SYSTEMATIC REVIEW

# Birth spacing and risk of adverse pregnancy and birth outcomes: A systematic review and dose–response meta-analysis

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## Abstract

**Introduction:** The association between extreme birth spacing and adverse outcomes is controversial, and available evidence is fragmented into different classifications of birth spacing.

**Material and methods:** We conducted a systematic review of observational studies to evaluate the association between birth spacing (i.e., interpregnancy interval and interoutcome interval) and adverse outcomes (i.e., pregnancy complications, adverse birth outcomes). Pooled odds ratios (ORs) with 95% confidence intervals (CI) were calculated using a random-effects model, and the dose–response relationships were evaluated using generalized least squares trend estimation.

**Results:** A total of 129 studies involving 46 874 843 pregnancies were included. In the general population, compared with an interpregnancy interval of 18–23 months, extreme intervals (<6 months and ≥60 months) were associated with an increased risk of adverse outcomes, including preterm birth, small for gestational age, low birthweight, fetal death, birth defects, early neonatal death, and premature rupture of fetal membranes (pooled OR range: 1.08–1.56; $p < 0.05$). The dose–response analyses further confirmed these J-shaped relationships ($p_{\text{non-linear}} < 0.001$–0.009). Long interpregnancy interval was only associated with an increased risk of preeclampsia and gestational diabetes ($p_{\text{non-linear}} < 0.005$ and $p_{\text{non-linear}} < 0.001$, respectively). Similar associations were observed between interoutcome interval and risk of low birthweight and preterm birth ($p_{\text{non-linear}} < 0.001$). Moreover, interoutcome interval of ≥60 months was associated with an increased risk of cesarean delivery (pooled OR 1.72, 95% CI 1.04–2.83). For pregnancies following preterm births, an interpregnancy interval of

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9 months was not associated with an increased risk of preterm birth, according to dose–response analyses ($p_{non-linear} = 0.008$). Based on limited evidence, we did not observe significant associations between interpregnancy interval or interoutcome interval after pregnancy losses and risk of small for gestational age, fetal death, miscarriage, or preeclampsia (pooled OR range: 0.76–1.21; $p > 0.05$).

**Conclusions:** Extreme birth spacing has extensive adverse effects on maternal and infant health. In the general population, interpregnancy interval of 18–23 months may be associated with potential benefits for both mothers and infants. For women with previous preterm birth, the optimal birth spacing may be 9 months.

**KEYWORDS**
adverse pregnancy outcome, adverse birth outcome, birth interval, interoutcome interval, interpregnancy interval

## 1 | INTRODUCTION

Optimal birth spacing is an important component of postpartum family planning criteria that can yield short- and long-term benefits for mothers children.[1,2] To reduce adverse events in subsequent pregnancies, the 2005 WHO guidelines recommend that women wait at least 2 years after a live birth and 6 months after a miscarriage or induced abortion before conceiving again.[3] When evaluating the evidence on birth spacing, WHO identified four intervals, including interpregnancy interval (IPI, the period between the previous live birth or pregnancy loss and the conception of the index pregnancy), interoutcome interval (IOI, the period between the outcome of the previous pregnancy and the outcome of the index pregnancy), birth-to-conception interval (the period from the previous live birth to the conception of the index pregnancy), and birth-to-birth interval (the period from the delivery of the previous livebirth to the subsequent live birth).[3] Compared with IPI, the use of birth intervals overestimates the risk of adverse outcomes for very short intervals between pregnancies.[4] Substantial differences were observed in risk estimates related to birth spacing according to the measurement of birth spacing used. However, differences in risk estimates related to birth spacing have not been well addressed in published systematic reviews, with a lack of stratification for the start of birth spacing or blurred distinction between birth and pregnancy intervals.[4-7] It is therefore important to quantify the differences by pooling current evidence.

To date, IPI has been among the most studied birth spacing intervals. Previous studies have reported on J-shaped dose–response relationships between IPI and the risk of adverse outcomes (eg gestational diabetes mellitus [GDM], low birthweight [LBW], preterm birth [PTB], and small for gestational age [SGA]).[8-10] Moreover, subsequent pregnancies after live birth or pregnancy loss have been variably associated with adverse pregnancy and birth outcomes.[11,12] Short intervals after a pregnancy loss might prevent adverse outcomes, including PTB, LBW, SGA, and recurrent preeclampsia.[12-14] However, risk factors associated with short intervals, such as poor socioeconomic status, are independently associated with increased risk of adverse pregnancy outcomes.[15,16] Given the increase of relevant large-scale population studies in recent years,[17-19] there is a need to incorporate empirical data and obtain robust estimates through meta-analytic approaches.

To inform the strategies for postpartum family planning, we systematically reviewed the evidence on the associations between birth spacing and adverse pregnancy and birth outcomes and evaluated these associations using meta-analytical synthesis with dose–response analysis.

> **Key message**
>
> Interpregnancy interval of 18 to 23 months could have benefits in the general population, and women with previous preterm birth should wait 9 months before conceiving again. To further explore this association and underlying unmeasured confounders, higher quality cohorts are needed.

## 2 | MATERIAL AND METHODS

The present study was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Appendix S1).[20] This review was not prospectively registered.

### 2.1 | Identification of studies

PubMed, Embase, and Web of Science Core Collection were searched from database inception until March 20, 2022, to identify observational studies that measured the association between birth spacing and risk of adverse pregnancy and birth outcomes. In accordance with the Peer Review of Electronic Search Strategies (PRESS) guideline,[21] two experienced medical information specialists (GXP, ZFF)
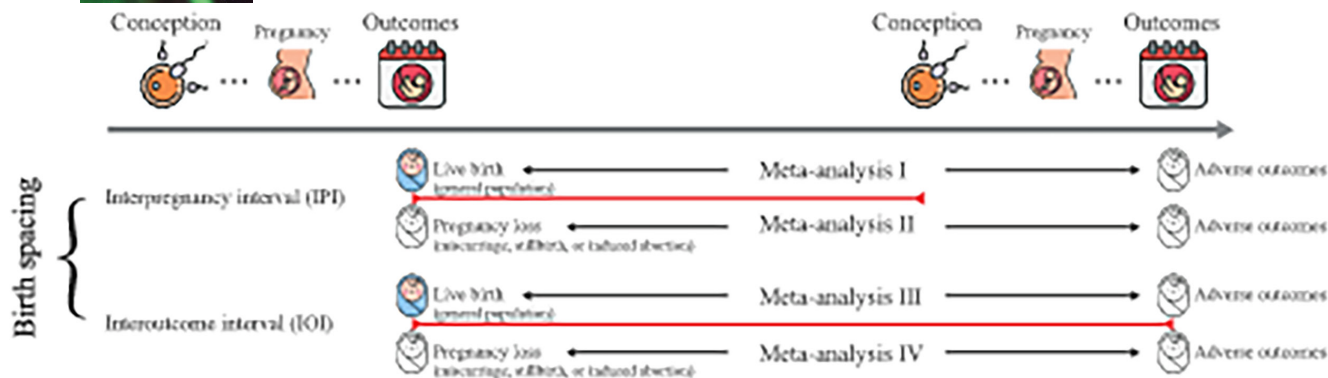
**FIGURE 1** The classification of birth spacing and analysis strategy. Four separate meta-analytical syntheses were conducted in accordance with the WHO definition of birth spacing as follows: (1) Meta I, the association between interpregnancy interval (IPI) and risk of adverse outcomes after a live birth (general population); (2) Meta II, the association between IPI and risk of adverse outcomes subsequent to pregnancy loss (miscarriage, stillbirth, or induced abortion) or preterm birth (PTB); (3) Meta III, the association between interoutcome interval (IOI) and risk of adverse outcomes after a live birth (general population); and (4) Meta IV, the association between IOI and risk of adverse outcomes subsequent to pregnancy loss (miscarriage, stillbirth, or induced abortion) or PTB. Free icons were obtained from Flaticon.com.

developed the search strategy and performed the literature search without language restrictions. The full list of outcomes of interest and details of search terms are listed in the Supporting information (Appendix S2). To identify additional items not retrieved by database searches, we analyzed the reference list of included articles. We additionally manually searched the related articles generated by PubMed and Google Scholar (https://scholar.google.com/).

The selection of potentially eligible studies was made by reviewing titles and abstracts by two independent reviewers (NWZ and GXP). In case of discrepancies, a third review author (ZFF) was involved, and consensus was reached by discussion. If the inclusion and exclusion criteria could not be determined from the titles and abstracts, the full articles were obtained to verify eligibility. The full text of potentially included studies was carefully reviewed by at least two reviewers.

## 2.2 | Selection criteria

To systematically review the current evidence on this topic, we included studies that met the following criteria: (1) Observational studies (cohort, cross-sectional, or case–control design) or experimental studies (analyzed as cohort design) evaluated the association between birth spacing and any adverse pregnancy or birth outcome. (2) The classification of birth spacing was defined in accordance with the standard proposed by WHO.[3] (3) Studies evaluated the risk of adverse outcomes of interest and reported effect estimates (i.e., odds ratios [ORs], risk ratios, or hazard ratios). Studies were excluded from systematic review if they were conference abstracts, letters, or review articles; if they had particularly short birth spacing that did not contain previous identified safe interval (i.e., 18–23 months); if they provided data for two or fewer birth spacing strata. Studies were further included in meta-analytical synthesis if they met the following additional criteria: (1) used multivariate analysis and adjusted for

at least maternal age and any socioeconomic variable; (2) reported either the number of cases and participants in each birth spacing stratum or the data necessary to calculate these; and (3) reported 95% confidence intervals (CIs) of risk estimates. For associations that involved overlapping data or populations, only the most recent study with the largest data set was included in meta-analytical synthesis.

## 2.3 | Data extraction and quality assessment

Two investigators (NWZ and GXP) independently extracted information on: first author, year of publication, setting (country and detailed geographical location if possible), specific data source (the name of cohort or database), sample size, birth spacing characteristics (definition of birth spacing, strata, details of previous birth or pregnancy loss, outcome of index pregnancy with corresponding definition or diagnostic criteria), maximally adjusted risk estimates with 95% CIs and confounders.

Newcastle–Ottawa Quality Assessment Scale (NOS) was used to evaluate the methodological quality of included studies on the basis of selection, comparability, exposure (for case–control or cross-sectional studies) or outcome (for cohort studies).[22] Studies could be awarded a maximum of nine stars, and a study with eight or more stars was of methodological high-quality. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidance was used to rate the certainty of evidence[23] and is presented in Table S1.

## 2.4 | Statistical analyses

For studies using different units to measure birth spacing (i.e., weeks, months, or years), we converted these different units of exposure to months. Based on the incidence of adverse pregnancy and birth

outcomes, OR were considered as the common approximations of all risk estimates. The DerSimonian & Laird method[24] random effects model was used to conduct all meta-analyses, because it accounted for both within- and between-study heterogeneity.[25] Different designs and measures of birth spacing could pose a threat to the internal validity of quantitative synthesis[4]; therefore, we conducted four separate meta-analytical syntheses (Figure 1).

## 2.4.1 | Pooled OR

Meta-analysis was applied for the association between birth spacing and specific adverse outcome with at least two eligible studies. Following the previous analytical procedure and taking into account the data availability in the original studies, birth spacing was categorized into six groups: 5 months or less, 6–11 months, 12–17 months, 18–23 months (18–35 months for Meta III), 24–59 months (36–59 months for Meta III), and 60 months or more. The reference category was set at 18 to 23 (35 for Meta III) months, as this interval has the lowest risk for most prevalent adverse outcomes (i.e., LBW, PTB, and SGA). To ensure the comparability between studies, risk estimates for studies using different reference categories were converted based on the Greenland and Longnecker method[26] using EXCEL macro file.[27] If study categories did not match the above intervals, we assigned categories based on their midpoints and favored the reference interval in case the midpoints fell on the boundary.

## 2.4.2 | Dose–response regression slopes

Under the assumption of the J-shaped dose-specific association, we evaluated the non-linear dose–response regression slopes of each meta-analytical synthesis (with eligible studies ≥5) using generalized least squares trend estimation based on the variance weighted least squares (VWLS) method.[28] This procedure requires the number of cases and population at risk (or controls), the midpoint of the exposure interval for at least three categories, and points that were half-width of the adjacent interval from open ends for open-ended intervals.[29] We examined a series of spline functions (3, 4, and 5 knots) and the significant model with highest goodness-of-fit chi-squared score was selected.

The heterogeneity between studies was evaluated with Cochran's Q test (statistically significant for $p$ value <0.10) and quantified with the $I^2$ metric.[30] Large heterogeneity was defined as an $I^2$ statistic of >50%.[31] In order to explore the potential modifying effects of study-level variables on the association, subgroup, and univariable random-effects, meta-regression analyses were carried out for a specific association with eligible studies ≥10. Subgroup analyses were stratified by publication year (2005 and before or after 2005), study design (cross-sectional, case–control, cohort study or trail), NOS score (≤8 or 9), adjustment of birth order/parity/ gravidity (Yes or No) and risk estimate (OR, risk ratio, or hazard ratio). Meta-regression analyses were performed for the Sociodemographic Index (SDI), a composite

indicator that effectively captures the level of development status.[32] SDI values for all estimated locations between 1950 and 2019 were obtained from the official website of the Global Burden of Disease Study 2019 (https://ghdx.healthdata.org/record/ihme-data/gbd-2019-socio-demographic-index-sdi-1950-2019). We assigned an SDI value to each study based on year of publication and study location. Publication bias was assessed using Egger's asymmetry tests, and was claimed at an Egger's $p$ value of <0.10.[33] All statistical analyses were performed using Stata software version 14.0 (StataCorp). The level of statistical significance was set at $p < 0.05$, and $p$ values were all two-tailed.

# 3 | RESULTS

## 3.1 | Study selection and characteristics

A total of 9276 articles were initially identified through database search. After removing duplicates and assessing titles and abstracts, 397 full-text articles were assessed for eligibility. Of these, articles were further excluded because of lack of risk estimates ($n=89$), having two or fewer birth spacing strata ($n=80$), birth spacing not measured ($n=36$), irrelevant or nonspecific outcomes ($n=53$), reviews or conference abstracts ($n=15$), short birth spacing ($n=6$), and overlapping population ($n=4$). With additional manual search, 129 studies comprising 46 874 843 participants were ultimately included in the systematic review (Figure S1), including 90 cohort studies,[11-14,17-19,34-116] 23 cross-sectional studies,[10,117-138] 15 case–control studies,[8,139-152] and 1 cluster-randomized trial.[153] The baseline characteristics of the eligible studies are presented in Table S2. The quality assessments of eligible studies ranged from four to nine stars, and most studies (99/129) were awarded with eight stars or more (Table S3 and S4). Based on GRADE guidance, a moderate rating was given for the association between interpregnancy interval and pregnancy-induced hypertension (PIH), whereas the certainty of evidence from other studies was deemed low.

Among studies eligible for systematic review, 23 studies were excluded from meta-analytical synthesis because of unadjusted risk estimates,[39,72,77,113,125,128,129,140,147,148] lack of 95% CI,[50,51,63,68,117,118,127] and lack of adjustment for maternal age.[37,66,81,110,137,142] Under the premise of data availability of individual studies, 77 studies were included in dose–response analyses, and 89 studies were included in meta-analyses (eight studies were further excluded from meta-analyses because of broad reference interval: 12–47, 12–60, and 18–59 months). Results of studies that were not included in meta-analytical synthesis are presented in Table S5.

## 3.2 | Meta I: Interpregnancy interval and risk of adverse outcomes after a live birth

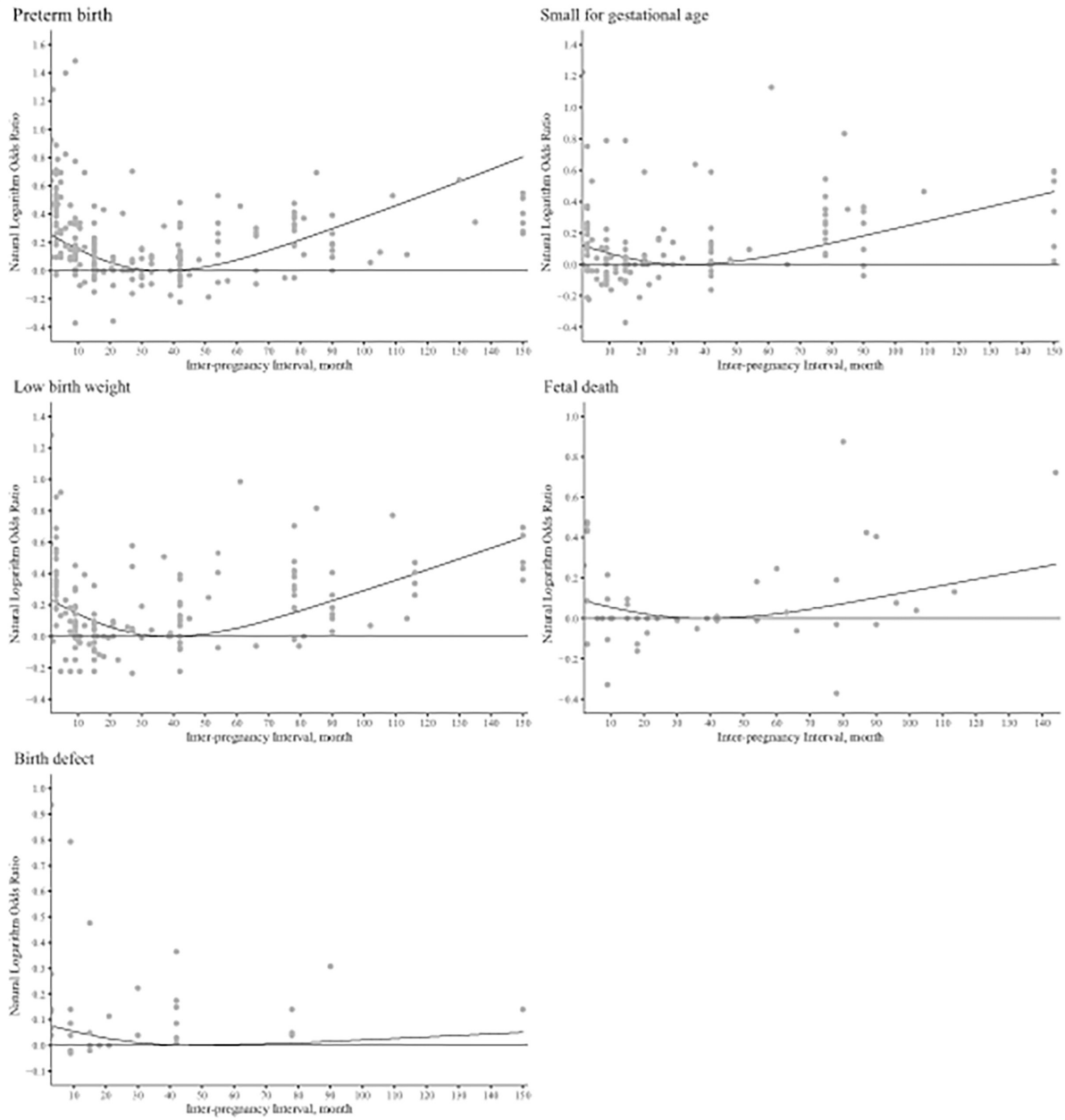### 3.2.1 | Adverse birth outcomes

Compared with an IPI of 18–23 months, extremely short intervals (<6 months) were associated with increased risk of PTB (pooled

**TABLE 1** Meta-analysis I for the associations between interpregnancy interval and risk of adverse pregnancy and birth outcomes subsequent to live births.

| Adverse outcomes | No. of studies | <6 months Pooled OR (95% CI) | $I^2$ (%) | 6–11 months Pooled OR (95% CI) | $I^2$ (%) | 12–17 months Pooled OR (95% CI) | $I^2$ (%) | 18–23 months OR | 24–59 months Pooled OR (95% CI) | $I^2$ (%) | ≥60 months Pooled OR (95% CI) | $I^2$ (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Birth outcomes** | | | | | | | | | | | | |
| Preterm birth | 37 studies[10,12,14,19,36,41,42,46,47,54,62,69,76,78,80,82,86,88,89,92,94,95,97,100-102,107,114,115,119,122,123,132,139,143,150,151] | 1.55 (1.47–1.63) | 92.2 | 1.16 (1.10–1.23) | 99.7 | 1.05 (1.01–1.09) | 98.5 | 1.00 | 1.05 (1.02–1.07) | 87.8 | 1.28 (1.20–1.35) | 96.9 |
| Small for gestational age | 24 studies[10,14,19,34,35,46,47,59,62,69,75,78,85,86,88,89,92,95,97,102,115,119,122,123] | 1.17 (1.12–1.23) | 79.9 | 1.05 (1.03–1.08) | 82.7 | 1.01 (0.99–1.03) | 43.9 | 1.00 | 1.06 (1.03–1.09) | 79.9 | 1.30 (1.22–1.40) | 94.8 |
| Low birthweight | 21 studies[10,14,34,41,42,46,49,69,78,82,86,88,89,92,102,107,119,122,123,132,135] | 1.42 (1.31–1.55) | 88.7 | 1.10 (1.06–1.13) | 48.8 | 1.01 (0.99–1.04) | 10.6 | 1.00 | 1.08 (1.05–1.12) | 70.9 | 1.37 (1.27–1.48) | 96.3 |
| Fetal death | 8 studies[48,53,55,82,98,122,123,149] | 1.52 (1.36–1.70) | 0.0 | 1.05 (0.93–1.19) | 61.7 | 1.02 (0.80–1.30) | 21.0 | 1.00 | 1.00 (0.97–1.03) | 27.6 | 1.14 (1.04–1.24) | 86.7 |
| Birth defects | 6 studies[8,10,62,73,79,87] | 1.12 (1.04–1.22) | 55.7 | 1.03 (0.97–1.10) | 56.0 | 1.01 (0.95–1.07) | 22.7 | 1.00 | 1.05 (1.02–1.09) | 0.0 | 1.08 (1.02–1.14) | 0.0 |
| Cleft lip with and without cleft palate | 4 studies[8,60,73,79] | 1.04 (0.68–1.60) | 0.0 | 1.20 (0.88–1.66) | 15.5 | 1.03 (0.74–1.45) | 0.0 | 1.00 | 1.28 (1.04–1.58) | 21.5 | — | — |
| Early neonatal death | 3 studies[48,62,122] | 1.32 (1.04–1.67) | 46.4 | 1.19 (1.03–1.36) | 32.0 | — | — | 1.00 | 1.01 (0.88–1.18) | 42.6 | 1.17 (1.06–1.28) | 0.0 |
| Large for gestational age | 3 studies[62,85,97] | 0.81 (0.78–0.84) | 18.1 | 0.91 (0.82–1.01) | 95.1 | — | — | 1.00 | 1.03 (0.93–1.13) | 97.1 | 0.94 (0.74–1.20) | 99.1 |
| **Pregnancy outcomes** | | | | | | | | | | | | |
| Preeclampsia | 7 studies[13,82,89,107,109,112,120] | 0.96 (0.87–1.06) | 55.1 | 0.91 (0.81–1.03) | 85.1 | 0.94 (0.83–1.06) | 74.3 | 1.00 | 1.08 (0.99–1.18) | 89.5 | 1.35 (1.18–1.54) | 95.2 |
| Gestational diabetes | 5 studies[89,99,100,107,120] | 1.07 (0.87–1.32) | 93.4 | 0.92 (0.91–0.94) | 0.0 | 0.98 (0.96–0.99) | 0.0 | 1.00 | 1.15 (1.08–1.22) | 16.8 | 1.37 (1.26–1.48) | 41.5 |
| Premature rupture of fetal membranes | 4 studies[96,107,120,123] | 1.56 (1.29–1.88) | 81.7 | 1.03 (0.96–1.11) | 0.0 | 1.02 (0.94–1.11) | 0.0 | 1.00 | 1.11 (0.96–1.28) | 80.0 | 1.53 (1.07–2.20) | 92.1 |
| Pregnancy-induced hypertension | 3 studies[100,107,123] | 1.07 (0.77–1.49) | 66.9 | 0.93 (0.91–0.95) | 0.0 | 0.95 (0.93–0.96) | 0.0 | 1.00 | 1.04 (0.78–1.39) | 0.0 | 1.47 (1.01–2.14) | 28.4 |
| Anemia, maternal | 2 studies[109,120] | — | — | — | — | — | — | 1.00 | 1.09 (0.89–1.33) | 28.1 | 0.98 (0.76–1.25) | 14.3 |
| Postpartum hemorrhage | 2 studies[109,120] | — | — | — | — | — | — | 1.00 | 1.00 (0.85–1.17) | 40.2 | 0.89 (0.78–1.02) | 0.0 |
| Miscarriage | 2 studies[11,53] | — | — | 1.00 (0.80–1.24) | 0.0 | — | — | 1.00 | 1.23 (1.08–1.42) | 0.0 | — | — |

Abbreviations: CI, confidence interval; OR, odds ratio.
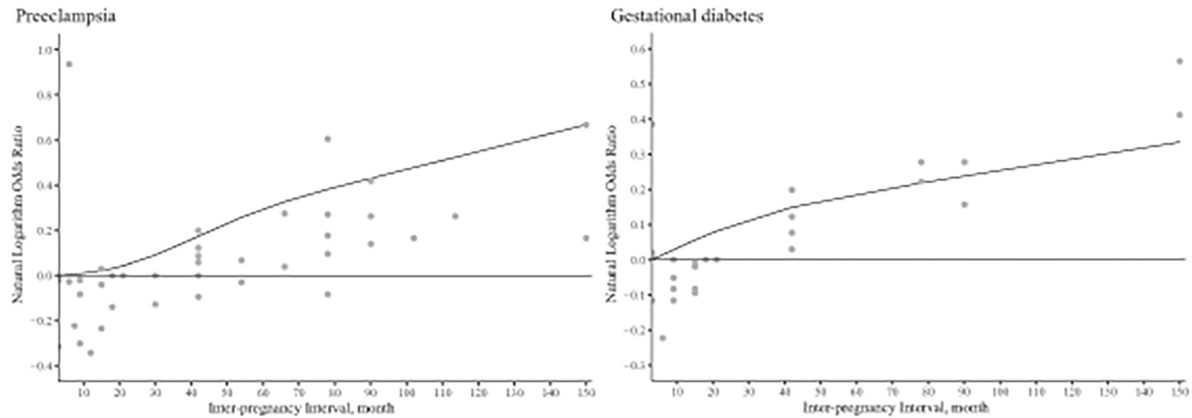
**(A)**



**(B)**



**FIGURE 2** Dose–response relationships between interpregnancy interval and risk of adverse pregnancy and birth outcomes subsequent to live births.

TABLE 2 Meta-analysis II for the associations between interpregnancy interval and risk of adverse pregnancy and birth outcomes subsequent to preterm birth or pregnancy loss (miscarriage, stillbirth, or induced abortion).

| Adverse outcomes | No. of studies | <6 months Pooled OR (95% CI) | I² (%) | 6–11 months Pooled OR (95% CI) | I² (%) | 12–17 months Pooled OR (95% CI) | I² (%) | 18–23 months OR | 24–59 months Pooled OR (95% CI) | I² (%) | ≥60 months Pooled OR (95% CI) | I² (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **After preterm births** | | | | | | | | | | | | |
| Preterm birth | 5 studies[18,54,71,90,105] | 1.45 (1.25–1.68) | 71.3 | 1.10 (1.00–1.21) | 56.1 | 1.03 (0.97–1.09) | 3.8 | 1.00 | 1.03 (0.94–1.14) | 75.0 | 1.29 (1.03–1.63) | 70.9 |
| **After pregnancy losses** | | | | | | | | | | | | |
| **Birth outcomes** | | | | | | | | | | | | |
| Preterm birth | 7 studies[12,14,65,70,91,103,121] | 1.21 (0.7–1.86) | 98.2 | 0.97 (0.88–1.06) | 84.1 | 0.99 (0.95–1.03) | 0.0 | 1.00 | 0.99 (0.96–1.01) | 0.0 | 1.03 (0.96–1.10) | 63.9 |
| Low birthweight | 5 studies[14,65,70,91,121] | 1.64 (1.10–2.44) | 93.8 | 1.03 (0.93–1.14) | 57.5 | 1.00 (0.96–1.05) | 0.0 | 1.00 | 1.02 (0.97–1.06) | 0.0 | 1.08 (0.93–1.24) | 93.0 |
| Small for gestational age | 5 studies[14,70,91,103,121] | 1.03 (0.83–1.29) | 70.2 | 1.00 (0.87–1.15) | 89.7 | 1.00 (0.86–1.17) | 19.1 | 1.00 | 0.99 (0.94–1.04) | 34.1 | 1.07 (0.99–1.15) | 31.3 |
| Fetal death | 3 studies[65,103,121] | 1.07 (0.83–1.38) | 0.0 | 1.00 (0.87–1.16) | 0.0 | 1.01 (0.87–1.16) | 0.0 | 1.00 | 1.01 (0.88–1.16) | 0.0 | — | — |
| **Pregnancy outcomes** | | | | | | | | | | | | |
| Miscarriage | 3 studies[11,65,93] | 0.76 (0.54–1.08) | 16.7 | — | — | 1.07 (0.81–1.41) | 2.2 | 1.00 | 0.98 (0.77–1.26) | 0.0 | — | — |
| Preeclampsia | 2 studies[65,121] | 1.04 (0.90–1.20) | 0.0 | 1.04 (0.87–1.23) | 33.2 | 1.10 (0.96–1.25) | 0.0 | 1.00 | 1.06 (0.94–1.20) | 0.0 | — | — |

Abbreviations: CI, confidence interval; OR, odds ratio.

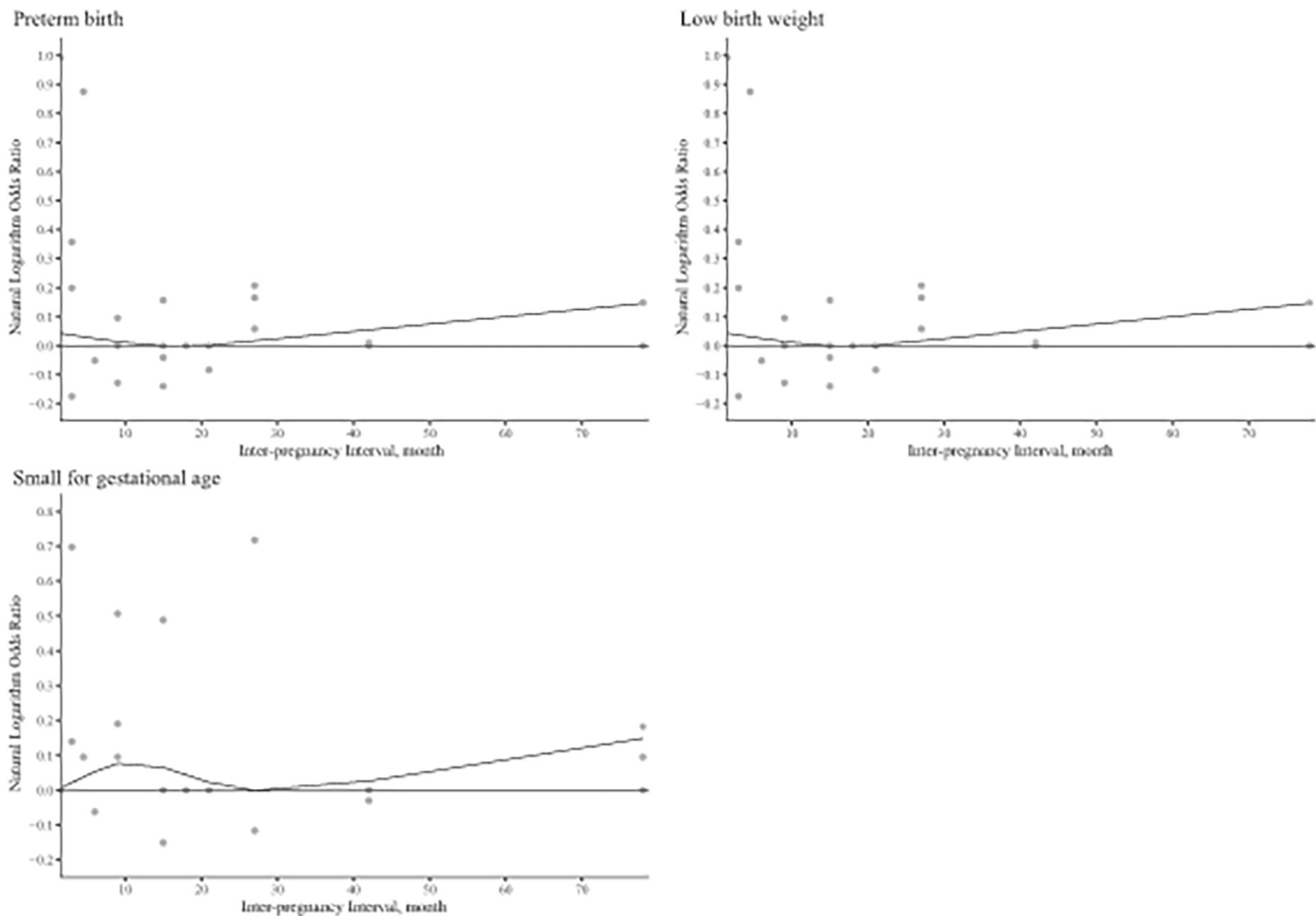Subsequent to preterm birth or pregnancy loss (miscarriage, stillbirth, or induced abortion)



**FIGURE 3** Dose–response relationships between interpregnancy interval and risk of adverse birth outcomes subsequent to pregnancy loss or preterm birth.

OR 1.55, 95% CI 1.47–1.63), SGA (pooled OR 1.17, 95% CI 1.12–1.23), LBW (pooled OR 1.42, 95% CI 1.31–1.55), fetal death (pooled OR 1.52, 95% CI 1.36–1.70), birth defects (pooled OR 1.12, 95% CI 1.04–1.22), and early neonatal death (pooled OR 1.32, 95% CI 1.04–1.67) (Table 1 and Figure S2). Likewise, there was an observed association between extremely long intervals (≥60 months) and an increased risk of PTB (pooled OR 1.28, 95% CI 1.20–1.35), SGA (pooled OR 1.30, 95% CI 1.22–1.40), LBW (pooled OR 1.37, 95% CI 1.27–1.48), and fetal death (pooled OR 1.14, 95% CI 1.04–1.24), birth defects (pooled OR 1.08, 95% CI 1.02–1.14), and early neonatal death (pooled OR 1.17, 95% CI 1.06–1.28) (Table 1 and Figure S2). We also observed an association between longer IPI (24–59 months) and an increased risk of cleft lip compared with the reference group (pooled OR 1.28, 95% CI 1.04–1.58).

Dose–response analyses indicated significant J-shaped relationships between IPI and risk of PTB, SGA, LBW, fetal death, and birth defects ($p_{non-linear}$ for 3 knots ranged from <0.001 to 0.009, best goodness-of-fit chi-squared scores ranged from 71.74 to 10 202.97) (Figure 2). The lowest risk estimates generally fell in the category of 30–40 months (Figure 2).

### 3.2.2 | Adverse pregnancy outcomes

Compared with an IPI of 18–23 months, shorter intervals were associated with an increased risk of premature rupture of fetal membranes (PROM) (pooled OR 1.56, 95% CI 1.29–1.88 for <6 months), but with a decreased risk of GDM (pooled OR 0.92, 95% CI 0.91–0.94 for 6–11 months) and PIH (pooled OR 0.93, 95% CI 0.91–0.95 for 6–11 months, 0.95, 95% CI 0.93–0.96 for 12–17 months). Except for maternal anemia and postpartum hemorrhage, longer IPI were associated with adverse pregnancy outcomes, including an increased risk of preeclampsia (pooled OR 1.35, 95% CI 1.18–1.54), GDM (pooled OR 1.37, 95% CI 1.26–1.48), PROM (pooled OR 1.53, 95% CI 1.07–2.20), PIH (pooled OR 1.47, 95% CI 1.01–2.14), and miscarriage (pooled OR 1.23, 95% CI 1.08–1.42) (Figure S2).

Dose–response analyses were performed for preeclampsia ($p_{non-linear}$<0.001, 4 knots, best goodness-of-fit $\chi^2$ score=213.28) and GDM ($p_{non-linear}$<0.001, 3 knots, best goodness-of-fit $\chi^2$ score=196.28). Consistent with the pooled estimates, the results showed that an increased IPI was positively associated with the risk of preeclampsia and GDM (Figure 2).

## 3.3 | Meta II: Interpregnancy interval and risk of adverse outcomes after a PTB or pregnancy loss

In the analysis of subsequent to preterm birth, compared with an IPI of 18–23 months, intervals shorter than 12 months were significantly associated with increased risk of PTB (pooled OR 1.10, 95% CI 1.00–1.21 for 6–11 months; 1.45, 95% CI 1.25–1.68 for <6 months), and extremely long intervals (≥60 months) also indicated an increased risk (pooled OR 1.29, 95% CI 95% CI 1.03–1.63) (Table 2). In the analysis of subsequent to pregnancy loss, none of the pooled risk estimates reached statistical significance, except for LBW with intervals <6 months (pooled OR 1.64, 95% CI 1.10–2.44) (Table 2 and Figure S3).

Dose–response analyses were conducted for PTB ($p_{non-linear}=0.008$, 5 knots, best goodness-of-fit $\chi^2$ score = 722.07), LBW ($p_{non-linear}<0.001$, 3 knots, best goodness-of-fit $\chi^2$ score = 741.32), and SGA ($p_{non-linear}=0.013$, 4 knots, best goodness-of-fit $\chi^2$ score = 35.50). The results indicated that for women whose most recent pregnancy had ended in preterm birth, safe intervals were generally shorter than for the general population. Additionally, conception at 9 months following a pregnancy loss was not associated with an increased risk of PTB in the subsequent pregnancy (Figure 3).

## 3.4 | Meta III and IV: Interoutcome interval and risk of adverse pregnancy and birth outcomes

Compared with an IOI of 18–35 months, shorter intervals were associated with increased risk of LBW (pooled OR 1.20, 95% CI 1.01–1.41 for 12–17 months; 1.66, 95% CI 1.46–1.89 for 6–11 months), fetal death (pooled OR 2.35, 95% CI 1.60–3.46 for 12–17 months), and PTB (pooled OR 1.37, 95% CI 1.25–1.51 for 12–17 months; 3.10, 95% CI 2.32–4.14 for 6–11 months). Likewise, extremely long intervals (≥60 months) were associated with increased risk of LBW (pooled OR 1.20, 95% CI 1.15–1.26), PTB (pooled OR 1.11, 95% CI 1.02–1.20), and cesarean delivery (pooled OR 1.72, 95% CI 1.04–2.83; Figure S4 and S5). However, no significant association was found between IOI and risk of early neonatal death, GDM, postpartum hemorrhage, preeclampsia, SGA, and miscarriage. (Table 3 and Table S6).

Dose–response analyses were conducted for LBW ($p_{non-linear}<0.001$, 3 knots, best goodness-of-fit $\chi^2$ score = 117.5) and fetal death ($p_{non-linear}<0.001$, 3 knots, best goodness-of-fit $\chi^2$ score = 493.75). The analyses revealed a J-shaped dose–response curve, indicating that the lowest risk was observed in the category of 30–40 months (Figure S6).

## 3.5 | Subgroup analysis and meta-regression

Subgroup analysis was carried out to explore the potential source of heterogeneity. In the preterm birth group of Meta I, the pooled

**TABLE 3** Meta-analysis III for the associations between interoutcome interval and risk of adverse pregnancy and birth outcomes subsequent to live births.

| | 6–11 months | | 12–17 months | | 18–35 months | 36–59 months | | ≥60 months | |
| Adverse outcomes | No. of studies | Pooled OR (95% CI) | $I^2$ (%) | Pooled OR (95% CI) | $I^2$ (%) | OR | Pooled OR (95% CI) | $I^2$ (%) | Pooled OR (95% CI) | $I^2$ (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Birth outcomes** | | | | | | | | | | |
| Low birthweight | 6 studies[38,57,104,133,136,145] | 1.66 (1.46–1.89) | 0.8 | 1.20 (1.01–1.41) | 95 | 1.00 | 1.08 (0.97–1.20) | 89.8 | 1.20 (1.15–1.26) | 4.5 |
| Fetal death | 5 studies[61,104,124,130,138] | — | — | 2.35 (1.60–3.46) | 97.4 | 1.00 | 1.08 (0.79–1.46) | 94.6 | 1.19 (0.84–1.69) | 89.6 |
| Preterm birth | 4 studies[57,74,83,104] | 3.10 (2.32–4.14) | 96.4 | 1.37 (1.25–1.51) | 97.3 | 1.00 | 1.07 (0.95–1.19) | 97.8 | 1.11 (1.02–1.20) | 93.8 |
| Early neonatal death | 2 studies[124,133] | — | — | — | — | 1.00 | 0.75 (0.46–1.24) | 44.7 | 0.76 (0.56–1.02) | 0.0 |
| Small for gestational age | 2 studies[83,131] | — | — | 0.98 (0.62–1.55) | 78.7 | 1.00 | 1.07 (0.89–1.28) | 27.4 | — | — |
| **Pregnancy outcomes** | | | | | | | | | | |
| Cesarean delivery | 3 studies[67,83,134] | — | — | — | — | 1.00 | 1.03 (0.71–1.48) | 88.1 | 1.72 (1.04–2.83) | 87.8 |
| Gestational diabetes | 2 studies[83,131] | — | — | 1.00 (0.96–1.04) | 0.0 | 1.00 | 0.99 (0.95–1.04) | 1.0 | — | — |
| Preeclampsia | 2 studies[58,152] | — | — | 1.64 (0.34–8.02) | 0.0 | 1.00 | 1.24 (0.98–1.57) | 68.1 | — | — |
| Postpartum hemorrhage | 2 studies[104,144] | — | — | — | — | 1.00 | 1.01 (0.93–1.10) | 0.0 | 2.31 (0.55–9.75) | 89.9 |

Abbreviations: CI, confidence interval; OR, odds ratio.

OR were higher for cohort studies than cross-sectional studies (OR 1.36 vs. 1.20; $p_{interaction}$=0.002), and higher for studies not adjusted for birth order/parity/ gravidity than studies adjusted for these variables (OR 1.47 vs. 1.25; $p_{interaction}$<0.001). Regarding the low-birthweight group of Meta II, the pooled OR were higher for studies with a NOS score of 9 compared with studies with a score lower than 9 (OR 1.61 vs. 1.25; $p_{interaction}$=0.012). However, no significant interaction was observed for between published year, or risk estimate ($p_{interaction}$ range 0.066–1.000) (Table S7–S9). In addition, results of meta-regression analysis indicated that SDI did not contribute to the inter-study heterogeneity ($p$ value range 0.052–0.265) (Table S10).

## 3.6  |  Publication bias

We conducted Egger's asymmetry tests for meta-analytical syntheses with 10 or more eligible studies. Most meta-analyses showed no significant publication bias ($p_{Egger's}$ range 0.107–0.826), except for pooled OR of LBW ($p_{Egger's}$ value was 0.006 for shortest IPI and 0.066 for longest IPI). Using the trim-and-fill method, the recalculated OR of LBW attenuated for ≥60 months (13 missing studies, imputed OR 1.17, 95% CI 1.09–1.27), and recalculated OR of LBW unchanged for <6 months (no trimming was performed, imputed OR 1.42, 95% CI 1.31–1.55).

## 4  |  DISCUSSION

In this comprehensive systematic review and meta-analysis, we found that, compared with a reference interval of 18–23 months, extreme IPI (<6 and ≥60 months) in the general population had adverse effects on several pregnancy and birth outcomes, including PTB, SGA, LBW, fetal death, birth defects, early neonatal death, and PROM. Similar associations were also observed between IOI and risk of LBW and PTB (<6 and ≥60 months), as well as longer than 60 months and risk of preeclampsia, GDM, PIH, and cesarean delivery. In addition, extreme IPI after a pregnancy loss or PTB (<6 and ≥60 months) were associated with an increased risk of PTB and LBW, with the optimum interval for conceiving again after a PTB being 9 months. Additionally, according to meta-regression analyses, the magnitude of increased risks of PTB, SGA, and LBW outcomes in Meta I was not correlated with the SDI, suggesting that the development status of the population from different countries may not be the reason for the inter-study heterogeneity. For adverse birth outcomes, results of three primary outcomes (i.e., PTB, SGA, and LBW) were consistent with previous meta-analyses.[4,154,155] Large cohort studies considered the birth spacing of 18 to 23 months as an appropriate reference interval, which was in line with our quantitative analysis.[78,88,89,102] However, dose–response analyses suggested that the minimum risk might occur after 23 months, possibly as a result of the wide intervals used in original studies (eg 18–35 months, 24–59 months, 36–59 months, and ≥60 months). For rare events such as fetal death and birth

defects, the results of meta-analyses and dose–response analyses showed adverse effects of extremely short and long birth spacing. Therefore, the optimal intervals are associated with potential benefits for both common and rare adverse birth outcomes. Additionally, we observed a decreased risk of LGA in birth spacing of <18 months, which was consistent with the results of each individual study.[62,85,97] This finding is reasonable as short birth spacing is associated with various disadvantages of fetal growth.

There is relatively limited evidence focusing on the association between birth spacing and maternal health. However, our results suggest that both short and long birth spacing are associated with an increased risk of PROM (one type of PTB), and that long intervals are associated with adverse effects on preeclampsia, GDM, PIH, and miscarriage. Consistent with the systematic review by Conde-Agudelo et al.,[16] our analysis found that long intervals were independently associated with increased risk of preeclampsia. Large population-based studies have shown that women with birth spacing longer than 23 months are at significantly increased risk of preeclampsia.[13,82,112,120] Similar effects were observed with long intervals (≥23 months) in GDM.[89,99,107] In addition, previous studies have suggested that intervals of 6–11 and 12–17 months have been associated with a lower risk on GDM and PIH.[99,100] Therefore, when considering birth spacing, it may be necessary to take into account its impact on maternal and infant health.

The findings of the meta-analysis by Kangatharan et al.[7] suggested that an IPI of <6 months following a miscarriage was not associated with adverse outcomes in the next pregnancy. Our study confirmed that IPI of <6 months might have no effect on SGA, fetal death, miscarriage, or preeclampsia. However, the meta-analytical synthesis indicated that both short and long IPI were associated with increased risk of recurrent PTB, which is consistent with previous cohort studies.[90,107] According to the WHO recommendation[3] that women should wait at least 6 months after a pregnancy loss before conceiving another child, our results further suggest that an IPI of 9 months after a PTB might be optimal for conceiving again.

Conde-Agudelo et al., in 2012, provided a comprehensive theoretical framework for possible causal mechanisms of birth spacing.[156] The most widely accepted interpretation of adverse outcomes due to short birth spacing includes postpartum nutritional depletion (especially folate deficiency),[157] vertical transmission of infection,[158,159] and cervical insufficiency (the major cause of spontaneous PTB).[160] Folate depletion is one of the most convincing causal mechanisms. The concentrations of folate levels in maternal serum and erythrocytes begin to decline in the fifth month of pregnancy and persist at low levels after delivery.[157] Low folate levels have been reported in women from 4 weeks to 12 months postpartum.[161-164] Data from a cohort study of 48 855 pairs of pregnancies with the second pregnancy found lower preconception folic acid use in women with both short and long inter-pregnancy intervals.[165] Folate depletion increases the risk of poor fetal growth associated with short birth spacing, therefore, postnatal folate supplementation may be beneficial.[59,166] For the adverse outcomes associated with long birth

spacing, the physiological regression hypothesis and reproductive wastage hypothesis are possible drivers.[167] Physiological regression suggests that the benefits attainable during pregnancy would gradually diminish after delivery, thereby affecting fetal growth[119] and maternal cardiovascular adaptation.[168] Population-based studies found the protective effect of previous pregnancy against preeclampsia was transient.[120,169] In addition, long birth spacing might reflect the deficiency in health and fertility of women who have been pregnant.[103]

The finding of a shorter optimum interval after pregnancy loss can be explained by two aspects. On the one hand, pregnancy loss may have less of an effect on the body's reserves of folate than live birth.[7] Most abortions often occur in the first trimester of pregnancy, when breastfeeding has not started, so women conceiving again soon after may not deplete vital nutrients.[53] On the other hand, women conceiving again within a short interval after pregnancy loss may not necessarily be poorer in education and family planning resources compared with women with a short interpregnancy interval after a live childbirth.[65] Additionally, women in this situation may have higher fecundity and be less likely to be obese, representing a higher level of reproductive health.[93]

The WHO recommends that women prioritize achieving ideal birth spacing before conceiving again. What is certain is that both short and long intervals are not conducive to the health of pregnant women and newborns. The previous recommendation of waiting at least 2 years after a livebirth before conceiving again may have been too long, although other factors such as breastfeeding were taken into account.[170] Given the great significance for guiding the postpartum pregnancy, more research is needed to evaluate the association between birth spacing after pregnancy loss and maternal and infant health, while markers of physiological depletion also warrant further exploration.

The main limitations of this systematic review are related to the primary studies that were included in the review. The measurements of birth spacing used in the primary studies may not reflect the true value because of the memory bias or the omission of pregnancies that ended in loss between two live births. Additionally, some studies failed to report the starting point for birth spacing, which could result in a study population that includes women who have experienced pregnancy loss. Moreover, adjustments for confounding variables varied among the included studies. One recent study suggested that women of all ages may be at increased risk of adverse pregnancy outcomes because of short birth spacing,[95] but we attempted to ensure that at least maternal age and other socioeconomic factors were adjusted in the maximally adjusted models. According to the NOS assessments, most cohort studies were rated as high quality, suggesting that the NOS might have limited power to identify potential risk of bias in these studies. Despite its widespread use, this topic warrants careful consideration when assessing the overall validity and reliability of the study. Finally, despite the fact that subgroup and meta-regression analyses were conducted, sources of heterogeneity were not well identified and findings should be interpreted with caution.

## 5 | CONCLUSION

Our results confirm a non-linear dose–response relationship between birth spacing and multiple adverse pregnancy and birth outcomes. Extreme IPI and IOI had adverse effects on PTB, SGA, LBW, fetal death, early neonatal death, birth defects, PROM, preeclampsia, GDM, PIH, and cesarean delivery. An IPI of 18–23 months could be optimal for the general population, and an IPI of 9 months after a preterm birth could be optimal for conceiving another child. Conceiving again and choosing an optimal birth spacing is a multifactorial decision, our findings can be used to assist policy-makers and healthcare providers in developing guidelines for postpartum family planning.

### AUTHOR CONTRIBUTIONS
ZFF and CWT designed the study. NWZ a GXP performed the literature search and screening, and extracted the data. NWZ, GXP, SX, and ZSW conducted the data analyses. NWZ, GXP, ZL, LJZ, FYH, CSY, and MJR created the figures and tables, and drafted the manuscript. All authors participated in the interpretation of results, and critically revised the manuscript. All authors approved the final version of the manuscript for publication. NWZ and GXP contributed equally to the manuscript as joint first authors. ZFF and CWT jointly take responsibility for the integrity of the data and the accuracy of the data analysis.

### CONFLICT OF INTEREST STATEMENT
None.

### DATA AVAILABILITY STATEMENT
All relevant data are within the manuscript and its Supporting Information files.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.