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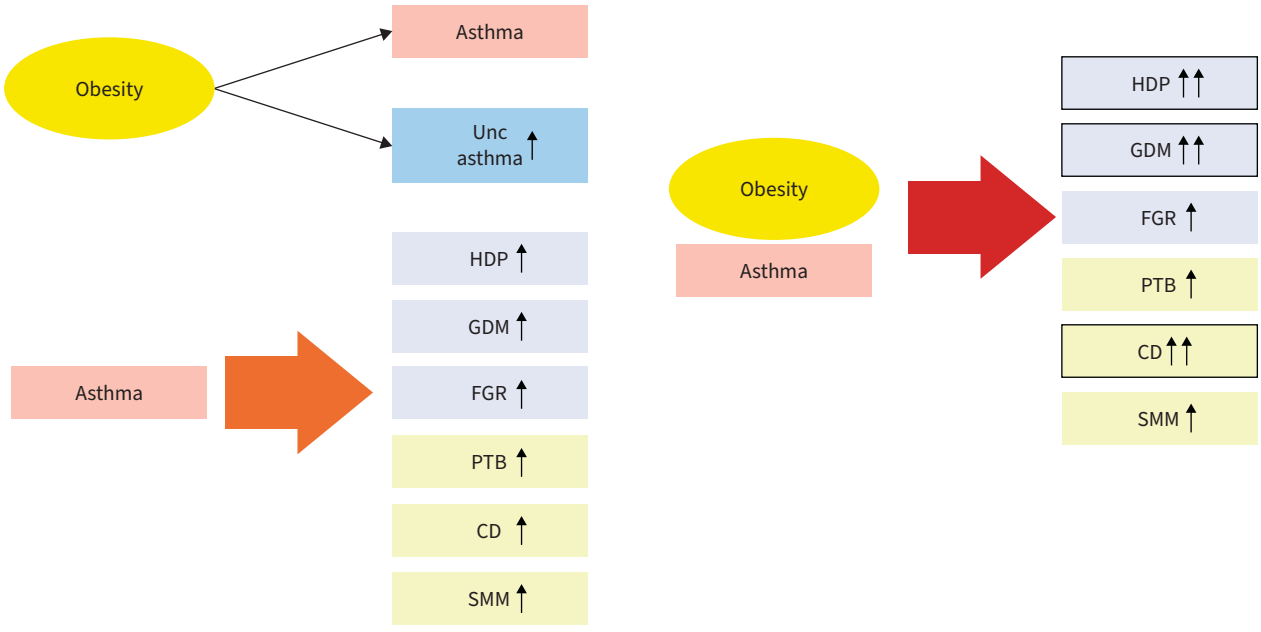

GRAPHICAL ABSTRACT Overview of the study findings. CD: caesarean delivery; FGR: fetal growth restriction; GDM: gestational diabetes mellitus; HDP: hypertensive disorders of pregnancy; PTB: preterm birth; SMM: severe maternal morbidity; Unc: uncontrolled.

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Obesity and asthma during pregnancy: a systematic review and meta-analysis

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Shareable abstract (@ERSpublications)
Obesity influenced the prevalence of asthma and uncontrolled asthma during pregnancy. Asthma was associated with adverse obstetric and delivery outcomes, and obesity was a risk factor for HDP, GDM and CD in pregnant women with asthma. https://bit.ly/41ZAgKq

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Abstract

Objective To assess the effect of obesity on the prevalence of asthma, obstetric outcomes and delivery outcomes in pregnant women with asthma.

Methods A comprehensive systematic review and meta-analysis were conducted up to 31 March 2024, using four public search engines. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines, both quantitative and qualitative data were collected and analysed.

Results We included 11 studies from 2006 to 2022 involving 77 611 386 pregnant patients (3.1% had asthma). Obesity increased the odds of asthma (n=2; OR 2.42, 95% CI 1.14–5.15) and increased that of uncontrolled asthma (n=6; OR 1.29, 95% CI 1.11–1.50) in pregnant women. In an adjusted pooled analysis, pregnant women with asthma were more likely to develop hypertensive disorders of pregnancy (HDP) (n=3; adjusted OR (aOR) 1.21, 95% CI 1.10–1.34), gestational diabetes mellitus (GDM) (n=3; aOR 1.14, 95% CI 1.04–1.26), fetal growth restriction (FGR) (n=2; aOR 1.18, 95% CI 1.15–1.21), preterm birth (PTB) (n=2; aOR 1.26, 95% CI 1.25–1.27), caesarean delivery (CD) (n=3; aOR 1.22, 95% CI 1.11–1.33) and severe maternal morbidity (n=1; aOR 1.50, 95% CI 1.45–1.55). Three comparator studies that examined the effect of obesity on obstetric outcomes cited obesity as a risk factor for HDP (n=1; aOR 1.7, 95% CI 1.3–2.3), GDM (n=1; aOR 4.2, 95% CI 2.8–6.3) and CD (n=1; aOR 1.6, 95% CI 1.3–2.0) in pregnant women with asthma.

Conclusions Pregnancy with asthma may increase the risk of HDP, GDM, FGR, PTB and CD, and obesity has the potential to further increase the risk of HDP, GDM and CD in pregnant women with asthma.

Introduction

Asthma is a common chronic noncommunicable disease with variable airflow obstruction, causing dyspnoea and wheezing [1]. The World Health Organization (WHO) [2] estimated 262 million asthma cases and 455 000 related deaths worldwide in 2019. Asthma during pregnancy is increasing worldwide, including in the US, where 8–12% of pregnant women are affected [3, 4]. A systematic review linked asthma to higher odds of preterm birth (PTB), fetal growth restriction (FGR) and low birthweight (LBW), with poor asthma control worsening perinatal outcomes [5]. Therefore, managing asthma during pregnancy is essential.

Obesity is a complex chronic disease defined by the WHO as “excess or abnormal fat accumulation that presents a risk to health” [6, 7]. Globally, 43% of adults aged ⩾18 years were overweight (body mass index (BMI) ⩾25 kg·m^{-2}) and 16% were obese (BMI ⩾30 kg·m^{-2}) in 2022. The rate of obesity is approximately 35% [8, 9], 30% [10], 30% [11], 15% [12] and 20% [13] in the US, Australia, Canada, France and Sweden, respectively. Obesity is associated with multiple healthcare problems [14]. A 2019 US

study found that the rate of pre-pregnancy obesity was approximately 30%, an increase of more than 10% from 2016 [15]. Studies show that obesity is linked to adverse obstetric outcomes [16–18]; thus, obesity management should ideally begin before pregnancy and continue through the postpartum period [19].

Asthma in individuals with obesity is associated with a higher prevalence of uncontrolled asthma, a lower response to conventional therapies and more adverse outcomes [20–22]. A recent meta-analysis identified obesity as an important risk factor for asthma exacerbation during pregnancy [23]. We hypothesised that 1) obesity is a risk factor for asthma during pregnancy, 2) pregnant women with obesity have an increased prevalence of uncontrolled asthma during pregnancy compared to nonobese pregnant women and 3) pregnant obese women with asthma have adverse obstetric outcomes. We conducted a systematic review and meta-analysis to assess the effects of obesity on asthma prevalence, asthma control and obstetric outcomes in pregnant women with concurrent obesity and asthma.

Methods

Ethical considerations

As we utilised publicly accessible, de-identified data, our Institutional Review Board waived the need for informed patient consent. This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration ID: CRD42023454562).

Eligibility criteria, information sources and search strategy

A comprehensive literature search was conducted for all articles published before 31 March 2024, without restrictions, across PubMed, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials databases, using keywords related to obesity, asthma and pregnancy (supplemental methods S1) [24, 25]. This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26]. Titles, abstracts and full texts were screened by two investigators (Sh. Matsuzaki and H. Matsuzaki) (supplemental methods S1). References in eligible studies were examined to identify additional literature.

Study selection

Study selection followed the patient/population, intervention, comparison, outcome and study (PICOS) framework [26]. Criteria for inclusion included the following: 1) comparative studies assessing obstetric outcomes between groups (pregnant women with asthma *versus* without asthma, well-controlled *versus* uncontrolled asthma and asthma with obesity *versus* asthma without obesity), 2) studies providing information on specific treatments for pregnant women with obesity and 3) studies with clear data on the number of pregnant women with concurrent asthma and obesity.

Criteria for exclusion included the following: 1) insufficient information on patient prognosis, 2) unclear numbers of experimental or control groups, 3) studies published in languages other than English and 4) conference abstracts, case reports, case series, narrative reviews, systematic reviews or meta-analyses, which were excluded because small case series and unpublished data are possibly prone to bias.

Data extraction

Data were extracted on study year, first author, study location, number of eligible cases, asthma severity and relevant outcomes. Severe maternal morbidity (SMM) was defined according to the Centers for Disease Control and Prevention [27]. Asthma, along with its exacerbations and severity, were defined according to each study's criteria. Uncontrolled asthma was defined as routinely poorly controlled asthma or severe exacerbations that could affect perinatal outcomes, while well-controlled asthma was defined as otherwise managed asthma.

Analysis of outcome measures and assessment of risk of bias

Bias risk was assessed using the Risk of Bias in Nonrandomised Studies of Interventions Tool-I by a blinded author (Sa. Matsuzaki) [28–30]. The co-primary objectives were to determine the effects of obesity on the prevalence of asthma and uncontrolled asthma during pregnancy. Co-secondary outcomes included obstetric outcomes, SMM, delivery outcomes (pregnant women with asthma *versus* without asthma, pregnant women with well-controlled asthma *versus* with uncontrolled asthma and pregnant asthmatic women with obesity *versus* without obesity) and risk of SMM in pregnant obese women with asthma. The effect of uncontrolled asthma on obstetric and delivery outcomes was also assessed.

Meta-analysis

The meta-analysis followed a previously described methodology [31]. Maternal outcome risks were evaluated in experimental and control groups, with odds ratios calculated using 95% confidence intervals.

Studies lacking raw data were excluded, as most reported odds ratios. Heterogeneity was assessed using I^2 percentages. Fixed-effect analysis was employed for low heterogeneity (I^2<30%), while random-effect analysis was conducted for moderate (I^2=30–60%), substantial (I^2=50–90%) and considerable heterogeneity (I^2=75–100%).

Meta-analysis and visualisation were performed using RevMan software version 5.4.1 (Cochrane Collaboration, Copenhagen, Denmark). Continuous and bivariate outcomes were included with a preference for active interventions because of their negative impact sizes or relative risks below 1.

Statistical analysis

Crude odds ratios and 95% confidence intervals were estimated. Cochrane RevMan version 5.4.1 was used to calculate the pooled common odds ratios and corresponding confidence intervals. The level of heterogeneity among the studies determined whether a fixed- or random-effects model was used for the pooled analysis.

Results

Article selection

Of the 1100 retrieved studies, 242 duplicates were excluded. Titles, abstracts and full-text reviews were screened, and 11 studies including 77 611 386 pregnant patients were eligible (figure 1) [32–42]. Although two studies with overlapping data were identified [32, 35], as the outcomes of each study were different, both studies were included in the analysis. A total of three studies used the National Inpatient Sample and the study durations overlapped (Friedman *et al.* [33] (2000–2018), Baghlaf *et al.* [38] (2003–2011) and Macmullen *et al.* [43] (2001)). One study was excluded due to overlapping study duration [43] and another was included only for the analysis of FGR [38]. The included studies and their metadata are summarised in supplemental table S1 [32–43] and table 1 [32–42], respectively. References in eligible studies were examined and no additional relevant literature was identified.

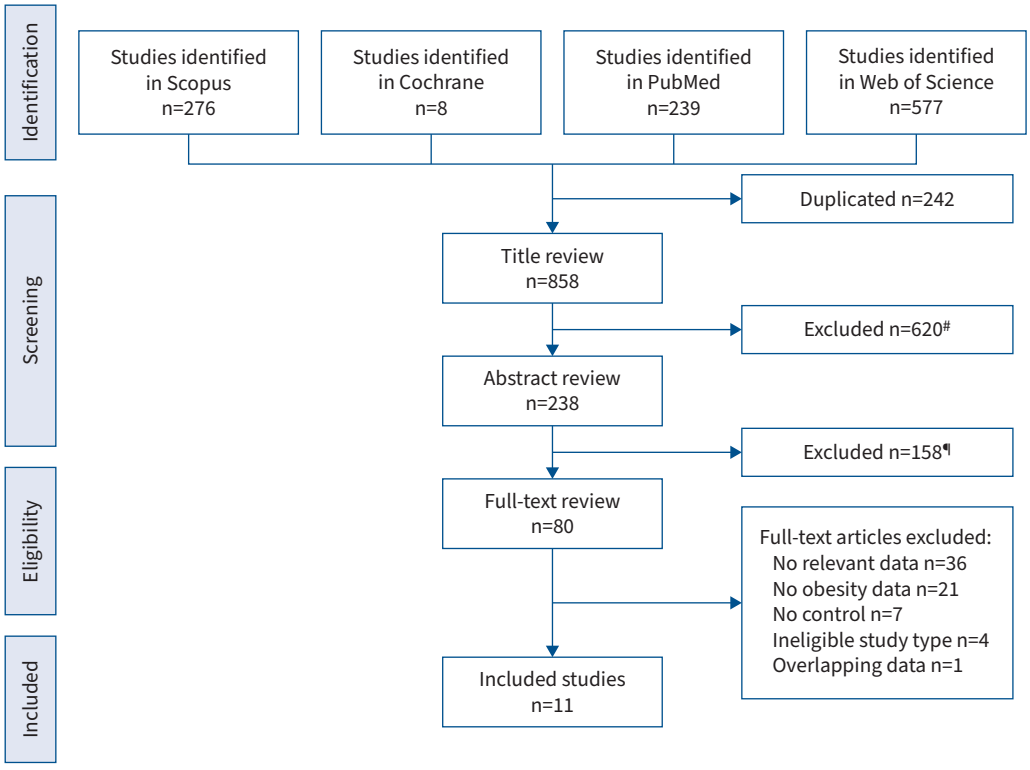


FIGURE 1 Scheme of the systematic literature search and study selection. #: During the title screening, 620 studies were excluded because they were nonasthma studies, nonpregnancy studies, ineligible study types or non-English articles. ¶: During the abstract screening, 158 studies were excluded because they were nonasthma studies, nonpregnancy studies, noncomparative studies, studies on asthma in childhood, ineligible study types or had no relevant outcomes.

TABLE 1 Summary of eligible studies

First author [ref.]	Year	n	Exp	Cont	n (exp)	n (cont)	Prevalence	Obesity prevalence
Stevens [32]	2022	299	Obesity	No obesity	91	102	NA	NA
Friedman [33]	2022	73 109 790	Asthma	No asthma	2 221 644	70 888 146	3.0%	4.1%
Bokern [34]	2021	1461	Exa	No exa	135	1326	NA	NA
Stevens [35]	2021	400	Asthma	No asthma	299	101	NA	NA
Yland [36]	2020	4 217 382	Asthma	No asthma	190 520	4 026 862	4.5%	2.9%[#]
Robijn [37]	2020	33 829	Exa	No exa	1430	32 399	NA	NA
Baghlaf [38]	2019	7 772 999	Asthma	No asthma	NA	NA	NA	NA
Murphy [39]	2017	164	Obesity	No obesity	66	45	NA	NA
Rejnö [40]	2014	284 214	Asthma	No asthma	26 586	257 628	9.4%	10.8%
Thuot [41]	2013	1386	Obesity	No obesity	225	888	NA	NA
Hendler [42]	2006	1772	Obesity	No obesity	542	1230	NA	NA
Cumulative	NA	77 611 386	Asthma	No asthma	2 438 750	75 172 636	3.1%	4.1%

Numbers or percentages are shown. [#]: Including overweight. Cumulative: cumulative rate of asthma [33, 36, 40]; cont: control group; exa: exacerbation; exp: experimental group; Obesity prevalence: the prevalence of obesity among pregnant patients; NA: not applicable.

Characteristics of the included studies

All 11 studies used a retrospective design and were published between 2006 and 2022 (table 1). Randomised controlled studies were not identified. Studies were conducted in the US (n=5; 45.5%) [32, 33, 35, 36, 42], Australia (n=3; 27.2%) [34, 37, 39], Canada (n=1; 9.1%) [38], France (n=1; 9.1%) [41] and Sweden (n=1; 9.1%) [40], and were comparator studies (supplemental table S1).

Risk of bias of included studies

Risk of bias assessments showed moderate bias (moderate quality) in seven studies [33, 34, 36–38, 40, 42] and severe bias (low quality) in four (supplemental table S2) [32, 35, 39, 41].

Primary outcomes

The rate of obesity and asthma during pregnancy in eligible studies

Three studies stated the number of asthma and obesity cases [33, 36, 40]. In these, the cumulative prevalence rate of asthma during pregnancy was 3.1% (2 438 750/77 611 386, range 3.0–9.4%) [33, 36, 40] and the prevalence of obesity among pregnant patients was 4.1% (3 159 640/77 611 386, range 2.9–10.8%).

Association between obesity and asthma during pregnancy

Pooled random-effects analysis in two studies showed that pregnant women with obesity were more likely to have asthma than those without obesity (n=2; OR 2.42, 95% CI 1.14–5.15) (figure 2a) [33, 40].

Association between obesity and uncontrolled asthma during pregnancy

Six studies examined the prevalence of uncontrolled asthma in pregnant women with asthma with and without obesity (table 2). Three compared well-controlled and uncontrolled asthma during pregnancy and the others compared pregnant patients with asthma who did or did not experience severe exacerbations during pregnancy. Patients were classified by obesity status in the pooled analysis comparing uncontrolled asthma rates between pregnant women with and without obesity (n=6; OR 1.29, 95% CI 1.11–1.50) (figure 2b).

Secondary outcomes

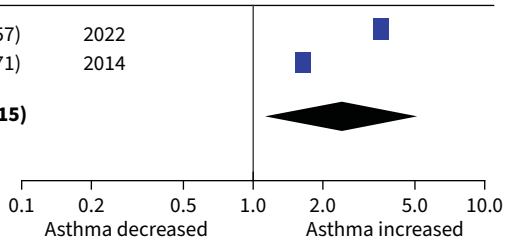
Effect of asthma on obstetric outcomes

The effect of asthma on obstetric outcomes was evaluated in eight studies (supplemental table S1, table 3). Unadjusted pooled random-effects analysis revealed that women with asthma were more likely to have hypertensive disorders of pregnancy (HDP) (n=2; OR 1.45, 95% CI 1.17–1.78), large for gestational age (LGA) (n=1; OR 1.10, 95% CI 1.03–1.17) and FGR (n=3; OR 1.28, 95% CI 1.15–1.42) (figures 3a and 3e), whereas the prevalence of gestational diabetes mellitus (GDM) (n=2; OR 1.22, 95% CI 0.99–1.49) was comparable between both groups (figure 3c). In the adjusted analysis, asthma was associated with an increased risk of HDP (n=3; adjusted OR (aOR) 1.21, 95% CI 1.10–1.34), GDM (n=3; aOR 1.14, 95% CI 1.04–1.26) and FGR (n=2; aOR 1.18, 95% CI 1.15–1.21) (figures 3b, 3d and 3f). The prevalence of LGA was lower in pregnant women with asthma compared to those without (n=1; aOR 0.93, 95% CI 0.86–0.99).

a) The rate of asthma in pregnant patients with and without obesity

Study	Obesity Asthma (n)	Obesity Total (n)	No obesity Asthma (n)	No obesity Total (n)	Weight	Odds ratio M-H, random, 95% CI	Year
Friedman *et al*. [33]	277078	3007996	1944566	70101794	50.0%	3.56 (3.54–3.57)	2022
Rejnö *et al*. [40]	4222	30693	22364	253521	50.0%	1.65 (1.59–1.71)	2014
Total (95% CI)		**3038689**		**70355315**	**100.0%**	**2.42 (1.14–5.15)**	
Total events	**281300**		**1966930**				

Heterogeneity: Tau^2=0.30; Chi^2=1805.52, df=1 (p< 0.00001); I^2=100%
Test for overall effect: Z=2.30 (p=0.02)



b) The rate of uncontrolled asthma in pregnant patients with and without obesity

Study	Obesity Unc (n)	Obesity Total (n)	No obesity Unc (n)	No obesity Total (n)	Weight	Odds ratio M-H, random, 95% CI	Year
Stevens *et al*. [32]	58	536	34	450	8.6%	1.48 (0.95–2.31)	2022
Bokern *et al*. [34]	56	91	38	102	5.6%	2.69 (1.50–4.83)	2021
Yland *et al*. [36]	4230	11432	61185	179088	33.9%	1.13 (1.09–1.18)	2020
Robijn *et al*. [37]	313	6012	1117	27817	27.7%	1.31 (1.15–1.49)	2020
Murphy *et al*. [39]	19	66	30	98	4.2%	0.92 (0.46–1.82)	2017
Hendler *et al*. [42]	190	521	359	1172	20.1%	1.30 (1.05–1.62)	2006
Total (95% CI)		**18658**		**208727**	**100.0%**	1.29 (1.11–1.50)	
Total events	**4866**		**62763**				

Heterogeneity: Tau^2=0.02; Chi^2=15.77, df=5 (p=0.008); I^2=68%
Test for overall effect: Z=3.34 (p=0.0008)

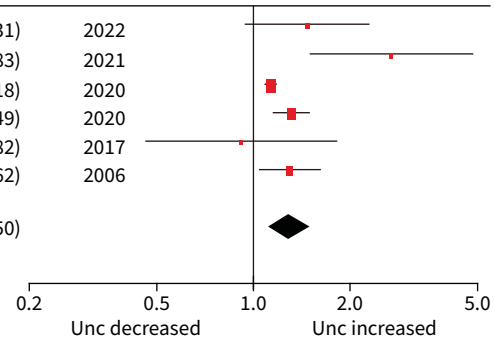


FIGURE 2 Meta-analysis of the association between obesity and asthma during pregnancy. The prevalence of a) asthma in pregnant women with and without obesity and b) the prevalence rates of uncontrolled asthma in pregnant women with and without obesity. Heterogeneity among the studies in each analysis was determined and a random-effects analysis was performed because of considerable heterogeneity (a) I^2=100%; b) I^2=68%). Some of the values listed above might be slightly different from the original values because of the calculations in RevMan^{TM} version 5.4.1. IV: inverse variance; M-H: Mantel–Haenszel test; Unc: uncontrolled asthma.

Effect of asthma on delivery outcomes

The effect of asthma on delivery outcomes, including preterm birth (PTB), caesarean delivery (CD) and postpartum haemorrhage (PPH), was investigated in four studies (table 4). On unadjusted pooled random-effects analysis, pregnant women with asthma were more likely to have PTB (n=3; OR 1.28, 95% CI 1.27–1.30), CD (n=2; OR 1.31, 95% CI 1.30–1.33), elective CD (n=1; OR 1.31, 95% CI 1.25–1.38) and emergent CD (n=1; OR 1.34, 95% CI 1.29–1.39) compared with those without asthma, whereas the rate of PPH was comparable between the two groups (n=2; OR 1.14, 95% CI 0.92–1.41) (figures 4a, 4c and 4e). Similarly, the adjusted pooled random-effects analysis revealed that asthma was associated with an increased rate of PTB (n=2; aOR 1.26, 95% CI 1.25–1.27), CD (n=3; aOR 1.22, 95% CI 1.11–1.33),

TABLE 2 The association between obesity and uncontrolled asthma during pregnancy

First author [ref.]	Year	n	Uncontrolled asthma[#]	
			Obesity	No obesity
Stevens [32][¶]	2022	299	56 (61.5)	38 (37.3)
Bokern [34][+]	2021	1461	58 (10.8)	34 (7.6)
Yland [36][¶]	2020	4 217 382	4230 (37.0)	61 185 (34.2)
Robijn [37][+]	2020	33 829	313 (5.2)	1117 (4.0)
Murphy [39][¶]	2017	164	19 (28.8)	30 (30.6)
Hendler [42][+]	2006	1693	190 (36.5)	359 (30.5)

Numbers (percentages per column) are shown. [#]: The rate of uncontrolled asthma among pregnant women with and without obesity. [¶]: Well-controlled *versus* poorly controlled. [+]: Severe exacerbation *versus* no severe exacerbation.

TABLE 3 The effect of asthma on the rate of obstetric outcomes

First author [ref.]	Year	HDP		GDM		LGA		FGR	
		OR	aOR	OR	aOR	OR	aOR	OR	aOR
Asthma *versus* no asthma									
Friedman [33]	2022	1.60 (1.58–1.63)	1.29 (1.26–1.30)[#]	1.34 (1.32–1.36)	1.20 (1.18–1.21)[#]	NA	NA	NA	NA
Yland [36]	2020	NA	NA	NA	NA	NA	NA	1.25 (1.22–1.29)[++]	NA
Baghlaf [38]	2019	NA	NA	NA	NA	NA	NA	1.42 (1.38–1.45)	1.17 (1.14–1.21)
Rejnö [40]	2014	1.30 (1.21–1.39)[¶]	1.15 (1.06–1.24)[¶,+]	1.22 (1.10–1.34)	1.09 (0.99–1.20)[+]	1.10 (1.03–1.17)	0.93 (0.86–0.99)[+]	1.16 (1.07–1.25)	1.23 (1.13–1.33)[+]
Hendler [42]	2006	NA	1.1 (0.8–1.5)	NA	0.8 (0.5–1.4)	NA	NA	NA	NA
Well *versus* uncontrolled asthma									
Yland [36]	2020	NA	NA	NA	NA	NA	NA	1.21 (1.10–1.33)[++]	NA
Rejnö [40]	2014	1.10 (0.89–1.35)	1.01 (0.81–1.26)[+]	0.99 (0.76–1.30)	0.97 (0.73–1.30)[+]	0.74 (0.60–0.91)	0.65 (0.52–0.81)[+]	1.68 (1.35–2.08)	1.71 (1.34–2.17)[+]
Obesity *versus* nonobesity (pregnant women with asthma)									
Murphy [39]	2017	0.73 (0.17–3.01)	NA	4.35 (1.11–17.08)	NA	NA	NA	NA	NA
Thuot [41]	2013	NA	NA	NA	NA	0.57 (0.35–0.92)[§]	1.2 (0.7–2.1)[§,f]	0.5 (0.3–0.8)[§]	0.6 (0.4–1.0)[§,##]
Hendler [42]	2006	NA	1.7 (1.3–2.3)[¶¶]	NA	4.2 (2.8–6.3)[¶¶]	NA	NA	NA	NA

Regarding maternal complications, unadjusted odds ratios (OR) or adjusted odds ratios (aOR) with corresponding 95% confidence intervals are shown. FGR: fetal growth restriction; GDM: gestational diabetes mellitus; HDP: hypertensive disorders of pregnancy; LGA: large for gestational age; NA: not applicable. [#]: Adjusted for year of delivery, maternal race, maternal age, payer, ZIP code income quartile, obesity, pregestational diabetes, chronic hypertension, singleton compared with multiple gestation, prior caesarean delivery and obesity. [¶]: Including eclampsia. [+]: Adjusted for age, body mass index (BMI), parity, smoking at antenatal care admission, country of birth, cohabitation/marital status and level of education. [§]: BMI >30 kg·m^{-2} *versus* BMI 18.5–25.0 kg·m^{-2}. [f]: Adjusted for number of years of education attained at delivery, nullipara, gestational diabetes and maternal weight during pregnancy. [##]: Adjusted for maternal age at the beginning of pregnancy, nullipara, maternal weight gain during pregnancy, low birthweight infant before the current delivery and maternal cigarette smoking during pregnancy. [¶¶]: Adjusted for obesity, asthma severity class (control, mild, moderate–severe), maternal age, African-American ethnicity, Hispanic ethnicity, chronic hypertension, pregestational diabetes and parity. [++]: Calculated by the authors.

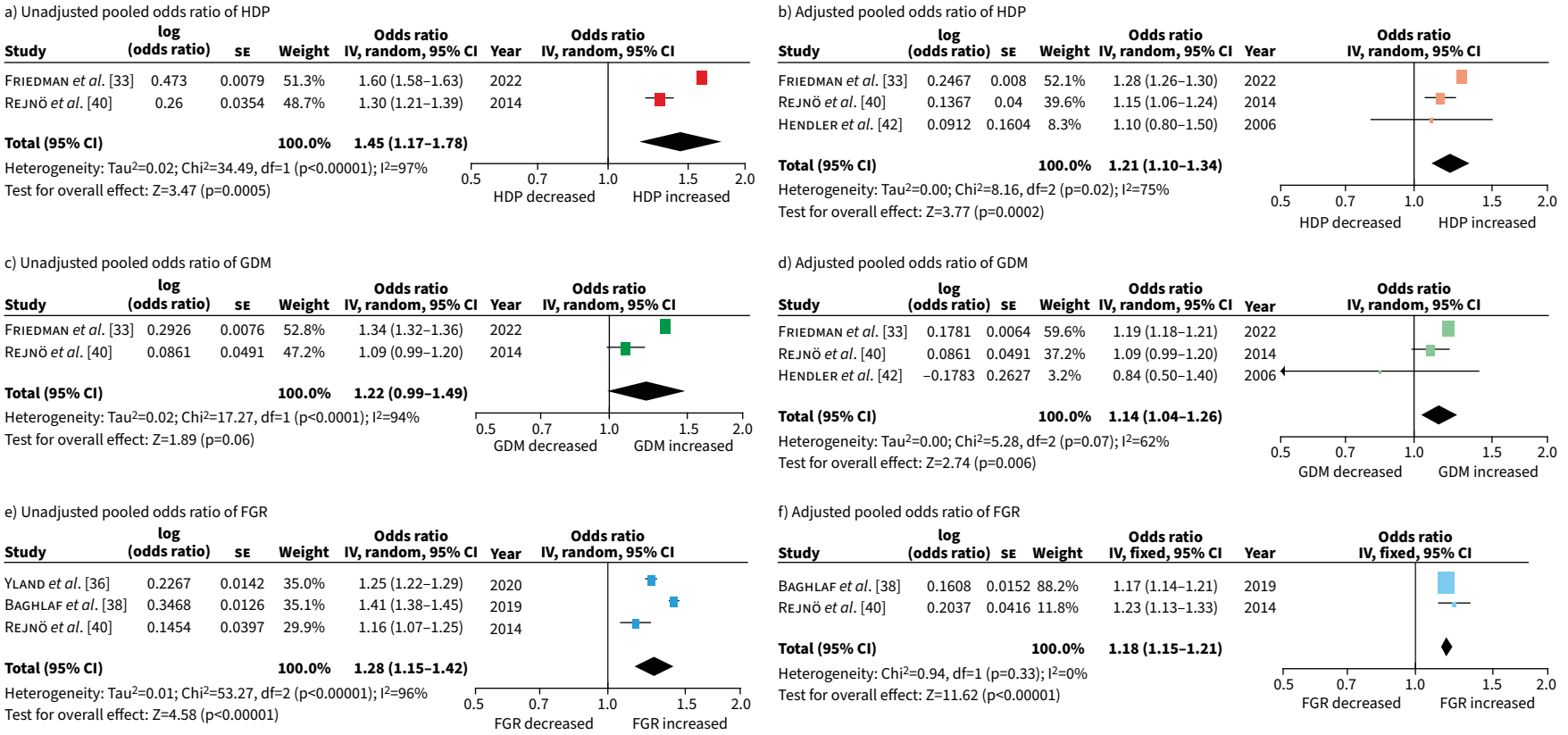


FIGURE 3 Meta-analysis of the effect of asthma on obstetric outcomes. Pooled odds ratios for a) unadjusted and b) adjusted analyses for hypertensive disorders of pregnancy (HDP), c) unadjusted and d) adjusted analyses for gestational diabetes mellitus (GDM), e) unadjusted and f) adjusted analyses for fetal growth restriction (FGR) are shown. Heterogeneity among the studies in each analysis was determined. Random-effects analysis was performed due to the considerable heterogeneity (a) I^2=97%; b) I^2=75%; c) I^2=94%; d) I^2=62%; e) I^2=96%). In the analysis with no heterogeneity (f) I^2=0%), a fixed analysis was applied. Some values listed above might be slightly different from the original values because of the calculation in Revman™ version 5.4.1. IV: inverse variance; M-H: Mantel–Haenszel test.

TABLE 4 The effect of asthma on the rate of delivery outcomes

First author [ref.]	Year	PTB		CD		PPH	
		OR	aOR	OR	aOR	OR	aOR
Asthma *versus* no asthma							
Friedman [33]	2022	1.29 (1.26–1.31)	1.27 (1.25–1.29)[#]	1.31 (1.29–1.33)	1.16 (1.15–1.18)[#]	1.27 (1.24–1.30)	1.21 (1.19–1.24)[#]
Yland [36]	2020	1.29 (1.26–1.31)	NA	NA	NA	NA	NA
Rejnö [40]	2014	1.26 (1.20–1.33)[¶]	1.24 (1.17–1.31)[¶]	1.33 (1.29–1.37)[¶]	1.29 (1.24–1.33)[¶]	1.03 (0.97–1.08)	1.03 (0.97–1.09)
Hendler [42]	2006	NA	1.1 (0.9–1.5)	NA	1.2 (0.9–1.5)	NA	NA
Well *versus* uncontrolled asthma							
Yland [36]	2020	1.12 (1.05–1.18)	NA	NA	NA	NA	NA
Rejnö [40]	2014	1.05 (0.89–1.23)[¶]	1.02 (0.87–1.21)[¶,+]	1.18 (1.08–1.29)[¶,§]	1.09 (0.99–1.20)[¶,f,+]	0.98 (0.83–1.15)	1.03 (0.86–1.24)[+]
Obesity *versus* nonobesity (pregnant women with asthma)							
Murphy [39]	2017	1.77 (0.64–4.85)	NA	2.08 (1.03–4.22)	NA	1.51 (0.36–6.26)	NA
Thuot [41]	2013	0.82 (0.50–1.37)[##]	0.7 (0.4–1.2)[##,¶¶]	NA	NA	NA	NA
Hendler [42]	2006	NA	0.8 (0.6–1.0)[++]	NA	1.6 (1.3–2.0)[++]	NA	NA

Regarding maternal complications, unadjusted odds ratios (OR) or adjusted odds ratios (aOR) with corresponding 95% confidence intervals are shown. CD: caesarean delivery; NA: not applicable; PPH: postpartum haemorrhage; PTB: preterm birth. [#]: Adjusted for year of delivery, maternal race, maternal age, payer, ZIP code income quartile, obesity, pregestational diabetes, chronic hypertension, singleton compared with multiple gestation, prior CD and obesity. [¶]: Calculated by the authors. [+]: Adjusted for age, body mass index (BMI), parity, smoking at antenatal care admission, country of birth, cohabitation/marital status and level of education. [§]: Elective CD 1.13 (0.99–1.30), emergent CD 1.21 (1.08–1.36). [f]: Elective CD 0.99 (0.85–1.14), emergent CD 1.18 (1.04–1.33). [##]: BMI >30 kg·m^{-2} *versus* BMI 18.5–25.0 kg·m^{-2}. [¶¶]: Adjusted for high-risk pregnancy, pregnancy-induced hypertension, number of prenatal visits, maternal weight gain during pregnancy, premature infant before current delivery and maternal cigarette smoking during pregnancy. [++]: Adjusted for obesity, asthma severity class (control, mild, moderate–severe), maternal age, African-American ethnicity, Hispanic ethnicity, chronic hypertension, pregestational diabetes and preterm labour.

elective CD (n=1; aOR 1.29, 95% CI 1.22–1.36) and emergent CD (n=1; OR 1.29, 95% CI 1.23–1.34), whereas the rate of PPH was similar (n=2; OR 1.12, 95% CI 0.95–1.32) in pregnant women with asthma compared with those without (figures 4b, 4d and 4f).

A study examining the effect of asthma on SMM found that pregnant women with asthma were more likely to have SMM in the unadjusted (n=1; OR 1.76, 95% CI 1.70–1.82) and adjusted analyses (n=1; aOR 1.50, 95% CI 1.45–1.55) [33]. No study examined the specific outcome of SMM in pregnant obese women with asthma compared with that in pregnant nonobese women with asthma.

Effect of uncontrolled asthma on obstetric and delivery outcomes

The effects of uncontrolled asthma on obstetric and delivery outcomes were determined in two studies [36, 40]. The risk of HDP, GDM, LGA, PTB, CD, elective CD and PPH was similar between pregnant women with well-controlled and uncontrolled asthma, whereas uncontrolled asthma was associated with increased rate of FGR in unadjusted (n=2; OR 1.27, 95% CI 1.17–1.39) and adjusted (n=1; aOR 1.71, 95% CI 1.34–2.17) pooled analyses (tables 3–4). Pregnant patients with uncontrolled asthma were more likely to have emergent CD in unadjusted (n=1; OR 1.21, 95% CI 1.08–1.36) and adjusted (n=1; aOR 1.18, 95% CI 1.04–1.33) pooled analyses (tables 3–4). No studies examined the specific outcomes of pregnant women with obesity and uncontrolled asthma compared with those of pregnant obese women with well-controlled asthma.

Effects of obesity on obstetric and delivery outcomes in pregnant women with asthma

The effects of obesity on obstetric and delivery outcomes in pregnant women with asthma were assessed in three studies [39, 41, 42]. One study found that pregnant women with both asthma and obesity were more likely to have GDM (n=1; OR 4.35, 95% CI 1.11–17.08) and CD (n=1; OR 2.08, 95% CI 1.03–4.22) than those with asthma but without obesity. However, the prevalence rates of HDP (n=1; OR 0.73, 95% CI 0.17–3.01), PTB (n=2; OR 1.06, 95% CI 0.53–2.11) and PPH (n=1; OR 1.51, 95% CI 0.36–6.26) were similar between both groups after unadjusted pooled analysis (tables 3–4).

Adjusted analysis showed comparable prevalence rates of LGA (n=1; aOR 1.2, 95% CI 0.7–2.1) and FGR (n=1; aOR 0.60, 95% CI 0.4–1.0) between both groups, whereas women with obesity were less likely to have PTB (n=2; aOR 0.76, 95% CI 0.60–0.96). Unlike the unadjusted analysis, obesity was associated with an increased rate of HDP in pregnant women with asthma (n=1; aOR 1.7, 95% CI 1.3–2.3). Obesity was also associated with higher odds of GDM (n=1; aOR 4.2, 95% CI 2.8–6.3) and CD (n=1; aOR 1.6, 95% CI 1.3–2.0) in pregnant women with obesity than in those without obesity in the adjusted analysis (tables 3–4).

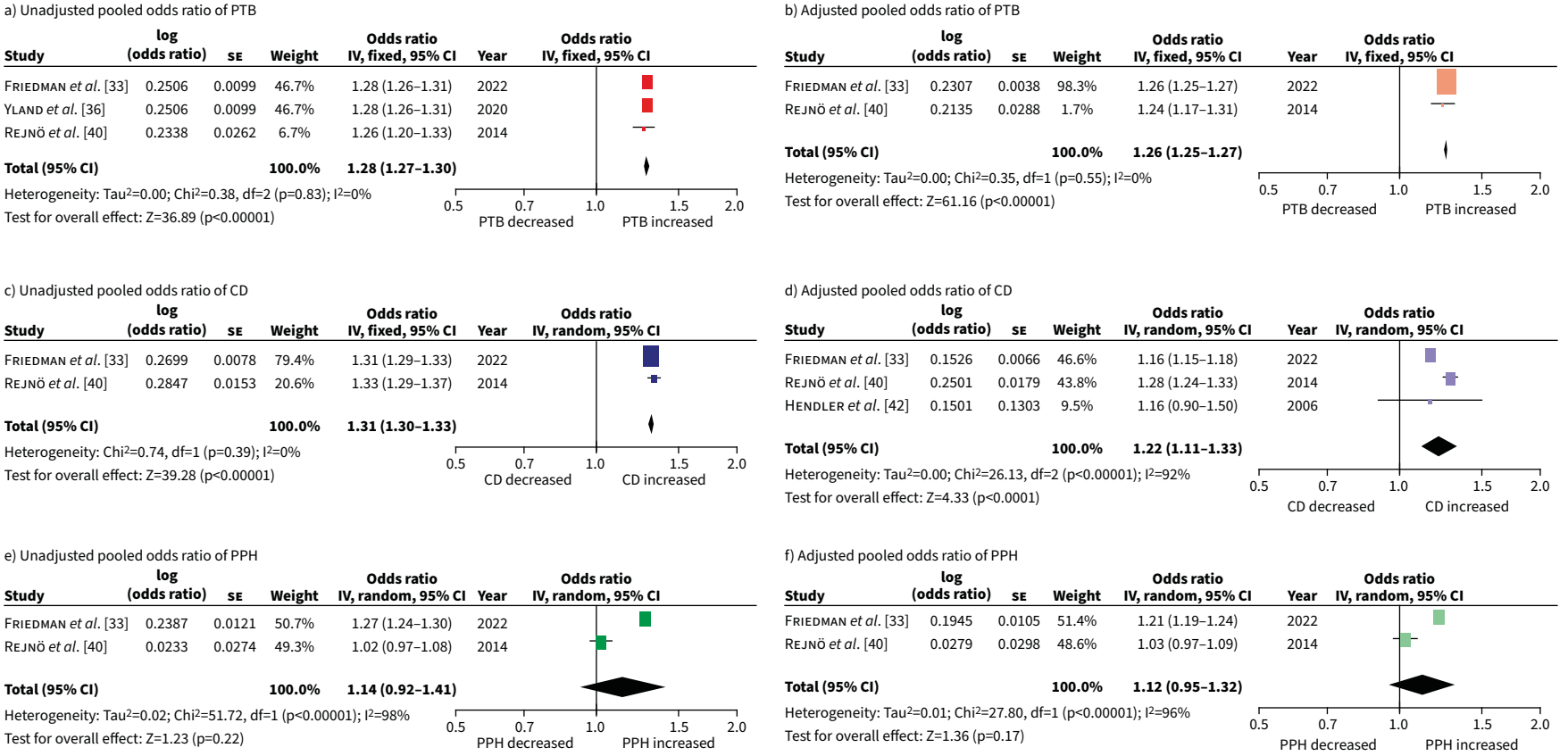


FIGURE 4 Meta-analysis of the effect of asthma on delivery outcomes. Pooled odds ratios for a) unadjusted and b) adjusted analyses for preterm birth (PTB), c) unadjusted and d) adjusted analyses for caesarean delivery (CD), and e) unadjusted and f) adjusted analyses for postpartum haemorrhage (PPH) between pregnant women with and without asthma. Heterogeneity among the studies in each analysis was determined. Random-effects analysis was applied due to the considerable heterogeneity among the studies (d) I^2=92%; e) I^2=98%; f) I^2=96%). In an examination of no heterogeneity (a, b and c) I^2= 0%), a fixed pooled analysis was performed. Some values listed above might be slightly different from the original values because of the calculation in Revman™ version 5.4.1. IV: inverse variance; M-H: Mantel–Haenszel test.

Discussion

Key findings

First, obesity was associated with an increased prevalence of asthma during pregnancy. Pregnant women with concurrent asthma and obesity were more likely to develop uncontrolled asthma than those without obesity. Second, asthma with or without obesity was a significant risk factor for adverse obstetric and delivery outcomes. Notably, pregnant women with asthma had an increased rate of SMM compared to those without asthma. Third, obesity was associated with increased odds of HDP, GDM and CD among pregnant women with asthma. Fourth, no study assessed the management or medication guidelines for patients with concurrent asthma and obesity during pregnancy.

Comparison with existing literature

Primary outcome: effect of obesity on asthma prevalence and uncontrolled asthma during pregnancy

Obesity is a major risk factor for developing asthma, with a higher prevalence in these individuals than in the general population [44]. People with obesity often have severe asthma and recent US studies report that 60% of adults with severe asthma are obese [22, 44]. In this study, obesity was linked to an increased asthma prevalence during pregnancy. A recent systematic review and meta-analysis also identified obesity as an important risk factor for asthma exacerbation during pregnancy [23]. In this study, uncontrolled asthma was defined as routinely uncontrolled asthma or severe exacerbations that could affect perinatal prognosis. We found an association between uncontrolled asthma and obesity, indicating that obesity influenced asthma and uncontrolled asthma prevalence in pregnant women. Therefore, obese pregnant women with asthma should be closely monitored for asthma control.

The relationship between obesity and asthma is complex and bidirectional [45]. The higher prevalence of asthma in obese women compared to nonobese women can be attributed to several factors, namely 1) inflammation, 2) mechanical factors, 3) hormonal factors, 4) comorbidities, 5) lifestyle factors, 6) gut microbiome and 7) genetic factors [46, 47]. Obesity is associated with systemic inflammation due to the increased production of pro-inflammatory cytokines by adipose tissue [23]. Increased body weight can lead to reduced lung volumes, a higher rate of comorbidities and increased production of leptin, which has been linked to increased airway hyperactivity and inflammation contributing to asthma [48]. Since pregnant women, especially obese pregnant patients [20, 49], have higher adipose tissue [50], reduced lung volumes [51] and higher levels of leptin [52, 53], these characteristics alone may worsen asthma during pregnancy. Since previous studies do not address the impact of obesity on the worsening of asthma during pregnancy, future studies are warranted to determine the mechanisms behind this exacerbation.

Excessive weight gain during pregnancy may worsen asthma control; however, limited information was available. One of the 11 studies reported that excessive first trimester gestational weight gain was associated with more frequent activity limitations in the first trimester and inhaler use across pregnancy [32]. However, this study reported few associations between gestational weight gain and lung function, except for an improvement in percent predicted peak flow with excessive gestational weight gain during the second trimester [32]. The mechanism by which weight gain during pregnancy affects asthma is unclear and more research is needed on its effects on asthma and obesity.

Secondary outcomes: effect of asthma on obstetric outcomes, SMM and delivery outcomes

These findings indicate the need to consolidate our understanding of the effects of obesity on obstetric and perinatal outcomes in pregnant women with asthma. Concurring with our findings, Friedman *et al.* [33] found that pregnant women with asthma had an increased risk of SMM, pre-eclampsia, gestational hypertension, PPH, CD, GDM, venous thromboembolism and preterm delivery compared to pregnant women without asthma. Therefore, asthma is a significant risk factor for adverse obstetric outcomes. However, as these outcomes were not available in most studies, further studies are warranted to examine the effect of obesity on obstetric outcomes, SMM and delivery outcomes in pregnant women with asthma.

Co-secondary outcomes: obstetric and delivery outcomes in pregnant women with concurrent asthma and obesity

Three studies investigated the effect of obesity on obstetric and delivery outcomes in pregnant women with asthma [39, 41, 42]. Hendler *et al.* [42] reported obesity as a risk factor for HDP, GDM and CD among pregnant women with asthma. Conversely, Thuot *et al.* [41] found no significant negative interactions between maternal asthma, obesity and adverse perinatal outcomes. However, that study did not adjust for the asthma severity and included a limited number of pregnant women with concurrent asthma and obesity. Thus, evidence regarding the effect of obesity on obstetric and perinatal outcomes in pregnant women with asthma needs to be consolidated.

No study has examined the specific management of pregnant women with concurrent asthma and obesity. Scott *et al.* [54] found that the sputum neutrophil count was higher in patients with asthma and obesity than in those with asthma without obesity. Similarly, blood neutrophil count, bronchial submucosal eosinophil count and sputum interleukin 5 were all higher in patients with obesity [54]. Therefore, patients with concurrent asthma and obesity exhibit a different pattern of airway inflammation than patients with asthma without obesity; however, the underlying mechanisms are poorly understood. The development of a specific management strategy for asthma exacerbated by obesity is desirable, especially in pregnant women with concurrent asthma and obesity. Investigations on the effects of weight loss on uncontrolled asthma and perinatal outcomes in this subgroup would also provide valuable insights.

One review highlighted the relationship between systemic inflammation and endothelial dysfunction, which is a key factor in HDP [55]. Persistent inflammation, a characteristic of asthma, intensifies endothelial damage, disrupts vascular function and increases the likelihood of HDP [55]. Furthermore, intermittent hypoxia due to asthma exacerbations increases oxidative stress, contributing to endothelial dysfunction and a higher risk of HDP [56].

In this study, a lower rate of PTB was observed in pregnant women with obesity and asthma than in women with asthma but without obesity in the adjusted pooled analysis. The results may be due to the following reasons: 1) the possible lower rate of FGR and increased rate of GDM may be associated with a decreased rate of iatrogenic PTB due to FGR, 2) publication bias due to the limited number of eligible studies or 3) a reduced risk of PTB associated with asthma treatment, as previously reported [57]. Pregnant women with obesity may have an increased risk of uncontrolled asthma and a higher rate of medical treatment. We hypothesised that asthma treatment may reduce the rate of PTB; however, detailed information about asthma treatments were unavailable in eligible studies. This point is a limitation of this study and further studies examining the effects of obesity on neonatal outcomes in pregnant women with asthma are warranted.

Limitations

This study had some limitations. First, an inherent bias was introduced through the inclusion of retrospective studies and confounding variables. Other possible bias is heterogeneity of difference of rate of obstetric and delivery outcomes among the different countries. For instance, the rate of varies significantly between countries, ranging from 10 to 50% [58, 59]. In addition, limited information was available regarding elective and emergent CD in the present study. These factors may lead to severe bias; thus, careful evaluation is needed to interpret the results of this study. Second, none of the studies comprehensively analysed the effect of obesity on obstetric outcomes after adjusting for confounding factors. Consequently, a causal relationship between obesity and obstetric outcomes in pregnant patients with asthma has not yet been established.

Third, the definition of asthma during pregnancy was ambiguous and could have varied with study. Asthma during pregnancy may have included a new case of asthma during pregnancy and pre-existing asthma. Uncontrolled asthma may also have included various patterns. This makes it difficult to discuss the prevalence of two coexisting conditions that can influence the morbidity or disease trajectory of each other. Another concern is the accuracy of asthma diagnosis in population-based database in the US (National Inpatient Sample) and this is widely recognised as a limitation of the National Inpatient Sample [60]. In fact, although a higher rate of asthma during pregnancy has also been reported (5–10%) [61, 62], the study from Friedman *et al.* [33], which included the largest number of pregnant patients in this review, reported the rate of asthma as 3.0%. This study included the largest number of patients and had the greatest impact on the cumulative rate of asthma during pregnancy. These points may have introduced selection bias.

Fourth, information on asthma phenotyping or subclassifications were lacking in the present study. For instance, the role of obesity in late onset asthma is important and this information has therapeutic implications; however, these discussions were difficult to include because of limited information. Fifth, none of the studies provided information on changes in asthma control during pregnancy, potentially causing considerable heterogeneity in the meta-analysis.

Sixth, the presence of publication bias may have skewed the findings toward a positive association between obstetric outcomes and asthma. Since three studies used the National Inpatient Sample database, one was completely removed from the descriptive analysis and another was used only in the analysis of FGR. These studies had similar results; thus, we believe that this exclusion method was appropriate (supplemental tables S3–S6). Seventh, most studies did not specify the asthma medications used and steroid medication may affect obstetric outcomes. Finally, studies lacking information on obesity in

pregnant women with asthma were excluded. Thus, the relationship between asthma and obstetric outcomes may not have included all eligible studies.

Conclusion

Obesity influenced the prevalence of asthma and uncontrolled asthma during pregnancy. Asthma was associated with adverse obstetric and delivery outcomes, and obesity was a risk factor for HDP, GDM and CD in pregnant women with asthma. Evidence on the effect of obesity on uncontrolled asthma and obstetric and perinatal outcomes should be consolidated to guide the management of pregnant women with concurrent asthma and obesity.

Points for clinical practice

- Asthma in pregnancy can cause adverse outcomes, especially with obesity.
- Pregnancy with asthma and obesity may require close asthma management.
- Evidence on the effect of obesity on asthma and obstetric outcomes needs consolidation.
- Obesity influences the prevalence of asthma or uncontrolled asthma during pregnancy.
- Obesity may be a possible risk factor for HDP, GDM and CD in pregnant women with asthma.

Data sharing statement: The data on which this study is based are the published articles. Sh. Matsuzaki and H. Matsuzaki had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Provenance: submitted article, peer reviewed.

Ethics statement: As the current systematic review used publicly available and de-identified data, the Institutional Review Board of Osaka University has exempted our present study from the requirements of informed patient consent.

Author contributors: Sh. Matsuzaki and H. Matsuzaki cleaned and analysed the data. Sh. Matsuzaki created the figures and tables, literature overview, intellectual inputs, interpreted the results, edited the manuscript, and wrote the manuscript. H. Matsuzaki and Sh. Matsuzaki wrote the manuscript together. H. Matsuzaki and Sa. Matsuzaki contributed to the literature review and extracted the data. K. Mimura, A. Okada, Y. Ueda, K. Hiramatsu and M. Kodama contributed to the discussion and intellectual inputs, interpreted the results, and edited the manuscript. T. Hisa contributed to the study concept, interpreted the results, and revised the manuscript with others. Y. Ueda, H. Kage and M. Kodama supervised the team and reviewed and edited the manuscript. H. Matsuzaki and K. Fukuda designed the study, initiated the collaborations, reviewed and edited the manuscript. Sh. Matsuzaki is the corresponding author of the study. The manuscript's corresponding author (Sh. Matsuzaki) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflict of interest: All authors have nothing to disclose.

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