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# Effect of maternal asthma exacerbations on perinatal outcomes: a population-based study

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ABSTRACT

**Background:** Although there is a growing body of literature about the impact of asthma exacerbations during pregnancy on adverse perinatal outcomes, it is still unclear whether asthma exacerbations themselves or asthma severity are the driving factor for negative outcomes. This study aimed to estimate the associations between maternal asthma exacerbations and perinatal outcomes, and whether this differed by asthma treatment regime as a proxy for severity.

**Methods:** We included births of women with asthma in Sweden from July 2006 to November 2013 (n=33 829). Asthma exacerbations were defined as unplanned emergency visits/hospitalisations or a short course of oral corticosteroids. Adjusted odds ratios (aOR) were estimated for the associations between exacerbations during pregnancy and perinatal outcomes (small for gestational age (SGA), preterm birth, birthweight and mode of delivery), stratified by preconception treatment regime.

**Results:** Exacerbations occurred in 1430 (4.2%) pregnancies. Exacerbations were associated with reduced birthweight (aOR 1.45, 95% CI 1.24–1.70), and elective (aOR 1.50, 95% CI 1.25–1.79) and emergency caesarean section (aOR 1.35, 95% CI 1.13–1.61). Multiple exacerbations were associated with a 2.6-fold increased odds of SGA (95% CI 1.38–4.82). Amongst women treated prepregnancy with combination therapy (proxy for moderate–severe asthma), exacerbators were at increased odds of elective (aOR 1.69, 95% CI 1.30–2.2) and emergency (aOR 1.62, 95% CI 1.26–2.08) caesarean section, and SGA (aOR 1.74, 95% CI 1.18–2.57) *versus* non-exacerbators.

**Conclusion:** Maternal asthma exacerbations increase the risk of SGA and caesarean sections, particularly in women with multiple exacerbations or moderate–severe asthma. Adequate antenatal asthma care is needed to reduce exacerbations and reduce risks of poor outcomes.

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**Maternal asthma exacerbations are associated with lower birthweight and increased caesarean sections, particularly in women with moderate–severe asthma. Adequate antenatal asthma care is needed to reduce exacerbations and reduce risks of poor outcomes.** https://bit.ly/3kF4x8N

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## Background

Asthma is highly prevalent during pregnancy [1, 2]. Previous cohort studies have found increased risks of adverse perinatal outcomes for women with asthma, including preeclampsia, low birthweight (LBW) and an infant born small for gestational age (SGA) [1, 3, 4]. Placental alterations during pregnancy can result in adverse perinatal outcomes among pregnant women with asthma [5]. Another proposed mechanism to explain negative perinatal outcomes is reduced oxygen transport to the fetus due to the reduced ability of maternal lungs to inhale oxygen-rich air [6]. Asthma exacerbations during pregnancy may further reduce oxygen transport, potentially increasing the risk conferred to the fetus. Studying the implications of exacerbations in women with asthma is especially important given that women with asthma often reduce their medications in early pregnancy out of concern for the growing fetus [7], which may increase the risk of asthma exacerbations.

However, few studies have investigated the association between maternal asthma exacerbations and adverse perinatal outcomes [3, 8–11], and even less so in a large population-based dataset [8, 9, 11], all with different definitions for exacerbations. This is largely because exacerbations are difficult to measure as they are not often reported, and it is difficult to determine whether the risk of negative outcomes is attributable to exacerbations or asthma severity. Furthermore, increasing asthma severity can increase the occurrence of asthma exacerbations among pregnant women with asthma [12, 13]. Therefore, when investigating the association between asthma exacerbations during pregnancy and adverse perinatal outcomes, underlying asthma severity should be taken into account.

The aims of this study were: 1) to estimate the associations of maternal asthma exacerbations with perinatal outcomes among pregnant women with asthma; and 2) to investigate whether asthma severity (using preconception asthma treatment regime as a proxy measure) modifies these associations.

## Methods

Ethical approval for this study was obtained from the Regional Ethical Review Board in Stockholm, Sweden. All data were pseudonymised prior to analysis.

### *Study population*

For this population-based register study, women in Sweden who gave birth to a singleton between July 1, 2006 and November 30, 2013 were identified through the Swedish Medical Birth Register (MBR). The study population consisted of women with asthma identified from the Prescribed Drug Register (PDR) and the National Patient Register (NPR), linked through a personal identity number [14, 15]. Asthma was defined using an adjusted validated algorithm based on asthma diagnoses and dispensed medications [16] as: 1) planned specialist care visits with a diagnosis of asthma (ICD-10 J45/J46) 24 months before or during pregnancy identified in the NPR; 2) an unplanned emergency department (ED) visit or hospitalisation with a diagnosis of asthma in the 24 months before pregnancy identified in the NPR; 3) at least two dispensed inhaled corticosteroids (ICS, R03BA), leukotriene receptor antagonists (LTRA, R03DCO3) or long-acting β-2-agonists (β2)/ICS (R03AK), up to 24 months before or during pregnancy; or 4) three or more dispensed ICS, LTRA, long-acting β2/ICS or short-acting β2 (R03AC02/R0AC03/R03AC12/R03AC13) within a 12-month period up to 24 months before or during pregnancy. The validated algorithm was extended to 24 months prior to pregnancy to be able to capture women with mild asthma.

The start of pregnancy was determined based on the delivery date and the infant's gestational age at birth; where the gestational age was missing, the start of pregnancy was set to 280 days before delivery date [17].

We excluded women who migrated to Sweden during pregnancy and pregnancies where the infant had a congenital malformation.

### *Exposure: asthma exacerbations*

Exacerbations were defined as a hospitalisation or unplanned ED visit for asthma (ICD J45/J46) and/or a short oral corticosteroid (OCS) course for asthma during pregnancy, identified in the NPR. The written text of all OCS prescriptions dispensed during pregnancy were manually checked to determine indication. Only those for which the written text indicated an asthma exacerbation, or described a similar course but without a specific indication or condition, were categorised as prescribed for an asthma exacerbation. Several exacerbations occurring within 14 days were grouped as one event. Women experiencing exacerbations during pregnancy were further categorised as "one exacerbation" or "multiple exacerbations".

### *Outcome definition*

Outcome measures included: mode of delivery, birthweight, gestational age at birth – categorised as preterm (<37 weeks) and term (≥37 weeks) – and SGA (defined as mean minus 2 standard deviations).

Birthweight was categorised as low birthweight (⩽2499 g), reduced birthweight (2500–2999 g), normal birthweight (3000–3999 g) and increased birthweight (⩾4 g).

### Covariates

Covariates were selected based on directed acyclic graphs [18]. From the MBR we obtained maternal age at delivery, body mass index (BMI in kilogrammes per metre squared, calculated from height and weight, usually measured by the midwife at first antenatal visit), parity, self-reported smoking status and country of birth. From the longitudinal integration database for health insurance and labour market studies (LISA) we obtained highest level of maternal education at the start of pregnancy, as a proxy for socioeconomic status. Based on diagnoses for anxiety and/or depression from the NPR (ICD-10 F30-34/F38-42/F44-45/F48), and/or prescriptions for antidepressants (NO6A) or antianxiolytics (NO5B) from the PDR, both in the 24 months before and during pregnancy, we identified maternal mood disorders [19].

As a proxy for asthma severity, we stratified women based on asthma medication dispensed in the 24 months preconception. We did not use pregnancy prescriptions because it has been shown that pregnant women change their medication despite exacerbations or changes in symptoms [7]. Since the PDR started on July 1, 2005, women with a conception date prior to July 1, 2007 were excluded from the preconception treatment analysis due to potential misclassification of treatment category. Women were grouped based on no asthma medication prescriptions, short-acting β-agonists (SABA)-only medication ("mild asthma"), ICS monotherapy ("mild asthma"), ICS/long-acting β-agonist (LABA) combination therapy ("moderate–severe asthma") and other combinations of asthma medications. These groups correspond with treatment steps one to four of the Global Initiative for Asthma (GINA) guidelines during our study period (2006–2013) [20].

### Statistical analysis

We used logistic and multinomial regression analysis to estimate odds ratios with 95% confidence intervals for the outcomes associated with asthma exacerbations during pregnancy. Additionally, we estimated odds ratios for the exacerbation categories (once/multiple) compared to no exacerbations. Separate odds ratios were estimated for asthma exacerbations within each treatment strata using a logistic model with interaction effects between exacerbations and preconception treatment category.

For all analyses we estimated crude and adjusted odds ratios (aOR) for maternal age, BMI, parity, self-reported smoking, education level, country of birth and maternal health problems (missing values for 8.3% of the population). To determine the impact of the missing data, we estimated the crude effects in both the full study population and the complete cases. The estimates were similar and we therefore reported the full study population crude estimates. To account for women with more than one birth in the study period, the sandwich estimator for standard errors was used.

We conducted three sensitivity analyses: firstly, an analysis including a non-asthma population; secondly, separating the exacerbation types; and thirdly, an E-value calculation.

The E-value was calculated as

$$\text{E-value} = \text{aOR} + \sqrt{\text{aOR} \cdot (\text{aOR}1)}$$

to determine the magnitude of effect that a potential unmeasured confounder/set of confounders would need to have on both the exposure and the outcome to reduce the odds ratio estimates or the lower confidence interval limit to null [21]. All data were analysed with STATA 15.1 TC (StataCorp, College Station, TX, USA). We report our results using the guidance given by Lederer *et al.* [22].

## Results

We identified 807 625 births in the MBR. After exclusion of multiple gestations, congenital malformations, immigration during pregnancy (n=49 732, 6.2%) and pregnancies without asthma (n=724 064, 89.7%), the study population consisted of 33 829 pregnancies in 27 081 mothers with asthma. Of these, we identified 1703 asthma exacerbation exposure episodes in 1430 (4.2%) pregnancies (figure 1). Multiple exacerbations occurred in 192 (0.6%) pregnancies. One-third of women with an exacerbation had an exacerbation in trimester 3, 30% in trimester 1, 28% in trimester 2 and 10% had exacerbations in multiple trimesters. Of the 1703 exacerbations, 882 (51.8%) were identified based on OCS only, 621 (36.5%) were identified based on ED/hospitalisation only and 200 (11.7%) were identified based on both OCS and ED/hospitalisation.

Maternal characteristics in relation to maternal asthma exacerbations are shown in table 1. Women who experienced at least one exacerbation during pregnancy (exacerbators) had a higher mean BMI, were more

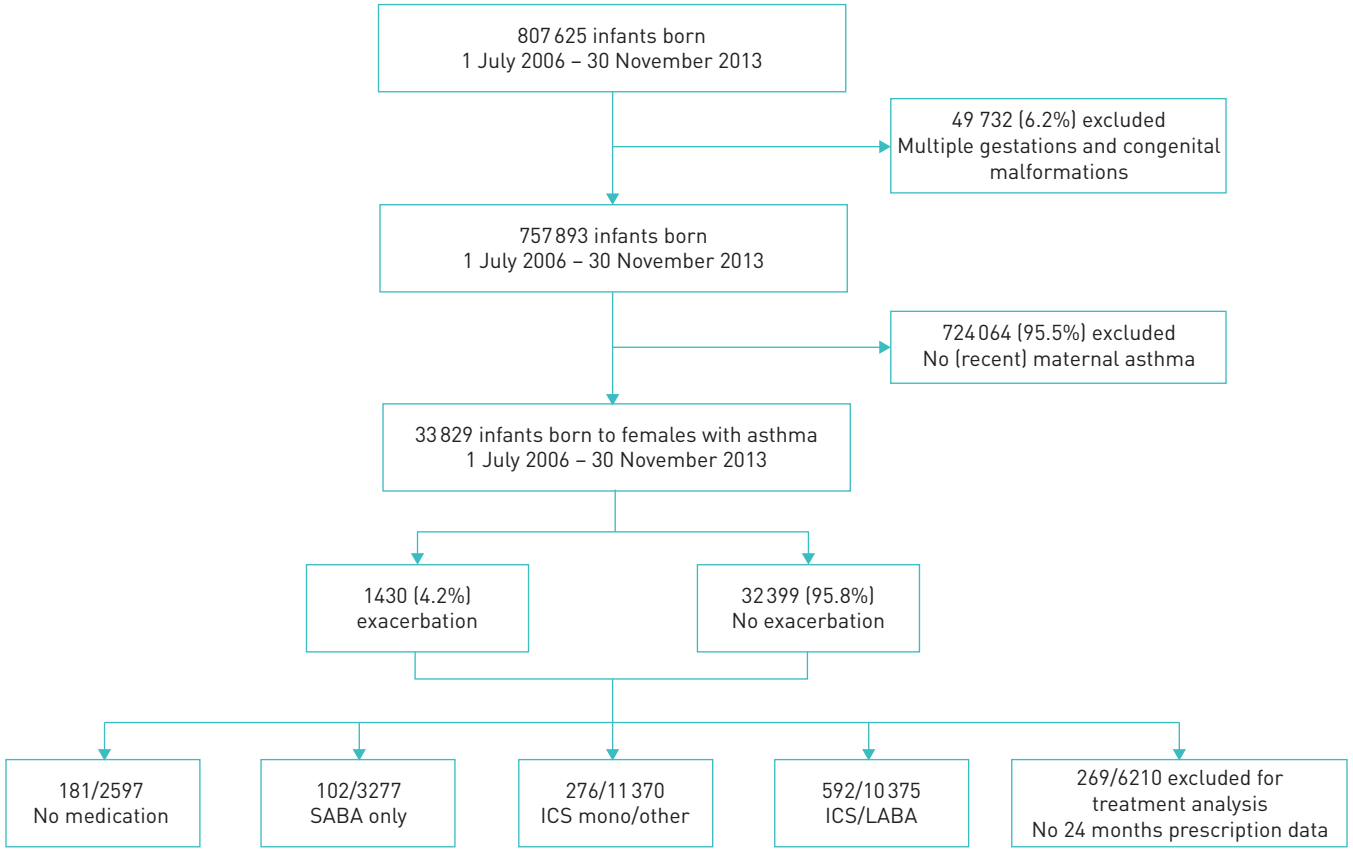


FIGURE 1 Study cohort flow diagram. For treatment groups, numbers displayed as n exacerbators/N total. SABA: short-acting-β2-agonists; ICS: inhaled corticosteroids; LABA: long-acting-β-agonist.

likely to be multiparous, to smoke, be born outside of Europe and have depression and/or anxiety than other women with asthma (non-exacerbators). There was no difference in ICS-only use between exacerbators (74.1%) and non-exacerbators (76.9%). However, more exacerbators were on ICS/LABA combinations preconception than non-exacerbators (51% *versus* 37%). Of the women who exacerbated in the ICS/LABA stratum, 14.5% had multiple exacerbations *versus* 11.8% and 11.9% in the SABA and ICS strata, respectively.

Maternal asthma exacerbations were associated with reduced birthweight (aOR 1.45, 95% CI 1.24–1.70), increased elective (aOR 1.50, 95% CI 1.25–1.79) and emergency (aOR 1.35, 95% CI 1.13–1.61) caesarean section, and increased SGA risk (aOR 1.28, 95% CI 0.94–1.75) compared to no exacerbations (table 2).

Both one exacerbation and multiple exacerbations increased the odds of reduced birthweight (aOR 1.39, 95% CI 1.17–1.65 and aOR 1.89, 95% CI 1.24–2.86, respectively) and the odds of having an elective caesarean section (aOR 1.37, 95% CI 1.13–1.67 and aOR 2.29, 95% CI 1.52–3.46, respectively) with a dose–response relationship. Multiple exacerbations increased the odds of babies being born SGA (aOR 2.58, 95% CI 1.38–4.82). Multiple exacerbations increased the odds of babies being born with a LBW (aOR 1.43, 95% CI 0.69–2.96), although the confidence interval crossed the null (table 3).

### *Preconception treatment analysis*

Stratification by preconception treatment regime as a proxy for asthma severity showed that for women on a single treatment regime – SABA only or ICS-only ("mild" asthma) – asthma exacerbations were not associated with worse perinatal outcomes (table 4), with the exception of reduced birthweight. In this case, among women who had been treated with SABA only, an exacerbation in pregnancy was associated with reduced birthweight (aOR 1.72, 95% CI 0.99–3.00), compared to no exacerbations. However, amongst women in the ICS/LABA treated group ("moderate/severe" asthma), experiencing an exacerbation during pregnancy increased the odds of being born SGA (aOR 1.74, 95% CI 1.18–2.57), reduced birthweight (aOR 1.65, 95% CI 1.29–2.24), LBW (aOR 1.54, 95% CI 1.05–2.24), and both elective and emergency caesarean section (aOR 1.69, 95% CI 1.30–2.20 and aOR 1.62, 95% CI 1.26–2.08, respectively), compared

TABLE 1 Baseline characteristics of pregnant women with asthma

| | No exacerbation | Exacerbation |
|---|---|---|
| **Subjects n** | 32399 | 1430 |
| **Maternal age at delivery years** | | |
| ⩽19 | 565 (1.7) | 22 (1.5) |
| 20–24 | 3989 (12.3) | 190 (13.3) |
| 25–29 | 8905 (27.5) | 366 (25.6) |
| 30–34 | 11078 (34.2) | 454 (31.7) |
| ⩾35 | 7862 (24.3) | 398 (27.8) |
| **Body mass index** | | |
| Underweight (<18 kg·m$^{-2}$) | 324 (1.0) | 15 (1.1) |
| Healthy weight (18–24 kg·m$^{-2}$) | 15591 (48.1) | 596 (41.7) |
| Overweight (25–29 kg·m$^{-2}$) | 8477 (26.2) | 390 (27.3) |
| Obese Class 1 (30–34 kg·m$^{-2}$) | 3646 (11.3) | 188 (13.1) |
| Obese ⩾Class 2 (⩾35 kg·m$^{-2}$) | 2053 (6.3) | 125 (8.7) |
| Missing | 2308 (7.1) | 116 (8.1) |
| **Parity** | | |
| 1 | 14918 (46.0) | 587 (41.0) |
| 2 | 11175 (34.5) | 489 (34.2) |
| ⩾3 | 6306 (19.5) | 354 (24.8) |
| **Cigarettes per day** | | |
| None | 28468 (87.9) | 1202 (84.0) |
| 1–9 | 1954 (6.0) | 106 (7.4) |
| ⩾10 | 746 (2.3) | 60 (4.2) |
| Missing | 1231 (3.8) | 62 (4.3) |
| **Country of birth** | | |
| Sweden | 28321 (87.4) | 1120 (78.3) |
| Nordic countries | 472 (1.5) | 20 (1.4) |
| Europe | 859 (2.7) | 44 (3.1) |
| Outside Europe | 2747 (8.5) | 246 (17.2) |
| **Maternal education** | | |
| ⩽9 years | 3475 (10.7) | 231 (16.1) |
| 10–12 years | 12476 (38.5) | 585 (40.9) |
| 13–14 years | 1749 (5.4) | 85 (5.9) |
| ⩾15 years | 14448 (44.6) | 504 (35.2) |
| Missing | 251 (0.8) | 25 (1.8) |
| **Depression/anxiety** | 6327 (19.5) | 377 (26.4) |
| **Treatment dispensed preconception** | | |
| SABA only[#] | 3175 (12.0) | 102 (8.8) |
| ICS monotherapy[#]/other mild asthma treatment combinations[#¶] | 11048 (41.9) | 286 (24.7) |
| ICS/LABA combination therapy[#] | 9783 (37.0) | 592 (51.0) |
| No medication[#] | 2416 (9.1) | 181 (15.6) |
| No 24-month preconception period | 5941 (18.3) | 269 (18.8) |

Data are presented as n (%), unless otherwise stated. ICS: inhaled corticosteroids; SABA: short-acting-β2-agonists; LABA: long-acting-β-agonist. [#]: percentage calculated based on 27619 pregnancies (1161 exacerbation) included for treatment analysis; [¶]: includes leukotriene receptor antagonist (LTRA) only, SABA+LABA and SABA+LTRA.

to no exacerbations (table 4 and figure 2). Women in the ICS/LABA group experiencing an exacerbation during pregnancy were also at increased risk of preterm birth (aOR 1.28, 95% CI 0.92–1.79), although the confidence interval crossed the null.

### *Sensitivity analyses*

Regardless of exacerbation status, women with asthma were at increased risk of adverse perinatal outcomes compared to women without asthma (table S1). Table S2 shows the association between the different exacerbation types and adverse perinatal outcomes. This analysis showed women treated with OCS for an asthma exacerbation were at increased risk of adverse perinatal outcomes.

Calculation of E-values found that the magnitude that potential unmeasured confounding would need to reduce the statistically significant odds ratio estimates to null ranged from OR=1.95 to 4.60 for the aORs and from 1.28 to 2.41 for the lower CI limits to fall below 1.00 (table S3).

TABLE 2 Odds ratios of maternal asthma exacerbations on adverse perinatal outcomes

| | No exacerbation | Exacerbation | OR (95% CI) | aOR[#] (95% CI) |
|---|---|---|---|---|
| **Subjects n** | 32399 | 1430 | | |
| **Birthweight categories** | | | | |
| ⩽2499 g | 1180 (3.6) | 60 (4.2) | 1.21 (0.92–1.59) | 1.02 (0.75–1.39) |
| 2500–2999 g | 3601 (11.1) | 224 (15.7) | 1.48 (1.27–1.72) | 1.45 (1.24–1.70) |
| 3000–3999 g[¶] | 21595 (66.7) | 909 (63.7) | Ref. | Ref. |
| ⩾4000 g | 5965 (18.4) | 235 (16.5) | 0.94 (0.81–1.09) | 0.94 (0.80–1.10) |
| Missing | 58 (0.2) | 2 (0.1) | | |
| **Preterm birth** | | | | |
| Yes | 1834 (5.7) | 85 (5.9) | 1.05 (0.84–1.32) | 1.00 (0.79–1.28) |
| Missing | 13 (0.04) | 2 (0.1) | | |
| **Small for gestational age** | | | | |
| Yes | 856 (2.6) | 52 (3.6) | 1.39 (1.05–1.85) | 1.28 (0.94–1.75) |
| Missing | 72 (0.2) | 3 (0.2) | | |
| **Mode of delivery** | | | | |
| Vaginal/instrumental | 25809 (79.7) | 1046 (73.1) | Ref. | Ref. |
| Elective caesarean section | 2807 (8.7) | 170 (11.2) | 1.49 (1.26–1.77) | 1.49 (1.24–1.78) |
| Emergency caesarean section | 3387 (10.5) | 187 (13.1) | 1.36 (1.16–1.60) | 1.32 (1.11–1.57) |
| Unknown caesarean section | 396 (1.2) | 27 (1.9) | | |

Data are presented as n (%), unless otherwise stated. [#]: adjusted for maternal smoking, obesity, education, country of birth, parity and depression/anxiety, and infant sex; [¶]: approximately mean±1SD in population.

## Discussion

To our knowledge, this is the largest population-based study reporting on the association of asthma exacerbations during pregnancy with perinatal outcomes including preconception asthma treatment stratification as proxy for asthma severity. Asthma exacerbations during pregnancy were associated with an increased risk of elective and emergency caesarean section, and an infant born SGA or with a reduced birthweight, compared to no exacerbations. Multiple exacerbations during pregnancy increased these risks further.

Although women with asthma are more likely to have a caesarean section [1], no previous studies have reported on the association between maternal asthma exacerbations and mode of delivery. Being born *via* caesarean section has also been associated with long-term risks for the child, including increased risk of asthma and allergy [23, 24]. In our study, the increased risk of having an elective caesarean section was a risk for all women who had exacerbations, but was even higher amongst women who experienced multiple exacerbations during pregnancy compared to women who exacerbated only once. Experiencing multiple asthma exacerbations may influence the decision of the obstetrician to recommend a caesarean section, or maternal preference.

A recently published study from Canada among women with asthma [9] found an increased risk of LBW (<2500 g) among those experiencing an exacerbation during pregnancy compared to those who did not. Although we did not find the same result for LBW in our main analysis, we did observe an association of LBW for the subgroup of women who had used ICS/LABA combination ("moderate/severe" asthma) and exacerbated in pregnancy. Furthermore, in the whole study population we did see that exacerbations were associated with a reduced birthweight (2500–3000 g), which was also true for the treatment subgroups of SABA only ("mild asthma") and combination therapy users ("moderate/severe" asthma). A previous study which investigated the relationship between maternal lung function measured by spirometry and fetal growth, suggested that one possible explanation of reduced birthweight among infants born to women with asthma is an impact of maternal hypoxia on infant birthweight [25]. During asthma exacerbations a state of maternal hypoxia might be present for an extended period of time and subsequently the lack of oxygen may affect fetal growth and development. However, this mechanistic factor has not been studied through direct assessment of hypoxia. Other possible mechanisms may include a direct effect of the asthma medication used [26], or upregulation of maternal inflammatory pathways [27], although there is limited evidence in the literature for specific mechanisms associated with reduced fetal growth.

In our study, women experiencing multiple exacerbations during pregnancy had a 2.6-fold increased risk of having an infant born SGA, and amongst women treated with ICS/LABA therapy preconception ("moderate/severe" asthma), asthma exacerbations were associated with a 1.7-fold increased risk of having an infant born SGA. This supports other studies which found increased risk of SGA among those with poorly controlled asthma *versus* well-controlled asthma in the 90 days prior to delivery (aRR 1.15, 95% CI 1.03–1.29) [8, 9].

TABLE 3 Odds ratios of maternal asthma exacerbation categories on adverse perinatal outcomes

| | No exacerbation | One exacerbation | | | Multiple exacerbations | | |
|---|---|---|---|---|---|---|---|
| | | Pregnancies | OR (95%CI) | aOR# (95%CI) | Pregnancies | OR (95%CI) | aOR# (95%CI) |
| **Subjects n** | 32399 | 1238 | | | 192 | | |
| **Birthweight categories** | | | | | | | |
| ⩽2499 g | 1180 (3.6) | 49 (4.0) | 1.14 (0.85–1.53) | 0.97 (0.69–1.35) | 11 (5.7) | 1.68 (0.90–3.12) | 1.43 (0.69–2.96) |
| 2500–2999 g | 3601 (11.1) | 191 (15.4) | 1.45 (1.24–1.70) | 1.39 (1.17–1.65) | 33 (17.2) | 1.65 (1.12–2.43) | 1.89 (1.24–2.86) |
| 3000–3999 g¶ | 21595 (66.7) | 789 (63.8) | Ref. | Ref. | 120 (62.8) | Ref. | Ref. |
| ⩾4000 g | 5965 (18.4) | 208 (16.8) | 0.95 (0.82–1.12) | 0.95 (0.80–1.13) | 27 (14.1) | 0.81 (0.54–1.24) | 0.85 (0.54–1.32) |
| Missing | 58 (0.2) | 1 (0.1) | | | 1 (0.5) | | |
| **Preterm birth** | | | | | | | |
| Yes | 1834 (5.7) | 71 (5.7) | 1.01 (0.79–1.29) | 0.95 (0.73–1.24) | 14 (7.3) | 1.31 (0.77–2.25) | 1.38 (0.78–2.43) |
| Missing | 13 (0.04) | 0 | | | 1 (0.5) | | |
| **Small for gestational age** | | | | | | | |
| Yes | 856 (2.6) | 40 (3.2) | 1.23 (0.89–1.70) | 1.11 (0.78–1.57) | 12 (6.3) | 2.48 (1.37–4.47) | 2.58 (1.38–4.82) |
| Missing | 72 (0.2) | 1 (0.1) | | | 2 (1.0) | | |
| **Mode of delivery** | | | | | | | |
| Vaginal/ instrumental | 25809 (79.7) | 913 (73.8) | Ref. | Ref. | 133 (69.3) | Ref. | Ref. |
| Elective caesarean section | 2807 (8.7) | 138 (11.2) | 1.39 (1.16–1.67) | 1.37 (1.13–1.67) | 32 (16.7) | 2.21 (1.48–3.29) | 2.29 (1.52–3.46) |
| Emergency caesarean section | 3387 (10.5) | 162 (13.1) | 1.35 (1.14–1.61) | 1.31 (1.10–1.58) | 25 (13.0) | 1.43 (0.93–2.20) | 1.37 (0.86–2.19) |
| Unknown caesarean section | 396 (1.2) | 25 (2.0) | | | 2 (1.0) | | |

Data are presented as n (%), unless otherwise stated. #: adjusted for maternal smoking, obesity, education, country of birth, parity and depression/anxiety, and infant sex; ¶: approximately mean±1SD in population.

Among these women, having an asthma exacerbation during pregnancy may worsen the hypoxic intrauterine environment compared to women with milder asthma, resulting in the increased risk of SGA. Children born SGA are at increased risk of Type 2 diabetes [28], cardiovascular disease [28], obesity [28] and childhood asthma [29]. Therefore, the impact of asthma exacerbations during pregnancy may still be observed later in life. Although not statistically significant, we observed increased odds of preterm birth for women who exacerbate during pregnancy, specifically among preconception ICS/LABA users ("moderate/severe" asthma). This supports two studies reporting increased risk of preterm birth for women experiencing an asthma exacerbation during pregnancy [9] or women with poorly controlled asthma in the 90 days prior to delivery [11]. These findings may explain in part the observations for the reduction in birthweight.

Among women with asthma treated with ICS/LABA therapy preconception as a proxy for moderate–severe asthma, exacerbations were associated with an increased risk of low and reduced birthweight, infant born SGA and caesarean section. These same risks were not seen for single use therapy as a proxy for mild asthma, except for an increased risk of reduced birthweight in those whose mothers used only SABA prior to pregnancy. A recent paper also used treatment stratification as a proxy for asthma severity; however, they used medications prescribed during pregnancy [11], whereas we did not due to the change in medication prescribing and/or use in pregnancy [7], which may introduce exposure misclassification. They concluded based on their results that exacerbations increase the risk of adverse perinatal outcomes rather than the underlying asthma severity. Our results indicate that exacerbations are associated with an increased risk of adverse perinatal outcomes, but the association is stronger among those with moderate–severe asthma. This difference between severities is unlikely to be explained by a higher rate of exacerbation in the moderate–severe asthma group, since the rate of multiple exacerbations was only slightly higher in that group compared to the mild asthma groups.

This study has several strengths. Firstly, this is a large population-based longitudinal register study. All data were collected prospectively, reducing recall bias. Asthma was defined with an adjusted previously validated algorithm [16]. Since OCS can be given during pregnancy for multiple indications, all OCS prescriptions dispensed during pregnancy were evaluated to determine indication. Only those that were indicated for asthma, or were most likely for an asthma exacerbation, *i.e.* short duration with no other written indication, were included to determine exposure to asthma exacerbations [8]. Although asthma

TABLE 4 Stratified analysis of maternal exacerbations on adverse perinatal outcomes by asthma treatment dispensed 24 months preconception

| | SABA only | | | ICS monotherapy/other mild asthma treatment | | | ICS/LABA therapy | | |
|---|---|---|---|---|---|---|---|---|---|
| | No exacerbation | Exacerbation | aOR[#] (95% CI) | No exacerbation | Exacerbation | aOR[#] (95% CI) | No exacerbation | Exacerbation | aOR[#] (95% CI) |
| **Subjects n** | 3175 | 102 | | 11 048 | 286 | | 9783 | 592 | |
| **Birthweight categories** | | | | | | | | | |
| ⩽2499 g | 109 (3.4) | 2 (2.0) | 0.69 (0.16–2.90) | 370 (3.3) | 10 (3.5) | 0.81 (0.40–1.67) | 426 (4.4) | 38 (6.4) | 1.54 (1.05–2.24) |
| 2500–2999 g | 354 (11.2) | 17 (16.7) | 1.72 (0.99–3.00) | 1166 (10.6) | 38 (13.3) | 1.09 (0.74–1.59) | 1121 (11.5) | 100 (16.9) | 1.65 (1.29–2.10) |
| 3000–3999 g[¶] | 2043 (64.4) | 59 (57.8) | Ref. | 7351 (66.5) | 193 (67.5) | Ref. | 6597 (67.4) | 362 (61.2) | Ref. |
| ⩾4000 g | 662 (20.9) | 24 (23.5) | 1.19 (0.71–2.00) | 2178 (19.7) | 45 (15.7) | 0.83 (0.58–1.17) | 1618 (16.5) | 91 (15.4) | 1.04 (0.81–1.34) |
| Missing | 7 (0.2) | 0 | | 19 (0.2) | 0 | | 22 (0.2) | 1 (0.2) | |
| **Preterm birth** | | | | | | | | | |
| Yes | 196 (6.2) | 9 (8.8) | 1.50 (0.76–3.00) | 625 (5.7) | 12 (4.2) | 0.62 (0.33–1.17) | 586 (6.0) | 47 (7.9) | 1.28 (0.92–1.79) |
| Missing | 1 (0.03) | 0 | | 6 (0.05) | 0 | | 5 (0.05) | 0 | |
| **Small for gestational age** | | | | | | | | | |
| Yes | 63 (2.0) | 2 (2.0) | 1.08 (0.26–4.5) | 274 (2.5) | 10 (3.5) | 1.04 (0.50–2.17) | 311 (3.2) | 31 (5.2) | 1.74 (1.18–2.57) |
| Missing | 8 (0.2) | 0 | | 25 (0.2) | 0 | | 26 (0.3) | 1 (0.2) | |
| **Mode of Delivery** | | | | | | | | | |
| Vaginal/instrumental | 2552 (80.4) | 81 (79.4) | Ref. | 8932 (80.8) | 219 (76.6) | Ref. | 7689 (78.6) | 402 (67.9) | Ref. |
| Elective caesarean section | 254 (8.0) | 10 (9.8) | 1.26 (0.64–2.47) | 905 (8.2) | 29 (10.1) | 1.26 (0.84–1.89) | 899 (9.2) | 84 (14.2) | 1.69 (1.30–2.20) |
| Emergency caesarean section | 330 (10.4) | 9 (8.8) | 0.87 (0.43–1.76) | 1133 (10.3) | 33 (11.5) | 1.09 (0.74–1.61) | 1057 (11.0) | 93 (15.7) | 1.62 (1.26–2.08) |
| Unknown caesarean section | 39 (1.2) | 2 (2.0) | | 114 (1.0) | 5 (1.7) | | 119 (1.2) | 13 (2.2) | |

Data are presented as n (%), unless otherwise stated. SABA: short-acting β-agonists; ICS: inhaled corticosteroids; LABA: long-acting β-agonist. [#]: adjusted for maternal smoking, obesity, education, country of birth, parity and depression/anxiety, and infant sex; [¶]: approximately mean±1SD in population.

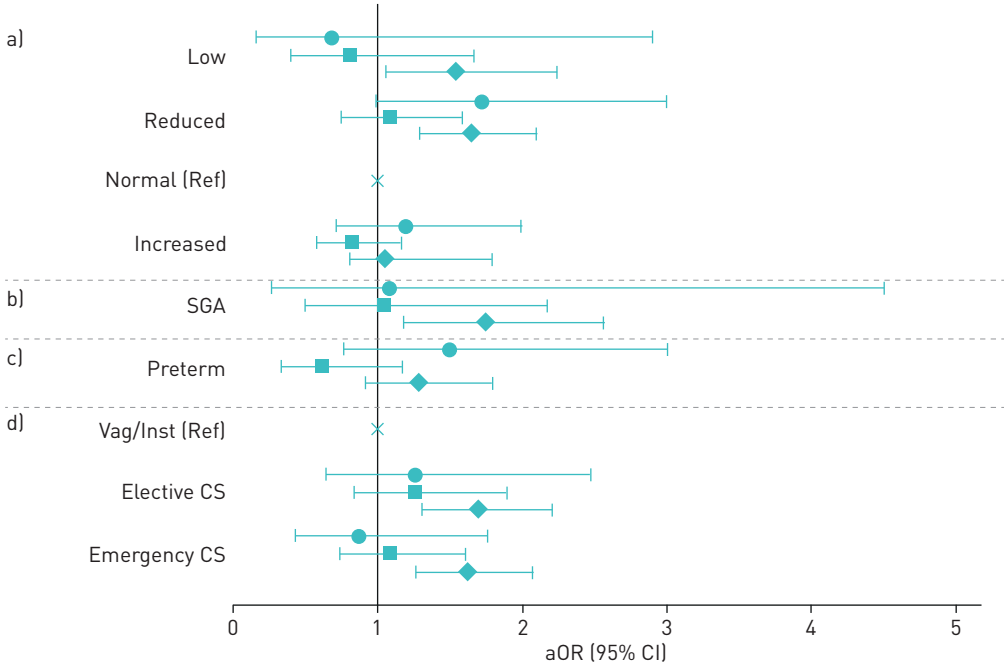


FIGURE 2 Odds ratios for association between maternal exacerbations and perinatal outcomes among pregnant women with asthma, stratified by prepregnancy asthma treatment (circles: SABA only; squares: ICS monotherapy/other; diamonds: ICS/LABA). a) Birthweight categories (low ⩽2499 g, reduced 2500–2999 g, normal 3000–3999 g, increased ⩾4000 g); b) small for gestational age (SGA); c) preterm delivery; and d) mode of delivery. SABA: short-acting-β2-agonists; ICS: inhaled corticosteroids; LABA: long-acting-β-agonist; CS: caesarean section; aOR: adjusted odds ratio; Vag/Inst: vaginal/instrumental.

severity could not be fully determined by treatment stratification due to the lack of clinical data, ICS/LABA combination therapy is usually prescribed to women with moderate–severe asthma; therefore, treatment stratification provides some insight into underlying asthma severity.

This study has some limitations. Although we used a validated algorithm to determine asthma, we may have missed women with very mild asthma who consulted a primary care doctor only, and who received less than two control medications or less than three prescriptions of β2-agonists in the 24 months before or during pregnancy. As these women would be less likely to have a severe exacerbation, the potential misclassification may have led to an overestimation of the prevalence of asthma exacerbations among pregnant women with asthma. Some potential confounders are not recorded in the databases, such as diet, alcohol use and physical activity. The results from the sensitivity analysis indicate that those factors need to have a combined impact of at least OR=1.3 on both the exposure and the outcome to reduce the effect to zero. However, given that adjustment was performed for commonly identified confounders, it is less likely but not impossible that residual confounding can explain the association. Another potential limitation was an inability to measure ICS non-adherence, which has been associated with exacerbations during pregnancy [12]. Research investigating the role of ICS non-adherence as an explanation for the association between asthma exacerbations and adverse perinatal outcomes is needed.

Studies examining Doppler ultrasounds during pregnancy, and especially during asthma exacerbations, may provide insight into the influence of blood flow and maternal hypoxia on birthweight reduction. In addition, asthma severity defined as per the GINA guidelines with clinical assessments could be used in future clinical studies to more accurately estimate the influence of asthma severity on the association between exacerbations and perinatal outcomes.

In conclusion, exacerbations during pregnancy among women with asthma increase the risk of having an elective or emergency caesarean section, and an infant born SGA, but do not increase the risk of preterm birth or LBW. These risks further increase when experiencing multiple exacerbations. Notably, these associations differ between preconception treatment regimes, suggesting that the associations between asthma exacerbations and adverse perinatal outcomes are stronger in women with moderate to severe asthma compared to those with mild asthma. Optimal antenatal asthma care during pregnancy is necessary to reduce asthma exacerbations and thereby reducing adverse perinatal outcomes which may have a long-lasting impact on the infant's health.

Conflict of interest: A.L. Robijn reports a Short-Term Research Fellowship from the European Respiratory Society during the conduct of the study. B.K. Brew has nothing to disclose. M.E. Jensen has nothing to disclose. G. Rejnö has nothing to disclose. C. Lundholm has nothing to disclose. V.E. Murphy has nothing to disclose. C. Almqvist reports grants from the Swedish Research Council, Swedish Heart–Lung Foundation, and Swedish Research Council for Health, Working Life and Welfare (FORTE), during the conduct of the study.

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## References

1 Rejnö G, Lundholm C, Gong T, *et al.* Asthma during pregnancy in a population-based study – pregnancy complications and adverse perinatal outcomes. *PLoS One* 2014; 9: e1047.
2 Sawicki E, Stewart K, Wong S, *et al.* Management of asthma by pregnant women attending an Australian maternity hospital. *Aust NZ J Obstet Gynaecol* 2012; 52: 183–188.
3 Murphy V, Namazy J, Powell H, *et al.* A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG* 2011; 118: 1314–1323.
4 Murphy VE, Wang G, Namazy JA, *et al.* The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. *BJOG* 2013; 120: 813–822.
5 Meakin AS, Saif Z, Jones AR, *et al.* Review: placental adaptations to the presence of maternal asthma during pregnancy. *Placenta* 2017; 54: 17–23.
6 Beckmann CA. The effects of asthma on pregnancy and perinatal outcomes. *J Asthma* 2003; 40: 171–180.
7 Robijn AL, Jensen ME, McLaughlin K, *et al.* Inhaled corticosteroid use during pregnancy among women with asthma: a systematic review and meta-analysis. *Clin Exp Allergy* 2019; 49: 1403–1417.
8 Firoozi F, Lemière C, Beauchesne MF, *et al.* Impact of maternal asthma on perinatal outcomes: a two-stage sampling cohort study. *Eur J Epidemiol* 2012; 27: 205–214.
9 Abdullah K, Zhu J, Gershon A, *et al.* Effect of asthma exacerbation during pregnancy in women with asthma: a population-based cohort study. *Eur Respir J* 2020; 55: 1901335.
10 Namazy JA, Murphy VE, Powell H, *et al.* Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. *Eur Respir J* 2013; 41: 1082–1090.
11 Yland JJ, Bateman BT, Huybrechts KF, *et al.* Perinatal outcomes associated with maternal asthma and its severity and control during pregnancy. *J Allergy Clin Immunol Pract* 2020; 8: 1928–1937.e3.
12 Murphy VE, Gibson P, Talbot PI, *et al.* Severe asthma exacerbations during pregnancy. *Obstet Gynecol* 2005; 106: 1046–1054.
13 Schatz M, Dombrowski MP, Wise R, *et al.* Asthma morbidity during pregnancy can be predicted by severity classification. *J Allergy Clin Immunol* 2003; 112: 283–288.
14 Ludvigsson JF, Almqvist C, Bonamy AKE, *et al.* Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol* 2016; 31: 125–136.
15 Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, *et al.* The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009; 24: 659–667.
16 Örtqvist AK, Lundholm C, Wettermark B, *et al.* Validation of asthma and eczema in population-based Swedish drug and patient registers. *Pharmacoepidemiol Drug Saf* 2013; 22: 850–860.
17 Bergsjø P, Denman DW, Hoffman HJ, *et al.* Duration of human singleton pregnancy: a population-based study. *Acta Obstet Gynecol Scand* 1990; 69: 197–207.
18 Textor J, Hardt J, Knüppel S. DAGitty. *Epidemiology* 2011; 22: 745.
19 Brew BK, Lundholm C, Viktorin A, *et al.* Longitudinal depression or anxiety in mothers and offspring asthma: a Swedish population-based study. *Int J Epidemiol* 2018; 47: 166–174.
20 Global Initiative for Asthma. Global Strategy for Asthma Management adn Prevention, 2019. Available from: www.ginasthma.org. Date accessed 12 November 2019.
21 Van Der Weele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-Value. *Ann Intern Med* 2017; 167: 268–274.
22 Lederer DJ, Bell SC, Branson RD, *et al.* Control of confounding and reporting of results in causal inference studies. *Ann Am Thorac Soc* 2019; 16: 22–28.
23 Darabi B, Rahmati S, Hafeziahmadi MR, *et al.* The association between caesarean section and childhood asthma: an updated systematic review and meta-analysis. *Allergy Asthma Clin Immunol* 2019; 15: 62.
24 Kuhle S, Tong OS, Woolcott CG. Association between caesarean section and childhood obesity: a systematic review and meta-analysis. *Obes Rev* 2015; 16: 295–303.
25 Schatz M, Zeiger RS, Hoffman CP, *et al.* Intrauterine growth is related to gestational pulmonary function in pregnant asthmatic women. *Chest* 1990; 98: 389–392.
26 Clifton VL, Giles WB, Smith R, *et al.* Alterations of placental vascular function in asthmatic pregnancies. *Am J Respir Crit Care Med* 2001; 164: 546–553.
27 Murphy VE, Gibson PG, Giles WB, *et al.* Maternal asthma is associated with reduced female fetal growth. *Am J Respir Crit Care Med* 2003; 168: 1317–1323.
28 Cho WK, Suh BK. Catch-up growth and catch-up fat in children born small for gestational age. *Korean J Pediatr* 2016; 59: 1–7.
29 Den Dekker HT, Sonnenschein-Van Der Voort AMM, De Jongste JC, *et al.* Early growth characteristics and the risk of reduced lung function and asthma: a meta-analysis of 25,000 children. *J Allergy Clin Immunol* 2016; 137: 1026–1035.