Leveraging Real-World Data, Including the Electronic Health Record, to Fill in Clinical Knowledge Gaps in Treating Pregnant People

Yeon Mi Hwang

A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2024

Reading Committee:

Peter Tarczy-Hornoch, Chair

Jennifer Hadlock

Nathan Price

Mary Hebert

Program Authorized to Offer Degree:

Molecular Engineering and Sciences

University of Washington

Abstract

Leveraging Real-World Data, Including the Electronic Health Record, to Fill in Clinical Knowledge Gaps in Treating Pregnant People

Yeon Mi Hwang

Chair of the Supervisory Committee:
Peter Tarczy-Hornoch
Department of Biomedical Informatics and Medical Education

There is a substantial knowledge gap in our understanding of treatment for pregnant people due to their exclusion from clinical trials. Despite this, the majority of pregnant people take prescription medication. The electronic health record (EHR), with its data on longitudinal phenotypes, confounders, and prescription orders, emerges as a promising resource for investigating medical treatments during pregnancy.

This dissertation addresses knowledge gaps regarding treatments for pregnant women through a comprehensive approach employing hypothesis-generating and testing methods on EHR data, with four primary aims. In Aim 1, we used propensity score matching to expedite the generation and prioritization of hypotheses regarding drug effect signals associated with preterm birth risk. Aim 2 validated drug effect signals, particularly the association between Selective Serotonin

Reuptake Inhibitors and preterm birth risk, using traditional pharmacoepidemiology methods. Aims 1 and 2 present a streamlined workflow for detecting known and unknown drug effect signals and validating by traditional epidemiological methods.

In Aim 3, we investigated the COVID-19 antithrombotic therapy guidelines for pregnant women, which lack evidence in favor of or against their clinical application. We examined the prophylactic anticoagulant prescription rate among hospitalized pregnant women with COVID-19 and its impact on risks related to coagulopathy, COVID-19, and maternal-fetal health outcomes. Surprisingly, a low (7.0%) prescribing rate for prophylactic anticoagulants was observed across healthcare systems.

In Aim 4, we leveraged EHRs to assess comorbidities during pregnancy, exploring the likelihood of adverse maternal-fetal health outcomes among pregnant individuals with immune-mediated inflammatory diseases (IMIDs). The association between IMIDs and elevated risk of adverse pregnancy outcomes depended on the specific type of IMIDs and presence of comorbidities.

Consequently, this dissertation introduces innovative approaches to aid in filling in the knowledge gap in treating pregnant individuals, focusing primarily on preterm birth, with potential applications to a broader spectrum of maternal-fetal outcomes requiring attention. Despite the rich longitudinal data EHR offered, we were limited by some inherent challenges when used for research purposes. Challenges included misclassification of variables, a range of good and bad standardization in the type and quality of data collected, and limited information derived from structured data. In corresponding chapters, we described these challenges and potential alternatives for future direction for each aim.

ABBREVIATIONS

APS: Antiphospholipid Syndrome
ASA: Acetylsalicylic Acid
ATC: Anatomical Therapeutic Chemical
AUC: Area Under the receiver operating characteristics Curve
BLyS: B Lymphocyte Stimulator
BMI: Body Mass Index
CDC: Centers for Diseases Control and Prevention
COVID-19: Coronavirus Diseases 2019
Csec: Caesarean section; surgical delivery
EHR: Electronic Health Record
FDA: Food and Drug Administration
GA: Gestational Age
IBD: Inflammatory Bowel Disease
ICU: Intensive Care Unit
IL: Interleukin
IMID: Immune-Mediate Inflammatory Disease
IMM: Immunomodulatory Medication
LBW: Low Birth Weight
MS: Multiple Sclerosis
NIH: National Institutes of Health
NLP: Natural Language Processing
OMOP: Observational Medical Outcomes Partnership
OR: Odds Ratio
PDE4: Phosphodiesterase-4
PHQ: Patient Health Questionnaire
PLLR: Pregnancy and Lactation Labeling Rule
PS: Propensity Score
PsA: Psoriatic Arthritis
PSJH: Providence St. Joseph Health
PsO: Psoriasis
PTB: Preterm Birth
PTL: Preterm Labor
RA: Rheumatoid Arthritis
RCT: Randomized Clinical Trial
ROC: Receiver Operating Characteristics
RR: Relative Risk
RWD: Real World Data
RWE: Real World Evidence
RxNorm: Medical prescription normalized medical prescription
S1P: Sphingosine-1-Phosphate
Sa: Sarcoidosis
SD: Standard Deviation
SGA: Small for Gestational Age
SHAP: Shapley Additive exPlanations

SjS: Sjörgen’s Syndrome
SLE: Systemic Lupus Erythematosus
SNOMED: Systemized Nomenclature of Medicine
SpA: Spondylarthritis
SS: Systemic Sclerosis
SSRI: Selective Serotonin Reuptake Inhibitor
TNF: Tumor Necrosis Factor
US: United States
Va: Vasculitides

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

Thank you everyone who has been a pillar of support throughout this challenging yet rewarding journey, offering both academic guidance and emotional encouragement.

First and foremost, I want to express my sincere thanks to Jennifer, Peter, Nathan, and Lee for invaluable advice and guidance. Special appreciation goes to Sam and Alison, whose mentorship has been instrumental in shaping the trajectory of my research. Thank you, Mary and Shelly, for serving as members of my committee.

I am deeply thankful to all the members of our lab (Hadlock and Hood-Price Lab) for fostering an environment of both intellectual stimulation and camaraderie.

To my family and friend, your unwavering support has been my anchor. Your encouragement and understanding have fueled my perseverance. This accomplishment is as much yours as it is mine.

Chapter 1. INTRODUCTION

1.0 INTRODUCTION

This chapter serves as an executive summary for the dissertation. We establish the motivation for the research, outlining the overarching background and objectives in Section 1.1. In Section 1.2, we briefly introduce the research approaches and highlight the contributions of each aim. The outcomes of the work concerning each of the four aims have been published, submitted, are under review, or are currently in preparation. Detailed summaries can be found below and in each corresponding chapter. Section 1.3 contains an outline of the organization of this dissertation, providing a roadmap for the reader. Finally, we characterize the clinical setting and study population we investigate in this dissertation in Section 1.4.

1.1 MOTIVATION FOR RESEARCH

1.1.1 *Background*

Pre-marketing randomized control trials (RCTs) rarely include pregnant women unless the product is specifically designed for them.[1] Efficacy, safety, and dosage determinations predominantly rely on data gathered from men and non-pregnant women. Remarkably, 97.7% (168 of 172) of newly approved drugs between 2000 and 2010 lacked sufficient data to assess teratogenicity, and 73.3% (126 of 168) had no information on human subjects regarding their safety during pregnancy.[2]

Although pregnant women are the most underrepresented population in clinical trials, they often face some of the most complex medical situations. During pregnancy, women undergo physiological changes that significantly alter the pharmacokinetics and pharmacodynamics of drugs.[3,4] Additionally, many drugs can pass through the placental barrier, potentially impacting fetal development.[5] Consequently, it is inappropriate to directly apply existing pharmacological knowledge to pregnant women because their limited information about the pharmacology during pregnancy places them at a considerable risk of experiencing unintended drug effects.

Despite the insufficient safety data, most pregnant women continue to use medications in the United States (US). In fact, 93.9% of pregnant women take at least one medication, whether over-the-counter or prescribed, with an average of 4.2 medications over the course of pregnancy.[6] Additionally, 49% of pregnant women had at least one prescription for a medication during the pregnancy.[6]

Aside from medications for pregnancy-related symptoms or complications, drugs are prescribed based on the patient's medical conditions, such as depression, diabetes, hypertension, cancer, or infections. When coupled with pregnancy, these comorbidities often further complicate pregnancy. Bateman et al., 2013[7] showed that primary and secondary outcome incidence rates rose as the maternal comorbidity score increased.[7] Primary outcomes were either maternal end-organ injury or death during the period between the delivery admission and 30 days postpartum. The secondary outcome was admission to the maternal intensive care unit during the period between the delivery hospitalization and 30 days postpartum.[7]

A notable knowledge gap exists in understanding the pharmacological aspects of these medications and their indications when combined with pregnancy, primarily because pregnant patients are frequently excluded from clinical trials. The electronic health record (EHR) contains rich data on longitudinal phenotypes, confounders, and prescription orders. Thus, it holds great promise as a data source for investigating medical treatments. Ongoing research aims to develop novel methodologies for investigating comorbidities,[8] drug repositioning,[9] adverse drug reactions

(ADR)[10], and drug-drug interactions[11]. Surprisingly, despite the significant progress in these areas, these methodologies have not yet been widely introduced into research on pregnant women at scale.

1.1.2 *Objective*

The overall goal of this dissertation was to **leverage real-world data (RWD) from Electronic Health Record (EHR) to fill the knowledge gap in treating pregnant women.** We selected preterm birth (PTB) as our primary outcome. We utilized both hypothesis-generating and hypothesis-testing approaches to meet our objective.

1.2 RESEARCH APPROACH AND CONTRIBUTION

Aim 1: Detect signals of previously identified and unidentified drug effects on preterm birth using statistical data mining methods on EHR

The work described in this aim is in preparation as a paper titled "Detection of drug effect signals associated with adverse pregnancy outcomes using propensity score matching at scale". The goal of Aim 1 was to capture both previously detected and novel drug effect signals associated with PTB, utilizing statistical methods. To achieve this, we harnessed the power of large-scale EHR data and employed propensity score matching techniques. Our objective was to generate and prioritize hypotheses related to the pharmacological factors influencing the risk of PTB. The significance of this approach lies in streamlining the process of hypothesis generation and prioritization through the use of EHR data, effectively addressing confounding by indication. For each medication, we conducted propensity score matching to assess the risk of PTB among exposed patients. Importantly, this framework can be adapted and applied to investigate other adverse pregnancy outcomes beyond PTB, including but not limited to conditions such as preeclampsia, gestational diabetes, gestational hypertension, surgical delivery, and maternal mortality. The findings related to Aim 1 significantly contribute to the overall goal of leveraging RWD EHR data to address knowledge gaps in the treatment of pregnant women. This is achieved by establishing a framework for detecting drug effect signals associated with adverse pregnancy outcomes at scale, utilizing propensity score matching on EHR data.

Aim 2: Validate detected drug effect signals from Aim 1 using traditional pharmacoepidemiology methods

The work described in this aim was submitted to and is under review for publication in *The Journal of Maternal-Fetal & Neonatal Medicine* as a paper titled "Timing of selective serotonin reuptake inhibitor use and risk for preterm birth and related adverse events."[12] The objective of Aim 2 was to confirm the drug effect signals identified in Aim 1. Specifically, among the associations identified in Aim 1, we focused on exploring the connection between prenatal exposure to sertraline and an elevated risk of PTB. We examined the risk of PTB, as well as related adverse events such as small for gestational age (SGA) and low birth weight (LBW) infants, in relation to sertraline and/or selective serotonin reuptake inhibitor (SSRI) exposure among patients who had experienced depression before becoming pregnant.

To ensure the robustness of our findings, we conducted a comprehensive analysis that accounted for various confounding factors. These factors included pregnancy-related characteristics, comorbidities, and environmental factors while considering the geographic region where the patients resided. We also delved into the impact of the timing of SSRI intake by categorizing SSRI exposure groups based on exposure occurring after the first trimester.

Our study included multiple sensitivity analyses to assess the influence of factors such as the COVID-19 pandemic period, pre-pregnancy/prenatal depressive symptoms, the use of other classes of antidepressants, and potential misclassification of prescription records. Additionally, we conducted drug-specific analyses for SSRIs and carried out supplementary analyses involving other classes of antidepressants (N06AA, N06AX). The findings related to Aim 2 advance the overall goal of leveraging RWD EHR to fill the knowledge gap on the medical treatment of pregnant women. This is accomplished by integrating Aim 1 and Aim 2 to present the complete workflow for detecting and validating drug effect signals associated with the risk of adverse pregnancy outcomes.

Aim 3: Investigate medical interventions targeting pregnant women using electronic health records

The work described in this aim is published as a paper by Hwang et al. (2023) titled "Adoption of a National Prophylactic Anticoagulation Guideline for Hospitalized Pregnant Women with COVID-19: Retrospective Cohort Study" in *JMIR Public Health and Surveillance* (9e45586).[13] The goal of Aim 3 was to investigate a controversial medical interventions targeting pregnant women using EHR. COVID-19 and pregnancy are associated with a heightened risk of hypercoagulability, which raises concerns about thrombosis. In response to this concern, the National Institute of Health recommended prophylactic use of anticoagulants in hospitalized pregnant patients with COVID-19 infection. Initially, this recommendation was limited to patients hospitalized for severe COVID-19 manifestations, but it was subsequently extended to include all hospitalized pregnant patients with COVID-19. These guideline updates occurred in three stages: the initial recommendation, the first update from December 27, 2020, to February

23, 2022, and the second update from February 24, 2022, to the present. However, there were no studies to evaluate the impact of these recommendations.

To address this gap, we characterized the prophylactic anticoagulant prescription rate among hospitalized pregnant patients with COVID-19 across different variants and guideline updates. Additionally, we examined the relationship between the prophylactic use of anticoagulants and the risks associated with coagulopathy, COVID-19, and maternal-fetal health outcomes. Importantly, we accounted for discrepancies in variables that could potentially influence these outcomes. Notably, this research represents the first assessment of the prophylactic use of anticoagulants in hospitalized pregnant patients with COVID-19 following the guideline update on February 24, 2022. The findings from Aim 3 contribute to overall goal of leveraging RWD EHR to fill in the knowledge gap in treating pregnant women. Specifically, we investigate the National Institute of Health antithrombotic therapy guideline, which lacked evidence about implementation.

Aim 4: Harness electronic health records to assess comorbidities in pregnancy course

The work described in this aim is under review in *eClinicalMedicine* as a paper titled "Maternal-fetal outcomes in patients with immune-mediated inflammatory diseases, with consideration of comorbidities: a retrospective cohort study in a large U.S. healthcare system."[14] The primary objective of Aim 4 was to conduct a retrospective analysis of pregnant patients diagnosed with comorbidities of interest. This study aimed to comprehensively characterize pregnant patients with immune-mediated inflammatory diseases (IMIDs) regarding their demographic profiles, pregnancy-related characteristics, comorbidities, and the use of immunomodulatory medications (IMMs). We assessed the impact of IMIDs on adverse pregnancy outcomes while carefully addressing disparities in the distribution of covariates associated with adverse pregnancy outcomes between patients with IMIDs and those without. We conducted disease-specific analyses and implemented sensitivity analyses to investigate how individual IMIDs and comorbid conditions might influence the relationship between IMIDs and adverse pregnancy outcomes. This study underscores the need to revisit current preconception counseling guidelines concerning patients with rheumatoid arthritis and inflammatory bowel disease. Preconception counseling entails risk assessment tailored to patient-specific health conditions[15]. Additionally, it highlights the importance of considering comorbidities when designing research studies investigating into the effects of IMIDs on maternal health. The findings related to Aim 4 contribute to the overall goal of leveraging EHR to fill in the knowledge gap in treating pregnant women by assessing influence of comorbidities in pregnancy course.

1.3 DISSERTATION ORGANIZATION

This dissertation comprises seven chapters, each contributing to a comprehensive exploration of various aspects of treating pregnant women and the associated medical challenges. Here is an overview of each chapter:

Chapter 1: Introduction This introductory chapter provides an overview (executive summary) of the entire dissertation, briefly outlining the contents of each subsequent chapter.

Chapter 2: Background and Prior Studies Chapter 2 offers background information and discusses previous research related to the research approach employed in this dissertation. Major themes covered in this chapter include the knowledge gap in treating pregnant women, the utilization of RWD, and PTB. It explores the exclusion of pregnant women in clinical trials, physiological changes during pregnancy, and policies concerning treating pregnant women. The chapter also delves into RWD types, their strengths and limitations, previous research using

RWD in pregnancy studies, and potential pitfalls associated with their usage. The knowledge gap addressed in the chapters 3 through 6 is also outlined in this chapter.

Chapters 3-6: Main Chapters Chapters 3 through 6 are the core of the dissertation, where research approaches are applied to narrow the knowledge gap in treating pregnant women. Each chapter is associated with a corresponding publication as detailed in each chapter (published, under review, or in preparation).

- **Chapter 3 (Aim 1: Validate detected drug effect signals from Aim 1 using traditional pharmacoepidemiology methods)** demonstrates a data-driven approach to identify drug effect signals linked to the risk of PTB. Propensity score matching at scale generates and prioritizes hypotheses regarding medication associated with PTB risk.
- **Chapter 4 (Aim 2: Validate detected drug effect signals from Aim 1 using traditional pharmacoepidemiology method)** tests the hypothesis selected from Chapter 3 (Aim 1). Specifically, we investigate the association between sertraline/SSRIs and the risk of PTB, addressing factors such as depression severity, individual and environmental variables, and classification bias.
- **Chapter 5 (Aim 3: Investigate medical interventions targeting pregnant women using electronic health records)** evaluates the controversial treatment guideline recommending prophylactic anticoagulation prescription for all hospitalized pregnant COVID-19 patients. No prior studies exist to support or challenge this recommendation.
- **Chapter 6 (Aim 4: Harness electronic health records to assess comorbidities in pregnancy course)** investigates the risk of adverse pregnancy outcomes in women with IMIDs before pregnancy. We assess the contributions of individual IMIDs and underlying comorbidities to adverse pregnancy outcomes.

Chapter 7: Summary of Primary Findings Chapter 7 serves as the conclusion of the dissertation. The overall goal of this dissertation was to leverage RWD EHR to address the knowledge gap in treating pregnant women. In Chapter 7, we summarize the primary findings, acknowledge limitations, and outline potential future research directions for each of the four aims covered in chapters 3 through 6.

Chapter 2. BACKGROUND AND PRIOR STUDIES

2.0 INTRODUCTION

2.0.1 *Overall goal*

The overall goal of this dissertation was **to leverage real world data (RWD), particularly electronic health record (EHR), to address the knowledge gap on the treatment of pregnant women**. The primary outcome of interest in this dissertation was preterm birth.

2.0.2 *Specific aims*

Table 2.1 Specific aims of this dissertation

	Aims	**Manuscript Title**
1	Detect signals of previously identified and unidentified drug effects on preterm birth using statistical data mining on electronic health records	Detection of drug effect signals associated with adverse pregnancy outcomes using propensity score matching at scale (In Preparation)
2	Validate detected drug effect signals from Aim 1 using traditional pharmacoepidemiology methods	Timing of selective serotonin reuptake inhibitor use and risk for preterm birth and related adverse events (Submitted)
3	Investigate medical interventions targeting pregnant women using electronic health records	Adoption of a national prophylactic anticoagulation guideline for hospitalized pregnant women with COVID-19: retrospective cohort study (Published)
4	Harness electronic health records to assess the comorbidities in pregnancy course	Maternal-fetal outcomes in patients with immune-mediated inflammatory diseases, with consideration of comorbidities: a retrospective cohort study in a large US healthcare system (Submitted)

2.1 THE KNOWLEDGE GAP IN TREATING PREGNANT WOMEN

Pregnant women are typically excluded from clinical trials, rendering them to be one of the most underrepresented populations in clinical studies, despite the fact that they face complex medical situations. Physiological changes during pregnancy significantly impact the pharmacodynamics and pharmacokinetics of drugs. This puts pregnant women vulnerable to unintended drug effects, highlighting a substantial knowledge gap in the treatment of this population.

2.1.1 *Exclusion of pregnant women in clinical trials*

The inclusion of pregnant women in pre-marketing randomized control trials (RCTs) is a rare occurrence.[1] Consequently, drug efficacy, safety, and dosage are predominantly determined based on studies involving men and non-pregnant women. The discovery of the teratogenic impact of thalidomide (used to treat morning sickness) and diethylstilbestrol (a medication for preventing miscarriage) in the 1960s and 1970s led to a Food and Drug Administration (FDA) guideline in 1977 recommending the exclusion of pregnant women from clinical trials[16,17].

Four decades have passed since the issuance of this guideline, but the exclusion of pregnant women from clinical trials remains a common practice. The teratogenic risk of 98% of drugs approved by the FDA between 2000 and 2010 remains undetermined.[2,18] Less than 0.5% of ongoing trials in 2013 and 2014 focused on pregnant women, and only 4% of ongoing trials in 2013 and 2014 examined the pharmacokinetics of medications during pregnancy[2,19,20]. Indeed, pregnancy and lactation are among the most common exclusion criteria in clinical trials.[21] As a result, medication efficacy and safety during pregnancy largely rely on observational data collected after the drugs are on the market.[22] This situation also persisted in the context of COVID-19 treatment trials. A search of the clinical studies registry for the timepoint of July 10 to 15, 2020, yielded 722 COVID-19 treatment trials. Out of these, 538 (75%) excluded pregnant women.[23]

2.1.2 *Physiological changes during pregnancy*

Pregnant women are the most underrepresented populations in clinical trials, despite facing some of the most unique and complex medical complications, which contributes to the knowledge gap. Pregnancy induces physiological changes that significantly alter the pharmacokinetics and pharmacodynamics of drugs.[3,4] These changes affect various organ systems, including the endocrine, circulatory, cardiovascular, respiratory, renal, gastrointestinal, and hematologic systems.[3]

2.1.2.1 Changes in endocrine system

Many physiological changes during pregnancy are triggered by shifts in hormonal production facilitated by the placenta. Once a fertilized egg successfully implants into the uterine wall, placental trophoblasts begin producing human chorionic gonadotropin.[24] The concentration of human chorionic gonadotropin rises throughout the first trimester, reaching its peak.[25] Human chorionic gonadotropin is a hormone that stimulates the production of progesterone and estrogen, with both hormones gradually increasing as the placenta grows.[26] Their concentrations peak during the third trimester.[27] Progesterone induces smooth muscle relaxation and changes in gastrointestinal, cardiovascular, and genitourinary systems.[25]

2.1.2.2 Changes in cardiovascular system

Alterations in the cardiovascular system during pregnancy encompass various changes, including a substantial expansion in plasma volume, increased heart rate, decline in systemic vascular resistance and blood pressure, and rise in cardiac output and red blood cell mass.[28] Plasma volume exhibits a remarkable expansion, with a notable increase of 40-50% observed from 6-12 weeks of gestation until reaching its peak at 30-34 weeks compared to pre-pregnancy levels.[28,29] The gradual reduction in systemic vascular resistance begins at five weeks of gestation, likely due to increased progesterone levels leading to smooth muscle relaxation.[28] The escalation in cardiac output is most prominent during the first trimester, surging by 30-50%.[25] Factors contributing to this rise in cardiac output include increased preload due to expanded blood volume, reduced afterload as systemic vascular resistance decreases, and an elevation in heart rate.[25]

2.1.2.3 Changes in respiratory system

Tidal volume, ventilation, and respiratory rates all increase during pregnancy to meet the oxygen demands of the pregnant individual and developing fetus.[25,30] Simultaneously, the expiratory reserve volume, total pulmonary capacity, and functional residual capacity decrease throughout pregnancy.[25] The increase in ventilation leads to a rise in the partial pressure of oxygen and a reduction in the partial pressure of carbon dioxide in the blood, facilitating efficient gas exchange across the placenta.[25]

2.1.2.4 Changes in renal system

Pregnancy increases kidney size, renal plasma flow, and glomerular filtration rate. The size of the kidney increases by 1 to 1.5 cm during pregnancy.[31] Renal plasma flow increases by up to 80% throughout the first and second trimesters but starts to decrease in the third trimester.[31] The increase in glomerular filtration rate occurs during the first month of conception, reaching approximately 50% above baseline levels by the early second trimester, and slightly declines toward the end of pregnancy.[32] At the same time, the capacity of the maternal bladder reduces due to the pressure from the growing placenta and fetus, resulting in an increase in the frequency urination.

2.1.2.5 Changes in gastrointestinal system

Elevated progesterone level during pregnancy relaxes smooth muscles.[33] This smooth muscle relaxation causes changes in gastrointestinal motility, slowing digestion in the stomach and intestines.[33] It also relaxes the lower esophageal sphincter, allowing stomach acid to flow back into the esophagus, which can lead to heartburn (gastroesophageal reflux; GERD).[33] Additionally, in the second half of pregnancy, the enlarging uterus obstructs the movement of the gastrointestinal contents of the digestive tract, leading to slowed digestion.[33]

2.1.2.6 Changes in hematologic system

With the marked increase in red blood cell production, the expansion in plasma volume outpaces the total red blood cell volume, leading to dilutional anemia.[25,28] This condition is often compounded by a surge in iron demand to support red blood cell production and sustain the placenta and fetus, often resulting in iron deficiency.[34] Studies have also demonstrated that platelet counts tend to decrease during pregnancy, primarily in the third trimester, a condition known as gestational thrombocytopenia. Furthermore, pregnancy is associated with elevated levels of coagulation factors, primarily due to increased estrogen concentrations during this period, resulting in a prothrombotic state, particularly in the third trimester.[35]

2.1.3 *Prevalent use of medication among pregnant women*

Despite the significant lack of information regarding dosage, safety, and efficacy during pregnancy, a substantial proportion of pregnant women use medications to address various health concerns. As detailed above, pregnant women are underrepresented in clinical trials yet there are many physiological reasons they or their fetuses might respond differently to drugs. Studies have reported that 93.9% of pregnant women use at least one medication during their pregnancies, whether over-the-counter or prescription.[6] On average, pregnant women take 4.2 medications throughout pregnancy. The use of prescribed medications during pregnancy varies across regions worldwide, with usage rates ranging from 23% to 96% of pregnant women addressing specific health needs. This demonstrates that medication use during pregnancy is a global phenomenon. Mitchell et al.[6] reported that nearly half (49%) of pregnant women in the US used prescribed medications during their pregnancies in 2011.

2.1.4 *Treatment guidelines in pregnant women*

In 2009, the FDA discovered that physicians heavily relied on FDA pregnancy categories when making treatment decisions for their pregnant patients (Table 2.2).[36] This discovery prompted the FDA to replace the overly simplistic pregnancy risk categories in medication labels, which poorly correlated with medication risk during pregnancy, with a more detailed description of what is known about medications during pregnancy, as outlined in the Pregnancy and Lactation Labeling Rule (PLLR; Table 2.3)[36,37]. The primary objectives of the PLLR were twofold: 1) to minimize misinformation and 2) to support informed and shared decision-making. The previous FDA pregnancy categories were simplistic and had the potential to lead to misunderstandings. Implementation of PLLR aimed to provide more comprehensive and accurate information to healthcare providers and patients, thus reducing the risk of misinformation. Another fundamental goal of the PLLR was to encourage both clinicians and patients to engage in shared decision-making. PLLR offers more detailed and context-specific information regarding the risks and benefits of medications during pregnancy and lactation. Table 2.3 shows the subcategories of PLLR.

Table 2.2 Pregnancy risk categories[36,37] used from 1979 to 2015

Category	**A**	**B**	**C**	**D**	**X**
Definition	No risk in human studies	No risk in animal studies	Risk cannot be ruled out	Evidence of risk	Contraindicated
Explanation	Studies on pregnant women have not demonstrated a risk to the fetus during the first trimester	There are no adequate human studies, but animal studies did not demonstrate a risk to the fetus	There are no satisfactory studies in pregnant women, but animal studies demonstrated a risk to the fetus; potential benefit of the drug may outweigh the risk	Studies on pregnant women have demonstrated a risk to the fetus; the potential benefits of the drug may outweigh the risks	Studies on pregnant women have demonstrated a risk to the fetus, and/or human or animal studies have shown fetal abnormalities; the risk of the drug outweigh the potential benefit

Table 2.3. Subcategories of PLLR[36,37]

Pregnancy (including labor and delivery) - **Mother and developing fetus**	**Lactation** - **Timing of breastfeeding, excretion in breast milk, lactation**	**Females and males of reproductive potential** - **Fertility, miscarriage, contraception, and pregnancy testing**
• Pregnancy exposure registry • Risk summary • Clinical considerations • Data	• Risk summary • Clinical considerations • Data	• Pregnancy testing • Contraception • Infertility

2.2 Real-world Data (RWD)

2.2.1 *Difference between RWD and RCT data*

We believe RWD from the EHRs might help us fill the knowledge gap on the medical treatment of pregnant women, which is the overall goal of this dissertation. Although pregnant women are underrepresented in clinical trials, they are not underrepresented in clinical care to nearly that extent. In the US in 2021, 75.6% of mothers who had delivered live births received adequate prenatal care.[38] Adequacy was measured using the Adequacy of Prenatal Care Utilization Index, combining information about the timing of prenatal care, the number of visits, and the infant's gestational age.[38] That said, RWD possesses several distinct characteristics compared to data collected from controlled settings such as RCTs that present some challenges. These characteristics help define the unique nature of RWD and include: (1) observational, (2) unstructured and inconsistent, (3) voluminous and dynamic, (4) high missingness, and (5) potential for bias.[39,40] Table 2.4 shows the comparison in characteristics of RCT data and RWD. First, RWD is inherently observational, meaning it is generated through the routine care of patients in real-world clinical settings rather than in a controlled and experimental environment like an RCT.[39,40] Second, most types of RWD are unstructured. This includes text-based health records, imaging data, and information from social media. These data are inconsistent due to variations in how information is entered and recorded across healthcare providers and systems.[39,40] Third, RWD tends to be dense and often continuously generated at high frequencies. For example, wearables can generate measurements at a millisecond level, contributing to large and dynamic datasets. Fourth, the primary purpose of RWD is not for research.[39,40] Therefore, it can often exhibit high levels of missing data, making it challenging to perform analyses that rely on complete datasets.[39,40] Fifth, RWD may be subject to various forms of bias, both random and non-random, and measurement errors. This can be due to factors such as variations in data collection practices or patient selection bias.[39,40]

Table 2.4 Comparison of evidence generated from RCT and RWD [10,39,41]

	RCT data	**RWD**
Purpose	Efficacy	Effectiveness
Focus	Investigator-centric	Patient-centric
Setting	Experimental	Real-world
Patients	Included as per strict criteria	No strict criteria
Concomitant medications and comorbid illness	Only those defined in the protocol allowed	As in real practice
Attending physician	Investigator/designated representative	Many practitioners as chosen by the patient
Comparator	Placebo/standard practice, as per the protocol	As per patient profile/real-world usage of available drugs in the market, at the physician's discretion
Patient monitoring	Continuous	Changeable
Treatment	Fixed pattern	Variable, at physician's discretion
Follow-up	Designed, as per protocol	Not planned; as per usual practice

2.2.2 *Types of RWD*

Widespread advancements in technology, such as the internet, social media platforms, and wearable devices, have led to the rapid generation of diverse forms of digital data.[40] In the medical and healthcare context, the US FDA defines RWD as "data related to patient health status and/or the delivery of healthcare that is routinely collected from various sources."[41] Examples of RWD include data from social media, wearable devices, mobile devices, claims and billing records, disease registries, and EHR. Additionally, Table 2.5 contains a comparison of characteristics between different types of RWD.

Table 2.5 Comparisons of different types of RWD

	EHR	**Registry data**	**Claims data**	**Wearable data**
Definition	Collected as part of routine care across healthcare system[40]	Organized systems that collect, analyze, and publish observational data on a patient population with specific characteristics in a prospective manner[42]	Data generated during healthcare claims processing in insurance plans or practice management systems[40]	Continuous streams of data generated through wearable devices [40]
Characteristics	Large source population,[43] noisy, heterogeneous, structured, and unstructured[44]	Standardized, continuous, prospective data collection in a real-world setting	Huge source population,[43] noisy, heterogeneous, structured, and unstructured[44]	Various format (temperature, electrocardiogram, movement, sound, location), high-density[40]
Disadvantage /Pitfall	Requires intensive pre-processing,[44] misclassification of exposure	High cost, takes time, often lack submission of exposure	Misclassification of exposure, upcoding, often lack important clinical information (eg. prior diagnosis)[40]	Data overload, lack of standardization[45]
Advantage /Potential	Large sample size, created unprecedented opportunities for data-driven approaches to learn patterns, make discoveries, assist preoperative planning, diagnostics, clinical prognostication, among others[46–49]	Enable identification and sharing best clinical practices, improve accuracy of estimates, and provide valuable data for supporting regulatory decision-making [50–53]. Rare disease registries provide a valuable data source to help understand the course of a disease[54–56]	Huge sample size, used in healthcare to understand patients' and prescribes' behavior and how they interact, to estimate disease prevalence, to learn disease progression, disease diagnosis, medication usage, and drug-drug interactions, and validate and replicate findings from clinical trials[57–60]	Unobtrusive, collect data in a natural environment[61]. When combined with contextual data (e.g., location data, social media), they provide an opportunity to conduct extensive research studies that are large in scale and scope [56] that would be otherwise infeasible in controlled trials[62–65]
Example	Providence, University of Washington EHR	Disease registries (ex. the European Cystic Fibrosis Society), Medical product registries	Medicaid and Medicare claims data, Ontario Pharmacy Evidence Network (OPEN)	Fitbit, Oura ring, Apple health

2.2.3 *Use of RWD*

RWD and RWE studies provide valuable avenues for exploring various aspects of health and disease. They offer insights into epidemiology, treatment patterns, disease burden, treatment outcomes, long-term impacts, and patient-reported outcomes, including satisfaction, quality of life, medication adherence, and the patient experience. Integrating RWE in the early stages of drug development can yield several benefits, such as shortened trial durations and cost savings. Furthermore, RWE complements the evidence obtained from RCTs by addressing gaps in existing clinical knowledge.[39]

RCTs, on their own, do not provide a comprehensive view of the safety of a medical product.[39] Regulatory authorities, therefore, require pharmaceutical companies to gather safety-related data after marketing approval, often through post-marketing surveillance studies. Notably, RWD from EHR and patient-generated sources have demonstrated the potential to offer unbiased insights into unexpected side effects associated with medical products.[39] For instance, in the field of pharmacovigilance, data from social networks were employed in the work of Nikfarjam et al. 2019 to detect cutaneous adverse drug reaction (ADR) signals related to cancer drugs (erlotinib, nivolumab, and pembrolizumab) several months before these signals were reported in the medical literature. Additionally, this study reported previously unrecognized ADR signals, including an association between erlotinib and hyperhidrosis.[66] RWD and RWE have recently been leveraged to support critical clinical and regulatory decisions, including new drug approvals, supplementary approvals, and label revisions. As an example, palbociclib, which was initially approved for the treatment of women with ER+/HER2- breast cancer, gained approval for use in men in 2019 based on RWE drawn from EHR studies related to its off-label use in male patients.[67]

2.2.4 *Potential pitfall in using the RWD*

The entire life cycle of RWD continues to face numerous pitfalls. These challenges encompass various aspects, including data collection, data quality control, and decision-making processes. Table 2.6 contains descriptions of key challenges in the RWD based on their characteristics and suggest alternative or solution.

Table 2.6 Potential pitfalls of RWD usage

RWD characteristics	**Types of challenge/bias/pitfall**	**Alternative/solution**
Inconsistent data collection[39]	Missing data[39]	Missing data imputation[39]
Real world data[39]	Lack of randomization, selection bias[39]	Biostatistical analytical methods (propensity score matching, inverse probability treatment weighting method), sensitivity analysis[39]
Ad hoc collection of unstandardized data[39,68]	Information bias[68]	Use of standardized data model, language (ex. SNOMED, OMOP, RxNorm), Use of natural language processing techniques [39]
Selective recollection of events by patients/caregivers[39]	Recall bias	Careful design of cohorts[39]
Likelihood of event being captured in one treatment group than other[39]	Detection bias	Careful design of cohorts, biostatistical analytical methods[39]
Confidentiality of patient data[39]	Limited data access, difficult to replicate and validate analysis	De-identification, federated data network[39]
Various system[39]	Source, format, method, quality discrepancy[39]	Standardized data model, language (ex. SNOMED, OMOP, RxNorm)[39]

2.2.5 *Usage of RWD in pregnancy research*

2.2.5.1 Epidemiology

RWD has been a critical data source for understanding the impact of SARS-CoV-2 infection and COVID-19 vaccination on maternal-fetal outcomes.[69] Pregnant women have encountered an elevated risk of SARS-CoV-2 infection and worse outcomes than non-pregnant women of reproductive age. This heightened risk of severe outcomes has resulted in higher hospitalization rates and increased intensive care unit (ICU) admission rates.[70–78] However, we have observed mixed results in the relative risk for mechanical ventilation (0.4-2.7).[69–72] and death (0.1-13.6).[69,70,72,73] Furthermore, pregnant women infected with SARS-CoV-2 have demonstrated a heightened risk of experiencing several adverse outcomes compared to those without the infection. These adverse outcomes include a higher likelihood of thrombotic events, ICU admissions, mechanical ventilation, PTB, low birth weight (LBW), small for gestational age (SGA), and stillbirth.[75,76,79–90]

The exclusion of pregnant women from all clinical trials for COVID-19 vaccination resulted in a significant knowledge gap regarding the risks and safety of vaccination in this specific population and fetus. This absence of critical information has, in turn, contributed to vaccine hesitancy among pregnant individuals globally.[91–95] Despite the hesitancy, RWE on COVID-19 vaccine safety was rapidly generated and was considered to have “no red flags” in February 2021, within two months after the vaccine's introduction by the CDC.[96] Vaccinated pregnant women experienced a significantly lower rate of maternal SARS-CoV-2 infection than unvaccinated pregnant women. Even among those vaccinated and later became infected, they exhibited a lower risk of severe outcomes compared to unvaccinated pregnant women. This included lower mortality rates, ICU admission, the need for supplemental oxygen, and the use of vasopressors. These findings underscore the potential benefits of COVID-19 vaccination for pregnant individuals in reducing the severity of the disease and its associated complications.[97–100]

Studies have reported neutral or positive effects on pregnancy and infant outcomes associated with COVID-19 vaccination during pregnancy. These outcomes include PTB, stillbirth, SGA infants, and infant mortality.[86,99,101–106] Additionally, it has been observed that vaccine efficacy in pregnant individuals waned similarly to that in non-pregnant women.[97] In summary, RWD has been a major resource for investigating the impact of SARS-CoV-2 infection and COVID-19 vaccination on pregnant women. As trials for COVID-19 therapeutics and vaccines did not include pregnant people, the public had to rely on evidence generated from RWD.

2.2.5.2 Drug effect signal detection

Although pregnancy research has not yet actively adopted innovative methodology in drug effect signal detection, some efforts have explored this avenue. In May 2008, the FDA initiated the Sentinel Initiative, a nationwide electronic system designed to monitor the safety of FDA-regulated medical products, including drugs, vaccines, biologics, and medical devices. As part of the mini-Sentinel pilot project, Andrade et al.[107] assessed outpatient prescription data to determine the prevalence rates of medication usage among pregnant women who gave birth to 1,678,410 live-born infants. Additionally, Suarez et al.[108] introduced a statistical method called tree scan statistics to analyze infant outcomes following maternal perinatal medication use. Specifically, they compared the risk of adverse outcomes associated with first-trimester exposure to fluoroquinolones and cephalosporins. Maric et al.[109] systematically investigated potential associations between prescribed medications during pregnancy and spontaneous PTB by analyzing claims databases. Their study encompassed 2,538,255 live, singleton births from 2007 to 2016 and identified 863 medications with statistically significant P-values. Although some efforts have been made to build a framework for detecting drug effect signals in pregnant women, there is still room for improvement.

2.3 PRETERM BIRTH (PTB)

2.3.1 *Background*

One example of the key knowledge gap is the impact of medication exposure associated with the risk of PTB. PTB, defined as birth occurring before 37 weeks of gestation, significantly contributes to perinatal morbidity and mortality in developed countries. PTB accounts for 75% of perinatal mortality cases and over half of long-term morbidity.[110] The US has a notably higher PTB rate (i.e., 10.2%), than other developed countries where rates typically range from 5 to 9%.[111] The prevalence of PTB has been on the rise in the US over the past three decades, despite advancements in understanding risk factors and efforts to reduce its incidence through medical interventions.[110] PTB is categorized by gestational age at delivery into three groups: extreme PTB (< 28 weeks of gestation), very PTB (28-32 weeks of gestation), and moderate to late PTB (32-37 weeks of gestation).[112] Alternatively, PTB can be classified into two categories: medically indicated PTB and spontaneous PTB, based on clinical pathways [113]. Medically indicated PTB occurs when the potential benefits to the mother or fetus outweigh continuing the pregnancy. Conversely, spontaneous PTB results from spontaneous preterm labor (PTL) or preterm premature rupture of membranes.[114] Preterm premature rupture of membranes[114] is characterized by the spontaneous rupture of the fetal membranes at least one hour before the onset of labor and before the 37th week of gestation.[114]

2.3.2 *PTB risk factors*

Understanding the risk factors associated with PTB is crucial. This knowledge allows healthcare providers, researchers, and policymakers to identify, target, and potentially mitigate the factors contributing to PTB. The risk factors of PTB can be categorized into several broad groups, including prior pregnancy, maternal demographics, nutritional status/physical activity, and current maternal/pregnancy characteristics. These risk factors are described in Table 2.7.

Table 2.7 PTB risk factors[115]

Prior OB/GYN history
• prior PTB • prior cervical surgery • uterine anomalies
Maternal demographics
• <17 or >35 maternal age • non-Hispanic Black and Indigenous women • lower education level • single marital status • lower socioeconomic status • short interpregnancy interval (<18 months) • other social factors (poor access to medical care, physical abuse)
Nutritional status/physical activity
• BMI <18.5 kg/m^2 or prepregnancy weight <50 kg • poor nutritional status • long working hours (>80 hours/week) • hard physical labor
Current maternal/pregnancy characteristics
• conception by assisted reproductive technology • multiple gestation • fetal disorder (eg. chromosome anomaly, structural abnormality, growth restriction, death) • vaginal bleeding • poly or oligohydramnios • maternal medical condition (eg. hypertension, diabetes, thyroid disease, asthma) • maternal abdominal surgery during pregnancy • psychological issues (eg. depression, anxiety) • substance use (smoking, heavy alcohol consumption, cocaine, heroin) • infection (bacterial vaginosis, trichomoniasis, chlamydia, gonorrhea, syphilis, urinary tract, intrauterine infection, severe viral infection) • short cervical length between 14 and 28 weeks • positive fetal fibronectin between 22 and 34 weeks

2.4 KEY GAPS IN THE CURRENT KNOWLEDGE ADDRESSED IN THIS DISSERTATION

The overall goal of this dissertation was **to leverage RWD, especially EHR, to fill in the knowledge gap in treating pregnant women**. In Section 2.4 we introduce key gaps in the current knowledge that are addressed in this dissertation.

2.4.1 *Aim 1 (Chapter 3)*

Aim 1 addresses a key knowledge gap in treating pregnant women by utilizing RWD EHR to discover drug effect signals at scale in pharmacology research for pregnancy. Current research actively seeks innovative methodologies for studying ADR,[10,116] drug repositioning,[9] and drug-drug interactions.[11,117] Although there have been some attempts to adopt these novel methodologies in pregnancy research, the efforts have been insufficient. There is a compelling need to establish a foundational framework for investigating drug reactions on a large scale using RWD in pregnancy research. Chapter 3 (Aim 1) discusses employing large-scale propensity score matching to efficiently prioritize and expedite the generation of hypotheses related to drug responses and their association with PTB risk. Unlike previous research that relied on claims data, we used EHR data that are more suitable due to their unique characteristics. EHR contain more comprehensive health service information, particularly for patients with discontinuous insurance coverage, and offer richer data on a patient's health condition, including lab results, vital signs, surveys, and prior complications.[43] This study is the first to use statistical data mining tools on EHR data to discover drug responses in pregnancy research.

2.4.2 *Aim 2 (Chapter 4)*

Aim 2 addresses a key knowledge gap in the treatment of pregnant women by evaluating the risk of PTB associated with the SSRI exposure during pregnancy. Despite the prevalent use of SSRI during pregnancy, existing findings have been inconsistent with the association between SSRI use and PTB. In Aim 2, we used EHR from a large US community healthcare system to comprehensively assess the association between SSRI exposure and PTB, SGA, and LBW. Aim 2 controlled for various confounding factors that could influence the association between SSRI exposures and adverse pregnancy outcomes investigated. This includes accounting for the potential impact of depression, considering the effects of the COVID-19 pandemic, and factoring in geospatial variables using the CDC social vulnerability index. Furthermore, we have considered the severity of pre-pregnancy and prenatal depression by utilizing standardized Patient Health Questionnaire (PHQ) assessments. To our knowledge, this is the first study to consider both the influence of the COVID-19 pandemic and social vulnerability when assessing the potential effects of SSRIs on adverse pregnancy outcomes. Aim 1 and Aim 2 collectively provided a powerful and streamlined process for detecting drug effect signals using EHR.

2.4.3 *Aim 3 (Chapter 5)*

Aim 3 addresses a knowledge gap within current medical treatment guidelines specifically targeted at pregnant women. The National Institutes of Health (NIH) issued a recommendation on February 24, 2022, advising the use of prophylactic doses of anticoagulants for all pregnant patients hospitalized with manifestations of COVID-19 due to the potential increased risk of thrombosis. However, up to this point, no studies have provided concrete evidence supporting or against this recommendation. Thus, in Aim 3, we utilized EHR obtained from a community healthcare system in the Western US states to characterize prophylactic anticoagulant use for hospitalized pregnant patients with COVID-19 across updates in NIH antithrombotic therapy guidelines and changes in the predominant SARS-CoV-2 variants. Additionally, we explored the impact of prophylactic anticoagulant use on outcomes such as coagulopathy, bleeding events, complications related to COVID-19, and maternal-fetal health outcomes. Our study represents the first effort to evaluate the NIH's antithrombotic therapy guideline in pregnant women. This effort sheds light on an essential aspect of managing COVID-19 in this population. Aims 1 through 3 collectively address crucial knowledge gaps in the medical treatment of pregnant women, with a specific focus on medication prescription.

2.4.4 *Aim 4 (Chapter 6)*

From Aim 1 to Aim 3, we observed that comorbidities significantly influence the associations between medication exposure and risk of adverse pregnancy outcomes. In Aim 4, we addressed a critical knowledge gap related to the association between comorbidities and adverse pregnancy outcomes. Specifically, we focused on immune-mediated inflammatory diseases (IMIDs), which are among the more understudied comorbidities in the context of pregnancy. Patients with IMIDs often face additional complications during pregnancy, leading many to voluntarily avoid getting pregnant.[118] However, previous research on pregnancy in patients with IMIDs is limited and often overlooks the impact of comorbidities. Many studies lack adequate control for these comorbid conditions, and the sample sizes are often small. In our study, we present a pioneering effort that leverages EHR from a large community healthcare system in the US to investigate the associations between twelve different IMIDs and the risks of adverse pregnancy outcomes. We investigated twelve selected IMIDs: psoriasis, inflammatory bowel disease, rheumatoid arthritis, spondyloarthritis, multiple sclerosis, systemic lupus erythematosus, psoriatic arthritis, antiphospholipid syndrome, Sjögren’s syndrome, vasculitides, sarcoidosis, and systemic sclerosis.

2.5 CLINICAL SETTING AND POPULATION

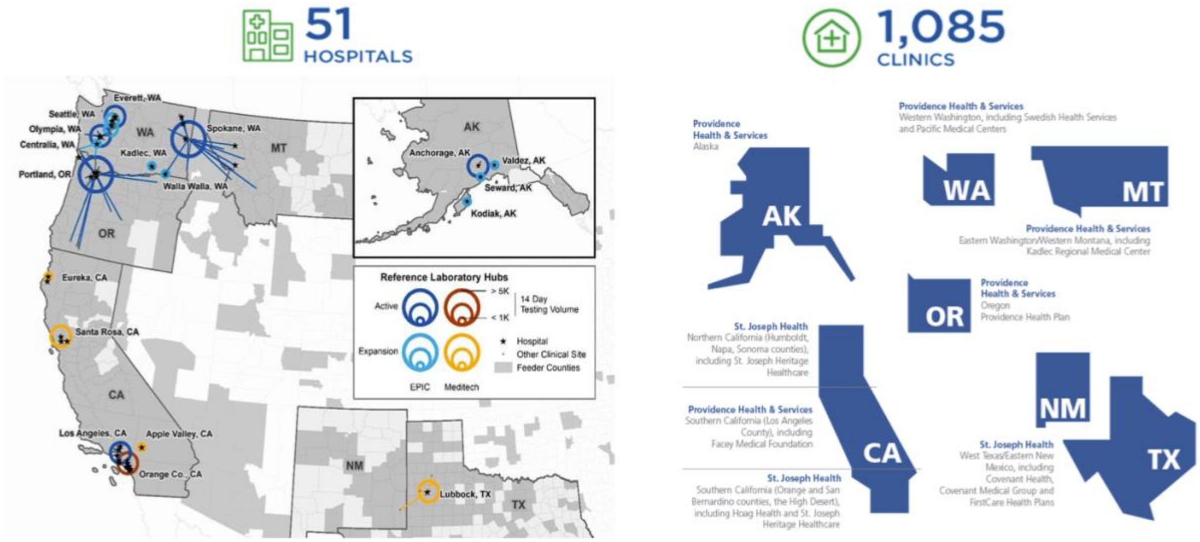


Figure 2.1. Clinical setting of study population

Providence St. Joseph Health (PSJH) is an integrated community healthcare system in the United States, providing medical services in both urban and rural settings across seven states: Alaska, California, Montana, Oregon, New Mexico, Texas, and Washington, as depicted in Figure 2.1. This dissertation utilized patient records from PSJH for pregnant individuals who gave birth between January 1, 2013, and December 31, 2022, resulting in a total sample size of 543,408.

Figure 2.2 outlines the process of selecting the source population. We excluded deliveries involving multifetal gestations before 20 weeks of gestation, resulting in a cohort size of 516,881 individuals. GA was limited to 20 weeks or greater because ascertainment bias is particularly high for EHR data earlier in pregnancy. We included pregnant individuals aged between 18 and 45 years, leading to a cohort of 510,488 individuals. Additionally, we focused on individuals continuously enrolled in PSJH to reduce surveillance bias. Continuous enrollment was defined as having at least one healthcare encounter within 180 days before conception and at least one encounter on or after the delivery date, resulting in a final cohort size of 368,459 individuals. Each study has its inclusion and exclusion criteria applied to the source population. The specific criteria for selecting the study's cohort are elaborated in the corresponding chapter.

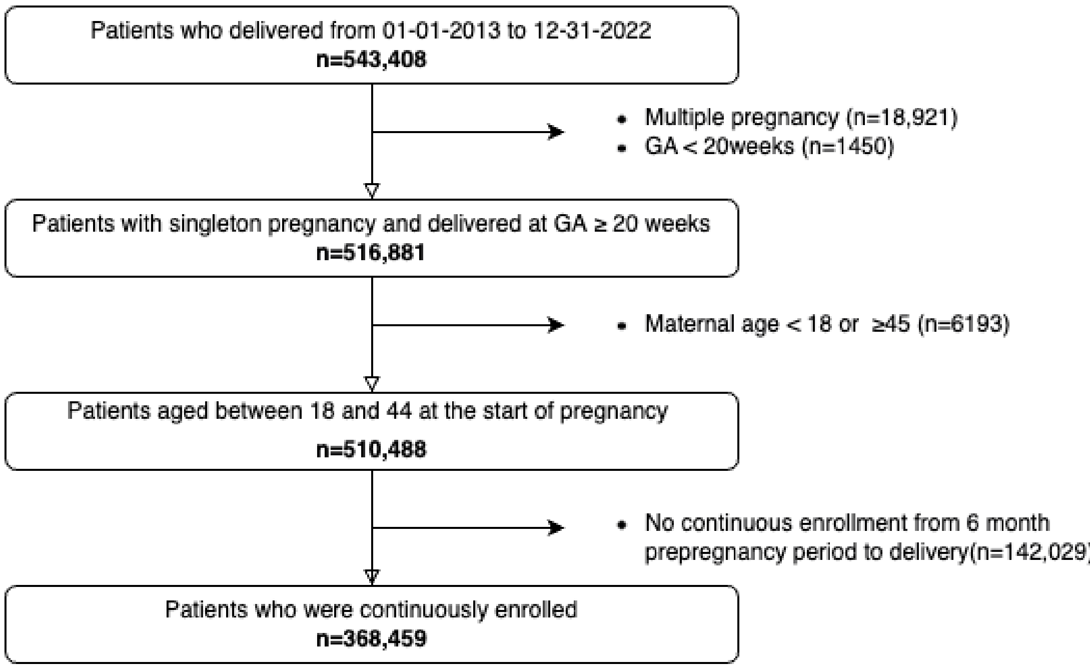


Figure 2.2 Source population selection flowchart

Chapter 3. **AIM 1** DETECT SIGNALS OF PREVIOUSLY IDENTIFIED AND UNIDENTIFIED DRUG EFFECTS ON PRETERM BIRTH USING STATISTICAL DATA MINING METHOD ON ELECTRONIC HEALTH RECORD

This chapter is expanded based on a manuscript titled "Detection of drug effect signals associated with adverse pregnancy outcomes using propensity score matching at scale". This manuscript still needs to be uploaded to a preprint server or submitted to a journal (as of December 15, 2023). Text from the planned manuscript is in italics and is in quotation marks.

3.0 INTRODUCTION

The overall goal of this dissertation was **to leverage RWD, especially EHR, to fill in the knowledge gap in treating pregnant women**. In **Aim 1 (Detect signals of previously identified and unidentified drug effects on preterm birth using statistical data mining method on electronic health record),** our approach to achieve this overall goal involved a data-driven methodology to generate many testable hypotheses about associations between prescribed medications and PTB risk. To accomplish this, we implemented a large-scale application of propensity score matching to generate and subsequently prioritize these hypotheses.

The central hypothesis of Aim 1 was there exist not yet characterized drug effect signals associated with risk of PTB. The objective was to apply propensity score matching method on patient records to confirm signals of known drug effects on PTB and detect previously unidentified potential drug effects.

3.1 MOTIVATION

3.1.1 *Background, literature review, and significance*

"Pharmaceutical companies primarily rely on pre-marketing randomized clinical trials to prevent and assess adverse drug reactions (ADRs). Despite the effort, studies conducted on inpatient populations estimated a serious ADRs incidence rate of 6.7% (N ≥ 2,216,000) with a fatality rate of 0.32% (N ≥ 106,000), placing ADRs as the fourth leading cause of morbidity and mortality in the United States (US) health care systems.[119,120] *The incidence rate of ADRs in outpatients is harder to estimate, with studies suggesting rates ranging from 3% to 38%.*[121–126] *Estimated incidence rate of ADRs in both inpatient and outpatient demonstrates that unintended drug response is common and expected."*

"Pre-marketing random clinical trials rarely include pregnant women unless the product targets pregnant women.[1] *Consequently, drug efficacy, safety, and dosages are determined based on data from men and non-pregnant women. While pregnant women are the most underrepresented population in clinical trials, they can experience some of the most complex medical situations. During pregnancy, women undergo marked physiological changes that significantly alter the pharmacokinetics and pharmacodynamics of drugs.*[127] *Therefore, current knowledge in pharmacology should not be directly applied to pregnant women, as inadequate information on the pharmacology of pregnancy exposes them to a high likelihood of experiencing unintended drug responses."*

"Despite the limited availability of safety information regarding medication use during pregnancy, many pregnant women continue to use medications. Overall, 93.9% of pregnant women take at least one medication (over-the-counter or prescribed) and typically use an average of 4.2 during pregnancy. Usage of prescribed medication by pregnant women varies

globally, ranging from 23% to 96%, with the US in 2008 reporting a usage rate of 49% among pregnant women.[6] *Given the prevalent use of medication among pregnant women and the challenges associated with conducting prospective clinical trials on this population, leveraging real-world data has emerged as a promising supplemental approach to investigate the effects of drugs during pregnancy. Electronic health records (EHRs) are particularly suitable candidates among these real-world data sources. EHRs contain rich and comprehensive information about patients' longitudinal health profiles, potential confounding factors, and prescription history. Active research on developing novel methodologies for not only ADRs*[10,116] *but also for drug repositioning*[9] *and drug-drug interactions*[11,117] *is ongoing."*

"However, despite these advancements in data-driven healthcare research, the field of pregnancy research has been slower in adopting these novel methodologies. In summary, there is a pressing need to establish a foundational framework for systematically investigating drug responses during pregnancy at scale using real-world data. Such an effort is crucial, as it can lead to the generation of testable hypotheses related to drug effects on pregnancy outcomes, both positive and negative. Furthermore, uncovering drug responses that do not pose risks to adverse pregnancy outcomes can provide valuable insights into drug safety during pregnancy. Here, we selected preterm birth (PTB) as our primary outcome of interest. PTB, defined as birth occurring before 37 weeks of gestation, significantly contributes to perinatal morbidity and mortality in developed countries. PTB accounts for 75% of perinatal mortality cases and over half of long-term morbidity.[110]*"*

3.1.2 *Objective*

"We employed a large-scale propensity score matching approach on patient records to expedite the generation and prioritization of testable hypotheses related to the risk of PTB. We

hypothesized there exist not yet characterized pharmacological signals with medication and risk of PTB. Beyond hypothesis generation, we investigated a few detected drug effect signals using traditional pharmacoepidemiology methods."

3.2 Methods

3.2.1 *Study design, setting, and participants*

"Providence St. Joseph Health (PSJH) is an integrated US community healthcare system that provides care in urban and rural settings across seven states: Alaska, California, Montana, Oregon, New Mexico, Texas, and Washington. We used PSJH pregnant patient records who delivered live infants from January 1, 2013, through December 31, 2022 (n=543,408). Figure A.3 1 describes the cohort selection. We excluded multiple pregnancies and deliveries with gestational age (GA) of less than 20 weeks (n=516,881). GA was limited to 20 weeks or greater because ascertainment bias is particularly high for EHR data earlier in pregnancy. This study population may be biased toward lower-risk pregnancy cases. This is because high-risk pregnancy cases are often transferred to third-level academic medical centers. We limited our analyses to pregnant patients aged between 18 and 45 years of age (n=510,488). We excluded patients who were not continuously enrolled from 180 days before the start of pregnancy (last menstrual period, LMP) to the time of delivery (n=365,075). Our definition of continuous enrollment was at least one encounter 180 days before LMP and one encounter on or after the delivery date. This was done to partially address surveillance bias"

"All procedures were reviewed and approved by the Institutional Review Board at the PSJH through expedited review on 11-04-2020 (study number STUDY2020000196). Consent was waived because disclosure of protected health information for the study involved no more than minimal risk to the privacy of individuals"

3.2.2 *Variable*

3.2.2.1 Exposure

"We mapped all prescription records during pregnancy to RxNorm code based on ingredients. We split the cohort into exposed and unexposed groups for individual medication ingredients. Women with medication orders that overlapped with at least one day of pregnancy were considered exposed. We excluded medications that did not reach a minimum sample size of the exposed, which was 600. This minimum sample size was calculated using Epitools,[128] *with the following parameters: PTB prevalence rate of the PSJH maternity cohort (7.7%), assumed relative risk (1.55), desired level of confidence (0.9), and desired power for the detection of significant difference (0.8). The calculated minimum sample size was 582, but we rounded it to 600."*

3.2.2.2 Outcome

"The primary outcome of interest was PTB, defined as gestational age at birth (GA; GA<37 weeks). Secondary outcomes were low birth weight (LBW; birth weight <2,500g) and small for gestational age (SGA; birth weight < 10th percentile of based on gestational age)."

3.2.2.3 Covariate

*"We extracted maternal, pre-pregnancy, and prenatal characteristics and comorbidities information from EHR data. Pregnancy and maternal characteristics were collected during prenatal care or at time of delivery. These included parity, preterm history, delivery year, fetal sex, age at LMP, race, ethnicity, insurance status, pregravid body mass index, smoking, and use of alcohol and illegal drugs (*Table A.3 1*)."*

"We conducted a parallel analysis with three different sets of covariates. First, we conducted propensity score matching at a scale with the aforementioned covariates without

comorbidities. Second, we addressed pre-pregnancy comorbidities based on the obstetric comorbidity index.[7] *Selected comorbidities were renal diseases, chronic lung diseases, diabetes, leukemia, pneumonia, sepsis, cardiovascular diseases, sickle cell diseases, anemia, cystic fibrosis, and asthma(Table A.3 2). A similar practice was done in an at-scale study conducted by Sentinel System, one of the US Food and Drug Administration (FDA) efforts in surveillance medical products.*[129] *We excluded comorbidities specific to the prenatal period, such as gestational diabetes; the obstetric comorbidity index is designed to assess the mortality risk at delivery. We did not consider comorbidities that happened after the start of pregnancy since covariates have to occur before the exposure by definition. Third, we selected the fifteen most common comorbidities before and during the pregnancy. We acknowledge prenatal comorbidities do not satisfy the covariate definition. However, this study aims to explore the usefulness of EHRs and generate hypotheses. To do so, we employed an exploratory approach beyond the conventional one."*

3.2.3 *Analysis*

3.2.3.1 Descriptive statistics

"We described the source population on maternal characteristics, outcomes, and covariates. The descriptive statistics are presented in Table A.3 3. We characterized the prescription rate within the PSJH pregnant population in Figure 3.1. We used the chi-square test and linear regression to evaluate the difference in prescription rate across categorical variables and continuous variables. Age distribution of this source population is described in Figure A.3 2. Prescription patterns from 2013 to 2022 based on their ingredient and ATC classification categories are displayed in Figure A.3 3."

3.2.3.2 Propensity score matching

"We calculated the risk ratio of PTB, LBW, and SGA for individual outpatient medications that reached the minimum sample size. For each medication, the unexposed group was matched to the exposed group using propensity score matching on the covariates listed above. We used propensity score matching to account for covariates associated with adverse pregnancy/maternal outcomes. Compared to other propensity score methods and covariate adjustment methods, propensity score matching provided exceptional covariate balance across most circumstances.[130] *An unsupervised learning model with k-nearest neighbors (k=1), as recommended by a prior study,*[131] *was used to match with replacement by the propensity logit metric. We evaluated the covariate balance using an average standardized mean difference. We excluded medication ingredients with an average standardized mean difference below 0.2. We categorized medications with statistically significant associations based on their indication in three categories: preterm labor(PTL) or PTB, PTB risk factors, and infection (Table A.3 4). Here, we considered association with a P value below 0.1 statistically significant. This is not a conventional practice in hypothesis-testing studies, but our study is hypothesis-generating. We are suggesting potential hypotheses to researchers to further investigate."*

3.2.4 *Validation*

"We selected sertraline, acyclovir, and ferrous sulfate for further investigation. They had relatively large exposure groups and were statistically significant in an analysis adjusted for pre-pregnancy/prenatal common diagnoses. Details of the method are described in the supplemental methods(Method A.3 1, Method A.3 2, and Method A.3 3)."

3.2.4.1 Sertraline

"Sertraline is a Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant. Depression is a treatable disease and a risk factor for PTB[132]*. We limited our analytic population to patients who had any depression diagnosis before pregnancy (*Table A.3 2*). We evaluated the risk of PTB in patients exposed to sertraline among patients who had depression onset before the pregnancy."* Additionally, we assessed the likelihood of delivering preterm in patients exposed to SSRI within the same analytic population that we used to evaluate the risk of PTB in those exposed to sertraline.

3.2.4.2 Acyclovir

"Acyclovir is a treatment for herpes virus infection, including shingles, chicken pox, and genital herpes. Genital herpes is a sexually transmitted disease, which is a risk factor for PTB. We determined the indication of treatment based on dosage[133]*. According to the CDC treatment guideline*[134]*, acyclovir is recommended starting at GA 36 weeks to suppress the reactivation of genital herpes among pregnant women. Patients who adhered to this treatment guideline delivered after 36 weeks of gestation, potentially introducing selection bias and leading to a lowered risk of PTB(delivery before 37 weeks of gestation). Initially, we characterized the number of patients who initiated their prescription at 36 weeks of gestation to assess the proportion of patients following this CDC treatment guideline. Subsequently, we examined the likelihood of PTB in patients exposed to acyclovir before 36 weeks of gestation. We replicated the analysis on a subsample of patients who had indications of genital herpes (*Table A.3 2*). We then evaluated the risk of PTB among patients exposed to acyclovir or valacyclovir (oral prodrug of acyclovir) before 36 weeks of gestation."*

3.2.4.3 Ferrous sulfate

*"Ferrous sulfate is a treatment for iron deficiency anemia, which is a risk factor for PTB. We assessed the impact of ferrous sulfate in the anemic group. The anemic group was determined based on the presence of iron-deficiency anemia diagnosis within 180 days before LMP to LMP (*Table A.3 2 *)."*

3.3 RESULTS

3.3.1 *Descriptive statistics*

"We identified 365,074 patients as our analytic population who had continuously enrolled singleton pregnant patients. This population was enriched with people who were aged 30-34 (32.7%), White or Caucasian (63.2%), non-Hispanic or Latino (77.2%), Medicaid/Medicare insured, living in metropolitan areas (84.2%), and delivered in 2022 (12.4%). Median maternal age increase from 30.3 to 31.5 (P<0.0001) from 2013 to 2022. The proportion of women aged 35 or older increased from 20.8% to 27.0% from 2013 to 2022 (Figure A.3 2). The mean gestational age at delivery was 275.0 days. The average prevalence rates of PTB, SGA, and LBW were 7.7%, 12.1%, and 5.4% (Table A.3 3).

The total medication prescription rate increased from 58.5% to 75.3% from 2013 to 2022 (P<0.0001). The inpatient prescription rate slightly increased from 29.3% to 32.4% (P=0.2) In contrast, outpatient medication prescriptions increased from 50.5% to 70.1% (P<0.0001) (Figure 3.1). The maternal age group of 18-24 had the highest prescription rate of 73.0%. Mothers aged 40 or older had the lowest prescription rate reporting 63.4%. The Medicare/Medicaid insurance group had a higher prescription rate reporting 72.2%, than the commercial insurance group (62.6%). Amongst the race group, pregnant women who reported

Black or African American race had the highest prescription rate of 77.3%, and Asian had the lowest, reporting 64.4%. We observed prescription rate increases as the number of comorbidities increased. This trend was similar for both pre-pregnancy and prenatal comorbidities. Approximately half of the pregnant people with no pre-pregnancy/prenatal problem diagnosis had a prescription during pregnancy. Patients with eleven or more pre-pregnancy/prenatal problem diagnoses had a prescription rate higher than 90% (Figure 3.1).”

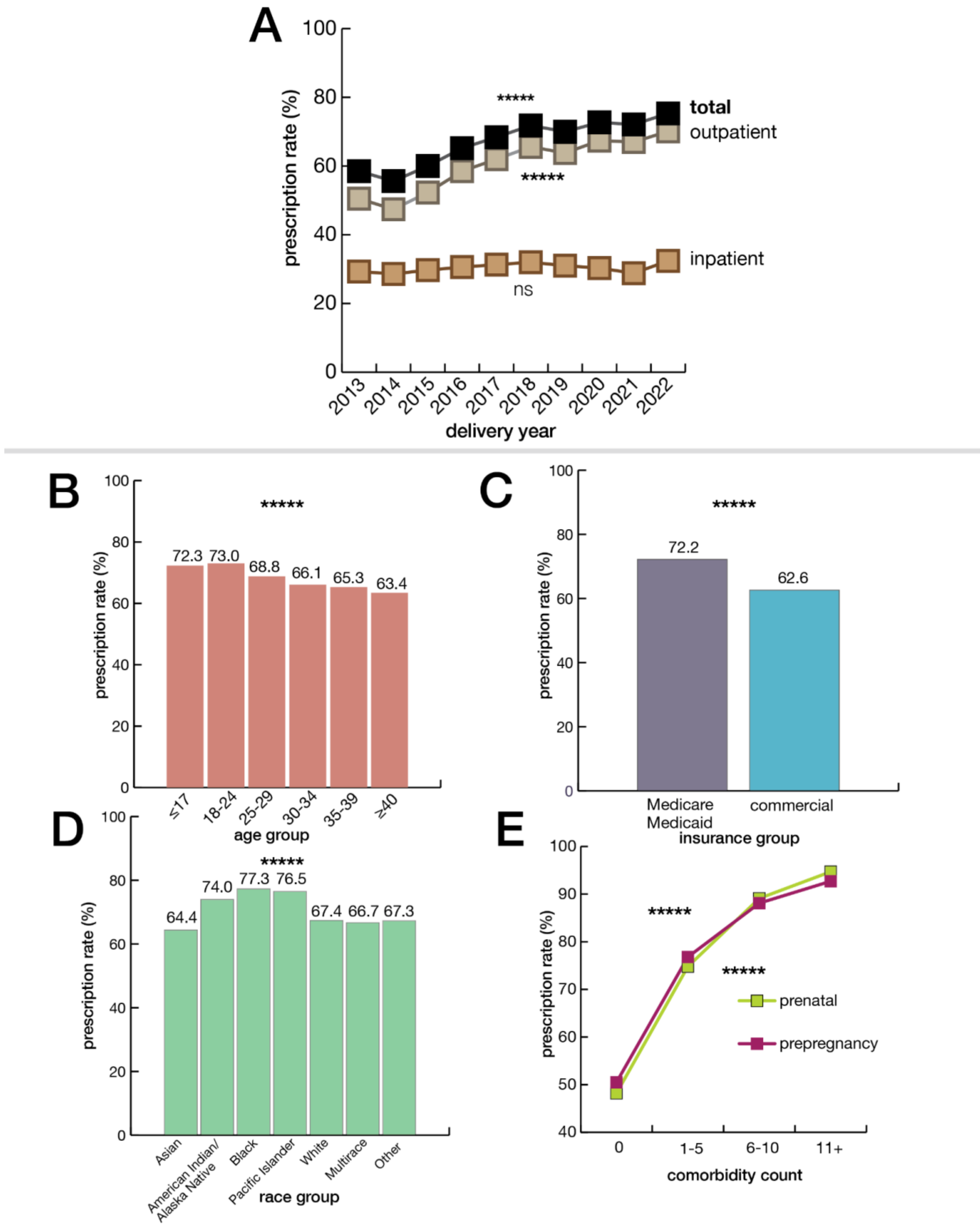


Figure 3.1 Overall prescription rate of PSJH pregnant population

(A) plot shows the increase in total prescription rate from 2013 to 2022. The total medication prescription rate increased from 58.5% to 75.3% from 2013 to 2022 (P<0.0001).

Figure 3.1 Overall prescription rate of PSJH pregnant population (continued); The inpatient prescription rate increased from 29.3% to 32.4% (P=0.2). In contrast, outpatient medication prescriptions increased from 50.5% to 70.1% (P<0.0001). We evaluated the increase in prescription rate using linear regression.

(B) plot shows the total prescription rate across age groups (P<0.0001). We evaluated the decrease in prescription rate across ages using linear regression. (C) plot shows the difference in prescription rates between insurance groups (P<0.0001). We evaluated the difference in prescription rate across categorical variables using the chi-square test.

(C) plot shows the difference in prescription rate across race groups (P<0.0001). We evaluated the difference in prescription rate across categorical variables using the chi-square test.

(D) plot shows the increase in prescription rate based on comorbidity count. The increase in prescription rate across comorbidity count using linear regression.

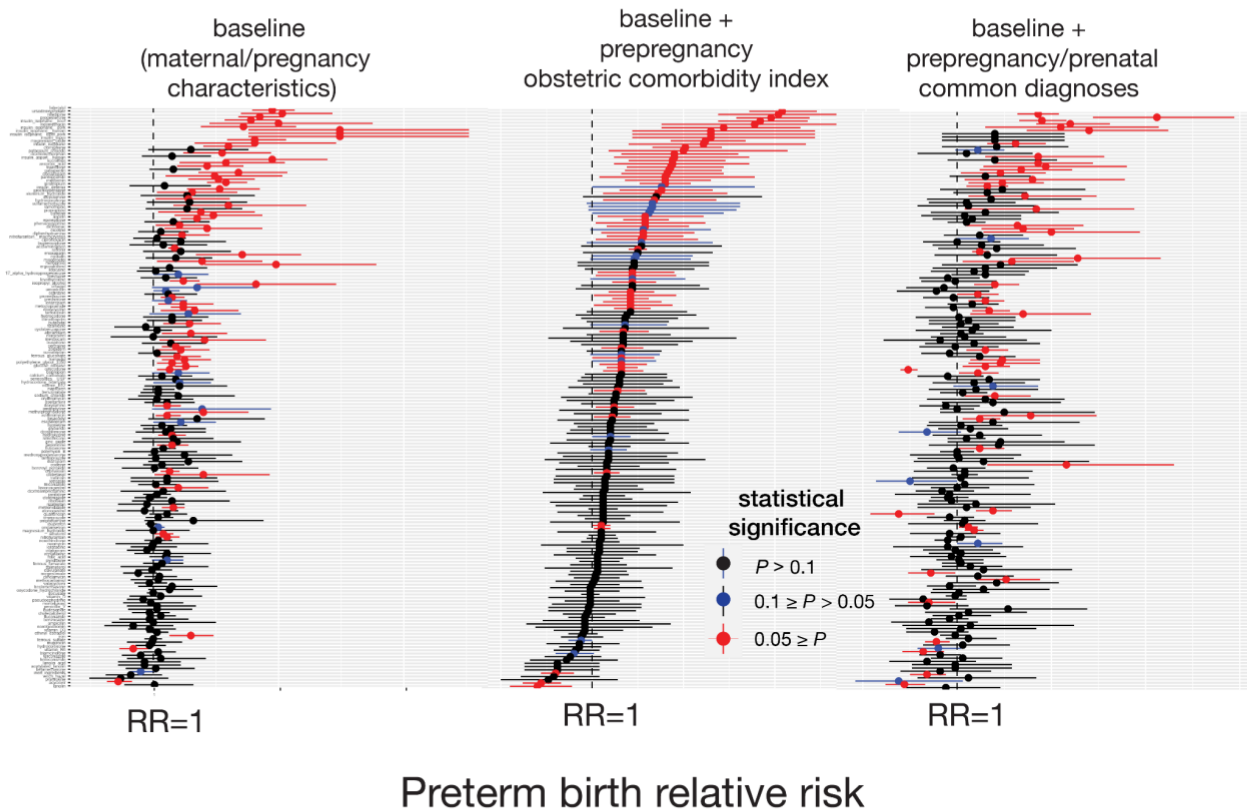


Figure 3.2 Forest plots of association between medication and risk of PTB

Left plot shows the forest plot of baseline analysis that adjusted maternal and pregnancy characteristics. The center plot shows a forest plot of analysis that adjusted for maternal and pregnancy characteristics and pre-pregnancy comorbidities from the obstetric comorbidity index. The right plot is a forest plot of analysis that adjusted for maternal and pregnancy characteristics and prenatal/pre-pregnancy common comorbidities. The Y axis is the list of medications that met the minimum sample size in descending order of RR of analysis in the center plot. This figure is summarized in Table 3.1. RR, confidence interval, and p-values are reported in supplementary data.

Table 3.1 Summary of associations based on statistical significance and relative risk

		Baseline (maternal/pregnancy characteristics)	**Baseline + prepregnancy comorbidity index**	**Baseline + prepregnancy/prenatal common comorbidity**
RR<1	**0.05≥P**	4	3	8
	0.1≥P>0.05	16	2	4
	P>0.1	23	26	36
RR≥1	**0.05≥P**	49	55	42
	0.1≥P>0.05	7	15	4
	P>0.1	77	75	82

3.3.2 *Propensity score matching*

"From the initial pool of 1329 medications, 175 prenatally prescribed medications met the minimum sample size. None of the medications had an effect size below 0.2 after matching all three analyses. When we adjusted for baseline characteristics, pregnancy and maternal characteristics, we identified a total of 76 (RR<1: 20, RR≥1:56) associations with a p-value below 0.1. The number of associations with statistical significance narrowed when additionally accounting for pre-pregnancy comorbidities in the obstetric comorbidity index. We observed 75 (RR<1: 5, RR≥1:70) medications associated with the risk of PTB with statistical significance. Finally, we identified 58 (RR<1: 12, RR≥1:46) medications associated with the risk of PTB in an analysis adjusted for common diagnoses during the pre-pregnancy and prenatal period (Figure 3.2, Figure 3.3, and

Table 3.1). Statistically significant correlations were categorized into three categories based on their indication: PTL/PTB, risk factor of PTB, and infection (Table A.3 4). Forty-three medications had indications categorized into at least one category. Four medications fell into the category of PTL/PTB indication. Thirty-two medications had indications that were risk factors for PTB. Nine medications were prescribed in case of infections, including bacterial, fungal, and viral."

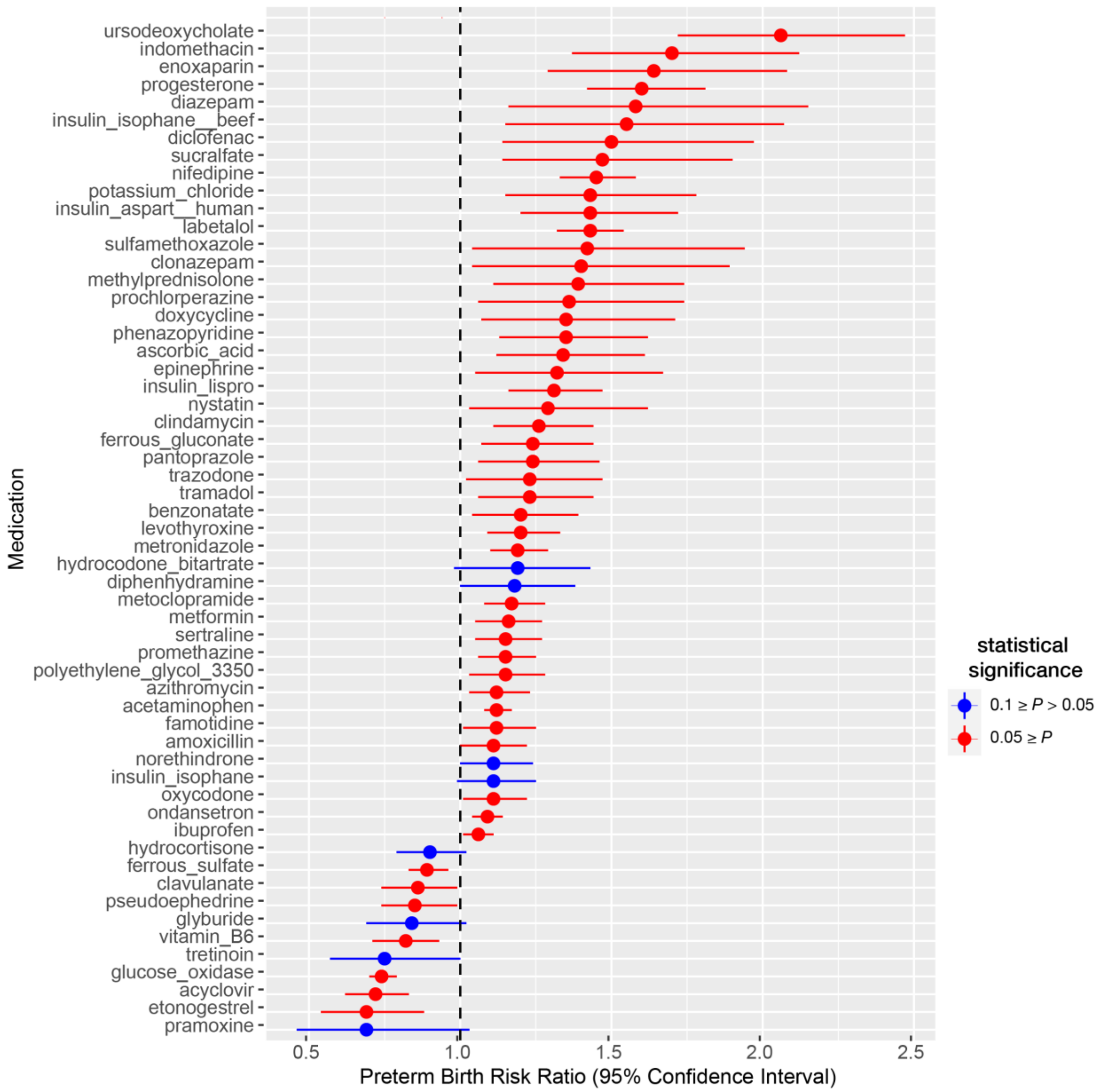


Figure 3.3 Forest plot of statistically significant association with risk of PTB

3.3.3 *Validation*

3.3.3.1 Sertraline

"There were 29,352 patients who had depression diagnosis before the pregnancy. Respectively, 3214 and 5910 patients were exposed to sertraline or any SSRI. They were 1.28 times [1.14, 1.45] and 1.16 times [1.05, 1.28] more likely to deliver preterm than patients without exposure."

3.3.3.2 Acyclovir

"The majority of patients (58.8%; 4947 out of 8420) who had prenatal acyclovir exposure started their prescription at or after 36 weeks of gestation. Those exposed to acyclovir before 36 weeks of pregnancy had 1.77 times (1.77 [1.52, 2.07]) higher likelihood of delivering preterm compared to patients without prenatal acyclovir exposure. However, within the subsample of patients diagnosed with genital herpes, we did not observe an elevated risk of PTB (OR=1.19 [0.94, 1.50]). Additionally, there was no observed association between exposure to acyclovir and elevated risk of PTB when comparing individuals exposed to acyclovir and valacyclovir before 36 weeks of gestation (OR=0.86 [0.74, 1.00])."

3.3.3.3 Ferrous sulfate

"There were 774 patients were diagnosed with iron deficiency anemia within a 180-day pre-pregnancy period. We observed 294 patients with a prescription for ferrous sulfate during pregnancy. Our analysis revealed no association between the prescription of ferrous sulfate and the risk of PTB (OR=0.85[0.48, 1.50])"

3.4 DISCUSSION

“To our knowledge, this was the first study to use propensity score matching at scale on EHR to generate and prioritize testable hypotheses on drug effects associated with risk of PTB. We retrospectively assessed 365,074 people who were continuously enrolled in PSJH. The majority of women took prescribed medication during pregnancy. From an initial pool of 1762 medications, we narrowed down to 172 medications for hypothesis evaluation. Three of these detected signals were selected based on their relatively large exposure groups and statistical significance in an analysis adjusted for pre-pregnancy/prenatal common diagnoses. We evaluated the heightened likelihood of delivering preterm associated with exposure to sertraline and decreased chance related to exposures to acyclovir and ferrous sulfate.”

“We employed propensity score matching at scale on EHR and produced hypotheses for 172 medications. Among them, 57 of 172 mediations had statistically significant associations with the risk of PTB. There were a few prior studies with similar aims. Maric et al., 2019[109] *assessed administrative claims data on 2,538,255 deliveries and identified 863 medications with statistically significant associations. Their number of signals, statistically significant association, far exceeds ours because their sample size was greater and did not eliminate medication that did not meet the minimum sample size. That study had only 5 medications with an odds ratio below 1, whereas we had 12. Another effort to establish a framework to detect drug effect signals in maternal-fetal medicine was conducted by the Sentinel working group. Sentinel initiative, led by the US Food and Drug Administration (FDA), has created novel methods to evaluate the safety of approved medical products, including medications, vaccines, and devices. They used propensity score matching tree-based scan statistics methods on Medicaid data to discover infant outcomes associated with prenatal cephalosporin exposure in*

the first trimester[129]*. That study utilized a different approach as they focused on multiple outcomes and single exposures; our study assessed single outcomes and multiple exposures. Both prior studies utilized claims data, whereas we used EHR."*

"The majority of patients were prescribed medications during pregnancy. This finding corresponds to observations in earlier studies. According to Mitchell et al. 2011[6]*, in the US, 48% of women were exposed to prescribed medication during pregnancy in 2008. A systemic review study conducted on peer-reviewed literature from 1989 to 2010 in developed countries reported that 27% to 93% of pregnant women used prescription drugs, depending on the country.*[135] *In our study, we observed an increase in prenatal prescription rate from 58.5% to 75.3% from 2013 to 2022. This rate is higher than the prescription rate reported in 2008. The discrepancy in the prescription rate for medication during pregnancy may be attributable to a gradual increase in usage. Mitchell et al. in 2011 described an incremental increase in the use of prescription medications by 60% from 1986 to 2008. We also observed a rise in the prescription rate from 2013 to 2022. As discussed in the introduction, the common use of medication during pregnancy underscores the necessity to promote pharmacology research in pregnant women and to leverage already generated real-world data to expand our understanding of the efficacy and safety of medications during pregnancy."*

"Surprisingly, the prescription rate decreased as the maternal age increased. We first assumed that the increased prescription rate over the study period was attributable to increasing maternal age based on observation from Mitchell et al. 2011.[6] *Indeed, the median maternal age increased, and the proportion of women aged 30 or older gradually increased over our study period. However, the prescription rate did not correlate with the maternal age, contrary to our speculation. Women in the oldest age group, 40 or older, had the lowest prescription rate,*

whereas women aged 24 or younger had the highest. The major difference between our study and Mitchell et al. 2011[6] *is the study period and population. Their observation was based on 5008 deliveries from 1997 to 2003 in the US. In contrast, our observation was relatively similar to that from a more recent study*[136] *on 2.3 million patients who delivered live births from 2000 to 2019. Their study reported that the most prevalent medication exposures (antibacterial agents, antiemetics, and contraceptives) during pregnancy had a prescription pattern across age groups similar to our study. The younger group, 24 or younger, had much higher prescription rates for these medications than those of the older group, 35 or older."*

"We employed traditional pharmacoepidemiology methods to evaluate the detected drug effect signals for sertraline, acyclovir, and ferrous sulfate. Specifically, we focused on assessing the negative association between sertraline/SSRI and the risk of PTB among patients who had an onset of depression before the pregnancy. We further validated this in a separate study[12]*. We confirmed the correlation between exposure to sertraline/SSRI and the risk of PTB, and this correlation remained strong and significant through extensive sensitivity analyses. However, our study faced limitations in properly evaluating ferrous sulfate association with a lower risk of PTB due to the small sample size. Only 774 patients received a diagnosis of iron deficiency anemia within the 180-day pre-pregnancy period. Despite the small sample size of our study, a recent study reported that patients exposed to iron supplementation(ferrous sulfate, ferrous gluconate, ferrous fumarate, and ferrous glycinate) experienced reduced odds of preeclampsia and/or PTB.*[137]*"*

"In contrast to sertraline and ferrous sulfate, the signal we observed for acyclovir was misleading. According to CDC treatment guidelines,[134] *acyclovir is recommended for administration at 36 weeks of gestation for patients with genital herpes. This practice likely*

introduced selection bias, as the exposure group included patients who surpassed 36 weeks of gestation. In fact, 60% of patients were exposed to acyclovir at or after GA 36 weeks. When we restricted our exposure group to patients exposed to acyclovir before 36 weeks, the protective result associated with the risk of PTB disappeared. Interestingly, our result slightly differed from prior studies. In a previous study, exposure to valacyclovir, not to acyclovir, was associated with a lower risk of spontaneous PTB.[109] *The investigation on sertraline and ferrous sulfate demonstrates the potential of our approach to produce and prioritize hypotheses to evaluate. However, misleading signals do exist. Thus, we must take a conservative stance and carefully verify detected drug effect signals."*

"We identified 118 medications with no statistical significance. Restricting our analyses to medications that satisfy minimum sample size ensures that associations lacking statistical significance are not dismissed as meaningless. Considering that pregnant women are typically excluded from clinical medication trials despite their medication use, the absence of an association with the risk of PTB is a valuable finding supporting the potential drug safety in relation PTB. It underscores the need for similar studies in pregnancy pharmacology to be conducted and repeated on real-world data to gather more evidence on medication's safety, risks, and benefits for pregnant women."

"We had one of the largest sample sizes for hypothesis-generating retrospective EHR studies for pregnant women. While similar studies exist, they often rely on claims data.[109,129] *Claims data may offer a larger sample size but EHR provides richer data on patient's longitudinal health conditions, encompassing lab results, vital signs, and surveys.*[43] *Moreover, our study setting PSJH serves community hospitals/clinics in both rural and urban settings in*

seven western states in the US. This setting better reflects the general population better than the third-level academic hospital, which may focus more on high-risk pregnancies."

"To ensure the integrity and reliability of our analyses, we implemented several measures to mitigate bias and ensure the robustness of our findings. We reduced the surveillance bias by restricting to continuously enrolled patients and leveraging propensity score matching. By limiting our study population to patients who were continuously enrolled, we excluded transient patients admitted for delivery who were likely to lack prenatal information. Furthermore, we mitigated the bias by matching patients in the treatment group to those in the control group with similar characteristics across covariates. Given that individuals exposed to medication may have more frequent doctor visits, ensuring comparability of patient health was crucial. Another noteworthy aspect of our approach was our commitment to evaluating all medications without introducing systemic bias. In research, there can be a tendency to focus on variables or hypotheses previously explored or considered more interesting. In research, there can be a tendency to focus on variables or hypotheses previously explored or considered more interesting. By conducting assessment on all medications that reached minimum sample size, we aimed to prevent such biases from influencing our analysis, which contributed to the overall rigor of our study."

"One major limitation of this study was the absence of multiple testing corrections. We recognize that conducting multiple comparisons increases the likelihood of producing false positives. However, we deliberately did not correct for multiple testing, as the primary objective of this study was to produce hypotheses rather than to test them. Furthermore, different methods for multiple testing correction can yield varying adjusted p-values. Instead of applying specific correction methods, we presented confidence intervals. This decision allows future researchers

to use them for meta-analysis, as recommended by a prior study.[138] *We underscore the need for cautious consideration of these associations and advocate for thorough evaluation through meticulously designed studies that reflect the characteristics of exposures of interest and their indications"*

"Another limitation was that we the use of uniform sets of comorbidities. Although we conducted multiple analyses with several groups of comorbidities, it is essential to note that individual medications are prescribed for specific indications. Medications with less common indications may not be adequately represented in the covariate we investigated. In the future, we can address this limitation by applying several promising approaches. One such approach is high-dimensional propensity score matching.[139] *High-dimensional propensity score matching offers a robust way to control for confounding variables in observational studies. Unlike traditional propensity score matching, which considers a limited number of covariates, high-dimensional matching can involve hundreds of empirical covariates. Another promising approach is leveraging external databases such as ChEMBL. ChEMBL provides valuable information about drug indications, contraindications, and other clinical data. Leveraging external databases like ChEMBL enables researchers to automatically select relevant analytic cohorts and covariates relevant to drug indication and treatment"*

3.5 Conclusion

In **Aim 1** (**Detect signals of previously identified and unidentified drug effects on preterm birth using statistical data mining method on electronic health record**), we implemented propensity score matching at scale to the delivery records of PSJH continuously enrolled pregnancy cohort. The hypothesis of Aim 1 was that there exist drug effects not yet characterized, which are associated with the risk of PTB. The objective of Aim 1 was **to identify both previously known and unknown drug effect signals linked to the risk of PTB.**

Several key findings emerged from Aim 1. First, a majority of pregnant women were prescribed/administered medication during pregnancy, emphasizing the importance of utilizing the wealth of already-generated data from EHR. This underscores the necessity to cultivate the groundwork for maternal pharmacology research. Second, from 1329 medications, we successfully narrowed down to 172 medications with hypotheses, further reducing it to 58 medications with statistically significant associations with the risk of PTB. This demonstrates our ability to accelerate and prioritize testable hypotheses on pharmacological effects associated with the risk of PTB. Third, we achieved our objective of detecting both previously identified and unidentified drug effects associated with the risk of PTB. Our findings were not confined to anticipated signals alone. Anticipated signals added reassurance to our findings and unanticipated ones provided interesting hypotheses that could be further investigated.

However, our study encountered certain limitations that are crucial to acknowledge. Firstly, we did not correct for multiple testing errors. It was a deliberate choice due to the primary goal of hypothesis generation rather than rigorous testing. In addition, there are several options for multiple testing corrections methods. Instead of selecting specific correction method, we instead provided confidence interval and sample size, thus future researchers can use them in meta-analysis. Another limitation involves the use of uniform set of comorbidities for different medications, potentially underrepresenting the specific indication individual medications were prescribed for.

To address these limitations in future studies, we suggest several promising approaches. One such strategy is the application of high-dimensional propensity score matching, involving hundreds of empirical covariates instead of a limited number. Additionally, leveraging external database such as ChEMBL presents an exciting opportunity, providing valuable information about drug indications, contraindications, and other clinical data. By automatically selecting relevant covariates directly related to drug indication and treatment, researchers can streamline the covariate selection process, enhancing the depth and accuracy of future studies.

From the signals detected in Aim 1, we selected sertraline for further investigation in Aim 2 due to its relatively large exposure group, well-documented depression diagnosis, and the existing controversy regarding its association with the risk of PTB. Aim 1 (Chapters 3) and the subsequent Aim 2 (**Validate detected drug effect signals from Aim 1 using traditional pharmacoepidemiology method**) collectively showcase the potential of our approach to generate and prioritize testable hypotheses at scale in pregnancy pharmacology research. This foundational method opens avenues for investigating various adverse pregnancy outcomes, including gestational diabetes, gestational hypertension, and preeclampsia. Aim 1 advances our overall goal of **leveraging RWD EHR to address knowledge gaps in treating pregnant women,** as we discovered drug effect signals at scale associated with adverse pregnancy outcomes.

Chapter 4. **AIM 2** VALIDATE DETECTED DRUG EFFECT SIGNALS USING TRADITIONAL PHARMACOEPIDEMIOLOGY METHOD

This chapter expands upon the manuscript[12] titled "Timing of selective serotonin reuptake inhibitor use and risk of preterm birth and related adverse events". This manuscript is uploaded to Medrxiv and currently under review in *the Journal of Maternal-Fetal Neonatal Medicine* (as of December 15, 2023). Text from manuscripts under review is italicized as is in quotation marks and any figures/tables from the submitted manuscript are marked as well.

4.0 INTRODUCTION

In the preceding chapter (Aim 1), we employed **a data-driven approach to EHR to detect drug effect signals associated with changes in the risk of PTB,** thereby advancing our overall goal **to leverage RWD from EHR to address knowledge gaps in treating pregnant women**. We were able to generate and prioritize interesting drug effect signals for further evaluation. From these signals, including those related to sertraline, acyclovir, and ferrous sulfate, we selected sertraline for further investigation in Aim 2. The signal associated with prenatal exposure to sertraline stood out as one of the most likely to be associated with PTB, due to its large sample size and well-documented indication diagnosis, albeit with controversial findings in prior studies.

In this chapter (Aim 2), we address our overall goal **to leverage RWD from EHR to address knowledge gaps in treating pregnant women** by **assessing the influence of the timing of SSRI on the risk of PTB, small for gestational age (SGA), and low birth weight (LBW)**. We distinguished the timing of SSRI exposure based on exposure status after the first trimester. Our assessment considered factors such as "*the influence of COVID-19 pandemic period, prenatal depressive symptoms, other classes of antidepressants, and misclassification of prescription records. We also conducted SSRI drug-specific analyses and additional analyses on the other classes of antidepressants (N06AA, N06AX).*"

4.1 Motivation

4.1.1 *Background, literature review, and significance*

"Depression is one of the most common comorbidities women experience during pregnancy or the postpartum period, occurring at a rate of 10-20% in the US from 2004 to 2012.[140] *In addition, the risk of maternal depression has significant increased during the COVID-19 pandemic period*[141]*and common symptoms of long COVID include depression.*[142] *Between 2004 and 2008, 8% of pregnant women took antidepressants.*[6,143–145] *As the rate of maternal depression has increased and some studies*[146,147] *suggest potential reduced risk of COVID-19 severity associated with SSRIs and SNRIs, we suspect more prevalent use of antidepressants among pregnant patients. Despite the high prevalence of prenatal antidepressant use, its safety during pregnancy is not fully understood. There is little agreement on the association between antidepressants and preterm birth (PTB; birth prior to 37 weeks of gestation). PTB is a key contributor to perinatal morbidity and mortality in developed and developing countries and occurs in 10% of all live births in the US.*[110,148] *"*

"*Although studies of varying size and design have reported results supporting the association between antidepressant use and PTB risk,*[144,149–153] *findings have been inconsistent, and inadequate control for underlying depression has raised concerns of potential confounding-by-indication.*[154,155] *Additionally, PTB risk may be influenced by the timing of antidepressant exposure.*[144,149,150,156,157] *Further, uncertainty around the safety of prenatal antidepressant use* *potentially contributed to high discontinuation rate(75%) before the second trimester of pregnancy.*[144] *SSRIs are the most commonly used class of antidepressants.*[144,150]*"*

4.1.2 *Objective*

"This study aims to evaluate the risk of PTB and other relevant adverse outcomes, low birthweight (LBW) and small for gestational age (SGA) infants, following SSRI use during the second or third trimester of pregnancy. To minimize confounding-by-indication, we conducted the study among women with depression onset before the pregnancy. We comprehensively addressed the influences of confounding factors, including not only pregnancy characteristics and comorbidities but also environmental factors based on the geographical region the patient resides. We characterized the influence of timing of SSRI intake by distinguishing SSRI exposure groups based on exposure status after the first trimester. We performed multiple sensitivity analyses to assess influence of COVID-19 pandemic, prenatal depressive symptoms, other classes of antidepressants, and misclassification of prescription records. We also conducted SSRI drug-specific analyses and additional analyses on the other classes of antidepressants."

4.2 METHODS

4.2.1 *Study setting and study population*

"We conducted a retrospective study among women who delivered between 2013/01/01 and 2022/12/31 (n=543,408) at Providence St. Joseph Health (PSJH) across Alaska, California, Montana, Oregon, and Washington. Figure 4.1 shows the study population selection. We selected mothers who were continuously enrolled from 180 days before the last menstrual period (LMP) to the date of delivery. We confirmed the date of delivery was at least 20 weeks apart from the LMP and 'living' delivery status of the baby. We limited our cohort to singleton

pregnancies. From this source population (n=365,075), women with depression onset before pregnancy were selected to avoid confounding-by-indication (n=8816). We first identified women diagnosed with depression any time before the pregnancy. From this population of women with a history of depression, we selected women with a diagnosis of depression or any antidepressant prescription order during the six-month pre-pregnancy period (LMP-180 days~LMP). Women with bupropion or trazodone prescriptions and no other antidepressants were excluded unless they had a diagnosis of depression because these are often prescribed for smoking cessation or insomnia.[158,159] *We excluded women with a diagnosis of psychosis or bipolar disorder during the two-year pre-pregnancy period (LMP-730 days~LMP) and fetal sex of 'other' category. The final analytic population consisted of 8406 women."*

4.2.2 *Measures*

4.2.2.1 Outcome

"Our primary outcome was PTB, determined by gestational age at birth (GA; GA<37 weeks). Gestational age at birth (GA) was a proxy outcome of PTB, calculated based on the expected date of delivery and actual delivery date. Secondary outcomes were LBW (birthweight < 2,500g) and SGA (birthweight < 10th percentile of the same gestational age)."

4.2.2.2 Exposure

"The main exposure of interest was SSRI exposure after the first trimester (GA≥13 weeks). The secondary exposure of interest was SSRI exposure only in the first trimester (Figure 4.2 and Figure A.4 1). Study participants were divided into three groups based on SSRI exposure status during pregnancy. The control group (no SSRI exposure) was women with no SSRI

prescribed during the pregnancy. The late SSRI exposure group was women who had any SSRI order after the first trimester. The early-only exposure group was of women with SSRI orders only in the first trimester."

4.2.2.3 Covariate

"We extracted information on maternal characteristics, pre-pregnancy/prenatal mental health conditions, and pre-pregnancy comorbidities from the EHR (Table A.4 1 and Table A.4 2). Pregnancy and maternal characteristics were collected during prenatal care or at the time of delivery. These included parity, preterm history, delivery year, fetal sex, age, race, ethnicity, insurance, pregravid body mass index (BMI) category, smoking status, illegal drug use status, ethanol consumption status, and Centers for Disease Control and Prevention social vulnerability index (CDC-SVI). CDC-SVI represents percentile ranking of each census tract on 15 social factors. Social factors themes include socioeconomic status, household composition, race/ethnicity/language, and housing/transportation.[160] *Pre-pregnancy mental health conditions were determined based on prescription orders (Table A.4 1 and Table A.4 3), clinical diagnoses (Table A.4 2), and Patient Health Questionnaire-9 (PHQ-9) scores.*[161,162] *We collected pre-pregnancy exposure status of N06AA, N06AB (SSRI), N06AF, N06AG, and N06AX during the six months prior to the pregnancy. We extracted diagnoses of adjustment disorders and anxiety disorders from the two-year pre-pregnancy period. Prenatal mental health was determined based on depression diagnosis and Patient Health Questionnaire-4 (PHQ-4) score during late pregnancy.*[163,164] *Other comorbid diagnoses (anemia, asthma, cardiovascular diseases, cystic fibrosis, chronic lung diseases, diabetes, renal diseases, leukemia, pneumonia, sepsis, and sickle cell diseases) were included when active during the two-year pre-pregnancy period (Table A.4 1 and Table A.4 2)."*

4.2.3 *Statistical analysis*

4.2.3.1 Descriptive statistics

"We calculated prevalence rate of maternal depression, use of antidepressant, and use of SSRI from 2013 to 2022 (Figure 4.3). We also compared these rates of the pandemic (2020-03-06~2022-12-31) and control period (2017-03-06~2019-12-31). Descriptive statistics for maternal characteristics, outcomes, covariates, prenatal mental health conditions are presented by exposure group (Table A.4 4). We examined the distribution of covariates across exposure groups (no, early-only, late SSRI) and outcome groups (PTB and non-PTB). We used chi-squared test for categorical variables. For continuous variables, we used one-way ANOVA test and Welch's t-test. Multiple testing was corrected using Benjamin-Hochberg method (Table A.4 4 and Table A.4 5)."

4.2.3.2 Main analysis

"We used propensity score adjusted log-binomial and linear regression to calculate the odds ratio (OR) of PTB, LBW, and SGA, and the difference in the mean of GA corresponding to exposure to SSRIs. We applied multivariable imputation for missing values. For each comparison, we selected the treatment group and calculated the propensity score using logistic regression. Covariates of the main model included pregnancy and maternal characteristics, pre-pregnancy mental health conditions, and pre-pregnancy comorbid conditions as defined above."

"We compared the late SSRI exposure group to the non-late, early-only, and no SSRI exposure group (Figure A.4 1 Flow diagram of exposure group selection*). We compared the early-only SSRI group to the no SSRI exposure group. Additionally, any SSRI exposure group*

was compared with the no SSRI exposure group. These associations were further assessed as follows."

"First, we subdivided the late SSRI exposure group into late-only and both SSRI exposure groups to evaluate the effect of late-only SSRI exposure. Both SSRI exposure groups consisted of women who had SSRI orders during and after the first trimester. Late-only SSRI exposure group consisted of women who had an SSRI order only after the first trimester. Second, drug-specific analyses were conducted on individual SSRI medications: citalopram, escitalopram, fluoxetine, paroxetine, sertraline and fluvoxamine."

4.2.3.3 Sensitivity analysis

"First, we evaluated the impact of COVID-19 pandemic period (n=3217). We assumed COVID-19 pandemic related changes, including reduced social interaction, would significantly influence both exposure and outcome. Second, the influence of late SSRI exposure was evaluated among women who had depression diagnoses during late pregnancy (n=5368)." This approach was adopted to partially adjust for the prenatal depression severity. Our goal was to investigate the association between late SSRI exposure and the risk of PTB within the subpopulation of patient experiencing severe depressive symptoms. We assumed women with severe prenatal depression symptoms were more likely to have recorded encounters associated with depression during second or third trimester. *"Third, we assessed the impact of pre-pregnancy depression severity on a subsample of women who completed the PHQ-9 during the two-year pre-pregnancy period (n=3532). Similarly, we assessed the impact of the prenatal depression severity using the Patient Health Questionnaire-4 (PHQ-4) score (n=3515). Fifth, we conducted an analysis by excluding women who were exposed to other categories of antidepressants (n=6603). Finally,*

we restricted analysis to women with more than one prescription during pregnancy (n=5986).” This was done to partially reduce the bias resulting from misclassification of exposure.

4.2.3.4 Additional analysis

“In addition, we examined the effect of other antidepressants (N06AA, N06AG, N06AF, N06AX) exposure on PTB, SGA, and LBW (Table A.4 1, Table A.4 2, and Table A.4 3). This approach was to further distinguish associations resulting from SSRI and other antidepressant exposures.”

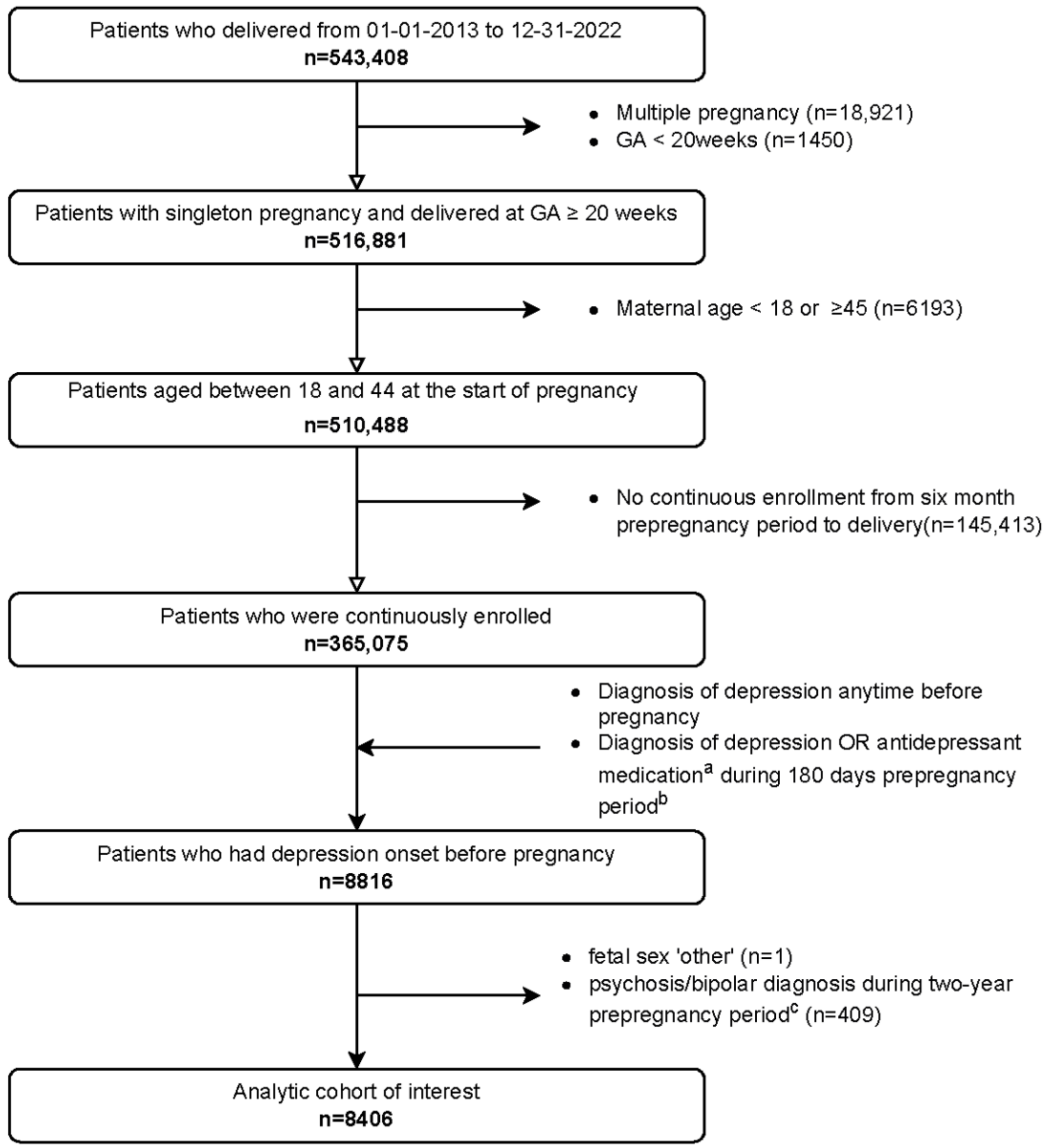


Figure 4.1 Analytic cohort selection flow chart[12]

Abbreviations: EHR, Electronic Health Record; LMP, Last Menstrual Period - the start of the pregnancy; PSJH, Providence St. Joseph Hospital. (a) women with only bupropion or trazodone order were excluded. (b) 6-month pre-pregnancy period is the time frame between 180 days before the LMP to LMP. (c) two-year pre-pregnancy period is the time frame between 730 days before the LMP to LMP. Inclusion criteria are indicated with arrows toward the flow arrow. Exclusion criteria are indicated with arrows away from the flow arrow.

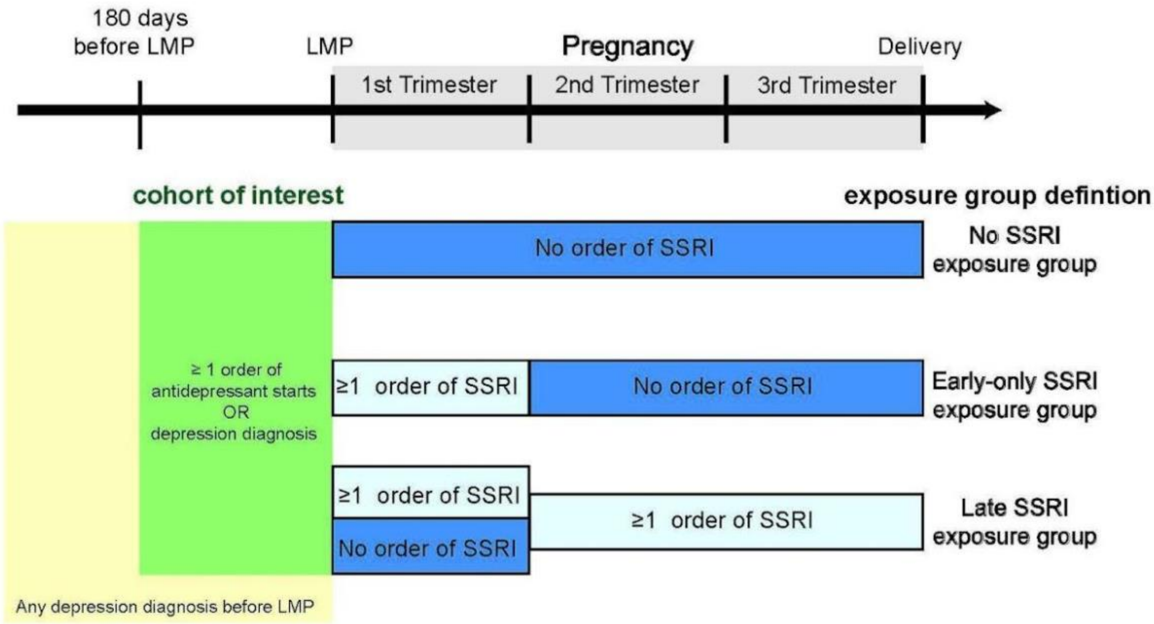


Figure 4.2 Study design[12]

Abbreviations: LMP, Last Menstrual Period; SSRI, Selective Serotonin Reuptake Inhibitor; Depressed cohort is subdivided into no, early-only, and late SSRI exposure groups. No SSRI exposure group has no order of SSRI during pregnancy. Early-only SSRI exposure group has SSRI order only at the first trimester, but none at the second or third trimester. Late SSRI exposure group has any order during the second or third trimester.

4.3 RESULTS

4.3.1 *Descriptive statistics*

"Figure 4.3 shows the trend in prevalence rate of maternal depression and prenatal use of SSRIs from 2013 to 2022. There were 50.3% and 40.3% increase in prenatal depression and SSRI prescriptions during the COVID-19 pandemic period. Table A.4 4 presents the descriptive statistics of covariates, outcomes, and maternal mental health. Of 365,075 women, 8406 women were eligible as our cohort of interest (Study Participants, Figure 4.1). The study cohort was divided into three groups (Figure 4.2 and Figure A.4 1): 3760 women in the no SSRI exposure group, 887 women in early-only SSRI exposure group, and 3759 women in late SSRI exposure

group. Among these three exposure groups, the late SSRI exposure group had the highest rate of PTB (11.7%), the no SSRI exposure had a rate of 9.1%, and the early-only SSRI exposure group had the lowest PTB prevalence rate (7.0%). Among the subpopulation with pre-pregnancy PHQ-9 score (n=3532), PHQ-9 score was not significantly different across outcome groups (P=0.8,Table A.4 4 and Table A.4 5)"

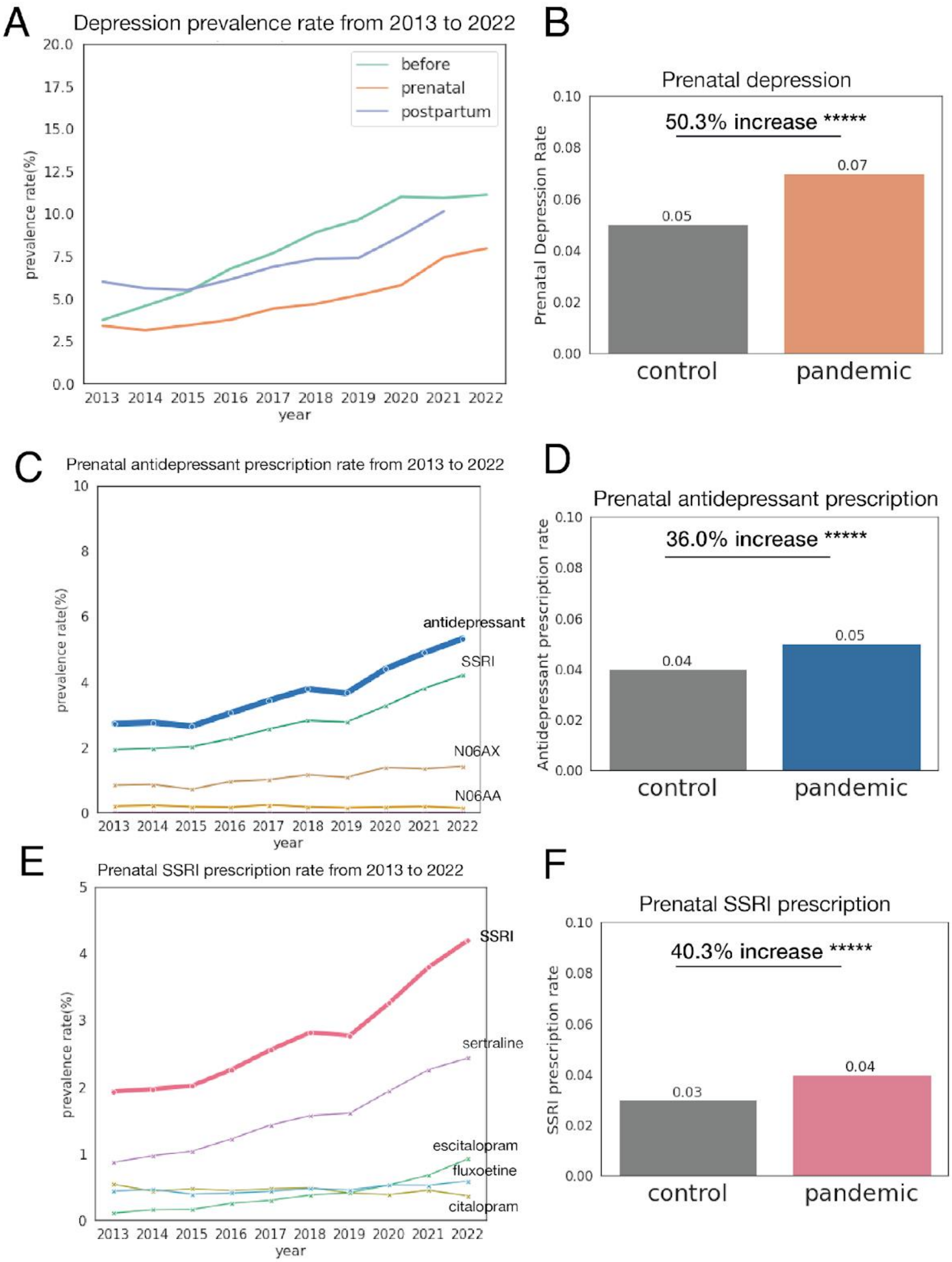


Figure 4.3 Increase in rate of maternal depression, prenatal antidepressant prescription, and prenatal SSRI prescription from 2013 to 2022[12]

Figure 4.3 Increase in rate of maternal depression prenatal antidepressant prescription, and prenatal SSRI prescription from 2013 to 2022[12] (continued);

(A) Maternal depression rate from 2013 to 2022. Green line indicates prevalence rate of women who had depression diagnosis before the start of the pregnancy. Orange line indicates prevalence rate of prenatal depression. Blue line indicates prevalence of postpartum depression. As the definition of postpartum depression indicates depression upto one-year postpartum period, we did not evaluate the rate of postpartum depression of patients who delivered in 2022.

(B) Comparison of prenatal depression rate in control period (2017-03-06~2019-12-31) and pandemic period (2020-03-06~2022-12-31). There was 50.3% increase in prenatal depression rate during pandemic period.

(C) Prenatal antidepressant prescription rate from 2013 to 2022. Antidepressant with prescription rate below 0.01% is not displayed. Comparison of prenatal antidepressant prescription rate in control period (2017-03-06~2019-12-31) and pandemic period (2020-03-06~2022-12-31). There was 36.0% increase in prenatal antidepressant prescription rate during pandemic period.

(D) Prenatal SSRI prescription rate from 2013 to 2022. SSRI with prescription rate below 0.01% is not displayed.

*(E) Comparison of prenatal SSRI prescription rate in control period (2017-03-06~2019-12-31) and pandemic period (2020-03-06~2022-12-31). There was 36.0% increase in prenatal SSRI prescription rate during pandemic period.; +: P < 0.1; *: P < 0.05; **: P < 0.01; ***: P < 0.001; ****: P < 0.0001; *****: P < 0.00001*

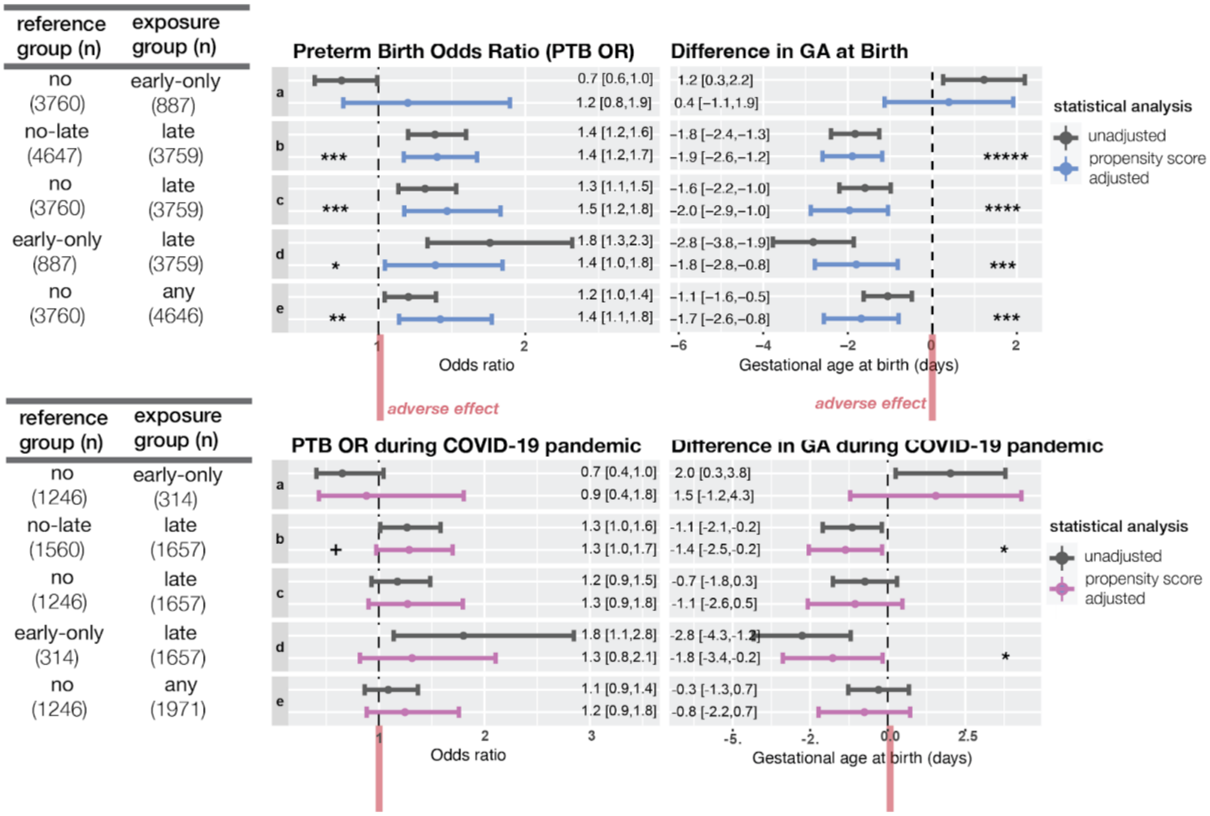


Figure 4.4 Increased risk of preterm birth and decreased gestational days at birth for women exposed to SSRI in second or third trimester[12]

*Abbreviations: CI, Confidence Interval; GA, Gestational Age. The odds ratio of preterm birth and difference in the mean of GA at birth were calculated using log-binomial regression and linear regression adjusting for propensity score (top). Exposure groups were defined as follows. No: women with no SSRI exposure during pregnancy. Early only: women with SSRI exposure only in the first trimester. Late: women with SSRI exposure in the second or third trimester. Any: women with any SSRI exposure during pregnancy (early only + late). No-late: women with no SSRI exposure in the 2nd nor 3rd trimester (no + early only). This increased risk of the late SSRI exposure group were similar among subsample of patients who delivered during COVID-19 pandemic period (bottom). Each comparison (a-e) is defined in the table on the left; +: P < 0.1; *: P < 0.05; **: P < 0.01; ***: P < 0.001; ****: P < 0.0001; *****: P < 0.00001*

4.3.2 *Main analysis*

4.3.2.1 Increased risk of preterm birth and low birthweight for late SSRI exposure

"Late SSRI exposure was associated with elevated risk of PTB and LBW after controlling for confounders (Figure 4.4,Table A.4 6). The odds ratios (OR) of PTB were 1.4 ([1.2,1.7], P<0.0001), 1.5 ([1.2,1.8], P<0.0001) and 1.4 ([1.1,1.9], P<0.05) and those of LBW were 1.6 ([1.3,2.0], P<0.0001), 1.5 ([1.2,2.0], P<0.01), and 1.8 ([1.3,2.7], P<0.01) when comparing late SSRI exposure group with no-late, no, and early-only SSRI exposure groups, respectively. Early-only SSRI exposure was not associated with either PTB (OR=1.2, [0.7,1.9]) and LBW (OR=0.7, [0.4,1.3]). Women exposed to SSRI at any time during pregnancy had 1.4 ([1.1,1.8], P<0.01) fold higher risk of PTB, 1.4 ([1.1,1.9], P<0.01) fold higher risk of LBW than the unexposed to SSRI group (Figure 4.4, Table A.4 6). Most (both SSRI exposure group, n=3328, 88.5%) of the late SSRI exposure group were taking SSRI throughout the pregnancy. The late-only SSRI exposure group (n=431) had similar PTB and LBW risk (PTB OR=1.1 [0.7,1.6]; LBW OR=1.0 [0.6,1.7]) compared with both SSRI exposure group (Table A.4 7)."

4.3.3 *Drug-specific analysis*

"In relation to PTB, drug-specific analyses demonstrated consistent results as the main SSRI analysis and remained statistically significant, except for paroxetine (Table A.4 8). There was increased risk of PTB with early-only exposure to paroxetine (OR=2.7 [1.1,6.8]). In relation to LBW, all drugs showed similar result as the main SSRI analysis."

4.3.4 *Sensitivity analysis*

"The strong and significant association between late SSRI exposure and PTB/LBW persisted throughout sensitivity analyses (Table A.4 9)."

4.4 DISCUSSION

"In this study, we examined the relationship between the timing of prenatal SSRI exposure and three outcomes (PTB, LBW and SGA) among women with a history of depression and adjusted for confounders that have been linked to PTB, including parity, preterm history, maternal mental health, and comorbidities. We found that women prescribed SSRIs in late pregnancy were 1.5 times more likely to deliver preterm when compared to women who were not prescribed SSRIs. Our findings were robust to several sensitivity analyses that accounted for pandemic, depression severity and exposure to other categories of antidepressants."

"Our findings are consistent with several prior observational studies that investigated the timing of prenatal antidepressant or SSRI-specific exposures and PTB.[144,149–153] *A systematic review and meta-analysis conducted on 41 observational studies reported that second and third trimester antidepressant exposure increased the risk of PTB*[149]*; and of which, 22 (53.6%) of studies examined SSRI exposure. A retrospective study on a similar-sized, singleton pregnancy cohort covered by Tennessee Medicaid also suggested an association between second trimester antidepressant (SSRI or non-SSRI antidepressant) exposure and PTB, but not with first trimester exposures.*[144]*"*

"In contrast with our study, some studies reported an elevated risk for PTB for first trimester SSRI or antidepressant (non-SSRI antidepressant) exposures.[150,156,157] *However, the first trimester exposure in these studies included women who continued the use throughout the pregnancy. Thus, the gestational timing of SSRI exposure on PTB risk cannot be determined in these studies. A population-based cohort study conducted in Finland reported lower risk of PTB for women who purchased SSRIs during pregnancy; the risk of PTB was 16% lower even when accounting for the underlying condition.*[165] *However, they compared women exposed to SSRI to*

unexposed ones with psychiatric diagnosis during the pregnancy. Our study compared only those participants experiencing depression before the pregnancy."

"Surprisingly, pre-pregnancy depression severity did not appear to be relevant to the risk of PTB, based on PHQ-9 score. These outcomes are contrary to earlier studies suggesting preconception stress and mental health correlation to PTB.[132,154,166] *However, we restricted our study to include participants with depression onset prior to the pregnancy, while those studies do not have such restrictions. Presence of pre-pregnancy depression may be a more significant contributor to PTB than severity of depressive symptoms. One possible explanation for this result is the saturation of maternal stress-induced response. Maternal stress may induce a response, such as hypothalamic-pituitary adrenal (HPA) axis dysfunction*[167,168] *or inflammatory immune response*[169] *which activates a mechanism leading to PTB but this response saturates and plateaus once stress hits the level of depression. In other words, once the patient has a depression the negative impact on risk of PTB does not proportionally increase based on the severity of depressive symptoms*."

"In this study, we minimized confounding-by-indication by analyzing women with depression onset prior to pregnancy. All study participants had a history of depression and had indication of depressive symptoms within the 6-month pre-pregnancy period. We analyzed a large sample to provide sufficient statistical power to examine PTB, SGA, and LBW. This allowed observation of statistically significant results in subgroup analyses and sensitivity analyses."

"We applied rigorous sensitivity analyses to test the robustness of associations observed in the main analysis. We accounted for the COVID-19 Pandemic period, depression severities before and during the pregnancy and exposure to antidepressant polytherapy. Many prior

studies on the association between SSRI and PTB were limited due to lack of severity data.[144,153,156,170–174]*"*

"We included the CDC social vulnerability index as a covariate. CDC uses US Census data to calculate social vulnerability of each census tract, a subdivision of counties.[160] *This index allows us to account for social disparity based on the location of residence. To our knowledge, this is the first study that accounted for the social vulnerability when assessing the impact of SSRIs on the risk of adverse pregnancy outcomes."*

"Additionally, we assessed SSRI drug-specific associations and N06AA/N06AX associations with PTB, SGA, and LBW. This helps us understand the magnitude of individual drug association with PTB, SGA, and LBW and to discern the contributions of other antidepressants (N06AA/N06AX)."

"A potential weakness of this study was the potential misclassification of exposures. Prescription orders do not necessarily indicate actual exposures. Non-differential misclassification of exposure biases toward the null, which could potentially attenuate the strength of the association. This is an inherent limitation of EHR, however we assessed the impact of misclassification of exposure in sensitivity analysis."

"Depression severity assessments, PHQ-9 and PHQ-4 were not administered to all pregnant women. Although we were able to perform sensitivity analyses on a subpopulation of people who took the assessments, we had an insufficient number of samples to perform stratified analyses based on the depression severity. SSRIs may have differential effects on women with more severe depressive symptoms.[175,176] *Going forward, stratified analysis based on pre-pregnancy and prenatal depression severity should be conducted to further evaluate the impact of SSRI on PTB."*

4.5 CONCLUSION

In Aim 2 (**Validate detected drug effect signals from Aim 1 using traditional pharmacoepidemiology method**), we explored the association between exposure to sertraline and/or SSRI and an increased risk of PTB. Our hypothesis was that there is an elevated likelihood of delivering preterm for patients exposed to SSRI after the first trimester and our objective was to assess this association. "*Among women with depression onset before pregnancy, SSRI exposure after the first trimester was associated with an increased risk for preterm birth and low birthweight. Although our findings suggest an association between SSRI exposure after the first trimester of pregnancy and risk of PTB and LBW, depression should not be left untreated during the pregnancy. Untreated depression increases the chance of adverse pregnancy outcomes and high-risk health behaviors*[177,178]*. Both patients and physicians should be informed on both the risk and benefit of medication treatment during pregnancy to make optimal patient-specific decisions given the patient's health conditions.*"

Aim 1 and 2 (Chapters 3 and 4) collectively advance our overall goal **to leverage RWD, particularly EHR, to address knowledge gaps in treating pregnant women**. These aims demonstrate a powerful and streamlined process to detect and validate drug effect signals associated with the risk of PTB. Together, Aim 1 and Aim 2 suggest the potential of our approach to generate and prioritize testable hypotheses at scale in pregnancy, laying the foundation for other adverse pregnancy outcomes, including gestational diabetes, gestational hypertension, and preeclampsia.

While our study offers valuable insights, it is essential to acknowledge certain limitations that may impact the interpretation of our findings. One notable limitation is the potential for exposure misclassification, as prescription orders may not always precisely reflect actual medication exposure. To address this bias, we conducted sensitivity analyses, aiming to understand the impact on our results. Additionally, the study faced a limitation concerning the assessment of depression severity. The use of standardized scoring systems like PHQ-9 and PHQ-4 allowed us to evaluate depression severity, but only a subsample of the study population completed these assessments. Although we performed sensitivity analysis using this subsample, the limited number prevented us from conducting subgroup analyses.

Looking ahead, with a larger sample size, we envision the opportunity to conduct various subgroup analyses. Large sample size would enhance our understanding of the relationship between SSRIs and the risk of PTB. Furthermore, we aim to apply the established workflow from Aim 1 and Aim 2 to explore the association between SSRIs and other pregnancy outcomes. By extending this methodology to different outcomes, we can broaden our understanding of the pharmacological factors influencing diverse aspects of pregnancy.

In Aim 3 (**Investigate medical interventions targeting pregnant women using electronic health records)**, we took a different approach. Instead of generating hypothesis, we selected a controversial and existing hypothesis in clinical practice that had not been previously investigated before. Specifically, we explored the National Institute of Health's antithrombotic therapy recommendation for hospitalized pregnant patients with manifestation of COVID-19. This study is the first to characterize the adoption rate of this guideline and evaluate the impact of prophylactic anticoagulant on this population, **addressing the knowledge gaps in treating pregnant women leveraging EHR**, as referenced in the overall goal.

Chapter 5. **AIM 3** INVESTIGATE MEDICAL INTERVENTIONS TARGETING PREGNANT WOMEN USING ELECTRONIC HEALTH RECORDS

This chapter expands upon on the manuscript published in *JMIR Public Health and Surveillance* 2023;9e45586[13]. The manuscript is titled “Adoption of a National Prophylactic Anticoagulation Guideline for Hospitalized Pregnant Women with COVID-19: Retrospective Cohort Study”. This manuscript was published (and can be reproduced) under the terms of Creative Commons Attribution 4.0 license. Text directly quoted from the published manuscript is italicized and is in quotation marks and any figures/tables from the published manuscript are marked as well.

5.0 INTRODUCTION

In the previous two Aims, we demonstrated a streamlined workflow to detect previously known and unknown drug effect signals and validate detected signals. This forms the foundational framework to advance our overall goal **to leverage RWD, particularly EHR, to address knowledge gaps in treating pregnant women.** In Aim 3 (**Investigate medical interventions targeting pregnant women using electronic health records**), we took a different and complementary approach to narrow the knowledge gap in treating pregnant women. Instead of generating hypothesis, we selected a controversial and existing hypothesis in clinical practice that had not been previously investigated before. Specifically, we explored the National Institute of Health’s antithrombotic therapy recommendation for hospitalized pregnant patients with manifestation of COVID-19.

"Both COVID-19 and pregnancy are associated with hypercoagulability. Due to increased risk for thrombosis, the National Institute of Health's recommendation for prophylactic anticoagulant use for pregnant patients has expanded from patients hospitalized for severe COVID-19 manifestation to all patients hospitalized for the manifestation of COVID-19 (no guideline: ~12-26-2020, first update: 12-27-2020~02-23-2022, second update: 02-24-2022~present). However, no study has evaluated this recommendation." The hypothesis of Aim 3 was that there is a high rate of prophylactic anticoagulant administration among pregnant patients hospitalized with COVID-19. In Aim 3, *"the objective of this study was to characterize prophylactic anticoagulant use among hospitalized pregnant people with COVID-19 from 03-20-2020~10-19-2022."*

5.1 MOTIVATION

5.1.1 *Background, literature review, and significance*

"Both coronavirus disease 2019 (COVID-19) and pregnancy are associated with thrombosis.[179–191] *Severe COVID-19 is accompanied by Virchow's triad of endothelial injury, stasis, and hypercoagulable state: categories of factors contributing to thrombosis.*[179–188] *The related virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), directly invades endothelial cells, leading to endothelial injury, exocytosis, and endotheliitis.*[179–182,186,192,193] *Hospitalization causes stasis of blood flow due to decreased mobility regardless of the presence of the SARS-CoV-2 virus.*[194] *COVID-19-induced changes in prothrombotic factors are linked to an increased risk of hypercoagulability.*[183–185,195–204] *Studies have reported elevated factor VIII, elevated fibrinogen, circulating prothrombotic microparticles, neutrophil extracellular traps, and hyperviscosity among severely ill COVID-19 patients.*[183–185,195–198] *Multiple meta-analyses studies*

report high rates of coagulopathy and thrombosis across multiple tissues and organ sites among COVID-19-infected patients since early in the pandemic.[199–204]*"*

"Hypercoagulability is a physiologically adaptive mechanism that prevents bleeding from miscarriage, childbirth, and postpartum hemorrhage. Women in pregnancy or the postpartum period are at a four to five-fold higher risk of thromboembolism than non-pregnant women.[189–191] *Normal pregnancy is accompanied by increased concentration of factors VII, VIII, X, and von Willebrand factor and by pronounced increases in fibrinogen.*[190,205,206] *Due to the combination of increased risk of hypercoagulability, the National Institute of Health (NIH) COVID-19 Treatment Guideline Panel recommends using a prophylactic dose of anticoagulation for pregnant patients who are hospitalized for COVID-19 unless a contraindication exists, since 02-24-2022.*[207]*"*

"We hypothesized that we would observe a high prophylactic anticoagulant administration rate after the second update in NIH COVID-19 treatment guidelines. As prophylactic anticoagulant was recommended to all hospitalized COVID-19 pregnant patients, we expected a minimal difference in clinical condition between the treatment and control group, leading to minimized confounding by indication. This would allow us to properly evaluate the impact of prophylactic anticoagulants on inpatient COVID-19 pregnant patients. No study yet has evidence for or against the guideline on recommending prophylactic anticoagulants on inpatient COVID-19 pregnant patients.[207]*"*

5.1.2 *Objective*

"Here, we aim to characterize prophylactic anticoagulant use among hospitalized pregnant COVID-19 patients. We assessed the difference in the prophylactic anticoagulant use across the timeline of NIH guideline changes and SARS-CoV-2 variants. We evaluated the association

between prophylactic anticoagulant use and risks of coagulopathy, COVID-19, and maternal-fetal health outcomes, after addressing the discrepancy in variables that could influence outcomes."

5.2 METHODS

5.2.1 *Study setting and population*

"Providence St. Joseph Health (PSJH) is an integrated not-for-profit US community healthcare system that provides care in urban and rural settings across seven states: Alaska, California, Montana, Oregon, New Mexico, Texas, and Washington. PSJH service includes 52 hospitals, 1,085 clinics, and 120,000 caregivers. We used PSJH electronic health records (EHR) of pregnant patients who delivered from 01-26-2020 through 10-19-2022(n=149,423). Figure 5.1 and Figure A.5 1 describe the cohort selection. Table S1 defines variables and terminology. We excluded multiple pregnancies, and deliveries with gestational age (GA) of less than 20 weeks (n=126,261). We limited our analyses to pregnant patients aged between 18 and 45 (n=144,114). Our inclusion criterion was COVID-19 diagnosis during the pregnancy period (n=9,271). We excluded patients who were not hospitalized with COVID-19 (n=2,829). The definition of this exclusion criterion was no overlap of hospitalization stay with an infection period, -7~+14 days from the COVID-19 diagnosis date. This infection period determined based on prior studies on incubation and symptomatic period. We excluded patients with any coagulopathy event prior to COVID-19 diagnosis, contraindication to anticoagulant administration, or a record of therapeutic anticoagulant dosage[208] *in the past two years (Table A.5 2, Table A.5 3, and Table A.5 4). We defined the remaining patients as our cohort of interest, relevant to the NIH antithrombotic therapy guideline (n=2,767). This study was reported following STROBE guidelines.*[209]*"*

5.2.2 *Variable*

5.2.2.1 Exposure

"Figure 5.1 and Figure A.5 1 describe definitions of exposure groups. From the cohort of interest (n=2,767), patients with no anticoagulant administration record during pregnancy or within -14~+60 days from the SARS-CoV-2 infection date comprised the control group (no anticoagulant administration group, n=2,534). We defined the treatment group (prophylactic anticoagulant administration group, n=191) as patients who received prophylactic anticoagulation from -2~+14 days from the potential COVID-19 treatment onset (Figure A.5 1,Table A.5 1, Table A.5 3, and Table A.5 4). Our definition of prophylactic included prophylactic and intermediate dosages (Table A.5 4).[208] *"*

5.2.2.2 Outcome

"Variables and diagnoses are defined in Table A.5 1 and Table A.5 2. Our primary outcome of interest was coagulopathy. We additionally observed diagnoses relevant to the consequences of COVID-19-associated coagulopathy.[186,210,211] *These included thrombosis, pulmonary embolism, thromboembolism, myocardial infarction, skin necrosis/purpura, and stroke (Table A.5 1). Secondary outcomes were COVID-19 severity and maternal-fetal health outcomes. COVID-19 complications included need for supplemental oxygen, vasopressor usage, mortality, length of hospital stay, unique diagnosis count, and unique medication count. Maternal-fetal outcomes were stillbirth, preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA). We also assessed the risk of bleeding during pregnancy and postpartum hemorrhage to evaluate the safety of anticoagulant use."*

5.2.2.3 Covariate

*"Maternal characteristics were evaluated including parity, gravidity, history of preterm delivery, age, race, ethnicity, insurance, pregravid body mass index (BMI), smoking, illegal drug use, Centers for Disease Control and Prevention social vulnerability index (CDC-SVI), and rural-urban classification (Table A.5 1). The count of unique diagnoses before COVID-19 was used to reflect the patient's prior comorbidity, and missing values were imputed using the cohort median for that feature. COVID-19-related features assessed were vaccination, prior SARS-CoV-2 infection, SARS-CoV-2 variant, timing of SARS-CoV-2 infection, and stage of NIH COVID-19 antithrombotic therapy guidelines (*Table A.5 1 *and Table A.5 5). We defined stages of guidelines based on major updates in NIH antithrombotic therapy guidelines on pregnant women.*[207] *Up until 12-20-2020, there was no specific guideline for pregnant women. On 12-21-2020, there was an update to recommend the prophylactic use of anticoagulants among pregnant patients with severe COVID-19. On 02-24-2022, a second update expanded the recommendation to any hospitalized patient with COVID-19."*

5.2.3 *Analysis*

5.2.3.1 Descriptive statistics

"Descriptive statistics of covariates by exposure group are in Table 5.1. Table 5.1 was generated using tableone PyPI package. P-value was calculated using the Chi-squared test, and the Two-sample t-test. Multiple testing error was corrected using Bonferroni correction. We performed pairwise Pearson Correlation between variables using python library scipy (version 1.6.2). We ranked the count of diagnoses each exposure group received between COVID-19 diagnosis and delivery."

5.2.3.2 Classification model, feature importance, and propensity score matching

*"We conducted classification model and feature importance to partially understand the potential difference between the treatment and control groups and select variables to be addressed in propensity score matching. Using 28 covariates (Table A.5 1) we built classification models, including logistic regression (LR), random forest (RF), and gradient boosting machine (GB) models (*Method A.5 2*). We applied random undersampling to address a class imbalance between the control and treatment groups. Due to the small sample size, we leveraged leave-one-out cross-validation (LOOCV). We then used Gini feature importance and SHAP*[212] *to identify which covariates were most important for classifying the administration of prophylactic anticoagulant during a COVID-19-related hospitalization in the best performing model (*Method A.5 2*). We evaluated whether the model trained with these top features achieved comparable performance to the original model with 28 features. We then performed propensity score matching to control for these top features between treatment and control groups. Compared to other propensity score methods and covariate adjustment methods, propensity score matching provided exceptional covariant balance across most circumstances.*[130] *k-nearest neighbors (k=1) was used to match with replacement across covariates using propensity logit and caliper of 0.2 using Python library PsmPy (version 0.2.8) to identify patients most similar on the top features and generate a matched control group.*[213] *Number of neighbors(k) and caliper threshold value were selected based on recommendations from prior studies.*[131,214] *Effect size of these matched features was evaluated using Cohen D's score before and after matching with a score of <.2 indicates a small effect size.*[215] *We evaluated outcome differences between the treatment and matched control groups using Fisher's exact test for categorical variables and Mann-*Whitney *U-test for continuous variables."*

5.2.3.3 Sensitivity analysis

"We assessed the influence of illness severity at the time of SARS-CoV-2 infection using the count of medication during the -3~+3 days period from the potential COVID-19 treatment onset. The date range for collecting the medication count was selected based on the distribution of the time gap between the anticoagulant administration date and the COVID-19 treatment onset date (Figure A.5 3). We conducted propensity score matching on this medication count at the time of SARS-CoV-2 infection, in addition to best-performing features. We also addressed the influence of maternal age and pregravid BMI, as these variables are known risk factors for coagulopathy."

5.2.3.4 Investigation of inpatient anticoagulant administration rate across multiple healthcare system using Truveta

"We calculated the rate of the inpatient anticoagulant administration rate in the Truveta patient population (Figure A.5 2). Truveta is a consortium of 28 healthcare systems, including PSJH, providing patient care in over 20,000 clinics and 700 hospitals across 43 states.[216] *Similar data fields across systems are mapped following the common schema referred to as the Truveta Data Model (TDM).*[217] *Among pregnant patients aged between 18 and 45 and delivered singleton from 01-26-2020 through 10-19-2022, we identified patients with COVID-19 diagnosis during pregnancy. We excluded patients who did not have any inpatient encounters during the active COVID-19 infection. We further excluded patients who had any anticoagulant use before pregnancy and defined the remaining patients as our Truveta cohort of interest, relevant to NIH antithrombotic therapy guidelines. From this analytic cohort, we calculated patients who were administered inpatient anticoagulants."*

5.3 RESULTS

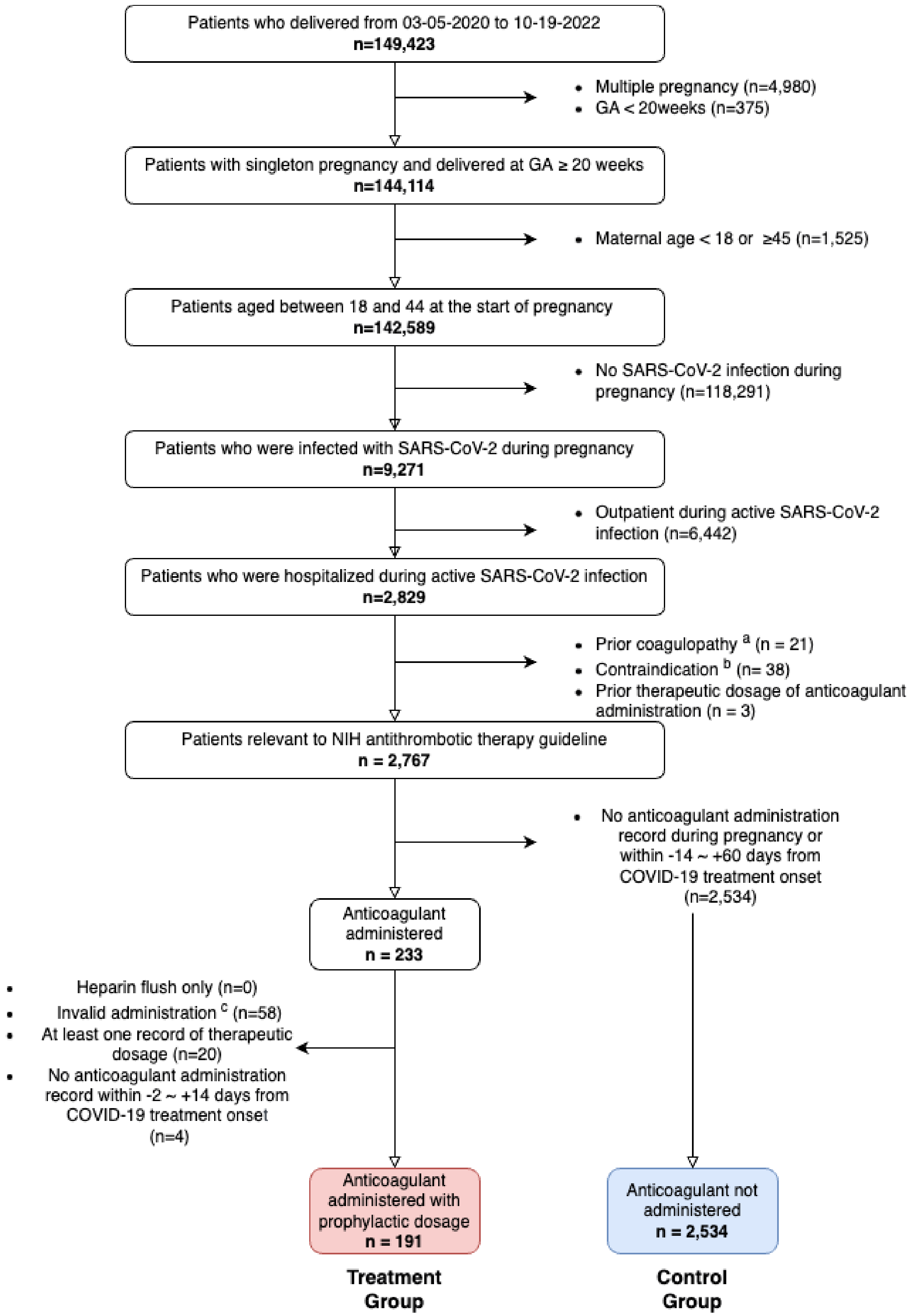


Figure 5.1 Analytic cohort selection flow chart[13]

Figure 5.1 Analytic cohort selection flow chart (continued); GA Gestational Age (a) We excluded patients with any history of coagulopathy before the time of SARS-CoV-2 infection. (b) We excluded patients with any contradiction to anticoagulant if the diagnosis was between two years prior to the pregnancy and the time of SARS-CoV-2 infection. Contraindications included major bleeding, peptic ulcer, stage 2 hypertension, esophageal varices, intracranial mass, end-stage liver diseases, aneurysm, proliferative retinopathy, and bleeding disorders. (c) We considered administration to be invalid if the administration status were either 'Canceled Entry', 'Held', 'Missed', 'Automatically Held', 'Held by Provider', 'MAR Hold', 'Stopped', 'Paused'

"Total of 2,767 patients composed our cohort of interest (Table 5.1). 191 and 2,534 patients were in the treatment and control groups respectively. The treatment group was older (mean age: 30.9; P<.05), less likely to be vaccinated (17.3%, P<.001), less likely to be infected during the third trimester (72.8%, P<.001), and more likely to be infected with Delta variant (42.4%, P<.001). The treatment group was exposed to enoxaparin and heparin only (Table 5.1). Date difference between anticoagulant administration date and potential COVID-19 treatment onset ranged from -2~14 days. 75% of the treatment group received anticoagulant prescriptions during the first three days of COVID-19 treatment (Figure A.5 3)."

Table 5.1 Descriptive statistics of treatment and control group[13]

Variables are defined in Table A.5 1. Table 5.1 was generated using tableone PyPI package. P-value was calculated using the Chi-squared test, and the Two-sample t-test. Multiple testing error was corrected using Bonferroni correction

		Missing	***Overall (n=2,736)***	***Control Group (n=2,545)***	***Treatment Group (n=191)***	***P-Value (adjusted)***
Maternal age (years), mean (SD)		*0*	*29.7 (5.7)*	*29.6 (5.7)*	*30.9 (5.3)*	*0.02*
Maternal age group (years), n(%)		*0*	*2736 (100.0)*	*2545 (100.0)*	*191 (100.0)*	*0.01*
	18 ~ 24		*647 (23.6)*	*619 (24.3)*	*28 (14.7)*	
	25 ~ 29		*758 (27.7)*	*713 (28.0)*	*45 (23.6)*	
	30 ~ 34		*797 (29.1)*	*718 (28.2)*	*79 (41.4)*	
	35 ~ 40		*435 (15.9)*	*402 (15.8)*	*33 (17.3)*	
	41 ~ 44		*99 (3.6)*	*93 (3.7)*	*6 (3.1)*	
	Unknown		*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	
Race group, n (%)		*0*	*2736 (100.0)*	*2545 (100.0)*	*191 (100.0)*	*0.02*
	American Indian or Alaska Native		*45 (1.6)*	*42 (1.7)*	*3 (1.6)*	
	Asian		*166 (6.1)*	*146 (5.7)*	*20 (10.5)*	
	Black or African American		*126 (4.6)*	*111 (4.4)*	*15 (7.9)*	
	Native Hawaiian or Other Pacific Islander		*46 (1.7)*	*38 (1.5)*	*8 (4.2)*	
	White or Caucasian		*1466 (53.6)*	*1381 (54.3)*	*85 (44.5)*	
	Multiracial		*150 (5.5)*	*138 (5.4)*	*12 (6.3)*	
	Other		*620 (22.7)*	*580 (22.8)*	*40 (20.9)*	
	Unknown		*117 (4.3)*	*109 (4.3)*	*8 (4.2)*	
Ethnic group, n (%)		*0*	*2736 (100.0)*	*2545 (100.0)*	*191 (100.0)*	*0.74*
	Hispanic or Latino	*0*	*1077 (39.4)*	*1013 (39.8)*	*64 (33.5)*	
	Not Hispanic or Latino		*1567 (57.3)*	*1444 (56.7)*	*123 (64.4)*	
	Unknown		*92 (3.4)*	*88 (3.5)*	*4 (2.1)*	
Pregravid BMI, n (%)		*1888*	*848 (100.0)*	*792 (100.0)*	*56 (100.0)*	*0.15*
	Underweight (Below 18.5)		*11 (1.3)*	*11 (1.4)*	*0 (0.0)*	
	Healthy weight (18.5 ~ 24.9)		*326 (38.4)*	*314 (39.6)*	*12 (21.4)*	
	Overweight (25.0 ~ 29.9)		*241 (28.4)*	*224 (28.3)*	*17 (30.4)*	
	Obesity (30.0~)		*270 (31.8)*	*243 (30.7)*	*27 (48.2)*	

Table 5.1. Descriptive statistics of treatment and control group[13](continued)						
		Missing	***Overall (n=2,736)***	***Control Group (n=2,545)***	***Treatment Group (n=191)***	***P-Value (adjusted)***
Gravidity, n (%)		*24*	*2712 (100.0)*	*2521 (100.0)*	*191 (100.0)*	*1.0*
	1 ~ 5		*2529 (93.3)*	*2354 (93.4)*	*175 (91.6)*	
	6 ~		*183 (6.7)*	*167 (6.6)*	*16 (8.4)*	
Parity, n (%)		*24*	*2712 (100.0)*	*2521 (100.0)*	*191 (100.0)*	*1.0*
	0		*381 (14.0)*	*355 (14.1)*	*26 (13.6)*	
	1 ~ 5		*2298 (84.7)*	*2136 (84.7)*	*162 (84.8)*	
	6 ~		*33 (1.2)*	*30 (1.2)*	*3 (1.6)*	
Preterm history, n (%)		*433*	*2303 (100.0)*	*2145 (100.0)*	*158 (100.0)*	*1.0*
	0		*2012 (87.4)*	*1879 (87.6)*	*133 (84.2)*	
	1		*291 (12.6)*	*266 (12.4)*	*25 (15.8)*	
Insurance status, n(%)		*1*	*2736 (100.0)*	*2545 (100.0)*	*191 (100.0)*	*1.0*
	Commercial		*959 (35.1)*	*890 (35.0)*	*69 (36.1)*	
	Medicaid		*1771 (64.8)*	*1649 (64.8)*	*122 (63.9)*	
	Medicare		*3 (0.1)*	*3 (0.1)*	*0 (0.0)*	
	Uninsured-Self-Pay		*2 (0.1)*	*2 (0.1)*	*0 (0.0)*	
Smoking status, n(%)		*0*	*2736 (100.0)*	*2545 (100.0)*	*191 (100.0)*	*0.49*
	No		*2488 (90.9)*	*2322 (91.2)*	*166 (86.9)*	
	Yes		*248 (9.1)*	*223 (8.8)*	*25 (13.1)*	
Illegal drug use status, n(%)		*0*	*2736 (100.0)*	*2545 (100.0)*	*191 (100.0)*	*1.0*
	No		*2399 (87.7)*	*2226 (87.5)*	*173 (90.6)*	
	Yes		*337 (12.3)*	*319 (12.5)*	*18 (9.4)*	
Rural-urban classification, n(%)		*538*	*2198 (100.0)*	*2029 (100.0)*	*166 (100.0)*	*1.0*
	Metropolitan		*1997 (90.9)*	*1846 (91.0)*	*151 (89.3)*	
	Micropolitan		*129 (5.9)*	*114 (5.6)*	*15 (8.9)*	
	Rural		*31 (1.4)*	*30 (1.5)*	*1 (0.6)*	
	Small Town		*41 (1.9)*	*39 (1.9)*	*2 (1.2)*	
Socioeconomic status vulnerability, mean (SD)		*455*	*0.5 (0.3)*	*0.5 (0.3)*	*0.5 (0.3)*	*1.0*
Household composition and disability vulnerability, mean (SD)		*452*	*0.4 (0.3)*	*0.4 (0.3)*	*0.5 (0.3)*	*1.0*
Minority status and language vulnerability, mean (SD)		*452*	*0.7 (0.3)*	*0.7 (0.3)*	*0.6 (0.2)*	*0.15*
Housing type and transportation vulnerability, mean (SD)		*455*	*0.6 (0.3)*	*0.6 (0.3)*	*0.6 (0.3)*	*1.0*
Vaccination status, n(%)		*0*	*2736 (100.0)*	*2545 (100.0)*	*191 (100.0)*	*<.001*
	No		*1803 (65.9)*	*1645 (64.6)*	*158 (82.7)*	
	Yes		*933 (34.1)*	*900 (35.4)*	*33 (17.3)*	

Table 5.1 Descriptive statistics of treatment and control group[13](continued)						
		Missing	***Overall (n=2,736)***	***Control Group (n=2,545)***	***Treatment Group (n=191)***	***P-Value (adjusted)***
Prior SARS-CoV-2 infection, n (%)		*0*	*2736 (100.0)*	*2545 (100.0)*	*191 (100.0)*	*1.000*
	No		*2690 (98.3)*	*2500 (98.2)*	*190 (99.5)*	
	Yes		*46 (1.7)*	*45 (1.8)*	*1 (0.5)*	
Trimester of SARS-CoV-2 infection, n (%)		*0*	*2736 (100.0)*	*2545 (100.0)*	*191 (100.0)*	*<.001*
	first trimester		*25 (0.9)*	*18 (0.7)*	*7 (3.7)*	
	second trimester		*120 (4.4)*	*75 (2.9)*	*45 (23.6)*	
	third trimester		*2591 (94.7)*	*2452 (96.3)*	*139 (72.8)*	
SARS-CoV-2 variant, n (%)		*0*	*2736 (100.0)*	*2545 (100.0)*	*191 (100.0)*	*<.001*
	Wild Type		*549 (20.1)*	*504 (19.8)*	*45 (23.6)*	
	Alpha		*129 (4.7)*	*111 (4.4)*	*18 (9.4)*	
	Delta		*507 (18.5)*	*426 (16.7)*	*81 (42.4)*	
	Omicron		*1551 (56.7)*	*1504 (59.1)*	*47 (24.6)*	
NIH antithrombotic therapy guideline, n (%)		*0*	*2736 (100.0)*	*2545 (100.0)*	*191 (100.0)*	*<.001*
	No Guideline		*262 (9.6)*	*235 (9.2)*	*27 (14.1)*	
	First Update		*1663 (60.8)*	*1518 (59.6)*	*145 (75.9)*	
	Second Update		*811 (29.6)*	*792 (31.1)*	*19 (9.9)*	
Diagnosis count prior to SARS-CoV-2 infection, mean (SD)		*0*	*1.9 (3.6)*	*1.9 (3.7)*	*2.0 (3.3)*	*1.0*

"Figure 5.2 displays the overall timeline of the prophylactic anticoagulant administration status from 03-20-2020 to 10-19-2022. The overall prevalence rate of prophylactic anticoagulant administration was 7.0%. The administration rate was the lowest when the Omicron variant was dominant (3%) and after the second guideline update (2%). It was the highest when the Delta variant was dominant (16%) and when there was no guideline (10%). The top ten diagnoses of the control group were subcategories of COVID-19 and pregnancy (Figure A.5 4). The treatment group additionally included COVID-19 complications such as pneumonia, acute respiratory failure with hypoxia, and hypokalemia (Figure A.5 4)."

"Figure A.5 2 displays the cohort selection procedure in the Truveta patient population. We identified 14,075 patients as our Truveta cohort of interest. Among these patients, 973 (6.9%) patients were administered inpatient anticoagulants."

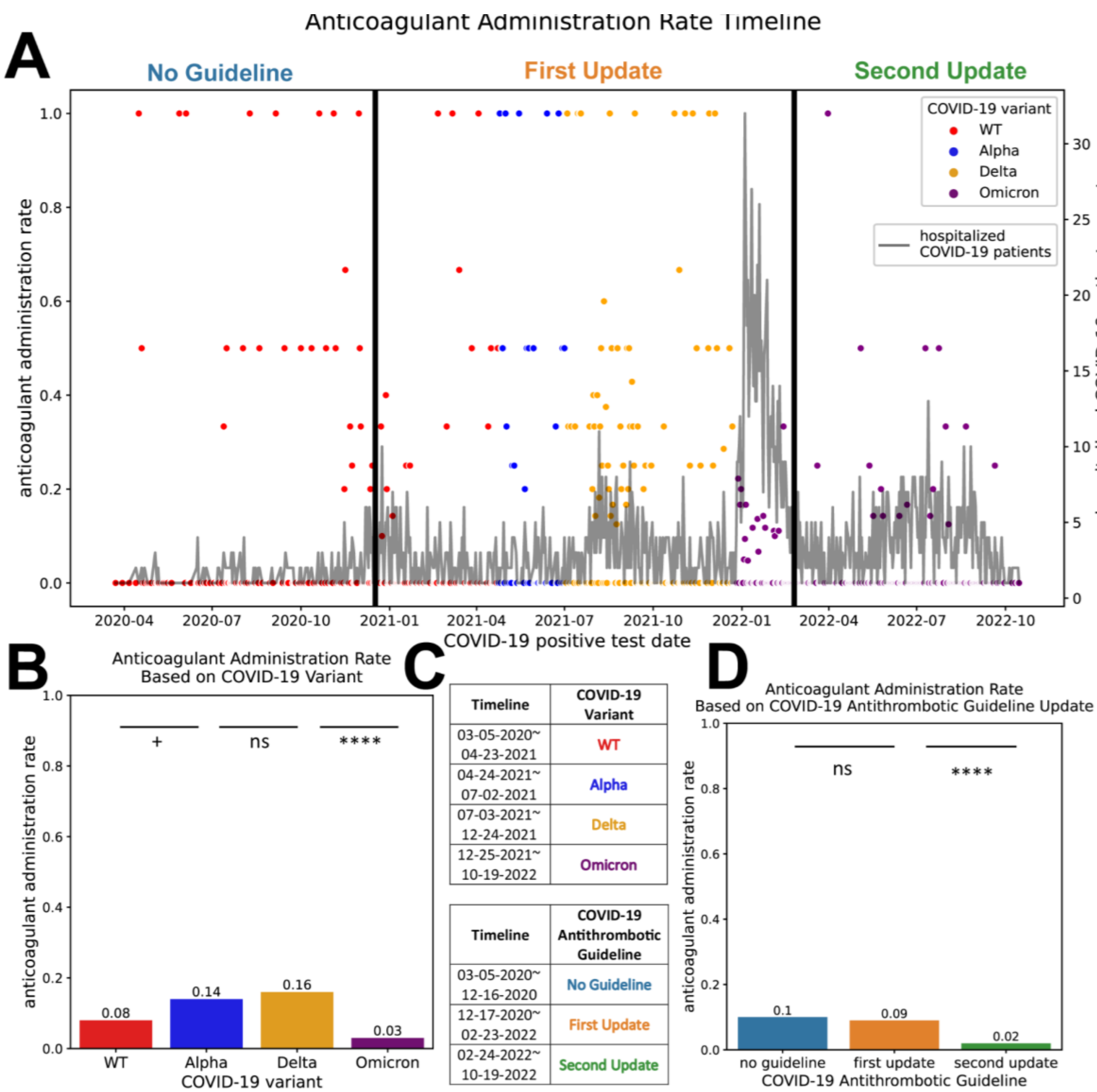


Figure 5.2 Timeline of prophylactic anticoagulant administration among hospitalized COVID-19 pregnant patients from 03-20-2020 to 10-19-2022[13]

*The anticoagulant administration rate is defined as the count of the patients who belong to the treatment group divided by the sum of patients who belong to the treatment group and control group. Statistical significance was represented as follows. ns : P>.05, * : P≤.05, ** : P≤.01, ***: P≤.001, ****: P≤.0001;*

(A) Timeline of prophylactic anticoagulant administration rate among hospitalized COVID-19 pregnant patients from 03-20-2020 to 10-19-2022.

Figure 5.2 Timeline of prophylactic anticoagulant administration among hospitalized COVID-19 pregnant patients from 03-20-2020 to 10-19-2022[13] *(continued); Marked time points are described in* ***C****. Timeline definitions: red, blue, yellow, and purple dots indicate the prophylactic anticoagulant administration rate among COVID-19 wild type, Alpha, Delta, and Omicron variants, respectively. Grayline chart indicates the count of hospitalized COVID-19 pregnant patients. The first (left) vertical line is on 12-17-2020, the first update date in COVID-19 antithrombotic therapy guidelines to recommend the administration of prophylactic anticoagulants on pregnant patients hospitalized with severe COVID-19 manifestation. The second (right) vertical line is on 02-24-2022, the second update date to expand the recommendation to all pregnant patients hospitalized with COVID-19 manifestation.*

(B) Prophylactic anticoagulant administration rate based on SARS-CoV-2 variant. The SARS-CoV-2 variant was determined based on the period during which each variant was the dominant variant accounting for >50% of cases as part of the CDC genomic surveillance for SARS-CoV-2 in region 10 (Alaska, Idaho, Oregon, and Washington; CDC 2022)

(C) Timeline definition. Text colors indicate the SARS-CoV-2 variant and COVID-19 antithrombotic therapy guideline time period in ***A, B, and D****.*

(D) Prophylactic anticoagulant administration rate based on COVID-19 antithrombotic therapy guideline. The first update was to recommend the administration of prophylactic anticoagulants on pregnant patients hospitalized with severe COVID-19 manifestations. The second update expanded the recommendation to all pregnant patients hospitalized with COVID-19 manifestation.

"The GBM model had the best performance with an area under the receiver operating characteristics curve (AUC-ROC) of 0.84 [0.81, 0.87] (Figure A.5 5 and Table A.5 6). Pre-COVID-19 diagnoses count, variant-omicron, socioeconomic status, third-trimester infection, housing type/transportation vulnerability, minority status/language vulnerability, and household composition/disability vulnerability were the most important seven features (Figure A.5 5). The GBM model trained with these seven features reached an AUC-ROC of 0.85 [0.83, 0.89] (Figure 5.3 and Figure A.5 5). In the SHAPley figure, red and blue dots indicate high and low feature values. Red dots of pre-COVID-19 diagnoses count were clustered in the positive end of the SHAP axis. Red dots of third-trimester infection and variant Omicron were clustered in the negative SHAP axis. The matched control group (n=188) was generated by propensity score matching on

the seven most important features. These features had small effect sizes after matching (Cohen's d values < 0.20,[215] *Table A.5 7).*"

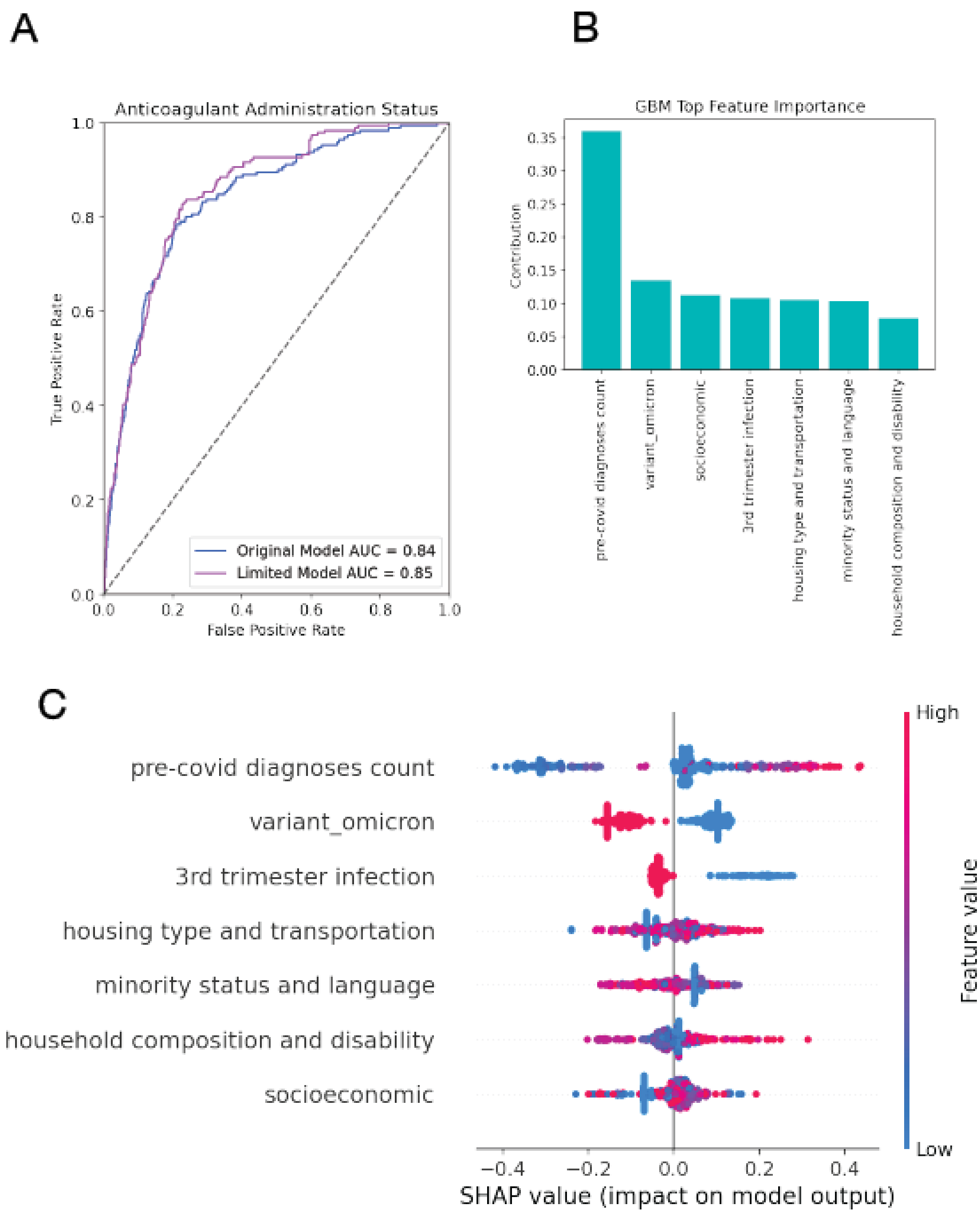


Figure 5.3 Performance of best performing classification model and feature importance[13]
(A) Performance of original and limited gradient boosted machine learning model classifying prophylactic anticoagulant administration status among hospitalized COVID-19 pregnant patients.

Figure 5.3 Performance of best performing classification model and feature importance[13] (continued); The limited model was trained with the seven most important features from the original model. The feature importance result of the original model is in Figure S5. The 95% confidence interval of the original and limited models were [0.81, 0.87] and [0.83, 0.89], respectively.

(B) Feature importance ranking of the limited model. Variables are defined in Table A 6.1

(C) Shapley permutation explainer of the feature contribution. SHAP value reflects the contribution of the seven most important features from the gradient boosting models towards classifying prophylactic anticoagulant administration status. SHAP value is the average marginal contribution of a feature value across all permutations of features. Each row represents an individual feature, and the dot represents a sample. The dot color reflects the value of the feature of the sample relative to all samples. The evaluation was done on the sample set composed of a treatment group and a 1:1 randomly undersampled matched control group (n=382).

"GBM model trained with seven top features and initial medication count reached AUC-ROC of 0.93 [0.91, 0.95] (Figure A.5 6). Feature importance showed initial medication count was the most important feature classifying prophylactic anticoagulant administration status (Figure A.5 6). Red and blue dots were spread out across extreme negative SHAP values and up to 0.2 SHAP value, but the end of the positive SHAP axis (SHAP value > 0.2) was clustered with red dots (Figure A.5 6)."

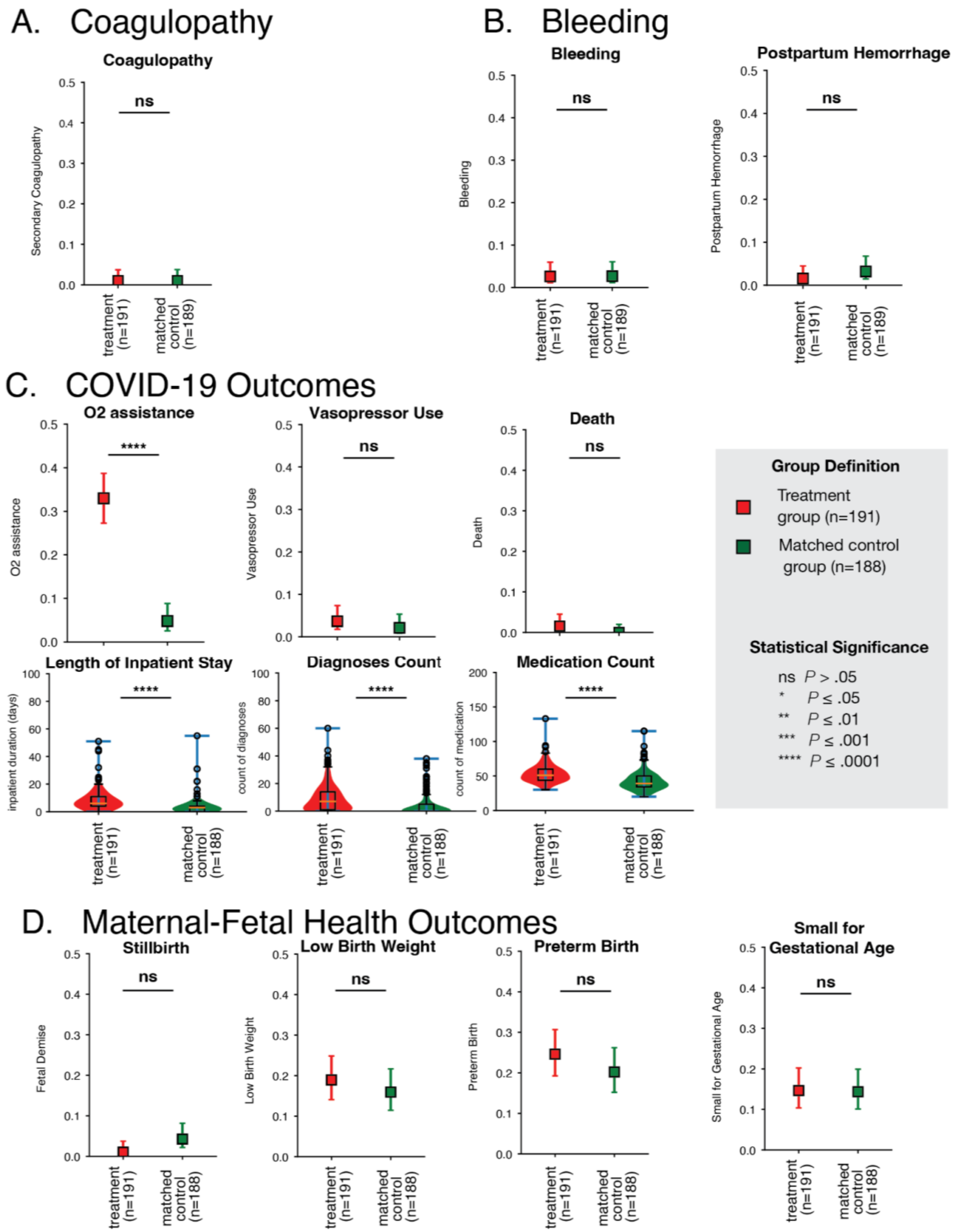


Figure 5.4 Clinical outcomes of the treatment and matched control[13]

Results are presented in Table A.5 8 and Table A.5 9. Unless specified, the observation cutoff was the delivery date.

Figure 5.4 Clinical outcomes of the treatment and matched control (continued); The observation start point was the anticoagulant exposure date and potential COVID-19 treatment onset date, respectively. (A)Coagulopathy prevalence rate of the treatment and matched control. SNOMED codes we used for coagulopathy diagnosis are listed in Table A.5 1. (B) Bleeding and postpartum hemorrhage prevalence rate of the treatment and matched control. SNOMED codes we used for bleeding and postpartum hemorrhage diagnoses are listed in Table A.5 1. Postpartum hemorrhage was collected from the delivery date to +12 weeks postpartum. (C) O2 assistance use, vasopressor use, and maternal death prevalence rates for the treatment, and matched control groups. Violin plots of the length of inpatient stay (days), medication counts 48 hours after the potential COVID-19 treatment onset, and diagnoses count after the potential COVID-19 treatment onset. The cutoff point was the delivery date. (D) Stillbirth, low birth weight, preterm birth, small for gestational age prevalence rate of the treatment, matched control and sensitivity analysis matched control group.

"Compared with the control group, the treatment group had an increased risk of maternal death (Relative risk, RR=not calculable due to small number of cases, 1.6% vs. 0%, P<.001), O_2 assistance (RR=9.3[6.9, 12.3], 33% vs. 3.6%, P<.001), low birth weight (RR=2.1[1.5, 2.8], 19% vs. 9.2%, P<.001), and preterm birth (RR=2.1[1.5, 2.8], 25% vs. 12%, P<.001), bleeding (RR=2.5[1.0,6.3], 2.6% vs. 1.1%, P=.08). After matching, risk of low birth weight (RR=1.2[0.8,1.8], P=0.50), preterm birth (RR=1.2[0.8,1.8], P=0.33), and bleeding (RR=1.0[0.3,3.3], P=1.0) were reduced and no longer statistically significant. We also did not observe an increase or decrease in risk between the treatment coagulopathy and other maternal-fetal health outcomes (Figure 5.4, Table A.5 8, and Table A.5 9). However, the treatment group had significantly worse outcomes regarding COVID-19 illness severity even after the matching. The treatment group had a higher likelihood of supplemental oxygen (RR=6.9[3.5, 13.4], 33% vs. 5%, P<.001), longer inpatient stay (6 vs. 3, P<.001; median), higher medication (51 vs. 39, P<.001; median), and diagnoses count (7 vs 0, P<.001; median). The statistical significance remained even in our sensitivity analysis (Table A.5 8 and Table A.5 9) where we additionally

addressed the initial illness severity. Maternal age and pregravid BMI did not influence the association between the treatment and outcomes of interest."

5.4 DISCUSSION

"To our knowledge, this was the first study evaluating the NIH antithrombotic therapy guideline for pregnant women. We initially hypothesized to observe a high prophylactic anticoagulant administration rate among hospitalized COVID-19 pregnant patients and minimal difference in patient characteristics between the treatment and control groups. However, we identified most patients relevant to NIH antithrombotic therapy guidelines, pregnant women hospitalized with COVID-19, did not receive prophylactic anticoagulants. Instead, patients with higher comorbidity levels, infected in the first or second trimester, and infected with a non-Omicron variant were more likely to receive prophylactic anticoagulants. Despite the worse COVID-19 symptoms, the treatment group did not have an elevated risk of coagulopathy, bleeding, and maternal-fetal health outcomes."

"The most important and interesting finding was an unexpectedly low prophylactic anticoagulant administration rate among hospitalized COVID-19 pregnant patients across healthcare systems despite the guidelines. A possible explanation for this observation is that clinicians administered prophylactic anticoagulants based on the patient's COVID-19 illness severity. The initial medication count, a proxy variable for COVID-19 illness severity at COVID-19 treatment onset, was the most important feature in the sensitivity analysis model classifying prophylactic anticoagulant administration status. It also enhanced the AUC score by 0.09 reaching 0.94. In addition, we noticed the treatment group was enriched with diagnoses indicative of severe COVID-19 symptoms such as pneumonia, acute respiratory failure with hypoxia, and hypokalemia. In contrast, the control group was not. We presume clinicians did not follow the

guideline because it was not strongly recommended and lacked studies to support it. The rating scheme of the NIH guideline is BIII. B and III, respectively, indicate a moderate recommendation and expert opinion evidence. This means no study yet has evidence for or against this recommendation.[37] *Few studies describing COVID-19-positive pregnant patients have reported prophylactic use of anticoagulants during hospitalization. In these studies, the sample size was small, ranging from 9 to 20, and complications following the treatment were not evaluated.*[218–220] *"*

"We noted an elevated risk of respiratory assistance among the treatment group. This was inconsistent with prior studies. Although there was no study on pregnant patients, there have been multiple observational studies supporting prophylactic anticoagulant use on non-pregnant hospitalized COVID-19 patients. Studies showed that prophylactic anticoagulants improved freedom from intubation and lowered mortality, indicating better COVID-19 outcomes.[221–223] *In these studies with a non-pregnant population, including men and older population, the rate of prophylactic anticoagulant administration ranged from 45 to 85% whereas that of our study was 7%. In addition, in our study, prophylactic anticoagulant administration was highly correlated with the comorbidity level before the SARS-CoV-2 infection and the initial illness severity. We do not think the increased risk in respiratory assistance in our study was influenced by the exposure to anticoagulants, but rather a byproduct of failure to overcome the confounding by indication."*

"Although we could only partially address the confounding by indication, we did not observe elevated risks of coagulopathy, bleeding, and maternal-fetal health outcomes among the treatment group. Given that severe COVID-19 is associated with coagulopathy and adverse pregnancy outcomes,[179–188,224,225] *this finding was somewhat promising as we expected worse outcomes in coagulopathy and maternal-fetal health outcomes. Based on our findings, we cannot support the benefit of the guideline but can, at least, support its potential safety regarding*

maternal-fetal health outcomes. Treatment group had similar likelihood to deliver low birthweight, preterm, and small for gestational age babies. This observation was less limited with small sample size, compared to rare outcomes of interest, due to the high incidence rate of cases across groups. Considering this is the first study to evaluate the guideline, our study can contribute to our knowledge in treating hospitalized pregnant COVID-19 patients. Future research should be conducted in larger and various study settings and minimize the confounding by indication to understand better the risk, safety, and benefit of the treatment."

"The small sample size despite our large database was an interesting observation and major limitation. We expected to observe a high prophylactic anticoagulant administration rate after the second guideline update as all hospitalized COVID-19 pregnant patients were relevant, but only 7% were administered prophylactic anticoagulants. This led to confounding by indication. The treatment group had higher pre-COVID-19 comorbidity levels and included more critically ill patients. Although we attempted to minimize the bias using propensity score matching, we could not overcome it due to the small sample size and lack of appropriate variables reflecting COVID-19 illness severity at the time of infection. EHR is retrospective data and structured data is insufficient to understand medical reasoning. In addition, individuals had a wide range of anticoagulant administration start times before and after the potential COVID-19 treatment onset. As covariates that occurred after the exposure are inappropriate for the propensity score method, we excluded them from the main matching model. Nevertheless, we performed sensitivity analysis on the impact of the initial medication count to partially address the COVID-19 illness severity at the time of treatment onset. Lastly, we did not verify whether the heightened risk of O_2 *assistance among the treatment group resulted from confounding by indication or not. We assumed it was due to confounding by indication based on the prior studies*

[221–223] *on hospitalized COVID-19 patients. To address these limitations, a similar study should be conducted in a larger prospective cohort, which collects appropriate variables reflecting the COVID-19 illness severity at the time of admission."*

"This was the first study assessing the prophylactic use of anticoagulants on hospitalized patients after the guideline update on 02-24-2022. Although the guideline recommends on all hospitalized patients regardless of COVID-19 severity, no study to date has assessed the exposure of anticoagulants among COVID-19 hospitalized patients. Another strength of our study includes adjustments for social and economic risk factors. We adjusted the difference CDC-SVI index and rural and urban classification between treatment and control groups based on the census tract level. Social vulnerability and rural health disparities are significant risk factors for adverse pregnancy outcomes and severe COVID-19 symptoms.[226–233] *As the census tract is more granular than the county level, it captures the environmental factors to which patients have been exposed more accurately. Indeed, all four CDC SVI indexes were important predictors of anticoagulant administration status. This study was conducted on a COVID-19 maternity population that has been investigated by other researchers,*[86,234]*allowing deeper insight into the study setting and population."*

"We validated the inpatient anticoagulant administration rates in Truveta's patient population, comprised of various healthcare systems. Overall inpatient anticoagulant administration rates in Truveta were similar to those observed in PSJH. This indicates that the unexpectedly low adaptation rate of NIH recommendations was not limited to the PSJH healthcare system. Here, we could not completely replicate our analysis as Truveta and Providence data models were different, and the leading researcher of this study had limited access to Truveta Studio. We did not exclude patients who had contraindications to

anticoagulants and did not differentiate between prophylactic and therapeutic dosage. Nevertheless, we expect our final estimation of the inpatient anticoagulant administration rate on the Truveta patient population would not drastically change based on the number we observed from the cohort selection procedure in the PSJH population."

5.5 CONCLUSION

In Aim 3 (**Investigate medical interventions targeting pregnant women using electronic health records**), we selected a controversial and existing hypothesis in clinical practice that had not been previously investigated before to narrow the knowledge gap in treating pregnant women. Specifically, we explored the National Institute of Health's antithrombotic therapy recommendation for hospitalized pregnant patients with manifestation of COVID-19. The hypothesis of Aim 3 was that there is a high rate of prophylactic anticoagulant administration among pregnant patients hospitalized with COVID-19 and the objective was to characterize this rate and to evaluate the impact of this treatment in the study population. Contrary to our hypothesis, *"we found that most patients across healthcare systems did not receive prophylactic anticoagulants despite the NIH antithrombotic therapy guideline. Patients who received prophylactic anticoagulants were more severely ill than those who did not. We were not able to show the efficacy of prophylactic anticoagulation. However, anticoagulation was not associated with elevated risks of coagulopathy, bleeding, and maternal-fetal health outcomes despite the worse health conditions of the treatment group."*

We recognize two significant limitations in our study. Firstly, the unexpectedly low rate of prophylactic anticoagulant administration led to a small sample size, potentially impacting the generalizability and statistical power of our findings. Secondly, we lacked an appropriate variable to reflect the severity of COVID-19 illness at the time of infection. The absence of an appropriate measure for illness severity limited our ability to understand the relationship between anticoagulant treatment and COVID-19 outcomes.

Moving forward, we recommend conducting similar studies in larger cohorts. Additionally, prospective studies that collect medical reasoning behind clinician's treatment decisions and include data on the severity of COVID-19 at the time of infection would provide a better understanding of the factors influencing treatment outcomes.

Across Aim 1 to 3, our evaluation has focused on understanding the impact of medical treatments administered to pregnant women within the context of **leveraging RWD EHR to address knowledge gaps in treating pregnant women** as outlined in our overall goal. In Aim 1 (Chapter 3; **Detect signals of previously identified and unidentified drug effects on preterm birth using statistical data mining methods on real-world data)**, we employed a statistical data mining approach to generate testable hypotheses regarding drug effect signals associated with the risk of PTB. In Aim 2 (Chapter 4; **Validate detected drug effect signals from aim 1 using traditional pharmacoepidemiology method**), we evaluated the detected drug effect signals from Aim 1. Building on this foundation in Aim 3, we assessed current treatment guideline lacking evidence to either support for or against it. Through these analyses, we observed how comorbidities significantly influence the associations between medical treatment and risk of adverse pregnancy outcomes.

Aim 4 (**Harness electronic health records to assess comorbidities in pregnancy course**) delved into selected comorbidities of interest and assessed how these conditions affect risk of adverse pregnancy outcomes. As comorbidities often accompany medical treatments, Aim 4 contributes to advancement of our overall goal **in leveraging EHR to address knowledge gaps in treating pregnant women**.

Chapter 6. **AIM 4** HARNESS ELECTRONIC HEALTH RECORDS TO ASSESS COMORBIDITIES IN PREGNANCY COURSE

This chapter expands upon the manuscript[14] titled "Maternal-fetal outcomes in patients with immune-mediated inflammatory diseases, with consideration of comorbidities: a retrospective cohort study in a large US healthcare system". This manuscript is currently under review in *eClinicalMedicine* and uploaded on Medrxiv (as of December 15, 2023). Text directly quoted from the Medrxiv/submitted version of the manuscript is italicized and in quotation marks and any figures/tables from the Medrxiv/submitted manuscript are marked as well.

6.0 INTRODUCTION

Through the work on Aim 1-3, we have demonstrated efforts to advance our overall goal **of leveraging RWD, particularly EHR, to address the knowledge gap pertaining to medical treatment in pregnant women**. Across Aim 1 to 3, we observed that comorbidities heavily influence drug effects on pregnant women. The combined insights from Aims 1 and 2, illustrated in *Figure 3.2*, revealed that different sets of comorbidities alter the associations between mediation exposure and the risk of PTB. In Aim 3, we found that the number of comorbidities before COVID-19 infection was the most important feature classifying the prophylactic anticoagulant administration status.

In Aim 4 (**Harness electronic health records to assess comorbidities in pregnancy course**), we selected specific comorbidities of interest and evaluated their influence on maternal health. We examined the risk of maternal-fetal health outcomes in patients with immune-mediated inflammatory disorders (IMIDs) before pregnancy and how underlying comorbidities affect these outcomes. The hypothesis was that there is an elevated risk of adverse pregnancy outcomes among patients who had IMIDs before pregnancy the objective was to test this population in our study population.

6.1 MOTIVATION

6.1.1 *Background, literature review, and significance*

"Immune-mediated inflammatory disorders (IMIDs) are a group of conditions with heterogeneous clinical presentation that share some common pathogenic immune pathways and affect multiple human body organ systems.[235] IMIDs are generally characterized by organ damage and chronic inflammation, resulting in reduced quality of life, comorbidities, and premature death.[236] Although each individual IMID has unique epidemiology and pathophysiology, its pathogenesis is primarily attributable to an imbalance in immune cellular activation and inflammatory cytokines.[235] The underlying causes and mechanisms for the pathogenesis of many IMIDs remains ill-defined, but there have been significant therapeutic advances over the past two decades.[235] We investigated a partial list of IMIDs in this study: psoriasis (PsO), inflammatory bowel disease (IBD), rheumatoid arthritis (RA), spondyloarthritis (SpA), multiple sclerosis (MS), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), antiphospholipid syndrome (APS), Sjögren's syndrome (SjS), vasculitis (Va), sarcoidosis (Sa), systemic sclerosis (SSc) (order based on number of IMIDs diagnosis in our study, see Figure 6.2C for more detail)."

"Although the degree of sexual bias varies widely across individual IMIDs, most IMIDs occur more frequently in females than males; 80% of patients with autoimmune diseases are female.[237] RA, IBD, MS, SLE, APS, SjS and SSc occur 2-3[238] (RA), 1.5[239] (IBD), 2[240] (MS), 7-10[241] (SLE), 3.5[242] (APS), 13[243] (SjS) , and 3-8[244] (SSc) times more often in females than males. Given

insufficient understanding of the pathology and mechanisms of IMIDs, the underlying reason for sexual dimorphism in IMIDs is still unknown."

"It is particularly important to evaluate the relationship between pregnancy and IMIDs because IMID are often first diagnosed during reproductive age. Pregnancy can ameliorate or exacerbate disease activity, depending on the specific IMID[245]*. Both MS and RA can improve during pregnancy and flare after the delivery*[245]*. SLE can induce unpredictable changes in disease activity during pregnancy and is one of the most significant risk factors for adverse pregnancy outcomes.*[245–248] *Less common autoimmune rheumatic diseases (e.g. PsA) were also shown to be associated with worse outcomes including PTB and SGA.*[249] *Recent meta-analysis studies on RA and IBD reported elevated risk of adverse pregnancy outcomes including PTB, LBW, caesarean section or stillbirth.*[250,251] *Pregnancy itself is a significant perturbation in the maternal immune system; the maternal immune system has to avoid rejecting a semi-allogeneic fetus while remaining immunocompetent.*[252] *Because IMIDs can further complicate pregnancy and patient's health, patients often voluntarily avoid pregnancy. Patients with IBD had significantly higher rate of voluntary childlessness, ranging from 14-18%, compared to 6·8% of the general population.*[253] *However, recent years have shown improvements in pregnancy outcomes through substantial progress in diagnosis, and in preconception and prenatal care.*[254]*"*

"Comorbid conditions, are common in patients with IMIDs, including cardiovascular disease, metabolic and bone disorders and cognitive deficit.[235] *Also, patients with IMIDs have increased incidence of psychiatric disorders including depression, anxiety, and bipolar disorder, compared to geographically- age-, and sex-matched controls.*[255] *Despite the high cooccurrence of comorbidities among patients with IMIDs condition, the impact of comorbidities on the relation between IMIDs and pregnancy course is insufficiently examined."*

6.1.2 *Objective*

"The objective of this study is to retrospectively characterize patients who had one or more diagnoses of IMIDs prior to pregnancy regarding their demographics, pregnancy characteristics, comorbidities, and use of immunomodulatory drugs. We will evaluate the impact of IMIDs on adverse pregnancy outcomes after assessing and addressing any discrepancies in the distribution of covariates associated with adverse pregnancy outcomes between patients with and without IMIDs. We will also conduct disease-specific and sensitivity analyses to examine the contribution of individual IMIDs and comorbidities on the relationship between IMIDs and adverse pregnancy outcomes."

6.2 METHODS

6.2.1 *Study setting and participants*

"Providence Health and Services and affiliates (PSJH) is an integrated US community healthcare system that provides care in urban and rural settings across seven states: Alaska, California, Montana, Oregon, New Mexico, Texas, and Washington. We used PSJH electronic health records (EHR) of pregnant people who had live births from January 1, 2013, through December 31, 2022 (n=543,408). PSJH database contains all EHR records. As such, the data may contain the types of errors and omissions typically observed in patient charts. Medication prescribed and diseases diagnosed outside of PSJH will be noted if the patient reports them when asked during an encounter. Figure 6.1 *describes the cohort selection. We included pregnant people with age between 18 and 45 years (n = 510,488). Delivery records with missing information regarding the living status of born babies were excluded because these records are susceptible to higher rates of missing data and potential surveillance bias. Analysis was limited to records with*

live births to prevent potential underestimation of miscarriage and stillbirth cases. To reduce surveillance bias, we included people who had continuity of care at PSJH. Continuous enrollment was defined as at least one encounter 180 days prior to conception and one encounter on or after the delivery date. We excluded multifetal gestations and deliveries with gestational age (GA) of less than 20 weeks (n = 516,881). GA was limited to 20 weeks or greater because ascertainment bias is particularly high for EHR data earlier in pregnancy. All procedures were reviewed and approved by the Institutional Review Board at the PSJH through expedited review on 11-04-2020 (study number STUDY2020000196). Consent was waived because disclosure of protected health information for the study involved no more than minimal risk to the privacy of individuals."

6.2.2 *Exposure and outcome*

"Our exposure of interest was pre-existing IMIDs conditions prior to pregnancy. The IMIDs group was people who had at least one type of IMIDs before pregnancy (n = 5784). The twelve IMIDs we investigated were PsO, IBD, RA, SpA, MS, SLE, PsA, APS, SjS, Va, Sa, and SSc. Systemized Nomenclature of Medicine (SNOMED) diagnoses of these IMIDs were clinically reviewed (Table S1). People with no IMIDs diagnosis before pregnancy comprised the control group, the non-IMID group (Figure 6.1*)."*

"Our outcomes of interest were adverse pregnancy outcomes: preterm birth (PTB; birth before 37 weeks of gestational age), low birthweight (LBW; birth of baby weighing less than 2,500g), small for gestational age (SGA; birth of baby weighing less than 10th percentile of babies born in same gestational age), and caesarean section (Table A.6 2)."

6.2.3 *Cohort characteristics*

"We collected information on maternal/pregnancy characteristics, comorbid conditions, and pre-pregnancy/prenatal IMMs prescription pattern (Table A.6 1, Table A.6 2, and Table A.6 3). The included maternal/pregnancy characteristics are parity, gravidity, preterm history, delivery year, fetal sex, maternal age, pregravid body mass index (BMI) category, self-reported smoking status, self-reported illegal drug use status, self-reported racial group, self-reported ethnic group, insurance, Centers for Disease Control and Prevention social vulnerability index (CDC-SVI), and rural-urban classification (Table A.6 2). CDC-SVI represents the percentile ranking of each census tract on 15 social factors. Social factor themes include socioeconomic status, household composition, race/ethnicity/language, and housing/transportation. CDC-SVI and rural/urban classification were collected based on the census tract in which the patient resided. Maternal and pregnancy characteristics were collected at the time of the prenatal visit. We included the following comorbidities: urinary tract infection, sexually transmitted disease, obesity, diabetes, asthma, depression, chronic kidney disease, chronic lung disease, pneumonia, and sepsis. Comorbidities that were active at the start of pregnancy (last menstrual period; LMP) were collected. Missing values were imputed using median values."

"We assessed the pre-pregnancy and prenatal prescription patterns of IMMs. We defined prescription status based on prescription records within the period of interest. We limited our search to records with administration routes of oral, intramuscular, intravenous, subcutaneous, and rectal. The pre-pregnancy study period was 180 days from LMP to LMP. Prenatal medication exposure was further categorized based on their administration status in each trimester. IMMs we investigated were hydroxychloroquine, methotrexate, leflunomide and teriflunomide, 5-ASA, azathioprine, mercaptopurine, mitoxantrone, mycophenolate, calcineurin inhibitors, TNF-α

inhibitor, fumarates, interferon, alkylating agent, hydroxyurea, dapsone, cladribine, IL-1 inhibitors, IL-6 inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, abatacept, anti-BLyS, S1P receptor modulator, JAK inhibitor, PDE4 inhibitor, anti-CD20, anti-CD52, budesonide, and systemic glucocorticoids (Table A.6 3).”

6.2.4 *Descriptive statistics*

“We described pregnancy/maternal characteristics, comorbidities, and pre-pregnancy/prenatal IMMs prescription patterns. We calculated the mean and standard deviation for continuous variables and the proportion of categories for binary and multi-class categorical variables (Table S4, S5, and S6). Differences in the distribution of variables between IMIDs and non-IMIDs groups were evaluated using the t-test, fisher exact test, and chi-square test for continuous, binary, and multi-class categorical variables (scipy v1.7.3). Multiple testing errors were corrected using the Benjamin-Hochberg method (statsmodel v.0.13.2)”

6.2.5 *Propensity score matching*

“We generated a matched non-IMIDs group using the propensity score matching method. Propensity score was calculated across covariates using logistic regression (scikit-learn v1.0.2). Covariates include parity, gravidity, preterm history, delivery year, fetal sex, maternal age, pregravid BMI, self-reported smoking status, self-reported illegal drug use status, self-reported racial group, self-reported ethnic group, race, ethnicity, insurance, pregravid BMI, smoking status, illegal drug use status, rural-urban classification, and comorbidities. People in the IMIDs group were 1:1 matched to the non-IMIDs group using the K-nearest neighbor algorithm in Euclidean metrics (k=1), which identifies for each IMIDs person the most similar non-IMIDs person across

several features in high-dimensional space (scikit-learn v1.0.2). We evaluated the balance across covariates after the matching using Cohen's d value (Figure A.6 2, Table A.6 7, and Table A.6 8)."

6.2.6 *Disease-specific analysis and sensitivity analysis*

"We replicated descriptive statistics and propensity score matching on individual IMIDs. Patients of individual IMID groups were 1:1 matched with non-IMIDs people to generate individual matched control groups (Table A.6 9). For sensitivity analysis, we conducted propensity score matching without comorbidities to examine the influence of comorbidities on the associations between IMIDs and adverse pregnancy outcomes (Figure 6.1*). Sensitivity analysis assessing the impact of comorbidities on the association was conducted on individual IMID groups (Table A.6 9). We additionally conducted a sensitivity analysis to confirm our assumption that patients with IMMs prescription during pregnancy had ongoing disease activities, affiliated with a higher chance of adverse pregnancy outcomes.*[256,257] *We evaluated the risk of adverse pregnancy outcomes among patients with IMIDs and IMM prescriptions and patients with IMIDs and no IMM prescriptions compared to non-IMIDs group (Table A.6 10)."*

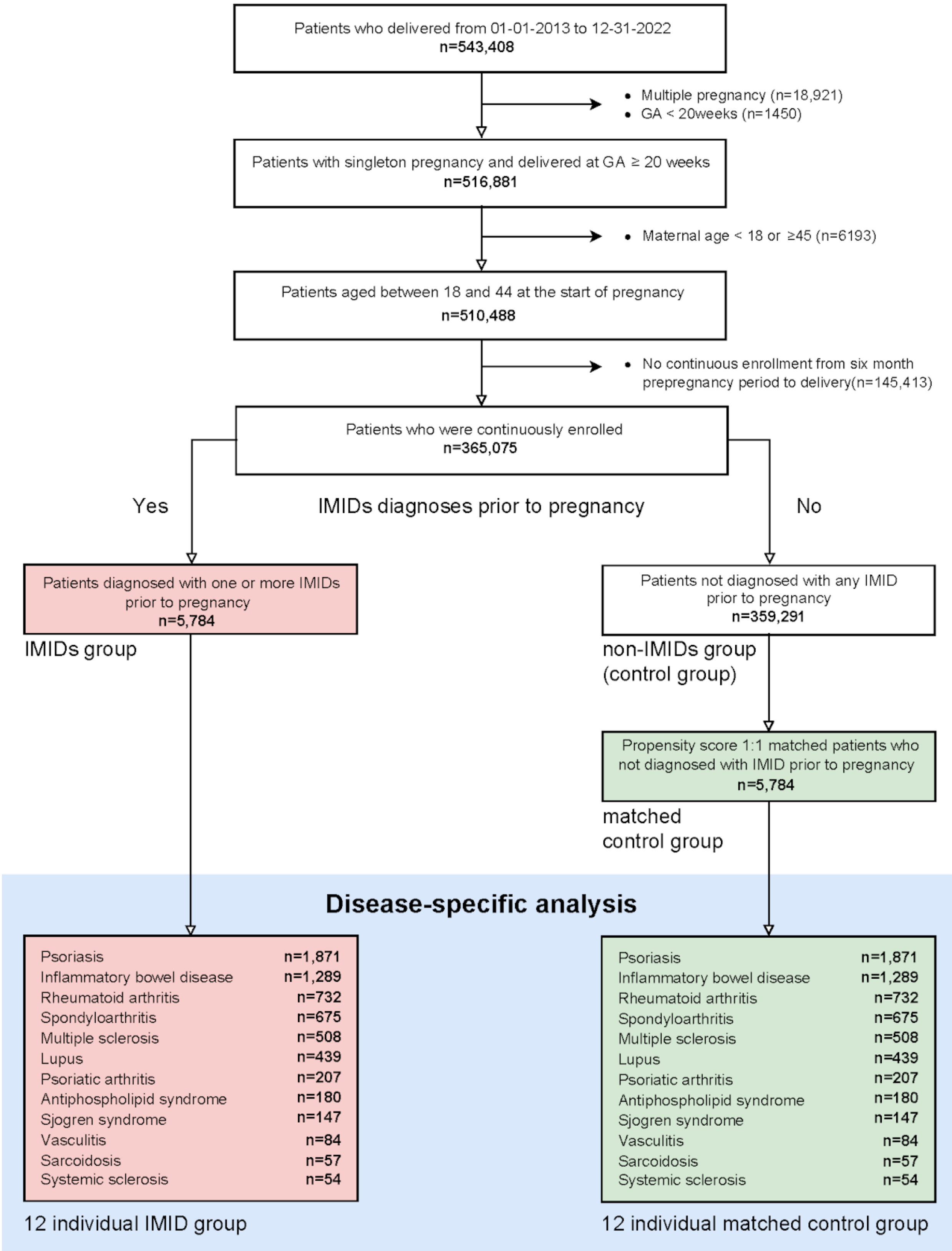


Figure 6.1 Cohort selection flow chart[14]

Figure 6.1 Cohort selection flow chart (continued); GA Gestational Age; IMIDs Immune-mediated Inflammatory Disease; IMIDs group was propensity score matched 1:1 on confounding variables to generate the matched non-IMIDs group. Individual IMID groups were propensity score matched 1:1 on pregnancy/maternal characteristics and comorbidities variables to generate corresponding matched control groups.

6.3 RESULT

6.3.1 *Identification of IMIDs, individual IMID, and matched control cohorts*

"Our analytic cohort had 365,075 people, of which 5784 were in the IMIDs group and 359,291 were in the non-IMIDs group (Figure 6.1*, continuously enrolled singleton pregnant people). The IMIDs group's most and least common IMID diagnoses were PsO and SSc respectively (PsO n = 1,871; IBD n = 1,289; RA n = 732; SpA n = 675; MS n = 508; SLE n = 439; PsA n = 207; APS n = 180; SjS n = 147; Va n = 84; Sc n = 57; SSc n = 54). IMIDs people were 1:1 matched to non-IMID people to generate matched non-IMIDs groups (n=5,784)."*

6.3.2 *Characteristics of IMIDs and individual IMID cohorts*

"Figure 6.1*,*

Table 6.1, and Table A.6 4 describe non-IMIDs, IMIDs, and the subclassification of the IMIDs group into twelve distinct IMID groups. The prevalence rate of pregnancy with prior IMIDs diagnoses increased from 1.1 to 2.0% in the recent ten years (Figure 6.2). It escalated steadily from 2013 to 2020 and plateaued from 2020 to 2022. Compared to the non-IMIDs group, people in the IMID group (n = 5,784) were more likely to identify as white (73·1% vs. 62·9%, p<0·0001) or non-Hispanic or Latino (86·2% vs. 76·6%, p<0·0001), be between the ages of 30-34 (54·8% vs. 43·1%, P < 0·0001), and have commercial insurance (55·2% vs. 46·3%, p<0·0001). Regarding comorbidities, the IMIDs group had significantly more people with cardiovascular disease (35·0% vs 13·9%, p< 0.0001), depression (22·1% vs 9·1%, p<0.0001), urinary tract infection (18·8% vs. 10·4%, p<0.0001), asthma (12·0% vs 5·2%, p<0.0001), obesity (7·0% vs 3·0%, p<0.0001), sexually transmitted disease (3·5% vs 1·7%, p<0.0001), and diabetes (1·5% vs 0·7%, p<0.0001)."

"Figure 6.2 describes the IMIDs cohort. 93% of people with IMIDs had one IMID diagnosis, and 7% of them had more than one IMID diagnosis. Figure 6.3 characterizes the IMMs prescription pattern of the IMIDs cohort. 83% of IMIDs people had no prenatal IMMs prescription (Figure A.6 3A). Among the individual IMIDs we investigated, people with SLE and PsO had the highest and lowest IMMs prescription rates of 39·4% and 6·7% (Figure 6.3B; SLE 39·4%, RA 32·1%, SjS 31·3%, IBD 27·8%, Va 21·4%, PsA 20·8%, Sc 19·3%, APS 15·6%, SSc 14·8%, MS 12·6%, SpA 10·8%, PsO 6·7%). Among patients with IMIDs, steroids, hydroxychloroquine, 5-ASA, and TNF inhibitors were the most commonly prescribed prenatal IMMs. Prescription rates were 8%, 5%, 4%, and 3% (Figure 6.3C). The ranking of IMMs prescription rate varied depending on the type of disease (Figure A.6 1). For further investigation, we focused on these four medications as the rest had a prescription rate below 2%. The prescription rate of these IMMs increased in the first trimester when compared to that of pre-pregnancy (Figure 6.3E). Most people prescribing

these IMMs before the pregnancy continued taking them with a continuation rate ranging from 49% to 70% (Figure 6.3D).”

6.3.3 *Association between IMIDs and risk of adverse pregnancy outcomes*

“When we controlled for comorbidities, having an IMID was only weakly associated with the risk of PTB (RR = 1·1[1·0, 1·3]), LBW (RR = 1·2 [1·0, 1·4]), SGA (RR = 1·1 [1·0,1·2]), and caesarean section (RR = 1·1 [1·1, 1·2]) (Figure 6.4 and Table A.6 9). Of those 12 individual IMIDs, SpA, SLE, and APS were associated with increased risk of PTB (SpA RR = 1·5 [1·0, 2·2]; SLE RR = 2·4 [1·6, 3·6]; APS RR = 2·1 [1·2, 3·8]). SLE was the only IMID significantly correlated with enhanced risk of LBW (RR = 3·5 [2·1, 5·8]). People with RA and SLE were 1·3 ([1·0, 1·6]) and 1·9 ([1·4, 2·6]) times more likely to deliver babies with SGA condition. Patients with IBD, RA, PsA, SpA, SLE, APS, and SjShad a high likelihood chance of to deliver babies in caesarean section (IBD RR = 1·3 [1·1, 1·4], RA RR = 1·2 [1·0, 1·4], PsA RR = 1·3 [1·0, 1·8], SpA RR = 1·3 [1·1, 1·5], SLE RR = 1·3 [1·1, 1·5], APS RR = 1·7 [1·3, 2·2], SjS RR = 1·5 [1·1, 2·1]).”

“When we did not control comorbidities to assess the impact of comorbidities on associations between IMIDs and adverse pregnancy outcomes, having any IMIDs showed 0.2 higher RR of PTB and LBW (Table A.6 9). In addition, the risk of PTB and LBW of IBD and RA patients was higher and showed statistical significance (IBD: PTB RR = 1·3[1·0, 1·7], LBW RR = 1·4[1·0, 1·9]; RA: PTB RR = 1·4[1·0, 2·0], LBW RR = 1·5[1·0, 2·3]). Association between APS and the risk of LBW also elevated and became statistically significant (APS LBW RR = 3·0[1·3, 6·9]). When compared with non-IMIDs group, patients with IMIDs and prenatal IMMs prescription had a higher RR across adverse pregnancy outcomes than patients with IMIDs and no prenatal IMMs prescription (Table A.6 10).”

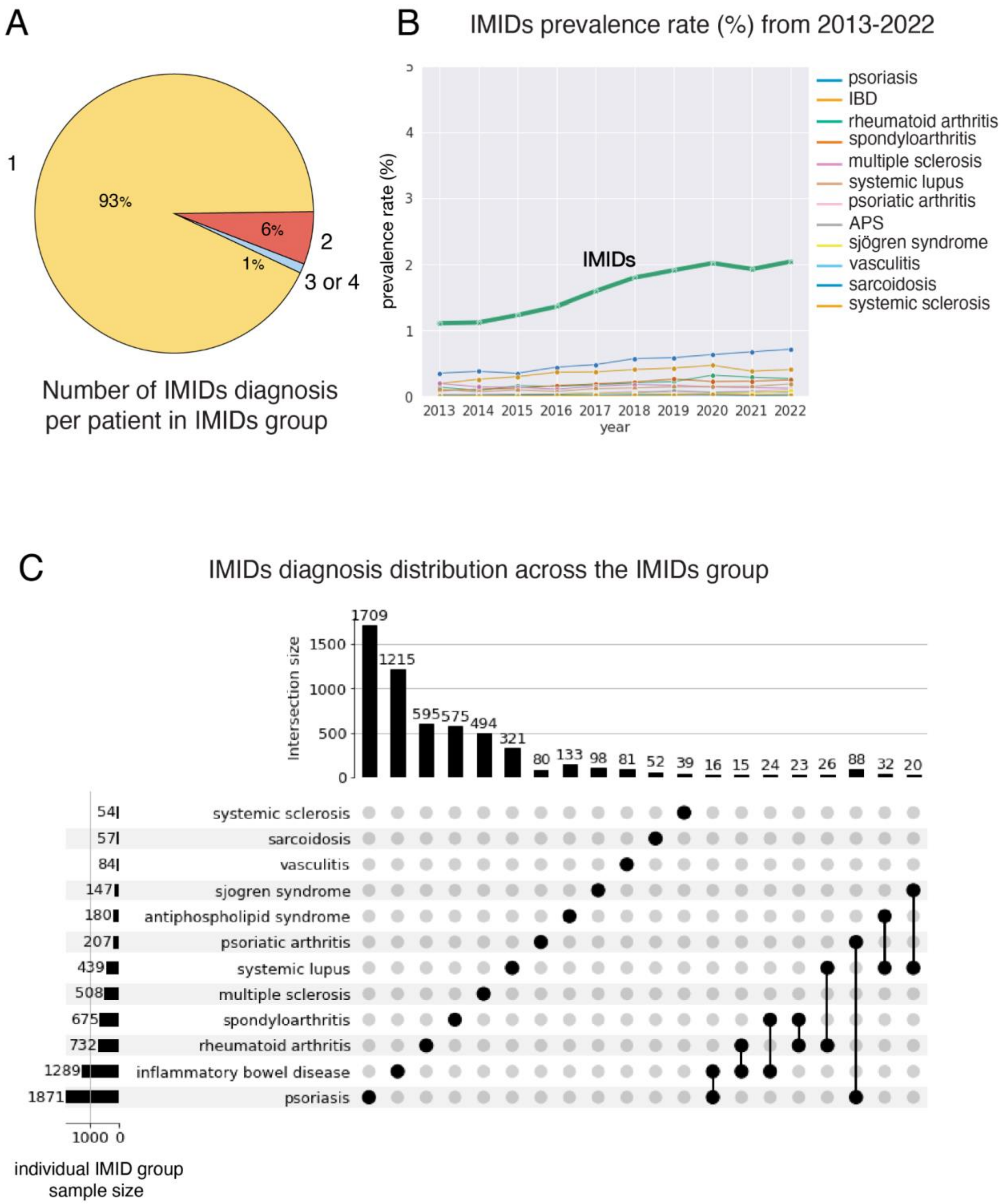


Figure 6.2 Characteristics of the IMIDs group[14]

APS Antiphospholipid Syndrome; IBD Inflammatory Bowel Disease; IMIDs Immune-mediated Inflammatory Disease;

Figure 6.2 Characteristics of the IMIDs group (continued);

(A) Number of IMIDs diagnosis per patient. 93% of the IMIDs group had one IMID diagnosis. 7% of the IMIDs group had more than one IMID diagnosis.

(B) IMIDs prevalence rate over time from 2013 to 2022. Prevalence rate was the proportion of patients with prior IMIDs delivered among patients delivered in the corresponding year. IMIDs prevalence rate gradually increased from 1% to 2% from 2013 to 2022, except in the year 2021.

(C) IMIDs diagnosis distribution across the IMIDs group. Subsets size below 15 were not displayed. The most common and least common diagnosis was psoriasis(n=1871) and systemic sclerosis(n=54), respectively.

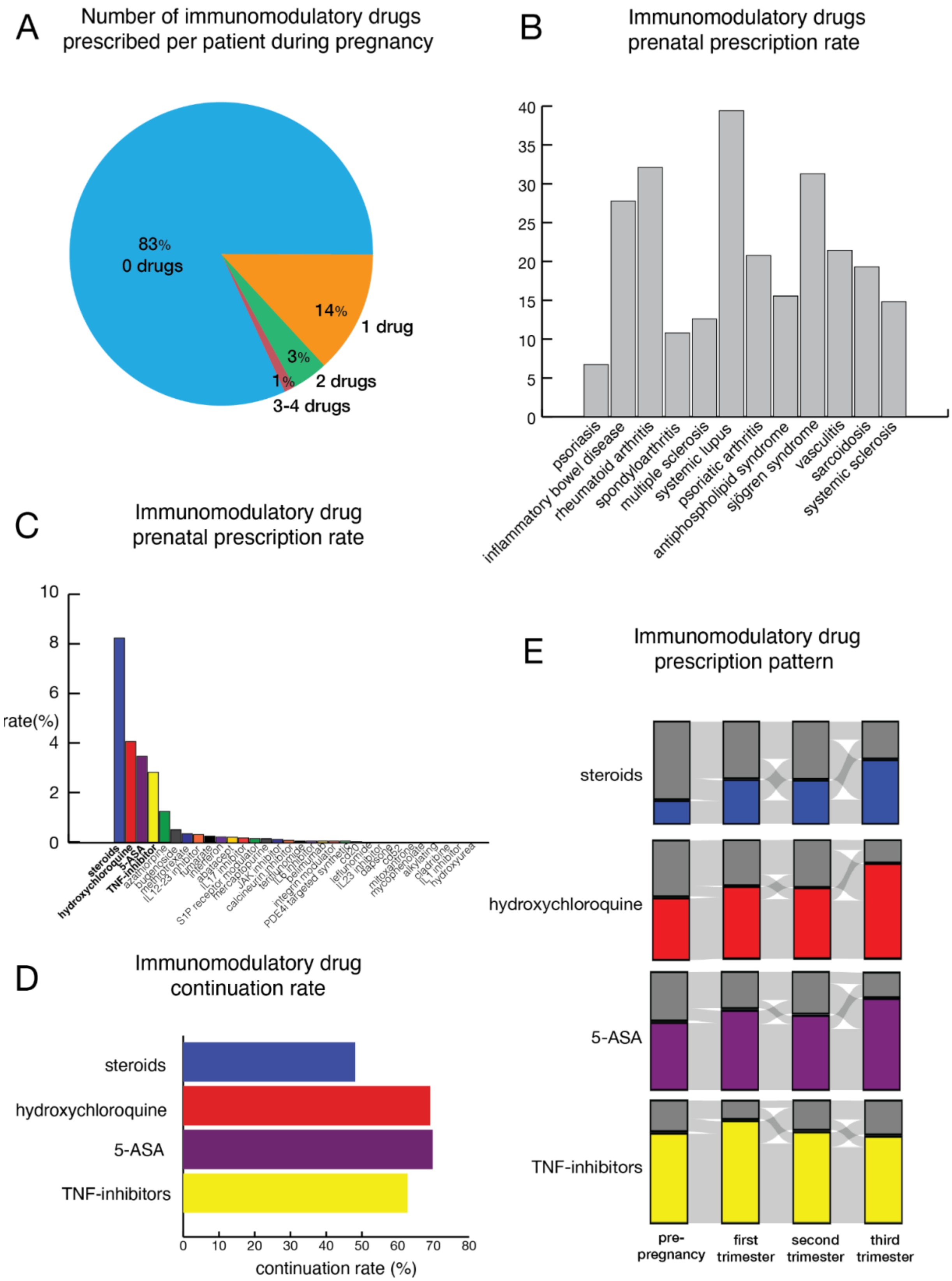


Figure 6.3 IMMs prescription pattern of the IMIDs group[14]

Figure 6.3 IMMs prescription pattern of the IMIDs group (continued); APS Antiphospholipid Syndrome; IBD Inflammatory Bowel Disease; IMID Immune-mediated Inflammatory Disease; IMMs Immunomodulatory Medications; LMP Last Menstrual Period; MS Multiple Sclerosis; PsO Psoriasis; PsA Psoriatic Arthritis; Sc Sarcoidosis; SLE Systemic Lupus Erythematosus; SpA Spondyloarthritis; SjS Sjörgen's Syndrome; SSc Systemic Sclerosis; Va Vasculitis;

(A) Number of IMMs prescribed per patient during pregnancy. 83% of the IMIDs group did not have any IMMs prescription. 17% had at least one IMMs prescription during pregnancy.

(B) Prenatal IMMs prescription rate of individual IMID groups. The descending order of prenatal IMMs prescription rate of individual IMID groups were SLE(39·4%), RA(32·1%), SjS(31·3%), IBD(27·8%), Va(21·4%), PsA(20·8%), Sc(19·3%), APS(15·6%), SSc(14·8%), MS(12·6%), SpA(10·8%), and PsO(6·7%).

(C) Prenatal IMMs prescription rate of the IMIDs group based on the type of IMMs. Glucocorticoids(steroids), hydroxychloroquine, 5-ASA, and TNF-α inhibitors were most commonly prescribed prenatally among the IMIDs group. Prenatal prescription rates were 8%, 5%, 4%, and 3%. Prenatal IMMs prescription rates of individual IMID groups based on the type of IMMs are displayed in Figure A.6 1.

(D) IMMs continuation rate. Majority of patients, who were exposed to IMMs during 180 days prepregnancy period, continued their prescription throughout the delivery. Continuation rates ranged from 48 to 70%.

(E) IMMs prescription patterns among patients who prescribed corresponding IMMs at least once from LMP-180 days to delivery date. Pre, first, second, and third columns indicate 180 days prepregnancy period, first second and third trimester. Colored and gray portions respectively indicate exposed and unexposed patients for corresponding time periods.

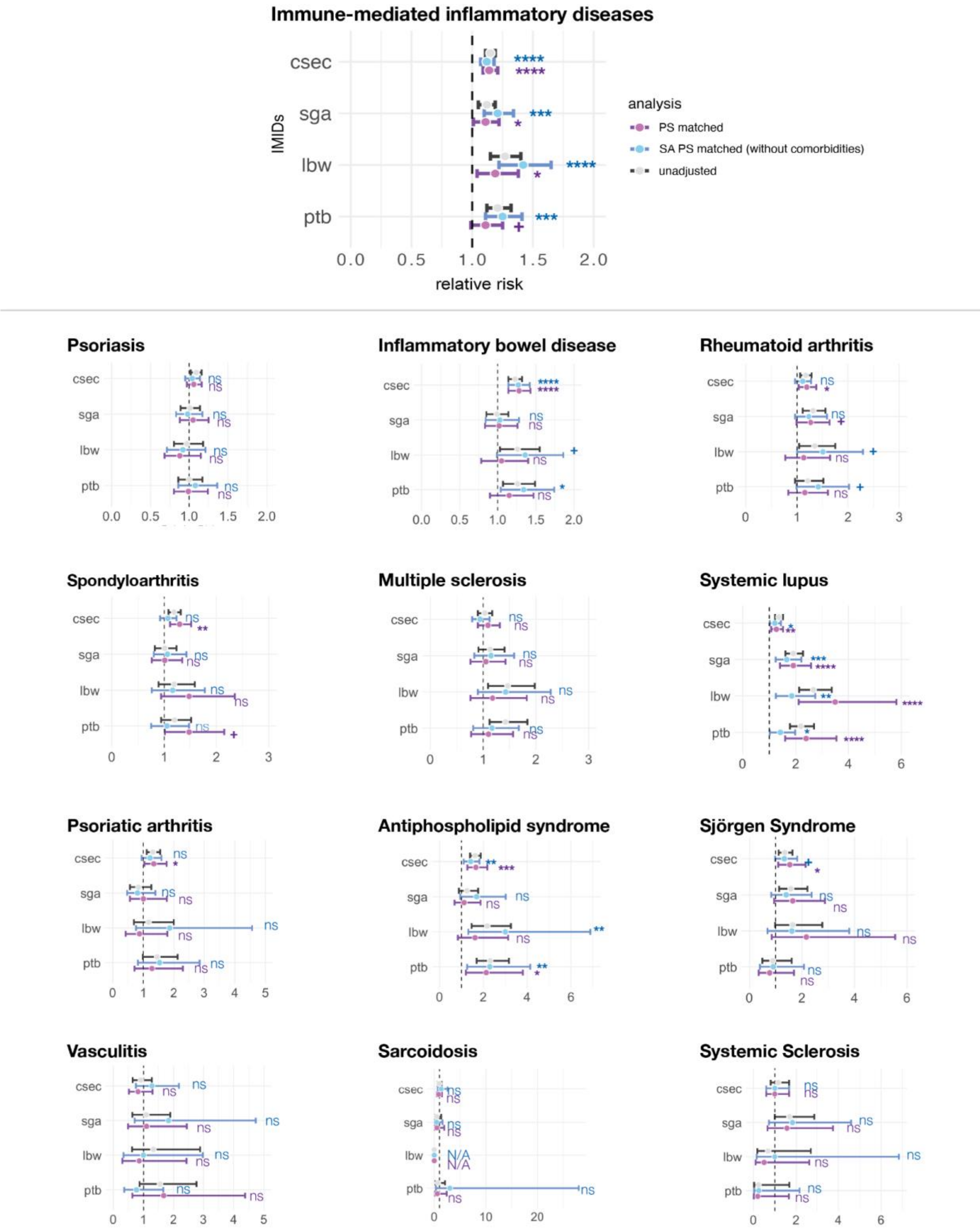


Figure 6.4 Adverse pregnancy outcomes of the IMIDs group, propensity score matched non-IMIDs group, and sensitivity analysis propensity score matched non-IMIDs group[14]

*Figure 6.4 Adverse pregnancy outcomes of the IMIDs group, propensity score matched non-IMIDs group, and sensitivity analysis propensity score matched non-IMIDs group (continued);APS Antiphospholipid Syndrome; Csec caesarean section; LBW Low Birth Weight; PTB Preterm Birth; IBD Inflammatory Bowel Disease; IMID Immune-mediated Inflammatory Disease; IMMs Immunomodulatory Medications; LMP Last Menstrual Period; MS Multiple Sclerosis; PsO Psoriasis; PsA Psoriatic Arthritis; RR Relative Risk; Sc Sarcoidosis; SGA Small for Gestational Age; SLE Systemic Lupus Erythematosus; SpA Spondyloarthritis; SjS Sjörgen's Syndrome; SSc Systemic Sclerosis; Va Vasculitis; Sensitivity analysis was performed to assess the influence of comorbidities on the association between IMIDs and risk of adverse pregnancy outcomes. The IMIDs group had slightly elevated risk of PTB (RR=1·1[1·0,1·3]), LBW (RR=1·2[1·0,1·4]), SGA (RR=1·1[1·0,1·2]), and c-section (RR=1·1[1·1,1·2]). Of 12 individual IMID, SpA, SLE, APS was associated with increased risk of PTB (SpA RR=1.5 [1.0,2.2]; SLE RR=2.4[1.6,3.6]; APS RR=2·1[1·2,3·8]). SLE was the only IMID correlated with enhanced risk of LBW (RR=3·5[2·1,5·8]). RA and SLE patients were 1·3([1·0,1·6]) and 1.9([1·4,2·6]) times more likely to deliver SGA babies. IBD, RA, PsA, SpA, SLE, APS, and SjS patients had elevated likelihood of caesarean section delivery(IBD RR=1·3[1·1,1·4], RA RR=1·2[1·0,1·4], PsA RR=1·3[1·0,1·8], SpA RR=1·3[1·1,1·5], SLE RR=1·3[1·1,1·5], APS RR=1.7[1·3,2·2], SjS RR=1·5[1·1,2·1]). When the comorbidities were not controlled, the IMIDs group's risk of PTB and LBW increased by 0.2. In addition, the risk of PTB and LBW of IBD and RA patients increased and gained statistical significance (IBD: PTB RR = 1·3[1·0, 1·7], LBW RR = 1·4[1·0, 1·9]; RA: PTB RR = 1·4[1·0, 2·0], LBW RR = 1·5[1·0, 2·3]). The association between APS and the risk of LBW also elevated and became statistically significant (APS LBW RR = 3·0[1·3, 6·9]). Statistical significance was reported as follows. $p<0·0001$:****, $0·0001\leq p<0·001$:***, $0·001\leq p<0·01$:**, $0·01\leq p<0·05$:*, $0·05\leq p<0·1$:+, $0.1<p$:ns*

Table 6.1 Descriptive statistics of non-IMIDs and IMIDs

HIV human immunodeficiency virus, acquired immunodeficiency syndrome; IMID Immune-mediated Inflammatory Disease; Variables are defined in Table A.6 2. SNOMED codes of diagnoses are listed in Table A.6 1. Mean and standard deviation are calculated for continuous variables. Proportions of each category are calculated for categorical variables.

Variable	***non-IMIDs (n=365,075)***	***IMIDs (n=5784)***
Maternal characteristics		
Maternal age	*31.0 (5.8)*	*32.7 (5.3)*
Age group		
17 or younger	*2893 (1.1)*	*12 (0.3)*
18-24	*57579 (22.1)*	*545 (13.8)*
25-29	*87759 (33.7)*	*1225 (31.1)*
30-34	*112308 (43.1)*	*2163 (54.8)*
Race group		
American Indian or Alaska Native	*4437 (1.3)*	*74 (1.3)*
Asian	*27513 (8.0)*	*332 (5.7)*
Black or African American	*14550 (4.2)*	*164 (2.8)*
Native Hawaiian or Other Pacific Islander	*3953 (1.2)*	*48 (0.8)*
White or Caucasian	*215895 (62.9)*	*4227 (73.1)*
Multirace	*17127 (5.0)*	*290 (5.0)*
Other	*57520 (16.8)*	*633 (10.9)*
Missing	*2162 (0.6)*	*16 (0.3)*
Ethnicity		
Hispanic or Latino	*72607 (21.2)*	*665 (11.5)*
Not Hispanic nor Latino	*262950 (76.6)*	*4986 (86.2)*
Unknown/Unreported	*7536 (2.2)*	*133 (2.3)*
BMI category		
Underweight	*2823 (0.8)*	*62 (1.1)*
Normal	*49346 (14.4)*	*985 (17.0)*
Obese	*29618 (8.6)*	*685 (11.8)*
Overweight	*29614 (8.6)*	*599 (10.4)*
Missing	*231756 (67.5)*	*3453 (59.7)*

Table 6.1 Descriptive statistics of non-IMIDs and IMIDs (continued)

Variable	***non-IMIDs (n=365,075)***	***IMIDs (n=5784)***
Maternal characteristics (continued)		
Insurance		
Commercial	*158995 (46.3)*	*3191 (55.2)*
Medicaid/Medicare	*181892 (53.0)*	*2575 (44.5)*
Self Pay	*76 (0.0)*	*0 (0.0)*
Missing	*2194 (0.6)*	*18 (0.3)*
Smoker	*24414 (7.1)*	*511 (8.8)*
Illegal drug user	*25745 (7.5)*	*578 (10.0)*
Alcohol user	*60516 (17.6)*	*1678 (29.0)*
Vulnerability index of socioeconomic status	*0.4 (0.2)*	*0.4 (0.2)*
Vulnerability index of housing composition	*0.4 (0.3)*	*0.4 (0.3)*
Vulnerability index of minority status and language	*0.6 (0.2)*	*0.6 (0.2)*
Vulnerability index of housing type and transportation	*0.6 (0.3)*	*0.6 (0.3)*
Rural/urban classification		
Metropolitan	*289998 (84.5)*	*4952 (85.6)*
Micropolitan	*16355 (4.8)*	*268 (4.6)*
Small Town	*5564 (1.6)*	*134 (2.3)*
Rural	*4378 (1.3)*	*84 (1.5)*
Missing	*26862 (7.8)*	*346 (6.0)*
Pregnancy characteristics		
Gravidity		
1	*78337 (22.8)*	*1240 (21.4)*
2-4	*189217 (55.1)*	*3052 (52.8)*
5≤	*39838 (11.6)*	*804 (13.9)*
Missing	*35765 (10.4)*	*688 (11.9)*
Parity		
0	*42250 (12.3)*	*717 (12.4)*
1	*121735 (35.5)*	*2006 (34.7)*
2-4	*135366 (39.4)*	*2254 (39.0)*
5≤	*8041 (2.3)*	*119 (2.1)*
Missing	*35765 (10.4)*	*688 (11.9)*

Table 6.1 Descriptive statistics of non-IMIDs and IMIDs (continued)		
Variable	***non-IMIDs (n=365,075)***	***IMIDs (n=5784)***
Pregnancy characteristics (continued)		
Preterm history		
Yes	*71978 (21.0)*	*1232 (21.3)*
No	*235414 (68.6)*	*3864 (66.8)*
Missing	*35765 (10.4)*	*688 (11.9)*
Fetal sex		
Female	*156624 (48.6)*	*2622 (48.4)*
Male	*165401 (51.4)*	*2791 (51.5)*
Unknown	*48 (0.0)*	*2 (0.0)*
Other	*15 (0.0)*	*1 (0.0)*
Delivery year		
2013	*20462 (6.0)*	*231 (4.0)*
2014	*30362 (8.8)*	*346 (6.0)*
2015	*34310 (10.0)*	*430 (7.4)*
2016	*35708 (10.4)*	*495 (8.6)*
2017	*35239 (10.3)*	*572 (9.9)*
2018	*34887 (10.2)*	*640 (11.1)*
2019	*36192 (10.5)*	*706 (12.2)*
2020	*34680 (10.1)*	*715 (12.4)*
2021	*39015 (11.4)*	*767 (13.3)*
2022	*42302 (12.3)*	*882 (15.2)*
Comorbidities		
Diabetes	*2510 (0.7)*	*88 (1.5)*
Chronic kidney disease	*218 (0.1)*	*18 (0.3)*
Obesity	*10296 (3.0)*	*407 (7.0)*
Chronic liver disease	*661 (0.2)*	*30 (0.5)*
Asthma	*17978 (5.2)*	*693 (12.0)*
Depression	*31365 (9.1)*	*1276 (22.1)*
Pneumonia	*3072 (0.9)*	*119 (2.1)*
Urinary tract infection	*35578 (10.4)*	*1086 (18.8)*
Sexually transmitted disease	*5712 (1.7)*	*203 (3.5)*
Cardiovascular disease	*47737 (13.9)*	*2024 (35.0)*
Sepsis	*1491 (0.4)*	*81 (1.4)*

6.4 Discussion

"To our knowledge, this is the first study that extensively evaluated the influence of IMIDs and comorbidities on women undergoing pregnancy. Here, we retrospectively assessed people diagnosed with one or more IMIDs before pregnancy. People who had IMIDs before pregnancy doubled from 2013 to 2022. Of the 5,784 pregnant people with IMIDs, only 17% were prescribed IMMs prenatally. Among people exposed to IMMs before the pregnancy, the majority, 48% to 70%, continued their prescriptions until delivery. People who had an IMID diagnosis before pregnancy were more likely to have comorbidities than those who did not. Overall, IMID patients had a similar but slightly elevated risk of adverse pregnancy outcomes after controlling for covariates when compared to controls. Patients with SLE had significantly elevated risk for all adverse pregnancy outcomes investigated. Out of the twelve selected IMIDs only three had an increased risk for PTB, one had an increased risk for LBW, two had an increased risk for SGA, and six had an increased risk for caesarean section. The risk of LBW and PTB of IMIDs was lower in analyses that controlled for comorbidities. We noted PTB and LBW risk on patients with RA or IBD are similar to patients without those conditions, unlike prior studies."

"Prevalence rate of pregnancy with a history of IMIDs diagnosis doubled in the recent ten years. There are several possible explanations for this trend. First, maternal age increased. According to US Census Bureau,[258], fertility rate of 15-29 age range gradually dropped, whereas that of the 30-44 age range rose from 1990 to 2019. As IMIDs usually develop during the reproductive age and are untreatable, older people have a higher likelihood to have IMIDs at the time of pregnancy. Second, enhanced understanding about classification and diagnosis of IMIDs could partially explain the trend. This explanation was considered as a possible reason for the

increase in IMIDs prevalence rate in the general population.[259] *Last but not least, it could be attributable to actual increase in the IMIDs prevalence rate. Although the exact reason of prevalence rate is not identified, there is a consensus that IMIDs prevalence is gradually increasing.*[260]*"*

"We found a strong association between specific IMIDs (SLE and APS) and adverse pregnancy outcomes. This finding is consistent with previous observations that SLE and APS are risk factors for adverse pregnancy outcomes. Gao et al., 2019[246] *built a deep learning model and predicted SLE as one of the most important features in predicting extremely preterm birth. A study conducted on the largest multicentric study to prospectively assess adverse pregnancy outcomes in SLE and/or APS pregnant patients (n=385) reported nearly a 20% chance of adverse pregnancy outcomes, regardless of disease activity.*[247] *Adverse pregnancy outcomes of that study were PTB, fetal/neonatal death, and fetal growth restriction. A meta-analysis of eleven observational case-control studies and thirteen cohort studies concluded that patients with SLE had twice the risk of delivering preterm when compared to controls.*[248]*"*

"Surprisingly, most individual IMIDs (9: PTB, 11: LBW, 9: SGA, 6: caesarean section) were not correlated with adverse pregnancy outcomes. Given that autoimmune conditions are often considered a risk factor for high-risk pregnancy, this finding was somewhat unexpected compared to recent studies.[261,262] *A meta-analysis conducted on twelve studies and 3907 IBD patients showed a correlation between IBD and higher incidence of PTB, LBW, and caesarean section.*[250] *Huang et al., 2023*[251] *evaluated eighteen studies to assess maternal outcomes of pregnant patients with RA. That study reported elevated odds of PTB, SGA, LBW, and stillbirth among patients with RA. Our study differed from these studies because we extensively controlled for comorbidities, addressing both physical and mental conditions. IBD and RA correlation with*

PTB and LBW decreased and lost statistical significance when we included comorbidities in the covariates used for propensity score matching. This suggests that comorbidities significantly influence the relationship between IBD and RA, and PTB and LBW. Our result implies that, for several IMIDs, underlying comorbidities may be more significant risk factors than IMID itself." It is also important to note our study population was restricted to continuously enrolled patients who delivered live infants after 20 weeks of gestation. In the context of this population, it is worth considering that IBD and RA may heighten the risk of early pregnancy loss, potentially leading to reduction in cases of PTB and LBW as pregnancy terminated before reaching the outcomes of interest. *"At the same time, the low rate of medication use in this cohort may suggest that the cohort had less severe cases of IMIDs, than populations studied in academic centers. To further understand IMIDs' relationship with adverse pregnancy outcomes, more research is needed to understand the trajectories of both IMIDs and comorbidities prior to pregnancy."*

"The observed co-occurrence of IMIDs within our study group was notably low, reporting 7%. Several factors may account for this finding. Firstly, our study focused specifically on the co-occurrence of IMIDs within the subset of twelve types of individual IMID, representing a fraction of the wide spectrum of autoimmune diseases. Second, cohorts of pregnant women are significantly younger than the overall population, and this study concentrated on pre-existing diagnoses before pregnancy. It is reasonable to expect an elevation in the total prevalence of IMIDs in this cohort to increase after pregnancy and as the cohort ages. Third, Providence St Joseph (PSJH) is a community healthcare system that serves patients in seven states that have relatively good health outcomes; there may be fewer patients with high-risk pregnancies and/or severe IMIDs than would be seen in an academic setting or in other regions of the United States."

"We observed a relatively low IMMs prescription rate and a high continuation rate. Low IMMs prescription rate is not reflective of the standard of care.[263] *A meta-analysis conducted on 39 studies characterizing the use of TNF-α inhibitors among pregnant patients with IMIDs condition noted that 6% of them (1786/34223) were exposed to TNF-α inhibitors during pregnancy.*[264] *This finding somewhat accords with the prenatal TNF-α inhibitors prescription rate of our findings, 2.8%, considering that the majority of their samples were IBD patients (58% vs. 22%). IMM prescription rate of patients with IBD was 1.6 times higher than for patients with IMIDs overall. The high continuation rate of IMM corresponds with that prior study. Allen et al. 2022,*[265] *a study on 338 patients with IMIDs, reported a 78% continuation rate of biologics, mostly TNF-α inhibitors. Our study found a similar rate of 70%."*

"The main strength of this study was the large sample size and use of longitudinal clinical observations from EHR data. We had some of the largest sample sizes of retrospective EHR records investigating the relationship between several IMIDs and pregnancy. EHR contains comprehensive and longitudinal information including but not limited to medical history, diagnosis, prescription, location of residence, and socioeconomic factors. We could control for many factors known to be associated with adverse pregnancy outcomes and IMIDs factors, including maternal and pregnancy characteristics comorbid health conditions and socioeconomic environmental factors."

"To reduce surveillance bias, we limited our analyses to continuously enrolled patients. People transiently enrolled for pregnancy are likely to lack information on medical history. Whereas, people with IMIDs may be more likely to receive more continuous care from the health system. Therefore, people with IMIDs have more detailed information on their health condition when compared to controls, leading to surveillance bias. In addition, we further addressed this

bias by conducting propensity score matching when evaluating the outcomes. The propensity score matching method matches individual people with IMID to people with similar characteristics except for the exposure to IMIDs."

"One major limitation of the study was that results were limited to live births with GA of 20 weeks or greater. Patients who experience early pregnancy loss or stillbirth may not always appear in their enrolled hospital's system when their pregnancy ends, leading to significant risk of missing data, misclassification, and ascertainment bias. Further research into early pregnancy loss before 20 weeks and stillbirth is essential but will require data beyond that available in EHR charts. This can also lead to bias toward fewer cases of adverse pregnancy outcomes we investigated as the pregnancy terminated before these outcomes occurred. Another significant limitation of this study is that we did not properly investigate the influence of IMMs on adverse pregnancy outcomes as structured EHR data does not provide clear measure for disease activity. We assumed people remaining on prescription were more likely to be experiencing ongoing disease activity, affiliated with a higher chance of adverse pregnancy outcome,[256,257] *which can induce confounding by indication. This assumption was further investigated in our sensitivity analysis. Patients with IMIDs who had IMMs prescriptions had higher RR across adverse pregnancy outcomes than patients with IMIDs who did not have IMMs prescriptions, although these associations did not reach statistical significance. This analysis did not evaluate the risks and benefits of IMMs exposure. Its risks and benefits could be better addressed with either natural language processing on free-text notes, or through prospective studies. An additional limitation was the low IMM prescription rate. Although this reflects real world care in the population studied, results from this study may show higher risk than might be achieved with recommended care guidelines. Factors influencing provider and patient decisions may include barriers to access to*

healthcare or medication, differences in IMID activity or severity, hesitancy regarding taking medications during pregnancy, and other differences found between community and academic healthcare settings.

Another limitation is that we considered the individual an independent entity, ignoring correlations among multiple pregnancies of a single person. As an alternative, we matched on parity and gravidity when generating matched control. Also, EHR data contains the types of errors and omissions typically observed in patient charts, including potential underdiagnosis, overdiagnosis and misclassification of IMIDs. Additionally, there was a significant amount of missing data for pregravid BMI information. We presumed that patients were not asked about it, potentially because clinicians did not consider as a relevant health concern. We classified individuals with missing pregravid BMI as belonging to the normal pregravid BMI category. Lastly, we are limited to a small sample size for a few individual IMID groups (SjS, Va, Sc, SSc). Although we had one of the largest samples for these individual IMIDs, it is difficult to draw conclusions out of these groups as a small sample size can extrapolate findings. As a result, we highlighted our findings on individual IMID groups with sufficient sample size and recommend future research with larger cohorts for IMIDs with lower prevalence"

6.5 Conclusion

In the context of the overall goal **to leverage RWD, especially EHR, to address the knowledge gap in treating pregnant women**, Aim 4 (**Harness electronic health records to assess the influence of comorbidities on pregnancy course**) assessed the influence of comorbidities on pregnancy course. Because medical treatment is given for specific indication, it is important to understand the relationship between comorbidities and adverse pregnancy outcomes. The hypothesis of Aim 4 was that there is an elevated risk of adverse pregnancy outcomes among patients who had IMIDs before pregnancy. The objective was to assess this association.

There were several noteworthy key findings from Aim 4. First, "*the association between IMIDs and increased risk of adverse pregnancy outcomes depended on the specific type of IMID and presence of comorbidities."* In our disease-specific analysis, SLE or APS exhibited strong associations with an elevated risk of PTB. This finding was particularly reassuring, aligning with existing knowledge that identifies SLE and APS as significant risk factors for PTB. Surprisingly, "*patients with RA or IBD had a similar likelihood to deliver preterm and low birthweight babies."* This finding contrasts with previous findings that have consistently reported associations between IBD/RA and elevated risks of PTB and LBW. In our sensitivity analysis, where underlying comorbidities were excluded from propensity score matching, the risk of PTB and LBW increased and gained statistical significance. This suggests that the inclusion of comorbidities play a crucial role in understanding the relationship between IBD/RA and PTB/LBW.

We acknowledge two significant limitations in our study. First, we lacked a proper measure for disease activity, preventing us from assessing the impact of the disease's activity on pregnancy outcomes. This limitation further hindered us to assess the influence of immunomodulatory medication on pregnancy outcomes. Patients with active flares are likely to be on medications. Thus, without the information on diseases' activity, we cannot properly evaluate the impact of immunomodulatory medications on pregnancy outcomes.

To overcome the limitation of lacking a proper measure for disease activity, future research could leverage natural language processing techniques, implementing advanced computational methods to extract information on disease activity. Additionally, considering our observations, there is a compelling need to revisit and enhance pre-pregnancy counseling guidelines for patients with RA and IBD. In the following chapter where we conclude this dissertation, we will provide an overview of major findings, limitations, and future directions across Aims 1-4.

Chapter 7. CONCLUSION

The overall goal of this dissertation was **to leverage real world data (RWD) electronic health records (EHR) to address knowledge gaps with a use case in preterm birth (PTB).**

7.0 INTRODUCTION

Table 7.1 contains a summary of the primary findings, limitations, and future directions encountered in Aims 1, 2, 3, and 4. Further details on Table 7.1 are provided in the following sections of Chapter 7. Across Aims 1 to 4, we presented our approach to leverage RWD EHR to address the knowledge gap in treating pregnant women in various aspects. We employed both hypothesis-generating and -testing approaches. Aim 1 utilized a data-driven statistical data mining approach on EHR to detect signals of previously identified and unidentified drug effects. Aim 2 validated detected drug effect signals from Aim 1 using traditional pharmacoepidemiology methods. We used a slightly different approach to achieve Aim 3 from Aims 1 and 2. Instead of discovering new hypotheses from EHR, we selected existing yet controversial hypotheses to test in our study population. Aim 3 investigated medical interventions that involve targeting pregnant women and lack evidence to support or oppose it using EHR. Across Aims 1 to Aim 3, we observed that underlying comorbidities heavily influence the drug effects on adverse pregnancy outcomes. In Aim 4, we harnessed EHR to assess the influence of comorbidity of interest on pregnancy course.

Table 7.1 Summary of primary findings, limitations, and future directions

	Findings	**Limitations**	**Future directions**
Aim 1 (Chapter 3) To detect signals of previously identified and unidentified drug effects using a statistical data mining approach on EHR	• common use of medication • 1329 -> 175 -> 58 • detected expected and unexpected signals	• no multiple testing correction • uniform set of comorbidities	• high dimensional propensity score matching • use of external database
Aim 2 (Chapter 4) To validate detected drug effect signals from Aim 1 using traditional pharmacoepidemiology methods	• late SSRI exposure and increased risk of PTB • streamlined workflow to detect and validate drug effect signals	• potential exposure misclassification • Limited number of patients took PHQ	• subgroup analysis • application of this workflow to other adverse outcomes
Aim 3 (Chapter 5) To investigate medical interventions targeting pregnant women using EHR	• low prophylactic anticoagulant administration rate • similar rate of coagulopathy, bleeding, and maternal-fetal health outcomes despite worse COVID-19	• small sample size • lack of variable to reflect COVID-19 symptom severity at admission	• larger sample • prospective study collecting information on clinician's decision
Aim 4 (Chapter 6) To harness EHR to assess the influence of comorbidities on pregnancy course	• strong association between SLE/APS and PTB • no association between IBD/RA and PTB/LBW	• lack of disease activity information	• use NLP to extract disease activity information • revisit pre-pregnancy counseling for IBD and RA

7.1 Aim 1: To detect signals of previously identified and unidentified drug effects using statistical data mining approach on electronic health record

Aim 1 advances our overall goal of **leveraging RWD, especially EHR, to fill in knowledge gaps in treating pregnant women** by **detecting signals of previously identified and unidentified drug effects using a statistical data mining approach on EHR**. The hypothesis of Aim 1 was that there exist not yet characterized drug effects that are associated with the risk of PTB. Our objective was to detect previously known and unknown drug effect signals associated with the risk of PTB using EHR.

7.1.1 *Summary of primary findings*

In Aim 1, we employed a data-driven approach to uncover signals of known and previously unidentified drug effects on PTB through statistical data mining of EHR. We leveraged propensity score matching at scale to identify these drug effect signals. This chapter presents a retrospective assessment of 365,074 individuals continuously enrolled in Providence. This population was enriched with individuals aged 30 to 34 years, of White or Caucasian race, non-Hispanic or Latino, covered by Medicaid/Medicare, and living in metropolitan areas. Our findings revealed that most patients received prescription medications during pregnancy, with the total prescription rate increasing from 58% in 2013 to 75.4% by 2022. The maternal age group of 18 to 24 years exhibited the highest prescription rate of 73.0% while mothers aged 40 or older had the lowest prescription rate, reporting 63.4%. The Medicare/Medicaid insurance group had a higher prescription rate, reporting 72.2%, compared to the commercial insurance group (62.6%). Among the racial groups, pregnant women identified as Black or African American had the highest prescription rate at 77.3% while Asians had the lowest, reporting 64.4%. We observed that the prescription rate increased as the number of comorbidities increased. This trend was similar for both pre-pregnancy and prenatal comorbidities. Approximately half of the pregnant individuals with no pre-pregnancy or prenatal problem diagnoses received prescriptions during pregnancy. Patients with eleven or more pre-pregnancy or prenatal problem diagnoses had a prescription rate higher than 90%.

We focused on outpatient medication when applying propensity score matching at scale. Our population had at least one prescription for 1,329 medications during pregnancy. Of these 1,329 medications, 175 met the minimum sample size of 600. We identified 58 medications (RR<1: 12, RR≥1: 46) associated with the risk of PTB in an analysis adjusted for common diagnoses during the pre-pregnancy and prenatal period. Medications with statistically significant correlations to the risk of PTB were categorized based on their indications: PTL/PTB, risk factors for PTB, and infection. Of these, 43 medications had indications categorized into at least one of these categories. Four medications fell into the PTL/PTB indications category, while 32 medications had indications as risk factors for PTB. Nine medications were prescribed in cases of infections, including bacterial, fungal, and viral infections.

7.1.2 *Limitations*

One major limitation of this study is the absence of multiple testing corrections. We acknowledge that multiple testing increases the risk of generating false positives. However, it was a deliberate choice not to apply multiple testing corrections. The study's primary goal was to generate hypotheses rather than to rigorously test them. Furthermore, the issue of p-values can be addressed and adjusted for through various multiple testing correction methods. Instead of imposing a specific correction method, we provided confidence intervals, enabling future researchers to use them in meta-analyses. We stress that these hypotheses should be interpreted cautiously and subjected to further evaluation in well-designed studies that account for the specific characteristics of the exposures of interest and their indications.

Another limitation of this study pertains to the uniform sets of comorbidities used. Although we conducted multiple analyses, both with and without the inclusion of common comorbidities before and during pregnancy, it is important to recognize that individual medications are prescribed for specific indications. Medications with less common indications may have been underrepresented in the covariate analyses. This limitation underscores the necessity for future research to consider the nuanced indications for each medication when assessing their impact on pregnancy outcomes.

7.1.3 *Future directions*

In the future, we can apply several promising approaches to address the limitations encountered in these studies. One such approach is high-dimensional propensity score matching. High-dimensional propensity score matching offers a robust way to control for confounding variables in observational studies. Unlike traditional propensity score matching, which involves considering a limited number of covariates, high-dimensional matching can involve hundreds of empirical covariates. This approach can enhance the precision of matching and reduce the potential for bias, ultimately leading to more reliable study results. It is a powerful tool for addressing confounding in complex datasets like EHRs. When applying this approach, we would need to empirically limit the number of covariates, considering the sample size of the exposure groups.

Another promising approach is leveraging external databases. Incorporating external databases, such as ChEMBL, is a valuable strategy for enhancing research in this field. These databases provide valuable information about drug indications, contraindications, and other clinical data. Researchers can automatically select relevant covariates directly related to drug indications and treatment by leveraging external databases, streamlining the covariate selection process. This approach can enhance the accuracy of propensity score matching and reduce the risk of confounding, particularly when assessing the effects of medications during pregnancy.

7.2 AIM 2: TO VALIDATE DETECTED DRUG EFFECT SIGNALS FROM AIM 1 USING TRADITIONAL PHARMACOEPIDEMIOLOGY METHODS

Aim 2 advances our overall goal to leverage RWD EHR to address knowledge gaps in treating pregnant women by **validating detected drug effect signals from Aim 1 using traditional**

pharmacoepidemiology methods. Among the detected drug effect signals, we selected sertraline to further investigate in Aim 2. Sertraline was chosen due to its relatively large exposure group, well-documented indications, and existing controversy regarding its association with the risk of PTB. The hypothesis of Aim 2 was that there is an elevated risk of PTB for SSRI, a broader category of sertraline, exposures after the first trimester. Our objective was to characterize the risk of PTB and other related adverse pregnancy outcomes based on the timing of SSRI exposure.

7.2.1 *Summary of primary findings*

In Aim 2, we validated the drug effect signals detected in Chapter 3 using traditional pharmacoepidemiology methods. We selected sertraline for further investigation. The association between exposure to sertraline and an increased risk of PTB has been previously reported in the literature. However, this association has been considered controversial because depression, the indication for sertraline, is a known risk factor for PTB. In this chapter, we limited our analyses to patients who had depression onset before pregnancy. We expanded our exposure of interest to SSRI, a broader category of sertraline. We comprehensively assessed the association between SSRI exposure and the risk of PTB, as well as other related adverse events, such as SGA and LBW. Our study controlled for potential confounding factors, including depression, the COVID-19 pandemic period, geospatial factors, and the severity of depressive symptoms. We also performed SSRI drug-specific analyses and additional analyses on other classes of antidepressants (N06AA and N06AX). It's worth noting that our analytic population had no patients with prenatal prescriptions for N06AC and N06AD.

In this study, we found that women prescribed SSRIs after the first trimester were 1.5 times more likely to experience PTB than those not exposed to SSRIs. Interestingly, we observed no such association for patients exposed to SSRIs only during the first trimester of pregnancy. Furthermore, our analysis revealed robust and statistically significant associations between late SSRI exposure and PTB, which persisted even in sensitivity analyses.

7.2.2 *Limitations*

The major limitation of this study was the potential for exposure misclassification. Prescription orders may not always accurately reflect the actual medication exposure of patients. Non-differential misclassification of exposure was a concern in this study because it tends to bias associations toward the null, potentially attenuating the strength of observed associations. This limitation is inherent in using EHR data; however, the study attempted to address the impact of exposure misclassification through sensitivity analysis.

Another limitation was the limited number of patients for whom depression severity was assessed. This study employed standardized scoring systems such as the PHQ-9 and PHQ-4 to assess depression severity. However, only a subsample of the study population completed these assessments. Although sensitivity analysis was performed on a subpopulation of individuals who underwent these assessments (3,532 out of 8,406; 42%), the sample size was insufficient to conduct stratified analyses based on depression severity. This is important to note because such an approach would further support our findings on the association between late SSRI exposure and the risk of PTB if a similar relative risk of PTB was observed between these subgroups (non-severe and severe).

7.2.3 *Future directions*

Moving forward, we can conduct stratified analyses based on multiple factors to elucidate the association between SSRI exposure and the risk of PTB. Firstly, we can perform a stratified analysis based on the severity of pre-pregnancy and prenatal depression. This approach can help us understand whether the impact of SSRIs varies among pregnant individuals with different levels of depressive symptoms. Tailoring clinical recommendations to specific patient characteristics can optimize maternal and fetal health outcomes. Furthermore, this approach would provide additional support for our findings regarding the association between late SSRI exposure and the risk of PTB if a similar relative risk of PTB was observed within these subgroups (non-severe and severe).

Secondly, to address a significant limitation of our analysis, we can conduct a subgroup analysis focusing on the subpopulation of nulliparous patients. One of the primary drawbacks of our previous analysis was the assumption of independence among individual pregnancy cases, disregarding potential correlations between multiple pregnancies within the same patients. This subgroup analysis will enhance the accuracy of our findings and recognize the unique characteristics of nulliparous pregnancies.

Thirdly, we can apply natural language processing (NLP) techniques to extract information from free-text clinical notes for a more granular understanding of PTB risk. This additional data source would enable us to conduct subgroup analyses on spontaneous PTB cases. The limitation of relying solely on structured EHR data is the inability to distinguish between spontaneous and medically indicated PTB.

7.3 Aim 3: To investigate medical interventions targeting pregnant women using electronic health records

Aim 3 advances our overall goal of leveraging RWD from EHR to address knowledge gaps in treating pregnant women by **investigating medical interventions targeting pregnant women using EHR**. In the previous two aims, we demonstrated a streamlined workflow to detect previously known and unknown drug effect signals and validate detected signals. This forms the foundational framework to advance our overall goal **to leverage RWD, particularly EHR, to address knowledge gaps in the treatment of pregnant women.** In Aim 3 (**Investigate medical interventions targeting pregnant women using electronic health records**), we took a different and complementary approach to narrow the knowledge gap in treating pregnant women. Instead of generating hypotheses, we selected a controversial and existing hypothesis in clinical practice that had not been previously investigated before. Specifically, we explored the National Institute of Health's antithrombotic therapy recommendation for hospitalized pregnant patients with manifestations of COVID-19. We hypothesized that there is a high rate of prophylactic anticoagulant administration rate among hospitalized pregnant patients with manifestation of COVID-19. The objective of Aim 3 was to characterize this rate and to evaluate the treatment in this study population.

7.3.1 *Summary of primary findings*

In Aim 3, we presented our approach to evaluating controversial medical treatment guideline for pregnancy, which lacks supporting evidence. We assessed the adoption rate of national prophylactic anticoagulation guidelines for hospitalized pregnant women with COVID-19. Although there is a lack of evidence about pregnant patients, the benefits of prophylactic anticoagulant administration on hospitalized patients have been studied in the non-pregnant population. Therefore, we hypothesized that we would observe a high rate of prophylactic anticoagulant administration among hospitalized pregnant patients with COVID-19. We expected to find minimal differences in patient characteristics between the treatment and control groups because the administration of prophylactic anticoagulation was recommended regardless of the severity of COVID-19. However, it turned out that most pregnant patients hospitalized with COVID-19 did not receive prophylactic anticoagulants. Instead, patients with higher comorbidities, those infected before the third trimester, and those infected with non-Omicron variants were more likely to receive prophylactic anticoagulants. Interestingly, despite experiencing more severe COVID-19 symptoms, the treatment group did not have an increased risk of coagulopathy, bleeding, or adverse maternal-fetal health outcomes.

7.3.2 *Limitations*

Despite having a large database, this study was constrained by a small sample size. One unexpected finding was the low rate of prophylactic anticoagulant administration, with only 7% of hospitalized COVID-19 pregnant patients receiving prophylactic anticoagulants. This discrepancy introduced a significant issue of confounding by indication. The treatment group had more pre-COVID-19 complications and included a greater proportion of critically ill patients. Although attempts were made to mitigate this bias through propensity score matching, the challenge persisted due to the small sample size and the absence of appropriate variables that could reflect the severity of COVID-19 illness at the time of infection.

Additionally, we highlighted the limitations caused by EHR data's retrospective and structured nature. Structured data in EHRs may not provide sufficient insight into medical reasoning, making it difficult to fully understand the clinical decision-making process. Moreover, the study noted that individuals had a wide range of start times for anticoagulant administration, both before and after the potential onset of COVID-19 treatment. As covariates occurring after the exposure are unsuitable for the propensity score method, they were excluded from the primary matching model. However, sensitivity analyses were conducted to assess the impact of the initial medication count as a partial means to address the potential influence of COVID-19 illness severity at the time of treatment initiation.

Lastly, this study did not verify whether the increased risk of requiring O_2 assistance among the treatment group was due to confounding by indication or other factors. The assumption was made that it was associated with confounding by indication based on prior studies involving hospitalized COVID-19 patients. This limitation underscores the complexity of disentangling the effects of treatments in real-world clinical settings and emphasizes the need for further investigation to elucidate causal relationships.

7.3.3 *Future directions*

In the future, we can assess the risks, benefits, and safety of exposure to IMMs on maternal-fetal health by utilizing NLP to analyze free-text clinical notes. NLP techniques can extract valuable insights about the disease's activity during pregnancy, enabling us to minimize confounding by indication and properly evaluate the impact of IMMs exposure on pregnancy outcomes. However, one of the most crucial next steps is revisiting existing guidelines for patients with RA and IBD. Unlike prior studies, our research revealed that RA and/or IBD patients had no elevated risk for PTB and LBW. To ensure that patients receive the most up-to-date and evidence-based care, it is essential to validate these findings in a separate study with a larger sample size and a different population. Furthermore, when designing research to investigate the impact of IMIDs on maternal health, it is essential to consider the presence of comorbidities. Many patients with IMIDs have comorbidities, which appear to impact maternal health more than the IMID itself for specific types of IMID.

7.4 AIM 4: TO HARNESS ELECTRONIC HEALTH RECORDS TO ASSESS THE INFLUENCE OF COMORBIDITIES ON PREGNANCY COURSE

Aim 4 advances our overall goal to leverage RWD EHR to address knowledge gaps in treating pregnant women by **harness electronic health records to assess the influence of comorbidities on pregnancy course**. Across Aim 1 to 3, we observed that comorbidities heavily influence drug effects on pregnant women. The combined insights from Aims 1 and 2, illustrated in *Figure 3.2*, revealed that different sets of comorbidities alter the associations between mediation exposure and the risk of PTB. In Aim 3, we found that the number of comorbidities before COVID-19 infection was the most important feature classifying the prophylactic anticoagulant administration status.

In Aim 4, we selected specific comorbidities of interest and evaluated their influence on maternal health. We examined the risk of IMIDs before pregnancy and how underlying comorbidities affect these outcomes. The hypothesis was that there is an elevated risk of adverse pregnancy outcomes among patients who had IMIDs before pregnancy the objective was to test this population in our study population.

7.4.1 *Summary of primary findings*

In Aim 4, we employed EHR data to investigate the influence of comorbidities on pregnancy outcomes. We specifically focused on Immune-mediated inflammatory diseases(IMIDs) as our comorbidity of interest. We aimed to assess the risk of adverse pregnancy outcomes in patients with IMIDs while considering the presence of other comorbidities. Our retrospective analysis covered patients diagnosed with at least one IMID before pregnancy. Interestingly, the number of patients with IMIDs before pregnancy doubled from 2013 to 2022. Among the 5,784 pregnant individuals with IMIDs, only 17% were prescribed immunomodulatory medications (IMMs) during pregnancy, while the majority, ranging from 48% to 70%, continued their IMMs prescriptions throughout pregnancy.

When comparing the IMIDs and non-IMIDs groups, we observed that the IMIDs group was more likely to experience complications. After adjusting for covariates, individuals with IMIDs had a slightly elevated risk of adverse pregnancy outcomes compared to the control group. Our analysis of twelve selected IMIDs revealed that the risk of adverse pregnancy outcomes depended on the specific type of IMID. Three of these conditions were associated with an increased risk of PTB, one with an increased risk of LBW, two with an increased risk of SGA births, and six with an increased risk of surgical delivery. Notably, the risk of LBW and PTB associated with IMIDs decreased when we controlled for comorbidities. However, patients with systemic lupus erythematosus (SLE) had a significantly elevated risk for all the adverse pregnancy outcomes we investigated. In contrast to prior studies, patients with rheumatoid arthritis (RA) or inflammatory bowel disease (IBD) had a similar risk of LBW and PTB compared to controls.

7.4.2 *Limitations*

This study had significant limitations in investigating the influence of immunomodulatory medications (IMMs) on adverse pregnancy outcomes. EHR data did not provide a proper measure for disease activity, making it challenging to assess the impact of IMMs. We assumed that individuals who remained on treatment were more likely to be experiencing ongoing disease activity, which could be associated with a higher likelihood of adverse pregnancy outcomes.

Another limitation was that we considered individual pregnancy cases as independent entities, overlooking potential correlations among multiple pregnancies of the same person. To address this limitation to some extent, we employed matching on parity and gravidity when generating matched controls. However, this approach does not sufficiently mitigate the limitations. Further research should account for the correlation between multiple pregnancies within individuals.

7.4.3 *Future directions*

In the future, we can assess the risks, benefits, and safety of exposure to IMMs on maternal-fetal health by utilizing NLP to analyze free-text clinical notes. NLP techniques can extract valuable insights about the disease's activity during pregnancy, allowing us to minimize confounding by indication and properly evaluate the impact of IMMs exposure on pregnancy outcomes. However, one of the most crucial next steps is revisiting existing guidelines for patients with RA and IBD. Unlike prior studies, our research revealed that RA and/or IBD patients had no elevated risk for PTB and LBW. To ensure that patients receive the most up-to-date and evidence-based care, it is essential to validate these findings in a separate study with a larger sample size and a different population. Furthermore, when designing research to investigate the impact of IMIDs on maternal health, it's essential to consider the presence of comorbidities. Many patients with IMIDs have comorbidities, which appear to impact maternal health more than the IMID itself for specific types of IMID.

7.5 Overall

7.5.1 *Summary of primary findings*

In this dissertation, we have addressed key knowledge gaps in treating pregnant women across various aspects. In Aim 1 (Chapter 3), we initially employed a data-driven approach to identify 58 medications out of 175 that displayed statistically significant associations with the risk of PTB. Aim 2 (Chapter 4) focused on validating these findings, particularly on sertraline. This validation revealed a 1.5-fold increased risk of PTB associated with late-pregnancy SSRI exposure. Aim 3 (Chapter 5) aimed to assess the adoption of prophylactic anticoagulation guidelines for pregnant COVID-19 patients. Surprisingly, despite being eligible, the majority of patients did not receive anticoagulation treatment. Higher levels of comorbidities were associated with an increased likelihood of receiving treatment. Remarkably, the treatment group did not exhibit elevated risks of bleeding, coagulopathy, or adverse maternal-fetal health outcomes (PTB, LBW, SGA, and stillbirth). Aim 4 (Chapter 6) delved into the impact of IMIDs on pregnancy outcomes, specifically focusing on PTB, LBW, SGA, and surgical delivery. Our findings indicated that patients with IMIDs showed a slightly elevated but generally similar risk of adverse pregnancy outcomes compared to controls.

7.5.2 *Limitations*

The consistent mention of the inherent limitations of EHR in these studies emphasizes a major challenge in using EHR data for research purposes. EHR data are valuable for their accessibility and comprehensive patient information but have major drawbacks. One of the recurring limitations is the potential for misclassification of variables. This refers to situations where the information recorded in the EHR may not reflect the actual exposure of patients to medications or the actual outcomes they experienced. For instance, prescription orders in the EHR do not often align with patients' actual medication usage, leading to exposure misclassification. Similarly, the recorded outcomes in the EHR may not capture the complete and correct clinical picture, potentially resulting in misclassified health outcomes.

Structured EHR data is another significant limitation. While EHRs provide structured information about patient demographics, diagnoses, medications, and procedures, they often lack the detailed clinical reasoning behind medical decisions. This can make it challenging to fully understand the rationale behind treatment choices or the context in which certain medications were prescribed. With this context, researchers will find distinguishing the factors driving observed associations or outcomes easier.

These limitations underscore the need for caution when interpreting findings from studies based on EHR data. Researchers must be aware of these inherent drawbacks and consider them when designing studies. Additionally, efforts to complement EHR data with more comprehensive clinical information, such as through NLP of free-text clinical notes, can mitigate some limitations and enhance the quality of research conducted using EHRs.

7.5.3 *Future directions*

In this dissertation, we have presented innovative approaches to effectively bridge the existing information gap in the treatment of pregnant women, with a primary focus on PTB. We believe these approaches can be applied to a broader spectrum of maternal-fetal health outcomes. By leveraging the methods and findings outlined in Aims 1-4, we can enhance care and understanding across various pregnancy-related conditions, including gestational diabetes and preeclampsia.

BIBLIOGRAPHY

1. Center for Drug Evaluation, Research. Clinical Trials in Pregnant Women. Accessed November 10, 2020. https://www.fda.gov/drugs/development-resources/division-pediatric-and-maternal-health-clinical-trials-pregnant-women

2. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. *Am J Med Genet C Semin Med Genet*. 2011;157C(3):175-182.

3. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. *Cardiovasc J Afr*. 2016;27(2):89-94.

4. Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. *Front Pharmacol*. 2014;5:65.

5. Tetro N, Moushaev S, Rubinchik-Stern M, Eyal S. The Placental Barrier: the Gate and the Fate in Drug Distribution. *Pharm Res*. 2018;35(4):71.

6. Mitchell AA, Gilboa SM, Werler MM, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. *Am J Obstet Gynecol*. 2011;205(1):51.e1-8.

7. Bateman BT, Mhyre JM, Hernandez-Diaz S, et al. Development of a comorbidity index for use in obstetric patients. *Obstet Gynecol*. 2013;122(5):957-965.

8. Wei Q, Mease PPJ, Chiorean M, et al. Risk factors for severe COVID-19 outcomes: a study of immune-mediated inflammatory diseases, immunomodulatory medications, and comorbidities in a large US healthcare system. *medRxiv*. Published online June 28, 2023. doi:10.1101/2023.06.26.23291904

9. Wu Y, Warner JL, Wang L, et al. Discovery of Noncancer Drug Effects on Survival in Electronic Health Records of Patients With Cancer: A New Paradigm for Drug Repurposing. *JCO Clin Cancer Inform*. 2019;3:1-9.

10. Park MY, Yoon D, Lee K, et al. A novel algorithm for detection of adverse drug reaction signals using a hospital electronic medical record database. *Pharmacoepidemiol Drug Saf*. 2011;20(6):598-607.

11. Liu S, Tang B, Chen Q, Wang X. Drug-Drug Interaction Extraction via Convolutional Neural Networks. *Comput Math Methods Med*. 2016;2016:6918381.

12. Hwang YM, Roper RT, Piekos SN, et al. Timing of selective serotonin reuptake inhibitor use and risk for preterm birth and related adverse events. *medRxiv*. Published online March 5, 2023:2023.03.03.23286717. doi:10.1101/2023.03.03.23286717

13. Hwang YM, Piekos S, Sorensen T, Hood L, Hadlock J. Adoption of a National Prophylactic Anticoagulation Guideline for Hospitalized Pregnant Women With COVID-19: Retrospective Cohort Study. *JMIR Public Health Surveill*. 2023;9:e45586.

14. Hwang YM, Wei Q, Piekos SN, et al. Maternal-fetal outcomes in patients with immune mediated inflammatory diseases, with consideration of comorbidities: a retrospective cohort study in a large U.S. healthcare system. *medRxiv*. Published online August 9, 2023. doi:10.1101/2023.08.07.23293726

15. Fowler J, Shields SG, Candib LM. Woman-centered risk assessment. In: *Women-Centered Care in Pregnancy and Childbirth*. Routledge; 2022:342-350.

16. Vargesson N. Thalidomide embryopathy: An enigmatic challenge. *ISRN Dev Biol*. 2013;2013:1-18.

17. Diethylstilbestrol (DES) Exposure and Cancer. National Cancer Institute. Published December 23, 2021. Accessed September 9, 2023. https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/des-fact-sheet

18. van Gelder MMHJ, de Jong-van den Berg LTW, Roeleveld N. Drugs associated with teratogenic mechanisms. Part II: a literature review of the evidence on human risks. *Hum Reprod*. 2014;29(1):168-183.

19. Gerbier E, Panchaud A. Specialty grand challenge editorial innovative approaches for pharmacoepidemiologic research in pregnancy: Shifting the paradigm of Thalidomide's impact on pregnant women. *Frontiers in Drug Safety and Regulation*. 2023;3. doi:10.3389/fdsfr.2023.1187070

20. Scaffidi J, Mol BW, Keelan JA. The pregnant women as a drug orphan: a global survey of registered clinical trials of pharmacological interventions in pregnancy. *BJOG*. 2017;124(1):132-140.

21. Duggal M, Sacks L, Vasisht KP. Eligibility criteria and clinical trials: An FDA perspective. *Contemp Clin Trials*. 2021;109:106515.

22. Schaefer C, Ornoy A, Clementi M, Meister R, Weber-Schoendorfer C. Using observational cohort data for studying drug effects on pregnancy outcome--methodological considerations. *Reprod Toxicol*. 2008;26(1):36-41.

23. Taylor MM, Kobeissi L, Kim C, et al. Inclusion of pregnant women in COVID-19 treatment trials: a review and global call to action. *Lancet Glob Health*. 2021;9(3):e366-e371.

24. Cole LA. Biological functions of hCG and hCG-related molecules. *Reprod Biol Endocrinol*. 2010;8:102.

25. Callahan T, Caughey AB. *Blueprints Obstetrics & Gynecology*. Wolters Kluwer; 2018.

26. Bosu WT, Johansson ED. Effect of HCG on plasma levels of estrogens and progesterone during the luteal phase of the menstrual cycle in rhesus monkeys (Macaca mulatta). Stimulation of sex steroid production in Rhesus monkeys. *Int J Fertil*. 1974;19(1):28-32.

27. Robinson DP, Klein SL. Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis. *Horm Behav*. 2012;62(3):263-271.

28. Valente AM. Maternal adaptations to pregnancy: Cardiovascular and hemodynamic changes. In: Lockwood CJ, Barss VA, eds. *UpToDate*. UpToDate; 2023.

29. Morton A. Physiological Changes and Cardiovascular Investigations in Pregnancy. *Heart Lung Circ*. 2021;30(1):e6-e15.

30. Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. *Clin Chest Med*. 2011;32(1):1-13.

31. Thadhani R, Maynard S. Maternal adaptations to pregnancy: Renal and urinary tract physiology. UptoDate. Published June 7, 2022. Accessed November 3, 2023. https://www.uptodate.com/contents/maternal-adaptations-to-pregnancy-renal-and-urinary-tract-physiology

32. Lopes van Balen VA, van Gansewinkel TAG, de Haas S, et al. Maternal kidney function during pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2019;54(3):297-307.

33. Bianco A. Maternal adaptations to pregnancy: Gastrointestinal tract. In: Lockwood CJ, Barss VA, eds. *UpToDate*. UpToDate; 2023.

34. Gandhi MH, Gupta V. *Physiology, Maternal Blood*. StatPearls Publishing; 2023.

35. Patel P, Balanchivadze N. Hematologic Findings in Pregnancy: A Guide for the Internist. *Cureus*. 2021;13(5):e15149.

36. Leek JC, Arif H. *Pregnancy Medications*. StatPearls Publishing; 2023.

37. Kux L. *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*. Food and Drug Administration ; 2014. https://s3.amazonaws.com/public-inspection.federalregister.gov/2014-28241.pdf

38. March of dimes. Prenatal care. March of dimes. Published January 2022. Accessed December 8, 2023. https://www.marchofdimes.org/peristats/data?reg=99&top=5&stop=34&lev=1&slev=4&obj=1

39. Dang A. Real-World Evidence: A Primer. *Pharmaceut Med*. 2023;37(1):25-36.

40. Liu F, Panagiotakos D. Real-world data: a brief review of the methods, applications, challenges and opportunities. *BMC Med Res Methodol*. 2022;22(1):287.

41. Office of the Commissioner. Real-World Evidence. U.S. Food and Drug Administration. Published April 25, 2023. Accessed September 9, 2023. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

42. Swift B, Jain L, White C, et al. Innovation at the Intersection of Clinical Trials and real-World Data science to Advance Patient Care. *Clin Transl Sci*. 2018;11(5):450-460.

43. Huybrechts KF, Bateman BT, Hernández-Díaz S. Use of real-world evidence from healthcare utilization data to evaluate drug safety during pregnancy. *Pharmacoepidemiol Drug Saf*. 2019;28(7):906-922.

44. Sun W, Cai Z, Li Y, Liu F, Fang S, Wang G. Data Processing and Text Mining Technologies on Electronic Medical Records: A Review. *J Healthc Eng*. 2018;2018:4302425.

45. Cho S, Ensari I, Weng C, Kahn MG, Natarajan K. Factors Affecting the Quality of Person-Generated Wearable Device Data and Associated Challenges: Rapid Systematic Review. *JMIR Mhealth Uhealth*. 2021;9(3):e20738.

46. Wu J, Roy J, Stewart WF. Prediction modeling using EHR data: challenges, strategies, and a comparison of machine learning approaches. *Med Care*. 2010;48(6 Suppl):S106-13.

47. Botsis T, Hartvigsen G, Chen F, Weng C. Secondary Use of EHR: Data Quality Issues and Informatics Opportunities. *Summit Transl Bioinform*. 2010;2010:1-5.

48. Shickel B, Tighe PJ, Bihorac A, Rashidi P. Deep EHR: A Survey of Recent Advances in Deep Learning Techniques for Electronic Health Record (EHR) Analysis. *IEEE J Biomed Health Inform*. 2018;22(5):1589-1604.

49. Poirier C, Hswen Y, Bouzillé G, et al. Influenza forecasting for French regions combining EHR, web and climatic data sources with a machine learning ensemble approach. *PLoS One*. 2021;16(5):e0250890.

50. Dreyer NA, Garner S. Registries for robust evidence. *JAMA*. 2009;302(7):790-791.

51. Larsson S, Lawyer P, Garellick G, Lindahl B, Lundström M. Use of 13 disease registries in 5 countries demonstrates the potential to use outcome data to improve health care's value. *Health Aff* . 2012;31(1):220-227.

52. Jandhyala R. Comment on: "Patient Registries: An Underused Resource for Medicines Evaluation: Operational Proposals for Increasing the Use of Patient Registries in Regulatory Assessments." *Drug Saf*. 2019;42(12):1515-1516.

53. Izmirly PM, Parton H, Wang L, et al. Prevalence of Systemic Lupus Erythematosus in the United States: Estimates From a Meta-Analysis of the Centers for Disease Control and Prevention National Lupus Registries. *Arthritis Rheumatol*. 2021;73(6):991-996.

54. McGettigan P, Alonso Olmo C, Plueschke K, et al. Patient Registries: An Underused Resource for Medicines Evaluation : Operational proposals for increasing the use of patient registries in regulatory assessments. *Drug Saf*. 2019;42(11):1343-1351.

55. Jansen-van der Weide MC, Gaasterland CMW, Roes KCB, et al. Rare disease registries: potential applications towards impact on development of new drug treatments. *Orphanet J Rare Dis*. 2018;13(1):154.

56. Lacaze P, Millis N, Fookes M, et al. Rare disease registries: a call to action. *Intern Med J*. 2017;47(9):1075-1079.

57. Bartlett VL, Dhruva SS, Shah ND, Ryan P, Ross JS. Feasibility of Using Real-World Data to Replicate Clinical Trial Evidence. *JAMA Netw Open*. 2019;2(10):e1912869.

58. Svarstad BL, Shireman TI, Sweeney JK. Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. *Psychiatr Serv*. 2001;52(6):805-811.

59. Izurieta HS, Wu X, Lu Y, et al. Zostavax vaccine effectiveness among US elderly using real-world evidence: Addressing unmeasured confounders by using multiple imputation after linking beneficiary surveys with Medicare claims. *Pharmacoepidemiol Drug Saf*. 2019;28(7):993-1001.

60. Sruamsiri R, Iwasaki K, Tang W, Mahlich J. Persistence rates and medical costs of biological therapies for psoriasis treatment in Japan: a real-world data study using a claims database. *BMC Dermatol*. 2018;18(1):5.

61. Dunn J, Runge R, Snyder M. Wearables and the medical revolution. *Per Med*. 2018;15(5):429-448.

62. Christensen JH, Saunders GH, Porsbo M, Pontoppidan NH. The everyday acoustic environment and its association with human heart rate: evidence from real-world data logging with hearing aids and wearables. *R Soc Open Sci*. 2021;8(2):201345.

63. Johnson KT, Picard RW. Advancing Neuroscience through Wearable Devices. *Neuron*. 2020;108(1):8-12.

64. Pickham D, Berte N, Pihulic M, Valdez A, Mayer B, Desai M. Effect of a wearable patient sensor on care delivery for preventing pressure injuries in acutely ill adults: A pragmatic randomized clinical trial (LS-HAPI study). *Int J Nurs Stud*. 2018;80:12-19.

65. Adams JL, Dinesh K, Snyder CW, et al. A real-world study of wearable sensors in Parkinson's disease. *NPJ Parkinsons Dis*. 2021;7(1):106.

66. Nikfarjam A, Ransohoff JD, Callahan A, et al. Early Detection of Adverse Drug Reactions in Social Health Networks: A Natural Language Processing Pipeline for Signal Detection. *JMIR Public Health Surveill*. 2019;5(2):e11264.

67. Wedam S, Fashoyin-Aje L, Bloomquist E, et al. FDA Approval Summary: Palbociclib for Male Patients with Metastatic Breast Cancer. *Clin Cancer Res*. 2020;26(6):1208-1212.

68. Rudrapatna VA, Butte AJ. Opportunities and challenges in using real-world data for health care. *J Clin Invest*. 2020;130(2):565-574.

69. Piekos SN, Price ND, Hood L, Hadlock JJ. The impact of maternal SARS-CoV-2 infection and COVID-19 vaccination on maternal-fetal outcomes. *Reprod Toxicol*. 2022;114:33-43.

70. Ellington S, Strid P, Tong VT, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(25):769-775.

71. Zambrano LD, Ellington S, Strid P, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-October 3, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(44):1641-1647.

72. Hsu AL, Ohler AM, Goldstein A, et al. Coronavirus Disease 2019 (COVID-19) Disease Severity: Pregnant vs Nonpregnant Women at 82 Facilities. *Clin Infect Dis*. 2022;74(3):467-471.

73. Lokken EM, Huebner EM, Taylor GG, et al. Disease severity, pregnancy outcomes, and maternal deaths among pregnant patients with severe acute respiratory syndrome coronavirus 2 infection in Washington State. *Am J Obstet Gynecol*. 2021;225(1):77.e1-77.e14.

74. Pineles BL, Goodman KE, Pineles L, et al. Pregnancy and the Risk of In-Hospital Coronavirus Disease 2019 (COVID-19) Mortality. *Obstet Gynecol*. 2022;139(5):846-854.

75. Ríos-Silva M, Murillo-Zamora E, Mendoza-Cano O, Trujillo X, Huerta M. COVID-19 mortality among pregnant women in Mexico: A retrospective cohort study. *J Glob Health*. 2020;10(2):020512.

76. McClymont E, Albert AY, Alton GD, et al. Association of SARS-CoV-2 Infection During Pregnancy With Maternal and Perinatal Outcomes. *JAMA*. 2022;327(20):1983-1991.

77. Shoji K, Tsuzuki S, Akiyama T, et al. Clinical Characteristics and Outcomes of Coronavirus Disease 2019 (COVID-19) in Pregnant Women: A Propensity Score–Matched Analysis of Data From the COVID-19 Registry Japan. *Clin Infect Dis*. 2022;75(1):e397-e402.

78. Magnus MC, Oakley L, Gjessing HK, et al. Pregnancy and risk of COVID-19: a Norwegian registry-linkage study. *BJOG*. 2022;129(1):101-109.

79. Chinn J, Sedighim S, Kirby KA, et al. Characteristics and Outcomes of Women With COVID-19 Giving Birth at US Academic Centers During the COVID-19 Pandemic. *JAMA Netw Open*. 2021;4(8):e2120456.

80. Ko JY, DeSisto CL, Simeone RM, et al. Adverse Pregnancy Outcomes, Maternal Complications, and Severe Illness Among US Delivery Hospitalizations With and Without a Coronavirus Disease 2019 (COVID-19) Diagnosis. *Clin Infect Dis*. 2021;73(Suppl 1):S24-S31.

81. Simon E, Gouyon JB, Cottenet J, et al. Impact of SARS-CoV-2 infection on risk of prematurity, birthweight and obstetric complications: A multivariate analysis from a nationwide, population-based retrospective cohort study. *BJOG*. 2022;129(7):1084-1094.

82. Villar J, Ariff S, Gunier RB, et al. Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study. *JAMA Pediatr*. 2021;175(8):817-826.

83. Metz TD, Clifton RG, Hughes BL, et al. Association of SARS-CoV-2 Infection With Serious Maternal Morbidity and Mortality From Obstetric Complications. *JAMA*. 2022;327(8):748-759.

84. Gulersen M, Rochelson B, Shan W, Wetcher CS, Nimaroff M, Blitz MJ. Severe maternal morbidity in pregnant patients with SARS-CoV-2 infection. *Am J Obstet Gynecol MFM*. 2022;4(4):100636.

85. Jering KS, Claggett BL, Cunningham JW, et al. Clinical Characteristics and Outcomes of Hospitalized Women Giving Birth With and Without COVID-19. *JAMA Intern Med*. 2021;181(5):714-717.

86. Piekos SN, Roper RT, Hwang YM, et al. The effect of maternal SARS-CoV-2 infection timing on birth outcomes: a retrospective multicentre cohort study. *Lancet Digit Health*. 2022;4(2):e95-e104.

87. Epelboin S, Labrosse J, De Mouzon J, et al. Obstetrical outcomes and maternal morbidities associated with COVID-19 in pregnant women in France: A national retrospective cohort study. *PLoS Med*. 2021;18(11):e1003857.

88. Doyle TJ, Kiros GE, Schmitt-Matzen EN, Propper R, Thompson A, Phillips-Bell GS. Maternal and Perinatal Outcomes Associated With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection During Pregnancy, Florida, 2020-2021: A Retrospective Cohort Study. *Clin Infect Dis*. 2022;75(Suppl 2):S308-S316.

89. Dileep A, ZainAlAbdin S, AbuRuz S. Investigating the association between severity of COVID-19 infection during pregnancy and neonatal outcomes. *Sci Rep*. 2022;12(1):3024.

90. Fallach N, Segal Y, Agassy J, et al. Pregnancy outcomes after SARS-CoV-2 infection by trimester: A large, population-based cohort study. *PLoS One*. 2022;17(7):e0270893.

91. Goncu Ayhan S, Oluklu D, Atalay A, et al. COVID-19 vaccine acceptance in pregnant women. *Int J Gynaecol Obstet*. 2021;154(2):291-296.

92. Battarbee AN, Stockwell MS, Varner M, et al. Attitudes toward COVID-19 illness and COVID-19 vaccination among pregnant women: A cross-sectional multicenter study during August-December 2020. *Am J Perinatol*. 2022;39(1):75-83.

93. Hosokawa Y, Okawa S, Hori A, et al. The Prevalence of COVID-19 Vaccination and Vaccine Hesitancy in Pregnant Women: An Internet-based Cross-sectional Study in Japan. *J Epidemiol*. 2022;32(4):188-194.

94. Skjefte M, Ngirbabul M, Akeju O, et al. COVID-19 vaccine acceptance among pregnant women and mothers of young children: results of a survey in 16 countries. *Eur J Epidemiol*. 2021;36(2):197-211.

95. Firouzbakht M, Sharif Nia H, Kazeminavaei F, Rashidian P. Hesitancy about COVID-19 vaccination among pregnant women: a cross-sectional study based on the health belief model. *BMC Pregnancy Childbirth*. 2022;22(1):611.

96. Rodriguez A. Should pregnant women get the COVID-19 vaccine? Dr. Anthony Fauci sees "no red flags" in safety data. *USA Today*. https://www.usatoday.com/story/news/health/2021/02/01/covid-vaccine-pregnant-women-dr-fauci-says-no-red-flags-so-far/4335747001/. Published February 1, 2021. Accessed October 19, 2023.

97. Piekos SN, Hwang YM, Roper RT, et al. Effect of COVID-19 vaccination and booster on maternal-fetal outcomes: a retrospective cohort study. *Lancet Digit Health*. 2023;5(9):e594-e606.

98. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med*. 2021;384(15):1412-1423.

99. Goldshtein I, Nevo D, Steinberg DM, et al. Association Between BNT162b2 Vaccination and Incidence of SARS-CoV-2 Infection in Pregnant Women. *JAMA*. 2021;326(8):728-735.

100. Butt AA, Chemaitelly H, Al Khal A, et al. SARS-CoV-2 vaccine effectiveness in preventing confirmed infection in pregnant women. *J Clin Invest*. 2021;131(23). doi:10.1172/JCI153662

101. Morgan JA, Biggio JR Jr, Martin JK, et al. Maternal Outcomes After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Vaccinated Compared With Unvaccinated Pregnant Patients. *Obstet Gynecol*. 2022;139(1):107-109.

102. Stock SJ, Carruthers J, Calvert C, et al. Author Correction: SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. *Nat Med*. 2022;28(3):599.

103. Wainstock T, Yoles I, Sergienko R, Sheiner E. Prenatal maternal COVID-19 vaccination and pregnancy outcomes. *Vaccine*. 2021;39(41):6037-6040.

104. Lipkind HS, Vazquez-Benitez G, DeSilva M, et al. Receipt of COVID-19 Vaccine During Pregnancy and Preterm or Small-for-Gestational-Age at Birth - Eight Integrated Health Care Organizations, United States, December 15, 2020-July 22, 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(1):26-30.

105. Dick A, Rosenbloom JI, Gutman-Ido E, Lessans N, Cahen-Peretz A, Chill HH. Safety of SARS-CoV-2 vaccination during pregnancy- obstetric outcomes from a large cohort study. *BMC Pregnancy Childbirth*. 2022;22(1):166.

106. Rottenstreich M, Sela HY, Rotem R, Kadish E, Wiener-Well Y, Grisaru-Granovsky S. Covid-19 vaccination during the third trimester of pregnancy: rate of vaccination and maternal and neonatal outcomes, a multicentre retrospective cohort study. *BJOG*. 2022;129(2):248-255.

107. Andrade SE, Toh S, Houstoun M, et al. Surveillance of Medication Use During Pregnancy in the Mini-Sentinel Program. *Matern Child Health J*. 2016;20(4):895-903.

108. Suarez EA, Nguyen M, Zhang D, et al. Presented at ICPE 2021 All Access. Accessed October 24, 2021. https://www.sentinelinitiative.org/sites/default/files/documents/ICPE%20Presentation%20-%20Use%20of%20Tree-Based%20Scan%20Statistics%20for%20Surveillance%20of%20Infant%20Outcomes.pdf

109. Marić I, Winn VD, Borisenko E, et al. Data-driven queries between medications and spontaneous preterm birth among 2.5 million pregnancies. *Birth Defects Res*. 2019;111(16):1145-1153.

110. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75-84.

111. Beck S, Wojdyla D, Say L, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ*. 2010;88(1):31-38.

112. Preterm birth. Accessed November 18, 2020. https://www.who.int/news-room/fact-sheets/detail/preterm-birth

113. Gracie S, Pennell C, Ekman-Ordeberg G, et al. An integrated systems biology approach to the study of preterm birth using "-omic" technology--a guideline for research. *BMC Pregnancy Childbirth*. 2011;11:71.

114. Menon R. Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiologic and genetic heterogeneities and racial disparity. *Acta Obstet Gynecol Scand*. 2008;87(6):590-600.

115. Robinson JN. Preterm birth: Risk factors, interventions for risk reduction, and maternal prognosis. In: Lockwood CJ, Barss VA, eds. *UpToDate*. UpToDate; 2021.

116. Liu R, Zhang P. Towards early detection of adverse drug reactions: combining pre-clinical drug structures and post-market safety reports. *BMC Med Inform Decis Mak*. 2019;19(1):279.

117. Rohani N, Eslahchi C. Drug-Drug Interaction Predicting by Neural Network Using Integrated Similarity. *Sci Rep*. 2019;9(1):13645.

118. Selinger CP, Ghorayeb J, Madill A. What Factors Might Drive Voluntary Childlessness (VC) in Women with IBD? Does IBD-specific Pregnancy-related Knowledge Matter? *J Crohns Colitis*. 2016;10(10):1151-1158.

119. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279(15):1200-1205.

120. Center for Drug Evaluation, Research. Preventable Adverse Drug Reactions: A Focus on Drug Interactions. Accessed November 10, 2020. https://www.fda.gov/drugs/drug-interactions-labeling/preventable-adverse-drug-reactions-focus-drug-interactions

121. Hutchinson TA, Flegel KM, Kramer MS, Leduc DG, Kong HH. Frequency, severity and risk factors for adverse drug reactions in adult out-patients: a prospective study. *J Chronic Dis*. 1986;39(7):533-542.

122. Hanlon JT, Schmader KE, Koronkowski MJ, et al. Adverse drug events in high risk older outpatients. *J Am Geriatr Soc*. 1997;45(8):945-948.

123. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*. 2003;289(9):1107-1116.

124. Overhage JM, Gandhi TK, Hope C, et al. Ambulatory Computerized Prescribing and Preventable Adverse Drug Events. *J Patient Saf*. 2016;12(2):69-74.

125. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med*. 2003;348(16):1556-1564.

126. Feng C, Le D, McCoy AB. Using Electronic Health Records to Identify Adverse Drug Events in Ambulatory Care: A Systematic Review. *Appl Clin Inform*. 2019;10(1):123-128.

127. Fuhler GM. The immune system and microbiome in pregnancy. *Best Pract Res Clin Gastroenterol*. 2020;44-45:101671.

128. Sample size for a cohort study. Accessed September 14, 2023. https://epitools.ausvet.com.au/cohortss

129. Suarez EA, Nguyen M, Zhang D, et al. Sentinel Methods. Accessed August 9, 2023. https://www.sentinelinitiative.org/sites/default/files/Methods/Sentinel_Protocol_TreeScan_Pregnancy_V3.pdf

130. Elze MC, Gregson J, Baber U, et al. Comparison of Propensity Score Methods and Covariate Adjustment: Evaluation in 4 Cardiovascular Studies. *J Am Coll Cardiol*. 2017;69(3):345-357.

131. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol*. 2010;172(9):1092-1097.

132. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch Gen Psychiatry*. 2010;67(10):1012-1024.

133. Taylor M, Gerriets V. *Acyclovir*. StatPearls Publishing; 2023.

134. Herpes - Genital (HSV) / In Pregnancy. Published July 21, 2021. Accessed September 15, 2023. https://www.cdc.gov/stiapp/herpes-genital_pregnancy.html

135. Daw JR, Hanley GE, Greyson DL, Morgan SG. Prescription drug use during pregnancy in developed countries: a systematic review. *Pharmacoepidemiol Drug Saf*. 2011;20(9):895-902.

136. Suarez EA, Haug N, Hansbury A, Stojanovic D, Corey C. Prescription medication use and baseline health status of women with live-birth deliveries in a national data network. *Am J Obstet Gynecol MFM*. 2022;4(1):100512.

137. Detlefs SE, Jochum MD, Salmanian B, McKinney JR, Aagaard KM. The impact of response to iron therapy on maternal and neonatal outcomes among pregnant women with anemia. *Am J Obstet Gynecol MFM*. 2022;4(2):100569.

138. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990;1(1):43-46.

139. Hamm N, Singal D, Dahl M, Chateau D, Brownell M. Linking health and social data to assess the performance of high dimensional propensity scores. *Int J Popul Data Sci*. 2020;5(5). doi:10.23889/ijpds.v5i5.1449

140. Van Niel MS, Payne JL. Perinatal depression: A review. *Cleve Clin J Med*. 2020;87(5):273-277.

141. Hessami K, Romanelli C, Chiurazzi M, Cozzolino M. COVID-19 pandemic and maternal mental health: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med*. 2022;35(20):4014-4021.

142. Kyzar EJ, Purpura LJ, Shah J, Cantos A, Nordvig AS, Yin MT. Anxiety, depression, insomnia, and trauma-related symptoms following COVID-19 infection at long-term follow-up. *Brain Behav Immun Health*. 2021;16(100315):100315.

143. Huybrechts KF, Palmsten K, Mogun H, et al. National trends in antidepressant medication treatment among publicly insured pregnant women. *Gen Hosp Psychiatry*. 2013;35(3):265-271.

144. Hayes RM, Wu P, Shelton RC, et al. Maternal antidepressant use and adverse outcomes: a cohort study of 228,876 pregnancies. *Am J Obstet Gynecol*. 2012;207(1):49.e1-9.

145. Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. *Am J Obstet Gynecol*. 2008;198(2):194.e1-5.

146. Oskotsky T, Maric I, Tang A, et al. Mortality risk among patients with COVID-19 prescribed selective serotonin reuptake inhibitor antidepressants. *JAMA Netw Open*. 2021;4(11):e2133090.

147. Nakhaee H, Zangiabadian M, Bayati R, Rahmanian M, Ghaffari Jolfayi A, Rakhshanderou S. The effect of antidepressants on the severity of COVID-19 in hospitalized patients: A systematic review and meta-analysis. *PLoS One*. 2022;17(10):e0267423.

148. Rush RW, Keirse MJNC, Howat P, Baum JD, Anderson ABM, Turnbull AC. Contribution of preterm delivery to perinatal mortality. *Obstet Gynecol Surv*. 1977;32(10):643-645.

149. Huybrechts KF, Sanghani RS, Avorn J, Urato AC. Preterm birth and antidepressant medication use during pregnancy: A systematic review and meta-analysis. *PLoS One*. 2014;9(3):e92778.

150. Sujan AC, Rickert ME, Öberg AS, et al. Associations of maternal antidepressant use during the first trimester of pregnancy with preterm birth, small for gestational age, autism spectrum disorder, and attention-deficit/hyperactivity disorder in offspring. *Obstet Gynecol Surv*. 2017;72(9):523-524.

151. Yonkers KA, Norwitz ER, Smith MV, et al. Depression and serotonin reuptake inhibitor treatment as risk factors for preterm birth. *Epidemiology*. 2012;23(5):677-685.

152. Reis M, Källén B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. *Psychol Med*. 2010;40(10):1723-1733.

153. Källén B. Neonate characteristics after maternal use of antidepressants in late pregnancy. *Arch Pediatr Adolesc Med*. 2004;158(4):312-316.

154. Phillips GS, Wise LA, Rich-Edwards JW, Stampfer MJ, Rosenberg L. Prepregnancy depressive symptoms and preterm birth in the Black Women's Health Study. *Ann Epidemiol*. 2010;20(1):8-15.

155. Li D, Liu L, Odouli R. Presence of depressive symptoms during early pregnancy and the risk of preterm delivery: a prospective cohort study. *Hum Reprod*. 2009;24(1):146-153.

156. Lennestål R, Källén B. Delivery outcome in relation to maternal use of some recently introduced antidepressants. *J Clin Psychopharmacol*. 2007;27(6):607-613.

157. Ericson A, Källén B, Wiholm B. Delivery outcome after the use of antidepressants in early pregnancy. *Eur J Clin Pharmacol*. 1999;55(7):503-508.

158. Wilkes S. The use of bupropion SR in cigarette smoking cessation. *Int J Chron Obstruct Pulmon Dis*. 2008;3(1):45-53.

159. Jaffer KY, Chang T, Vanle B, et al. Trazodone for insomnia: A systematic review. *Innov Clin Neurosci*. 2017;14(7-8):24-34.

160. Centers for Disease Control and Prevention/ Agency for Toxic Substances and Disease Registry/ Geospatial Research, Analysis, and Services Program. CDC/ATSDR Social Vulnerability Index. Published online 2020. Accessed 2022. https://www.atsdr.cdc.gov/placeandhealth/svi/data_documentation_download.html

161. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *J Gen Intern Med*. 2001;16(9):606-613.

162. Levis B, Sun Y, He C, et al. Accuracy of the PHQ-2 alone and in combination with the PHQ-9 for screening to detect major depression: Systematic review and meta-analysis. *JAMA*. 2020;323(22):2290-2300.

163. Kroenke K, Spitzer RL, Williams JBW, Löwe B. An ultra-brief screening scale for anxiety and depression: The PHQ–4. *Psychosomatics*. 2009;50(6):613-621.

164. Löwe B, Wahl I, Rose M, et al. A 4-item measure of depression and anxiety: validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. *J Affect Disord*. 2010;122(1-2):86-95.

165. Malm H, Sourander A, Gissler M, et al. Pregnancy complications following prenatal exposure to SSRIs or maternal psychiatric disorders: Results from population-based national register data. *Am J Psychiatry*. 2015;172(12):1224-1232.

166. Gavin AR, Chae DH, Mustillo S, Kiefe CI. Prepregnancy depressive mood and preterm birth in black and white women: findings from the CARDIA Study. *J Womens Health (Larchmt)*. 2009;18(6):803-811.

167. Stephens MAC, Wand G. Stress and the HPA axis: role of glucocorticoids in alcohol dependence. *Alcohol Res*. 2012;34(4):468-483.

168. Najafzadeh A. Stress and preterm birth: biological and vascular mechanisms affecting the feto-placental circulation and the length of gestation. *Sonography*. 2016;3(3):95-102.

169. Liu YZ, Wang YX, Jiang CL. Inflammation: The common pathway of stress-related diseases. *Front Hum Neurosci*. 2017;11:316.

170. Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal

depression using population-based linked health data. *Arch Gen Psychiatry*. 2006;63(8):898-906.

171. Calderon-Margalit R, Qiu C, Ornoy A, Siscovick DS, Williams MA. Risk of preterm delivery and other adverse perinatal outcomes in relation to maternal use of psychotropic medications during pregnancy. *Obstet Anesth Dig*. 2011;31(1):46-47.

172. Lund N, Pedersen LH, Henriksen TB. Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. *Arch Pediatr Adolesc Med*. 2009;163(10):949-954.

173. Colvin L, Slack-Smith L, Stanley FJ, Bower C. Dispensing patterns and pregnancy outcomes for women dispensed selective serotonin reuptake inhibitors in pregnancy. *Birth Defects Res A Clin Mol Teratol*. 2011;91(3):142-152.

174. Davis RL, Rubanowice D, McPhillips H, et al. Risks of congenital malformations and perinatal events among infants exposed to antidepressant medications during pregnancy. *Pharmacoepidemiol Drug Saf*. 2007;16(10):1086-1094.

175. Hieronymus F, Lisinski A, Nilsson S, Eriksson E. Influence of baseline severity on the effects of SSRIs in depression: an item-based, patient-level post-hoc analysis. *Lancet Psychiatry*. 2019;6(9):745-752.

176. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA*. 2010;303(1):47-53.

177. Gentile S. Untreated depression during pregnancy: Short- and long-term effects in offspring. A systematic review. *Neuroscience*. 2017;342:154-166.

178. Chan J, Natekar A, Einarson A, Koren G. Risks of untreated depression in pregnancy. *Can Fam Physician*. 2014;60(3):242-243.

179. Otifi HM, Adiga BK. Endothelial Dysfunction in Covid-19 Infection. *Am J Med Sci*. 2022;363(4):281-287.

180. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nat Rev Immunol*. 2020;20(7):389-391.

181. Lowenstein CJ, Solomon SD. Severe COVID-19 Is a Microvascular Disease. *Circulation*. 2020;142(17):1609-1611.

182. Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J*. 2020;41(32):3038-3044.

183. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost*. 2020;18(7):1738-1742.

184. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost*. 2020;18(7):1747-1751.

185. Maier CL, Truong AD, Auld SC, Polly DM, Tanksley CL, Duncan A. COVID-19-associated hyperviscosity: a link between inflammation and thrombophilia? *Lancet*. 2020;395(10239):1758-1759.

186. Conway EM, Mackman N, Warren RQ, et al. Understanding COVID-19-associated coagulopathy. *Nat Rev Immunol*. 2022;22(10):639-649.

187. Levy JH, Iba T, Gardiner EE. Endothelial Injury in COVID-19 and Acute Infections. *Arterioscler Thromb Vasc Biol*. 2021;41(5):1774-1776.

188. Huertas A, Montani D, Savale L, et al. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)? *Eur Respir J*. 2020;56(1). doi:10.1183/13993003.01634-2020

189. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med*. 2005;143(10):697-706.

190. James AH. Pregnancy-associated thrombosis. *Hematology Am Soc Hematol Educ Program*. Published online 2009:277-285.

191. Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJM. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. *J Thromb Haemost*. 2008;6(4):632-637.

192. Montiel V, Lobysheva I, Gérard L, et al. Oxidative stress-induced endothelial dysfunction and decreased vascular nitric oxide in COVID-19 patients. *eBioMedicine*. 2022;77. doi:10.1016/j.ebiom.2022.103893

193. Xu SW, Ilyas I, Weng JP. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. *Acta Pharmacol Sin*. Published online October 17, 2022:1-15.

194. CDC. Hospitalization and Blood Clots. Centers for Disease Control and Prevention. Published June 9, 2022. Accessed December 3, 2022. https://www.cdc.gov/ncbddd/dvt/hospitalization-infographic.html

195. Gorog DA, Storey RF, Gurbel PA, et al. Current and novel biomarkers of thrombotic risk in COVID-19: a Consensus Statement from the International COVID-19 Thrombosis Biomarkers Colloquium. *Nat Rev Cardiol*. 2022;19(7):475-495.

196. Semeraro N, Colucci M. The Prothrombotic State Associated with SARS-CoV-2 Infection: Pathophysiological Aspects. *Mediterr J Hematol Infect Dis*. 2021;13(1):e2021045.

197. Acherjee T, Behara A, Saad M, Vittorio TJ. Mechanisms and management of prothrombotic state in COVID-19 disease. *Ther Adv Cardiovasc Dis*. 2021;15:17539447211053470.

198. von Meijenfeldt FA, Havervall S, Adelmeijer J, et al. Prothrombotic changes in patients with COVID-19 are associated with disease severity and mortality. *Res Pract Thromb Haemost*. 2021;5(1):132-141.

199. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine*. 2020;29-30:100639.

200. Tan BK, Mainbourg S, Friggeri A, et al. Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis. *Thorax*. 2021;76(10):970-979.

201. Suh YJ, Hong H, Ohana M, et al. Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis. *Radiology*. 2021;298(2):E70-E80.

202. Katsoularis I, Fonseca-Rodríguez O, Farrington P, et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after covid-19: nationwide self-controlled cases series and matched cohort study. *BMJ*. 2022;377. doi:10.1136/bmj-2021-069590

203. Xiao D, Tang F, Chen L, Gao H, Li X. Cumulative Evidence for the Association of Thrombosis and the Prognosis of COVID-19: Systematic Review and Meta-Analysis. *Front Cardiovasc Med*. 2021;8:819318.

204. Kollias A, Kyriakoulis KG, Lagou S, Kontopantelis E, Stergiou GS, Syrigos K. Venous thromboembolism in COVID-19: A systematic review and meta-analysis. *Vasc Med*. 2021;26(4):415-425.

205. Brenner B. Haemostatic changes in pregnancy. *Thromb Res*. 2004;114(5-6):409-414.

206. Battinelli EM, Marshall A, Connors JM. The role of thrombophilia in pregnancy. *Thrombosis*. 2013;2013:516420.

207. *NIH COVID-19 Treatment Guidelines*. National Institute of Health Accessed November 10, 2022. https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/

208. Bauer KA. Use of anticoagulants during pregnancy and postpartum. In: Leung LLK, Tirnauer JS, eds. *UpToDate*. UpToDate; 2022.

209. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453-1457.

210. Leentjens J, van Haaps TF, Wessels PF, Schutgens REG, Middeldorp S. COVID-19-associated coagulopathy and antithrombotic agents—lessons after 1 year. *The Lancet Haematology*. 2021;8(7):e524-e533.

211. Görlinger K, Dirkmann D, Gandhi A, Simioni P. COVID-19–Associated Coagulopathy and Inflammatory Response: What Do We Know Already and What Are the Knowledge Gaps? *Anesthesia & Analgesia*. 2020;131(5):1324.

212. Lundberg SM, Lee SI. A Unified Approach to Interpreting Model Predictions. In: Guyon I, Luxburg UV, Bengio S, et al., eds. *Advances in Neural Information Processing Systems*. Vol 30. Curran Associates, Inc.; 2017. https://proceedings.neurips.cc/paper/2017/file/8a20a8621978632d76c43dfd28b67767-Paper.pdf

213. Kline A, Luo Y. PsmPy: A Package for Retrospective Cohort Matching in Python. *Conf Proc IEEE Eng Med Biol Soc*. 2022;2022:1354-1357.

214. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res*. 2011;46(3):399-424.

215. Sullivan GM, Feinn R. Using Effect Size-or Why the P Value Is Not Enough. *J Grad Med Educ*. 2012;4(3):279-282.

216. Truveta. Truveta's health system members. Truveta. Published October 21, 2022. Accessed March 30, 2023. https://www.truveta.com/members/

217. Althouse BM, Baker C, Smits PD, et al. Racial inequality in COVID-treatment and in-hospital length of stay in the US over time. *Front Public Health*. 2022;10:1074775.

218. Koyuncu K. Thromboprophylaxis in Covid-19 positive pregnant women. *South Clin Istanb Eurasia*. Published online 2020. doi:10.14744/scie.2020.86548

219. Pierce-Williams RAM, Burd J, Felder L, et al. Clinical course of severe and critical coronavirus disease 2019 in hospitalized pregnancies: a United States cohort study. *Am J Obstet Gynecol MFM*. 2020;2(3):100134.

220. Jevtic SD, Malinowski AK, Othman M, Abdul Kadir RA. Physician experiences in management of COVID-19-associated coagulopathy in pregnancy: Communication from the ISTH SSC Subcommittee on Women's Health Issues in Thrombosis and Haemostasis. *J Thromb Haemost*. 2021;19(10):2539-2545.

221. Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19. *J Am Coll Cardiol*. 2020;76(16):1815-1826.

222. Rentsch CT, Beckman JA, Tomlinson L, et al. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. *BMJ*. 2021;372:n311.

223. Vaughn VM, Yost M, Abshire C, et al. Trends in Venous Thromboembolism Anticoagulation in Patients Hospitalized With COVID-19. *JAMA Netw Open*. 2021;4(6):e2111788.

224. Smith ER, Oakley E, Grandner GW, et al. Adverse maternal, fetal, and newborn outcomes among pregnant women with SARS-CoV-2 infection: an individual participant data meta-analysis. *BMJ Glob Health*. 2023;8(1). doi:10.1136/bmjgh-2022-009495

225. DeSisto CL, Wallace B, Simeone RM, et al. Risk for Stillbirth Among Women With and Without COVID-19 at Delivery Hospitalization - United States, March 2020-September 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(47):1640-1645.

226. Shah LM, Varma B, Nasir K, et al. Reducing disparities in adverse pregnancy outcomes in the United States. *Am Heart J*. 2021;242:92-102.

227. Kent ST, McClure LA, Zaitchik BF, Gohlke JM. Area-level risk factors for adverse birth outcomes: trends in urban and rural settings. *BMC Pregnancy Childbirth*. 2013;13:129.

228. Sharma Garima, Ying Wendy, Vaught Arthur Jason. Understanding the Rural and Racial Disparities in Pre-Pregnancy Hypertension. *J Am Coll Cardiol*. 2020;76(22):2620-2622.

229. Oates GR, Juarez LD, Horswell R, et al. The Association Between Neighborhood Social Vulnerability and COVID-19 Testing, Positivity, and Incidence in Alabama and Louisiana. *J Community Health*. 2021;46(6):1115-1123.

230. Raja R, Mukherjee I, Sarkar BK. A Machine Learning-Based Prediction Model for Preterm Birth in Rural India. *J Healthc Eng*. 2021;2021:6665573.

231. Mah JC, Andrew MK. Social vulnerability indices: A pragmatic tool for COVID-19 policy and beyond. *Lancet Reg Health Eur*. 2022;14:100333.

232. Biggs EN, Maloney PM, Rung AL, Peters ES, Robinson WT. The Relationship Between Social Vulnerability and COVID-19 Incidence Among Louisiana Census Tracts. *Front Public Health*. 2020;8:617976.

233. Salmanian B, McKinney JR, Moufarrij S, et al. 1011 Pregnancy affected by COVID-19, patient characteristics and outcomes based on Social Vulnerability Index (SVI). *Am J Obstet Gynecol*. 2021;224(2):S626.

234. Piekos SN, Hwang YM, Roper RT, et al. The effect of COVID-19 vaccination and booster on maternal-fetal outcomes: a retrospective multicenter cohort study. *medRxiv*. Published online August 18, 2022. doi:10.1101/2022.08.12.22278727

235. McInnes IB, Gravallese EM. Immune-mediated inflammatory disease therapeutics: past, present and future. *Nat Rev Immunol*. 2021;21(10):680-686.

236. Kuek A, Hazleman BL, Ostör AJK. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. *Postgrad Med J*. 2007;83(978):251-260.

237. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol*. 1997;84(3):223-243.

238. MacGregor AJ, Silman AJ. Rheumatoid arthritis and other synovial disorders: classification and epidemiology. *Rheumatology*. Published online 2003.

239. Betteridge JD, Armbruster SP, Maydonovitch C, Veerappan GR. Inflammatory bowel disease prevalence by age, gender, race, and geographic location in the U.S. military health care population. *Inflamm Bowel Dis*. 2013;19(7):1421-1427.

240. Ahlgren C, Odén A, Lycke J. High nationwide prevalence of multiple sclerosis in Sweden. *Mult Scler*. 2011;17(8):901-908.

241. Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. *Arthritis Rheum*. 2007;56(6):2092-2094.

242. Cervera R, Serrano R, Pons-Estel GJ, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. *Ann Rheum Dis*. 2015;74(6):1011-1018.

243. Ramírez Sepúlveda JI, Kvarnström M, Eriksson P, et al. Long-term follow-up in primary Sjögren’s syndrome reveals differences in clinical presentation between female and male patients. *Biol Sex Differ*. 2017;8(1):25.

244. Abbot S, Bossingham D, Proudman S, de Costa C, Ho-Huynh A. Risk factors for the development of systemic sclerosis: a systematic review of the literature. *Rheumatol Adv Pract*. 2018;2(2):rky041.

245. Merz WM, Fischer-Betz R, Hellwig K, Lamprecht G, Gembruch U. Pregnancy and Autoimmune Disease. *Dtsch Arztebl Int*. 2022;119(9):145-156.

246. Gao C, Osmundson S, Velez Edwards DR, Jackson GP, Malin BA, Chen Y. Deep learning predicts extreme preterm birth from electronic health records. *J Biomed Inform*. 2019;100:103334.

247. Fazzari MJ, Guerra MM, Salmon J, Kim MY. Adverse pregnancy outcomes in women with systemic lupus erythematosus: can we improve predictions with machine learning? *Lupus Sci Med*. 2022;9(1). doi:10.1136/lupus-2022-000769

248. Wei S, Lai K, Yang Z, Zeng K. Systemic lupus erythematosus and risk of preterm birth: a systematic review and meta-analysis of observational studies. *Lupus*. 2017;26(6):563-571.

249. Strouse J, Donovan BM, Fatima M, et al. Impact of autoimmune rheumatic diseases on birth outcomes: a population-based study. *RMD Open*. 2019;5(1):e000878.

250. Cornish J, Tan E, Teare J, et al. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut*. 2007;56(6):830-837.

251. Huang W, Wu T, Jin T, et al. Maternal and fetal outcomes in pregnant women with rheumatoid arthritis: a systematic review and meta-analysis. *Clin Rheumatol*. 2023;42(3):855-870.

252. Adams Waldorf KM, Nelson JL. Autoimmune disease during pregnancy and the microchimerism legacy of pregnancy. *Immunol Invest*. 2008;37(5):631-644.

253. Marri SR, Ahn C, Buchman AL. Voluntary childlessness is increased in women with inflammatory bowel disease. *Inflamm Bowel Dis*. 2007;13(5):591-599.

254. Yamamoto Y, Aoki S. Systemic lupus erythematosus: strategies to improve pregnancy outcomes. *Int J Womens Health*. 2016;8:265-272.

255. Marrie RA, Walld R, Bolton JM, et al. Increased incidence of psychiatric disorders in immune-mediated inflammatory disease. *J Psychosom Res*. 2017;101:17-23.

256. de Man YA, Dolhain RJEM, van de Geijn FE, Willemsen SP, Hazes JMW. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum*. 2008;59(9):1241-1248.

257. Kim MA, Kim YH, Chun J, et al. The Influence of Disease Activity on Pregnancy Outcomes in Women With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *J Crohns Colitis*. 2021;15(5):719-732.

258. U.S. Census Bureau. Stable Fertility Rates 1990-2019 Mask Distinct Variations by Age. Accessed April 26, 2023. https://www.census.gov/library/stories/2022/04/fertility-rates-declined-for-younger-women-increased-for-older-women.html?utm_campaign=20220406msacos1ccstors&utm_medium=email&utm_source=govdelivery

259. Aringer M, Brinks R, Dörner T, et al. European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) SLE classification criteria item performance. *Ann Rheum Dis*. 2021;80(6):775-781.

260. Miller FW. The increasing prevalence of autoimmunity and autoimmune diseases: an urgent call to action for improved understanding, diagnosis, treatment, and prevention. *Curr Opin Immunol*. 2023;80:102266.

261. Mazzucchelli I, Decembrino L, Garofoli F, et al. Maternal and neonatal outcomes in pregnant women with autoimmune diseases in Pavia, Italy. *BMC Pediatr*. 2015;15:217.

262. Park KY, Kwon HJ, Wie JH, et al. Pregnancy outcomes in patients with vitiligo: A nationwide population-based cohort study from Korea. *J Am Acad Dermatol*. 2018;79(5):836-842.

263. Paizis K. Immunomodulatory drugs in pregnancy and lactation. *Aust Prescr*. 2019;42(3):97-101.

264. Barenbrug L, Groen M te, Hoentjen F, et al. Pregnancy and neonatal outcomes in women with immune mediated inflammatory diseases exposed to anti-tumor necrosis factor-α during pregnancy: A systemic review and meta-analysis. *J Autoimmun*. 2021;122:102676.

265. Allen KD, Kiefer MK, Butnariu M, Afzali A. Pregnant women with immune mediated inflammatory diseases who discontinue biologics have higher rates of disease flare. *Arch Gynecol Obstet*. 2022;306(6):1929-1937.

266. U.S. Department of Agriculture's Economic Research Service (ERS). Rural-Urban Commuting Area Codes. Published online 2010 (revised 2019). Accessed 2022. https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/

267. Luketic VA, Sanyal AJ. The current status of ursodeoxycholate in the treatment of chronic cholestatic liver disease. *Gastroenterologist*. 1994;2(1):74-79.

268. Mawson AR. A Role for the Liver in Parturition and Preterm Birth. *J Transl Sci*. 2016;2(3):154-159.

269. Haas DM, Benjamin T, Sawyer R, Quinney SK. Short-term tocolytics for preterm delivery - current perspectives. *Int J Womens Health*. 2014;6:343-349.

270. Jupalli A, Iqbal AM. *Enoxaparin*. StatPearls Publishing; 2022.

271. Flickr F us on. What are the risk factors for preterm labor and birth? https://www.nichd.nih.gov/. Accessed September 13, 2023. https://www.nichd.nih.gov/health/topics/preterm/conditioninfo/who_risk

272. Updated Clinical Guidance for the Use of Progesterone Supplementation for the Prevention of Recurrent Preterm Birth. Accessed September 13, 2023. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2023/04/updated-guidance-use-of-progesterone-supplementation-for-prevention-of-recurrent-preterm-birth

273. Dhaliwal JS, Rosani A, Saadabadi A. *Diazepam*. StatPearls Publishing; 2022.

274. Männistö T, Mendola P, Kiely M, et al. Maternal psychiatric disorders and risk of preterm birth. *Ann Epidemiol*. 2016;26(1):14-20.

275. Saleem F, Sharma A. *NPH Insulin*. StatPearls Publishing; 2023.

276. Crump C, Sundquist J, Sundquist K. Preterm birth and risk of type 1 and type 2 diabetes: a national cohort study. *Diabetologia*. 2020;63(3):508-518.

277. Alfaro RA, Davis DD. *Diclofenac*. StatPearls Publishing; 2023.

278. Smith CJF, Förger F, Bandoli G, Chambers CD. Factors Associated With Preterm Delivery Among Women With Rheumatoid Arthritis and Women With Juvenile Idiopathic Arthritis. *Arthritis Care Res* . 2019;71(8):1019-1027.

279. Van Calsteren K, Heyns L, De Smet F, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. *J Clin Oncol*. 2010;28(4):683-689.

280. Khan KM, Patel JB, Schaefer TJ. *Nifedipine*. StatPearls Publishing; 2023.

281. Conde-Agudelo A, Romero R, Kusanovic JP. Nifedipine in the management of preterm labor: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2011;204(2):134.e1-134.e20.

282. McMahon RS, Bashir K. *Potassium Chloride*. StatPearls Publishing; 2023.

283. Yang CW, Li S, Dong Y. The Prevalence and Risk Factors of Hypokalemia in Pregnancy-Related Hospitalizations: A Nationwide Population Study. *Int J Nephrol*. 2021;2021:9922245.

284. Rubin R, Khanna NR, McIver LA. *Aspart Insulin*. StatPearls Publishing; 2022.

285. Kemnic TR, Coleman M. *Trimethoprim Sulfamethoxazole*. StatPearls Publishing; 2022.

286. Baer RJ, Nidey N, Bandoli G, et al. Risk of Early Birth among Women with a Urinary Tract Infection: A Retrospective Cohort Study. *AJP Rep*. 2021;11(1):e5-e14.

287. Basit H, Kahwaji CI. *Clonazepam*. StatPearls Publishing; 2023.

288. Rose MS, Pana G, Premji S. Prenatal Maternal Anxiety as a Risk Factor for Preterm Birth and the Effects of Heterogeneity on This Relationship: A Systematic Review and Meta-Analysis. *Biomed Res Int*. 2016;2016:8312158.

289. Yonkers KA, Gilstad-Hayden K, Forray A, Lipkind HS. Association of Panic Disorder, Generalized Anxiety Disorder, and Benzodiazepine Treatment During Pregnancy With Risk of Adverse Birth Outcomes. *JAMA Psychiatry*. 2017;74(11):1145-1152.

290. Ocejo A, Correa R. *Methylprednisolone*. StatPearls Publishing; 2022.

291. Crowley P. Prophylactic corticosteroids for preterm birth. *Cochrane Database Syst Rev*. 2000;(2):CD000065.

292. Din L, Preuss CV. *Prochlorperazine*. StatPearls Publishing; 2023.

293. Fabre C, Pauly V, Baumstarck K, et al. Pregnancy, delivery and neonatal complications in women with schizophrenia: a national population-based cohort study. *Lancet Reg Health Eur*. 2021;10:100209.

294. Patel RS, Parmar M. *Doxycycline Hyclate*. StatPearls Publishing; 2023.

295. Rours GIJG, Duijts L, Moll HA, et al. Chlamydia trachomatis infection during pregnancy associated with preterm delivery: a population-based prospective cohort study. *Eur J Epidemiol*. 2011;26(6):493-502.

296. Eastham JH, Patel P. *Phenazopyridine*. StatPearls Publishing; 2023.

297. Maxfield L, Crane JS. *Vitamin C Deficiency*. StatPearls Publishing; 2022.

298. Hauth JC, Clifton RG, Roberts JM, et al. Vitamin C and E supplementation to prevent spontaneous preterm birth: a randomized controlled trial. *Obstet Gynecol*. 2010;116(3):653-658.

299. Dalal R, Grujic D. *Epinephrine*. StatPearls Publishing; 2023.

300. Kelly YJ, Brabin BJ, Milligan P, Heaf DP, Reid J, Pearson MG. Maternal asthma, premature birth, and the risk of respiratory morbidity in schoolchildren in Merseyside. *Thorax*. 1995;50(5):525-530.

301. Islam N, Khanna NR, Zito PM. *Insulin Lispro*. StatPearls Publishing; 2023.

302. *Nystatin*. National Institute of Diabetes and Digestive and Kidney Diseases; 2020.

303. Maki Y, Fujisaki M, Sato Y, Sameshima H. Candida Chorioamnionitis Leads to Preterm Birth and Adverse Fetal-Neonatal Outcome. *Infect Dis Obstet Gynecol*. 2017;2017:9060138.

304. Murphy PB, Bistas KG, Le JK. *Clindamycin*. StatPearls Publishing; 2023.

305. McDonald HM, O'Loughlin JA, Jolley P, Vigneswaran R, McDonald PJ. Vaginal infection and preterm labour. *Br J Obstet Gynaecol*. 1991;98(5):427-435.

306. Ferrous gluconate. Drugs.com. Accessed September 13, 2023. https://www.drugs.com/mtm/ferrous-gluconate.html

307. Rahmati S, Azami M, Badfar G, Parizad N, Sayehmiri K. The relationship between maternal anemia during pregnancy with preterm birth: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med*. 2020;33(15):2679-2689.

308. Bernshteyn MA, Masood U. *Pantoprazole*. StatPearls Publishing; 2023.

309. Lee KS, Kim ES, Kim DY, Song IS, Ahn KH. Association of Gastroesophageal Reflux Disease with Preterm Birth: Machine Learning Analysis. *J Korean Med Sci*. 2021;36(43):e282.

310. Shin JJ, Saadabadi A. *Trazodone*. StatPearls Publishing; 2022.

311. Dhesi M, Maldonado KA, Maani CV. *Tramadol*. StatPearls Publishing; 2023.

312. Philip Thornton D. Benzonatate. Drugs.com. Accessed September 13, 2023. https://www.drugs.com/benzonatate.html

313. Eghtedari B, Correa R. *Levothyroxine*. StatPearls Publishing; 2022.

314. Parizad Nasirkandy M, Badfar G, Shohani M, et al. The relation of maternal hypothyroidism and hypothyroxinemia during pregnancy on preterm birth: An updated systematic review and meta-analysis. *Int J Reprod Biomed*. 2017;15(9):543-552.

315. Isola S, Hussain A, Dua A, Singh K, Adams N. *Metoclopramide*. StatPearls Publishing; 2023.

316. Nasri H, Rafieian-Kopaei M. Metformin: Current knowledge. *J Res Med Sci*. 2014;19(7):658-664.

317. Singh HK, Saadabadi A. *Sertraline*. StatPearls Publishing; 2023.

318. Southard BT, Al Khalili Y. *Promethazine*. StatPearls Publishing; 2022.

319. Dabaja A, Dabaja A, Abbas M. *Polyethylene Glycol*. StatPearls Publishing; 2023.

320. Sandman Z, Iqbal OA. *Azithromycin*. StatPearls Publishing; 2023.

321. Lim WS, Macfarlane JT, Colthorpe CL. Pneumonia and pregnancy. *Thorax*. 2001;56(5):398-405.

322. Gerriets V, Anderson J, Nappe TM. *Acetaminophen*. StatPearls Publishing; 2023.

323. Nguyen K, Dersnah GD, Ahlawat R. *Famotidine*. StatPearls Publishing; 2022.

324. Akhavan BJ, Khanna NR, Vijhani P. *Amoxicillin*. StatPearls Publishing; 2022.

325. Norethindrone. Drugs.com. Accessed September 13, 2023. https://www.drugs.com/mtm/norethindrone.html

326. Sadiq NM, Dice TJ, Mead T. *Oxycodone*. StatPearls Publishing; 2022.

327. Griddine A, Bush JS. *Ondansetron*. StatPearls Publishing; 2023.

328. Ngo VTH, Bajaj T. *Ibuprofen*. StatPearls Publishing; 2023.

329. Hydrocortisone. Drugs.com. Accessed September 13, 2023. https://www.drugs.com/mtm/hydrocortisone.html

330. Sinha S. Ferrous Sulfate: Uses, Dosage & Side Effects. Drugs.com. Accessed September 13, 2023. https://www.drugs.com/ferrous_sulfate.html

331. Uto LR, Gerriets V. *Clavulanic Acid*. StatPearls Publishing; 2023.

332. Pseudoephedrine: medicine for a stuffy or blocked nose. nhs.uk. Accessed September 13, 2023. https://www.nhs.uk/medicines/pseudoephedrine/

333. Hardin MD, Jacobs TF. *Glyburide*. StatPearls Publishing; 2023.

334. Vitamin B6. Accessed September 13, 2023. https://ods.od.nih.gov/factsheets/VitaminB6-HealthProfessional/

335. Schmidt N, Gans EH. Tretinoin: A Review of Its Anti-inflammatory Properties in the Treatment of Acne. *J Clin Aesthet Dermatol*. 2011;4(11):22-29.

336. Liu B, Dai Q, Liu P, Gopinath SCB, Zhang L. Nanostructure-mediated glucose oxidase biofunctionalization for monitoring gestational diabetes. *Process Biochem*. 2021;110:19-25.

337. Li DK, Raebel MA, Cheetham TC, et al. Genital herpes and its treatment in relation to preterm delivery. *Am J Epidemiol*. 2014;180(11):1109-1117.

338. Gilbert AL, Hoffman BL. Contraceptive Technology: Present and Future. *Obstet Gynecol Clin North Am*. 2021;48(4):723-735.

339. Pramoxine. Memorial Sloan Kettering Cancer Center. Accessed September 13, 2023. https://www.mskcc.org/cancer-care/patient-education/medications/adult/pramoxine

340. CDC. COVID Data Tracker. Accessed March 8, 2022. https://covid.cdc.gov/covid-data-tracker/#variant-proportions

341. Andrade C. Mean Difference, Standardized Mean Difference (SMD), and Their Use in Meta-Analysis: As Simple as It Gets. *J Clin Psychiatry*. 2020;81(5). doi:10.4088/JCP.20f13681

342. Anatomical Therapeutic Chemical (ATC) Classification. Accessed November 21, 2021. https://www.who.int/tools/atc-ddd-toolkit/atc-classification

343. CDC. Symptoms of COVID-19. Centers for Disease Control and Prevention. Published December 14, 2022. Accessed April 25, 2023. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html?s_cid=11722:covid%20variant%20symptoms:sem.ga:p:RG:GM:gen:PTN:FY22

344. Wu Y, Kang L, Guo Z, Liu J, Liu M, Liang W. Incubation Period of COVID-19 Caused by Unique SARS-CoV-2 Strains: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2022;5(8):e2228008.

345. Sun X, Xu W. Fast Implementation of DeLong's Algorithm for Comparing the Areas Under Correlated Receiver Operating Characteristic Curves. *IEEE Signal Process Lett*. 2014;21(11):1389-1393.

APPENDIX A

Supplementary method

Method A.3 1 Investigation on the association between exposure to sertraline/SSRI and elevated risk of PTB

We limited our analytic population to patients with at least one depression diagnosis before the pregnancy (Table A.3 2). We calculated the risk of PTB using the propensity score adjustment method. We chose propensity score adjustment because it performs well compared to other covariate adjustment methods[130], and our analytic population shares similar characteristics and is balanced. Propensity score was calculated on maternal and pregnancy characteristics. This includes delivery year, parity, gravidity, maternal age, race, ethnicity, preterm history, ethanol consumption status, smoking status, and illegal drug use status.

Method A.3 2 Investigation on negative correlation between exposure to acyclovir and PTB risk

We first assessed the risk of PTB in patients exposed to acyclovir before the GA of 36 weeks using propensity score matching. We used matching here because the control and treatment groups were highly imbalanced. Second, we calculated the chance of delivering before 37 weeks on a subsample of patients with an indication of genital herpes, determined based on a diagnosis before delivery (Table A.3 2). Third, we compared PTB risk between patients exposed to acyclovir and valacyclovir before GA 36 weeks. We used the propensity score adjustment method for the second and third analyses because the control and treatment groups were balanced; both the control and treatment groups had genital herpes. Propensity score was calculated on maternal and pregnancy characteristics. This includes delivery year, parity, gravidity, maternal age, race, ethnicity, preterm history, ethanol consumption status, smoking status, and illegal drug use status.

Method A.3 3 Investigation on the association between exposure to ferrous sulfate and decreased risk of PTB

We limited our analytic population to patients diagnosed with iron deficiency anemia (Table A.3 2) within 180 days of the prepregnancy period. We used propensity score adjustment because the control and treatment groups were balanced; both had iron deficiency anemia before pregnancy. The propensity score was calculated on maternal/pregnancy characteristics. This includes delivery year, parity, gravidity, maternal age, race, ethnicity, preterm history, ethanol consumption status, smoking status, and illegal drug use status.

Method A.5 1 CDC Social Vulnerability Index (CDC-SVI) and rural-urban classification

Patient's address was converted to a U.S. census tract. We imported publicly available CDC-SVI[160] and rural-urban classification[266] resources from the CDC Agency for Toxic Substance and Disease Registry and the U.S. Department of Agriculture Economic Research Service into our HIPPA-compliant workspace. Individuals' census tract was mapped to CDC SVI and rural-urban classification code. CDC-SVI represents the percentile ranking of each census tract on 15 social factors. Social factor themes include socioeconomic status, household composition, race/ethnicity/language, and housing/transportation. CDC scores range from 0 to 1. A higher SVI score indicates a higher vulnerability of an individual's U.S. census tract exposed for each theme. For rural-urban classification, we specifically used SecondaryRUCACode2010 (last updated in 2019) to categorize an individual's census tract into metropolitan (<4), micropolitan (4-6), small town(7-9), and rural (10-99).

Method A.5 2 Classification models

Models were generated using python package sklearn (version 1.0.2) with default settings for logistic regression, gradient boosting regression, and random forest. Due to the imbalance of dataset, we randomly undersampled control group to 1:1 match the treatment group. We leveraged leave-one-out-cross-validation (LOOCV). LOOCV is an extreme version of k-fold cross-validation where k equals n. We left one sample as a test set at a time, and this step was repeated for all samples. Model performance was evaluated using mean absolute error, mean squared error, root mean squared error, area under the curve of receiver operating characteristics (AUC-ROC), AUC of the precision-recall curve, R^2. Gini feature importance was used to assess the marginal contribution and contribution of an individual feature to the model. Due to the computational cost, we did not use our final model to run Shapley additive explanation (SHAP). We 1:1 randomly undersampled the control group to match the treatment group. We leveraged SHAP on these 1:1 matched samples to evaluate the average marginal contribution of a feature value across all permutations of features. This provided insight into the degree of influence of the feature on an individual's classification prophylactic anticoagulant administration status for the gradient boosting model, the final model.

Method A.6 1 CDC Social Vulnerability Index (CDC-SVI) and rural-urban classification

Patient's address was converted to a U.S. census tract. We imported publicly available CDC-SVI[160] and rural-urban classification[266] resources from the CDC Agency for Toxic Substance and Disease Registry and the U.S. Department of Agriculture Economic Research Service into our HIPPA-compliant workspace. Individuals' census tract was mapped to CDC SVI and rural-urban classification code. CDC-SVI represents the percentile ranking of each census tract on 15 social factors. Social factor themes include socioeconomic status, household composition, race/ethnicity/language, and housing/transportation. CDC scores range from 0 to 1. A higher SVI score indicates a higher vulnerability of an individual's U.S. census tract exposed for each theme. For rural-urban classification, we specifically used SecondaryRUCACode2010 (last updated in

2019) to categorize an individual's census tract into metropolitan (<4), micropolitan (4-6), small town(7-9), and rural (10-99).

Supplementary table

Table A.3 1 Variable definition

Category	Variable	Definitions
Maternal/pregnancy characteristics	Race	Race noted in medical record. Missing values were encoded as Unknown; American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White or Caucasian, Multiracial, Other, Unknown
	Ethnicity	Ethnicity noted in medical record. Missing values were encoded as unknown; Hispanic or Latino, Not Hispanic or Latino, Unknown
	Maternal age	Maternal age at the start of pregnancy; 18 ~ 24, 25 ~ 29, 30 ~ 34, 35 ~ 40, 41 ~ 44
	Pregravid BMI	Pregravid Body Mass Index (kg/m2). Missing value was encoded as unknown; Underweight (<18.5 BMI), Normal (18.5 - 24.9 BMI), Overweight (25.0 - 29.9 BMI), Obese (>30.0)
	Insurance status	Commercial, Medicaid, Medicare, Uninsured-Self-Pay
	Smoker	Self-reported smoking status; 0,1
	Illegal drug use	Self-reported illegal drug use status; 0,1
	Preterm history	History of preterm delivery; 0,1
	Parity	Number of times a patient has delivered a fetus older than 20 weeks of gestation prior to the current pregnancy; 0, 1~5, 6
	Gravidity	Number of times a patient has been pregnant; 0, 1~5, 6
	Delivery year	Year of delivery; 2013~2022
Maternal-fetal health outcomes	Low birth weight	Infant birth weight ≤ 2,500g
	Preterm birth	Infant gestational age (GA) at birth < 37 weeks
	Small for gestational age	Infant birth weight < 10th percentiles for infants of same GA

BMI Body Mass Index; CDC Center for Disease Control and Prevention; GA Gestational age; SVI Social Vulnerability Index

Table A.3 2 SNOMED diagnosis codes

Diagnosis	SNOMED Concept ID
Abnormal fetal movement	276369006, 363093002, 364755008
anemia	271737000
anxiety	48694002
asthma	195967001
Bacterial infection	87628006,442635007,170488007, 710954001
Breech presentation	6096002
Cardiovascular diseases	49601007
Chronic kidney diseases	709044004
Cystic fibrosis	190905008
Depression	35489007
Diabetes	73211009
Excessive fetal growth	22173004, 199616008
Fatigue	84229001
Gastroesophageal reflux diseases	235595009
History of cesarean section	161805006
Hypertensive disorder	10725009,720568003,48146000,59621000,429198000, 71701000119105,71421000119105, 397748008, 706882009, 697929007, 1078301000112109, 206596003, 23130000, 5501000119106, 118781000119108, 84094009, 31992008, 38341003, 24184005 69909000, 198941007, 367390009, 48194001
Intrauterine device birth control	737288007
insomnia	193462001
Irregular period	80182007, 237055002 (polycystic ovary syndrome)
Leukemia	93143009
Placenta previa	36813001, 445122007
Pneumonia	233604007
Poor fetal growth	2033007, 397949005
Preterm labor	289733005, 6383007
Premature rupture of membrane	44223004
Rhesus D negative	165746003
sepsis	91302008
Sickle cell diseases	417357006
Vitamin D deficiency	34713006

All descendant SNOMED codes are included

Table A.3 3 Descriptive statistics of source population

	Source population (n=367,459)
Maternal-fetal health outcome	
Gestational days	275.0 (12.8)
Preterm birth	28185 (7.7)
Small for gestational age	43905 (12.1)
Low birth weight	19611 (5.4)
Delivery method	
vaginal	252001 (69.0)
c-section	110386 (30.2)
other	277 (0.1)
Missing	2411 (0.7)
Maternal/pregnancy characteristics	
Maternal age	31.0 (5.8)
Age group	
17 or younger	3112 (1.1)
18-24	61214 (22.1)
25-29	93220 (33.6)
30-34	119530 (43.1)
Race group	
American Indian or Alaska Native	4764 (1.3)
Asian	29448 (8.1)
Black or African American	15478 (4.2)
Native Hawaiian or Other Pacific Islander	4249 (1.2)
White or Caucasian	230765 (63.2)
Multirace	17932 (4.9)
Other	60175 (16.5)
Missing	2264 (0.6)
Ethnic group	
Hispanic/Latino	75271 (20.6)
Not Hispanic/Latino	281675 (77.2)
Unknown/Not Reported	8061 (2.2)
BMI category	
underweight	3002 (0.8)
normal	52389 (14.4)
obese	31243 (8.6)
overweight	31300 (8.6)
Missing	247141 (67.7)
Insurance	
Commercial	170164 (46.6)
Medicaid/Medicare	192453 (52.7)
Self Pay	84 (0.0)
Missing	2374 (0.7)
Smoker	26108 (7.2)
Illegal drug user	27071 (7.4)
Alcohol user	64577 (17.7)
Vulnerability index of socioeconomic status	0.4 (0.2)
Vulnerability index of housing composition	0.4 (0.3)
Vulnerability index of minority status and language	0.6 (0.2)
Vulnerability index of housing type and transportation	0.6 (0.3)

Rural/urban classification	
Metropolitan	307464 (84.2)
Micropolitan	17425 (4.8)
Small Town	5871 (1.6)
Rural	4567 (1.3)
Missing	29747 (8.1)
Gravidity	
1	82176 (22.5)
2-4	198452 (54.4)
5≤	42011 (11.5)
Missing	42436 (11.6)
Parity	
0	45275 (12.4)
1	127735 (35.0)
2-4	141207 (38.7)
5≤	8422 (2.3)
Missing	42436 (11.6)
Preterm history	
Yes	76632 (21.0)
No	246007 (67.4)
Missing	42436 (11.6)
Fetal sex	
Female	164049 (48.6)
Male	173160 (51.3)
Unknown	51 (0.0)
Other	16 (0.0)
Delivery year	
2013	20799 (5.9)
2014	30834 (8.8)
2015	34844 (10.0)
2016	36288 (10.4)
2017	35895 (10.3)
2018	35587 (10.2)
2019	36953 (10.6)
2020	35431 (10.1)
2021	39791 (11.4)
2022	43188 (12.4)

Table A.3 4 Categorization of medications with statistically significant association with risk of PTB based on their indication

		indication		
medication	**usage/usage during pregnancy**	**preterm labor/birth**	**PTB risk factor**	**infection**
ursodeoxyholate	dissolve gallstones. treat cholestatic liver diseases[267]	N	Y(liver disorder[268])	N
indomethacin	pain treatment. tocolytics for preterm labor[269]	Y[269]	N	N
enoxaparin	anticoagulation[270]	N	Y(blood clot[271])	N
progesterone	treatment option for preterm birth[272]	Y	N	N

diazepam	treat anxiety, muscle spasm, and seizures[273]	N	Y(anxiety[274])	N
insulin isophane beef	insulin given to help control blood sugar levels in people with diabetes[275]	N	Y(diabetes[276])	N
diclofenac	treat pain, migraines, and arthritis[277]	N	Y (arthritis[278])	N
sucralfate	medication used to treat duodenal ulcers, chemotherapy-induced mucostasis	N	Y(cancer[279])	N
nifedipine	treat high blood pressure[280]	Y[281]	Y (diabete[276])	N
potassium chloride	treat and prevent low blood potassium[282]	N	Y(hypokalemia[283])	N
insulin aspart human	treat diabetes[284]	N	Y(diabetes[276])	N
sulfamethoxazole	antibiotics used for bacterial infection such as urinary tract infection[285]	N	Y(urinary tract infection[286])	Y
clonazepam	sedative. treatment for seizures, panic disorder, and anxiety[287]	N	Y(anxiety[288], panic[289])	N
methylprednisolone	treatment for inflammation, flares of chronic illness[290]	Y[291]	N	N
prochlorperazine	treatment for nausea, vomiting, anxiety, and schizophrenia[292]	N	Y(schizophrenia[293])	N
doxycycline	antibiotics used for bacterial infection including acne, urinary tract infection, gonorrhea, chlamydia, etc[294]	N	Y(chlamydia[295])	Y
phenazopyridine	relieve symptoms caused by urinary tract infection[296]	N	Y(urinary tract infection[286])	Y
ascorbic acid	treat vitamin c deficiency[297]	N	Y[298]	N
epinephrine	treatment for severe asthma attack and allergic reactions[299]	N	Y(asthma[300]	N
insulin lispro	treament for diabetes[301]	N	Y[276]	N
nystatin	treat fungal infection[302]	N	Y(candida[303])	Y
clindamycin	antibiotic for skin and vaginal infection[304]	N	Y[305]	Y
ferrous gluconate	used to treat or prevent iron deficiency anemia[306]	N	Y(anemia[307])	N
pantoprazole	reduce the amount of stomach acid. used for heartburn, acid reflux, gastroesophegal reflux diseases[308]	N	Y(GERD[309])	N
trazodone	antidepresssant[310]	N	Y(depression[132])	N
tramadol	strong pain medication[311]	N	N	N
benzonatate	treat cough caused by common cold and other breathing problems(asthma, pneumonia)[312]	N	Y[300]	N
levothyroxine	treat hypothyroidism[313]	N	Y(hypothyroidism[314])	N
metochlorompramide	treat GERD, and gastroparesis in patients with diabetes[315]	N	Y[309]	N
metformin	treat type 2 diabetes[316]	N	Y(diabetes[276])	N
sertraline	antidepressant, selective serotonin reuptake inhibitor[317]	N	Y(depression[274])	N
promethazine	antihistamine treating allergies and motion sickness[318]	N	N	N
polyethylene glycol 3350	treat occasional constipation[319]	N	N	N

azithromycin	antibiotic medicine treating pneumonia, ear, nose, throat, and sinus[320]	N	Y(pneumonia[321])	Y
acetaminophen	treat minor aches, pains, and fevers[322]	N	N	N
famotidine	used to treat GERD[323]	N	Y(GERD[309])	N
amoxicillin	penicillin antibiotic treating infection and stomach ulcers[324]	N	N	Y
norethindrone	used to prevent pregnancy[325]	N	N	N
insulin isophane	control blood sugar with diabetes[275]	N	Y(diabete[276])	N
oxycodone	treat moderate to severe pain[326]	N	N	N
ondansetron	prevent nausea and vomiting[327]	N	N	N
ibuprofen	treat fever and mild to severe pain[328]	N	N	N
hydrocortisone	calm down body's immune response to reduce pain, itching, swelling, inflammation[329]	N	N	N
ferrous sulfate	iron supplement used for iron deficient anemia[330]	N	Y[307]	N
clavulanate	used in conjuction with amoxicillin to treat certain bacterial infection[331]	N	N	Y
pseudoephedrine	treat stuffy nose and sinuses[332]	N	N	N
glyburide	treat type 2 diabetes[333]	N	Y[276]	N
vitamin b6	vitamin for healthy nervous system and immune system[334]	N	N	N
tretinoin	acne treatment[335]	N	N	N
glucose oxidase	probe for sensing gestational diabetes[336]	N	N	N
acyclovir	treat herpes virus infection[133]	N	Y(genital herpes[337])	Y
etonogestrel	birth control[338]	N	N	N
pramoxine	relieve pain and itching from insect bites or hemorrhoids[339]	N	N	N

Table A.4 1 Variable definition[12]

Variable Definition		
Category	Feature	Definition
pregnancy characteristics	parity	number of times a women has given birth to a fetus older than 24 weeks of gestational age; 0, 1~4, ≥5
	preterm history	number of times a women has given preterm birth
	delivery year	year of delivery; 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020
	fetal sex	fetal sex; female, male
maternal characteristics	age at LMP	maternal age at the start of pregnancy
	racial group	maternal race group; white/caucasian, black/african american, asian, american indian, alaska native, native hawaiian/other pacific islanders, multirace, unknown/not reported
	ethnic group	maternal ethnicity group; hispanic/latino, not hispanic/latino, unknown/not reported

	insurance status	insurance status; commercial, medicaid/medicare
	pregravid BMI category	pregravid body mass index (BMI); underweight, normal, overweight, obese
	smoking status	smoking history reported during prenatal visit; 1,0
	illegal drug use status	illegal drug use history reported during prenatal visit; 1,0
	alcohol drinking status	alcohol drinking status reported during prenatal visit; 1,0
social vulnerability	social vulnerability index	social vulnerability percentile ranking of women's census tract; 0~1
comorbidities	anemia	any diagnosis of anemia or descendent disorders during two-year pre-pregnancy period; 1,0
	asthma	any diagnosis of asthma or descendent disorders during two-year pre-pregnancy period; 1,0
	chronic lung disease	any diagnosis of chronic lung disease or descendent disorders during two-year pre-pregnancy period; 1,0
	cardiovascular disease	any diagnosis of cardiovascular disease or descendent disorders during two-year pre-pregnancy period; 1,0
	cystic fibrosis	any diagnosis of cystic fibrosis or descendent disorders during two-year pre-pregnancy period; 1,0
	diabetes	any diagnosis of diabetes or descendent disorders during two-year pre-pregnancy period; 1,0
	leukemia	any diagnosis of leukemia or descendent disorders during two-year pre-pregnancy period; 1,0
	pneumonia	any diagnosis of pneumonia or descendent disorders during two-year pre-pregnancy period; 1,0
	renal diseases	any diagnosis of renal diseases or descendent disorders during two-year pre-pregnancy period; 1,0
	sepsis	any diagnosis of sepsis or descendent disorders during two-year pre-pregnancy period; 1,0
	sickle cell diseases	any diagnosis of sickle cell diseases or descendent disorders during two-year pre-pregnancy period; 1,0

pre-pregnancy mental health condition	adjustment disorder	any diagnosis of adjustment disorder or descendent disorders during 6-month pre-pregnancy period; 1,0
	anxiety disorder	any diagnosis of anxiety disorder or descendent disorders during 6-month pre-pregnancy period; 1,0
	PHQ-9 score	latest patient health questionnaire-9 (PHQ-9) score during two-year pre-pregnancy period
	PHQ-9 category	category of PHQ-9 score; minimal: 1-4, mild: 5-9, moderate: 10-14, moderately severe: 15-19, severe: 20-27
	N06AA exposure	any prescription order of N06AA during 6-month pre-pregnancy period; 1,0
	N06AB exposure	any prescription order of SSRI(N06AB) during 6-month pre-pregnancy period; 1,0
	N06AG exposure	any prescription order of N06AG during 6-month pre-pregnancy period; 1,0
	N06AF exposure	any prescription order of N06AF during 6-month pre-pregnancy period; 1,0

	N06AX exposure	any prescription order of N06AX during 6-month pre-pregnancy period; 1,0
prenatal mental health condition	late pregnancy depression diagnosis	any depression diagnosis during second or third trimester; 1,0
	PHQ-4 score	latest patient health questionnaire-4 (PHQ-4) score during two-year pregnancy
	PHQ-4 category	category of PHQ-4 score; normal: 0-2, mild:3-5, moderate: 6-8, severe: 9-12

Abbreviations: LMP, Last Menstrual Period; BMI, Body Mass Index.
Comorbidity diagnoses were collected using SNOMED codes from Table A.4 2

Table A.4 2 SNOMED diagnosis codes[12]

Diagnosis	**SNOMED Code[a]**
anemia	271737000
adjustment disorder	17226007
asthma	195967001
anxiety disorder	197480006
bipolar	13746004
cardiovascular disease	233604007
chronic lung disease	413839001
cystic fibrosis	190905008
depression	69322001
diabetes	46635009, 44054006
leukemia	93143009
pneumonia	233604007
psychosis	69322001
renal diseases	90708001
sepsis	91302008
sickle cell diseases	417357006

[a]All descendant codes of listed SNOMED were collected

Table A.4 3 RxNorm codes for medication order[12]

Medication	**RxNorm Code**
N06AA	17698, 704, 722, 19895, 2597, 3247, 3332, 3634, 3638, 5691, 5979, 6465, 6646, 446248, 7531, 7674, 8886, 35242, 10834
N06AB	citalopram: 2556, escitalopram: 321988, fluoxetine: 4493, fluvoxamine: 42355, paroxetine: 32937, sertraline: 36437
N06AF	6011, 7394, 8123, 10734
N06AG	30121, 38382
N06AX	94, 47111, 42347, 734064, 72625, 2119365, 29434, 6929, 588250, 30031, 15996, 31565, 7500, 60842, 258326, 38252, 10737, 10898, 39786, 1086769, 11196, 1455099

Table A.4 4 Descriptive statistics for women who had depression onset before pregnancy who went on to deliver, by SSRI exposure[12]

	SSRI exposure during pregnancy

Maternal and birth characteristics	Total No. (%)	No exposure No. (%)	Early-only exposure No. (%)	Late exposure No. (%)
Total	8406	3760	887	3759
Term birth (GA≥37w)	7562 (90.0)	3417 (90.0)	825 (93.0)	3320 (88.3)
≥39w	5051 (60.1)	1988 (63.7)	459 (66.6)	1508 (58.1)
37-39w	2511 (29.9)	864 (27.7)	185 (26.8)	791 (30.5)
Preterm birth (GA<37w)	844 (10.0)	343 (9.1)	62(7.0)	439 (11.7)
32-37w	740 (8.8)	296 (7.9)	57 (6.4)	387 (10.3)
28-32w	71 (0.8)	29 (0.8)	1 (0.1)	41 (1.1)
<28w	33 (0.4)	18 (0.5)	4 (0.5)	11 (0.3)
Gestational age at birth (days)	271.3±13.3	271.9±13.5	273.1±11.8	270.3±13.4
Low birthweight	546 (6.5)	233 (6.2)	33 (4.0)	280 (7.4)
Not low birthweight	7823 (93.1)	3509 (93.8)	852 (96.0)	3462 (92.1)
Birthweight missing	37 (0.4)	18 (0.5)	2 (0.2)	17 (0.5)
Small for gestational age				
SGA	1047 (12.5)	475 (12.6)	96 (10.8)	476 (12.5)
Not SGA	7322 (87.1)	3267 (86.9)	789 (89.0)	3266 (86.9)
Missing	37 (0.4)	18 (0.5)	2 (0.2)	17 (0.5)
Parity				
0	1116 (13.2)	547 (14.5)	101 (11.4)	468 (12.5)
1-4	6342 (75.4)	2799 (74.4)	692 (78.0)	2851 (75.8)
≥5	166 (2.0)	73 (1.9)	14 (1.6)	33 (2.1)
Missing	782 (9.3)	341 (9.1)	80 (9.0)	361 (9.6)
Maternal age (years), mean±std	30.2±6.0	29.7±6.1	29.1±6.0	30.9±5.7
Fetal sex				
Male	3864 (46.0)	1726 (45.9)	433 (48.8)	1705 (45.4)
Female	4140 (49.2)	1846 (49.1)	407 (45.9)	1885 (50.1)
Missing	402 (4.8)	188 (5.0)	47 (5.3)	167 (4.4)
Maternal preterm birth history				
0	5742 (68.3)	2547 (67.7)	634 (71.5)	2543 (67.7)
1	676 (9.5)	315 (8.4)	54 (6.1)	307 (8.2)
≥2	92 (1.1)	29 (0.7)	9 (1.0)	54 (1.4)
Missing	1914 (22.8)	869 (23.1)	190 (21.4)	855 (22.7)
Maternal race				
White	6347 (75.5)	2723 (72.4)	530 (77.0)	2962 (78.8)
Black	286 (3.4)	159 (4.2)	27 (3.9)	93 (2.5)
Asian	314 (3.7)	137 (3.6)	23 (3.3)	148 (3.9)
American Indian/Alaskan Native	158 (1.9)	76 (2.0)	9 (1.3)	68 (1.8)
Native Hawaiian/other Pacific Islander	60 (0.7)	37 (1.0)	3 (0.4)	19 (0.5)
Multirace	438 (5.2)	222 (5.9)	26 (3.8)	176 (4.7)
Unknown/not reported/missing	783 (9.3)	406 (10.8)	72 (10.4)	293 (7.8)
Ethnicity				
Hispanic/Latino	1000 (11.9)	491 (13.1)	138 (15.6)	371 (9.9)
Not Hispanic/Latino	7302 (86.9)	3224 (85.7)	742 (83.7)	3335 (88.7)
Unknown/not reported/missing	104 (1.2)	45 (1.2)	7 (0.8)	53 (1.4)
Pregravid BMI				
Underweight (<18.5)	105 (1.2)	51 (1.4)	11 (1.2)	43 (1.1)
Normal (18.5-25)	1433 (17.0)	595 (15.8)	201 (22.7)	637 (16.9)
Overweight (25-30)	1199 (14.3)	456 (12.1)	148 (16.7)	595 (15.8)
Obese (>30)	1626 (19.3)	659 (17.5)	205 (23.1)	762 (20.3)
Unknown	4043 (48.4)	1999 (73.4)	322 (36.3)	1722 (45.8)

Maternal and birth characteristics	SSRI exposure during pregnancy (continued) Total No. (%)	No exposure No. (%)	Early-only exposure No. (%)	Late exposure No. (%)
Smoking status				
No	7055 (83.9)	3088 (82.1)	746 (84.4)	3221 (85.7)
Yes	1212 (14.4)	580 (15.4)	138 (15.6)	494 (13.1)
Unknown	139 (1.7)	92 (2.4)	3 (0.3)	44 (1.1)
Illegal drug use status				
No	6732 (80.0)	2987 (79.4)	713 (80.4)	3032 (80.7)
Yes	1535 (18.3)	681 (18.1)	171 (19.3)	683 (18.2)
Unknown	139 (1.7)	92 (2.4)	3 (0.3)	44 (1.1)
Ethanol consumption status				
No	5424 (64.5)	2480 (66.0)	568 (64.0)	2376 (63.2)
Yes	2843 (33.8)	1188 (31.6)	316 (35.6)	1339 (35.6)
Unknown	139 (1.7)	92 (2.4)	3 (0.3)	44 (1.1)
Insurance				
Commercial	3272 (38.9)	1344 (35.7)	310 (34.9)	1618 (43.0)
Medicaid/Medicare	5112 (60.8)	2406 (64.0)	576 (64.9)	2117 (56.3)
Other/unknown	22 (0.3)	10 (0.2)	1 (0.0)	11 (0.3)
Social vulnerability index (percentile), mean±std	0.5±0.3	0.5±0.3	0.5±0.3	0.5±0.3
Missing	160 (1.9)	67 (1.8)	17 (1.9)	760(2.0)
Pre-pregnancy comorbidities				
Anemia	1666 (19.8)	692 (18.4)	185 (20.9)	789 (21.0)
Asthma	1034 (12.3)	464 (12.3)	112 (12.6)	458 (12.2)
Cardiovascular diseases	2411 (28.7)	1062 (28.2)	254 (28.6)	1095 (29.1)
Cystic fibrosis	4 (0.0)	2 (0.1)	1 (0.0)	1 (0.0)
Diabetes	167 (2.0)	69 (1.8)	8 (0.9)	90 (2.4)
Leukemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	132 (1.6)	60 (1.6)	11 (1.2)	61 (1.6)
Renal diseases	298 (3.5)	151 (4.0)	30 (3.4)	117 (3.1)
Sepsis	64 (0.8)	36 (1.0)	5 (0.6)	23 (0.6)
Sickle cell diseases	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Pre-pregnancy mental health				
Adjustment disorder	359 (4.3)	161 (4.3)	34 (3.8)	164 (4.4)
Anxiety disorder	3538 (42.1)	1373 (36.5)	384 (43.3)	1781 (47.4)
PHQ-9 category	8406	3760	887	3759
Minimal (1-4)	735 (8.7)	253 (6.7)	71 (8.0)	411 (10.9)
Mild (5-9)	930 (11.1)	354 (9.4)	110 (12.4)	466 (12.4)
Moderate (10-14)	833 (9.9)	301 (8.0)	121 (13.6)	411 (10.9)
Moderately severe (15-19)	625 (7.4)	243 (6.5)	92 (10.3)	290 (7.7)
Severe (20-27)	409 (4.9)	154 (4.1)	66 (7.4)	189 (5.0)
PHQ-9 not available	4874 (57.9)	2455 (65.3)	427 (48.1)	1992 (52.9)
PHQ-9 score mean±std	10.7±6.6	10.9±6.6	11.8±6.5	10.3±6.6
Pre-pregnancy medication				
N06AA	263 (3.1)	169 (4.5)	22 (2.5)	72 (1.9)
N06AB	4496 (53.5)	439 (11.7)	859 (96.8)	3198 (85.1)
N06AG	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
N06AF	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
N06AX	1633 (19.4)	946 (25.2)	110 (12.4)	577 (15.3)
Other psychotropic medication	1557 (18.5)	640 (17.0)	162 (18.3)	755 (20.1)

Maternal and birth characteristics	SSRI exposure during pregnancy (continued) Total No. (%)	No exposure No. (%)	Early-only exposure No. (%)	Late exposure No. (%)

Prenatal mental health	8406	3760	887	3759
Late pregnancy depression	5368 (63.9)	2026 (53.9)	577 (65.1)	2765 (73.6)
PHQ-4 category				
normal (0-2)	2427 (69.0)	1100 (70.8)	246 (73.0)	1081 (28.8)
mild (3-5)	837 (23.8)	358 (23.0)	76 (22.6)	403 (10.7)
moderate (6-8)	192 (5.5)	68 (4.4)	12 (3.6)	112 (3.0)
severe (9-12)	59 (1.7)	28 (1.8)	3 (0.9)	28 (0.7)
PHQ-4 not available	4891 (58.1)	2206 (58.7)	550 (62.0)	2135 (56.8)
PHQ-4 score mean±std	2.0±2.2	1.9±2.1	1.7±1.9	2.1±2.2
Delivery year				
2013	351 (4.2)	202 (5.4)	35 (3.9)	114 (3.0)
2014	533 (6.3)	271 (7.2)	70 (7.9)	192 (5.1)
2015	576 (6.9)	255 (6.8)	80 (9.0)	241 (6.4)
2016	766 (9.1)	387 (10.3)	82 (9.2)	297 (7.9)
2017	795 (9.5)	341 (9.1)	107 (12.1)	347 (9.2)
2018	938 (11.2)	437 (11.6)	99 (11.2)	402 (10.7)
2019	1041 (12.4)	509 (13.5)	88 (9.9)	444 (11.8)
2020	1135 (13.5)	541 (14.4)	93 (10.5)	501 (13.3)
2021	1228 (14.6)	507 (13.5)	118 (13.3)	603 (16.0)
2022	1046 (12.4)	310 (8.2)	115 (13.0)	618 (16.4)

a. For categorical variables, the number of samples and proportion (%) in each exposure group are reported. For continuous variables, mean and standard deviation were reported.

b. Abbreviations: BMI, Body Mass Index; LMP, Last Menstrual Period; PHQ, Patient Health Questionnaire; SSRI, Selective Serotonin Reuptake Inhibitor, N06AA (non-selective monoamine reuptake inhibitor), N06AB, SSRI); N06AF, monoamine oxidase inhibitors, non-selective; N06AG, monoamine oxidase A inhibitors; N06AX, other antidepressants; std, standard deviation.

Table A.4 5 Result of contingency table chi-squared test, Welch's t-test and one-way ANOVA test on distribution of variable across exposure groups and outcome groups[12]

	Exposure group				Outcome group
	no early-only late (P-value)[c]	no late (P-value)[d]	no early-only (P-value)[d]	early-only late (P-value)[d]	non-PTB PTB (P-value)[e]
pregnancy characteristics					
parity [a]	5.2E-01	7.4E-01	7.4E-01	7.4E-01	1.3E-03
parity group [b]	2.4E-02	5.0E-02	5.0E-02	3.6E-01	1.6E-90
preterm birth history [a]	6.3E-02	1.9E-01	1.9E-01	8.1E-02	2.7E-108
delivery year [b]	2.1E-32	4.3E-31	2.8E-07	3.0E-06	2.7E-02
maternal characteristics					
maternal age [a]	3.1E-23	1.3E-16	4.2E-03	2.9E-15	3.4E-02
race group [b]	1.1E-09	8.8E-11	4.6E-01	5.3E-03	8.9E-02
ethnic group [b]	1.0E-06	9.3E-05	9.8E-02	9.0E-06	5.6E-01
insurance group [b]	2.2E-11	3.0E-10	6.6E-01	1.6E-05	1.4E-05
pregravid BMI [a]	3.5E-01	4.2E-01	6.2E-01	4.2E-01	4.9E-04
pregravid BMI group [b]	1.0E-01	1.4E-01	5.7E-01	3.7E-01	1.0E-05

smoking status [b]	6.6E-03	7.3E-03	9.2E-01	1.2E-01	4.1E-01
illegal drug use status [b]	8.0E-01	8.6E-01	8.6E-01	8.6E-01	5.7E-02
ethanol consumption status [b]	2.6E-08	2.0E-06	8.3E-05	8.2E-02	2.1E-01
social vulnerability index [b]	5.0E-08	5.9E-08	6.2E-01	2.7E-03	6.3E-01
comorbidities					
anemia [b]	1.4E-02	1.6E-02	1.5E-01	9.7E-01	2.7E-01
asthma [b]	9.3E-01	8.6E-01	8.6E-01	8.6E-01	5.1E-02
cardiovascular diseases [b]	7.0E-01	8.5E-01	8.5E-01	8.5E-01	5.2E-05
cystic fibrosis [b]	5.6E-01	1.0E+00	1.0E+00	1.0E+00	1.0E+00
diabetes [b]	1.1E-02	1.1E-01	1.0E-01	2.4E-02	1.1E-28
leukemia [b]	1.0E+00	1.0E+00	1.0E+00	1.0E+00	1.0E+00
pneumonia [b]	7.0E-01	1.0E+00	8.0E-01	8.0E-01	7.0E-03
renal diseases [b]	1.0E-01	1.2E-01	6.5E-01	7.6E-01	1.1E-03
sepsis [b]	1.8E-01	3.5E-01	5.3E-01	1.0E+00	9.8E-01
sickle cell diseases [b]	N/A	N/A	N/A	N/A	N/A
pre-pregnancy condition					
adjustment disorder [b]	7.8E-01	9.1E-01	9.1E-01	9.1E-01	6.5E-01
anxiety disorder [b]	1.3E-20	5.1E-21	3.2E-04	3.1E-02	2.0E-01
PHQ-9 score [b]	4.7E-05	1.4E-02	1.4E-02	4.9E-05	7.4E-01
PHQ-9 category [b]	2.6E-03	9.8E-02	9.8E-02	1.8E-03	6.5E-01
N06AA exposure [b]	5.5E-10	9.9E-10	1.3E-02	3.5E-01	3.9E-01
N06AB exposure [b]	0.0E+00	0.0E+00	0.0E+00	4.6E-21	9.5E-01
N06AG exposure [b]	N/A	N/A	N/A	N/A	N/A
N06AF exposure [b]	N/A	N/A	N/A	N/A	N/A
N06AX exposure [b]	1.3E-32	1.5E-25	7.5E-16	3.0E-02	1.5E-02
prenatal depression					
late pregnancy depression [b]	2.6E-69	9.4E-70	3.2E-09	4.9E-07	7.5E-02
PHQ-4 score [a]	1.3E-03	5.3E-03	1.9E-01	3.6E-03	1.9E-03
PHQ-4 category [b]	8.2E-03	2.2E-02	5.6E-01	5.7E-02	2.6E-03

Abbreviations: BMI, Body Mass Index; LMP, Last Menstrual Period; PHQ, Patient Health Questionnaire.

a. Continuous variable

b. Categorical variable

c. Contingency table chi-squared test was conducted to assess the difference in the distribution of categorical variables. One-way ANOVA test was conducted to assess the difference in the distribution of continuous variables

d. Contingency table chi-squared test was conducted on categorical variables. Welch’s t-test was conducted on continuous variables. P-value was corrected with post-hoc multiple comparison post hoc using the Benjamin-Hochberg procedure

e. Welch’s t-test was conducted on continuous variables.

Table A.4 6 Result of the main analysis on preterm birth, gestational age at birth (top), low birthweight and small for gestational age (bottom)

reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no SSRI exposure (3760)	early-only SSRI exposure (887)	0.8 [0.6,1.0] *	1.2 [0.7,1.9]	4.8E-01	1.2 [0.3,2.2]*	0.5 [-1.1,2.0]	5.6E-01
no-late SSRI exposure (4647)	late SSRI exposure (3759)	1.4 [1.2,1.6] ****	1.4 [1.2,1.7] ****	1.9E-05	-1.8 [-2.4,-1.3]*****	-1.9 [-2.6,-1.2]*****	1.6E-07
no SSRI exposure (3760)	late SSRI exposure (3759)	1.3 [1.1,1.5] ***	1.5 [1.2,1.8] ***	6.9E-05	-1.6 [-2.2,-1.0]*****	-2.0 [-2.9,-1.1]****	2.5E-05
early-only SSRI exposure (887)	late SSRI exposure (3759)	1.8 [1.3,2.3] ***	1.4 [1.1,1.9] *	2.0E-02	-2.8 [-3.8,-1.9]*****	-1.8 [-2.8,-0.8]***	3.1E-04
no SSRI exposure (3760)	any SSRI exposure (4646)	1.2 [1.0,1.4] *	1.4 [1.1,1.8] **	1.8E-03	-1.1 [-1.6,-0.5]***	-1.7 [-2.6,-0.8]***	1.9E-04

reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	unadjusted SGA OR p-value
no SSRI exposure (3122)	early-only SSRI exposure (690)	0.6 [0.4,0.8]**	0.7 [0.4,1.3]	2.8E-01	0.8 [0.7,1.1]	1.0 [0.7,1.4]	8.1E-01
no-late SSRI exposure (3812)	late SSRI exposure (2596)	1.3 [1.1,1.6]**	1.6 [1.3,2.0]****	3.1E-05	1.0 [0.9,1.2]	1.1 [1.0,1.3]	1.4E-01
no SSRI exposure (3122)	late SSRI exposure (2596)	1.2 [1.0,1.5]*	1.5 [1.2,2.0]**	1.3E-03	1.0 [0.9,1.1]	1.1 [0.9,1.4]	3.0E-01
early-only SSRI exposure (690)	late SSRI exposure (2596)	2.1 [1.4,3.0]****	1.8 [1.3,2.7]**	1.8E-03	1.2 [0.9,1.5]	1.2 [0.9,1.5]	2.2E-01
no SSRI exposure (3122)	any SSRI exposure (3286)	1.1 [0.9,1.4]	1.4 [1.1,1.9]**	6.6E-03	1.0 [0.9,1.1]	1.1 [0.9,1.3]	3.9E-01

Abbreviations: GA, Gestational age; LBW, Low birthweight; OR, Odds ratio; PTB, Preterm birth; SGA, Small for gestational age; SSRI, Selective Serotonin Reuptake Inhibitors.
Adjusted with pregnancy characteristics, maternal characteristics, pregnancy mental health conditions, and comorbidities (main model)
Significance level
+: P < 0.1; *: P < 0.05; **: P < 0.01; ***: P < 0.001; ****: P < 0.0001; *****: P < 0.00001

Table A.4 7 Result of the exposure group supplementary analysis on preterm birth, gestational age at birth (top), low birthweight and small for gestational age (bottom) [12]

reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no SSRI exposure (3760)	both SSRI exposure (3328)	1.3 [1.1,1.5]**	1.5 [1.1,2.0]**	6.1E-03	-1.4 [-2.0,-0.7]****	-1.6 [-2.7,-0.5]**	3.9E-03
no SSRI exposure (3760)	late-only SSRI exposure (431)	1.7 [1.3,2.2]***	1.5 [1.1,2.0]**	7.7E-03	-3.4 [-4.7,-2.0]*****	-2.7 [-4.1,-1.3]***	1.4E-04
both SSRI exposure (3328)	late-only SSRI exposure (431)	1.3 [1.0,1.8]+	1.1 [0.7,1.6]	7.2E-01	-2.0 [-3.3,-0.7]**	-0.4 [-2.3,1.5]	6.7E-01
early-only SSRI exposure (887)	late-only SSRI exposure (431)	2.2 [1.5,3.2]****	1.8 [0.9,3.5]	1.1E-01	-4.6 [-6.1,-3.0]*****	-2.2 [-5.0,0.6]	1.3E-01
early-only SSRI exposure (887)	both SSRI exposure (3328)	1.7 [1.3,2.2]***	1.4 [1.0,1.8]*	2.4E-02	-2.6 [-3.5,-1.6]*****	-1.8 [-2.8,-0.8]***	2.2E-04

reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no SSRI exposure (3122)	both SSRI exposure (2259)	1.2 [1.0,1.4]+	1.5 [1.1,2.2]*	1.2E-02	0.9 [0.8,1.1]	1.1 [0.8,1.4]	5.2E-01
no SSRI exposure (3122)	late-only SSRI exposure (337)	1.6 [1.1,2.2]**	1.6 [1.1,2.2]*	1.4E-02	1.1 [0.8,1.6]	1.2 [0.9,1.6]	3.0E-01
both SSRI exposure (2259)	late-only SSRI exposure (337)	1.4 [1.0,1.9]+	1.0 [0.6,1.7]	9.3E-01	1.2 [0.8,1.7]	1.1 [0.7,1.7]	6.3E-01
early-only SSRI exposure (690)	late-only SSRI exposure (337)	2.7 [1.7,4.4]****	2.0 [0.8,4.8]	1.2E-01	1.5 [1.0,2.2]+	1.1 [0.6,2.1]	7.2E-01
early-only SSRI exposure (690)	both SSRI exposure (2252)	2.0 [1.4,2.9]***	1.8 [1.3,2.7]**	1.7E-03	1.2 [0.9,1.6]	1.2 [0.9,1.5]	2.3E-01

Abbreviations: GA, Gestational age; LBW, Low birthweight; OR, Odds ratio; PTB, Preterm birth; SGA, Small for gestational age; SSRI, Selective Serotonin Reuptake Inhibitors.
Adjusted with pregnancy characteristics, maternal characteristics, pregnancy mental health conditions, and comorbidities (main model)
Significance level

+: P < 0.1; *: P < 0.05; **: P < 0.01; ***: P < 0.001; ****: P < 0.0001; *****: P < 0.00001

Table A.4 8 Result of drug specific analyses[12]

citalopram							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no citalopram exposure (3760)	early-only citalopram exposure (221)	1.0 [0.6,1.6]	1.4 [0.8,2.7]	2.5E-01	1.5 [-0.4,3.3]	0.8 [-1.5,3.1]	5.1E-01
no-late citalopram exposure (3981)	late citalopram exposure (554)	1.1 [0.8,1.4]	1.2 [0.8,1.7]	4.4E-01	-0.5 [-1.7,0.7]	-0.8 [-2.3,0.6]	2.7E-01
no citalopram exposure (3760)	late citalopram exposure (554)	1.1 [0.8,1.4]	1.3 [0.8,1.9]	2.7E-01	-0.4 [-1.6,0.8]	-0.7 [-2.3,1.0]	4.3E-01
early-only citalopram exposure (221)	late citalopram exposure (554)	1.1 [0.6,1.8]	1.0 [0.5,1.7]	8.7E-01	-1.9 [-3.8,0.1]+	-1.4 [-3.5,0.6]	1.8E-01
no citalopram exposure (3760)	any citalopram exposure (775)	1.0 [0.8,1.4]	1.3 [0.9,1.9]	2.1E-01	0.1 [-0.9,1.2]	-0.2 [-1.7,1.3]	7.6E-01

citalopram (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted SGA OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no citalopram exposure (3760)	early-only citalopram exposure (221)	0.4 [0.2,1.0]*	0.5 [0.2,1.3]	1.78E-01	0.8 [0.5,1.2]	0.9 [0.5,1.5]	5.76E-01
no-late citalopram exposure (3981)	late citalopram exposure (554)	1.2 [0.9,1.7]	1.6 [1.0,2.6]*	3.22E-02	1.0 [0.7,1.3]	1.2 [0.9,1.7]	2.94E-01
no citalopram exposure (3760)	late citalopram exposure (554)	1.2 [0.8,1.7]	1.4 [0.9,2.3]	1.83E-01	1.0 [0.7,1.3]	1.2 [0.8,1.7]	4.57E-01
early-only citalopram exposure (221)	late citalopram exposure (554)	2.8 [1.2,6.7]*	2.9 [1.2,7.4]*	2.08E-02	1.2 [0.7,2.0]	1.2 [0.7,2.0]	6.01E-01
no citalopram exposure (3760)	any citalopram exposure (775)	1.0 [0.7,1.3]	1.2 [0.7,1.9]	4.94E-01	0.9 [0.7,1.2]	1.1 [0.8,1.6]	5.84E-01

escitalopram							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value

no escitalopram exposure (3760)	early-only escitalopram exposure (184)	0.9 [0.5,1.5]	1.3 [0.7,2.6]	4.3E-01	0.6 [-1.4,2.6]	-0.0 [-2.5,2.4]	9.8E-01
no-late escitalopram exposure (3944)	late escitalopram exposure (565)	1.1 [0.9,1.5]	1.4 [1.0,2.1]+	8.1E-02	-0.8 [-1.9,0.4]	-1.1 [-2.6,0.4]	1.4E-01
no escitalopram exposure (37)	late escitalopram exposure (565)	1.1 [0.8,1.5]	1.5 [1.0,2.3]+	6.3E-02	-0.7 [-1.9,0.4]	-1.2 [-2.8,0.5]	1.6E-01
early-only escitalopram exposure (184)	late escitalopram exposure (565)	1.3 [0.7,2.3]	1.0 [0.6,1.9]	9.5E-01	-1.4 [-3.3,0.5]	-0.9 [-2.9,1.0]	3.5E-01
no escitalopram exposure (3760)	any escitalopram exposure (749)	1.1 [0.8,1.4]	1.5 [1.0,2.2]+	5.0E-02	-0.4 [-1.4,0.6]	-0.9 [-2.4,0.6]	2.6E-01

escitalopram (continued)

reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no escitalopram exposure (3760)	early-only escitalopram exposure (184)	0.5 [0.2,1.2]	0.6 [0.2,1.6]	3.1E-01	1.1 [0.7,1.7]	1.1 [0.7,1.9]	6.5E-01
no-late escitalopram exposure (3944)	late escitalopram exposure (565)	1.3 [0.9,1.8]	2.1 [1.3,3.3]**	1.3E-03	1.1 [0.9,1.5]	1.3 [0.9,1.8]	1.4E-01
no escitalopram exposure (37)	late escitalopram exposure (565)	1.2 [0.9,1.7]	2.0 [1.2,3.2]**	6.8E-03	1.2 [0.9,1.5]	1.4 [1.0,2.0]+	5.7E-02
early-only escitalopram exposure (184)	late escitalopram exposure (565)	2.5 [1.0,5.9]*	2.3 [0.9,5.5]+	7.5E-02	1.0 [0.6,1.6]	1.0 [0.6,1.7]	9.4E-01
no escitalopram exposure (3760)	any escitalopram exposure (749)	1.1 [0.8,1.5]	1.6 [1.0,2.7]*	4.1E-02	1.1 [0.9,1.4]	1.3 [0.9,1.8]	1.1E-01

fluoxetine

reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no fluoxetine exposure (3760)	early-only fluoxetine exposure (219)	0.9 [0.6,1.5]	1.4 [0.8,2.7]	2.4E-01	0.5 [-1.4,2.3]	-0.4 [-2.6,1.9]	7.6E-01
no fluoxetine exposure (3979)	late fluoxetine exposure (656)	1.4 [1.1,1.8]**	1.6 [1.2,2.2]**	5.2E-03	-2.4 [-3.5,-1.2]****	-2.5 [-3.9,-1.1]***	4.9E-04

early-only fluoxetine exposure (3760)	late fluoxetine exposure (656)	1.4 [1.1,1.8]**	1.6 [1.1,2.3]**	8.1E-03	-2.3 [-3.5,-1.2]****	-2.5 [-4.1,-1.0]**	1.4E-03
early-only fluoxetine exposure (219)	late fluoxetine exposure (656)	1.5 [0.9,2.5]	1.4 [0.8,2.3]	2.7E-01	-2.8 [-5.0,-0.6]*	-2.0 [-4.3,0.4]	1.0E-01
no fluoxetine exposure (3760)	any fluoxetine exposure (875)	1.3 [1.0,1.6]*	1.6 [1.1,2.3]**	8.5E-03	-1.6 [-2.6,-0.6]**	-2.1 [-3.5,-0.6]**	5.4E-03

fluoxetine (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no fluoxetine exposure (3760)	early-only fluoxetine exposure (219)	0.8 [0.4,1.5]	1.0 [0.5,2.1]	9.8E-01	0.8 [0.5,1.2]	0.8 [0.5,1.4]	4.0E-01
no fluoxetine exposure (3979)	late fluoxetine exposure (656)	1.2 [0.9,1.6]	1.5 [1.0,2.3]+	6.1E-02	1.0 [0.7,1.2]	1.1 [0.8,1.5]	5.7E-01
early-only fluoxetine exposure (3760)	late fluoxetine exposure (656)	1.2 [0.8,1.6]	1.6 [1.0,2.5]*	4.4E-02	0.9 [0.7,1.2]	1.0 [0.7,1.5]	8.4E-01
early-only fluoxetine exposure (219)	late fluoxetine exposure (656)	1.5 [0.8,2.9]	1.3 [0.6,2.5]	5.3E-01	1.2 [0.7,2.0]	1.3 [0.8,2.3]	2.7E-01
no fluoxetine exposure (3760)	any fluoxetine exposure (875)	1.1 [0.8,1.5]	1.5 [1.0,2.3]+	7.6E-02	0.9 [0.7,1.1]	1.0 [0.7,1.4]	9.8E-01

paroxetine							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no paroxetine exposure (3760)	early-only paroxetine exposure (56)	1.4 [0.6,3.2]	2.7 [1.1,6.8]*	3.1E-02	0.2 [-3.3,3.8]	-1.0 [-5.0,2.9]	6.0E-01
no-late paroxetine exposure (3816)	late paroxetine exposure (55)	0.4 [0.1,1.5]	0.5 [0.1,2.6]	4.4E-01	0.4 [-3.2,4.0]	-0.4 [-4.8,4.1]	8.8E-01
no paroxetine exposure (3760)	late paroxetine exposure (55)	0.4 [0.1,1.5]	0.6 [0.1,2.9]	5.0E-01	0.4 [-3.2,4.0]	-0.5 [-5.1,4.0]	8.2E-01
early-only paroxetine exposure (56)	late paroxetine exposure (55)	0.3 [0.1,1.3]	0.2 [0.0,1.4]+	9.4E-02	0.1 [-4.3,4.6]	3.9 [-2.6,10.5]	2.4E-01

no paroxetine exposure (3760)	late paroxetine exposure (111)	0.9 [0.4,1.8]	1.7 [0.7,3.9]	2.0E-01	0.3 [-2.2,2.9]	-1.1 [-4.2,1.9]	4.7E-01

paroxetine (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no paroxetine exposure (3760)	early-only paroxetine exposure (56)	0.9 [0.3,2.7]	1.1 [0.3,3.8]	9.4E-01	1.0 [0.4,2.2]	1.0 [0.4,2.3]	9.1E-01
no-late paroxetine exposure (3816)	late paroxetine exposure (55)	1.5 [0.6,3.8]	2.4 [0.7,8.0]	1.4E-01	1.7 [0.9,3.4]	1.8 [0.7,4.3]	1.9E-01
no paroxetine exposure (3760)	late paroxetine exposure (55)	1.5 [0.6,3.8]	2.3 [0.7,7.7]	1.9E-01	1.7 [0.9,3.4]	1.6 [0.7,4.0]	2.8E-01
early-only paroxetine exposure (56)	late paroxetine exposure (55)	1.8 [0.4,7.8]	1.3 [0.1,11.4]	8.1E-01	1.8 [0.6,4.9]	1.9 [0.4,8.6]	4.1E-01
no paroxetine exposure (3760)	late paroxetine exposure (111)	1.2 [0.6,2.4]	1.4 [0.6,3.4]	4.6E-01	1.3 [0.8,2.2]	1.3 [0.7,2.4]	4.7E-01

sertraline							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no sertraline exposure (3760)	early-only sertraline exposure (401)	0.6 [0.4,0.9]*	1.1 [0.6,1.9]	8.6E-01	0.7 [-0.7,2.1]	-0.5 [-2.4,1.4]	6.2E-01
no-late sertraline exposure (4161)	late sertraline exposure (2081)	1.5 [1.2,1.7]*****	1.5 [1.2,1.9]***	3.7E-04	-2.0 [-2.7,-1.3]*****	-1.9 [-2.8,-1.0]****	3.3E-05
no sertraline exposure (3760)	late sertraline exposure (2081)	1.4 [1.2,1.7]****	1.5 [1.2,1.9]***	9.9E-04	-1.9 [-2.7,-1.2]*****	-2.2 [-3.2,-1.1]****	4.9E-05
early-only sertraline exposure (401)	late sertraline exposure (2081)	2.3 [1.5,3.6]***	1.6 [1.0,2.6]*	3.2E-02	-2.7 [-4.1,-1.3]***	-1.3 [-2.8,0.1]+	7.8E-02
no sertraline exposure (3760)	any sertraline exposure (2482)	1.3 [1.1,1.5]**	1.5 [1.1,1.9]**	3.3E-03	-1.5 [-2.2,-0.8]****	-2.0 [-3.0,-0.9]***	1.7E-04

sertraline (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no sertraline exposure (3760)	early-only sertraline exposure (401)	0.8 [0.5,1.2]	1.0 [0.5,2.0]	9.0E-01	0.7 [0.5,1.1]+	0.9 [0.6,1.5]	8.2E-01
no-late sertraline exposure (4161)	late sertraline exposure (2081)	1.3 [1.1,1.6]*	1.6 [1.2,2.0]**	1.1E-03	1.0 [0.9,1.2]	1.2 [1.0,1.5]+	8.2E-02
no sertraline exposure (3760)	late sertraline exposure (2081)	1.3 [1.0,1.6]*	1.7 [1.3,2.3]***	4.5E-04	1.0 [0.9,1.2]	1.2 [0.9,1.5]	1.6E-01
early-only sertraline exposure (401)	late sertraline exposure (2081)	1.7 [1.0,2.8]*	1.4 [0.8,2.3]	2.0E-01	1.4 [1.0,1.9]+	1.3 [0.9,1.8]	2.0E-01
no sertraline exposure (3760)	any sertraline exposure (2482)	1.2 [1.0,1.5]+	1.6 [1.2,2.2]**	1.2E-03	1.0 [0.8,1.1]	1.2 [0.9,1.4]	2.3E-01

Abbreviations: GA, Gestational age; LBW, Low birthweight; OR, Odds ratio; PTB, Preterm birth; SGA, Small for gestational age; SSRI, Selective Serotonin Reuptake Inhibitors.
Adjusted with pregnancy characteristics, maternal characteristics, pregnancy mental health conditions, and comorbidities (main model). No woman was exposed to fluvoxamine during pregnancy; thus fluvoxamine was excluded from the drug-specific analysis.
No exposure group of each medication excluded patients exposed to other SSRI.
Significance level
+: P < 0.1; *: P < 0.05; **: P < 0.01; ***: P < 0.001; ****: P < 0.0001; *****: P < 0.00001

Table A.4 9 Result of sensitivity analyses[12]

subsample of women who delivered during COVID-19 pandemic[a]							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no SSRI exposure (1246)	early-only SSRI exposure (314)	0.7 [0.4,1.0]+	0.9 [0.4,1.8]	6.9E-01	2.0 [0.3,3.8]*	1.8 [-1.0,4.5]	2.1E-01
no-late SSRI exposure (1560)	late SSRI exposure (1657)	1.3 [1.0,1.6]*	1.3 [1.0,1.7]+	7.9E-02	-1.1 [-2.1,-0.2]*	-1.3 [-2.5,-0.2]*	2.5E-02

no SSRI exposure (1246)	late SSRI exposure (1657)	1.2 [0.9,1.5]	1.3 [0.9,1.8]	1.7E-01	-0.7 [-1.8,0.3]	-1.1 [-2.6,0.5]	1.7E-01
early-only SSRI exposure (314)	late SSRI exposure (1657)	1.8 [1.1,2.8]*	1.3 [0.8,2.1]	2.7E-01	-2.8 [-4.3,-1.2]***	-1.7 [-3.3,-0.1]*	3.5E-02
no SSRI exposure (1246)	any SSRI exposure (1971)	1.1 [0.9,1.4]	1.2 [0.9,1.8]	2.1E-01	-0.3 [-1.3,0.7]	-0.8 [-2.2,0.7]	3.1E-01

subsample of women who delivered during COVID-19 pandemic[a] (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no SSRI exposure (1246)	early-only SSRI exposure (314)	0.5 [0.3,0.9]*	0.9 [0.3,2.1]	7.3E-01	1.1 [0.7,1.5]	1.1 [0.6,2.0]	6.4E-01
no-late SSRI exposure (1560)	late SSRI exposure (1657)	1.2 [0.9,1.5]	1.3 [1.0,1.9]+	7.9E-02	1.0 [0.8,1.2]	1.0 [0.7,1.2]	7.0E-01
no SSRI exposure (1246)	late SSRI exposure (1657)	1.1 [0.8,1.4]	1.2[0.8,1.8]	4.4E-01	1.0 [0.8,1.2]	1.0 [0.7,1.3]	8.1E-01
early-only SSRI exposure (314)	late SSRI exposure (1657)	2.1 [1.2,3.9]*	1.8 [1.0,3.3]+	6.3E-02	0.9 [0.7,1.3]	1.0 [0.7,1.4]	8.2E-01
no SSRI exposure (1246)	any SSRI exposure (1971)	1.0 [0.7,1.3]	1.1 [0.8,1.7]	5.3E-01	1.0 [0.8,1.3]	1.0 [0.7,1.3]	8.3E-01

subsample of women with depression diagnosis during late pregnancy[b]							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no-late SSRI exposure (2603)	late SSRI exposure (2765)	1.1 [1.0,1.4]	1.2 [0.9,1.4]	1.8E-01	-1.1 [-1.8,-0.4]**	-1.2 [-2.0,-0.3]*	1.0E-02
no SSRI exposure (2026)	late SSRI exposure (2765)	1.1 [0.9,1.3]	1.2 [0.9,1.6]	1.8E-01	-0.8 [-1.6,-0.0]*	-1.1 [-2.2,0.1]+	6.5E-02
early-only SSRI exposure (577)	late SSRI exposure (2765)	1.4 [1.0,1.9]*	1.2 [0.8,1.6]	3.6E-01	-2.1 [-3.3,-0.9]***	-1.3 [-2.5,-0.1]*	3.2E-02

subsample of women with depression diagnosis during late pregnancy[b] (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no-late SSRI exposure (2603)	late SSRI exposure (2765)	1.1 [0.9,1.4]	1.3 [1.0,1.7]+	6.2E-02	0.9 [0.8,1.1]	1.0 [0.8,1.2]	1.0E+00
no SSRI exposure (2026)	late SSRI exposure (2765)	1.0 [0.8,1.3]	1.3 [0.9,1.7]	1.8E-01	0.9 [0.8,1.1]	1.0 [0.8,1.3]	9.9E-01
early-only SSRI exposure (577)	late SSRI exposure (2765)	1.6 [1.0,2.4]*	1.4 [0.9,2.2]+	8.9E-02	1.1 [0.8,1.4]	1.0 [0.8,1.4]	8.1E-01

subsample of women with phq-9 score during two-year prepregnancy period[c]							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no SSRI exposure (1305)	early-only SSRI exposure (460)	0.8 [0.6,1.2]	1.5 [0.7,2.9]	2.8E-01	0.8 [-0.6,2.2]	-0.0 [-2.2,2.2]	9.9E-01
no-late SSRI exposure (1765)	late SSRI exposure (1767)	1.3 [1.1,1.7]*	1.3 [1.0,1.7]+	7.2E-02	-2.1 [-3.0,-1.3]*****	-1.9 [-2.9,-0.9]***	3.5E-04
no SSRI exposure (1305)	late SSRI exposure (1767)	1.3 [1.0,1.6]+	1.5 [1.0,2.1]*	3.7E-02	-1.9 [-2.8,-1.0]****	-2.3 [-3.7,-0.8]**	1.8E-03
early-only SSRI exposure (460)	late SSRI exposure (1767)	1.5 [1.1,2.2]*	1.1 [0.7,1.6]	6.8E-01	-2.7 [-4.0,-1.4]****	-1.4 [-2.8,-0.0]*	4.3E-02
no SSRI exposure (1305)	any SSRI exposure (2227)	1.2 [0.9,1.5]	1.4 [1.0,2.1]*	4.7E-02	-1.3 [-2.2,-0.4]**	-1.9 [-3.3,-0.5]**	6.3E-03

subsample of women with phq-9 score during two year prepregnancy period[c] (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no SSRI exposure (1305)	early-only SSRI exposure (460)	0.7 [0.4,1.1]	1.0 [0.5,2.3]	9.7E-01	1.0 [0.8,1.5]	0.8 [0.5,1.4]	4.9E-01
no-late SSRI exposure (1765)	late SSRI exposure (1767)	1.2 [0.9,1.5]	1.4 [1.0,1.9]*	4.8E-02	1.2 [1.0,1.4]	1.1 [0.9,1.5]	2.6E-01

no SSRI exposure (1305)	late SSRI exposure (1767)	1.1 [0.8,1.4]	1.4 [0.9,2.2]+	8.6E-02	1.2 [0.9,1.5]	1.2 [0.8,1.6]	3.8E-01
early-only SSRI exposure (460)	late SSRI exposure (1767)	1.6 [1.0,2.6]*	1.3 [0.8,2.2]	2.3E-01	1.1 [0.8,1.5]	1.2 [0.8,1.6]	3.8E-01
no SSRI exposure (1305)	any SSRI exposure (2227)	1.0 [0.8,1.3]	1.4 [0.9,2.1]	1.3E-01	1.1 [0.9,1.4]	1.1 [0.8,1.5]	5.6E-01

subsample of women with phq-4 score during pregnancy[d]							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no SSRI exposure (1554)	early-only SSRI exposure (337)	0.8 [0.5,1.1]	1.3 [0.7,2.4]	4.9E-01	1.7 [-0.1,3.5]+	0.0 [-2.8,2.8]	9.9E-01
no-late SSRI exposure (1891)	late SSRI exposure (1624)	1.2 [1.0,1.5]*	1.2 [0.9,1.5]	1.9E-01	-2.0 [-3.0,-1.0]***	-2.0 [-3.3,-0.8]**	1.4E-03
no SSRI exposure (1554)	late SSRI exposure (1624)	1.2 [1.0,1.4]	1.2 [0.9,1.7]	1.6E-01	-1.7 [-2.7,-0.6]**	-2.3 [-3.8,-0.7]**	4.0E-03
early-only SSRI exposure (337)	late SSRI exposure (1624)	1.6 [1.1,2.3]*	1.1 [0.7,1.7]	6.5E-01	-3.4 [-5.2,-1.6]***	-1.7 [-3.6,0.1]+	5.9E-02
no SSRI exposure (1554)	any SSRI exposure (1961)	1.1 [0.9,1.3]	1.2 [0.9,1.6]	1.8E-01	-1.1 [-2.1,-0.1]*	-2.0 [-3.5,-0.5]*	1.1E-02

subsample of women with phq-4 score during pregnancy[d] (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no SSRI exposure (1554)	early-only SSRI exposure (337)	0.5 [0.3,0.8]*	0.6 [0.3,1.4]	2.5E-01	0.5 [0.4,0.8]**	0.6 [0.3,1.1]	1.3E-01
no-late SSRI exposure (1891)	late SSRI exposure (1624)	1.4 [1.1,1.8]**	1.6 [1.2,2.1]**	2.6E-03	1.1 [0.9,1.4]	1.3 [1.0,1.6]+	5.6E-02
no SSRI exposure (1554)	late SSRI exposure (1624)	1.3 [1.0,1.6]+	1.5 [1.1,2.1]*	2.3E-02	1.0 [0.9,1.3]	1.1 [0.8,1.5]	4.9E-01

early-only SSRI exposure (337)	late SSRI exposure (1624)	2.6 [1.5,4.6]***	2.0 [1.1,3.6]*	1.7E-02	1.9 [1.3,2.9]**	1.8 [1.2,2.7]**	7.3E-03
no SSRI exposure (1554)	any SSRI exposure (1961)	1.1 [0.9,1.4]	1.4 [1.0,2.0]+	5.5E-02	1.0 [0.8,1.2]	1.0 [0.8,1.4]	8.7E-01

subsample of women exposed to SSRI only[e]

reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no SSRI exposure (2759)	early-only SSRI exposure (750)	0.9 [0.6,1.2]	1.2 [0.7,2.1]	4.2E-01	0.6 [-0.4,1.6]	0.1 [-1.6,1.7]	9.4E-01
no-late SSRI exposure (3509)	late SSRI exposure (3094)	1.4 [1.2,1.7]****	1.4 [1.1,1.7]**	3.0E-03	-2.0 [-2.6,-1.4]*****	-1.9 [-2.6,-1.1]*****	2.0E-06
no SSRI exposure (2759)	late SSRI exposure (3094)	1.4 [1.2,1.7]***	1.5 [1.1,2.0]**	4.4E-03	-1.9 [-2.5,-1.2]*****	-2.2 [-3.2,-1.1]****	4.6E-05
early-only SSRI exposure (750)	late SSRI exposure (3094)	1.6 [1.2,2.2]**	1.3 [0.9,1.7]	1.2E-01	-2.5 [-3.5,-1.5]*****	-1.5 [-2.5,-0.4]**	5.5E-03
no SSRI exposure (2759)	any SSRI exposure (3844)	1.3 [1.1,1.5]**	1.5 [1.1,1.9]**	6.2E-03	-1.4 [-2.0,-0.8]****	-2.0 [-3.0,-0.9]***	1.5E-04

subsample of women exposed to SSRI only[e] (continued)

reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted PTB OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no SSRI exposure (2759)	early-only SSRI exposure (750)	0.7 [0.5,1.1]	0.9 [0.5,1.7]	7.0E-01	0.8 [0.7,1.1]	0.9 [0.6,1.4]	8.1E-01
no-late SSRI exposure (3509)	late SSRI exposure (3094)	1.3 [1.1,1.7]**	1.6 [1.2,2.0]***	5.8E-04	1.0 [0.9,1.2]	1.2 [1.0,1.4]	1.2E-01
no SSRI exposure (2759)	late SSRI exposure (3094)	1.3 [1.0,1.6]*	1.7 [1.2,2.3]**	2.1E-03	1.0 [0.8,1.2]	1.2 [0.9,1.5]	1.7E-01
early-only SSRI	late SSRI exposure (3094)	1.7 [1.2,2.5]**	1.5 [1.0,2.3]*	3.7E-02	1.2 [0.9,1.5]	1.1 [0.9,1.5]	3.3E-01

exposure (750)							
no SSRI exposure (2759)	any SSRI exposure (3844)	1.2 [0.9,1.4]	1.6 [1.1,2.2]**	6.9E-03	1.0 [0.8,1.1]	1.2 [0.9,1.5]	2.5E-01

exposure status to psychotropic medication as an additional covariate[f]							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no SSRI exposure (3760)	early-only SSRI exposure (887)	0.7 [0.6,1.0]*	1.2 [0.7,1.8]	5.4E-01	1.2 [0.3,2.2]*	0.4 [-1.1,1.9]	6.0E-01
no-late SSRI exposure (4647)	late SSRI exposure (3759)	1.4 [1.2,1.6]*****	1.4 [1.2,1.7]***	1.9E-04	-1.8 [-2.4,-1.3]*****	-1.9 [-2.6,-1.2]*****	1.5E-07
no SSRI exposure (3760)	late SSRI exposure (3759)	1.3 [1.1,1.5]***	1.5 [1.2,1.8]***	5.6E-04	-1.6 [-2.2,-1.0]*****	-2.0 [-2.9,-1.1]****	1.6E-05
early-only SSRI exposure (887)	late SSRI exposure (3759)	1.8 [1.3,2.3]****	1.4 [1.0,1.8]*	2.4E-02	-2.8 [-3.8,-1.9]*****	-1.8 [-2.8,-0.8]***	3.9E-04
no SSRI exposure (3760)	any SSRI exposure (4646)	1.2 [1.0,1.4]*	1.4 [1.1,1.8]**	1.6E-03	-1.1 [-1.6,-0.5]***	-1.7 [-2.6,-0.8]***	1.3E-04

exposure status to psychotropic medication as an additional covariate[f] (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted PTB OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no SSRI exposure (3760)	early-only SSRI exposure (887)	0.6 [0.4,0.8]**	0.7 [0.4,1.3]	2.6E-01	0.8 [0.7,1.1]	1.0 [0.7,1.4]	7.8E-01
no-late SSRI exposure (4647)	late SSRI exposure (3759)	1.3 [1.1,1.6]**	1.6 [1.3,2.0]****	3.1E-05	1.0 [0.9,1.2]	1.1 [1.0,1.3]	1.4E-01
no SSRI exposure (3760)	late SSRI exposure (3759)	1.2 [1.0,1.5]*	1.6 [1.2,2.0]***	9.8E-04	1.0 [0.9,1.1]	1.1 [0.9,1.4]	2.9E-01
early-only SSRI	late SSRI exposure (3759)	2.1 [1.4,3.0]****	1.8 [1.2,2.6]**	2.0E-03	1.2 [0.9,1.5]	1.2 [0.9,1.5]	2.2E-01

exposure (887)							
no SSRI exposure (3760)	any SSRI exposure (4646)	1.1 [0.9,1.3]	1.5 [1.1,1.9]**	5.3E-03	1.0 [0.9,1.1]	1.1 [0.9,1.3]	3.9E-01

exclusion of women with single SSRI prescription during pregnancy[g]							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no SSRI exposure (3760)	early-only SSRI exposure (136)	0.8 [0.4,1.5]	1.1 [0.5,2.5]	7.8E-01	1.4 [-0.9,3.7]	0.3 [-2.5,3.1]	8.3E-01
no-late SSRI exposure (3896)	late SSRI exposure (2090)	1.5 [1.3,1.8]*****	1.6 [1.3,2.1]****	5.8E-05	-2.5 [-3.2,-1.8]*****	-2.7 [-3.7,-1.7]*****	1.4E-07
no SSRI exposure (3760)	late SSRI exposure (2090)	1.5 [1.3,1.8]*****	1.7 [1.3,2.1]****	5.3E-05	-2.4 [-3.2,-1.7]*****	-2.7 [-3.8,-1.6]*****	8.4E-07
early-only SSRI exposure (136)	late SSRI exposure (2090)	1.9 [1.0,3.7]+	1.4 [0.7,2.8]	3.0E-01	-3.8 [-6.2,-1.4]**	-2.4 [-4.9,0.1]+	5.6E-02
no SSRI exposure (3760)	any SSRI exposure (2226)	1.5 [1.2,1.7]*****	1.6 [1.3,2.1]****	8.3E-05	-2.2 [-2.9,-1.5]*****	-2.6 [-3.7,-1.5]*****	1.8E-06

exclusion of women with single SSRI prescription during pregnancy[g] (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted PTB OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no SSRI exposure (3122)	early-only SSRI exposure (96)	0.6 [0.2,1.4]	0.7 [0.3,2.1]	5.5E-01	0.8 [0.5,1.4]	0.9 [0.5,1.8]	7.8E-01
no-late SSRI exposure (3218)	late SSRI exposure (1378)	1.4 [1.1,1.7]**	1.7 [1.3,2.2]***	4.7E-04	1.0 [0.9,1.2]	1.1 [0.9,1.4]	3.7E-01
no SSRI exposure (3122)	late SSRI exposure (1378)	1.4 [1.1,1.7]**	1.7 [1.2,2.3]***	8.8E-04	1.0 [0.8,1.2]	1.1 [0.9,1.4]	4.4E-01

early-only SSRI exposure (96)	late SSRI exposure (1378)	2.4 [1.0,5.9]+	1.8 [0.7,4.6]	2.0E-01	1.3 [0.7,2.2]	1.2 [0.7,2.1]	5.9E-01
no SSRI exposure (3122)	any SSRI exposure (1474)	1.3 [1.1,1.6]**	1.6 [1.2,2.2]**	1.5E-03	1.0 [0.8,1.2]	1.1 [0.9,1.4]	4.3E-01

Abbreviations: GA, Gestational age; LBW, Low birthweight; OR, Odds ratio; PHQ, Patient Health Questionnaire; PTB, Preterm birth; SGA, Small for gestational age; SSRI, Selective Serotonin Reuptake Inhibitors.

a. Limited to patients delivered during COVID-19 pandemic (2020-03-06~2022-12-31) and adjusted with pregnancy characteristics, maternal characteristics, pre-pregnancy mental health conditions, and comorbidities (main model)
b. Adjusted with pregnancy characteristics, maternal characteristics, pre-pregnancy mental health conditions, and comorbidities (main model)
c. Pre-pregnancy PHQ-9 score was additionally adjusted to the main model
d. Prenatal PHQ-4 score was additionally adjusted to the main model
e. Excluded patients exposed to other antidepressants (N06AA, N06AX) and adjusted with pregnancy characteristics, maternal characteristics, pre-pregnancy mental health conditions, and comorbidities (main model)
f. Exposure status to psychotropic medication was additionally adjusted to the main model
g. Excluded patients with single SSRI prescription during pregnancy

+: P < 0.1; *: P < 0.05; **: P < 0.01; ***: P < 0.001; ****: P < 0.0001; *****: P < 0.00001

Table A.4 10 Result of other antidepressants analyses (N06AA, N06AX)[12]

N06AA exposure							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no N06AA exposure (3626)	early-only N06AA exposure (115)	0.7 [0.4,1.5]	0.6 [0.2,1.8]	3.2E-01	-1.2 [-3.8,1.3]	0.4 [-4.0,4.9]	8.4E-01
no-late N06AA exposure (3741)	late N06AA exposure (106)	1.9 [1.1,3.2]*	1.4 [0.7,2.8]	2.8E-01	-3.6 [-6.3,-1.0]**	-0.9 [-4.0,2.2]	5.6E-01
no N06AA exposure (3626)	late N06AA exposure (106)	1.9 [1.1,3.2]*	1.0 [0.4,2.4]	9.4E-01	-3.6 [-6.3,-1.0]**	-0.2 [-3.9,3.6]	9.3E-01
early-only N06AA exposure (115)	late N06AA exposure (106)	2.6 [1.1,6.2]*	2.1 [0.8,5.7]	1.3E-01	-2.4 [-6.6,1.8]	-1.5 [-6.2,3.2]	5.3E-01

no N06AA exposure (3626)	any N06AA exposure (221)	1.3 [0.8,1.9]	0.9 [0.4,1.9]	7.2E-01	-2.4 [-4.2,-0.5]*	-0.2 [-3.4,3.0]	8.9E-01

N06AA exposure (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no N06AA exposure (3626)	early-only N06AA exposure (115)	1.0 [0.5,2.1]	1.4 [0.3,5.4]	6.6E-01	1.4 [0.8,2.2]	0.9 [0.4,2.2]	8.3E-01
no-late N06AA exposure (3741)	late N06AA exposure (106)	2.3 [1.3,4.1]**	2.0 [1.0,4.1]+	6.7E-02	1.1 [0.6,1.9]	1.0 [0.5,1.9]	1.0E+00
no N06AA exposure (3626)	late N06AA exposure (106)	2.3 [1.3,4.1]**	2.1 [0.8,5.1]	1.2E-01	1.1 [0.6,2.0]	1.2 [0.6,2.8]	6.1E-01
early-only N06AA exposure (115)	late N06AA exposure (106)	2.3 [0.9,6.1]+	1.8 [0.6,5.3]	2.6E-01	0.8 [0.4,1.7]	0.7 [0.3,1.7]	4.5E-01
no N06AA exposure (3626)	any N06AA exposure (221)	1.6 [1.0,2.5]+	1.8 [0.8,4.2]	1.9E-01	1.2 [0.9,1.8]	1.2 [0.6,2.3]	6.1E-01

N06AX exposure							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no N06AX exposure (2862)	early-only N06AX exposure (504)	1.6 [1.2,2.1]**	1.3 [0.7,2.2]	4.1E-01	-1.5 [-2.7,-0.2]*	0.2 [-2.0,2.4]	8.9E-01
no-late N06AX exposure (3366)	late N06AX exposure (1127)	1.7 [1.4,2.1]*****	1.5 [1.2,2.0]**	2.4E-03	-2.8 [-3.7,-1.9]*****	-2.4 [-3.5,-1.2]****	5.5E-05
no N06AX exposure (2862)	late N06AX exposure (1127)	1.8 [1.5,2.2]*****	2.2 [1.5,3.1]****	1.9E-05	-3.0 [-3.9,-2.1]*****	-3.4 [-4.9,-1.9]****	1.2E-05
early-only N06AX exposure (504)	late N06AX exposure (1127)	1.1 [0.8,1.6]	1.1 [0.8,1.6]	4.2E-01	-1.6 [-3.1,-0.0]*	-1.7 [-3.3,-0.1]*	4.2E-02

no N06AX exposure (2862)	any N06AX exposure (1631)	1.7 [1.4,2.1]*****	2.0 [1.4,2.8]****	9.1E-05	-2.5 [-3.4,-1.7]*****	-2.8 [-4.2,-1.3]***	2.1E-04

N06AX exposure (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no N06AX exposure (2862)	early-only N06AX exposure (504)	1.3 [0.9,1.9]	1.3 [0.7,2.7]	4.1E-01	0.8 [0.6,1.1]	0.9 [0.5,1.6]	7.7E-01
no-late N06AX exposure (3366)	late N06AX exposure (1127)	1.7 [1.3,2.1]****	1.8 [1.3,2.5]***	3.1E-04	1.2 [1.0,1.5]*	1.4 [1.1,1.7]*	1.4E-02
no N06AX exposure (2862)	late N06AX exposure (1127)	1.7 [1.3,2.3]****	2.5 [1.7,3.8]****	1.3E-05	1.2 [1.0,1.5]+	1.4 [1.0,1.9]*	4.7E-02
early-only N06AX exposure (504)	late N06AX exposure (1127)	1.4 [0.9,2.0]	1.3 [0.9,2.0]	2.0E-01	1.4 [1.0,2.0]*	1.4 [1.0,2.0]*	3.5E-02
no N06AX exposure (2862)	any N06AX exposure (1631)	1.6 [1.3,2.0]***	2.3 [1.5,3.4]****	6.3E-05	1.1 [0.9,1.3]	1.3 [0.9,1.7]	1.5E-01

SNRI exposure							
reference group (n)	comparison group (n)	unadjusted PTB OR	adjusted PTB OR	adjusted PTB OR p-value	unadjusted GA β	adjusted GA β	adjusted GA β p-value
no SNRI exposure (2867)	early-only SNRI exposure (501)	1.6 [1.2,2.1]**	1.3 [0.8,2.2]	3.5E-01	-1.4 [-2.7,-0.2]*	0.1 [-2.1,2.3]	9.3E-01
no-late SNRI exposure (3368)	late SNRI exposure (1121)	1.7 [1.4,2.1]*****	1.5 [1.2,2.0]**	1.3E-03	-2.8 [-3.7,-1.9]*****	-2.4 [-3.6,-1.3]****	3.7E-05
no SNRI exposure (2867)	late SNRI exposure (1121)	1.8 [1.5,2.3]*****	2.2 [1.5,3.1]****	1.5E-05	-3.0 [-4.0,-2.1]*****	-3.4 [-4.9,-1.9]*****	1.0E-05
Early-only SNRI exposure (501)	late SNRI exposure (1121)	1.2 [0.8,1.6]	1.2 [0.8,1.7]	3.3E-01	-1.6 [-3.1,-0.0]*	-1.8 [-3.4,-0.1]*	3.4E-02

no SNRI exposure (2867)	any SNRI exposure (1622)	1.7 [1.4,2.1]*****	2.0 [1.4,2.8]****	6.8E-05	-2.5 [-3.4,-1.7]*****	-2.8 [-4.2,-1.3]***	1.7E-04

SNRI exposure (continued)							
reference group (n)	comparison group (n)	unadjusted LBW OR	adjusted LBW OR	adjusted LBW OR p-value	unadjusted SGA OR	adjusted SGA OR	adjusted SGA OR p-value
no SNRI exposure (2434)	early-only SNRI exposure (371)	1.3 [0.9,1.9]	1.4 [0.7,2.8]	3.6E-01	0.9 [0.6,1.2]	0.9 [0.5,1.5]	7.0E-01
no-late SNRI exposure (2811)	late SNRI exposure (823)	1.7 [1.3,2.2]****	1.8 [1.3,2.5]***	2.4E-04	1.2 [1.0,1.5]*	1.4 [1.1,1.7]*	1.5E-02
no SNRI exposure (2434)	late SNRI exposure (823)	1.8 [1.4,2.3]****	2.5 [1.7,3.8]****	1.0E-05	1.2 [1.0,1.5]+	1.4 [1.0,1.9]+	5.2E-02
early-only SNRI exposure (377)	late SNRI exposure (823)	1.4 [0.9,2.0]	1.3 [0.9,2.0]	1.9E-01	1.4 [1.0,2.0]*	1.4 [1.0,2.0]*	3.9E-02
no SNRI exposure (2434)	any SNRI exposure (1194)	1.6 [1.3,2.0]****	2.3 [1.5,3.4]****	4.8E-05	1.1 [0.9,1.3]	1.3 [0.9,1.7]	1.6E-01

Abbreviations: GA, Gestational age; LBW, Low birthweight; OR, Odds ratio; PHQ, Patient Health Questionnaire; PTB, Preterm birth; SGA, Small for gestational age; SSRI, Selective Serotonin Reuptake Inhibitors.
Adjusted with pregnancy characteristics, maternal characteristics, pre-pregnancy mental health conditions, and comorbidities
Significance level
+: P < 0.1; *: P < 0.05; **: P < 0.01; ***: P < 0.001; ****: P < 0.0001; *****: P < 0.00001

Table A.5 1 Variable definition[13]

Category	Variable	Definitions
COVID-19 related	SARS-CoV-2 infection date	Either the date of COVID-19 diagnosis or positive SARS-CoV-2 PCR/NAAT test, whichever preceded
	COVID-19 treatment onset	Starting time of COVID-19 treatment. If patient was hospitalized more than 7 days before the SARS-CoV-2 infection date, SARS-CoV-2 infection date was defined as COVID-19 treatment onset. If patient was hospitalized less

		than 7 days before or after the COVID-19 infection date, patient's admission date was defined as COVID-19 treatment onset.
	Active SARS-CoV-2 infection period	-2~14 days from the SARS-CoV-2 infection date
	Hospitalization with COVID-19	Any overlap of hospitalization and active SARS-CoV-2 infection period
	SARS-CoV-2 variant	Dominant variant at the time of SARS-CoV-2 infection. Variant was considered predominant when the variant account for >50% cases as part of the CDC genomic surveillance for SARS-CoV-2 in region 10 (Alaska, Idaho, Oregon, and Washington); Wild Type, Alpha, Delta, Omicron
	Trimester of SARS-CoV-2 infection	Trimester of SARS-CoV-2 infection date; first, second, third trimester
	NIH antithrombotic therapy guideline	Status of NIH antithrombotic therapy guideline on pregnant women. There was no specific guideline on pregnant women until December 16, 2020. The first major update was on December 17, 2020, recommending prophylactic anticoagulant use on pregnant women hospitalized with severe COVID-19 manifestation. The second major update was on February 24, 2022 recommending prophylactic anticoagulant use on pregnant women hospitalized with COVID-19 manifestation; no guideline, first update, second update
	Vaccination status	History of COVID-19 vaccination (Pfizer-BioNTech BNT162B2, Moderna mRNA-1273, Janssen Ad26.COV2.S) based on immunization record; 0,1
	Prior infection status	History of COVID-19 based on diagnosis or positive SARS-CoV-2 PCR/NAAT test; 0,1
COVID-19 illness severity	Oxygen assistance	Any oxygen assistance after SARS-CoV-2 infection and before delivery; 0, 1 (low flow, high flow oxygen devices)
	Vasopressor use	Vasopressor administration record after SARS-CoV-2 infection and before delivery; 0, 1
	Death	Maternal death occurred after SARS-CoV-2 infection and before delivery
	Days in hospital after COVID-19 diagnosis	Length of hospitalization stay from SARS-CoV-2 infection to delivery date
	Unique medication count	Count of unique medication ingredient from SARS-CoV-2 infection to delivery date
	Unique diagnosis count	Count of unique diagnosis from SARS-CoV-2 infection to delivery date
Demographic	Race	Race noted in medical record. Missing values were encoded as Unknown; American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White or Caucasian, Multiracial, Other, Unknown
	Ethnicity	Ethnicity noted in medical record. Missing values were encoded as unknown; Hispanic or Latino, Not Hispanic or Latino, Unknown
	Maternal age	Maternal age at the start of pregnancy; 18 ~ 24, 25 ~ 29, 30 ~ 34, 35 ~ 40, 41 ~ 44
	Pregravid BMI	Pregravid Body Mass Index (kg/m2). Missing value was encoded as unknown; Underweight (<18.5 BMI), Normal (18.5 - 24.9 BMI), Overweight (25.0 - 29.9 BMI), Obese (>30.0)
	Insurance status	Commercial, Medicaid, Medicare, Uninsured-Self-Pay
	Smoker	Self-reported smoking status; 0,1

	Illegal drug use	Self-reported illegal drug use status; 0,1
	Preterm history	History of preterm delivery; 0,1
	Parity	Number of times a patient has delivered a fetus older than 20 weeks of gestation prior to the current pregnancy; 0, 1~5, 6
	Gravidity	Number of times a patient has been pregnant; 0, 1~5, 6
Comorbidity	Diagnosis count before COVID-19	Number of unique diagnoses from two year before the start of the pregnancy to SARS-CoV-2 infection date
	Initial medication count	Number of unique medications during -3~+3 days from the COVID-19 treatment onset
Geographical features	Socioeconomic status	CDC SVI Socioeconomic (RPL_THEME1) theme ranking mapped to patient's U.S. Census tract; scores are 0-1. score of 0 and 1 indicate low and high level of social vulnerability regarding socioeconomic status
	Housing composition	CDC SVI Housing Composition & Disability (RPL_THEME2) theme ranking mapped to patient's U.S. Census tract; scores are 0-1. score of 0 and 1 indicate low and high levels of social vulnerability regarding housing composition.
	Minority status and language	CDC SVI Minority Status & Language (RPL_THEME3) theme ranking mapped to patient's U.S. Census tract; scores are 0-1. score of 0 and 1 indicate low and high levels of social vulnerability in terms of minority status and language. Census tract with high RPL_THEME3 score is enriched with residents of minority (non-White) and/or have low English language skills
	Housing type and transportation	CDC SVI Housing Type & Transportation (RPL_THEME4) theme ranking mapped to patient's U.S. Census tract; scores are 0-1. score of 0 and 1 indicate low and high levels of social vulnerability regarding housing type and transportation. Census tract with high RPL_THEME4 score is area of lower income housing and/or population dense housing options
	Rural/urban categorization	U.S. Department of Agriculture Economic Research Service (USDA ERS) Rural-Urban Commuting Area (RUCA) codes; SecondaryRUCACode2010 (last updated in 2019) were mapped using patient U.S. Census Tract; Categorized as Metropolitan (> 4 score), Micropolitan (4 - 6 score), Small Town (7 - 9 score), Rural (10 - 99 score), or Unknown
Maternal-fetal health outcomes	Low birth weight	Infant birth weight ≤ 2,500g
	Preterm birth	Infant gestational age (GA) at birth < 37 weeks
	Small for gestational age	Infant birth weight < 10th percentiles for infants of same GA
	Stillbirth	Fetal demise in the womb ≥ GA 20 weeks

CDC: Center for Disease Control and Prevention
SVI: Social Vulnerability Index

Table A.5 2 SNOMED diagnosis code[13]

Category	Diagnosis	SNOMED hypernym code
Coagulopathy	Coagulopathy	64779008
	Thrombosis	439127006
	Arterial thrombosis	65198009
	Venous thrombosis	111293003
	Deep vein thrombosis	128053003

	Thromboembolism	371039008
	Pulmonary embolism	59282003
	Pulmonary necrosis	7159003
	Skin necrosis/purpura	95347000, 423902002
	Stroke	230690007
	Myocardial infarction	22298006
Bleeding	Bleeding	131148009
	Postpartum hemorrhage	47821001
Anticoagulant contraindications	Peptic ulcer	1320003
	Stage 2 hypertension	827068008
	Esophageal varices	26870008
	Intracranial mass	85974009
	End stage liver disease	7082480004
	Aneurysm	85659009
	Proliferative retinopathy	430801000124103
	Major bleeding	74474003 (gastrointestinal) 98478000 (intraocular) 1386000 (intracranial) 95549001 (retroperinatal)

Table A.5 3 Medication ingredient RxNorm codes

Drug	**RxNorm Code**	**RxNorm Ingredient**
Anticoagulant(heparin)	1009	Antithrombin III
	280611	Bemiparin
	67109	Dalteparin
	78484	Danaparoid
	67108	Enoxaparin
	5224	Heparin
	67031	Nadroparin
	69528	Parnaparin
	75960	Reviparin
	69646	Tinzaparin
Anticoagulant(other)	154	Acenocoumarol
	1364430	Apixaban
	15202	Argatroban
	1927851	Betrixaban
	60819	Bivalirudin
	1037042	Dabigatran etexilate
	114934	Desirudin
	1598	Dicumarol
	1599538	Edoxaban
	50097	Fluindione
	321208	Fondaparinux
	237057	Lepirudin
	8150	Phenprocoumon
	8130	Phenindione
	1114195	Rivaroxaban
	163426	Tioclomarol
	11289	Warfarin
Vasopressor	3616	Dobutamine
	3628	Dopamine

	3966	Ephedrine
	3992	Epinephrine
	6963	Midodrine
	7512	Norepinephrine
	8163	Phenylephrine
	11149	Vasopressin (USP)

Table A.5 4 Prophylactic, intermediate, and therapeutic dosage of anticoagulant[13]

Heparin	**Dose level**	**Dose**
LMW heparin	Prophylactic	Enoxaparin 40mg SC once daily
	Intermediate	Enoxaparin 40mg SC once daily, increases as pregnancy progresses to 1mg/kg once daily
	Therapeutic	Enoxaparin 1mg/kg SC every 12 hours
Unfractionated heparin	Prophylactic	5000 unit SC every 12 hours
	Intermediate	First trimester: 5000-7500 unit SC every 12 hours
		Second trimester: 7500-10000 unit SC every 12 hours
		Third trimester: 10000 unit SC every 12 hours
	Therapeutic	Continuous IV infusion or SC dose every 12 hours

Anticoagulation dose during pregnancy[208]

Table A.5 5 Timeline of dominant SARS-CoV-2 variant in the U.S Western states used in this study[13]

Dominant Variant	**Start Date**	**End Date**
Wild-Type	3/5/2020	4/23/2021
Alpha	4/24/2021	7/2/2021
Delta	7/3/2021	12/24/2021
Omicron	12/25/2021	10/19/2022

Variant was considered dominant when a specific variant exceeded 50% of cases of U.S. Region 10 (Alaska, Idaho, Oregon, Washington) CDC's national genomic surveillance system[340]

Table A.5 6 Propensity score matching effect size comparison for matched and sensitivity analysis matched control groups[13]

	Mean Absolute Error	**Mean Squared Error**	**Root Mean Squared Error**	**ROC-AUC**	**Coefficient of determination**	**Precision-recall AUC**
Logistic Regression	0.26	0.26	0.51	0.72	-2.98	0.30
Random Forest	0.36	0.18	0.43	0.80	-1.80	0.24
Gradient Boost Machine	0.33	0.17	0.41	0.84	-1.54	0.31
Gradient Boost Machine Limited	0.31	0.16	0.40	0.85	-1.47	0.31

ROC Receiver operating characteristics, AUC Area under the curve

Table A.5 7 Propensity score matching effect size comparison for matched control and sensitivity analysis matched control groups[13]

Main matching model effect size comparison		
Variable	**Before matching effect size**	**After matching effect size**
Variant omicron	-0.71	0.04
CDC SVI socioeconomic status	-0.10	-0.10
CDC SVI household composition and disability	0.08	-0.14
CDC SVI minority status and language	-0.22	-0.09
CDC SVI housing type and transportation	-0.07	-0.11
3rd trimester infection	-1.09	-0.04
Pre-COVID-19 diagnoses count	0.70	0.11
Sensitivity analysis matching model effect size comparison		
Variable	**Before matching effect size**	**After matching effect size**
Variant omicron	-0.71	0.15
CDC SVI socioeconomic status	-0.10	-0.12
CDC SVI household composition and disability	0.08	-0.25
CDC SVI minority status and language	-0.22	0.00
CDC SVI housing type and transportation	-0.07	-0.14
3rd trimester infection	-1.09	-0.01
Pre-COVID-19 diagnoses count	0.70	0.25
COVID-19 initial medication count	-0.06	0.14

Effect size was calculated using Cohen D’s value. The absolute value of effect size < 0.2 is considered a small effect size.

Table A.5 8 Outcome statistics for treatment, control, matched control, and sensitivity analysis matched control group[13]

Variable	**Categories**	**Treatment (n=191)**	**Control (n=2545)**	**Matched Control (n=188)**	**SA Matched Control (n=189)**
Secondary Coagulopathy, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	189 (99.0)	2536 (99.6)	186 (98.9)	188 (99.5)
	Yes	2 (1.0)	9 (0.4)	2 (1.1)	1 (0.5)
Skin Necrosis/Purpura, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)

	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombosis, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	190 (99.5)	2543 (99.9)	188 (100.0)	188 (99.5)
	Yes	1 (0.5)	2 (0.1)	0 (0.0)	1 (0.5)
Arterial Thrombosis, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Venous Thrombosis, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	191 (100.0)	2543 (99.9)	188 (100.0)	188 (99.5)
	Yes	0 (0.0)	2 (0.1)	0 (0.0)	1 (0.5)
Deep Vein Thrombosis, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	191 (100.0)	2544 (100.0)	188 (100.0)	188 (99.5)
	Yes	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.5)
Thromboembolism, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	190 (99.5)	2545 (100.0)	188 (100.0)	189 (100.0)
	Yes	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary Embolism, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	190 (99.5)	3112 (100.0)	188 (100.0)	189 (100.0)
	Yes	1 (0.5)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Myocardial Infarction, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	190 (99.5)	2545 (100.0)	188 (100.0)	189 (100.0)
	Yes	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Stroke, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	190 (99.5)	2545 (100.0)	188 (100.0)	189 (100.0)
	Yes	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Bleeding, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)

	No	186 (97.4)	2518 (98.9)	183 (97.3)	188 (99.5)
	Yes	5 (2.6)	27 (1.1)	5 (2.7)	1 (0.5)
Postpartum Hemorrhage, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	188 (98.4)	2482 (97.5)	182 (96.8)	186 (98.4)
	Yes	3 (1.6)	63 (2.5)	6 (3.2)	3 (1.6)
WHO Score, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	2	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
	3	128 (67.0)	2459 (96.6)	181 (96.3)	178 (94.2)
	4	50 (26.2)	81 (3.2)	5 (2.7)	9 (4.8)
	5	7 (3.7)	4 (0.2)	2 (1.1)	2 (1.1)
	6	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
	7	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
	8	3 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Oxygen Assistance, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	High-Flow	7 (3.7)	4 (0.2)	1 (0.5)	1 (0.5)
	Low-Flow	50 (26.2)	87 (3.4)	8 (4.3)	10 (5.3)
	None	134 (70.2)	2454 (96.4)	179 (95.2)	178 (94.2)
Vasopressor Use, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	184 (96.3)	2484 (97.6)	184 (97.9)	182 (96.3)
	Yes	7 (3.7)	61 (2.4)	4 (2.1)	7 (3.7)
COVID-19 Severity, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	Mild	123 (64.4)	2377 (93.4)	166 (88.3)	157 (83.1)
	Moderate	55 (28.8)	164 (6.4)	21 (11.2)	31 (16.4)
	Severe	10 (5.2)	4 (0.2)	1 (0.5)	1 (0.5)
	Deceased	3 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal Death, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	188 (98.4)	2545 (100.0)	188 (100.0)	189 (100.0)
	Yes	3 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)

Days in Hospital After COVID-19 diagnosis (days), mean (SD)		9.5 (7.8)	5.3 (7.9)	5.5 (6.4)	6.6 (10.4)
Diagnosis Count After COVID-19 diagnosis, mean (SD)		9.3 (10.1)	2.2 (4.9)	4.3 (8.0)	4.6 (7.6)
Unique Medication Ingredient Count After COVID-19 diagnosis, mean (SD)		53.3 (13.4)	40.7 (10.6)	43.4 (16.1)	46.3 (17.5)
Gestational Age (days), mean (SD)		262.3 (25.3)	271.2 (15.5)	263.2 (30.2)	263.1 (27.4)
Preterm Birth, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	144 (75.4)	2250 (88.4)	150 (79.8)	148 (78.3)
	Yes	47 (24.6)	295 (11.6)	38 (20.2)	41 (21.7)
Infant Birth Weight (oz), mean (SD)		109.1 (29.8)	115.1 (21.0)	109.8 (33.3)	108.9 (31.2)
Low Birth Weight, n (%)		190 (100.0)	2539 (100.0)	188 (100.0)	187 (100.0)
	No	154 (81.1)	2306 (90.8)	158 (84.0)	157 (84.0)
	Yes	36 (18.9)	233 (9.2)	30 (16.0)	30 (16.0)
Fetal Growth Percentile, mean (SD)		50.2 (30.6)	46.0 (28.9)	48.4 (29.9)	45.9 (29.9)
Small for Gestational Age, n (%)		190 (100.0)	2539 (100.0)	188 (100.0)	187 (100.0)
	No	163 (85.3)	2174 (85.4)	161 (85.6)	158 (83.6)
	Yes	28 (14.7)	371 (14.6)	27 (14.4)	31 (16.4)
Stillbirth, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	No	189 (99.0)	2526 (99.3)	180 (95.7)	182 (96.3)
	Yes	2 (1.0)	19 (0.7)	8 (4.3)	7 (3.7)
Delivery Method, n (%)		191 (100.0)	2545 (100.0)	188 (100.0)	189 (100.0)
	C-section	101 (52.9)	885 (34.8)	84 (44.7)	76 (40.2)
	Vaginal	90 (47.1)	1660 (65.2)	104 (55.3)	113 (59.8)

The observation endpoint was the delivery date, except for postpartum hemorrhage. Variables are defined in Table A.5 1. SNOMED codes of diagnoses are presented in Table A.5 2.

Table A.5 9 Outcome comparison between treatment group and control, matched control, and sensitivity analysis matched control group[13]

	Treatment group	**Control group**			**Matched control group**			**Sensitivity analysis matched control group**		
Outcome	**Case (prevalence rate, 95% CI)**	**Case (prevalence rate, 95% CI)**	**Relative risk, 95% CI**	***P*-value**	**Case (prevalence rate, 95% CI)**	**Relative risk, 95% CI**	***P*-value**	**Case (prevalence rate, 95% CI)**	**Relative risk, 95% CI**	***P*-value**
Coagulopathy	2 (0.011, [0.003,0.037]	9 (0.004, [0.002,0.007]	3.0 [0.6,13.6]	0.18	2 (0.011, [0.002,0.038]	1.0 [0.1,6.9]	1.0	1 (0.005, [0.001,0.029]	2.0[0.2,21.6]	1.0
Bleeding	5 (0.026, [0.011,0.06]	27 (0.011, [0.007,0.015]	2.5 [1.0,6.3]	0.07	5 (0.027, [0.007,0.061]	1.0 [0.3,3.3]	1.0	1 (0.005, [0.001,0.029]	5.0 [0.6,42.0]	0.22
Postpartum hemorrhage	3 (0.016, [0.005,0.045]	63 (0.025, [0.019,0.032]	0.6 [0.2,2.0]	0.62	6 (0.032, [0.019,0.068]	0.5 [0.1,1.9]	0.34	3 (0.016, [0.005,0.046]	1.0 [0.2,4.8]	1.0
O2 assistance	63 (0.33, [0.273,0.387]	91 (0.036, [0.029,0.044]	9.2 [6.9,12.3]	<.001	9 (0.048, [0.029,0.088]	6.9 [3.5,13.5]	<.001	11 (0.058, [0.033,0.101]	5.7 [3.1,10.4]	<.001
Vasopressor use	7 (0.037, [0.018,0.074]	61 (0.024, [0.019,0.031]	1.5 [0.7,3.3]	0.33	4 (0.021, [0.019,0.053]	1.7 [0.5,5.8]	0.54	7 (0.037, [0.018,0.074]	1.0 [0.4,2.8]	1.0
Death	3 (0.016, [0.005,0.045]	0 (0.0, [0.0,0.002]	NA	<.001	0 (0.0, [0.0,0.02]	NA	0.25	0 (0.0, [0.0,0.02]	NA	0.25
Stillbirth	2 (0.011, [0.003,0.037]	19 (0.007, [0.005,0.012]	1.4 [0.3,6.0]	0.65	8 (0.043, [0.005,0.082]	0.2 [0.0,1.1]	0.06	7 (0.037, [0.018,0.074]	0.3 [0.0,1.3]	0.10
Low birth weight	36 (0.19, [0.141,0.248]	233 (0.092, [0.081,0.104]	2.1 [1.5,2.8]	<.001	30 (0.16, [0.081,0.217]	12 [0.8,1.8]	0.50	30 (0.16, [0.115,0.218]	1.2 [0.8,1.8]	0.50
Preterm birth	47 (0.246, [0.192,0.307]	295 (0.116, [0.104,0.129]	2.1 [1.6,2.8]	<.001	38 (0.202, [0.104,0.262]	1.2 [0.8,1.8]	0.33	41 (0.217, [0.165,0.277]	1.1 [0.8,1.6]	0.54
Small for gestational age	28 (0.147, [0.104,0.202]	371 (0.146, [0.133,0.16]	1.0 [0.7,1.4]	1.0	27 (0.144, [0.133,0.2]	1.0 [0.6,1.7]	1.0	31 (0.164, [0.118,0.222]	0.9 [0.6,1.4]	0.67

NA: Not applicable, too few cases to calculate

	Treatment group	**Control group**		**Matched control group**		**Sensitivity analysis matched control group**	
Outcome	**0, 25, 50, 75, 100 percentile**	**0, 25, 50, 75, 100 percentile**	***P*-value**	**0, 25, 50, 75, 100 percentile**	***P*-value**	**0, 25, 50, 75, 100 percentile**	***P*-value**

Days in hospital after COVID-19 diagnosis (days), mean (SD)	0,4,6,11,51	0,0,3,4,189	<.001	0,0,3,4,55	<.0001	0,1,3,5,62	<.001
Diagnosis count	0,1,7,14,60	0,0,0,2,59	<.001	0,0,0,5,38	<.0001	0,0,1,6,33	<.001
Medication count	30,44,51,60,133	18,34,39,46,129	<.001	20,34,39,50,115	<.0001	20,36,44,51,115	<.001

Categorical and continuous outcome variables were evaluated using Fisher's exact test and Mann Whitney U test.

Table A.5 10 Influence of maternal age and pregravid BMI on relations between prophylactic anticoagulant administration and risks of outcomes[13]

	Before adjustment		**After adjustment**	
Outcome	**RR, 95% CI**	***P*-value**	**RR, 95% CI**	***P*-value**
Coagulopathy	1.0[0.1,13.7]	1.0	0.9[0.1,6.8]	0.95
Bleeding	1.0[0.2,4.4]	1.0	0.9[0.3,3.3]	0.90
Postpartum hemorrhage	0.5[0.1,2.3]	0.34	0.5[0.1,1.9]	0.27
O2 assistance	9.7[4.6,23.1]	<.001	9.5[4.5,19.8]	<.001
Vasopressor use	1.7[0.4,8.3]	0.54	1.8[0.5,6.4]	0.36
Death	NA[0.4,inf]	0.25	NA[0.0,inf]	1.0
Preterm birth	1.3[0.8,2.2]	0.33	1.3[0.8,2.1]	0.29
Small for gestational age	1.0[0.6,1.9]	1.0	1.1[0.6,1.9]	0.82
Low birth weight	1.2[0.7,2.2]	0.50	1.2[0.7,2.1]	0.42
Stillbirth	0.2[0.0,1.2]	0.06	0.3[0.1,1.5]	0.15

NA: Not applicable, too few cases to calculate

Table A.6 1 SNOMED codes for diagnoses[14]

Diagnosis	SNOMED Concept ID
inflammatory bowel disease	295046003, 733157003, 721686000, 128600008, 24829000, 56689002, 71833008, 52506002, 3815005, 50440006, 1085131000119105, 426549001, 737195007, 410485009, 414156000, 966011731000119103, 61424003, 239814006, 1085901000119101, 235664007, 8161000119106, 444546002, 235714007, 1085231000119100, 201727001, 34000006, 10743231000119101, 697969008, 24526004, 1092841000119100, 1085801000119106, 15342002, 14311001, 414153008, 397173003, 414154002, 201807008, 91390005, 56287005, 239809007,

	201805000, 1085851000119105, 196987008, 732966008, 13470001, 235607002, 196977009, 70622003, 1085751000119100, 78324009, 397172008, 444548001, 722850002, 7620006, 196578009, 1144956000, 359664009, 445243001, 453720571000119100, 441971007, 64766004, 442159003, 234999001, 788718000, 38106008, 969688801000119108, 78712000, 721702009, 410484008
rheumatoid arthritis	319871000119100, 319951000119101, 319061000119100, 1073741000119109, 15691841000119102, 15691121000119103, 239792003, 11055151000119108, 16050071000119108, 402433007, 193180002, 318891000119108, 1073771000119102, 201772009, 15691081000119100, 459911000124100, 402431009, 239804002, 1156774008, 193250002, 735599007, 319031000119108, 1073681000119109, 1073781000119104, 201766009, 15691881000119107, 201784006, 201780002, 1073791000119101, 410798004, 319091000119107, 201774005, 15692041000119104, 287008006, 16606721000119107, 201785007, 239803008, 82939003, 201768005, 15691321000119101, 402426007, 402428008, 410802003, 201771002, 287006005, 410801005, 1156765006, 319051000119102, 38877003, 201778008, 143441000119108, 402427003, 59165007, 318901000119107, 28880005, 15691761000119107, 427770001, 201783000, 319141000119100, 10713006, 399923009, 1073691000119107, 1073811000119102, 318941000119109, 15686321000119106, 239791005, 1073831000119107, 318921000119103, 15691241000119101, 15687841000119108, 86219005, 15691921000119100, 16606681000119101, 201769002, 201773004, 319131000119109, 410796000, 318951000119106, 318861000119101, 54867000, 239799007, 318841000119100, 15686001000119104, 52661003, 201770001, 402434001, 15687201000119107, 318871000119107, 410800006, 33719002, 318911000119105, 15685921000119102, 410502007, 15685961000119107, 201779000, 318931000119100, 1156766007, 1073711000119105, 201767000, 201777003, 7607008, 398726004, 319121000119106, 1156817001, 319071000119106, 319081000119109, 781206002, 77522006, 201775006, 318961000119108, 15673521000119101, 318851000119103, 402432002, 62131000000107, 201791009, 1073601000119101, 1156779003, 15686281000119101, 1073761000119108, 1073611000119103, 201764007, 1073721000119103, 1149218009, 16024431000119108, 15691161000119108, 410797009, 319861000119106, 287007001, 16044751000119106, 239802003, 1156777001, 318971000119102, 1073731000119100, 57160007, 429192004, 15673361000119100, 15687321000119109, 15691801000119104, 1156778006, 201776007, 239943002, 1073821000119109, 1073701000119107, 15691721000119102, 1073751000119106, 1149219001, 300961000119108, 301051000119101, 308143008, 1073801000119100, 15691961000119105, 201789001, 398640008, 400054000, 319151000119103, 319941000119103, 319041000119104, 318881000119105, 459921000124108, 410799007, 69896004, 319011000119103, 201781003, 15692001000119101, 1156819003, 319111000119104, 129563009, 201796004
multiple sclerosis	703621006, 230372003, 439567002, 724778008, 816984002, 426373005, 425500002, 445967004, 24700007, 903741000000102, 733028000, 434321000124107, 428700003, 192929006, 766246000, 192927008, 438511000, 192926004, 703622004
psoriatic arthritis	239803008, 10629311000119107, 33339001, 200956002, 239813000, 19514005, 239802003, 239804002, 410482007, 156370009, 239812005
psoriasis	238600001, 200969003, 402316001, 402314003, 238616004, 402319008, 402317005, 402326008, 402311006, 402333008, 238611009, 200966005, 402308005, 402336000, 402331005, 238605006, 402330006, 784327005, 238608008, 200965009, 200962007,

	3533007, 27520001, 200967001, 111188005, 402309002, 402324006, 402318000, 238601002, 402307000, 200968006, 402320002, 28840001, 81271001, 238617008, 238603004, 200975007, 200973000, 238602009, 200972005, 238609000, 200970002, 402312004, 37042000, 238612002, 200971003, 200977004, 402315002, 200974006, 238606007, 83839005, 402313009, 402334002, 9014002, 721538000, 200963002, 402322005, 402332003, 238607003, 402323000, 402327004, 200964008, 402325007, 238613007, 784339002, 402335001, 402310007, 402321003, 402329001, 719810000, 1052325005, 238604005, 784328000, 400069004, 402337009, 25847004, 238615000
systemic sclerosis	196133001, 322461000119108, 236502006, 403519001, 298285004, 236503001, 443872005, 403517004, 402712002, 724603009, 193252005, 774080007, 403520007, 403516008, 715401008, 444133002, 201443009, 22784002, 128461001, 403518009, 1144925008, 87442008, 403514006, 402713007, 35719004, 62382002, 51156002, 89681000119101, 89155008, 299276009, 403515007, 128460000, 31848007
spondyloarthritis	239806000, 67224007, 239808004, 724606001, 1153369009, 239810002, 235066005, 236744002, 9350004, 786077003, 239805001, 201568008, 723116002, 55146009, 15630971000119102, 239815007, 784332006, 713777005, 239811003, 15972981000119101, 1074981000119100, 201736002, 9631008, 1074971000119103, 110041000119104
systemic lupus erythematosus	25380002, 54912002, 773333003, 309762007, 724767000, 19682006, 402711009, 724781003, 239888002, 397856003, 200936003, 61458006, 403487009, 80258006, 403486000, 77753005, 238652000, 201436003, 698694005, 4676006, 239886003, 196138005, 68815009, 55464009, 54072008, 239889005, 713225000, 239890001, 76521009, 36402006, 200940007, 239887007, 11013005, 73286009, 295121000119101, 22888007, 95609003, 52042003, 707301001, 295101000119105, 95644001, 403488004, 295111000119108
vasculitis	988111000000106, 239926000, 724599009, 359789008, 128971000119101, 239936008, 402662002, 402433007, 1144932004, 53485006, 232460001, 1144914004, 38675009, 11352009, 58144006, 722020006, 239946005, 28807005, 190815001, 30911005, 1144919009, 57484009, 724783000, 75053002, 191306005, 3275009, 722191003, 310701003, 21542005, 718217000, 195353004, 724600007, 239935007, 239947001, 232369001, 155441006, 239927009, 54034003, 1144805008, 235000001, 44371002, 239922003, 403443000, 57390009, 239938009, 1149218009, 723674005, 402856005, 82275008, 239939001, 239945009, 762302008, 230732009, 239925001, 239921005
sarcoidosis	724780002, 402369000, 58870009, 735433009, 187233002, 697921005, 75403004, 64757003, 233743002, 233744008, 238676008, 402371000, 238680003, 91259005, 402370004, 55941000, 234528007, 54515008, 234524009, 233771008, 707238003, 197368002, 193195000, 232368009, 402372007, 238678009, 111937006, 233769008, 111292008, 195033009, 402380000, 238679001, 9529007, 24369008, 193251003, 37061001, 192673008, 402368008, 233770009, 361197009, 402373002, 231799005, 234526006, 233767005, 72470008, 230193008, 361198004, 400127001, 31541009, 232458003, 233768000, 21787007, 238677004, 234529004, 111936002, 233772001, 234530009, 870334009, 4416007, 234531008, 425384007, 310607007, 80941006, 238674006, 17363001, 1144986007, 234527002, 238681004, 402379003
antiphospholipid syndrome	239895006, 239894005, 774084003, 239897003, 239892009, 72161000119100, 402865003, 19267009, 26843008, 609329007

Sjögren's syndrome	196137000, 239915006, 762303003, 126766000, 83901003, 78946008, 724782005, 239912009

Diabetes type 1 and 2	395204000, 23045005, 97341000119105, 426875007, 761000119102, 359642000, 609566000, 137931000119102, 421847006, 368581000119106, 422166005, 81531005, 713706002, 16745651000119101, 16747901000119104, 721284006, 713703005, 82551000119103, 313436004, 46635009, 16747141000119104, 190389009, 769220000, 138941000119105, 368591000119109, 138911000119106, 314902007, 368101000119109, 97621000119107, 44054006, 31321000119102, 791000119109, 428007007, 421631007, 190368000, 1531000119102, 16747661000119109, 16745531000119108, 28032008, 72061000119104, 16745051000119107, 102621000119101, 781000119106, 16746261000119108, 1501000119109, 82541000119100, 1481000119100, 10660471000119109, 16746901000119101, 110181000119105, 1521000119100, 237599002, 72051000119101, 421750000, 421779007, 16746341000119103, 199230006, 427027005, 87441000119104, 422034002, 16749661000119102, 701000119103, 199229001, 609567009, 87921000119104, 16747021000119109, 712883005, 1551000119108, 16891151000119103, 9859006, 420436000, 1491000119102, 609564002, 15936501000119100, 703137001, 237627000, 97331000119101, 138921000119104, 140391000119101, 41911000119107, 10661671000119102, 140521000119107, 789567007, 16745131000119100, 313435000, 1511000119107, 10656271000119102, 110171000119107, 420756003, 87461000119100, 16745931000119102, 722454003, 789568002, 703138006, 16746131000119105, 368521000119107, 314903002, 190372001, 111231000119109, 60951000119105, 104961000119108, 16748141000119100, 28331000119107, 427134009
chronic kidney disease	731000119105, 709044004, 324311000000101, 71701000119105, 431856006, 90751000119109, 118781000119108, 127991000119101, 691421000119108, 286371000119107, 284981000119102, 104931000119100, 722150000, 285871000119106, 8501000119104, 751000119104, 324211000000106, 700378005, 90771000119100, 49708008, 950291000000103, 723190009, 368461000119103, 236436003, 897311008, 324251000000105, 285841000119104, 236435004, 10757481000119107, 324341000000100, 96441000119101, 713313000, 284971000119100, 950061000000103, 949881000000106, 714153000, 434431000124103, 46177005, 111411000119103, 949401000000103, 897312001, 722149000, 140101000119109, 90741000119107, 433146000, 324471000000100, 449631000124102, 285061000119106, 129161000119100, 153891000119101, 90761000119106, 324121000000109, 711000119100, 128001000119105, 949481000000108, 950251000000106, 285861000119100, 96741000119109, 96721000119103, 368421000119108, 708975004, 285001000119105, 722098007, 897308007, 96731000119100, 425369003, 324441000000106, 431855005, 950231000000104, 285881000119109, 950311000000102, 90731000119103, 1801000119106, 741000119101, 950181000000106, 140121000119100, 284991000119104, 96751000119106, 949921000000100, 722467000, 949421000000107, 949521000000108, 140111000119107, 140131000119102, 129181000119109, 153851000119106, 90791000119104, 285831000119108, 90721000119101, 16726004, 117681000119102, 236433006, 71421000119105, 324371000000106, 897310009, 712487000, 704667004, 285851000119102, 285041000119107, 368431000119106, 721000119107, 700379002, 950101000000101, 285911000119109, 90688005, 324281000000104, 950081000000107, 776416004, 950211000000107, 10757401000119104, 57557005, 285081000119102,

	368441000119102, 285921000119102, 707324008, 236434000, 284961000119106, 714152005, 285011000119108, 324151000000104, 120261000119101, 433144002, 96711000119105, 324501000000107, 771000119108, 324411000000105, 324181000000105, 285101000119109, 368451000119100, 129151000119102, 96701000119107, 431857002, 368471000119109, 324541000000105, 949561000000100, 949621000000109, 129171000119106, 949901000000109
obesity	292464007, 72894001, 722051004, 294493008, 295509007, 238135003, 190965006, 724137002, 415530009, 248312008, 722053001, 10750551000119100, 80660001, 238134004, 717269008, 57337005, 5036006, 770680004, 702949005, 715628009, 1076701000119104, 190966007, 82793005, 248311001, 722037004, 360566006, 721231007, 297500005, 788996008, 296526005, 238136002, 414920002, 290439001, 783719006, 83911000119104, 783549006, 414917005, 717761005, 461341000124106, 414916001, 62999006, 773663004, 293481008, 444862003, 719160009, 785722006, 298464002, 63702009, 1076711000119101, 171000119107, 238133005, 414919008, 722596001, 783556000, 763350002, 719834005, 770750002, 53146006, 414438005, 270486005, 776204008, 774102003, 238132000, 1003380001, 111036000, 15750121000119108
chronic liver disease	197286002, 103611000119102, 767809001, 1010616001, 128302006, 708198006, 768006009, 45256007, 235889003, 776981000000103, 838305005, 79720007, 1155913007, 89789003, 725940006, 235896001, 21861000, 74162007, 197303009, 37688005, 699189004, 33144001, 703866000, 715401008, 19943007, 76301009, 713370005, 713181003, 197305002, 197296006, 109819003, 123605001, 123606000, 266468003, 768127002, 235895002, 38662009, 86454000, 197301006, 328383001, 425413006, 1761006, 863957008, 76783007, 314963000, 735451005, 725939009, 723829000, 838377003, 266470007, 12368000, 10295004, 735733008, 774204006, 197291001, 16070004, 9843006, 768289009, 235897005, 31155007, 536002, 450880008, 838380002, 725416005, 78208005, 768126006, 715864007, 58282009, 197293003, 57339008, 307757001, 767810006, 197284004, 419728003, 266469006, 50167007, 197299004, 41889008, 871619002, 1116000, 1155841005, 768288001, 725938001, 31712002, 123604002, 235869004, 831000119103, 713966008, 61977001, 27156006, 66870002, 420054005, 768125005, 123717006, 43904005, 60037002, 43634002, 432908002, 716203000, 266471006, 123716002, 74669004, 15999000, 197310003, 197294009, 34736002, 16098491000119109, 371139006, 271440004, 702969000, 6183001, 1092801000119102, 89580002
asthma	266361008, 426656000, 405944004, 10676431000119103, 10742121000119104, 233678006, 56968009, 2360001000004109, 125011000119100, 195949008, 1086701000000102, 34015007, 10675991000119100, 829976001, 16584951000119101, 782513000, 786836003, 370220003, 735588005, 703953004, 734905008, 10692681000119108, 1086711000000100, 418395004, 708093000, 10674711000119105, 733858005, 707445000, 401000119107, 708090002, 93432008, 72301000119103, 233683003, 424643009, 707981009, 424199006, 10675551000119104, 10674991000119104, 404808000, 407674008, 370218001, 707513007, 404806001, 901000119100, 782520007, 10675391000119101, 703954005, 63088003, 233688007, 1103911000000103, 12428000, 735589002, 1751000119100, 708094006, 389145006, 10675911000119109, 233679003, 16055311000119107, 707512002, 10676391000119108, 707447008, 425969006, 92807009, 10675751000119107, 707979007, 370219009, 18041002, 10692761000119107, 10675871000119106, 708096008, 225057002, 125021000119107, 707444001, 195967001, 866881000000101, 59786004, 442025000, 10692721000119102, 1741000119102, 19849005, 427679007, 707980005, 404804003, 423889005, 31387002, 762521001, 11641008, 370221004, 10675471000119109, 734904007, 55570000, 124991000119109, 708095007, 707511009, 57607007, 281239006, 41553006, 195977004, 409663006, 37981002, 445427006, 427295004, 103781000119103,

	10675431000119106, 426979002, 99031000119107, 233687002, 427603009, 10676511000119109, 5281000124103, 707446004, 125001000119103
HIV	735521001, 713733003, 713530002, 713325002, 186707002, 713503007, 405631006, 48794007, 714083007, 713571008, 713505000, 713260006, 91948008, 1142055000, 713349004, 81000119104, 713718006, 713497004, 15928141000119107, 713278001, 186708007, 235009000, 713695001, 771119002, 713527009, 111880001, 713545009, 713731001, 713722001, 397763006, 713881001, 230598008, 1142045004, 713734009, 713339002, 186706006, 713490002, 713897006, 840442003, 713340000, 735527002, 721166000, 713491003, 713508003, 713844000, 713526000, 90681000119107, 713487008, 713510001, 10746341000119109, 838377003, 771126002, 713299003, 713275003, 713298006, 713543002, 713845004, 276665006, 713483007, 735526006, 713444005, 95892003, 713507008, 840498003, 733834006, 398329009, 40780007, 713546005, 713523008, 713445006, 79019005, 713342008, 713341001, 735525005, 421020000, 235726002, 713316008, 713489006, 735523003, 86406008, 713696000, 713967004, 713533000, 713570009, 713964006, 719522009, 722557007, 713446007, 733835007, 713572001, 713880000, 315019000, 80191000119101, 713511002, 943041000000105, 713320007, 276666007, 713730000, 735522008, 713504001, 713318009, 230180003, 713531003, 52079000, 236406007, 91947003, 713297001, 735528007, 735524009, 713729005, 713732008, 90691000119105, 713887002, 713300006, 713484001, 713532005, 62479008, 714464009, 713506004, 10755671000119100, 713544008, 240103002, 713488003, 87117006, 771127006
chronic lung disease	1010670004, 123713005, 840351007, 33325001, 233674008, 724500003, 836477007, 233615002, 233675009, 18354001, 4981000, 313299006, 47938003, 417688002, 195958001, 846637007, 789574002, 70756004, 430476004, 196049002, 313296004, 713525001, 771306007, 233762004, 847091000000104, 413839001, 314954002, 195957006, 1010334009, 713526000, 1751000119100, 723829000, 266404004, 16846004, 23958009, 68328006, 707553005, 704345008, 10236100011910 4, 10692761000119107, 196001008, 86680006, 240742009, 700250006, 46847001, 106001000119101, 699014000, 28791000119105, 2912004, 63841001, 18121009, 87433001, 266355005, 737180005, 707534000, 13645005, 135836000, 313297008, 36599006, 77690003, 195951007, 430969000, 196028003, 783182004, 432958009, 240747003, 26427008, 733171006, 37180002, 195959009, 1010333003, 66987001, 57686001, 266356006, 60805002, 708030004, 31898008, 293991000000106, 434301000124102, 460561000124109, 196026004, 840350008, 233677001, 16003001, 426437004, 47895001, 233713004, 285381006
depression‡	36923009, 16238181000119101, 310495003, 83458005, 720453001, 63778009, 764711000000106, 718636001, 33736005, 426578000, 16265951000119109, 191629006, 191604000, 15193003, 76441001, 765176007, 16266991000119108, 16238221000119109, 762329003, 67711008, 40568001, 69392006, 442057004, 10835871000119104, 720451004, 247803002, 723928009, 15639000, 268621008, 832007, 29929003, 16264901000119109, 755321000000106, 19527009, 2506003, 25922000, 310497006, 16264621000119109, 30605009, 1086471000000103, 1089631000000109, 79298009, 724677009, 16265301000119106, 762345001, 191611001, 237349002, 596004, 281000119103, 430852001, 237350002, 38451003, 191676002, 18818009, 300706003, 1086681000000104, 723930006, 87842000, 191613003, 450714000, 724676000, 279225001, 764701000000109, 71336009, 16265061000119105, 84788008, 1086691000000102, 310496002, 94631000119100, 712823008, 85080004, 764691000000109, 719592004, 36474008, 231500002, 321717001, 16266831000119100, 755331000000108, 191616006, 104851000119103, 724678004, 39809009, 38694004, 274948002, 75084000, 42925002, 1153570009, 68019004, 133121000119109, 192080009, 1086661000000108, 35489007, 82218004, 60099002, 720454007, 58703003, 698957003, 1089641000000100, 838530009, 2618002, 720455008, 288751000119101, 66344007, 3109008, 36170009, 46244001,

	77911002, 73867007, 191659001, 1089511000000100, 16264821000119108, 42810003, 191627008, 84760002, 10811161000119107, 10211000132109, 319768000, 231504006, 370143000, 14183003, 788120007, 762512002, 231499006, 191495003, 724690002, 78667006, 231542000, 191610000, 251000119105, 70747007, 720452006, 762321000, 28475009, 63412003, 191630001, 48589009, 231485007, 20250007, 764611000000100, 79842004, 320751009, 14070001, 726772006, 87512008, 10811121000119102, 1153575004, 33135002, 87414006, 719593009, 762336002, 1086671000000101, 33078009, 19694002, 83176005, 40379007, 192079006, 762339009, 191634005
pneumonia	206286008, 196112005, 1010670004, 80003002, 233608005, 78895009, 301004001, 724500003, 10311000175107, 10625391000119100, 441658007, 1149093006, 10625191000119102, 233728004, 408681003, 51530003, 35031000119100, 105977003, 72656004, 425464007, 41269000, 206287004, 471272001, 240741002, 10625711000119105, 40786001, 445096001, 129451001, 206284006, 430395005, 35339003, 434931000124106, 417688002, 3487004, 266350000, 191727003, 276695003, 420787001, 10625591000119108, 10301000175109, 789574002, 10625671000119106, 1092361000119109, 1010650005, 31561003, 50804000, 409664000, 60485005, 421047005, 10625471000119108, 124691000119101, 195902009, 1092951000119106, 713525001, 10624991000119103, 84753008, 71926009, 276693005, 75426006, 707552000, 422588002, 700249006, 64479007, 233607000, 233609002, 707503004, 72854003, 301003007, 312342009, 10291000175108, 277869007, 713526000, 233731003, 240635003, 10625111000119106, 10625751000119106, 233618000, 68409003, 723829000, 724499007, 22754005, 1033111000000104, 266404004, 44549008, 713084008, 772839003, 308906005, 55679008, 233730002, 438764004, 142931000119100, 10625071000119104, 707553005, 10625551000119103, 10625271000119109, 300999006, 704345008, 236302005, 102361000119104, 233617005, 195888009, 57702005, 240742009, 123589003, 700250006, 396286008, 385093006, 10625151000119107, 32204007, 58890000, 61884008, 41381004, 441590008, 1082721000119101, 75570004, 123591006, 421508002, 719218000, 240391001, 2523007, 35037009, 181007, 195900001, 195881003, 699014000, 10625511000119104, 8549006, 28791000119105, 206283000, 76090006, 763888005, 707508008, 195908008, 64880000, 233604007, 408680002, 53084003, 32286006, 233621003, 195911009, 724498004, 7063008, 195896004, 111900000, 733051000, 195886008, 39172002, 420544002, 123588006, 59475000, 64667001, 233624006, 441942006, 233625007, 426696003, 10625631000119108, 42004004, 430969000, 64917006, 415125002, 85469005, 7678002, 195909000, 10281000175105, 67525007, 128711000119106, 45556008, 240747003, 708031000, 409665004, 10625351000119105, 233610007, 83608006, 44274007, 276692000, 10625311000119109, 195878008, 301001009, 882784691000119100, 425996009, 16311000119108, 7548000, 278516003, 301000005, 421671002, 396285007, 38976008, 70036007, 10625231000119106, 123590007, 407671000, 371072008, 65141002, 46970008, 42680007, 64703005, 10625431000119105, 442094008, 195904005, 1087061000119106, 707507003, 34020007, 206289001, 426437004, 195889001, 187052004, 45312009, 233613009, 10625031000119102, 206285007, 10271000175107, 129452008, 301002002, 707449006, 870573008, 1010634002, 233623000, 314978007, 41207000, 38699009, 233614003, 713544008, 233713004, 66429007, 429271009, 233619008, 233622005, 233620002, 240387006, 123587001
urinary tract infection	197850006, 236706006, 66892003, 48278001, 301011002, 8776008, 721817004, 236620008, 197849006, 199110003, 95889002, 66993009, 371061003, 29500006, 7448003, 788962001, 301012009, 16916631000119104, 197761005, 422747000, 236721000, 240577006, 44412000, 301010001, 236702008, 51105006, 197927001, 85495007, 72225002, 111830007, 236378005, 44323002, 99631000119101, 36689008, 838353009, 431737008, 197764002, 713453003, 52123000, 4181000119109, 4009004, 1087041000119107, 129128006, 45816000, 27810000, 37133005, 307426000, 80375002, 1090711000000102, 275410008, 32268008, 33046001, 197760006, 426479005, 1723008,

	1148932007, 197769007, 444834005, 1469007, 24868007, 429728004, 236602004, 707208009, 236622000, 236685000, 81359005, 197782004, 85884009, 1086071000119103, 1148870007, 236599009, 10812041000119103, 236683007, 423322005, 110041000119104, 425562008, 236600007, 236590008, 17121006, 431309003, 240578001, 700372006, 12301009, 368991000119100, 29864006, 197757004, 84619001, 88813005, 431308006, 312221005, 609491002, 369011000119102, 59530001, 123755001, 187144000, 240721007, 123754002, 1092831000119109, 199111004, 240574004, 312124009, 10751431000119104, 788961008, 236690002, 369001000119100, 197848003, 30116001, 123611003, 199206009, 91195006, 53991003, 236703003, 838301001, 373611003, 42231000009109, 370368007, 63302006, 236377000, 40635000, 236681009, 236682002, 75712001, 68566005, 54026009, 5945005, 186796004, 838302008, 307534009, 1084821000119103, 197926005, 197763008, 197768004, 23754003, 713886006, 236684001, 38176009, 179101003, 236406007, 48631008, 428091000, 199205008, 197903003, 424551004, 96171000119103, 236686004, 197606008, 1092371000119103, 1149232006, 1149233001, 236373001, 236375008, 22352007, 60867007, 236379002, 16271000119108, 236687008, 197928006, 236376009, 240579009, 197770008, 236374007, 16751003, 240576002, 5093001
sexually transmitted disease‡	26135000, 197850006, 186846005, 85857008, 15677801000119103, 46699001, 237446005, 449773001, 237095000, 186946009, 402956009, 77939001, 1142043006, 60528006, 91554004, 194910001, 32735002, 1052319006, 1142092000, 402958005, 26039008, 237046000, 54825009, 37430004, 21523006, 240573005, 240564002, 239825002, 307423008, 81339006, 1092491000000102, 736686006, 59721007, 28198007, 240602008, 444834005, 762257007, 28867007, 266130009, 312955002, 237104007, 237096004, 235861001, 402942007, 20943002, 402950003, 186842007, 240586001, 55768006, 59233003, 444150000, 88813005, 240567009, 402126004, 194907008, 67125004, 82355002, 199164000, 11906007, 722520001, 202933002, 38523005, 266143009, 9941009, 276700005, 10754701000119100, 236682002, 237042003, 272262003, 402890001, 4082005, 402940004, 402889005, 237038001, 197348008, 240587005, 6267005, 4483005, 402952006, 35742006, 23975003, 402943002, 9241004, 4359001, 266128007, 90428001, 67391006, 15679681000119101, 230152000, 42746002, 240568004, 86028001, 86443005, 230735006, 713261005, 16217981000119107, 402951004, 312934004, 186850003, 58392004, 240577006, 44412000, 402947001, 240604009, 186878002, 240560006, 199166003, 61048000, 235863003, 427578006, 27681008, 266126006, 10759841000119105, 51960003, 1052322008, 65295003, 278480000, 235064008, 13731006, 192008, 33839006, 402949003, 54274001, 402941000, 240584003, 428230005, 423391007, 80604007, 58056005, 30168008, 402888002, 788975001, 104011000119109, 735515000, 46235002, 240554006, 28438004, 199161008, 278068003, 22386003, 109436001, 45058001, 29864006, 402894005, 302812006, 31015008, 151004, 1142095003, 59530001, 240552005, 88943008, 80770009, 274118001, 74372003, 402896007, 186833000, 789121002, 240572000, 76272004, 230563005, 449776009, 272006008, 12373006, 37754005, 2390000, 8098009, 237447001, 405635002, 240555007, 235062007, 240563008, 27648007, 301086002, 49923008, 39085002, 236687008, 410470003, 15685441000119102, 278481001, 240576002, 62861003, 193786000, 64102008, 36276008, 186868000, 240585002, 232313005, 194947001, 315826004, 186893003, 721583004, 40149008, 240582004, 72225002, 197967000, 402945009, 402895006, 186867005, 402944008, 232367004, 402955008, 53664003, 1052321001, 266136003, 15677841000119101, 1087021000119101, 186875004, 28572009, 240583009, 240558009, 1137693003, 240039005, 266133006, 9091006, 59819007, 10345003, 186931002, 186915005, 240603003, 721585006, 890115009, 35526001, 27075004, 65049003, 31999004, 235065009, 58227000, 1107004, 62207008, 94851000119107, 199165004, 15679561000119109, 240608007, 129670002, 27420004, 8555001, 68863007, 240578001, 52414005, 10754031000119105, 45377007, 20735004, 35089004, 197848003, 186847001, 240581006, 114881000119108, 197347003, 240575003, 198175009, 721587003, 66887000, 301990003, 11056091000119105, 866115006, 240557004, 83883001, 240561005, 277499006, 240569007, 59307008, 71011005, 240571007, 44743006, 1087051000119109,

	439912007, 236766009, 236772009, 276877003, 240606006, 68764005, 402954007, 13310005, 1142031005, 12232008, 240579009, 237083000, 112121000119105, 233849007, 72083004, 440714005, 719755001, 10227000, 44568006, 42770003, 111807001, 60335002, 60893000, 3589003, 266125005, 31137003, 266127002, 82323002, 240565001, 5085001, 230182006, 15679481000119104, 17305005, 15677881000119106, 51928006, 406581000, 1087041000119107, 371237000, 27460003, 186854007, 237069002, 342381000119109, 11338007, 890114008, 1010615002, 838317007, 111806005, 19206003, 24868007, 827006, 61612001, 50970007, 1142099009, 16070004, 402946005, 192647003, 331151000119109, 15993391000119102, 197757004, 186861006, 240556008, 66281009, 80388004, 199163006, 186863009, 314840009, 410478005, 240574004, 240545008, 302813001, 82959004, 439913002, 35876006, 77028001, 76802005, 788998009, 240566000, 231858009, 59934002, 53529004, 197966009, 238419002, 15628003, 13095005, 186939000, 721589000, 87318008, 63751007, 50528008, 721588008, 54069001, 1087061000119106, 186903006, 19290004, 1621000119101, 1087001000119105, 198242009, 235032001, 713251003, 240562003, 275376007, 69595007, 75299005, 1052323003, 186877007
cardiovascular disease	49601007‡
sepsis	1089000, 79587009, 39246002, 2858002, 714083007, 238152004, 713866007, 447898000, 707271004, 700055009, 16060271000119109, 698819004, 700051000, 127251000119102, 449335002, 5085001, 700053002, 448421008, 715070000, 448482003, 8554002, 735638009, 1153534006, 1149494008, 762528007, 206379003, 16060311000119109, 436741000124105, 750511000000101, 448812000, 1149486001, 1125006, 199711007, 4089001, 448418006, 944071000000101, 449546000, 957431000000102, 449505005, 127091000119100, 127201000119101, 277639002, 721278008, 1092461000119104, 765106006, 1092591000119105, 206380000, 128381000119104, 276229008, 721104000, 235657005, 240389009, 447894003, 944061000000108, 276669000, 1149481006, 447897005, 735637004, 765107002, 770349000, 126811000119102, 448813005, 91302008, 448420009, 870588003, 443980004, 1036671000000106, 51831006, 700054008, 77206006, 196853004, 127181000119102, 447684006, 448422001, 277638005, 127191000119104, 127261000119100, 1092511000119101, 447843005, 1092531000119106, 10751351000119104, 32751000119100, 957421000000104, 127121000119101, 9012003, 609485004, 713865006, 240385003, 435181000124108, 127751000119108, 42939002, 789043007, 700052007, 449504009, 10001005, 448784003, 127231000119108, 1149482004, 371044001, 1092541000119102, 276741000, 733142005, 67465009, 721572008, 1076281000000108, 240426001, 46848006, 447841007, 272006008, 127311000119106, 199710008, 700050004, 200196001, 1092601000119103, 194394004, 1092471000119105, 447685007, 206378006, 11373009, 206376005, 762529004, 448417001, 186365005, 449083008, 1092501000119104, 448483008, 127171000119100, 448419003, 397843005, 447899008, 449084002, 22241000175107, 1092491000119106, 713854001, 127331000119101, 1092481000119108, 436751000124107, 1092571000119109, 449082003, 127241000119104, 24444009, 127141000119107, 16751003, 715071001, 10812001000119100

‡ indicate all descendant SNOMED codes are included

Table A.6 2 Variable definition[14]

Category	Variable	Definitions
Maternal/pregnancy characteristics	Race	Race noted in medical record. Missing values were encoded as Unknown; American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White or Caucasian, Multiracial, Other, Unknown

	Ethnicity	Ethnicity noted in medical record. Missing values were encoded as unknown; Hispanic or Latino, Not Hispanic or Latino, Unknown
	Maternal age	Maternal age at the start of pregnancy; 18 ~ 24, 25 ~ 29, 30 ~ 34, 35 ~ 40, 41 ~ 44
	Pregravid BMI	Pregravid Body Mass Index (kg/m2). Missing value was encoded as unknown; Underweight (<18.5 BMI), Normal (18.5 - 24.9 BMI), Overweight (25.0 - 29.9 BMI), Obese (>30.0)
	Insurance status	Commercial, Medicaid, Medicare, Uninsured-Self-Pay
	Smoker	Self-reported smoking status; 0,1
	Illegal drug use	Self-reported illegal drug use status; 0,1
	Preterm history	History of preterm delivery; 0,1
	Parity	Number of times a patient has delivered a fetus older than 20 weeks of gestation prior to the current pregnancy; 0, 1~5, 6
	Gravidity	Number of times a patient has been pregnant; 0, 1~5, 6
	Delivery year	Year of delivery; 2013~2022
Geographical features	Vulnerability index of socioeconomic status	CDC SVI Socioeconomic (RPL_THEME1) theme ranking mapped to patient's U.S. Census tract; scores are 0-1. score of 0 and 1 indicate low and high level of social vulnerability regarding socioeconomic status
	Vulnerability index of housing composition	CDC SVI Housing Composition & Disability (RPL_THEME2) theme ranking mapped to patient's U.S. Census tract; scores are 0-1. score of 0 and 1 indicate low and high levels of social vulnerability regarding housing composition.
	Vulnerability index of minority status and language	CDC SVI Minority Status & Language (RPL_THEME3) theme ranking mapped to patient's U.S. Census tract; scores are 0-1. score of 0 and 1 indicate low and high levels of social vulnerability in terms of minority status and language. Census tract with high RPL_THEME3 score is enriched with residents of minority (non-White) and/or have low English language skills
	Vulnerability index of housing type and transportation	CDC SVI Housing Type & Transportation (RPL_THEME4) theme ranking mapped to patient's U.S. Census tract; scores are 0-1. score of 0 and 1 indicate low and high levels of social vulnerability regarding housing type and transportation. Census tract with high RPL_THEME4 score is area of lower income housing and/or population dense housing options
	Rural/urban categorization	U.S. Department of Agriculture Economic Research Service (USDA ERS) Rural-Urban Commuting Area (RUCA) codes; SecondaryRUCACode2010 (last updated in 2019) were mapped using patient U.S. Census Tract; Categorized as Metropolitan (> 4 score), Micropolitan (4 - 6 score), Small Town (7 - 9 score), Rural (10 - 99 score), or Unknown
Maternal-fetal health outcomes	Low birth weight	Infant birth weight ≤ 2,500g
	Preterm birth	Infant gestational age (GA) at birth < 37 weeks
	Small for gestational age	Infant birth weight < 10th percentiles for infants of same GA
	C-section	Cesarean section

CDC Center for Disease Control and Prevention; GA Gestational Age; SVI Social Vulnerability Index

Table A.6 3 RxNorm codes for medication order

Drug class	Example of medications and ingredients	Ingredients RxNorm codes
hydroxychloroquine	hydroxychloroquine	5521
methotrexate	methotrexate	6851
leflunomide	leflunomide	27169
teriflunomide	teriflunomide	1310520
5-ASA	balsalazide, sulfasalazine, mesalamine	18747, 9524, 52582
azathioprine	azathioprine	1256
mercaptopurine	mercaptopurine	103
mitoxantrone	mitoxantrone	7005
mycophenolate	mycophenolate	265323
calcineurin inhibitor	cyclosporine, sirolimus, tacrolimus	3008, 35302, 42316
TNF-α inhibitor	adalimumab, certolizumab pegol, etanercept, golimumab, infliximab	327361, 709271, 214555, 819300, 191831
fumarates	dimethyl fumarate, diroximel fumarate, monomethyl fumarate	1373478, 2261783, 1546433
interferons	interferon beta-1a, interferon beta-1b	75917, 72257
alkylating agent	chlorambucil, cyclophosphamide	2346, 3002
hydroxyurea	hydroxyurea	5552
dapsone	dapsone	3108
cladribine	cladribine	44157
IL-1 inhibitor	canakinumab, anakinra, rilonacept	853491, 72435, 763450
IL-6 inhibitor	sarilumab, tocilizumab, satralizumab	1923319, 612865, 2391541
IL-12/23 inhibitor	ustekinumab	847083
IL-17 inhibitor	ixekizumab, brodalumab, secukinumab	1745099, 1872251, 1599788
IL-23 inhibitor	guselkumab, tildrakizumab, risankizumab	1928588, 2053436, 2166040
abatacept	abatacept	614391
anti-BLyS	belimumab	1092437
S1P receptor modulator	siponimod, ponesimod, fingolimod, ozanimod	2121085, 2532300, 1012892, 2288236
JAK inhibitor	tofacitinib, upadacitinib, baricitinib	1357536, 2196092, 2047232
Integrin modulator	vedolizumab, natalizumab	1538097, 354770
PDE4 inhibitor	apremilast	1492727
anti-CD20	rituximab, ocrelizumab, ofatumumab	121191, 1876366, 712566
anti-CD52	alemtuzumab	117055
budesonide	budesonide	19831
systemic glucocorticoids	prednisone, dexamethasone, prednisolone, triamcinolone, methylprednisolone, hydrocortisone	8638, 3264, 8638, 10759, 6902, 5492

Table A.6 4 Descriptive statistics of twelve individual IMIDs group[14]

variable	IBD (n=1289)	RA (n=732)	MS (n=508)	PsA (n=207)	PsO (n=1871)	SSc (n=54)	SpA (n=675)	SLE (n=439)	Va (n=84)	Sc (n=57)	APS (n=180)	SjS (n=147)
Maternal characteristics												
Maternal age	32.6 (5.2)	32.4 (5.5)	33.0 (5.0)	33.8 (4.7)	32.8 (5.2)	33.7 (6.4)	32.1 (5.2)	32.6 (5.2)	31.4 (5.4)	34.8 (6.0)	34.0 (5.7)	33.0 (4.6)
Age group												

17 or younger	1 (0.1)	2 (0.4)	0 (0.0)	0 (0.0)	4 (0.3)	1 (3.2)	1 (0.2)	0 (0.0)	2 (2.6)	0 (0.0)	1 (1.0)	0 (0.0)
18-24	114 (12.7)	88 (17.8)	33 (10.2)	11 (9.2)	178 (13.9)	5 (16.1)	74 (15.4)	39 (13.1)	18 (23.7)	7 (22.6)	11 (10.5)	5 (5.1)
25-29	269 (30.1)	157 (31.8)	107 (32.9)	32 (26.7)	392 (30.7)	11 (35.5)	155 (32.2)	97 (32.6)	14 (18.4)	8 (25.8)	37 (35.2)	36 (36.4)
30-34	511 (57.1)	246 (49.9)	185 (56.9)	77 (64.2)	704 (55.1)	14 (45.2)	252 (52.3)	162 (54.4)	42 (55.3)	16 (51.6)	56 (53.3)	58 (58.6)
Race group												
American Indian or Alaska Native	12 (0.9)	20 (2.7)	4 (0.8)	1 (0.5)	21 (1.1)	2 (3.7)	6 (0.9)	7 (1.6)	1 (1.2)	3 (5.3)	3 (1.7)	3 (2.0)
Asian	43 (3.3)	45 (6.1)	13 (2.6)	14 (6.8)	133 (7.1)	2 (3.7)	35 (5.2)	38 (8.7)	2 (2.4)	3 (5.3)	10 (5.6)	19 (12.9)
Black or African American	34 (2.6)	16 (2.2)	15 (3.0)	2 (1.0)	45 (2.4)	0 (0.0)	20 (3.0)	28 (6.4)	4 (4.8)	2 (3.5)	4 (2.2)	4 (2.7)
Native Hawaiian or Other Pacific Islander	1 (0.1)	7 (1.0)	5 (1.0)	1 (0.5)	28 (1.5)	0 (0.0)	3 (0.4)	2 (0.5)	1 (1.2)	0 (0.0)	1 (0.6)	0 (0.0)
White or Caucasian	1051 (81.5)	482 (65.8)	410 (80.7)	162 (78.3)	1336 (71.4)	38 (70.4)	495 (73.3)	250 (56.9)	67 (79.8)	37 (64.9)	121 (67.2)	94 (63.9)
Multirace	47 (3.6)	50 (6.8)	22 (4.3)	11 (5.3)	93 (5.0)	2 (3.7)	36 (5.3)	36 (8.2)	2 (2.4)	2 (3.5)	16 (8.9)	7 (4.8)
Other	99 (7.7)	110 (15.0)	39 (7.7)	16 (7.7)	210 (11.2)	10 (18.5)	78 (11.6)	76 (17.3)	6 (7.1)	10 (17.5)	22 (12.2)	20 (13.6)
Missing	2 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	5 (0.3)	0 (0.0)	2 (0.3)	2 (0.5)	1 (1.2)	0 (0.0)	3 (1.7)	0 (0.0)
Ethnicity												
Hispanic or Latino	84 (6.5)	128 (17.5)	44 (8.7)	13 (6.3)	201 (10.7)	8 (14.8)	90 (13.3)	101 (23.0)	9 (10.7)	6 (10.5)	28 (15.6)	20 (13.6)
Not Hispanic nor Latino	1182 (91.7)	580 (79.2)	457 (90.0)	190 (91.8)	1621 (86.6)	44 (81.5)	566 (83.9)	331 (75.4)	74 (88.1)	50 (87.7)	151 (83.9)	124 (84.4)
Unknown/Unreported	23 (1.8)	24 (3.3)	7 (1.4)	4 (1.9)	49 (2.6)	2 (3.7)	19 (2.8)	7 (1.6)	1 (1.2)	1 (1.8)	1 (0.6)	3 (2.0)
BMI category												
Underweight	17 (1.3)	6 (0.8)	5 (1.0)	0 (0.0)	15 (0.8)	1 (1.9)	6 (0.9)	4 (0.9)	2 (2.4)	0 (0.0)	3 (1.7)	3 (2.0)
Normal	238 (18.5)	118 (16.1)	92 (18.1)	34 (16.4)	330 (17.6)	13 (24.1)	116 (17.2)	42 (9.6)	20 (23.8)	7 (12.3)	20 (11.1)	17 (11.6)
Obese	106 (8.2)	99 (13.5)	42 (8.3)	28 (13.5)	276 (14.8)	7 (13.0)	85 (12.6)	47 (10.7)	9 (10.7)	9 (15.8)	18 (10.0)	12 (8.2)
Overweight	136 (10.6)	78 (10.7)	43 (8.5)	14 (6.8)	206 (11.0)	3 (5.6)	80 (11.9)	37 (8.4)	8 (9.5)	5 (8.8)	17 (9.4)	14 (9.5)

Missing	792 (61.4)	431 (58.9)	326 (64.2)	131 (63.3)	1044 (55.8)	30 (55.6)	388 (57.5)	309 (70.4)	45 (53.6)	36 (63.2)	122 (67.8)	101 (68.7)
Insurance												
Commercial	796 (61.8)	381 (52.0)	292 (57.5)	114 (55.1)	1057 (56.5)	29 (53.7)	296 (43.9)	197 (44.9)	44 (52.4)	30 (52.6)	88 (48.9)	94 (63.9)
Medicaid/Medicare	492 (38.2)	349 (47.7)	213 (41.9)	93 (44.9)	803 (42.9)	25 (46.3)	378 (56.0)	242 (55.1)	40 (47.6)	27 (47.4)	92 (51.1)	53 (36.1)
Self Pay	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	1 (0.1)	2 (0.3)	3 (0.6)	0 (0.0)	11 (0.6)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Smoker	85 (6.6)	67 (9.2)	52 (10.2)	21 (10.1)	174 (9.3)	5 (9.3)	70 (10.4)	38 (8.7)	10 (11.9)	8 (14.0)	18 (10.0)	7 (4.8)
Illegal drug user	139 (10.8)	74 (10.1)	51 (10.0)	20 (9.7)	170 (9.1)	2 (3.7)	87 (12.9)	49 (11.2)	12 (14.3)	6 (10.5)	15 (8.3)	7 (4.8)
Alcohol user	409 (31.7)	184 (25.1)	161 (31.7)	57 (27.5)	579 (30.9)	20 (37.0)	159 (23.6)	114 (26.0)	22 (26.2)	23 (40.4)	36 (20.0)	42 (28.6)
Vulnerability index of socioeconomic status	0.3 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.3)	0.3 (0.2)	0.4 (0.2)	0.4 (0.2)
Vulnerability index of housing composition	0.3 (0.3)	0.4 (0.3)	0.4 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.3 (0.3)
Vulnerability index of minority status and language	0.5 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.3)	0.6 (0.2)
Vulnerability index of housing type and transportation	0.5 (0.3)	0.6 (0.3)	0.6 (0.3)	0.5 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.7 (0.3)	0.6 (0.3)	0.6 (0.3)
Rural/urban classification												
Metropolitan	1106 (85.8)	621 (84.8)	435 (85.6)	181 (87.4)	1649 (88.1)	43 (79.6)	569 (84.3)	353 (80.4)	71 (84.5)	43 (75.4)	141 (78.3)	128 (87.1)
Micropolitan	67 (5.2)	37 (5.1)	17 (3.3)	5 (2.4)	61 (3.3)	2 (3.7)	42 (6.2)	27 (6.2)	6 (7.1)	3 (5.3)	14 (7.8)	6 (4.1)
SmallTown	30 (2.3)	18 (2.5)	6 (1.2)	4 (1.9)	42 (2.2)	2 (3.7)	18 (2.7)	11 (2.5)	1 (1.2)	3 (5.3)	6 (3.3)	5 (3.4)
Rural	17 (1.3)	14 (1.9)	9 (1.8)	3 (1.4)	25 (1.3)	0 (0.0)	9 (1.3)	7 (1.6)	0 (0.0)	0 (0.0)	4 (2.2)	1 (0.7)
Missing	69 (5.4)	42 (5.7)	41 (8.1)	14 (6.8)	94 (5.0)	7 (13.0)	37 (5.5)	41 (9.3)	6 (7.1)	8 (14.0)	15 (8.3)	7 (4.8)

Pregnancy characteristics												
Gravidity												
1	306 (23.7)	163 (22.3)	100 (19.7)	38 (18.4)	399 (21.3)	8 (14.8)	132 (19.6)	94 (21.4)	26 (31.0)	10 (17.5)	19 (10.6)	37 (25.2)
2-4	683 (53.0)	393 (53.7)	275 (54.1)	108 (52.2)	988 (52.8)	29 (53.7)	370 (54.8)	232 (52.8)	41 (48.8)	24 (42.1)	74 (41.1)	77 (52.4)
5≤	146 (11.3)	103 (14.1)	57 (11.2)	37 (17.9)	258 (13.8)	11 (20.4)	110 (16.3)	73 (16.6)	7 (8.3)	8 (14.0)	54 (30.0)	22 (15.0)
Missing	154 (11.9)	73 (10.0)	76 (15.0)	24 (11.6)	226 (12.1)	6 (11.1)	63 (9.3)	40 (9.1)	10 (11.9)	15 (26.3)	33 (18.3)	11 (7.5)
Parity												
0	169 (13.1)	97 (13.3)	57 (11.2)	28 (13.5)	228 (12.2)	5 (9.3)	76 (11.3)	57 (13.0)	18 (21.4)	5 (8.8)	23 (12.8)	15 (10.2)
1	465 (36.1)	254 (34.7)	184 (36.2)	59 (28.5)	635 (33.9)	19 (35.2)	238 (35.3)	158 (36.0)	32 (38.1)	13 (22.8)	50 (27.8)	64 (43.5)
2-4	484 (37.5)	293 (40.0)	186 (36.6)	88 (42.5)	729 (39.0)	23 (42.6)	279 (41.3)	174 (39.6)	24 (28.6)	24 (42.1)	72 (40.0)	52 (35.4)
5≤	17 (1.3)	15 (2.0)	5 (1.0)	8 (3.9)	53 (2.8)	1 (1.9)	19 (2.8)	10 (2.3)	0 (0.0)	0 (0.0)	2 (1.1)	5 (3.4)
Missing	154 (11.9)	73 (10.0)	76 (15.0)	24 (11.6)	226 (12.1)	6 (11.1)	63 (9.3)	40 (9.1)	10 (11.9)	15 (26.3)	33 (18.3)	11 (7.5)
Preterm history												
Yes	288 (22.3)	169 (23.1)	120 (23.6)	50 (24.2)	355 (19.0)	13 (24.1)	141 (20.9)	117 (26.7)	19 (22.6)	7 (12.3)	48 (26.7)	30 (20.4)
No	847 (65.7)	490 (66.9)	312 (61.4)	133 (64.3)	1290 (68.9)	35 (64.8)	471 (69.8)	282 (64.2)	55 (65.5)	35 (61.4)	99 (55.0)	106 (72.1)
Missing	154 (11.9)	73 (10.0)	76 (15.0)	24 (11.6)	226 (12.1)	6 (11.1)	63 (9.3)	40 (9.1)	10 (11.9)	15 (26.3)	33 (18.3)	11 (7.5)
Fetal sex												
Female	599 (49.0)	349 (50.8)	218 (48.0)	91 (46.7)	816 (46.5)	27 (52.9)	302 (46.6)	209 (50.9)	42 (52.5)	28 (62.2)	81 (48.2)	75 (52.8)
Male	623 (51.0)	338 (49.2)	235 (51.8)	104 (53.3)	937 (53.4)	24 (47.1)	346 (53.4)	201 (48.9)	38 (47.5)	17 (37.8)	87 (51.8)	67 (47.2)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Delivery year												

2013	40 (3.1)	29 (4.0)	41 (8.1)	6 (2.9)	73 (3.9)	1 (1.9)	17 (2.5)	22 (5.0)	1 (1.2)	4 (7.0)	2 (1.1)	4 (2.7)
2014	80 (6.2)	27 (3.7)	44 (8.7)	10 (4.8)	117 (6.3)	3 (5.6)	33 (4.9)	21 (4.8)	5 (6.0)	4 (7.0)	8 (4.4)	4 (2.7)
2015	104 (8.1)	56 (7.7)	47 (9.3)	12 (5.8)	122 (6.5)	3 (5.6)	43 (6.4)	34 (7.7)	4 (4.8)	8 (14.0)	10 (5.6)	11 (7.5)
2016	133 (10.3)	55 (7.5)	39 (7.7)	13 (6.3)	161 (8.6)	4 (7.4)	59 (8.7)	27 (6.2)	4 (4.8)	9 (15.8)	13 (7.2)	11 (7.5)
2017	133 (10.3)	63 (8.6)	55 (10.8)	18 (8.7)	173 (9.2)	4 (7.4)	68 (10.1)	42 (9.6)	10 (11.9)	4 (7.0)	18 (10.0)	16 (10.9)
2018	145 (11.2)	73 (10.0)	64 (12.6)	27 (13.0)	204 (10.9)	5 (9.3)	78 (11.6)	45 (10.3)	12 (14.3)	6 (10.5)	20 (11.1)	16 (10.9)
2019	159 (12.3)	83 (11.3)	62 (12.2)	22 (10.6)	217 (11.6)	7 (13.0)	97 (14.4)	54 (12.3)	9 (10.7)	7 (12.3)	31 (17.2)	13 (8.8)
2020	167 (13.0)	114 (15.6)	51 (10.0)	21 (10.1)	225 (12.0)	10 (18.5)	80 (11.9)	52 (11.8)	15 (17.9)	6 (10.5)	22 (12.2)	16 (10.9)
2021	152 (11.8)	115 (15.7)	52 (10.2)	32 (15.5)	269 (14.4)	9 (16.7)	92 (13.6)	60 (13.7)	9 (10.7)	4 (7.0)	28 (15.6)	19 (12.9)
2022	176 (13.7)	117 (16.0)	53 (10.4)	46 (22.2)	310 (16.6)	8 (14.8)	108 (16.0)	82 (18.7)	15 (17.9)	5 (8.8)	28 (15.6)	37 (25.2)
Comorbidities												
Diabetes	13 (1.0)	16 (2.2)	5 (1.0)	6 (2.9)	39 (2.1)	0 (0.0)	10 (1.5)	5 (1.1)	1 (1.2)	1 (1.8)	1 (0.6)	1 (0.7)
Chronic kidney disease	3 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	10 (2.3)	2 (2.4)	0 (0.0)	2 (1.1)	1 (0.7)
Obesity	42 (3.3)	60 (8.2)	24 (4.7)	23 (11.1)	175 (9.4)	0 (0.0)	59 (8.7)	40 (9.1)	5 (6.0)	7 (12.3)	15 (8.3)	12 (8.2)
Chronic liver disease	4 (0.3)	5 (0.7)	1 (0.2)	0 (0.0)	8 (0.4)	6 (11.1)	4 (0.6)	1 (0.2)	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.7)
Asthma	138 (10.7)	91 (12.4)	49 (9.6)	33 (15.9)	231 (12.3)	5 (9.3)	101 (15.0)	59 (13.4)	12 (14.3)	6 (10.5)	28 (15.6)	29 (19.7)
HIV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depression	229 (17.8)	175 (23.9)	134 (26.4)	58 (28.0)	410 (21.9)	15 (27.8)	208 (30.8)	91 (20.7)	16 (19.0)	11 (19.3)	36 (20.0)	37 (25.2)
Hypercoagulability	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	4 (0.9)	0 (0.0)	0 (0.0)	9 (5.0)	0 (0.0)
Pneumonia	16 (1.2)	16 (2.2)	10 (2.0)	7 (3.4)	31 (1.7)	0 (0.0)	16 (2.4)	14 (3.2)	4 (4.8)	7 (12.3)	11 (6.1)	1 (0.7)
Urinary tract infection	205 (15.9)	137 (18.7)	94 (18.5)	41 (19.8)	342 (18.3)	8 (14.8)	188 (27.9)	85 (19.4)	25 (29.8)	13 (22.8)	38 (21.1)	21 (14.3)
Sexually transmitted disease	44 (3.4)	24 (3.3)	18 (3.5)	3 (1.4)	66 (3.5)	3 (5.6)	29 (4.3)	10 (2.3)	3 (3.6)	1 (1.8)	8 (4.4)	8 (5.4)

Cardiovascular disease	417 (32.4)	276 (37.7)	175 (34.4)	78 (37.7)	579 (30.9)	21 (38.9)	260 (38.5)	184 (41.9)	81 (96.4)	25 (43.9)	96 (53.3)	59 (40.1)
Sepsis	35 (2.7)	11 (1.5)	4 (0.8)	4 (1.9)	8 (0.4)	2 (3.7)	11 (1.6)	10 (2.3)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)

APS Antiphospholipid Syndrome; IBD Inflammatory Bowel Disease; IMID Immune-mediated Inflammatory Disease; MS Multiple Sclerosis; Ps Psoriasis; PsA Psoriatic Arthritis; Sc Sarcoidosis; SLE Systemic Lupus Erythematosus; SpA Spondyloarthritis; SjS Sjörgen's Syndrome; SSc Systemic Sclerosis; Va Vasculitis;
Variables are defined in Table A.6 2. SNOMED codes of diagnoses are listed in Table A.6 1.

Table A.6 5 Statistical significance of descriptive statistics[14]

variable	**IMIDs**	**IBD**	**RA**	**MS**	**PsA**	**Ps**	**SSc**	**SpA**	**SLE**	**Va**	**Sc**	**APS**	**SjS**
Maternal age	****	****	****	****	****	****	*	****	****	ns	**	****	****
Age group	****	****	*	****	***	****	ns	****	***	ns	ns	+	**
Race group	****	****	***	****	**	****	ns	****	*	ns	ns	+	ns
Ethnicity	****	****	*	****	****	****	ns	****	ns	ns	ns	+	ns
BMI category	****	****	****	ns	+	****	ns	****	+	ns	ns	ns	ns
insurance	****	****	*	****	ns	****	ns	ns	ns	ns	ns	ns	**
smoker	****	ns	+	*	ns	***	ns	**	ns	ns	ns	ns	ns
Illegal drug user	****	****	*	+	ns	*	ns	****	*	ns	ns	ns	ns
Alcohol user	****	****	****	****	**	****	**	***	****	ns	***	ns	**
Vulnerability index of socioeconomic status	****	****	***	****	**	****	ns	ns	ns	ns	ns	ns	ns
Vulnerability index of housing composition	***	**	ns	ns	+	****	ns	**	ns	ns	ns	ns	ns
Vulnerability index of minority status and language	****	****	****	****	**	****	ns	****	ns	ns	*	ns	ns
Vulnerability index of housing type and transportation	***	****	ns	ns	*	ns	ns	ns	ns	ns	ns	ns	ns
Rural/urban classification	****	**	+	ns	ns	****	ns	*	ns	ns	ns	ns	ns
Gravidity	****	ns	ns	*	*	**	ns	**	*	ns	**	****	ns

Parity	**	+	ns	**	ns	ns	ns	ns	ns	ns	**	*	ns
Preterm_history	***	+	ns	**	ns	*	ns	ns	*	ns	**	***	ns
Fetal sex	ns	ns	ns	****	ns	ns	ns	ns	**	ns	ns	ns	ns
Delivery year	****	****	****	ns	***	****	ns	****	****	ns	ns	**	**
Diabetes	****	ns	***	ns	*	****	ns	+	ns	ns	ns	ns	ns
Chronic kidney disease	****	+	ns	ns	ns	ns	ns	ns	****	*	ns	*	ns
Obesity	****	ns	****	+	****	****	ns	****	****	ns	**	**	**
Asthma	****	****	****	***	****	****	ns	****	****	*	ns	****	****
Chronic lung disease	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Depression	****	****	****	****	****	****	***	****	****	*	+	****	****
Pneumonia	****	ns	**	+	**	**	ns	**	***	*	****	****	ns
Urinary tract infection	****	****	****	****	***	****	ns	****	****	****	*	****	ns
Sexually transmitted disease	****	****	**	**	ns	****	ns	****	ns	ns	ns	*	*
Cardiovascular disease	****	****	****	****	****	****	****	****	****	****	****	****	****
Sepsis	****	****	**	ns	*	ns	ns	***	****	ns	ns	ns	ns

APS Antiphospholipid Syndrome; IBD Inflammatory Bowel Disease; IMID Immune-mediated Inflammatory Disease; MS Multiple Sclerosis; Ps Psoriasis; PsA Psoriatic Arthritis; Sc Sarcoidosis; SLE Systemic Lupus Erythematosus; SpA Spondyloarthritis; SjS Sjörgen's Syndrome; SSc Systemic Sclerosis; Va Vasculitis;

Variables are defined in Table A.6 2. SNOMED codes of diagnoses are listed in Table A.6 1. Difference in distribution of corresponding variable between IMIDs and control was evaluated using t-test, fisher exact test, and chi-square test for continuous, binary, and categorical variables. Multiple testing error was corrected using Benjamin-Hochberg Statistical significance was reported as follows. p<0·0001:****, 0·0001≤p<0·001:***, 0·001≤p<0·01:**, 0·01≤p<0·05:*, 0·05≤p<0·1:+, 0.1<p:ns

Table A.6 6 IMMs prescription pattern[14]

	IMIDs	**IBD**	**RA**	**MS**	**PsA**	**Ps**	**SSc**	**SpA**	**SLE**	**Va**	**Sc**	**APS**	**SjS**

	(n=5784)	(n=1289)	(n=732)	(n=508)	(n=207)	(n=1871)	(n=54)	(n=675)	(n=439)	(n=84)	(n=57)	(n=180)	(n=147)
hydroxychloroquine													
prepregnancy	123 (2.1)	1 (0.1)	53 (7.2)	0 (0.0)	0 (0.0)	4 (0.2)	3 (5.6)	5 (0.7)	63 (14.4)	1 (1.2)	1 (1.8)	7 (3.9)	15 (10.2)
prenatal	235 (4.1)	3 (0.2)	93 (12.7)	0 (0.0)	2 (1.0)	8 (0.4)	6 (11.1)	12 (1.8)	133 (30.3)	2 (2.4)	1 (1.8)	12 (6.7)	36 (24.5)
first trimester	144 (2.5)	1 (0.1)	63 (8.6)	0 (0.0)	1 (0.5)	6 (0.3)	3 (5.6)	5 (0.7)	72 (16.4)	2 (2.4)	1 (1.8)	7 (3.9)	23 (15.6)
second trimester	141 (2.4)	2 (0.2)	52 (7.1)	0 (0.0)	2 (1.0)	6 (0.3)	4 (7.4)	6 (0.9)	77 (17.5)	1 (1.2)	1 (1.8)	6 (3.3)	26 (17.7)
third trimester	190 (3.3)	3 (0.2)	70 (9.6)	0 (0.0)	1 (0.5)	6 (0.3)	4 (7.4)	10 (1.5)	114 (26.0)	1 (1.2)	1 (1.8)	11 (6.1)	32 (21.8)
methrotrexate													
prepregnancy	14 (0.2)	0 (0.0)	9 (1.2)	0 (0.0)	1 (0.5)	4 (0.2)	0 (0.0)	2 (0.3)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	15 (0.3)	0 (0.0)	9 (1.2)	0 (0.0)	1 (0.5)	4 (0.2)	0 (0.0)	2 (0.3)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	15 (0.3)	0 (0.0)	9 (1.2)	0 (0.0)	1 (0.5)	4 (0.2)	0 (0.0)	2 (0.3)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	4 (0.1)	0 (0.0)	4 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	3 (0.1)	0 (0.0)	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
leflunomide													
prepregnancy	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
teriflunomide													
prepregnancy	3 (0.1)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

prenatal	3 (0.1)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	3 (0.1)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	2 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Five ASA													
prepregnancy	116 (2.0)	98 (7.6)	14 (1.9)	1 (0.2)	1 (0.5)	5 (0.3)	0 (0.0)	8 (1.2)	1 (0.2)	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.7)
prenatal	200 (3.5)	169 (13.1)	25 (3.4)	1 (0.2)	4 (1.9)	7 (0.4)	0 (0.0)	15 (2.2)	4 (0.9)	0 (0.0)	1 (1.8)	1 (0.6)	1 (0.7)
first trimester	137 (2.4)	117 (9.1)	17 (2.3)	1 (0.2)	2 (1.0)	6 (0.3)	0 (0.0)	11 (1.6)	1 (0.2)	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.7)
second trimester	128 (2.2)	111 (8.6)	13 (1.8)	1 (0.2)	2 (1.0)	6 (0.3)	0 (0.0)	8 (1.2)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	157 (2.7)	135 (10.5)	16 (2.2)	1 (0.2)	2 (1.0)	5 (0.3)	0 (0.0)	9 (1.3)	4 (0.9)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
azathioprine													
prepregnancy	40 (0.7)	20 (1.6)	10 (1.4)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	3 (0.4)	8 (1.8)	2 (2.4)	0 (0.0)	1 (0.6)	2 (1.4)
prenatal	72 (1.2)	38 (2.9)	14 (1.9)	0 (0.0)	0 (0.0)	1 (0.1)	1 (1.9)	6 (0.9)	19 (4.3)	2 (2.4)	0 (0.0)	3 (1.7)	2 (1.4)
first trimester	50 (0.9)	27 (2.1)	12 (1.6)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	4 (0.6)	10 (2.3)	2 (2.4)	0 (0.0)	2 (1.1)	2 (1.4)
second trimester	40 (0.7)	23 (1.8)	6 (0.8)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	4 (0.6)	11 (2.5)	1 (1.2)	0 (0.0)	2 (1.1)	2 (1.4)
third trimester	49 (0.8)	26 (2.0)	7 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	6 (0.9)	16 (3.6)	1 (1.2)	0 (0.0)	2 (1.1)	2 (1.4)
mercaptopurine													
prepregnancy	2 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	7 (0.1)	7 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	3 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	4 (0.1)	4 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	5 (0.1)	5 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

mitoxantrone													
prepregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
mycophenolate													
prepregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
calcineurin inhibitor													
prepregnancy	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	4 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.7)
first trimester	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	1 (1.2)	0 (0.0)	0 (0.0)	1 (0.7)
TNF-α inhibitor													
prepregnancy	121 (2.1)	38 (2.9)	61 (8.3)	0 (0.0)	19 (9.2)	22 (1.2)	0 (0.0)	16 (2.4)	3 (0.7)	1 (1.2)	1 (1.8)	0 (0.0)	0 (0.0)
prenatal	163 (2.8)	52 (4.0)	82 (11.2)	0 (0.0)	21 (10.1)	23 (1.2)	0 (0.0)	26 (3.9)	5 (1.1)	1 (1.2)	1 (1.8)	0 (0.0)	1 (0.7)
first trimester	138 (2.4)	45 (3.5)	68 (9.3)	0 (0.0)	20 (9.7)	23 (1.2)	0 (0.0)	20 (3.0)	3 (0.7)	1 (1.2)	1 (1.8)	0 (0.0)	0 (0.0)

second trimester	121 (2.1)	41 (3.2)	57 (7.8)	0 (0.0)	16 (7.7)	20 (1.1)	0 (0.0)	20 (3.0)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
third trimester	117 (2.0)	44 (3.4)	53 (7.2)	0 (0.0)	13 (6.3)	18 (1.0)	0 (0.0)	20 (3.0)	4 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
fumarates													
prepregnancy	9 (0.2)	0 (0.0)	0 (0.0)	9 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	11 (0.2)	0 (0.0)	0 (0.0)	11 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	9 (0.2)	0 (0.0)	0 (0.0)	9 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	5 (0.1)	0 (0.0)	0 (0.0)	5 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	5 (0.1)	0 (0.0)	0 (0.0)	5 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
interferons													
prepregnancy	9 (0.2)	0 (0.0)	0 (0.0)	9 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	10 (0.2)	0 (0.0)	0 (0.0)	10 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	10 (0.2)	0 (0.0)	0 (0.0)	10 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	7 (0.1)	0 (0.0)	0 (0.0)	7 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	5 (0.1)	0 (0.0)	0 (0.0)	5 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
alkylating agent													
prepregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
hydroxyurea													
prepregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

prenatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
dapsone													
prepregnancy	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
cladribine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prepregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IL1 inhibitor													
prepregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

IL6 inhibitor													
prepregnancy	2 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	3 (0.1)	0 (0.0)	2 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	3 (0.1)	0 (0.0)	2 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IL12/IL23 inhibitor													
prepregnancy	11 (0.2)	8 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)	3 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	14 (0.2)	10 (0.8)	0 (0.0)	0 (0.0)	1 (0.5)	4 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	12 (0.2)	8 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)	4 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	12 (0.2)	10 (0.8)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	12 (0.2)	10 (0.8)	0 (0.0)	0 (0.0)	1 (0.5)	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IL17 inhibitor													
prepregnancy	8 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (1.0)	6 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	8 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (1.0)	6 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	8 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (1.0)	6 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	5 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.5)	3 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	2 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.5)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IL23 inhibitor													
prepregnancy	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

second trimester	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
abatacept													
prepregnancy	8 (0.1)	0 (0.0)	8 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	9 (0.2)	0 (0.0)	9 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	9 (0.2)	0 (0.0)	9 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	4 (0.1)	0 (0.0)	4 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	2 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
anti-BLyS													
prepregnancy	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
prenatal	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)
first trimester	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)
second trimester	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
S1P receptor modulator													
prepregnancy	7 (0.1)	0 (0.0)	0 (0.0)	7 (1.4)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	7 (0.1)	0 (0.0)	0 (0.0)	7 (1.4)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	7 (0.1)	0 (0.0)	0 (0.0)	7 (1.4)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	5 (0.1)	0 (0.0)	0 (0.0)	5 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	3 (0.1)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
JAK inhibitor													
prepregnancy	5 (0.1)	1 (0.1)	5 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

prenatal	6 (0.1)	1 (0.1)	6 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	6 (0.1)	1 (0.1)	6 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	6 (0.1)	1 (0.1)	6 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	3 (0.1)	1 (0.1)	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
integrin modulator													
prepregnancy	3 (0.1)	2 (0.2)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	3 (0.1)	2 (0.2)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	3 (0.1)	2 (0.2)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	3 (0.1)	2 (0.2)	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	2 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PDE4 inhibitor targeted synthetic													
prepregnancy	3 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	2 (1.0)	3 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
prenatal	3 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	2 (1.0)	3 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
first trimester	3 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	2 (1.0)	3 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
second trimester	3 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	2 (1.0)	3 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
third trimester	2 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (1.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
anti-cd20													
prepregnancy	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	2 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

third trimester	2 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
anti-cd52													
prepregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
budesonide													
prepregnancy	10 (0.2)	10 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
prenatal	22 (0.4)	22 (1.7)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
first trimester	14 (0.2)	14 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
second trimester	14 (0.2)	14 (1.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
third trimester	15 (0.3)	15 (1.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
steroids													
prepregnancy	108 (1.9)	37 (2.9)	27 (3.7)	2 (0.4)	4 (1.9)	13 (0.7)	1 (1.9)	10 (1.5)	22 (5.0)	2 (2.4)	3 (5.3)	5 (2.8)	3 (2.0)
prenatal	479 (8.3)	154 (11.9)	108 (14.8)	28 (5.5)	18 (8.7)	79 (4.2)	2 (3.7)	38 (5.6)	73 (16.6)	13 (15.5)	9 (15.8)	18 (10.0)	13 (8.8)
first trimester	208 (3.6)	77 (6.0)	51 (7.0)	11 (2.2)	8 (3.9)	24 (1.3)	1 (1.9)	20 (3.0)	29 (6.6)	4 (4.8)	3 (5.3)	9 (5.0)	4 (2.7)
second trimester	205 (3.5)	67 (5.2)	48 (6.6)	8 (1.6)	7 (3.4)	31 (1.7)	1 (1.9)	18 (2.7)	32 (7.3)	7 (8.3)	4 (7.0)	6 (3.3)	5 (3.4)
third trimester	304 (5.3)	99 (7.7)	68 (9.3)	15 (3.0)	12 (5.8)	52 (2.8)	2 (3.7)	23 (3.4)	45 (10.3)	9 (10.7)	7 (12.3)	10 (5.6)	8 (5.4)

GA Gestational Age; LMP Last Menstrual Period; IMMs Immunomodulatory Medication;
RxNorm codes of IMMs are listed in Table A.6 3. Prepregnancy exposure indicates exposure status during 180 days prepregnancy period (LMP-180days~LMP). Prenatal exposure indicates exposure status from LMP to

delivery. First trimester exposure indicates exposure status from LMP to end of first trimester (LMP≤exposure<GA 13 weeks). Second trimester exposure indicates exposure status from end of first trimester to end of second trimester (GA 13 weeks≤exposure<GA 28 weeks). Third trimester exposure indicates exposure status from end of second trimester to delivery date (GA 28 weeks≤exposure<date of delivery)

Table A.6 7 Standardized mean differences after propensity score matching for individual IMIDs group[14]

variable	**IMIDs**	**IBD**	**RA**	**MS**	**PsA**	**Ps**	**SSc**	**SpA**	**SLE**	**Va**	**Sc**	**APS**	**SjS**
Pregravid BMI	0.05	0.05	-0.02	0.03	0.09	0.01	0.19	-0.02	0.04	-0.03	0.02	0.16	-0.04
Maternal age	0.02	0.02	-0.04	-0.08	0.00	-0.04	0.02	-0.06	-0.04	0.07	0.00	0.05	-0.02
Ethnic group	0.04	0.04	0.03	0.06	-0.14	0.02	-0.04	0.01	-0.02	0.00	0.00	-0.06	0.13
Fetal sex	-0.00	-0.00	-0.01	0.01	0.04	0.03	-0.13	-0.05	-0.05	0.02	0.03	-0.16	-0.04
Parity	-0.02	-0.02	-0.04	-0.01	0.06	-0.04	-0.16	-0.03	0.03	0.03	-0.07	-0.05	0.17
Gravidity	0.00	0.00	-0.03	-0.01	0.03	-0.02	-0.03	0.07	-0.04	-0.09	-0.03	0.04	0.05
Preterm history	0.01	0.01	0.01	-0.03	-0.03	0.04	-0.11	0.04	0.00	0.07	-0.22	0.06	-0.06
Illegal drug user	0.02	0.02	0.08	-0.02	0.02	0.01	-0.16	-0.01	0.04	0.00	-0.11	-0.08	-0.03
smoker	-0.02	-0.02	0.05	0.02	0.12	0.01	-0.12	0.01	0.09	-0.04	0.00	0.04	-0.03
Vulnerability index of socioeconomic status	0.00	0.00	0.06	-0.00	0.08	0.04	-0.16	0.07	0.02	0.01	0.05	-0.14	-0.08
Vulnerability index of housing composition	-0.01	-0.01	0.02	-0.02	0.12	-0.01	0.00	0.05	0.01	-0.07	0.00	0.04	0.12
Vulnerability index of minority status and language	0.02	0.02	0.04	-0.02	0.09	0.03	-0.13	0.05	0.03	0.07	0.13	-0.06	-0.12
Vulnerability index of housing type and transportation	0.02	0.02	0.01	-0.08	0.15	0.02	-0.18	0.06	0.03	0.11	0.04	-0.17	-0.16
Rural/urban classification	0.04	0.04	-0.08	-0.04	-0.06	-0.05	0.13	-0.03	-0.08	-0.15	-0.02	-0.06	-0.01
Diabetes	0.04	0.04	0.05	-0.02	-0.08	0.00	NaN	-0.04	0.00	-0.09	-0.11	0.11	0.12
Chronic kidney disease	0.02	0.02	0.05	NaN	NaN	0.03	NaN	NaN	0.05	0.00	NaN	0.06	0.00
Obesity	0.03	0.03	0.06	0.02	0.06	0.09	NaN	-0.05	0.02	0.05	0.18	0.11	0.08
Chronic liver disease	0.01	0.01	-0.03	-0.06	NaN	-0.05	0.00	-0.02	0.07	-0.09	NaN	NaN	0.00
Asthma	0.01	0.01	0.03	-0.04	0.01	0.03	-0.12	0.03	0.01	0.11	-0.15	0.08	0.09
Depression	0.04	0.04	0.02	0.06	-0.04	0.01	-0.24	0.07	-0.06	-0.09	0.00	-0.01	-0.12

Pneumonia	0.04	0.04	0.03	0.00	0.03	0.05	NaN	0.05	0.00	-0.05	0.00	0.07	-0.12
Urinary tract infection	0.02	0.02	0.01	0.04	-0.04	-0.03	0.17	0.00	0.02	0.13	-0.08	0.11	0.08
Sexually transmitted disease	-0.00	-0.00	-0.09	-0.06	0.06	0.01	0.09	0.04	-0.01	0.07	-0.11	0.00	0.10
Cardiovascular disease	0.02	0.02	-0.00	0.05	-0.05	0.01	-0.15	0.01	0.00	0.00	0.07	-0.04	-0.04
Sepsis	0.03	0.03	0.00	-0.02	0.04	-0.03	0.27	0.03	-0.01	-0.07	NaN	NaN	NaN
Year_2013	-0.01	-0.01	-0.05	-0.02	-0.03	0.00	0.19	0.05	0.06	0.15	-0.18	0.00	-0.04
Year_2014	0.03	0.03	0.01	0.05	-0.08	-0.03	0.20	0.03	0.03	0.00	0.00	0.09	0.10
Year_2015	-0.01	-0.01	-0.03	0.02	0.00	0.01	-0.07	0.05	-0.01	-0.05	0.16	0.05	0.03
Year_2016	-0.02	-0.02	-0.06	0.00	-0.11	0.02	0.07	0.04	-0.01	0.06	-0.13	0.00	-0.03
Year_2017	-0.06	-0.06	0.08	-0.10	0.00	-0.02	-0.07	-0.04	0.03	0.26	0.16	0.02	-0.04
Year_2018	0.02	0.02	0.00	-0.03	-0.04	0.03	-0.06	-0.06	0.00	-0.10	-0.15	0.02	-0.14
Year_2019	-0.01	-0.01	0.04	0.05	-0.12	-0.03	0.12	-0.04	0.02	0.00	0.18	-0.09	0.08
Year_2020	0.00	0.00	-0.01	0.05	0.14	0.00	-0.09	0.03	-0.01	0.03	0.06	0.07	0.04
Year_2021	0.01	0.01	0.02	0.00	0.05	-0.03	-0.05	0.01	0.01	0.04	0.16	-0.07	-0.04
Year_2022	0.04	0.04	-0.01	-0.01	0.12	0.05	0.00	0.00	-0.08	-0.17	-0.11	0.00	0.08
Race_white	-0.09	-0.09	-0.01	-0.02	-0.10	-0.05	-0.21	-0.01	-0.08	0.03	0.11	-0.06	-0.01
Race_asian	0.04	0.04	-0.01	0.00	0.11	-0.02	-0.09	-0.01	0.02	-0.07	0.00	0.05	-0.13
Race_black	0.05	0.05	0.04	0.00	0.06	0.05	NaN	0.02	0.08	0.13	-0.08	-0.07	-0.11
Race_other	0.03	0.03	0.03	0.02	0.02	0.04	0.16	0.03	0.01	-0.13	-0.09	0.08	0.19
Commercial insurance	-0.01	-0.01	-0.04	-0.07	0.02	-0.04	-0.07	-0.01	0.01	-0.02	0.03	0.00	-0.07

APS Antiphospholipid Syndrome; IBD Inflammatory Bowel Disease; IMID Immune-mediated Inflammatory Disease; MS Multiple Sclerosis; Ps Psoriasis; PsA Psoriatic Arthritis; Sc Sarcoidosis; SLE Systemic Lupus Erythematosus; SpA Spondyloarthritis; SjS Sjörgen’s Syndrome; SSc Systemic Sclerosis; Va Vasculitis; IMM Immunomodulatory Medication; LMP Last Menstrual Period; GA Gestational Age

The standardized mean difference below 0.2 is considered a small effect size. [341]

Table A.6 8 Standardized mean difference after propensity score matching for individual IMIDs group in the sensitivity analysis[14]

variable	IMIDs	IBD	RA	MS	PsA	Ps	SSc	SpA	SLE	Va	Sc	APS	SjS
Pregravid BMI	0.03	-0.01	0.03	0.03	0.11	0.03	-0.15	0.06	-0.02	-0.13	-0.06	-0.09	0.06
Maternal age	-0.02	0.01	-0.04	-0.08	-0.11	0.00	-0.07	-0.00	0.03	-0.07	0.23	-0.14	-0.03
Ethnic group	-0.01	0.04	0.01	-0.02	-0.07	0.00	0.04	-0.02	0.01	-0.03	0.11	0.01	-0.05
Fetal sex	0.00	0.01	0.00	0.07	0.00	-0.01	0.00	0.03	-0.08	0.02	0.11	0.00	0.00
Parity	0.01	-0.04	-0.01	0.00	-0.04	0.06	-0.14	0.09	-0.07	0.16	0.03	0.00	0.03
Gravidity	0.03	0.01	0.03	0.03	-0.08	0.08	0.03	0.09	-0.05	0.02	0.11	0.07	0.05
Preterm history	0.00	0.03	-0.01	0.06	0.10	0.01	-0.11	0.04	-0.05	0.00	0.11	0.00	-0.06
Illegal drug user	0.05	0.03	0.03	0.03	0.05	0.05	0.27	0.04	-0.01	0.03	0.12	-0.08	0.11
Smoker	0.03	0.02	0.00	0.14	0.12	0.04	0.00	0.03	-0.04	-0.10	0.00	-0.09	0.03
Vulnerability index of socioeconomic status	0.03	-0.00	0.02	-0.00	0.24	0.06	-0.17	0.04	0.01	0.08	0.12	0.02	0.07
Vulnerability index of housing composition	0.05	0.01	0.02	0.05	0.18	0.02	0.05	0.01	-0.05	0.13	0.06	-0.09	0.13
Vulnerability index of minority status and language	0.01	0.01	0.01	-0.07	0.07	0.02	-0.06	0.05	-0.03	-0.12	0.10	-0.02	0.12
Vulnerability index of housing type and transportation	0.01	-0.03	0.02	-0.00	0.09	0.04	-0.06	0.01	-0.02	0.16	-0.02	0.03	0.12
Rural/urban classification	-0.06	-0.01	-0.01	0.09	-0.06	-0.05	-0.07	-0.03	-0.09	-0.11	-0.17	-0.13	-0.07
Year_2013	-0.00	-0.02	-0.01	-0.02	-0.05	0.00	0.19	-0.01	0.06	0.00	-0.06	0.06	-0.07
Year_2014	-0.01	-0.01	-0.03	0.00	0.02	-0.02	-0.07	-0.03	0.02	0.05	-0.06	0.00	0.10
Year_2015	0.00	-0.04	0.02	-0.01	0.07	-0.02	0.20	-0.02	0.02	0.00	0.00	-0.02	0.08
Year_2016	-0.01	0.03	0.04	-0.01	-0.07	0.00	-0.13	0.04	0.02	-0.18	0.00	-0.17	-0.03
Year_2017	-0.02	-0.03	0.04	0.08	-0.08	0.01	0.00	0.00	-0.09	0.04	0.39	-0.04	-0.08
Year_2018	0.00	0.03	-0.00	-0.01	-0.08	0.03	0.22	0.01	0.02	-0.07	-0.05	0.00	0.02
Year_2019	0.00	0.02	0.00	-0.04	-0.06	-0.03	0.00	0.01	-0.01	0.00	-0.10	-0.03	-0.07

Year_2020	-0.00	-0.03	-0.05	-0.01	0.05	-0.01	-0.18	0.10	-0.02	0.10	-0.05	-0.05	-0.02
Year_2021	0.01	-0.02	-0.01	-0.01	0.19	-0.01	0.10	-0.04	0.08	0.00	0.07	0.20	0.02
Year_2022	0.02	0.04	0.01	0.03	0.01	0.04	-0.05	-0.05	-0.05	0.03	0.06	0.06	0.06
Race_white	-0.02	-0.02	0.01	0.03	0.00	-0.06	0.12	-0.08	0.07	-0.09	-0.15	-0.05	-0.03
Race_asian	0.01	-0.01	-0.05	-0.04	0.04	0.01	-0.16	0.01	-0.05	-0.07	0.00	0.02	0.04
Race_black	-0.01	0.00	-0.01	0.04	-0.08	-0.01	NaN	0.02	-0.09	0.13	-0.16	0.00	0.04
Race_other	-0.01	0.03	-0.04	0.02	-0.09	0.03	-0.05	0.02	0.03	0.05	0.10	0.06	-0.04
Commercial insurance	-0.05	-0.01	-0.03	-0.04	-0.10	-0.06	-0.23	-0.03	0.08	-0.14	0.14	-0.08	-0.03

The standardized mean difference below 0.2 is considered a small effect size[341]

Table A.6 9 Risk of adverse pregnancy outcomes of IMIDs group and individual IMID group[14]

		unadjusted		**PS matched**		**SA PS matched (without comorbidities)**	
	outcome	**RR**	**P value**	**RR**	**P value**	**RR**	**P value**
	PTB	1.2[1.1,1.3]	6.8E-06	1.1[1.0,1.3]	7.7E-02	1.3[1.1,1.4]	3.3E-04
	LBW	1.1[1.0,1.2]	3.3E-06	1.1[1.0,1.2]	1.5E-02	1.2[1.1,1.3]	4.0E-06
	SGA	1.3[1.2,1.4]	1.3E-03	1.2[1.0,1.4]	3.4E-02	1.4[1.2,1.6]	1.2E-04
	Csec	1.2[1.1,1.2]	1.8E-13	1.1[1.1,1.2]	5.7E-07	1.1[1.1,1.2]	1.2E-05
IMIDs	ND	1.5[0.8,3.1]	2.6E-01	1.1[0.4,3.1]	1.0E+00	1.1[0.4,3.1]	1.0E+00
	PTB	1.0[0.9,1.2]	9.7E-01	1.0[0.8,1.2]	1.0E+00	1.1[0.9,1.4]	5.3E-01
	LBW	1.0[0.9,1.1]	8.0E-01	1.1[0.9,1.3]	3.9E-01	1.0[0.8,1.2]	6.1E-01
	SGA	1.0[0.8,1.2]	8.9E-01	0.9[0.7,1.1]	6.1E-01	0.9[0.7,1.2]	8.8E-01
Psoriasis	Csec	1.1[1.0,1.2]	1.2E-02	1.1[1.0,1.2]	2.3E-01	1.0[0.9,1.1]	4.4E-01
	PTB	1.3[1.1,1.5]	8.7E-03	1.1[0.9,1.5]	3.0E-01	1.3[1.0,1.7]	2.8E-02
	LBW	1.0[0.8,1.1]	3.0E-02	1.0[0.8,1.3]	8.1E-01	1.0[0.8,1.3]	6.5E-02
Inflammatory bowel diseases	SGA	1.3[1.0,1.5]	9.0E-01	1.0[0.8,1.4]	9.0E-01	1.4[1.0,1.9]	8.1E-01
	Csec	1.2[1.1,1.3]	1.7E-07	1.3[1.1,1.4]	1.6E-05	1.3[1.1,1.4]	2.3E-05
	PTB	1.2[1.0,1.5]	1.1E-01	1.2[0.8,1.6]	4.6E-01	1.4[1.0,2.0]	6.6E-02
	LBW	1.3[1.1,1.6]	2.6E-02	1.3[1.0,1.6]	6.0E-01	1.2[1.0,1.6]	6.1E-02
	SGA	1.4[1.0,1.8]	2.5E-03	1.1[0.8,1.6]	7.2E-02	1.5[1.0,2.3]	1.2E-01
Rheumatoid arthritis	Csec	1.2[1.1,1.3]	2.9E-03	1.2[1.0,1.4]	2.2E-02	1.1[1.0,1.3]	1.8E-01
	PTB	1.2[0.9,1.5]	1.5E-01	1.5[1.0,2.2]	5.2E-02	1.1[0.7,1.5]	8.5E-01
	LBW	1.0[0.8,1.2]	2.3E-01	1.0[0.8,1.4]	1.1E-01	1.1[0.8,1.4]	5.6E-01
	SGA	1.2[0.9,1.6]	9.1E-01	1.5[0.9,2.3]	1.0E+00	1.2[0.8,1.8]	7.4E-01
Spondyloarthritis	Csec	1.2[1.1,1.3]	1.4E-03	1.3[1.1,1.5]	1.3E-03	1.1[0.9,1.2]	3.9E-01
	PTB	1.4[1.1,1.8]	7.4E-03	1.1[0.8,1.6]	6.8E-01	1.2[0.8,1.7]	4.7E-01
	LBW	1.1[0.9,1.4]	1.7E-02	1.0[0.8,1.4]	5.5E-01	1.2[0.8,1.6]	1.7E-01
	SGA	1.5[1.1,2.0]	2.8E-01	1.2[0.8,1.8]	8.5E-01	1.4[0.9,2.3]	4.5E-01
Multiple sclerosis	Csec	1.0[0.9,1.2]	6.6E-01	1.1[0.9,1.3]	4.1E-01	0.9[0.8,1.1]	5.5E-01
	PTB	2.2[1.8,2.7]	2.4E-10	2.4[1.6,3.6]	9.9E-06	1.4[1.0,2.0]	4.3E-02

	LBW	1.9[1.6,2.3]	1.8E-12	1.9[1.4,2.6]	1.5E-07	1.7[1.2,2.2]	2.4E-03
Systemic lupus erythematosus	SGA	2.7[2.1,3.4]	1.5E-10	3.5[2.1,5.8]	2.7E-05	1.9[1.2,2.8]	6.6E-04
	Csec	1.4[1.2,1.5]	1.2E-06	1.3[1.1,1.5]	7.8E-03	1.2[1.0,1.4]	3.1E-02
	PTB	1.4[1.0,2.1]	6.8E-02	1.3[0.7,2.3]	5.1E-01	1.5[0.8,2.9]	2.3E-01
	LBW	0.8[0.6,1.3]	5.3E-01	1.0[0.6,1.8]	8.5E-01	0.8[0.5,1.4]	2.5E-01
	SGA	1.2[0.7,2.0]	4.6E-01	0.9[0.4,1.8]	1.0E+00	1.9[0.8,4.6]	5.4E-01
Psoriatic arthritis	Csec	1.3[1.1,1.6]	4.0E-03	1.3[1.0,1.8]	3.9E-02	1.2[0.9,1.6]	1.5E-01
	PTB	2.3[1.7,3.2]	8.1E-06	2.1[1.2,3.8]	1.2E-02	2.3[1.3,4.1]	6.8E-03
	LBW	1.2[0.9,1.8]	7.5E-04	1.1[0.7,1.9]	2.1E-01	1.7[0.9,3.0]	9.4E-03
	SGA	2.2[1.5,3.3]	2.1E-01	1.6[0.8,3.1]	7.6E-01	3.0[1.3,6.9]	1.0E-01
Antiphospholipid syndrome	Csec	1.6[1.4,1.9]	2.1E-07	1.7[1.3,2.2]	2.3E-04	1.4[1.1,1.8]	7.4E-03
	PTB	0.9[0.5,1.6]	8.8E-01	0.8[0.3,1.7]	6.6E-01	0.9[0.4,2.1]	1.0E+00
	LBW	1.6[1.1,2.2]	6.6E-02	1.6[0.9,2.9]	1.5E-01	1.4[0.8,2.4]	3.7E-01
	SGA	1.7[1.0,2.8]	1.5E-02	2.2[0.8,5.5]	1.0E-01	1.6[0.7,3.8]	2.7E-01
Sjögren's syndrome	Csec	1.3[1.1,1.6]	6.9E-03	1.5[1.1,2.1]	1.3E-02	1.3[1.0,1.8]	8.8E-02
	PTB	1.5[0.9,2.8]	1.5E-01	1.7[0.6,4.4]	4.3E-01	0.8[0.4,1.7]	6.5E-01
	LBW	1.1[0.6,1.9]	4.6E-01	1.1[0.5,2.5]	1.0E+00	1.8[0.7,4.7]	1.0E+00
	SGA	1.3[0.6,2.9]	7.4E-01	0.9[0.3,2.4]	1.0E+00	1.0[0.3,3.0]	3.1E-01
Vasculitis	Csec	0.9[0.6,1.3]	6.4E-01	0.8[0.5,1.3]	5.0E-01	1.3[0.7,2.2]	4.7E-01
	PTB	0.7[0.2,2.1]	8.0E-01	0.6[0.2,2.4]	7.2E-01	3.0[0.3,28.0]	6.2E-01
	LBW	0.4[0.1,1.3]	7.5E-02	0.5[0.1,1.9]	1.0E+00	0.4[0.1,1.6]	1.0E+00
	SGA	0.0[0.0,nan]	1.5E-01	0.0[0.0,nan]	4.9E-01	0.0[0.0,nan]	3.2E-01
Sarcoidosis	Csec	0.9[0.6,1.4]	7.7E-01	0.8[0.5,1.5]	6.9E-01	1.3[0.7,2.6]	5.1E-01
	PTB	0.2[0.0,1.7]	1.3E-01	0.2[0.0,1.7]	2.1E-01	0.2[0.0,2.2]	3.6E-01
	LBW	1.7[1.0,2.9]	1.0E+00	1.6[0.7,3.7]	6.8E-01	1.8[0.7,4.6]	1.0E+00
	SGA	0.7[0.2,2.7]	8.9E-02	0.5[0.1,2.6]	4.4E-01	1.0[0.1,6.8]	2.9E-01
Systemic sclerosis	Csec	1.2[0.8,1.7]	4.6E-01	1.0[0.6,1.7]	1.0E+00	1.0[0.6,1.7]	1.0E+00

Csec Caesarean section; IMID Immune-mediated inflammatory disease, LBW Low Birth Weight; PTB Preterm Birth; PS Propensity Score; RR Relative Risk; SA Sensitivity Analysis; SGA Small for Gestational Age;

Table A.6 10 Risk of adverse pregnancy outcomes on subpopulation of IMIDs group with IMM prescription and IMIDs group without IMM prescription[14]

	Outcome	**RR**	**Statistical significance**	**P value**
IMIDs group without IMM prescription	PTB	1.2[1.0,1.4]	*	1.0E-02
	LBW	1.2[1.1,1.3]	*	1.1E-02
	SGA	1.2[1.1,1.5]	**	4.1E-03
	Csec	1.1[1.1,1.2]	***	1.0E-04
	ND	2.7[0.7,10.0]	ns	2.3E-01
IMIDs group with IMM prescription	PTB	1.5[1.2,1.9]	**	1.9E-03
	LBW	1.4[1.2,1.8]	**	7.7E-03
	SGA	1.5[1.1,2.0]	**	1.0E-03

Csec	1.1[1.0,1.3]	+	8.2E-02
ND	nan[nan,nan]	ns	1.0E+00

Csec Caesarean section; IMID Immune-mediated Inflammatory Disease; IMM Immunomodulatory Medication; LBW Low Birth Weight; PTB Preterm Birth; PS Propensity Score; RR Relative Risk; SA Sensitivity Analysis; SGA Small for Gestational Age;

Table A.6 11 List of packages and version number[14]

Package name	Version number
imbalanced-learn	0.10.1
ipython	8.5.0
joblib	1.1.1
joblibspark	0.5.1
matplotlib	3.5.1
matplotlib-inline	0.1.2
numpy	1.21.5
pandas	1.4.2
pip	21.2.4
scikit-learn	1.0.2
scipy	1.7.3
seaborn	0.11.2
statsmodels	0.13.2

Supplementary figure

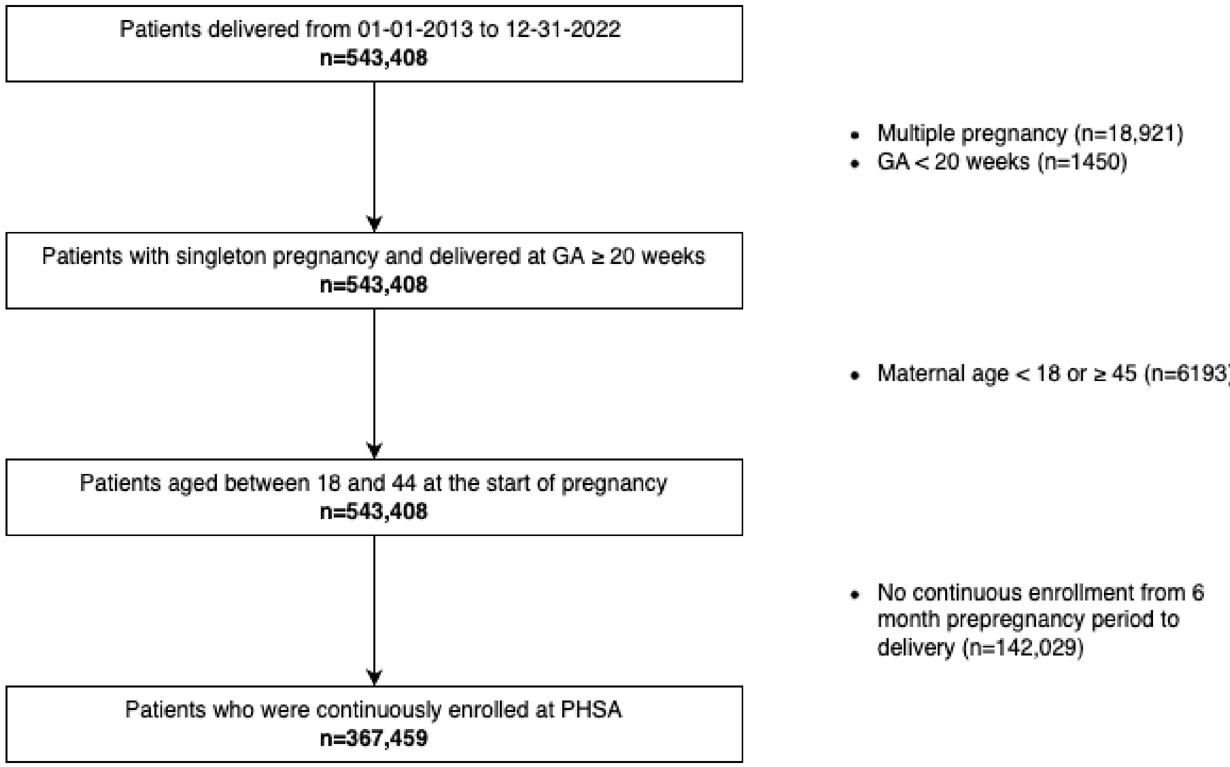


Figure A.3 1 Source population selection flow diagram

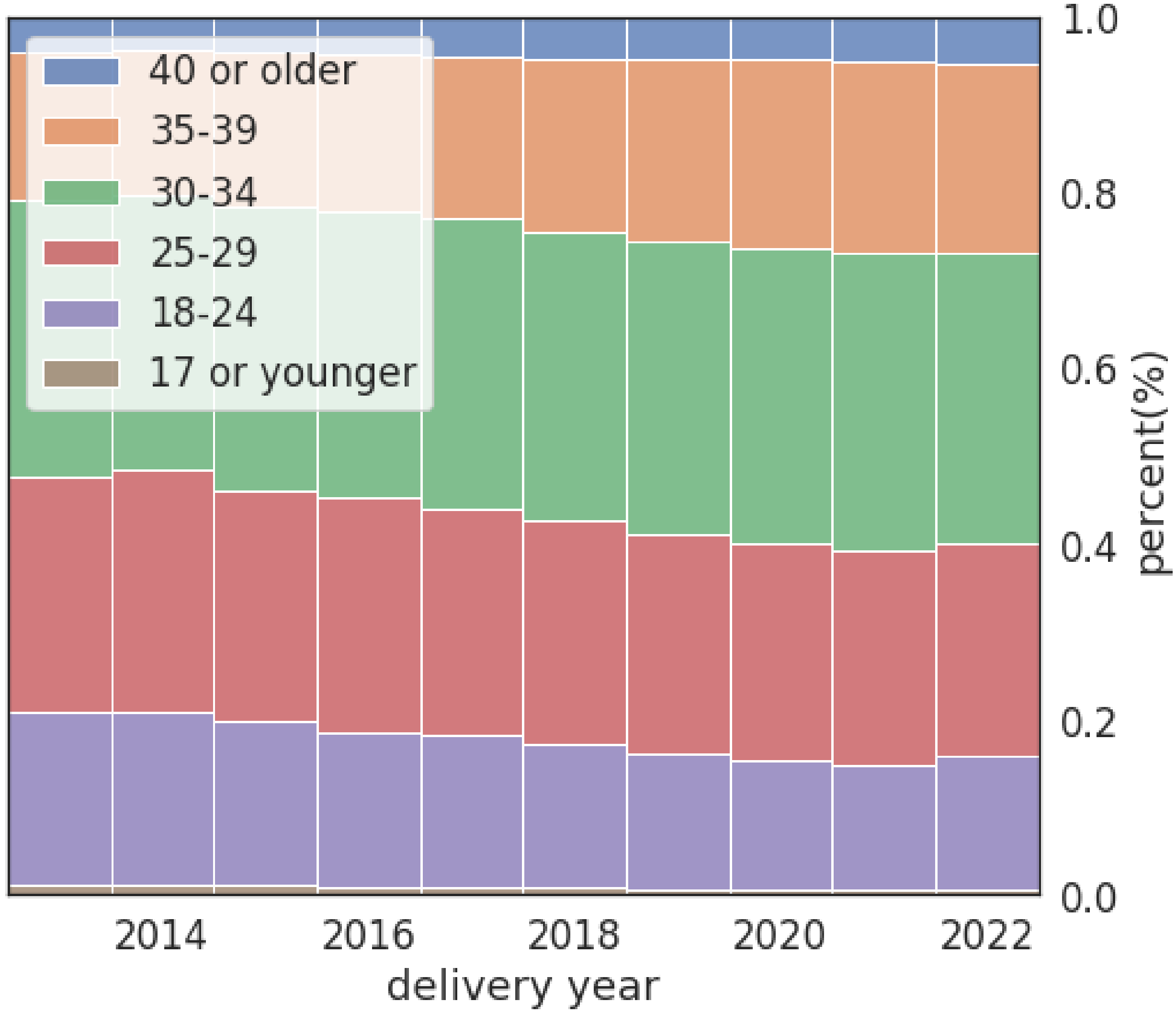


Figure A.3 2 Maternal age distribution from 2013 to 2022

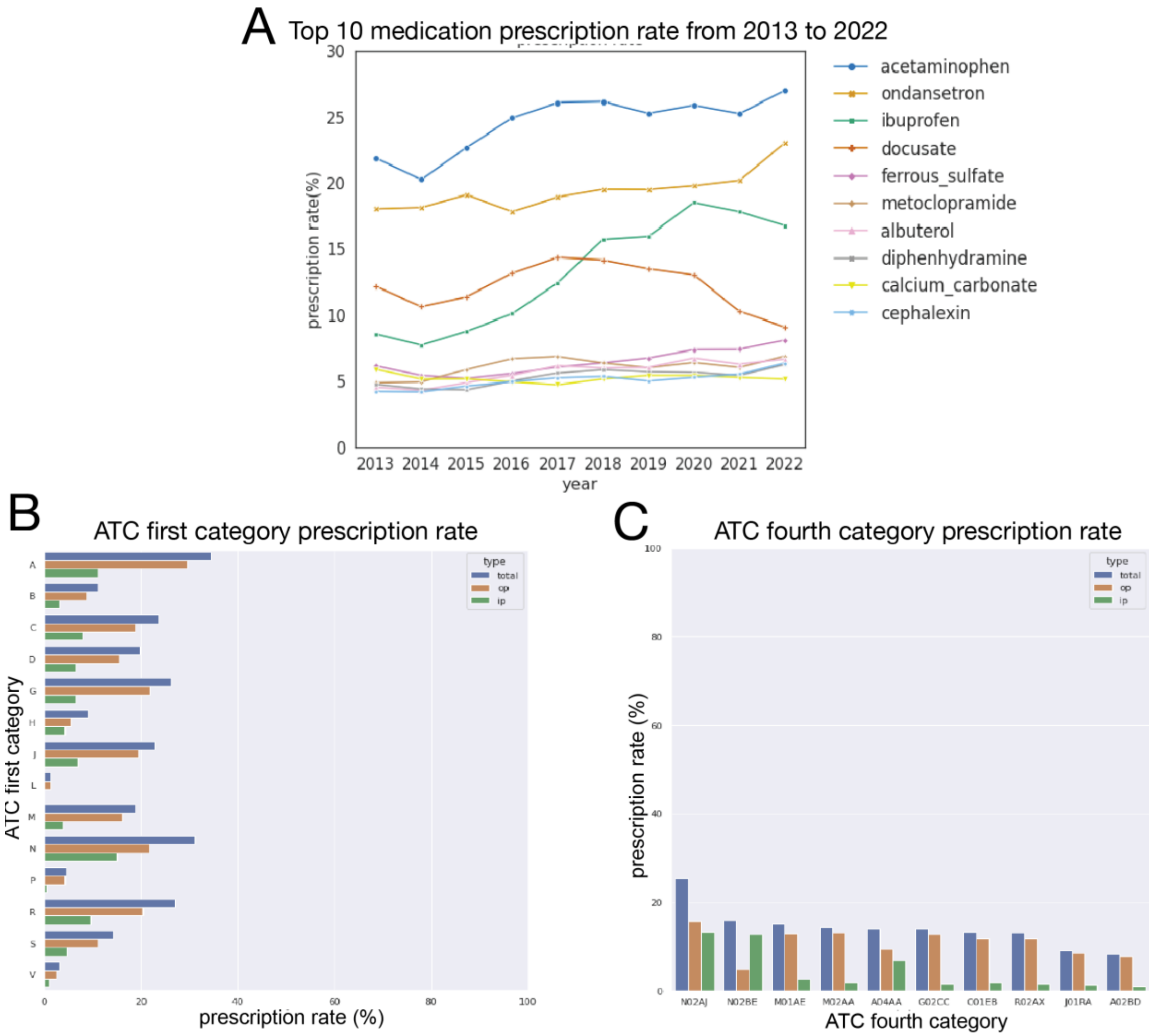


Figure A.3 3 Prescription rate of medication based on RxNorm ingredient and ATC category

A. Prescription rate of top ten commonly prescribed medications from 2013 to 2022. Top ten commonly prescribed medications were acetaminophen, ondansetron, ibuprofen, docusate, ferrous sulfate, metoclopramide, albuterol, and diphenhydramine in order.

B. Prescription rate of top ten commonly prescribed medication based on ATC first level. ATC first level has fourteen main anatomical or pharmacological groups. A: Alimnetary tract and metabolism; B: Blood and blood forming organs; C: Cardiovascular system; D: Dermatologicals; G: Genito urinary system and sex hormones; H: Systemic hormonal preparations, excluding sex hormones and insulins; J: Antiinfective for systemic use; L: Antineoplastic and immunomodulating agents; M: Musculoskeletal system; N: Nervous system; P: Antiparasitic products, insecticides and repellants; R: Respiratory system; S: Sensory organs; V: Various.[342]

C. Prescription rate of top ten commonly prescribed medication based on ATC fourth level. ATC fourth level indicates chemical subgroup. N02AJ: Opioids in combination with non-opiod analgesics; N02BE: Anilides; M01AE: Propionics acid derivative; M02AA: Antiinflammatory preparations, non-steroids for topical use; A04AA: Serotonin antagonist; G02CC: Antiinflammatory products for vaginal administration; C01EB: Other cardiac preparation; R02AX: Other throat preparation; J01RA: Combinations of antibacterials; A02BD: Combinations for eradications of helicobacter pylori

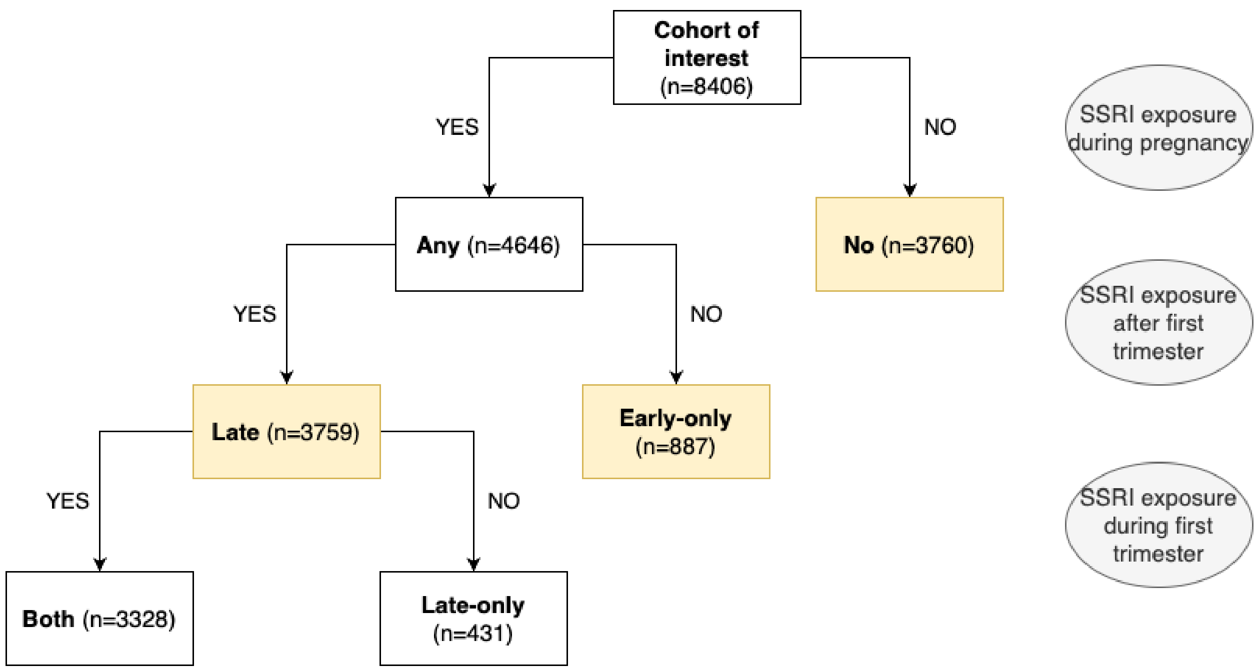


Figure A.4 1 Flow diagram of exposure group selection[12]

Abbreviation: SSRI, Selective Serotonin Reuptake Inhibitor.

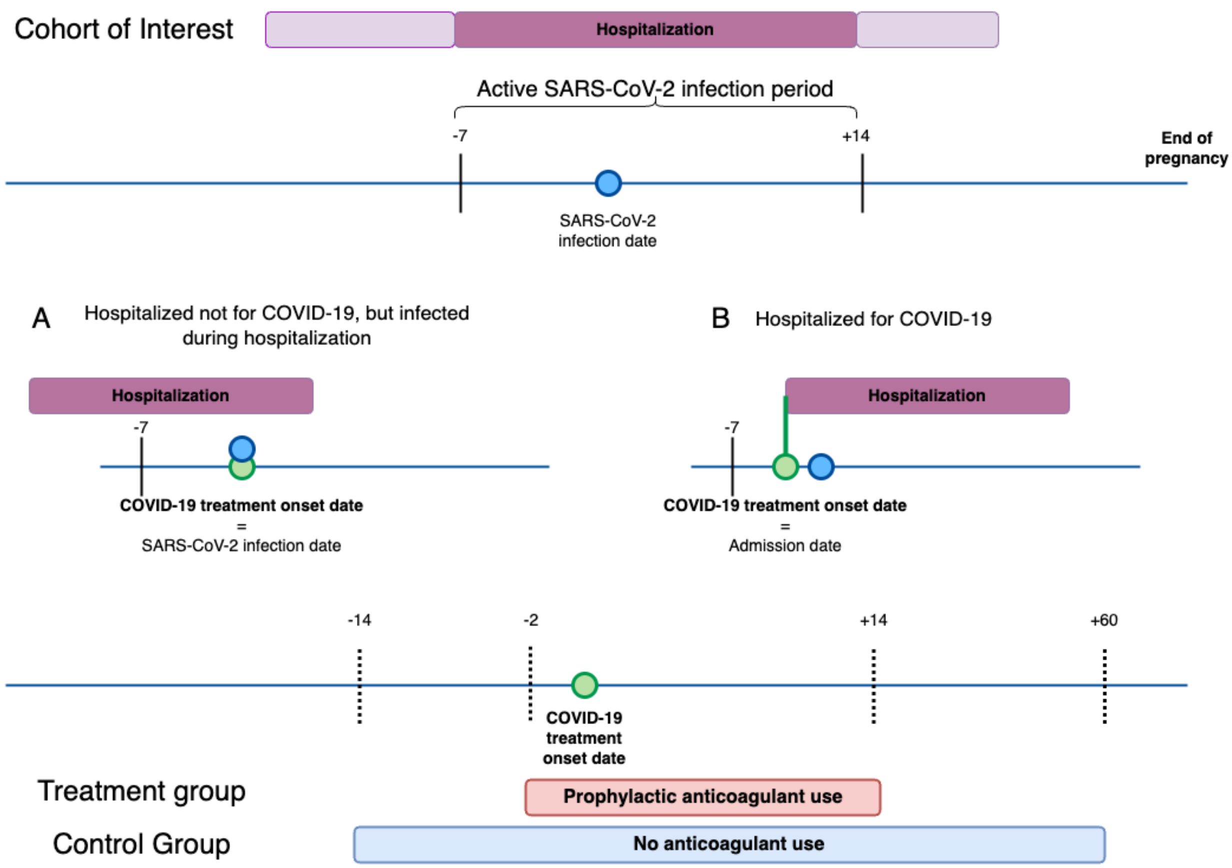


Figure A.5 1 Timeline and exposure group definition[13]

Cohort of interest was defined as pregnant patients hospitalized anytime during the active SARS-CoV-2 infection. We defined the active COVID-19 infection period as -7~+14 days from the COVID-19 infection date. This date range was determined based on the COVID-19 incubation period and symptomatic period.[343,344] SARS-CoV-2 infection date was either the date of COVID-19 diagnosis or the date of the SARS-CoV-2 NAAT positive test result, whichever preceded. We considered two possible scenarios for hospitalization: A) Hospitalized not for COVID-19, but infected during hospitalization, and B) Hospitalized for COVID-19. If patients were admitted before the start of active SARS-CoV-2 infection period, we categorized them into A scenario. If not, they were categorized into B scenario. For category A, SARS-CoV-2 infection date was considered as the COVID-19 treatment onset. For category B, admission date was considered as the COVID-19 treatment onset. We used COVID-19 treatment onset as our index date for exposure, instead of the infection date, because our exposure of interest was inpatient prophylactic anticoagulant administration relevant to COVID-19 treatment. The treatment group was defined as patients who had only prophylactic anticoagulant administration during -2~+14 days from the COVID-19 treatment onset date. The control group was defined as patients who had no anticoagulant administration during -14~+60 days from the COVID-19 treatment onset date.

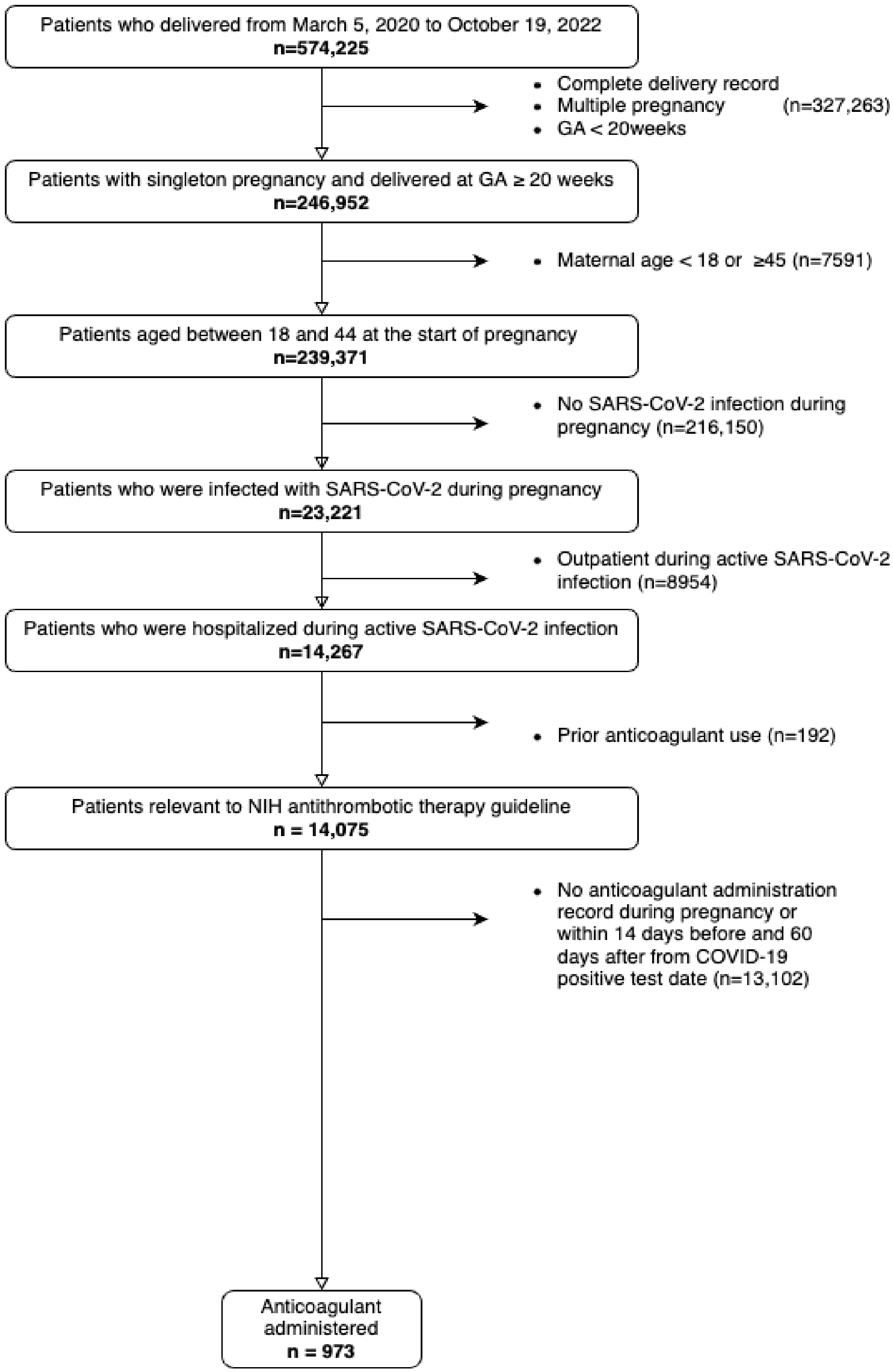
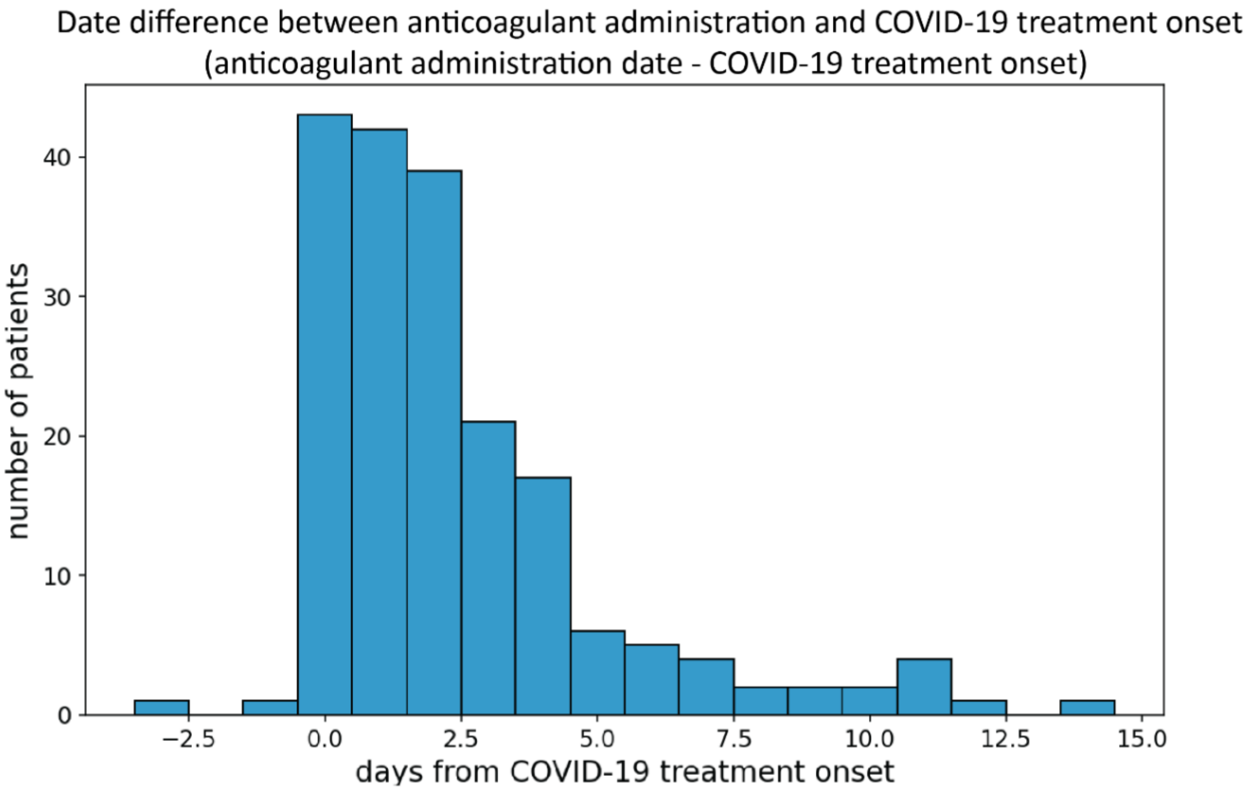


Figure A.5 2 Truveta cohort selection flow chart[13]

Variables are defined in Table A.5 1

A



B

mean	2.4
std	2.7
min	-3.0
25 percentile	1.0
50 percentile	2.0
75 percentile	3.0
max	14.0

Figure A.5 3 Distribution of the time gap (in days) between COVID-19 treatment onset and anticoagulant administration[13]

A.Histogram of the distribution of date difference between the prophylactic anticoagulant administration date and COVID-19 treatment onset (anticoagulant administration date - COVID-19 treatment onset)B.Descriptive statistics (mean, standard deviation, minimum, 25 percentile, median, 75 percentile, maximum) of the distribution of the time gap between anticoagulant administration date and

COVID-19 treatment onset. 75 percent of patients took anticoagulants within the first three days of the COVID-19 treatment onset date

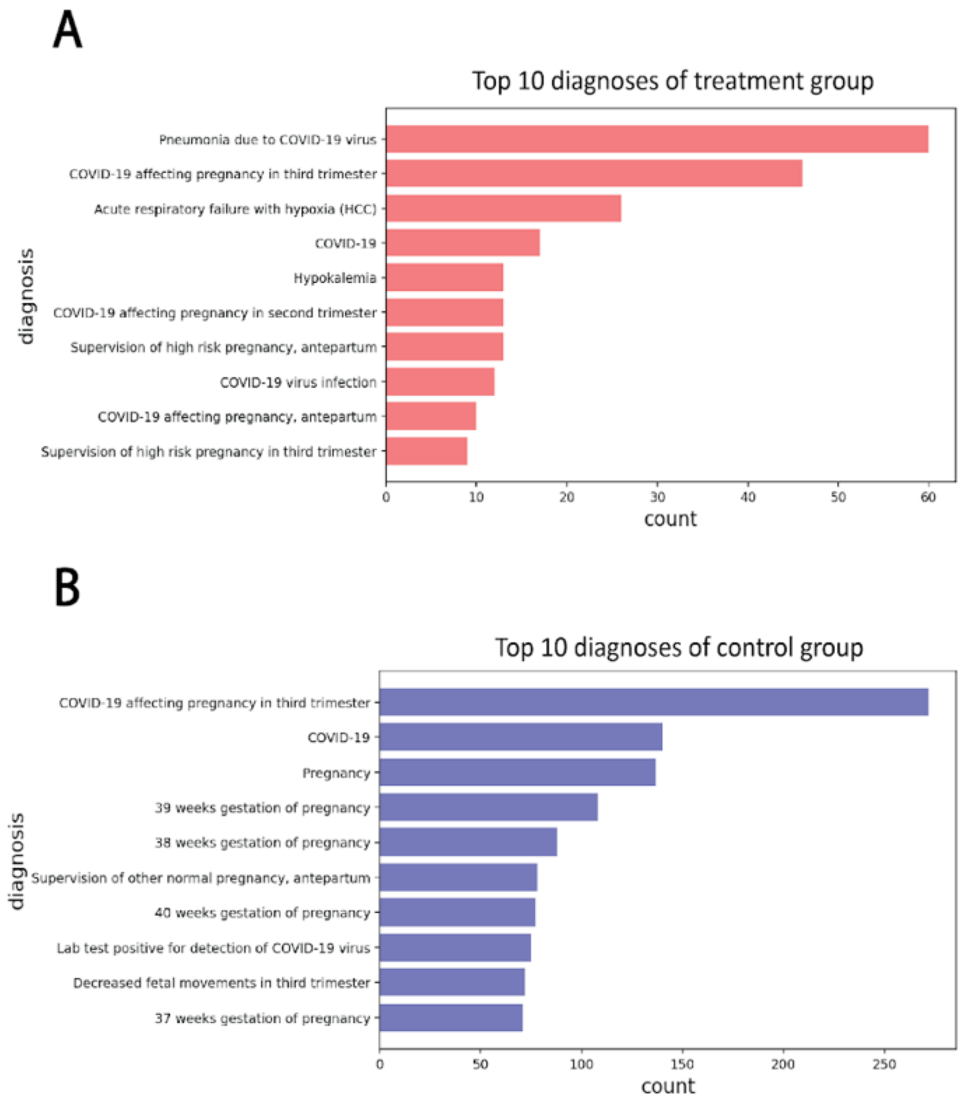


Figure A.5 4 Top 10 diagnoses of treatment and control group during the period between SARS-CoV-2 infection and delivery date[13]

(A)Top 10 diagnoses of the treatment group during SARS-CoV-2 infection and date of delivery. If the same diagnosis was given more than once to the patient during the study period, we counted it as one. (B)Top 10 diagnoses of the control group during SARS-CoV-2 infection and date of delivery. If the same diagnosis was given more than once to the patient during the study period, we counted it as one.

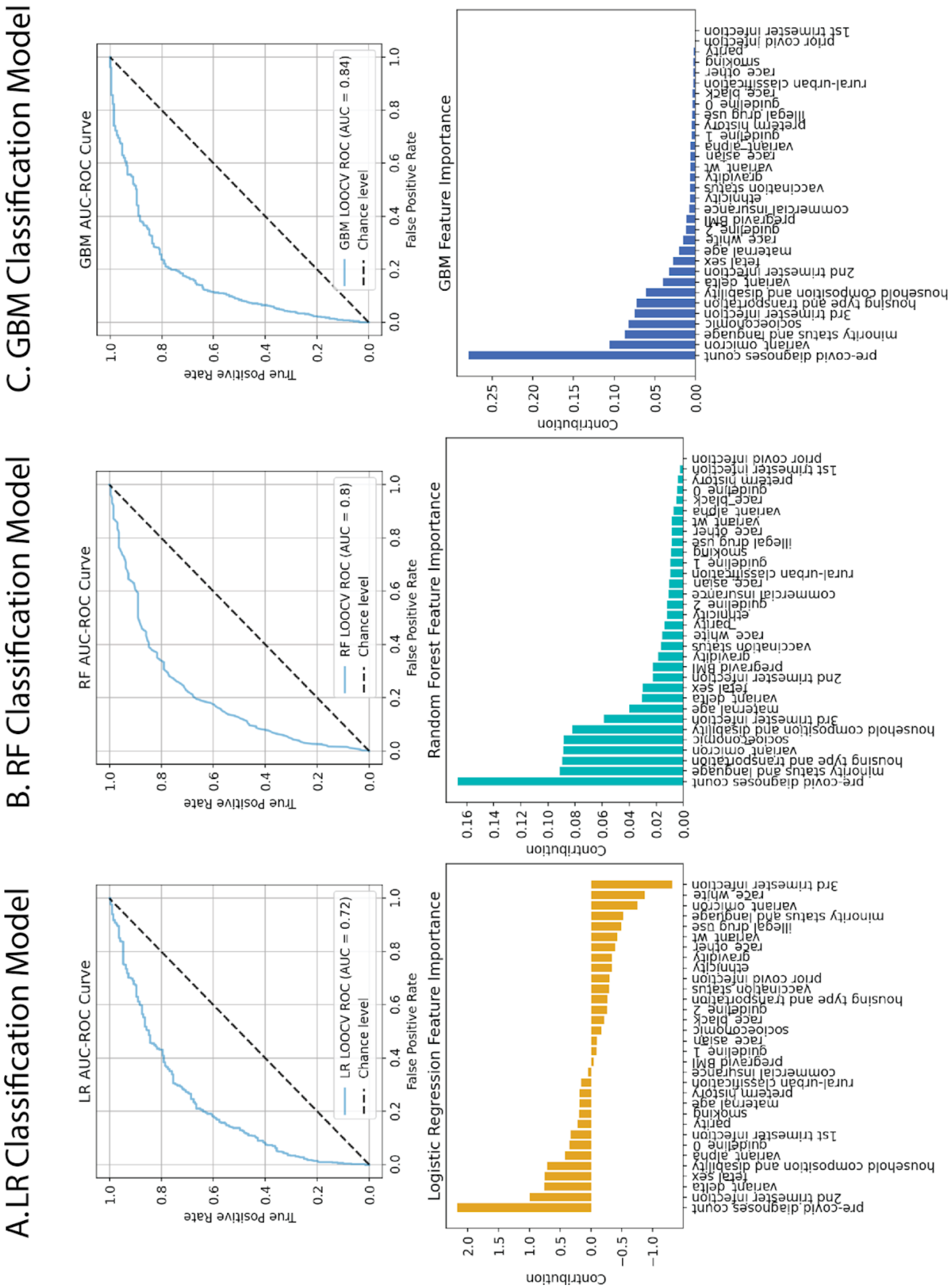


Figure A.5 5 Classification model performance[13]

AUC-ROC Area under the receiver operator characteristics curve
Each model was trained with 28 features in the feature importance plot to classify prophylactic anticoagulant administration status among our cohort of interest. Impurity-based feature importance evaluated the contribution of 28 features on demographic, comorbidity, geographical, pregnancy, maternal, clinical recommendation, and SARS-CoV-2 variant characteristics. The confidence interval of AUC-ROC was calculated using DeLong's method[345]

A. Logistic regression classification model performance based on AUC-ROC and feature importance plot. 95% confidence interval of AUC-ROC was [0.68, 0.75]

B. Random forest classification model performance based on AUC-ROC and feature importance plot. 95% confidence interval of AUC-ROC was [0.76, 0.83]

C. Gradient boosting machine classification model performance based on AUC-ROC and feature importance plot. 95% confidence interval of AUC-ROC was [0.81, 0.87]

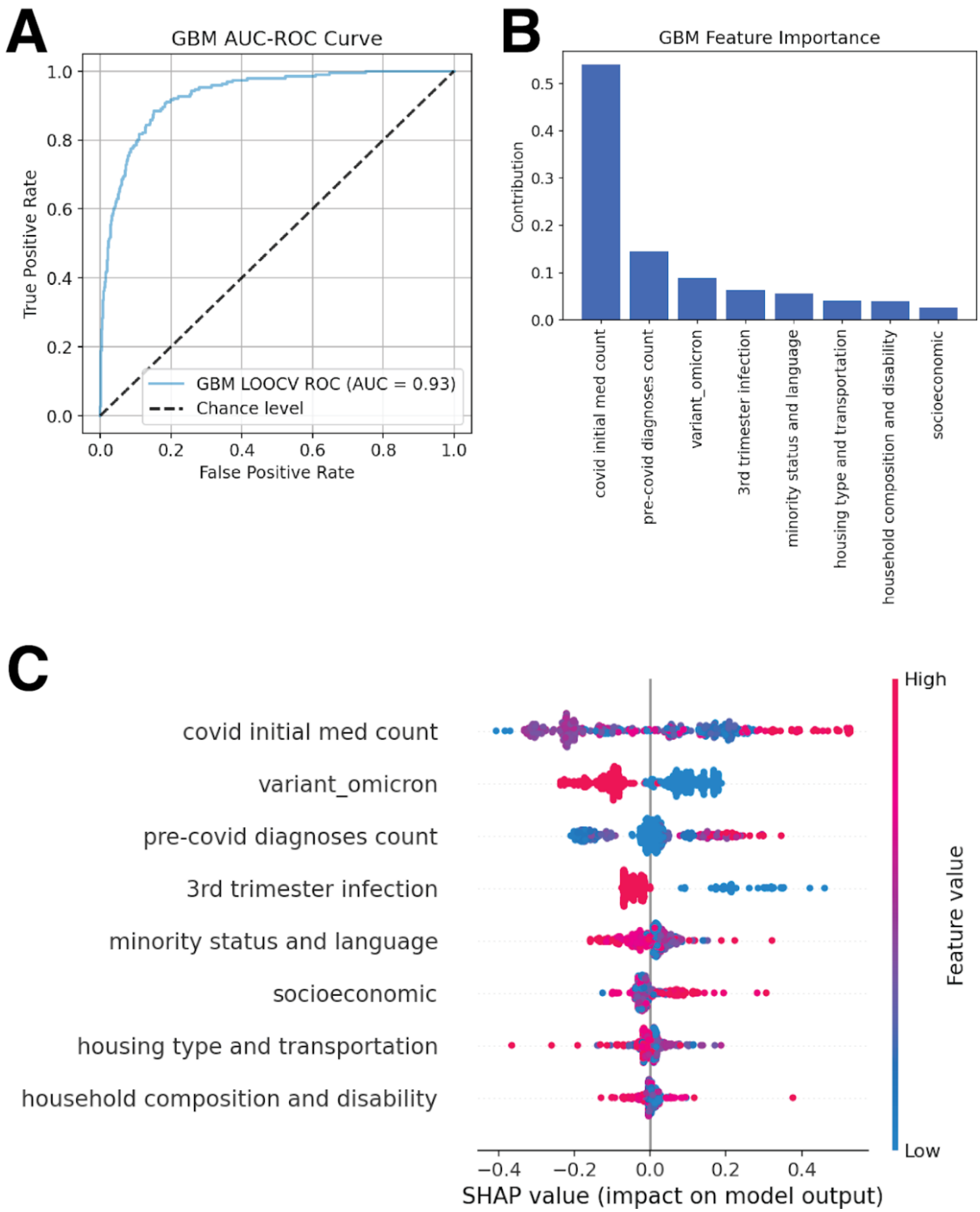


Figure A.5 6 Sensitivity analysis result of classification model performance, feature importance, and propensity score matching result[13]

We performed a sensitivity analysis to assess the impact of COVID-19 illness severity at the time of COVID-19 treatment onset. The definition of COVID-19 initial medication count is the count of unique medication ingredients -3-+3 days from the COVID-19 treatment onset. We used this variable to reflect the COVID-19 illness severity. This date range was determined based on the distribution of the time gap between COVID-19 treatment onset and anticoagulant administration date. 75 percentile patients were exposed to anticoagulants within the first three days from the COVID-19 treatment onset date. We used the model with the best performance from the main analysis, the gradient boosting machine classification model. We trained this model with the seven most important features from the main analysis and results were as follows.

A. Gradient boosting machine classification model performance based on AUC-ROC. 95% confidence interval of AUC-ROC was [0.91, 0.95].

B. Feature importance ranking of the limited model. Variables are defined in Table A.5 1. COVID-19 initial medication count contributed the most toward classifying prophylactic anticoagulant administration status.

C. Shapley permutation explainer of the feature contribution (Supplemental Method). SHAP value reflects the contribution of the seven most important features from the gradient boosting models towards classifying prophylactic anticoagulant administration status. SHAP value is the average marginal contribution of a feature value across all permutations of features. Each row represents an individual feature, and the dot represents a sample. The dot color reflects the value of the feature of the sample relative to all samples. The evaluation was done on the sample set comprised of a treatment group and a 1:1 randomly undersampled matched control group (n=382). For the row of COVID-19 initial medication count, red and blue dots were spread out across extreme negative SHAP values and up to 0.2 SHAP value, but the end of the positive SHAP axis (SHAP value > 0.2) was clustered with red dots. This describes a positive correlation between COVID-19 initial medication count and prophylactic anticoagulant administration status.

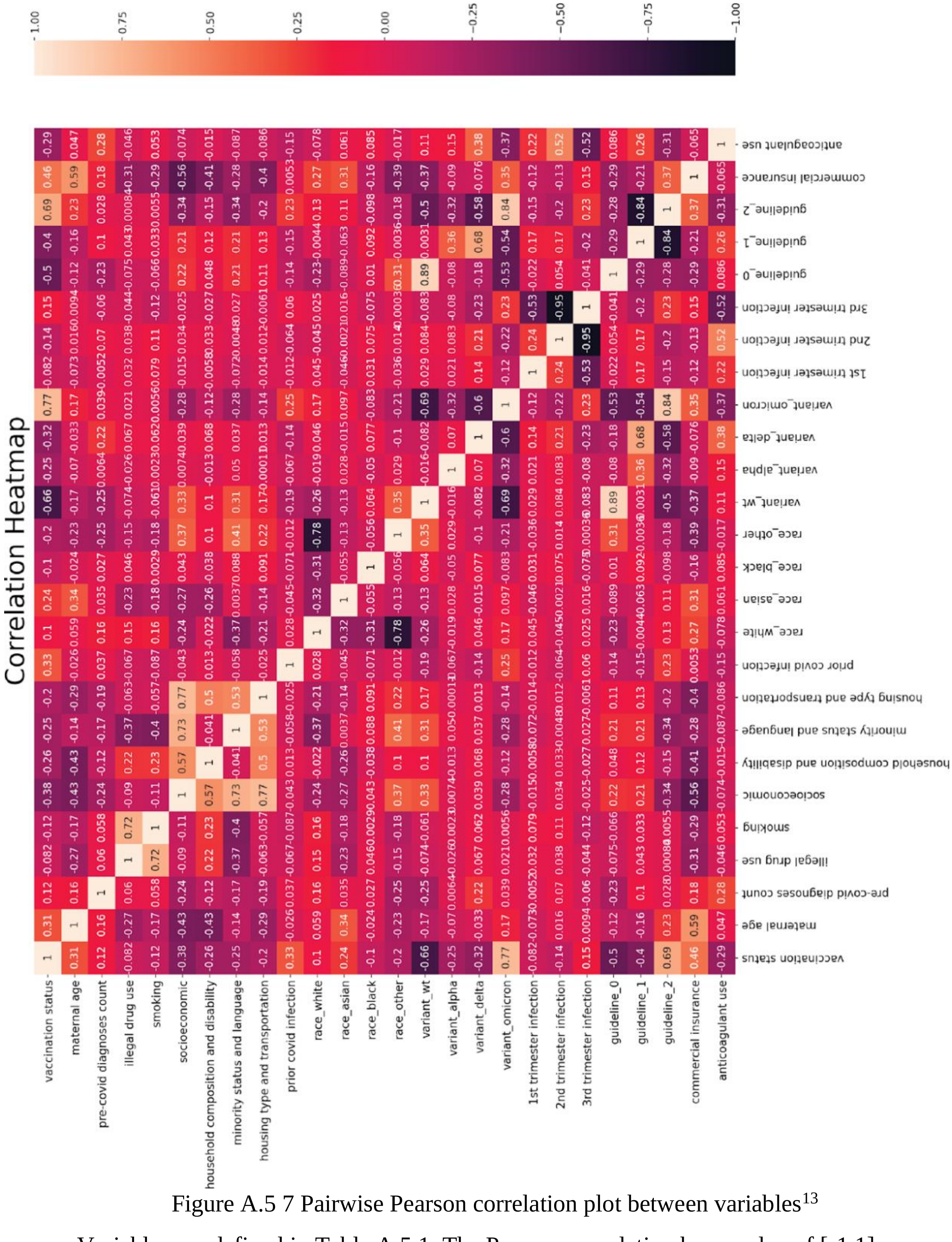


Figure A.5 7 Pairwise Pearson correlation plot between variables[13]

Variables are defined in Table A.5 1. The Pearson correlation has a value of [-1,1] and measures the strength of the linear relationship between variables. A negative value means a negative linear correlation, and a positive value means a positive one. 0 means no linear correlation

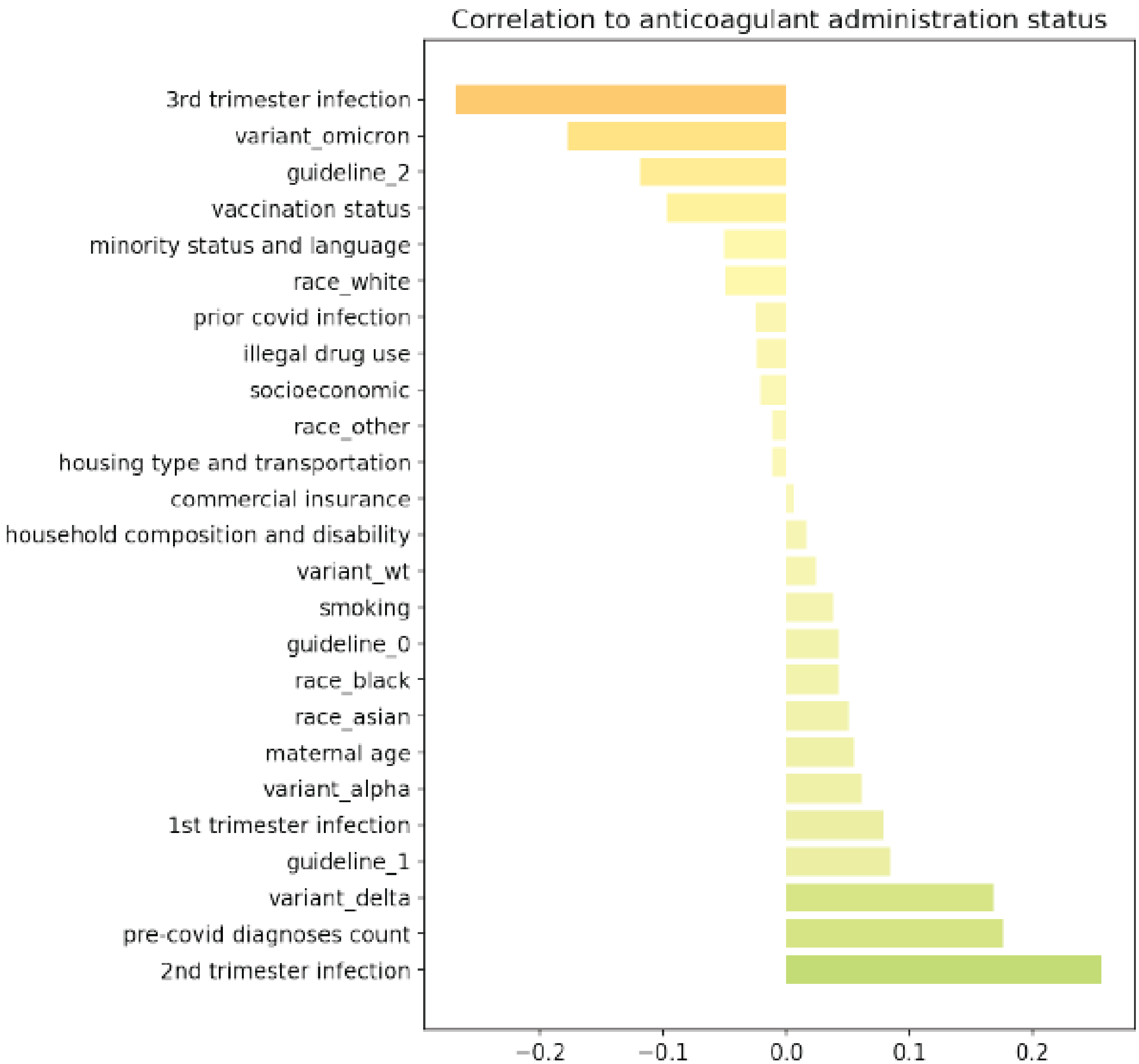


Figure A.5 8 Pearson correlation between individual variables and prophylactic anticoagulant administration status[13]

Variables are defined in Table A.5 1. The Pearson correlation has a value of [-1,1] and measures the strength of the linear relationship between variables. A negative value means a negative linear correlation, and a positive value means a positive one. 0 means no linear correlation.

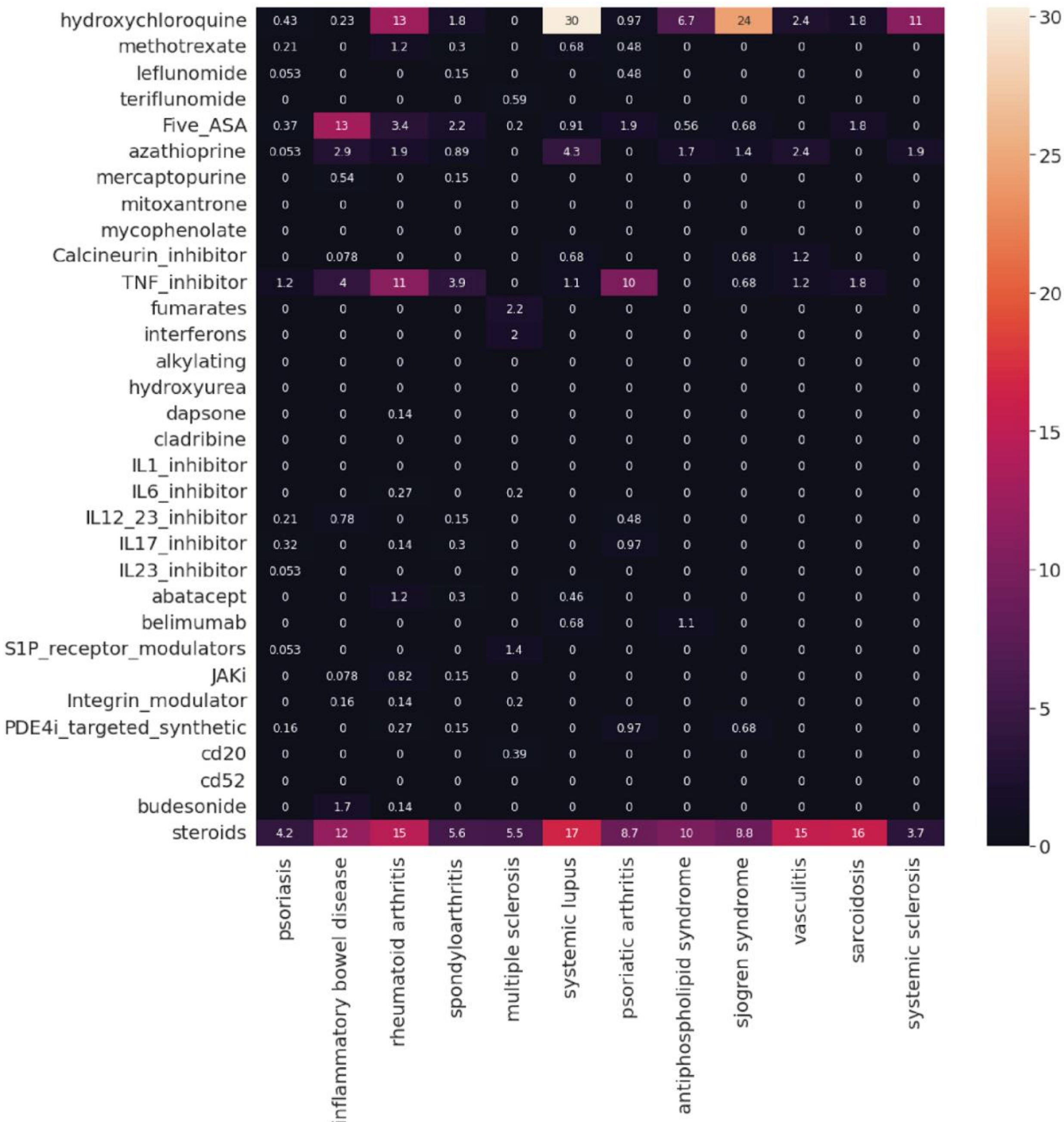


Figure A.6 1 Prenatal IMM prescription rate of individual IMIDs[13]

APS Antiphospholipid Syndrome; IBD Inflammatory Bowel Disease; IMIDs Immune-mediated Inflammatory Disease; MS Multiple Sclerosis; Ps Psoriasis; PsA Psoriatic Arthritis; Sc Sarcoidosis; SLE Systemic Lupus Erythematosus; SpA Spondyloarthritis; SjS Sjörgen's Syndrome; SSc Systemic Sclerosis; Va Vasculitis;

RxNorm codes of immunomodulatry medications (IMMs) are listed in the Table S3. Each column indicates ranking of individual IMID's prenatal IMMs prescription rate. Prenatal IMMs prescription rate are displayed in the descending order. IMMs with prescription rate below 1% are not displayed. IMMs prescription rate widely varied depending on the individual IMID.

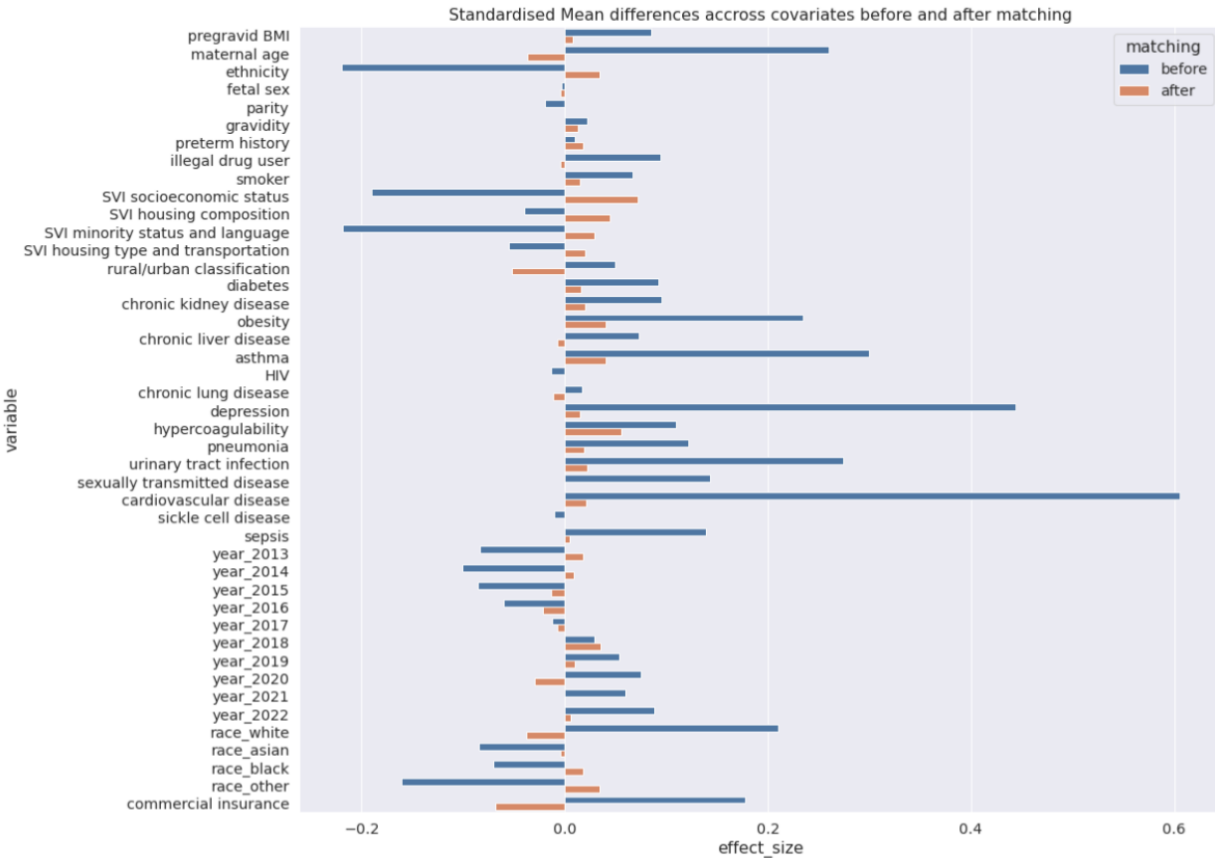


Figure A.6 2 Standardized mean difference before and after propensity score matching for the IMIDs group[13]

Variables are defined in Table A.6 2 Variable definition. The standardized mean difference after propensity score matching for individual IMIDs groups is shown in Table A.6 7. The standardized mean difference of sensitivity analysis is shown in Table A.6 8.

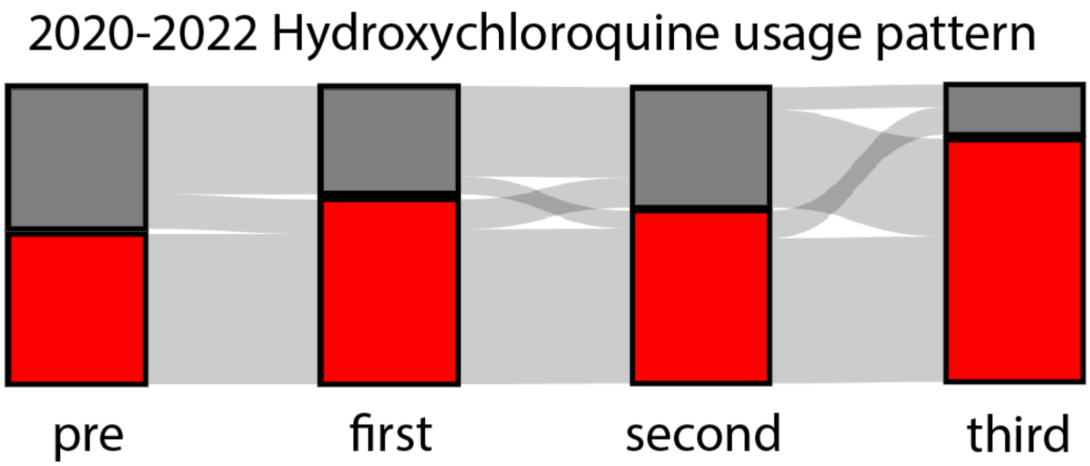


Figure A.6 3 Hydroxychloroquine usage pattern from 2020 to 2022

Hydroxychloroquine prescription patterns among patients who prescribed at least once from LMP-180 days to delivery date in 2020-2022. Pre, first, second, and third columns indicate 180 days prepregnancy period, first second and third trimester. Red and gray portions respectively indicate