

*Original article***Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes**

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Background: Asthma is a common condition during pregnancy. **Objective:** We sought to determine the effect of asthma on the rates of adverse pregnancy and fetal outcomes.

Methods: We identified pregnancies among black and white women age 15 to 44 with singleton gestations enrolled in the Tennessee Medicaid program over a period of 9 consecutive years, from 1995 to 2003, and used claims data to determine the relationship of maternal asthma and asthma exacerbations on pregnancy and infant outcomes.

Results: Among the 140,299 pregnancies, 6.5% were in women with asthma. Among women with asthma, 23% had a hospital or emergency department visit (exacerbated asthma); 40% of black and 23% of white women received hospital or emergency department care for asthma during pregnancy. After controlling for race and other covariates, birth weights among infants of women with asthma were, on average, 38 g lower, and among infants of women with exacerbated asthma they were, on average, 56 g lower. There were moderate, dose-dependent relationships between asthma alone and exacerbated asthma with hypertensive disorders of pregnancy, membrane-related disorders, preterm labor, antepartum hemorrhage, and cesarean delivery. Maternal asthma was not associated with preterm birth or birth defects.

Conclusion: Asthma is a risk factor for several common adverse outcomes of pregnancy, and poorly controlled asthma during pregnancy increases these risks.

Clinical implications: It is possible that both maternal and infant outcomes could be improved in this population with appropriate asthma care, especially among black women. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, pregnancy, Medicaid database, outcomes, birth weight

Asthma is one of the most common chronic medical conditions complicating pregnancy, affecting as many as 8% of pregnant women.¹⁻⁵ Studies of inhaled asthma medication use during pregnancy have not identified risks to mother or fetus, and national guidelines recommend the continued use of appropriate asthma medications because adverse maternal and neonatal outcomes have been described among women with more severe asthma or asthma requiring hospital care.^{3,5-19} However, results have been inconsistent and weak.

In the largest US population studied to date, we report the relationship between maternal asthma, exacerbated asthma, and pregnancy outcomes. This population includes a large number of African American women (41%). African Americans are disproportionately affected by both asthma morbidity and adverse pregnancy outcomes, and any adverse effect of exacerbated asthma on pregnancy outcomes could be a cause of existing health disparities. The current study population also includes persons at greater risk of exacerbated asthma²⁰ and therefore was designed to estimate the effect of lack of asthma control on pregnancy and perinatal outcomes.

METHODS

We conducted a cohort study of 140,299 pregnancies among black or white women age 15 to 44 years enrolled in the Tennessee Medicaid program during the period 1995 to 2003 who had at least 180 days of continuous enrollment before their last menstrual period (LMP). These requirements captured 44% of deliveries to mothers enrolled in Medicaid and approximately 19% of all births to Tennessee residents during the 9 consecutive study years. Maternal race was available for all TennCare enrollees, and 97.6% of enrollees were white or black; nonwhite, nonblack women were too few to evaluate during the study years.

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Abbreviations used

ED: Emergency department
 ICD-9: International Classification of Diseases,
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 LMP: Last menstrual period
 SGA: Small for gestational age

Data were obtained from linked Tennessee Medicaid database and vital records files provided by the Tennessee Department of Health, Division of Health Statistics. These linked data files were developed for studying medication use and pregnancy outcomes among pregnant women enrolled in the Tennessee Medicaid Program.^{21,22} Demographics and race were obtained from Tennessee birth certificates (infants) and Tennessee Medicaid enrollment files (mothers). Birth certificates include the date of the LMP, which was used to estimate week of pregnancy.

Asthma-specific medication use was determined by using Tennessee Medicaid pharmacy claims files, which included prescriptions filled and the number of days supplied as previously described.²³ Rescue corticosteroid use was defined as a single prescription of at least 3 days' supply, with each new course separated by at least 7 days. Terbutaline was excluded because of its use for preterm labor, and dexamethasone, betamethasone, and hydrocortisone were excluded because these medications may have been used in pregnant women at risk for preterm labor during the study years to prevent infant respiratory distress syndrome and are rarely used in clinical practice for the treatment of asthma exacerbations.

Mothers with an International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code of 493 (asthma) in any of the 9 diagnostic fields for inpatient, other hospital care (23-hour observation) or outpatient physician visit claims and/or women with 2 prescriptions for any short-acting β -agonist or a single prescription for any other asthma medication from the 180 days before LMP through 150 days after LMP were classified as having asthma. In previous studies, this definition was validated by chart reviews and found to be highly sensitive and specific.^{4,23} Although asthma medication use was recorded throughout pregnancy, women could be classified as having asthma only if they met the definition of asthma from LMP – 180 days to LMP + 150 days. Exacerbated asthma was defined as hospital or emergency department (ED) care for asthma during pregnancy, and asthma alone was asthma with no record of hospital or ED care during pregnancy.

Infant birth weight, gestational age, and maternal smoking were abstracted from birth certificates, whereas remaining maternal and infant outcomes were determined from ICD-9 diagnostic codes (see this article's [Tables E1 and E2](#) in the Online Repository at www.jacionline.org). Adequacy of prenatal care was defined by using the Kotelchuck index, which classifies prenatal care on the basis of the timing of the initiation of care and service use in the following categories: none, inadequate, intermediate, adequate, and adequate plus.²⁴ Maternal comorbidity was defined as inpatient or outpatient claims for bipolar affective disorder, depression, schizophrenia, mental retardation, chronic kidney disease, diabetes (not gestational), heart disease, immunodeficiency, malignancy, other chronic lung diseases, and sexually transmitted infections. Women with prevalent hypertension were included in the cohort, and pregnancy-induced hypertension was identified by using pregnancy-specific ICD-9 codes (642.3–642.9) and was defined from LMP + 150 through date of delivery. A complete list of disease definitions and data sources can be found in this article's [Tables E1 and E2](#) in this article's Online Repository at www.jacionline.org.

Clinical characteristics were compared between pregnant women with and without asthma by using Pearson χ^2 tests for categorical variables and *t* tests for birth weight and gestational age. Multiple linear regression models assessed the relationship between asthma and exacerbated asthma on infant birth weight after adjustment for maternal race (black/white), maternal age (continuous), smoking (yes/no), education (<12 years, 12 years, >12 years, missing), comorbidity (yes/no), adequacy of prenatal care (adequate plus, adequate, intermediate, inadequate, missing), and gestational age (continuous), which is strongly associated with birth weight. In multiple logistic regression models, dichotomous indicator variables were used to estimate the independent effects of nonexacerbated and exacerbated asthma on the outcomes depicted in [Fig 2](#). The logistic regression models were adjusted for maternal race, maternal age, smoking, education, comorbidity, and adequacy of prenatal care. Subsequently, an ordinal variable for asthma severity (none, asthma alone, exacerbated asthma) was used to estimate the significance of the observed dose response. All models included 140,299 observations except for the logistic regression model for cesarean section, which omitted 57 observations in which the method of delivery was unknown. Statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC).

The protocol was approved by the Institutional Review Boards of Vanderbilt University and the Tennessee Department of Health.

RESULTS

The study cohort included 83,008 (59.2%) white and 57,291 (40.8%) black pregnant women enrolled in the Tennessee Medicaid program ([Table I](#)). Black women were more likely to be unmarried and have an urban residence, and white women were more likely to be smokers. Overall, 9154 (6.5%) of women had asthma; white women (7.8%) were more likely than black women (4.6%) to be classified as having asthma. In addition, women with asthma were more likely to smoke and had more comorbidities than women without asthma. During pregnancy, 60% of women with asthma used inhaled β -agonists, less than 25% used inhaled corticosteroids, and 23% of white women and 40% of black women had a hospitalization or ED visit for asthma during pregnancy ([Table I](#)). Of women with asthma who used inhaled corticosteroids, 72% filled only 1 prescription during pregnancy; β -agonist use was more frequent, with 46% of users obtaining at least 2 reliever medication inhalers during pregnancy. Among women who used any asthma medication, on average 3.4 reliever medications were dispensed for every controller medication.

Several complications of pregnancy were observed more frequently among women with than without asthma, including hypertensive disorders, antepartum hemorrhage, membrane-related disorders, gestational diabetes, cesarean section, low birth weight, and small size for gestational age (SGA; [Table II](#)). Preterm birth, congenital defects, and postpartum hemorrhage were not associated with maternal asthma.

We estimated the effect of asthma and exacerbated asthma on infant birth weight adjusted for maternal race, maternal age, smoking, education, comorbidities, adequacy of prenatal care, and gestational age ([Fig 1](#)). Asthma

TABLE I. Demographic and clinical characteristics of pregnant women with and without asthma carrying singleton gestations (N = 140,299 pregnancies)*

Characteristics	Pregnant women with asthma (N = 9154) (6.5%)		Pregnant women without asthma (N = 131,145) (93.5%)	
	White (N = 6509)	Black (N = 2645)	White (N = 76,499)	Black (N = 54,646)
Age (y), mean (SD)	23.7 (5.5)	23.0 (5.3)	23.2 (5.1)	23.0 (5.2)
Education				
<12 y	3014 (46.3)	1149 (43.4)	32,162 (42.0)	21,889 (40.5)
12 y	2699 (41.5)	1076 (40.7)	34,148 (44.6)	24,055 (44)
>12 y	777 (11.9)	411 (15.5)	10,019 (13.1)	8558 (15.7)
Unknown	19 (0.3)	9 (0.3)	170 (0.2)	144 (0.3)
Marital status†				
Married	3348 (51.4)	381 (14.4)	41,484 (54.2)	7298 (13.4)
Not married	3160 (48.6)	2264 (85.6)	35,007 (45.8)	47,347 (86.6)
Residence‡				
Urban	1262 (19.4)	2035 (76.9)	15,133 (19.8)	43,732 (80)
Standard metropolitan statistical area	2060 (31.6)	350 (13.2)	24,921 (32.6)	6281 (11.5)
Rural	3187 (49)	260 (9.8)	36,444 (47.6)	4632 (8.5)
Parity				
Nulliparous	2185 (33.6)	757 (28.6)	24,937 (32.6)	14,048 (25.7)
Multiparous	4324 (66.4)	1888 (71.4)	51,562 (67.4)	40,598 (74.3)
Adequacy of prenatal care				
Adequate plus	2097 (32.2)	653 (24.7)	21,820 (28.5)	12,405 (22.7)
Adequate	2666 (41)	1030 (38.9)	32,846 (42.9)	19,063 (34.9)
Intermediate	1015 (15.6)	409 (15.5)	12,299 (16.1)	8671 (15.9)
Inadequate	650 (10)	502 (19)	8569 (11.2)	13,543 (24.8)
Unknown	81 (1.2)	51 (1.9)	965 (1.3)	964 (1.8)
Maternal exposures during pregnancy (%)				
Smoking during pregnancy	48.2	13.0	39.1	11.2
Alcohol use during pregnancy	1.5	1.6	0.9	1.9
Drug use during pregnancy	3.3	3.7	2.5	3.3
Comorbid condition‡	17.8	14.7	7.3	7.1
Short-acting β -agonist use during pregnancy	3906 (60)	1631 (61.7)	—	—
Inhaled corticosteroid use during pregnancy	1451 (22.3)	638 (24.1)	—	—
Asthma hospitalization and/or ED visit during pregnancy	1489 (22.9)	990 (39.9)	—	—

*Values in parentheses are percentages unless noted otherwise.

†Missing values are not reported.

‡Comorbid conditions include chronic kidney disease, depression, bipolar, diabetes, heart disease, immune deficiency, chronic lung disease (excluding asthma), malignancy, mental retardation, schizophrenia, and sexually transmitted infections.

not requiring ED or hospital care during pregnancy was associated with a 38-g decrease in birth weight ($P = .0002$); asthma requiring hospitalization or ED visit during pregnancy was associated with a 56-g decrease in birth weight ($P < .0001$), and there was a significant dose-response trend ($P < .0001$) between lower birth weight and increasing use of oral corticosteroids during pregnancy.

We estimated the effect of asthma alone and exacerbated asthma on the odds ratios for any birth defect, cesarean delivery, preterm birth, antepartum hemorrhage, preterm labor, membrane-related disorders, and hypertensive disorders of pregnancy. These odds were calculated with respect to the children of mothers without asthma and were adjusted for maternal age, race, smoking, education, and comorbidities. Significant, consistent associations with asthma alone and exacerbated asthma, respectively, were observed for low birth weight, cesarean delivery, antepartum hemorrhage, preterm labor, membrane-related

disorders, and hypertensive disorders of pregnancy (Fig 2). Although the observed associations were moderate, with odds ratio estimates of <1.5 , we found consistent dose-response relationships, and results were highly statistically significant with $P \leq .002$ for all outcomes. Asthma was not associated with preterm birth or birth defects.

Maternal race did not modify the relationship between maternal asthma and adverse pregnancy and perinatal outcomes; an interaction term was nonsignificant ($P > .1$ for all outcomes). However, maternal asthma exacerbations were significantly more common among African American women.

DISCUSSION

Asthma is one of the most common conditions complicating pregnancy. In this population, 77% of women with asthma did not use asthma controller medications,

TABLE II. Maternal and perinatal outcomes among 140,299 singleton gestation pregnancies by maternal asthma status

Variable	With asthma (N = 9154) (6.5%)	Without asthma (N = 131,145) (93.5%)	P value
Hypertensive disorder of pregnancy	823 (9)	9354 (7.1)	<.0001
Antepartum hemorrhage	236 (2.6)	2524 (1.9)	<.0001
Postpartum hemorrhage	131 (1.4)	1556 (1.2)	.04
Membrane-related disorder	517 (5.6)	6229 (4.7)	.0001
Gestational diabetes	375 (4.1)	3569 (2.7)	<.0001
Preterm labor	747 (8.2)	9825 (7.5)	.02
Method of delivery*			
Normal, spontaneous vaginal delivery	6758 (73.8)	102,526 (78.2)	<.0001
Cesarean section	2341 (25.6)	27,765 (21.2)	
Assisted delivery	52 (0.6)	800 (0.6)	
Length of hospital stay at delivery (d)			
Vaginal delivery	3 (2-3)	3 (1-3)	.3
Median (interquartile range)			
Cesarean section	4 (3-4)	4 (3-4)	.3
Birth weight (g), mean (SD)	3131 (615)	3173 (607)	<.0001
Size for gestational age [N (%)]			
Very SGA	590 (6.5)	7043 (5.4)	<.0001
SGA	1058 (11.6)	12,710 (9.7)	
Appropriate for gestational age	6329 (69.1)	90,679 (69.2)	
Large for gestational age	1175 (12.8)	20,705 (15.8)	
Gestational age (d)			
Mean (SD)	272 (19.9)	272 (20)	.3
Any congenital defect	284 (3.1)	3754 (2.9)	.2

*Missing values are not reported.

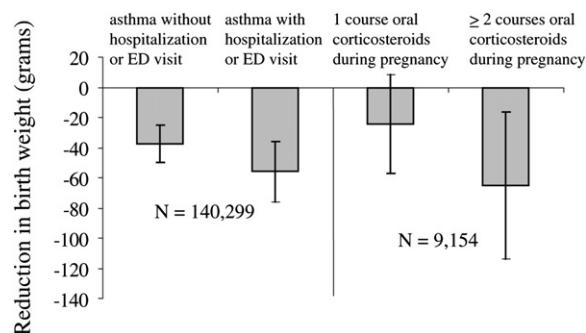


FIG 1. Reduction in birth weight (95% CI) associated with maternal asthma, and indicators of maternal asthma severity. These reductions are with respect to the children of women without asthma. They are adjusted for maternal race, age, smoking, education, comorbidity, adequacy of prenatal care, and gestational age.

26% used excessive quantities of reliever medications (>30 days' supply during pregnancy), the ratio of reliever to controller medication dispensing events was 3.4:1, and 27% had an asthma-associated hospitalization or ED visit during pregnancy. We previously reported that there was a 23% decline in inhaled corticosteroid prescriptions in this population during early pregnancy.²⁵ In the current study, there were few women who regularly filled controller medications, which precluded specifically examining this subset. Previous research indicates that asthma treatment during pregnancy is safe and effective.^{10,12,14,15,26,27}

The current study showed that asthma in pregnancy was associated with complications of pregnancy. These

negative effects on pregnancy and infant outcomes increased in those with exacerbated asthma. Although effect sizes were small, these data suggest that exacerbated asthma may have contributed to adverse pregnancy outcomes.

We also demonstrated that asthma and exacerbated asthma were associated with increasing decrements of infant birth weight, independent of length of gestation. This is consistent with the preponderance of evidence from other studies that indicates asthma, and in particular uncontrolled asthma, is associated with lower birth weights that are not the result of preterm birth.^{10,12,19,28} Slightly decreased oxygenation levels in the blood may have a significant effect on infant growth, as suggested by Schatz et al,¹¹ Olesen et al,¹² Clifton et al,²⁸ and Bracken et al.¹⁰ Although the average decrement in infant birth weight (38 g) was statistically significant, this decrement is not clinically significant. However, in addition to the small decrement in average birth weight, we also report that low birth weights and SGA are observed more frequently in pregnancies affected by asthma. In addition, there are consistent associations between asthma alone and exacerbated asthma, with cesarean delivery, antepartum hemorrhage, preterm labor, membrane-related disorders, and hypertensive disorders of pregnancy. These findings confirm previous reports.^{3,6-9,16,17,19,29,30} A recent British study of 281,019 pregnancies found that maternal asthma was associated only with antepartum or postpartum hemorrhage and cesarean section.³¹ The authors of that study did not have data on birth weight or gestational age but did examine the relationship of

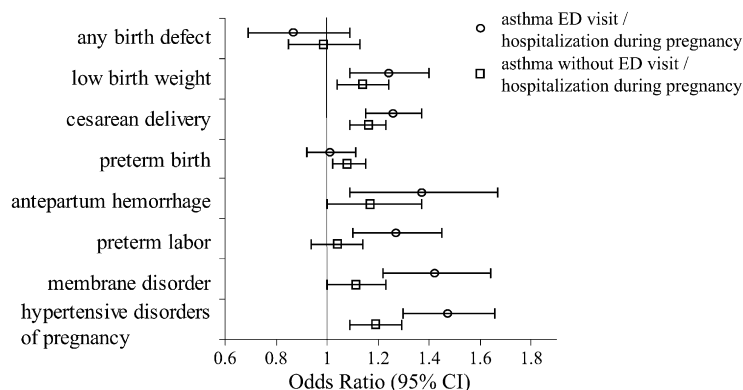


FIG 2. Odds ratios and 95% CIs for associations between maternal asthma and selected pregnancy and infant outcomes; pregnancies not affected by maternal asthma are referent. ORs were adjusted for maternal race, age, smoking, education, comorbidity, and adequacy of prenatal care.

asthma with hypertension or diabetes in pregnancy and assisted deliveries. The British study population was wealthier and more likely to use controller medications than the population of the current study. In addition, the reported prevalence of hypertension in the population was 0.7% and the prevalence of diabetes was 0.4%, suggesting that adverse outcomes may not have been fully ascertained.

The associations reported here were stronger for exacerbated asthma, and significant dose effects were also observed for exposure to increasing amounts of rescue corticosteroids, used to treat acute asthma exacerbations. The significant associations between maternal asthma and adverse maternal and perinatal outcomes were highly significant ($P \leq .002$) for all outcomes and were unlikely to be a result of sampling error alone. However, unmeasured confounding and bias could explain these small effect sizes.

In this analysis, we inferred asthma exacerbations through claims for asthma ED visits and hospitalizations. Black women were 1.6 (95% CI, 1.5-1.7) times more likely than white women to receive care for exacerbated asthma during pregnancy.

Our findings add another report to the literature that confirms maternal asthma was not associated with birth defects,^{3,7,26,27,32} which should be reassuring to expectant mothers. However, birth defects are rare events, and even this large study has insufficient power to detect moderate effects between specific treatments and defects.

Analyses of administrative data are limited by the completeness of claims data and the lack of detail on the severity of treated conditions. The very large size of the population, the standardized data collection methods, and our previous experience confirming the diagnosis of asthma in pregnant women^{4,23} minimize these concerns. More worrisome is the possibility that women with complicated pregnancies have increased contact with the medical care system and more opportunities for the recording of an asthma diagnosis in their claims file. We believe this is unlikely because we defined asthma only through the first 5 months of pregnancy, before many

complications of pregnancy and childbirth became apparent (however, asthma medication use was recorded throughout pregnancy).

We described the largest and most diverse population of pregnant women with asthma studied in the United States. A large proportion of pregnant women with asthma in this study population have exacerbated asthma, increased rates of adverse pregnancy outcomes, and lower infant birth weights compared with subjects without asthma in Tennessee Medicaid. Given that only 592 women with asthma (6.5%) filled 2 or more prescriptions for controller medications, although 1164 women had an ED visit for asthma, it appears that medication is either is not prescribed or not refilled by pregnant women with asthma during pregnancy. Although actual adherence to controller medication was not assessed in this study, medication refilling is a surrogate for use and persistence. The explanation for why controller medication was not refilled by the majority of women could not be assessed in this study. On the basis of the work of others, however, it seems likely that women do not refill these medications because they believe either the medications are not beneficial or the medications might harm their unborn child.³³ Although the effect sizes of asthma and exacerbated asthma on maternal and infant outcomes were small, appropriate asthma control during pregnancy has the potential to prevent adverse outcomes, particularly among African American women who have disproportionate asthma, maternal, and infant morbidity.

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TABLE E1. Maternal outcomes

Idiopathic preterm labor	Idiopathic preterm labor (those women with preterm labor = 644.2, excluding those with uterine malformations = 654.0, known uterine tumors = 654.1, cervical incompetence = 654.5, placenta previa = 641.0-641.1, premature separation of placenta = 641.2, type I or insulin-dependent diabetes mellitus = 250.0-250.9 with a fifth digit code of 1, type II or noninsulin-dependent diabetes mellitus = 250.0-250.9 with a fifth digit code of 0, gestational diabetes = 648.0, preexisting hypertension = 401.0-405.0 and 642.0-642.2, polyhydramnios = 657.0, or medical or surgical induction of labor = ICD-9 procedure code = 730 to 734); defined from LMP + 150 through DDEL.	Yes/no
Hypertensive disorders of pregnancy	Pre-eclampsia (642.4-642.5); transient hypertension of pregnancy (642.3); pregnancy-induced hypertension (defined as either of pre-eclampsia, transient hypertension of pregnancy, pre-eclampsia superimposed on preexisting hypertension, or unspecified hypertension of pregnancy = 642.3-642.9). Defined from LMP + 150 through DDEL.	Yes/no
Antepartum hemorrhage	Placenta previa (641.0 to 641.1); premature separation of placenta (641.2). Defined from LMP + 150 through DDEL.	Yes/no
Membrane-related disorders	Premature rupture of membranes (658.1); infection of the amniotic cavity (658.4). Defined from LMP + 150 through DDEL.	Yes/no
Method of delivery, birth certificate	Vital record file: birth certificate.	1. Unassisted vaginal 2. Cesarean section 3. Forceps 4. Vacuum
Postpartum hemorrhage	Postpartum hemorrhage (666.0-666.2) Defined DDEL – DDEL + 5.	Yes/no
Length of delivery hospital stay	Enrollment file.	Days
Gestational diabetes	Gestational diabetes (648.8) from LMP to DDEL AND No codes for diabetes 250.x from LMP – 180 through LMP + 6 AND No prescriptions for antidiabetic agents from LMP – 180 through LMP + 6.	Yes/no

TABLE E2. Infant outcomes

Variables	Ascertainment and definition	Operational definition
Birth weight (g)	Birth weight from birth certificate	Number in grams
Birth weight category	Very low birth weight is defined as birth weight <1500 g; low birth weight 1500 to <2500 g; normal birth weight 2500 g to <4000 g; high birth weight ≥ 4000 g	Very low birth weight yes/no; low birth weight yes/no; normal birth weight yes/no; high birth weight yes/no
Gestational age	Gestational age in days	Number
Preterm birth	Early preterm birth is defined as as gestational age <32 wk; preterm 32 to <37 completed wk; term ≤ 37 to <42 wk; postterm ≥ 42 wk	Early preterm; preterm; term; postterm
Size for gestational age	Very SGA is defined as a fetal growth ratio <0.75; SGA <0.85; appropriate for gestational age 0.85 to <1.15; large for gestational age >1.15	Very SGA; SGA; appropriate for gestational age; large for gestational age
Any birth defect	Birth certificate indicates any congenital anomaly or 740-759 in infant or maternal record after date of birth	Yes/no
Down syndrome	Birth certificate check box or 758.0 in infant record or 758.0 in maternal record after infant date of birth	Yes/no