



Maternal Asthma, Preterm Birth, and Risk of Bronchopulmonary Dysplasia

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Objective To study the relationship between maternal asthma and the development of bronchopulmonary dysplasia (BPD).

Study design Using a large population-based California cohort, we investigated associations between maternal asthma and preterm birth subtype, as well as maternal asthma and BPD. We used data from 2007-2010 maternal delivery discharge records of 2 009 511 pregnancies and *International Classification of Diseases, Ninth Revision* codes. Preterm birth was defined as <37 weeks gestational age (GA), with subgroups of <28 weeks, 28-32 weeks, and 33-37 weeks GA, as well as preterm subtype, defined as spontaneous, medically indicated, or unknown. Linkage between the 2 California-wide datasets yielded 21 944 singleton preterm infants linked to their mother's records, allowing estimation of the risk of BPD in mothers with asthma and those without asthma.

Results Maternal asthma was associated with increased odds (OR, 1.42; 95% CI, 1.38-1.46) of preterm birth at <37 weeks GA, with the greatest risk for 28-32 GA (aOR, 1.60; 95% CI, 1.47-1.74). Among 21 944 preterm infants, we did not observe an elevated risk for BPD in infants born to mothers with asthma (aOR, 1.03; 95% CI, 0.9-1.2). Stratification by maternal treatment with antenatal steroids revealed increased odds of BPD in infants whose mothers had asthma but did not receive antenatal steroids (aOR, 1.54; 95% CI, 1.15-2.06), but not in infants whose mothers had asthma and were treated with antenatal steroids (aOR, 0.85; 95% CI, 0.67-1.07).

Conclusion Asthma in mothers who did not receive antenatal steroid treatment is associated with an increased risk of BPD in their preterm infants. (*J Pediatr* 2015;167:875-80).

Asthma is a common, if not the most common, chronic disease to complicate pregnancy and has been associated with poor obstetric outcomes.¹ Despite medical advances in both asthma and preterm birth, mothers with asthma are at greater risk for preterm birth (defined as delivery at <37 weeks gestational age [GA]).^{2,3} In the US, preterm birth occurred in 13% of all births⁴ (during the study time frame), and infants born preterm are at increased risk for substantial morbidity, one of the most common being bronchopulmonary dysplasia (BPD).

Previous studies involving relatively small numbers of patients have reported that infants with BPD, or those who require prolonged supplemental oxygen in the neonatal intensive care unit (NICU), are more likely to have a family member with asthma.^{5,6} This has led to speculation that maternal asthma may be casually linked to the development of BPD.^{5,6} Given these findings, we endeavored to explore the potential relationship among maternal asthma, preterm birth, and BPD in a large population-based cohort.

A further motivation to explore such a relationship is the biological underpinnings that may be common to asthma and preterm birth. Of note, these include inflammatory pathways with transcription factors nuclear factor kappa light chain enhancer of activated B cells, specific chemokines and leukotrienes (interleukin-6 and tumor necrosis factor 2),⁷ and beta receptors in smooth muscle.⁸ For example, Bertrand et al⁹ observed a relationship between the degree of bronchial reactivity and preterm birth. The authors speculated that there might be a common physiological basis for the reactivity of uterine and bronchial smooth muscle, which would suggest a common origin of underlying disease. These may be inherited conditions or innate risk factors that predispose the fetus to spontaneous preterm birth and BPD.

The objectives of the present study were: (1) to estimate preterm birth risks, by subtype (ie, GA-specific and spontaneous vs medically indicated), among mothers with asthma using California-wide data; and (2) to estimate the risk of BPD in singleton preterm infants whose mothers have asthma. We hypothesized that maternal asthma is associated with increased risk of

BMI	Body mass index
BPD	Bronchopulmonary dysplasia
BW	Birth weight
CPQCC	California Perinatal Quality Care Collaborative
GA	Gestational age
ICD-9	<i>International Classification of Diseases, Ninth Revision</i>
ID	Identification number
NICU	Neonatal intensive care unit
OSHDP	California Office of Statewide Health Planning and Development
RDS	Respiratory distress syndrome

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spontaneous preterm birth and subsequent BPD owing to these conditions having an innate predisposition associated with maternal asthma.

Methods

Our analyses used 2 large California-wide datasets. The first dataset was from the California Office of Statewide Health Planning and Development (OSHPD). The OSHPD administrative database captures all hospital discharge diagnoses associated with each woman, including diagnoses antecedent to the pregnancy. We extracted data from this dataset informative of births in the period 2007-2010 and obtained information on maternal delivery discharge records of 2 009 511 pregnancies and their *International Classification of Diseases, Ninth Revision* (ICD-9) codes. This dataset served as the information for demographic and some clinical data; variables considered included maternal age, maternal body mass index (BMI), maternal education, race/ethnicity, payer type, maternal diabetes, maternal asthma, gestational diabetes, hypertension, preeclampsia, polyhydramnios, oligohydramnios, GA, birth weight (BW), and preterm birth subtype. The second dataset was from the California Perinatal Quality Care Collaborative (CPQCC; www.cpqcc.org). The CPQCC data represent >90% of NICU admissions in California. The study protocol was approved by Stanford University's Investigational Review Board.

First, we examined the frequency of maternal asthma in the OSHPD cohort of 2 009 511 singleton live births using ICD-9 code 493 at delivery discharge. Then, using OSHPD data, we examined the frequency of preterm birth by the presence of maternal asthma among singleton births.

GA was based on an obstetric estimate of gestation at delivery in weeks provided on the birth certificate. Preterm birth was defined as <37 weeks and was stratified into groups by GA at birth to <28 weeks, 28-32 weeks, and 33-37 weeks. Preterm birth was further subtyped as spontaneous, medically indicated, and unknown. The algorithm for these subtypes is shown in [Table I](#). Data were analyzed by logistic regression models, with ORs adjusted for maternal BMI,

maternal education, maternal race/ethnicity, and payer status at delivery.

Data linkage was performed between the OSHPD and CPQCC datasets from 2007-2010. The CPQCC-OSHPD linkage was created using a probabilistic method based on CPQCC stay identification number (ID) and NICU ID for the NICU that discharged the infant to home, infant's age at discharge (in days), infant's date of birth, infant's sex, location of birth, mother's date of birth, BW, GA at birth (days), multiple birth status, number of multiples in the set, and birth order.

The majority of matches found were based on the CPQCC stay ID and NICU ID for the NICU that discharged the infant home. For these matches, the other data elements listed must have shown a minimum level of concordance. In the absence of the CPQCC stay ID and/or NICU ID, the agreement for the other matching data elements must be very strong. The goal of the linkage is to match CPQCC records to infants registered in the OSHPD database with near 100% certainty.

We were able to link 21 944 premature infants in the CPQCC database from the 2 009 511 pregnancies in the OSHPD database. Using the linked data, we evaluated rates of BPD in preterm infants, defining the use of supplemental oxygen at 28 days after birth but room air at 36 weeks postmenstrual age as mild BPD and the requirement for supplemental oxygen at 36 weeks postmenstrual age as moderate/severe BPD.¹⁰ The CPQCC database does not provide information on the amount of supplemental oxygen or the use of nasal positive pressure, so we were unable to differentiate between moderate and severe BPD as defined elsewhere.¹⁰ We used the ICD-9 code from the OSHPD database to identify mothers with asthma. We compared CPQCC and OSHPD data GA, sex, and maternal age for data rigor.

Associations among maternal asthma, preterm birth, preterm birth subtype, BPD, and BPD with and without antenatal steroid use were estimated with ORs and their 95% CIs. Antenatal steroid use was defined as corticosteroids given to expectant women in anticipation of a preterm delivery. Regarding preterm birth and subtype, ORs were adjusted for maternal BMI, maternal education, maternal race/ethnicity, payer status at delivery, and maternal age. When we analyzed the data for odds of BPD, in addition to the foregoing characteristics, we adjusted for sex and BW, and then stratified separately for the use of antenatal steroids.

All analyses were performed with SAS version 9.3 (SAS institute, Cary, North Carolina).

Table I. Categorization tool for preterm type coding using OSHPD and VS data

Preterm birth group (specific)	ICD-9/VS code
Spontaneous	(Preterm premature rupture of membranes, premature labor, and/or tocolytics) 658.1 VS labor/delivery code 10 644.0-645.0 VS complications/procedure of pregnancy code 28
Indicated	(Not spontaneous, "induced," or cesarean section before 37 wk) Procedure codes 73.0, 73.1, and/or 73.4 VS labor/delivery codes 11 and/or 12; procedure codes 74.0-75.0 VS method of delivery codes 01, 11, 21, 31, 02, 12, 22, and 32
Unknown	Not spontaneous or indicated

VS, Vital Statistics.

Results

To reproduce and compare with results from previous studies and to validate our database, we present in [Table II](#) (available at www.jpeds.com) the characteristics of the 2 009 511 singleton live births that provided our initial basis of analysis for those with mothers with asthma (2.4%) and those with mothers without asthma. Compared with mothers without asthma, those with asthma were

more likely to be obese, to have private insurance, and to be non-Latina black or non-Latina white, and less likely to be Latina or Asian.

Preterm Birth

Compared with the mothers without asthma, those with asthma were at increased risk for preterm birth at <37 weeks GA; further analysis found that this risk was greatest in the 28-32 weeks GA group (Figure 1). Analyses of preterm birth subtype, defined as spontaneous or medically indicated, revealed increased rates of both spontaneous and medically indicated preterm births in mothers with asthma (Figure 2; available at www.jpeds.com).

BPD

With the linked CPQCC and OSHPD data, we investigated 21 944 preterm infants with or without BPD for their association with maternal history of asthma. The characteristics of these preterm infants are shown in Table III. We found no substantially elevated risk for BPD when all mothers with asthma were analyzed together (Figure 3); however, stratification for maternal treatment with antenatal steroids revealed an increased rate of BPD in infants whose mothers had asthma but did not receive antenatal steroids (Figure 3). In contrast, BPD was not increased in infants whose mothers had asthma and were treated with antenatal steroids, and the odds of BPD were slightly reduced in mothers both with and without asthma who did not receive antenatal steroids (Figure 3). In the group with

maternal asthma, BPD was increased in infants whose mothers did not receive antenatal steroids (crude OR, 1.29; 95% CI, 1.22-1.37; aOR, 1.54; 95% CI, 1.15-2.06) compared with infants whose mothers did not have asthma (adjusted for maternal race, maternal BMI, maternal age, maternal education, BW, and sex).

Discussion

We found that women with asthma were at greater odds of delivering preterm infants regardless of whether the preterm birth was spontaneous or medically indicated. Interestingly, women with asthma were at higher odds of delivering preterm infants who subsequently developed BPD if they did not receive antenatal steroids.

Our observed prevalence of maternal asthma (2.4%) is similar to that reported in other studies that used a similar approach as ours.^{11,12} In contrast, surveys using direct interviews, such as the National Center for Health Statistics and Vital Statistics system, have found much a higher percentage of asthma (eg, 9.5%) in similar populations of childbearing-age women. One potential explanation for this discrepancy is that only asthma that was being actively treated during pregnancy was recorded in discharge records.

Compared with mothers without asthma, those with asthma were more likely to be obese, have private insurance, be non-Latina black or non-Latina white, and less likely to be Latina or Asian. Mendola et al³ reported that women with asthma in their study population also were more likely to be non-Latina black, and obese, but to have public insurance. This discrepancy regarding insurance status may reflect the California-wide nature of our study vs the more restricted cohort nature of the Mendola et al³ study. In our analysis of the association between maternal asthma and BPD, we adjusted for these and other characteristics, including maternal BMI, maternal education, payer status, race/ethnicity, and maternal age.

We found that pregnant women with asthma had increased odds of preterm delivery of singleton births. This finding is consistent with recent studies. In a meta-analysis of 40 publications, Murphy et al¹³ reported an elevated risk for preterm delivery in women with asthma (OR, 1.41; 95% CI, 1.22-1.61). Similarly, Mendola et al¹⁴ reported on a retrospective cohort using electronic medical records data on 223 512 deliveries during 2002-2008 and showed that women with asthma were at greater odds of preterm birth (OR, 1.17; 95% CI, 1.12-1.23). Hyperactivity of smooth muscle in both the lung and the uterine myometrium has been suggested to explain the relationship between the increased risk of preterm birth and maternal asthma.^{8,9} We also found that the increased risk of preterm birth in mothers with asthma was greatest in the 28-32 weeks GA group; this finding differs from the results of Mendola et al,¹⁴ who found the greatest risk of preterm birth in mothers with asthma at weeks 34, 35, and 36 GA. Regardless, the present study and all of the previous studies demonstrate that maternal asthma

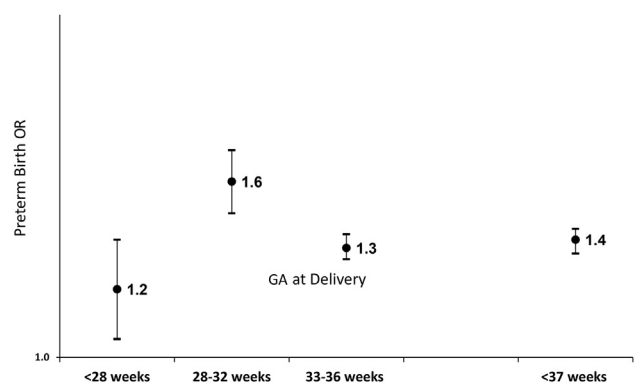


Figure 1. Odds of preterm birth in mothers with asthma compared with those without asthma. OR adjusted for maternal BMI, maternal education, payer status at delivery, race/ethnicity, and maternal age. Data from the OSHPD. Total, n = 2 009 511; term births, n = 1 864 345; term births with maternal asthma, n = 43 299. Births at <37 wk GA, crude OR, 1.42; 95% CI, 1.38-1.46; aOR, 1.37; 95% CI, 1.32-1.41. Births at 33-36 wk GA, crude OR, 1.38; 95% CI, 1.38-1.42; aOR, 1.34; 95% CI, 1.30-1.39. Births at 28-32 wk GA, crude OR, 1.70; 95% CI, 1.58-1.84; aOR, 1.60; 95% CI, 1.47-1.74. Births at <28 wk, crude OR, 1.70; 95% CI, 1.58-1.84; aOR, 1.61; 95% CI, 1.47-1.74.

Table III. Characteristics of infant and mother in the preterm infant cohort from the CPQCC database

Characteristics	BPD (n = 9520; 43.4%)	No BPD (n = 12 424; 56.6%)
Asthma (ICD code 493.xx)		
No	9182 (96.4)	11 970 (96.3)
Yes	338 (3.6)	454 (3.7)
Maternal race/ethnicity		
White	2303 (24.7)	3046 (25.0)
Black	1057 (11.3)	1288 (10.6)
Hispanic	4994 (53.5)	6328 (52.0)
Other	980 (10.5)	1510 (12.4)
Maternal age		
<20 y	1119 (11.8)	1301 (10.5)
20-29 y	4285 (45.0)	5465 (44.0)
30-39 y	3580 (37.6)	4987 (40.1)
40-49 y	531 (5.6)	668 (5.4)
50+ y	3 (0.0)	3 (0.0)
Principal source of payment for delivery		
Medi-Cal	4944 (52.1)	6362 (51.4)
Private	3976 (41.9)	5296 (42.8)
Uninsured	285 (3.0)	313 (2.5)
Other	277 (2.9)	412 (3.3)
Maternal prepregnancy BMI		
Underweight	322 (3.8)	543 (4.9)
Normal weight	3512 (41.8)	5028 (45.5)
Overweight	2197 (26.2)	2795 (25.3)
Obese	2370 (28.2)	2687 (24.3)
Cigarette during pregnancy		
No	8963 (96.3)	11 691 (96.1)
Yes	344 (3.7)	473 (3.9)
Cigarette 3 mo before pregnancy		
No	8838 (95.0)	11 569 (95.1)
Yes	464 (5.0)	591 (4.9)
Maternal education		
Less than high school	2535 (27.8)	3288 (27.6)
High school graduate or GED	2687 (29.4)	3263 (27.4)
Some college	1835 (20.1)	2365 (19.8)
Associate degree	486 (5.3)	644 (5.4)
Undergraduate degree	1081 (11.8)	1590 (13.3)
Postgraduate degree	506 (5.5)	780 (6.5)
BW		
<750 g	1873 (19.7)	133 (1.1)
750-999 g	2321 (24.4)	738 (5.9)
1000-1249 g	1508 (15.8)	1875 (15.1)
1250-1500 g	746 (7.8)	3094 (24.9)
1500+ g	3072 (32.3)	6584 (53.0)
Sex		
Female	4049 (42.6)	5606 (45.2)
Male	5466 (57.4)	6809 (54.8)
Antenatal steroids ever received before delivery		
No	3460 (36.6)	5136 (41.8)
Yes	5983 (63.4)	7163 (58.2)
PDA intervention		
No PDA	3552 (37.4)	9582 (77.2)
Medication and surgery	1085 (11.4)	77 (0.6)
Medication only	2850 (30.0)	1376 (11.1)
Surgery only	501 (5.3)	68 (0.5)
None or unknown treatment	1516 (16.0)	1308 (10.5)

GED, general education development; PDA, patent ductus arteriosus.

is associated with an increased risk of delivery at <37 weeks GA.

Mendola et al³ reported that mothers with asthma had higher odds of having a medically indicated preterm delivery. However, we found that asthma was more closely associated with the spontaneous preterm birth subtype (OR, 1.45; 95%

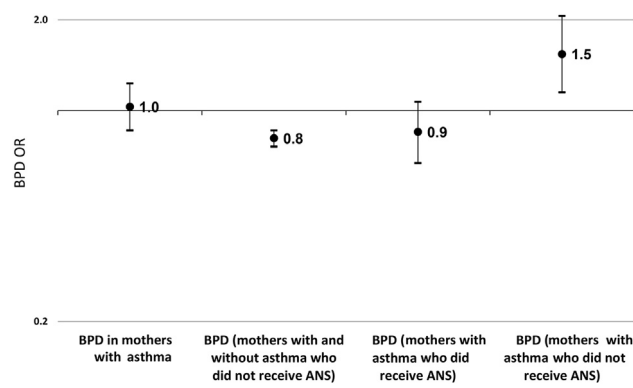


Figure 3. Odds of BPD among mothers with and without asthma and mothers with asthma compared with mothers without asthma among singleton preterm infants in the CPQCC. Odds of BPD stratified by mothers with asthma who received antenatal steroid (ANS) therapy and mothers with asthma who did not receive antenatal steroids. Total, n = 21 944; BPD, n = 9520; mothers with asthma, n = 792. Mothers with asthma and infants with BPD, crude OR, 0.97; 95% CI, 0.84-1.12; aOR, 1.03; 95% CI, 0.86-1.23. Mothers with and without asthma who did not receive ANS, mothers who did receive ANS and infants with BPD, crude OR, 0.81; 95% CI, 0.76-0.85; aOR, 0.81; 95% CI, 0.76-0.86. BPD odds in mothers with asthma who did not receive ANS. ANS in mothers with asthma, n = 540; ANS in mothers with asthma with infants with BPD, n = 220; crude OR, 0.82; 95% CI, 0.69-0.97; aOR, 0.85; 95% CI, 0.67-1.07. Mothers who did not receive ANS with asthma, n = 240; no ANS mothers with asthma, infants with BPD, n = 115; BPD in mothers with asthma no ANS, crude OR, 1.38; 95% CI, 1.07-1.78; aOR, 1.54; 95% CI, 1.15-2.06. *PTB*, preterm birth.

CI, 1.4-1.5), with the medically indicated subtype having a positive, but somewhat weaker association (OR, 1.28; 95% CI, 1.19-1.37). One potential explanation for this finding is related to the shift away from cesarean delivery, because our study involves data from 2007-2010, whereas the study by Mendola et al³ examined data from 2002-2008. We noted a reduced risk for BPD in infants who had preterm birth recorded as “unknown.” One potential explanation is that these infants may be small for GA and mislabeled as preterm based on their BW, and thus there would not be documentation regarding the reason for their preterm delivery.

Previous studies have indicated a relationship between lung disease in preterm infants and a family history of asthma. Bertrand et al⁹ studied mothers and preterm sibling pairs with and without respiratory distress syndrome (RDS) and found a correlation between bronchial reactivity development in the children who survived RDS and their mothers’ degree of bronchial hyperactivity. Given that bronchial reactivity is a hallmark of asthma, that study suggests that maternal predisposition to asthma increases the likelihood of a preterm-born infant developing long-term reactive airway disease or asthma. Similarly, Nickerson et al⁵ found

that preterm infants born at <36 weeks GA with RDS who had a family history for asthma were more likely to develop BPD. In a study by Hagan et al,⁶ preterm infants born at <30 weeks GA with RDS were more likely to receive supplemental oxygen at term if they had a family member with asthma.

We examined maternal asthma as opposed to family history, because maternal history confers a greater risk for the development of asthma in childhood compared with a paternal history of asthma.¹⁵ Our analyses did not find a substantially elevated risk of asthma in all mothers of singleton preterm infants associated with the development of BPD, however (aOR, 1.03; 95% CI, 0.9-1.2), unless the mother did not receive antenatal steroids. This finding differs substantially from the results of 2 previous studies on the relationship of family history of asthma with the development of BPD.^{5,6} One potential explanation for this apparent discrepancy is that the infants in both of those studies had “old” BPD, as first described by Northway et al,¹⁶ which was largely influenced by mechanical ventilation and oxygen exposure. In contrast, the infants in our cohort had “new” BPD, or BPD in the postsurfactant era. Thus, the apparently divergent findings regarding familial influence could represent 2 separate disease phenotypes, the development of which might be influenced by different factors. Another potential explanation is that the infants in the previous studies did not receive antenatal steroid therapy.

There is a complex relationship between antenatal corticosteroid use and the development of BPD. Some previous studies have not identified such a relationship,¹⁷⁻²⁰ whereas other studies have found this relationship.^{21,22} Gagliardi et al²³ suggested that previous studies overcorrected in their modeling, including mediators for the development of BPD such as severity of early disease, duration of mechanical ventilation, and patent ductus arteriosus, and concluded that antenatal steroids do have an effect on BPD.²³ When we stratified for antenatal steroid use and evaluated its effect on the relationship between maternal asthma and development of BPD, we found that the mothers with asthma who have preterm infants and did not receive antenatal steroids were at increased odds for having an infant with BPD (OR, 1.54; 95% CI, 1.15-2.06) compared with infants of mothers without asthma. This relationship has not been studied previously and may provide an explanation for the discrepancies in earlier studies, which did not stratify for antenatal steroid use. A possible explanation may be that asthma is an inflammatory disease, and that the use of antenatal steroids may confer protection for these infants. One theory is that the inflammatory cascade that is heightened in a mother with asthma is attenuated with the use of antenatal steroids and reduces the triggering of these inflammatory pathways in the preterm infant, which causes pulmonary inflammation, leading to lung injury and remodeling, as well as disruption of lung morphogenesis.²⁴⁻²⁷ Another explanation could be that antenatal steroid therapy is a marker of the quality of overall antenatal care.

The strengths of the present study lie in its large population-based approach, large numbers of singleton preterm infants, and ability to examine various specific factors affecting both maternal asthma and preterm birth. Limitations include the lack of information regarding asthma severity, medication use during pregnancy, and type and dose of antenatal steroids used in the setting of preterm labor. We also lacked data regarding mode of conception, as well as some important covariates, such as maternal cigarette smoking, owing to poor reporting. Approximately 5% of mothers reported smoking 3 months before pregnancy, and 3.7% reported smoking during pregnancy. Given these limited results, we stratified for smokers and nonsmokers, but this did not change the odds of BPD in preterm infants. Currently, the CPQCC does not require a physiological definition of BPD, and thus we are limited to oxygen data provided in the CPQCC. In addition, the current CPQCC data do not allow us to differentiate between moderate and severe BPD. We were limited by the birth certificate to understanding the preterm birth subtype; thus, there was a small percentage of unknown subtype.

This study extends our understanding of the relationships among maternal asthma and preterm birth, preterm birth subtype, and BPD. Our novel finding that maternal asthma is associated with increased odds of BPD in infants whose mothers did not receive antenatal steroids is clinically important. This information may further inform the care of women with asthma during pregnancy, and help guide the use of antenatal steroids in maternal asthma and preterm birth. ■

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References

1. Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: estimates from national health surveys. *Ann Epidemiol* 2003;13:317-24.
2. Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, Attia J, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *Br J Obstet Gynecol* 2011;118:1314-23.
3. Mendola P, Laughon SK, Mannisto TI, Leishear K, Reddy UM, Chen Z, et al. Obstetric complications among US women with asthma. *Am J Obstet Gynecol* 2013;208:127.e1-8.
4. Martin JA, Kung HC, Mathews TJ, Hoyert DL, Strobino DM, Guyer B, et al. Annual summary of vital statistics: 2006. *Pediatrics* 2008;121:788-801.
5. Nickerson BG, Taussig LM. Family history of asthma in infants with bronchopulmonary dysplasia. *Pediatrics* 1980;65:1140-4.
6. Hagan R, Minutillo C, French N, Reese A, Landau L, LeSouef P. Neonatal chronic lung disease, oxygen dependency, and a family history of asthma. *Pediatr Pulmonol* 1995;20:277-83.
7. Voltolini C, Torricelli M, Conti N, Vellucci FL, Severi FM, Petraglia F. Understanding spontaneous preterm birth: from underlying mechanisms to predictive and preventive interventions. *Reprod Sci* 2013;20:1274-92.
8. Kramer MS, Coates AL, Michoud MC, Dagenais S, Moshonas D, Davis GM, et al. Maternal asthma and idiopathic preterm labor. *Am J Epidemiol* 1995;142:1078-88.

9. Bertrand JM, Riley SP, Popkin J, Coates AL. The long-term pulmonary sequelae of prematurity: the role of familial airway hyperreactivity and the respiratory distress syndrome. *N Engl J Med* 1985;312:742-5.
10. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723-9.
11. Berg CJ, Mackay AP, Qin C, Callaghan WM. Overview of maternal morbidity during hospitalization for labor and delivery in the United States: 1993-1997 and 2001-2005. *Obstet Gynecol* 2009;113:1075-81.
12. Fridman M, Korst LM, Chow J, Lawton E, Mitchell C, Gregory KD. Trends in maternal morbidity before and during pregnancy in California. *Am J Public Health* 2014;104(Suppl 1):S49-57.
13. Murphy VE, Wang G, Namazy JA, Powell H, Gibson PG, Chambers C, et al. The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. *Br J Obstet Gynecol* 2013;120:812-22.
14. Mendola P, Mannisto TI, Leishear K, Reddy UM, Chen Z, Laughon SK. Neonatal health of infants born to mothers with asthma. *J Allergy Clin Immunol* 2014;133:85-90.e1-4.
15. Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med* 1998;158:176-81.
16. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease: bronchopulmonary dysplasia. *N Engl J Med* 1967;276:357-68.
17. Van Marter LJ, Allred EN, Leviton A, Pagano M, Parad R, Moore M, et al. Antenatal glucocorticoid treatment does not reduce chronic lung disease among surviving preterm infants. *J Pediatr* 2001;138:198-204.
18. Egreteau L, Pauchard JY, Semama DS, Matis J, Liska A, Romeo B, et al. Chronic oxygen dependency in infants born at less than 32 weeks' gestation: incidence and risk factors. *Pediatrics* 2001;108:e26.
19. Wells LR, Papile LA, Gardner MO, Hartenberger CR, Merker L. Impact of antenatal corticosteroid therapy in very low birth weight infants on chronic lung disease and other morbidities of prematurity. *J Perinatol* 1999;19:578-81.
20. Marshall DD, Kotelchuck M, Young TE, Bose CL, Krueyer L, O'Shea TM, North Carolina Neonatologists Association. Risk factors for chronic lung disease in the surfactant era: a North Carolina population-based study of very low birth weight infants. *Pediatrics* 1999;104:1345-50.
21. Van Marter LJ, Leviton A, Kuban KC, Pagano M, Allred EN. Maternal glucocorticoid therapy and reduced risk of bronchopulmonary dysplasia. *Pediatrics* 1990;86:331-6.
22. Doyle LW, Kitchen WH, Ford GW, Rickards AL, Lissenden JV, Ryan MM. Effects of antenatal steroid therapy on mortality and morbidity in very low birth weight infants. *J Pediatr* 1986;108:287-92.
23. Gagliardi L, Bellu R, Rusconi F, Merazzi D, Mosca F. Antenatal steroids and risk of bronchopulmonary dysplasia: a lack of effect or a case of over-adjustment? *Paediatr Perinat Epidemiol* 2007;21:347-53.
24. Kunzmann S, Collins JJ, Kuypers E, Kramer BW. Thrown off balance: the effect of antenatal inflammation on the developing lung and immune system. *Am J Obstet Gynecol* 2013;208:429-37.
25. Kramer BW, Kramer S, Ikegami M, Jobe AH. Injury, inflammation, and remodeling in fetal sheep lung after intra-amniotic endotoxin. *Am J Physiol Lung Cell Mol Physiol* 2002;283:L452-9.
26. Kramer BW, Kallapur S, Newnham J, Jobe AH. Prenatal inflammation and lung development. *Semin Fetal Neonatal Med* 2009;14:2-7.
27. Benjamin JT, Carver BJ, Plosa EJ, Yamamoto Y, Miller JD, Liu JH, et al. NF-kappaB activation limits airway branching through inhibition of Sp1-mediated fibroblast growth factor-10 expression. *J Immunol* 2010;185:4896-903.

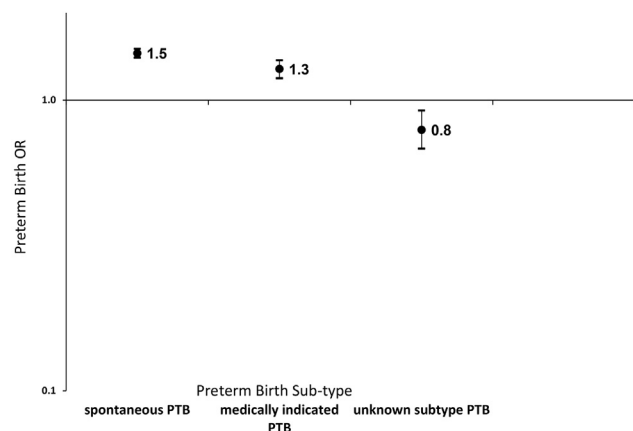


Figure 2. Odds of preterm birth subtype among mothers with asthma compared with mothers without asthma. OR adjusted for maternal BMI, maternal education, payer status at delivery, race/ethnicity, and maternal age. Data from the OSHPD. Spontaneous preterm birth (PTB), $n = 104\,859$; spontaneous PTB mothers with asthma, $n = 3624$; crude OR, 1.51; 95% CI, 1.45-1.56; aOR, 1.45; 95% CI, 1.40-1.50. Medically indicated PTB, $n = 283\,398$; medically indicated PTB mothers with asthma, $n = 908$; crude OR, 1.39; 95% CI, 1.30-1.49; aOR, 1.28; 95% CI, 1.19-1.37. Unknown PTB subtype, $n = 11\,909$; unknown PTB subtype mothers with asthma, $n = 202$; crude OR, 0.73; 95% CI, 0.63-0.83; aOR, 0.79; 95% CI, 0.68-0.92.2.

Table II. Characteristics of the study population of women with or without asthma with singleton births, California, 2007-2010

Characteristics	Asthma ($n = 48\,033$; 2.4%)	No asthma ($n = 1\,961\,478$; 97.6%)
GA		
20-23 w	59 (0.1)	2217 (0.1)
24-31 w	665 (1.4)	17 208 (0.9)
32-36 w	4010 (8.3)	121 007 (6.2)
37+ w	43 299 (90.1)	1 821 046 (92.8)
BW		
<750 g	144 (0.3)	4437 (0.2)
750-999 g	123 (0.3)	3386 (0.2)
1000-1249 g	165 (0.3)	3812 (0.2)
1250-1500 g	191 (0.4)	4809 (0.2)
1500+ g	47 410 (98.7)	1 945 030 (99.2)
Term birth	43 299 (90.1)	1 821 046 (92.8)
Sex		
Female	23 414 (48.7)	956 106 (48.7)
Male	24 619 (51.3)	1 005 360 (51.3)
Diabetes		
No	47 186 (98.2)	1 945 372 (99.2)
Yes	847 (1.8)	16 106 (0.8)
Gestational diabetes		
No	43 698 (91.0)	1 826 084 (93.1)
Yes	435 (9.0)	135 394 (6.9)
Hypertension		
No	45 817 (95.4)	1 928 568 (98.3)
Yes	2216 (4.6)	32 910 (1.7)
Gestational hypertension		
No	46 469 (96.7)	1 920 270 (97.9)
Yes	1564 (3.3)	41 208 (2.1)
Preeclampsia		
No	45 782 (95.3)	1 905 706 (97.2)
Yes	2251 (4.7)	55 772 (2.8)
Polyhydramnios		
No	47 748 (99.4)	1 953 010 (99.6)
Yes	285 (0.6)	8468 (0.4)
Oligohydramnios		
No	46 334 (96.5)	1 909 085 (97.3)
Yes	1699 (3.5)	52 393 (2.7)
Maternal race/ethnicity		
Non-Latina white	17 961 (38.1)	521 082 (27.0)
Non-Latina black	6522 (13.8)	107 107 (5.5)
Non-Latina Asian	2078 (4.4)	188 910 (9.8)
Non-Latina Pacific Islander	2142 (4.5)	65 014 (3.4)
Latina	17 966 (38.1)	1 040 637 (53.8)
Non-Latina Asian	435 (0.9)	8468 (0.4)
Non-Latina Other	50 (0.1)	1477 (0.1)
Maternal age		
<20 y	5204 (10.8)	183 573 (9.4)
20-29 y	23 304 (48.5)	956 031 (48.7)
30-39 y	17 751 (37.0)	752 870 (38.4)
40-49 y	1766 (3.7)	68 739 (3.5)
50+ y	7 (0.0)	234 (0.0)
Principal source of payment for prenatal care		
Medi-Cal	18 314 (38.2)	943 813 (48.2)
Private	27 461 (57.3)	907 648 (46.4)
Uninsured	626 (1.3)	46 878 (2.4)
Other	1556 (3.2)	59 649 (3.0)
Principal source of payment for delivery		
Medi-Cal	18 554 (38.7)	951 432 (48.6)
Private	27 549 (57.4)	910 877 (46.5)
Uninsured	467 (1.0)	40 766 (2.1)
Other	1398 (2.9)	55 425 (2.8)
Maternal prepregnancy BMI		
Underweight	1266 (2.8)	74 834 (4.2)
Normal weight	18 113 (40.5)	897 919 (50.2)
Overweight	11 653 (26.0)	459 028 (25.7)
Obese	13 717 (30.7)	355 399 (19.9)