Challenges in estimating effects of COVID-19 on preterm birth

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1. Why is this a complex question to answer?
2. What additional problems emerge from the data?
3. Analytic methods to address these issues
4. Results and conclusions

COVID-19 during pregnancy

- Infections known to be harmful during pregnancy
  - Pregnant people may be at higher risk of infection or, more likely, bad outcomes from infection
- Preterm birth (delivery before 37 weeks' gestation) is an outcome of concern
  - A leading cause of neonatal death
  - Potential long-term outcomes

TABLE 4 Mode of delivery and preterm birth in pregnant women in the included studies.

Authors	Gestational age, w	Mode of delivery			Preterm birth
		Cesarean for maternal COVID-19 infection	Cesarean for obstetric indication	Vaginal delivery	
Chen et al.[4]	36–39	9[a]/9	7[a]/9	–	4/9
Chen et al.[20]	38–40	–	2/5	3/5	0/5
Dong et al.[11]	37	1/1	–	–	0/1
Fan et al.[12]	36, 37	2/2	–	–	1/2
Lee et al.[18]	37	–	1/1		0/1
Li et al.[13]	35	–	1[b]/1	–	1/1
Liu et al.[14]	Nr	5[c]/10	5[d]/10	–	6/10
Liu et al.[15]	Nr	9/11	1/11	1/11	Nr
Wang et al.[16]	40	1/1	–	–	0/1
Wang et al.[6]	30	1/1	–	–	1/1
Yu et al.[17]	37–41	7/7	–	–	0/7
Zeng et al.[19]	Nr	6/6[g]	–	–	Nr
Zhu et al.[5]	31–39	1/9	6[e]/9	2[f]/9	6 (2 twins)/10

Abbreviation: Nr, not reported.

Some initial case series

Parazzini F, Bortolus R, Mauri PA, Favilli A, Gerli S, Ferrazzi E. Delivery in pregnant women infected with SARS-CoV-2: A fast review. *International Journal of Gynecology & Obstetrics*. 2020;150(1):41-46.

Estimates of absolute risk of preterm birth

- If someone gets COVID-19 at week 38, they will not have a preterm birth
  - % preterm LOW if COVID-19 preferentially leads to hospitalization later in pregnancy
  - Preferentially counting people who were already past the preterm threshold at infection
- If someone gets COVID-19 at week 18, we can't yet assess preterm delivery
  - % preterm HIGH if we ignore people who haven't yet delivered
  - Preferentially counting short pregnancies that finished soon enough for us to assess whether they were preterm or not

Comparative measures

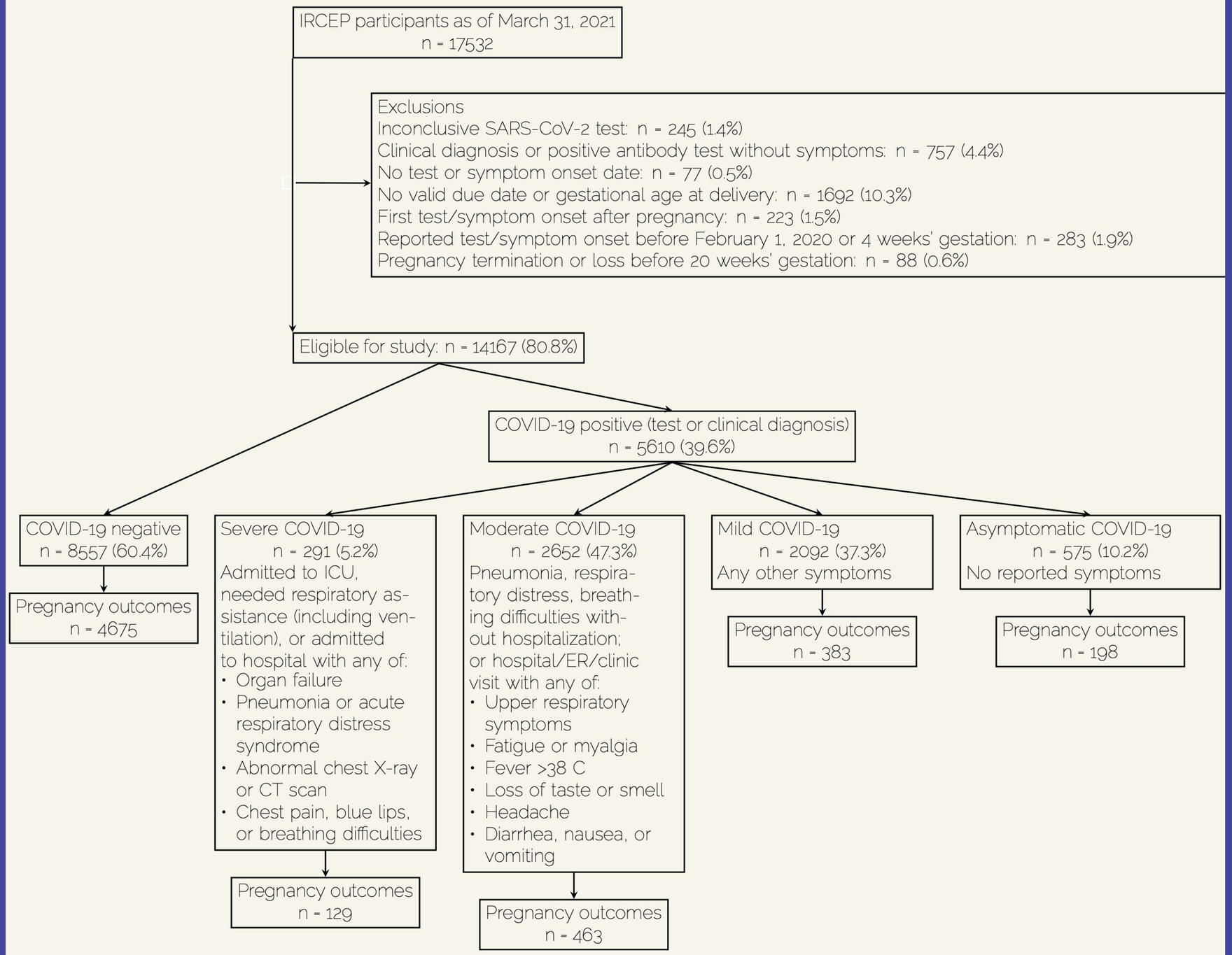
- Maybe the estimates of *absolute* risk have problems, but what about measures of *relative* risk?
  - What if we count the preterm deliveries among people who had COVID-19 in pregnancy and compare to those who never did?
- If we just look at deliveries overall, we may underestimate the effect of COVID-19 on preterm birth
  - Shorter pregnancies are less likely to have been affected by COVID-19… just because they were shorter!
  - Immortal time bias: we need both the exposed and unexposed groups defined at the same time zero

Study design and population

IRCEP
International Registry of Coronavirus Exposure in Pregnancy

- Enrollment during pregnancy or within 6 months afterward
- Must have had a COVID-19 test or clinical diagnosis of COVID-19 during pregnancy
- Study is advertised online in countries around the world
- Survey modules completed via internet
  - Demographics, reproductive and health history, COVID-19 symptoms/tests/treatments, pregnancy outcomes, infant outcomes at birth and 3 months

Participants in IRCEP



Enrollment and testing throughout pregnancy

Completed pregnancies by March 31

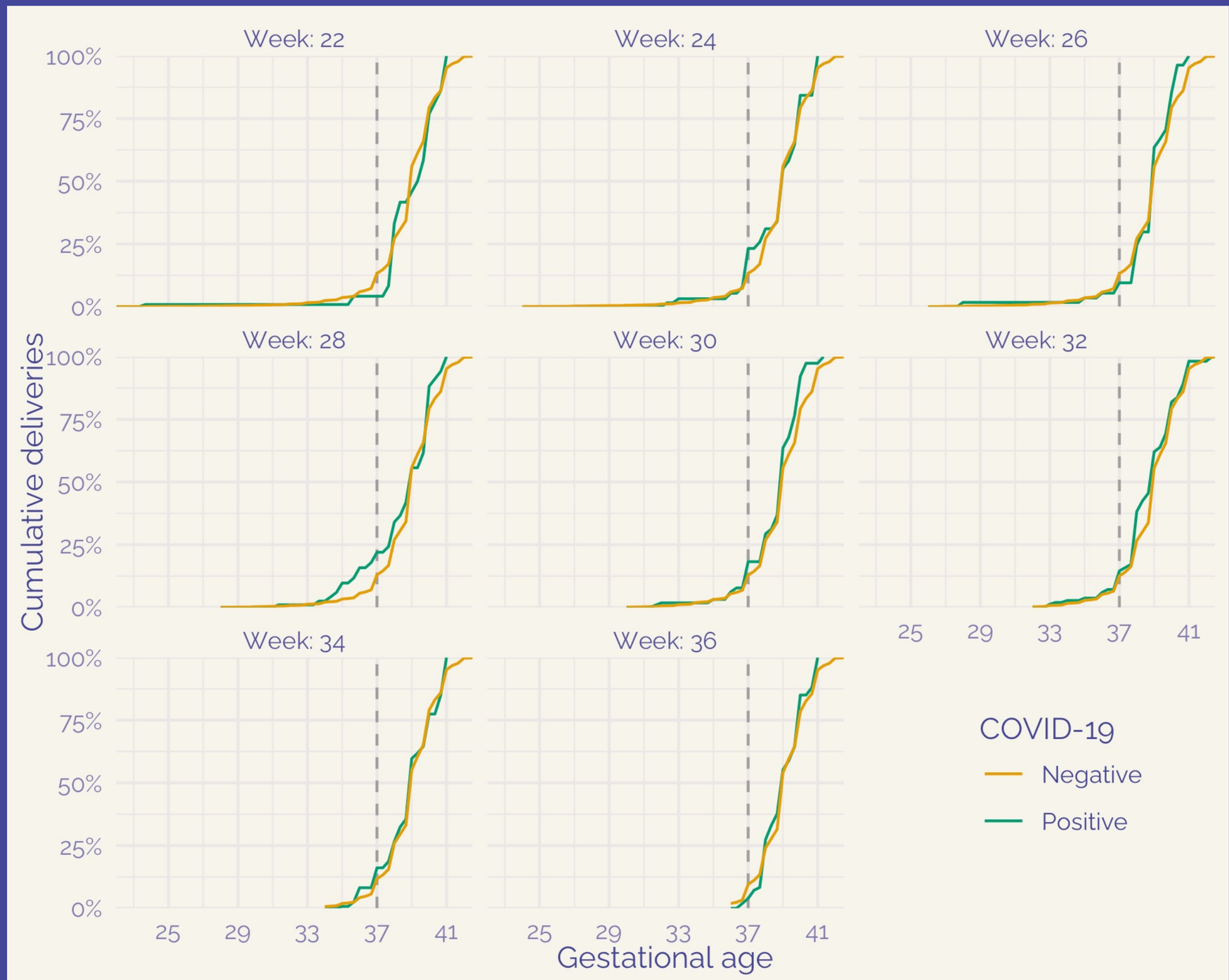
	Negative	Asymp.	Mild	Moderate	Severe
Enrolled during pregnancy	237 (5%)	7 (11%)	63 (19%)	73 (18%)	6 (5%)
Enrolled after pregnancy	**4438 (95%)**	**59 (89%)**	265 (81%)	341 (82%)	**111 (95%)**

Completed pregnancies by March 31

	Preterm delivery	Term delivery
Negative	411 (9%)	4264 (91%)
Asymptomatic	**22 (33%)**	44 (67%)
Mild	35 (11%)	293 (89%)
Moderate	54 (13%)	360 (87%)
Severe	**39 (33%)**	78 (66%)

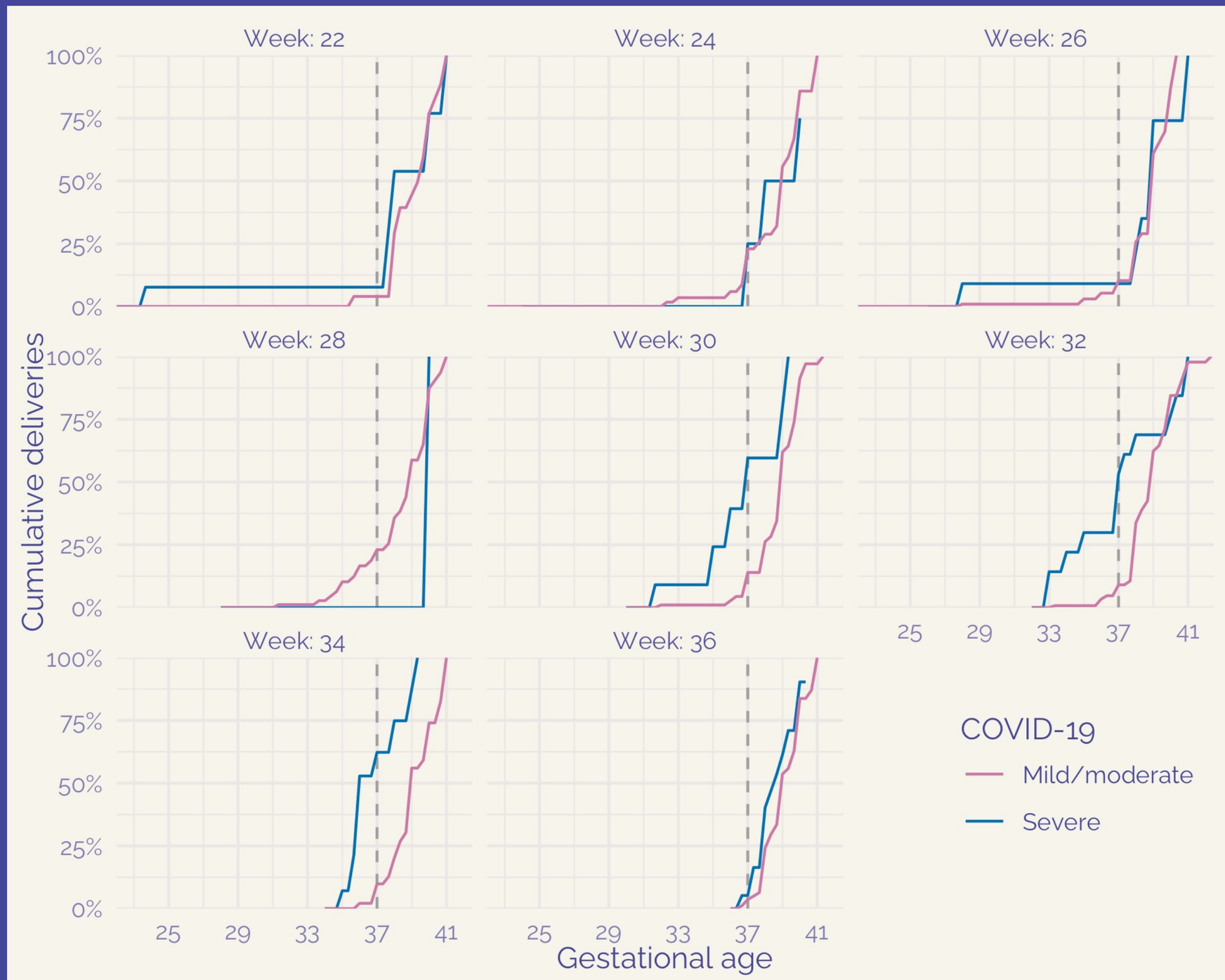
Analysis plan

- At each week of gestation (time zero), choose the people who developed COVID-19 that week
- At that same week of gestation, choose the participants whose pregnancies were ongoing but who didn't have COVID-19
  - They might be part of multiple comparison groups
- Censor observations at last known date of continued pregnancy
- Compare risks of delivery by end of week 37



Unadjusted cumulative deliveries

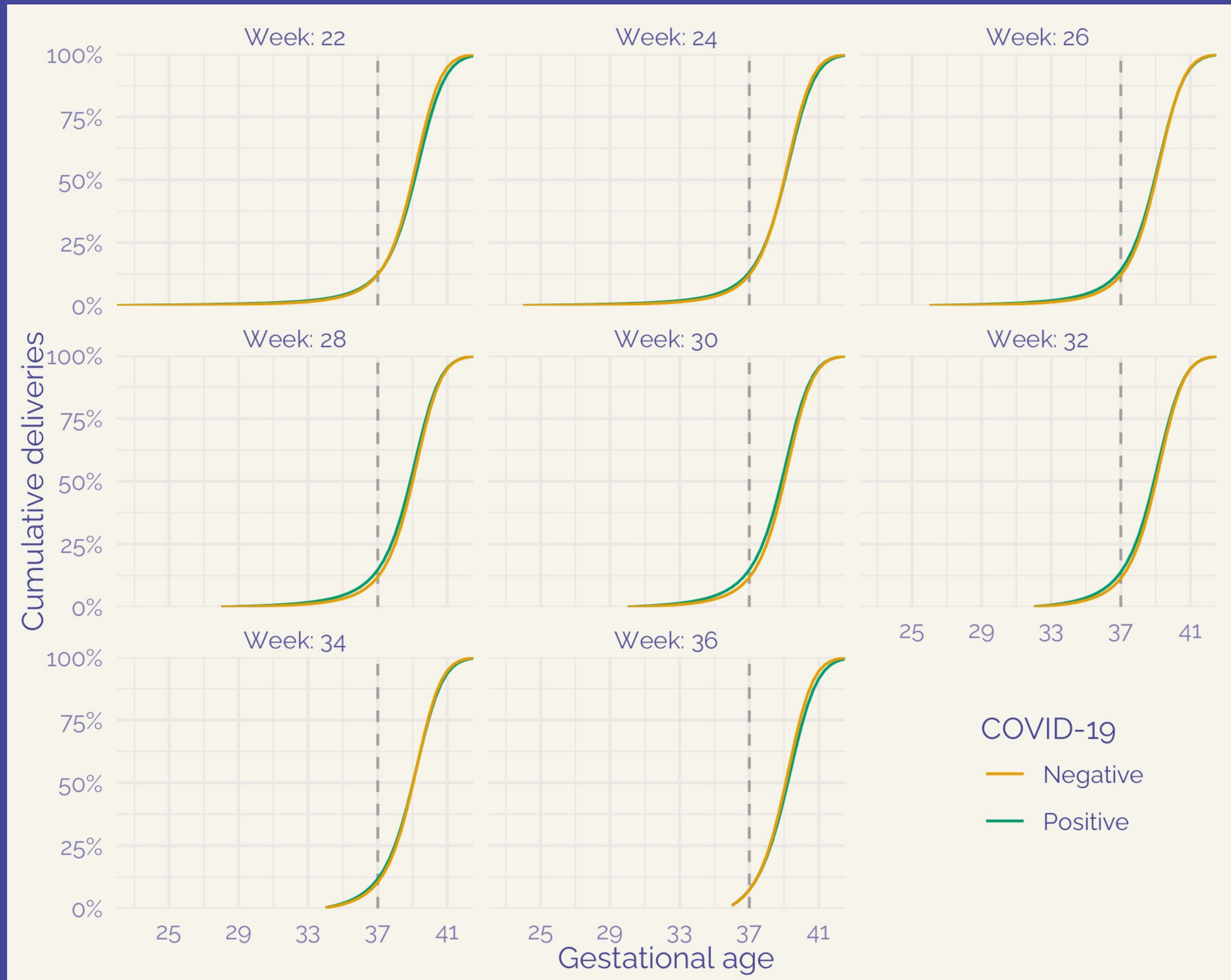
Unadjusted cumulative deliveries



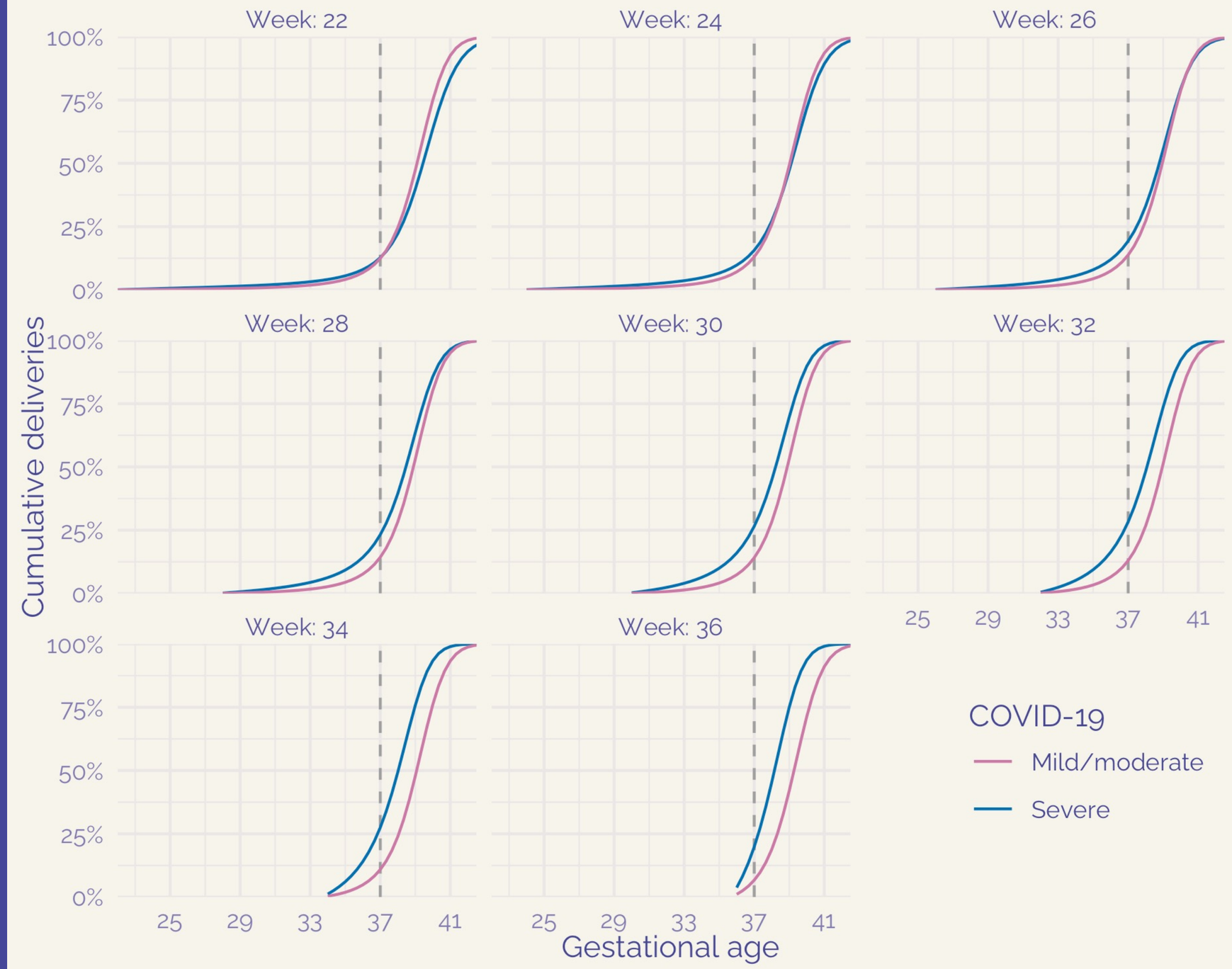
Standardized cumulative delivery curves

- Fit a model for daily hazard of delivery
  - Pooled logistic regression model conditional on confounders (continent, maternal age, pre-pregnancy BMI, parity, race/ethnicity, pre-existing condition, healthcare coverage, reason for testing), infection/severity, time since infection
  - Allow delivery rate to vary over gestational age (cubic splines), and effects of infection to vary over gestational age as well (interaction terms)
- For every “time zero” week, estimate delivery hazards in weeks 20+ given observed distribution of covariates in test-negative participants still pregnant
  - Had everyone been negative but still pregnant that week, positive with mild/moderate infection that week, positive with severe infection that week

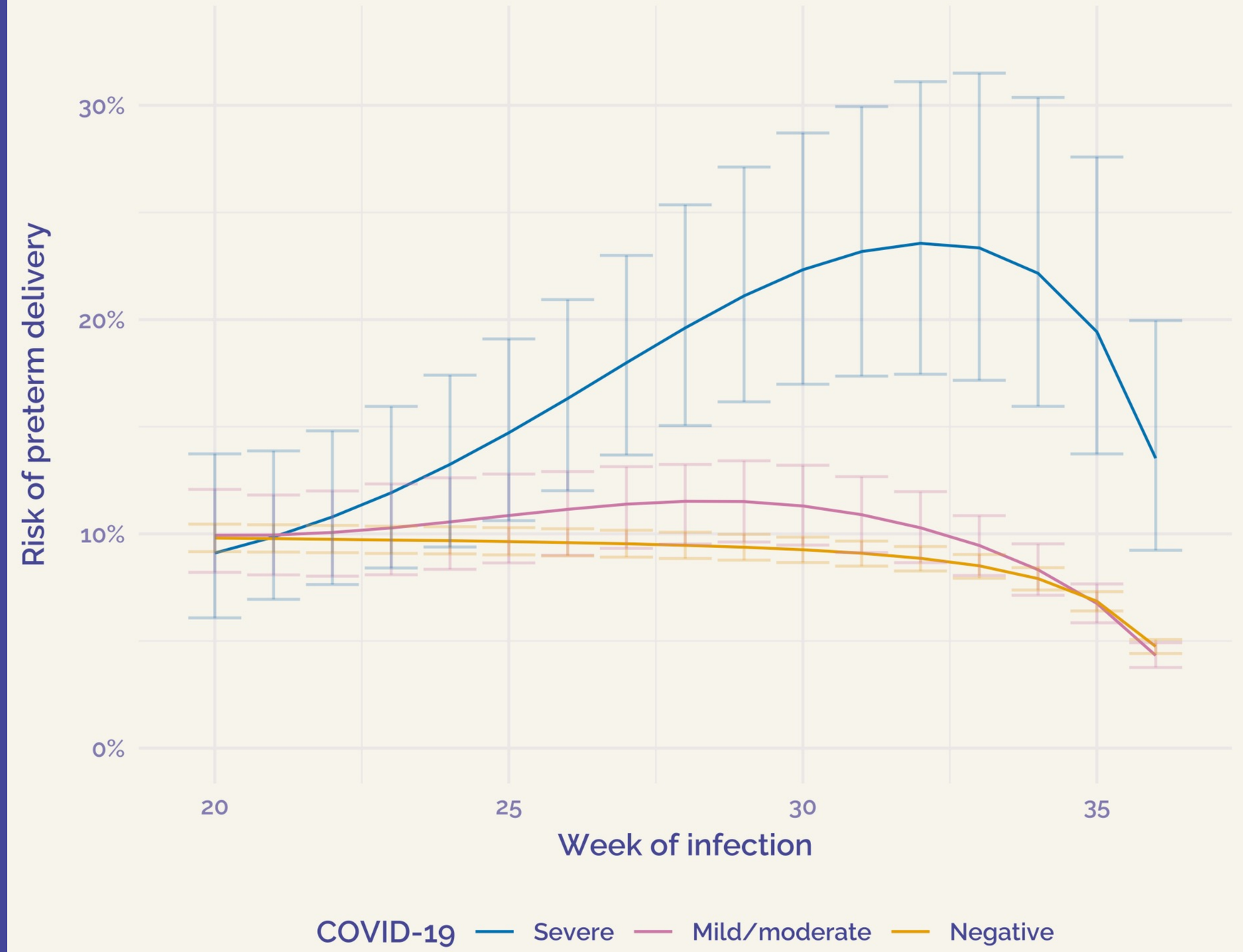
Adjusted cumulative deliveries



Adjusted cumulative deliveries



Risks over pregnancy



Strengths and Limitations

Loss to follow-up

Outcomes are missing for most prospective participants – some still pregnant, others lost to follow-up.

Gestational-age-specific absolute and relative risks

We considered effects throughout gestation, including early infections.

Self-report

We did not have clinical measures to classify severity (e.g., oxygen levels).

Additional analyses

We conducted multivariable regression analyses and a case-time-control analysis to support our findings, along with sensitivity analyses.