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# Impacts of COVID-19 pandemic on preterm birth: a systematic review and meta-analysis

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# Impacts of COVID-19 pandemic on preterm birth: A systematic review and meta-analysis


## ABSTRACT

**Objectives:** The coronavirus disease 2019 (COVID-19) pandemic has significantly affected healthcare systems and daily wellbeing. However, the reports of the indirect impacts of the pandemic on preterm birth remain conflicting. We performed a meta-analysis to examine whether the pandemic altered the risk of preterm birth.

**Study Design:** A systematic review and meta-analysis of the previous literature.

**Methods**: We searched MEDLINE and Embase databases until March 2022 using appropriate keywords and extracted 63 eligible studies that compared preterm between the COVID-19 pandemic period and the pre-pandemic period. A random-effects model was used to obtain the pooled odds of each outcome. The study protocol was registered with PROSPERO (No. CRD42022326717).

**Results:** The search identified 3827 studies, of which 63 reports were included. A total of 3,220,370 pregnancies during the COVID-19 pandemic period and 6,122,615 pregnancies during the pre-pandemic period were studied. Compared with the pre-pandemic period, we identified a significant decreased odds of preterm birth (PTB, < 37 weeks' gestation) [pooled OR (95%CI) = 0.96 (0.94, 0.98); $I^2$ = 78.7%; 62 studies] and extremely preterm birth (EPTB, < 28 weeks' gestation) [pooled OR (95%CI) = 0.92 (0.87, 0.97); $I^2$ = 26.4%; 25 studies] during the pandemic, while there was only a borderline significant reduction in the odds of very preterm birth (VPTB, < 32 weeks' gestation) [pooled OR (95%CI) = 0.93 (0.86, 1.01); $I^2$ = 90.1%; 33 studies] between the two periods. There was significant publication bias for PTB.

**Conclusion:** Pooled results suggested the COVID-19 pandemic was associated with preterm birth, even though there was only a borderline significant reduction for VPTB during the pandemic compared with the pre-pandemic period. Large studies showed conflicting results, and further research on whether the change is related to pandemic mitigation measures was warranted.

**Keywords:** preterm, birth outcomes, COVID-19 pandemic, lockdown, meta-analysis.



## Introduction

The coronavirus disease 2019 (COVID-19) pandemic has resulted in substantial morbidity and mortality, and also created a profound impact on healthcare systems, social functioning, and daily wellbeing[1,2]. To restrict the spread of the disease, countries imposed national or regional lockdowns, which consisted of multiple restrictions measures including stay-at-home orders, working at home, health care disruption, and school or shop closure except for emergency services[3,4]. The widespread lockdown is unprecedented, and the impact on human physical and mental health is not fully understood[5].

Previous studies have found that the COVID-19 pandemic may have influenced obstetric interventions and birth outcomes due to the disruption of maternal and neonatal health services and massive stress from psychosocial and economic consequences of the pandemic[6,7]. Most attention has been paid to the impact of the pandemic on preterm birth, but with inconsistent results and insufficient analysis. Reductions in preterm birth rates during the COVID-19 pandemic compared with before the pandemic has been reported in many countries, such as Australia[8], the United States[9–12], Israel[13,14], England[15], Denmark and Ireland[16,17], while studies in China, Netherlands, and Spain have not found such changes[18–20]. Vaccaro et al[21] reported no difference in the risk of preterm birth (< 37 weeks' gestation) during the pandemic as compared with the pre-pandemic period based on a rapid review of 13 studies. In other studies, preterm was not significantly changed overall but was decreased in high-income countries[22], and Yang et al[23] only found a significantly reduced risk in the data from unadjusted estimates and single-center studies. However, the indirect effect of the COVID-19 pandemic on preterm birth may be affected by more confounding factors, such as sample size, countries, study population, comparative period (seasonality), and study quality. A comprehensive and thorough study with further subgroup analysis for these factors is needed to assess the association between the pandemic and preterm.

Given the inconsistent conclusions from previous studies, the meta-analysis of these articles was conducted to estimate the impact of the global COVID-19 pandemic on preterm birth and further assess the confounding factors' effects by subgroup analysis.

## Methods

We conducted a meta-analysis of previous studies to determine the effects of the COVID-19 pandemic on preterm delivery. This review was performed according to the Preferred Reporting Items in Systematic Reviews and Meta-analyses (PRISMA) guidelines[24]. The study protocol was registered with PROSPERO (No. CRD42022326717).

### Sources: Search strategy and selection criteria

We electronically retrieved MEDLINE and Embase databases up to March 2022 for relevant articles. The following terms were used in the search: "preterm" or "premature" or "PTB" in combination with "2019-nCoV" or "COVID-19" or "SARS-COV-2". Studies were included if 1) preterm birth was compared between the pandemic period *vs.* the pre-pandemic period; 2) effect size [odds ratios (OR) or risk ratios (RR)] with 95%CI was provided or could be calculated; 3) published in English. We excluded studies that were case reports or not published as full reports; studies with wrong study design (women with SARS-COV-2 infection were not excluded or the outcomes were not compared in general populations) or without control subjects (only reports on the rate of preterm during the pandemic) or with inappropriate comparison groups; studies of only SARS-COV-2 infected women.

**Quality assessment**

Sixty-three eligible studies included in this study were scored according to the Newcastle-Ottawa Scale (NOS)[25]. Quality assessment of these studies was based on three categories: selection, comparability, and outcomes. The studies with scores ranged from 0 to 9, those with a score of 0 to 3 were considered to have a high risk of bias, 4 to 6 had a moderate risk of bias, and 7 to 9 had a low risk of bias, respectively.

**Statistical analyses**

The following data were extracted: authors, publication date, study design, sample size, study population, pandemic period definition, pre-pandemic period definition, effect size, and other related information. For studies adopting multivariate logistic regression for adjustment of confounders, we extracted adjusted OR and 95%CI. Otherwise, we calculated OR and 95%CI based on the extracted data for unadjusted studies. The outcome of interest in this review was preterm. Furthermore, we calculated preterm birth (PTB, < 37 weeks of gestation), very preterm birth (VPTB, < 32 weeks of gestation), and extremely preterm birth (EPTB, < 28 weeks of gestation) based on the clinician's best estimate of gestational age. A random-effects model was used to obtain the pooled odds of each outcome. Statistical heterogeneity among studies was evaluated by using the $\chi^2$ test, $I^2$ statistics, and $P$ values. The small study effects were assessed by funnel plots and asymmetry was assessed with Egger's test[26].

We conducted a subgroup analysis for factors that could potentially affect the association between the pandemic and preterm birth: effect size (adjusted OR or crude OR), sample size (<10,000, 10,000-100,000, or ≥ 100,000), study population (single-center, multicenter, or regionwide/nationwide), country classification (low/middle-income or high-income country according to World Bank classifications), published year (2020, 2021, or 2022), pre-pandemic period definition (equivalent period in previous years or near before the lockdown period), and quality assessment of included studies (moderate or low risk of bias). In addition, we performed sensitivity analysis by omitting each study individually and recalculating the pooled effect size estimates for the remaining studies to assess the effect of individual studies on the pooled results. All statistical analyses were two-sided and performed using STATA software (version 11.0).

## Results

Initially, 3827 studies were retrieved, and 63 previously published articles were eligible for inclusion with further screening[1,3–5,7–20,27–71]. There were 62 reports provided data on the odds of PTB during the pandemic compared with the pre-pandemic period, 33 reports included the odds of VPTB, and 25 studies included the data of EPTB (**Figure 1**). **Table S1** shows the characteristics of included studies in the quantitative synthesis. All of the studies used a historical cohort design. A total of 3,220,370 pregnancies during the COVID-19 pandemic period and 6,122,615 pregnancies during the pre-pandemic period were studied. Twenty-nine countries were represented, with substantial variation in pandemic mitigation measures among countries. There were 31 reports from single-center studies, 12 multicenter studies, and 14 national registries, the remaining 6 were regional reports. The duration of the "pandemic period" studied varied from 1 month to 15 months, and the duration of the "pre-pandemic period" studied varied from 2 months to 15 years. And the sample sizes varied from 81 to 2,219,914 pregnancies. The scores of quality assessments of the studies ranged from 5 to 9 (**Table S2**). There were 33 articles with moderate risk of bias and 30 articles with low risk of bias.

PTB (< 37 weeks of gestation) was reported in 62 studies. There was a significant reduction in the rate of PTB during the pandemic period compared with the pre-pandemic period [pooled OR (95%CI) = 0.96 (0.94, 0.98), $I^2$ = 78.7%, 62 studies, **Figure 2**]. Test for heterogeneity among subgroups revealed significant differences besides effect size and pre-pandemic period (*P* < 0.1). VPTB (< 32 weeks of gestation) was reported in 33 studies with varying gestational weeks thresholds and conflicting findings. There was a reduction in the odds of VPTB with a borderline significance [pooled OR (95%CI) = 0.93 (0.86, 1.01), $I^2$ = 90.1%, 33 studies, **Figure 3**]. Further heterogeneity test showed significant difference among subgroups (*P* < 0.1). Twenty-five studies reported EPTB (< 28 weeks of gestation), which showed a significant decrease in EPTB [pooled OR (95%CI) = 0.92 (0.87, 0.97), $I^2$ = 26.4%, 25 studies, **Figure 4**]. Then subgroups analyses suggested that there was no heterogeneity (*P* > 0.1). Moreover, we found evidence of a small study effect for PTB (Egger's *P* = 0.018), but not for VPTB (Egger's *P* = 0.235) and EPTB (Egger's *P* = 0.441) (**Figure 5**).

In the sensitivity analysis, the pooled estimates of PTB and EPTB were not significantly changed when a study was omitted; suggesting that no one study had a large effect on the pooled estimate. However, for VPTB, when study conducted by Main et al was omitted[10], the pooled result became significant and the heterogeneity became nonsignificant [pooled OR (95%CI) = 0.93 (0.90, 0.97), $I^2$ = 27.2%].

## Discussion

The present meta-analysis aimed to investigate and systematically analyze the relationship between the COVID-19 pandemic and preterm birth. We specifically excluded articles that only reported outcomes of the pregnant population infected with COVID-19. The indirect impact of the COVID-19 lockdown on preterm was more noticed. The results showed that significant reduction in PTB and EPTB, but no difference in VPTB during the pandemic compared with before the pandemic.

In this meta-analysis, PTB was significantly decreased overall, but the previous meta-analysis reported by Chmielewska et al[22], Vaccaro et al[21], and Yang et al[23] suggested no differences in pooled odds ratios. Further subgroups analysis, Chmielewska et al[22] found PTB was decreased in high-income countries, and Yang et al[23] found the reduction of PTB was only noted in unadjusted estimates and single-center studies. Moreover, they reported no reduction in unadjusted odds of preterm birth < 34 weeks', < 32 weeks', and < 28 weeks' gestation. Inconsistency among conclusions from different studies and a lack of detailed evidence to inform the effects of the COVID-19 pandemic on VPTB and EPTB prompted us to conduct a more specifically quantitative synthesis.

We identified an overall reduction in the odds of PTB during the pandemic compared with before the pandemic. However, the further subgroup analysis showed there was no difference in PTB in specific subgroups, such as the data from adjusted odds, the studies from multicenter or low- and middle-income countries, and the pre-pandemic period defined as near before the lockdown. There could be several reasons for this conflict, such as the heterogeneity of the study populations, variation in sample sizes, lengths or definition of the pandemic and pre-pandemic periods, and the quality of studies. In addition, the significant statistical heterogeneity was also partly explained by the methodological heterogeneity of the studies and the variation in lockdown measures among countries based on the results of subgroup analysis.

The researchers have proposed that COVID-19 related lockdown may cause socio-environmental and behavioral modifications, including maternal workload reduction, improved air quality, reduced maternal non-COVID-19 related infections, reductions in physical activity, and better nutritional support, thus playing a role in pregnancy prolongation and exert a beneficial impact on preterm birth[3,5,30,40]. On the other hand, several recent studies have shown that COVID-19 pandemic related stressors and quarantine measures have exacerbated perinatal anxiety and depression[72,73]. Stress, worries, and anxieties during pregnancy are often associated with preterm birth[74]. Moreover, COVID-19 lockdown may result in a reduction in antenatal care and fetal surveillance. Therefore, the impact of the pandemic on preterm birth is a double-edged sword. And for the risk of VPTB, there was no overall difference during the pandemic, but analyses of adjusted odds and $10{,}000 \leq$ sample size $\leq 100{,}000$ studies only suggested VPTB might be reduced. Furthermore, we found the high heterogeneity disappeared for VPTB and the risk of VPTB became significant reduction when the study of Main et al[10] was omitted. The study reported the preterm change in the peak period of the COVID-19 outbreak in California compared with before the pandemic, which was conducted from April 2020 to July 2020 without any response measures or even masks in the period. Specific local political and epidemic circumstances may have contributed to the heterogeneity of the study. Although the previous meta-analysis showed there was no difference in preterm birth before 32 gestational weeks[23], we conducted a larger number of subjects included in pooled analyses and found a significant change in EPTB.

The advantages of this review included the comprehensive search and synthesis of a broad range of articles for preterm birth. In addition, our meta-analysis included large populations from 29 countries, mainly arising from national or state, or provincial data. We summarized the available global data on the impact of the COVID-19 pandemic on preterm birth. Nevertheless, this study had some limitations. There was the heterogeneity in methodology, study populations, and the definitions of the groups, leading to the limiting the comparability of results. Also, we only included the impact of the pandemic on preterm birth for improving the precision of pooled estimates, more birth outcomes should be assessed.

Preterm birth is a major determinant of neonatal mortality and morbidity with long-term adverse consequences during childhood and adulthood[75,76]. Further research needs more attention on whether changes in preterm birth are related to changes in health-related behaviors during the pandemic. There is also a need to assess the availability of maternal and newborn health services. Research in these areas will allow us to draw up plans and allocate resources effectively for immediate care after the pandemic and for future health system crises.

## Conclusion

Our study suggested that the pandemic period was marked by an overall substantial decrease in PTB and EVPTB. However, there was heterogeneity between the subgroups and publication bias in PTB. VPTB was not significantly changed overall but was decreased in studies with adjusted odds and 10,000 ≤ sample size ≤ 100,000. The results show the considerable disparity between countries. Further research was warranted to investigate if the change is related to pandemic mitigation measures.

**Abbreviations**

PTB: preterm birth; VPTB: very preterm birth; EPTB: extremely preterm birth.

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**Competing interests:** None declared.

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## Figure Legends:

**Figure 1.** Flow chart of study selection.

**Figure 2.** Forest plot for odds of preterm birth < 37 weeks' gestation [*Test for heterogeneity between subgroups (*P* < 0.1)].

**Figure 3.** Forest plot for odds of very preterm birth < 32 weeks' gestation [*Test for heterogeneity between subgroups (*P* < 0.1)].

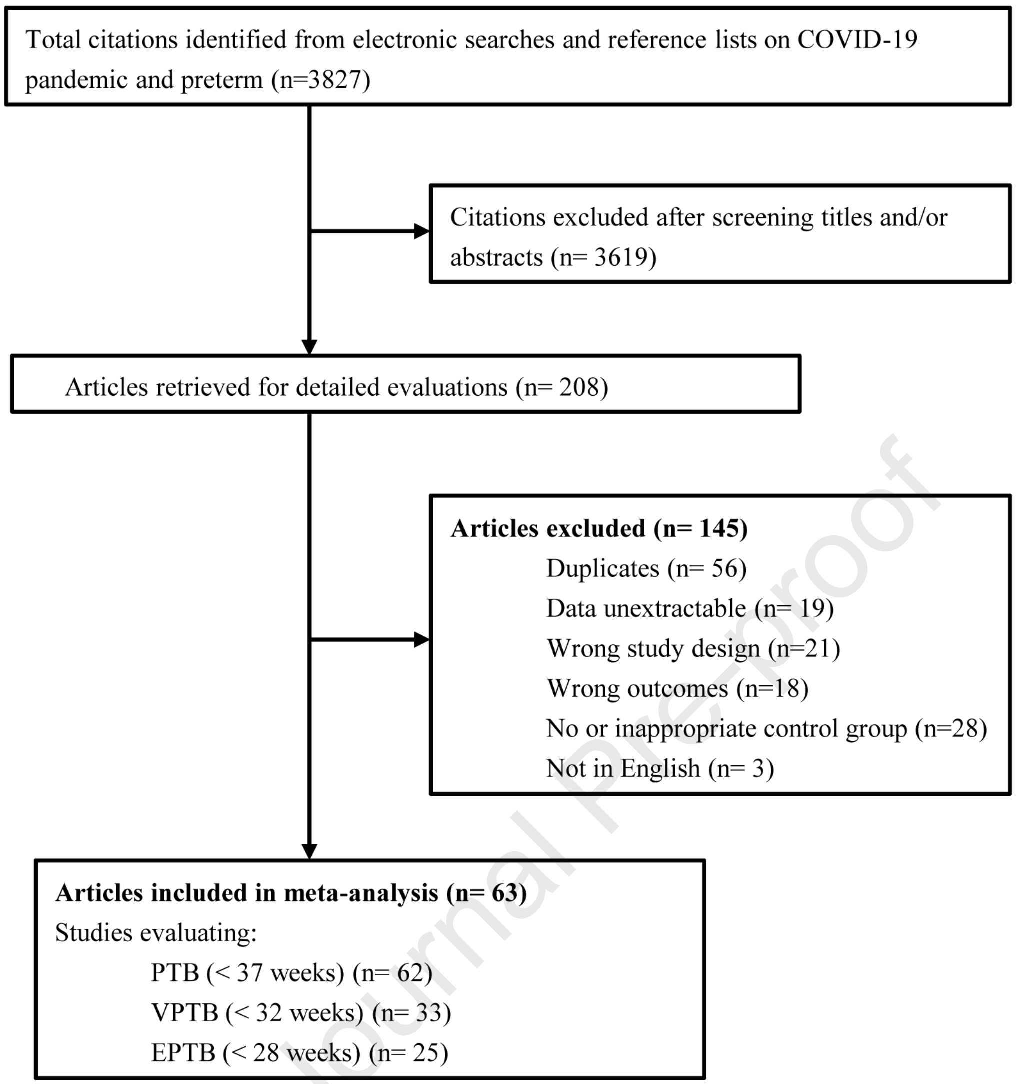
**Figure 4.** Forest plot for odds of extremely preterm birth < 28 weeks' gestation.

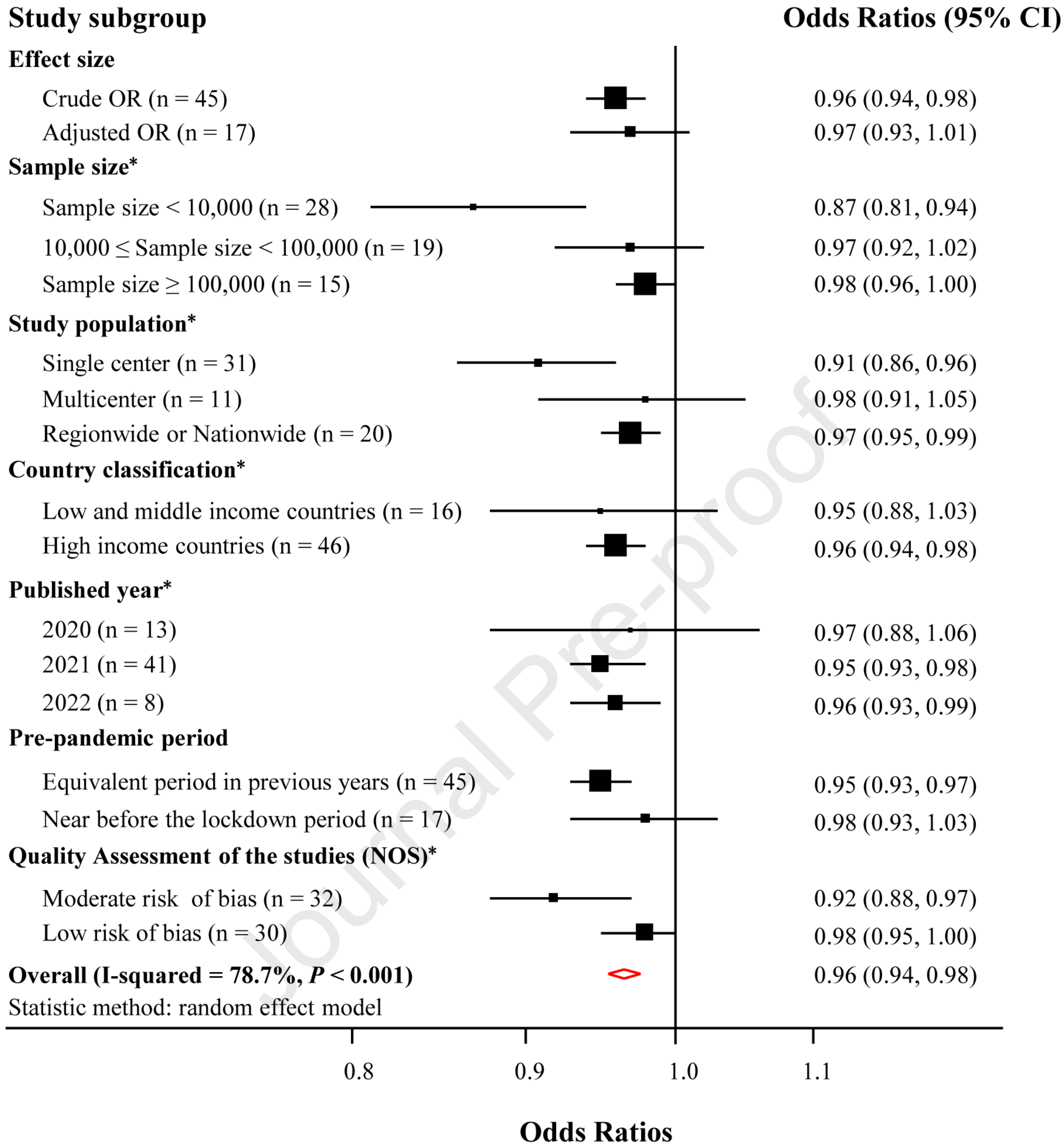
**Figure 5.** Funnel plots for studies reporting on preterm birth.

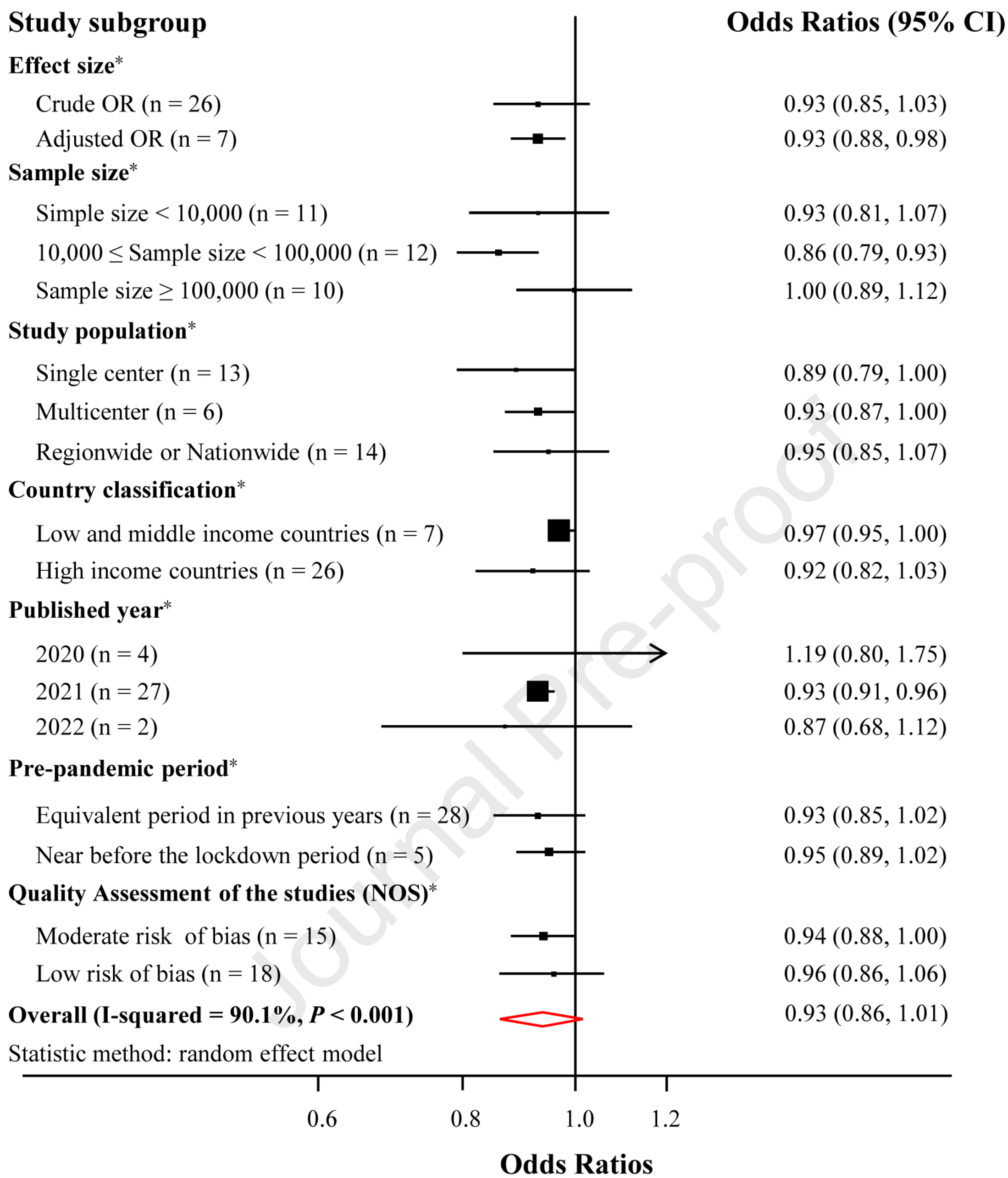
## Appendix:

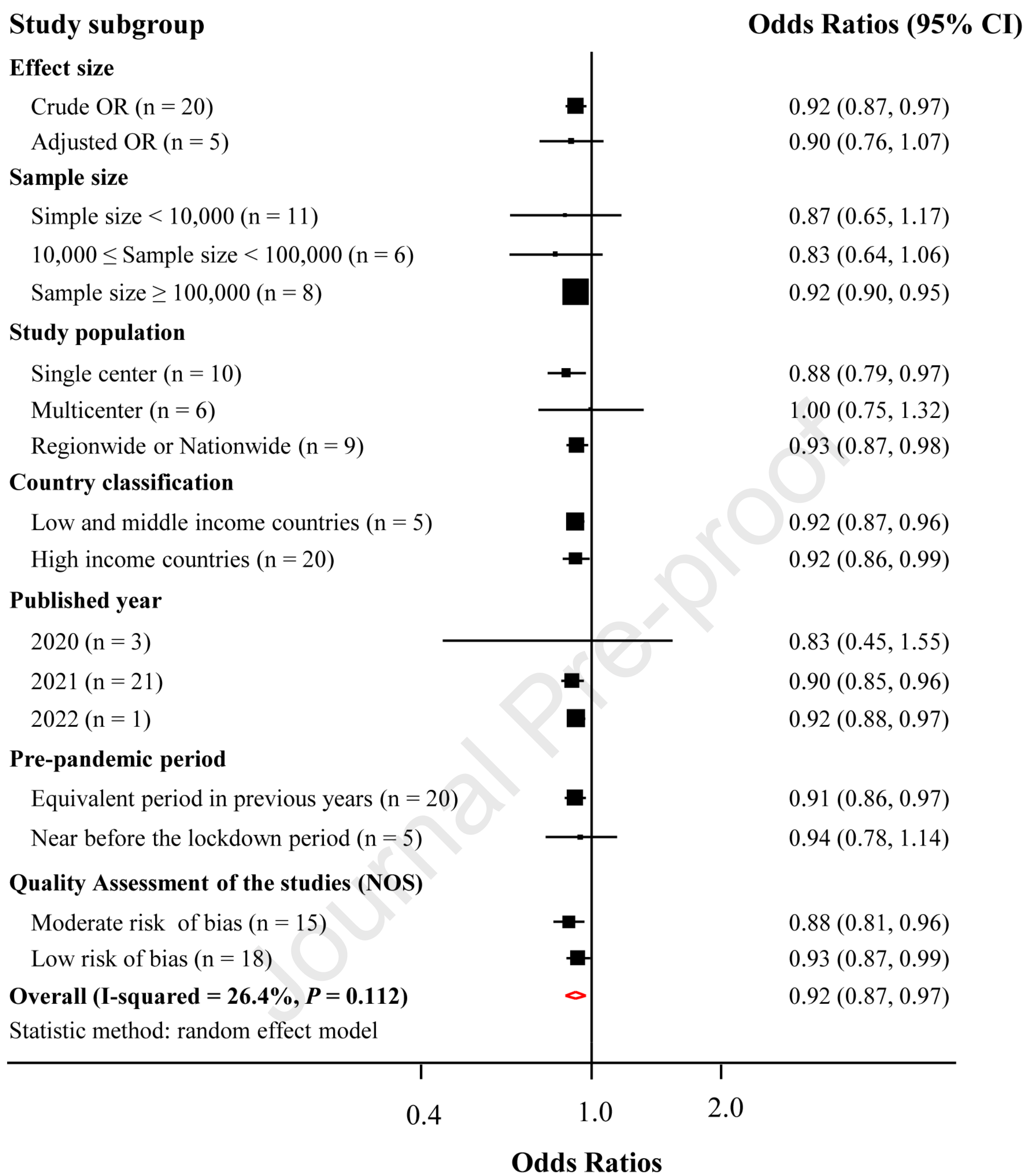
**Table S1.** Characteristics of included studies in meta-analysis.

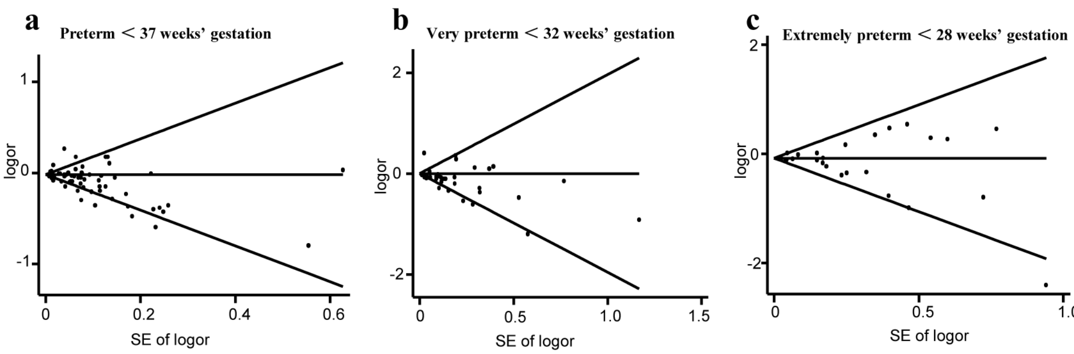
**Table S2.** Quality assessment of the included studies using the Newcastle-Ottawa Scale (NOS).


Total citations identified from electronic searches and reference lists on COVID-19 pandemic and preterm (n=3827)
Citations excluded after screening titles and/or abstracts (n= 3619)
Articles retrieved for detailed evaluations (n= 208)
Articles excluded (n= 145)
Duplicates (n= 56)
Data unextractable (n= 19)
Wrong study design (n=21)
Wrong outcomes (n=18)
No or inappropriate control group (n=28)
Not in English (n= 3)
Articles included in meta-analysis (n= 63)
Studies evaluating:
PTB (< 37 weeks) (n= 62)
VPTB (< 32 weeks) (n= 33)
EPTB (< 28 weeks) (n= 25)


Study subgroup
Odds Ratios (95% CI)
Effect size
Crude OR (n = 45)
0.96 (0.94, 0.98)
Adjusted OR (n = 17)
0.97 (0.93, 1.01)
Sample size*
Sample size < 10,000 (n = 28)
0.87 (0.81, 0.94)
10,000 ≤ Sample size < 100,000 (n = 19)
0.97 (0.92, 1.02)
Sample size ≥ 100,000 (n = 15)
0.98 (0.96, 1.00)
Study population*
Single center (n = 31)
0.91 (0.86, 0.96)
Multicenter (n = 11)
0.98 (0.91, 1.05)
Regionwide or Nationwide (n = 20)
0.97 (0.95, 0.99)
Country classification*
Low and middle income countries (n = 16)
0.95 (0.88, 1.03)
High income countries (n = 46)
0.96 (0.94, 0.98)
Published year*
2020 (n = 13)
0.97 (0.88, 1.06)
2021 (n = 41)
0.95 (0.93, 0.98)
2022 (n = 8)
0.96 (0.93, 0.99)
Pre-pandemic period
Equivalent period in previous years (n = 45)
0.95 (0.93, 0.97)
Near before the lockdown period (n = 17)
0.98 (0.93, 1.03)
Quality Assessment of the studies (NOS)*
Moderate risk of bias (n = 32)
0.92 (0.88, 0.97)
Low risk of bias (n = 30)
0.98 (0.95, 1.00)
Overall (I-squared = 78.7%, P < 0.001)
0.96 (0.94, 0.98)
Statistic method: random effect model
0.8
0.9
1.0
1.1
Odds Ratios


Study subgroup
Odds Ratios (95% CI)
Effect size*
Crude OR (n = 26) 0.93 (0.85, 1.03)
Adjusted OR (n = 7) 0.93 (0.88, 0.98)
Sample size*
Simple size < 10,000 (n = 11) 0.93 (0.81, 1.07)
10,000 ≤ Sample size < 100,000 (n = 12) 0.86 (0.79, 0.93)
Sample size ≥ 100,000 (n = 10) 1.00 (0.89, 1.12)
Study population*
Single center (n = 13) 0.89 (0.79, 1.00)
Multicenter (n = 6) 0.93 (0.87, 1.00)
Regionwide or Nationwide (n = 14) 0.95 (0.85, 1.07)
Country classification*
Low and middle income countries (n = 7) 0.97 (0.95, 1.00)
High income countries (n = 26) 0.92 (0.82, 1.03)
Published year*
2020 (n = 4) 1.19 (0.80, 1.75)
2021 (n = 27) 0.93 (0.91, 0.96)
2022 (n = 2) 0.87 (0.68, 1.12)
Pre-pandemic period*
Equivalent period in previous years (n = 28) 0.93 (0.85, 1.02)
Near before the lockdown period (n = 5) 0.95 (0.89, 1.02)
Quality Assessment of the studies (NOS)*
Moderate risk of bias (n = 15) 0.94 (0.88, 1.00)
Low risk of bias (n = 18) 0.96 (0.86, 1.06)
Overall (I-squared = 90.1%, P < 0.001) 0.93 (0.86, 1.01)
Statistic method: random effect model
0.6
0.8
1.0
1.2
Odds Ratios


Study subgroup
Odds Ratios (95% CI)
Effect size
Crude OR (n = 20)
0.92 (0.87, 0.97)
Adjusted OR (n = 5)
0.90 (0.76, 1.07)
Sample size
Simple size < 10,000 (n = 11)
0.87 (0.65, 1.17)
10,000 ≤ Sample size < 100,000 (n = 6)
0.83 (0.64, 1.06)
Sample size ≥ 100,000 (n = 8)
0.92 (0.90, 0.95)
Study population
Single center (n = 10)
0.88 (0.79, 0.97)
Multicenter (n = 6)
1.00 (0.75, 1.32)
Regionwide or Nationwide (n = 9)
0.93 (0.87, 0.98)
Country classification
Low and middle income countries (n = 5)
0.92 (0.87, 0.96)
High income countries (n = 20)
0.92 (0.86, 0.99)
Published year
2020 (n = 3)
0.83 (0.45, 1.55)
2021 (n = 21)
0.90 (0.85, 0.96)
2022 (n = 1)
0.92 (0.88, 0.97)
Pre-pandemic period
Equivalent period in previous years (n = 20)
0.91 (0.86, 0.97)
Near before the lockdown period (n = 5)
0.94 (0.78, 1.14)
Quality Assessment of the studies (NOS)
Moderate risk of bias (n = 15)
0.88 (0.81, 0.96)
Low risk of bias (n = 18)
0.93 (0.87, 0.99)
Overall (I-squared = 26.4%, P = 0.112)
0.92 (0.87, 0.97)
Statistic method: random effect model
0.4
1.0
2.0
Odds Ratios


a
Preterm < 37 weeks' gestation
1
0
-1
logor
0
0.2
0.4
0.6
SE of logor
b
Very preterm < 32 weeks' gestation
2
0
-2
logor
0
0.5
1.0
1.5
SE of logor
c
Extremely preterm < 28 weeks' gestation
2
0
-2
logor
0
0.5
1.0
SE of logor