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REVIEW ARTICLE

Maternal diabetes mellitus and risk of neonatal respiratory distress syndrome: a meta-analysis

Yan Li[1] · Weijing Wang[1] · Dongfeng Zhang[1]

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Abstract

Aim The relationship between maternal diabetes mellitus (DM) and neonatal respiratory distress syndrome (RDS) has long been recognized, but the conclusions of this relationship were non-consistent. We conducted this meta-analysis to explore the association between maternal DM and the risk of neonatal RDS.

Methods We searched PubMed and Web of Science databases for cohort or case–control studies related to the association of maternal DM and neonatal RDS risk up to 25 August 2018. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were estimated by the use of random effect model. Meta-regression was used to explore potential sources of between-study heterogeneity.

Results A total of 24 studies from 23 available articles were included in this meta-analysis. For the association between maternal DM and the risk of neonatal RDS, the pooled OR was 1.47 (95% CI 1.24–1.74), especially for cohort studies (1.39, 95% CI 1.17–1.65). The pooled OR of the risk of neonatal RDS was 1.57 (95% CI 1.28–1.93) for gestational diabetes mellitus (GDM) and 2.66 (95% CI 2.06–3.44) for pre-gestational diabetes mellitus (PGDM).

Conclusions This meta-analysis suggests that maternal DM, including GDM and PGDM, is linked to an increased risk of neonatal RDS.

Keywords Epidemiology studies · Maternal diabetes · Meta-analysis · Neonatal respiratory distress syndrome

Introduction

Neonatal respiratory distress syndrome (RDS) was defined by the clinical signs of early neonatal respiratory distress with consistent radiologic features and a requirement for supplemental oxygen to maintain a saturation over 85% within the first 24 h following birth [1, 2]. It is more likely to cause morbidity and mortality during infancy and childhood than any other diseases and remains a significant health problem [3]. Even survivors of RDS seem more likely to suffer from severe sequelae [4]. Actual potential risk factors for RDS include low gestational age, male, maternal age, maternal chorioamnionitis, and multifetal pregnancy among others [5, 6].

Maternal diabetes mellitus (DM), including gestational (GDM) and pre-gestational diabetes mellitus (PGDM), is the most common cause of complications during pregnancy [7]. It is estimated that the prevalence of GDM is up to 9.2%, and the prevalence of PGDM is as high as 1% in the United States [8–12]. Maternal DM increases the risk of cardiovascular disease in offspring and in pregnant mothers [13, 14]. In addition, maternal DM is associated with several adverse obstetric risks including malformations, macrosomia, and neonatal metabolic disorders [14–17]. Furthermore, neonatal respiratory complication is also one of the most common and life-threatening diseases [18, 19]. The relationship between maternal DM and neonatal RDS has been recognized since the early 1970s [20, 21]. However, the conclusions of this relationship are non-consistent. Some studies showed that maternal DM significantly increased the risk of neonatal

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✉ Dongfeng Zhang
zhangdf1961@126.com

[1] Department of Epidemiology and Health Statistics, Public Health College, Qingdao University, No. 38 Dengzhou Road, Qingdao, Shandong 266021, China

RDS [22–33], whereas other studies [7, 34–43] did not find this relationship.

Therefore, we conducted this meta-analysis to further investigate the associations between maternal DM, GDM, and PGDM and the risk of neonatal RDS, respectively.

Materials and methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to carried out this meta-analysis [44].

Search strategy

We searched PubMed and Web of Science up to 25 August 2018 to identify all available studies related to the association of maternal DM and neonatal RDS. Searches were limited to English-language studies in humans and search terms were as follows: "maternal diabetes" (or "gestational diabetes" or "pre-gestational diabetes" or "pre-pregnancy diabetes" or "infants of diabetic mothers" or "DM" or "GDM" or "diabetes") and "respiratory distress syndrome" (or "hyaline membrane disease" or "RDS" or "respiratory distress"). To identify additional eligible studies not captured by our databases, we reviewed the reference lists of retrieved articles.

Study selection criteria

The inclusion criteria were as follows: (a) cohort or case–control studies; (b) the exposure group was infants born to women with DM (gestational and/or pre-gestational); (c) the control group was infants born to women without DM; (d) the outcome of interest was neonatal RDS; (e) relative risk (RR), odds ratio (OR), or hazard ratio with 95% confidence interval (CI) was provided.

Two investigators (YL and WW) searched articles and reviewed all retrieved studies independently, and the discrepancy was resolved by the third investigator (DZ).

Data extraction and quality assessment

The following data were extracted by two investigators (YL and WW) independently: (a) name of the first author; (b) year of publication; (c) country where the study was performed; (d) study design; (e) exposure (maternal DM, GDM or PGDM); (f) diagnosis method of DM; (g) sample size and number of cases; (h) number of fetuses; (i) range of gestational age; (j) OR with 95% CI for the risk of RDS; (k) variables adjusted for; and (l) score of quality assessment. If the same control group was used in the included studies, the relationship between maternal DM and neonatal RDS was analyzed using the exposure group with a larger sample size.

The study quality was assessed by the Newcastle–Ottawa quality assessment scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), and score no less than 7 represents better methodological quality.

Statistical analysis

The pooled measure was calculated as the inverse variance-weighted mean of the logarithm of the OR with 95% CI to evaluate the relationship of maternal DM, GDM, and PGDM with the risk of neonatal RDS, respectively. Heterogeneity among studies was assessed using the I^2 [45]. We used a random effect model (REM) as the pooling method in this analysis [46]. Meta-regression was conducted to investigate the potential sources of heterogeneity [47], including the covariates of publication year, sample size, continent, study design (cohort or case–control study), study quality assessment score, number of fetuses, whether adjusted for covariates, whether adjusted for mode of delivery, whether adjusted for gestational age and whether adjusted for maternal age. We also performed subgroup analyses by continent, study design (cohort or case–control study), number of fetuses, whether adjusted for covariates, whether adjusted for mode of delivery, whether adjusted for gestational age, and whether adjusted for maternal age. Influence analysis was used to assess the existence of a single study that had a significant impact on the pooled results. Cumulative meta-analysis was conducted to indicate the dynamic trend of results by adding one study at a time according to the publication year. Egger's test [48] was used as a formal test of funnel plot asymmetry and publication bias.

All statistical analyses were performed with Stata V.15.0 (Stata Corp, College Station, TX, USA). All reported probabilities (P values) were two-sided, with $P \leq 0.05$ considered statistically significant.

Results

Literature search and study characteristics

Initially, 1565 articles from PubMed and 748 articles from Web of Science were identified. 1894 articles were excluded after reviewing titles and abstracts. We further excluded 45 articles after reviewing 68 possibly relevant articles in full text. One additional article was found from reference lists. Thus, 24 studies from 23 articles [7, 22–43] were eligible for this meta-analysis (Fig. 1).

A total of 24 studies from 23 articles [7, 22–43] evaluated the association between maternal DM and the risk of neonatal RDS; 13 studies from 12 articles [22, 24, 26, 28–31, 33, 34, 36, 39, 40] evaluated the association between GDM and the risk of neonatal RDS; 4 studies from 3 articles [23,

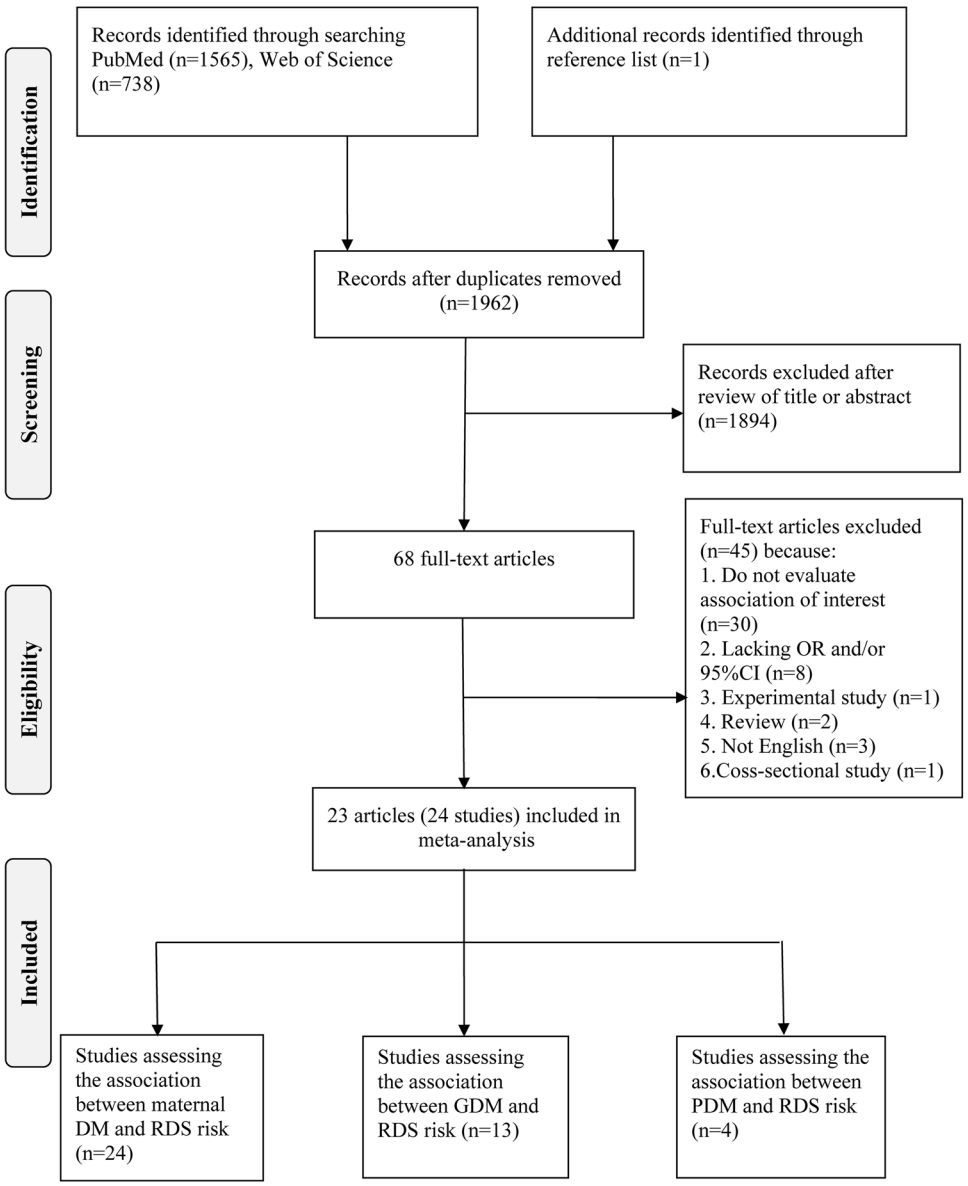

Fig. 1 Flow diagram of literature search. *CI* confidence interval, *DM* diabetes mellitus, *GDM* gestational diabetes mellitus, *PGDM* pre-gestational diabetes mellitus, *OR* odds ratio, *RDS* respiratory distress syndrome

29, 31] assessed the association between PGDM and the risk of neonatal RDS; 3 studies from 2 articles [29, 31] not only evaluated the association between PGDM and RDS, but also the association between GDM and RDS.

The Newcastle–Ottawa score of each study showed that the methodological quality was generally good. The score of quality assessment and baseline characteristics of included studies are shown in the Table 1.

Quantitative synthesis

Maternal DM and the risk of RDS

Among the 24 studies from 23 articles evaluated the relationship between maternal DM and the risk of neonatal RDS, 10 studies [24–27, 35, 36, 39, 40, 42, 43] were conducted in Europe, 7 studies [7, 23, 29, 31, 32, 34] in North America, 5 studies [28, 30, 33, 38, 41] in Asia, 1 study [37] in South America, and 1 study [22] in Oceania. In subgroup analysis stratified by study design, there were 20 cohort studies [7, 22, 23, 25–27, 29–32, 34, 35, 37–43], and 4 case–control studies [24, 28, 33, 36]. The pooled OR of the relationship between maternal DM and the risk of neonatal RDS was 1.47 (95% CI 1.24–1.74; $I^2 = 81.0\%$, $P_{\text{heterogeneity}} < 0.001$; Fig. 2). In subgroup analysis stratified by study design, the pooled OR was 1.39 (95% CI 1.17–1.65; $I^2 = 81.3\%$, $P_{\text{heterogeneity}} < 0.001$) for cohort studies, and 2.02 (95% CI 1.20–3.40; $I^2 = 59.6\%$, $P_{\text{heterogeneity}} = 0.060$) for case–control studies. In subgroup analysis stratified by continents, except Europe, the results were still significant in other continents. Regarding the subgroup of whether adjusted for

Table 1 Characteristics of studies on the associations between maternal DM, GDM and PGDM and risk of neonatal RDS

Author (year)	Country	Study type	Exposure	Diagnosis method of DM	Sample size (cases)	No. of fetuses	Range of gestational age (week)	OR (95%CI)	Adjustment for covariates	Score of quality assessment
Luerti (1993)	Italy	Cohort	Maternal DM	Retrieved from the mother's medical record	1624 (131)	Both[a]	26–37	1 (0.3, 3.4)	Calendar period, study center, sex, weight and, in term, hypertension, rupture of membranes, maternal smoking in pregnancy	8
Rehan (2002)	Canada	Matched-cohort (GA, sex, and the year of birth)	Maternal DM	OGTT	582 (409)	NA	NA	0.7 (0.35, 1.42)	NA	8
Le Ray (2006)	France	Cohort	Maternal DM	NA	189 (53)	Both[a]	34–37	0.8 (0.2, 2.9)	None	7
Bental (2011)	Israel	Cohort	Maternal DM	OGTT	15,874 (10,749)	Both[a]	24–33	1.12 (0.92, 1.32)	Ethnicity, maternal age, multiple pregnancy, maternal hypertensive disorders, prenatal steroid treatment, mode of delivery gender, GA, birth weight z score, and need for delivery room resuscitation	9
Anadkat (2012)	USA	Cohort	Maternal DM	ICD 9 codes	287,454 (895)	Both[a]	34–42	2.31 (1.81, 2.94)	Sex, race/ethnicity GA, size for GA, mode of delivery, multiplicity of gestation, pre-eclampsia/eclampsia, chorioamnionitis, and prolonged rupture of membranes	9
Fung (2014)	China	Cohort	Maternal DM	Random venous blood glucose test + OGTT	911 (12)	NA	34–36	0.83 (0.1, 6.87)	Gender, advanced maternal age, mode of delivery (cesarean section), small-for-gestation, and antenatal steroids	9
Grandi (2015)	Argentina, Brazil, Chile, Paraguay, Peru, and Uruguay	Cohort	Maternal DM	OGTT	11,991 (8486)	Both[a]	22–36	1.18 (0.9, 1.56)	Maternal age, multiple pregnancy, maternal hypertensive disorders, prenatal steroid treatment, mode of delivery, need for delivery room resuscitation, gender, GA, and birth weight *Z* score	9
Becquet (2015)	France	Cohort	Maternal DM	OGTT	17,467 (412)	Single birth	≥ 34	0.95 (0.68, 1.32)	GA and maternal and infant characteristics	7
Lloreda-Garcia (2016)	Spain	Cohort	Maternal DM	NA	996 (17)	NA	NA	2.9 (1.4, 6.7)	NO	7

Table 1 (continued)

Author (year)	Country	Study type	Exposure	Diagnosis method of DM	Sample size (cases)	No. of fetuses	Range of gestational age (week)	OR (95%CI)	Adjustment for covariates	Score of quality assessment
Persson (2018)	Canada, Finland, Israel, Italy, Japan, Sweden, and the United Kingdom	Cohort	Maternal DM	Recorded in tick boxes or defined according to ICD 10 codes	76,360 (47,402)	Single birth	24–31	1.01 (0.91, 1.11)	Maternal age of 35 years or older, maternal hypertensive disease in pregnancy, GA, sex, birth weight z score, and network, antenatal corticosteroids, mode of delivery, and out-born	9
Stone (2002)	Australia	Cohort	GDM	Record in database	60,400 (929)	Single birth	NA	1.6 (1.2, 2.2)	Maternal country of birth, aboriginality, marital status, age, gestation, parity, socioeconomic status based on postcode, previous perinatal death, and congenital malformation in current pregnancy. macrosomia, hypertension or pre-eclampsia, sex of the child and the birth condition, GA, and prematurity	9
Abolfazl (2008)	Iran	Cohort	GDM	NA	420 (33)	NA	NA	5.16 (2.45, 10.85)	None	7
Rauh-Hain (2009)	USA	Cohort	GDM	OGTT	1106 (87)	Twin	NA	1.2 (0.2, 2.8)	GA and birth weight	9
Fadl (2010)	Sweden	Cohort	GDM	OGTT	1,260,297 (2532)	Single birth	NA	1.03 (0.67, 1.59)	Maternal age, BMI, parity, chronic hypertensive disorder, smoking habits, and ethnicity	9
Simoes (2011)	Portugal	Matched-case–control (GA, chorionicity, and year of birth)	GDM	OGTT	840 (73)	Twin	≥24	2.2 (1.3, 3.7)	None	8
Abdalrahman Almarzouki (2013)	Saudi Arabia	Case–control	GDM	ICD-9 codes	149 (20)	Single birth	NA	4.2 (1.4, 12.2)	None	7

Table 1 (continued)

Author (year)	Country	Study type	Exposure	Diagnosis method of DM	Sample size (cases)	No. of fetuses	Range of gestational age (week)	OR (95%CI)	Adjustment for covariates	Score of quality assessment
Guillen (2014)	Spain	Matched-case–control (maternal age and year of delivery)	GDM	OGTT	272 (75)	Twin	> 24	0.756 (0.32, 1.79)	Maternal age, maternal hypertension, pre-eclampsia, pre-pregnancy BMI, smoking habit, mode of conception, chorionicity, severe fetal malformations, GA, and cesarean delivery	8
Boghossian (2014)	USA	Cohort	GDM	Electronic medical records + ICD-9 codes	59,506 (1927)	Single birth	≥ 20	1.33 (1.05, 1.68)	Study site, maternal age, race, parity, interpregnancy interval, pre-pregnancy BMI, and smoking status	9
			PGDM		59,026 (1934)			2.24 (1.76, 2.86)		
Liu (2014)	China	Case–control	GDM	NA	615 (205)	NA	≥ 37	2.415 (1.721, 4.053)	Selective cesarean section, birth asphyxia, small GA, maternal–fetal infection, premature rupture of membranes, male, low birth weight	8
Mortier (2017)	France	Cohort	GDM	Fasting blood glucose detection + OGTT	444 (32)	Single birth	≥ 34	3.6 (1.5, 8.6)	Obesity, mode of delivery, macrosomia	9
Bricelj (2017)	Slovenian	Cohort	GDM	OGTT	7763 (328)	Single birth	34–37	0.7 (0.4, 1.3)	None	8
Kawakita (2017)	USA	Cohort	GDM[b]	Medical records + ICD-9 codes	193,411 (4142)	Single birth	24–42	1.5 (1.3, 1.7)	Maternal age, BMI at delivery, race, insurance, parity, marital status, smoking, precursor for delivery (spontaneous labor, premature rupture of membranes, indicated, elective, and no recorded information), and hospital site	9
			GDM[c]		26,271 (2649)			1.2 (1, 1.5)		
			PGDM[b]		186,008 (4021)			3.1 (2.6, 3.7)		
			PGDM[c]		25,643 (2643)			2.2 (1.8, 2.7)		
Spain (2015)	USA	Cohort	PGDM	NA	4954 (170)	NA	≥ 37	5.7 (2.5, 12.9)	Nulliparity, fever, induction of labor, BMI, and mode of delivery	8

DM diabetes mellitus, *GDM* gestational diabetes mellitus, *PGDM* pre-gestational diabetes mellitus, *RDS* respiratory distress syndrome, *OR* odds ratio, *CI* confidence interval, *OGTT* oral glucose tolerance test, *NA* not available, *GA* gestational age, *ICD* International Classification of Diseases, *BMI* body mass index

[a]Including both single and multiple births

[b]High probability of delivery at term

[c]Low probability of delivery at term

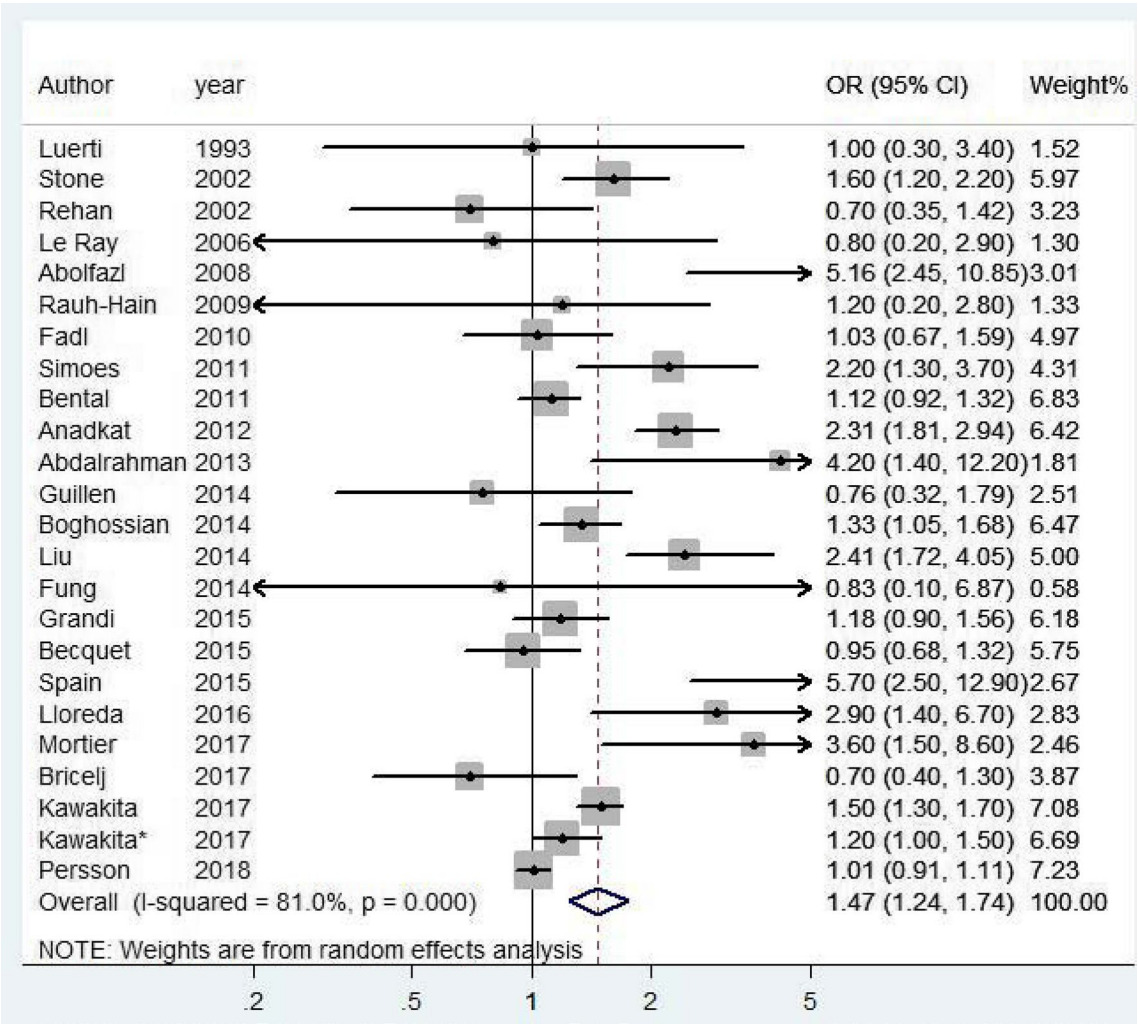

Fig. 2 Forest plot of maternal diabetes and the risk of neonatal respiratory distress syndrome. The size of gray box is positively proportional to the weight assigned to each study, which is inversely proportional to the standard error of the OR, and horizontal lines represent the 95% Cis. *OR* odds ratio, *CI* confidence interval; *low probability of delivery at term

covariates, the pooled OR was 1.40 (95% CI 1.18–1.66; $I^2 = 81.6\%$, $P_{\text{heterogeneity}} < 0.001$) for subgroup that adjusted for covariates, 1.77 (95% CI 0.93–3.36; $I^2 = 80.0\%$, $P_{\text{heterogeneity}} < 0.001$) for not adjusted for covariates. The results of all subgroup analyses are shown in Table 2.

Cumulative meta-analysis for the association between maternal DM and the risk of neonatal RDS was also conducted to indicate the dynamic trend of results and assess the influence of individual study on the overall results. The result indicated that the association between maternal DM and the risk of neonatal RDS became statistically significant (OR = 1.40, 95% CI 1.01–1.93) until adding the ninth study conducted by Bental et al. in 2011 and gradually stabilized. Details are provided in electronic supplementary materials (ESM) Fig S1.

GDM and the risk of RDS

Among the 13 studies from 12 articles evaluated the relationship between GDM and the risk of neonatal RDS, 5 studies [24, 26, 36, 39, 40] were conducted in Europe, 4 studies [29, 31, 34] in North America, 3 studies [28, 30, 33] in Asia, and 1 study [22] in Oceania. In subgroup analysis stratified by study design, there were 9 cohort studies [22, 26, 29–31, 34, 39, 40], and 4 case–control studies [24, 28, 33, 36]. The pooled OR of the relationship between GDM and the risk of neonatal RDS was 1.57 (95% CI 1.28–1.93; $I^2 = 71.4\%$, $P_{\text{heterogeneity}} < 0.001$; Fig. 3). In subgroup analysis stratified by study design, the pooled OR was 1.44 (95% CI 1.16–1.78; $I^2 = 71.2\%$, $P_{\text{heterogeneity}} = 0.001$) for cohort studies. Regarding the subgroup of continents,

Table 2 Summary of pooled ORs for the associations between maternal DM, GDM, and neonatal RDS risk

Exposure	Subgroup	No. of studies	Pooled OR (95%CI)	I^2 (%)	$P_{heterogeneity}$
Maternal DM	All studies	24	1.47 (1.24, 1.74)	81.0	< 0.001
	Study design				
	Cohort	20	1.39 (1.17, 1.65)	81.3	< 0.001
	Case–control	4	2.02 (1.20, 3.40)	59.6	0.060
	Continent				
	Europe	10	1.21 (0.92, 1.59)	64.4	0.003
	North America	7	1.56 (1.19, 2.04)	81.6	< 0.001
	Asia	5	2.32 (1.15, 4.66)	85.7	< 0.001
	Others	2	1.36 (1.01, 1.84)	53.0	0.145
	No. of fetuses				
	Single birth	14	1.71 (1.25, 2.33)	79.7	< 0.001
	Others[a]	10	1.26 (1.05, 1.52)	79.1	< 0.001
	Adjusted for covariates				
	Yes	17	1.40 (1.18, 1.66)	81.6	< 0.001
	No	7	1.77 (0.93, 3.36)	80.0	< 0.001
	Adjusted for gestational age				
	Yes	7	1.27 (0.93, 1.73)	86.7	< 0.001
	No	17	1.60 (1.29, 1.97)	75.5	< 0.001
	Adjusted for mode of delivery				
	Yes	9	1.64 (1.19, 2.25)	88.8	< 0.001
	No	15	1.38 (1.14, 1.68)	67.6	< 0.001
	Adjusted for maternal age				
	Yes	8	1.28 (1.14, 1.44)	44.1	0.085
	No	16	1.77 (1.27, 2.46)	86.0	< 0.001
GDM	*All studies*	13	1.57 (1.28, 1.93)	71.4	< 0.001
	Study design				
	Cohort	9	1.44 (1.16, 1.78)	71.2	0.001
	Case–control	4	2.02 (1.20, 3.40)	59.6	0.060
	Continent				
	Europe	5	1.31 (0.75, 2.28)	74.9	0.003
	North America	4	1.37 (1.23, 1.54)	12.8	0.329
	Asia	3	3.36 (1.99, 5.69)	41.1	0.183
	Oceania	1	1.60 (1.18, 2.17)	–	–
	No. of fetuses				
	Single birth	8	1.37 (1.13, 1.67)	64.7	0.006
	Others[a]	5	2.07 (1.22, 3.53)	66.5	0.018
	Adjusted for covariates				
	Yes	9	1.44 (1.21, 1.71)	57.2	0.017
	No	4	2.30 (0.93, 5.66)	85.2	< 0.001
	Adjusted for gestational age				
	Yes	3	1.32 (0.85, 2.07)	25.4	0.262
	No	10	1.66 (1.30, 2.11)	77.1	< 0.001
	Adjusted for mode of delivery				
	Yes	3	1.92 (0.88, 4.20)	72.5	0.026
	No	10	1.48 (1.20, 1.83)	70.0	< 0.001
	Adjusted for maternal age				
	Yes	4	1.30 (1.04, 1.62)	32.2	0.219
	No	9	1.86 (1.37, 2.52)	77.7	< 0.001

DM diabetes mellitus, *GDM* gestational diabetes mellitus, *CI* confidence interval, *OR* odds ratio, *RDS* respiratory distress syndrome

[a]Not describing the number of fetuses in studies, twins or including both single and multiple births

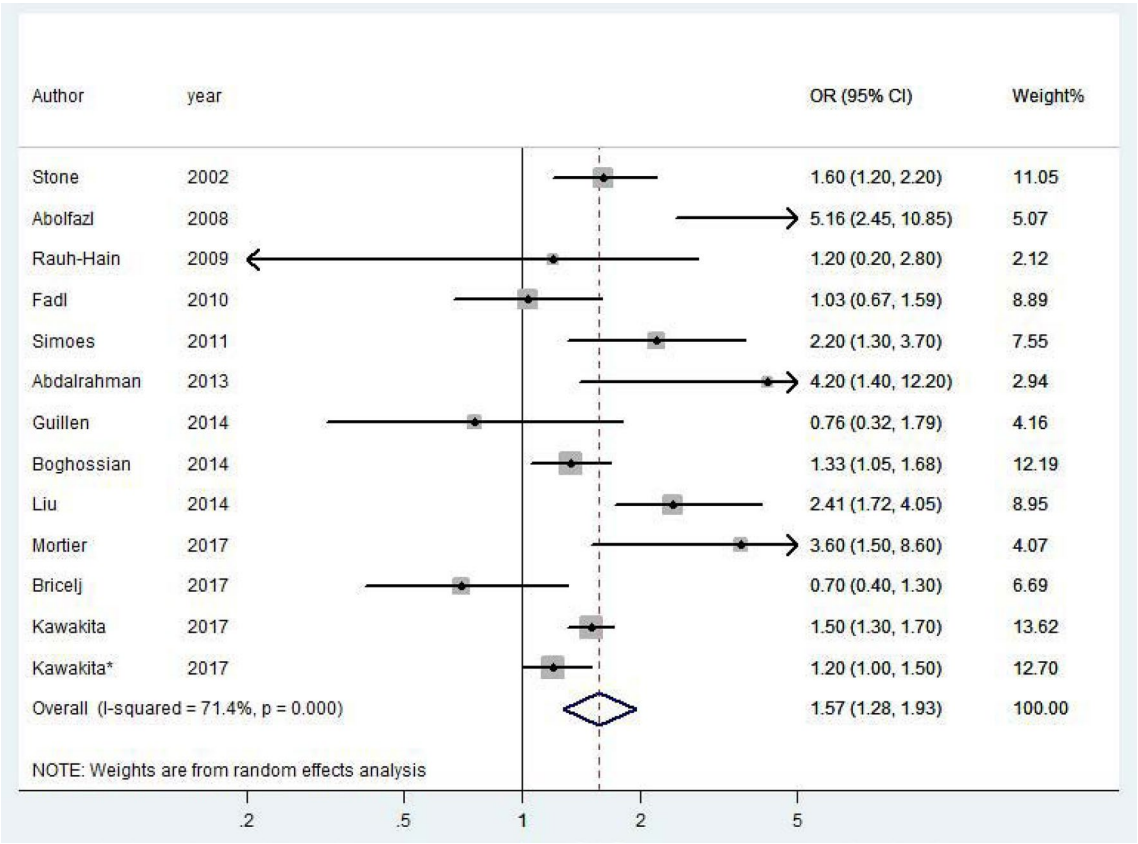

Fig. 3 Forest plot of gestational diabetes mellitus and the risk of neonatal respiratory distress syndrome. The size of gray box is positively proportional to the weight assigned to each study, which is inversely proportional to the standard error of the OR, and horizontal lines represent the 95% CIs. *OR* odds ratio, *CI* confidence interval; *low probability of delivery at term

except Europe, the significance of the results in other continents still existed. Regarding the subgroup of whether adjusted for confounders, the pooled OR was 1.44 (95% CI 1.21–1.71; $I^2 = 57.2\%$, $P_{\text{heterogeneity}} = 0.017$) for subgroup that adjusted for covariates, 2.30 (95% CI 0.93–5.66; $I^2 = 85.2\%$, $P_{\text{heterogeneity}} < 0.001$) for not adjusted for covariates. The results of subgroup analyses are listed in Table 2.

PGDM and the risk of RDS

All studies that evaluated the association between PGDM and the risk of neonatal RDS were cohort studies and conducted in North America. The pooled OR of the association between PGDM and the risk of neonatal RDS was 2.66 (95% CI 2.06–3.44; $I^2 = 73.7\%$, $P_{\text{heterogeneity}} = 0.010$). Details are provided in ESM Fig S2.

Meta-regression analysis

Taking into that high heterogeneity was found in the analysis of the association between maternal DM and the risk of neonatal RDS, meta-regression analyses were performed. The results showed that the covariates, including publication year ($P = 0.687$), sample size ($P = 0.119$), continent ($P = 0.758$), study design ($P = 0.305$), study quality assessment score ($P = 0.727$), number of fetuses ($P = 0.275$), whether adjusted for covariates ($P = 0.486$), whether adjusted for mode of delivery ($P = 0.898$), whether adjusted for gestational age ($P = 0.715$), and whether adjusted for maternal age ($P = 0.053$), did not have significant impacts on the between-study heterogeneity. Similarly, meta-regression analyses of the association between GDM and the risk of neonatal RDS did not find any covariates having significant impacts on the between-study heterogeneity. The results of meta-regression analyses are summarized in ESM **Table S1**.

Influence analysis and small-study effect evaluation

Influence analysis revealed that one study [25] had excessive influence on the pooled OR for the relationship between maternal DM and the risk of neonatal RDS, and that the pooled OR (1.74) fell to 1.52 (95% CI 1.27–1.80) after excluding this study. Regarding the relationship

between GDM and the risk of neonatal RDS, no study had excessive influence on the pooled OR.

Egger's tests and the funnel plots showed no evidence of significant small-study effect for the analyses of neonatal RDS risk with maternal DM ($P = 0.092$; ESM Fig S3) and GDM ($P = 0.364$; ESM Fig S4), respectively.

Discussion

Main findings

This meta-analysis assessed the association of maternal DM, GDM, and PGDM with the risk of neonatal RDS, and the results showed that maternal DM, GDM, and PGDM might be linked to an increased risk of neonatal RDS. In subgroup analysis, significant associations of maternal DM and GDM with the risk of neonatal RDS were observed in cohort studies. It was also found that maternal DM and GDM were significantly related to an increased risk of neonatal RDS among studies conducted in North America, South America, and Oceania but not in Europe, which may be due to the differences in race or medical conditions among continents. Furthermore, the results were still significant whether or not there was an adjustment for covariates.

The potential mechanism underlying the association between maternal DM and the increased risk of neonatal RDS is associated with the integrity and composition of fetal pulmonary surfactant. DM is related to delayed secretion of phosphatidylglycerol, which is an essential lipid component of surfactant [49, 50]. In addition, insulin inhibits gene expression of surfactant proteins A and B in lung epithelial cells, which in newborns exposed to hyperglycemia during pregnancy is usually high [51, 52].

In our meta-analysis, high heterogeneity was found. To find out the sources of between-study heterogeneity, meta-regression analyses were carried out. However, no covariate was found to contribute to between-study heterogeneity in the analyses of associations of maternal DM and GDM with the risk of neonatal RDS. We speculate that several other factors might lead to the heterogeneity. First, the variables adjusted for included studies were diverse, including maternal age, gestational age, body mass index, multiple pregnancies, maternal hypertensive disorders, mode of delivery and ethnicity, etc. Second, the severity of maternal DM was different, which might contribute to the between-study heterogeneity. Third, diagnostic criteria of neonatal RDS and maternal DM of included studies were not completely consistent.

Strengths and limitations of the study

The present meta-analysis has several strengths. First, 20 out of the 24 included studies were cohort studies, making our results more convincing. Second, most studies had adjusted for the potential confounders, such as gestational age and maternal age, which would increase the precision of the findings. Third, we further investigated the associations of GDM and PGDM with the risk of neonatal RDS, and the results showed that GDM and PGDM were both related to an increased risk of neonatal RDS, indicating the stableness of the associations.

However, our study also has several limitations. First, although the included study had adjusted for the major confounders, such as mode of delivery and maternal age, other unknown confounders might exaggerate or underestimate the observed associations. Second, definitions of neonatal RDS of included studies were not necessarily subject to a single standard. In some studies, neonatal RDS was as recorded in the data sets without a clear definition. Meanwhile, participants of included studies were not all necessarily subject to the same screening methods and diagnostic criteria of maternal DM. These might influence the results of our meta-analysis. Third, we did not differentiate the influence of the severity of maternal DM, mode of treatment on maternal DM, neonatal hypoglycemia, and the degree of glycemic control on these observed associations due to the absence of relevant information. Meanwhile, the absence of information on steroid therapy in the included studies led to inability to determine the effects of steroid therapy on observed outcomes. Fourth, infant weight has an effect on neonatal RDS [5, 53], but many of the included studies did not clearly provide the range of infant weight. Therefore, our study did not conduct a subgroup analysis based on infant weight.

Conclusions

Our meta-analysis showed that maternal DM, including GDM and PGDM, is linked to an increased risk of neonatal RDS. The findings can help to clarify the important clinical question about the impact of maternal DM on neonatal RDS, which is a hitherto controversial problem. To ensure the best maternal and fetal outcome, glucose impairment in pregnancy should be diagnosed in time, and obstetricians should evaluate and monitor the clinical situation of pregnant women with maternal DM closely. The effects of different modes of treatment, diagnostic method, degree of diabetic control, infant weight, and neonatal hypoglycemia on the association between maternal DM and the risk of neonatal RDS warrant further study.

Author contributions Li and Zhang conceived the study, participated in its design and coordination, and were involved in drafting the manuscript. Li and Wang carried out the literature search, data extraction, and interpretation of the data. Li, Wang, and Zhang reviewed and revised the manuscript critically for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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

Informed consent Not applicable.

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