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LIVING SYSTEMATIC REVIEW

Coronavirus disease 2019 pandemic and pregnancy and neonatal outcomes in general population: A living systematic review and meta-analysis (updated Aug 14, 2021)

Jie Yang[1] | Rohan D'Souza[2,3] | Ashraf Kharrat[1] | Deshayne B. Fell[4,5] | John W. Snelgrove[2] | Kellie E. Murphy[2,3,6] | Prakesh S. Shah[1,3,6]

[1]Department of Pediatrics, Mount Sinai Hospital, Toronto, Ontario, Canada

[2]Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

[3]Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada

[4]Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada

[5]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada

[6]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

Correspondence
Prakesh S. Shah, Department of Pediatrics, Mount Sinai Hospital, 19-231, 600 University Avenue, Toronto, ON M5G 1X5, Canada.
Email: Prakeshkumar.shah@sinaihealth.ca

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Abstract

Introduction: Conflicting reports of increases and decreases in rates of preterm birth (PTB) and stillbirth in the general population during the coronavirus disease 2019 (COVID-19) pandemic have surfaced. The objective of our study was to conduct a living systematic review and meta-analyses of studies reporting pregnancy and neonatal outcomes by comparing the pandemic and pre-pandemic periods.

Material and methods: We searched PubMed and Embase databases, reference lists of articles published up until August 14, 2021 and included English language studies that compared outcomes between the COVID-19 pandemic time period and the pre-pandemic time periods. Risk of bias was assessed using the Newcastle–Ottawa scale. We conducted random-effects meta-analysis using the inverse variance method.

Results: Forty-five studies with low-to-moderate risk of bias, reporting on 1 843 665 pregnancies during the pandemic period and 23 564 552 pregnancies during the pre-pandemic period, were included. There was significant reduction in unadjusted estimates of PTB (35 studies, unadjusted odds ratio [uaOR] 0.95, 95% CI 0.92–0.98), but not in adjusted estimates (six studies, adjusted OR [aOR] 0.95, 95% CI 0.80–1.13). This reduction was noted in studies from single centers/health areas (25 studies, uaOR 0.90, 95% CI 0.86–0.96) but not in regional/national studies (10 studies, uaOR 0.99, 95% CI 0.95–1.02). There was reduction in spontaneous PTB (six studies, uaOR 0.89, 95% CI 0.81–0.96) and induced PTB (five studies, uaOR 0.89, 95% CI 0.81–0.97). There was no difference in the odds of stillbirth between the pandemic and pre-pandemic time periods (24 studies, uaOR 1.11, 95% CI 0.97–1.26 and four studies, aOR 1.06, 95% CI 0.81–1.38). There was an increase in mean birthweight during the pandemic period compared with the pre-pandemic period (six studies, mean difference 17 g, 95% CI 7–28 g). The odds of maternal mortality were increased (four studies, uaOR

Abbreviations: aOR, adjusted odds ratio; COVID-19, coronavirus disease 2019; ELBW, extremely low birthweight; LBW, low birthweight; PTB, preterm birth; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; uaOR, unadjusted odds ratio; VLBW, very low birthweight.

This version updates the previous Living Systematic Review (https://doi.org/10.1111/aogs.14206)

1.15, 95% CI 1.05–1.26); however, only unadjusted estimates were available and the result was mostly influenced by one study from Mexico. There was significant publication bias for the outcome of PTB.

Conclusions: The COVID-19 pandemic may be associated with a reduction in PTB; however, referral bias cannot be excluded. There was no statistically significant difference in stillbirth between pandemic and pre-pandemic periods.

KEYWORDS
birthweight, epidemic, maternal mortality, neonatal mortality, preterm birth, severe acute respiratory syndrome coronavirus 2, stillbirth, stress

1 | INTRODUCTION

Most pregnancies end with healthy mothers and healthy children, but a small proportion result in adverse outcomes for the mother, fetus, or neonate. Among others, such outcomes include stillbirth, preterm birth (PTB), neonatal mortality, and maternal mortality—all of which can have devastating and long-lasting effects on families.[1–3] Preterm birth (birth before 37 weeks of gestation) is a major determinant of neonatal mortality and morbidity[4] with long-term adverse consequences during childhood and adulthood.[5] Medical, social, psychological, environmental, and economic factors have all been implicated in the etiopathogenesis of PTB and other adverse pregnancy outcomes.

The coronavirus disease 2019 (COVID-19) pandemic has had an unprecedented impact on society worldwide and provided a natural experiment allowing us to study the effects of these factors on adverse pregnancy outcomes. During the early stages of the pandemic, reports emerged describing reduced PTB rates in Denmark[6] and Ireland.[7] However, these were followed by reports of increased PTB rates (births between 28 and 32 weeks of gestation) in Nepal[8] and no changes in PTB rates in the UK[9] and Sweden.[10] At the same time, increases in stillbirth rates were reported from the UK[9] and Nepal,[8] with or without changes in PTB rates, whereas no change in the stillbirth rate was reported from Ireland.[2]

In light of these mixed reports, it is uncertain whether or not the COVID-19 pandemic has affected pregnancy outcomes at the population level. Inconsistency among conclusions from different studies and a lack of evidence to inform the creation of evidence-based population health guidance prompted us to undertake a comprehensive review of the influence of the COVID-19 pandemic on pregnancy outcomes. Our objective was to systematically review and meta-analyze studies reporting defined local, regional, or national population-based rates for maternal, fetal, and neonatal outcomes during the pandemic period compared with the pre-pandemic period.

Key message

Preterm birth may have reduced during the pandemic, especially spontaneous preterm births, but there was no difference in stillbirths. The reduction in preterm birth was only noted in single-center studies and in unadjusted estimates, raising the possibility of referral bias. Further studies from countries with high prevalence are needed and this review will be updated periodically.

Update findings

This is update #1 for this living systematic review and meta-analyses. The search was updated to August 14, 2021. Nine new eligible studies were identified, and their data were incorporated into this new analysis. An additional nine potentially eligible studies were identified; however, they are currently in abstract or pre-print format, so are not included in this update. One study, which was included in our previous version, is now excluded because of the availability of data from a larger cohort from the same region. The findings in this update are consistent with our previous version: the odds of PTB during the pandemic were significantly reduced in unadjusted estimates and in single-center/single-health-authority studies, but there was no difference in odds of PTB in studies using regional/national data. There was no difference in the odds of stillbirth between the pandemic and non-pandemic periods. There still exists the possibility of publication bias for outcome of preterm birth.

2 | MATERIAL AND METHODS

The review was conducted using standardized methods for systematic reviews of observational studies and reported according to the Preferred Reporting Items in Systematic Reviews and Meta-analyses guidelines.[11] No ethical approval was obtained because all data used for these analyses were published previously. The review protocol was registered in PROSPERO (CRD42021234036).[12] This is update #1 of a previously published review.[13]

2.1 | Data sources: Search strategy and selection criteria

We searched PubMed and Embase databases, reference lists of included articles, and personal files for studies published up to August 14, 2021. The search strategy used a combination of the

MeSH terms "preterm" or "stillbirth" AND "Covid19" or "SARS-CoV-2" and included any type of study design published in the English language (Appendix S1). As this is a living systematic review, it will be updated 3-monthly for the duration of the pandemic, using the same search strategy. Studies were included if they compared pregnancy outcomes between the COVID-19 pandemic period and pre-pandemic time periods and reported on any of the outcomes of interest. We excluded studies that only reported outcomes of pregnant women with COVID-19. Screening of articles was conducted by two authors (PS and JY) and disagreements were resolved through discussion (JY, RD and PS) and consensus. As we were interested in overall pregnancy outcomes, we did not restrict studies based on plurality (including both singleton and multiple pregnancies).

2.2 | Exposure

In most studies, the pandemic period was defined as the period beginning from the date or month of the implementation of emergency lockdown measures in relevant countries or states or cities, or when there was an emergence of cases or a surge of cases in the population studied. Some studies assessed "post-lockdown" period which for the purpose of this study was included as "pandemic" period as we are still not out of the pandemic yet. The pre-pandemic period was defined either as the period ending immediately before lockdown measures were implemented or before the emergence of the first case or high case numbers in the population, or as a historical period, such as births in the same population in previous year(s). The lengths of these periods varied across studies.

We included studies that reported outcomes of pregnancy in general population. The review was not designed to evaluate outcomes of pregnancies where only women affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were reported.

2.3 | Outcomes

The primary outcomes in this study were rates of PTB and stillbirth. Secondary outcomes included mean birthweight (continuous) and rates of low birthweight (LBW), spontaneous PTB, medically indicated PTB, and neonatal, perinatal, or maternal mortality. We contacted authors to obtain data on stillbirth and neonatal mortality when the outcomes were reported as "intrauterine fetal death" and "perinatal mortality". The outcomes of intrauterine fetal death and perinatal mortality, though specified in the protocol, were not included ultimately in the review (deviation from protocol). Outcomes were defined as follows:

1. Preterm birth: Live births between 22^{+0} and 36^{+6} weeks of gestation were classified as PTB. Data on PTB at <28 weeks, <32 weeks, and <34 weeks of gestation were reported separately in some studies and were analyzed independently.
2. Stillbirth: Death before the complete expulsion or extraction from the parturient of a product of human conception at or after 20 weeks of gestation.[14]
3. Birthweight: Infant weight in grams, measured as soon as possible after live birth. Birthweight <2500 g was defined as LBW, birthweight <1500 g was defined as very low birthweight (VLBW), and birthweight <1000 gram was defined as extremely low birthweight (ELBW).
4. Spontaneous PTB: Birth of a baby between 22^{+0} and 36^{+6} weeks of gestation following spontaneous preterm labor or preterm prelabor rupture of membranes.[3]
5. Medically indicated PTB: Preterm birth initiated by a healthcare provider for maternal or fetal indications.[3]
6. Neonatal mortality: Death of a newborn due to any cause before 28 days of age.
7. Maternal mortality: Death of a woman either during pregnancy or childbirth from any cause related to or aggravated by pregnancy or its management, or within 42 days of end of pregnancy, irrespective of the duration and site of the pregnancy.[9]

2.4 | Data extraction and risk of bias assessment

Data from the eligible studies were independently extracted by two authors (JY and PS) using a predefined, standardized extraction form. Disagreements between the authors were resolved by consensus and involving a third author (RD). The information extracted included details of the publication, study setting and size, pre-pandemic period definition, pandemic period definition, and rates of the reported outcomes in pre-pandemic and pandemic time periods. We relied only on published information.

We anticipated that primarily observational studies would be included in this review, so we used the Newcastle–Ottawa Scale[15] for cohort studies to assess risk of bias. This scale assesses risk of bias in the domains of selection, comparability, and outcomes, and assigns a maximum score of 9. Studies with scores of 0 to 3 were considered to have high risk of bias, those with scores of 4 to 6 had moderate risk of bias, and those with scores of 7 to 9 had low risk of bias.

2.5 | Statistical analyses

We planned for meta-analyses of studies that reported similar outcomes and were methodologically homogeneous. For binary outcomes, we calculated the summary unadjusted odds ratios (uaOR), adjusted OR (aOR) when available and 95% CI, whereas for birthweight we calculated the mean difference and 95% CI. Statistical heterogeneity was assessed using Cochran's *Q* statistic and quantified by calculating the I^2 values. We expected clinical and methodological heterogeneity between studies, so planned a priori for random effect meta-analyses using the inverse variance method. We planned to meta-analyze adjusted estimates from studies that reported them, understanding that studies will have adjusted for different factors

based on data availability and baseline differences. We also expected that the duration of the "pre-pandemic" period would vary across studies, so we conducted meta-regression on the variable "duration of the pre-pandemic period" as a covariate to explain any heterogeneity in the results. Post-hoc subgroup analyses were conducted for the two primary outcomes after dividing studies into single-center (or selected hospitals/centers in an area), regional (statewide or province-wide) or national in scope. Publication bias was assessed qualitatively, using funnel plots, and quantitatively, by calculating Egger's regression intercept when more than 10 studies were included in the meta-analyses. For the Egger test, values less than 0.10 were considered indicative of publication bias. Meta-analyses were conducted using STATA v11.0 (StataCorp, College Station, TX, USA) and REVIEW MANAGER v5.3 (Cochrane Collaboration).

3 | RESULTS

3.1 | General study characteristics

Of 9953 records in the initial search, 45 articles were eligible for inclusion, of which 44 were used in the quantitative synthesis[2,6–10,16–53] (Figure 1). Twenty-six full-text reports were excluded: reasons for the exclusions are provided in Appendix S2. For one study conducted in the Netherlands by Been et al,[54] data were presented using multiple cut-offs to define the pre- and post-pandemic periods, with several different comparisons, making it difficult to select one comparison that aligned well with the other studies; we, therefore, included this study in the systematic review but not in meta-analyses. Khalil et al[9] had overlapping data for stillbirth outcome with another study; however, preterm birth data were not overlapping, so only preterm birth data were used in this review. Study characteristics are reported in Table 1: eight studies were national in scope, 11 were regional, and 24 were local, including single-center studies. Two studies did not report data settings. One study included in the previous version of this review, by Simpson et al,[55] was replaced by data from a new study Shah et al[49] because the latter contained a larger pandemic and pre-pandemic period from the same province of Ontario, Canada. Liu et al.[41] published another study from Canada, including data from Ontario. As they reported Ontario data separately and for an overlapping period with Shah et al[49], we extracted the data for Canada excluding Ontario from Liu et al. to avoid double counting of data. Across the included studies, totals of 1 843 665 pregnancies during the pandemic period (excluding numbers from Been et al[54]) and 23 564 552 pregnancies during the pre-pandemic period were

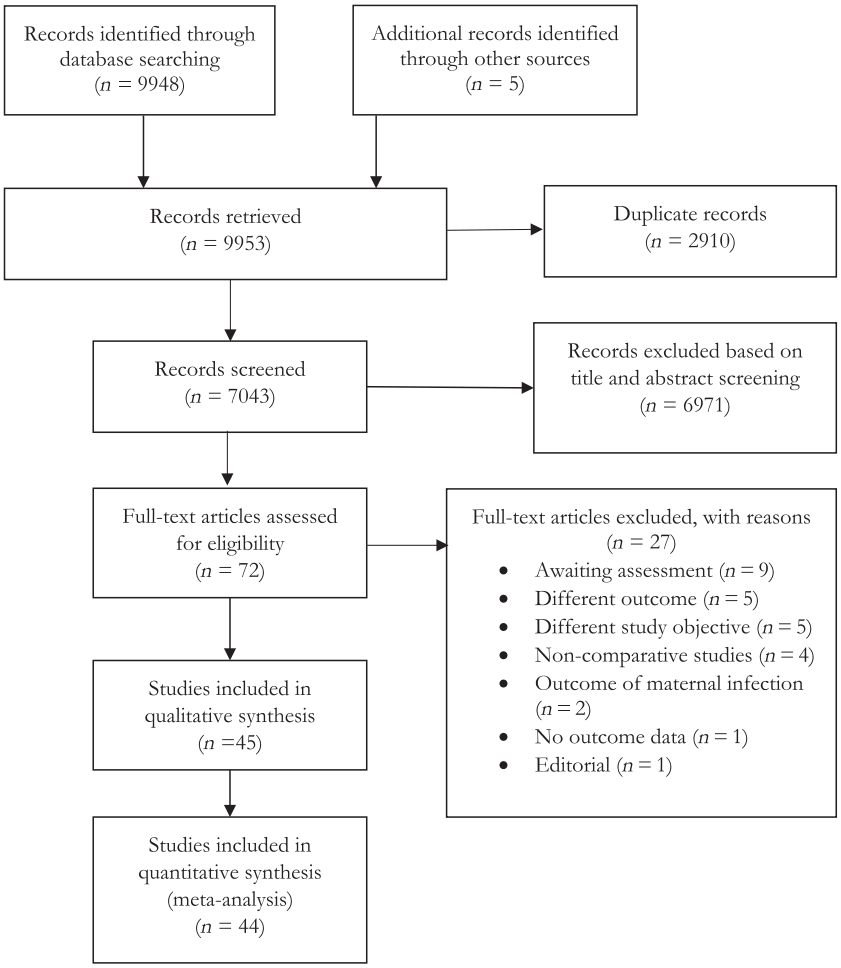

FIGURE 1 PRISMA flow diagram: article selection

TABLE 1 Characteristics of included studies (update #1)

First author, Country	Population level	Neonatal	Exposed cohort (Pandemic period)	Non-exposed cohort (Pre-pandemic period)	Outcomes	Statistical approach	Factors adjusted for if any
Arnaez[16] Spain	13 regional hospitals	Singleton	March 15–May 3, 2020	March 15–May 3, 2015–2019	PTB <37 weeks; PTB <32 weeks; PTB <28 weeks; Stillbirth; LBW; VLBW; ELBW	Join-point regression analysis; Multivariate binomial logistic regression models	Hospital, sex, type of delivery and multiples
Been[54] Netherlands	Nationwide	Singleton	1 month, 2 months, 3 months and 4 months after March 9, 2020; 1 month, 2 months, 3 months and 4 months after March 15, 2020; 1 month, 2 months, 3 months and 4 months before March 23, 2020	1 month, 2 months, 3 months and 4 months before March 9, 2020; 1 month, 2 months, 3 months and 4 months before March 15, 2020; 1 month, 2 months, 3 months and 4 months before March 23, 2020	PTB <37 weeks; PTB <32 weeks	Difference-in-regression-discontinuity analysis	
Berghella[17] USA	Single center	Singleton	March 1–July 31, 2020	March 1–July 31, 2019	PTB <37 weeks; PTB <34 weeks; PTB <28 weeks; Stillbirth; Spontaneous PTB; Medically indicated PTB	Chi-squared test; multivariable logistic regression	
Bian,[18] China	Single center	Singleton	2020	2014–2019	PTB <37 weeks; PTB <32 weeks; Stillbirth	Chi-squared test; Student's t-test; logistic regression	Maternal age, pre-pregnant body mass index, education, insurance status, type of conception, parity, maternal chronic medical conditions, pregnancy complications, gender of fetus
Briozzo,[19] Uruguay	Not reported	Not reported	March 15–September 30, 2020	March 15–September 30, 2019	PTB <37 weeks; LBW	Not reported	
Caniglia[20] Botswana	Nationwide	Singleton	April 3–July 20, 2020	April 3–July 20, 2017–2019	PTB <37 weeks; PTB <32 weeks; Stillbirth; Neonatal mortality	Difference-in-differences	
De Curtis[21] Italy	Single center	Singleton	March–May, 2020	March–May, 2019	PTB <37 weeks; PTB <32 weeks; Stillbirth	Z-test	
Dell'Utri[22] Italy	Single center	Not reported	February 23–June 24, 2020	February 23–June 24, 2019	Stillbirth	Chi-squared test;	

(Continues)

TABLE 1 (Continued)

First author, Country	Population level	Neonatal	Exposed cohort (Pandemic period)	Non-exposed cohort (Pre-pandemic period)	Outcomes	Statistical approach	Factors adjusted for if any
Du[23] China	Single center	Singleton	January 20–July 31, 2020	May 20–November 30, 2019	PTB <37 weeks; Stillbirth; LBW	Chi-squared test; t-test; Univariate and multivariate log-binomial regression models	Age, ethnicity, occupation, education, gravidity, parity, h/o miscarriage, h/o induced abortion, BMI, GWG, f/h chronic diseases, prenatal visits
Einarsdóttir,[24] Iceland	Nationwide	Singleton	2020	2016–2019	PTB <37 weeks; PTB <32 weeks; Spontaneous PTB; Medically indicated PTB	Generalized linear mixed models (proc glimmix) with binomial distribution and logit link	Parity (primipara/multipara), maternal age (continuous), country of origin (Iceland, other), residential area (capital area, outside capital area), cohabitation (yes/no), employment (employed/student/homemaker/disability pension/unemployed), essential hypertension (yes/no), and pre-existing diabetes mellitus (yes/no)
Gallo[25] Australia	Single center	Singleton	March 30–May 1, 2020	March 30–May 1, 2013–2019	PTB <37 weeks; PTB <32 weeks; PTB <28 weeks	Analysis of variance (ANOVA) (scale); chi-squared testing (categorical); Logistic regressions	Maternal age, body mass index, ethnicity, parity, socioeconomic status, and history of or current asthma, diabetes mellitus, and/or hypertensive disorder
Goyal[26] India	Single center	Not reported	April 1–August 30 2020	October 1 2019–February 29, 2020	Maternal mortality	Chi-squared test; Student's *t*-test	
Greene[27] USA	Single center	Not reported	March–April, 2020	January–February, 2020	PTB <37 weeks	Student's *t*-test; Wilcoxon test; chi-squared test; Fisher's exact test	
Gu[28] China	Single center	Not reported	January–February, 2020	January–February, 2019	PTB <37 weeks; Stillbirth; Birthweight	*t* test; Chi-squared test	
Handley[29] USA	2 Penn Medicine hospitals in Philadelphia	Singleton	March–June, 2020	March–June, 2018–2019	PTB <37 weeks; Stillbirth; Spontaneous PTB; Medically indicated PTB	Fisher's exact test	

(Continues)

TABLE 1 (Continued)

First author, Country	Population level	Neonatal	Exposed cohort (Pandemic period)	Non-exposed cohort (Pre-pandemic period)	Outcomes	Statistical approach	Factors adjusted for if any
Harvey[30] USA	Regionwide	Not reported	March 22–April 30, 2020	March 22–April 30, 2015–2019	PTB <37 weeks; PTB <32 weeks; LBW; VLBW	Logistic regression models	Maternal age, education, race/ethnicity, diabetes, and hypertension
Hedermann[6] Denmark	Nationwide	Singleton	March 12–April 14, 2020	March 12–April 14 of 2015–2019	PTB <37 weeks; PTB <32 weeks; PTB <28 weeks	Logistic regression	
Huseynova[31] Saudi Arabia	Single health authority	Singleton	March 1–June 30, 2020	March 1–June 30, 2017–2019	PTB <37 weeks; PTB <32 weeks; PTB <28 weeks	One-sample test for binomial proportion; Chi-squared test, Fisher's exact test; Poisson regression model	
Janevic[32] USA	Single center	Not reported	March 28–July 31, 2020	March 28–July 31, 2019	PTB <37 weeks; PTB <32 weeks	Log binomial regression	
Justman[33] Israel	Single center	Not reported	March-April, 2020	March-April, 2019	PTB <37 weeks; PTB <32 weeks; Stillbirth; Birthweight	Chi-squared and *t*-test or Mann–Whitney *U* test	
Kassie[34] Ethiopia	Regionwide	Not reported	March–June, 2020	March–June, 2019	Stillbirth; Neonatal mortality	*t* test	
Kasuga[35] Japan	Single center	Not reported	April 1–June 30, 2020	April 1–June 30, 2017–2019	PTB <37 weeks	Not reported	
KC[8] Nepal	9 hospitals across seven provinces	Not reported	March 21–May 30, 2020	January 1–March 20, 2020	PTB <37 weeks; Stillbirth; LBW; Neonatal mortality	Generalized linear model with Poisson regression; Pearson's chi-squared test	Ethnicity, maternal age, and complication during admission
Khalil[9] UK	Single center	Singleton; twin; triplet	February 1–June 14, 2020	October 1, 2019–January 31, 2020	PTB <37 weeks; PTB <34 weeks; Stillbirth[a]	Mann–Whitney and Fisher's exact tests	
Kirchengast[36] Austria	Single center	Singleton	March to July, 2020	March to July, 2005–2019	PTB <37 weeks; PTB <32 weeks; LBW; VLBW; ELBW	*t* test; Chi-squared test; Linear regression	
Kumar[37] India	Not reported	Not reported	March to September, 2020	March to September, 2019	Stillbirth; LBW; ELBW; VLBW	Fisher's exact test	
Kumari[38] India	4 regional hospitals	Not reported	March 25 June 2, 2020	January 15–March 24, 2020	Stillbirth; Maternal mortality	Not reported	

(Continues)

TABLE 1 (Continued)

First author, Country	Population level	Neonatal	Exposed cohort (Pandemic period)	Non-exposed cohort (Pre-pandemic period)	Outcomes	Statistical approach	Factors adjusted for if any
Lemon[39] USA	Single center	Singleton	April 1–October 27, 2020	January 1, 2018–January 31, 2020	PTB <37 weeks; PTB <34 weeks; PTB <28 weeks; Spontaneous PTB; Medically indicated PTB	Pearson chi-squared or *t* tests	
Li[40] China	Single center	Not reported	January 23–March 24, 2020	January 1, 2019–January 22, 2020	PTB <37 weeks; Birthweight	Chi-squared, *t* test and Fishers exact	
Liu[41] Canada	Nationwide	Singleton	March–August, 2020	March–August, 2015–2019	PTB <37 weeks; PTB <34 weeks; PTB <32 weeks; PTB <28 weeks; Stillbirth	Not reported	
Llorca[42] Spain	Single center	Not reported	May 26–October 22, 2020	January 1–August 31, 2018	PTB <37 weeks; PTB <34 weeks; LBW	Goodman–Kruskal γ test; Chi-squared test; Logistic regression	Age at delivery, educational level, and occupational status
Lumbreras-Marquez[43] Mexico	Nationwide	Not reported	January 1–August 9, 2020	2011–2019	Maternal mortality	Not reported	
Main[44] USA	Statewide	Singleton	April–July, 2020	April–July, 2016–2019	PTB <37 weeks; PTB <32 weeks; PTB <28 weeks	Logistic regression	
Matheson[45] Australia	3 regional hospitals	Singleton and multiple pregnancies	July–September, 2019	July–September, 2020	PTB <37 weeks; PTB <34 weeks; PTB <28 weeks; Stillbirth; Spontaneous PTB; Medically indicated PTB	Interrupted time-series analysis; Auto-regressive integrated moving average (ARIMA) model	
McDonnell[7] Ireland	Single center	Not reported	January–July, 2020	January–July, 2018–2019	PTB <37 weeks; Stillbirth	Pearson correlation; chi-squared, Fisher's exact test	
Meyer 1[46] Israel	Single center	Singleton	March 20–June 27, 2020	March 20–June 27, 2011–2019	PTB <37weeks; PTB <34 weeks; PTB <32 weeks; Stillbirth; Birthweight; Neonatal mortality	Multivariate regression	
Meyer 2[47] Israel	Single center	Not reported	February–March, 2020	February–March, 2019	PTB <37 weeks; PTB <34 weeks; Birthweight	Chi-squared; Fisher's exact test; Mann–Whitney U test	

(Continues)

TABLE 1 (Continued)

First author, Country	Population level	Neonatal	Exposed cohort (Pandemic period)	Non-exposed cohort (Pre-pandemic period)	Outcomes	Statistical approach	Factors adjusted for if any
Mor[48] Israel	Single center	Singleton	February 21–April 30, 2020	February 21–April 30, 2017–2019	PTB <37 weeks; PTB <34 weeks; PTB <28 weeks; Stillbirth; Birthweight	Chi-squared test or Fisher's exact test	
Pasternak[10] Sweden	Nation-wide	Singleton	April 1–May 31, 2020	April 1–May 31, 2015–2019	PTB <37 weeks; PTB <32 weeks; PTB <28 weeks; Stillbirth	Logistic regression	Maternal age, birth country, parity, body mass index and smoking
Philip[2] Ireland	Region-wide	Not reported	January–April, 2020; And March–June, 2020	January–April of 2001–2019; And March–June 2016–2019	Stillbirth; LBW; ELBW; VLBW	Poisson regression	
Shah[49] Canada	Regionwide	All births	January 1–December 31, 2020	July 1, 2002–December 31, 2019	PTB <37 weeks; PTB <32 weeks; PTB <28 weeks; Stillbirth	Laney control P′ charts; the interrupted time-series analysis;	
Shakespeare[50] Zimbabwe	Single center	Not reported	April–June, 2020	January–March, 2020	Stillbirth; Neonatal mortality; Maternal mortality	Not reported	
Stowe[51] UK	Nation-wide	Not reported	April–June, 2020	April–June, 2019	Stillbirth	Fisher's exact test	
Sun[52] Brazil	Single center		March 11–June 11, 2020	March 11–June 11, 2019	PTB <37weeks; LBW	Not reported	
Wood[53] USA	4 level 3 or 4 neonatal intensive care units	Singleton	April–July, 2020	April–July, 2019	PTB <37 weeks; PTB <34 weeks; PTB <32 weeks; PTB <28 weeks; Spontaneous PTB	Not reported	

Abbreviations: ELBW, extremely low birthweight, GWG, gestational weight gain; LBW, low birthweight, PTB, preterm birth, VLBW, very low birthweight.

[a]Data not used because of overlapping cohort.

TABLE 2 Risk of bias assessment using the Newcastle–Ottawa Scale (update #1).

	Selection				Comparability	Outcome			
First Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur?	Adequacy of follow up of cohorts	Total score
Arnaez[16]	☆	☆	☆	☆	☆		☆	☆	7
Been[54]			☆	☆		☆	☆	☆	5
Berghella[17]	☆	☆	☆	☆		☆	☆	☆	7
Bian[18]		☆	☆	☆	☆☆	☆	☆	☆	8
Briozzo[19]		☆	☆	☆			☆	☆	5
Caniglia[20]			☆	☆	☆☆	☆	☆	☆	7
De Curtis[21]			☆	☆	☆	☆	☆	☆	6
Dell'Utri[22]		☆	☆	☆		☆	☆	☆	6
Du[23]		☆	☆	☆	☆☆	☆	☆	☆	8
Einarsdóttir[24]	☆	☆	☆	☆	☆	☆	☆	☆	8
Gallo[25]		☆	☆	☆	☆	☆	☆	☆	7
Goyal[26]		☆	☆	☆		☆	☆	☆	6
Greene[27]		☆	☆	☆	☆	☆	☆	☆	7
Gu[28]		☆		☆	☆		☆	☆	5
Handley[29]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Harvey[30]	☆	☆	☆	☆	☆	☆	☆	☆	8
Hedermann[6]		☆	☆	☆	☆	☆	☆	☆	7
Huseynova[31]			☆	☆	☆	☆	☆	☆	6
Janevic[32]		☆		☆	☆		☆	☆	5
Justman[33]			☆	☆	☆	☆	☆	☆	6
Kassie[34]		☆	☆	☆	☆	☆	☆	☆	7
Kasuga[35]		☆	☆	☆		☆	☆	☆	6
KC[8]			☆	☆	☆☆	☆	☆	☆	7
Khalil[9]		☆	☆	☆	☆	☆	☆	☆	7
Kirchengast[36]		☆	☆	☆	☆	☆	☆	☆	7
Kumar[37]			☆	☆	☆	☆	☆	☆	6
Kumari[38]	☆			☆	☆☆	☆	☆		6
Lemon[39]		☆	☆	☆	☆	☆	☆	☆	7

(Continues)

TABLE 2 (Continued)

	Selection				Comparability	Outcome			
First Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur?	Adequacy of follow up of cohorts	Total score
Liu[41]	☆	☆	☆	☆	☆	☆	☆	☆	8
Li[40]			☆	☆	☆	☆	☆	☆	6
Llorca[42]		☆		☆	☆☆	☆	☆	☆	7
Lumbreras-Marquez[43]	☆	☆		☆		☆	☆	☆	6
Main[44]		☆	☆	☆	☆	☆	☆	☆	7
Matheson[45]		☆		☆	☆		☆	☆	5
McDonnell[7]		☆		☆	☆	☆	☆	☆	6
Meyer 1[46]		☆	☆	☆	☆		☆	☆	6
Meyer 2[47]		☆	☆	☆	☆		☆	☆	6
Mor[48]		☆	☆	☆	☆		☆	☆	6
Pasternak[10]	☆	☆	☆	☆	☆☆		☆	☆	8
Philip[2]		☆	☆	☆	☆	☆	☆	☆	7
Shakespeare[50]		☆	☆	☆			☆	☆	5
Shah[49]		☆	☆☆	☆	☆	☆	☆	☆	7
Stowe[51]	☆	☆	☆	☆	☆	☆	☆	☆	8
Sun[52]		☆	☆	☆			☆	☆	5
Wood[53]		☆	☆	☆	☆		☆	☆	6

Note: A study can be awarded a maximum of one star for each item within the Selection and Outcome categories. A maximum of two stars can be given for comparability.

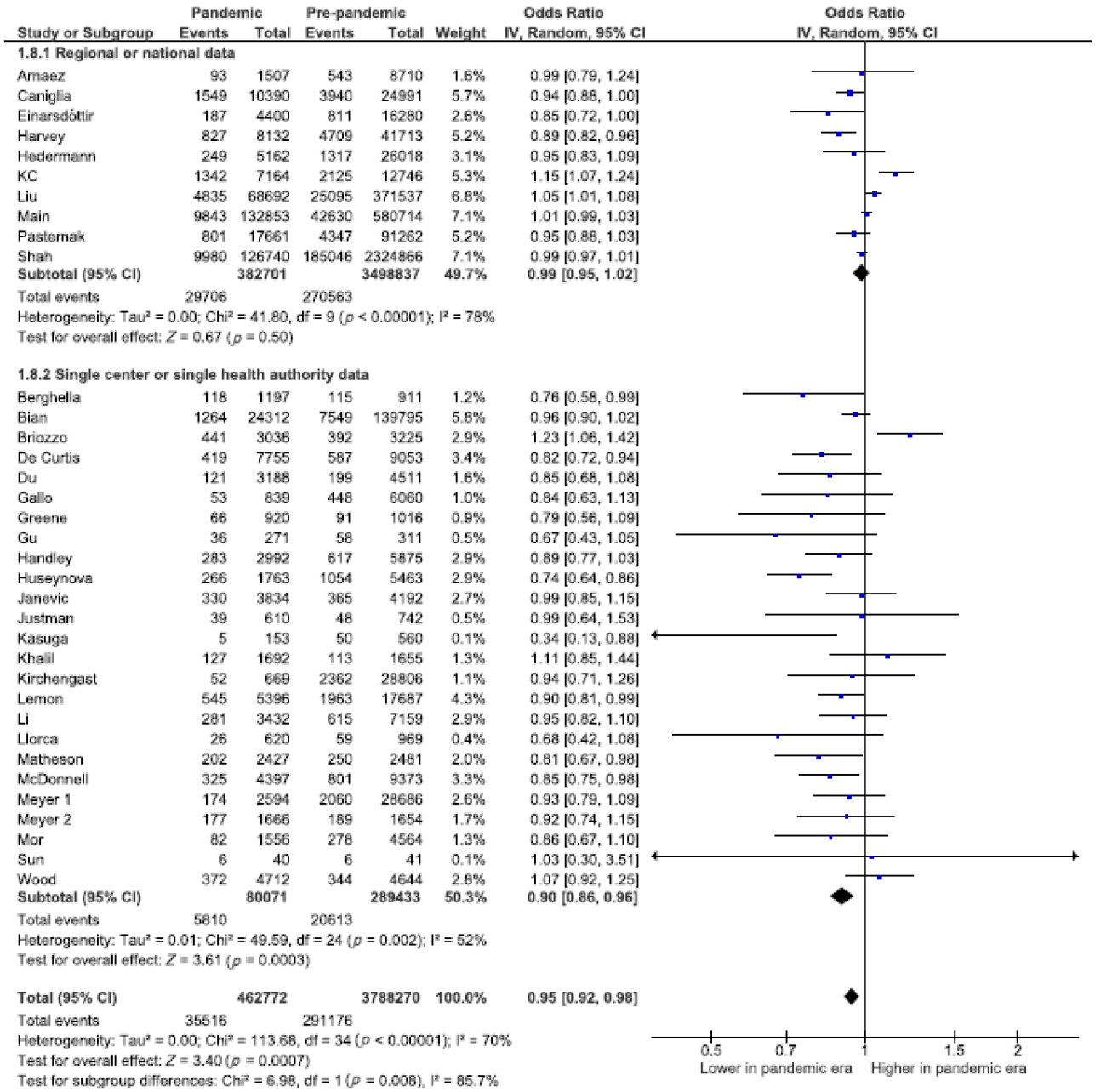

FIGURE 2 Forest plot for odds of preterm birth <37 weeks of gestation in pandemic vs pre-pandemic periods. CI, confidence interval, IV, inverse variance

studied. The duration of the "pandemic period" studied varied from 4 weeks to 12 months, and the duration of the "pre-pandemic period" varied from 2 months to 19 years across studies. The risk of bias scores for the included studies ranged from 5 to 9 (Table 2). Twenty-two studies had moderate risk of bias and 23 studies had low risk of bias. Thirty-three studies included pregnant populations from local/regional/national data, which may have included those with COVID-19, whereas eight studies specifically excluded women known to have COVID-19. However, it is difficult to be completely certain as testing on pregnant women was not universally applied in any of the studies.

3.2 | Synthesis: Outcomes

3.2.1 | Preterm birth and its subgroups

Thirty-five studies including 462 772 women during the pandemic period and 3 788 270 women in the pre-pandemic period reported PTB <37 weeks of gestation; there was a small reduction in the unadjusted odds of PTB during the pandemic period compared with the pre-pandemic period (pooled uaOR 0.95, 95% CI 0.95–0.98, $I^2 = 70\%$, Figure 2). Subgroup analyses revealed no differences in odds of PTB during the pandemic period in national or regional studies (pooled uaOR

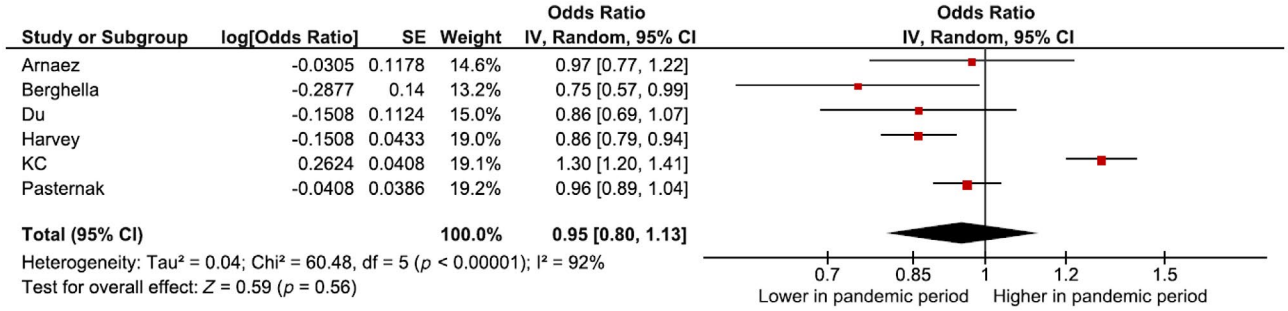

FIGURE 3 Forest plot for adjusted odds of preterm birth <37 weeks of gestation in pandemic vs pre-pandemic periods. CI, confidence interval, IV, inverse variance

TABLE 3 Results of studies reporting other outcomes (update #1)

Outcome	Number of studies	Pandemic period (*n*/*N*)	Pre-pandemic period (*n*/*N*)	OR (95% CI)	I^2 (%)
PTB <34 weeks	10	1798/90 552	8985/434 788	0.86 (0.74–1.01)	67
PTB <32 weeks	18	5552/422 625	51604/3 713 532	0.93 (0.79–1.10)	95
PTB <28 weeks	13	1755/370 505	18710/3 444 917	0.90 (0.81–1.00)	48
Spontaneous PTB	6	856/21 124	2072/47 878	0.89 (0.81–0.96)	0
Induced PTB	5	679/16 412	1882/43 234	0.89 (0.81–0.97)	0
Low birthweight	10	2194/32 177	8094/120 141	0.92 (0.81–1.04)	70
Very low birthweight	5	205/15 292	1366/114 636	1.03 (0.71–1.49)	65
Extremely low birthweight	4	33/7167	299/73 001	0.83 (0.32–2.17)	72
Neonatal mortality	6	1549/25 705	1599/73 659	1.56 (0.98–2.49)	94
Birthweight, grams	6	13871[a]	49 152[a]	17.3 (6.9–27.6)[b]	0

Abbreviation: PTB, preterm birth.

[a]Birthweight is shown as total numbers.

[b]Value shown is mean difference (95% CI) in grams.

0.99, 95% CI 0.95–1.02, I^2 = 78%); however, there was a reduction in odds of PTB in single-center studies (pooled uaOR 0.90, 95% CI 0.86–0.96, I^2 = 52%, subgroup differences p = 0.008, Figure 2). Six of the studies examining PTB reported adjusted estimates (with different factors adjusted, reported in Table 1) and pooled analyses did not show any significant differences in the odds of PTB during the pandemic, though the magnitude of the adjusted pooled estimate was the same as the unadjusted pooled estimate (pooled aOR 0.95, 95% CI 0.80–1.13; I^2 = 92%; Figure 3). There was no reduction in the unadjusted odds of PTB <34 weeks (Table 3, Appendix S3), <32 weeks (Table 3, Appendix S4), or <28 weeks (Table 3, Appendix S5) of gestation. Meta-analysis of six studies reporting data on spontaneous PTB (Table 3, Appendix S6) and six studies of medically indicated PTB and five studies of spontaneous PTB revealed reductions in unadjusted odds of PTB during the pandemic period of similar magnitude (Table 3, Appendix S7).

Although most of the studies presented data for the entire pregnant population, some explicitly excluded individuals with a known confirmed diagnosis of COVID-19. When such studies were included in meta-analyses, we identified no difference in the odds of PTB or stillbirth—for PTB: regional/national data from two studies had pooled uaOR 1.05 (95% CI 0.87–1.26), while six single-center studies had pooled uaOR of 0.89 (95% CI 0.79–1.01); for stillbirth: regional/national data from two studies had a pooled uaOR of 1.14 (95% CI 0.58–2.22), whereas four single-center studies had uaOR of 1.97 (95% CI 0.85–4.55).

3.2.2 | Stillbirth

Twenty-five studies of 498 231 women during the pandemic period and 3 569 667 women in the pre-pandemic period assessed stillbirth. There was no difference in the odds of stillbirth between the pandemic and pre-pandemic periods (pooled uaOR 1.10, 95% CI 0.98–1.24, I^2 = 54%, Figure 4). Subgroup analyses also revealed no difference in stillbirth during the pandemic period compared with the pre-pandemic period in single-center studies and regional/national studies (Figure 4). Meta-analysis of adjusted estimates from four studies revealed no difference in stillbirth between pandemic and pre-pandemic periods (aOR 1.06, 95% CI 0.81–1.38; I^2 = 72%; Appendix S8).

3.2.3 | Birthweight

Seven studies of 13 871 women during the pandemic period and 49 152 women in the pre-pandemic period reported

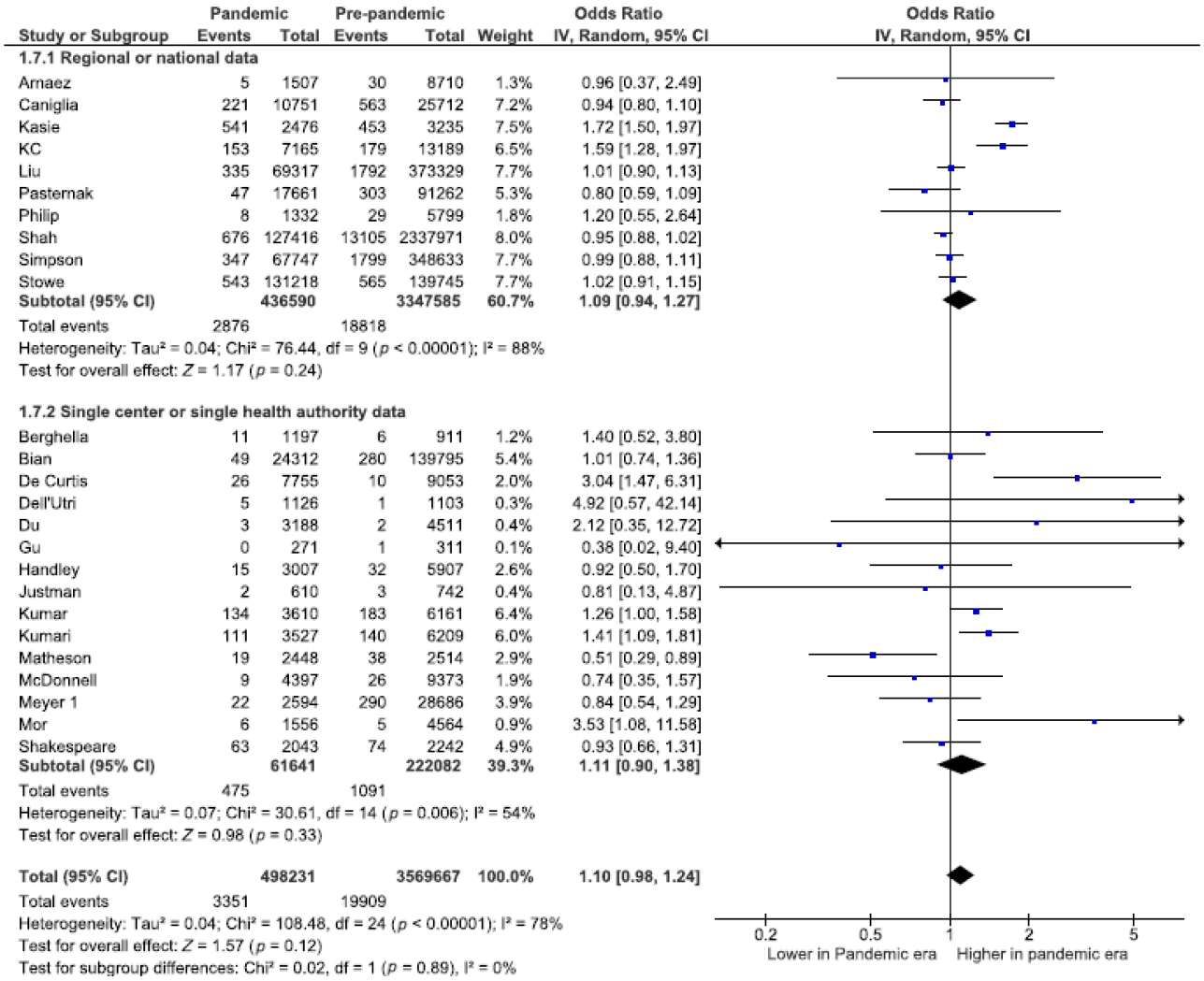

FIGURE 4 Forest plot for odds of stillbirth in pandemic vs pre-pandemic periods. IV, inverse variance

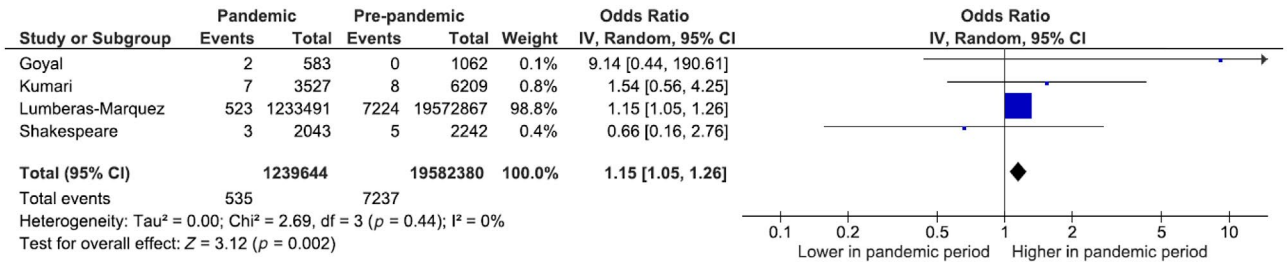

FIGURE 5 Forest plot for odds of maternal mortality in pandemic vs pre-pandemic periods. IV, inverse variance

birthweight. There was a small increase in mean birthweight during the pandemic compared with the pre-pandemic period (pooled mean difference 17 g, 95% CI 7–28g, I^2 = 0%) (Table 3, Appendix S9). There was no difference in the odds of LBW (Table 3, Appendix S10), VLBW (Table 3, Appendix S11), or ELBW (Table 3, Appendix S12).

3.2.4 | Neonatal mortality

Six studies of 99 364 neonates during the pandemic period did not show any difference in neonatal mortality between the pandemic and pre-pandemic periods (pooled uaOR 1.56, 95% CI 0.98–2.49, I^2 = 94%, Table 3, Appendix S13), however, the heterogeneity of

results across studies was very high. One national study from nine hospitals in Nepal[8] reported a higher neonatal mortality rate during the pandemic period, which may reflect significant local impact on access to care during the lockdown period.

3.2.5 | Maternal mortality

Four studies reported on maternal mortality. Three reported no significant difference in maternal mortality; however, one study from Mexico[43] reported a significant increase in maternal mortality during the pandemic (Figure 5). The study from Mexico contributed to 98.7% of the weight in this meta-analysis and it also reported that a significant portion of excess mortality was due to respiratory infections including COVID-19.

In meta-regression analyses, duration of the pre-pandemic study period did not emerge as a significant covariate for any outcome ($p > 0.05$ for all outcomes). We found evidence of publication bias for PTB (Egger's $p = 0.002$, Appendix S14) but not for stillbirth (Appendix S15), with fewer studies reporting higher rates of PTB during the pandemic period.

4 | DISCUSSION

In this updated systematic review and meta-analysis, we identified a 5% reduction in the unadjusted odds of PTB in pandemic compared with pre-pandemic time periods, in both spontaneous PTB and medically indicated PTB. However, in subgroup analyses, a significant reduction in PTB was only observed in single-center studies, not in regional or national studies. Although there was no statistically significant difference in the pooled adjusted odds of PTB the magnitude of the pooled estimate was the same as the pooled unadjusted estimate. We identified no difference in any other fetal/neonatal outcomes, including stillbirths and neonatal mortality, and only a marginal increase of 17 g in mean birthweight during the pandemic period compared with the pre-pandemic period. The increased incidence of maternal mortality noted in our meta-analysis was mostly driven by one study from Mexico[43] that included deaths due to COVID-19; these were the leading cause of maternal mortality during the pandemic period.

This review was designed to evaluate the impact of the COVID-19 pandemic on pregnancy and neonatal outcomes and not to evaluate studies that report only on maternal COVID-19 itself, which has been discussed in other reviews.[56–58] We specifically excluded studies that only reported outcomes of pregnant individuals infected with COVID-19. We identified conflicting evidence from the included studies based on whether they were single-center or regional/national studies. There could be several reasons for this. In addition to potential referral bias, other potential explanations include variation in sample sizes, outcome definitions, lengths of the pandemic and pre-pandemic periods, differences in timing and enforcement of lockdown orders, failure of some studies to account for natural variation in pregnancy outcomes over time, and dissimilarities among COVID-19 mitigation strategies.[8,10,20,29,47] Moreover, the study populations were heterogeneous; for example, baseline PTB rates ranged from 4.8% to 16.7% during the pre-pandemic period across the included studies; however, the change in PTB rate between periods was not baseline rate dependent. Although we did not observe any differences in subgroups of PTB using different gestational age cut-offs (ie <34, <32, and <28 weeks), not all studies contributed to these analyses.

Recently, Chmielewska[59] et al reported results from a systematic review and meta-analyses including studies evaluating studies assessing population-level impact during the pandemic period published up to January 8, 2021. They reported no difference in the PTB rate (15 studies, uaOR 0.94, 95% CI 0.87–1.02) and an increase in stillbirth (12 studies, uaOR 1.28, 95% CI 1.07–1.54) and maternal mortality. With the availability of data from 13 more studies on PTB and nine more studies for stillbirth, the results have remarkably changed, although this could also partly relate to minor differences in study inclusion criteria and data extraction. The larger number of subjects included in pooled analyses in our review has improved the precision of pooled estimates, increasing confidence in the findings particularly for less common secondary outcomes. However, this is the main reason for conducting this as a living systematic review, so that the information can be updated regularly.

The effects of lockdowns and mitigation strategies had contrasting effects in high-income vs low- and middle-income countries.[59] Reports from low-resource settings described increased fear and stress among pregnant individuals, reluctance to access in-hospital care during a pandemic, financial or employment issues, childcare or home schooling challenges, maternity staff shortages, reduced access to in-hospital care, and perceived or actual reductions in available obstetric services, resulting in a significant reduction in institutional births.[8,9,20,37,38] Some reports noted a reduction in PTB and attributed this to a number of social and health behaviors associated with the pandemic,[2,7] including decreased physical and mental stress due to better work-life balance,[6,17,46] better support systems and financial assistance,[17,35] improved nutrition, better hygiene,[8,12] reduced physical activity,[6,17,35,40] reduced exposure to infection,[8,17,46,60] lower incidence of smoking and drug use due to reduced access and being indoors,[17] lower pollution exposure and levels in environment,[17,61] and fewer medical interventions secondary to reduced antenatal surveillance.[7,17,46,54] The differences in PTB findings between single-center/adjacent hospitals studies and national/regional studies could reflect a change in referral patterns due to reduced access or the fact that pregnant individuals opted to give birth in hospitals with lower prevalence of COVID-19 or in non-COVID designated hospitals.[33] Future studies are needed to explore these differences.

Although we did not observe an overall change in the odds of stillbirth during the pandemic period, several individual studies, mostly single center in scope, reported increased odds of stillbirth compared with pre-pandemic time periods. The increase in stillbirth reported by these studies was attributed to reduced antenatal surveillance, a

reluctance to access in-hospital care due to increased stress and anxiety,[9,21,37,40,48] or missed appointments due to rapid changes in maternity services during the pandemic.[60] These reasons may also explain an increase in maternal mortality identified in Mexico;[43] however, according to the authors the data from the government website were preliminary in scope and may change as more data are available. This could be a signal to be vigilant in attending the mother–fetus dyad during difficult public health emergency situations.

We did not find any significant differences between the pandemic and pre-pandemic periods for other outcomes, except for a marginal difference in birthweight. As these data came from only five studies, further studies are needed to clarify this association, as a difference of 17 g is unlikely to be of clinical significance. Other factors that could be responsible for the differences between study findings include variations in the etiology of adverse pregnancy outcomes in different countries,[2,20] initiatives by local governments to provide support to those at risk for higher stress,[7] and changes to national legislation on pregnancy termination during the study period potentially influencing the incidences of stillbirth and PTB.[2,7]

A key strength of our review was the inclusion of large populations from 18 countries, mainly arising from national or state/provincial data. Most included studies came from registries or similar types of data sets. In addition, we only included studies that reported on temporal changes in outcomes in the overall population, and not data specifically from women affected by COVID-19. However, our study also has limitations. There may be other relevant studies that are not yet published (and so not included) as the pandemic is still ongoing and many countries are facing additional waves of infections and associated public health restrictions. There was clinical and methodological heterogeneity across studies regarding pandemic and pre-pandemic period definitions, population bases (single center/adjacent hospitals vs. regional/national), and choices of statistical methodologies. To overcome these limitations, we planned a priori to include pre-pandemic duration in meta-regression analyses, and we conducted post-hoc subgroup analyses on type of studies. We were able to explain statistical heterogeneity to an extent for both of our primary outcomes. Some studies included the entire population of pregnant women, comprising those who did and did not have COVID-19 in their sample. When studies that categorically excluded women with COVID-19 were included in our review, we identified no difference in PTB or stillbirth. Finally, there were insufficient studies to assess some of the pre-specified outcomes, including maternal mortality.

The COVID-19 pandemic has affected many countries with very high case numbers, such as India, Brazil, the UK, and Italy, but large, population-based estimates on pregnancy outcomes from these countries are lacking in this review. National registries from these and other countries would be ideally suited to investigate the impact of the pandemic on perinatal health at a population level. A harmonization of methodological approaches would also facilitate the assessment of the effects of the pandemic period on fetal, neonatal, and maternal outcomes, as high methodological heterogeneity makes direct comparisons challenging. One important point to consider going forward will be that the rates of these outcomes fluctuate with natural variation over time. We hope to capture these fluctuations through further 3-monthly updates of this living systematic review. Future investigations should use approaches that can elucidate whether any fluctuation observed in a particular setting during the pandemic period is outside the range of expected natural variation.

5 | CONCLUSION

In pooled analyses, we observed reductions in the unadjusted odds of PTB between the pandemic and pre-pandemic periods; in both induced and spontaneous PTB. However, this finding was driven by single-center studies. There was no difference in analyses of adjusted estimates of PTB or within subgroups of PTB. Although we did not observe meaningful differences in other outcomes, including odds of stillbirth, the data were more limited and precluded a robust assessment. Higher maternal mortality reported from Mexico indicates that further studies from low- and middle-income regions highly affected by COVID-19 are needed where drastic changes in the healthcare access, healthcare availability, and personal, social, and environmental factors contributed disproportionately to adverse pregnancy outcomes. As the findings have changed between the review published recently and this current review, there is a need for this type of living systematic review that can be updated regularly.

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CONFLICT OF INTEREST

None.

ORCID

Rohan D'Souza https://orcid.org/0000-0002-4049-2017
John W. Snelgrove https://orcid.org/0000-0002-7128-8916
Prakesh S. Shah https://orcid.org/0000-0002-9920-0488

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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