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Effect of Maternal Asthma Exacerbations on Perinatal Outcomes: A Population-based Study

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Maternal asthma exacerbations are associated with lower birth weight 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.

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-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, birth weight and mode of delivery), stratified by pre-conception treatment regime.

Results: Exacerbations occurred in 1,430 (4.2%) pregnancies. Exacerbations were associated with reduced birth weight (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 pre-pregnancy 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) vs. 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.

Short title: Maternal asthma exacerbations and perinatal outcomes

Keywords

Pregnancy, asthma, birth weight, caesarean section, inhaled corticosteroid

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 birth weight (LBW) and an infants 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 pre-conception 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 medication dispenses[16] as either: 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 beta-2-agonists(β2)/ICS (R03AK), up to 24 months before, or during pregnancy; or 4) three or more dispenses of 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 categorized 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, birth weight, gestational age at birth - categorized as pre-term (<37 weeks) and term (≥37 weeks), and SGA (defined as mean minus two standard deviations). Birth weight was categorized as low birth weight (≤2499 grams), reduced birth weight (2500-2999 grams), normal birth weight (3000-3999 grams) and increased birth weight (≥4000 grams).

Covariates

Covariates were selected based on directed acyclic graphs[18]. From the MBR we obtained maternal age at delivery, Body Mass Index (BMI in kg/m^2, 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 socio-economic 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 dispenses 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 1 July 2005, women with a conception date prior to 1 July 2007 were excluded from the pre-conception treatment analysis due to potential misclassification of treatment category. Women were grouped based on no asthma medication dispenses, SABA only medication ['mild asthma'], ICS mono-therapy ['mild asthma'], ICS/LABA combination therapy ['moderate-severe asthma'], and other combinations of asthma medication. 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 (OR) with 95% confidence intervals (CI) for the outcomes associated with asthma exacerbations during pregnancy. Additionally, we estimated ORs for the exacerbation categories (once/multiple) compared to no exacerbations. Separate ORs were estimated for asthma exacerbations within each treatment strata using a logistic model with interaction effects between exacerbations and pre-conception treatment category.

For all analyses we estimated crude and adjusted ORs (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

there 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 exacerbations types and thirdly an E-value calculation.

The E-value was calculated as

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

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 OR estimates or the lower CI 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 1,703 asthma exacerbation exposure episodes in 1,430 (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/hospitalization only and 200 (11.7%) were identified based on both OCS and ED/hospitalization.

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 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 pre-conception than non-exacerbators (51% vs 37%). Of the women who exacerbated in the ICS/LABA stratum, 14.5% had multiple exacerbations vs 11.8% and 11.9% in the SABA and ICS strata respectively.

Maternal asthma exacerbations were associated with reduced birth weight (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) CS, 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 birth weight (aOR 1.39, 95%CI 1.17-1.65, aOR 1.89, 95%CI 1.24-2.86 respectively) and the odds of having an elective CS (aOR 1.37 95%CI 1.13-1.67, aOR 2.29 95%CI 1.52-3.46, respectively) with a dose response relationship. Multiple exacerbations increased the odds being born SGA (aOR 2.58, 95%CI 1.38-4.82). Multiple exacerbations increased the odds of being born with a low birth weight (aOR1.43, 95%CI 0.69-2.96), although the confidence interval crossed the null, Table 3.

Pre-conception 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 birth weight. In this case, among women who had been treated with SABA-only, an exacerbation in pregnancy was associated with reduced birth weight (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 birth weight (aOR 1.65, 95%CI 1.29-2.24), low birth weight (aOR 1.54, 95%CI 1.05-2.24), and both elective and emergency CS (aOR 1.69, 95%CI 1.30-2.20 and aOR

1.62, 95%CI 1.26-2.08, respectively), compared to no exacerbations, Table 4, 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. Supplement Table 1. Supplemental Table 2 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 OR 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, Supplement Table 3.

Discussion

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

Although women with asthma are more likely to have a CS[1], no previous studies have reported on the association between maternal asthma exacerbations and mode of delivery. Being born via CS 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 CS was a risk for all women who exacerbated, 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 CS, or maternal preference.

A recently published study from Canada among women with asthma[9] found an increased risk of LBW (<2500 grams) 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 sub-group 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 birth weight (2500-3000 grams), 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 birth weight among infants born to women with asthma is an impact of maternal hypoxia on infant birth weight[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 up-regulation 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 a an infant born SGA. This supports other studies which found increased risk of SGA among those with poorly-controlled asthma vs well-controlled asthma in the 90 days prior to delivery (aRR 1.15, 95%CI 1.03-1.29)[8, 9]. 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 birth weight.

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 birth weight, infant born SGA and CS. These same risks were not seen for single use therapy as a proxy for mild asthma, except for an increased risk of reduced birth weight 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 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 whom received less than two controller medications or less than three dispenses 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 birth weight 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 small for gestational age, but do not increase the risk of preterm birth or LBW. These risks further increase when experiencing multiple exacerbations. Notably, these associations differ between pre-conception 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.

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Figure legends

Figure 1. Study cohort flow diagram. For treatment groups, numbers displayed as n exacerbators / N total.

Figure 2. Odds ratios for association between maternal exacerbations and perinatal outcomes among pregnant women with asthma, stratified by pre-pregnancy asthma treatment (●: SABA only, ■: ICS mono-therapy/other, ◆: ICS/LABA). A) Birth weight categories (low ≤2499 grams, reduced 2500-2999 grams, normal 3000-3999 grams, high ≥4000 grams; B) small for gestational age (SGA); C) Preterm delivery; and D) Mode of Delivery. Abbreviations used: SABA short-acting-beta2-agonists, ICS inhaled corticosteroids, LABA long-acting-beta-agonist, CS caesarean section.

Tables

Table 1. Baseline characteristics of pregnant women with asthma		
	No Exacerbation (N=32,399)	Exacerbation (N=1,430)
Maternal age at delivery (years)		
≤19	565 (1.7)	22 (1.5)
20-24	3,989 (12.3)	190 (13.3)
25-29	8,905 (27.5)	366 (25.6)
30-34	11,078 (34.2)	454 (31.7)
≥35	7,862 (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)	15,591 (48.1)	596 (41.7)
Overweight (25-29 kg/m^2)	8,477 (26.2)	390 (27.3)
Obese Class 1 (30-34 kg/m^2)	3,646 (11.3)	188 (13.1)
Obese ≥Class 2 (≥35 kg/m^2)	2,053 (6.3)	125 (8.7)
Missing	2,308 (7.1)	116 (8.1)
Parity		
1	14,918 (46.0)	587 (41.0)
2	11,175 (34.5)	489 (34.2)
≥3	6,306 (19.5)	354 (24.8)
Cigarettes per day		
None	28,468 (87.9)	1,202 (84.0)
1-9	1,954 (6.0)	106 (7.4)
≥10	746 (2.3)	60 (4.2)

Missing	1,231 (3.8)	62 (4.3)
Country of birth		
Sweden	28,321 (87.4)	1,120 (78.3)
Nordic Countries	472 (1.5)	20 (1.4)
Europe	859 (2.7)	44 (3.1)
Outside Europe	2,747 (8.5)	246 (17.2)
Maternal Education		
≤9 years	3,475 (10.7)	231 (16.1)
10-12 years	12,476 (38.5)	585 (40.9)
13-14 years	1,749 (5.4)	85 (5.9)
≥15 years	14,448 (44.6)	504 (35.2)
Missing	251 (0.8)	25 (1.8)
Depression/Anxiety	6,327 (19.5)	377 (26.4)
Treatment dispensed preconception		
SABA only[#]	3,175 (12.0)	102 (8.8)
ICS monotherapy[#] / Other mild asthma treatment combinations[#]*	11,048 (41.9)	286 (24.7)
ICS/LABA combination therapy[#]	9,783 (37.0)	592 (51.0)
No Medication[#]	2,416 (9.1)	181 (15.6)
No 24 Month preconception period	5,941 (18.3)	269 (18.8)

All data presented as n (%).
[#]Percentage calculated based for 27,619 pregnancies (1,161 exacerbation) included for treatment analysis.
*includes LTRA only, SABA + LABA, SABA + LTRA.

Table 2. Odds ratios of maternal asthma exacerbations on adverse perinatal outcomes				
	No exacerbation N=32,399	**Exacerbation N=1,430**	**OR (95%CI)**	**aOR* (95%CI)**
Birth Weight Categories				
≤2499 grams	1,180 (3.6)	60 (4.2)	1.21 (0.92-1.59)	1.02 (0.75-1.39)
2500-2999 grams	3,601 (11.1)	224 (15.7)	**1.48 (1.27-1.72)**	**1.45 (1.24-1.70)**
3000-3999 grams[#]	21,595 (66.7)	909 (63.7)	*Reference*	*Reference*
≥4000 grams	5,965 (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	1,834 (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	25,809 (79.7)	1,046 (73.1)	*Reference*	*Reference*
Elective C-Section	2,807 (8.7)	170 (11.2)	**1.49 (1.26-1.77)**	**1.49 (1.24-1.78)**
Emergency C-Section	3,387 (10.5)	187 (13.1)	**1.36 (1.16-1.60)**	**1.32 (1.11-1.57)**
Unknown C-Section	396 (1.2)	27 (1.9)	-	-
*Adjusted for maternal smoking, obesity, education, country of birth, parity, and depression/anxiety, and infant sex. [#] Approximately mean+/- one standard deviations in population.				

Table 3. Odds ratios of maternal asthma exacerbations categories on adverse perinatal outcomes							
	No exacerbation N=32,399	**One Exacerbation**			**Multiple Exacerbations**		
		Pregnancies (n=1,238)	**OR (95%CI)**	**aOR* (95%CI)**	**Pregnancies (n=192)**	**OR (95%CI)**	**aOR* (95%CI)**
Birth Weight Categories							
≤2499 grams	1,180 (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 grams	3,601 (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 grams[#]	21,595 (66.7)	789 (63.8)	*Reference*	*Reference*	120 (62.8)	*Reference*	*Reference*
≥4000 grams	5,965 (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	1,834 (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	1.11	12 (6.3)	***2.48***	***2.58***

			(0.89-1.70)	(0.78-1.57)		***(1.37-4.47)***	***(1.38-4.82)***
missing	72 (0.2)	1 (0.1)	-	-	2 (1.0)	-	-
Mode of Delivery							
Vaginal/Instrumental	25,809 (79.7)	913 (73.8)	*Reference*	*Reference*	133 (69.3)	*Reference*	*Reference*
Elective C-Section	2,807 (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 C-Section	3,387 (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 C-Section	396 (1.2)	25 (2.0)	-	-	2 (1.0)	-	-
*Adjusted for maternal smoking, obesity, education, country of birth, parity, and depression/anxiety, and infant sex. [#] Approximately mean+/- one standard deviations in population.							

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

	SABA Only			**ICS mono therapy /Other mild asthma treatment**			**ICS/LABA therapy**		
	No exacerbation N= 3,175	**Exacerbation N = 102**	**aOR* (95%CI)**	**No exacerbation N= 11,048**	**Exacerbation N=286**	**aOR* (95%CI)**	**No exacerbation N= 9,783**	**Exacerbation N=592**	**aOR* (95%CI)**
Birth Weight Categories									
≤2499 grams	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 grams	354 (11.2)	17 (16.7)	1.72 (0.99-3.00)	1,166 (10.6)	38 (13.3)	1.09 (0.74-1.59)	1,121 (11.5)	100 (16.9)	**1.65 (1.29-2.10)**
3000-3999 grams[#]	2,043 (64.4)	59 (57.8)	*Reference*	7,351 (66.5)	193 (67.5)	*Reference*	6,597 (67.4)	362 (61.2)	*Reference*
≥4000 grams	662 (20.9)	24 (23.5)	1.19 (0.71-2.00)	2,178 (19.7)	45 (15.7)	0.83 (0.58-1.17)	1,618 (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	2,552 (80.4)	81 (79.4)	*Reference*	8,932 (80.8)	219 (76.6)	*Reference*	7,689 (78.6)	402 (67.9)	*Reference*
Elective C-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 C-Section	330 (10.4)	9 (8.8)	0.87 (0.43-1.76)	1,133 (10.3)	33 (11.5)	1.09 (0.74-1.61)	1,057 (11.0)	93 (15.7)	**1.62 (1.26-2.08)**
Unknown C-Section	39 (1.2)	2 (2.0)	-	114 (1.0)	5 (1.7)	-	119 (1.2)	13 (2.2)	**-**

*Adjusted for maternal smoking, obesity, education, country of birth, parity, and depression/anxiety, and infant sex. [#] Approximately mean+/- one standard deviations in population. Abbreviations used: SABA short-acting beta-agonists, ICS inhaled corticosteroids, LABA long-acting beta-agonist

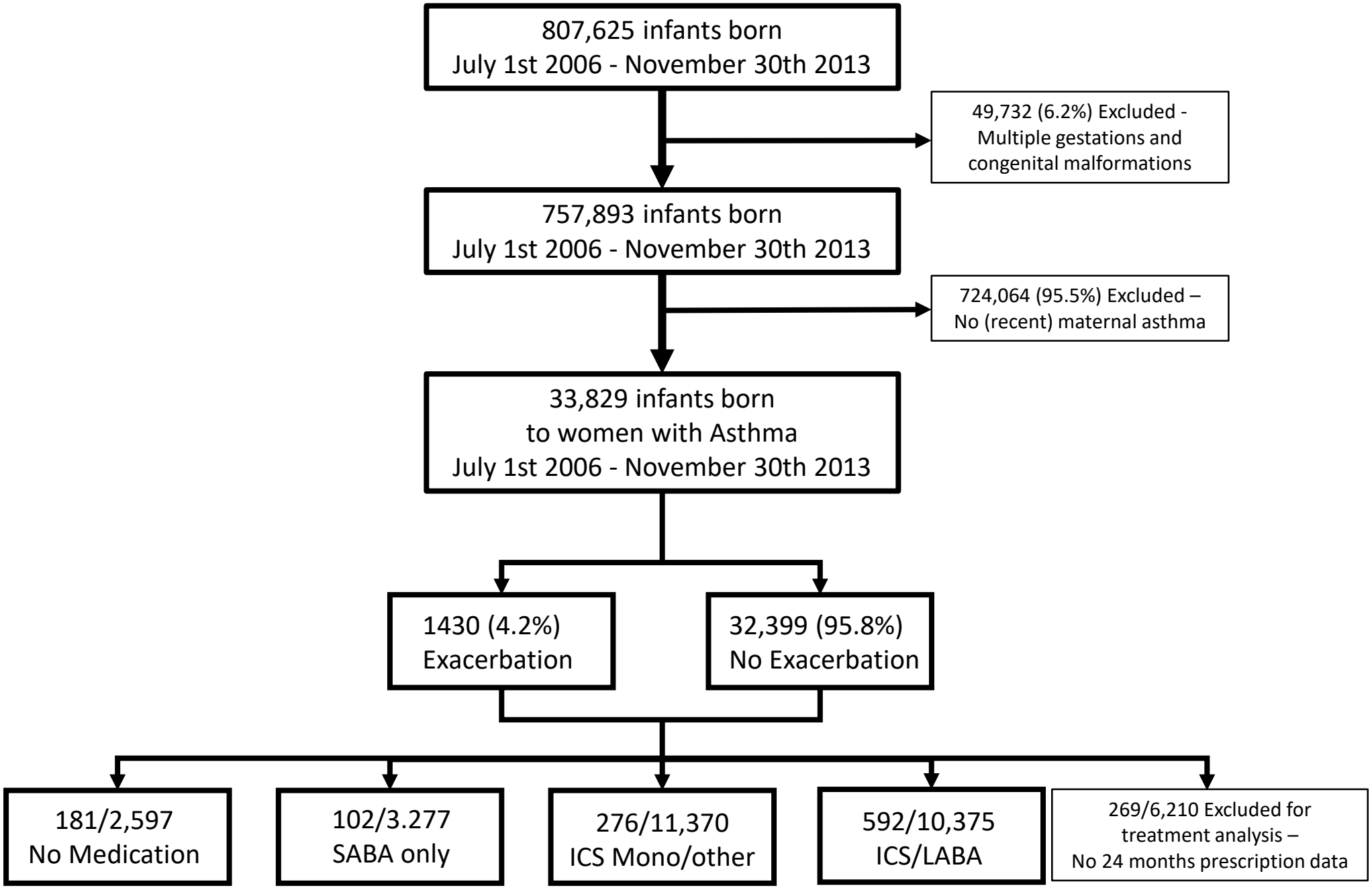

Figure 1. Study cohort flow diagram. For treatment groups numbers displayed as n exacerbators / N total

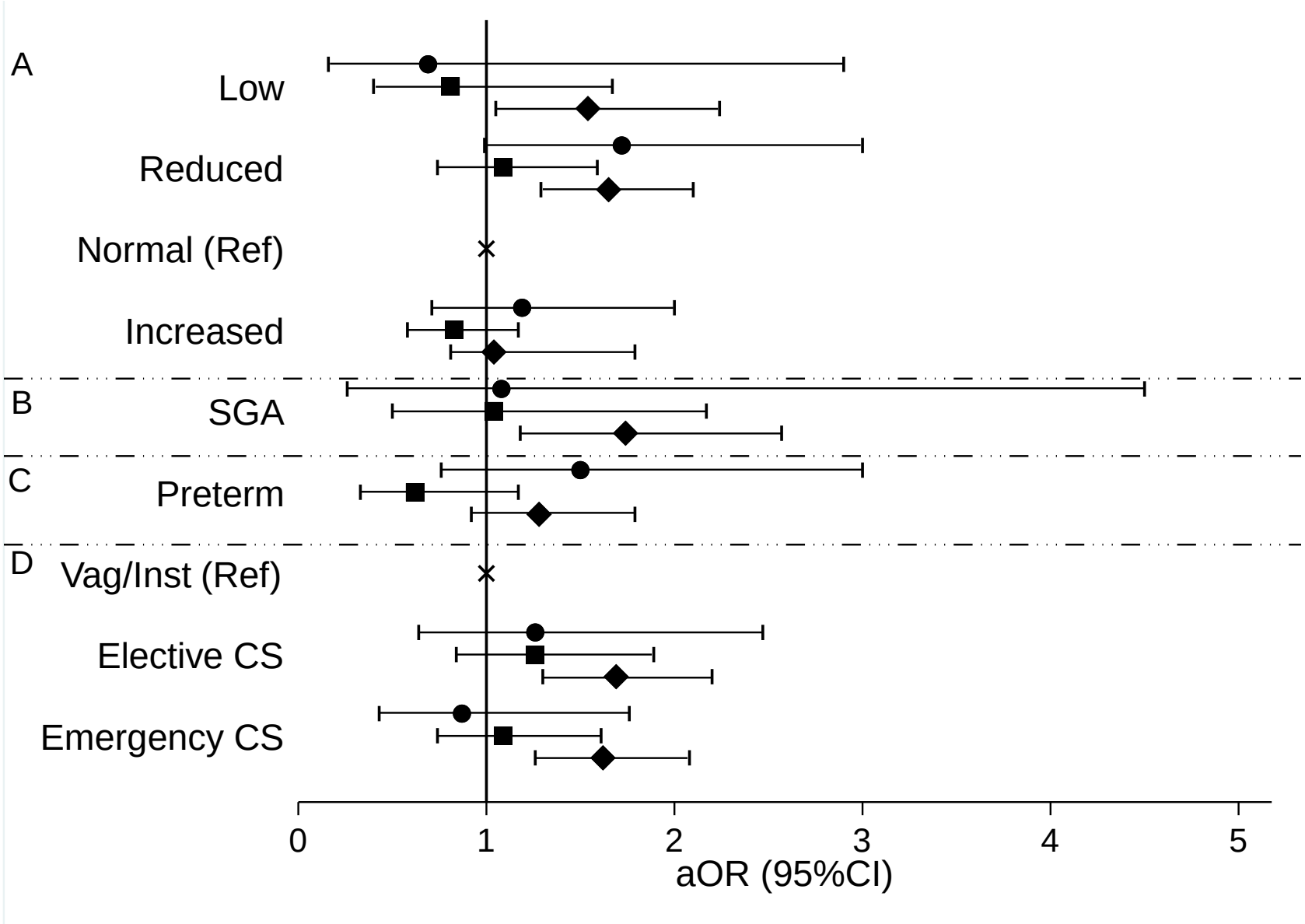

Figure 2. Odds ratios for association between maternal exacerbations and perinatal outcomes among pregnant women with asthma, stratified by pre-pregnancy asthma treatment (●: SABA only, ■: ICS mono-therapy/other, ◆: ICS/LABA). A) Birth weight categories (low ≤2499 grams, reduced 2500-2999 grams, normal 3000-3999 grams, high ≥4000 grams; B) small for gestational age (SGA); C) Preterm delivery; and D) Mode of Delivery. Abbreviations used: SABA short-acting-beta2-agonists, ICS inhaled corticosteroids, LABA long-acting-beta-agonist, CS caesarean section.

Supplemental information

The Effect of Maternal Asthma Exacerbations on Adverse Perinatal Outcomes in Mother and Infant

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Methods

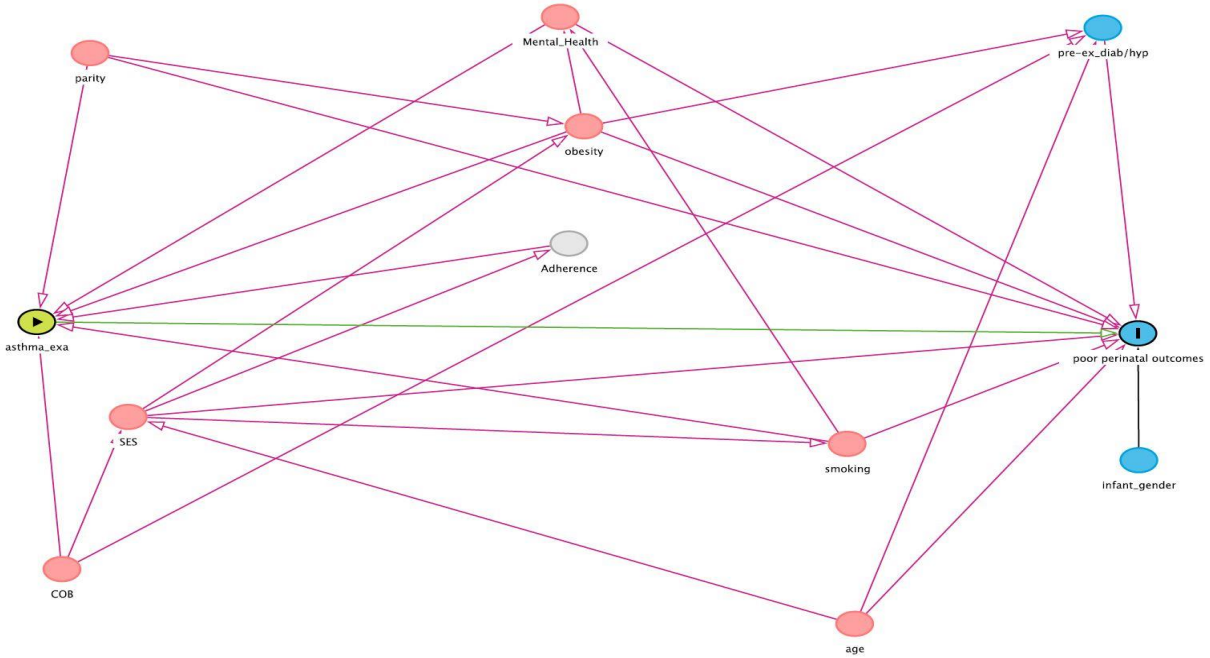

Figure S1. Directed Acyclic Graph used to determine covariates to be included for analysis, developed using Dagitty.

Results

Supplemental Table 1. Odds ratios of maternal asthma with and without exacerbations on adverse perinatal outcomes compared to no asthma							
	No Asthma N=678,454	**Asthma - No Exacerbation**			**Asthma - Exacerbations**		
		Pregnancies (n=32,399)	**OR (95%CI)**	**aOR* (95%CI)**	**Pregnancies (n=1,430)**	**OR (95%CI)**	**aOR* (95%CI)**
Birth Weight Categories							
≤2499 grams	20,605 (3.0)	1,180 (3.6)	***1.22 (1.15-1.30)***	***1.20 (1.12-1.28)***	60 (4.2)	***1.47 (1.13-1.92)***	1.24 (0.92-1.67)
2500-2999 grams	68,676 (10.1)	3,601 (11.1)	***1.12 (1.07-1.16)***	***1.17 (1.13-1.22)***	224 (15.7)	***1.65 (1.42-1.91)***	***1.69 (1.45-1.98)***
3000-3999 grams[#]	459,365 (67.7)	21,595 (66.7)	*Reference*	*Reference*	909 (63.7)	*Reference*	*Reference*
≥4000 grams	128,806 (19.0)	5,965 (18.4)	0.99 (0.96-1.02)	**0.91 (0.88-0.94)**	235 (16.5)	0.92 (0.80-1.07)	**0.84 (0.72-0.98)**
missing	1,002 (0.2)	58 (0.2)	-	-	2 (0.1)	-	-
Preterm Birth							
Yes	31,736 (4.7)	1,834 (5.7)	***1.22 (1.16-1.29)***	***1.17 (1.11-1.23)***	85 (5.9)	***1.29 (1.03-1.61)***	1.21 (0.96-1.54)
missing	199 (0.03)	13 (0.04)	-	-	2 (0.1)	-	-
Small for Gestational Age							
Yes	14,801 (2.2)	856 (2.6)	***1.22 (1.13-1.31)***	***1.29 (1.19-1.39)***	52 (3.6)	***1.69 (1.28-2.23)***	***1.63 (1.21-2.20)***
missing	1,230 (0.2)	72 (0.2)	-	-	3 (0.2)	-	-
Mode of Delivery							
Vaginal/Instrumental	568,838 (83.8)	25,809 (79.7)	*Reference*	*Reference*	1,046 (73.1)	*Reference*	*Reference*
Elective C-Section	45,651 (6.7)	2,807 (8.7)	***1.36 (1.30-1.41)***	***1.32 (1.27-1.39)***	170 (11.2)	***2.03 (1.72-2.39)***	***2.02 (1.69-2.40)***
Emergency C-Section	57,444 (8.5)	3,387 (10.5)	***1.30 (1.25-1.35)***	**1.25 (1.20-1.31)**	187 (13.1)	***1.77 (1.51-2.07)***	**1.69 (1.43-2.00)**
Unknown C-Section	6,521 (1.0)	396 (1.2)	-	-	27 (1.9)	-	-
*Adjusted for maternal smoking, obesity, education, country of birth, parity, and infant sex. [#] Approximately mean+/- one standard deviations in population.							

Supplemental Table 2. Odds ratios of different exacerbation types and adverse perinatal outcomes

	No exacerbation N=32,399	OCS only		ED/Hospitalisation only		OCS + ED/Hospitalisation		Mixed categories	
		Pregnancies (n=687)	aOR* (95%CI)	Pregnancies (n=514)	aOR* (95%CI)	Pregnancies (n=153)	aOR* (95%CI)	Pregnancies (n=76)	aOR* (95%CI)
Birth Weight Categories									
≤2499 grams	1,180 (3.6)	30 (4.4)	1.20 (0.79-1.83)	19 (3.7)	0.65 (0.36-1.17)	7 (4.6)	1.32 (0.57-3.03)	4 (5.3)	1.88 (0.66-5.34)
2500-2999 grams	3,601 (11.1)	115 (16.7)	***1.64 (1.31-2.05)***	70 (16.7)	1.11 (0.84-1.46)	25 (16.3)	1.60 (1.00-2.56)	14 (18.4)	***2.22 (1.16-4.23)***
3000-3999 grams[#]	21,595 (66.7)	427 (62.2)	*Reference*	342 (66.5)	*Reference*	94 (61.4)	*Reference*	46 (60.5)	*Reference*
≥4000 grams	5,965 (18.4)	114 (16.6)	0.99 (0.79-1.24)	82 (16.0)	0.83 (0.63-1.08)	27 (17.7)	1.07 (0.68-1.67)	12 (15.8)	1.00 (0.50-2.00)
missing	58 (0.2)	1 (0.2)	-	1 (0.2)	-	0	-	0	-
Preterm Birth									
Yes	1,834 (5.7)	36 (5.2)	0.88 (0.61-1.27)	29 (5.6)	0.88 (0.58-1.32)	15 (9.8)	***1.89 (1.08-3.31)***	5 (6.6)	*1.17 (0.48-2.88)*
missing	13 (0.04)	0		1 (0.2)		0		0	
Small for Gestational Age									
Yes	856 (2.6)	25 (3.6)	1.28 (0.82-2.00)	17 (3.3)	1.09 (0.64-1.84)	4 (2.6)	1.02 (0.37-2.83)	6 (7.8)	***3.37 (1.44-7.88)***
missing	72 (0.2)	1 (0.2)		2 (0.4)		0		0	
Mode of Delivery									
Vaginal/ Instrumental	25,809 (79.7)	491 (71.5)	*Reference*	388 (75.5)	*Reference*	113 (73.9)	*Reference*	54 (71.1)	*Reference*
Elective C-Section	2,807 (8.7)	93 (13.5)	***1.68 (1.33-2.14)***	48 (9.3)	1.12 (0.81-1.55)	15 (9.8)	1.36 (0.78-2.36)	14 (18.4)	***2.62 (1.40-4.88)***
Emergency C-Section	3,387 (10.5)	89 (13.0)	***1.42 (1.12-1.81)***	68 (13.2)	1.17 (0.88-1.55)	22 (14.4)	1.57 (0.96-2.55)	8 (10.5)	1.03 (0.46-2.30)
Unknown C-Section	396 (1.2)	14 (2.0)	-	10 (2.0)	-	3 (2.0)	-	0	-

*Adjusted for maternal smoking, obesity, education, country of birth, parity, and depression/anxiety, and infant sex. [#] Approximately mean+/- one standard deviations in population.

Supplemental Table 3. E-Values for adjusted Odds Ratio's (aOR) and lower confidence interval (LCI) limit of statistically significant aOR from main analyses by analysis		
	E-Value aOR	E-Value LCI
Analysis 1.		
Reduced Birth Weight	2.26	1.79
Elective Caesarean Section	2.34	1.79
Emergency Caesarean Section	1.97	1.46
Analysis 2.		
One Exacerbation		
Reduced Birth Weight	2.13	1.62
Elective Caesarean Section	2.08	1.51
Emergency Caesarean Section	1.95	1.43
Multiple Exacerbations		
Reduced Birth Weight	3.19	1.79
Small for Gestational Age	4.60	2.10
Elective Caesarean Section	4.01	2.41
Analysis 3. Stratified by Treatment		
ICS/LABA therapy		
Low Birth Weight	2.45	1.28
Reduced Birth Weight	2.67	1.90
Small for Gestational Age	2.88	1.64
Elective Caesarean Section	2.77	1.92
Emergency Caesarean Section	2.62	1.83