Sleep Breath
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REVIEW

A systematic review and quantitative assessment of sleep-disordered breathing during pregnancy and perinatal outcomes

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Abstract
Purpose Previous investigations have suggested a strong association between sleep-disordered breathing (SDB) during pregnancy and perinatal outcomes. However, the results of the following replication studies were not always concordant. Therefore, this meta-analysis was conducted to evaluate the more reliable estimate.
Methods A systematic literature search was performed on PubMed, Springer Link, and EMBASE to identify all eligible studies published before August 2013. Summary odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated using fixed or random effects model.
Results A total of 24 publications met the inclusion criteria and were included in this meta-analysis. Findings demonstrated that moderate-to-severe SDB during pregnancy was associated with gestational diabetes mellitus (OR=1.78; 95 % CI, 1.29 to 2.46), pregnancy-related hypertension (OR=2.38; 95 % CI, 1.63 to 3.47), preeclampsia (OR=2.19; 95 % CI, 1.71 to 2.80), preterm delivery (OR=1.98; 95 % CI, 1.59 to 2.48), low birth weight (OR=1.75; 95 % CI, 1.33 to 2.32), neonatal intensive care unit (NICU) admission (OR=2.43; 95 % CI, 1.61 to 3.68), intrauterine growth restriction (OR=1.44; 95 % CI, 1.22 to 1.71), and Apgar score of <7 at 1 min (OR=1.78; 95 % CI, 1.10 to 2.91) based on all studies but not gestational age and birth weight.
Conclusions This meta-analysis revealed that moderate-to-severe SDB during pregnancy may be associated with most of adverse perinatal outcomes. Further well-designed studies are warranted to confirm our findings.

Keywords Gestational diabetes · Pregnancy · Preeclampsia · Meta-analysis · Sleep-disordered breathing

Introduction

Pregnancy along with physiological, hormonal, and physical changes placed pregnant women at a risk for the development of sleep-disordered breathing (SDB) [1]. Both epidemiological and physiological data have suggested that pregnant women might be predisposed to SDB. SDB is a common sleep disorder in pregnant women, referring to the spectrum of breathing disorders during sleep, ranging from uncomplicated snoring to the most severe forms of SDB, such as upper-airway resistance syndrome, obstructive sleep apnea (OSA) and the obesity-hypoventilation syndrome [2]. Snoring and OSA are the most frequent SDB issues among pregnant women [3, 4]. Habitual snoring was usually defined as the presence of loud snoring at least three nights per week [3]. OSA is a condition marked by repetitive upper-airway obstruction, hypoventilation, and intermittent nocturnal hypoxia [5]. OSA affects 5 % of the population, and the prevalence of snoring is approximately 6.7 % in women, which appears to

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increase during pregnancy with a prevalence of 14–28 % of women [6]. However, there is a paucity of data regarding the exact prevalence of SDB among pregnant women.

Given the evidence supporting a relationship between OSA and hypertension in the general population, investigators have long speculated that the combination of pregnancy and SDB may be related to maternal–fetal outcomes. It has been postulated that intermittent hypoxia induced by maternal SDB is likely to exacerbate placental ischemia, triggering oxidative stress and endothelial activation [7, 8]. In recent years, numerous studies have focused on the association between SDB in pregnant women and adverse maternal–fetal outcomes, such as gestational diabetes mellitus [9, 10], pregnancy-related hypertension [10, 11], preeclampsia [10, 12], preterm delivery [10, 13], gestational age [14, 15], low birth weight [12, 13], neonatal intensive care unit (NICU) admission [5, 12], and fetal growth restriction [13, 14], but with conflicting results. It is plausible that most of the studies were limited by small sample size, inherent limitations of study design, based on questionnaires and insufficient polysomnographic confirmation of SDB to draw definite conclusions. One meta-analysis has been completed, which examined the relationship between maternal SDB and several adverse pregnancy outcomes [16].

Our present study aims to create an evidence-based reference guide for clinicians to help pregnant women with SDB in reaching treatment plans. We included more new studies in comparison with the previous meta-analysis [16] (included studies in the previous meta-analysis performed by Pamidi et al. were published before June 2012; whereas our included studies in this meta-analysis were published until August 2013) and examined more adverse maternal–fetal outcomes, such as gestational age, preterm delivery, birth weight, NICU admission, intrauterine growth restriction, and Apgar score. Therefore, this comprehensive meta-analysis was conducted including several updated original studies to clarify if maternal moderate-to-severe SDB was associated with adverse pregnancy and birth outcomes.

Materials and methods

Identification and selection of studies

A systematic literature search was performed on PubMed, Springer Link, and EMBASE to identify all studies published before August 2013, which investigated the association between SDB and perinatal outcomes. Keywords utilized included *apnea, obstructive sleep apnea, OSA, sleep disordered breathing, SDB, snoring, gestational diabetes, pregnancy-related hypertension, pregnancy-induced hypertension (PIH), preeclampsia, preterm delivery, gestational age, birth weight, low birth weight, NICU admission, intrauterine growth restriction, and Apgar score*. Furthermore, references of systematic reviews and retrieved articles were also searched for eligible articles. Two reviewers independently reviewed all potentially relevant articles, according to the preset inclusion criteria. Discrepancies were resolved by consensus.

Inclusion and exclusion criteria

The original studies meeting the following criteria were included: (1) studies which defined SDB as the presence of symptoms consistent with intermittent upper-airway obstruction during sleep: snoring or apneas, (2) studies comparing clinical outcomes in populations that were exposed to SDB during pregnancy compared with those unexposed, (3) studies that provided odd ratio (OR) with 95 % confidence interval (CI) or sufficient data to calculate them for perinatal outcomes in pregnant women with moderate-to-severe SDB in relation to pregnant women with mild or no SDB, and (4) if there were multiple publications from the same population, the article that most closely explored our research topic was included. Abstracts, case reports, and editorials were excluded from this study.

Data extraction

Two reviewers (Xiu-Xiu Ding and Yi-Le Wu) extracted data independently referring to the meta-analysis of observational studies in epidemiology guidelines [17]. The following information was extracted from all eligible studies: first author, year of publication, country, study design, participants, type of SDB, ORs and 95 % CIs from case–control studies, or RRs and 95 % CIs from cohort studies (in the few articles where adjusted RRs were provided, these were considered as ORs, since, maternal–fetal outcomes were rare, ORs in case–control studies and RRs in cohort studies yield similar estimates of OR). In this meta-analysis, moderate-to-severe SDB was used to describe the study participants with the most severe SDB in each eligible study, whereas the control (without SDB) or least severe group was considered as no or mild SDB. Outcomes examined included: gestational diabetes mellitus, pregnancy-related hypertension, preeclampsia, preterm delivery (<37 completed weeks of gestation), gestational age, birth weight, low birth weight (birth weight, <2500 g), NICU admission, intrauterine growth restriction (birth weight, <10th percentile for gestational age), and Apgar score.

Adjusted estimates were first choice. When adjusted estimates were not available, the crude ORs were calculated. For studies which provided several ORs from different multivariate models, the ORs from multivariate models with the most complete adjustment for potential confounders were selected.

Statistical analysis

In this meta-analysis, the pooled estimates of odds ratio for binary outcomes or the weighted mean difference (WMD) for continuous outcomes were estimated using fixed effects (Mantel–Haenszel) or random effects (DerSimonian and Laird) models [18, 19]. Heterogeneity among studies was investigated using Q test and I^2 statistic [20]. We considered that heterogeneity was present when the P value of Q test was <0.1 and I^2 statistic was >50 %. The fixed effects model was selected when the heterogeneity was not present; otherwise, the random effects model was selected. Subgroup analyses were performed according to country (Europe, North America, and Asia), adjusted estimates (adjusted findings and unadjusted findings), and study design (prospective and nonprospective). We also did a sensitivity analysis by removing each individual study from the meta-analysis. Finally, publication bias was estimated through visual inspection of a funnel plot and with the Begg's and Egger's tests [21, 22]. All statistical analyses were conducted using Stata 9.0 (StataCrop, College station, Tex). A two-tailed P value of less than 0.05 was considered statistically significant.

Results

Characteristics of eligible studies

A total of 384 publications met our initial criteria, of which 24 publications [5, 9–15, 23–38] met the inclusion criteria and were included in this meta-analysis (search flow chart is presented in Fig. 1; characteristics of the included studies are summarized in Table 1). In terms of geographic region, 8 were conducted in Europe, 13 in North America, and 3 in Asia. For study design, there were 12 prospective cohort studies and 12 nonprospective studies. Of the studies that could be pooled, most provided data on more than 1 outcome: 12 provided data on gestational diabetes mellitus, 12 on pregnancy-related hypertension, 12 on preeclampsia, 7 on preterm delivery, 9 on birth weight, 3 on low birth weight, 6 on gestational age, 4 on NICU admission, 11 on intrauterine growth restriction, and 4 on Apgar score.

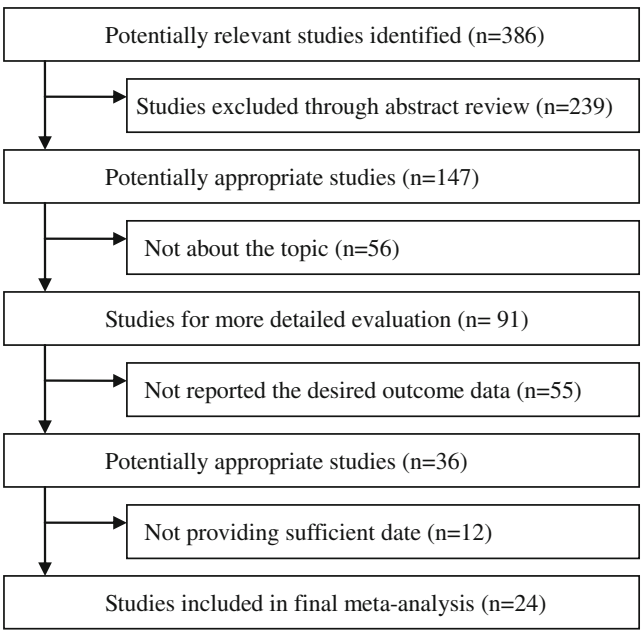

Fig. 1 Flow diagram of the study selection process

Quantitative synthesis

Gestational diabetes mellitus

Based on 12 pooled studies, gestational diabetes mellitus was significantly associated with maternal moderate-to-severe SDB during pregnancy (OR=1.78; 95 % CI, 1.29 to 2.46; P<0.001; Fig. 2). Significant heterogeneity was detected among studies in the medium range (I^2=55.2 %). Heterogeneity was decreased when stratified by study design. The OR between exposure to moderate-to-severe SDB during pregnancy and gestational diabetes mellitus was not significant in the prospective design group. Similarly, two other subgroups (unadjusted data group and Asia group) were not significant after stratification (Table 2).

Pregnancy-related hypertension

There was a significant association between moderate-to-severe SDB during pregnancy and pregnancy-related hypertension when the 12 studies were pooled (OR=2.38; 95 % CI, 1.63 to 3.47; P<0.001). Significant heterogeneity across studies was noted (I^2=52.7 %). However, subgroup analyses results suggested that there were nonsignificant ORs with significant heterogeneity (I^2=78.5 %) from studies conducted in North America; whereas other subgroups had significant ORs (Table 2).

Preeclampsia

The pooled OR for the 12 studies investigating preeclampsia was significant (OR=2.19; 95 % CI, 1.71 to 2.80; P<0.001), which indicated that moderate-to-severe SDB during pregnancy was associated with increased risk of preeclampsia. Heterogeneity was not significant among studies (I^2= 34.4 %). Subgroup analyses results indicated no significant differences were found in all the groups (Table 2).

Preterm delivery

Seven studies evaluated the association between SDB during pregnancy and preterm delivery. Using the fixed effects model, moderate-to-severe SDB during pregnancy was

Table 1 Study characteristics of 24 studies included in the meta-analysis

Study	Country	Study design	Participants	Type of SDB	Results
Loube et al. [23]	USA	Prospective cohort	350	FS	BW
Franklin et al. [24]	Sweden	Cross-sectional	502	FS	PRH, PEC, GA, IUGR, and Apgar score
Köken et al. [25]	Turkey	Prospective cohort	83	FS	BW and Apgar score
Pérez-Chada et al. [26]	Sweden	Cross-sectional	456	FS	GA, BW, and IUGR
Sahin et al. [27]	Turkey	Prospective cohort	35	OSA	GA, BW, IUGR, and Apgar score
Yin et al. [28]	UK	Cross-sectional	178	FS	PRH, PEC, and IUGR
Ursavas et al. [29]	Turkey	Case–control	469	FS	PRH and PEC
Champagne et al. [11]	Canada	Case–control	50	OSA	PRH
Bourjeily et al. [10]	USA	Cross-sectional	1000	FS	GDM and IUGR
Facco et al. [30]	USA	Prospective cohort	189	FS	GDM
Louis et al. [5]	USA	Prospective cohort	173	OSA	PEC, PTB, NICU admission, and IUGR
Qiu et al. [9]	USA	Prospective cohort	1,290	FS	GDM
Ayrım et al. [31]	Turkey	Prospective cohort	200	FS	PRH, PEC, PTB, and BW
Reutrakul et al. [32]	USA	Case–control	169	FS	GDM
Micheli et al. [14]	Greece	Prospective cohort	1,091	FS	GDM, PRH, PEC, PTB, GA, LBW, BW, and IUGR
Olivarez et al. [33]	USA	Prospective cohort	220	OSA	GDM, PRH, PEC, IUGR, and Apgar score
O'Brien et al. [34]	USA	Prospective cohort	1,712	FS	GDM, PRH, and PEC
Tauman et al. [15]	Israel	Cross-sectional	246	FS	GA, BW, IUGR, and Apgar score
Louis et al. [35]	USA	Prospective cohort	175	OSA	GDM, PEC, PTB, GA, BW, and NICU admission
Chen et al. [13]	China	Cross-sectional	4,746	OSA	GDM, PRH, PEC, PTB, LBW, BW, and IUGR
Facco et al. [36]	USA	Retrospective cohort	143	OSA	GDM, PRH, and PTB
Ko et al. [37]	Korea	Prospective cohort	276	OSA	GDM, PRH, PEC, PTB, NICU admission, IUGR, and Apgar score
Izci Balserak et al. [38]	USA	Case–control	104	OSA	GDM
Owusu et al. [12]	USA	Cross-sectional	220	FS	PRH, PEC, LBW, and NICU admission

FS frequent snoring, *OSA* obstructive sleep apnea, *GDM* gestational diabetes mellitus, *PRH* pregnancy-related hypertension, *PEC* preeclampsia, *PTB* preterm birth, *GA* gestational age, *LBW* low birth weight, *BW* birth weight, *NICU* neonatal intensive care unit, *IUGR* intrauterine growth restriction

significantly associated with preterm delivery (OR=1.98; 95 % CI, 1.59 to 2.48; $P<0.001$). Heterogeneity across studies was not significant ($I^2=42.9$ %). However, subgroup analyses results indicated that the significant ORs could just be found from studies conducted in North America and nonprospective design group (Table 2).

Low birth weight

Low birth weight was significantly associated with moderate-to-severe SDB during pregnancy based on the OR of the three pooled studies (OR=1.75; 95 % CI, 1.33 to 2.32; $P<0.001$). Study heterogeneity was not significant ($I^2=32.5$ %). However, the ORs for the unadjusted data group and North America group were not significant, based on one study, respectively (Table 2).

Birth weight

No significant association between exposure to moderate-to-severe SDB during pregnancy and birth weight was detected when pooling nine eligible studies (WMD=-36.4 g; 95 % CI, −106.0 to 33.2; $P=0.306$). Heterogeneity was significant across studies ($I^2=72.7$ %). Furthermore, none of the subgroup analyses results were significant (Table 2).

Gestational age

The pooled standardized mean difference for the six studies investigating the association between moderate-to-severe SDB during pregnancy and gestational age was not significant (WMD=−0.18 weeks; 95 % CI, −0.57 to 0.21; $P=0.362$). Heterogeneity was significant across studies ($I^2=76.8$ %). There was also no significant association in subgroup analyses (Table 2).

NICU admission

The pooled OR based on four studies indicated that moderate-to-severe SDB during pregnancy was significantly associated with NICU admission (OR=2.43; 95 % CI, 1.61 to 3.68; $P<0.001$). No heterogeneity was found among pooled studies

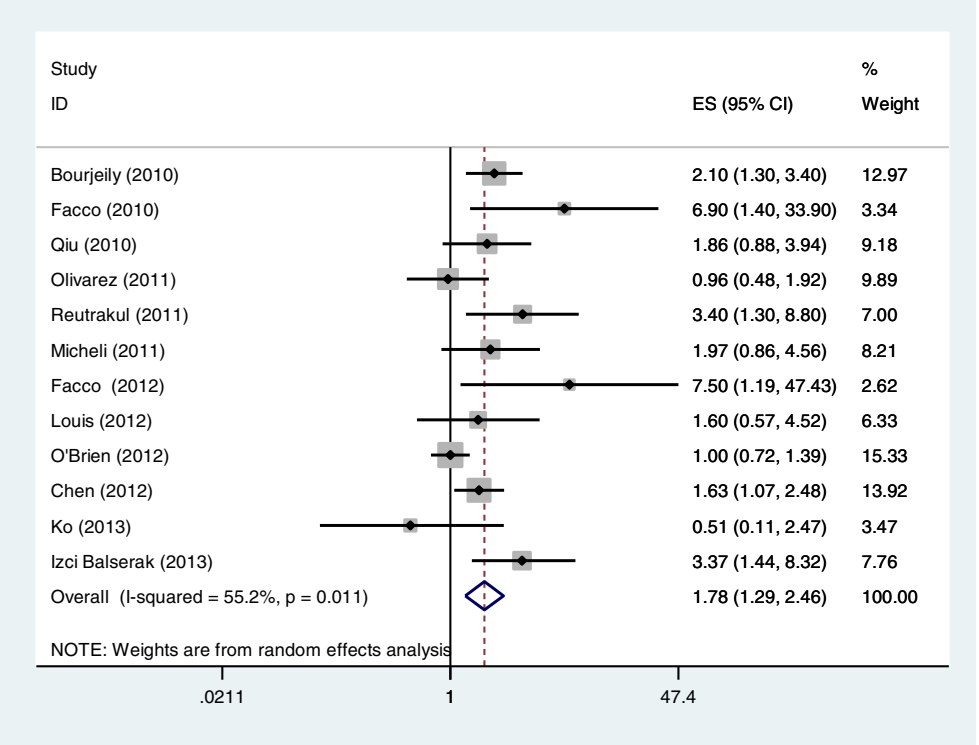

Fig. 2 Forest plot for the association between SDB during pregnancy and gestational diabetes mellitus in overall populations with random effect model

(I^2=0.0 %). In addition, significant association could be found in all of the subgroup analyses (Table 2).

Intrauterine growth restriction

Meta-analysis results including 11 studies suggested that pregnant women with moderate-to-severe SDB had high odd of developing intrauterine growth restriction compared with those without SDB (OR=1.44; 95 % CI, 1.22 to 1.71; P<0.001). Heterogeneity among studies was not significant (I^2=26.9 %). The significant association as well as existed in all the subgroups (Table 2).

Apgar score

The results from meta-analysis indicated that moderate-to-severe SDB during pregnancy was associated with Apgar score of <7 at 1 min (OR=1.78; 95 % CI, 1.10 to 2.91; P=0.020). There was significant heterogeneity among studies (I^2=50.0 %). However, no association was detected on Apgar score of <7 at 5 min (Table 2).

Sensitivity analyses

Sensitivity analyses indicated that no single study substantially altered the pooled ORs of the association between moderate-to-severe SDB during pregnancy and those perinatal outcomes, suggesting that the results of this meta-analysis were robust.

Publication bias diagnostics

No publication bias was detected in the analyses of the association between moderate-to-severe SDB and gestational diabetes mellitus (Begg's test, P=0.12; Egger's test, P=0.07. Funnel plot is shown in Fig. 3), pregnancy-related hypertension (Begg's test, P=0.97; Egger's test, P=0.26), preeclampsia (Begg's test, P=0.45; Egger's test, P=0.03), preterm delivery (Begg's test, P=1.00; Egger's test, P=0.20), birth weight (Begg's test, P=0.75; Egger's test, P=0.84), low birth weight (Begg's test, P=1.00; Egger's test, P=0.84), gestational age (Begg's test, P=1.00; Egger's test, P=0.63), NICU admission (Begg's test, P=1.00; Egger's test, P=0.68), intrauterine growth restriction (Begg's test, P=1.00; Egger's test, P=0.93), Apgar at 1 min (Begg's test, P=1.00; Egger's test, P=0.48), Apgar at 5 min (Begg's test, P=0.30; Egger's test, P=0.44), Apgar score of <7 at 1 min (Begg's test, P=0.73; Egger's test, P=0.39), and Apgar score of <7 at 5 min (Begg's test, P=0.73; Egger's test, P=0.39).

Discussion

The present study performed on a systematic review and meta-analysis examing the association of moderate-to-severe SDB

Table 2 Effect of sleep-disordered breathing during pregnancy on perinatal outcomes: meta-analysis results

Analysis	No. of studies	Odds ratio or mean difference (95 % CI)	*P* value	Heterogeneity		
				Q within	*P* value	I^2
Gestational diabetes mellitus						
All studies	12	1.78 (1.29, 2.46)	<0.001	24.53	0.011	55.2
Any adjusted data						
Adjusted findings	7	1.98 (1.32, 2.96)	0.001	17.60	0.007	65.9
Unadjusted findings	5	1.38 (0.89, 2.14)	0.156	6.65	0.156	39.8
Country						
Europe	2	2.50 (1.33, 4.68)	0.004	0.71	0.399	0.0
North America	8	1.85 (1.19, 2.87)	0.006	19.29	0.007	63.7
Asia	2	1.17 (0.42, 3.27)	0.762	2.00	0.158	49.9
Study design						
Prospective	7	1.20 (0.93, 1.53)	0.157	10.34	0.111	41.9
Nonprospective	5	2.11 (1.60, 2.80)	<0.001	5.32	0.256	24.8
Pregnancy-related hypertension						
All studies	12	2.38 (1.63, 3.47)	<0.001	23.24	0.016	52.7
Any adjusted data						
Adjusted findings	5	2.81 (1.85, 4.27)	<0.001	10.17	0.038	60.7
Unadjusted findings	7	1.72 (1.02, 2.88)	0.041	10.22	0.116	41.3
Country						
Europe	5	2.43 (1.38, 4.25)	0.002	0.70	0.705	0.0
North America	5	1.71 (0.68, 4.30)	0.255	18.64	0.001	78.5
Asia	2	2.86 (2.05, 3.99)	<0.001	3.18	0.365	5.6
Study design						
Prospective	5	2.53 (1.70, 3.78)	<0.001	2.44	0.655	0.0
Nonprospective	7	2.16 (1.23, 3.82)	0.008	20.79	0.002	71.1
Preeclampsia						
All studies	12	2.19 (1.71, 2.80)	<0.001	32.11	0.001	34.4
Any adjusted data						
Adjusted findings	4	1.87 (1.34, 2.61)	<0.001	3.84	0.279	21.9
Unadjusted findings	8	2.65 (1.84, 3.81)	<0.001	5.74	0.571	0.0
Country						
Europe	3	3.19 (1.62, 6.29)	0.001	3.24	0.198	38.2
North America	5	2.02 (1.49, 2.74)	<0.001	3.96	0.412	0.0
Asia	4	2.22 (1.32, 3.74)	0.003	2.80	0.423	0.0
Study design						
Prospective	6	1.85 (1.33, 2.86)	<0.001	7.51	0.186	33.4
Nonprospective	6	2.67 (1.86, 3.83)	<0.001	1.87	0.866	0.0
Preterm delivery						
All studies	7	1.98 (1.59, 2.48)	<0.001	10.50	0.105	42.9
Any adjusted data						
Adjusted findings	4	1.57 (0.87, 2.84)	0.137	8.49	0.037	64.7
Unadjusted findings	3	1.69 (0.85, 3.36)	0.136	1.78	0.410	0.0
Country						
Europe	1	1.00 (0.50, 2.00)	1.000	–	–	–
North America	3	1.81 (0.69, 4.74)	0.229	4.06	0.131	50.8
Asia	3	2.19 (1.70, 2.81)	<0.001	2.10	0.351	4.6
Study design						
Prospective	4	1.03 (0.64, 1.68)	0.894	1.37	0.712	0.0
Nonprospective	3	2.36 (1.84, 3.03)	<0.001	0.33	0.847	0.0

Table 2 (continued)

Analysis	No. of studies	Odds ratio or mean difference (95 % CI)	*P* value	Heterogeneity		
				Q within	*P* value	I^2
Low birth weight						
All studies	3	1.75 (1.33, 2.32)	<0.001	2.96	0.227	32.5
Any adjusted data						
Adjusted findings	2	1.87 (1.40, 2.49)	<0.001	0.88	0.348	0.0
Unadjusted findings	1	0.89 (0.34, 2.33)	0.812	–	–	–
Country						
Europe	1	2.60 (1.20, 5.40)	0.013	–	–	–
North America	1	0.89 (0.34, 2.33)	0.812	–	–	–
Asia	1	1.76 (1.28, 2.40)	<0.001	–	–	–
Study design						
Prospective	1	2.60 (1.20, 5.40)	0.013	–	–	–
Nonprospective	2	1.65 (1.22, 2.22)	0.001	1.74	0.187	42.6
Birth weight						
All studies	9	−36.4 (−106.0, 33.2)	0.306	29.31	<0.001	72.7
Country						
Europe	5	−48.9 (−183.2, 85.6)	0.476	16.74	0.002	76.1
North America	2	43.6 (−85.2, 172.4)	0.507	0.97	0.324	0.0
Asia	2	−35.1 (−149.9, 79.6)	0.549	4.07	0.044	75.4
Study design						
Prospective	6	−30.9 (−168.8, 107.0)	0.661	20.85	0.001	76.0
Nonprospective	3	−33.7 (−112.7, 45.3)	0.403	4.81	0.090	58.4
Gestational age						
All studies	6	−0.18 (−0.57, 0.21)	0.362	21.53	0.001	76.8
Country						
Europe	4	−0.27 (−0.51, −0.03)	0.028	2.79	0.248	28.4
North America	1	−0.60 (−1.58, 0.38)	0.229	–	–	–
Asia	1	0.30 (0.15, 0.45)	<0.001	–	–	–
Study design						
Prospective	3	−0.50 (−0.98, −0.02)	0.042	0.86	0.652	0.0
Nonprospective	3	−0.02 (−0.15, 0.11)	0.795	13.52	0.001	85.2
NICU admission						
All studies	4	2.43 (1.61, 3.68)	<0.001	1.74	0.628	0.0
Any adjusted data						
Adjusted findings	1	3.39 (1.23, 9.33)	0.018	–	–	–
Unadjusted findings	3	2.28 (1.45, 3.58)	<0.001	1.25	0.536	0.0
Country						
North America	3	2.48 (1.55, 3.97)	<0.001	1.71	0.426	0.0
Asia	1	2.26 (0.94, 5.43)	0.068	–	–	–
Study design						
Prospective	2	2.69 (1.39, 5.22)	0.003	0.35	0.553	0.0
Nonprospective	2	2.28 (1.34, 3.88)	0.002	1.25	0.264	19.8
Intrauterine growth restriction						
All studies	11	1.44 (1.22, 1.71)	<0.001	13.69	0.188	26.9
Any adjusted data						
Adjusted findings	3	1.41 (1.16, 1.72)	0.001	1.76	0.414	0.0
Unadjusted findings	8	1.56 (1.08, 2.24)	0.018	11.72	0.110	40.3
Country						
Europe	5	1.77 (1.19, 2.62)	0.004	2.20	0.699	0.0

Table 2 (continued)

Analysis	No. of studies	Odds ratio or mean difference (95 % CI)	*P* value	Heterogeneity		
				Q within	*P* value	I^2
North America	3	1.81 (0.85, 3.88)	0.125	4.08	0.130	51.1
Asia	3	1.29 (1.05, 1.59)	0.016	3.54	0.171	43.4
Study design						
Prospective	4	1.28 (0.75, 2.17)	0.369	5.64	0.130	46.8
Nonprospective	7	1.46 (1.22, 1.76)	<0.001	7.82	0.252	23.2
Apgar score						
Apgar at 1 min (mean)	3	−0.09 (−0.29, 0.11)	0.355	2.07	0.355	3.5
Apgar at 5 min (mean)	3	−0.01 (−0.10, 0.09)	0.921	2.03	0.362	1.5
Apgar score <7 at 1 min (*n*)	4	1.78 (1.10, 2.91)	0.020	6.00	0.111	50.0
Apgar score <7 at 5 min (*n*)	4	1.43 (0.56, 3.67)	0.460	4.94	0.176	39.3

NICU neonatal intensive care unit

during pregnancy and adverse maternal–fetal outcomes. To our knowledge, this is the first study to investigate various perinatal outcomes, involving gestational diabetes mellitus, pregnancy-related hypertension, preeclampsia, preterm delivery, gestational age, birth weight, low birth weight, NICU admission, intrauterine growth restriction, and Apgar score. Of the diverse outcomes, the majority associations were significantly found. However, few outcomes had no significant associations.

SDB and adverse maternal outcomes

Results from the present study indicated that maternal moderate-to-severe SDB during pregnancy was associated with pregnancy complications, including gestational diabetes mellitus, pregnancy-related hypertension and preeclampsia based on overall populations. In addition, those associations can consistently be detected after pooling the adjusted findings. However, subgroup analyses results indicated that there was no significant in some countries. It suggested that country was likely to be a potential moderator factor. This may contribute to racial differences. In the further study, this underlying difference should be taken into consideration.

The mechanisms linking to SDB and cardiovascular disease are likely multifactorial, involving sympathetic overactivity, oxidative stress, and inflammation [34]. Intermittent hypoxia induced by maternal SDB may lead to increased sympathetic activity. Such increases in sympathetic activity

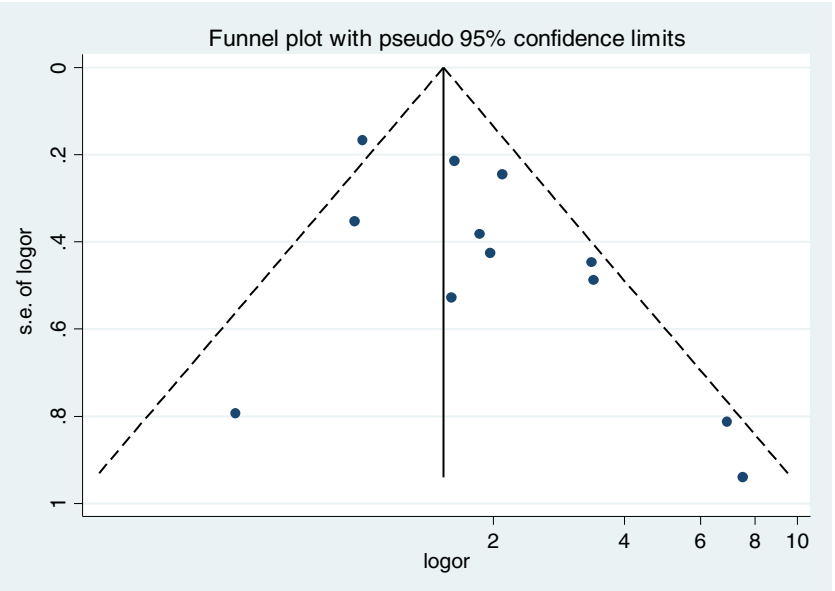

Fig. 3 Funnel plot for the association between SDB during pregnancy and gestational diabetes mellitus in overall populations

may potentially contribute to blood pressure changes and glucose intolerance [39]. Evidence that women with preeclampsia have enhanced levels of sympathetic activity has been observed [40]. Sympathetic overactivity may alter glucose homeostasis and induce insulin resistance by increasing glycogen breakdown and gluconeogenesis [9]. Intermittent hypoxia also induces increased oxidative stress and elevated levels of proinflammatory cytokines. Studies have suggested that preeclampsia was associated with increased oxidative stress owing to ischemia–reperfusion events and with reduced antioxidant defenses [41]. Similarly, increased oxidative stress induced by intermittent hypoxia is likely to play an important role in the mechanism for insulin resistance and in the onset of gestational diabetes. An investigation by Jelic et al found that SDB were linked to elevated levels of proinflammatory cytokines and oxidative stress markers [42]. It is thought that enhanced inflammatory and oxidative stress response promotes insulin resistance, ultimately leading to impaired glucose tolerance and diabetes [43].

SDB and adverse fetal outcomes

Results from this study indicated that maternal SDB during pregnancy was associated with increased risk of preterm delivery, NICU admission, low birth weight, intrauterine growth restriction, and Apgar score based on overall populations. However, no significant association between maternal SDB during pregnancy and birth weight, gestational age was detected in overall populations.

Preterm delivery, an adverse birth outcome, is rather a recognized public health concern. An evaluated 14.9 million babies are born preterm each year with a prevalence of 11.1 % worldwide [44]. Preterm delivery is the leading cause of neonatal morbidity and mortality [45]. In the present study, the result indicated that maternal SDB during pregnancy was significantly associated with increased risk of preterm delivery. However, biologic plausibility for these associations has not been fully elucidated. Elevated inflammatory cytokines and markers induced by SDB in maternal circulation are likely predictive of preterm birth [46]. Subgroup analyses by country indicated that only in Asia a significant association existed, but not in Europe and North America. The most potential reason is likely due to racial differences and socioeconomic status of the countries. Generally, public health care in western developed countries is more sufficient compared with developing countries in Asia. Consequently, the ultimate effect size in developed countries may be moderated.

More than 20 million infants worldwide are born with low birth weight representing 15.5 % of all births [47]. Low birth weight also increased the risk of infant mortality and morbidity [48]. Similar with preterm delivery, low birth weight has raised major public health concerns [49]. The result from the present study suggested that maternal SDB during pregnancy significantly increased the risk of low birth weight. Subgroup analyses by country indicated that a significant association existed in Asia, but not in North America. This evidence further confirmed that racial differences should be taken into consideration.

Intrauterine growth restriction is the main cause of intrauterine fetal death and the second leading cause of death during the neonatal period [50]. Approximately 7–10 % of newborns are affected by intrauterine growth restriction [51]. Infants with intrauterine growth restriction have a higher risk for congenital malformations [52], decreased cognitive function in young adults [53], and developing adult cardiovascular disease [54]. Our present study indicated that maternal SDB during pregnancy was significantly associated with intrauterine growth restriction among overall populations. Some potential mechanisms linked to this association have been proposed, but yet obscure. Pregnant women with SDB can develop hypoxemia during sleep owing to decreased cardiorespiratory reserve. Even small declines in maternal oxygenation can endanger oxygen delivery to the fetus [55]. Animal studies have consistently shown that gestational exposure to hypoxia is likely to impair fetal growth [56]. Moreover, chronic hypoxia due to women residence at high altitude was also associated with reduced fetal growth [57].

Increased NICU admission was correlated with maternal SDB during pregnancy in the main analysis and most of the subgroup analyses. The association between Apgar score of <7 at 1 min and maternal SDB was statistically significant. However, none of the included studies specially evaluated the relationship between maternal SDB and NICU admission, and Apgar score. Studies in this area is scarce, thus more investigations should be performed to further confirm a precise estimate.

To some extent, several limitations of this meta-analysis should be noted. First, the sample sizes of some adverse pregnancy outcomes (i.e., low birth weight and NICU admission) are not big enough in the present study. More original studies are needed to make our conclusions more reliable and accurate. Second, this meta-analysis is unable to solve problems with some confounding factors which are inherent in the included studies. Some important confounders such as smoking and body mass index have not been measured with sufficient precision in most of published studies. However, they are the most potential confounders of the association between SDB and adverse perinatal outcomes. Despite these limitations, this meta-analysis also demonstrated some advantages. First, no publication bias was detected indicating that the whole pooled results should be unbiased. Second, the quality of included studies in the present meta-analysis was satisfactory and met our inclusion criterion. Third, the most adverse perinatal outcomes were taken into account in this meta-analysis.

Conclusions

In conclusion, this meta-analysis evaluated the association between SDB during pregnancy and adverse perinatal outcomes and revealed that moderate-to-severe SDB may be associated with most adverse perinatal outcomes including gestational diabetes mellitus, pregnancy-related hypertension, preeclampsia, preterm delivery, low birth weight, NICU admission, intrauterine growth restriction, and Apgar score of <7 at 1 min based on all studies, but not gestational age and birth weight. Further well-designed studies taking potential confounding factors into account may eventually provide a better, comprehensive understanding of the association between the SDB during pregnancy and perinatal outcomes.

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