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Short interpregnancy intervals and adverse perinatal outcomes in high-resource settings: An updated systematic review

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Abstract

Background: This systematic review summarises association between short interpregnancy intervals and adverse perinatal health outcomes in high-resource settings to inform recommendations for healthy birth spacing for the United States.

Methods: Five databases and a previous systematic review were searched for relevant articles published between 1966 and 1 May 2017. We included studies meeting the following criteria: (a) reporting of perinatal health outcomes after a short interpregnancy interval since last livebirth; (b) conducted within a high-resource setting; and (c) estimates were adjusted for maternal age and at least one socio-economic factor.

Results: Nine good-quality and 18 fair-quality studies were identified. Interpregnancy intervals <6 months were associated with a clinically and statistically significant increased risk of adverse outcomes in studies of preterm birth (eg, aOR ≥ 1.20 in 10 of 14 studies); spontaneous preterm birth (eg, aOR ≥ 1.20 in one of two studies); small-for-gestational age (eg, aOR ≥ 1.20 in 5 of 11 studies); and infant mortality (eg, aOR ≥ 1.20 in four of four studies), while four studies of perinatal death showed no association. Interpregnancy intervals of 6-11 and 12-17 months generally had smaller point estimates and confidence intervals that included the null. Most studies were population-based and few included adjustment for detailed measures of key confounders.

Conclusions: In high-resource settings, there is some evidence showing interpregnancy intervals <6 months since last livebirth are associated with increased risks for preterm birth, small-for-gestational age and infant death; however, results were inconsistent. Additional research controlling for confounding would further inform recommendations for healthy birth spacing for the United States.

KEYWORDS
birth spacing, birth-to-conception interval, interpregnancy interval, perinatal, preterm, review

1 | BACKGROUND

A short interpregnancy interval since last livebirth—the time between one birth and the start of the next pregnancy—may increase the risk of adverse perinatal outcomes in the subsequent pregnancy. This increased risk could be due to inadequate maternal repletion of nutritional status following the delivery of a live infant, increased cervical insufficiency or vertical transmission of

infections following a short interpregnancy interval.[1] A previous systematic review and meta-analysis found that an interpregnancy interval <6 months is associated with 40% higher odds of preterm birth, 61% higher odds of low birthweight and 26% higher odds of small-for-gestational age in the subsequent pregnancy.[2] Short interpregnancy intervals up to 17 months were also associated with greater risks for these outcomes.[2] These findings, along with other supportive evidence, informed the 2005 World Health Organization (WHO) recommendation that women should wait for a minimum of 24 months between livebirth and conception of the next child in order to reduce the risk of adverse maternal, perinatal and infant outcomes.[3]

The applicability of the WHO recommendations to the United States is unclear because breast feeding, nutrition, age at first birth and parity differ between the United States and the lower-resource countries upon which most of the evidence reviewed for the WHO recommendation is based.[4-7] Further, the evidence for the WHO recommendations does not include the findings of research conducted since 2006. Recent studies using maternally linked birth records and employing matched study design have found mostly null associations between short interpregnancy interval and adverse outcomes,[8-11] prompting renewed concern that previously observed associations may be due to confounding.[12]

The purpose of this systematic review is to summarise research on the associations between short interpregnancy intervals and adverse perinatal outcomes in high-resource settings. The association between short interpregnancy intervals and adverse maternal outcomes in high-resource settings is reported separately in this journal supplement.[13] Findings from this review can be used to inform evidence-based recommendations for healthy birth spacing for the United States.[14] At present, although short interpregnancy interval is a recognised risk factor for preterm birth and low birthweight,[15,16] and the American College of Obstetricians and Gynecologists recommends women be advised to avoid interpregnancy intervals shorter than 6 months,[16] there are no federal recommendations on healthy birth spacing for the United States.

2 | METHODS

This systematic review adhered to established methodological standards.[17,18] Investigators developed an analytic framework outlining the target population and relationships between interpregnancy intervals and outcomes (Figure S1). The key question guiding this systematic review was "In postpartum women in the United States, what is the effect of short interpregnancy intervals (any interval <24 months) versus a longer interval on short-term perinatal health outcomes: low birthweight, preterm birth, small-for-gestational age, intrauterine growth restriction, APGAR score, neonatal intensive care unit admission, stillbirth, neonatal mortality, infant mortality, and congenital anomaly?" In this study, we synthesise findings for the most commonly examined perinatal outcomes, including preterm birth, spontaneous preterm birth, small-for-gestational age, perinatal death and infant mortality. Although low birthweight was a commonly studied outcome, we did not synthesise the evidence for this outcome because its value as a health indicator is limited primarily to lower-resource settings where accurate estimates of gestational age are unavailable.[19] However, all relevant perinatal findings are presented in a supplemental table (Table S1).

The protocol (available upon request) is based on a previous systematic review published in 2006 on the effects of birth spacing on adverse perinatal outcomes.[2] The 2006 review included studies published between 1966 and January 2006 in PubMed/MEDLINE; between 1980 and January 2006 in EMBASE, POPLINE and ECLA; and between 1982 and January 2006 in CINAHL and LILACS using a combination of medical subject headings and keyword terms to identify relevant studies.

In contrast to the 2006 review, the updated review includes only studies published in English and conducted in the United States, Canada, Australia, New Zealand and the European countries categorised as "very high" on the United Nations Human Development Index[20] to identify studies most applicable to women in the United States. In addition, the updated review concerns potential consequences of short rather than long interpregnancy intervals because the former are more amenable to prevention, such as through the provision of postpartum contraception services.

The 2006 review included 67 studies with statistical adjustment for maternal age and at least one socio-economic position measure (52 cohort or cross-sectional studies and 15 case-control studies). Twenty-nine studies were conducted on study populations from the United States and other high-resource countries, of which 19 examined interpregnancy intervals (as opposed to birth-to-birth intervals).[21-39]

2.1 | Literature search

Using the same search terms as the 2006 review,[2] we conducted electronic searches of PubMed/Medline, POPLINE, EMBASE, CINAHL and the Cochrane Database of Systematic Reviews for relevant articles published between 1 January 2006 and 1 May 2017. In addition to search terms for specific outcomes, we also included general terms, such as "perinatal outcome," "perinatal morbidity," "pregnancy outcome," "adverse outcome," "obstetric outcome" and "infant outcome." Specific search terms and publication date ranges are listed in Table S2.

2.2 | Inclusion/exclusion criteria

Inclusion criteria for studies were developed a priori using the PICOTSS (population, intervention/exposure, comparison group, outcome, time, setting and study design) framework[40] and independently applied to the search results by two study authors (KAA and JAH) in a two-stage review process (Table S3).[41] Studies from the 2006 review meeting new, more restrictive inclusion criteria were also included. Included studies met the following criteria:

1. The study population consisted of women of reproductive age with at least one livebirth who became pregnant again. Women whose last delivery was a stillbirth were also included, as long as they comprised <5% of the study population (ie, the cohort was not specifically drawn from women with a prior stillbirth).
2. The study measured interpregnancy interval since last livebirth—defined as the interval between delivery of a birth (liveborn or stillborn) and start of the subsequent pregnancy (also known as birth-to-conception interval)—rather than other types of intervals (eg, post-abortion or post-pregnancy loss interpregnancy interval, birth-to-birth interval). This definition was imposed because there are separate recommendations for interpregnancy interval following pregnancy losses.[3] Further, birth-to-birth intervals are the sum of the interpregnancy interval and the duration of the subsequent pregnancy; therefore, women with adverse pregnancy outcomes associated with shorter pregnancy duration (such as stillbirth or preterm birth) will have systematically shorter birth-to-birth intervals than women without these outcomes. This systematic difference creates the potential for bias due to reverse causation (ie, a short birth-to-birth interval being the result of, rather than the cause of, an adverse outcome).
3. The study compared a short interpregnancy interval, defined as any interval shorter than 24 months, to a longer interpregnancy interval (the reference interval). The reference interval had to

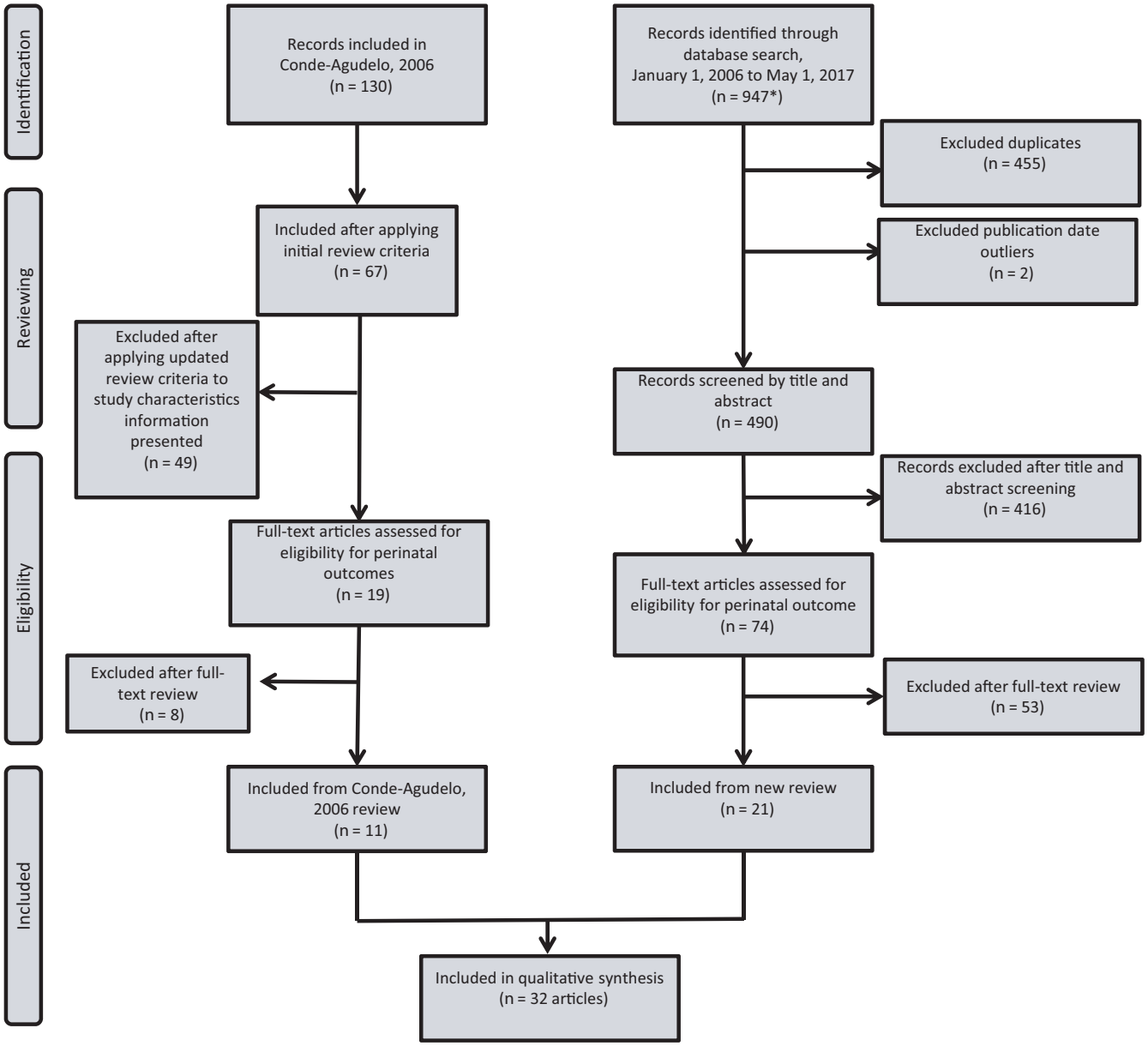

FIGURE 1 Literature flow diagram. *947 records include eight unique records identified from a targeted review conducted on September 22, 2017 to find articles on interpregnancy intervals and uterine rupture, placental abruption and placenta previa, which were outcomes relevant to the maternal outcomes systematic review

TABLE 1 Characteristics and quality of 32 included studies

Author Year	Location	Design and data source	Study population (N)	Inter pregnancy intervals (mo)	Outcomes[a]
Klebanoff et al (1988)[27,b]	USA	Cohort; interviews and medical record data	Women with two consecutive singleton pregnancies resulting in livebirth during 1959-1966 (N = 5938)	<3[c,d] 3-5.9 6-8.9 9-11.9 12-14.9 15-17.9 18-20.9 21-23.9 ≥24	Birthweight; low birthweight; small-for-gestational age
Lieberman et al (1989)[29,b]	Boston, MA, USA	Cohort; interviews and medical record data	Women with full-term live born infants delivered during 1977-1980 whose last pregnancy was a full-term livebirth (N = 4467)	≤3 3-6 6-12 12-18 18-24 24-36[c] 36-48 48-60 60-72 72-96 ≥96	Small-for-gestational age
Lang et al (1990)[28,b]	Boston, MA, USA	Cohort; interviews and medical record data	Women with appropriate-for-gestational age liveborn infants delivered during 1977-1980 whose last pregnancy was a full-term livebirth (N = 4489)	≤3 4-6 7-12 13-18 29-24 25-36[c] 37-48 ≥49	Spontaneous preterm
Adams et al (1997)[21,b]	Georgia, USA	Cohort; birth certificate data maternally linked to foetal death data	Low-risk women with a second consecutive pregnancy of singleton livebirth during 1989-1992 (N = 23 388 white; N = 4885 black)	0-5 6-8 9-1 12-17 18-23 24-35[c] 36-47 ≥48	Preterm
Basso et al (1998)[22,b]	Denmark	Cohort; random sample from population-based registry of pregnancies maternally linked with education, employment, and income	First two consecutive live singleton births during 1980-1992, (N = 10 187)	≤4 4-≤8 8-≤12 12-≤24 24-≤36[c] >36	Preterm; low birthweight
Zhu et al (1999)[36,b]	Utah, USA	Cohort; birth certificate data	Singleton infants born alive during 1989-1996 to women who had previously delivered at least one live infant (N = 173 205)	0-5 6-11 12-17 18-23[c] 24-59 60-119 ≥120	Low birthweight; preterm birth; small-for-gestational age

Covariates in adjusted analysis	Subgroup/stratified analyses	Quality ratings
Assessed at first pregnancy: maternal age (number of levels not stated), education (number levels not stated), socio-economic index (number of levels not stated), smoking, birthweight of first child, weight at start of first pregnancy, maternal race/ethnicity.	None	Fair internal validity *Strengths:* measure of interpregnancy interval accounted for intervening miscarriages; adjusted for time-varying covariates at the time of the first rather than the second pregnancy. *Weaknesses:* did not account for pregnancy intention or past neonatal death. *Fair external validity:* based on women who agreed to participate in a prospective cohort study; drop in participation between eligible first and second pregnancy.
Assessed at time of subsequent pregnancy: maternal age (2 level), welfare recipient (2 level), race, education (2 level), smoking, alcohol use, prepregnancy weight, weight gain, maternal height, infant sex, chronic hypertension.	None	Fair internal validity *Strengths:* data obtained from medical record abstraction and interview, increased accuracy compared with birth certificate records; accounted for prior stillbirth. *Weaknesses:* adjusted for confounders at subsequent pregnancy rather than initial pregnancy, which may be an overadjustment; did not adjust for pregnancy intention, past neonatal death, or intervening pregnancy losses. *Fair external validity*: single-centre hospital in Boston.
Assessed at time of subsequent pregnancy: maternal age (number of levels not stated), insurance status (number of levels not stated), race, education (number of levels not stated), marital status, prenatal care, planned pregnancy, smoking, prepregnancy weight, parity, among several others.	None	Good internal validity *Strengths:* controlled for multiple potential confounders including pregnancy intention, prior stillbirth or neonatal death and multiple measures of socio-economic position. *Weaknesses:* adjusted for confounders at the time of the subsequent pregnancy rather than the initial pregnancy, which may be an overadjustment. *Fair external validity:* single-centre hospital in Boston.
Assessed at time of second delivery: maternal age (4 level), education (3 level), prenatal care initiation in first trimester, paternity same as first pregnancy.	Maternal race (white, black)	Fair internal validity *Strengths:* large, population-based study; restricted to low-risk women reduces some potential for confounding. *Weaknesses:* accuracy of many birth certificate variables is poor; did not control for pregnancy intention, prior neonatal death or intervening miscarriages. *Good external validity*: population-based sample from Georgia.
Assessed at time of first delivery: maternal age (5 levels), parity, social status (3 levels); Assessed at time of second delivery: change in social status, gestational age (for low birthweight outcome only).	Gestational age of the first pregnancy (<37, 37-38, 39-40, ≥41 wk)	Good internal validity *Strengths:* large population-based sample with detailed information from database linkages; socio-economic position adequately measured; excluded births after past stillbirth or infant death. *Weaknesses:* did not account for pregnancy intention. *Good external validity*: national population-based sample from Denmark.
Assessed at time of subsequent pregnancy: maternal age at delivery (4 levels), marital status, education (2 levels), outcome of most recent recognised pregnancy, previous living children, previous liveborn children who died, previous spontaneous or induced abortions, among others.	Age, education, weight, previous stillbirths or abortion, and rural or urban residence. pregnancy.	Fair internal validity *Strengths:* large, population-based cohort. *Weaknesses:* accuracy of many birth certificate variables is poor; did not control for pregnancy intention; limited measure of socio-economic position; did not account for intervening early pregnancy losses. *Good external validity:* population-based sample from Utah.

(Continues)

TABLE 1 (Continued)

Author Year	Location	Design and data source	Study population (N)	Inter pregnancy intervals (mo)	Outcomes[a]
Fuentes-Afflick et al (2000)[25,b]	USA	Cohort; national birth certificate data; Hispanic and non-Hispanics matched on birth county	Singleton infants born during 1991 to women with a previous livebirth (N = 246 726)	<6 6-11 12-17 18-59[c] >59	Preterm (23-32; 33-37 wk)
Zhu et al (2001)[37,b]	Michigan, USA	Cohort; birth certificate data	Singleton infants born alive during 1993-1998 to women with previous livebirth (N = 346 250 white; N = 89 077 black)	0-5 6-11 12-17 18-23[c] 24-59 60-119 ≥120	Low birthweight; preterm birth; small-for-gestational age
Smith et al (2003)[34,b]	Scotland	Cohort; hospital discharge data linked to registry of infant and foetal death data	Women with second birth during 1992-1998 whose first infant was full term and liveborn (N = 69 055)	1-5 6-11 12-17 18-23[c] 24-59	Low birthweight (<5th percentile); preterm (24-32; 33-36 wk); foetal abnormality; stillbirth; other neonatal deaths
Stephansson et al (2003)[35,b]	Sweden	Cohort; population-based birth registry linked to cause of death registry, education registry, and immigration registry, maternally linked	Women who delivered consecutive first and second singletons during 1983-1997 (N = 362 368)	0-3 4-7 8-11 12-35[c] 36-71 ≥72	Stillbirth; early neonatal death
Zhu et al (2003)[38,b]	Michigan, USA	Cohort; birth certificate data, maternally linked	Singleton infants born alive during 1989-2000 to women with previous live infant (N = 565 911)	0-5 6-11 12-17 18-23[c] 24-59 60-95 96-136	Low birthweight
Smith et al (2007)[53]	Scotland	Cohort; hospital discharge data linked to registry of infant and foetal death data	Women with second birth during 1992-2001 whose first infant was liveborn (N = 133 163)	<6 6-11 12-23[c] 24-5 y 6-10 y >10 y	Antepartum unexplained stillbirth
van Eijsden et al (2008)[52]	Amsterdam, the Netherlands	Cohort; prospective community-based pregnancy study	Multiparae giving birth to a viable full-term infant during 2003-2004 (N = 3153)	<6 6-11 12-17 18-23[c] 24-59 ≥60	Birthweight; small-for-gestational age

Covariates in adjusted analysis	Subgroup/stratified analyses	Quality ratings
Assessed at time of subsequent pregnancy: maternal race/ethnicity, maternal age (5 level), education (5 level), country of birth, parity, previous preterm or small-for-gestational age infant, prenatal care and infant sex.	None	Fair internal validity rating *Strengths*: large, population-based cohort. *Weaknesses*: accuracy of many birth certificate variables is poor; did not control for pregnancy intention, prior neonatal death, or intervening miscarriages. *Fair external validity*: study population limited to Mexican-origin Hispanic and non-Hispanic white women in the United States.
Assessed at time of subsequent pregnancy: maternal age at delivery (6 levels), education (2 levels), marital status, outcome of most recent pregnancy, number of previous pregnancies, adequacy of prenatal care, smoking, alcohol.	Race, education, other covariates	Fair internal validity *Strengths:* large, population-based cohort. *Weaknesses:* accuracy of many birth certificate variables is poor; did not control for pregnancy intention; limited measure of socio-economic status; did not account for early pregnancy losses. *Good external validity*: population-based sample from Michigan.
Assessed at time of subsequent pregnancy: maternal age (3 levels), marital status, height, socio-economic deprivation category (5 levels), smoking, previous birthweight, previous caesarean section.	Married, non-smokers, age ≥25	Good internal validity *Strengths:* use of hospital discharge records increased accuracy of diagnoses; controlled for detailed individual-level measure of socio-economic position, prior stillbirth or neonatal death and intervening pregnancy losses; adjusted for covariates at time of first, not second pregnancy. *Weaknesses:* did not account for pregnancy intention. *Good external validity*: population-based sample from Scotland, UK.
Assessed at time of subsequent pregnancy: smoking status, maternal age (4 levels), education (2 levels), cohabitating with father, maternal country of birth, diabetes, hypertensive disease, year of delivery, outcome of first pregnancy.	None	Good internal validity *Strengths:* data obtained from high-quality population birth registry linked with individual records on educational achievement and immigration status; accounted for prior stillbirth or neonatal death. *Weaknesses:* did not account for pregnancy intention or intervening losses; adjustment for covariates at time of second pregnancy such as maternal age may be an overadjustment. *Good external validity*: national population-based sample from Sweden.
Assessed at time of subsequent pregnancy: Preceding infant's birthweight, paternal acknowledgement, maternal age at delivery (6 levels), race, education (2 levels), adequacy of prenatal care utilisation, outcome of most recent pregnancy, smoking, alcohol.	Factors included as covariates and birth-order pair	Poor internal validity *Strengths:* large, population-based cohort. *Weaknesses:* control for socio-economic position limited; did not control for pregnancy intention, prior neonatal death, or account for losses between pregnancies. *Good external validity:* population-based sample from Michigan.
Assessed at time of first delivery: preterm, small-for-gestational age/preeclampsia and caesarean section. Assessed at time of subsequent delivery: maternal age (6 levels), social deprivation category (7 levels), height, smoking, marital status.	Size for age at birth (small vs appropriate-for-gestational age)	Fair internal validity *Strengths:* large population-based sample; hospital discharge records increased accuracy; individual-level measure of socio-economic position. *Weaknesses:* no adjustment for pregnancy intention or prior neonatal death; does not account for intervening miscarriages. *Good external validity:* population-based study from Scotland, UK.
Assessed at time of subsequent delivery: maternal age (3 levels), prepregnancy BMI, infant sex, height, parity, gestational age, smoking, alcohol, psychosocial stress, pregnancy intention, cohabitant status, education (3 levels), country of birth.	Folic acid supplementation	Fair internal validity *Strengths:* controlled for pregnancy intention, psychosocial stress and multiple measures of socio-economic position. *Weaknesses:* did not account for prior neonatal death or stillbirth; does not account for intervening miscarriages. *Fair external validity:* limited to 67% who agreed to participate; folic acid supplementation lower than in the United States.

(Continues)

TABLE 1 (Continued)

Author Year	Location	Design and data source	Study population (N)	Inter pregnancy intervals (mo)	Outcomes[a]
Villamor et al (2008)[60]	Sweden	Cohort; population-based birth registry, maternally linked	Women with first two consecutive births during 1992-2004, whose first-born did not have oral cleft malformation (N = 219 983)	<12[c,e] 12-23 24-35 36-47 ≥48	Isolated cleft palate; all cleft palate
de Weger et al (2011)[48]	The Netherlands	Cohort; population-based registry of pregnancies, deliveries, and readmissions	Women with singleton delivery by gynaecologist in a hospital during 2000-2007 with one previous delivery (N = 263 142)	<6 6-11 12-17 18-23[c] ≥24	Preterm; low birthweight; small-for-gestational age
Salihu et al (2012)[55]	Hillsborough County, Florida, USA	Cohort; birth certificate data linked to Healthy Start Program data	Women with consecutive singleton first and second pregnancies during 2002-2009 (N = 36 718)	<6 6-<18 18-<24[c] ≥24	Low birthweight; preterm; small-for-gestational age; any feto-infant morbidity
Howard et al (2013)[49]	Louisiana, USA	Cohort; birth certificate data	Women with a singleton birth during 1995-2007 with single previous pregnancy that ended in livebirth or foetal death (>20 wk or ≥350 g) (N = 96 387)	<9 9-23[c]	Preterm
Hussaini et al (2013)[54]	Arizona, USA	Case-control: birth certificate data linked to infant mortality data	Non-first-born singleton infant deaths during 2003-2007 and a random sample of non-first-born singleton survivors (N = 1466 cases; N = 2000 controls)	<6 6-11 12-17 18-23[c] 24-59 ≥60	Infant deaths; neonatal deaths; post-neonatal deaths
Ball et al (2014)[8]	Perth, Western Australia	Cohort (sibling comparison); population-wide database of births, maternally linked	Women with their first three births as liveborn singletons during 1980-2010 (N = 40 441)	0-5 6-11 12-17 18-23[c] 24-59 60-119 ≥120	Preterm; small-for-gestational age; low birthweight
Hinkle et al (2014)[56]	Utah, USA	Cohort; maternal and infant hospital electronic medical records supplemented with ICD9 discharge codes, maternally linked	Women with two singleton deliveries >20 wks' gestation in their first and second pregnancy during 2002-2010 (N = 25 241)	<12 12-≤18 18-23[c] >23	Incident small-for-gestational age in second pregnancy; recurrent small-for-gestational age in second pregnancy

Covariates in adjusted analysis	Subgroup/stratified analyses	Quality ratings
Maternal height, country of origin; Assessed at time of first pregnancy: BMI, maternal age (4 levels), paternal age, maternal education (6 levels), preeclampsia, gestational diabetes, preterm delivery, small- or large-for-gestational age, stillbirth or infant death; Assessed at time of subsequent pregnancy: year of delivery, smoking, pregestational diabetes.	None	Fair internal validity *Strengths:* high-quality, validated database (Swedish Medical Birth Register). *Weaknesses:* did not control for pregnancy intention; does not account for intervening miscarriages. *Good external validity*: national population-based sample from Sweden.
Assessed at time of subsequent delivery: maternal age at first delivery (6 levels), mean household income of neighbourhood (5 levels), use of artificial reproductive techniques, ethnic origin, year of birth.	None	Fair internal validity *Strengths:* large, population-based registry, excluded women with losses <20 wk. *Weaknesses:* limited measure of socio-economic position; did not control for pregnancy intention or prior stillbirth or neonatal death. *Poor external validity:* only women delivered by a gynaecologist (~65%); health behaviours and risks likely differ by caregiver.
Assessed at time of subsequent delivery: maternal age (2 level), parity, race/ethnicity, smoking, maternal education (2 level), marital status, adequacy of prenatal care, conditions during pregnancy.	Programme participation status	Poor internal validity *Strengths:* stratified analyses by zip code to examine effects in neighbourhoods served by Healthy Start Program. *Weaknesses:* control for socio-economic position limited to a binary variable; did not control for pregnancy intention, prior neonatal death or stillbirth, or account for early pregnancy losses. *Fair external validity:* limited to a population-based sample from a single county in Florida.
Assessed at time of subsequent delivery: maternal age (y) and race, smoking, number of prenatal visits, timing of first prenatal visit, low birthweight, marital status, education (3 levels), number of terminations, previous foetal death and previous caesarean section.	None	Fair internal validity *Strengths:* large, population-based sample; propensity score analysis to control for confounding. *Weaknesses:* accuracy of many birth certificate variables is poor; did not account for early pregnancy losses, prior neonatal death or pregnancy intention. *Good external validity:* population-based sample from Louisiana.
Assessed at time of subsequent delivery: preterm birth, low birthweight, small-for-gestational age, maternal medical risk factor, infant sex, smoking, history of preterm birth, number of living children, maternal race/ethnicity, weight gained during pregnancy, no prenatal care, marital status, maternal age (3 levels), education (2 levels), insurance status (3 levels), geographic area of residence.	None	Fair internal validity *Strengths:* large, population-based sample. *Weaknesses:* accuracy of many birth certificate variables is poor; did not account for early pregnancy losses, prior neonatal death or pregnancy intention. *Good external validity:* cases included all infant deaths in Arizona during study period, controls drawn from random sampling of birth certificates in the state during same period.
Assessed at time of second and third birth: maternal age (6 levels), parity, birth year, socio-economic disadvantage index (5 levels).	None	Good internal validity *Strengths:* use of sibling comparison design to control for confounding by time-invariant characteristics. *Weaknesses:* no adjustment for potentially time-varying confounding such as smoking or pre-pregnancy BMI. *Poor external validity*: limited to women with three or more births with discordant perinatal outcomes representing a small subset of the target population.
Assessed at time of subsequent delivery: maternal age (5 levels), race/ethnicity, marital status, insurance (2 levels), smoking, alcohol, prepregnancy weight, gestational weight gain, diabetes, hypertension, asthma, thyroid disease, depression or other mental health condition.	Small-for-gestational age birth in first pregnancy	Poor internal validity *Strengths*: data based on medical record abstraction increased accuracy of diagnoses and gestational age estimation. *Weaknesses:* control for socio-economic position limited to a binary variable; did not control for pregnancy intention, prior neonatal death or stillbirth, or account for intervening early pregnancy losses. *Good external validity*: sample of multiparae from 20 Utah hospitals.

(Continues)

Author Year	Location	Design and data source	Study population (N)	Inter pregnancy intervals (mo)	Outcomes[a]
Naimi et al (2014)[47]	Quebec, Canada	Cohort; birth certificate records linked with area-level measures of social and material deprivation	Singleton livebirths during 1989-2010 to women with at least one previous birth (N = 847 618)	0-18 18-23[c] 24-<60 ≥60	Preterm
Chen et al (2015)[50]	Northern Alberta, Canada	Cohort; province-wide delivery records from hospital and midwife attended deliveries, linked to maternal demographic database	Women with two consecutive singleton deliveries in northern Alberta during 1999-2007 (N = 46 243)	0-5 6-11 12-17[c] 18-23 24-35 ≥36	Preterm (<28; <34 wk); low birthweight (<1500; <1000 g); small-for-gestational age (<3rd percentile); perinatal death; Apgar scores; NICU admission
Jelliffe-Pawlowski et al (2015)[57]	California, USA	Cohort; birth certificate data linked to hospital discharge record and prenatal screening data	Singleton livebirths with expected dates of delivery during 2009-2010, with 1st and 2nd trimester prenatal aneuploidy serum screening (N = 125 202)	<6 6-23 24-59[c] ≥60	Preterm (<32; 32-36 wk); medically indicated (<32; 32-36 wk)
Mburia-Mwalili et al. (2015)[58]	Nevada, USA	Cohort; population-based birth defects surveillance system, linked to birth certificate data	Singleton livebirths during 2006-2011 to women with at least one previous livebirth (N = 124 341)	0-5 6-11 12-17 18-23[c] 24-35 ≥36	At least one birth defect
Merklinger-Gruchala et al (2015)[61]	Krakow, Poland	Cohort; birth registry records	Singleton livebirths during 1995-2009 to women with at least one previous livebirth (N = 39 968)	0-5 6-11 12-17 18-23[c] 24-59 60-119 ≥120	Low birthweight
Appareddy et al (2016)[51]	Tennessee, USA	Cohort; birth certificate data linked to infant mortality data	Women with a previous livebirth, who gave birth during 2012-2014 and had IPI <5 y (N = 101 912)	<6 6-12 12-18 18 ≤ 60[c]	Low birthweight; preterm birth (<34 wk); NICU admission; infant mortality
Shachar et al (2016)[11]	California, USA	Cohort (sibling comparison); birth certificate data linked to hospital discharge records, infant death, and foetal death data, maternally linked	Women with three consecutive livebirths during 1991-2010 (N = 302 706)	<6 6-11 12-17 18-23[c] 24-59 60-119 ≥120	Preterm
Coo et al (2017)[46]	Manitoba, Canada	Cohort; province-wide hospital discharge data linked with 8 other provincial datasets	Sibling pairs representing two consecutive singleton livebirths in Manitoba during 1985-2014 (N = 171 688)	<6 6-11 12-17 18-23[c] 24-59 ≥60	Preterm (<34; 34-36; 37-38 wk); low birthweight; small-for-gestational age; medically indicated preterm; spontaneous preterm

Covariates in adjusted analysis	Subgroup/stratified analyses	Quality ratings
Assessed at time of subsequent delivery: maternal education (4 levels) and birth year; maternal age (y), paternal ages, countries of birth, native languages; area-level measures of material and social deprivation (levels not stated).	None	Fair internal validity *Strengths:* large population-based study, controlled for multiple measures of socio-economic position. *Weaknesses:* no control for pregnancy intention or prior neonatal death; does not account for intervening stillbirths or miscarriages; material and social deprivation measures from the neighbourhood rather than individual level. *Good external validity:* population-based sample from the province of Quebec, Canada.
Assessed at time of subsequent delivery: maternal age (3 levels), smoking, social assistance (3 levels), parity, diabetes, maternal/gestational hypertension, previous stillbirth, previous small-for-gestational age, infant sex, congenital anomalies	None	Fair internal validity *Strengths:* high-quality data from population-based clinical records. *Weaknesses:* no adjustments for previous neonatal death or pregnancy intention; early pregnancy losses during interpregnancy interval not identified. *Good external validity:* population-based study from Northern Alberta, Canada.
Assessed at time of subsequent delivery: maternal race/ethnicity, maternal age (3 levels), insurance (4 levels), education (3 levels), nativity, BMI at onset of pregnancy, pre-existing hypertension, preeclampsia, preexisting diabetes, gestational diabetes, primiparity, previous caesarean sections and preterm births, mid-pregnancy serum biomarkers.	None	Fair internal validity *Strengths:* linkage of birth certificate records with hospital discharge data improves data quality for medical diagnoses. *Weaknesses:* accuracy of many birth certificate variables is poor; did not control for pregnancy intention, prior stillbirth or neonatal death, or intervening miscarriages. *Good external validity:* population-based sample from California.
Assessed at time of subsequent delivery: infant sex, maternal age (5 levels), race/ethnicity, education (3 levels), number of previous births, smoking and/or alcohol use, prescription drug use.	None	Fair internal validity *Strengths:* linkage with state birth defects surveillance system ensures higher data quality for outcome assessment. *Weaknesses:* accuracy of many birth certificate variables is poor; did not control for pregnancy intention, prior stillbirth or neonatal death or intervening miscarriages. *Good external validity:* population-based sample from Nevada.
Assessed at time of subsequent delivery: marital status, maternal employment and education indicator (4 levels), parity, infant sex, maternal age (y), gestational age.	Parity	Fair internal validity *Strengths:* population-based sample includes maternal employment and education. *Weaknesses:* did not control for pregnancy intention, prior stillbirth or neonatal death, or intervening miscarriages; no information on day of birth. *Fair external validity:* population-based study from Krakow, Poland.
Assessed at time of subsequent delivery: maternal age (y), marital status, education (2 levels), race; WIC use during pregnancy (2 levels), pre-pregnancy BMI, number of previous pregnancies, timing of prenatal care initiation, smoking.	WIC use during pregnancy	Fair internal validity *Strengths:* large, population-based sample. *Weaknesses* accuracy of many birth certificate variables is poor. *Good external validity*: based on all vital statistics records from Tennessee.
Parity, education (4 levels), maternal age (y), year of birth, previous preterm birth.	None	Good internal validity *Strengths*: use of sibling comparison design to control for confounding by time-invariant characteristics. *Weaknesses*: did not control for risk factors such as smoking and pre-pregnancy BMI that vary between a woman's pregnancies. *Poor external validity*: limited to women with three or more births with discordant perinatal outcomes.
Assessed at time of subsequent delivery: birth year, child's sex, maternal age at delivery (6 levels); parity, adequacy of prenatal care, high school graduate (3 levels); received income assistance (3 levels); socio-economic index (6 levels), smoking, alcohol, substance use, chronic hypertension, maternal/gestational diabetes, previous pregnancy losses or stillbirths, perinatal outcome of previous birth.	None	Good internal validity *Strengths:* detailed measures of socio-economic position and multiple other confounders; accounted for prior stillbirth and early pregnancy losses during the interpregnancy interval. *Weaknesses:* did not account for pregnancy intention or previous neonatal loss. *Good external validity:* population-based study from the Canadian province of Manitoba.

(Continues)

TABLE 1 (Continued)

Author Year	Location	Design and data source	Study population (N)	Inter pregnancy intervals (mo)	Outcomes[a]
Hanley et al (2017)[9]	British Columbia, Canada	Cohort (sibling comparison); database of obstetric and neonatal medical charts, British Columbia Perinatal Data Registry, with deliveries linked maternally	Women with at least three singleton deliveries during 2000-2015 delivered at 20-44 wks' gestation (N = 38 178)	0-5 6-11 12-17 18-23[c] 24-59 ≥60	Preterm; small-for-gestational age; NICU; low birthweight
Koullali et al (2017)[10]	The Netherlands	Cohort; population-based registry of pregnancies, deliveries, and readmissions, maternally linked	Women with three sequential singleton pregnancies during 1999-2009, with the first pregnancy resulting in spontaneous preterm birth (N = 2361)	0-5 6-11 12-17 18-23[c] 24-59 ≥60	Preterm (<32 wk); low birthweight; small-for-gestational age
Goyal et al (2017)	Ohio, USA	Cohort; birth certificate data for home-visiting programme participants and matched controls	Women with consecutive singleton first birth (>23 wks' gestation and no neonatal death) during 2007-2009 and second births during 3-y follow-up (N = 854)	≤6 7-<36[c]	Preterm
McKinney et al (2017)[59]	Ohio, USA	Cohort; birth certificate data linked to infant mortality data	Livebirths during 2007-2014 to multiparae (N = 604 217)	0-5 6-<12 12-<24[c] 24-<60 ≥60	Infant mortality

BMI, body mass index; IPI, interpregnancy interval; NICU, Neonatal Intensive Care Unit; WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

[a]Unless otherwise specified, preterm was defined as livebirth/delivery <37 wks' gestational age, low birthweight as livebirth/delivery and <2500 g, small-for-gestational age as livebirth/delivery and <10th percentile by gestational age in weeks (or by sex and gestational age in weeks), perinatal death as foetal death plus neonatal death within the first week of life, infant death as death within the first year of life, neonatal death as death within the first 28 d of life and post-neonatal death as death within the first 39 d to 1 y of life.

[b]Identified from previous review.

[c]Reference group.

[d]For calculating relevant odds ratios, estimates for <3 mo were inverted so that reference group was 18-20.9 mo.

[e]For calculating relevant odds ratios, estimates for <12 mo were inverted so that reference group was 12-23 months.

Covariates in adjusted analysis	Subgroup/stratified analyses	Quality ratings
Maternal age at each delivery (6 levels); delivery year, maternal diabetes, maternal hypertension, smoking, history of perinatal death.	None	Good internal validity *Strengths:* use of sibling comparison design to control for confounding by time-invariant characteristics. *Weaknesses:* adjustment for maternal age at pregnancy following IPI an over-adjustment. *Poor external validity:* Limited to women with three or more births with discordant perinatal outcomes.
Assessed at time of previous delivery: maternal age (3 levels), race/ethnicity, socio-economic position (3 levels), artificial reproductive techniques, year of birth.	None	Good internal validity *Strengths:* use of sibling comparison design to control for confounding by time-invariant characteristics. *Weaknesses:* did not adjust for potential time-varying confounders such as smoking or pre-pregnancy BMI. *Poor external validity:* limited to women with three or more births with discordant perinatal outcomes; women with prior spontaneous preterm birth in first pregnancy; delivered by a gynaecologist.
Assessed at time of second birth: prior preterm birth; race/ethnicity; education level (3 level), insurance paid for delivery (4 level), maternal age (2 level), breast-feeding status, marital status, pre- or during pregnancy hypertension, diabetes, and obesity (separately); sexually transmitted infection during pregnancy; and (assessed at time of first birth): enrolment in Healthy Start Program, delivery method, smoking, year of birth.	Programme participants	Poor internal validity *Strengths:* excluded prior neonatal deaths. *Weaknesses:* small sample size; did not account for pregnancy intention or intervening early pregnancy losses; propensity score matching performed for primary analysis was not intended to balance covariates for IPI comparison; adjustment for covariates at time of second pregnancy such as maternal age may be an overadjustment. *Fair external validity:* limited to first time mothers participating in home-visiting programme and their matched controls from seven counties in Ohio.
Assessed at time of subsequent delivery: marital status, Medicaid (2 levels), smoking, maternal age (y), race/ethnicity.	Maternal race	Poor internal validity *Strengths:* large, population-based cohort. *Weaknesses:* socio-economic position limited to a binary variable; did not control for pregnancy intention, prior neonatal death, stillbirth, early pregnancy losses; selection bias from missing IPI information among those with high infant mortality rates. *Good external validity:* population-based sample from Ohio.

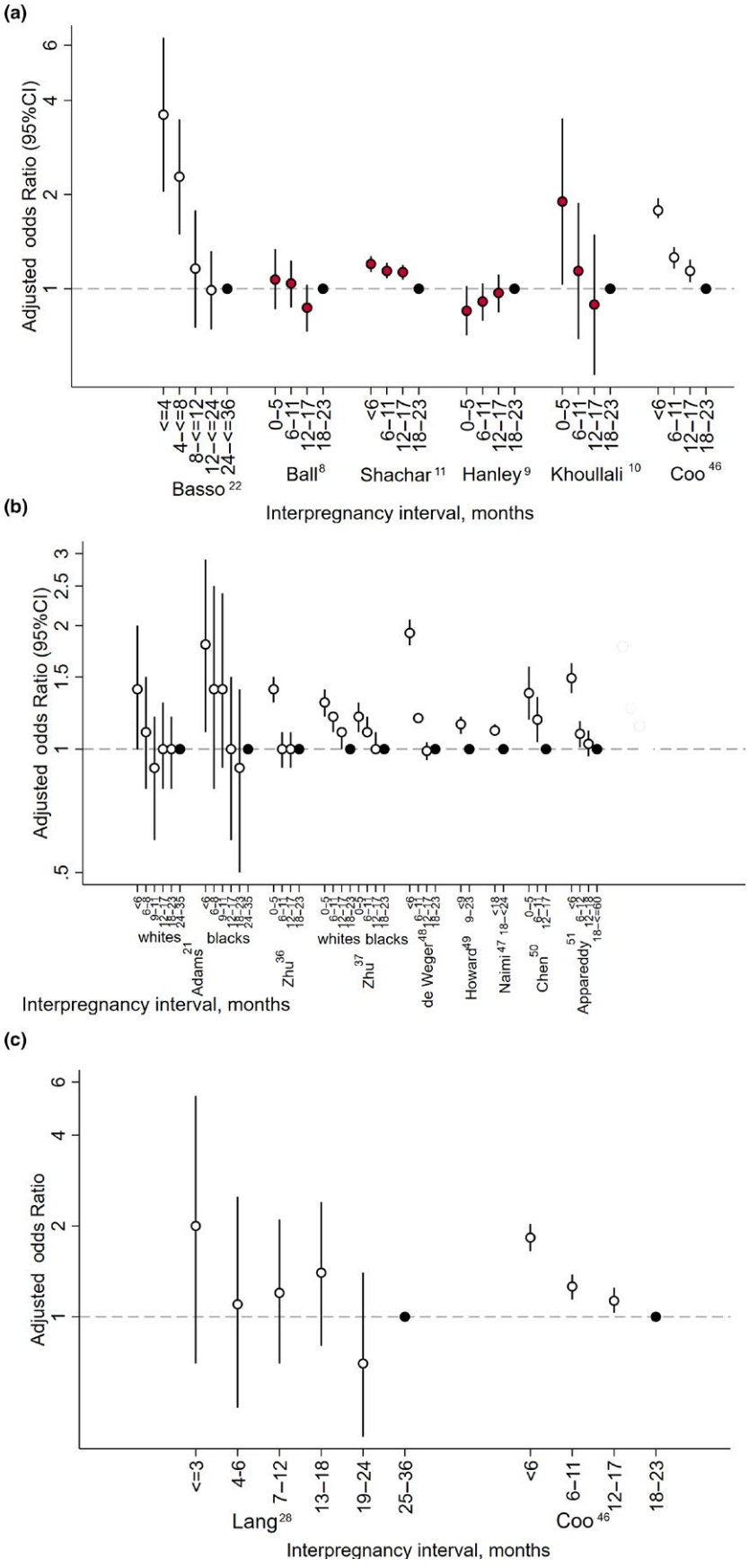
(a)
Adjusted odds Ratio (95%CI)
Basso 22
Ball 8
Shachar 11
Hanley 9
Khoullali 10
Coo 46
Interpregnancy interval, months
(b)
Adjusted odds Ratio (95%CI)
whites
blacks
whites blacks
Adams 21
Zhu 36
Zhu 37
de Weger 48
Howard 49
Naimi 47
Chen 50
Appareddy 51
Interpregnancy interval, months
(c)
Adjusted odds Ratio
Lang 28
Coo 46
Interpregnancy interval, months

FIGURE 2 A, Adjusted odds ratios and 95% confidence intervals for the association between interpregnancy interval and preterm birth among studies rated as having "good" internal validity from high-resource settings. Black solid circles indicate the reference category, and red solid circles indicate studies using a sibling comparison design; B, Adjusted odds ratios and 95% confidence intervals for the association between interpregnancy interval and preterm birth among studies rated as having "fair" internal validity from high-resource settings. Black solid circles indicate the reference category. Confidence intervals are not discernible for some studies because they fell within the range covered by the point estimate symbol (black hollow circle); C, Adjusted odds ratios and 95% confidence intervals for the association between interpregnancy interval and spontaneous preterm birth among studies from high-resource settings. Black solid circles indicate the reference category

have clearly defined lower and upper boundaries (ie, "18-23 months" rather than ">18 months"). Clearly defined boundaries were required because of the reverse J-shaped relationship between interpregnancy interval and many adverse perinatal outcomes.[36] Reference categories without an upper boundary can represent a heterogeneous risk group. For similar reasons, studies that modelled interpregnancy interval assuming a continuous, linear association with the adverse perinatal outcome were also excluded.

4. The study examined at least one of the following outcomes: preterm birth, small-for-gestational age, foetal death, perinatal death, neonatal death, infant death, low birthweight, intrauterine growth restriction, Apgar score, neonatal intensive care unit or congenital anomaly.
5. The study was published between 1 January 2006 and 1 May 2017.
6. The study was designed as a randomised controlled trial, cohort, cross-sectional or case-control study and could use unmatched (between-woman) or matched (within-sibling) designs. The study adjusted for maternal age and at a least one measure of socioeconomic position.
7. The study included at least 100 individuals.

In addition, included studies were available as full-text English-language publications (ie, not an abstract from a conference presentation) and presented the relevant findings and estimates of precision numerically (eg, 95% confidence interval [CI] or standard error).

2.3 | Data abstraction, study quality assessment, data synthesis

A structured Excel-based abstraction form was developed for data abstraction (available on request). Two study authors independently abstracted relevant data from full-text articles of included studies; discrepancies were resolved through discussion.[41] Data included study design, source, setting, numbers and characteristics of participants, interpregnancy intervals, comparisons, adjustment for confounders, perinatal outcomes and results.

Included studies were assessed for internal and external study quality using criteria outlined by the U.S. Preventive Services Task Force and rated as good, fair or poor.[42,43] Two reviewers independently assessed quality and discrepancies were resolved through consensus. In a few instances, we contacted study authors to discuss study details needed for completing the quality assessment.

Internal validity was determined by evaluating sources of potential information bias (misclassification), confounding and selection bias. Assessments were guided by the key study design considerations identified by a recent Office of Population Affairs' expert work group reviewing the evidence on short birth spacing

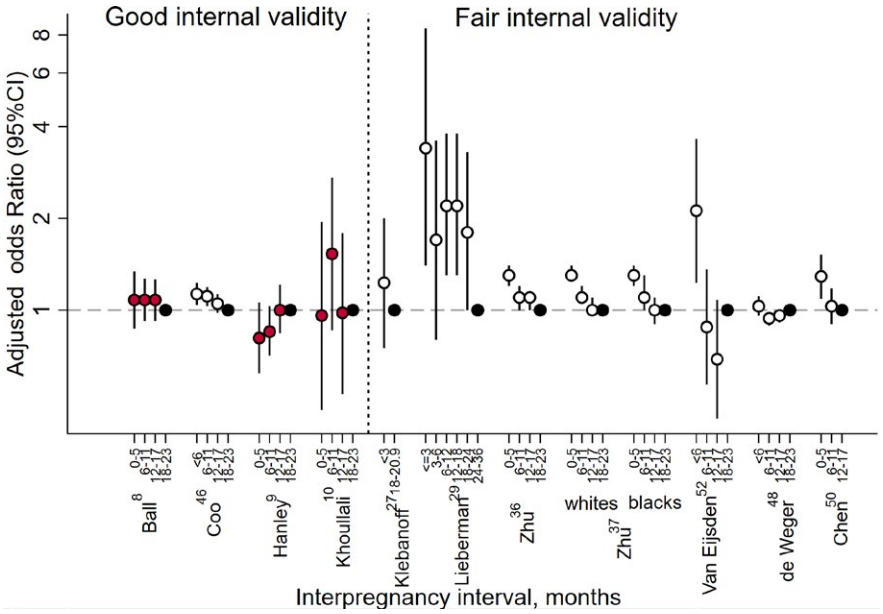

FIGURE 3 Adjusted odds ratios and 95% confidence intervals for the association between interpregnancy interval and small for gestational age birth among studies from high-resource settings. Black solid circles indicate the reference category, red solid circles indicate studies using a sibling comparison design, and vertical dashed line separates studies with good internal validity from those with fair internal validity. Confidence intervals are not discernible for some studies because they fell within the range covered by the point estimate symbol (black hollow circle)

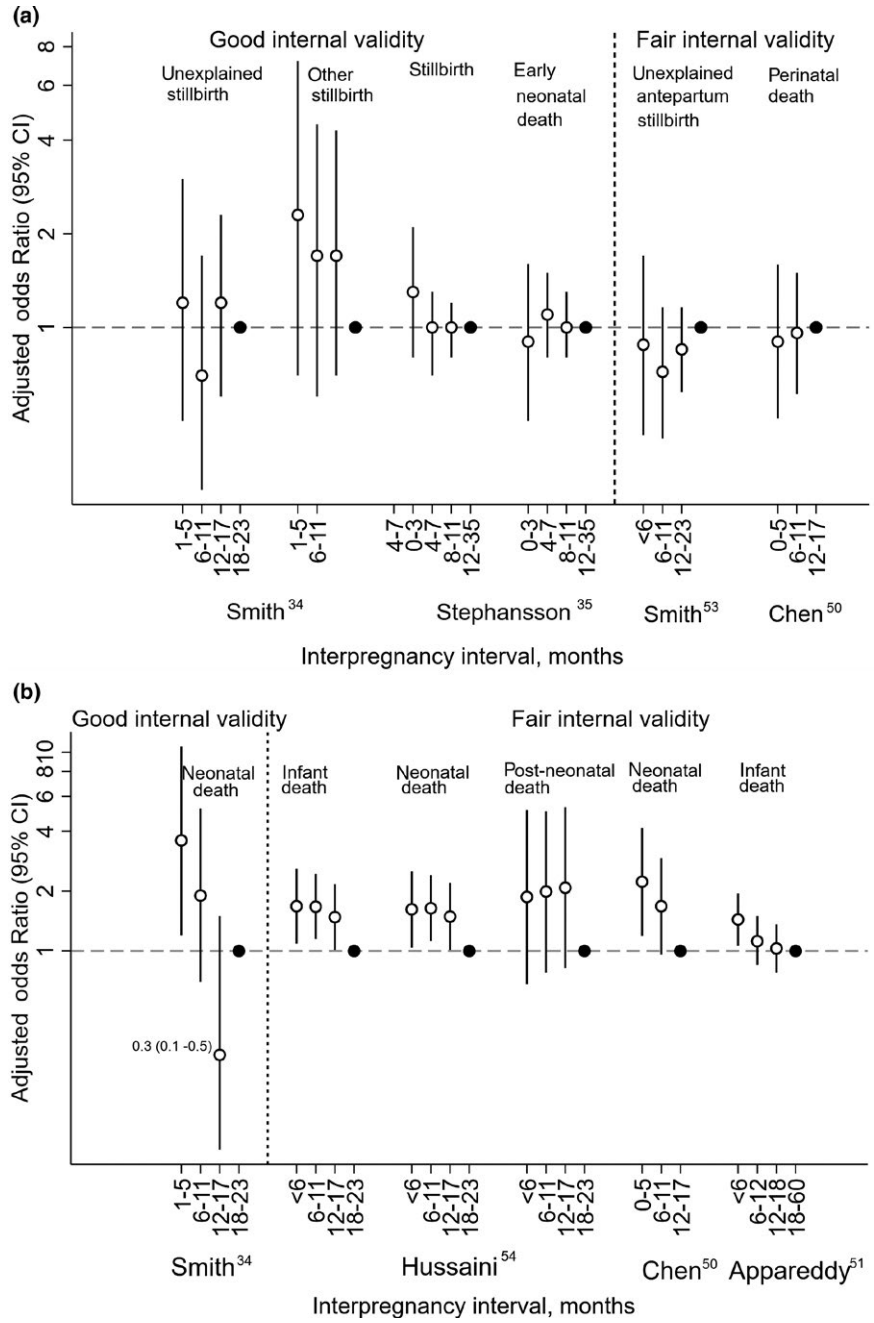

FIGURE 4 A, Adjusted odds ratios and 95% confidence intervals for the association between interpregnancy interval and perinatal death among studies from high-resource settings. Black solid circles indicate the reference category, and vertical dashed line separates studies with good internal validity from those with fair internal validity; B, Adjusted odds ratios and 95% confidence intervals for the association between interpregnancy interval and infant death among studies from high-resource settings. Black solid circles indicate the reference category, and vertical dashed line separates studies with good internal validity from those with fair internal validity

and adverse pregnancy outcomes.[44] These included the extent to which the study incorporated a detailed measure of socioeconomic position, accounted for pregnancy intention, identified early pregnancy losses occurring between the last birth and the subsequent pregnancy being evaluated (which could result in differential misclassification of interpregnancy interval) and accounted for perinatal death (stillbirth or neonatal death) in the previous pregnancy.[44]

External validity (generalisability) was determined by comparing the study population to either the general obstetric population in the United States or, for studies of women with specific obstetric history, a population with similar history in the United States.

Study design classification was based on when interpregnancy interval information was most likely documented in relation to when perinatal outcomes were assessed. As many of the studies were population-based samples of birth records, information on interpregnancy interval was assumed to originate from the prenatal medical record, which would have therefore been captured prior to the pregnancy outcome being known.[45] Consequently, population-based record samples were considered cohort studies.

Results of studies rated as having good or fair internal validity were qualitatively synthesised, taking into account both the magnitude and precision of relative risk estimates.

TABLE 2 Summary of evidence

Outcome	Studies (k) Study designs Observations (n)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
Preterm birth	14 studies (cohort); N = 2 557 668	Risk was significantly higher with shorter IPI in 10 studies (aOR ≥ 1.20 for ~<6 mo in 10 studies, but only four of six good-quality studies; point estimates decreased with increasing IPI).	Inconsistent in good quality studies, precise	Limited adjustment for confounders and validity of US vital statistics-based data sources.	Moderate	High
Spontaneous preterm birth	2 studies (cohort); N = 176 177	Risk was significantly higher with shorter IPI in 1 study (aOR = 1.83 for <6 mo; aOR = 1.26 for 6-11).	Inconsistent, imprecise	Few studies; limited adjustment for confounders and validity of US vital statistics-based data sources.	Low	Moderate
Small-for-gestational age	11 studies (cohort); N = 1 184 143	Risk was significantly higher with shorter IPI in 5 studies (aOR ≥ 1.20 for <6 mo in five studies, but none were good-quality studies).	Inconsistent, precise	Limited adjustment for confounders and validity of US vital statistics-based data sources.	Low	High
Perinatal death	4 studies (cohort); N = 610 829	There were non-significant increased risks with shorter IPI in two studies for <6 mo.	Inconsistent, imprecise	Few studies; variation in outcome definition, limited adjustment for confounders and validity of US vital statistics-based data sources.	Low	Moderate
Infant mortality	4 studies (3 cohort and 1 case-control); N = 220 676	Risk was significantly higher with shorter IPI in 4 studies (aOR ≥ 1.20 for <6 mo in 4 studies; 6-11 mo in 1 study; 12-17 mo in 1 study).	Consistent, precise	Few studies; variation in outcome definition, limited adjustment for confounders, and validity of US vital statistics-based data sources.	Moderate	Moderate

IPI, interpregnancy interval; aOR, adjusted odds ratio.

3 | RESULTS

Figure 1 shows a literature flow diagram of inclusions and exclusions. The literature search identified 490 unique references of which 416 were excluded after reviewing the title and abstract, most commonly because the studies were conducted outside the United States or other high-resource settings or did not describe original research. A total of 74 articles were identified for full-text review for perinatal outcomes, of which 21 studies met eligibility criteria in addition to 11 studies from the 2006 review. The most common reasons for exclusion at the full-text review stage were that the studies did not measure interpregnancy intervals, did not have a well-defined comparison group or did not adjust for maternal age and at least one measure of socio-economic position. Multiple reasons for exclusion were possible at each stage of review, but all exclusion reasons were not documented because once a study met one exclusion criterion it was then not further reviewed.

The 32 included studies are described in Table 1.[8-11,21,22,25,27-29,34-38,46-62] The majority of studies were conducted in the United States (n = 18),[11,21,25,27-29,36-38,49,51,54-59,62] 78% of which used U.S. birth certificate data (n = 14).[11,21,25,36-38,49,51,54,55,57-59,62] Other study settings included Canada (n = 4),[9,46,47,50] the Netherlands (n = 3),[10,48,52] Scotland (n = 2),[34,53] Sweden (n = 2),[35,60] Australia (n = 1),[8] Denmark (n = 1)[22] and Poland (n = 1).[61] Variations in birth registration practices across study settings (and thus, what is documented as a life birth) could have limited the validity of comparison across studies.[63] Most studies had large sample sizes (only two studies had sample size <3000[10,62] and the largest study was 847 618 individuals[47]), and over half of studies (n = 17) used 18-23 months as the interpregnancy interval reference group for analyses (Table 1). One study was a case-control study,[54] and the rest were cohort studies, which included four studies with interview data.[27-29,52] No studies evaluated the effects of an intervention designed to reduce short interpregnancy intervals on subsequent perinatal outcomes. Most studies evaluated more than one perinatal outcome.

Nine of the 32 studies met criteria for good internal validity,[8-11,22,28,34,35,46] 18 fair[21,25,27,29,36,37,47-54,57,58,60,61] and five poor[38,55,56,59,62] (Table 1). Most studies included a limited set of covariates for adjustment, and no study accounted for all the study design considerations outlined above. However, previous pregnancy stillbirth or neonatal death was accounted for in eight studies,[9,35-38,46,50,60] pregnancy intention was measured in two studies,[28,52] and intervening pregnancy loss was accounted for—usually in the study cohort definition—in seven studies.[10,21,28,29,49,55,56]

Generally, studies rated as good-quality accounted for a measure of socio-economic position beyond maternal education (the primary socio-economic measure on the U.S. birth certificate), in addition to at least one of the key study design considerations listed above. These higher quality studies included four studies that used a matched (within-sibling comparison) design,[8-11] which controls for time-fixed confounders by using a woman as her own control. Studies rated as poor-quality generally adjusted for only a single binary measure of socio-economic position, usually maternal education. All studies, except one,[27] included adjustment for covariates measured during or after the end of the interpregnancy interval, which can introduce overadjustment bias if these covariates operate as causal intermediates.[64] Most studies found attenuated estimates after adjustment for covariates, but the magnitude of that attenuation varied by perinatal outcome, length of interpregnancy interval and covariate adjustment set; generally, the shortest interpregnancy intervals evaluated showed the greatest attenuation after adjustment (Table S1). In the light of the potential for residual confounding and overadjustment bias, statistical meta-analysis was not performed and results were synthesised qualitatively.

Most studies (n = 19) were rated as having good external validity, reflecting the common use of population-based data (including birth certificate records and population perinatal registries). Eight studies met criteria for fair-quality[25,27-29,52,55,61,62] and five for poor.[8-11,48] The eight studies meeting criteria for fair-quality[25,27-29,52,55,61,62] were limited by including populations from only a single hospital or county;[28,29,55] including Healthy Start Program participants and matched controls from selected counties;[62] excluding certain race/ethnicity groups[25]; having low participation or follow-up rates[27,52] or taking place in settings with markedly different access to reproductive health services compared to the United States.[61] The five poor-quality studies[8-11,48] included four matched studies, which, by design, were restricted to women with three or more pregnancies and discordant pregnancy outcomes.[8-11] The other poor-quality study included only hospital births delivered by gynaecologists in the Netherlands,[48] which represents higher risk pregnancies compared to those among women delivered in other settings in that country.

3.1 | Preterm birth

Preterm birth (defined as <37 weeks' gestation) was assessed in 14 cohort studies (Figure 2A,B). Among the six good-quality studies (Figure 2A),[8-11,22,46] four reported statistically significant adjusted odds ratios (aORs) for interpregnancy intervals of approximately <6 months[10,11,22,46] of which all had effect sizes ≥1.20 (ranging from 1.2 [95% CI 1.13, 1.27] for <6 vs 18-23 months[11] to 3.6 [95% CI 2.04, 6.35] for ≤4 vs 24-36 months).[22] One study reported an aOR = 1.26 (95% CI 1.16, 1.36) for 6-11 vs 18-23 months.[46] The remaining aOR estimates from these studies were smaller in magnitude or not statistically significant.

Among the eight fair-quality studies (Figure 2B), all reported statistically significant aORs for the shortest interpregnancy interval examined in each study.[21,36,37,47-51] Six of these studies found significant associations for <6-month interpregnancy intervals (estimates ranged in magnitude from an aOR = 1.2 (95% CI 1.1, 1.3)[37] for <6 vs 18-23 months to an aOR = 1.92 (95% CI 1.79, 2.07)[48] for <6 vs 18-23 months). One study reported an aOR = 1.2 (95% CI 1.1, 1.2) for interpregnancy intervals 6-11 months,[37] and the remaining studies that reported statistically significant estimates were small in magnitude (eg, aOR<1.20). The good-quality studies usually reported

lower estimates for a given interpregnancy interval compared with fair-quality studies. Generally, for all studies, the shorter the interpregnancy interval, the higher the reported estimate.

3.2 | Spontaneous preterm birth

Spontaneous preterm birth was assessed in two good-quality cohort studies (Figure 2C).[28,46] Odds ratios were significantly higher with shorter intervals in one study (aOR = 1.83 [95% CI 1.65, 2.03] for <6 vs 18-23 months; aOR = 1.26 [95% CI 1.14, 1.38] for 6-11 vs 18-23 months).[46]

3.3 | Small-for-gestational age

Small-for-gestational age (defined as <10th percentile) was assessed in 11 cohort studies; eight studies used external weight-for-gestational age charts to define small-for-gestational age, one used an internally derived chart, and in two studies, the choice of charts was not stated (Figures 3 and S1). Among the four good-quality studies,[8-10,46] interpregnancy intervals <6, 6-11 or 12-17 months were associated with increased risks in one study, although the magnitude of increased risk was small (eg, aOR = 1.13 [95% CI 1.04, 1.23] for <6 months vs 18-23 months).[46]

Among the seven fair-quality studies,[27,29,36,37,48,52,65] five reported statistically significant aORs for interpregnancy intervals approximately <6 months.[29,36,37,52,65] Of these, all had aORs ≥1.20. One study also reported statistically significant aORs ≥1.20 for interpregnancy intervals 6-12, 12-18 and 18-24 months vs 24-36 months.[29] The remaining aOR estimates were small in magnitude or not statistically significant. As with preterm birth, generally the good-quality studies reported lower estimates than the fair-quality studies for interpregnancy intervals <6 months.

3.4 | Perinatal death

Perinatal death was assessed in four cohort studies (Figure 4A).[34,35,50,53] The two good-quality studies[34,35] reported increased risks for interpregnancy intervals <6 months (stillbirth ≥28 weeks aOR = 1.3 [95% CI 0.8, 2.1][35] for 0-3 vs 12-35 months and "other stillbirth" aOR = 2.3 [95% CI 0.7, 7.2][34] for 1-5 vs 18-23 months); however, neither estimate was statistically significant. The two fair-quality studies[50,53] also did not find significantly increased risks for interpregnancy intervals <6 months (unexplained antepartum stillbirth aOR = 0.88 [95% CI 0.45, 1.70][53] for <6 vs 24-60 months and perinatal death aOR = 0.90 [95% CI 0.51, 1.59][50] for 0-5 vs 12-17 months).

3.5 | Infant mortality

Infant mortality was assessed in four studies (three cohort studies and one case-control study) (Figure 4B).[34,50,51,54] A good-quality study reported an aOR of 3.6 (95% CI 1.2, 10.7) for neonatal death (death within the first four weeks of life) for interpregnancy intervals <6 vs 18-23 months.[34]

In the three fair-quality studies, interpregnancy intervals of <6 months were consistently associated with significantly increased risks of infant mortality and neonatal mortality,[50,51,54] with point estimates ranging from aOR = 1.44 (95% CI 1.06, 1.95)[51] to aOR = 2.23 (95% CI 1.19, 4.16).[50] There were significantly increased risks in one study for interpregnancy intervals of 6-11 months for infant mortality (aOR = 1.68) and neonatal mortality (aOR = 1.62);[54] and in the same study for interpregnancy intervals of 12-17 months for infant mortality (aOR = 1.48) and neonatal mortality (aOR = 1.49).[54]

3.6 | Other perinatal outcomes

Additional good or fair quality studies examined the following outcomes: alternative preterm birth definitions (n = 6);[25,34,46,50,51,57] birthweight (n = 2);[27,52] low birthweight (including alternative definitions such as very low birthweight) (n = 13);[8-10,22,27,34,36,37,46,48,50,51,61] alternative small-for-gestational age definitions (n = 1);[50] neonatal intensive care unit (n = 3);[9,50,51] Apgar score (n = 1);[50] and congenital anomalies (n = 3).[34,58,60] Estimates reported from each study are presented in a supplemental table (Table S1). As with the adverse perinatal outcomes already described, the highest risks (mostly aOR<2.0) were found for the shortest interpregnancy intervals, and there was attenuation of estimates after adjustment for confounders. Several studies found statistically significant increased risks for interpregnancy intervals <6 months[10,36,37,46,48,50,51] and 6-11 months[37,46,50] for low birthweight and for interpregnancy intervals <6 months,[25,34,46,51] 6-11 months[25,46] or 12-17 months[25,46] for alternative preterm birth definitions. No significant associations were found between interpregnancy interval and alternative small-for-gestational age definitions (<3rd percentile), neonatal intensive care unit admission, Apgar scores or congenital anomalies.[9,34,50,51,58,60]

4 | DISCUSSION

Among births in high-resource settings, clinically relevant and statistically significant associations between short interpregnancy intervals since last livebirth and perinatal health were supported by some studies, but not all studies. The most consistent evidence of an association was seen for intervals <6 months vs a longer interval (most commonly 18-23 months) and in studies of preterm birth and infant death, less consistent evidence was found for small-for-gestational age, while studies of perinatal death showed no relationship. However, the number of studies, precision of estimates and consistency of results varied (Table 2). Often, lower quality studies reported higher estimates for short interpregnancy intervals compared with higher quality studies, estimates were attenuated after covariate adjustment, and, within each study, estimates were highest for the shortest interpregnancy interval examined. Most studies examined population-based samples of births, most commonly using U.S. vital records, and many accounted for a similar set of covariates. Generally the highest quality studies, in terms of internal validity, had limited external generalisability.

Our findings are generally consistent with a previously published 2006 review[2] upon which our systematic review protocol was based. The previous review also observed an inverse relationship between shorter interpregnancy intervals and adverse perinatal outcomes and an attenuation of estimates after covariate adjustment. The previous review also reported increased adjusted odds of preterm birth and small-for-gestational age birth for interpregnancy intervals <6 months, but found significantly greater risks for these adverse outcomes for interpregnancy intervals up to 17 months. The reviews differ by study aims, methods of study inclusion and data synthesis. While the 2006 review used statistical meta-analysis to determine combined estimates, we opted against producing a single summary measure due to concerns about study quality and heterogeneity. In addition, we tiered our qualitative synthesis of studies based on our assessment of internal validity and considered both magnitude and statistical significance when synthesising the evidence.

While results of our review support associations between an interpregnancy interval <6 months and some adverse perinatal outcomes, our findings provide less support for intervals of 6-11 months and 12-17 months, particularly for small-for-gestational age, compared with the previous review, and a more recent review of studies from low- and middle-income countries.[66] Our conclusions are generally consistent with a recent systematic review and meta-analysis[67] of high-quality studies from largely high- and moderate-income countries showing that risks were mostly confined to interpregnancy intervals <6 months. Together, this suggests that adverse associations from short interpregnancy intervals for high-resource settings may be limited to very short interpregnancy intervals (<6 months or possibly 6-11 months) as opposed to up to 18 or 24 months for lower-resource settings.

Future research using additional data sources and methods and with more rigorous control for confounding would be valuable for informing the development of recommendations for healthy birth spacing for U.S. women. Although we synthesised evidence only from studies rated as having "Good" or "Fair" internal validity, no study included in our review accounted for all the factors we identified as being important for ruling out major concerns of bias: detailed information on maternal socio-economic position, pregnancy intention and history of perinatal losses to reduce confounding, and accounting for intervening pregnancy losses in order to reduce exposure misclassification, which could potentially be differential by perinatal outcome. Most (78%) of the studies from the United States used information on interpregnancy interval and covariates from U.S. birth certificates, essentially replicating the same study design in different geographic areas across the country. Now that interpregnancy interval is available on national files from states that have adopted the 2003 revised U.S. birth certificate (all states as of 2016), new analyses of national data can be expected, with presumably similar findings, albeit greater precision.

Further research conducted among populations at high risk of adverse perinatal outcomes is also needed, as most of the studies conducted to date have been among population-based samples, which can obscure important differences among subgroups. In addition, research is lacking on the effects of interventions aimed at reducing short interpregnancy intervals on subsequent pregnancy outcomes in high-resource settings, although a recently published intervention study from Bangladesh suggests these types of interventions may lead to decreased risk of preterm birth.[68] These types of studies in the U.S. would be useful in targeting health care services.

Limitations of this review include using only English-language articles and restricting the focus to the more commonly studied adverse perinatal health outcomes. Also, our systematic review protocol may have excluded some potentially germane studies, because of our strict inclusion and exclusion criteria. For example, several studies were excluded because they did not adjust for socio-economic position and/or maternal age, but did investigate the influence of these factors in exploratory analysis[65,69-73] or restricted their analysis to certain age groups, thereby controlling for socio-economic position to some extent.[74] We opted against inclusion of such studies in order to maintain consistency with the previous review. We also excluded otherwise eligible studies that did not provide precision estimates for their measures of effect[24,26] and those that modelled interpregnancy interval as a continuous, linear variable.[75-77] In addition, since the publication end date, several relevant studies of interpregnancy intervals and adverse perinatal outcomes from high-resource settings have been published using data from Missouri, Canada and Denmark,[78-80] including a matched analysis study among births in Sweden[81] and a study using linked birth certificate and assisted reproductive technology surveillance data from the United States;[82] findings were generally in line with the evidence we present in this review.

This is the first systematic review of interpregnancy interval and adverse perinatal outcomes restricted to studies from high-resource settings, which enhances the applicability of our findings to women in the United States. We present evidence tiered by assessed internal validity quality, helping to highlight the potential role of bias in our current understanding of the evidence base. Finally, our systematic review is unique, because it includes a number of recently published studies that used maternally linked births to conduct matched sibling comparison analyses, which provide a novel approach to control for confounding by difficult-to-measure characteristics, such as socio-economic position. Inclusion of the findings from these new study designs is critical for enhancing the overall internal validity of the evidence for this topic, though the limited external generalisability of these study cohorts is a concern.

In conclusion, we found that among higher quality studies conducted in high-resource settings, short interpregnancy intervals (<6 or <12 months) are associated with increased risks for preterm birth, small-for-gestational age and infant death, although associations were less consistent in the highest quality studies. It remains unclear whether these associations represent causal effects given the limited study designs and data sources used, inconsistency of findings and comparison groups, similar confounder adjustments and limited generalisability of the highest quality studies. Additional research targeting high-risk populations and controlling for confounding

would further inform recommendations for healthy birth spacing in the United States.

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DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Office of Population Affairs, Office of the Secretary for Health, Department of Health and Human Services.

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SUPPORTING INFORMATION

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

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