates	Score of quality assessment
Livingston	USA (2010)	Cohort	Elective CS	978	Single birth	≥ 20	2.32 (0.95–5.67)	Maternal race and ethnicity, infant sex, maternal plasma viral load closest to delivery, infant GA, infant birth weight	8
			Emergency CS	782			2.56 (1.01–6.48)		
Mortier	France (2017)	Cohort	Elective CS	344	Single birth	> 34	1.9 (0.6–6)	NA	7
			Emergency CS	353			2.9 (0.9–9.2)		
Dani	Italy (1999)	Cohort	Elective CS	54962	Both	NA	1.88 (1.42–2.48)	Birthweight, GA, sex maternal age	9
			Emergency CS	45292			3.46 (2.69–4.44)		
Zanardo	Italy (2004)	Cohort	Elective CS	2568	NA	$37–41^{+6}$	5.85 (2.27–32,4)	NA	8
Kreitchmann	Latin America (2011)	Cohort	Emergency CS	926	Single birth	> 20	3.18 (1.41–7.16)	NA	7

CS cesarean section, *RDS* respiratory distress syndrome, *OR* odds ratio, *CI* confidence interval, *GA* gestational age, *SNAP II* Score for Neonatal Acute Physiology version II, *NA* not available, *BMI* body mass index

[a]Appropriately grown preterm neonates

[b]Small-for-gestational-age newborns

[c]The second infant of twins with birth weights < 1500 g;

[d]The second infant of twins with birth weights ≥ 1500 g

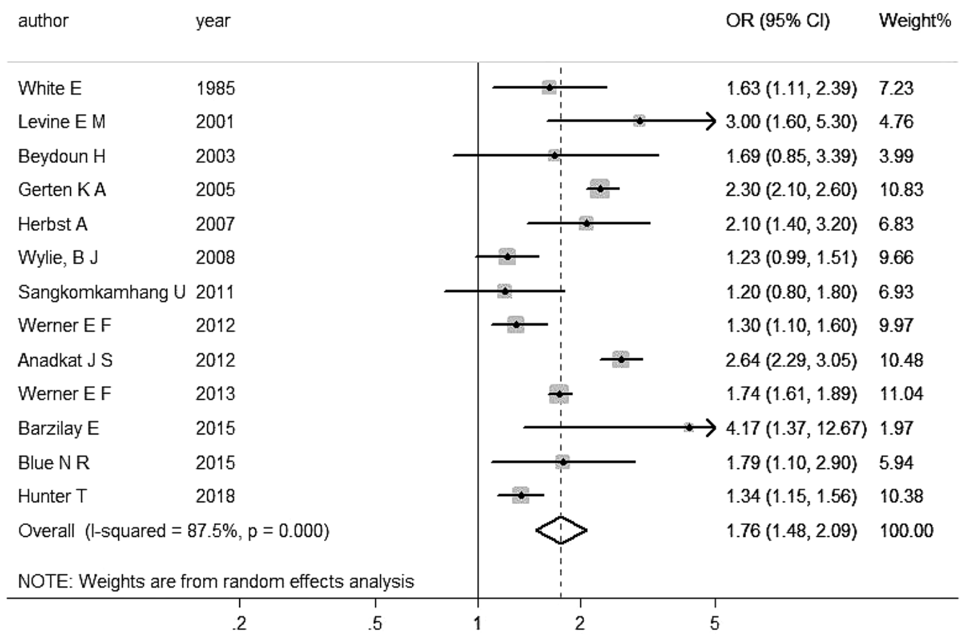

Fig. 2 Forest plot of cesarean section and the risk of respiratory distress syndrome. The size of gray box is positively proportional to the weight assigned to each study, which is inversely proportional to the standard error of the OR, and horizontal lines represent the 95% CIs (OR, odds ratio; CI, confidence interval)

1.48–2.09; $I^2 = 87.5\%$, $P_{heterogeneity} < 0.05$; Fig. 2). In subgroup analysis stratified by study design, the pooled OR of neonatal RDS was 1.71 (95% CI 1.40–2.09; $I^2 = 87.6\%$, $P_{heterogeneity} < 0.05$) for cohort studies, and 2.03 (95% CI 1.57–2.61; $I^2 = 42.9\%$, $P_{heterogeneity} = 0.173$) for case–control studies. Regarding the subgroup by continents, the pooled OR of neonatal RDS was 1.76 (95% CI 1.45–2.13; $I^2 = 91.1\%$, $P_{heterogeneity} < 0.05$) in North America and 1.79 (95% CI 1.18–2.71; $I^2 = 52.6\%$, $P_{heterogeneity} = 0.097$) in other continents. In subgroup analysis stratified by number of fetuses, the pooled OR of the risk of neonatal RDS was 1.76 (95% CI 1.43–2.16; $I^2 = 87.6\%$, $P_{heterogeneity} < 0.05$) for single birth and was 1.77 (95% CI 1.22–2.59; $I^2 = 85.9\%$, $P_{heterogeneity} < 0.05$) for others. The results of subgroup analyses are summarized in Table 2.

Elective CS and the risk of neonatal RDS

Among the 15 studies [5, 7, 17, 19, 22, 35–42, 44] assessing the association between elective CS and the risk of neonatal RDS, 8 studies [17, 19, 22, 37–40] were conducted in North America, 6 studies [5, 7, 35, 36, 42, 44] in Europe and 1 study [41] in Asia. As for study design, there were 11 cohort studies [5, 7, 19, 35, 37–42] and 4 case–control studies [17, 22, 36, 44]. The pooled OR of the risk of neonatal RDS associated with elective CS was 2.38 (95% CI 1.89–2.99; $I^2 = 45.3\%$, $P_{heterogeneity} = 0.029$; Fig. 3). In subgroup analysis stratified by study design, the pooled OR of neonatal RDS was 2.27 (95% CI 1.52–3.38; $I^2 = 57.4\%$, $P_{heterogeneity} = 0.009$) for cohort studies, and 2.59 (95% CI 2.10–3.19; $I^2 = 0\%$, $P_{heterogeneity} = 0.985$) for case–control studies. Regarding the subgroup analysis by continents, the pooled OR of neonatal RDS was 2.68 (95% CI 1.85–3.89; $I^2 = 40.2\%$, $P_{heterogeneity} = 0.111$) in North America and 2.13 (95% CI 1.64–2.77; $I^2 = 39.2\%$, $P_{heterogeneity} = 0.131$) in other countries. In subgroup analysis stratified by number of fetuses, the pooled OR of neonatal RDS for single birth was 2.81 (95% CI: 2.24 to 3.52; $I^2 = 17.9\%$, $P_{heterogeneity} = 0.284$) and 1.82 (95% CI: 1.33 to 2.49; $I^2 = 25.6\%$, $P_{heterogeneity} = 0.242$) for the others.

Among the 15 studies assessing the association between elective CS and the risk of neonatal RDS, 5 studies [19, 35, 38, 41, 44] were conducted in newborn delivered at term. The pooled OR of neonatal RDS associated with elective CS for full-term newborn was 3.27 (95% CI 1.91–5.59; $I^2 = 53.2\%$, $P_{heterogeneity} = 0.073$).

Emergency CS and the risk of neonatal RDS

Among the 13 studies [5, 7, 17, 36–44] assessing the association between emergency CS and the risk of neonatal RDS, 6 studies [17, 37–40] were conducted in North America, 5 studies [5, 7, 36, 42, 44] in Europe, 1 study [41] in Asia and 1 study [43] in Latin America. As for study design, there were 10 cohort studies [5, 7, 37–41, 43, 45] and 3 case–control studies [17, 36, 44]. For emergency CS, the pooled OR of the risk of neonatal RDS was 1.85 (95% CI 1.34–2.56; $I^2 = 70.9\%$, $P_{heterogeneity} < 0.05$; Fig. 4). In subgroup analysis stratified by study design, the pooled OR of neonatal RDS was 1.78 (95% CI 1.05–3.02; $I^2 = 75.1\%$, $P_{heterogeneity} < 0.05$) for cohort studies, and 1.97 (95% CI 1.62–2.40; $I^2 = 14.6\%$, $P_{heterogeneity} = 0.310$) for case–control studies. Regarding the subgroup analysis by continents, the pooled OR of

Table 2 Summary of pooled ORs for the associations between CS, elective CS, and emergency CS and neonatal RDS risk

Exposure	Subgroup	No. of studies	Pooled OR (95% CI)	I^2 (%)	$P_{heterogeneity}$
CS	All studies	13	1.76 (1.48, 2.09)	87.5	0.000
	Study design				
	Cohort	10	1.71 (1.40, 2.09)	87.6	0.000
	Case–control	3	2.03 (1.57, 2.61)	42.9	0.173
	Continent				
	North America	9	1.76 (1.45, 2.13)	91.1	0.000
	Others	4	1.79 (1.18, 2.71)	52.6	0.097
	Number of fetuses				
	Single birth	7	1.76 (1.43, 2.16)	87.6	0.000
	Others[a]	6	1.77 (1.22, 2.59)	85.9	0.000
	Adjusted for birth weight				
	Yes	4	1.90 (1.21, 2.96)	89.6	0.000
	No	9	1.73 (1.41, 2.12)	86.8	0.000
	Adjusted for gestational age				
	Yes	10	1.65 (1.36, 1.99)	87.0	0.000
	No	3	2.30 (2.08, 2.55)	0.0	0.468
	Adjusted for maternal age				
	Yes	8	1.66 (1.35, 2.03)	86.4	0.000
	No	5	1.95 (1.33, 2.86)	90.8	0.000
Elective CS	All studies	15	2.38 (1.89, 2.99)	45.3	0.029
	Study design				
	Cohort	11	2.27 (1.52, 3.38)	57.4	0.009
	Case–control	4	2.59 (2.10, 3.19)	0.0	0.985
	Continent				
	North America	8	2.68 (1.85, 3.89)	40.2	0.111
	Others	7	2.13 (1.64, 2.77)	39.2	0.131
	Number of fetuses				
	Single birth	9	2.81 (2.24, 3.52)	17.9	0.284
	Others[a]	6	1.82 (1.33, 2.49)	25.6	0.242
	Adjusted for birth weight				
	Yes	7	1.91 (1.52, 2.38)	9.6	0.356
	No	8	2.90 (2.17, 3.89)	35.2	0.147
	Adjusted for gestational age				
	Yes	8	2.59 (1.84, 3.66)	53.5	0.036
	No	7	2.15 (1.54, 3.01)	40.5	0.121
	Adjusted for maternal age				
	Yes	5	2.33 (1.96, 2.76)	0.0	0.408
	No	10	2.27 (1.42, 3.64)	58.3	0.010

Table 2 (continued)

Exposure	Subgroup	No. of studies	Pooled OR (95% CI)	I^2 (%)	$P_{heterogeneity}$
Emergency CS	All studies	13	1.85 (1.34, 2.56)	70.9	0.000
	Study design				
	Cohort	10	1.78 (1.05, 3.02)	75.1	0.000
	Case–control	3	1.97 (1.62, 2.40)	14.6	0.310
	Continent				
	North America	6	1.67 (1.23, 2.26)	0.0	0.583
	Others	7	1.97 (1.25, 3.10)	81.9	0.000
	Number of fetuses				
	Single birth	8	2.13 (1.77, 2.57)	0.0	0.673
	Others[a]	5	1.45 (0.59, 3.54)	88.9	0.000
	Adjusted for birth weight				
	Yes	6	1.57 (0.61, 4.01)	84.0	0.000
	No	7	1.99 (1.63, 2.43)	9.7	0.355
	Adjusted for gestational age				
	Yes	8	2.10 (1.52, 2.91)	61.9	0.010
	No	5	1.60 (0.74, 3.46)	76.8	0.002
	Adjusted for maternal age				
	Yes	5	2.28 (1.63, 3.18)	68.9	0.012
	No	8	1.57 (0.92, 2.70)	58.4	0.018

CS cesarean section, *CI* confidence interval, *OR* odds ratio, *RDS* respiratory distress syndrome

[a]Not described the number of fetus in studies, twins or include both single and multiple births

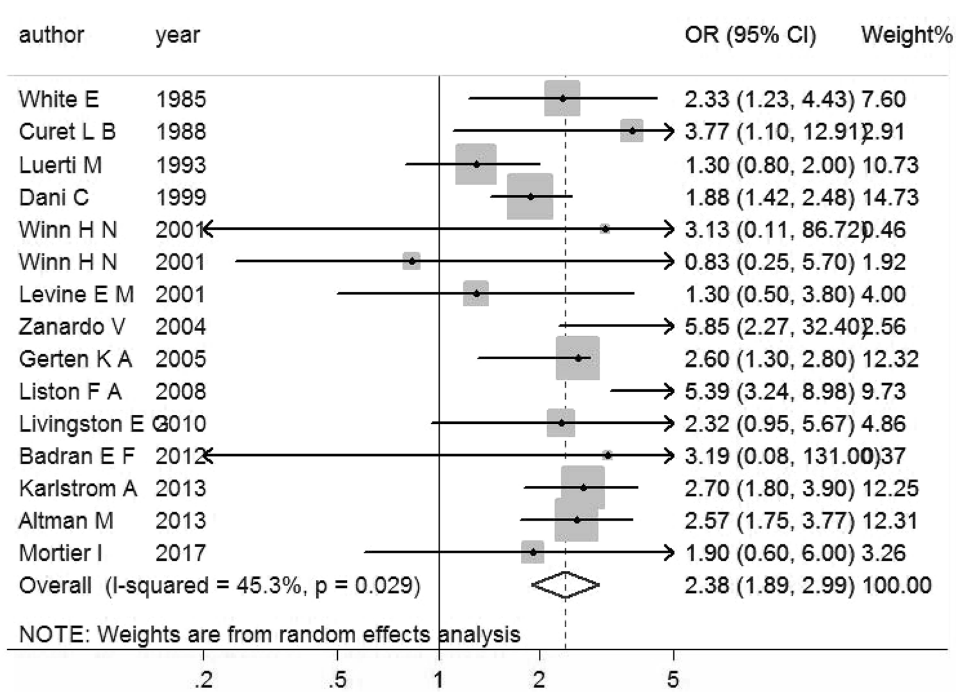

Fig. 3 Forest plot of elective cesarean section and the risk of neonatal respiratory distress syndrome (OR, odds ratio; CI, confidence interval)

neonatal RDS was 1.67 (95% CI 1.23–2.26; $I^2 = 0.0\%$, $P_{heterogeneity} = 0.583$) in North America and 1.97 (95% CI 1.25–3.10; $I^2 = 81.9\%$, $P_{heterogeneity} < 0.05$) in other countries. In subgroup analysis stratified by number of fetuses, the pooled OR of neonatal RDS was 2.13 (95% CI 1.77–2.57; $I^2 = 0\%$, $P_{heterogeneity} = 0.673$) for single birth and 1.45 (95% CI 0.59–3.54; $I^2 = 88.9\%$, $P_{heterogeneity} < 0.05$) for the others.

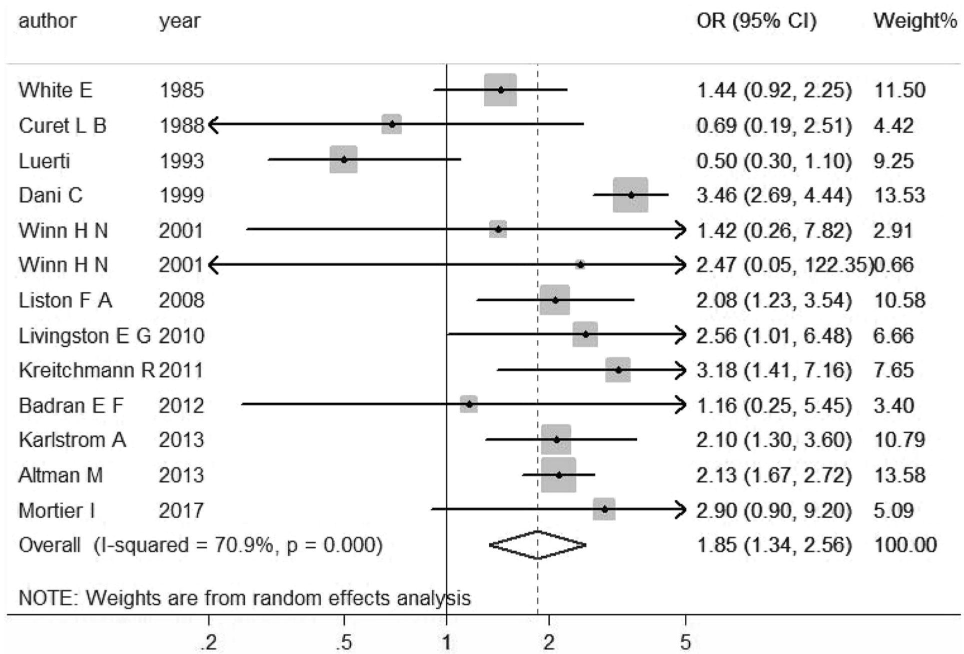

Fig. 4 Forest plot of emergency cesarean section and the risk of neonatal respiratory distress syndrome (OR, odds ratio; CI, confidence interval)

Sources of heterogeneity and sensitivity analysis

Univariate meta-regression analyses with the covariates of publication year, sample size, continent, study design (cohort study or case–control study), study quality, number of the fetuses, and adjustment (yes or no) for maternal age, birthweight, and gestational age were performed to explore the sources of heterogeneity. None of these covariates was found to have a significant impact on the between-study heterogeneity in the analyses of the associations between CS, emergency CS, and the risk of neonatal RDS. However, the results showed that the number of fetuses ($P=0.042$) contributed to heterogeneity in the analysis of the association between elective CS and the risk of neonatal RDS. The corresponding P values are shown in Table 3.

We performed leave-one-out sensitivity analysis to further investigate potential sources of heterogeneity. In the analysis of the association between CS and the risk of neonatal RDS, after excluding 4 studies [18, 19, 22, 26], the heterogeneity was reduced to 33.6% ($P_{\text{heterogeneity}}=0.349$) and the result was still significant (OR = 1.42, 95% CI 1.25–1.62). In the analysis of the association between elective CS and the risk of neonatal RDS, the pooled OR of neonatal RDS was 2.29 (95% CI 1.96–2.69; $I^2=0$, $P_{\text{heterogeneity}}=0.710$) after further excluding 2 studies [38, 42]. In the analysis of the association between emergency CS and risk of neonatal RDS, after excluding 1 study [44], the heterogeneity was reduced to 0.0% ($P_{\text{heterogeneity}}=0.672$) and the result was still significant (OR = 2.00, 95% CI 1.69–2.38).

Table 3 Results of meta-regression

Exposure	Covariates	*P* value	*t*
CS	Continent	0.962	0.05
	Sample size	0.257	1.20
	Study design	0.591	0.55
	Study quality	0.566	−0.59
	Publication year	0.668	0.44
	Number of fetuses	0.955	−0.06
	Adjusted for birth weight	0.756	−0.32
	Adjusted for maternal age	0.441	0.80
	Adjusted for gestational age	0.136	1.61
Elective CS	Continent	0.358	0.95
	Sample size	0.760	−0.31
	Study design	0.625	0.50
	Study quality	0.552	0.61
	Publication year	0.227	1.27
	Number of fetuses	0.042	−2.25
	Adjusted for birth weight	0.065	2.02
	Adjusted for maternal age	0.789	−0.27
	Adjusted for gestational age	0.479	−0.73
Emergency CS	Continent	0.630	0.50
	Sample size	0.124	1.66
	Study design	0.937	0.08
	Study quality	0.187	1.41
	Publication year	0.098	1.81
	Number of fetuses	0.419	−0.84
	Adjusted for maternal age	0.339	−1.00
	Adjusted for gestational age	0.529	−0.65
	Adjusted for birth weight	0.651	0.47

CS cesarean section

Influence analysis and small-study effect evaluation

Influence analysis indicated that 2 studies [22, 26] had excessive influence on the pooled OR of the association between CS and the risk of neonatal RDS. After excluding these two studies, the result was still significant (OR = 1.56, 95% CI 1.35–1.81). No individual study had excessive influence on the pooled OR for the association between elective CS and the risk of neonatal RDS. Regarding the association between emergency CS and the risk of neonatal RDS, 1 study [5] had excessive influence on the pooled OR. After excluding this single study, the pooled OR of neonatal RDS was 1.69 (95% CI 1.24–2.30).

Egger's tests and the funnel plot showed no evidence of a significant small-study effect in the analyses of associations of CS ($P = 0.788$; Fig. 5), elective CS ($P = 0.769$; Fig. 6), and emergency CS ($P = 0.199$; Fig. 7) with the risk of neonatal RDS.

Discussion

Main findings

Our meta-analysis included 26 studies from 25 available articles. The results showed that CS, elective CS, and emergency CS were associated with an increased risk of neonatal RDS. In addition, the associations of CS and elective CS with the risk of neonatal RDS remained significant in subgroup analysis by continent, study design, number of fetuses, and adjustment status of gestational age, birthweight, and maternal age. In addition, we also found that elective CS significantly increased the risk of neonatal RDS for full-term newborn.

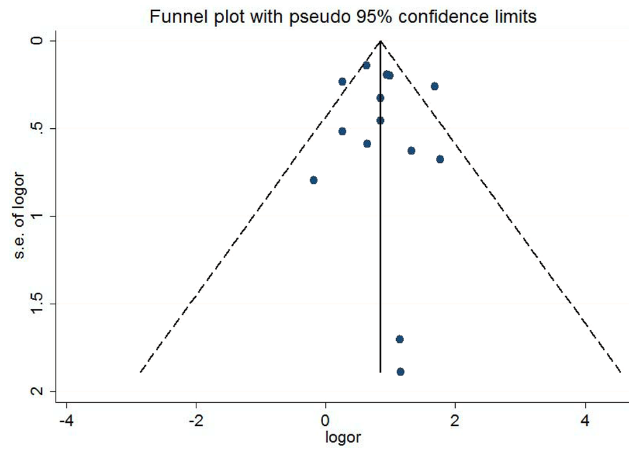

Fig. 6 Funnel plot of relative risk (OR) for the analysis of the association between elective cesarean section and the risk of neonatal respiratory distress syndrome. Each dot represents a different study

The potential mechanism underlying the association between CS and the risk of neonatal RDS is that labor is associated with catecholamine release [46], and a high concentration of catecholamine in newborn infants is conducive to promoting the absorption of lung fluid and increasing the release of surfactants [47, 48].

Moderate-to-high heterogeneities were demonstrated for the associations of CS, elective CS, and emergency CS with the risk of neonatal RDS. To explore the sources of between-study heterogeneity, meta-regression analyses with the covariates of publication year, sample size, continent, study design, study quality assessment score, number of fetuses, and adjustment (yes or no) for maternal age, birthweight, and gestational age were performed. However, except number of fetuses ($P = 0.042$) in the

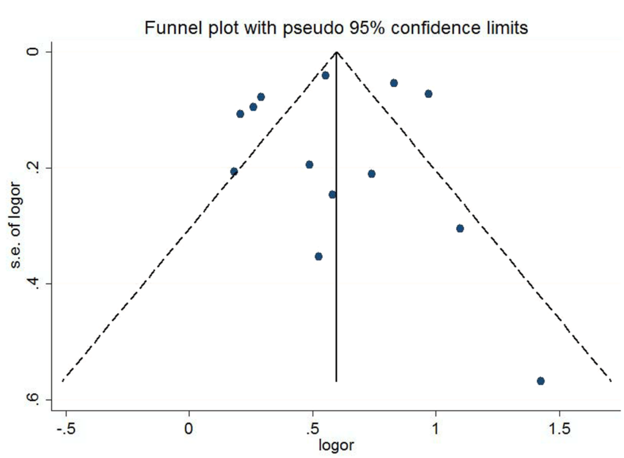

Fig. 5 Funnel plot of relative risk (OR) for the analysis of the association between cesarean section and the risk of neonatal respiratory distress syndrome. Each dot represents a different study

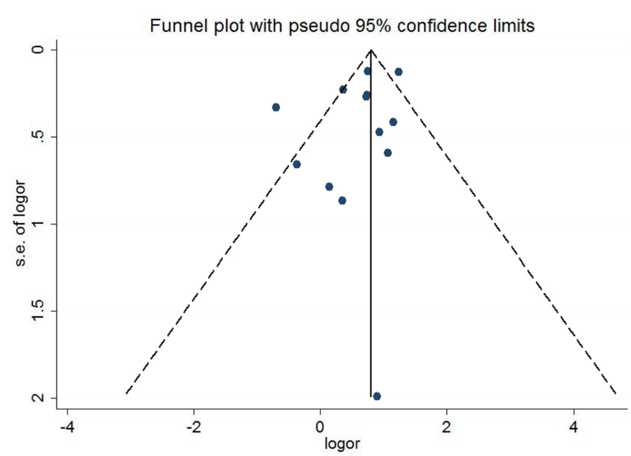

Fig. 7 Funnel plot of relative risk (OR) for the analysis of the association between emergency cesarean section and the risk of neonatal respiratory distress syndrome. Each dot represents a different study

analysis of the association between elective CS and the risk of neonatal RDS, the other covariates were not found to contribute to between-study heterogeneity. The results of our subgroup analysis also found that the number of fetuses might be the source of heterogeneity in the analyses between elective CS and the risk of neonatal RDS. In addition, to further investigate the potential sources of between-study heterogeneity in the analyses of CS, elective CS, and emergency CS with the risk of neonatal RDS, leave-one-out sensitivity analyses were performed. In the analyses of CS, elective CS, and emergency CS with the risk of neonatal RDS, after excluding 4 studies [18, 19, 22, 26], 2 studies [38, 42], and 1 study [43], the heterogeneity was reduced and all the results remained significant. Considering that heterogeneity still exists, we speculated that the possible factors leading to heterogeneity might be: (1) the confounders adjusted for in the included studies were diverse and (2) the definitions of neonatal RDS in the included studies were not completely consistent.

Strengths and limitations of the study

There are several strengths in our analysis. First, this is the first quantitative meta-analysis assessing the associations of CS (not differentiating between elective CS and emergency CS), elective CS, and emergency CS with the risk of neonatal RDS. Second, the present meta-analysis included a large number of participants, which was likely to draw a more reasonable conclusion. Third, almost all studies have adjusted the potential confounders, such as gestational age, birth weight or maternal age, and maternal chronic disease (preeclampsia, diabetes mellitus and chronic hypertension), improving the credibility of the findings. Fourth, most of the included studies are cohort studies, which could produce more convincing results.

However, this meta-analysis also has several limitations. First, although the major confounders have been adjusted in the included studies, some potential confounders, such as birth asphyxia and neonatal infection, might also have an impact on the observed associations. Second, the high heterogeneity was found in our meta-analysis. However, after excluding the studies that have a significant impact on between-study heterogeneity, the heterogeneity was reduced and the results did not change substantially. Third, we did not further analysis the influence of prenatal steroid treatment and the type of elective CS (mother's requirement or medical indication) on these observed associations due to the absence of relevant information. Fourth, our search excluded non-English or unpublished studies, which might result in some data being lost. In addition, some included articles did not have a precise definition of neonatal RDS, which might lead to misclassification and affect the results.

Conclusions

This meta-analysis suggests that CS, elective CS, and emergency CS were associated with an increased risk of neonatal RDS and that elective CS might increase the risk of neonatal RDS even for full-term newborn. Our meta-analysis might provide constructive guidance for clinicians when making decisions with respect to mode of delivery of newborn.

Author's contribution YL: conceived the study, designed the study, drafted the manuscript, carried out the literature search and data extraction, interpreted the result of the analysis, and reviewed and revised the manuscript critically. CZ: carried out the literature search and data extraction, interpreted the result of the analysis, and reviewed and revised the manuscript critically. DZ: conceived the study, designed the study, drafted the manuscript, and reviewed and revised the manuscript critically. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Tochie JN, Choukem SP, Langmia RN, Barla E, Koki-Ndombo P (2016) Neonatal respiratory distress in a reference neonatal unit in Cameroon: an analysis of prevalence, predictors, etiologies and outcomes. Pan Afr Med J 24:152
2. De Luca D, van Kaam AH, Tingay DG, Courtney SE, Danhaive O, Carnielli VP, Zimmermann LJ, Kneyber MCJ, Tissieres P, Brierley J, Conti G, Pillow JJ, Rimensberger PC (2017) The Montreux definition of neonatal ARDS: biological and clinical background behind the description of a new entity. Lancet Respir Med 5:657–666
3. Hermansen CL, Mahajan A (2015) Newborn respiratory distress. Am Fam Phys 92:994
4. Lewis S (1968) A follow-up study of the respiratory distress syndrome. Proc R Soc Med 61:771–773
5. Dani C, Reali MF, Bertini G, Wiechmann L, Spagnolo A, Tangucci M, Rubaltelli FF, Italian Grp Neonatal P (1999) Risk factors for the development of respiratory distress syndrome and transient tachypnoea in newborn infants. Eur Respir J 14:155–159
6. Reed DM, Bakketeig LS, Nugent RP (1978) The epidemiology of respiratory distress syndrome in Norway. Am J Epidemiol 107:299–310
7. Mortier I, Blanc J, Tosello B, Gire C, Bretelle F, Carcopino X (2017) Is gestational diabetes an independent risk factor of neonatal severe respiratory distress syndrome after 34 weeks of gestation? a prospective study. Arch Gynecol Obstet 296:1071–1077

8. Alfirevic Z, Milan SJ, Livio S (2012) Caesarean section versus vaginal delivery for preterm birth in singletons. Cochrane Database Syst Rev.https://doi.org/10.1002/14651858.CD000078.pub2
9. Santas G, Santas F (2018) Trends of caesarean section rates in Turkey. J Obstet Gynaecol 38:658–662
10. Caughey AB, Cahill AG, Guise JM, Rouse DJ (2014) Safe prevention of the primary cesarean delivery. Am J Obstet Gynecol 210:179–193
11. Alexander JM, Leveno KJ, Hauth J, Landon MB, Thom E, Spong CY, Varner MW, Moawad AH, Caritis SN, Harper M, Wapner RJ, Sorokin Y, Miodovnik M, O'Sullivan MJ, Sibai BM, Langer O, Gabbe SG (2006) Fetal injury associated with cesarean delivery. Obstet Gynecol 108:885–890
12. Kamath BD, Todd JK, Glazner JE, Lezotte D, Lynch AM (2009) Neonatal outcomes after elective cesarean delivery. Obstet Gynecol 113:1231
13. Soltanifar S, Russell R (2012) The National Institute for Health and Clinical Excellence (NICE) guidelines for caesarean section, 2011 update: implications for the anaesthetist. Int J Obstet Anesth 21:264–272
14. Baumfeld Y, Walfisch A, Wainstock T, Segal I, Sergienko R, Landau D, Sheiner E (2018) Elective cesarean delivery at term and the long-term risk for respiratory morbidity of the offspring. Eur J Pediatr 177:1653–1659
15. Greenough A, Lagercrantz H, Pool J, Dahlin I (1987) Plasma catecholamine levels in preterm infants. Effect of birth asphyxia and Apgar score. Acta Paediatr Scand 76:54–59
16. Morley GM (2001) Mode of delivery and risk od respiratory diseases in newborns. Obstet Gynecol 97:439–442
17. White E, Shy KK, Daling JR (1985) An investigation of the relationship between cesarean section birth and respiratory distress syndrome of the newborn. Am J Epidemiol 121:651–663
18. Werner EF, Han CS, Savitz DA, Goldshore M, Lipkind HS (2013) Health outcomes for vaginal compared with cesarean delivery of appropriately grown preterm neonates. Obstet Gynecol 121:1195–1200
19. Levine EM, Ghai V, Barton JJ, Strom CM (2001) Mode of delivery and risk of respiratory diseases in newborns. Obstet Gynecol 97:439–442
20. Hunter T, Shah J, Synnes A, Shivananda S, Ryan G, Shah PS, Murphy KE, Canadian Neonatal N (2018) Neonatal outcomes of preterm twins according to mode of birth and presentation. J Matern Fetal Neonatal Med 31:682–688
21. Herbst A, Kallen K (2007) Influence of mode of delivery on neonatal mortality and morbidity in spontaneous preterm breech delivery. Eur J Obstet Gynecol Reprod Biol 133:25–29
22. Gerten KA, Coonrod DV, Bay RC, Chambliss LR (2005) Cesarean delivery and respiratory distress syndrome: does labor make a difference? Am J Obstet Gynecol 193:1061–1064
23. Blue NR, Van Winden KR, Pathak B, Barton L, Opper N, Lane CJ, Ramanathan R, Ouzounian JG, Lee RH (2015) Neonatal outcomes by mode of delivery in preterm birth. Am J Perinatol 32:1292–1297
24. Barzilay E, Mazaki-Tovi S, Amikam U ,de Castro H ,Haas J, Mazkereth R, Sivan E ,Schiff E, Yinon Y (2015) Mode of delivery of twin gestation with very low birthweight: is vaginal delivery safe? Am J Obstet Gynecol. https://doi.org/10.1016/j.ajog.2015.03.030
25. Werner EF, Savitz DA, Janevic TM, Ehsanipoor RM, Thung SF, Funai EF, Lipkind HS (2012) Mode of delivery and neonatal outcomes in preterm, small-for-gestational-age newborns. Obstet Gynecol 120:560–564
26. Anadkat JS, Kuzniewicz MW, Chaudhari BP, Cole FS, Hamvas A (2012) Increased risk for respiratory distress among white, male, late preterm and term infants. J Perinatol 32:780–785
27. Wylie BJ ,Davidson LL, Batra M, Reed SD (2008) Method of delivery and neonatal outcome in very low-birthweight vertex-presenting fetuses. Am J Obstet Gynecol 198: 640.e1-7 (**discussion e1–4**)
28. Sangkomkamhang U, Pattanittum P, Laopaiboon M, Lumbiganon P (2011) Mode of delivery and outcomes in preterm births. J Med Assoc Thail 94: 415–420.
29. Beydoun H, Yunis KA, Khogali M, Usta I, Tamim H (2003) Caesarean route of delivery and hyaline membrane disease: a hospital-based case-control study in Greater Beirut. Paediatr Perinat Epidemiol 17:363–368
30. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Chin Integr Med 18:e123
31. Higgins JPT, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558
32. Higgins JPT, Thompson SG (2004) Controlling the risk of spurious findings from meta-regression. Stat Med 23:1663–1682
33. Patsopoulos NA, Evangelou E, Ioannidis JP (2008) Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. Int J Epidemiol 37:1148–1157
34. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634
35. Zanardo V, Simbi AK, Franzoi M, Solda G, Salvadori A, Trevisanuto D (2004) Neonatal respiratory morbidity risk and mode of delivery at term: influence of timing of elective caesarean delivery. Acta Paediatr (Oslo, Norway: 1992) 93: 643–647.
36. Altman M, Vanpee M, Cnattingius S, Norman M (2013) Risk factors for acute respiratory morbidity in moderately preterm infants. Paediatr Perinat Epidemiol 27:172–181
37. Curet LB, Zachman RD, Rao AV, Poole WK, Morrison J, Burkett G (1988) Effect of mode of delivery on incidence of respiratory distress syndrome. Int J Gynaecol Obstet 27:165–170
38. Liston FA, Allen VM, O'Connell CM, Jangaard KA (2008) Neonatal outcomes with caesarean delivery at term. Arch Dis Child Fetal Neonatal Ed 93:F176–F182
39. Livingston EG, Huo Y, Patel K, Brogly SB, Tuomala R, Scott GB, Bardeguez A, Stek A, Read JS (2010) Mode of delivery and infant respiratory morbidity among infants born to HIV-1-infected women. Obstet Gynecol 116:335–343
40. Winn HN, Cimino J, Powers J, Roberts M, Holcomb W, Artal R, Amon E (2001) Intrapartum management of nonvertex second-born twins: a critical analysis. Am J Obstet Gynecol 185:1204–1208
41. Badran EF, Abdalgani MM, Al-Lawama MA, Al-Ammouri IA, Basha AS, Al Kazaleh FA, Saleh SS, Al-Katib FA, Khader YS (2012) Effects of perinatal risk factors on common neonatal respiratory morbidities beyond 36 weeks of gestation. Saudi Med J 33:1317–1323
42. Luerti M, Parazzini F, Agarossi A, Bianchi C, Rocchetti M, Bevilacqua G (1993) Disparities in the risk of gestational diabetes by race-ethnicity and country of birth—a multicenter Italian survey. Acta Obstet Gynecol Scand 72:359–364
43. Kreitchmann R, Cohen RA, Stoszek SK, Pinto JA, Losso M, Pierre R, Alarcon J, Succi R, Szyld E, Abreu T, Read JS (2011) Mode of delivery and neonatal respiratory morbidity among HIV-exposed newborns in Latin America and the Caribbean: NISDI Perinatal-LILAC Studies. Int J Gynecol Obstet 114:91–96
44. Karlstrom A, Lindgren H, Hildingsson I (2013) Maternal and infant outcome after caesarean section without recorded medical indication: findings from a Swedish case-control study. BJOG 120: 479–86 (**discussion 486**)
45. Luerti M, Parazzini F, Agarossi A, Bianchi C, Rocchetti M, Bevilacqua G (1993) RISK-factors for respiratory-distress syndrome in the newborn—a multicenter Italian survey. Acta Obstet Gynecol Scand 72:359–364

46. Lagercrantz H, Bistoletti P (1977) Catecholamine release in the newborn infant at birth. Pediatr Res 11:889–893
47. Fedrick J, Butler NR (1972) Hyaline-membrane disease. Lancet (London, England) 2:768–769
48. Jain L, Dudell GG (2006) Respiratory transition in infants delivered by cesarean section. Semin Perinatol 30:296–304

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.