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Oral Corticosteroids and Risk of Preterm Birth in the California Medicaid Program

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Abstract

BACKGROUND: There is limited information regarding the impact of dose and gestational timing of oral corticosteroid (OCS) use on preterm birth (PTB), especially among women with asthma.

OBJECTIVES: To evaluate OCS dose and timing on PTB for asthma and, as a comparison, systemic lupus erythematosus (SLE).

METHODS: We used health care data from California Medicaid enrollees linked to birth certificates (2007–2013), identifying women with asthma (n = 22,084) and SLE (n = 1174). We estimated risk ratios (RR) for OCS cumulative dose trajectories and other disease-related medications before gestational day 140 and hazard ratios (HR) for time-varying exposures after day 139.

RESULTS: For asthma, PTB risk was 14.0% for no OCS exposure and 14.3%, 16.8%, 20.5%, and 32.7% in low, medium, medium-high, and high cumulative dose trajectory groups, respectively, during the first 139 days. The high-dose group remained associated with PTB after adjustment (adjusted RR [aRR]: 1.46; 95% confidence interval [CI]: 1.00, 2.15). OCS dose after day 139 was not clearly associated with PTB, nor were controller medications. For SLE, PTB risk for no OCS exposure was 24.9%, and it was 39.1% in low- and 61.2% in high-dose trajectory groups. aRR were 1.80 (95% CI: 1.34, 2.40) for high and 1.24 (95% CI: 0.97, 1.58) for low groups. Only prednisone equivalent dose >20 mg/day after day 139 was associated with increased PTB (adjusted HR: 2.54; 95% CI: 1.60, 4.03).

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CONCLUSIONS: For asthma, higher OCS doses early in pregnancy, but not later, were associated with increased PTB. For SLE, higher doses early and later in pregnancy were associated with PTB.

Keywords

Adrenergic β_2 receptor agonists; Antirheumatic agents; Asthma; Glucocorticoids; Inflammatory bowel disease; Leukotriene antagonist; Oral corticosteroids; Pregnancy; Preterm birth; Systemic lupus erythematosus

The treatment goal for pregnant women with asthma is to maintain asthma control with optimal therapy.[1] Oral corticosteroids (OCSs) may be used during pregnancy to treat acute exacerbations or less commonly for severe persistent asthma.[2,3] For pregnant women with other autoimmune diseases, including systemic lupus erythematosus (SLE) and inflammatory bowel disease (IBD), OCSs may be used to manage flares or as maintenance therapy.[4–7]

Many studies have reported an increased risk of preterm birth (PTB) or shorter gestational length after *any* OCS use during pregnancy, primarily among women with asthma, but also for other autoimmune diseases including SLE and IBD.[8–25] As a potential mechanism underlying the association, Schatz et al[13] proposed that the immunosuppressive effects of OCSs could increase the risk of PTB mediated through subclinical intraamniotic infection, which is believed to be an important contributor to PTB.[26] Systemic corticosteroid use in higher doses of approximately ≥10 mg of prednisone-equivalent per day has been associated with infection in individuals with autoimmune diseases, including pregnant women, independent of other immunosuppressives.[27–31] An alternative explanation for the association between OCS use and PTB is confounding by indication as lower asthma control and greater autoimmune disease severity are also associated with increased PTB risk.[24,32–39]

There is limited information regarding the impact of dose and gestational timing of OCS use on gestational length,[18,20,25,40] especially among women with asthma.[25] Therefore, we evaluated the impact of OCS dose and gestational timing of use among women with asthma, adjusting for proxies of asthma control. We also considered the association in women with SLE and as an exploratory analysis among women with IBD to determine whether findings for asthma would be observed for other OCS indications.

METHODS

Data source and study population

We used enrollment and outpatient, inpatient, and pharmacy claims data from 2007 to 2013 from the California Medicaid program (known as Medi-Cal), which were compiled by the California Department of Health Care Services and linked to birth certificate data from the California Birth Statistical Master Files and to California's Office of Statewide Health Planning and Development hospital discharge data. The study was approved by the Committee for the Protection of Human Subjects, California Health and Human Services Agency and was determined exempt by the University of California San Diego Human Research Protections Program. A data use agreement was in place with the California

Department of Health Care Services. Counts and numbers that could be used to calculate counts of less than 16 were suppressed.

Last menstrual period (LMP) date was calculated from the birth certificate by subtracting the obstetric estimate of gestational age at delivery from the delivery date; the birth certificate LMP estimate of gestational age at delivery was used when obstetric estimate was unavailable.[41] Most (84%) of the women meeting inclusion criteria (described below) had the obstetric estimate available.

Among the 1,767,164 linked deliveries (Figure 1), we included women with gestational age at delivery of ≥20 weeks and <45 weeks, an LMP date on or after January 1, 2007, and on or before March 1, 2013, maternal age ≥12 and <49 years at delivery, continuous Medi-Cal enrollment between the LMP month and delivery month (to help ensure completeness of claims during pregnancy), and an inpatient or outpatient International Classification of Diseases, Ninth Revision diagnosis codes for asthma (493.x), SLE (710.0), Crohn's disease (555.x), or ulcerative colitis (556.x) during pregnancy through gestational day 258 (<37 gestational weeks). After applying inclusion criteria, there were 23,647 pregnancies ending in live birth. Women were assigned to at least one of 3 subcohorts based on asthma (n = 22,084), SLE (n = 1174), or IBD (Crohn's disease or ulcerative colitis; n = 469) diagnosis; 54 women had asthma and SLE, 24 women had asthma and IBD, and less than 16 women had SLE and IBD. Given the small number of women with IBD exposed to OCS, the IBD analysis was exploratory and is presented in Tables E1–E4 (available in this article's Online Repository at www.jaci-inpractice.org).

Outcome

The primary outcome was PTB (delivery at <37 gestational weeks, ie, <259 days). We considered early PTB (<32 gestational weeks, ie, <224 days) as exploratory given the small number with the outcome.

Exposure

We obtained medication exposure information from outpatient pharmacy claims between LMP and gestational day 258. We used the dispensing dates plus the number of days of medication supplied to estimate exposure. The primary exposure of interest was OCS. Because nearly all OCS dispensings were for prednisone (96%), strength was converted to prednisone-equivalent dose per day.[42] Doses from dispensings that had supply on overlapping days were summed. Prednisone-equivalent doses ≥80 mg/day (<16 women) was assigned to 80 mg/day. We calculated cumulative dose on each day by summing daily dose from previous days.

Other exposures of interest were as follows: for asthma, inhaled corticosteroids, long-acting β-agonist (LABA) or LABA and inhaled corticosteroid combinations, leukotriene modifiers, and other asthma medications excluding inhaled short-acting β-agonists (SABA); for SLE, disease-modifying antirheumatic drugs (DMARDs) (collapsed over biologic and nonbiologic DMARDs given the small number with these medications and our previous study indicating that neither were associated with an increased PTB risk).[25]

Exposure modeling

k-means is a statistical learning method used to cluster individuals with similar patterns of a measurement over time.[43] We used k-means to group women with similar trajectories of cumulative OCS dose during the first 139 days of pregnancy with "KmL" package in R software.[43] Recently this method has been used to characterize patterns of medications in pregnancy.[40,44–46] We previously observed pronounced differences in OCS daily dose between individual observations and the cluster mean due to sporadic OCS use[25]; therefore, we focused on cumulative dose. We selected the number of k clusters, that is, trajectory groups, based on relevance and size. For asthma, we selected k = 5 because setting k < 5 produced a cluster containing >85% of the subcohort and k = 6 produced a cluster with only 1 individual. For SLE, we selected k = 2 because k = 3 produced a cluster containing only 19 individuals. We modeled exposure as any or none for non-OCS medications before gestational day 140.

We could not apply the trajectory method when modeling OCS dose later in pregnancy because the same gestational length is required to avoid including postpartum days for shorter gestations.[40] Furthermore, we avoided studying cumulative dose or a fixed exposure window after gestational day 139 because women become at risk for PTB on day 140 and pregnancies with longer gestations have more opportunity for exposure, which could lead to immortal time bias.[47,48] Instead, we modeled time-dependent changes in OCS daily dose on each gestational day between 140 and 259, allowing for daily changes in high, medium, low, or no dose for OCS and any or no non-OCS medications. Because previous studies reported increased infection risk associated with prednisone doses of around 10 mg and increasing risk with increasing doses,[27–31] we evaluated prednisone-equivalent doses of <10, 10 to <20, and ≥20 mg/day. To characterize the amount of exposure time, we calculated the average number of weeks of exposure to each OCS dose level and to no OCS by dividing the person-weeks in each exposure category by the number of women with any exposure to each level after day 139. Women could contribute weeks to multiple dose levels.

Statistical analysis

To estimate risk ratios (RR) and 95% confidence intervals (CI) between exposure groups before day 140 and PTB and early PTB, we used modified Poisson regression.[49] To estimate hazard ratios (HR) for time-dependent medication exposure after day 139 and PTB and early PTB, we used Cox proportional hazards models with time since day 140 as the time scale. Women with term deliveries were censored at day 259. We used robust variance estimators in models to account for correlation within women who had more than 1 delivery in the data.[49,50]

We adjusted for the following covariates: delivery year, maternal age (<21, 21–34, ≥35 years), race/ethnicity (white, black, Hispanic, other or unknown), education (less than high school, high school graduate or equivalent, some college or associate's degree or higher), nulliparity, multifetal gestation (singleton, higher order), prepregnancy body mass index (underweight or normal <25 kg/m^2, overweight ≥25 to <30 kg/m^2, obesity ≤30 kg/m^2), and smoking during pregnancy from the birth certificate, and Medicaid eligibility based on disability. We adjusted for mental health and hypertension diagnoses between LMP and day

140 because both were associated with PTB. We also adjusted for the following between LMP and day 140 as markers of comorbidity: any inpatient admissions, outpatient visits (none, 1–5, ≥6), and emergency department visits (none, 1, ≥2).[51] Models for medication exposures before day 140 and after day 139 were mutually adjusted for the other medication exposures during the same period of interest.

For asthma, we also adjusted for the following between LMP and day 140 as asthma control proxies: any inpatient admissions with an asthma diagnosis, outpatient visits with an asthma diagnosis (none, 1, ≥2), emergency department visits with an asthma diagnosis (none, 1, ≥2), and SABA dispensings (none, 1, 2, ≥3).[52,53] For models of asthma medication exposure after day 139, we adjusted for exposure to OCS cumulative dose trajectory groups, inhaled corticosteroids, LABA or LABA and inhaled corticosteroid combinations, leukotriene modifiers, and other asthma medications excluding SABA before day 140.

For SLE, we also adjusted for the following SLE severity proxies: number of outpatient visits with an SLE diagnosis (none, 1, ≥2) and any inpatient admissions with an SLE diagnosis before day 140. For models of SLE medication exposure after day 139, we adjusted for exposure to OCS cumulative dose trajectory groups and DMARDs before day 140.

We imputed values with single imputation using predicted values from multivariable models including county, maternal age, and race/ethnicity for the following covariates with missing data: body mass index (7% missing), education (3% missing), smoking (2% missing), and parity (0.1% missing).

We conducted a *post hoc* mediation analysis, as described by Valeri and Vanderweele,[54] to explore whether preeclampsia, based on diagnosis codes,[55] mediated the association between early OCS and PTB. We collapsed exposure levels to increase statistical power.

RESULTS

Cohort and trajectory group characteristics

The average maternal age was 25.8 (standard deviation [SD], 6.1) and 27.9 (SD, 5.8) years in the asthma and SLE subcohorts, respectively. The majority of women were Hispanic (51% for asthma and 61% for SLE) (Tables I and II). Approximately a third of women were in each of the 3 education levels, with slightly more women with at least some college or an associate's degree in the SLE subcohort (30% for asthma and 36% for SLE). The average gestational age at delivery was 267.5 (SD, 15.4) and 259.1 (SD, 21.2) days in the asthma and SLE subcohorts, respectively.

Figure 2 illustrates mean cumulative dose for each trajectory group on each gestational day. The 2 groups with the highest OCS exposure in the asthma subcohort were combined into one "high-dose" group in analyses given their smaller size. When examining the high-dose trajectory groups, women with SLE had on average more days of OCS exposure (mean, 87.3 vs 56.8 days; Table III) but lower average daily dose (mean, 15.2 vs 24.1 mg; Table III) than women with asthma.

Among women with asthma, those with OCS exposure more often had Medicaid eligibility based on disability, hypertension, and proxies of lower asthma control, that is, more outpatient and emergency department visits and any inpatient admission with an asthma diagnosis, and more SABA dispensings, especially those in higher trajectories (Table I). Women with OCS more often had non-OCS asthma medication exposures, with more LABA or LABA and inhaled corticosteroid combinations, leukotriene modifiers, and other asthma medications in medium-high and high trajectories compared with low and medium trajectories. Among women with SLE, women with OCS more often had hypertension and DMARD exposure and had greater health care utilization than women without OCS (Table II).

OCS earlier in pregnancy and PTB

For asthma, PTB risk among women with no OCS exposure was 14.0%, and it was 14.3% in low, 16.8% in medium, 20.5% in medium-high, and 32.7% in high cumulative dose trajectory groups before day 140 (Table IV). After adjusting for covariates, only the high-dose group remained moderately associated with PTB (adjusted RR [aRR]: 1.46; 95% CI: 1.00, 2.15). Controller therapies were not associated with PTB.

Among women with SLE, PTB risk among women with no OCS exposure was 24.9%, and it was 39.1% in low and 61.2% in high cumulative dose trajectory groups (Table IV). Adjusting for covariates attenuated associations, with the high-dose group associated with a 1.80-fold increased PTB risk for PTB (95% CI: 1.34, 2.40) and the low-dose group associated with a borderline increased risk of 1.24 (95% CI: 0.97, 1.58). DMARDs were not associated with PTB.

OCS later in pregnancy and PTB

After gestational day 139, the average weeks of exposure at each OCS dose level was approximately 3 times greater among women with SLE than those with asthma (Figure 3).

For asthma, there was no clear pattern of association between OCS dose after day 139 and PTB (adjusted HR [aHR]: 0.85 [95% CI: 0.54, 1.34; Table V] for >20 mg/day of prednisone equivalent dose; aHR: 1.16 [95% CI: 0.67, 2.02] for 10–20 mg/day; aHR: 1.40 [95% CI: 0.62, 3.16] for <10 mg/day).

Among women with SLE, only exposure to >20 mg/day of prednisone equivalent dose after day 139 was strongly associated with an increased PTB rate (aHR: 2.54 [95% CI: 1.60, 4.03]; Table V), whereas the aHR were 1.37 (95% CI: 0.80, 2.36) for 10 to 20 mg/day and 1.15 (95% CI: 0.68, 1.95) for <10 mg/day.

Exploratory analyses

Among women with IBD, OCS exposure before day 140 was not associated with PTB (aRR: 1.06 [95% CI: 0.59, 1.89]; Table E3, available in this article's Online Repository at www.jaci-inpractice.org). In contrast, OCS exposure after day 140 was associated with an increased PTB rate; however, results were imprecise (aHR: 2.13 [95% CI: 0.99, 4.59]; Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

There was no increased risk of early PTB after either period of OCS exposure in women with asthma although results were imprecise. Among women with SLE, only high doses of OCS were associated with an elevation in early PTB (aRR: 1.88 [95% CI: 1.02, 3.48] for high OCS cumulative dose trajectory group before day 140; aHR: 4.32 [95% CI: 1.85, 10.10] for >20 mg/day of prednisone-equivalent dose after day 139; Tables E5 and E6, available in this article's Online Repository at www.jaci-inpractice.org).

Among women with asthma, preeclampsia risk was 3%; preeclampsia mediated 8% of the association between the highest 2 trajectory groups before day 140 versus no OCS exposure and PTB, although the CI for this association contained the null. Among women with SLE, preeclampsia risk was 11%; preeclampsia mediated 20% of the association between any OCS exposure before day 140 and PTB.

DISCUSSION

In this study of California Medicaid enrollees, we observed very high absolute risks for PTB among women with asthma, ranging from 14% in women with no OCSs to 33% for the highest OCS doses, and for SLE, ranging from 25% in women with no OCSs to 61% for the highest OCS doses. These PTB risks are notably higher than the general population of pregnant Medi-Cal enrollees (10%) and national estimates including women with a broader range of socioeconomic status during similar years (10%−12%; Department of Health Care Services, 2011, Unpublished data).[56] The high baseline PTB risk may in part reflect effects of poorly controlled disease among some women.[32,33,37,38]

We observed some differences in the association between OCS dose and PTB by gestational timing between women with asthma and SLE. Among women with asthma, we observed a moderate association between the highest OCS cumulative dose trajectory group during the first half of pregnancy and PTB. However, we did not observe a clear association between OCS exposures late in pregnancy and PTB for asthma. In contrast, for SLE, we observed an increase in PTB associated with higher doses of OCS exposure both earlier and later in pregnancy. We did not observe associations for other asthma- or SLE-related medications. As discussed below, differences in results between asthma and SLE may reflect disease-related differences in the intensity of OCS exposure, if there is a true effect of OCSs on PTB, or differences in confounding, if the association between OCS and PTB is spurious due to confounding by disease severity, or a combination of these explanations.

There were differences in the typical daily dose and days of OCS exposure between women with asthma and SLE that may contribute to differences in results. During the first half of pregnancy, the average daily dose across each trajectory group in the asthma subcohort was higher than for SLE, and the average number of OCS days tended to be lower for asthma than SLE. Later in pregnancy, the average number of exposure weeks for each level of OCS dose was higher in women with SLE than asthma. It is possible that chronic OCS exposure at relatively high daily doses, as was more frequently observed among women with SLE than asthma, impacts PTB risk, whereas shorter OCS durations do not.

The generally stronger associations between higher OCS dose versus no OCS exposure and PTB among women with SLE, as compared with asthma, may reflect greater confounding by disease severity for SLE and differences in disease course during pregnancy. Meta-analyses indicate that SLE confers greater increased risk for PTB than asthma (a 2-fold vs 1.4-fold), although such estimates vary by the severity of women included.[33,38] The current study only had disease severity proxies and potential residual confounding is a limitation.

In our previous study using MotherToBaby Pregnancy Studies data, we also observed a possible difference in the association between early and late OCS exposure and PTB risk for women with asthma.[25] Specifically, the point estimate was larger for any early OCS exposure versus none (aRR: 2.28 [95% CI: 0.89, 5.81]) than for late OCS exposure versus none (aHR: 1.23 [95% CI: 0.27, 5.56]), although CIs overlapped.[25] One possible explanation for the association between early, but not late, high-dose OCS exposure and PTB is that early asthma exacerbations, that is, the indication for high dose OCS, are impacting PTB through a mechanism occurring earlier in pregnancy, for example, through the development of preeclampsia. Our mediation analyses indicate that preeclampsia may explain a small portion of the association between early OCS and PTB, although there was likely some misclassification of preeclampsia.[55]

In line with the current study, a previous study reported that prednisone dose >10 mg/day anytime during pregnancy was associated with PTB for SLE, although results were unadjusted.[20] There is some evidence from studies of rheumatoid arthritis that higher OCS doses are associated with increased PTB; however, confounding by disease severity has not been ruled out.[18,25,40]

Besides residual confounding by disease control or severity, our study had additional limitations. First, we relied on pharmacy dispensing data with medication dispensing dates and days' supply to estimate gestational timing and dose, and we could not confirm that women were taking medications as assumed. Exposure misclassification may have biased results toward the null. Second, we relied on diagnosis codes to identify women with each condition. We would expect women who are false positives for the condition not to have a disease-related medication, and this may have resulted in a healthier unexposed comparison group than if we could confirm the assumed conditions. Third, results may reflect selection bias if the exposures are associated with pregnancy loss and stillbirth, as we included only livebirths. Fourth, we required women to be enrolled in Medi-Cal throughout pregnancy. In more recent years since the Patient Protection and Affordable Care Act, Medicaid has expanded to include women without children, nonpregnant women, and higher income women than during the study period. Results could differ for women who are Medicaid eligible before pregnancy and for Medicaid-eligible women with higher socioeconomic status, especially if such women differ from the study population by disease severity. Finally, the number of women with IBD and OCS exposures was small, resulting in imprecise estimates.

A major strength of the study is that we used claims data linked to birth certificate data to obtain gestational age at delivery. Therefore, we avoided relying on diagnosis codes to estimate LMP and identify PTBs, which results in greater misclassification of gestational

timing of exposure and outcome misclassification. Other strengths include the use of non-OCS disease-related medications for comparisons, the large number of women with asthma and SLE, which allowed us to study OCS dose, and a diverse, in terms of race and ethnicity, and low-income population.

In summary, the highest OCS doses early in pregnancy, but not later, were associated with moderately increased PTB among women with asthma. In contrast, higher dose OCSs both early and later in pregnancy were associated with increased PTB for SLE. There was no clear association between lower OCS doses and PTB and no association between the other medications we studied and PTB, including asthma controller therapy. Our findings support the current guidelines to control asthma and treat exacerbations during pregnancy.[1] Although the positive associations may reflect residual confounding by disease activity, results are reassuring for women who can manage asthma and SLE with non-OCS medications or lower OCS doses. Regardless of confounding, the absolute risk for PTB was notably high in this population of low-income women with asthma and SLE, especially for women with OCS. Providers treating similar women should be aware of the potential for PTB.

ONLINE REPOSITORY

METHODS

We describe additional details pertaining to the exploratory analysis in the inflammatory bowel disease (IBD) subcohort below.

Exposure modeling—Medications of interest for the IBD subcohort included oral corticosteroids (OCSs), immunosuppressives, and oral aminosalicylates. For IBD, we considered any exposure versus none to each medication group of interest during the first 139 days of pregnancy and after gestational day 139. We did not consider OCS dose because of the small number of women who used OCSs.

Additional covariates—In addition to the variables that we adjusted for across each subcohort, we also adjusted the IBD models for the following covariates: Crohn's disease diagnosis (vs ulcerative colitis diagnosis), number of outpatient visits with IBD diagnosis (none, 1, ≥2), and any inpatient admissions with an IBD diagnosis before gestational day 140. For models of IBD medication exposure after gestational day 139, we adjusted for exposure to OCS, oral aminosalicylates, and immunosuppressives before gestational day 140.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

aHR	Adjusted hazard ratio
aRR	Adjusted risk ratio
CI	Confidence interval
DMARD	Disease-modifying antirheumatic drug
HR	Hazard ratio
IBD	Inflammatory bowel disease
LABA	Long-acting β-agonist
LMP	Last menstrual period
OCS	Oral corticosteroid
PTB	Preterm birth
RR	Risk ratio
SABA	Short-acting β-agonists
SD	Standard deviation
SLE	Systemic lupus erythematosus

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What is already known about this topic?

Oral corticosteroids are associated with an increased risk of preterm birth (PTB) among women with asthma.

What does this article add to our knowledge?

For asthma, only higher oral corticosteroid doses early in pregnancy, but not later, were associated with increased PTB risk. There was no association between asthma controller therapies and PTB.

How does this study impact current management guidelines?

Our findings support the treatment goal of controlling asthma symptoms during pregnancy and are reassuring for women who can manage asthma during pregnancy with lower oral corticosteroid doses and controller therapies.

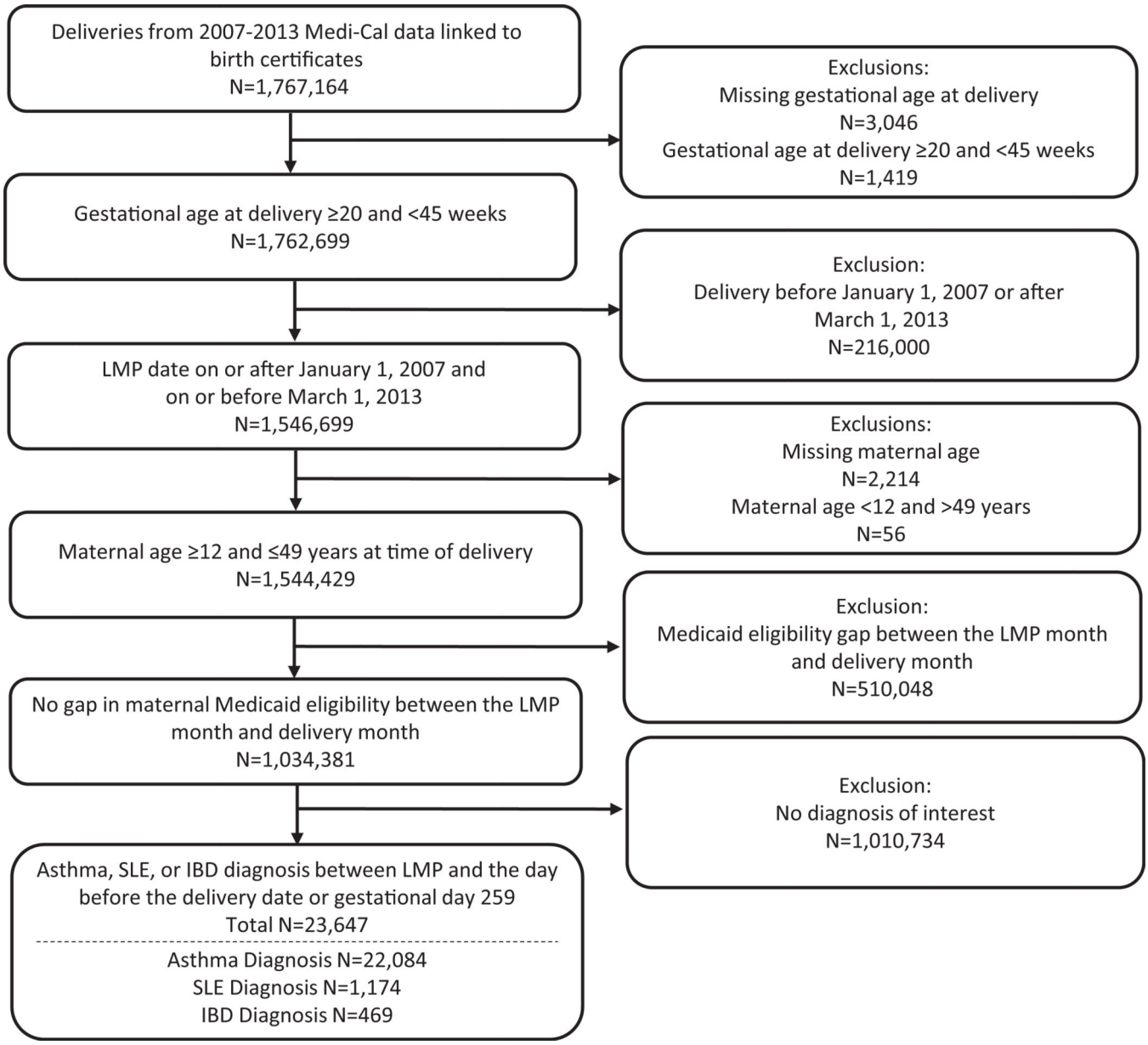

FIGURE 1.

Study flow diagram. Fifty-four women had asthma and SLE, 24 women had asthma and IBD, and <16 women had SLE and IBD. *IBD,* Inflammatory bowel disease; *LMP,* last menstrual period; *SLE,* systemic lupus erythematosus.

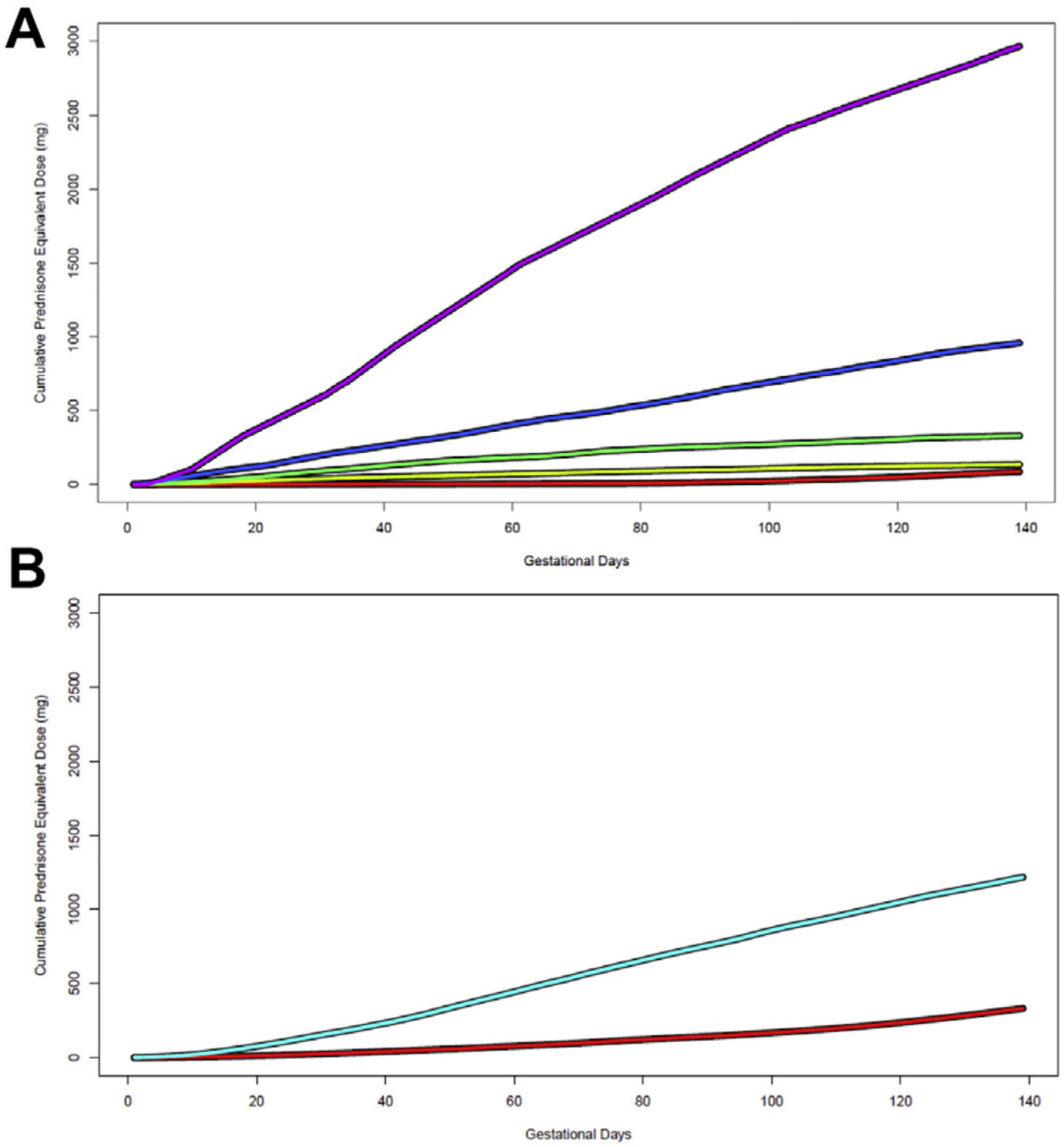

FIGURE 2.

Oral corticosteroid cumulative dose trajectories between the last menstrual period and gestational day 139. Lines represent the mean cumulative dose on each gestational day for each trajectory group. Women with (**A**) asthma (n = 2591) (purple and blue = high, green = medium-high, yellow = medium, red 1/4 low-dose trajectories) and (**B**) systemic lupus erythematosus (n = 223) (light blue = high and red = low-dose trajectories).

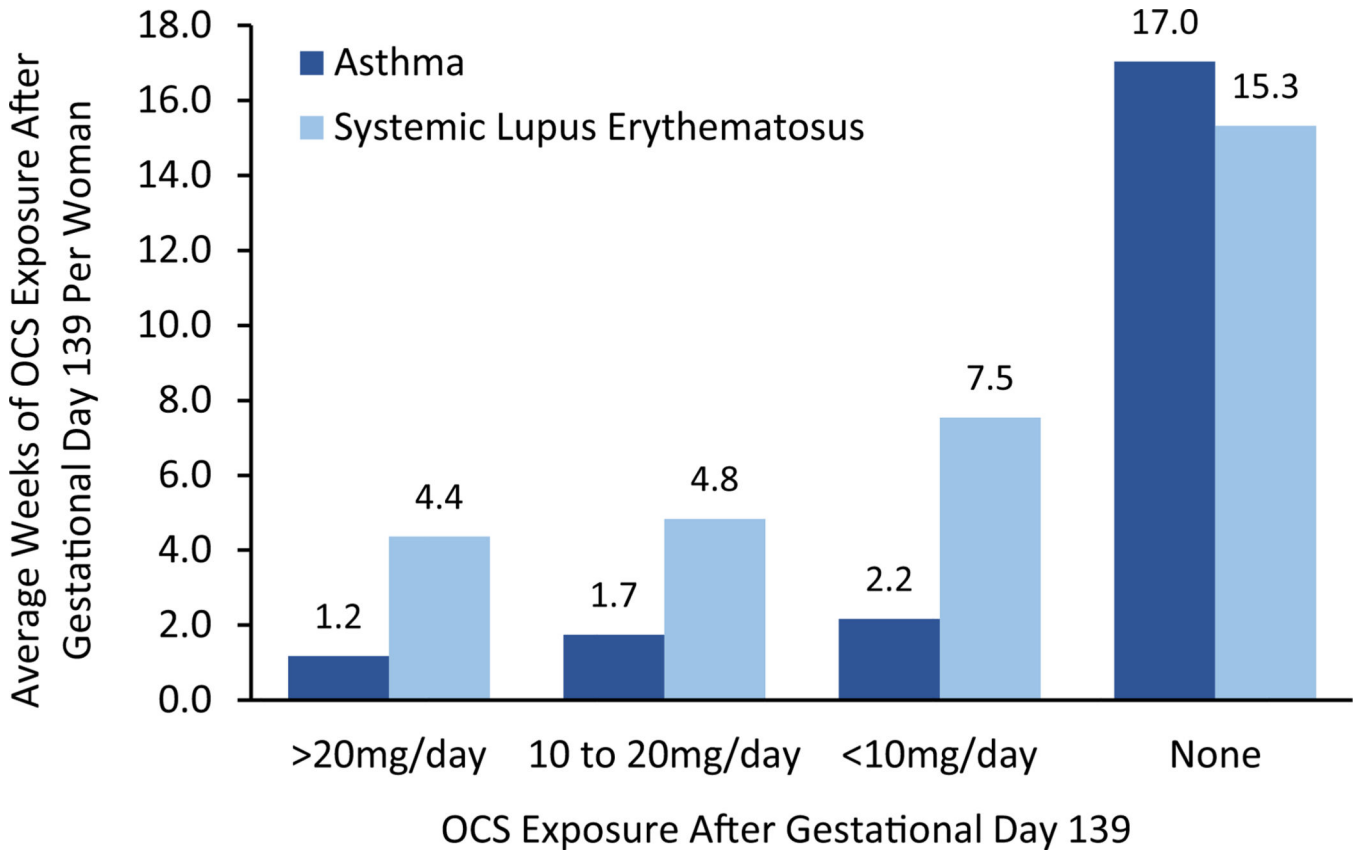

FIGURE 3.

Average weeks of oral corticosteroid (OCS) exposure after gestational day 139 by dose level per woman for asthma (n = 22,084) and systemic lupus erythematosus (n = 1174). For asthma, 99.0% of all person-weeks were unexposed to OCS. For systemic lupus erythematosus, 89.0% of all person-weeks were unexposed to OCS. mg/day in prednisone equivalent dose.

TABLE I.

Characteristics by oral corticosteroid cumulative dose trajectory group before gestational day 140 among women with asthma (n = 22,084)

	Trajectory group				
Characteristic	**None (n = 19,493)**	**Low (n = 1360)**	**Medium (n = 928)**	**Medium-high (n = 254)**	**High (n = 49)**
Maternal age (y)					
12–20	4515 (23.2)	234 (17.2)	178 (19.2)	43 (16.9)	-
21–34	13,055 (67.0)	969 (71.3)	640 (69.0)	175 (68.9)	-
≥35	1923 (9.9)	157 (11.5)	110 (11.9)	36 (14.2)	-
Race/ethnicity					
White	4334 (22.2)	236 (17.4)	192 (20.7)	56 (22.0)	-
Black	3507 (18.0)	216 (15.9)	192 (20.7)	53 (20.9)	-
Hispanic	9891 (50.7)	790 (58.1)	458 (49.4)	117 (46.1)	19 (38.8)
Other or unknown	1761 (9.0)	118 (8.7)	86 (9.3)	28 (11.0)	-
Education					
Less than high school	6651 (34.1)	534 (39.3)	345 (37.2)	83 (32.7)	17 (34.7)
High school graduate	6945 (35.6)	475 (34.9)	309 (33.3)	85 (33.5)	-
Some college, associate’s degree, or higher	5897 (30.3)	351 (25.8)	274 (29.5)	86 (33.9)	-
Nulliparous	6005 (30.8)	293(21.5)	192 (20.7)	54 (21.3)	-
Multifetal gestation	278 (1.4)	25 (1.8)	-	-	-
Prepregnancy body mass index					
Underweight or normal	6366 (32.7)	377 (27.7)	238 (25.7)	53 (20.9)	-
Overweight	5619 (28.8)	401 (29.5)	270 (29.1)	78 (30.7)	-
Obese	7508 (38.5)	582 (42.8)	420 (45.3)	123 (48.4)	16 (32.7)
Smoking during pregnancy	1650 (8.5)	95 (7.0)	78 (8.4)	18 (7.1)	-
Medicaid eligibility based on disability	1125 (5.8)	74 (5.4)	75 (8.1)	33 (13.0)	-
Mental health diagnosis *	2387 (12.2)	160 (11.8)	139 (15.0)	47 (18.5)	-
Hypertension diagnosis *	472 (2.4)	41 (3.0)	42 (4.5)	18 (7.1)	-
No. of outpatient visits *					
None	6848 (35.1)	296 (21.8)	227 (24.5)	54 (21.3)	19 (38.8)
1–5	8182 (42.0)	712 (52.4)	433 (46.7)	108 (42.5)	-

Characteristic	Trajectory group				
	None (n = 19,493)	Low (n = 1360)	Medium (n = 928)	Medium-high (n = 254)	High (n = 49)
≥6	4463 (22.9)	352 (25.9)	268 (28.9)	92 (36.2)	-
No. of emergency department visits *					
None	9044 (46.4)	206 (15.2)	162 (17.5)	36 (14.2)	-
1	4363 (22.4)	404 (29.7)	243 (26.2)	50 (19.7)	-
≥2	6086 (31.2)	750 (55.1)	523 (56.4)	168 (66.1)	31 (63.3)
≥1 inpatient admission *	874 (4.5)	156 (11.5)	102 (11.0)	56 (22.0)	-
No. of outpatient visits with asthma diagnosis *					
None	13,696 (70.3)	594 (43.7)	390 (42.0)	108 (42.5)	30 (61.2)
1	4827 (24.8)	530 (39.0)	334 (35.0)	63 (24.8)	-
≥2	970 (5.0)	236 (17.4)	204 (22.0)	83 (32.7)	-
No. of emergency department visits with asthma diagnosis *					
None	15,417 (79.1)	445 (32.7)	349 (37.6)	92 (36.2)	25 (51.0)
1	3595 (18.4)	683 (50.2)	404 (43.5)	77 (30.3)	-
≥2	481 (2.5)	232 (17.1)	175 (18.9)	85 (33.5)	-
≥1 inpatient admission with asthma diagnosis *	246 (1.3)	115 (8.5)	66 (7.1)	37 (14.6)	-
No. of SABA dispensings *					
None	11,984 (61.5)	234 (17.2)	151 (16.3)	38 (15.0)	-
1	4645 (23.8)	504 (37.1)	307 (33.1)	52 (20.5)	-
2	1450 (7.4)	284 (20.9)	174 (18.8)	36 (14.2)	-
≥3	1414 (7.3)	338 (24.9)	296 (31.9)	128 (50.4)	26 (53.1)
Inhaled corticosteroid *	2007 (10.3)	342 (25.1)	277 (29.9)	84 (33.1)	-
LABA or LABA and inhaled corticosteroid combination *	1054 (5.4)	209 (15.4)	164 (17.7)	69 (27.2)	17 (34.7)
Leukotriene modifier *	642 (3.3)	102 (7.5)	102 (11.0)	47 (18.5)	16 (32.7)
Other asthma medication *	336 (1.7)	135 (9.9)	89 (9.6)	48 (18.9)	-

LABA, Long-acting β-agonist; *SABA*, short-acting β-agonist.

Data are presented as n (%).

-Small numbers or numbers that could be used to calculate small numbers suppressed.

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* Between last menstrual period and gestational day 140.

TABLE II.

Characteristics by oral corticosteroid cumulative dose trajectory group before gestational day 140 among women with systemic lupus erythematosus (SLE) (n = 1174)

	Trajectory group		
Characteristic	**None (n = 951)**	**Low (n = 174)**	**High (n = 49)**
Maternal age (y)			
12–20	100 (10.5)	16 (9.2)	-
21–34	712 (74.9)	129 (74.1)	-
≥35	139 (14.6)	29 (16.7)	-
Race/ethnicity			
White	149 (15.7)	-	-
Black	110 (11.6)	24 (13.8)	-
Hispanic	575 (60.5)	114 (65.5)	-
Other or unknown	117 (12.3)	-	-
Education			
Less than high school	253 (26.6)	53 (30.5)	-
High school graduate	346 (36.4)	68 (39.1)	-
Some college, associate's degree, or higher	352 (37.0)	53 (30.5)	-
Nulliparous	252 (26.5)	41 (23.6)	18 (36.7)
Multifetal gestation	-	-	0 (0)
Prepregnancy body mass index			
Underweight or normal	346 (36.4)	74 (42.5)	-
Overweight	291 (30.6)	55 (31.6)	-
Obese	314 (33.0)	45 (25.9)	-
Smoking during pregnancy	49 (5.2)	-	-
Medicaid eligibility based on disability	76 (8.0)	26 (14.9)	-
Mental health diagnosis *	79 (8.3)	20 (11.5)	-
Hypertension diagnosis *	62 (6.5)	22 (12.6)	-
No. of outpatient visits *			
None	327 (34.4)	50 (28.7)	-
1–5	395 (41.5)	70 (40.2)	-
≥6	229 (24.1)	54 (31.0)	24 (49.0)
No. of emergency department visits *			
None	569 (59.8)	77 (44.3)	17 (34.7)
1	165 (17.4)	43 (24.7)	-
≥2	217 (22.8)	54 (31.0)	-
≥1 inpatient admission *	63 (6.6)	27 (15.5)	-
No. of outpatient visits with SLE diagnosis *			
None	705 (74.1)	92 (52.9)	-
1	147 (15.5)	32 (18.4)	-
≥2	99 (10.4)	50 (28.7)	21 (42.9)

	Trajectory group		
Characteristic	**None (n = 951)**	**Low (n = 174)**	**High (n = 49)**
≥1 inpatient admissions with SLE diagnosis *	-	-	-
DMARD *	105 (11.0)	99 (56.9)	31 (63.3)

DMARD, Disease-modifying antirheumatic drug.

Data are presented as n (%).

- Small numbers or numbers that could be used to calculate small numbers suppressed.

* Between last menstrual period and gestational day 140.

TABLE III.

Average total days with oral corticosteroid (OCS) exposure and average daily and total cumulative prednisone equivalent dose between last menstrual period and gestational day 139 by oral corticosteroid cumulative dose trajectory group for women with asthma (n = 2591) and systemic lupus erythematosus (n = 223)

		Total days with OCS exposure	Average daily prednisone equivalent dose* (mg), gestational days 0–139	Total cumulative prednisone equivalent dose (mg), gestational days 0–139
Trajectory group	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Asthma				
High dose	49	56.8 (36.9)	24.1 (14.3)	1086.6 (713.3)
Medium-high dose	254	17.2 (15.2)	27.2 (14.7)	334.5 (148.5)
Medium dose	928	7.7 (5.7)	19.7 (7.5)	134.8 (73.2)
Low dose	1360	5.7 (3.6)	16.9 (8.1)	89.2 (61.8)
Systemic lupus erythematosus				
High dose	49	87.3 (28.3)	15.2 (6.4)	1225.5 (501.9)
Low dose	174	46.4 (34.5)	10.0 (9.1)	338.2 (247.0)

SD, Standard deviation.

*Average daily dose on days with any oral corticosteroid exposure.

TABLE IV.

Association between oral corticosteroid cumulative dose trajectory groups and other medications of interest before gestational day 140 and preterm birth among women with asthma (n = 22,084) and systemic lupus erythematosus (n = 1174)

Medication exposure before gestational day 140*	n	Preterm birth	% Preterm birth	Crude RR (95% CI)	Adjusted RR‡ (95% CI)
Asthma					
Oral corticosteroid trajectory					
High dose	49	16	32.7	2.28 (1.52, 3.42)	1.46 (1.00, 2.15)
Medium-high dose	254	52	20.5	1.48 (1.16, 1.88)	1.16 (0.91, 1.48)
Medium dose	928	156	16.8	1.20 (1.03, 1.39)	1.06 (0.91, 1.24)
Low dose	1360	195	14.3	1.02 (0.89, 1.17)	0.92 (0.80, 1.06)
No oral corticosteroid	19,493	2728	14.0	Reference	Reference
Inhaled corticosteroid	19,359	2752	14.5	1.02 (0.92, 1.12)	0.95 (0.86, 1.06)
No inhaled corticosteroid	2725	395	14.2	Reference	Reference
LABA or LABA and inhaled corticosteroid combination	1513	240	15.9	1.11 (0.99, 1.26)	0.99 (0.87, 1.12)
No LABA or LABA and inhaled corticosteroid combination	20,571	2907	14.1	Reference	Reference
Leukotriene modifier	909	139	15.3	1.08 (0.93, 1.27)	1.00 (0.85, 1.17)
No leukotriene modifier	21,175	3008	14.2	Reference	Reference
Other asthma medication†	619	109	17.6	1.24 (1.03, 1.48)	1.01 (0.84, 1.21)
No other asthma medication†	21,465	3038	14.2	Reference	Reference
No medication of interest	16,098	2240	13.9	NA	NA
Systemic lupus erythematosus					
Oral corticosteroid trajectory					
High dose	49	30	61.2	2.46 (1.93, 3.13)	1.80 (1.34, 2.40)
Low dose	174	68	39.1	1.56 (1.26, 1.93)	1.24 (0.97, 1.58)
No oral corticosteroid	951	237	24.9	Reference	Reference
DMARD	235	86	36.6	1.38 (1.13, 1.69)	0.97 (0.77, 1.22)
No DMARD	939	249	26.5	Reference	Reference
No medication of interest	328	125	38.1	NA	NA

CI, Confidence interval; *DMARD*, disease-modifying antirheumatic drug; *LABA*, long-acting β-agonist; *NA*, not applicable; *RR*, risk ratio.

*Mutually exclusive oral corticosteroid trajectory groups and any vs none for other medication exposure groups.

[†]Excluding short-acting β-agonists.

[‡]RR for asthma mutually adjusted for medications of interest, delivery year, maternal age, race/ethnicity, education, nulliparity, multifetal gestation, prepregnancy body mass index, smoking during pregnancy, Medicaid eligibility based on disability, and mental health diagnosis, hypertension diagnosis, number of outpatient visits, emergency department visits, outpatient visits with an asthma diagnosis, emergency department visits with an asthma diagnosis, and inhaled short-acting β-agonist dispensings, any inpatient admissions and any inpatient admissions with an asthma diagnosis between last menstrual period (LMP) and day 140. RR for systemic lupus erythematosus (SLE) mutually adjusted for medications of interest, delivery year, maternal age, race/ethnicity, education, nulliparity, multifetal gestation, prepregnancy body mass index, smoking during pregnancy, Medicaid eligibility based on disability, and mental health diagnosis, hypertension diagnosis, number of outpatient visits, emergency department visits, and outpatient visits with an SLE diagnosis, any inpatient admissions and any inpatient admissions with an SLE diagnosis between LMP and day 140.

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TABLE V.

Association between oral corticosteroids and other medications of interest after gestational day 139 and preterm birth among women with asthma (n = 22,084) and systemic lupus erythematosus (n = 1174)

Time-dependent medication exposure after gestational day 139	n	Preterm birth	Person-weeks	Rate (per 1000/week)	Crude HR (95% CI)	Adjusted HR‡(95% CI)
Asthma						
Oral corticosteroid (mg/day*)						
>20	1922	16	2257	7.1	0.95 (0.59,1.54)	0.85 (0.54, 1.34)
10–20	-	-	-	9.8	1.25 (0.72, 2.18)	1.16 (0.67, 2.02)
<10	-	-	-	12.9	1.77 (0.79, 3.95)	1.40 (0.62, 3.16)
No oral corticosteroid	22,077	3109	375,053	8.3	Reference	Reference
Inhaled corticosteroid	3329	131	193,271	6.8	0.87 (0.73, 1.03)	0.85 (0.72, 1.02)
No inhaled corticosteroid	22,053	3012	359,724	8.4	Reference	Reference
LABA or LABA and inhaled corticosteroid combination	1713	99	11,576	8.6	1.05 (0.86, 1.28)	0.99 (0.81, 1.21)
No LABA or LABA and inhaled corticosteroid combination	22,060	3044	367,420	8.3	Reference	Reference
Leukotriene modifier	915	51	7191	7.1	0.89 (0.68, 1.18)	0.82 (0.62, 1.09)
No leukotriene modifier	22,063	3092	371,804	8.3	Reference	Reference
Other asthma medications†	541	27	2893	9.3	1.10 (0.76, 1.60)	0.90 (0.62, 1.31)
No other asthma medications†	22,069	3116	376,102	8.3	Reference	Reference
No medication of interest	21,978	2850	340,572	8.4	NA	NA
Systemic lupus erythematosus						
Oral corticosteroid (mg/day*)						
>20	118	29	515	56.3	3.86 (2.68, 5.55)	2.54 (1.60, 4.03)
10–20	132	19	637	29.8	2.16 (1.38, 3.37)	1.37 (0.80, 2.36)
<10	138	25	1040	24.0	1.68 (1.12, 2.52)	1.15 (0.68, 1.95)
No oral corticosteroid	1159	262	17,763	14.7	Reference	Reference
DMARD	213	39	1913	20.4	1.29 (0.92,1.79)	0.72 (0.48, 1.11)
No DMARD	1159	296	18,042	16.4	Reference	Reference
No medication of interest	1136	246	16,747	14.7	NA	NA

CI, Confidence interval; *DMARD*, disease-modifying antirheumatic drug; *HR*, hazard ratio; *LABA*, long-acting β-agonist; *NA*, not applicable.

-Small numbers or numbers that could be used to calculate small numbers are suppressed.

[*] Prednisone equivalent dose.

[†] Excluding short-acting β-agonists.

[‡] HR for asthma mutually adjusted for medications of interest, delivery year, maternal age, race/ethnicity, education, nulliparity, multifetal gestation, prepregnancy body mass index, smoking during pregnancy, Medicaid eligibility based on disability, and mental health diagnosis, hypertension diagnosis, oral corticosteroid cumulative dose trajectory groups, inhaled corticosteroids, LABA or LABA and inhaled corticosteroid combinations, leukotriene modifiers, and other asthma medications excluding short-acting β-agonists between last menstrual period (LMP) and day 140, number of outpatient visits, emergency department visits, outpatient visits with an asthma diagnosis, emergency department visits with an asthma diagnosis, and short-acting β-agonist dispensings, any inpatient admissions and any inpatient admissions with an asthma diagnosis between LMP and day 140. HR for systemic lupus erythematosus (SLE) mutually adjusted for medications of interest, delivery year, maternal age, race/ethnicity, education, nulliparity, multifetal gestation, prepregnancy body mass index, smoking during pregnancy, Medicaid eligibility based on disability, and mental health diagnosis, hypertension diagnosis, oral corticosteroid cumulative dose trajectory groups and DMARDs between LMP and day 140, number of outpatient visits, emergency department visits, and outpatient visits with an SLE diagnosis, any inpatient admissions and any inpatient admissions with an SLE diagnosis between LMP and day 140.

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