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ORIGINAL ARTICLE

Association between SARS-CoV-2 infection during pregnancy and postpartum depressive and anxiety symptoms: finding from the International Registry of Coronavirus Exposure in Pregnancy (IRCEP) study

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Abstract
While there has been concern over the perinatal mental health implications of the COVID-19 outbreak, evidence on the risk of postpartum depression and anxiety following SARS-CoV-2 infection is limited. We studied this question using the International Registry of Coronavirus Exposure in Pregnancy, which included both a prospective and retrospective cohort. Study participants were required to have been tested for SARS-CoV-2 between the date of last menstrual period and delivery. The exposure of interest was SARS-CoV-2 infection during pregnancy, as well as COVID-19 severity (severe, moderate, mild, and asymptomatic). The outcome was postpartum depression and anxiety symptoms, assessed by the 4-item Patient Health Questionnaire. The final analytic cohort consisted of 3819 participants (COVID-19 positive: 771; COVID-19 negative: 3048). After adjusting for confounding by socio-demographics, prior obstetric and maternal health comorbidities, mothers with severe COVID-19 had an increased risk of depressive (aRR: 1.72; 95%CI: 1.18–2.52) and anxiety (aRR: 1.40; 0.98–2.00) symptoms. The strength of the association was attenuated for women with moderate COVID-19 (aRR = 1.12; 0.86–1.44 for depressive symptoms; aRR = 1.18; 0.96–1.44 for anxiety symptoms). No increased risk was observed for mild or asymptomatic illness. The findings can inform targeted interventions to minimize the risk of adverse COVID-19-related mental health outcomes for pregnant women.

Keywords COVID-19 · Pregnancy · Mental health · Postpartum · Depression · Anxiety

Introduction

The coronavirus disease (COVID-19) pandemic has disrupted healthcare practices, disproportionately affecting vulnerable patients, including pregnant women.[1] Services were abruptly suspended, transitioning obstetric consultation visits to telehealth visits (Aziz et al. 2020; Fryer et al. 2020). Especially at the beginning of the pandemic, hospitals took unprecedented approaches regarding delivery visitor policies to reduce the exposures, including restricting families from entering maternity wards or imposing mother-neonate separation (Yeo et al. 2020; Bo et al. 2021). Fear of contagion by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or feelings of isolation due to social distancing are some important psychosocial factors that may worsen mental health. Due to these disruptions and concerns about the effect of the virus, the initial COVID-19 outbreak has been a collective anxiety-provoking experience that has imposed great emotional stress on pregnant mothers (Grumi et al. 2021). The psychological consequences of the pandemic warrant attention because it has been well documented that significant prenatal stress is associated with the risk of postpartum depression and anxiety (Boyce 2003;

[1] Use of inclusive language: The terms "woman" or "mother" are being used throughout the manuscript. These should be taken to include people who do not identify as women but are pregnant or have given birth.

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Dennis et al. 2017). Furthermore, a bidirectional association between depression and inflammatory conditions has been suggested; those who were affected with COVID-19 may experience physiological responses that can also exacerbate mental health (Senra 2021).

Several prior studies have assessed the perinatal mental health impact of the COVID-19 pandemic and reported that pandemic-related distress is associated with an increased risk of postpartum mental health symptoms (Effati-Daryani et al. 2020; Fallon et al. 2021; Farrell et al. 2020; Basu et al. 2021). However, most of these cross-sectional studies were conducted among pregnant women who were never tested nor confirmed for SARS-CoV-2 (Bo et al. 2021; Effati-Daryani et al. 2020; Fallon et al. 2021; Farrell et al. 2020). Consequently, while it is well accepted that the risk of postpartum depression and anxiety is increased during the pandemic, it is unclear whether the risk differs between pregnant women with versus without confirmed SARS-CoV-2 infection. The few existing studies addressing this question had insufficient power to detect small to moderate increases in risk and did not evaluate the effect of disease severity (Ceulemans et al. 2021; Kotabagi et al. 2020).

Our study objectives were therefore (1) to evaluate whether SARS-CoV-2 infection during pregnancy elevates the risk of depressive and/or anxiety symptoms during the postpartum period compared to individuals who tested negative during pregnancy and (2) to determine whether the risk of depressive and anxiety symptoms increases with greater COVID-19 severity levels in comparison to the negative group.

Methods

Study design and setting

The data source is the International Registry of Coronavirus Exposure in Pregnancy (IRCEP), a multinational web-based registry that includes participants residing in 68 countries. Recruitment occurred though a dedicated IRCEP website (https://corona.pregistry.com/), through social media platforms (e.g., Facebook and Instagram) and maternal health interest websites. Enrollment was voluntary, and eligible women gave consent through the IRCEP website. The survey was made available in 10 languages (English, Spanish, French, German, Italian, Portuguese, Hindi, Russian, Mandarin, and Urdu). The IRCEP protocol was approved by the Harvard Longwood Campus Institutional Review Board (IRB20-0622).

Pregnant women > 18 years, or those who had been pregnant within the last 6 months, who had been tested for SARS-CoV-2 (regardless of the result) or had been clinically diagnosed with COVID-19, were eligible. The registry included both *prospective* and *retrospective* enrollees (Hernández-Díaz et al. 2022). The prospective cohort included pregnant women who enrolled before delivery or pregnancy loss and were followed from the time of testing or diagnosis until 3 months after delivery or pregnancy loss. At enrollment, the prospective enrollees completed modules on baseline characteristics, the timing of SARS-CoV-2 testing and COVID-19 clinical signs, duration, severity, and treatment. Monthly follow-up was conducted until delivery when obstetric and neonatal outcomes were collected. The retrospective cohort included pregnant women who enrolled during the first 180 days after delivery. These retrospective enrollees completed most modules at enrollment and postpartum outcomes at the latest of 90 days or enrollment.

The study data timeframe is between June 2020 and August 2021; 19,753 subjects enrolled during this timeframe; all gave birth to a liveborn infant (Fig. 1). We excluded individuals who did not meet the registry eligibility criteria: not having SARS-CoV-2 infection status nor COVID-19 related clinical confirmation ($n = 1993$), inconclusive SARS-CoV-2 test results or unknown clinical diagnosis ($n = 227$), and COVID-19 diagnosis after delivery ($n = 60$). Among the 17,473 remaining individuals, 9394 (54%) were prospective, and 8079 (46%) were retrospective enrollees.

We subsequently excluded participants (1) who had missing mental health outcome information ($N = 12,157$) or (2) answered "Unsure" for mental health outcomes ($N = 564$) resulting in uncertain outcome status, (3) who tested negative but were symptomatic ($N = 412$) resulting in uncertain exposure status, and (4) who had missing information on baseline covariates ($N = 521$). Among the remaining 3819 participants, 3557 (93.1%) were retrospective, and 262 (6.86%) were prospective enrollees, indicating a large loss to follow-up in the prospective cohort. In comparison to participants included in our final analytic cohort, excluded participants were more likely to have tested positive, less likely to be White, to have graduated from college, to have come from higher socioeconomic status, or to have health insurance, and less likely to be considered a high-risk pregnancy. Excluded participants were also more likely to be from Asia or South America (Supplemental Table 2).

Exposure and outcome definition

Pregnant women with a positive nucleic acid or serologic test for SARS-CoV-2 *or* clinically confirmed COVID-19 between LMP and delivery were considered exposed ($N = 771$). Our reference group consisted of those with a negative SARS-CoV-2 test who displayed no clinical symptoms ($N = 3048$). In addition, we defined SARS-CoV-2 exposure across multiple severity levels by assessing patients' self-reported COVID-19-related symptoms during pregnancy

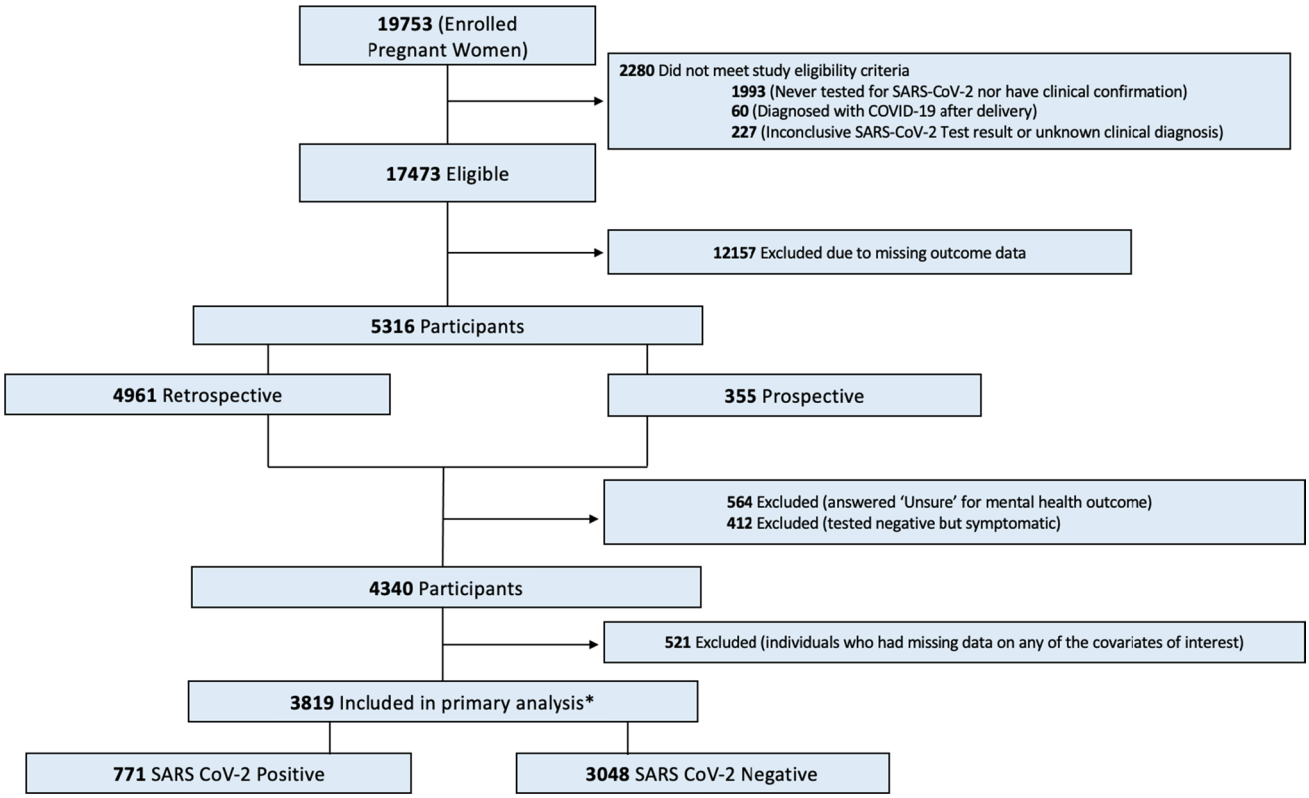

Fig. 1 Flow diagram of pregnant women exposed and unexposed to SARS-CoV-2 infection in IRCEP Registry. *Among the remaining 3819 participants, 3557 (93.1%) were retrospective, and 262 (6.86%) were prospective enrollees. Among the 3557 retrospective enrollees, 2298 participants (65%) were enrolled within 90 days, and 1259 participants (35%) were enrolled greater than 90 days after delivery

and any self-reported adverse events experienced due to COVID-19. We categorized the COVID-19 exposure as "severe" ($N=70$), "moderate" ($N=286$), "mild" ($N=233$), or "asymptomatic" ($N=182$) using the CDC's severity classification guideline (CDC 2021) (Supplemental Table 1).

The primary outcome was depressive and anxiety symptoms during the postpartum period, assessed within 180 days after delivery. We used the Patient Health Questionnaire-4 (PHQ-4), a four-item Likert scale which was found to be valid and reliable in an international sample of pregnant women (Barrera et al. 2021). Anxiety symptoms were defined as a score ≥ 3 on the anxiety subscale, and depressive symptoms were defined as a score ≥ 3 on the depression subscale. The PHQ-4 is a tool to screen for the presence of anxious and/or depressive symptoms; it does not determine a diagnosis of postpartum depression and anxiety. However, for simplicity, we will use the term "depression" and/or "anxiety" when referring to the outcomes of interest.

Covariates

All covariates were self-reported. We considered the following sociodemographic variables: age, race, education, employment status, socio-economic class, health insurance, and continent. Potential obstetric confounders included primiparity, pre-pregnancy BMI, and high-risk pregnancy as determined by the healthcare provider. From this list of candidate maternal conditions alleged to be risk factors for the outcome, confounders were selected based on a priori belief and based on between exposure group imbalances: chronic asthma, anxiety, depression, bipolar disorder, alcohol abuse, drug/prescription abuse, and eating disorder. Neonatal-related variables (e.g., preterm birth) and COVID-19 related variables (e.g., mother-baby separation after delivery) were not included to avoid adjusting for causal intermediates (Karasek et al. 2021; de Paula Eduardo et al. 2019; Richiardi et al. 2013).

Analyses

Balance with respect to baseline characteristics between COVID-19-positive and -negative women was assessed using absolute standardized mean differences (SMD), with an SMD > 0.1 considered evidence of imbalance. We performed a complete case analysis to handle missing data in our covariates, excluding 521 subjects with missing covariate information. We used log-binomial models to calculate absolute risks, unadjusted and adjusted relative risks with 95% confidence intervals.

Table 1 Unadjusted baseline characteristics of study cohort (binary exposure)

	Negative ($N=3048$)	Positive ($N=771$)	Standardized difference
Age			
Mean (SD)	30.6 (4.85)	30.4 (4.92)	0.0450
Median [min, max]	31.0 [18.0, 47.0]	30.0 [18.0, 42.0]	
Race/ethnicity			
White	2197 (72.1%)	457 (59.3%)	0.2607
Black	94 (3.1%)	30 (3.7%)	0.0417
Latina	383 (12.6%)	158 (20.5%)	0.1964
Asian/Pacific Islander	150 (4.9%)	35 (4.5%)	0.0183
Mixed	213 (7.0%)	87 (10.6%)	0.1183
Other	11 (0.4%)	9 (1.2%)	0.0751
Education			
Graduate education	840 (27.6%)	205 (26.6%)	0.0220
College	1197 (39.3%)	310 (40.2%)	0.0191
High school	896 (29.4%)	226 (29.3%)	0.0018
Less than high school	115 (3.8%)	30 (3.9%)	0.0061
Employment status			
Unemployed	212 (7.0%)	58 (7.5%)	0.0215
Unemployed, not looking	517 (17.0%)	125 (16.2%)	0.0203
Usually, but not now (pregnancy/pandemic)	825 (27.1%)	195 (25.3%)	0.0408
Working away from home	629 (20.6%)	188 (24.4%)	0.0873
Working from home	865 (28.4%)	205 (26.6%)	0.0405
Economic class			
Wealthy	574 (18.8%)	131 (17.0%)	0.0490
Middle class	1442 (47.3%)	370 (48.0%)	0.0136
Lower-middle class	726 (23.8%)	211 (27.4%)	0.0796
Poor	306 (10.0%)	59 (7.7%)	0.0898
Has health insurance	2733 (89.7%)	667 (86.5%)	0.0923
Pre-pregnancy BMI category			
<18.5	96 (3.1%)	25 (3.2%)	0.0052
18.5–25	1277 (41.9%)	353 (45.8%)	0.0780
25–30	781 (25.6%)	195 (25.3%)	0.0076
≥ 30	894 (29.3%)	198 (25.7%)	0.0835
Continent			
North America	1430 (46.9%)	301 (39.0%)	0.1614
Europe	1064 (34.9%)	224 (29.1%)	0.1290
South America	274 (9.0%)	168 (21.8%)	0.3101
Asia	129 (4.2%)	42 (5.4%)	0.0535
Others	151 (5.0%)	36 (4.7%)	0.0135
Primiparous	1465 (48.1%)	324 (42.0%)	0.1224
High-risk pregnancy			
Yes	993 (32.6%)	208 (27.0%)	0.1262
No	2018 (66.2%)	555 (72.0%)	0.1286
I don't know	37 (1.2%)	8 (1.0%)	0.0174
Asthma	300 (9.8%)	42 (5.4%)	0.1937
Anxiety	676 (22.2%)	119 (15.4%)	0.1867
Depression	412 (13.5%)	65 (8.4%)	0.1831
Bipolar disorder	65 (2.1%)	7 (0.9%)	0.1291
Drug abuse	10 (0.3%)	1 (0.1%)	0.0551
Eating disorder	44 (1.4%)	4 (0.5%)	0.1287

Table 1 (continued)

	Negative ($N=3048$)	Positive ($N=771$)	Standardized difference
Alcohol abuse	9 (0.3%)	2 (0.3%)	0.0071
Testing reason: clinical evaluation (I had symptoms)	45 (1.5%)	383 (49.7%)	0.9640
Testing reason: routine surveillance (healthy population screening)	1126 (36.9%)	102 (13.2%)	0.6999
Testing reason: travelled to a risk zone	92 (3.0%)	6 (0.8%)	0.2549
Testing reason: contact with an infected person	206 (6.8%)	221 (28.7%)	0.4844
Testing reason: other	1717 (56.3%)	192 (24.9%)	0.7268

We utilized propensity scores (PS)—estimated using logistic regression including the above specified covariates—to account for potential confounding by observed baseline characteristics. We implemented different PS adjustment approaches. First, COVID-positive versus negative women were matched 1:2 on the logit of the PS using a nearest-neighbor approach with a 0.2 caliper distance. Second, we performed inverse probability of treatment weighting (IPTW) and set the estimand to the average treatment effect for the treated (ATT), defining the COVID-positive group as the treated group. Analyses were performed with 2 levels of adjustment: (1) adjustment for pre-existing depression and anxiety and (2) further adjustment for all confounding variables. A robust sandwich variance estimator was used to calculate the 95% CI. Given the similarity of results across adjustment approaches for the binary exposure, only the IPTW approach was implemented for the analysis by severity level.

Sensitivity analyses were conducted to test the robustness of our primary results. First, we restricted our cohort to pregnant women without self-reported affective disorders (depression, anxiety, and bipolar disorder) at baseline to further reduce the risk of confounding by pre-existing disease. Second, since the study population was restricted to pregnant women who were tested for SARS-Cov-2 or received a COVID-19 diagnosis, there is potential for collider bias if we were not adjusting for all factors associated with testing and the outcome; that is, women with a negative SARS-Cov-2 test may not be representative of the entire population of pregnant women without SARS-Cov-2 and may have higher levels of depression and/or anxiety at baseline. For the analyses by severity level, we therefore redefined the study reference group to consist of women who tested positive but had mild symptoms since these women are likely to be more comparable to other COVID-19 severity levels than women who tested negative. All analyses were performed using R studio, version 4.0.2.

Results

Overall, the SARS-Cov-2-positive and -negative groups were well balanced, with a few exceptions. Infected women were less likely than non-infected women to be White and more likely to be Latina. They were also less likely to be primiparous, to have a high-risk pregnancy, and to have comorbid illnesses at baseline (Table 1, Supplement Table 3). When stratified by severity groups, severely infected groups were more likely to be Black or Asian than the less severely infected or negative group. They were also more likely to be of lower socioeconomic status than the other severity groups. In addition, the severely infected group had lower prevalence of baseline chronic depression and anxiety levels than the negative group (Table 2).

Among 771 infected women, 128 reported depression (16.6%), and 174 reported anxiety (22.6%) during the postpartum period. Among 3048 non-infected women, 495 reported depression (16.2%), and 736 reported anxiety (24.2%). This corresponds to an unadjusted relative risk (RR) of 1.02 (95% CI: 0.86–1.22) for depression and 0.93 (95% CI: 0.81–1.08) for anxiety (Table 3).

We observed sufficient distributional overlap of the PS between the binary exposure groups (Supplemental Fig. 1), and all covariates were balanced after PS adjustment through matching and weighting (Supplemental Figs. 2, 3, 4, and 5). The effect estimate remained largely unchanged across either method of adjustment. For example, PS matching resulted in a RR of 0.98 [0.80, 1.19] for depression and 0.91 [0.77, 1.06] for anxiety (Fig. 2).

The risk of depression was 31.4% among women with severe, 19.2% among women with moderate, 12.5% among women with mild, and 12.1% among women with asymptomatic infection, corresponding to unadjusted RR of 1.94 (95% CI: 1.31–2.67), 1.18 (95% CI: 0.91–1.50), 0.77 (95% CI: 0.53–1.07), and 0.74 (95% CI: 0.48–1.07), respectively, compared with non-infected women. For

Table 2 Unadjusted baseline characteristics of study cohort stratified by COVID-19 severity (multilevel exposure)

	Severe ($N=70$)	Moderate ($N=286$)	Mild ($N=233$)	Asymptomatic ($N=182$)	Negative ($N=3048$)	Standardized difference (pooled)
Age						
Mean (SD)	31.0 (4.23)	30.3 (5.13)	30.4 (4.67)	30.3 (5.15)	30.6 (4.85)	0.1381
Median [min, max]	31.0 [22.0, 40.0]	30.0 [19.0, 42.0]	30.0 [18.0, 40.0]	30.0 [19.0, 41.0]	31.0 [18.0, 47.0]	
Race/ethnicity						
White	32 (45.7%)	175 (61.2%)	149 (63.9%)	101 (55.5%)	2197 (72.1%)	0.5463
Asian/Pacific Islander	8 (11.4%)	4 (1.4%)	7 (3.0%)	16 (8.8%)	150 (4.9%)	0.4309
Black	6 (8.6%)	11 (3.8%)	8 (3.4%)	5 (2.7%)	94 (3.1%)	0.2883
Latina	13 (18.6%)	57 (19.9%)	44 (18.9%)	44 (24.2%)	383 (12.6%)	0.2950
Mixed	8 (11.4%)	38 (13.3%)	22 (9.4%)	14 (7.7%)	213 (7.0%)	0.2128
Other	3 (4.3%)	1 (0.3%)	3 (1.3%)	2 (1.1%)	11 (0.4%)	0.3288
Education						
Graduate education	12 (17.1%)	78 (27.3%)	66 (28.3%)	49 (26.9%)	840 (27.6%)	0.2508
College	34 (48.6%)	118 (41.3%)	93 (39.9%)	65 (35.7%)	1197 (39.3%)	0.2664
High school	20 (28.6%)	81 (28.3%)	66 (28.3%)	59 (32.4%)	896 (29.4%)	0.0861
Less than high school	4 (5.7%)	9 (3.1%)	8 (3.4%)	9 (4.9%)	115 (3.8%)	0.1281
Employment status						
Unemployed	3 (4.3%)	25 (8.7%)	12 (5.2%)	18 (9.9%)	212 (7.0%)	0.2183
Unemployed, not looking	10 (14.3%)	47 (16.4%)	42 (18.0%)	26 (14.3%)	517 (17.0%)	0.1064
Usually, but not now (pregnancy/pandemic)	26 (37.1%)	67 (23.4%)	46 (19.7%)	56 (30.8%)	825 (27.1%)	0.3908
Working away from home	10 (14.3%)	81 (28.3%)	65 (27.9%)	32 (17.6%)	629 (20.6%)	0.3431
Working from home	21 (30.0%)	66 (23.1%)	68 (29.2%)	50 (27.5%)	865 (28.4%)	0.1551
Economic class						
Wealthy	4 (5.7%)	50 (17.5%)	44 (18.9%)	33 (18.1%)	574 (18.8%)	0.3629
Middle class	37 (52.9%)	125 (43.7%)	124 (53.2%)	84 (46.2%)	1442 (47.3%)	0.1955
Lower-middle class	22 (31.4%)	77 (26.9%)	60 (25.8%)	52 (28.6%)	726 (23.8%)	0.1711
Poor	7 (10.0%)	34 (11.9%)	5 (2.1%)	13 (7.1%)	306 (10.0%)	0.3568
Has health insurance	63 (90.0%)	253 (88.5%)	202 (86.7%)	149 (81.9%)	2733 (89.7%)	0.2426
Pre-pregnancy BMI category						
<18.5	2 (2.9%)	10 (3.5%)	10 (4.3%)	3 (1.6%)	96 (3.1%)	0.1545
18.5–25	23 (32.9%)	116 (40.6%)	124 (53.2%)	90 (49.5%)	1277 (41.9%)	0.4108
25–30	19 (27.1%)	78 (27.3%)	55 (23.6%)	43 (23.6%)	781 (25.6%)	0.0867
≥ 30	26 (37.1%)	82 (28.7%)	44 (18.9%)	46 (25.3%)	894 (29.3%)	0.4091
Continent						
North America	18 (25.7%)	140 (49.0%)	92 (39.5%)	51 (28.0%)	1430 (46.9%)	0.4887
Europe	24 (34.3%)	68 (23.8%)	75 (32.2%)	57 (31.3%)	1064 (34.9%)	0.2409
Asia	6 (8.6%)	7 (2.4%)	10 (4.3%)	19 (10.4%)	129 (4.2%)	0.3371
South America	18 (25.7%)	62 (21.7%)	42 (18.0%)	46 (25.3%)	274 (9.0%)	0.4237
Others	4 (5.7%)	9 (3.1%)	14 (6.0%)	9 (4.9%)	151 (5.0%)	0.1332
Primiparous	23 (32.9%)	107 (37.4%)	101 (43.3%)	93 (51.1%)	1465 (48.1%)	0.3779
High-risk pregnancy						
Yes	27 (38.6%)	91 (31.8%)	48 (20.6%)	42 (23.1%)	993 (32.6%)	0.3970
No	41 (58.6%)	193 (67.5%)	184 (79.0%)	137 (75.3%)	2018 (66.2%)	0.4457

Table 2 (continued)

	Severe ($N=70$)	Moderate ($N=286$)	Mild ($N=233$)	Asymptomatic ($N=182$)	Negative ($N=3048$)	Standardized difference (pooled)
I don't know	2 (2.9%)	2 (0.7%)	1 (0.4%)	3 (1.6%)	37 (1.2%)	0.2094
Asthma	3 (4.3%)	21 (7.3%)	12 (5.2%)	6 (3.3%)	300 (9.8%)	0.2781
Anxiety	7 (10.0%)	59 (20.6%)	29 (12.4%)	24 (13.2%)	676 (22.2%)	0.3379
Depression	3 (4.3%)	38 (13.3%)	17 (7.3%)	7 (3.8%)	412 (13.5%)	0.3526
Bipolar disorder	2 (2.9%)	2 (0.7%)	1 (0.4%)	2 (1.1%)	65 (2.1%)	0.2041
Drug abuse	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	10 (0.3%)	0.0951
Eating disorder	0 (0%)	1 (0.3%)	2 (0.9%)	1 (0.5%)	44 (1.4%)	0.1813
Alcohol abuse	0 (0%)	2 (0.7%)	0 (0%)	0 (0%)	9 (0.3%)	0.1573
Testing reason: clinical evaluation (i had symptoms)	50 (71.4%)	206 (72.0%)	122 (52.6%)	5 (2.7%)	45 (1.5%)	1.8910
Testing reason: routine surveillance (healthy population screening)	4 (5.7%)	18 (6.3%)	22 (9.5%)	58 (31.7%)	1126 (36.9%)	0.8674
Testing reason: travelled to a risk zone	0 (0%)	2 (0.7%)	3 (1.3%)	1 (0.5%)	92 (3.0%)	0.2893
Testing reason: contact with an infected person	22 (31.4%)	88 (30.8%)	84 (36.2%)	27 (14.8%)	206 (6.8%)	0.7149
Testing reason: other	6 (8.6%)	37 (12.9%)	48 (20.7%)	101 (55.2%)	1717 (56.3%)	1.1595

anxiety, the risks were 32.9% for severe, 28.7% for moderate, 15.9% for mild, and 17.5% for asymptomatic infection, corresponding to unadjusted RR of 1.36 (95% CI: 0.93–1.85), 1.19 (95% CI: 0.97–1.43), 0.66 (95% CI: 0.48–0.88) and 0.72 (95% CI: 0.51–0.98), respectively, compared with non-infected women (Table 3).

We again observed sufficient distributional overlap of the PS between the exposure groups (Supplemental Figs. 6, 7, 8, and 9), and all covariates were balanced after PS weighting (Supplemental Figs. 10, 11, 12, and 13). Compared with non-infected women, fully adjusted analyses for severe infection resulted in a RR of 1.72 (95% CI: 1.18–2.52) for depression and a RR of 1.40 (95% CI: 0.98–2.00) for anxiety. The corresponding estimates for moderate infection were 1.12 (95% CI: 0.86–1.44) for depression and 1.18 (95% CI: 0.96–1.44) for anxiety. No association was observed for mild and asymptomatic infection (Figs. 3 and 4).

Restricting the cohort to those without baseline affective disorders in sensitivity analyses did not substantially alter the adjusted estimates (Table 4; Supplemental Figs. 14 and 15). Using mild and asymptomatic COVID-19 as alternative reference groups strengthened the adjusted estimates somewhat. For severe infection, results were consistent with a 2- to threefold increase for depression and a twofold increase for anxiety. For moderate infection, results were consistent with a 50% increase for both depression and anxiety (Supplemental Fig. 16).

Discussion

Among 3819 participants, no association was observed between testing positive for SARS-CoV-2 during pregnancy and the risk for depression and anxiety during the postpartum period. However, women with severe COVID-19 had a 1.7-fold increased risk of depression and a 1.4-fold increased risk of anxiety, compared to the non-infected group.

Our null findings for depression and anxiety among the SARS-CoV-2-infected versus non-infected group is consistent with results from a pilot case–control study conducted in the UK ($n=14$ COVID-19-positive pregnant women) (Kotabagi et al. 2020) and from a cross-sectional study conducted in Europe ($n=56$ COVID-19-positive pregnant and breastfeeding women) (Ceulemans et al. 2021). However, neither study stratified on disease severity.

No prior studies have assessed the effect of COVID-19 disease severity on pregnant women's mental health during the postpartum period. However, a study by Magnúsdóttir et al. (2022) assessed the prevalence of depression

Table 3 Prevalence of depression and anxiety among COVID-19 positive vs. negative; severity levels vs. negative pregnant women

Target population	Depression				Anxiety			
	No. of patients	No. of events	Absolute risk (%) [95% CI]	Unadjusted RR [95% CI]	No. of patients	No. of events	Absolute risk (%) [95% CI]	Unadjusted RR [95% CI]
Positive vs. negative								
Infected (overall)	771	128	16.6 [14.1, 19.4]	1.02 [0.86, 1.22]	771	174	22.6 [19.8, 25.7]	0.93 [0.81, 1.08]
Non-infected	3048	495	16.2 [15.0, 17.6]		3048	736	24.2 [22.7, 25.7]	
Severe vs. negative								
Infected (overall)	70	22	31.4 [21.4, 43.0]	1.94 [1.31, 2.67]	70	23	32.9 [23.0, 44.5]	1.36 [0.93, 1.85]
Non-infected	3048	495	16.2 [15.0, 17.6]		3048	736	24.2 [22.7, 25.7]	
Moderate vs. negative								
Infected (overall)	286	55	19.2 [15.0, 24.1]	1.18 [0.91, 1.50]	286	82	28.7 [23.7, 34.2]	1.19 [0.97, 1.43]
Non-infected	3048	495	16.2 [15.0, 17.6]		3048	736	24.2 [22.7, 25.7]	
Mild vs. negative								
Infected (overall)	233	29	12.5 [8.8, 17.3]	0.77 [0.53, 1.07]	233	37	15.9 [11.8, 21.1]	0.66 [0.48, 0.88]
Non-infected	3048	495	16.2 [15.0, 17.6]		3048	736	24.2 [22.7, 25.7]	
Asymptomatic vs. negative								
Infected (overall)	182	22	12.1 [8.1, 17.6]	0.74 [0.48, 1.07]	182	32	17.5 [12.7, 23.8]	0.72 [0.51, 0.98]
Non-infected	3048	495	16.2 [15.0, 17.6]		3048	736	24.2 [22.7, 25.7]	

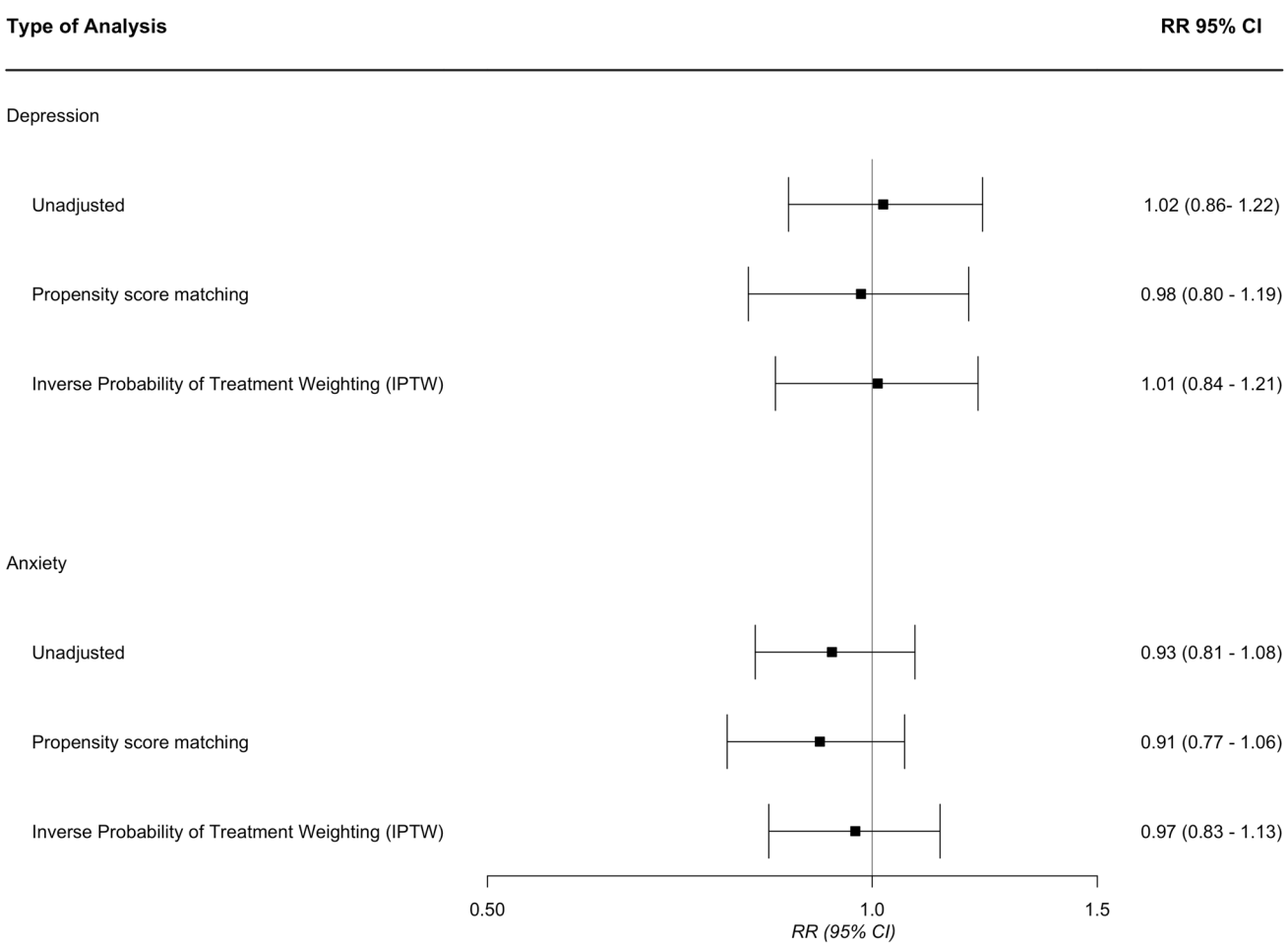

Fig. 2 Relative risk of depression and anxiety among COVID-19-positive vs. -negative (ref.) pregnant women

and anxiety in the general population and found that individuals with severe COVID-19 (indicated by number of days confined to bed) were at higher risk of depression (PR = 1.61 [95% CI: 1.27–2.05]) and anxiety (PR = 1.43 [95% CI: 1.26–1.63]) than those not diagnosed with COVID-19. In addition, the study reported that individuals with mild COVID-19 were consistently at lower risk of depression (PR = 0.83 [95% CI: 0.75–0.91]) and anxiety (PR = 0.77 [0.63–0.94]) than those not diagnosed with COVID-19. These findings highlighted the importance of providing clinical vigilance among individuals with the most severe COVID-19 illness, an observation that is compatible with our study result among pregnant women.

Study strengths include the large cohort size, its international nature, and the availability of infection severity. However, the study has several limitations.

First, both the SARS-Cov-2-positive and -negative groups had been tested at least once for the virus in our cohort. Although most were the result of screening around delivery, the negative group may have been enriched by a self-selected sample of women who had high baseline anxiety and therefore "chose" to receive testing despite being asymptomatic. This group might therefore not be representative of the non-infected pregnant women in the general population; they might be more susceptible to increased anxiety and depression levels postpartum which would bias towards the null. To explore this potential collider bias, we switched our reference group from the negative to the mild group in the analyses by COVID-19 severity level. This slightly strengthened the results for both depression and anxiety although the confidence intervals largely overlapped. These result hint at the possibility of selection bias in that the negative group may already have had high baseline anxiety and depression levels (which are not necessarily self-reported at baseline), and as a result, the effect estimates might be somewhat diluted.

Other limitations include the loss to follow-up in our prospective cohort, resulting in the retrospective cohort

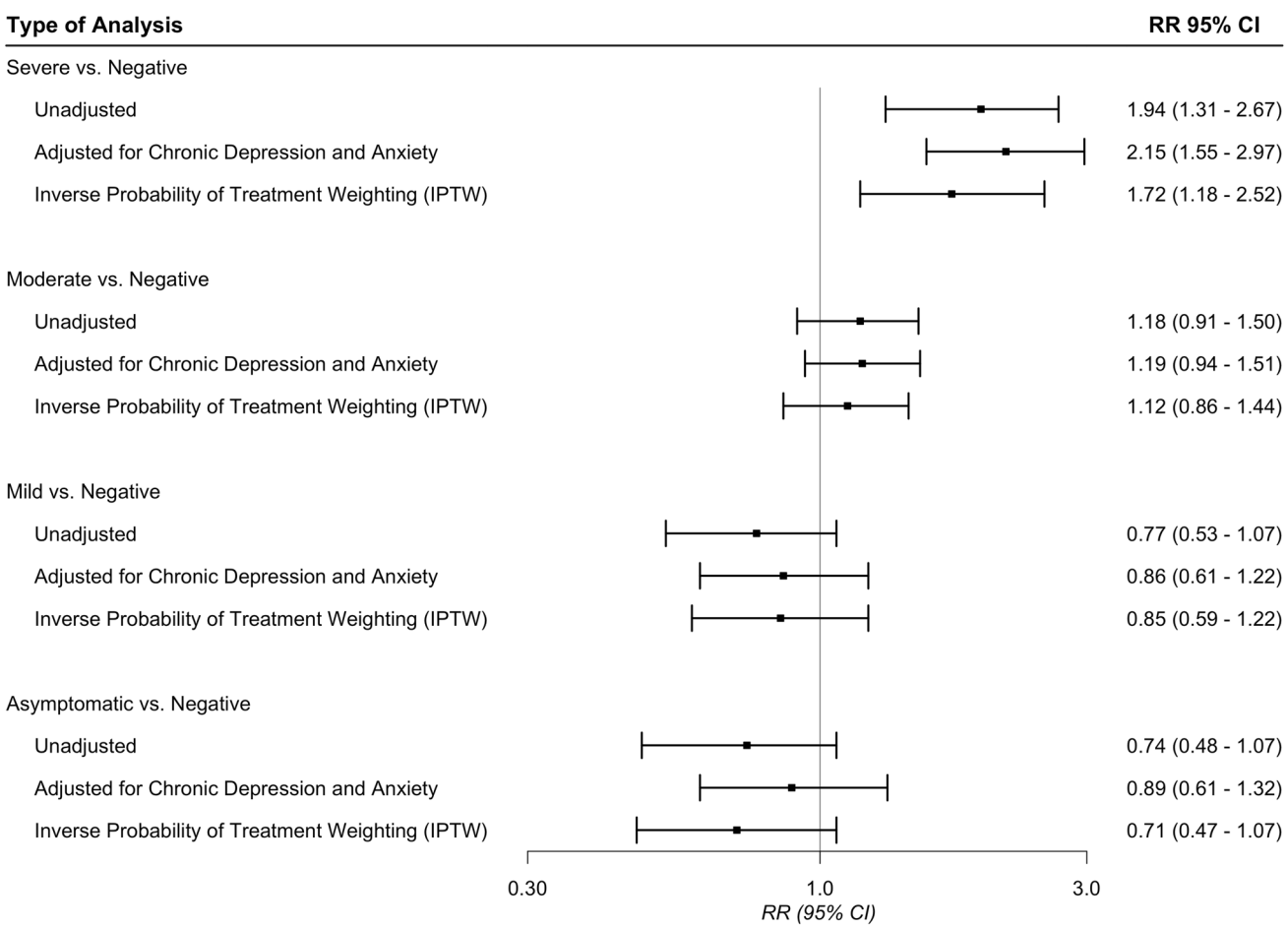

Fig. 3 Relative risk of depression across COVID-19 severity levels vs. negative (ref)

comprising most of our study population. Although exposure was assessed retrospectively in that group, we do not suspect recall bias being present because it is unlikely that subjects with the outcome will recall and self-report SARS-CoV-2 infection during pregnancy more accurately than subjects without the outcome. The variable timing of the outcome assessment among the retrospective enrollees, who enrolled more than 90 days following delivery ($N = 1259$, 33%), however, is a limitation. This sub-group completed the PHQ-4 anytime between 90 and 180 days postdelivery. Women lost to follow-up were more likely to be non-White and of lower educational and socio-economic status, which could affect the generalizability of the findings. A more personalized and proactive contact with enrollees might help to attain higher retention rates in future studies (Hernández-Díaz et al. 2022).

Pre-existing mental health diagnoses (i.e., chronic anxiety and depression) were self-reported, as were all the other variables. Baseline pre-existing mental health diagnoses may have been underreported, and it is possible that women with postpartum symptoms are more likely to accurately report baseline mental health diagnoses than women who do not experience the outcome. While this misclassification will likely be non-differential according to exposure level, it could have resulted in an underestimate of the association. There is also potential for misclassification between the severe and moderate groups in the definition of the severity level of exposure. This could have resulted in an underestimation of the strength of the association for the severe group and an overestimation for the moderate group.

Recruitment was solely conducted through social media platforms and websites, possibly resulting in a sample of women with higher socioeconomic status and easy internet access. Although vaccination was not available in the data, 97% of our study participants completed the survey in 2020 when the vaccine was

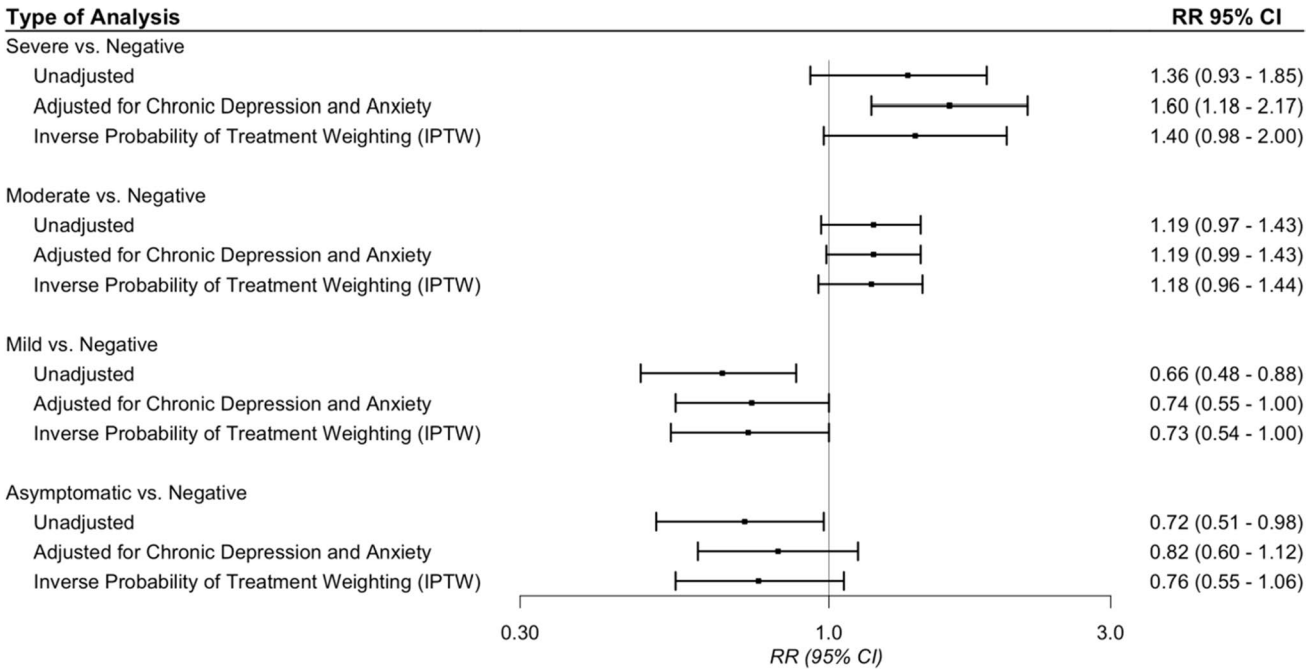

Fig. 4 Relative risk of anxiety across COVID-19 severity levels vs. negative (ref)

generally not available to the public. Due to the study being observational in nature, there is potential for unmeasured confounding. For example, we lacked data on the use of psychotropic medications that can inform the severity of pre-existing psychiatric diagnoses, and potentially important psychosocial factors (e.g., loss of loved ones). Although we adjusted for continent in our analyses, regional differences may still result in some residual confounding. It should also be emphasized that the PHQ-4 screens for the presence of anxious and/or depressive symptoms and does not determine a diagnosis of postpartum depression and anxiety (Rodríguez-Muñoz et al. 2020). Whether the severity of COVID-19 infection also affects clinical diagnoses is a potential area for future research. The translations of the PHQ-4 were not formally validated. Considering how there may be cross-cultural differences in the way women understand and interpret the items in the PHQ, this may have resulted in some non-differential misclassification of the outcome, which could have biased towards the null. Lastly, our study presents findings from survey data between June 2020 and August 2021. Due to the ongoing nature of COVID-19 pandemic with differing surging periods and viral mutations, the mental health impact on pregnant women is likely to change over time. For example, mental health symptoms may manifest differently depending on each emerging variant of concern due to the differing viral transmission speed, risk of severe outcomes such as hospitalization and death, and vaccine uptake in the community. Thus, our study findings need to be interpreted in the context of this dynamic COVID-19 situation.

Despite limitations, the study findings provide vital information about whom to target for perinatal mental health interventions. Our findings highlight the important risks associated with severe COVID-19, as the severity of the infection can lead to a unique stressful perinatal experience, exacerbated by the isolating pandemic contextual factors (Choi et al. 2022; Wyszynski et al. 2021). The finding that postpartum mental health is worse for women who experience severe infection during pregnancy beyond the already high level of depression experienced by non-infected postnatal women during the COVID-19 pandemic (Fallon et al. 2021; Jackson et al. 2021) calls for clinical attention to mitigate maternal mental health risk in this vulnerable group.

This pregnancy registry study suggests that pregnant women exposed to SARS-CoV-2 during pregnancy with severe COVID-19 symptoms are at considerably heightened risk of experiencing depressive symptoms and—to a lesser degree—anxiety symptoms during the postpartum period in comparison to a non-infected group. This group warrants clinical attention and targeted mental health intervention during the COVID-19 pandemic.

Table 4 Prevalence of depression and anxiety among COVID-19 positive vs. negative; severity levels vs. negative pregnant women stratified by baseline affective disorders (sensitivity analysis)

Target population	Depression				Anxiety			
	No. of patients	No. of events	Absolute risk (%) [95% CI]	Unadjusted RR [95% CI]	No. of patients	No. of events	Absolute risk (%) [95% CI]	Unadjusted RR [95% CI]
Positive (overall) vs. negative								
Restricted to affective disorders at baseline								
Infected	132	40	30.3 [23.1, 38.6]	1.06 [0.80, 1.41]	132	55	41.7 [33.6, 50.2]	1.01 [0.81, 1.25]
Non-infected	776	221	28.5 [25.4, 31.8]		776	321	41.4 [38.0, 44.9]	
Excluded affective disorders at baseline								
Infected	639	88	13.8 [11.3, 16.7]	1.14 [0.91, 1.43]	639	119	18.6 [15.8, 21.8]	1.02 [0.85, 1.23]
Non-infected	2272	274	12.1 [10.8, 13.5]		2272	415	18.3 [16.7, 19.9]	
Severe vs. negative								
Restricted to affective disorders at baseline								
Infected	8	4	50.0 [20.0, 80.0]	1.76 [0.87, 3.54]	8	4	50.0 [20.0, 80.0]	1.21 [0.60, 2.43]
Non-infected	776	221	28.5 [25.4, 31.8]		776	321	41.4 [38.0, 44.9]	
Excluded affective disorders at baseline								
Infected	62	18	29.0 [19.2, 41.3]	2.41 [1.53, 3.47]	62	19	30.6 [20.6, 43.0]	1.68 [1.09, 2.37]
Non-infected	2272	274	12.1 [10.8, 13.5]		2272	415	18.3 [16.7, 19.9]	
Moderate vs. negative								
Restricted to affective disorders at baseline								
Infected	66	22	33.3 [23.2, 45.3]	1.17 [0.79, 1.62]	66	31	47.0 [35.4, 58.8]	1.14 [0.84, 1.45]
Non-infected	776	221	28.5 [25.4, 31.8]		776	321	41.4 [37.9, 44.9]	
Excluded affective disorders at baseline								
Infected	220	33	15.0 [10.9, 20.4]	1.24 [0.87, 1.71]	220	51	23.2 [18.1, 29.2]	1.27 [0.97, 1.62]
Non-infected	2272	274	12.1 [10.8, 13.5]		2272	415	18.3 [16.7, 19.9]	
Mild vs. negative								
Restricted to affective disorders at baseline								
Infected	33	7	21.2 [10.7, 37.8]	0.74 [0.34, 1.32]	33	12	36.4 [22.2, 53.4]	0.88 [0.52, 1.30]
Non-infected	776	221	28.5 [25.4, 31.8]		776	321	41.4 [37.9, 44.9]	
Excluded affective disorders at baseline								
Infected	199	22	11.1 [7.42, 16.2]	0.92 [0.59, 1.34]	199	25	12.6 [8.66, 17.9]	0.69 [0.46, 0.98]
Non-infected	2272	274	12.1 [10.8, 13.5]		2272	415	18.3 [16.7, 19.9]	
Asymptomatic vs. negative								
Restricted to affective disorders at baseline								
Infected	25	7	28.0 [14.3, 47.6]	0.98 [0.46, 1.86]	25	8	32.0 [17.2, 51.6]	0.77 [0.39, 1.25]
Non-infected	776	221	28.5 [25.4, 31.8]		776	321	41.4 [37.9, 44.9]	
Excluded affective disorders at baseline								
Infected	158	15	9.50 [5.8, 15.1]	0.79 [0.46, 1.24]	158	24	15.2 [10.4, 21.6]	0.83 [0.55, 1.18]
Non-infected	2272	274	12.1 [10.8, 13.5]		2272	415	18.3 [16.7, 19.9]	

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00737-022-01274-0.

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Declarations

Ethics approval Approval was obtained from the Harvard Longwood Campus Institutional Review Board (IRB20-0622) and the procedures used in the study adhere to the ethical standards as laid down in the 1964 Declaration of Helsinki.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

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