Review Paper

COVID-19 pandemic and neonatal birth weight: a systematic review and meta-analysis

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A B S T R A C T

Objectives: Lockdown was implemented in many countries during the pandemic, which led to myriad changes in pregnant women's lives. However, the potential impacts of the COVID-19 pandemic on neonatal outcomes remain unclear. We aimed to evaluate the association between the pandemic and neonatal birth weight.
Study design: This was a systematic review and meta-analysis of the previous literature.
Methods: We searched the MEDLINE and Embase databases up to May 2022 and extracted 36 eligible studies that compared neonatal birth weight between the pandemic and the prepandemic period. The following outcomes were included: mean birth weight, low birth weight (LBW), very low birth weight (VLBW), macrosomia, small for gestational age (SGA), very small for gestational age (VSGA), and large for gestational age (LGA). Statistical heterogeneity among studies was assessed to determine whether a random effects model or fixed effects model was conducted.
Results: Of the 4514 studies identified, 36 articles were eligible for inclusion. A total of 1,883,936 neonates during the pandemic and 4,667,133 neonates during the prepandemic were reported. We identified a significant increase in mean birth weight (pooled mean difference [95% confidence interval (CI)] = 15.06 [10.36, 19.76], I^2 = 0.0%, 12 studies) and a reduction in VLBW (pooled OR [95% CI] = 0.86 [0.77, 0.97], I^2 = 55.4%, 12 studies). No overall effect was identified for other outcomes: LBW, macrosomia, SGA, VSGA, and LGA. There was publication bias for mean birth weight with a borderline significance (Egger's P = 0.050).
Conclusion: Pooled results showed the pandemic was significantly associated with an increase in mean birth weight and a reduction in VLBW, but not for other outcomes. This review provided clues about the indirect effects of the pandemic on neonatal birth weight and more healthcare measures needed to improve neonatal long-term health.

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Introduction

The outbreak of COVID-19 has profound effects on the global economy, social structures, and health services systems.[1,2] Then, many governments implemented national or regional blockades and restrictions on free activities, which led to myriad changes in how pregnant women live their lives.[3,4] Pregnant women are vulnerable to not only the direct effects of infection with COVID-19 but also the indirect effects of disruption of essential healthcare services and restrictions on social interaction. However, the indirect impact of the pandemic on pregnancy outcomes, including neonatal birth weight, remains unclear.

Birth weight, a sensitive indicator of intrauterine growth, is well documented that stress during pregnancy, prenatal care, and change in social life may result in adverse infant birth weight.[5,6] As the important predictive indicator of neonatal health, the changes of low birth weight (LBW), very low birth weight (VLBW), small for gestational age (SGA), very small for gestational age (VSGA), and other adverse outcomes during the pandemic have drawn more attention, but it is mainly regarded as the secondary outcome in

previous studies and with inconsistent results. A large sample study showed a significant increase of 13 g in mean birth weight during the pandemic compared with before the pandemic,[7] but there were no differences in other studies.[8,9] For LBW, there were no significant differences in some countries, such as Ireland,[10] China,[11,12] and Australia,[13] whereas the studies from Spain[14] and Turkey[15] observed a significant increase in the pandemic period. Moreover, the recent two large sample sizes and nationwide studies reported a significant reduction in the rate of SGA during the pandemic (the United States[16] and England[17]), but not for other studies.[13,18,19] The COVID-19 lockdown and population response measures, as well as risk factors for adverse birth outcomes, vary from region to region, which may partly explain the differences between studies.[20]

Inconsistency among results from previous reports and a lack of evidence prompted us to conduct further exploration of neonatal birth weight changes during the pandemic. We aimed to assess the indirect effects on birth outcomes of the global COVID-19 pandemic.

Methods

We did a meta-analysis of studies on the effects of the pandemic on neonatal birth weight. This review was reported according to the Preferred Reporting Items in Systematic Reviews and Meta-analyses guidelines.[21] The study protocol was registered with PROSPERO (No. CRD42022337886).

Search strategy and selection criteria

We searched the MEDLINE and Embase databases and reference lists of included studies up to May 2022 for relevant articles. The keywords used in this study were 'COVID-19' or '2019-nCoV' or 'SARS-COV-2' or 'n-COV' or 'coronavirus' and combined them with terms related to outcomes, such as 'birth outcome,' 'neonates,' 'bw,' 'birth weight,' 'LBW,' 'VLBW,' 'macrosomia,' 'SGA,' 'VSGA,' and 'LGA' (Table S1). The search strategy was appropriately translated for the database. Studies were included if (1) the following outcomes were compared: mean birth weight, LBW, VLBW, macrosomia, SGA, VSGA, or large for gestational age (LGA) between the pandemic and the prepandemic period; (2) effect size (odds ratios [ORs] or risk ratios or β) with 95% confidence interval (CI) or mean with standard deviation were provided or could be calculated; (3) published in English. We excluded studies that were case reports or not published as full reports, studies with data unextractable or inappropriate design, and studies of only SARS-COV-2—infected women. Two investigators (X.D.Y. and H.J.) independently reviewed all the articles, and disagreements were resolved after discussion with the third author (J.Q.M.).

Data extraction

The characteristics of included studies were extracted based on authors, year of publication, sample size, study population and location, pandemic period definition, prepandemic period definition, effect size with 95% CI or mean with standard deviation, and other related information.

Neonatal birth weight assessed were mean birth weight, LBW, VLBW, macrosomia, SGA, VSGA, and LGA. LBW was defined as <2500 g, VLBW was defined as <1500 g, and macrosomia was defined as >4000 g. SGA was defined as birth weight less than the 10th percentile, VSGA was defined as birth weight less than the 3rd percentile, and LGA was defined as birth weight greater than the 90th percentile by gestational week at birth.[22—24]

Quality assessment

Each study was scored according to the Newcastle—Ottawa Scale[25] independently by two assessors (X.D.Y. and H.J.). Quality assessment of these studies was based on three domains: selection, comparability, and outcomes. A study that scored 0—3 was considered to have a high risk of bias, 4—6 have a moderate risk of bias, and 7—9 have a low risk of bias. A lower risk of bias denotes higher quality.

Statistical analyses

For binary outcomes, if adjusted OR was not given, crude OR was used. For continuous outcomes, mean difference (MD) with 95% CI was calculated by pooling the mean with standard deviation. Statistical heterogeneity among studies was evaluated using the Chi-squared test, I^2 statistics, and P values. If the homogeneous test was not significant ($I^2 < 50\%$ and/or $P > 0.10$), a fixed effects model was used to obtain a summary OR or MD. Otherwise, a random effects model was used. Publication bias was evaluated by using funnel plots and Egger's test. Then, we conducted a subgroup analysis for factors that could potentially affect COVID-19 pandemic definition, lockdown measures, or neonatal birth weight: effect size (adjusted OR or crude OR), sample size (<10,000 or ≥10,000), study population (single center, multicenter, or regionwide/nationwide), country classification (low-/middle-income or high-income country according to World Bank classifications), prepandemic 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 analyses 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; College Station, TX, USA).

Results

Of the 4514 studies identified, 36 articles were eligible for inclusion with further screening (Fig. 1).[4,5,7—20,26—45] Table S2 shows the characteristics of included studies in the quantitative synthesis. All the studies used a historical cohort design. Across the included studies, a total of 1,883,936 neonates during the COVID-19 pandemic and 4,667,133 neonates during the prepandemic were reported. Of the 36 primary studies, 12 reported mean birth weight, 23 reported adverse birth weight (LBW, VLBW, or macrosomia), and nine reported birth weight for gestational age (SGA, VSGA, or LGA). Twenty-two countries were represented, with substantial variation in pandemic mitigation measures among countries. There were 21 reports from single-center studies, four multicenter studies, and six regional reports, and the remaining five were national registries. Total sample sizes varied from 81 to 2,219,914 neonates. The duration of the 'pandemic period' studied varied from 1 month to 11 months, and the duration of the 'prepandemic period' studied varied from 2 months to 18 years. The scores of quality assessments of the studies ranged from 5 to 9 (Table S3). There were 21 articles with moderate risk of bias and 15 articles with low risk of bias.

There was an increase in mean birth weight during the pandemic compared with the prepandemic period (pooled MD [95% CI] = 15.06 [10.36, 19.76], I^2 = 0.0%, 12 studies; Fig. 2). We only found a significant decrease in the rate of VLBW (pooled OR [95% CI] = 0.86 [0.77, 0.97], I^2 = 55.4%, 12 studies), but there was no difference for LBW and macrosomia during the pandemic compared with the prepandemic period (LBW: pooled OR [95% CI] = 0.96 [0.90, 1.03], I^2 = 69.2%, 20 studies; macrosomia: pooled
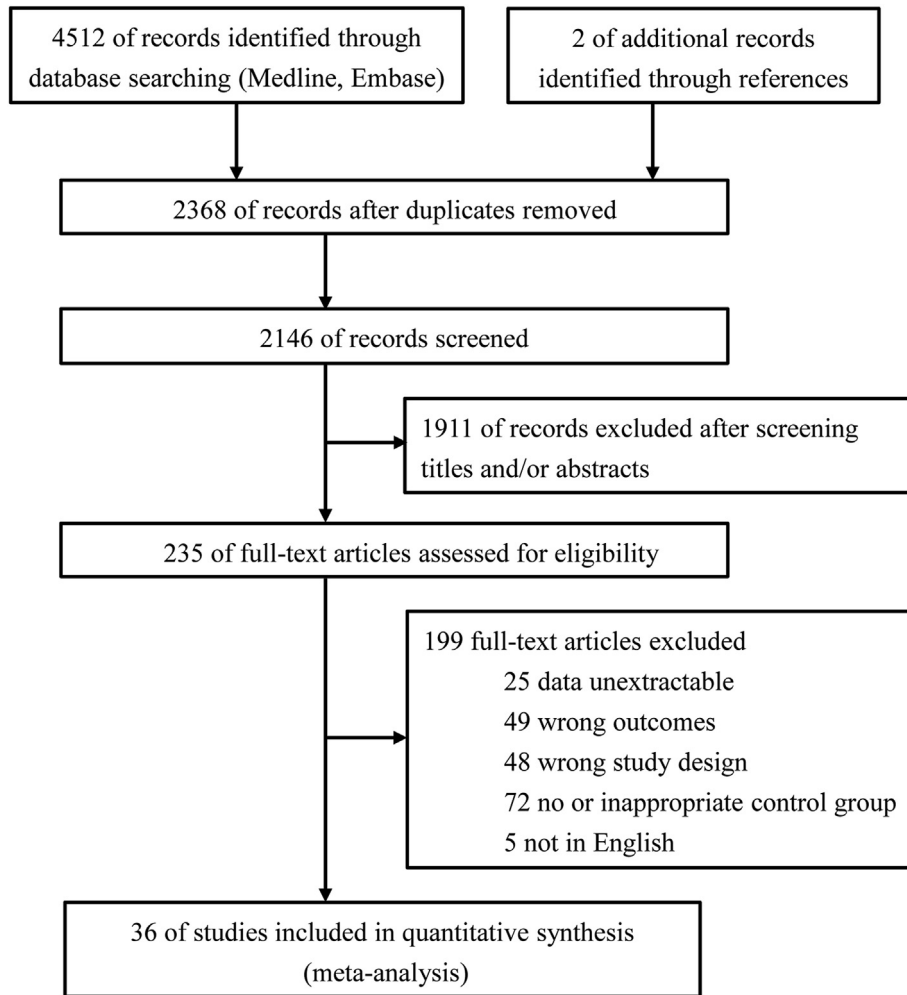
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Fig. 1. Flowchart of study selection.

Study	Mean difference (95% CI)	% Weight
Gu et al, 2020[33]	43.65 (-62.17, 149.47)	0.2
Justman et al, 2020[35]	11.70 (-40.87, 64.27)	0.8
Kim et al, 2021[36]	93.40 (25.47, 161.33)	0.5
Kirchengast et al, 2021[5]	39.50 (-45.90, 124.90)	0.3
Meyer et al, 2020[40]	21.00 (-19.89, 61.89)	1.3
Mor et al, 2020[8]	24.00 (-4.00, 52.00)	2.8
Ornaghi et al, 2021[28]	16.60 (-21.79, 54.99)	1.5
Wang et al, 2021[45]	-10.00 (-111.67, 91.67)	0.2
Friedrich et al, 2021[32]	32.00 (8.29, 55.71)	3.9
Kc et al, 2020[9]	10.60 (-4.05, 25.25)	10.3
Meyer et al, 2021[39]	25.00 (4.39, 45.61)	5.2
Wagner et al, 2021[7]	13.00 (7.50, 18.50)	73.0
Overall (I-squared = 0.0%, P = 0.514)	15.06 (10.36, 19.76)	100.0

Note: Weights are from fixed effects analysis

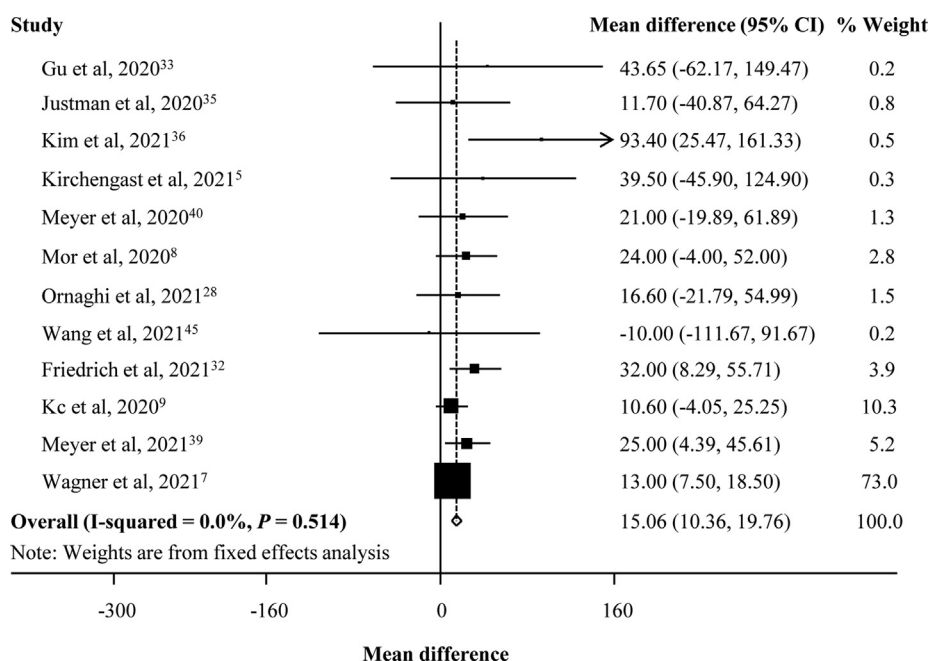Mean difference axis: -300   -160   0   160

Mean difference

Fig. 2. Forest plot for mean birth weight.

OR [95% CI] = 0.70 [0.49, 1.02], I^2 = 87.7%, five studies; Fig. 3). Moreover, there was publication bias for mean birth weight with a borderline significance (Egger's P = 0.050) but not for LBW (Egger's P = 0.681) and VLBW (Egger's P = 0.071). Fig. 4 shows the funnel plots of the included studies for neonatal birth weight ($\geq$10 studies). In studies with birth weight for gestational age, we found a

reduction for SGA in the pandemic period with a borderline significance (SGA: pooled OR [95% CI] = 0.97 [0.94, 1.01], I^2 = 55.1%, nine studies), whereas there was no significant difference for VSGA and LGA (VSGA: pooled OR [95% CI] = 1.10 [0.95, 1.28], I^2 = 33.7%, three studies; LGA: pooled OR [95% CI] = 0.93 [0.76, 1.14], I^2 = 98.0%, two studies; Fig. 5).
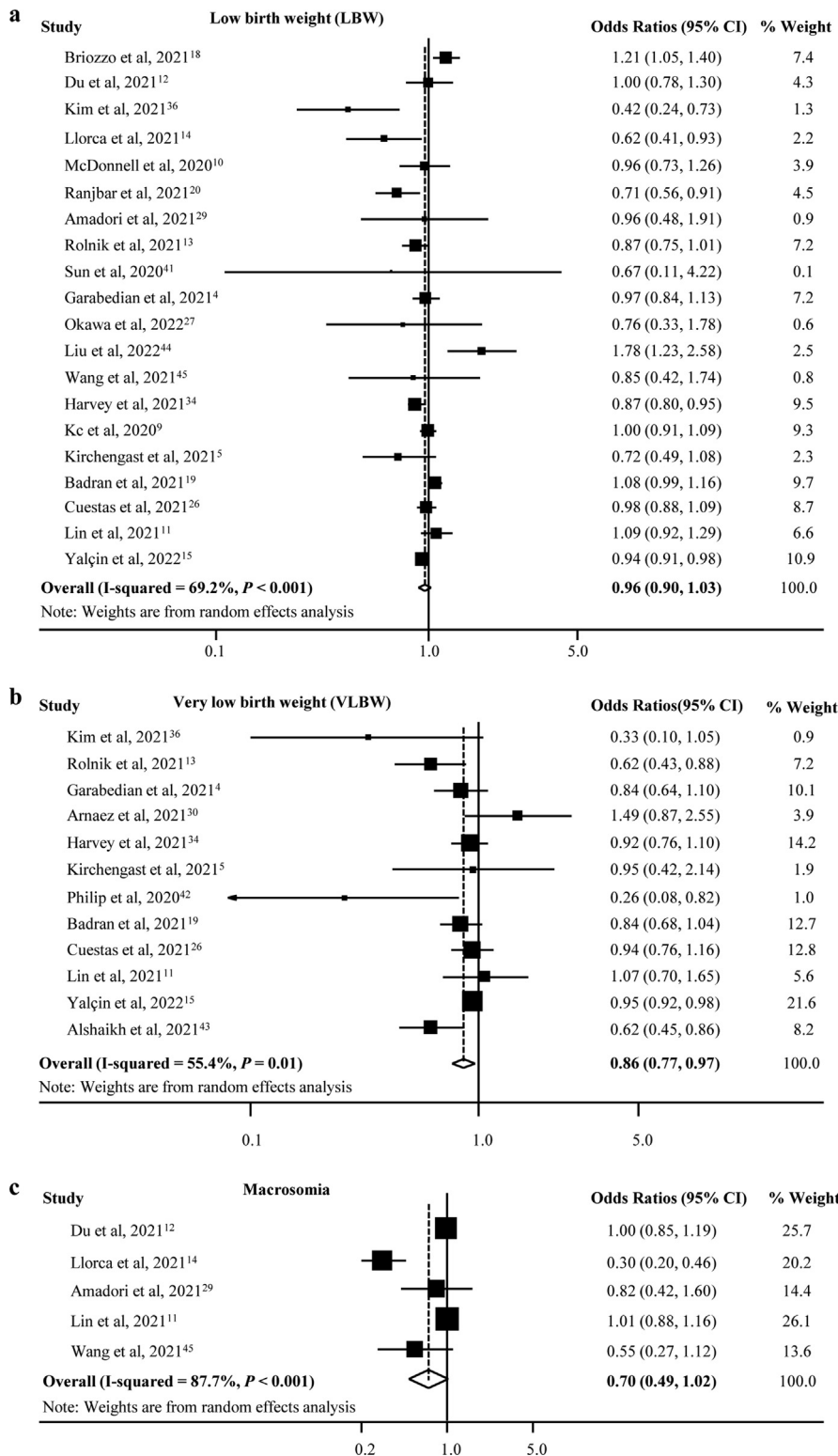
Fig. 3. Forest plot for odds of birth weight.
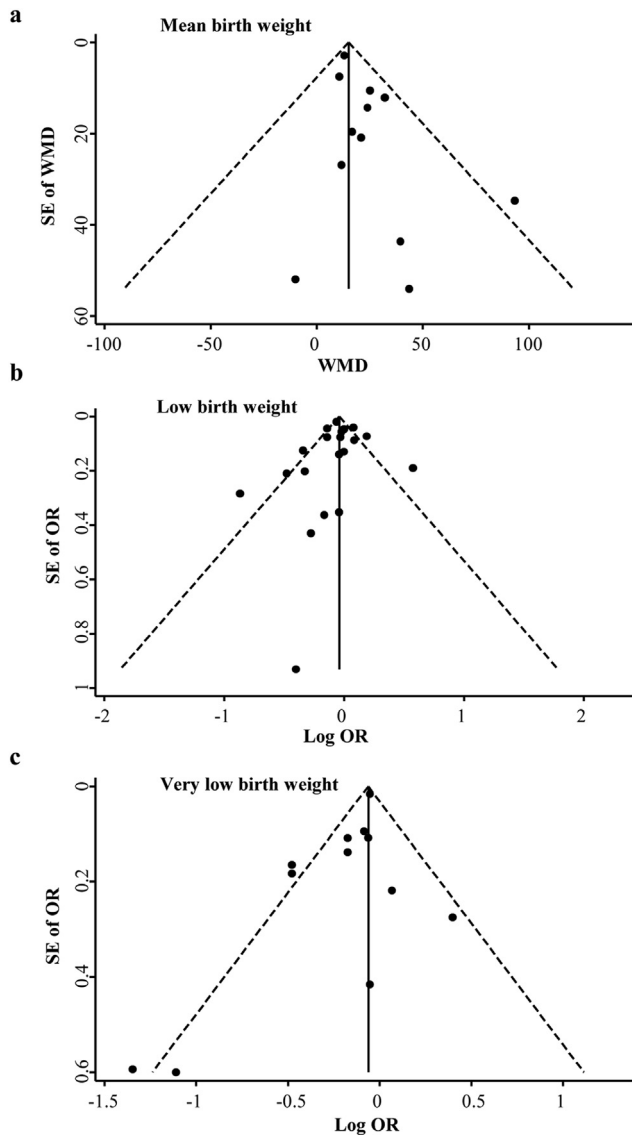
Fig. 4. Funnel plots for studies reporting on birth weight.

Further subgroup analyses were performed to assess the effect of potential confounders on the pooled results. For mean birth weight, there was a significant increase during the pandemic, which was supported by most study subgroups ($P < 0.01$), except for the data from low-/middle-income countries (Table S4). Although the pooled odds of LBW had no change during the pandemic, the subgroups analysis showed a significant decrease in the studies from regionwide/nationwide and high-income countries (studies from regionwide/nationwide: pooled OR [95% CI] = 0.92 [0.86, 0.97], $I^2 = 29.7\%$, three studies; studies from high-income countries: pooled OR [95% CI] = 0.85 [0.77, 0.95], $I^2 = 37.7\%$, nine studies; Table S5). Furthermore, we also found a significant reduction for VLBW in most subgroups, including the data from adjusted odds, low-/middle-income or high-income countries, and the studies with moderate risk of bias or total sample size <10,000, but not for other subgroups (Table S6). Different from summary odds of SGA, there was a significant reduction in specific subgroups: the studies from regionwide/nationwide or high-income countries, the studies with a low risk of bias or total sample size ≥10,000, and the prepandemic period defined as equivalent period in previous years ($P < 0.01$; Table S7).

In sensitivity analysis, most pooled estimates were not significantly different when a study was omitted, whereas the pooled estimate effect became significant for SGA when Briozzo et al.[18] or Badran et al.[19] were omitted ($P < 0.001$ and $P = 0.002$).

Discussion

We have provided quantitative estimates for the associations between the COVID-19 pandemic and neonatal birth weight through a systematic search and comprehensive meta-analysis. The results showed a significant increase of 15 g in mean birth weight in the pandemic period compared with before the pandemic period. We also identified a reduction in the rate of VLBW, but not for LBW and macrosomia. Besides, there was a reduction in the rate of SGA with a borderline significance but not for VSGA and LGA with a few studies included.

Recently, some reviews mainly reported the effects of COVID-19 infection on pregnancy outcomes[46–48] and the major birth outcomes, such as preterm birth and stillbirths.[49–51] This meta-analysis was designed to evaluate the indirect impacts of the COVID-19 pandemic on secondary birth outcomes and excluded studies that reported outcomes of maternal COVID-19 infection. In this review, pooled results showed that LBW did not significantly change during the COVID-19 pandemic, which was supported by the previous review.[50,51] However, we identified a significant decrease for LBW in the data from regionwide/nationwide and high-income countries. Yang et al.[49] found a reduction in LBW during the pandemic using regional/national data, but there was no overall difference in LBW and VLBW. In contrast, there was a significant decrease in the rate of VLBW during the pandemic compared with the prepandemic period in our study. Nevertheless, we also found substantial heterogeneity and discordant results among the subgroups. Inconsistency among conclusions from different studies possibly be attributed to variations in sample sizes, location of the population, socio-economic status, lengths or definition of the pandemic and prepandemic periods, and different blockade measures between countries.

The previous meta-analyses mainly reported the effects of the COVID-19 pandemic on preterm, stillbirths, maternal mortality, and LBW.[49–51] As a more sensitive indicator of neonatal health, SGA infants are more likely to have intensive care therapy, morbidity due to perinatal fetal distress and neonatal asphyxia, and perinatal mortality compared with appropriate for gestational age.[52] However, the effect of the pandemic on SGA has not received much attention in the previous review. To improve this deficiency, our study investigated the association between SGA and the pandemic. Although we found no difference in the rate of SGA during the pandemic compared with the prepandemic period, there was a significant decrease in the data from regionwide/nationwide, high-income countries, and the studies with low risk of bias. Besides, we found a significant change when Briozzo et al.[18] or Badran et al.[19] were omitted, and the studies were from single-center and low-/middle-income countries. Explanations for these results may be related to substantial variation in pandemic mitigation measures and population responses among countries.

The researchers have proposed that COVID-19–related lockdown may cause maternal behavioral modifications, potential reduction in work-related stresses, optimal opportunities for rest and sleep, reduced exposure to infections, and improved opportunities for nutritional support and exercise.[19,42] While the pandemic has caused disruption to healthcare systems, economic crises, and rising unemployment, people with high income and people in developed countries have experienced faster restructuring of healthcare systems and timely increased access to care through telehealth.[53] In addition, their family assets may ease the burden of unemployment
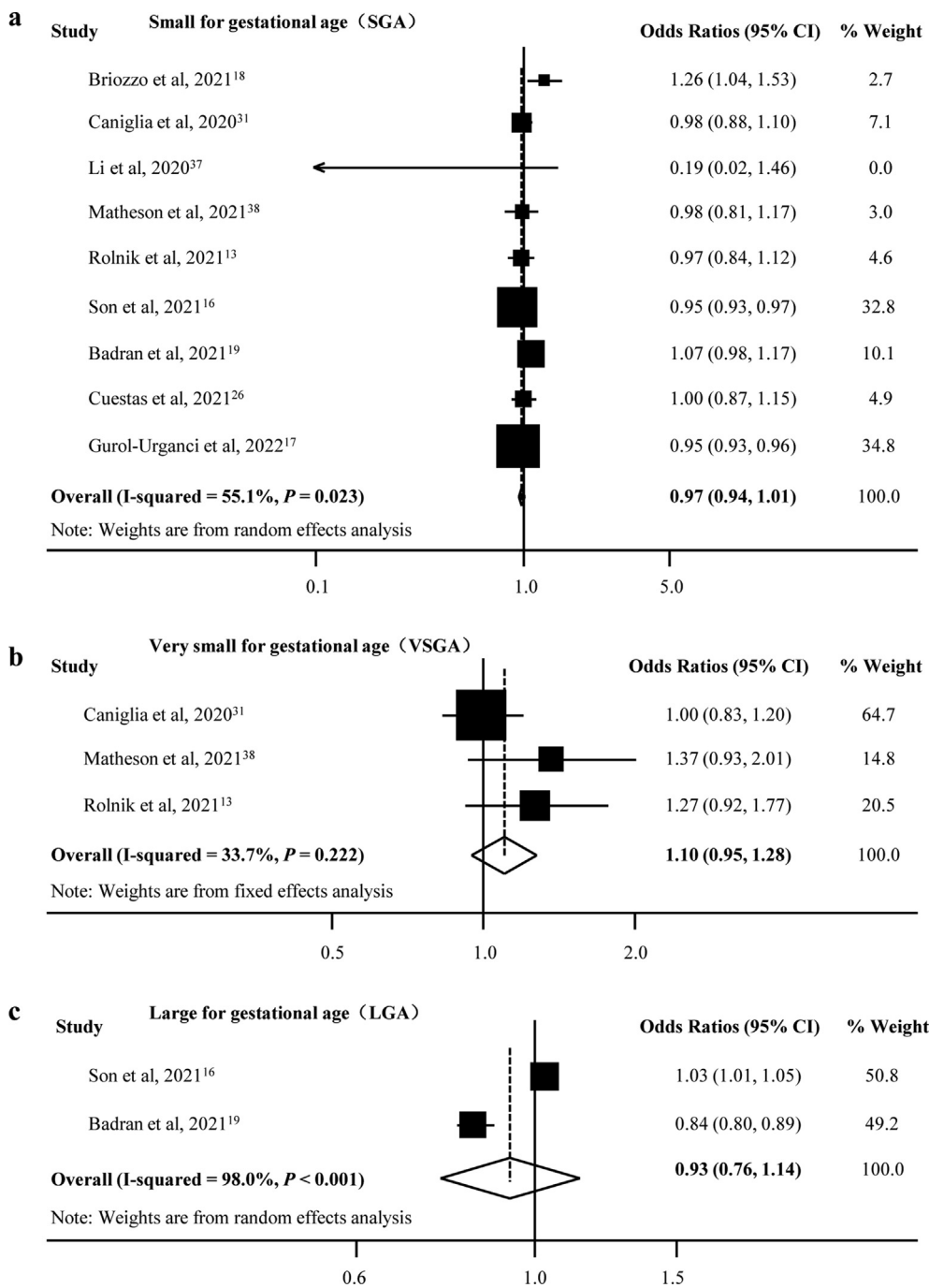
Fig. 5. Forest plot for odds of birth weight for gestational age.

and allow them to spend more time enjoying life. However, for low-income families, it may have exacerbated socio-economic inequalities in health, limitation of health services, family conflicts, perinatal anxiety, and depression.[26,54] In low-income countries, where remote consultations are less feasible, financial or employment issues are prominent, and maternity staff shortages exist, resulting in reduced access to preventive antenatal care and nutritional support for pregnant women.[55] As a result, pregnant women can suffer negative physical and mental health outcomes. Stress, worries, and anxieties during pregnancy are often associated with LBW.[56] Therefore, the effect of the pandemic on neonatal adverse birth weight is a double-edged sword. COVID-19 is not only a

pandemic and global health crisis but also a psychosocial and economic disaster. The potential influence of a multitude of biological, physical, and environmental factors could cumulatively modify the birth outcomes of neonates.

The strength of this review was the inclusion of large populations from 22 countries and the synthesis of a broad range of articles. We mainly investigate the potential effects of the COVID-19 pandemic on secondary birth outcomes, and deep subgroup analysis was conducted to clarify the source of heterogeneity. Nevertheless, our study had some limitations. First, the included studies all used a retrospective design, and the heterogeneity of study countries, the definitions of comparable groups, and statistical

methodology all affected the comparability of results. Besides, we only reported the non—COVID-19 infection population, and more birth outcomes during the pandemic should be further assessed.

Conclusion

In this study, we found the COVID-19 pandemic was significantly associated with an increase in mean birth weight and a reduction in VLBW, but not for other outcomes. However, subgroup analysis showed that LBW and SGA had a significant reduction in specific subgroups. This review provided clues about the indirect effects of the pandemic on neonatal birth weight. Further studies should be conducted to clarify the underlying mechanisms of the findings, and more healthcare measures needed to improve neonatal long-term health.

Author statements

Author contributions

J.W. initiated, conceived, and supervised the study. X.Y., H.J., J.M., and Y.L. did data collection and performed the data analysis. All authors approved the final format of the submitted manuscript.

Ethical approval

None sought.

Funding

Competing interests

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.04.009.

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