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Mediation of Adverse Pregnancy Outcomes in Autoimmune Conditions by Pregnancy Complications

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Abstract

Objective—Autoimmune conditions are associated with an increased risk of adverse pregnancy complications and outcomes, suggesting that pregnancy complications may mediate the excess risk. We performed a causal mediation analysis to quantify the mediated effects of autoimmune conditions on adverse pregnancy outcomes.

Methods—We queried a California birth cohort created from linked birth certificates and hospital discharge summaries. From 2,963,888 births, we identified women with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriasis and inflammatory bowel disease (IBD). Pregnancy complications included preeclampsia/hypertension, gestational diabetes and infection in pregnancy. Adverse pregnancy outcomes were preterm birth, cesarean delivery and small for gestational age. We performed a mediation analysis to estimate the total effects of each autoimmune condition and adverse pregnancy outcome, and the indirect effects through pregnancy complications.

Results—All four autoimmune conditions were associated with preterm birth and cesarean delivery, and RA, SLE and IBD were associated with small for gestational age offspring. The strongest mediator of RA, SLE, and psoriasis was preeclampsia/hypertension, accounting for 20–33% of the excess risk of preterm births and 10–19% of excess cesarean deliveries. Gestational

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diabetes and infections generally mediated <10% of excess adverse pregnancy outcomes. Of the four autoimmune conditions, selected pregnancy complications mediated the least amount of adverse pregnancy outcomes among women with IBD.

Conclusions—We found evidence that some excess risk of adverse pregnancy outcomes is mediated through pregnancy complications, particularly preeclampsia/hypertension. Quantifying excess risk and associated pathways provides insight into the underlying etiologies of adverse pregnancy outcomes and can inform intervention strategies.

The increased risk of adverse pregnancy outcomes associated with select autoimmune conditions is well documented, and has been replicated across multiple data sources (1–9). Rheumatic conditions such as rheumatoid arthritis (RA), psoriatic arthritis and systemic lupus erythematosus (SLE) have been associated with increased risk of preterm birth, low birth weight, caesarean delivery, and small for gestational age offspring (1,2,5–7,9–11). Further, although less consistent, psoriasis and inflammatory bowel disease (IBD) have also been associated with increased risk for preterm birth and caesarean delivery (1,3,4,8,12). Many of these same autoimmune conditions are also associated with pregnancy complications, including preeclampsia (1,7,10,12,13), gestational diabetes (12,13), and infections (7,13,14). Taken together, these findings suggest that autoimmune conditions may, in part, increase the risk of adverse pregnancy outcomes through their relationship with pregnancy complications. Termed ‘indirect’ or ‘mediated’ pathways, these models propose that in addition to autoimmune diseases directly causing adverse pregnancy outcomes, that the autoimmune conditions are also causing pregnancy complications, which in turn cause adverse pregnancy outcomes (15).

In order to determine whether or not, and to what extent, these mediated relationships exist, it is necessary to perform a mediation analysis, where the total effect is decomposed into direct (non-mediated) and indirect (mediated) effects. Previous strategies for mediation analysis included regression-based approaches of estimating the effect of the exposure on the outcome in the presence and absence of the mediator and assessing the difference in effect estimates (15). However, if there are unmeasured common causes of the mediator and outcome (Figure 1, variable U (16)), conditioning on the mediator will introduce a collider stratification bias (17,18). Further, if there is an interaction between the exposure and mediator, traditional regression-based approaches may result in incorrect estimates. In order to avoid these biases, a counterfactual approach may be employed, which is a framework for estimating causal effects from observational data. Through various methodological techniques, including marginal structural models and inverse probability weighting, counterfactual models are robust to interactions between exposure and mediator variables and mediator-outcome confounding. Under this approach, one can estimate the total effect, the direct and indirect effects, and the proportion the effect that is mediated through the indirect effect.

These four autoimmune conditions are relatively rare, with prevalence estimates that range from less than 1% for RA to 3% for psoriasis (19–22). Similarly, pregnancy complications are not common, with 8% experiencing gestational hypertension (23), and 6% experiencing gestational diabetes (24). The prevalence of the outcomes range from 8–10% (preterm birth

and SGA (25,26)) to 30% (cesarean deliveries (26)). In order to partition the total effect into these component pathways, it is necessary to query large datasets. Recently, the authors estimated the total effects of several rheumatic diseases on adverse pregnancy and birth outcomes from a retrospective birth cohort of 3 million singleton births in California (2). To extend that work, the objective of this study was to perform a causal mediation analysis to determine the extent to which pregnancy complications (preeclampsia/hypertensive disorder, gestational diabetes and infections) mediate the association between selected autoimmune conditions (RA, SLE, psoriasis and IBD) and adverse pregnancy outcomes (preterm birth, caesarean delivery and small for gestational age). Identifying pathways that mediate adverse pregnancy outcomes will inform the clinical care of pregnant women with autoimmune conditions through quantifying the potential impact of intervention on select mediators.

Materials and methods

Study population

Subjects in this retrospective cohort were women with live-born singletons in California between 2007–2012. Deliveries were identified from hospital discharge database maintained by the California Office of Statewide Health Planning and Development, which includes linked birth certificates, detailed information on maternal and infant characteristics, hospital discharge diagnoses and procedures recorded as early as 1 year before delivery (27). Clinical characteristics were based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) four digit codes contained in the hospital discharge database (28). Of the 3,160,268 live births, the study was restricted to singletons born between 20–44 weeks of gestation (n=3,067,839), and then further restricted to mother-infant dyads with linked hospital discharge records (n=2,963,888). Methods and protocols for the study were approved by the Committee for the Protection of Human Subjects within the Health and Human Services Agency of the State of California.

Exposures, outcomes and mediators

Autoimmune conditions were identified via ICD-9 codes as follows (29,30): RA: 714.0 (rheumatoid arthritis and other inflammatory polyarthropathies); SLE: 710.0 (systemic lupus erythematosus, organ or system involvement unspecified); psoriasis: 696.1 (other psoriasis); and IBD: 555.5x (regional enteritis) and 556.x (ulcerative enterocolitis). Gestational age was determined using best obstetric estimate and was obtained from birth certificate records. Preterm birth was defined as less than 37 weeks of completed gestation, and small for gestational age was defined as birth weight in the lowest 10th percentile for gestational age (31). Cesarean delivery was identified from maternal (669.7: cesarean delivery without mention of indication) or infant (763.4: cesarean delivery affecting fetus or newborn) ICD-9 codes, or maternal procedure codes (74.0, 74.1, 74.2, 74.4, 74.99). Potential mediators were identified as: preeclampsia/hypertensive disorder (642: hypertension complicating pregnancy childbirth and the puerperium), gestational diabetes (648.0: diabetes mellitus complicating pregnancy childbirth or the puerperium, 648.8: abnormal glucose tolerance of mother complicating pregnancy childbirth or the puerperium), and any infection complicating the pregnancy (ICD-9 codes: 647 (infectious and parasitic conditions in the mother classifiable elsewhere but complicating pregnancy childbirth or the puerperium), 646.5 (asymptomatic

bacteriuria in pregnancy), 646.6 (infections of genitourinary tract in pregnancy) or infant ICD-9 codes 760.2 (maternal infections affecting fetus or newborn), 760.1 (maternal renal and urinary tract diseases affecting fetus or newborn)).

Covariates

Maternal age, race and ethnicity were derived from birth record variables. Maternal pre-pregnancy BMI was created from height and weight variables on the birth records (kg/m^2) and categorized into <25, 25–30, and >30 kg/m^2. Expected source of delivery payment was categorized from birth records as private, public, or other, and maternal education was dichotomized as less than or equal to 12^{th} grade. Finally, maternal smoking was created from indication of smoking from either birth records or ICD-9 codes (649.0).

Mediation analysis

Causal mediation analysis was performed using a SAS macro (*%mediation*) developed by Valeri and VanderWeele (15). This macro was selected for its ability to determine causal direct (non-mediated) and indirect (mediated) effects, allowance for interaction of exposure and mediator variables, and the ability to model binary outcomes with log-linear regression. In this analysis, we present the total effect (mediated and unmediated pathways), the natural direct (unmediated) effect, and the natural indirect (mediated) effect. The natural direct effect (Figure 1, arrow from RA to caesarean delivery) is the effect of the exposure if the effect of the mediator was what it would have been in the absence of the exposure. The natural indirect effect (Figure 1, arrow from RA to caesarean delivery through preeclampsia) is the effect when the exposure is present and the mediator is set to what it would have been without vs. with the exposure. As an example, in the case of the risk of caesarean delivery with RA and mediation by preeclampsia (Figure 1), the natural direct effect compares the risk of caesarean delivery between those with and without RA if, in both cases, the occurrence of preeclampsia was what it would have been without RA. The natural indirect effect is the effect among those with RA, the risk of caesarean delivery if preeclampsia status was changed from the level in those without RA to the level in those with RA. Finally, the proportion mediated is also reported, which is the excess risk of the outcome among exposed women that is mediated by the variable of interest. Following the example, the proportion mediated is the excess risk of caesarean delivery among women with RA that is mediated through preeclampsia. Mathematically, the total effect is the product of the natural direct and indirect effects, and the proportion mediated is the ratio of the natural indirect effect over the total effect, with a transformation of the ratio scale (15).

Statistical analyses

Women with ICD-9 codes for more than one autoimmune condition were considered exposed to each and included in each appropriate model. To prepare for mediation analyses, we first performed multivariable adjusted Poisson log-linear regression to estimate the risk of each autoimmune condition with each outcome. We then repeated models with the mediator and a mediator-exposure product term to assess interaction. Mediation analyses were then performed in SAS using the macro *%mediation.* All models had a Poisson distribution and log link, and were adjusted for race and ethnicity, age, insurance provider, education, BMI and smoking (all coded into dummy variables as required for the macro).

For models with evidence of an exposure-mediator interaction, the model was coded to allow for interaction. Standard errors and confidence intervals were obtained via the default delta method. Separate models were constructed for each exposure-mediator-outcome combination, and total effect, natural direct effect, natural indirect effect, and proportion mediated were all reported. Of note, due to random fluctuations and estimations inherent to modeling, the total effects may vary slightly between models for each exposure-outcome pair. Thus, the total effects from each model are reported. When total effects were not statistically significant, mediation analyses were not performed.

To assess whether mediation differs by race/ethnicity, we repeated all models stratified into samples of non-Hispanic White, Latina, Black and Asian women.

Results

In the full sample, there were 3,129 (0.11%) deliveries from women with RA, 3,863 (0.13%) deliveries from women with SLE, 1,255 (0.04%) deliveries from women with psoriasis, and 2,714 (0.09%) deliveries from women with IBD (Table 1). Compared to the full sample, women with an autoimmune disease were more likely to be older, have private insurance, and have more education. Mediators of interest also differed by the presence of autoimmune conditions. Women with autoimmune conditions were more likely to have preeclampsia/hypertension and infection, and all conditions with the exception of IBD were more likely to have gestational diabetes. Further, women with RA, SLE and psoriasis were more likely to have all outcomes of interest: preterm birth, caesarean delivery, and small for gestational age, and women with IBD were more likely to have a preterm birth and a cesarean delivery. These findings prompt further investigation into mediation mechanisms.

Mediation analyses

Rheumatoid arthritis—Women with RA had a two-fold increase in the risk for preterm birth compared with women without RA (Table 2). One-fifth of the excess preterm birth associated with RA was due to preeclampsia/hypertension, while 7% was mediated by infection in pregnancy, and 2% by gestational diabetes. Relative to the excess risk of preterm birth, preeclampsia/hypertension accounted for less of the excess cesarean delivery and SGA in women with RA (13% and 8%, respectively).

Systemic lupus erythematosus—There was a 3-fold increase in the risk of preterm birth, and almost two-fold increase in the risk of SGA among women with SLE compared to women without SLE (Table 3). Preeclampsia/hypertension was the strongest mediator for all outcomes, accounting for 18–30% of the excess adverse pregnancy outcomes among women with SLE. An additional 7% of the excess preterm births among women with SLE were attributable to infection in pregnancy. Gestational diabetes contributed essentially no excess risk of any of the pregnancy outcomes.

Psoriasis—Women with psoriasis had a 50% increased risk of preterm birth and a 22% increased risk of caesarean delivery (Table 4); there was no evidence of an increased risk of SGA offspring. Approximately 33% of excess preterm births and 12% of excess cesarean deliveries in women with psoriasis were mediated by preeclampsia. Additionally, gestational

diabetes accounted for an additional 9% and infections in pregnancy an additional 16% of excess preterm births.

Inflammatory bowel disease—The total risk estimates for adverse pregnancy outcomes in women with IBD were quite similar in magnitude to women with RA. However, preeclampsia/hypertension, gestational diabetes and infection in pregnancy explained much less of the excess risk of outcomes among women with IBD relative to the other autoimmune conditions (Table 5). Unlike the other autoimmune conditions, pregnancy complications mediated less than 10% of excess risk of any outcome, with the only notable mediation occurring through infections and the risk of preterm birth (11.5%).

Race/ethnicity

Rheumatoid arthritis and race/ethnicity—Among women with RA, there was heterogeneity in the strength of the total effect of the disease on outcomes, with Black women having the highest risk of preterm birth, Latina women having the highest risk of cesarean delivery, and Latinas and Asian women having the highest risk of SGA (Supplemental Table 1). The proportion mediated by the select pregnancy complications also varied markedly. Of excess preterm births among women with RA, Latina women had the highest proportion attributed to preeclampsia/hypertension (25.6%) and infection in pregnancy (9%), while Black women had the highest proportion attributed to gestational diabetes (6.8%). Of excess SGA births among women with RA, Black women had the highest proportion attributable to preeclampsia/hypertension.

Systemic lupus erythematosus and race/ethnicity—When stratified by race/ethnicity, the magnitude of the association between preterm birth and SLE was strongest in Latinas and Asian women, and equivalent among White and Black women (Supplemental Table 2). Of the excess preterm deliveries due to SLE, Latinas and Asian women had the highest proportion mediated by preeclampsia/hypertension (34.7% and 36.4%, respectively), and White women had the lowest (19.5%). The proportion of preterm births mediated by gestational diabetes or infection in pregnancy was substantially lower than the proportion mediated by preeclampsia/hypertension with little heterogeneity between race/ethnicities. Although there was little heterogeneity by race/ethnicity in the overall risk of cesarean delivery, Latinas, Black and Asian women had much higher proportion mediated by preeclampsia/hypertension than White women.

Psoriasis and race/ethnicity—There was little heterogeneity in total effect estimates by race/ethnicity of psoriasis on preterm birth or cesarean delivery, and little heterogeneity on the proportion mediated by pregnancy complications (Supplemental Table 3). Of note, the total effect of psoriasis on preterm birth or cesarean delivery among Black women was not statistically significant; however, only 36 Black women in the sample had evidence of psoriasis, and thus statistical power was limited. There was also no evidence of an increased risk of cesarean delivery among Asian women with psoriasis.

IBD and race/ethnicity—Although the total effect of IBD on preterm birth was strongest among Black women, the proportion mediated by preeclampsia/hypertension was highest

among Latinas, although still less than 10% (Supplemental Table 4). There was little other heterogeneity by race/ethnicity of the proportion mediated by pregnancy complications for any of the other outcomes.

Discussion

The purpose of a causal mediation analysis is to investigate the underlying mechanisms that contribute to an observed relationship. We performed such an analysis to determine the extent to which select pregnancy complications contribute to the previously documented association between autoimmune conditions and adverse pregnancy outcomes. Using a large cohort of approximately 3 million births in the state of California, we found increased risks of preterm birth, cesarean delivery, and SGA among women with RA, SLE, and IBD, and increased risk of preterm birth and cesarean delivery among women with psoriasis. There was tremendous heterogeneity between and within autoimmune conditions with respect to the proportion mediated by pregnancy complications. In general, preeclampsia/hypertension accounted for the largest proportion of excess adverse pregnancy outcomes due to autoimmune conditions, particularly preterm births. There, the proportion mediated was highest among women with psoriasis (32.9%) or SLE (30.2%), followed by RA (20.4%). There was not an appreciable contribution from preeclampsia/hypertension to preterm birth among women with IBD. Generally, gestational diabetes and infections in pregnancy contributed to much less of the excess risk of adverse pregnancy outcomes across the autoimmune conditions, although infections did contribute over 10% of the excess preterm births among women with psoriasis and IBD. Finally, there was variation in the proportion mediated by race/ethnicity. Among women with RA, pregnancy complications generally mediated higher proportions of preterm births in Latinas compared to White or Black women. Among women with SLE, excess preterm births and cesarean deliveries were more commonly mediated by preeclampsia/hypertension among Latinas, Asian or Black women than White women.

By performing a counterfactual mediation analysis, we quantified the extent to which select pregnancy complications contribute to associations between autoimmune conditions and adverse pregnancy outcomes. Although mediation of adverse pregnancy outcomes by pregnancy complications among women with autoimmune conditions has been suggested (10,32,33), to our knowledge it has never been formally investigated using causal mediation analyses. These results are clinically meaningful both in the findings of the proportion mediated and the proportion not mediated. From the knowledge that upwards of one-third of excess cases of preterm birth are mediated by preeclampsia/hypertension among women with psoriasis and SLE, we may better appreciate the mechanisms through which these conditions affect pregnancy outcomes. However, by recognizing that two-thirds of the excess cases of preterm births were not due to preeclampsia/hypertension, we demonstrate the work that remains in understanding the underlying etiology of this outcome. Similarly, the contrast in proportions mediated between autoimmune conditions, even though many of the conditions use the same medications in pregnancy, suggest that different mechanisms underlie the risk of adverse pregnancy outcomes in women with different autoimmune conditions. This contrast is the most pronounced in the results for IBD, where although total effects on adverse pregnancy outcomes are just as strong as other autoimmune conditions,

very little of any of the excess risk was attributed to any pregnancy complications studied. This strongly highlights the importance of continued investigation into each of the conditions individually.

Strengths of this study include the large sample created from birth records and hospital discharge summaries. This birth cohort has been used by others to estimate associations between maternal conditions and pregnancy outcomes (2,34,35). By relying on a large, administrative database, we were able to quantify mediated pathways of relatively rare complications, with further stratification by race/ethnicity to improve generalizability to specific populations. Additional strengths include the use of a counterfactual mediation analysis that is robust to unmeasured confounding of the mediator-outcome, and estimation of natural indirect effects to allow for examination of exposure-mediator interaction. Limitations include the well-documented underreporting of certain behaviors or medical conditions in hospital discharge summaries and in birth records, including information on licit and illicit substances and mental health diagnoses. As with all observational data, unmeasured confounding should be assumed. If the frequency of unmeasured confounders differed by the presence of autoimmune conditions, our estimates may be biased. In addition, autoimmune conditions were likely under-recorded (as evidence by our prevalence estimates being much lower than national estimates), potentially with biased capture towards more severe cases. This may result in overstated effect estimates when applied to a less severe sample. Also, with respect to models assessing preterm birth, we did not have information on the timing of pregnancy complications. Preeclampsia, gestational diabetes and infections can occur after 37 weeks of gestation, resulting in a misclassification of exposure among individuals no longer at risk of preterm birth. We anticipate this would attenuate the total and indirect effect estimates due to misclassification of exposure, but cannot guarantee the strength or direction of the potential bias. Finally, these select autoimmune conditions were chosen based on frequency of occurrence and reported increased risk with adverse pregnancy outcomes. Exposures that occurred with less frequency in our sample (e.g.- psoriatic arthritis (n=116) (2) or ankylosing spondylitis (n=128) (2)) could not be estimated with a mediation analysis, but should be pursued in other datasets with more exposures. Likewise, we were only able to assess pregnancy complications that are coded in discharge summaries and occur with enough frequency to investigate. Other potential mediators of interest (smoking, weight gain) were not well defined or captured in this data source and could not be assessed, but should be quantified using other sources of data. Furthermore, this database did not capture medications, so we were unable to assess whether medications like disease modifying antirheumatic drugs or corticosteroids mediate the severity of autoimmune conditions and adverse pregnancy outcomes.

In summary, by leveraging a large retrospective birth cohort, we were able to perform a causal mediation analysis to estimate direct and indirect effects across relatively rare exposures and outcomes. We confirmed previous findings of increased risk of adverse pregnancy outcomes associated with select autoimmune conditions, and quantified the extent to which preeclampsia/hypertension, gestational diabetes and infections in pregnancy mediate these associations. We showed that although the select pregnancy complications do mediate the outcomes, there is considerable heterogeneity by complication and by

autoimmune condition. This analysis demonstrates that there are many unrecognized pathways that mediate risk for adverse pregnancy outcomes in women with autoimmune conditions. However, we simultaneously demonstrate the potential magnitude of improvement of these outcomes through intervention efforts targeted towards preventing pregnancy complications. Clinically, this could be implemented by additional counseling and prevention efforts, particularly around preeclampsia/hypertension, extended to women with RA, SLE and psoriasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and innovation (2–4 bullet points)

- For rheumatoid arthritis, systemic lupus erythematosus and psoriasis, preeclampsia/hypertension was the strongest mediator of all three pregnancy outcomes (preterm birth, caesarean delivery and small for gestational age), accounting for approximately 10–33% of the excess risk.
- Infections were the next strongest mediator, but generally accounted for less than 10% of the excess risk of pregnancy outcomes.
- Efforts to prevent or mitigate preeclampsia/ hypertension would have the largest impact on reducing disparities in adverse pregnancy outcomes associated with rheumatoid arthritis, systemic lupus erythematosus and psoriasis.

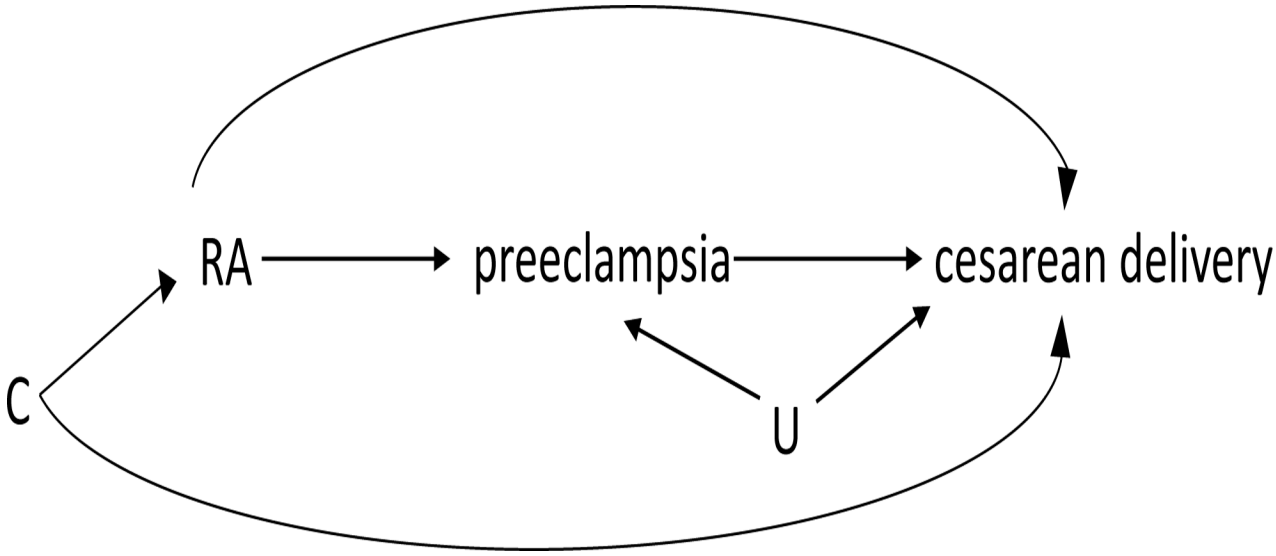

Figure 1.

Simplified directed acyclic graph (16) of rheumatoid arthritis (RA) and caesarean delivery, with mediation by preeclampsia. Maternal characteristics (C) of pre-pregnancy body mass index, race and ethnicity, age, education, insurance provider and smoking are assumed baseline confounders. U represents potential unmeasured confounders of preeclampsia and cesarean delivery.

Table 1.

Maternal characteristics (n, %) of 3 million births in the State of California (2007–2012) by autoimmune conditions *

	All births n=2,963,888	Rheumatoid arthritis n=3,129	System iclupus erythematosus n=3,863	Psoriasis n=1,255	Inflammatory bowel disease n=2,714
Sociodemographic characteristics					
Race/ethnicity					
non-Hispanic White	773352 (26.1)	1134 (36.2)	1050 (27.2)	543 (43.3)	1703 (62.8)
Hispanic	1445356 (48.8)	1313 (42.0)	1568 (40.6)	353 (28.1)	509 (18.8)
Black	158802 (5.4)	202 (6.5)	388 (10.0)	36 (2.9)	135 (5.0)
Asian	366732 (12.4)	210 (6.7)	469 (12.1)	199 (15.9)	145 (5.3)
Other	219646 (7.4)	270 (8.6)	388 (10.0)	124 (9.9)	222 (8.2)
Maternal age					
<18	85717 (2.9)	26 (0.8)	36 (0.9)	11 (0.9)	9 (0.3)
18–34	2351645 (79.4)	2228 (71.2)	2917 (75.5)	934 (74.4)	1998 (73.6)
>34	526415 (17.8)	875 (28.0)	910 (23.6)	310 (24.7)	707 (26.1)
Pre-pregnancy BMI (kg/m^2)					
<25	1479287 (49.9)	1513 (48.4)	1888 (48.9)	488 (38.9)	1678 (61.8)
25–30	728096 (24.6)	788 (25.2)	936 (24.2)	320 (25.5)	543 (20.0)
>30	556623 (18.8)	655 (20.9)	805 (20.8)	369 (29.4)	351 (12.9)
missing	199882 (6.7)	173 (5.5)	234 (6.1)	78 (6.2)	142 (5.2)
Insurance provider					
Private	1373539 (46.3)	1837 (58.7)	2019 (52.3)	824 (65.7)	2044 (75.3)
Public	1475205 (49.8)	1199 (38.3)	1705 (44.1)	403 (32.1)	599 (22.1)
Other	115144 (3.9)	93 (3.0)	139 (3.6)	28 (2.2)	71 (2.6)
Education ≤ 12th grade	1466653 (49.5)	1123 (35.9)	1550 (40.1)	455 (36.3)	609 (22.4)
missing	109457 (3.7)	118 (3.8)	150 (3.9)	42 (3.3)	121 (4.5)
Pregnancy smoking	134682 (4.5)	202 (6.5)	280 (7.3)	145 (11.6)	167 (6.2)
Pregnancy complications					
Preeclampsia or hypertension	212590 (7.2)	448 (14.3)	875 (22.7)	175 (13.9)	258 (9.5)
Gestational Diabetes	274102 (9.3)	392 (12.5)	426 (11.0)	213 (17.0)	230 (8.5)
Infection in pregnancy	234043 (7.9)	475 (15.2)	698 (18.1)	178 (14.2)	382 (14.1)

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	All births	Rheumatoid arthritis	System iclupus erythematosus	Psoriasis	Inflammatory bowel disease
	n=2,963,888	n=3,129	n=3,863	n=1,255	n=2,714
Adverse pregnancy outcomes					
Preterm birth	211802 (7.2)	447 (14.3)	901 (23.3)	135 (10.8)	371 (13.7)
Cesarean delivery	956710 (32.3)	1317 (42.1)	1823 (47.2)	528 (42.1)	1097 (40.4)
Small for gestational age	252848 (8.5)	376 (12.0)	636 (16.5)	98 (7.8)	279 (10.3)

* 369 women had ICD9 codes for more than one autoimmune condition

Table 2.

Effectde composition of the influence of rheumatoid arthritis and potential mediators on adverse pregnancy outcomes in 3 million live births in the state of California

	Total effect[a]		Direct effect[b]		Indirect effect[c]		
Mediator	**aRR**	**95%CI**	**aRR**	**95%CI**	**aRR**	**95%CI**	**Proportion mediated[d]**
				Preterm Birth			
Preeclampsia/hypertension	1.97	(1.78, 2.17)	1.77	(1.60, 1.96)	1.11	(1.08, 1.13)	20.4%
Gestational diabetes	1.98	(1.80, 2.19)	1.96	(1.78, 2.17)	1.01	(1.00, 1.02)	2.2%
Infection in pregnancy	1.99	(1.81, 2.20)	1.92	(1.74, 2.12)	1.04	(1.03, 1.05)	7.4%
				Cesarean Delivery			
Preeclampsia/hypertension	1.22	(1.15, 1.29)	1.19	(1.12, 1.26)	1.02	(1.02, 1.03)	13.3%
Gestational diabetes	1.23	(1.16, 1.30)	1.22	(1.15, 1.29)	1.01	(1.00, 1.01)	3.0%
Infection in pregnancy	1.23	(1.16, 1.30)	1.22	(1.15, 1.29)	1.01	(1.01, 1.01)	3.6%
				Small for Gestational Age			
Preeclampsia/hypertension[*]	1.53	(1.37, 1.73)	1.49	(1.33, 1.66)	1.03	(1.01, 1.05)	8.3%
Gestational diabetes	1.53	(1.37, 1.73)	1.53	(1.38, 1.71)	0.99	(0.99, 0.99)	3.0%
Infection in pregnancy	1.53	(1.37, 1.73)	1.52	(1.36, 1.69)	1.01	(1.00, 1.01)	1.5%

Models adjusted for race/ethnicity, maternal age, insurance provider, maternal education, overweight/obesity, and smoking

[a] Effect of rheumatoid arthritis on adverse pregnancy outcomes

[b] Effect of rheumatoid arthritis on adverse pregnancy outcomes that is not mediated by each pregnancy complication

[c] Effect of rheumatoid arthritis on adverse pregnancy outcomes mediated by each pregnancy complication

[d] Proportion of effect of rheumatoid arthritis on adverse pregnancy outcomes mediated by each pregnancy complication

[*] modeled with interaction term between exposure and mediator

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Table 3.

Effect decomposition of the influence of systemic lupus erythematosus and potential mediators on adverse pregnancy outcomes in 3 million live births in the state of California

	Total effect[a]		Direct effect[b]		Indirect effect[c]		
Mediator	**aRR**	**95%CI**	**aRR**	**95%CI**	**aRR**	**95%CI**	**Proportion mediated[d]**
				Preterm Birth			
Preeclampsia/hypertension	3.09	(2.87, 3.32)	2.46	(2.29, 2.63)	1.25	(1.23, 1.28)	30.2%
Gestational diabetes	3.12	(2.91, 3.35)	3.10	(2.89, 3.32)	1.00	(1.00, 1.01)	1.0%
Infection in pregnancy	3.11	(2.91, 3.34)	2.96	(2.76, 3.18)	1.05	(1.04, 1.05)	7.0%
				Cesarean Delivery			
Preeclampsia/hypertension	1.40	(1.33, 1.47)	1.32	(1.26, 1.39)	1.06	(1.05, 1.06)	18.9%
Gestational diabetes*	1.41	(1.35, 1.48)	1.41	(1.34, 1.48)	1.00	(1.00, 1.00)	0.5%
Infection in pregnancy	1.40	(1.34, 1.48)	1.39	(1.32, 1.46)	1.01	(1.01, 1.01)	3.1%
				Small for Gestational Age			
Preeclampsia/hypertension*	1.89	(1.74, 2.06)	1.73	(1.59. 1.09)	1.09	(1.05, 1.13)	17.6%
Gestational diabetes	1.91	(1.76, 2.06)	1.91	(1.76, 2.07)	0.99	(0.99, 0.99)	0.0%
Infection in pregnancy	1.89	(1.76, 2.07)	1.89	(1.74, 2.05)	1.01	(1.01, 1.01)	1.4%

Models adjusted for race/ethnicity, maternal age, insurance provider, maternal education, overweight/obesity, and smoking

[a] Effect of systemic lupus erythematosus on adverse pregnancy outcomes

[b] Effect of systemic lupus erythematosus on adverse pregnancy outcomes that is not mediated by each pregnancy complication

[c] Effect of systemic lupus erythematosus on adverse pregnancy outcomes mediated by each pregnancy complication

[d] Proportion of effect of systemic lupus erythematosus on adverse pregnancy outcomes mediated by each pregnancy complication

* modeled with interaction term between exposure and mediator

Table 4.

Effect decomposition of the influence of psoriasis and potential mediators on adverse pregnancy outcomes in 3 million live births in the state of California

Mediator	Total effect[a]		Direct effect[b]		Indirect effect[c]		Proportion mediated[d]
	aRR	95%CI	aRR	95%CI	aRR	95%CI	
Preterm birth							
Preeclampsia/hypertension*	1.46	(1.22, 1.76)	1.31	(1.08, 1.58)	1.11	(1.05, 1.18)	32.9%
Gestational diabetes	1.48	(1.25, 1.78)	1.44	(1.19, 1.74)	1.03	(1.00, 1.06)	8.9%
Infection in pregnancy*	1.49	(1.25, 1.79)	1.41	(1.18, 1.70)	1.06	(1.01, 1.11)	15.9%
Cesarean Delivery							
Preeclampsia/hypertension	1.22	(1.11, 1.33)	1.19	(1.09, 1.31)	1.02	(1.01, 1.03)	11.8%
Gestational diabetes	1.22	(1.12, 1.34)	1.21	(1.10, 1.32)	1.01	(1.01, 1.02)	7.3%
Infection in pregnancy	1.22	(1.12, 1.34)	1.22	(1.12, 1.33)	1.01	(1.00, 1.01)	3.3%
Small for Gestational Age[e]							

Models adjusted for race/ethnicity, maternal age, insurance provider, maternal education, overweight/obesity, and smoking

[a] Effect of psoriasis on adverse pregnancy outcomes

[b] Effect of psoriasis on adverse pregnancy outcomes that is not mediated by each pregnancy complication

[c] Effect of psoriasis on adverse pregnancy outcomes mediated by each pregnancy complication

[d] Proportion of effect of psoriasis on adverse pregnancy outcomes mediated by each pregnancy complication

[e] Total effects observed between psoriasis and small for gestational age were null (aRR 1.00, 95% CI 0.81, 1.24); no mediation analysis performed

* modeled with interaction term between exposure and mediator

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Table 5.

Effect decomposition of the influence of inflammatory bowel disease and potential mediators on adverse pregnancy outcomes in 3 million live births in the state of California

	Total effect[a]		Direct effect[b]		Indirect effect[c]		
Mediator	**aRR**	**95%CI**	**aRR**	**95%CI**	**aRR**	**95%CI**	**Proportion mediated[d]**
				Preterm Birth			
Preeclampsia/hypertension *	2.01	(1.80, 2.24)	1.97	(1.77, 2.21)	1.02	(1.01, 1.04)	4.9%
Gestational diabetes	2.03	(1.82, 2.26)	2.02	(1.81, 2.24)	1.00	(1.00, 1.01)	0.5%
Infection in pregnancy *	2.02	(1.82, 2.26)	1.90	(1.70, 2.13)	1.06	(1.02, 1.10)	11.5%
				Cesarean Delivery			
Preeclampsia/hypertension *	1.24	(1.17, 1.34)	1.23	(1.16, 1.31)	1.00	(1.00, 1.01)	1.4%
Gestational diabetes	1.24	(1.16, 1.31)	1.23	(1.16, 1.31)	1.00	(1.00, 1.01)	1.2%
Infection in pregnancy	1.24	(1.16, 1.31)	1.22	(1.15, 1.30)	1.00	(1.00, 1.00)	3.5%
				Small for Gestational Age			
Preeclampsia/hypertension	1.38	(1.22, 1.56)	1.35	(1.20, 1.53)	1.02	(1.00, 1.03)	6.6%
Gestational diabetes	1.38	(1.22, 1.56)	1.38	(1.22, 1.56)	1.00	(1.00, 1.00)	0.0%
Infection in pregnancy	1.38	(1.22, 1.56)	1.38	(1.22, 1.56)	1.01	(1.00, 1.01)	1.9%

Models adjusted for race/ethnicity, maternal age, insurance provider, maternal education, overweight/obesity, and smoking

[a] Effect of inflammatory bowel disease on adverse pregnancy outcomes

[b] Effect of inflammatory bowel disease on adverse pregnancy outcomes that is not mediated by each pregnancy complication

[c] Effect of inflammatory bowel disease on adverse pregnancy outcomes mediated by each pregnancy complication

[d] Proportion of effect of inflammatory bowel disease on adverse pregnancy outcomes mediated by each pregnancy complication

* modeled with interaction term between exposure and mediator

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