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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

The prevalence of obstructive sleep apnea and its association with pregnancy-related health outcomes: a systematic review and meta-analysis

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Abstract

Purpose Obstructive sleep apnea (OSA) is common during pregnancy. Nevertheless, prevalence estimates of OSA have varied widely due to variabilities in the assessment methods. This meta-analysis aimed to examine the prevalence of objectively assessed OSA and its association with pregnancy-related health outcomes in pregnant women.

Methods This review was developed following the PRISMA guideline. A systematic search was conducted in major electronic databases to identify studies conducted from inception to January 2018. The pooled estimates with 95% confidence interval were calculated using the inverse variance method. Forest plots were used to present the results of individual studies and the pooled effect sizes.

Results Thirty-three studies were included. The mean gestational age was between 21.2 (8.5) and 37.3 (2.1) weeks. The pooled worldwide prevalence of OSA was 15% (95% CI 12–18%). The prevalence estimates ranged from 5% in the European Region to 20% in the Region of Americas. The prevalence estimates for different trimesters ranged from 15 to 19%. OSA was related to an increased risk for gestational hypertension, gestational diabetes, pre-eclampsia, C-section, postoperative wound complication, and pulmonary edema. The pooled adjusted odds ratio (aOR) values were 1.97, 1.55, 2.35, 1.42, 1.87, and 6.35, respectively. OSA was also related to an increased risk for preterm birth (aOR = 1.62) and neonatal intensive care unit admission (aOR = 1.28).

Conclusions OSA is a common health issue in pregnant women. OSA is associated with various pregnancy-related health outcomes. Routine screening, early diagnosis, and effective treatment of OSA are recommended in pregnant women, particularly during mid and late pregnancy.

Keywords Meta-analysis · Observational · Pregnancy · Prevalence · Sleep apnea

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway obstruction and significant reductions in airflow during sleep, which results in intermittent hypoxia and sleep fragmentation [1]. OSA is a common problem in the general population; it has been reported that 12% of the US adults had OSA [2]. The prevalence of OSA in women of reproductive age was 5% [3], which likely increases during pregnancy because of normal physiological changes, such as respiratory changes and weight gain [4]. However, due to variations in sample characteristics and assessment of OSA, prevalence estimates of OSA in the current literature have varied widely from 2.1% [5] to 37.5% [6]. Polysomnography (PSG) has been the gold standard for the diagnosis of OSA [7]. The prevalence of OSA has also been reported based on subjective questionnaires in numerous studies [8–10]. These questionnaires include the Epworth Sleepiness Scale [11], STOP-Bang [12], and Berlin Questionnaire [13]. Although questionnaires are cheap and can be easily administered, they may bring recall bias and impair the accuracy of prevalence estimates of OSA. During pregnancy, women typically

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experience fatigue and daytime sleepiness [14, 15]. Those symptoms are similar to normal pregnancy-related symptoms and thus being ignored or under-reported by pregnant women. Currently, there is a gap in our knowledge about the prevalence of OSA based on objective assessments, such as PSG.

Accumulating evidence suggests that OSA was associated with adverse pregnancy-related outcomes, such as gestational hypertension [16], gestational diabetes [17], pre-eclampsia [18], preterm birth [18], and low birth weight [19]. Nonetheless, results have been inconsistent. Two previous reviews have examined the effect of maternal OSA on perinatal and neonatal outcomes. Since the publication of these reviews, more studies have been conducted. Additionally, the previous reviews included both self-reported OSA based on symptoms and confirmed OSA based on PSG. There is a need to synthesize current evidence on the relationship between objectively measured OSA and pregnancy-related outcomes.

Early diagnosis and in-time treatment of OSA may help to decrease the risk for adverse maternal and neonatal outcomes. Nevertheless, OSA is frequently under-recognized by healthcare providers. There is a clear need to determine the prevalence of OSA and related health outcomes during pregnancy and thereby increase health care professionals' awareness of the importance of OSA and facilitate the development of healthcare planning. Thus, the aim of this study was two-fold: (1) evaluate the overall prevalence of OSA during pregnancy based on objective assessments and (2) the relationship between OSA and pregnancy-related outcomes.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol [20] was developed to investigate the prevalence of OSA in pregnant women. The PRISMA guideline was used in developing this review [21].

Search strategy

We conducted a systematic search of electronic databases, including PubMed, CINAHL, Embase, and PsycINFO, to identify studies conducted from inception to January 2018. We also searched bibliographies of included studies to identify additional eligible studies. The search was conducted using combinations of the following terms: (1) sleep disordered breathing OR SDB OR sleep apn* OR OSA and (2) pregnan* OR gestation*. The inclusion criteria were (1) studies reported the prevalence of OSA among pregnant women and (2) objective assessment OSA was used. The exclusion criteria were (1) studies conducted specifically in subjects diagnosed with other types of sleep disorders, such as restless leg syndrome or insomnia, (2) variables of interest were not measured, and (3) other types of articles: review, case study, editorial, or abstract. We also excluded studies conducted exclusively in subjects diagnosed with comorbidities such as diabetes and hypertension. Compared to the general population, the prevalence of OSA in people with diabetes or hypertension is higher [22, 23]. The inclusion of studies exclusively conducted in subjects with diabetes or hypertension may inflate the estimation of OSA prevalence.

We used the PRISMA flow chart to select eligible studies [21]. One reviewer (LL) completed the initial screening based on title and abstract. Two reviewers (LL and SW) independently reviewed the full text of potential studies. Whether a study was eligible for final inclusion was determined by the two reviewers based on inclusion/exclusion criteria. Discrepancies were resolved by a third reviewer (GS). If more than one article using the same sample was eligible, only the more recent one was included in the analysis.

Data extraction

Data were independently extracted by two reviewers (LL and SW). A standardized table was developed by the research team to tabulate main study information. Extracted information included study-related characteristics (e.g., design, sample size, response rate, and prevalence of OSA) and participant-related characteristics (e.g., age, gestational age, and comorbidities). Discrepancies were resolved by a third reviewer (BZ).

OSA diagnosis

The primary outcome is the prevalence of OSA. Diagnosis and definition of OSA were based on the American Academy of Sleep Medicine (AASM) [24]. There are several commonly used indices for OSA. The most common one is the apnea-hypopnea index (AHI), which is the number of episodes of apnea and hypopnea per hour of sleep. Another one is oxygen desaturation index (ODI), which is the number of oxygen desaturations of over 3% below baseline per hour of sleep. The respiratory disturbance index (RDI) has also been used. RDI is the number of episodes of apnea, hypopnea, and respiratory event-related arousals per hour of sleep. Based on AHI, the severity of OSA can be categorized into: no OSA (AHI < 5), mild OSA (AHI ≥ 5 but < 15), moderate OSA (AHI ≥ 15 but < 30), and severe OSA (AHI ≥ 30).

Data analysis

Stata 13.0 (StataCorp LP, College Station, TX) was used for statistical analysis. Statistical significance was set at $P < 0.05$. For studies that consisted of both pregnant cases and non-pregnant controls, only the prevalence of OSA in the cases was used. We obtained the pooled estimates of the prevalence of OSA during pregnancy. Odds ratio (OR) with 95% CI was

used to assess the relationship between OSA and pregnancy-related outcomes. The pooled OR was calculated using the inverse variance method. Forest plots were used to present the results of individual studies and the pooled effect size. Funnel plot for the primary outcome (prevalence of OSA) was used to examine publication bias, and asymmetry of the plot suggests publication bias. Begg's test was also conducted to test the publication bias [25]. Heterogeneity among studies was examined by the I^2 value ($I^2 > 50\%$ considered significant) [26]. A fixed effect model was used if no heterogeneity was detected and a random effect model was used otherwise [27]. Subgroup analyses were conducted based on the regions of the study (i.e., Region of Americas, European Region, and Western Pacific Region) and trimester. The AASM has proposed several guidelines on how to define hypopnea, such as the 1999 recommended definition (1999_{rec}), 2007 recommended definition (2007_{rec}), 2007 alternative definition (2007_{alt}), and 2012 recommended definition (2012_{rec}) [28]. The definition of hypopnea can largely influence the prevalence estimates. Therefore, subgroup analysis was also conducted based on the definition of hypopnea. In the case of heterogeneity, we performed sensitivity analyses to test the robustness of the pooled estimates, using leave-one-out approach. We also used qualitative analysis to summarize the findings on the relationship between OSA and pregnancy-related outcomes when the meta-analysis was not applicable.

Results

Searching results

The initial literature search yielded 848 relevant records after excluding duplications across databases. A total of 75 articles underwent the full-text review and were excluded based on reasons listed in Fig. 1. A total of 33 studies met the inclusion and exclusion criteria and thus were included in this review. No eligible studies were identified through other sources. The searching process is shown in Fig. 1.

Study characteristics

Study characteristics are shown in Table 1. The studies were conducted between 2000 and 2017. Over half of the studies were conducted in the USA. Other countries included Canada, Australia, and UK. A majority of the studies used a prospective design ($n = 25$), eight studies used a retrospective design, and 12 studies also used a case-control design. Most of the studies used PSG to diagnose OSA. Other methods used included pulse-oximeter [44, 53, 55], RUSleeping meter [5], and WatchPat device [29]. AHI ≥ 5 was most commonly used as the indicator for OSA. AHI ≥ 10, AHI ≥ 15, RDI ≥ 5, ODI ≥ 5, and ODI ≥ 3 were also used. The participant mean age was between 25.5 (4.6) and 37.0 years. Participants were typically in their second or third trimester. The mean gestational age was between 21.2 (8.5) and 37.3 (2.1) weeks.

Prevalence of OSA during pregnancy

Among the 33 studies, two studies [35, 39] did not report the prevalence of OSA, six studies reported the incidence rate [17, 18, 30, 34, 41, 52], and one study [37] reported a prevalence of 0%. Therefore, findings from the remaining 24 studies were meta-analyzed. The 24 studies included a total of 4556 participants. The individual sample size ranged from 15 to 4166. Heterogeneity was detected ($I^2 = 86.2\%$, $p < 0.001$). Therefore, the random effects analysis was used. The pooled overall prevalence of OSA during pregnancy was 15% (95% CI 12–18%), as is shown in Fig. 2.

Subgroup analysis was conducted based on the regions of the studies. There was a lack of data from Southeast Asian Region, African Region, and Eastern Mediterranean Region. Based on the forest plot (Fig. 2a), the prevalence of OSA in European Region, Region of Americas, and Western Pacific Region were 5% (95% CI 1–9%), 20% (95% CI 15–25%), and 17% (95% CI 8–26%), respectively. The prevalence of OSA in the European Region was significantly lower than in the Region of Americas and Western Pacific Region.

Additional subgroup analysis was conducted based on trimester. There was a lack of data from the first trimester and only one study assessed the prevalence of OSA during the second trimester (11%, 95% CI 3–19%). Based on the forest plot (Fig. 2b), the prevalence of OSA during the third trimester was 15% (95% CI 10–20%). Three studies assessed the overall prevalence of OSA across all trimesters. The pooled prevalence was 19% (95% CI 10–28%). Six studies consisted of participants during their second and third trimester. The pooled prevalence was 17% (95% CI 9–24%).

Another subgroup analysis was conducted based on the definition of hypopnea. Based on the forest plot (Fig. 2c), the prevalence estimates produced by the 1999_{rec} definition and 2007_{rec} definition were 22% and 24%, respectively, higher than the one (15%) produced by the 2007_{alt} definition.

Sensitivity analysis and publication bias

Sensitivity analysis was conducted by excluding those two studies [5, 29] that employed the less commonly used method for OSA diagnosis. Based on the forest plot, the pooled prevalence of OSA was 15% (95% CI 12–19%), suggesting the result was robust (Supplementary Fig. 1). A funnel plot was performed for the primary outcome. Although not statistically significant ($z = 1.95$, $p = 0.052$), visual inspection of the funnel plot suggested a slight publication bias (Supplementary Fig. 2).

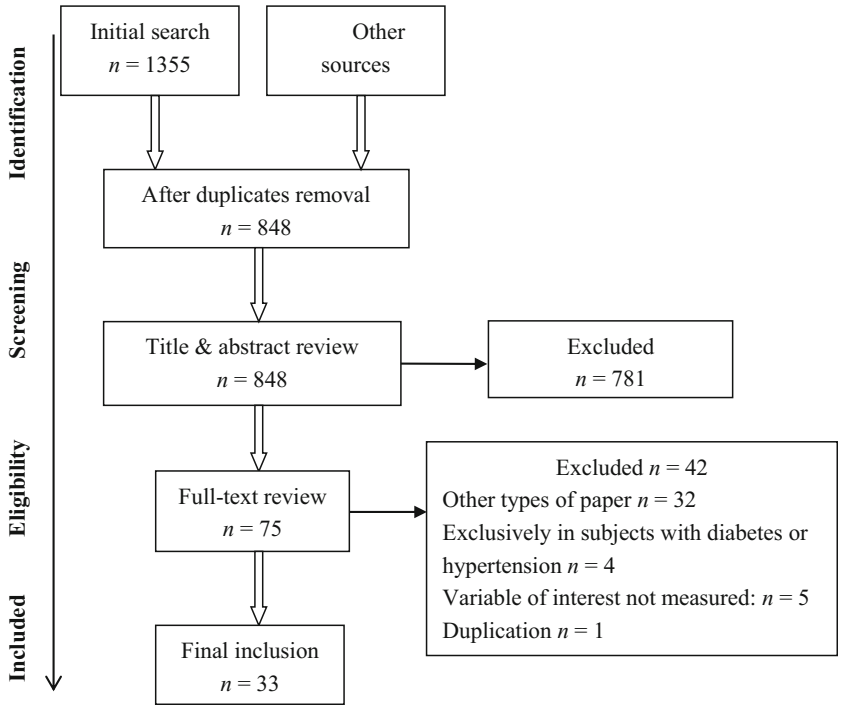

Fig. 1 PRISMA flowchart for study selection

Association between OSA and pregnancy-related outcomes

Among the 33 studies, 15 evaluated the association between OAS and maternal-related outcomes and 13 evaluated the association between OSA and infant-related outcomes. The main findings from each study are listed in Table 2. The pooled estimates for each outcome are presented in Table 3. The forest plots are shown in Supplementary Fig. 3.

Maternal-related outcomes

Based on Table 3, OSA was related to an increased risk for gestational hypertension, gestational diabetes, and pre-eclampsia ($p < 0.001$). The pooled adjusted odds ratio (aOR) values were 1.97 (95% CI 1.51–2.56), 1.55 (95% CI 1.51–2.56), and 2.35 (95% CI 2.15–2.58), respectively. OSA was also related to an increased risk for C-section (aOR = 1.42, 95% CI 1.12–1.79), postoperative wound complication (aOR = 1.87, 95% CI 1.56–2.24), and pulmonary edema (aOR = 6.35, 95% CI 4.25–9.50). In contrast, OSA was not significantly related to prolonged hospital stay (aOR = 1.94, $p = 0.10$).

Findings that cannot be meta-analyzed were summarized here. Specifically, OSA was reported to be associated with an increased risk for intensive care unit admission (aOR = 2.74, 95% CI 2.36–3.18) [17], a composite measure of adverse outcomes (e.g., preterm birth and prolonged hospital stay) [34, 39], and decreased resting heart rate variability [53]. Reutrakul et al. [50] also reported a strong association between OSA and gestational diabetes, but OSA was the outcome.

Infant-related outcomes

Based on Table 3, OSA was related to an increased risk for preterm birth (aOR = 1.62, 95% CI 1.29–2.02) and neonatal intensive care unit (NICU) admission (aOR = 1.28, 95% CI 1.13–1.46). In comparison, the association between OSA with small for gestational age infant, stillbirth, and poor fetal growth was not statistically significant.

Findings that cannot be meta-analyzed were summarized here. OSA was associated with an increased risk for low birth weight (aOR = 1.76, 95% CI 1.28–2.40) [18] and the low Apgar score [18, 19, 30]. The association between OSA with neurological function and perinatal complication of the infant [29] and fetal heart rate abnormality [47] was also examined, but no significance was detected.

Discussion

The aim of this systematic review and meta-analysis was to examine the prevalence of OSA during pregnancy and to explore the association between OSA and pregnancy-related health outcomes. This study, to our best knowledge, is among the first that exclusively included studies relied on the objective assessment of OSA, which enhanced the reliability of the findings. In this study, we provided a pooled estimate of the OSA prevalence during pregnancy around the globe. We found that the overall prevalence of OSA during mid and late pregnancy was 15% (95% CI 12–18%). We also provided an up-to-date assessment of health outcomes related to OSA

Table 1 Study characteristics and participant description ($n = 33$)

Author, year	Country	Design	Sample size	Age (years)	Gestational age (weeks) and trimester	OSA assessment; hypopnea definition; diagnosis criteria	Comorbid with diabetes or hypertension
Bassan, 2016 [29]	Israel	Prospective	44	32.5 (4.2)	33–36; 3rd trimester	WatchPat device; $AASM\ 1999_{rec}$; AHI ≥ 5	None
Bin, 2016 [30]	Australia	Retrospective	636,227	NA	NA	ICD-10	Diabetes: 6.6% Hypertension: 4.4%
Bisson, 2014 [31]	Canada	Prospective, case-control	26 healthy controls and 26 with GMD	32.7 (3.8)	32.3 (1.0); 2nd and 3rd trimester	Unattended PSG; $AASM\ 1999_{rec}$; AHI ≥ 5	Diabetes: 0% Hypertension: 4%
Bourjeily, 2015 [32]	USA	Prospective, case-control	25 non-pregnant women and 25 pregnant women	31.1 (5.8)	26.6 (7.9); any trimester	Attended PSG; $AASM\ 2007_{rec}$; AHI ≥ 5	Diabetes: 36% Hypertension: 24%
Bourjeily, 2017 [17]	USA	Retrospective	1,577,632	29.6 (6.0)	NA	ICD-9	Diabetes: 1.2% Hypertension: 2.9%
Champagne, 2009 [33]	Canada	Prospective, case-control	33 healthy pregnant women and 17 pregnant women with GHT	32.7 (5.5)	32.4 (4.6); 2nd and 3rd trimester	Unattended PSG: $AASM\ 1999_{rec}$; AHI ≥ 15	Diabetes: 6.0% Hypertension: 0%
Chen, 2012 [18]	Taiwan	Retrospective, case-control	3955 healthy pregnant women and 791 pregnant women with OSA	30.3 (4.4)	NA	ICD-9	None
Facco,2012 [34]	USA	Retrospective	143	32.1 (5.6)	NA	Attended PSG; $AASM\ 2007_{rec}$; AHI ≥ 5	Diabetes:4% Hypertension: 17%
Facco, 2017 [16]	USA	Prospective	Mid: 2474	NA	2nd and 3rd trimester	Unattended PSG; $AASM\ 2007_{rec}$; AHI ≥ 5	Diabetes: 7.0% Hypertension:32.5%
Felder, 2017 [35]	USA	Retrospective, case-control	2172 pregnant women with sleep disorder and 2172 healthy pregnant women	NA	NA	ICD-9	NA
Fung, 2013 [36]	Australia	Prospective	41	36.0 (4.4)	37; 3rd trimester	Attended PSG; NA; RDI ≥ 5	Diabetes: 29% Hypertension: 14%
Guilleminault, 2000 [37]	USA	Prospective	26	25.5 (4.6)	25–27; 2nd trimester	Attended PSG; NA; AHI ≥ 5	NA
Lockhart, 2015 [38]	USA	Prospective	248	28 (6.2)	32 (3.1); 3rd trimester	Attended PSG; $AASM\ 1999_{rec}$; AHI ≥ 5	Diabetes: 15% Hypertension: 27%
Longworth, 2017 [5]	UK	Prospective	47	29.6 (6.1)	28; 3rd trimester	RUSleeping Meter; NA; AHI ≥ 15	NA
Louis, 2010 [39]	USA	Retrospective, case-control	57 pregnant women with OSA and 114 healthy pregnant women	30 (6)	NA	Attended PSG; $AASM\ 2012_{rec}$; AHI ≥ 5	
Louis, 2012 [40]	USA	Prospective	175	30.0 (6.4)	21.2 (8.5); any trimester	Unattended PSG; $AASM\ 2007_{alt}$; AHI ≥ 5	Diabetes: 31% Hypertension: 33%
Louis, 2014 [41]	USA	Retrospective	55,781,965	NA	NA	ICD-9	
Maasilta, 2001 [42]	Finland	Prospective, case-control	11 obese and 11 non-obese pregnant women	31.8 (1.1)	3rd trimester	Attended PSG; $AASM\ 2007_{alt}$; AHI ≥ 10	Diabetes: 40.9% Hypertension: NA
McIntyre, 2016 [43]	New Zealand	Prospective	30	30.8 (5.2)	37; 3rd trimester	Unattended PSG; $AASM\ 2012_{rec}$; AHI ≥ 5	None
Miyagawa, 2011 [44]	Japan	Prospective	179	32.4 (4.7)	35.9 (1.5); 3rd trimester	Pulse-oximeter; NA; 3%ODI ≥ 5	NA
O'Brien, 2012 [45]	USA	Prospective	31	30.2 (7.1)	33.4 (3.0); 3rd trimester	Unattended PSG; $AASM\ 2007_{alt}$; AHI ≥ 5	NA
O'Brien, 2014 [46]	USA			28.1 (9.2)		Attended PSG;	None

Table 1 (continued)

Author, year	Country	Design	Sample size	Age (years)	Gestational age (weeks) and trimester	OSA assessment; hypopnea definition; diagnosis criteria	Comorbid with diabetes or hypertension
		Prospective, case-control	16 healthy pregnant women and 51 pregnant women with hypertensive disorder		33.8 (3.8); any trimester	AASM 2007_{alt}; AHI ≥ 5	
Olivarez, 2010 [47]	USA	Prospective	100	26.6 (7.1)	32.3 (3.5); 3rd trimester	Attended PSG; NA; AHI ≥ 5	Diabetes: 28% Hypertension: 16%
Pamidi, 2016 [48]	USA	Prospective	234	31.0 (4.3)	36.6 (1.4); 3rd trimester	Attended PSG; AASM 1999_{rec}; AHI ≥ 15	None
Pien, 2013 [49]	USA	Prospective	105	26.7 (7.2)	33.6 (2.5); 3rd trimester	Attended PSG; AASM 1999_{rec}; AHI ≥ 5	Diabetes: 13.3%
Reutrakul, 2013 [50]	USA	Prospective, case-control	15 healthy pregnant women and 15 pregnant women with GDM	28.5 (5.9)	2nd and 3rd trimester	Attended PSG; AASM 2007_{rec}; AHI ≥ 5	None
Sahin, 2008 [19]	Turkey	Prospective	35	34.8 (3.3)	37.3 (2.1); 3rd trimester	Attended PSG; AASM 2007_{alt}; AHI ≥ 5	Diabetes: 11.4% Hypertension:14.3%
Sarberg, 2016 [51]	Sweden	Prospective, case-control	100 pregnant women and 80 non-pregnant women	31	24–34; 2nd and 3rd trimester	Unattended PSG; AASM 2007_{alt}; AHI ≥ 5	Diabetes: none Hypertension: NA
Sharkey, 2014 [6]	USA	Prospective	16	29.8 (5.4)	28.6 (6.3); 2nd and 3rd trimester	Attended PSG; AASM 2007_{rec}; AHI ≥ 5	NA
Spence, 2017 [52]	USA	Retrospective, case-control	266 pregnant women with OSA and 304,735 healthy pregnant women	30.7 (6.4)	NA	ICD-9	NA
Watanabe, 2015 [53]	Japan	Prospective	64	28.8 (4.8)	25.8 (1.6); 2nd trimester	Pulse-oximeter; NA; 3%ODI ≥ 3 or minimum $_{O2}$ saturation < 90%	None
Wilson, 2013 [54]	Australia	Prospective	43	33.5 (5.1)	37; 3rd trimester	Attended PSG; AASM 2007_{alt}; RDI ≥ 5	Diabetes: 19% Hypertension: 19%
Yin, 2008 [55]	UK	Prospective, case-control	50 non-pregnant women and 150 pregnant women	29 (7)	35 (2.7); 3rd trimester	Pulse-oximeter; NA; 4%ODI ≥ 5	None

AASM the American Academy of Sleep Medicine, *AHI* apnea-hypopnea index, *ICD* the International Statistical Classification of Diseases and Related Health Problems, *NA* not available or not applicable, *ODI* oxygen desaturation index, *OSA* obstructive sleep apnea, *PSG* polysomnography, *RDI* respiratory disturbance index, 1999_{rec} 1999 recommended definition, 2007_{rec} 2007 recommended definition, 2007_{alt} 2007 alternative definition, 2012_{rec} 2012 recommended definition

during pregnancy. OSA was related to an increased risk for various adverse health outcomes. Maternal-related outcomes included gestational diabetes, gestational hypertension, pre-eclampsia, C-section, postoperative wound complication, and pulmonary edema. Infant-related outcomes included pre-term birth and NICU admission.

The overall prevalence of OSA during pregnancy was high, suggesting that pregnancy-related factors may increase the risk for OSA during this special time. During pregnancy, many changes can predispose pregnant women to the development of OSA. Such changes include progressive weight gain, upward placement of the diagram, and levels of estrogen and progesterone during pregnancy [56]. Lee et al. [57] found that controlling for gestational age and weight, progesterone levels were lower in pregnant women with OSA than pregnant women without OSA. This finding suggests that progesterone, as a known respiratory drive stimulant, may protect pregnant women against OSA [57]. However, the increasing level of estrogen during pregnancy may result in narrowing of the upper airway with increased

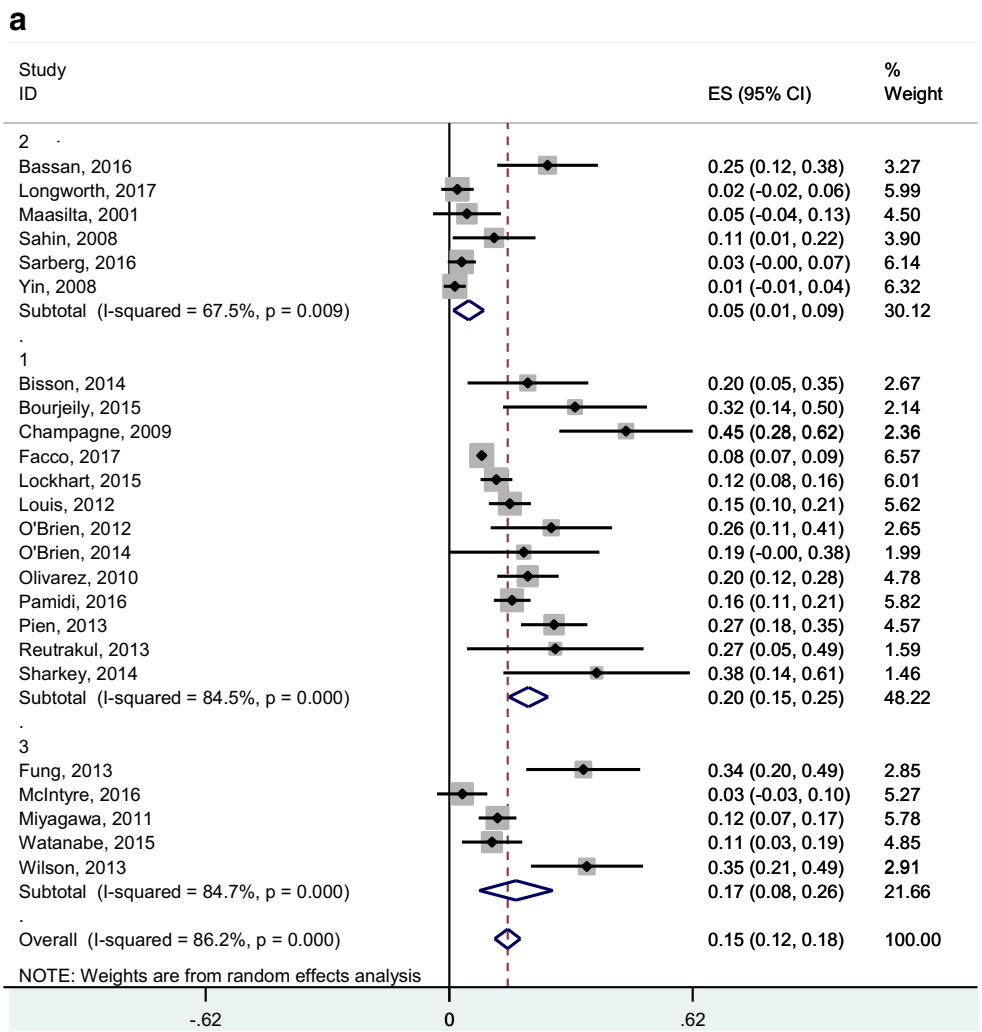

Fig. 2 **a** Forest plot for the prevalence of sleep apnea during pregnancy based on regions. Results are shown as effect size (ES) and 95% CI. Dotted line represents the pooled prevalence ratio. 1: Region of Americas, ES = 0.20, $z = 7.39$, $p < 0.001$. 2: European Region, ES = 0.05, $z = 2.50$, $p = 0.012$. 3: Western Pacific Region, ES = 0.17, $z = 3.58$, $p < 0.001$. Overall, ES = 0.15, $z = 8.96$, $p < 0.001$. **b** Forest plot for the prevalence of sleep apnea during pregnancy based on trimesters. Results are shown as effect size (ES) and 95% CI. Dotted line represents the pooled prevalence ratio. 3: Third trimester, ES = 0.15, $z = 5.75$, $p < 0.001$. 2.5: Second and third trimester, ES = 0.17, $z = 4.30$, $p < 0.001$. 2: Second trimester, ES = 0.11, $z = 2.80$, $p = 0.005$. 0: Across all trimesters, ES = 0.19, $z = 4.20$, $p < 0.001$. Overall, ES = 0.15, $z = 8.96$, $p < 0.001$. **c** Forest plot for the prevalence of sleep apnea during pregnancy based on definitions of hypopnea. Results are shown as effect size (ES) and 95% CI. Dotted line represents the pooled prevalence ratio. 4: Following the 2012 recommended definition, ES = 0.03, $z = 1.01$, $p = 0.312$. 3: Following the 2007 alternative definition, ES = 0.15, $z = 3.66$, $p < 0.001$. 2: Following the 2007 recommended definition, ES = 0.24, $z = 2.74$, $p = 0.006$. 1: Following the 1999 recommended definition, ES = 0.22, $z = 5.98$, $p < 0.001$. 0: Information not available or not applicable, ES = 0.12, $z = 3.29$, $p = 0.001$. Overall, ES = 0.15, $z = 8.96$, $p < 0.001$

resistance to airflow [56]. Those two hormones, working together, play a role in the development of OSA. Additionally, it was also reported that increasing neck circumference and waistline during pregnancy were risk factors for symptoms of OSA [58]. Similarly, Pien and colleagues [49] found that baseline BMI and age were significant risk factors for OSA during the third trimester, which were similar to those found in the general population [59]. Overall, both common and pregnancy-specific factors may put pregnant women at a higher risk for the development of OSA. An important finding of this review is the regional differences in OSA prevalence during pregnancy. The prevalence of OSA in the European Region (5%) was significantly lower than in the Region of Americas (20%) and Western Pacific Region (17%). However, there was a lack of data from the Southeast Asian Region, African Region, and Eastern Mediterranean Region. This finding can be a result of language criteria we used, but it also demonstrates the need to conduct similar studies in those regions.

Prevalence of OSA during pregnancy may vary in women with different characteristics, including gestational age (or trimester) and coexistence with hypertension or diabetes. It has

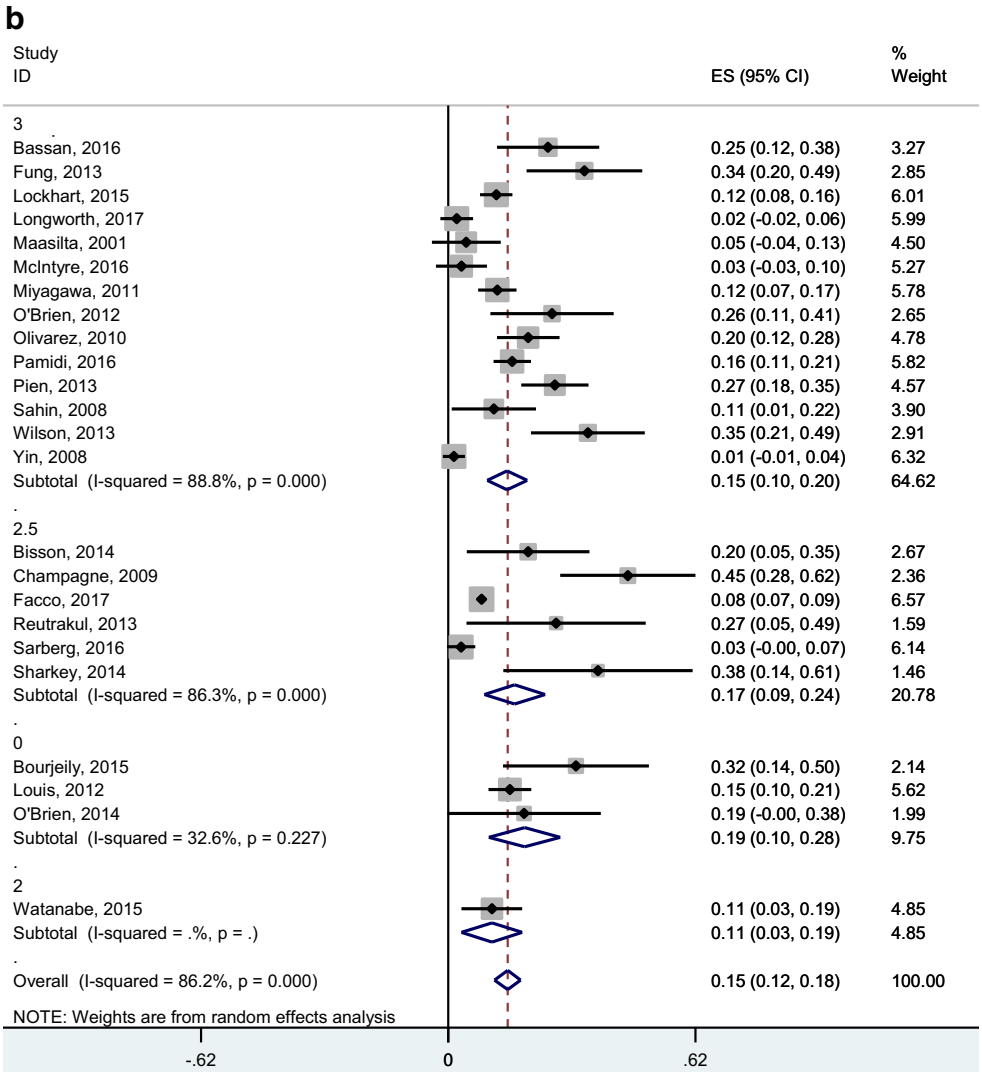

Fig. 2 continued.

been reported that the prevalence of OSA increases with the increase of gestational age [49]. In this review, there was a lack of data from the first trimester or the second trimester alone. The pooled prevalence rates of OSA during the third trimester alone and across all trimesters were 15% and 19%, respectively. The pooled prevalence of OSA during the second and third trimester was 17%. The prevalence of OSA found in this review may be more representative of women during mid and late pregnancy. The prevalence rates of OSA in the general population with diabetes or hypertension are high [22, 23]. The prevalence of OSA in pregnant women with these conditions is likely to be higher. A review suggests that OSA and gestational diabetes and hypertension share a number of common mechanistic pathways [60]. Empirical evidence also indicates that pregnant women with hypertension [46] and diabetes [61] are at a high risk for OSA. In this review, we did not include studies conducted exclusively in women with high-risk pregnancy, such as those with hypertension or diabetes. Nevertheless, it was very challenging to recruit only healthy pregnant women with no other conditions. The prevalence of diabetes and hypertension in this review were 0 to 40.9% and 4 to 57.7%, respectively. Variations in the proportion of pregnant women with those conditions may influence the prevalence estimate of OSA.

We found that OSA was related to an increased risk for maternal-related health outcomes including gestational hypertension, gestational diabetes, and pre-eclampsia. These findings are in line with the reviews by Ding et al. [62] and Pamidi et al. [63]. In addition, we found that OSA was associated with an increased risk for complications, such as C-section, postoperative wound complication, and pulmonary edema after adjusting for covariates. It has been suggested that poor tissue perfusion may explain the increased risk for postoperative wound complications [17]. However, mechanisms underlying those relationships have not been fully understood, which warrants more

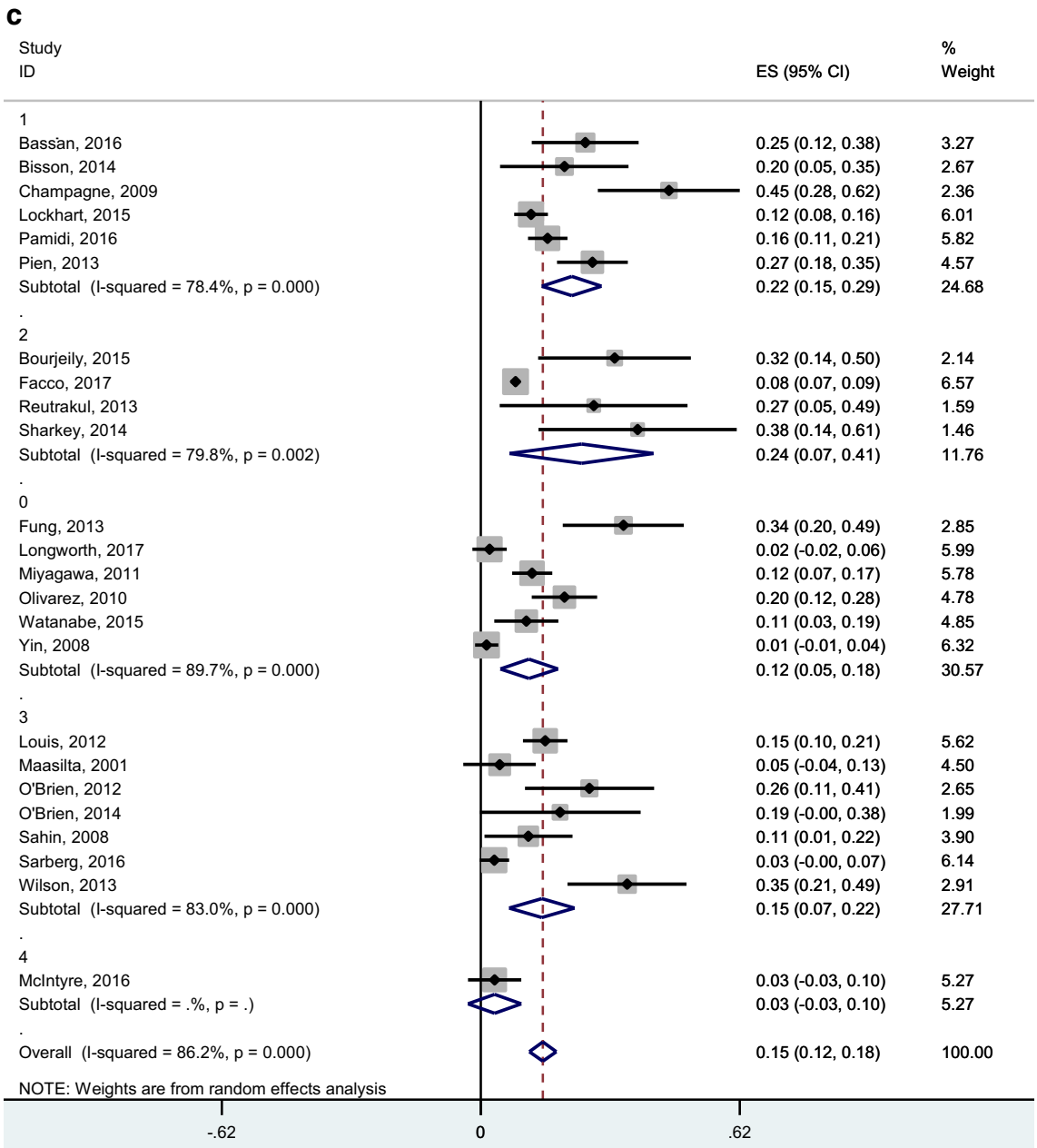

Fig. 2 continued.

studies. Similar to Ding et al. findings [62], OSA during pregnancy was related to an increased risk for preterm birth (aOR = 1.62), NICU admission (aOR = 1.28), and the low Apgar score. In contrast to Ding et al.'s study, we did not observe a significant association between OSA with poor fetal growth. Variabilities in OSA diagnosis may largely explain the discrepancy. OSA assessment in the previous review was typically based on self-reported symptoms as compared to the objective assessment in this review. Previous studies [64, 65] conducted in rats demonstrated that gestational exposure to intermittent hypoxia was related to asymmetrical growth restriction and overall reduced birth weights. However, in this review, we did not find a significant relationship between OSA and small for gestational age infant or stillbirth. These findings were primarily based on retrospective studies. More prospective studies are needed to confirm the findings.

In this review, we determined the prevalence of OSA in different regions and trimesters. One strength of this study lies in the diagnosis of OSA using objective methods. However, findings from this review need to be interpreted in light of the limitations. First, although we did an exhaustive search, not all literature was captured in this review, such as papers published in non-English. Second,

Table 2 Summary of main study findings ($n = 33$)

Author, year	OSA, prevalence (%)	Maternal-related outcomes	Infant-related outcomes
Bassan, 2016	25		No association with neonatal neurological function and perinatal complication
Bin, 2016	0.08	Increased risk for gestational hypertension (aRR = 1.43, 1.18–1.73) No association with GDM (aRR = 1.09, 0.82–1.46) and C-section (aRR = 1.06, 0.96–1.17)	Increased risk for 5-min Apgar score < 7 (aRR = 1.60, 1.07–1.23), NICU admission (aRR = 1.26, 1.11–1.44), and preterm birth (aRR = 1.50, 1.21–1.84) No association with small for gestational age infant (aRR = 0.81, 0.61–1.08)
Bisson, 2014	20	No association with GDM (aOR = 1.90, 0.52–6.88)	
Bourjeily, 2015	32		
Bourjeily, 2017	0.12	Increased risk for pre-eclampsia (aOR = 2.22, 1.94–2.54), gestational hypertension (aOR = 1.67, 1.42–1.92), eclampsia (aOR = 2.95, 1.08–8.02), GDM (aOR = 1.52, 1.34–1.72), IUC admission (aOR = 2.74, 2.36–3.18), longer stay (aOR = 1.18, 1.05–1.32), pulmonary edema (aOR = 5.06, 2.29–11.1), and wound complication (aOR = 1.77, 1.24–2.54)	No association with growth restriction (aOR = 1.05, 0.84–1.31) and stillbirth (aOR = 1.17, 0.79–1.73)
Champagne, 2009	45	Increased risk for gestational hypertension (aOR = 7.5, 3.5–16.2)	
Chen, 2012	0.4	Increased risk for C-section (aOR = 1.74, 1.48–2.04), pre-eclampsia (aOR = 1.60, 2.16–11.26), gestational hypertension (aOR = 3.18, 2.14–4.73), and GDM (aOR = 1.63, 1.07–2.48)	Increased risk for low birth weight (aOR = 1.76, 1.28–2.40), preterm birth (aOR = 2.31, 1.77–3.01), small size for gestational age (aOR = 1.34, 1.09–1.66), and 5-min Apgar score < 7 (OR = 10.1, 3.45–29.67)
Facco,2012	42	Associated with an increased risk for a composite measure of adverse outcomes (e.g., pregnancy-related hypertension, GDM, or preterm birth): NOT control for confounders	
Facco, 2017	8.3	Increased risk for pre-eclampsia (aOR = 1.95, 1.18–3.23), gestational hypertension (aOR = 1.73, 1.19–2.52), and GDM (aOR = 2.79, 1.63–4.77)	
Felder, 2017	NA		Increased risk for preterm birth (OR = 1.5, 1.2–1.8)
Fung, 2013	34.1		No association with impaired fetal growth (aOR = 5.3, 0.93–30.34)
Guilleminault, 2000	0		
Lockhart, 2015	12		
Longworth, 2017	2.1		
Louis, 2010	NA	Increased risk for maternal morbidity (e.g., prolonged stay and ICU admission) (aOR = 4.6, 1.5–13.7)	Increased risk for preterm birth (aOR = 2.6, 1.0–6.6)
Louis, 2012	15.4	Increased risk for C-section (aOR = 3.04, 1.14–8.1) and pre-eclampsia (aOR = 3.54, 1.1–11.3)	Increased risk for NICU admission (aOR = 3.39, 1.23–9.32) No association with preterm birth (aOR = 0.63, 0.18–2.24)
Louis, 2014	0.03	Increased risk for GDM (aOR = 1.89, 1.67–2.14), gestational hypertension (aOR = 1.28, 1.08–1.52), pre-eclampsia (aOR = 2.50, 2.19–2.85), eclampsia (aOR = 5.42, 3.29–8.92), C-section (aOR = 1.12, 1.01–1.23), longer stay (aOR = 3.06, 2.76–3.40), wound complication (aOR = 1.89, 1.53–2.34), pulmonary edema (aOR = 7.50, 4.63–12.15)	Increased risk for preterm birth (aOR = 1.20, 1.06–1.37) No association with poor fetal growth (aOR = 1.21, 0.96–1.53) and stillbirth (aOR = 1.01, 0.66–1.53)
Maasilta, 2001	4.5		
McIntyre, 2016	3.3		
Miyagawa, 2011	12.3	Increased risk for C-section (aOR = 3.03, 1.10–8.33)	No association with small for gestational age infant (aOR = 3.15, 0.31–32.13)
O'Brien, 2012	26		
O'Brien, 2014	19		

Table 2 (continued)

Author, year	OSA, prevalence (%)	Maternal-related outcomes	Infant-related outcomes
Olivarez, 2010	20		No association with fetal heart rate abnormality
Pamidi, 2016	16		Increased risk for small for gestational age (aOR = 2.57, 1.02–6.48)
Pien, 2013	26.7		
Reutrakul, 2013	27	Strong association between GDM and OSA, but GDM was the predictor of OSA	
Sahin, 2008	11.4		Related to lower Apgar score and more NICU admissions (based on *t* tests)
Sarberg, 2016	3.2		
Sharkey, 2014	37.5		
Spence, 2017	0.09	Increased risk for C-section (aOR = 1.60, 1.06–2.40), gestational hypertension (aOR = 2.46, 1.30–4.68), and pre-eclampsia (aOR = 2.42, 1.43–4.09) No association with GDM (aOR = 1.00, 0.63–1.60) and longer stay (aOR = 2.06, 0.88–4.81), wound complication (aOR = 2.47, 0.60–10.14), pulmonary edema (aOR = 1.82, 0.41–18.14)	Increased risk for preterm birth (aOR = 1.90, 1.09–3.30) No association with poor fetal healthy (aOR = 1.40, 0.57–3.43) and stillbirth (aOR = 2.09, 0.55–7.95)
Watanabe, 2015	10.9	Associated with resting heart rate variability	
Wilson, 2013	35		
Yin, 2008	1.4	No association with fetal growth restriction or hypertensive disease (based on *t* tests)	

aOR adjusted odds ratio, *GDM* gestational diabetes mellitus, *NICU* neonatal intensive care unit, *OSA* obstructive sleep apnea

women in the first trimester were under-represented, possibly due to difficulty in recruiting pregnant women during early pregnancy. Therefore, findings from this study may not be generalized to women during early pregnancy. Third, some of the studies did not differentiate women who experienced OSA for the first time during pregnancy and those with pre-existing OSA. It is possible that pregnant women diagnosed with OSA during pregnancy already had pre-existing unrecognized OSA that may have overestimated the prevalence estimates. It is also worth

Table 3 Relationships between sleep apnea and pregnancy-related outcomes

Outcomes	No. of studies	Adjusted OR (95% CI)	*p*	Heterogeneity	
				I^2 (%)	*p*
Maternal-related					
Gestational hypertension	7	1.97 (1.51, 2.56)	< 0.001	83.9	< 0.001
Gestational diabetes	7	1.55 (1.26, 1.90)	< 0.001	73.1	0.001
Pre-eclampsia	5	2.35 (2.15, 2.58)	< 0.001	0.0	0.636
C-section	6	1.42 (1.12, 1.79)	< 0.001	86.5	< 0.001
Prolonged hospital stay	3	1.94 (0.88, 4.28)	0.100	98.6	< 0.001
Wound complication	3	1.87 (1.56, 2.24)	< 0.001	0.0	0.883
Pulmonary edema	3	6.35 (4.25, 9.50)	< 0.001	18.2	0.294
Infant-related					
Preterm birth	8	1.62 (1.29, 2.02)	< 0.001	72.9	0.001
Small for gestational age	4	1.26 (0.80, 2.01)	0.321	73.8	0.010
Stillbirth	3	1.12 (0.85, 1.49)	0.413	0.0	0.572
Poor fetal growth	4	1.15 (0.98, 1.34)	0.091	24.3	0.266
NICU admission	2	1.28 (1.13, 1.46)	< 0.001	72.3	0.057

CI confidence interval, *NICU* neonatal intensive care unit, *OR* odds ratio

mentioning that a slight publication bias for the estimate of OSA prevalence was detected. Publication bias suggests a lack of publication of small trials with negative findings [66] or an inflation of estimates by small studies [67]. However, evidence also suggests that publication bias may not affect the conclusions in most cases [68].

Findings from this review have important implications for both research and clinical practice. Given the limited data from early pregnancy, more studies are warranted. These studies ideally should be longitudinal studies that include pregnant women during different trimesters. Determining the OSA prevalence during different trimesters may shed lights on the time window that could be targeted for interventions. Experimental studies are needed to examine the effect of treating OSA on pregnancy-related health outcomes. In clinical practice, routine screening of OSA is recommended so that early diagnosis and treatment of OSA can be initiated, which may further decrease the risk of adverse maternal and neonatal outcomes. For instance, healthcare providers are recommended to offer pregnant women a quick screening for the risk of OSA, particularly starting from the mid-pregnancy. Referral to an overnight PSG diagnosis should be made for those with a high risk. Continuous positive airway pressure (CPAP) treatment has been the most commonly used method to treat OSA. Thus, early use of CPAP is encouraged for those with established OSA. Additionally, we also demonstrated that estimates of OSA prevalence varied based on the definition of hypopnea. Therefore, clinicians and researchers need to take that into consideration when interpreting the results obtained using different scoring standards.

Conclusion

In conclusion, OSA is a common health problem during pregnancy. The overall prevalence of objectively assessed OSA was 15%, and there were likely regional differences in the prevalence. OSA was related to various pregnancy-related health outcomes, such as gestational diabetes, gestational hypertension, pre-eclampsia, C-section, and preterm birth. Findings from this review highlight the need to include OSA-related assessment and intervention in the overall health care during pregnancy.

Compliance with ethical standards

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

Informed consent For this type of study, formal consent is not required.

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