

Poorly Controlled Asthma During Pregnancy Remains Common in the United States



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What is already known about this topic? Asthma complicates more than 5% of pregnancies. Smoking is a risk factor for poor asthma control.

What does this article add to our knowledge? Asthma exacerbations are common during pregnancy, particularly among publicly insured women with asthma. A large proportion of pregnant women with poorly controlled asthma do not fill a prescription for the indicated long-term asthma controllers during their pregnancy.

How does this study impact current management guidelines? Reasons for the apparent incomplete uptake of current guidelines in pregnant women, and the potential consequences, warrant further investigation.

BACKGROUND: Asthma is among the most common preexisting medical conditions in pregnancy. Uncontrolled asthma may increase the risk of adverse pregnancy outcomes. **OBJECTIVES:** To describe the prevalence, severity, and control of asthma during pregnancy in the United States. **METHODS:** We identified 2 cohorts of pregnancies ending in a live birth within 2 large US health care claims databases: the Truven Health MarketScan Commercial Claims and Encounters Database (MarketScan, private insurance) for the period 2011 to 2015 and the nationwide Medicaid Analytic eXtract (MAX, public insurance) for the period 2000 to 2013. We defined asthma prevalence, severity, and control on the basis of *International Classification of Diseases, 9th Revision* diagnoses and asthma-related treatments. *Severe asthma* was defined as dispensing of 1 or more medium/high-dose inhaled corticosteroid plus additional therapy within the 12 months preceding delivery. Poor control was defined as having at least 1 of the following: 1 or more exacerbation (asthma-related hospitalization or emergency room visit, or a course of oral corticosteroids) or 5 or more filled prescriptions for

short-acting β -agonists between the last menstrual period and delivery.

RESULTS: Among 604,420 pregnant women in MarketScan and 2,071,359 in MAX, 20,104 (3.3%) and 120,745 (5.8%) had asthma, respectively. Among pregnant women with asthma, 19.0% and 18.8% had severe asthma and 16.5% and 28.0% had poorly controlled asthma in MarketScan and MAX, respectively. Many women with poorly controlled asthma during pregnancy were not dispensed a long-term controller (38.4% in MarketScan and 43.3% in MAX). Within both cohorts, women with poor control were more often smokers and obese, had more comorbidities, and used more concomitant nonasthma medications. **CONCLUSIONS:** Poorly controlled asthma is more frequent among publicly versus privately insured pregnancies in the United States. Dispensing of long-term controller medications during pregnancy remains low, even for symptomatic patients. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2672-80)

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Abbreviations used

COPD- Chronic obstructive pulmonary disease

GINA- Global Initiative for Asthma

ICS- inhaled corticosteroid

LABA- Long-acting β -agonist

LMP- Last menstrual period

LTRA- Leukotriene receptor antagonist

MarketScan- Truven Health MarketScan Commercial Claims and Encounters Database

MAX- Medicaid Analytic eXtract

SABA- Short-acting β -agonist

INTRODUCTION

The prevalence of asthma in the United States has increased since 1980,¹ reaching 8.3% among adults in 2016.² This trend has affected pregnant women^{3,4}; asthma is currently estimated to complicate between 3% and 10% of pregnancies depending on the definition, ascertainment method, and population.⁵⁻⁹ In parallel, the bronchodilators and inhaled anti-inflammatory drugs used to treat asthma have become among the most commonly prescribed medications in pregnancy.^{8,10-12} Asthma medications are divided into long-term controllers and rescue therapy.⁶ Long-term controller medications, including inhaled corticosteroids (ICSs), long-acting β -agonists (LABAs), combinations of ICS/LABA, and leukotriene receptor antagonists (LTRAs), are used to prevent symptoms. Rescue therapy, most commonly inhaled short-acting β -agonists (SABAs), provides immediate relief from symptoms.¹³ Oral corticosteroids can be used as rescue therapy or as chronic maintenance therapy for severe cases.⁶

Pregnant women with uncontrolled asthma may have an elevated risk for adverse maternal and neonatal outcomes including preeclampsia, major congenital malformations, preterm birth, intrauterine growth restriction, and fetal, neonatal, and maternal mortality.^{3,5,9,14-22} Findings suggest that both maternal and infant outcomes could be improved with proper asthma management.^{5,9,18,23,24} Because no consistent increased risk of pregnancy complications or fetal toxicity has been demonstrated for those asthma treatments with some information on their safety during pregnancy,^{25,26} their benefits are considered to outweigh the potential risks. The American College of Obstetricians and Gynecologists and other national guidelines recommend the continued use of indicated asthma medications in pregnancy.^{13,27}

To maintain asthma control during pregnancy, the National Asthma Education and Prevention Program advises a stepwise approach to pharmacologic therapy, and recommends low-dose ICS as first-line treatment for persistent asthma when symptoms cannot be controlled with SABA.²⁷ If still not controlled, the guidelines recommend either addition of a LABA or increasing the ICS dose. These steps are consistent with the Global Initiative for Asthma (GINA)²⁸ treatment guidelines, which have also been used to assess asthma severity on the basis of level of treatment required to control symptoms and exacerbations. However, the extent to which these guidelines are followed in the real world is unclear and use of ICSs during pregnancy has not increased as much as expected since the

guidelines' publication in 2005.^{7,8,29-31} Moreover, around one-third of women may discontinue asthma controller medications early in pregnancy³² to avoid fetal toxicity³³ or because of uncertainty about the appropriate asthma medications.^{34,35} This behavior raises concerns because a major trigger of exacerbations during pregnancy, within levels of initial asthma severity, is nonadherence to ICSs early in pregnancy.^{36,37} Indeed, using asthma medication according to guidelines reduces the risk of worsening asthma symptoms during pregnancy.³⁸ Moreover, it has been suggested that the increase in asthma symptoms described in a proportion of pregnant women³⁹ may be attributable to inadequate medication rather than worsening of asthma due to the pregnancy itself.³⁶

In the present study, we identified pregnancies within 2 large US health care claims databases to describe the prevalence of asthma, levels of asthma severity, dispensing patterns for specific asthma therapies, and risk of asthma exacerbations during pregnancy.

METHODS

Study population

We conducted a cohort study nested in the nationwide Medicaid Analytic eXtract (MAX), which included health care utilization claims for public health insurance beneficiaries for the period 2000 to 2013, and in the Truven Health MarketScan Commercial Claims and Encounters Database (MarketScan), which included claims for private health insurance beneficiaries for the period 2011 to 2015. The study population included pregnancies in women aged 12 to 55 years that were linked to liveborn infants. Women were required to have insurance with prescription drug coverage from at least 3 months before the last menstrual period (LMP) through 1 month after pregnancy. Infants were required to have insurance coverage for at least the first month after birth unless they died sooner, in which case we allowed an eligibility period of shorter duration. In MAX, we implemented a linkage algorithm based on state, insurance case number (which identifies family units), and date of delivery.⁴⁰ The proportion of pregnancies linked to infants was more than 80%.⁴⁰ A similar protocol was applied to MarketScan data, where the linkage was performed using the unique ID number, shared by family members on the same insurance plan, and year of birth. The proportion of pregnancies linked to liveborn infants in MarketScan was approximately 75%.⁴¹

We estimated the first day of LMP on the basis of delivery date combined with diagnostic codes indicative of preterm delivery using a previously validated algorithm that accurately classifies gestational length within 2 weeks for 99% of deliveries and has both a sensitivity and a specificity of more than 96% for correctly classifying trimester-specific exposure status for chronic medications.⁴²⁻⁴⁴ Given that asthma is a chronic condition, misclassification of LMP by a few weeks is not expected to result in meaningful exposure misclassification.

Asthma

The presence of clinically diagnosed asthma was based on *International Classification of Diseases, 9th Revision* asthma codes (493.xx excluding 493.2, which indicates chronic obstructive pulmonary disease [COPD]) and dispensing of asthma-specific prescription medications recorded from 90 days before LMP to delivery. Asthma was defined as 1 or more inpatient or 2 or more outpatient *International Classification of Diseases, 9th Revision* asthma codes on different dates; or 1 outpatient code for asthma and 1 or more

dispensed prescription for SABA, ICS, ICS/LABA, or LTRA; or 2 or more dispensed prescriptions for ICS or ICS/LABA.^{42,43} We excluded patients with 2 or more codes for COPD (*International Classification of Diseases, 9th Revision* codes 491.xx, 492.xx, 496.xx, or 493.2x) from consideration as asthma cases, regardless of the presence of asthma-related diagnoses.^{45,46} In previous health care claims database studies, similar asthma definitions were validated by chart reviews and found to be highly sensitive and specific, with a positive predictive value of 95%.^{32,47}

GINA classification of asthma severity

Following the GINA guidelines,²⁸ we defined asthma severity according to medications dispensed from 90 days before LMP to delivery. Asthma severity was defined as step 0 (asthma diagnosis without treatment); step 1 treatment (only SABA); step 2 treatment (low-dose ICS or LTRA or low-dose theophylline); step 3 treatment (low-dose ICS/LABA, low-dose ICS plus LTRA or plus low-dose theophylline, or medium/high-dose ICS); step 4 treatment (medium/high-dose ICS/LABA or high-dose ICS alone plus LTRA or plus low-dose theophylline); or step 5 treatment (step 4 plus additional therapy with tiotropium, anti-IgE, or low-dose oral corticosteroids). Dose classification of ICSs as low, medium, or high was determined on the basis of strength (milligram/actuation) of the formulation dispensed and typical drug regimens (eg, we assumed 2 inhalations, twice daily). Dose classification of ICS/LABA was dependent on the ICS component. A summary of the GINA classification steps and the medication groups and subgroups used for their operationalization in the data is presented in Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org.

For severity assessment, the GINA steps were combined into the following asthma severity categories: mild (steps 0, 1, 2), moderate (step 3), and severe (steps 4 and 5). Asthma severity was classified according to the highest intensity treatments received during the following time windows: pre-pregnancy and pregnancy (LMP – 90 days to delivery); pre-pregnancy (LMP – 90 days to LMP – 1 day); first trimester (LMP to LMP + 90 days); second trimester (LMP + 91 days to LMP + 180 days); and third trimester (LMP + 181 days to delivery).

Asthma control

We considered the following as markers for asthma control: (a) *number of SABA canisters dispensed from LMP to delivery* and (b) *number of unique acute asthma exacerbations*, identified as asthma-related emergency department visit, asthma-related hospitalization, or course of oral corticosteroids (≥ 20 mg prednisone equivalents for 3–28 days associated with an asthma diagnosis within 14 days) from LMP to delivery (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). *Poor asthma control* was then defined as 5 or more SABA prescriptions dispensed or 1 or more asthma exacerbation from LMP to delivery.^{45,46} In addition to the entire pregnancy period,^{42,43} we considered exacerbations by trimester, including the pre-pregnancy period.

Data analyses

We compared the distributions of sociodemographic, clinical, and health care utilization characteristics between women with asthma and women without asthma. We further compared these characteristics between women with poorly controlled asthma and women with well-controlled asthma. Information on covariates was obtained from eligibility files (eg, maternal age), inpatient and/or outpatient diagnoses and procedures (eg, diabetes), and outpatient pharmacy dispensing records (eg, concomitant medications). The ascertainment

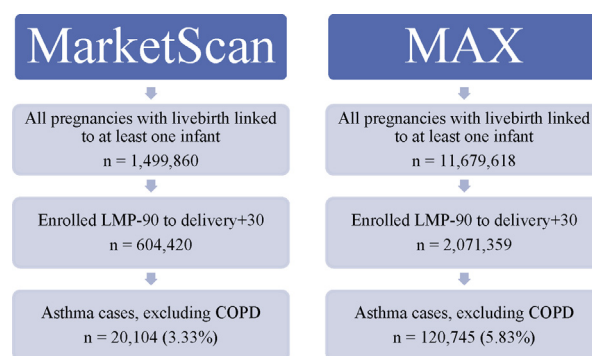


FIGURE 1. Population flowchart.

window for covariates was LMP – 90 to LMP + 245 unless otherwise specified (eg, health care utilization pre-pregnancy LMP – 90 to LMP – 1). We used 245 days instead of delivery to ensure a more uniform time window for covariate assessment (eg, number of prenatal visits) for preterm and term births. We then assessed the association between asthma control and asthma severity and described treatment patterns in pregnancy.

All results (counts, proportions, means, and SDs) are presented separately for each cohort. In accordance with the data use agreement, cell sizes less than 11 are not presented. All statistical analyses were conducted using SAS (SAS Institute, Cary, NC). This study received ethics board approval by the Harvard T.H. Chan School of Public Health, and use of the MAX database was approved by the Partners Institutional Review Board.

RESULTS

We identified 604,420 eligible pregnancies in the MarketScan database and 2,071,359 in the MAX database (Figure 1). We excluded 249 ($<0.1\%$) and 2790 (0.1%) patients with 2 or more codes for COPD from consideration as asthma cases in MarketScan and MAX, respectively. The number of pregnancies complicated by asthma was 20,104 (3%) in MarketScan and 120,745 (6%) in MAX. The prevalence in MAX increased from around 5% in 2000 to close to 7% in 2013 (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Overall, women in the MarketScan cohort were older on average than women in the MAX cohort (32 vs 24 years) and had fewer comorbidities. However, the pattern of differences between women with and without asthma was consistent in both cohorts. Women with asthma in both cohorts used about twice as many different prescription medications in pregnancy as did women without asthma, including opioids. They were also twice as likely to have claims for tobacco use, obesity, anxiety, depression, hypertension, or diabetes and to be hospitalized before and during pregnancy (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

Among women with asthma, the proportion with severe asthma (GINA steps 4 and 5) was 19% in MarketScan and 19% in MAX (Figure 2 and Table I). However, there was a larger proportion of women with poorly controlled asthma in MAX (28%) than in MarketScan (17%). A summary of the different measures of asthma control is presented in Figure 3. Asthma severity based on treatments received during the 3 months before LMP and each trimester afterwards was similar across pregnancy within both the MarketScan and MAX populations; a large

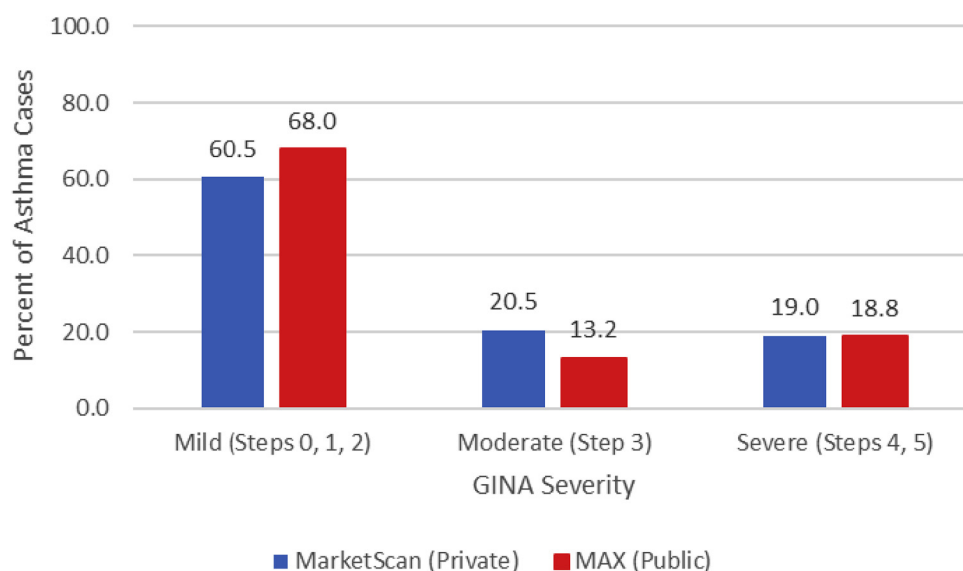


FIGURE 2. GINA Severity category (%) for women with asthma identified in MarketScan and MAX, assessed during the primary 12-month window.

TABLE I. Comparison of control by severity among asthma cases during pregnancy (LMP to delivery)

Cohort	Severity	≥1 Exacerbation		≥5 SABA Rx		Poor control		Total	
	GINA Step	n	%	n	%	n	%	n	%
MarketScan	0	218	6.8	0	0.0	218	6.8	3,222	16.0
	1	858	12.9	247	3.7	1,058	15.9	6,655	33.1
	2	261	11.4	111	4.9	337	14.7	2,288	11.4
	3	562	13.6	268	6.5	767	18.6	4,118	20.5
	4	633	17.3	375	10.3	876	24.0	3,654	18.2
	5	55	32.9	21	12.6	66	39.5	167	0.8
	Total	2,587	12.9	1,022	5.1	3,322	16.5	20,104	100
MAX	0	2,028	10.3	0	0.0	2,028	10.3	19,662	16.3
	1	10,372	20.1	3,072	6.0	12,604	24.5	51,525	43.7
	2	2,250	20.6	1,410	12.9	3,175	29.1	10,909	9.0
	3	4,410	27.6	2,760	17.3	5,968	37.4	15,975	13.2
	4	6,541	30.0	5,463	25.1	9,556	43.8	21,807	18.1
	5	353	40.7	226	26.1	452	52.1	867	0.7
	Total	25,954	21.5	12,931	10.7	33,783	28.0	120,745	100

proportion (around 50%) were classified as mild in each period because they had no asthma drugs dispensed in those 3 months. Similar to severity, exacerbations were almost equally likely to occur in any trimester (see [Table E5](#) in this article's Online Repository at www.jaci-inpractice.org).

We compared women with poorly controlled asthma to those with well-controlled asthma (see [Table E6](#) in this article's Online Repository at www.jaci-inpractice.org). In MAX, those with poor control tended to be older. In both cohorts, those with poor control were more likely to have claims associated with smoking, obesity, chronic conditions such as diabetes, and nonasthma medications including opioids; and they had more outpatient visits, emergency department visits, and hospitalizations.

During pre-pregnancy and pregnancy, in the MarketScan population, 69% of women received at least 1 dispensing for SABA, 26% for ICS alone, 25% for ICS/LABA, and 1% for

rescue low-dose oral corticosteroids. The corresponding frequencies in MAX were 80% for SABA, 22% for ICS alone, 18% for ICS/LABA, and 1% for low-dose rescue oral corticosteroids. The proportions were more similar between populations when comparing the overlapping study years. The most commonly dispensed specific asthma medications during pre-pregnancy and pregnancy in MarketScan and MAX were albuterol (69% and 78%), montelukast (19% and 13%), combination fluticasone propionate and salmeterol xinafoate (17% and 17%), budesonide (14% and 5%), and fluticasone propionate monotherapy (7% and 12%) ([Table II](#)). Trends in utilization of the main classes of asthma medications over the study period, within MAX, are presented in [Figure E1](#). The proportion of women with asthma with at least 1 dispensing for SABA declined over the study period, whereas the proportion with ICS/LABA increased from 2001 to 2005, following their approval in 2000. We observed a

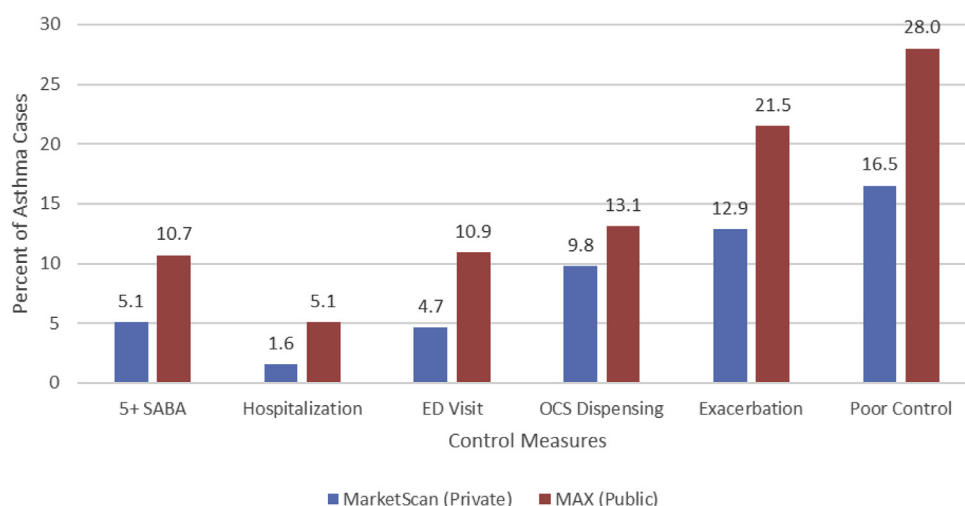


FIGURE 3. Summary of the measures of poor asthma control for women with asthma identified in MarketScan and MAX. Groups are not mutually exclusive. *ED*, Emergency department. *5+ SABA*, At least 5 SABA canisters dispensed during pregnancy; *Hospitalization*, asthma-related hospitalization; *ED Visit*, asthma-related ED visit; *OCS Dispensing*, greater than or equal to 20 mg prednisone equivalents for 3 to 28 days associated with an asthma diagnosis within 14 days; *Exacerbation*, the occurrence of Hospitalization, ED Visit, or OCS Dispensing; *Poor control*, the occurrence of 5+ SABA or Exacerbation. Ascertainment window was LMP to delivery. Control measures are described in more detail in Table E3.

TABLE II. Number and % of pregnancies in women with asthma with at least 1 dispensation for each drug type, as included in the GINA classification system (LMP – 90 d to delivery)*

Drug group	Drug name†	MarketScan (N = 20,104), n (%)	MAX (N = 120,745), n (%)
SABA	Albuterol	13,882 (69.1)	93,687 (77.6)
	Pirbuterol	70 (0.4)	698 (0.6)
ICS	Beclomethasone dipropionate	766 (3.8)	4,830 (4.0)
	Budesonide	2,720 (13.5)	5,644 (4.7)
	Fluticasone propionate	1,311 (6.5)	14,215 (11.8)
	Mometasone furoate	742 (3.7)	942 (0.8)
	Triamcinolone acetonide	0 (0.0)	3,213 (2.7)
	Ciclesonide	0 (0.0)	<11 (0.0)
	Fluticasone furoate	0 (0.0)	0 (0.0)
	Fluticasone furoate/vilanterol trifenatate	<11 (0.0)	0 (0.0)
ICS/LABA	Budesonide/formoterol fumarate	1,274 (6.3)	1,571 (1.3)
	Fluticasone propionate/salmeterol xinafoate	3,457 (17.2)	20,559 (17.0)
	Formoterol fumarate/mometasone furoate	349 (1.7)	115 (0.1)
	Montelukast	3,830 (19.1)	15,575 (12.9)
LTRA	Zafirlukast	26 (0.1)	363 (0.3)
	Tiotropium bromide‡	40 (0.2)	289 (0.2)
Other	Theophylline	20 (0.1)	735 (0.6)
	Omalizumab	35 (0.2)	48 (0.0)
	Prednisone (5 mg)	150 (0.8)	698 (0.6)
	Methylprednisolone (4 mg)	31 (0.2)	227 (0.2)

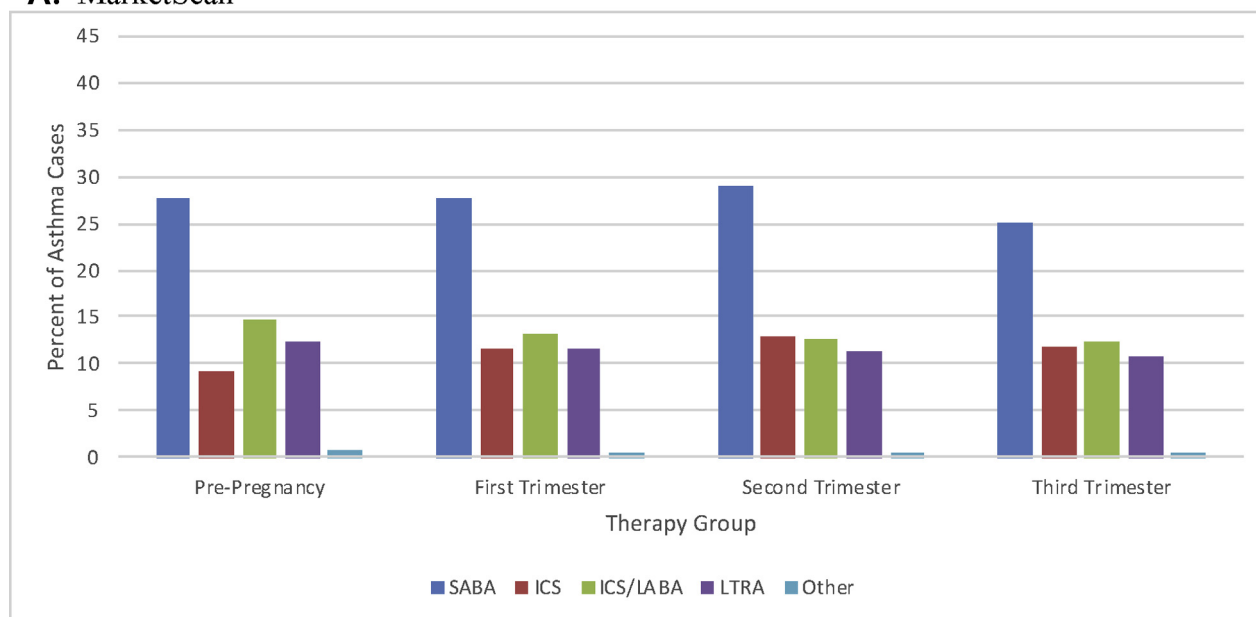
*Only dispensations meeting the inclusion criteria for the GINA classification system were counted. For example, when counting dispensations for prednisone (Other), only 5-mg doses were included. Likewise, we excluded drugs matching the generic names for ICS but with “oral” or “nasal” routes of administration.

‡Tiotropium bromide, a long-acting muscarinic antagonist, was not yet approved during the study period.

concurrent decline in ICS alone, such that the overall ICS use remained relatively constant. The prevalence of 1 or more dispensing for each class of asthma medication by trimester is presented in Figure 4. Restriction of the population to term infants to avoid the shorter opportunity for exposure in preterm deliveries during the third trimester shows the same lack of trend

(data not shown). Of patients on ICS at baseline in MarketScan, including ICS/LABA, the proportions with ICS or ICS/LABA dispensing in the first, second, and third trimesters were 59%, 54% and 52%. The corresponding proportions were 44%, 38%, and 32% in MAX (data not shown). Overall, prescription patterns were scattered, with few women consistently filling

A. MarketScan



B. MAX

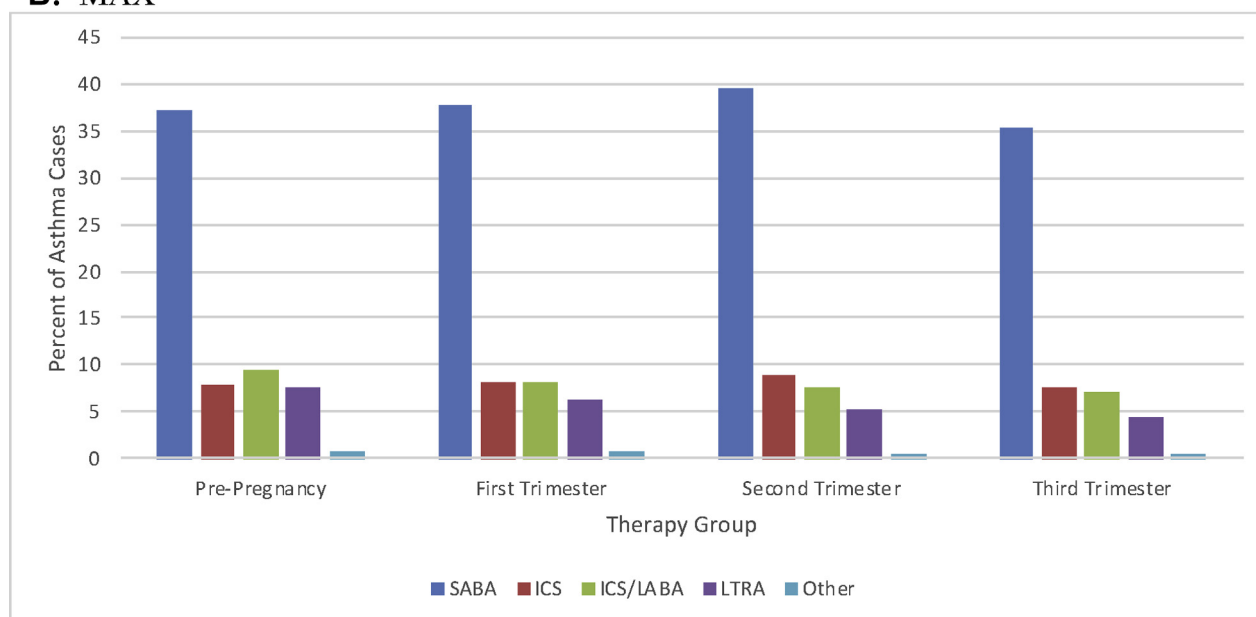


FIGURE 4. Dispensing of specific medication by trimester among women with asthma for MarketScan (A) and MAX (B), as included in the GINA classification system. Note that third trimester is shorter in women with preterm delivery, reducing the opportunity for exposure with respect to other trimesters.

prescriptions in all trimesters (see Table E7 in this article's Online Repository at www.jaci-inpractice.org).

Poor asthma control during pregnancy was associated with severe asthma, that is, higher treatment intensity (Table I; see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Yet, 38% (MarketScan) and 43% (MAX) of women whose asthma symptoms were poorly controlled did not fill a prescription for a long-acting control medication during pregnancy. When considering longitudinal associations, initial asthma severity (based on medications pre-pregnancy) was not a

good predictor for asthma control during pregnancy. The proportion of women with 1 or more exacerbations during pregnancy was similar for women with mild asthma at baseline (14% in MarketScan and 21% in MAX) compared with those with severe asthma at baseline (12% in MarketScan and 25% in MAX) (see Table E8 in this article's Online Repository at www.jaci-inpractice.org). Within women on long-acting controllers at baseline, those without refills during the first trimester (ie, the 41% and 56% discontinuers in MarketScan and MAX, respectively) were similarly likely to have asthma exacerbations during

the second trimester (4% MarketScan and 9% MAX) compared with those who continued filling prescriptions during the first trimester (5% MarketScan and 9% MAX).

DISCUSSION

We identified 2 large cohorts of pregnancies complicated by asthma in the United States during the period 2000 to 2015. Asthma was approximately twice as common in publicly versus privately insured pregnant women. Despite publicly insured women having apparently milder asthma based on treatments dispensed, the proportion of patients with poorly controlled asthma during pregnancy was higher in publicly insured than in privately insured women. In both cohorts, a high proportion of those with poorly controlled asthma symptoms were not dispensed a long-acting controller medication during pregnancy.

Publicly insured pregnant women tended to be younger and had more chronic conditions, dispensing of medications, and health care utilization. However, within both cohorts, women with asthma were more likely to smoke, be obese, have other comorbidities, and use more prescription medications compared with women without asthma. Among pregnant women with asthma, women with poor asthma control were more likely to smoke, use nonasthma medications, and have more health care utilization compared with women with well-controlled asthma. The higher prevalence of smoking among women with poorly controlled asthma is disturbing, because it is a known asthma trigger, but not surprising because the association has been repeatedly reported.^{1,7} Other characteristics previously associated with uncontrolled asthma include black race and low socioeconomic status.^{1,7} Within our Medicaid population we did not find racial differences in asthma or asthma severity.⁴⁸ However, publicly insured women more often had poorly controlled asthma than did privately insured women. Because insurance type is an indicator of socioeconomic status, socioeconomic differences might explain part of the racial disparity in asthma during pregnancy that has been previously reported.⁴⁹ Whether the differences between privately and publicly insured populations are explained by differences in asthma severity underlying risk factors, health awareness and utilization, access to care, or clinical care affected by insurance type warrants further investigations.

Having more severe asthma based on higher GINA treatment steps was associated with worse asthma control during pregnancy overall, as had been previously reported.³⁷ This is expected because the GINA classification does not differentiate between cause and effect of treatment; that is, worse control would require more aggressive treatment. Thus, we also considered clinical manifestations that indicate a level of control (ie, hospitalizations, exacerbations, intensity of rescue SABA use).

During pregnancy, the frequency of asthma-related hospitalizations was 1.6% in MarketScan and 5.1% in MAX. These observations are in agreement with other reports, where exacerbations requiring medical intervention occurred in about 20% of women with asthma, with approximately 3% to 6% of women being admitted to hospital.³¹ Some studies have linked the severity of asthma with asthma control during pregnancy.³⁸ In a clinical cohort, pregnant women diagnosed with mild asthma had an 8% risk of exacerbation compared with a 65% risk in women with severe asthma.^{36,37} Although we found the same qualitative association, our risk of exacerbation was lower

(ranging from close to 9% to 44% for GINA step 0 to step 5 in MarketScan) likely because we considered only hospitalizations, emergency department visits, and prescriptions recorded in claims, whereas the clinical cohort included physiologic measurements. In another health care database study, the proportion of pregnancies with at least 1 asthma exacerbation was up to 2% for those with mild, 8% for those with moderate, and 16% for those with severe asthma.³¹

Exacerbations of asthma during pregnancy have been related to poor pregnancy outcomes.¹⁴ Controlling asthma may reduce the risk of exacerbations and prevent obstetric and neonatal complications.^{3,19,25} Current guidelines emphasize continuing treatment of asthma throughout pregnancy.²⁷ Although in some populations initial asthma severity is a main predictor of exacerbations,³⁶ a trigger within levels of severity might be the lack of appropriate treatment with ICSs or their discontinuation during pregnancy. It has been suggested that 29% of severe exacerbations are a consequence of nonadherence to ICSs.³⁷ However, we did not find an increased risk of exacerbations among ICS discontinuers in early pregnancy, similar to other studies.⁷ Potential explanations for this observed lack of association include ICS misclassification (ie, some women may fill the prescription and still discontinue taking the medication and others may use old prescriptions) and channeling bias (ie, those with better control or milder disease might be more likely to discontinue their medication and are at lower risk of exacerbations).

About 50% of women with asthma discontinued their controller therapy early in pregnancy. The explanation for discontinuation of controller use does not seem to reflect improved asthma control during the first trimester and less need for medication for a proportion of women.¹³ Moreover, the decrease in medication use has been reported mainly for controllers rather than rescue medications for symptoms.³² Rather, women might discontinue ICS use on learning that they are pregnant because of fears of adverse effects on the developing fetus.^{32,33} Of note, despite the discontinuation, the prevalence of controller drug use was similar through trimesters because users may not represent the same women starting and stopping medications. Particularly in the Medicaid population, a reduction in prescriptions filled by some women early in pregnancy could have been balanced by an increase in asthma drug prescriptions as health care contacts increase.

Consistent with other studies, the most commonly prescribed therapies, as included in the GINA classification system, in pregnant women with asthma were albuterol, montelukast, and fluticasone propionate/salmeterol xinafoate.^{8,10-12,50} Overall, among women with asthma, dispensing of ICS-only products during pregnancy (26% in MarketScan, 22% in MAX) was similar to that of ICS/LABA (24% in MarketScan, 18% in MAX), and remained lower than that of SABA (69% in MarketScan, 80% in MAX). Within overlapping study years, drug utilization was similar between MarketScan and MAX. Moreover, only about 60% of women with poorly controlled asthma filled prescriptions for controller medications during pregnancy, supporting the suggestion that asthma symptoms in pregnancy may be inadequately treated.⁷ Although temporal prescription tendencies are in alignment with current National Asthma Education and Prevention Program clinical guidelines, which highlight the importance of maintenance medication use in pregnancy,²⁷ the use of controllers remains suboptimal worldwide. By 2007, the prevalence of controllers dispensing among

pregnant women with asthma had increased in the United States (ICS alone to 27.1%, leukotriene modifiers to 7.4%, and combination of ICS and LABA to 6.1%),⁸ but remained below that of SABA (50%-60%).³² In Canada, prescription of ICS/LABA therapy in pregnancy to women with asthma increased from 3.5% in 1999 to 13.4% in 2008.²⁹ In Europe, ICS products were infrequently prescribed in pregnancy during that decade,³⁰ while almost 70% of women with asthma used SABA.³¹

The major strength of this study was the combination of 2 large complementary data sets to identify more than 2.5 million pregnancies among women enrolled in public or private health insurance plans between 2001 and 2015. We studied a Medicaid population with a large proportion of minority women, which provides important health information for traditionally understudied populations. The combination with MarketScan, which includes privately insured women, provides complementary results generalizable to the US population.

There were 4 main limitations to this study. First, the prevalence of asthma is likely underestimated in claims, particularly when using algorithms that prioritize specificity over sensitivity. The prevalence of asthma among adult females in the United States increased from 8.3% in 2001 to 9.2% in 2009.⁵¹ The lower prevalence in our study is at least partially due to incomplete capture of diagnoses in administrative data, for example, if women with preexisting asthma did not have an encounter where the diagnosis was required for billing purposes or medication prescriptions during the period of ascertainment. Because we are more likely missing mild cases with no clinical encounters for asthma or asthma-specific treatments, our results may overestimate the proportion of women with severe asthma. Also, though it is theoretically possible to misclassify some COPD cases as asthma, given the young population, it is unlikely for them to represent a meaningful proportion as suggested by the very small number of COPD cases excluded on the basis of 2 codes. Second, drug utilization was determined on the basis of filled prescriptions, which does not guarantee that the medication was taken or inhaled, therefore overestimating exposure and underestimating discontinuations. Moreover, treatments used may have been missed if prescriptions were filled before the exposure window (eg, an old prescription was still being used). The observed irregular prescription dispensing patterns support the difficulties of assessing asthma treatment use on the basis of pharmacy claims. For this reason, a larger proportion of the pregnancies were defined as mild (and predominantly untreated) when considering 3-month windows versus the 12-month window in the primary definition (9 months of pregnancy plus 3 months of pre-pregnancy baseline). Therefore, the primary definition considering GINA overall likely provides a more accurate reflection of severity of asthma during pregnancy than do the trimester-specific estimates. Patients with apparently inactive asthma (step 0) may have stockpiled SABA or other medications. Third, information on some potentially relevant risk factors cannot be sufficiently assessed given the limited information in health care claims databases (eg, smoking and obesity). Fourth, as discussed above, confounding by indication (ie, asthma severity) likely explains why we observed more exacerbations for women who required ICS-containing therapy during pregnancy than for those who discontinued or did not use ICS-containing therapy during pregnancy.

In summary, we identified a high prevalence of poorly controlled asthma among pregnant women in the United

States, particularly in the Medicaid population. Factors associated with low socioeconomic status, smoking, obesity, and comorbidities may contribute to poor asthma control during pregnancy. Dispensing of long-acting controllers remains low, even for symptomatic patients, potentially out of fear regarding fetal toxicity. Because appropriate therapeutic management during pregnancy could improve the health of both mothers and children, there is a need to provide additional evidence on the risks and benefits of asthma medications in pregnancy.

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ONLINE REPOSITORY

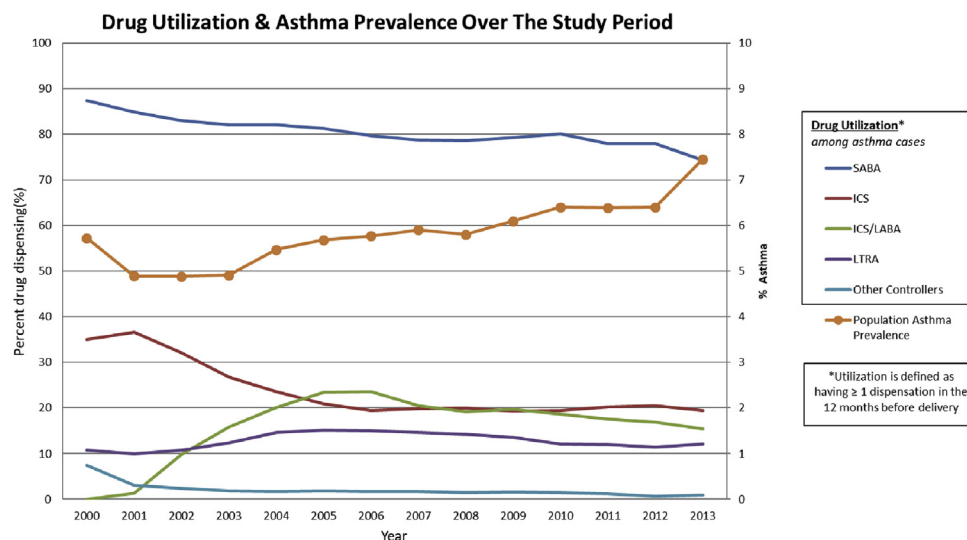


FIGURE E1. Trends of asthma prevalence in pregnancy and main classes of asthma medications dispensed within the pre-pregnancy and pregnancy window during the study period among women with asthma identified in MAX.

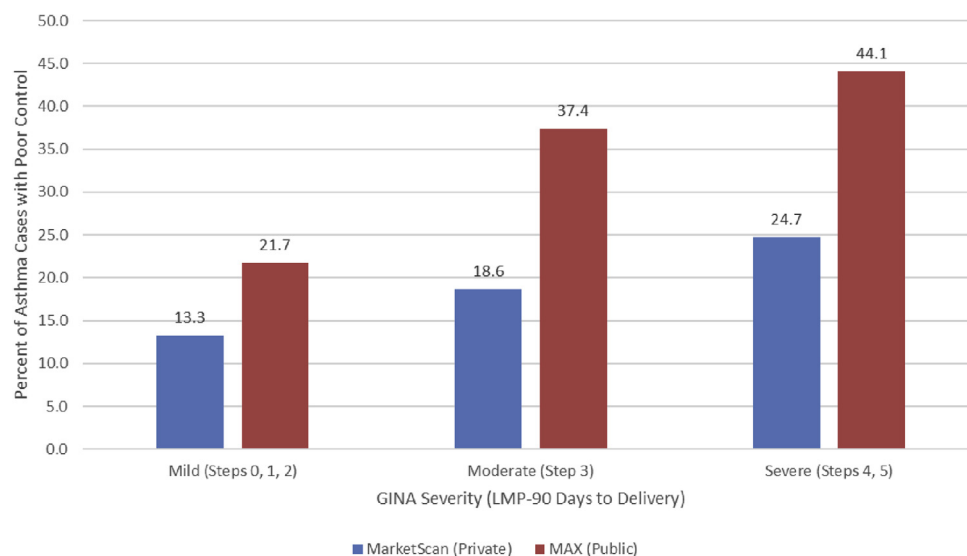


FIGURE E2. Proportion of women with poor control within asthma severity category, based on GINA classification, among women with asthma identified in MarketScan and MAX.

TABLE E1. Medication groups and doses for severity classification according to the 2015 GINA guidelines

Medication group	Subgroup	Detailed specification (drug, dose)*
1. SABA		Albuterol Levalbuterol Pirbuterol
2. ICS (alone; not including combination drugs)	A. Low dose	Beclomethasone dipropionate, 100-200 µg Budesonide, 200-400 µg Ciclesonide, >160 µg Fluticasone propionate, 100-250 µg Mometasone furoate, 110-220 µg Triamcinolone acetonide, 400-1000 µg
	B. Medium dose	Beclomethasone dipropionate, >200-400 µg Budesonide, >400-800 µg Ciclesonide, >160-320 µg Fluticasone propionate, >250-500 µg Mometasone furoate, >220-440 µg Triamcinolone acetonide, >1000-2000 µg
	C. High dose	Beclomethasone dipropionate, >400 µg Budesonide, >800 µg Ciclesonide, >320 µg Fluticasone propionate, >500 µg Mometasone furoate, >440 µg Triamcinolone acetonide, >2000 µg
3. ICS/LABA	A. Low dose*	Budesonide/formoterol fumarate Fluticasone furoate/vilanterol trifenatate Fluticasone propionate/salmeterol xinafoate Formoterol fumarate/mometasone furoate
	B. Medium/high dose*	Budesonide/formoterol fumarate Fluticasone furoate/vilanterol trifenatate Fluticasone propionate/salmeterol xinafoate Formoterol fumarate/mometasone furoate
4. LTRA		Montelukast Zafirlukast
5. Other controllers†	A. Tiotropium	Tiotropium bromide
	B. Theophylline	Theophylline
	C. Anti-IgE	Omalizumab
	D. Low-dose OCS	Prednisone (5 mg) Methylprednisolone (4 mg)

*See ICS dose ranges above.

†The 2018 GINA guidelines include anti-IL-5 therapies (mepolizumab, benralizumab, reslizumab) for treatment of severe asthma.

TABLE E2. Overview of GINA steps definitions and operationalization in claims

GINA Steps definition	Operational definition in claims
Step 1: Preferred controller choice: Other controller options: Low-dose ICS* Reliever: As-needed SABA	SABA (group 1) = YES <u>AND</u> All other medications (groups 2, 3, 4, 5) = NO
Step 2: Preferred controller: Low-dose ICS Other controller options: LTRA, low-dose theophylline† Reliever: As-needed SABA	ICS, low dose (group 2a) = YES <u>OR</u> LTRA (group 4) = YES <u>OR</u> Theophylline (group 5b) = YES
Step 3: Preferred controller: Low-dose ICS/LABA Other controller options: Medium/high-dose ICS, low-dose ICS + LTRA (or + theophylline) Reliever: As-needed SABA or low- dose ICS/formoterol‡	ICS/LABA, low dose (group 3a) = YES <u>OR</u> ICS, medium dose (group 2b) = YES <u>OR</u> ICS, high dose (group 2c) = YES <u>OR</u> (ICS, low dose (group 2a) = YES <u>AND</u> LTRA (group 4) = YES) <u>OR</u> (ICS, low dose (group 2a) = YES <u>AND</u> Theophylline (group 5b) = YES)
Step 4: Preferred controller: Medium/high- dose ICS/LABA Other controller options: Add tiotropium,§ high-dose ICS + LTRA (or + theophylline) Reliever: As-needed SABA or low- dose ICS/formoterol‡	ICS/LABA, medium/high dose (group 3b) = YES <u>OR</u> (ICS, high dose (group 2c) = YES <u>AND</u> LTRA (group 4) = YES) <u>OR</u> (ICS, high dose (group 2c) = YES <u>AND</u> Theophylline (group 5b) = YES)
Step 5: Preferred controller: Refer for add-on treatment, eg, anti-IgE Other controller options: Add tiotropium, add low-dose OCS Reliever: As-needed SABA or low- dose ICS/formoterol‡	(ICS/LABA, medium/high dose (group 3b) = YES <u>OR</u> (ICS, high dose (group 2c) = YES <u>AND</u> LTRA (group 4) = YES) <u>OR</u> (ICS, high dose (group 2c) = YES <u>AND</u> Theophylline (group 5b) = YES)) <u>AND</u> (Tiotropium (5a) = YES <u>OR</u> anti-IgE (5c) = YES <u>OR</u> Low-dose OCS (5d) = YES)
Step 0: We defined this as failing to meet the definition for steps 1-5 (no treatment)	If any of these pregnancies have received medications during the period after initial classification into step 0, reclassify: Tiotropium (group 5a), theophylline (group 5b) → step 2 Omalizumab (group 5c), low-dose OCS (group 5d) → step 5

OCS, Oral corticosteroid.

*Did not consider low-dose ICS in step 1 because then we do not have a clear way to separate from step 2, ie, cannot differentiate between ICS dispensed as a preferred controller or as an “other option.”

†Consider any theophylline as a controller, regardless of dose.

‡Low-dose ICS/formoterol not used as both controller and reliever in US context.

§Did not consider those with add-on tiotropium in step 4 because then we do not have a clear way to separate from step 5.

TABLE E3. Definitions used for asthma exacerbation components

Asthma exacerbation	Definition
Oral corticosteroids	Dispensing of prednisone and methylprednisolone • At average daily dose ≥ 20 mg prednisone equivalents (ie, prednisone ≥ 20 mg or methylprednisolone ≥ 16 mg) • AND with days' supply ≥ 3 d and ≤ 28 d • AND an asthma code (493.xx) in inpatient or outpatient services claims within ± 14 d of dispensing date
ED visit	Identify ED visits in outpatient claims with: • DX = 493.02, 493.12, 493.92 (asthma w/ acute exacerbation) OR • DX = 493.xx (asthma) AND (PROC = ICD-9 9394 OR CPT 94xxx) (respiratory therapy) • Consider codes within ± 1 d as 1 event • No hospital admission within ± 1 d
Hospitalization	Inpatient services claims with: • PDX = 493.xx (asthma), OR • PDX = 648.93 (maternal condition in pregnancy) and DX = 493.xx (asthma), OR • DX = 493.02, 493.12, 493.92 (asthma w/ acute exacerbation)

CPT, Current procedural terminology; DX, diagnosis codes; ED, emergency department; ICD-9, *International Classification of Diseases, 9th Revision*; PDX, primary diagnosis; Rx, prescriptions.

For subsequent exacerbations to be considered independent, at least 7 d must elapse from the end date of oral corticosteroid script (dispense date + days supplied + 7 d), date of ED visit, or hospital discharge date.

TABLE E4. Characteristics of pregnancies with asthma vs no asthma

Characteristic	MarketScan (privately insured pregnancies)					MAX (publicly insured pregnancies)				
	Asthma		No asthma		Standardized difference	Asthma		No asthma		Standardized difference
	(n or mean)	(% or SD)	(n or mean)	(% or SD)		(n or mean)	(% or SD)	(n or mean)	(% or SD)	
Total	20,104		584,316			120,745		1,950,614		
Sociodemographic										
Age at delivery (y)	32.1	4.7	31.7	4.5	0.09	24.2	5.9	24.4	5.9	−0.03
≤19	66	0.3%	1,189	0.2%	0.03	30,617	25.4%	445,768	22.9%	0.06
20-29	5,781	28.8%	188,017	32.2%	−0.07	67,735	56.1%	1,137,940	58.3%	−0.05
30-39	13,062	65.0%	367,622	62.9%	0.04	20,856	17.3%	339,383	17.4%	0.00
≥40	1,195	5.9%	27,488	4.7%	0.06	1,537	1.3%	27,523	1.4%	−0.01
Region										
Northeast	4,543	22.6%	105,792	18.1%	0.11	26,272	21.8%	334,026	17.1%	0.12
North central/midwest	4,801	23.9%	138,400	23.7%	0.00	38,914	32.2%	553,538	28.4%	0.08
South	6,206	30.9%	213,590	36.6%	−0.12	31,603	26.2%	509,640	26.1%	0.00
West	4,263	21.2%	118,443	20.3%	0.02	23,956	19.8%	553,410	28.4%	−0.20
Unknown	291	1.5%	8,091	1.4%	0.01					
Race/ethnicity										
White						50,609	41.9%	761,953	39.1%	0.06
Black/African American						42,930	35.6%	629,539	32.3%	0.07
American Indian						1,714	1.4%	33,720	1.7%	−0.02
Hispanic/Latino						12,085	10.0%	312,500	16.0%	−0.18
Asian/Pacific Islander						2,332	1.9%	79,208	4.1%	−0.13
Unknown						2,860	2.4%	44,437	2.3%	0.01
Other						8,215	6.8%	89,257	4.6%	0.10
Multiparity						85,577	70.9%	1,494,586	76.6%	−0.13
Maternal lifestyle habits										
Tobacco use*	671	3.3%	8,792	1.5%	0.12	13,776	11.4%	105,872	5.4%	0.22
Alcohol abuse or dependence†	61	0.3%	732	0.1%	0.04	1,189	1.0%	10,677	0.6%	0.05
Drug abuse or dependence	156	0.8%	2,408	0.4%	0.05	3,396	2.8%	31,476	1.6%	0.08
Opioid abuse	<11	0.0%	129	0.0%	0.01	211	0.2%	1,495	0.1%	0.03
Health care utilization, pre-pregnancy										
No. of drugs used	3.3	3.3	1.5	2.3	0.62	3.7	3.6	1.6	2.3	0.68
No. of outpatient visits	3.9	4.6	2.3	3.5	0.40	3.5	4.8	2.0	3.4	0.35
No. of ED visits	0.1	0.5	0.1	0.3	0.19	0.7	1.3	0.3	0.8	0.33
Any hospitalization	279	1.4%	3,680	0.6%	0.08	7,587	6.3%	67,524	3.5%	0.13
Medications and comorbidities										
Antidepressants	2,788	13.9%	45,870	7.9%	0.19	22,828	18.9%	201,502	10.3%	0.24
Anticonvulsants	497	2.5%	7,223	1.2%	0.09	5,834	4.8%	40,784	2.1%	0.15
Opioids	5,286	26.3%	87,865	15.0%	0.28	54,340	45.0%	577,929	29.6%	0.32
Codeine	2,089	10.4%	28,475	4.9%	0.21	27,384	22.7%	264,543	13.6%	0.24
Antibiotic use	11,257	56.0%	192,938	33.0%	0.00	78,232	64.8%	831,075	42.6%	0.46
Epilepsy or convulsions	139	0.7%	2,617	0.5%	0.03	2,543	2.1%	18,930	1.0%	0.09
Depression	1,774	8.8%	26,197	4.5%	0.17	17,819	14.8%	150,494	7.7%	0.22
Anxiety	1,897	9.4%	28,841	4.9%	0.17	11,151	9.2%	89,638	4.6%	0.18
Obesity or overweight‡	2,666	13.3%	36,061	6.2%	0.24	9,917	8.2%	73,059	3.8%	0.19
Antihypertensive medication	1,269	6.3%	20,401	3.5%	0.13	6,732	5.6%	58,407	3.0%	0.13

(continued)

TABLE E4. (Continued)

Characteristic	MarketScan (privately insured pregnancies)					MAX (publicly insured pregnancies)				
	Asthma		No asthma		Standardized difference	Asthma		No asthma		Standardized difference
	(n or mean)	(% or SD)	(n or mean)	(% or SD)		(n or mean)	(% or SD)	(n or mean)	(% or SD)	
Antidiabetic medication	1,164	5.8%	22,491	3.9%	0.09	3,278	2.7%	30,447	1.6%	0.08
Hypertension diagnosis	1,197	6.0%	18,194	3.1%	0.14	6,245	5.2%	50,717	2.6%	0.13
Diabetes diagnosis	577	2.9%	9,547	1.6%	0.08	4,085	3.4%	36,399	1.9%	0.10
Hypertension§	1,708	8.5%	27,633	4.7%	0.15	9,393	7.8%	80,817	4.1%	0.15
Diabetes	1,373	6.8%	26,001	4.5%	0.10	4,916	4.1%	45,317	2.3%	0.10

ED, Emergency department; ICD-9, *International Classification of Diseases, 9th Revision*.

*Tobacco use identified by ≥ 1 of the following ICD-9 codes: 305.1x, 649.0x, 989.84, V15.82.

†Alcohol abuse or dependence identified by ≥ 1 of the following ICD-9 codes: 291.xx, 303.xx, 305.0x, 357.5x, 425.5x, 571.0x, 571.2x, 571.3x, E860.0, V11.3.

‡Obesity or overweight identified by ≥ 1 of the following ICD-9 codes: 278.0x, 649.1x, V85.3x, V85.4.

§Hypertension was defined as having claims for either antihypertensive medication or hypertension diagnosis.

||Diabetes was defined as having claims for either antidiabetic medication or diabetes diagnosis.

TABLE E5. Proportion of asthma cases with exacerbations, by trimester

Cohort	Period	Exacerbations, n (%)	
		0	≥ 1
MarketScan	Pre-pregnancy	19,033 (94.7)	1,071 (5.3)
	Trimester 1	19,299 (96.0)	805 (4.0)
	Trimester 2	19,091 (95.0)	1,013 (5.0)
	Trimester 3	19,070 (94.9)	1,025 (5.1)
MAX	Pre-pregnancy	110,157 (91.2)	10,588 (8.8)
	Trimester 1	111,248 (92.1)	9,497 (7.9)
	Trimester 2	109,593 (90.8)	11,152 (9.2)
	Trimester 3	111,186 (92.1)	9,559 (7.9)

TABLE E6. Characteristics of pregnancies with poorly controlled asthma vs well-controlled asthma

Characteristic	MarketScan (privately insured pregnancies)					MAX (publicly insured pregnancies)				
	Poorly controlled asthma		Well-controlled asthma		Standardized difference	Poorly controlled asthma		Well-controlled asthma		Standardized difference
	(n or mean)	(% or SD)	(n or mean)	(% or SD)		(n or mean)	(% or SD)	(n or mean)	(% or SD)	
Total	3,322		16,782			33,783		86,962		
Sociodemographic										
Age at delivery (y)	32.1	4.9	32.1	4.6	−0.01	24.9	6.0	23.9	5.9	0.18
≤19	12	0.4%	54	0.3%	0.01	6,907	20.5%	23,710	27.3%	−0.16
20-29	1,009	30.4%	4,772	28.4%	0.04	19,530	57.8%	48,205	55.4%	0.05
30-39	2,092	63.0%	10,970	65.4%	−0.10	6,804	20.1%	14,052	16.2%	0.10
≥40	209	6.3%	986	5.9%	0.02	542	1.6%	995	1.1%	0.04
Region										
Northeast	744	22.4%	3,799	22.6%	0.00	7,598	22.5%	18,674	21.5%	0.02
North central/midwest	879	26.5%	3,922	23.4%	0.07	11,145	33.0%	27,769	31.9%	0.02
South	1,075	32.4%	5,131	30.6%	0.04	8,043	23.8%	23,560	27.1%	−0.08
West	578	17.4%	3,685	22.0%	−0.10	6,997	20.7%	16,959	19.5%	0.03
Unknown	46	1.4%	245	1.5%	0.00					
Race/ethnicity										
White						14,074	41.7%	36,535	42.0%	−0.01
Black/African American						11,963	35.4%	30,967	35.6%	0.00
American Indian						437	1.3%	1,277	1.5%	−0.01
Hispanic/Latino						3,447	10.2%	8,638	9.9%	0.01
Asian/Pacific Islander						604	1.8%	1,728	2.0%	−0.01
Unknown						851	2.5%	2,009	2.3%	0.01
Other						2,407	7.1%	5,808	6.7%	0.02
Multiparity						25,273	74.8%	60,304	69.4%	0.12
Maternal lifestyle habits										
Tobacco use*	175	5.3%	496	3.0%	0.12	4,282	12.7%	9,494	10.9%	0.05
Alcohol abuse or dependence†	15	0.5%	46	0.3%	0.03	371	1.1%	818	0.9%	0.02
Drug abuse or dependence	31	0.9%	125	0.7%	0.02	1,019	3.0%	2,377	2.7%	0.02
Opioid abuse	<11	0.1%	<11	0.0%	0.01	77	0.2%	134	0.2%	0.02
Health care utilization, pre-pregnancy										
No. of drugs used	3.7	3.6	3.0	3.0	0.16	4.0	3.8	3.5	3.5	0.12
No. of outpatient visits	3.8	4.6	3.9	4.5	0.00	3.3	4.7	3.6	4.9	−0.05
No. of ED visits	0.2	0.6	0.1	0.5	0.09	0.7	1.4	0.7	1.3	0.04
Any hospitalization in baseline	43	1.3%	236	1.4%	0.00	1,948	5.8%	5,639	6.5%	−0.03
Medications and comorbidities										
Antidepressants	595	17.9%	2,193	13.1%	0.13	6,631	19.6%	16,197	18.6%	0.03
Anticonvulsants	120	3.6%	377	2.3%	0.08	1,681	5.0%	4,153	4.8%	0.01
Opioids	1,124	33.8%	4,162	24.8%	0.20	16,095	47.6%	38,245	44.0%	0.07
Codeine	478	14.4%	1,611	9.6%	0.15	8,447	25.0%	18,937	21.8%	0.08
Antibiotic use	2,330	70.1%	8,927	53.2%	0.35	23,937	70.9%	54,295	62.4%	0.18
Epilepsy or convulsions	26	0.8%	113	0.7%	0.01	673	2.0%	1,870	2.2%	−0.01
Depression	344	10.4%	1,430	8.5%	0.06	4,903	14.5%	12,916	14.9%	−0.01
Anxiety	357	10.8%	1,540	9.2%	0.05	3,169	9.4%	7,982	9.2%	0.01
Obesity or overweight‡	533	16.0%	2,133	12.7%	0.10	3,059	9.1%	6,858	7.9%	0.04

(continued)

TABLE E6. (Continued)

Characteristic	MarketScan (privately insured pregnancies)					MAX (publicly insured pregnancies)				
	Poorly controlled asthma		Well-controlled asthma		Standardized difference	Poorly controlled asthma		Well-controlled asthma		Standardized difference
	(n or mean)	(% or SD)	(n or mean)	(% or SD)		(n or mean)	(% or SD)	(n or mean)	(% or SD)	
Antihypertensive medication	238	7.2%	1,031	6.1%	0.04	2,057	6.1%	4,675	5.4%	0.03
Antidiabetic medication	204	6.1%	960	5.7%	0.02	952	2.8%	2,326	2.7%	0.01
Hypertension diagnosis	218	6.6%	979	5.8%	0.03	1,907	5.6%	4,338	5.0%	0.03
Diabetes diagnosis	110	3.3%	467	2.8%	0.03	1,165	3.5%	2,920	3.4%	0.01
Hypertension§	317	9.5%	1,391	8.3%	0.04	2,830	8.4%	6,563	7.6%	0.03
Diabetes	239	7.2%	1,134	6.8%	0.02	1,405	4.2%	3,511	4.0%	0.01

ED, Emergency department; ICD-9, *International Classification of Diseases, 9th Revision*.*Tobacco use identified by ≥ 1 of the following ICD-9 codes: 305.1x, 649.0x, 989.84, V15.82.†Alcohol abuse or dependence identified by ≥ 1 of the following ICD-9 codes: 291.xx, 303.xx, 305.0x, 357.5x, 425.5x, 571.0x, 571.2x, 571.3x, E860.0, V11.3.‡Obesity or overweight identified by ≥ 1 of the following ICD-9 codes: 278.0x, 649.1x, V85.3x, V85.4.

§Hypertension was defined as having claims for either antihypertensive medication or hypertension diagnosis.

||Diabetes was defined as having claims for either antidiabetic medication or diabetes diagnosis.

TABLE E7. Assessment of prescription patterns during pregnancy among women with asthma

A. Drug dispensation across pregnancy in MarketScan						
Exposure period				Drug group, n (%)		
Pre-pregnancy	T1	T2	T3	SABA	ICS	ICS/LABA
✓				2354 (11.71)	563 (2.80)	792 (3.94)
✓	✓			517 (2.57)	220 (1.09)	352 (1.75)
✓		✓		484 (2.41)	135 (0.67)	167 (0.83)
✓			✓	408 (2.03)	115 (0.57)	147 (0.73)
✓	✓	✓		328 (1.63)	135 (0.67)	230 (1.14)
✓		✓	✓	281 (1.40)	116 (0.58)	172 (0.86)
✓	✓		✓	255 (1.27)	120 (0.60)	174 (0.87)
✓	✓	✓	✓	952 (4.74)	457 (2.27)	936 (4.66)
	✓			2272 (11.30)	664 (3.30)	380 (1.89)
	✓	✓		470 (2.34)	251 (1.25)	160 (0.80)
	✓		✓	404 (2.01)	157 (0.78)	142 (0.71)
	✓	✓	✓	365 (1.82)	295 (1.47)	244 (1.21)
		✓		2461 (12.24)	808 (4.02)	348 (1.73)
		✓	✓	515 (2.56)	388 (1.93)	265 (1.32)
			✓	1868 (9.29)	724 (3.60)	412 (2.05)
B. Drug dispensation across pregnancy in MAX						
Exposure period				Drug group, n (%)		
Pre-pregnancy	T1	T2	T3	SABA	ICS	ICS/LABA
✓				13,158 (10.90)	4,745 (3.93)	4,621 (3.83)
✓	✓			4,574 (3.79)	1,351 (1.12)	1,687 (1.40)
✓		✓		3,558 (2.95)	707 (0.59)	565 (0.47)
✓			✓	2,917 (2.42)	469 (0.39)	409 (0.34)
✓	✓	✓		3,462 (2.87)	625 (0.52)	858 (0.71)
✓		✓	✓	2,626 (2.17)	335 (0.28)	462 (0.38)
✓	✓		✓	2,262 (1.87)	343 (0.28)	433 (0.36)
✓	✓	✓	✓	12,442 (10.30)	856 (0.71)	2303 (1.91)
	✓			12,098 (10.02)	4,111 (3.40)	2,749 (2.28)
	✓	✓		3,935 (3.26)	1,065 (0.88)	727 (0.60)
	✓		✓	2,943 (2.44)	626 (0.52)	385 (0.32)
	✓	✓	✓	3,968 (3.29)	737 (0.61)	742 (0.61)
		✓		13,044 (10.80)	4,747 (3.93)	2,224 (1.84)
		✓	✓	4,876 (4.04)	1,581 (1.31)	1,141 (0.95)
			✓	10,597 (8.78)	4,301 (3.56)	2,598 (2.15)

T1, Trimester 1; T2, trimester 2; T3, trimester 3.

TABLE E8. GINA Severity* at baseline (pre-pregnancy trimester) vs exacerbations during pregnancy for MarketScan (A) and MAX (B)**A. MarketScan**

GINA Severity at baseline	Exacerbations (≥1), n (%)			
	Trimester 1	Trimester 2	Trimester 3	LMP-Delivery
Mild (n = 15,947)	675 (4.2)	835 (5.2)	831 (5.2)	2,157 (13.5)
Moderate (n = 1,970)	53 (2.7)	59 (3.0)	75 (3.8)	164 (8.3)
Severe (n = 2,187)	77 (3.5)	119 (5.4)	119 (5.4)	265 (12.1)

B. MAX

GINA Severity at baseline	Exacerbations (≥1), n (%)			
	Trimester 1	Trimester 2	Trimester 3	LMP-Delivery
Mild (n = 102,820)	7,604 (7.4)	9,062 (8.8)	7,907 (7.7)	21,659 (21.1)
Moderate (n = 6,225)	569 (9.1)	615 (9.9)	515 (8.3)	1,342 (21.6)
Severe (n = 11,700)	1,324 (11.3)	1,475 (12.6)	1,137 (9.7)	2,953 (25.2)

*Severity categories: mild (GINA steps 0-2), moderate (GINA step 3), severe (GINA steps 4-5).