Sentinel

Comparing Risk of Adverse Infant Outcomes Among Pregnancies with and without COVID-19 in the Sentinel System

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Disclosures

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- The views expressed in this presentation represent those of the presenters and do not necessarily represent the official views of the U.S. FDA.

Background

- Pregnant individuals are at higher risk for developing severe illness related to respiratory infections including COVID-19
- Pregnant individuals with COVID-19 have higher rates of hospitalization and are more likely to be admitted to ICU and receive mechanical ventilation than non-pregnant individuals with COVID-19
- Increased risk of preterm birth, stillbirth, cesarean section, and other pregnancy-related complications associated with COVID-19 infection during pregnancy
- Impact of timing of COVID-19 infection during pregnancy on risk of adverse infant and pregnancy outcomes is not known

Zambrano LD. 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.
Son M, Gallagher K, Lo JY, et al. Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy Outcomes in a U.S. Population. Obstet Gynecol. 2021;138(4):542-551. doi:10.1097/AOG.0000000000004547
Ferrara A, Hedderson MM, Zhu Y, et al. Perinatal Complications in Individuals in California With or Without SARS-CoV-2 Infection During Pregnancy. JAMA Intern Med. Published online March 21, 2022.
Karasek D, Baer RJ, McLemore MR, et al. The association of COVID-19 infection in pregnancy with preterm birth: A retrospective cohort study in California. Lancet Reg Health Am. 2021;2:100027.
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 Int J Obstet Gynaecol. Published online March 7, 2022.

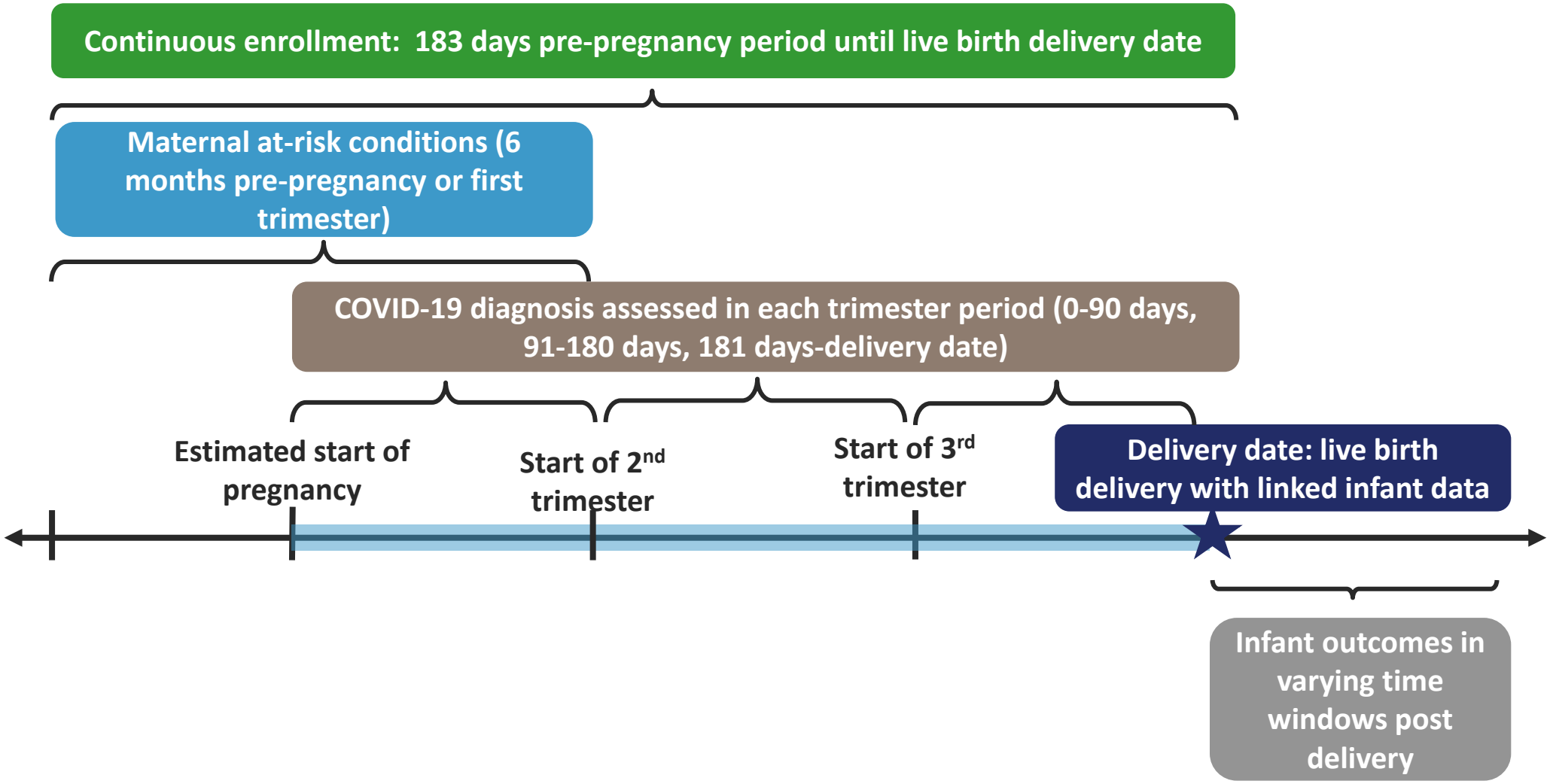
Study Objectives

CONSIGN (**C**OVID-19 Infecti**O**n a**N**d Medicine**S** **I**n Pre**GN**ancy), a European Medicines Agency (EMA)-funded, international collaboration across various countries to understand the natural history of COVID-19 in pregnant individuals

- U.S. (Sentinel) was one of several international collaborators, including Canada, United Kingdom, Norway, Denmark, Germany, Spain, Italy, France, and Sweden

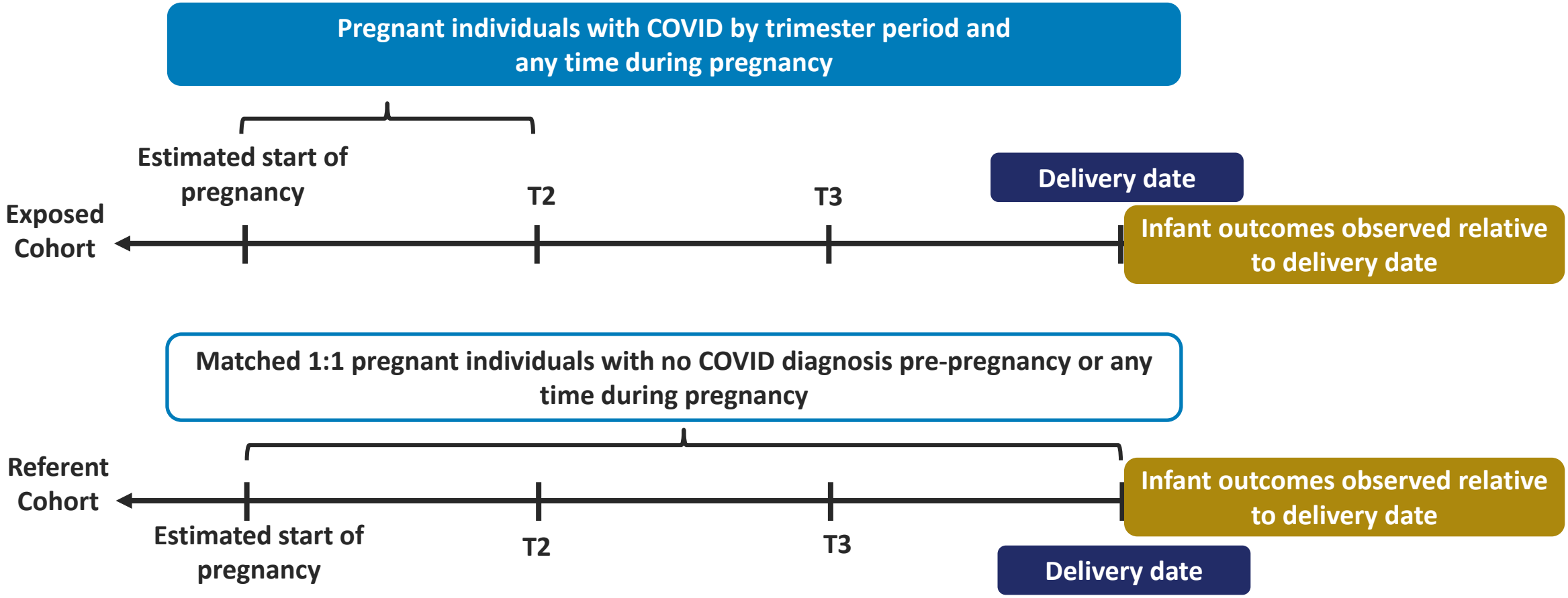
Aim: To evaluate the impact of COVID-19 on adverse infant outcomes in pregnant individuals with COVID-19 compared to those without COVID-19, stratified by trimester of COVID-19 infection during pregnancy and COVID-19 severity

Methods
Study Design: Pregnancy Cohort Creation



Methods

Study Design: Propensity Score Matching



1) Estimated pregnancy start for referent cohort within +/-14 days of pregnancy start in exposed cohort;
2) Matched exposed and referent individuals have same categorical gestational age (preterm, term, postterm, unknown term);
3) Matched exposed and referent individuals have same categorical maternal age (12-24, 25-39, 40-55 years)

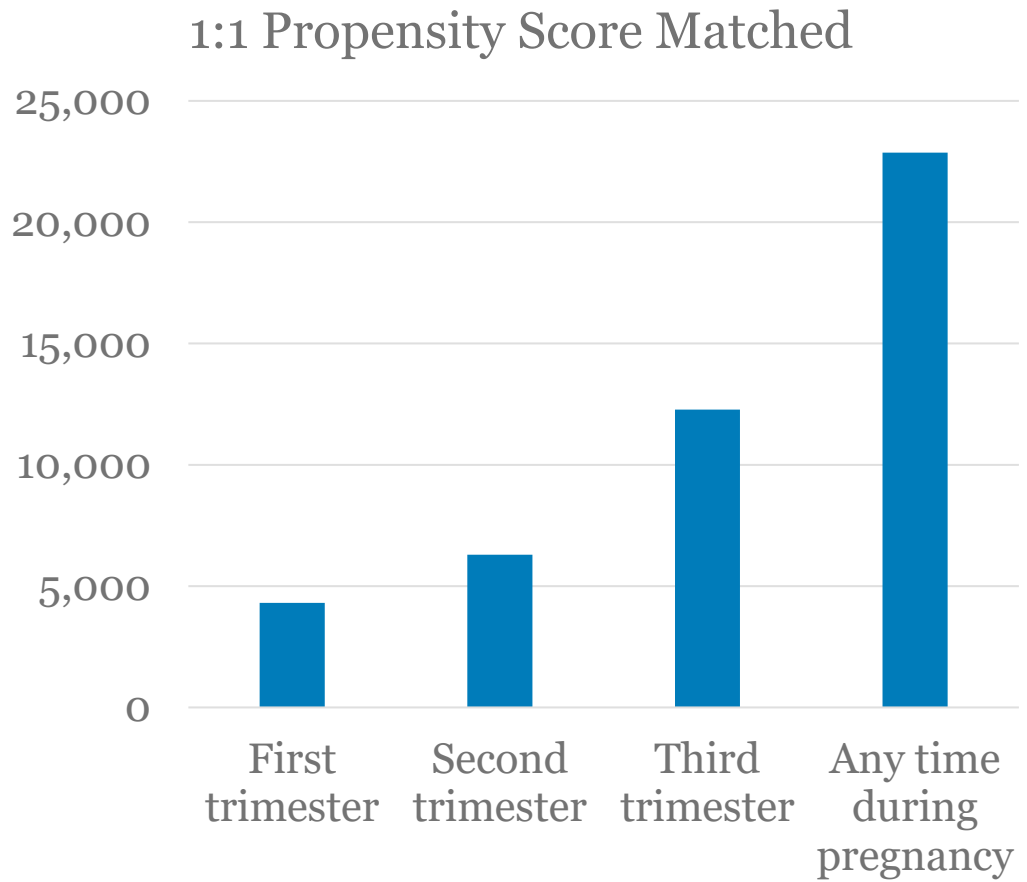
Infant Outcomes Assessment Windows

Infant outcome	Evaluation period start	Evaluation period end	Claims to observe outcome
Low birth weight	Admission date for live birth delivery	+7 days after Admission date for live birth delivery	Mother or infant claims
Small for gestational age			
Microcephaly		+90 days after Admission date for live birth delivery	Infant claims only
Any congenital malformations			

Results: Cohort Attrition

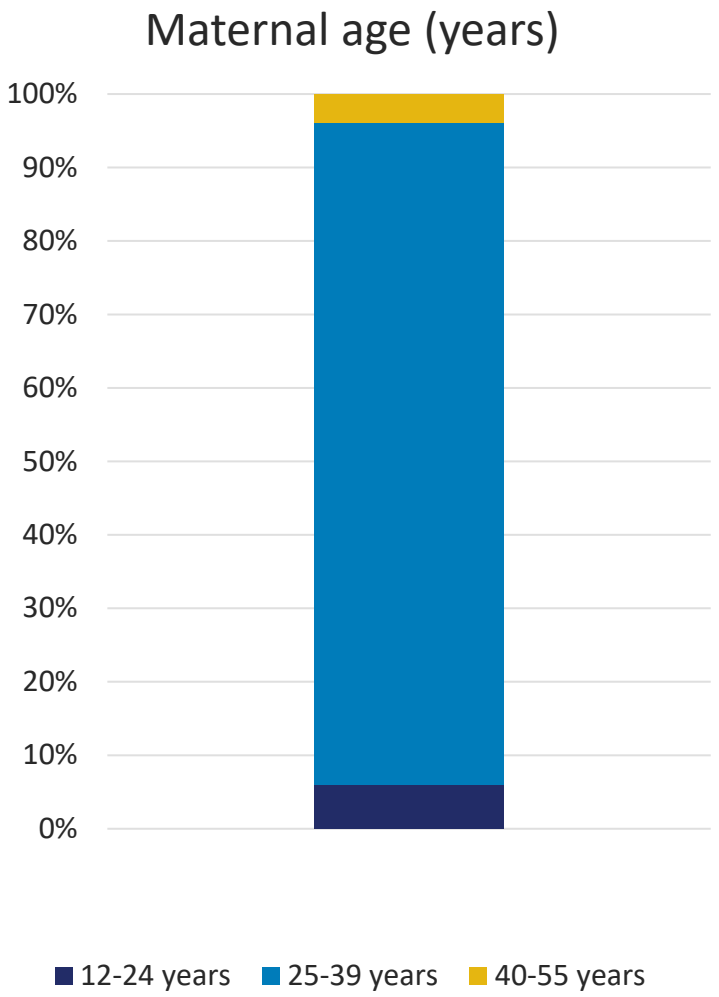
Pregnant Individuals with and without COVID-19 using data from 4 Data Partners with Mother-Infant Linkage from January 2020 – December 2022

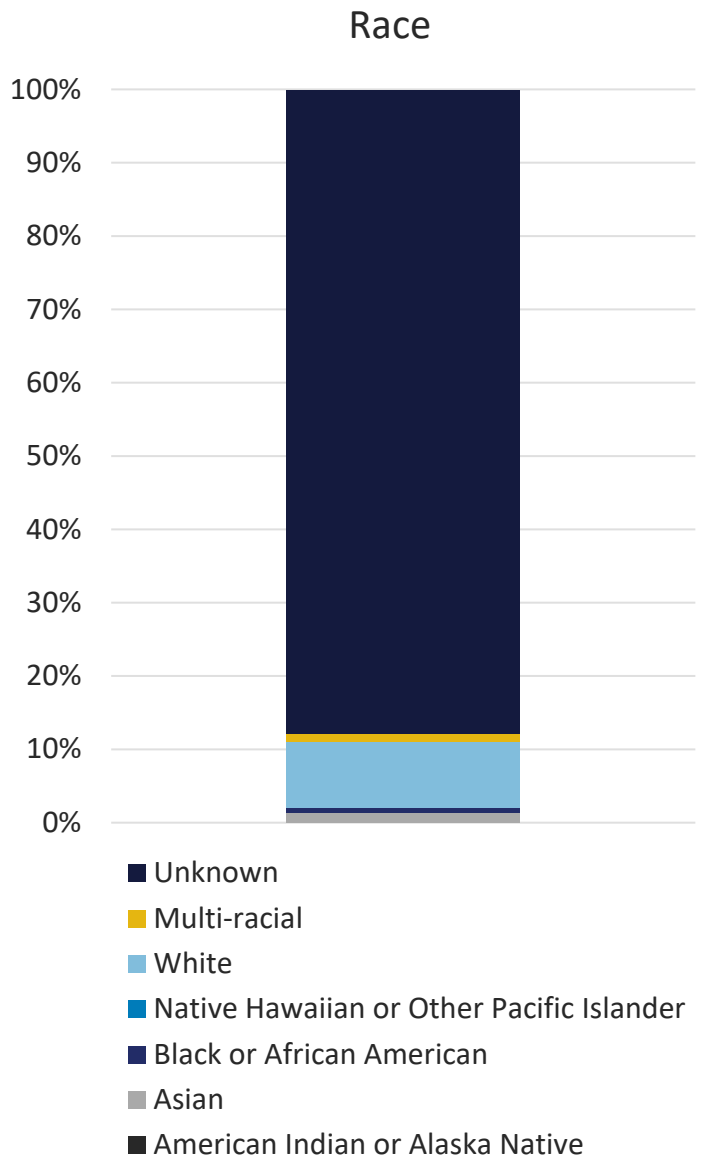
COVID-19 assessment period	Pregnant individuals **with COVID-19**	Pregnant individuals **without COVID-19**
First trimester	4,314	259,927
Second trimester	6,302	259,927
Third trimester	12,286	259,927
Any time during pregnancy	22,893	259,927

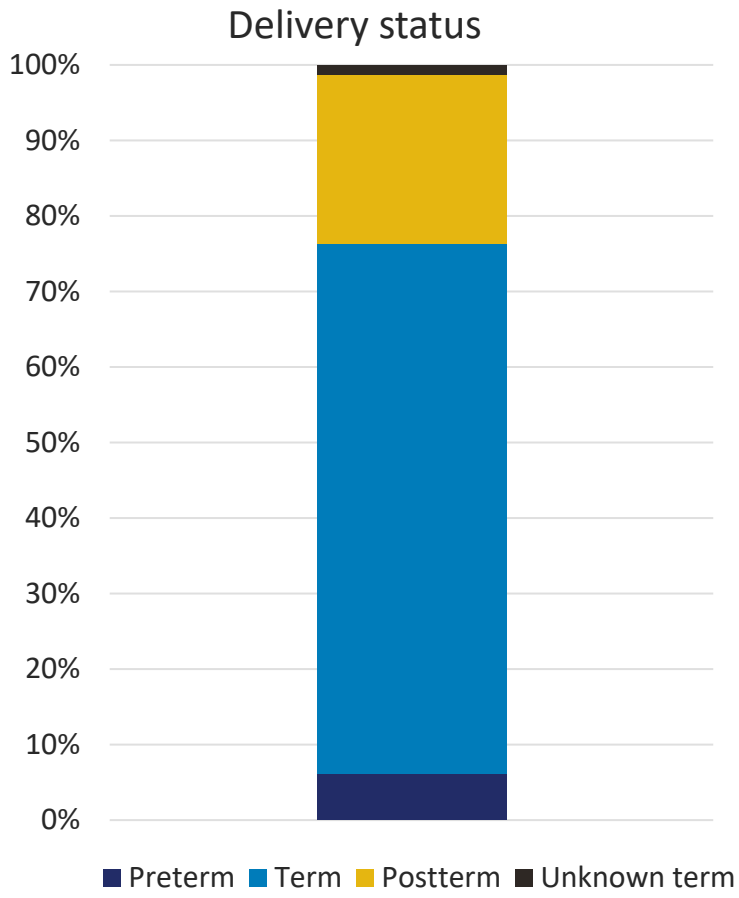


COVID-19 was defined using COVID-19 related International Classification of Diseases (ICD)-10-Clinical Modification (CM) diagnosis codes (U07.1, B34.2, B97.21, B97.29, J12.81) or a positive result of reverse transcription polymerase chain reaction (RT-PCR) test for severe acute respiratory syndrome (SARS)-CoV-2

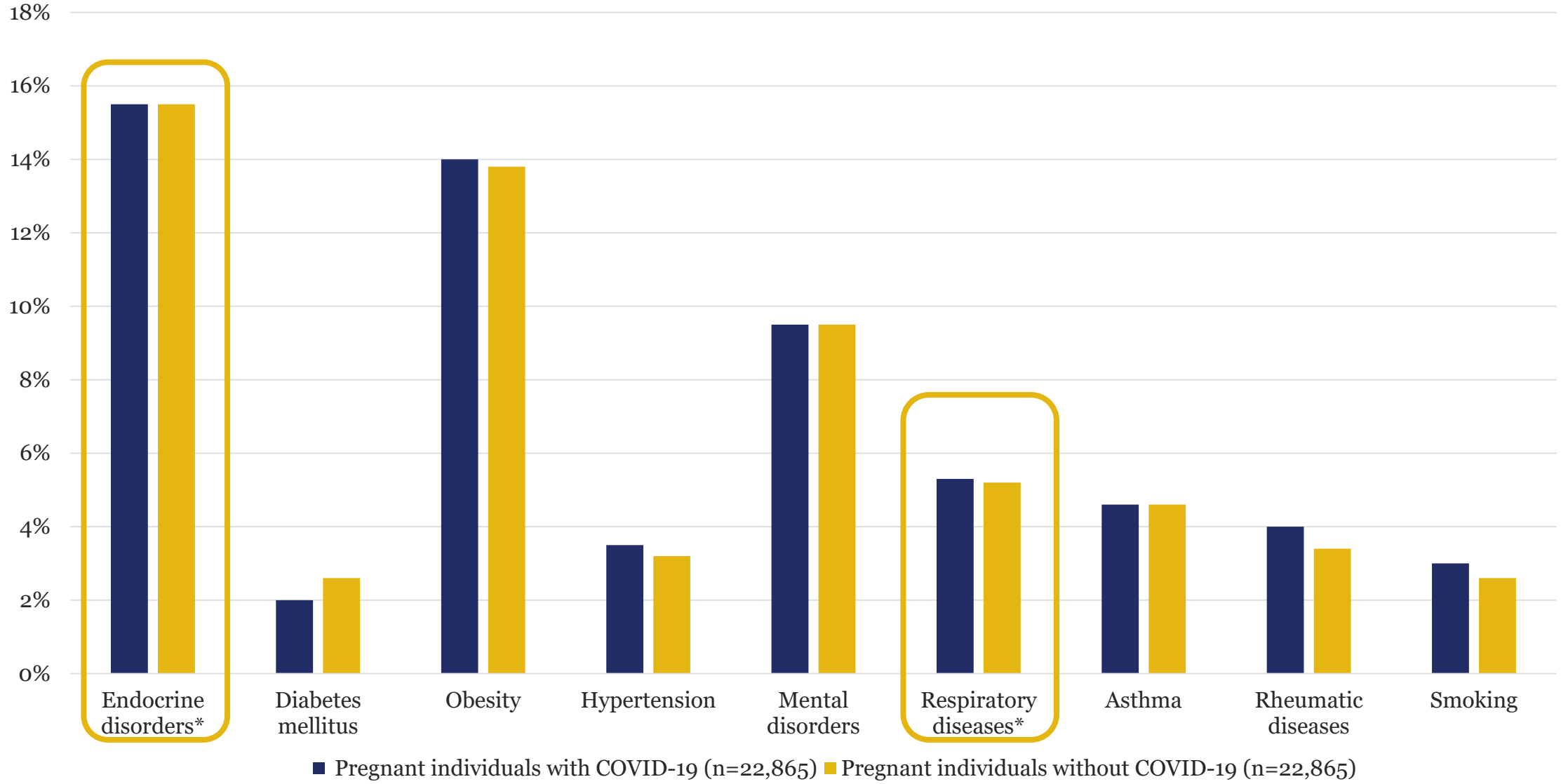
Demographic Characteristics of Pregnancies with COVID-19 (n=22,865)







Maternal Pre-existing Conditions in 6 Months Pre-pregnancy Through First Trimester- After Matching

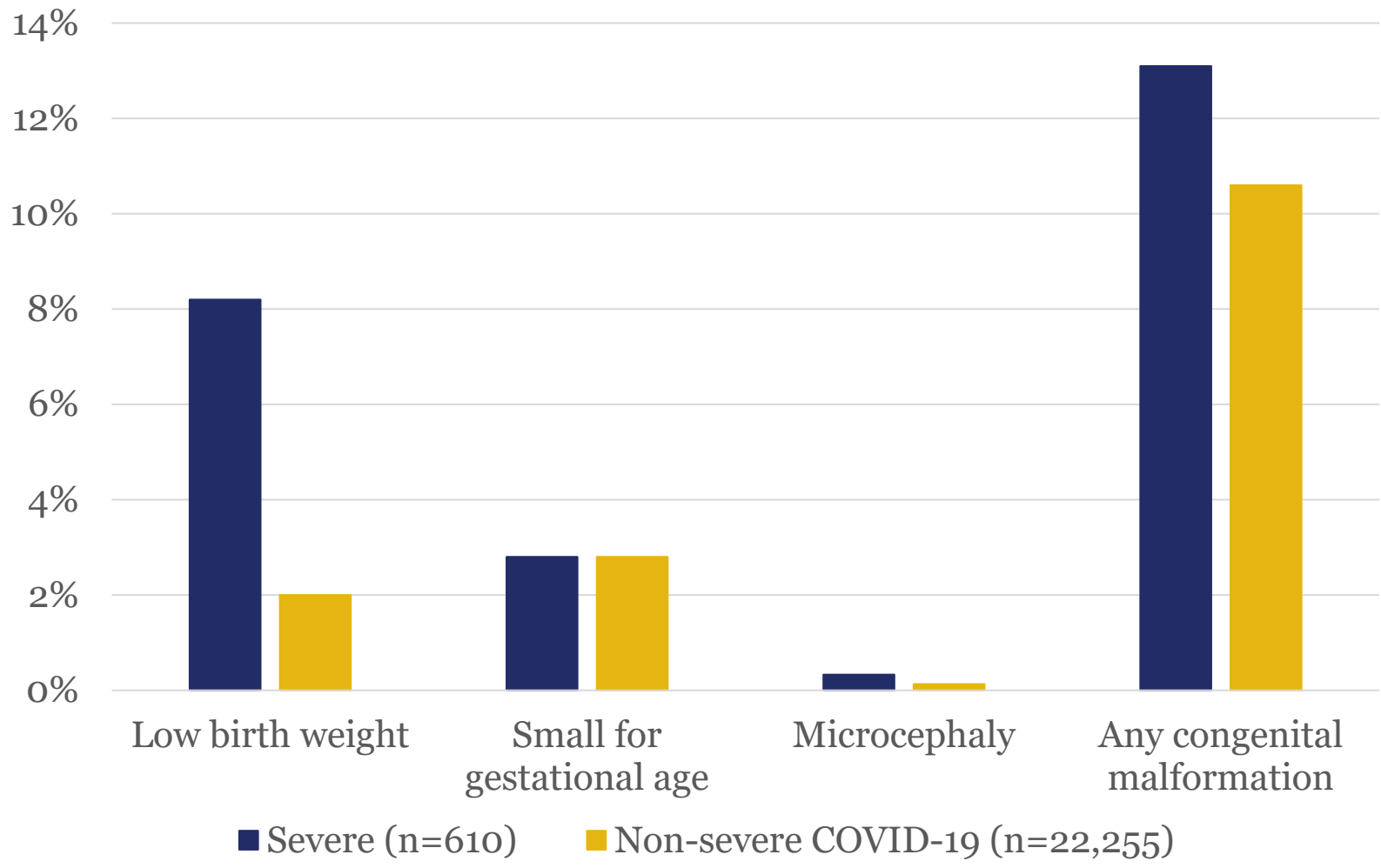


*adjusted for Endocrine disorders and Respiratory diseases in 1:1 Propensity Score model

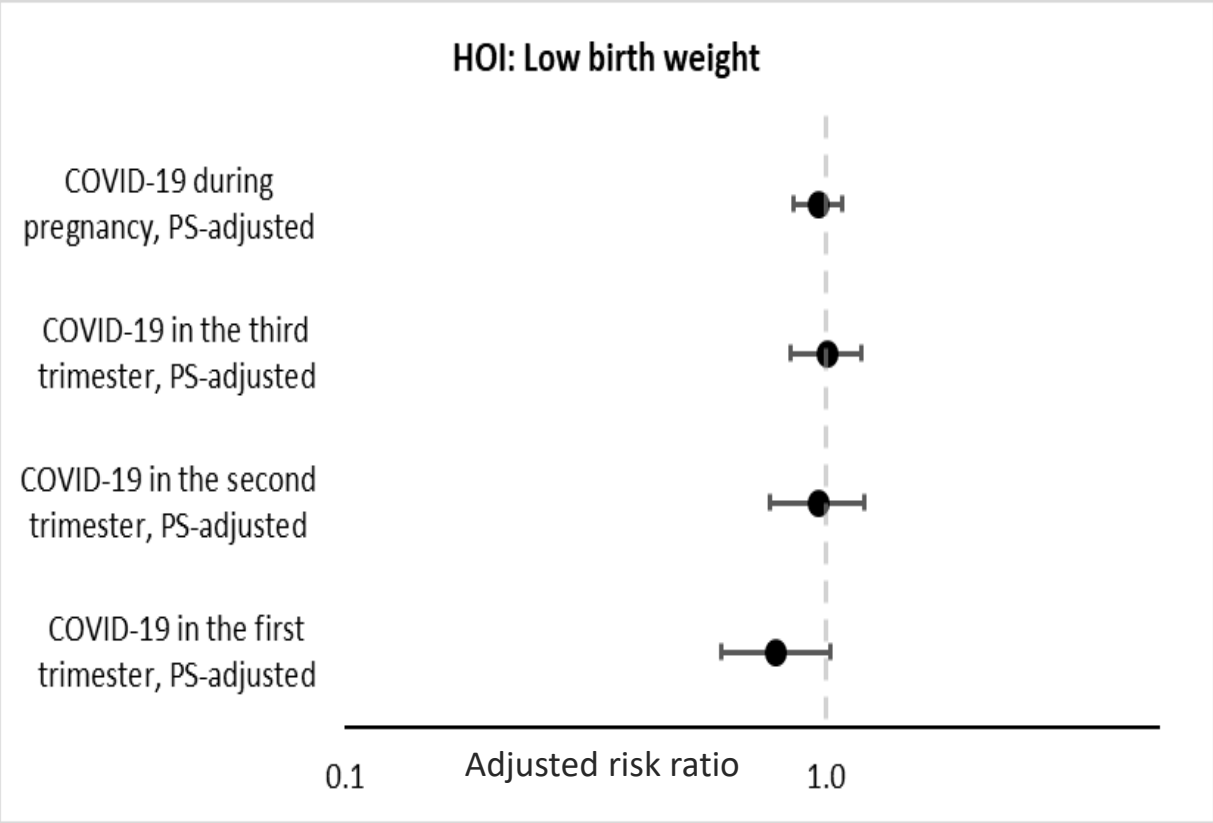
Hierarchical COVID-19 Severity

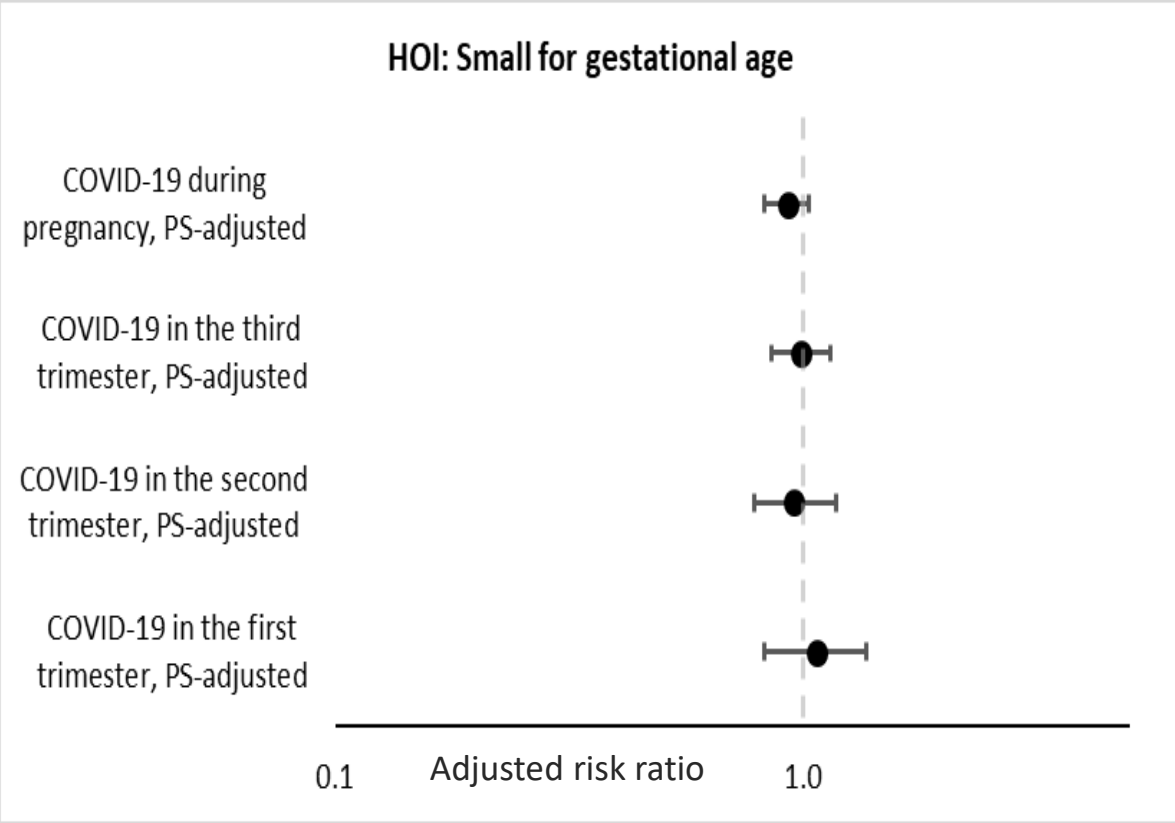
	COVID-19 in the **first trimester**	COVID-19 in the **second trimester**	COVID-19 in the **third trimester**	COVID-19 **during pregnancy**
Total adjusted cohort size	N=4,310	N=6,298	N=12,274	N=22,865
Level 5: Hospitalization for COVID-19 with expired discharge status	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)
Level 4: Hospitalization for COVID-19 with ARDS requiring ventilation	12 (0.3%)	44 (0.7%)	178 (1.5%)	239 (1.0%)
Level 3: Hospitalization for COVID-19 with ICU stay	3 (0.1%)	9 (0.1%)	124 (1.0%)	145 (0.6%)
Level 2: Hospitalization for COVID-19 with pneumonia, dyspnea, hypoxia, hypoxemia, supplemental oxygen, or non-invasive oxygen therapy	4 (0.1%)	20 (0.3%)	190 (1.5%)	225 (1.0%)
Non-severe COVID-19 (Level 1: any other occurrence of COVID-19)	4,291 (99.6%)	6,225 (98.8%)	11,782 (96.0%)	22,255 (97.3%)
Severe COVID-19 (Levels 2-5)	19 (0.4%)	73 (1.2%)	492 (4.0%)	610 (2.7%)

Incidence of Infant Outcomes by COVID-19 Severity



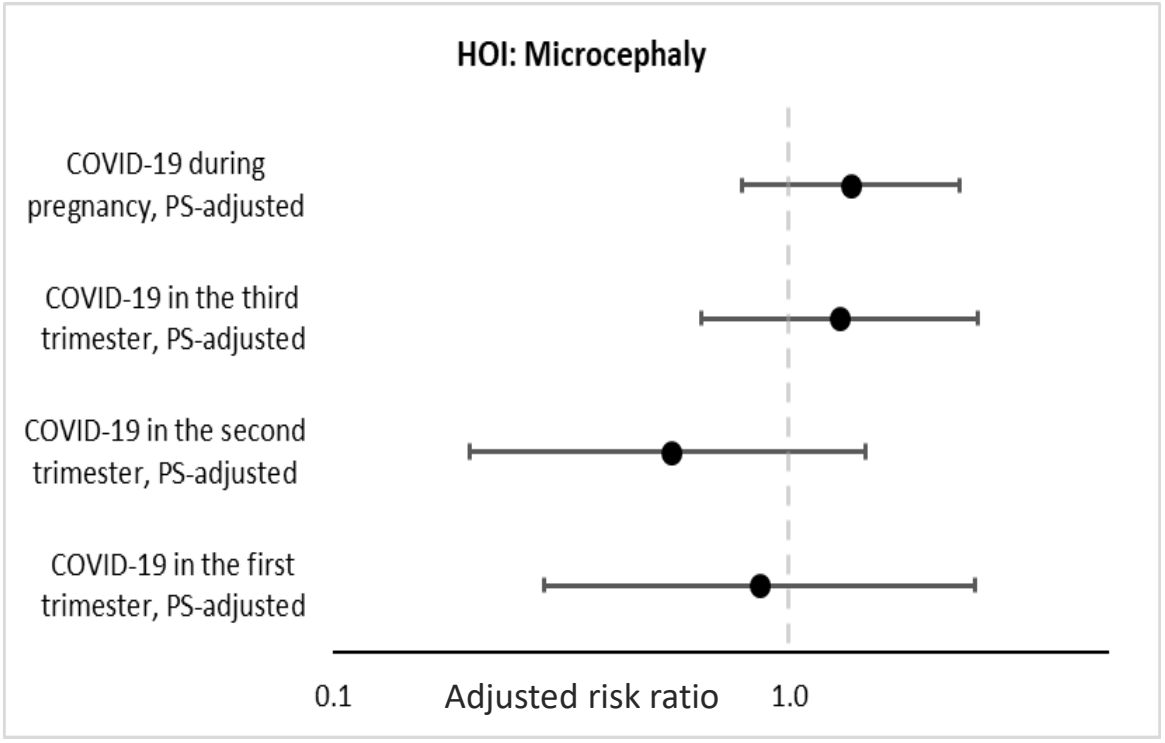
Risk of Infant Outcomes by Trimester of COVID-19 Infection During Pregnancy

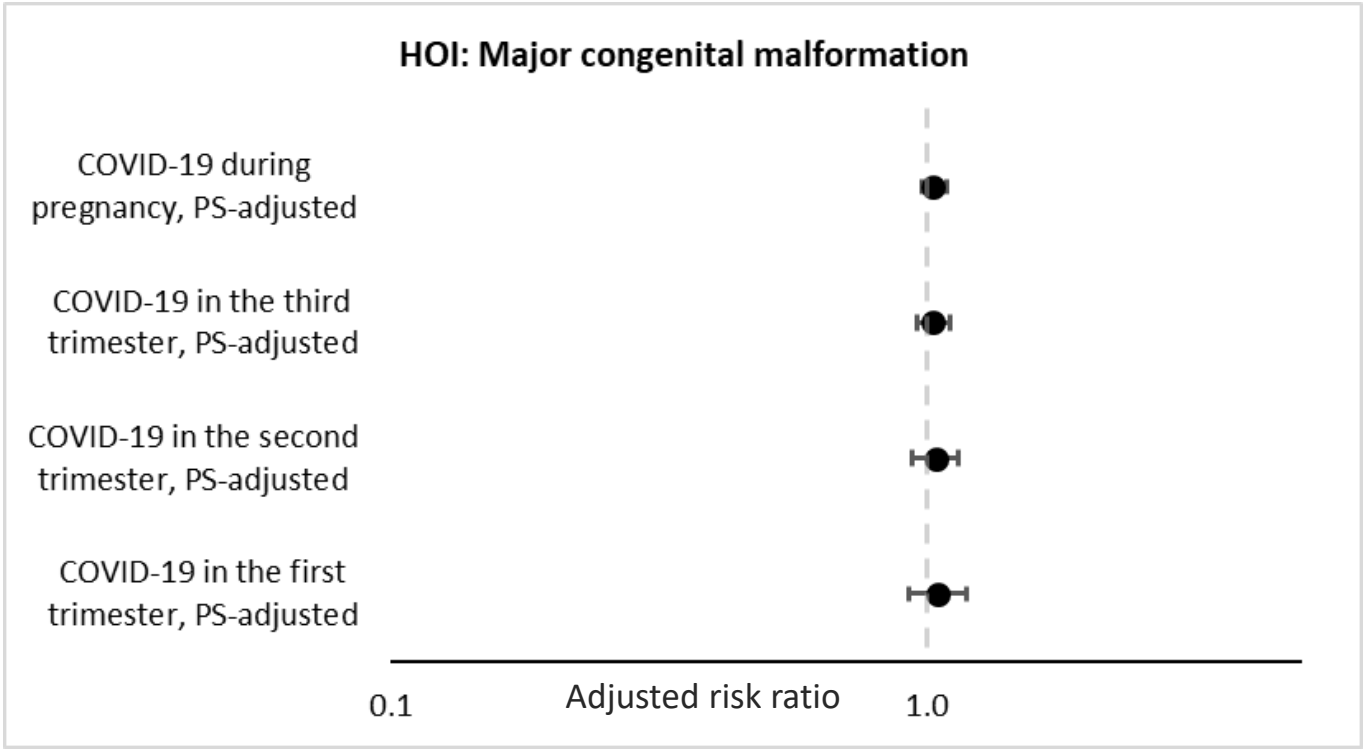




*Low birth weight and small for gestational age observed in the 7 days after and including live birth delivery in the mother or infant's claims.

Risk of Infant Outcomes by Trimester of COVID-19 Infection During Pregnancy Continued





*Microcephaly and any congenital malformation observed in the 90 days after and including live birth delivery in only the infant's claims.

Conclusion

- We identified nearly 23,000 pregnancies with COVID-19 linked to infant records from January 2020-December 2022
- No statistically significant increased risk of any infant outcome among pregnant individuals with COVID-19 compared to pregnant individuals without COVID-19
- Less than 5% of pregnancies had severe COVID-19, a higher risk of low birth weight was noted among severe COVID-19 pregnancies in the third trimester
- Findings may be difficult to interpret due to changing patterns of COVID-19 over time, variations in COVID-19 treatment management and prevention recommendations that may impact the COVID-19 severity and risk of adverse outcomes

Thank You

Harvard Pilgrim Health Care Institute

U.S. Food and Drug Administration

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- HealthPartners Institute, Minneapolis, Minnesota;
- Humana Healthcare Research Inc., Louisville, KY;
- Kaiser Permanente Colorado Institute for Health Research, Aurora, CO;
- Kaiser Permanente Northwest Center for Health Research, Portland, OR;
- OptumInsight Life Sciences Inc., Boston, MA.

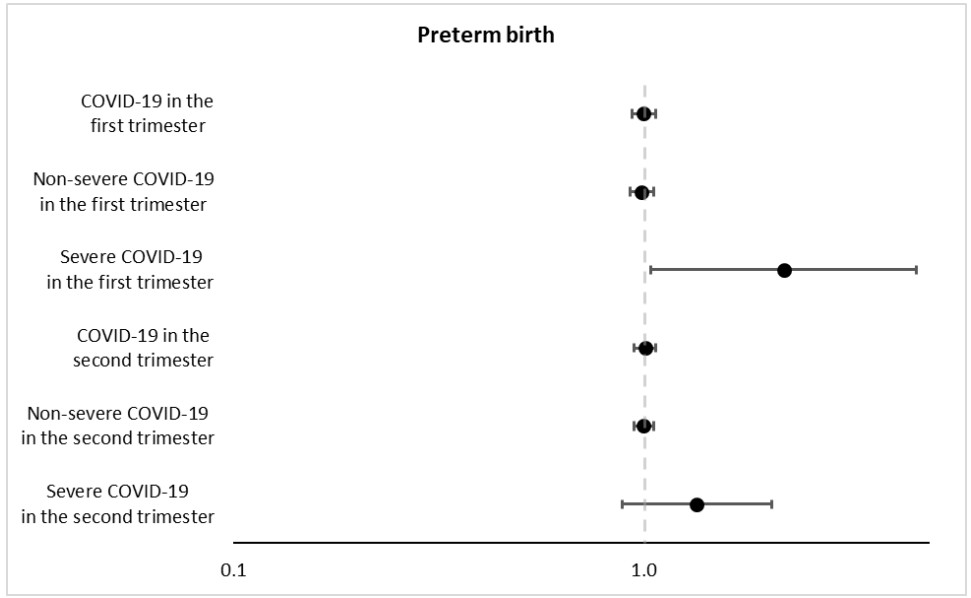
Maternal Outcome Analysis: Pregnant Individuals with and without COVID-19 (stratified by COVID-19 severity) from January 2020 – November 2023 from 7 Data Partners (DP)

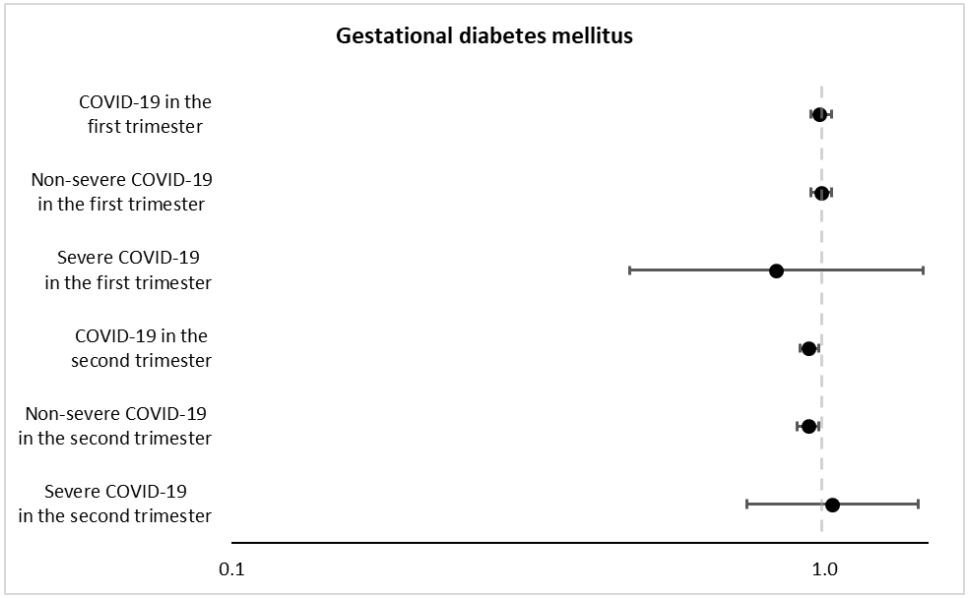
COVID-19 assessment period	Pregnant individuals **with COVID-19**	Pregnant individuals **without COVID-19**	1:1 PS Matched	Pregnant individuals **with severe COVID-19**	Pregnant individuals **with non-severe COVID-19**
First trimester	15,842	642,374	15,841	67 (0.4%)	15,774 (99.6%)
Second trimester	20,121	642,374	20,121	237 (1.2%)	19,884 (98.8%)
Third trimester	33,979	642,374	33,979	1,472 (4.3%)	32,503 (95.7%)
Any time during pregnancy	69,910	642,374	69,901	1,860 (2.7%)	68,041 (97.3%)

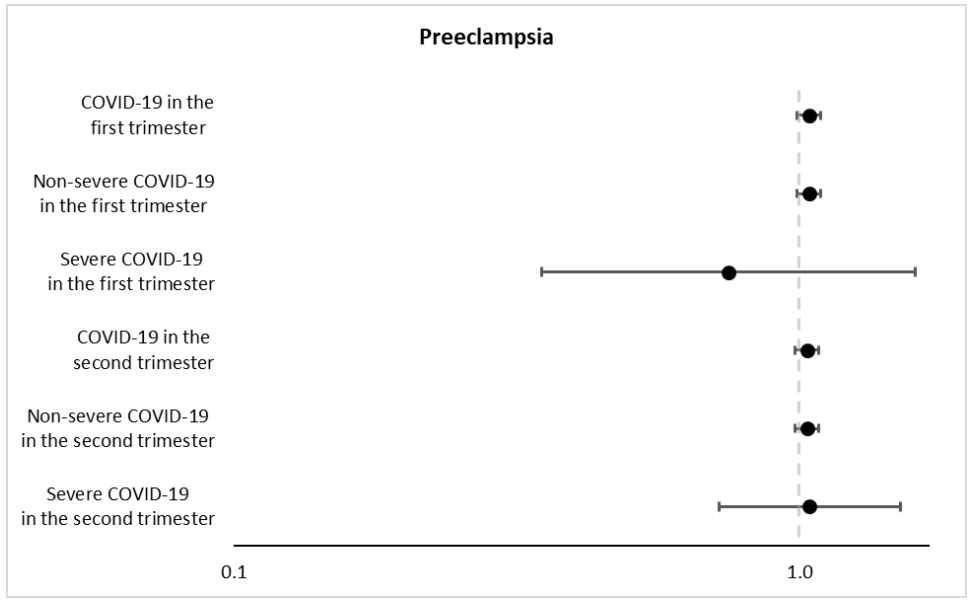
Maternal Outcomes Assessment Windows

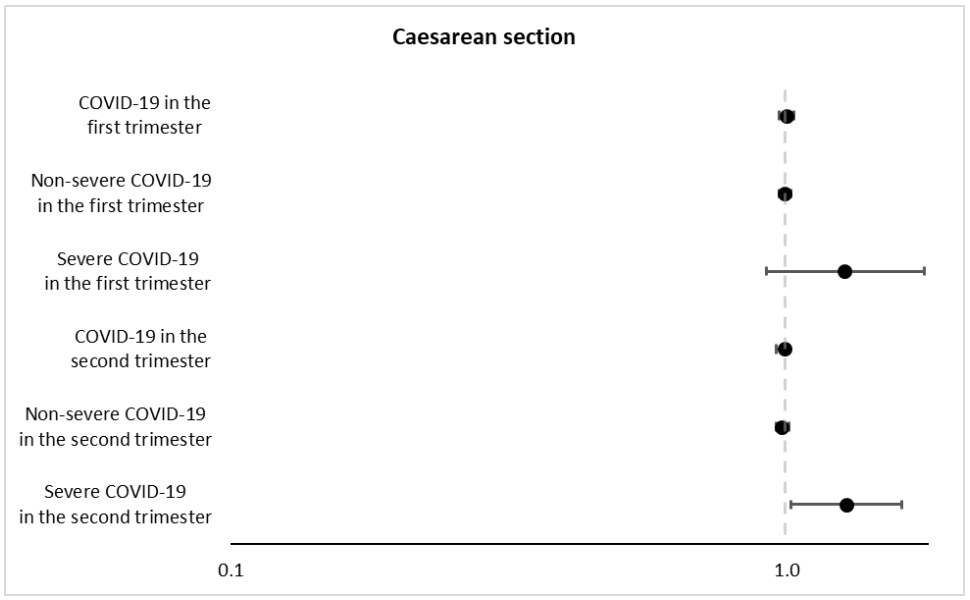
Maternal outcome	Evaluation period start	Evaluation period end
Preterm birth	22 weeks 0/7 days of gestation	36 weeks 6/7 days of gestation
Gestational diabetes		Admission date for live birth delivery
Preeclampsia		Admission date for live birth delivery
Caesarean section	-7 days from Admission date for live birth delivery	+7 days after Admission date for live birth delivery
Maternal death	ADate for live birth delivery	+42 days after Admission date for live birth delivery

Risk of Maternal Outcomes Comparing Pregnant Individuals with and without COVID-19, by Trimester and Severity of COVID-19 Infection

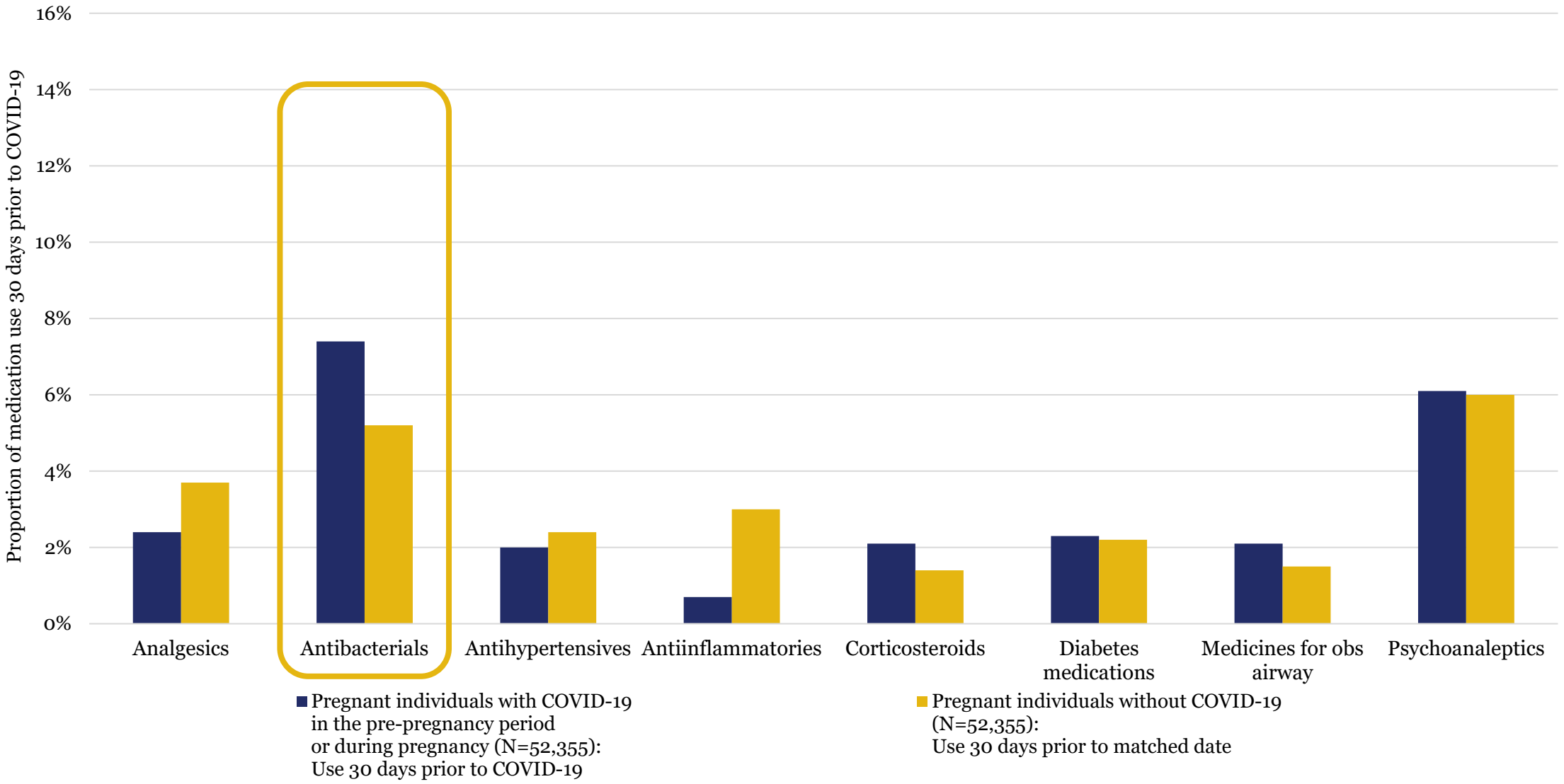




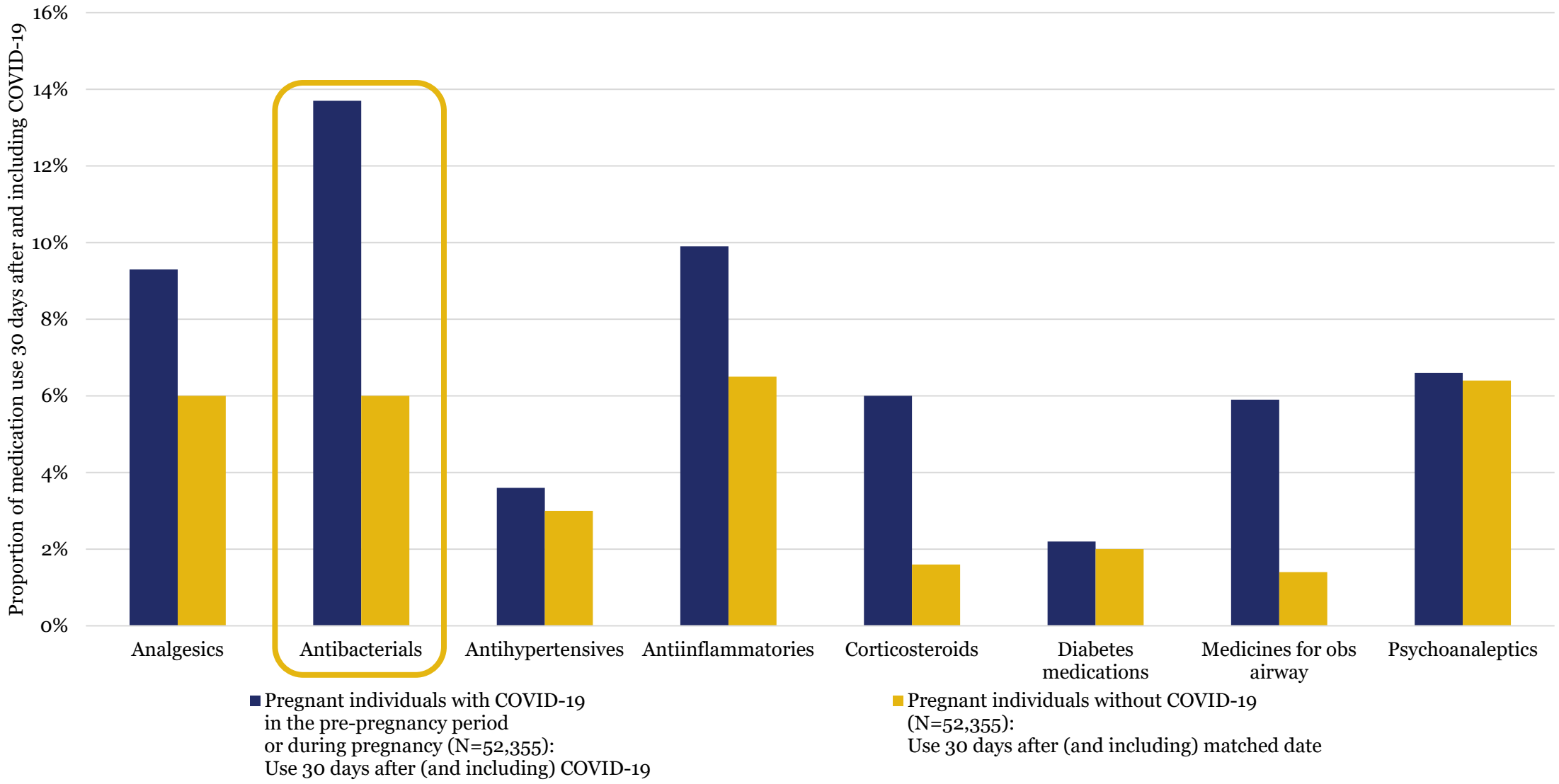




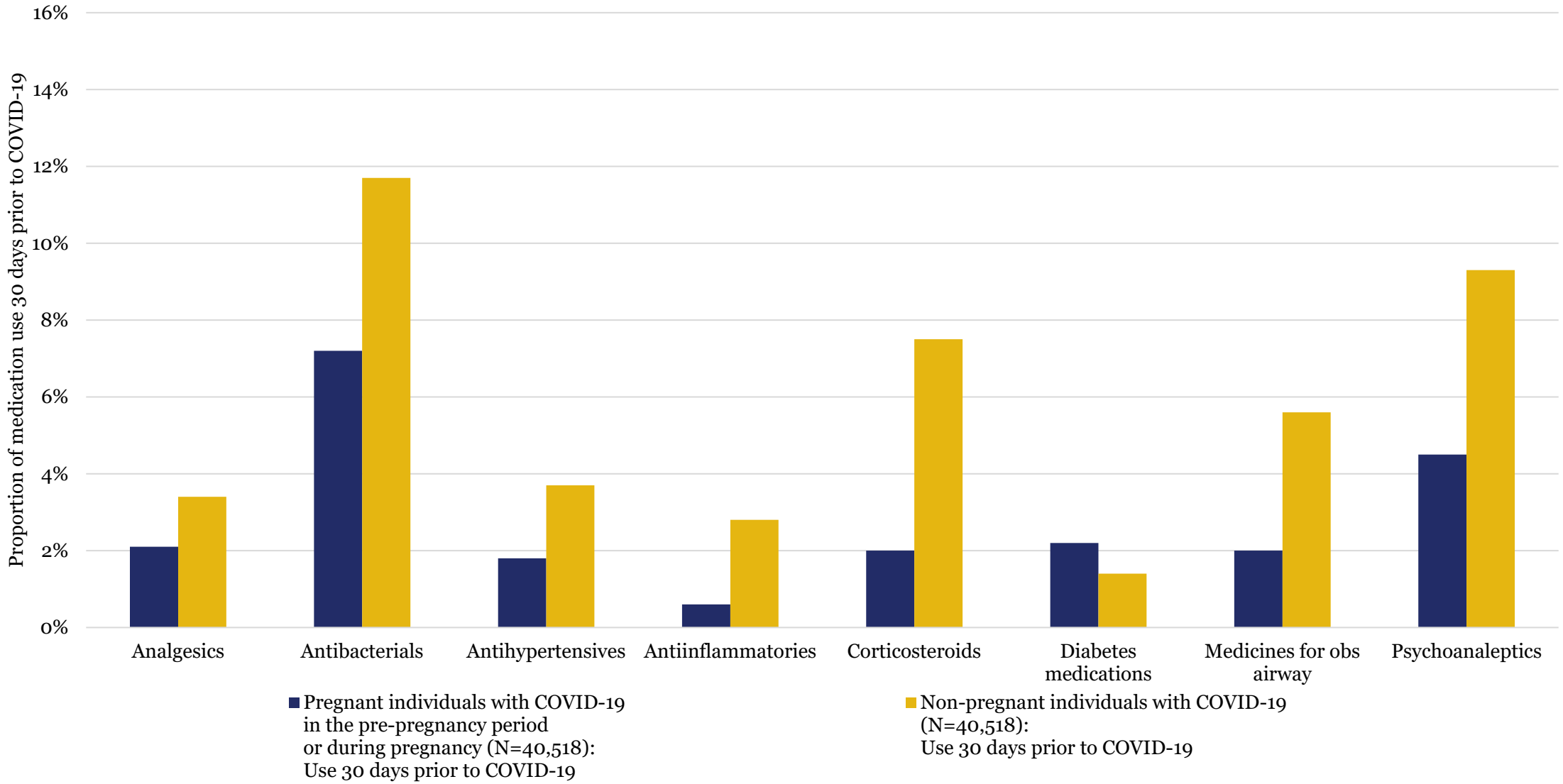
Selected Medication Use 30 Days Prior to COVID-19 among Pregnant Individuals with and without COVID-19



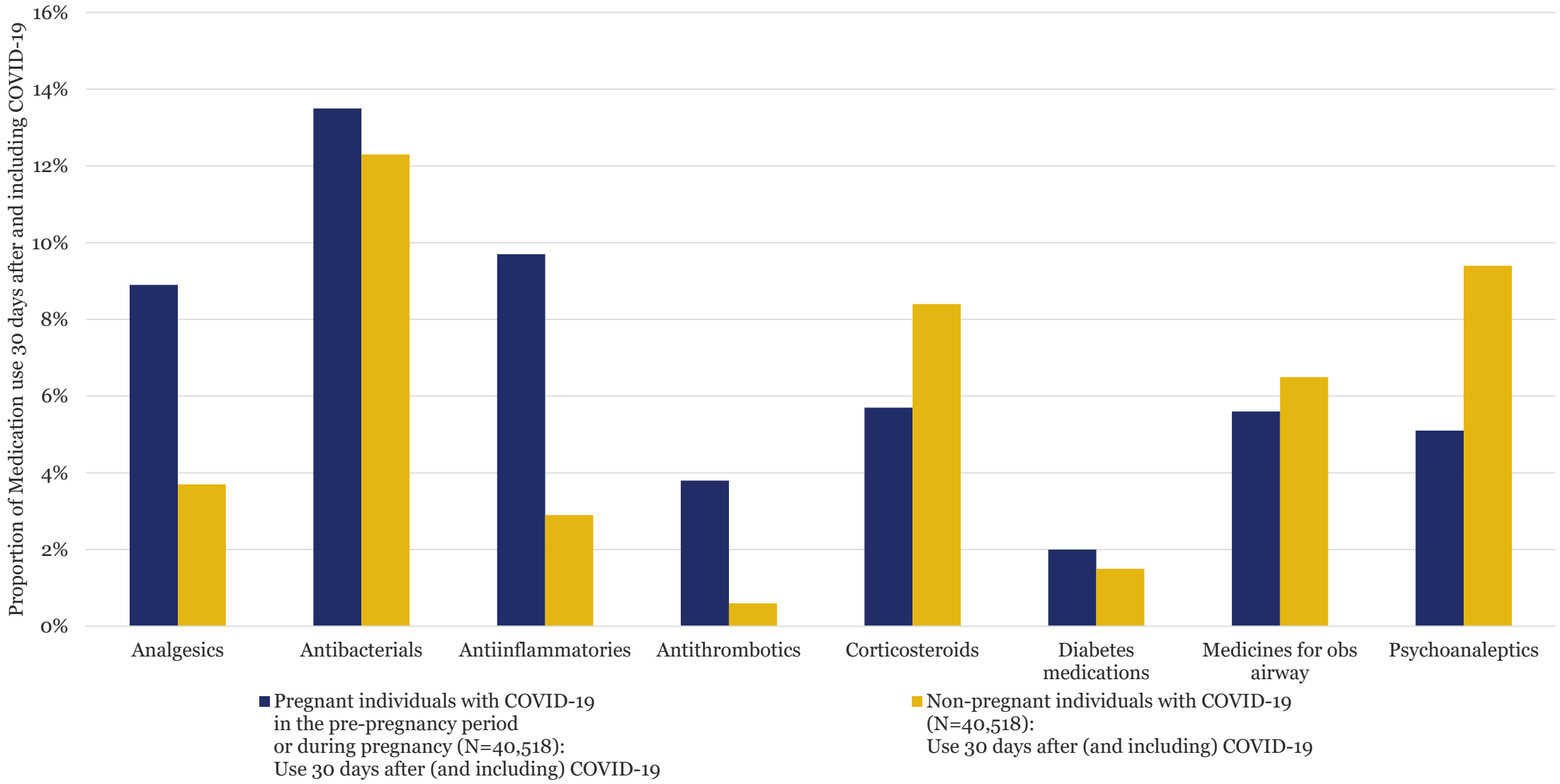
Selected Medication Use 30 Days After COVID-19 among Pregnant Individuals with and without COVID-19



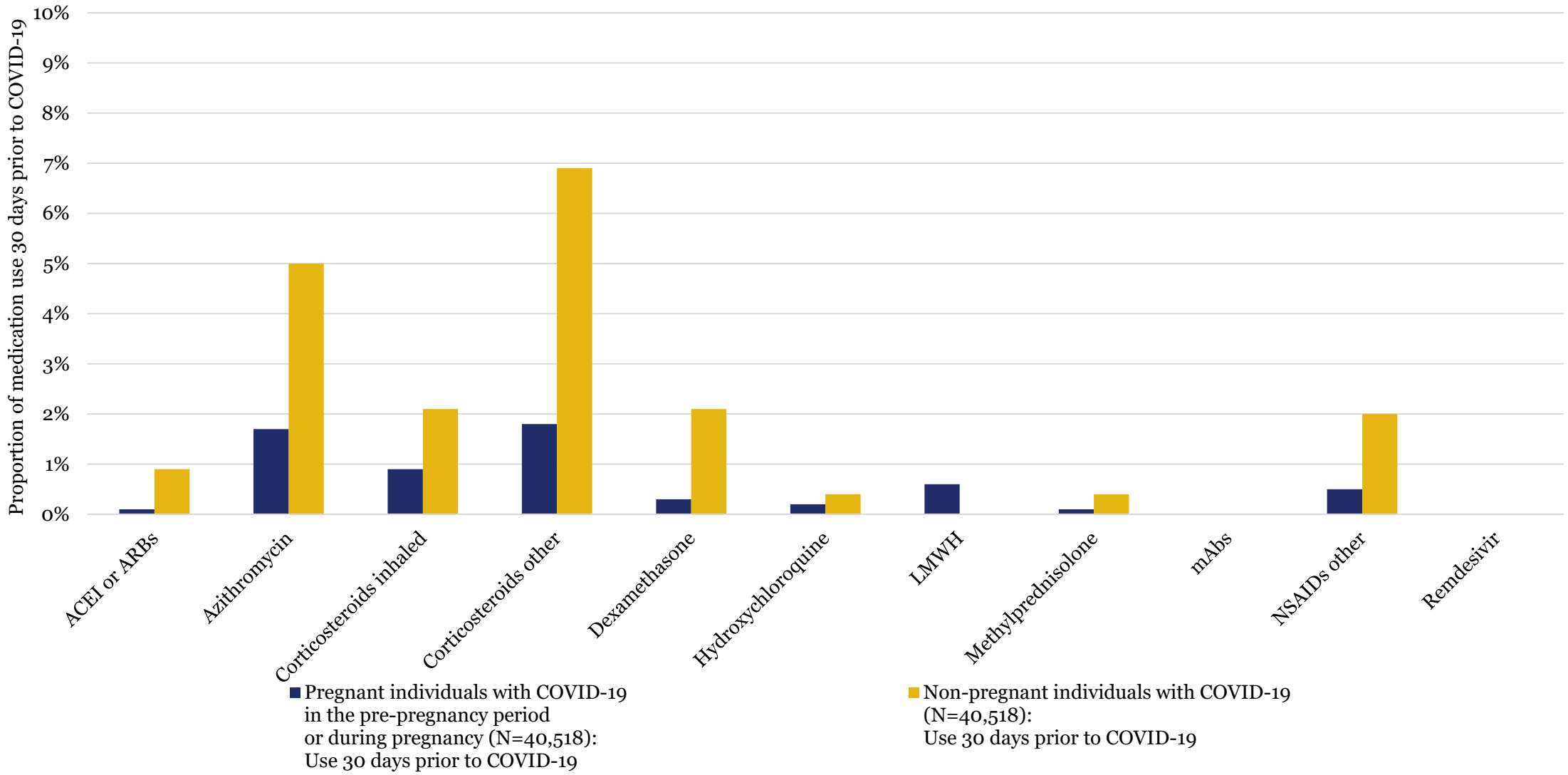
Selected Medication Use 30 Days Prior to COVID-19 among Pregnant and Non-Pregnant Individuals with COVID-19



Comparing Medication Use 30 Days After COVID-19 among Pregnant and Non-Pregnant Individuals with COVID-19



Potential COVID-19 Medication Use 30 Days Prior to COVID-19 among Pregnant and Non-Pregnant Individuals with COVID-19



Potential COVID-19 Medication Use 30 Days After COVID-19 among Pregnant and Non-Pregnant Individuals with COVID-19