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Impact of Increasing Inter-pregnancy Interval on Maternal and Infant Health

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Abstract

Short inter-pregnancy intervals (IPIs) have been associated with adverse maternal and infant health outcomes in the literature. However, many studies in this area have been lacking in quality and appropriate control for confounders known to be associated with both short IPIs and poor outcomes. The objective of this systematic review was to assess this relationship using more rigorous criteria, based on GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. We found too few higher-quality studies of the impact of IPIs (measured as the time between the birth of a previous child and conception of the next child) on maternal health to reach conclusions about maternal nutrition, morbidity or mortality. However, the evidence for infant effects justified meta-analyses. We found significant impacts of short IPIs for extreme preterm birth [<6 m adjusted odds ratio (aOR): 1.58 [95% confidence interval (CI) 1.40, 1.78], 6–11 m aOR: 1.23 [1.03, 1.46]], moderate preterm birth (<6 m aOR: 1.41 [1.20, 1.65], 6–11 m aOR: 1.09 [1.01, 1.18]), low birthweight (<6 m aOR: 1.44 [1.30, 1.61], 6–11 m aOR: 1.12 [1.08, 1.17]), stillbirth (aOR: 1.35 [1.07, 1.71] and early neonatal death (aOR: 1.29 [1.02, 1.64]) outcomes largely in high- and moderate-income countries. It is likely these effects would be greater in settings with poorer maternal health and nutrition. Future research in these settings is recommended. This is particularly important in developing countries, where often the pattern is to start childbearing at a young age, have all desired children quickly and then control fertility through permanent contraception, thereby contracting women's fertile years and potentially increasing their exposure to the ill effects of very short IPIs.

Keywords

interpregnancy intervals; *maternal nutrition status*; *maternal morbidity*; *maternal mortality*; *preterm*; *low birthweight*; *stillbirth*; *early neonatal death*

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For nearly a century, public health investigators have reported that the length of time between delivery and conception of the next pregnancy (inter-pregnancy interval or IPI) or birth of the next child (inter-birth interval) is associated with outcomes of the subsequent pregnancy.[1–4] Both short and long intervals have been associated with poor pregnancy outcomes, although along different hypothesised causal pathways. Long intervals are thought to be a consequence of infecundity and its associated poor pregnancy outcomes, while short intervals are thought to affect maternal, infant and child mortality through a `maternal depletion syndrome',[5,6] when the mother does not have enough time between pregnancies to recover micro- and macronutrient stores. This recovery is additionally affected by breastfeeding practices. Especially for women who were undernourished before pregnancy, the energy needed to breastfeed increases time required to fully recover for the next conception.[6] Both very short and long intervals can also be associated with other factors such as socio-economic status (SES), which can cloud investigations of any independent physiological impact of pregnancy intervals.

For women of normal fecundity, the length of IPI is a function of sexual activity, breastfeeding and contraception. In a population with high fertility, higher fertility is associated with shorter IPIs.[7] Thus, increasing IPI is a major goal for international health agencies' population and family planning programmes.[8–11] Because of the observed negative association on maternal, infant and child health of short IPIs, family planning advocates have long identified increasing IPIs as a common goal for both maternal and child health and family planning programmes.[7] However, for women with two or three children, IPI can vary depending on age at first childbearing and cultural values. For example, in India, which traditionally has promoted population control through sterilisation, average IPI is relatively short even for families with two or three children.[12] Thus, to maintain a programmatic affinity between maternal and child health and family planning in lower-fertility settings, it would be important to show strong evidence that short IPIs cause poor pregnancy outcomes irrespective of number of previous births.

A number of systematic reviews have evaluated the evidence for a causal linkage between short IPI and maternal and child health outcomes (e.g. Conde-Agudelo 2006[13] and 2007,[14] Hogue 2011,[15] Dewey 2007[6]). Many have concluded that short intervals, variously defined, may increase preterm birth risk and other child health outcomes.[6,13,15] However, it is not clear that the weight of the evidence is sufficient to argue that programmes aimed at improving maternal and infant health through improved maternal nutrition should prioritise programming to lengthen IPI. All published studies are observational, and many are of poor quality. To attempt to clarify whether the evidence is sufficient for decision making, in this review we examine studies with high enough quality to rate a grade of `moderate' in the GRADE system (Grading of Recommendations Assessment, Development and Evaluation), which was developed by the GRADE Working Group and is described in detail elsewhere.[16] We conducted a meta-analysis when there are at least three moderate-quality studies of a particular health outcome. Ideally, a study would examine the effect of IPI on maternal nutrition directly, but there are few such studies. Therefore, we included studies of preterm birth, low birthweight, infant and maternal mortality and maternal morbidity, which are indirect measures of maternal health.

Methods

Systematic review

The objective of this review was to assess the impact of increasing IPIs, defined as the time from birth to conception, on maternal and child health outcomes in any setting. The systematic literature search was conducted by the authors and a research assistant. All attended a 1-day training workshop on the methodology for conducting the systematic review, data abstraction and assessing the overall quality of evidence using the GRADE method. The training was led by experts in systematic reviews and the GRADE and Lives Saved Tools methods.[17] During and following training, the abstraction table developed for this review was piloted and the GRADE technique was examined for appropriateness to observational studies. This led to minor modifications to the abstraction protocol and table. Information on the specific modifications made to the GRADE method and abstraction table is available upon request.

Literature search

We utilised six major search engines (PubMed/MEDLINE, POPLINE, ISI Web of Science, EMBASE, Cochrane Reference Libraries and CINAHL); we limited searches to English only and human subjects. Our search terms varied slightly according to the required syntax particular to each search engine. Search terms listed in Appendix 1 are formatted for the PubMed search engine. We retrieved and reviewed both electronic and non-electronic sources. When a database returned unpublished results, we attempted to find the studies with the help of a reference librarian. In addition, we manually searched the references of a limited number of studies. We did not contact authors to identify additional studies. Our methods were similar to those used for a recent review of the impact of contraception on perinatal mortality.[18]

Eligibility criteria

Trained screeners examined all titles and abstracts returned by the search and excluded those deemed not relevant per eligibility criteria. In general, we excluded descriptive studies, general review articles and commentaries in the systematic review. We screened abstracts for relevance according to specific inclusion and exclusion criteria for each outcome (described below). If multiple papers were published on the same data set, only one paper was included in the review to represent that information. GRADE assesses the quality of evidence based on study design, limitations/biases, consistency of results, applicability of evidence, precision and publication bias. Evidence may be downgraded (e.g. if there are serious limitations) or upgraded (e.g. if consistency is high).[19] With respect to individual studies, the GRADE system states that observational studies begin at `low' quality, but they may be upgraded. To assure that all studies in this systematic review were at least moderate quality, we excluded studies that reported only inter-birth intervals because of their inherent bias (i.e. short gestation is associated with poor pregnancy outcomes). Categorisation of countries as high-, middle- or low-income countries was done using the World Bank country classifications.[20] We included studies only if the IPI exposures were, for the `exposed' group, <12 months or some subcategory of <12 months and, for the `unexposed' group, categories that did not include the `exposed' group. This was defined as ≥12 months or a

subcategory of this. We also only included studies examining outcomes associated with births, the main focus of this review.

Additionally, we excluded studies that did not define the outcome (e.g. low birthweight or preterm birth), did not examine confounding or effect modification, or did not control for some measure of SES by matching or by multivariable analysis. Across the studies, there were numerous differences in how SES and other potential confounders were defined. For clarity in comparison, rather than aggregating these variables, we chose to code and list them as defined in the studies (see Appendix 2). Our inclusion criteria were somewhat similar to those in other recent reviews;[13–15] however, for the purpose of grading evidence, we were more restrictive in choice of studies for meta-analyses.[13–15] We also classified studies by whether they were conducted in low-income, middle-income or high-income countries.

Infant outcome inclusion criteria were early neonatal mortality (with weeks specified), stillbirth (if defined), low birthweight (if defined) or preterm birth (with weeks specified). Because infant death after the early neonatal period may be affected more by the infant's postnatal environment than the mother's nutritional status and/or infant health at birth, we excluded studies of post-neonatal or overall infant mortality. Studies that did not define the outcome and outcomes of small-for-gestational age and intrauterine growth restriction (IUGR) were also excluded because of imprecise definitions and difficulty in comparing growth standards across studies.

Possible maternal morbidity outcomes included pregnancy-induced hypertension including eclampsia, HELLP (Haemolysis, Elevated Liver Enzymes, Low Platelet count) and pre-eclampsia; obstetric labour complications, including abruptio placentae, cephalo-pelvic disproportion, dystocia, placenta accreta, placenta previa, post-partum haemorrhage, uterine inversion, uterine rupture and vasa previa; oligohydramnios and polyhydramnios; haematological pregnancy complications; infectious pregnancy complications, including parasitic and puerperal infections; puerperal disorders, including post-partum depression, mastitis, post-partum haemorrhage, post-partum thyroiditis, pubic symphysis diastasis and puerperal infection; and obstetric fistula. Placental diseases included abruptio placentae, chorioamnionitis, retained placenta and placental insufficiency. We also searched for maternal mortality.

Nutrition outcomes included anaemia, vitamin status, pre-pregnant weight and/or weight change, and anthropometric measures if they defined their outcomes. Studies of gestational body composition change were excluded if they did not account for initial weight and/or body composition.

Data extraction

Studies meeting inclusion criteria were abstracted into an abstraction table. A random subsample of 30% of the included articles was double abstracted by the senior author to ensure the accuracy and completeness of the abstraction procedure. Key variables abstracted were related to the study identifiers and context, study design and limitations, intervention specifics and effects on outcomes.

Statistical analysis and comparative assessment

When at least three studies of moderate quality and comparable outcomes were abstracted, we conducted meta-analyses using the inverse-variance method for weighting and a random-effects model to calculate a summary odds ratio (OR), transformed to a natural log scale. Weights were derived from the standard error estimated from the reported 95% confidence interval (CI). We tested for heterogeneity using both the χ^2 and the I^2 statistic based on a random-effects model. Meta-analyses were conducted using Review Manager Software, version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark). CI [in brackets] are 95% CI, unless otherwise noted.

Because our review is more restrictive than previous reviews, we also present a comparative analysis of our results with results from recent reviews.[6,14] The major differences were our exclusions of studies with birth intervals instead of IPIs. We also excluded those that reported IPI as a continuous variable because of evidence that IPI is associated with pregnancy outcomes in a curvilinear fashion.[14]

Level of evidence

The quality of the evidence was evaluated and graded according to the Child Health Epidemiology Reference Group (CHERG) adaptation of the GRADE technique.[21,22] The overall assessment of evidence in the systematic review depends on both the quantity and quality of evidence presented. The GRADE system classifies the quality of evidence as very low (very uncertain effect estimates), low (further research will likely change the effect estimate), moderate (further research may change the estimate and our confidence in it) or high (further research is `very unlikely to change our confidence in the estimate of effect').

Results

Our initial searches retrieved 3171 total studies for all outcomes combined (maternal nutritional status: 571; maternal outcomes: 1551; infant outcomes: 1039). After removal of duplicates and irrelevant articles, we retrieved and read 585 articles for further evaluation. Initial screening for study designs, relevance (e.g. not outcomes of interest) and IPI exclusions (e.g. <24 months as `exposed' group) reduced the search to 107 studies. An additional 84 studies were then removed either for outcome definitions that did not fit our inclusion criteria, no multivariable analysis or lack of controlling for SES variables, or inappropriate `unexposed' categories. For example, an inappropriate comparison would be primiparous women, whereas an appropriate group would be women with longer IPI ranges.[23] For the studies that met our criteria for at least one outcome, only those outcomes that met our criteria were included.

Infant outcomes: stillbirth and early neonatal death

We abstracted 43 stillbirth and early neonatal death studies. Three stillbirth studies (two in middle-income countries) met inclusion criteria, and two found significant results (Table 1). Our meta-analysis results show an overall random-effects OR of 1.35 [1.07, 1.71] (Figure 1).

Stephansson *et al*. divided their IPI categories into 0–3 m and 4–7 m and reported non-significant associations in both IPI categories once adjusting for confounders.[24] In a study of 19 Latin American countries, Conde-Agudelo *et al*. reported adjusted odds ratios (aORs) of 1.54 [1.28, 1.83] and 1.24 [1.14, 1.35] for stillbirths of ≥20 weeks' gestation among women with IPIs of less than 6 months and 6–11 months, respectively.[25] Da Vanzo *et al*. reported an aOR of 1.61 [1.20, 2.18] for stillbirths ≥28 weeks' gestation in Bangladesh.[26]

Three studies of early neonatal death (death within 1 week of birth) met inclusion criteria (Table 2). The majority of excluded studies did not meet our narrow inclusion criteria for IPI definition. The meta-analysis found an overall random-effects OR of 1.29 [1.02, 1.64] (Figure 2).

Conde-Agudelo *et al*.[25] reported a significant relationship for both IPI groups (<6 and 6–11 m), and Stephansson *et al*.[24] reported a non-significant association between early neonatal death and IPI. Grisaru-Granovsky *et al*.[27] found a significant association for the shortest IPI group (0–5 m) but not 6–11 m.[27]

Preterm birth

We abstracted 24 preterm birth studies and included 12 in the review[25,27–37] (Table 3). Six of these studies stratified by both length of IPI and gestational age of the following pregnancy, which we used to conduct four meta-analyses: <6 months IPI with extreme prematurity (<33 weeks), <6 months IPI with either all prematurity (<37 weeks) or moderate prematurity (between 32 and 37 weeks), >6 months IPI with extreme prematurity and >6 months IPI with all or moderate prematurity (Figures 3–6). In the moderate prematurity group, our rationale for including studies of all prematurity is that the majority of premature livebirths in these studies would have been at least 33 weeks of gestation. For an IPI of <6 months and extreme preterm birth, the aOR was 1.58 [1.40, 1.78]. The meta-analysis for <6 months IPI and all or moderate prematurity had an aOR of 1.41 [1.20, 1.65]. For an IPI >6 months and extreme prematurity, the aOR was 1.23 [1.03, 1.46] whereas for an IPI of >6 months and all or moderate preterm birth, the aOR was 1.09 [1.01, 1.18].

Conde-Agudelo *et al*. reported similar results in their meta-analysis of preterm birth (defined as <37 weeks), with an aOR of 1.40 [1.24, 1.58] for an IPI of <6 months and an aOR of 1.14 [1.10, 1.17] for an IPI of 6–11 months.[13] Hogue *et al*. found that risk of preterm birth was increased by approximately 40% for IPIs of <6 months.[15]

Low birthweight

We abstracted 25 studies of low birthweight (birthweight <2500 g), of which only six met inclusion criteria[25,29,33,38–40] (Table 4). Jafari *et al*. was excluded from the meta-analyses because their analysis was not separated into IPIs of <6 months and >6 months. The meta-analysis for the IPI of <6 months resulted in an overall aOR of 1.44 [1.30, 1.61] (Figure 7). The meta-analysis for the IPI of >6 months resulted in an overall aOR of 1.12 [1.08, 1.17] (Figure 8).

Only one included study examined the outcome of very low birthweight, defined as less than 1500 g. Conde-Agudelo *et al*. found an increased risk of very low birthweight associated

with an IPI of < 6 months (aOR of 2.01 [1.73, 2.31]) and even with an IPI of 6–11 months (aOR of 1.23 [1.12, 1.35]) in comparison with 18- to 23-month intervals.[25] With less stringent inclusion criteria, a Conde-Agudelo *et al*. review found a similar aOR for low birthweight of 1.61 [1.39, 1.86] for an IPI of less than 6 months and 1.14 [1.10, 1.18] for an IPI of 6–11 months.[13]

Maternal morbidity/mortality

We abstracted nine articles that examined the association between IPI and maternal morbidity/mortality. However, four studies did not meet additional inclusion criteria[41–44] (e.g. inappropriate comparison groups, IPI range not specified). Five moderate-quality studies investigated 10 maternal outcomes[45–48] (Table 5). Although three studies for the maternal outcomes of haemorrhage and premature rupture of membranes (PPROM) met inclusion criteria, Razzaque *et al*. did not report CI with their estimates, so we were not able to perform meta-analyses.

Overall, the evidence did not present a clear picture with any included outcome. Only one out of three studies examining haemorrhage/bleeding found a significant association; this study found a significant increase in third trimester bleeding (which combined two outcomes) for an IPI of 0–5 months compared to an IPI of 18–23 months.[46] The study by Conde-Agudelo *et al*. was also the only study to find a significant association between PPROM and IPI.[46] Cecatti *et al*. and Razzaque *et al*. did not find a significant association.[45,47] All other outcomes (pre-eclampsia/eclampsia,[46,47] hypertensive disorders,[45,47] maternal death,[46,47] maternal infection,[45] proteinuria,[47] puerperal endometritis,[46] uterine rupture[48] and composite morbidity[48]) were evaluated by only one to two included studies.

Maternal nutritional status

Three studies met inclusion criteria for anaemia:[46,47,49] one study in the high-income country Singapore;[49] one multi-country study in middle-income Latin American and the Caribbean nations;[46] and one study in the low-income country of Bangladesh[47] (Table 6). Only two of these studies presented aORs for anaemia.[46,48] Conde-Agudelo *et al*. reported an adjusted relative risk of 1.30 [1.18, 1.43] for IPIs < 6 months, while Razzaque *et al*. reported no significantly increased risk (aOR for IPIs < 6 months of 1.03). The study in Singapore found an association between short IPIs and maternal anaemia, although there was no difference in mean birth intervals between anaemic and non-anaemic mothers.[50]

Two other systematic reviews, Dewley *et al*. and Conde-Agudelo *et al*., have also examined the relationship between maternal anaemia and IPI. Dewey's assessment of eight studies of maternal anthropometry in relation to IPI or recuperative interval obtained mixed results.[6] Conde-Agudelo *et al*.[14] also reported mixed results concerning anaemia and short IPI in their review of five studies. Three of their five studies were also included in this review.[46,48,50] The other two were excluded because of IPI as a continuous variable[51] and birth interval as the exposure.[52]

Only one study met inclusion criteria for pre-pregnancy weight and IPIs.[53] This study was conducted in Guatemala, a middle-income country. All weight measures were standardised to the women's height. Authors found that an IPI of <9 months was associated with a higher pre-pregnancy weight when compared with an IPI of ≥15 months ($P < 0.05$). When they included non-breastfeeding recuperative intervals into their model, the trend remained but was non-significant ($0.05 < P < 0.10$). The results for pre-pregnancy weight were unexpected. Authors proposed that this might have been because women at higher weights might reflect better nutritional status and ability to get pregnant sooner. After review, no study of gestational weight change met inclusion criteria.

No studies assessing specific micronutrient maternal levels were included in this review because of IPI categorisations that did not meet inclusion criteria. Although some evidence indicates that decreases in some micronutrients may be more prevalent in women with short IPIs,[54–57] differences in vitamins and IPIs assessed and possible residual confounding are factors that need to be explored as research in this area expands.

Overall assessment

The overall quality of evidence varied across outcomes (Table 7). There were several studies examining the association between IPI and infant morbidity and mortality. Three studies were included for stillbirth and three for early neonatal death. For each of these outcomes, the quality of evidence was graded as moderate. Two studies for stillbirth and one for early neonatal death were conducted in middle/low-income countries for a moderate and low generalisability, respectively, to countries of interest. However, limitations such as imprecision, misclassification bias and a sample that was not population based prevented a higher quality rating.

The outcome of preterm birth as a whole included 12 studies and three designs: retrospective cohort, nested case–control and cross-sectional. Each meta-analysis showed a significant association between both very preterm birth (<33 weeks) and all or moderate preterm birth (<37 or 32–37 weeks) and IPI, leading to a moderate grade for quality of evidence, even though not all studies were population based and some suffered from imprecision. Similar findings for meta-analyses of low birthweight suggest that the impact of IPI on infant health is significant, especially if the IPI is <6 months, and this association is present among women in high- and moderate-income countries, where maternal nutrition is presumed to be adequate.

The quality of evidence assessing the relationship between IPI and anaemia is low. One of three studies (two cross-sectional and one retrospective cohort) showed a decrease in haemoglobin levels in women with shorter IPIs. However, two of the studies were conducted in middle/low-income countries, which led to moderate generalisability to our population of interest. Only one study was included that examined pre-pregnancy weight and IPI, resulting in a very low quality of evidence. For the relationship between IPI and maternal morbidity/mortality, five studies fit the inclusion criteria. Consistency of evidence was low because of varying results for two outcomes (haemorrhage and PPROM). For the rest, consistency could not be determined, as only one to two included studies examined

each outcome (eight in total). Generalisability was high for this outcome because four of the five studies were conducted in middle- or low-income countries.

Comments

We found moderate evidence that an IPI of < 12 months increases the risk of stillbirth, early neonatal death, preterm birth and low birthweight. Evidence for other outcomes is insufficient to warrant definitive conclusions. In general, there is no issue of the exposure (IPI) preceding the outcome. In addition, our inclusion criteria required that studies specify the length of IPI investigated as well as an appropriate comparison group and that they provide a control for SES and other confounders. Because of these restrictions, we believe that the included studies represent evidence of at least moderate quality. Interestingly, our findings are similar to those of other reviews that used less restrictive criteria. In general the studies support the hypothesis that mothers in low-resource countries require a recuperative period of at least 1 year for their health as well as the health of their offspring.

However, lack of accounting for other factors such as breastfeeding frequency and duration or initial maternal nutritional status may lead to an incomplete picture. Some studies that had to be excluded because they used IPI as a continuous variable or did not specify IPI did account for recuperative intervals. Their findings highlight the complexities inherent in the relationship between IPI and maternal nutritional outcomes. Winkvist *et al*. divided IPI to measure duration of breastfeeding, recuperative period (non-pregnant non-lactating) and overlap period (breastfeeding and pregnant). They reported a positive association of overlap and parity with weight gain over one reproductive cycle, while late breastfeeding (>6 m) was associated with increased weight loss in the middle weight group only (45–56 kg).[51,58] A Guatemalan study that examined two consecutive pregnancies and varying intervals[59] found that women who had a recuperative interval followed by an overlap were more likely to have significant weight loss during their first and second trimesters, but not their third trimester. Although these studies did not fit the inclusion criteria, they reveal a complex association in which measuring for IPI alone may not account for the impact of breastfeeding, previous pregnancy intervals and pre-pregnancy nutritional status.

In our meta-analyses, only three included studies were from low- and middle-income countries. However, the limited data from low-income countries is consistent with results in this review. It may be that our definition of high-risk IPI (i.e. <12 months) is too restrictive for investigating the impact on infants' survival of pregnancy spacing in low-income environments. For example, in a retrospective cohort study in Uttar Pradesh, India, Williams found an aOR for early neonatal death of 4.39 [3.97, 4.87] for an IPI of < 18 months. Lawoyin and Oyediran reported that in a retrospective study in Ibadan, Nigeria, the risk of having a low-birthweight baby was at its peak for IPIs < 3 years.[61] Dhar found the frequency of low birthweight to be higher with an IPI < 18 months ($\chi^2 = 14.33$, $P < 0.005$) in a hospital-based cross-sectional study in Srinagar, India.[61] Future, high-quality studies in low-income settings are warranted to determine an ideal IPI for infant health and survival in these contexts.

Biological plausibility

The mechanisms of how a short IPI may lead to adverse maternal and infant outcomes have not been fully elucidated. A major theory used to explain this phenomenon is called `Maternal Depletion Syndrome'.[5] The overall premise is that closely spaced pregnancies do not allow sufficient recovery time for the mother. This depletion in both macro- and micronutrients for the subsequent pregnancy may lead to adverse outcomes for the mother and infant.[63] These stores must then be replenished prior to the next pregnancy for optimal outcomes.

A related hypothesis to maternal depletion focuses on the specific role of folate depletion.[64] The depressed red blood cell and serum folate levels that happen in the fifth month of pregnancy remain lowered for several weeks after delivery. Conceptions during this period before folate repletion suffer higher risks of adverse pregnancy outcomes including neural tube defects, lower birthweights, preterm births and intrauterine growth restriction.[64] van Eijsden *et al*. examined this in a cohort of women with intervals of 1–24 months and found that folate supplementation both early and late in pregnancy attenuated the effects of short IPI on birthweight and small-for-gestational age risk.[65]

The time to recover from the increased inflammatory changes from the previous pregnancy has also been posed as a mechanism to explain poor maternal and infant outcomes, specifically PPROM. Getahun *et al*. found that the risk of recurrent PPROM was elevated in women (especially African-Americans) that had an IPI of <18 months. The authors believe that chronic inflammation may be the cause of the association; a short IPI may not provide sufficient time for the mother's body to recover from previous inflammation, thus contributing to an increased risk of PPROM (and preterm birth) in the next pregnancy.[66]

Other factors have been mentioned as possibly confounding the association of short IPI with poor pregnancy outcomes. Lower SES, less access or utilisation of antenatal care, unintended or unplanned pregnancies and unstable life styles are associated with short IPIs as well as adverse pregnancy outcomes.[67,68] However, Conde-Agudelo noted that socio-economic and maternal characteristics did not confound the IPI/pregnancy outcomes association in their meta-analysis.[13] In this systematic review, to reduce the impact of confounding, we included only studies that adjusted for SES.

Additionally, another major factor, which can deplete nutrient stores and increase needs for the mother, is duration, frequency and intensity of lactation. The increased requirements for lactation in some ways tax the mother's body even more than pregnancy with increases in energy needs and some vitamins.[6] Not accounting for different breastfeeding practices could lead to exposure misclassification. Winkvist *et al*. proposed a change in the maternal depletion definition to account for this factor, measuring full and partial breastfeeding and non-pregnant non-lactating intervals. Situations of overlap where there is no non-pregnant non-lactating period are seen as particularly depleting.[58,69] Winkvist *et al*. proposed that maternal depletion as described currently takes place in marginally malnourished women who can provide nutrients for the foetus but deplete their own stores while under more severe malnutrition, the mother's needs take priority and birth-weight suffers.[70] Therefore, it would be difficult to measure this phenomenon without differentiating the groups.[69]

Other studies indicated that women with low initial nutritional stores may adapt by developing a slower metabolic rate to increase energy efficiency during high stress situations[58,71] or by partitioning energy differently, replenishing maternal energy stores over foetus growth.[70,72] Additionally, in rat models, food restriction led to increased weight gain during the repletion phase and lower-weight pups, lending evidence to this theory.[73] In addition to these complexities, other key factors can mediate the relationship between IPI and maternal and child outcomes. Initial body mass index can affect both IPI (higher body mass index can lead to a faster return to fertility) and nutritional stores (which can mean a shorter repletion phase is necessary).[6]

In conclusion, there is great need for high-quality studies of the potential impact of short IPI on maternal nutrition and morbidity in low-income settings. In this systematic review, we found too few higher-quality studies of the impact of IPI on maternal health to reach conclusions about nutrition, morbidity or mortality. However, the evidence for infant effects – particularly preterm birth and low birthweight – justified meta-analyses. The results were consistent with small, but significant impacts of short IPIs largely in high- and moderate-income countries. It is likely that effects would be greater in settings with poorer maternal health and nutrition. Future, prospective studies on the effect of maternal nutrition during and between pregnancies on infant health outcomes in subsequent pregnancies are warranted. This is particularly important in developing countries, where women often start childbearing at a young age, have all desired children quickly, and then control fertility through permanent contraception, thereby contracting their fertile years and potentially exposing themselves and their offspring to the ill effects of very short IPIs.

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Appendix 1: Search Terms

All searches for each maternal or child outcome included the following terms to search for inter-pregnancy intervals: birth interval* OR birth spacing OR pregnancy interval* OR interbirth interval* OR `birth to conception' OR `delivery to conception' OR `interdelivery interval' and when appropriate, the MeSH term `Birth Intervals'.

In order to narrow the search down to the desired maternal and child health (MNCH) outcomes, different groupings of terms were added and then formatted in the following way: [birth interval search terms] AND [outcome search terms]. For example, papers retrieved from the search for IPI and maternal nutritional status (MNS) had at least one search term from the birth interval grouping and at least one term specified from the MNS search terms listed. Outcome search terms are outlined below (MeSH terms were used with PubMed only).

Infant outcomes

`Infant, Low Birth Weight'[MeSH] OR `Infant, Very Low Birth Weight'[MeSH] OR `Infant, Extremely Low Birth Weight'[MeSH] OR low birth weight* OR `premature birth'[MeSH] OR preterm deliver* OR preterm birth* OR `small for gestational age' OR intrauterine growth retardation OR `intrauterine growth restriction' OR `Infant Mortality'[MeSH] OR `fetal death' OR stillbirth OR `perinatal death' OR fetal mortalit* OR perinatal mortalit* OR `neonatal death' OR neonatal mortality OR infant mortality.

Maternal outcomes

Maternal mortality OR Gestational diabetes OR pregnancy-Induced hypertension OR eclampsia OR HELLP Syndrome OR pre-eclampsia OR Obstetric Labor Complications OR obstetric labor complication OR Abruptio Placentae OR Breech Presentation OR Cephalopelvic Disproportion OR Dystocia OR Premature Rupture Fetal membranes OR Premature obstetric labor OR Placenta Accreta OR Placenta Previa OR Postpartum Hemorrhage OR Uterine Inversion OR Uterine Rupture OR Vasa Previa OR Oligohydramnios OR Placental Diseases OR Placental Disease OR Abruptio Placentae OR Chorioamnionitis OR Retained Placenta OR Placental Insufficiency OR Polyhydramnios OR Cardiovascular Pregnancy Complications OR Cardiovascular Pregnancy Complication OR Amniotic Fluid Embolism OR Hematologic Pregnancy Complications OR Hematologic Pregnancy Complication OR Infectious Pregnancy Complications OR Infectious Pregnancy Complication OR septic abortion OR Parasitic Pregnancy Complications OR Puerperal Infection OR Prolonged pregnancy OR Puerperal Disorders OR Postpartum depression OR Lactation Disorders OR Mastitis OR Postpartum Hemorrhage OR Postpartum Thyroiditis OR Pubic Symphysis Diastasis.

Maternal nutritional status outcomes

`Maternal Nutritional Physiological Phenomena' [Mesh] OR `maternal nutrition' OR `maternal malnutrition' OR `maternal undernutrition' OR undernourished OR malnourished OR `weight gain' OR `prepregnancy weight' OR `nutritional status' OR `iron deficiency' OR `folate deficiency' OR folate insufficiency OR `folic acid deficiency' OR `folic acid insufficiency' OR maternal depletion OR maternal nutritional stores OR `calcium deficiency' OR `vitamin d deficiency' OR `zinc deficiency' OR `multiple micronutrient supplement' OR `vitamin deficiency' OR `catch-up growth' OR `anemia' OR `anemic' OR `hemoglobin'.

Appendix 2: Grouped Confounders

Race/ethnicity (Class)

(1 = race/ethnicity/Indig status/foreign born mother/caste/mother's country of origin)

SES (SES)

(2 = maternal education/literacy; 3 = marital status; 4 = SES; 34 = community dev't/ proportion non HS graduates/census tract income; 35 = log income; 36 = maternal

occupation/working status; 37 = insurance status; 38 = latrine ownership; 39 = electricity in home; 40 = cattle ownership; 50 = paternal education; 52 = paternal occupation; 53 = paternal acknowledgement on birth certificate; 54 = no housework help; 55 = mother's living arrangements; 56 = work during pregnancy; 57 = consanguinity; 75 = religion; 76 = household space (sq. ft.); 96 = social status of the couple at the birth of the index child 97 = change of social status between the two births).

Drug or alcohol use during pregnancy (Drug/alc use)

(5 = smoking during pregnancy; 6 = alcohol use during pregnancy; 44 = cocaine use).

Infant characteristics (Infant char)

(11 = sex of infant; 19 = plurality; 26 = Gestational Age/Preterm Birth; 27 = birth weight/ LBW; 28 = SGA; 29 = congenital anomalies; 30 = perinatal death; 101 = Premature rupture of the membranes).

Maternal body composition/nutritional indicators (Mat body comp)

(13 = maternal BMI; 14 = weight gain during pregnancy; 15 = triceps skinfold thickness; 16 = mid-arm circumference, 17 = maternal height; 47 = maternal pre-pregnancy weight; 41 = maternal night blindness during pregnancy; 58 = diabetes; 59 = hypertensive disease; 60 = ferrous use; 61 = maternal vitamin use; 81 = pre-pregnancy BMI; 86 = history of anemia in previous pregnancy; 87 = Hb level at booking; 89 = current pregnancy status; 93 = meat consumption; 98 = Maternal obesity; 99 = cardiopathy; 102 = Increased blood pressure during pregnancy; 103 = Infectious diseases during pregnancy; 104 = Hemorrhage during pregnancy; 105 = preeclampsia; 106 = eclampsia; 107 = abruptio placentae; 108 = Anemia; 109 = Gestational diabetes mellitus; 110 = Syphilis; 111 = Rhisoimmunization; 112 = Urinary tract infection; 116 = diethylstilbestrol exposure; 117 = cervical incompetence; 118 = uterine anomaly; 120 = Maternal hematocrit).

Quality of medical care (QoC)

(7 = prenatal care; 21 = level of hospital; 22 = private hospital; 23 = non-hospital birth; 71 = use of IPT for malaria during pregnancy; 72 = use of bednets; 73 = *P. falciparum* infection at delivery; 80 = Hospital Type; 82 = gestational age at first ANC visit; 83 = Number of prenatal care visits; 90 = onset of prenatal care; 92 = length of time between ANC visits; 94 = clinic payment status; 100 = Less than 5 prenatal visits/entering after 3 months; 114 = Antenatal care).

Pregnancy history/complications (Pg hx)

(10 = parity/gravidity/birth order; 12 = medical complications of pregnancy or delivery; 18 = IPI/recent live birth; 24 = history of previous miscarriage or abortion; 25 = had child who died; 31 = cervical dilation; 62 = number of previous live-born children who were still alive; 63 = number of previous live-born children who had died; 64 = preceding infant's birth weight; 65 = previous medical history; 66 = previous obstetric history; 67 = previous

preterm birth; 68 = history of low birth weight; 69 = outcome of previous pregnancy; 77 = number of previous deliveries; 78 = previous Caesarean delivery; 85 = previous pregnancy losses; 79 = number of weeks postpartum; 95 = hx of perinatal death; 113 = vaginal bleeding; 115 = planned pregnancy; 119 = Previous induced abortion; 121 = stillbirth and early neonatal death; 122 = history of chronic hypertension).

Parental age (Parental age)

(45 = paternal age; 46 = age difference of parents; 48 = chronologic age; 49 = age^2; 51 = maternal age, <18 years; 84 = age at first index pregnancy; 88 = gestational age at delivery; 91 = age of menarche).

Details/setting of delivery (Setting)

(8 = year of delivery; 9 = geographic area [state/county/country of birth]; 20 = delivery mode; 33 = city size/rural residence; 123 = calendar year)

Type of study/biases (Study/biases)

(32 = memory bias; 43 = type of study/treatment (in cohorts from cluster RCTs).

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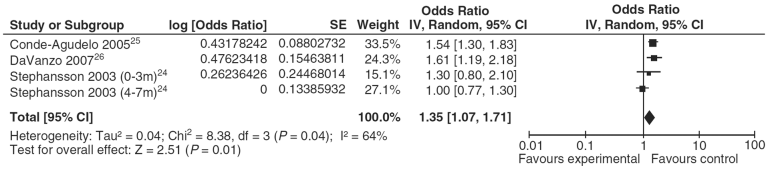

Figure 1.

Forest plot for inter-pregnancy intervals (IPIs) (<7 months) and stillbirth. Included studies are listed, along with the IPI of exposed and unexposed groups and stillbirth definition: Conde-Agudelo *et al*. 2005[25] (<6 vs. 18–23 months) (stillbirth: birth of a foetus at 20 weeks of gestation or later, which shows no sign of life); Da Vanzo *et al*. 2007[26] (IPI: <6 vs. 27–50 months) (stillbirth: foetal loss at 28 weeks or more since last menstrual period after a livebirth); Stephansson *et al*. 2003[24] (IPI: 0–3 vs. 12–35 months and 4–7 vs. 12–35 months) (stillbirth: foetal loss at 28 weeks or more since last menstrual period after a livebirth). IV, inverse variance; CI, confidence interval.

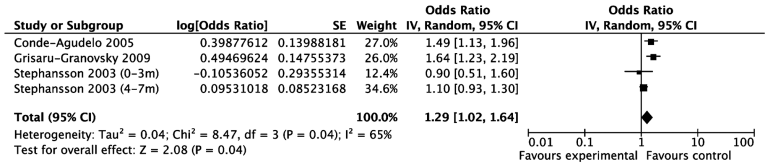

Figure 2.

Forest plot for inter-pregnancy intervals (IPIs) and early neonatal death. Included studies are listed, along with the IPI of exposed and unexposed groups and early neonatal death definition: Conde-Agudelo *et al*. 2005[25] (<6 vs. 18–23 months) (early neonatal death: death of a liveborn infant in the first week of life); Grisaru-Granovsky *et al*. 2009[27] (IPI: 0–5 vs. 12–23 months) (early neonatal death: death within 0–6 days after delivery); Stephansson *et al*. 2003[24] (IPI: 0–3 vs. 12–35 months and 4–7 vs. 12–35 months) (early neonatal death: death during the first week after delivery). IV, inverse variance; CI, confidence interval.

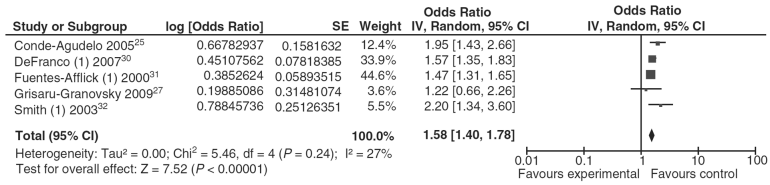

Figure 3.

Forest plot for inter-pregnancy intervals (IPIs) (<6 months) and extreme preterm birth. Included studies are listed, along with the IPI of exposed and unexposed groups and preterm birth (PTB) definition: Conde-Agudelo *et al*.[25] 2005 (<6 vs. 18–23 months) (PTB: <32 weeks); DeFranco *et al*. 2007[30] (<6 vs. >18 months) (PTB: 28–32 weeks); Fuentes-Afflick *et al*. 2000[31] (<6 vs. 18–59 months) (PTB: 23–32 weeks); Grisaru-Granovsky *et al*. 2009[27] (0–5 vs. 12–23 months) (PTB: <33 weeks); Smith *et al*. 2003[32] (1–5 vs. 18–23 months) (PTB: 24–32 weeks). IV, inverse variance; CI, confidence interval.

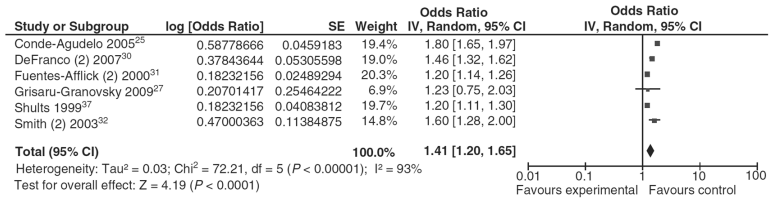

Figure 4.

Forest plot for inter-pregnancy interval (IPIs) (<6 months) and all or moderate preterm birth. Included studies are listed, along with the IPI of exposed and unexposed groups and preterm birth (PTB) definition: Conde-Agudelo *et al*. 2005[25] (<6 vs. 18–23 months) (PTB: < 37 weeks); DeFranco *et al*. 2007[30] (<6 vs. >18 months) (PTB: 32–35 weeks); Fuentes-Afflick *et al*. 2000[31] (<6 vs. 18–59 months) (PTB: 33–37 weeks); Grisaru-Grovsky *et al*. 2009[27] (0–5 vs. 12–23 months) (PTB: <37 weeks); Shults *et al*. 1999[37] (0–3 vs. 13–24 months) (PTB: <37 weeks); Smith *et al*. 2003[32] (1–5 vs. 18–23 months) (PTB: 33–35 weeks). IV, inverse variance; CI, confidence interval.

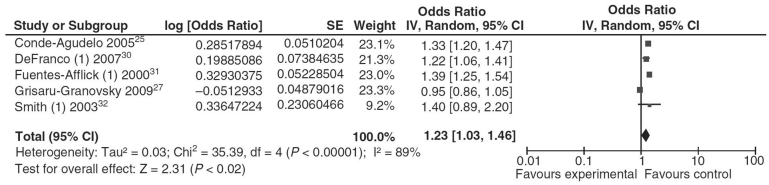

Figure 5.

Forest plot for inter-pregnancy interval (IPIs) (>6 months) and extreme preterm birth. Included studies are listed, along with the IPI of exposed and unexposed groups and preterm birth (PTB) definition: Conde-Agudelo *et al*. 2005[25] (6–11 vs. 18–23 months) (PTB: < 32 weeks); DeFranco *et al*. 2007[30] (6–12 vs. >18 months) (PTB: 28–32 weeks); Fuentes-Afflick *et al*. 2000[31] (6–11 vs. 18–59 months) (PTB: 23–32 weeks); Grisaru-Granovsky *et al*. 2009[27] (6–11 vs. 12–23 months) (PTB: <33 weeks); Smith *et al*. 2003[32] (6–11 vs. 18–23 months) (PTB: 24–32 weeks). IV, inverse variance; CI, confidence interval.

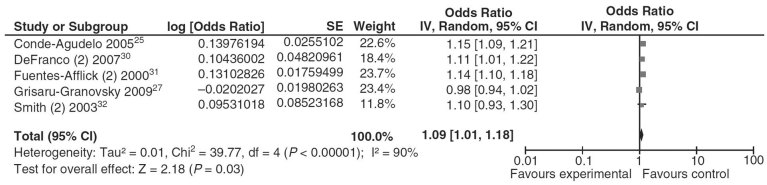

Figure 6.

Forest plot for inter-pregnancy interval (IPIs) (>6 months) and all or moderate preterm birth. Included studies are below, along with the IPI of exposed and unexposed groups and preterm birth (PTB) definition: Conde-Agudelo *et al*. 2005[25] (6–11 vs. 18–23 months) (PTB: < 37 weeks); DeFranco *et al*. 2007[30] (6–12 vs. >18 months) (PTB: 32–35 weeks); Fuentes-Afflick *et al*. 2000[31] (6–11 vs. 18–59 months) (PTB: 33–37 weeks); Grisaru-Granovsky *et al*. 2009[27] (6–11 vs. 12–23 months) (PTB: <37 weeks); Smith *et al*. 2003[32] (6–11 vs. 18–23 months) (PTB: 33–35 weeks). IV, inverse variance; CI, confidence interval.

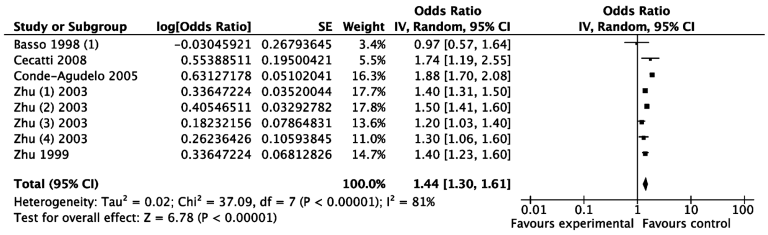

Figure 7.

Forest plot for inter-pregnancy interval (IPIs) (<6 months) and low birthweight. Included studies are listed, along with the IPI of exposed and unexposed groups: Basso *et al*. 1998[29] (<4 vs. 24–36 months); Cecatti *et al*. 2008[45] (<4 vs. 18–23 months); Conde-Agudelo *et al*. 2005[25] (<6 vs. 18–23 months); Zhu *et al*. 2003[39] (<6 vs. 18–23 months); Zhu *et al*. 1999[33] (0–5 vs. 18–23 months). Numbers in parentheses in Zhu *et al*. 2003[39] refer to the birth pair of focus: (1) first–second birth pair, (2) second–third birth pair, (3) third–fourth birth pair, (4) fourth–fifth pair. IV, inverse variance; CI, confidence interval.

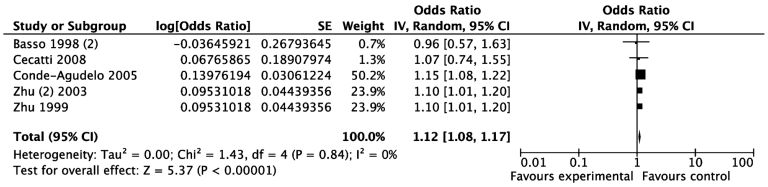

Figure 8.

Forest plot for inter-pregnancy interval (IPIs) (>6 months) and low birthweight. Included studies are listed, along with the IPI of exposed and unexposed groups: Basso *et al*. 1998[29] (8–12 vs. 24–36 months); Cecatti *et al*. 2008[45] (6–11 vs. 18–23 months); Conde-Agudelo *et al*. 2005[25] (6–11 vs. 18–23 months); Zhu *et al*. 2003[39] (6–11 vs. 18–23 months); Zhu *et al*. 1999[33] (6–11 vs. 18–23 months). IV, inverse variance; CI, confidence interval.

Table 1

Included studies of stillbirth and inter-pregnancy intervals (IPIs)

Source	Study type[a] Country	Exposed IPI (No.) *Unexposed IPI*	Stillbirth definition	Variables controlled[b]	Crude OR [95% CI]	Adjusted OR [95% CI]
Middle/low-income country						
Conde-Agudelo *et al*. 2005[25]	RC Multiple countries[c]	<6 months (34 888) *18–23 months*	Birth of a foetus at 20 weeks of gestation or later, which shows no sign of life	SES (2, 3), Mat body comp (59, 81), QoC (80, 82, 83), Pg hx (10, 69), Paternal age (51) Setting (8, 9)	3.41 [3.20, 3.64][d]	1.54 [1.28, 1.83]
		6–11 months (165 438)			1.47 [1.39, 1.55][d]	1.24 [1.14, 1.35]
Da Vanzo *et al*. 2007[26]	RC BD	<6 months (1640) *27–50 months*	Foetal loss at 28 weeks or more since last menstrual period after a livebirth	SES (2, 50, 75, 76), Pg hx (10, 115), Paternal age (51), Setting (8)	1.57 [1.17, 2.12]	1.61 [1.20, 2.18]
High-income country						
Stephansson *et al*. 2003[24]	RC SE	0–3 months (6835) *12–35 months*	Foetal loss at 28 weeks or more since last menstrual period after a livebirth	Race (1), SES (2), Drug/ale use (5), Mat body comp (58, 59), Pg hx (69), Parental age (51), Setting (8, 55)	1.82 [1.68, 2.06][d]	1.3 [0.8, 2.1]
		4–7 months (27 299)			1.49 [1.44, 1.54][d]	1.0 [0.7, 1.3]

UY, Uruguay; AR, Argentina; PE, Peru; CO, Colombia; HN, Honduras; PY, Paraguay; SV, EI Salvador; CL, Chile; BO, Bolivia; CR, Costa Rica; PA, Panama; DO, Dominican Republic; NI, Nicaragua; BR, Brazil; EC, Ecuador; MX, Mexico; BS, Bahamas; BZ, Belize; VE, Venezuela; BD, Bangladesh; SE, Sweden.

[a] RC, retrospective cohort.

[b] See Appendix 2 for confounder definitions.

[c] UY, AR, PL, CO, HN, PY, SV, CL, BO, CR, PA, DO, NI, BR, EC, MX, BS, BZ, VE.

[d] Calculated from the paper.

Table 2

Included studies of early neonatal death and inter-pregnancy intervals (IPIs)

Source	Study type[a] Country	Exposed IPI (No.) *Unexposed IPI*	Early neonatal death definition	Variables controlled[b]	Crude OR [95% CI]	Adjusted OR [95% CI]
Middle/low-income country						
Conde-Agudelo *et al*. 2005[25]	RC Multiple countries[c]	<6 months (34 888) *18–23 months* 6–11 months (165 438)	Death of a liveborn infant in the first week of life	SES (2, 3), Mat body comp (59, 81), QoC (80, 82, 83), Pg hx (10, 69), Paternal age (51) Setting (8, 9)	4.74 [4.35, 5.17][d] 1.54 [1.43, 1.67][d]	1.49 [1.06, 1.96] 1.27 [1.12, 1.44]
High-income country						
Grisaru-Granovsky *et al*. 2009[27]	RC IL	0–5 months (36 020) *12–23 months* 6–11 months (77 899)	Death within 0–6 days after delivery.	SES (2 3), Pg hx (10, 69), Parental age (51)	1.84 [1.3, 2.45][d] 1.23 [1.3, 2.45][d]	1.64 [1.22, 2.19] 1.22 [0.94, 1.58]
Stephansson *et al.* 2003[24]	RC SE	0–3 months (6 835) *12–35 months* 4–7 months (27 299)	Death during the first week after delivery	Race (1), SES (2), Drug/ale use (5), Mat body comp (58, 59), Pg hx (69), Parental age (51), Setting (8, 55)	1.8 [1.2, 2.8][d] 1.4 [1.1, 1.8][d]	0.9 [0.5, 1.6] 1.1 [0.8, 1.3]

UY, Uruguay; AR, Argentina; PE, Peru; CO, Colombia; HN, Honduras; PY, Paraguay; SV, EI Salvador; CL, Chile; BO, Bolivia; CR, Costa Rica; PA, Panama; DO, Dominican Republic; NI, Nicaragua; BR, Brazil; EC, Ecuador; MX, Mexico; BS, Bahamas; BZ, Belize; VE, Venezuela; IL, Israel; SE, Sweden.

[a] RC, retrospective cohort.

[b] See Appendix 2 for confounder definitions.

[c] UY, AR, PE, CO, HN, PY, SV, CL, BO, CR, PA, DO, NI, BR, EC, MX, BS, BZ, VE.

[d] Calculated from the paper.

Table 3

Included studies of preterm birth and inter-pregnancy intervals (IPSs)

Source	Study type[a] Country	Exposed IPI (No.) *Unexposed IPI*	Preterm Definition (weeks of gestation)	Variables controlled[b]	Crude OR [95% CI]	Adjusted OR [95% CI]
Middle/low-income country						
Al-Eissa *et al.* 1994[36]	CC SA	<12 months (236) ≥22 *months*	<37	SES (2, 54, 55, 57), Mat body comp (13), Pg hx (10, 65, 66), Parental age (51)	2.82 [1.48, 5.36]	2.22 [1.06, 4.65]
Arafa *et al.* 2004[28]	NCC EG	<12 months (103) >*60 months*	<37	Mat body comp (14, 108, 112), QoC (114), Pg hx (10, 24, 67, 113), Paternal age (51)	1.1 [0.4, 2.5]	1.2 [0.5, 3.1]
Conde-Agudelo *et al.* 2005[25]	RC Multiple countries[c]	<6 months (34 888) *28–23 months*	<37	SES (2, 3), Mat body comp (59, 81), QoC (80, 82, 83), Pg hx (10, 69), Paternal age (51), Setting (8, 9)	2.61 [2.53, 2.70][d]	1.80 [1.71, 1.89]
			<32		3.86 [3.62, 4.12][d]	1.95 [1.67, 2.26]
		6–11 months (165 438)	<37		1.15 [1.12, 1.18][d]	1.15 [1.10, 1.20]
			<32		6.97 [6.59, 7.38][d]	1.33 [1.24, 1.43]
Hsieh *et al.* 2002[35]	RC TW	<12 months (1640) >*12 months*	<37	SES (2, 3, 56), Mat body comp (13), Pg hx (65, 66), Parental age (51)	0.79 [0.37, 1.74][d]	1.3 [1.0, 1.7]
High-income country						
Basso *et al.* 1998[29]	RC DK	<4 months 24–36 *months*	<37	SES (96, 97), Pg hx (10), Parental age (51)	3.71 [2.14, 6.42]	3.60 [2.04, 6.35]
		4.01–8 months			2.32 [1.53, 3.52]	2.28 [1.49, 3.48]
		8.01–12 months (559: 0–8 months IPI)			1.16 [0.76, 1.78]	1.16 [0.75, 1.78]
DeFranco *et al.* 2007[30]	RC US	<6 months (15 200) >*18 months*	<35	Class (1), SES (37), QoC (7), Pg hx (67), Paternal age (70)	2.28 [2.12, 2.46]	1.48 [1.37, 1.61]
			32–35		2.11 [1.92, 2.31]	1.46 [1.32, 1.62]
			28–32		2.62 [2.28, 3.02]	1.57 [1.35, 1.83]
			20–28		2.55 [2.09, 3.10]	1.41 [1.13, 1.76]
		6–12 months (27 405)	<35		1.41 [1.31, 1.51]	1.14 [1.06, 1.23]
			32–35		1.32 [1.21, 1.44]	1.11 [1.01, 1.22]
			28–32		1.61 [1.41, 1.85]	1.22 [1.06, 1.41]
			20–28		1.45 [1.20, 1.76]	1.12 [0.91, 1.38]
Fuentes-Afflick and Hessol 2000[31]	CS US	<6 months (26 022) 28–59 *months*	33–37	Class (1), SES (2), Infant char (11), QoC (7), Pg hx (10, 69), Parental age (51), Setting (9)	1.31 [1.26, 1.34]	1.20 [1.15, 1.26]
			23–32		1.85 [1.65, 2.07]	1.47 [1.30, 1.65]
		6–11 months (41 454)	33–37		1.17 [1.13, 1.21]	1.14 [1.10, 1.18]
			23–32		1.53 [1.39, 1.69]	1.39 [1.25, 1.54]
Grisaru-Granovsky *et al.* 2009[27]	RC IL	0–5 months (36 020) *22–23 months*	<37	SES (2, 3), Pg hx (10, 69), Parental age (51)	1.32 [1.26, 1.39][d]	1.23 [1.17, 1.29]
			<33		0.97 [0.94, 1.02][d]	0.98 [0.93, 1.02]
		6–11 months (77 899)	<37		1.35 [1.21, 1.52][d]	1.22 [1.08, 1.37]

Source	Study type[a] / Country	Exposed IPI (No.) / *Unexposed IPI*	Preterm Definition (weeks of gestation)	Variables controlled[b]	Crude OR [95% CI]	Adjusted OR [95% CI]
			<33		0.96 [0.87, 1.06][d]	0.95 [0.86, 1.05]
Lang *et al*. 1990[34]	RC US	<3 months (72) *25–36 months*	<37	Class (1), SES (2, 3, 37), Drug/ale use (5), Infant char (29), Mat body comp (47, 58, 112,116, 117,118,120), QoC (7), Pg hx (10, 113, 115, 119), Paternal age (51)	3.3 [1.3, 8.3]	2.0 [0.7, 5.4]
		4–6 months (202)			1.9 [0.9, 4.0]	1.1 [0.5, 2.5]
		7–12 months (614)			1.7 [1.0, 3.0]	1.2 [0.7, 2.1]
Shults *et al*. 1999[37]	RC US	0–3 months (11 451) 23–24 *months*	<37	Class (1), SES (2, 3), QoC (7)	1.7 [1.6, 1.8]	1.2 [1.1, 1.3]
		4–12 months (10 668)			1.3 [1.2, 1.5]	1.1 [1.0, 1.2]
Smith *et al*. 2003[32]	RC SF	1–5 months (3282) *28–23 months*	24–32	SES (3, 4), Drug/ale use (5), Mat body comp (17), Pg hx (68, 78), Parental age (51)	3.1 [1.9, 4.9]	2.2 [1.4, 3.6]
			33–36		2.0 [1.6, 2.4]	1.6 [1.3, 2.0]
		6–11 months (8999)	24–32		1.6 [1.0, 2.4]	1.4 [0.9, 2.2]
			33–36		1.2 [1.0, 1.4]	1.1 [0.9, 1.3]
Zhu *et al*. 1999[33]	RC US	0–5 months (9311) *28–23 months*	<37	Class (1), SES (2, 3), Drug/ale use (5, 6), Mat body comp (14, 17, 47), QoC (83, 90), Pg hx (24, 62, 63, 69, 119), Paternal age (51), Setting (33)	Could not be calculated	1.4 [1.3, 1.5]
		6–11 months (23 700)			Could not be calculated	1.0 [0.9, 1.1]

SA, Saudi Arabia; EG, Egypt; UY, Uruguay; AR, Argentina; PE, Peru; CO, Colombia; HN, Honduras; PY, Paraguay; SV, EI Salvador; CL, Chile; BO, Bolivia; CR, Costa Rica; PA, Panama; DO, Dominican Republic; NI, Nicaragua; BR, Brazil; EC, Ecuador; MX, Mexico; BS, Bahamas; BZ, Belize; VE, Venezuela; TW, Taiwan; DK, Denmark; US, United States; IL, Israel; SF, Finland.

[a] NCC, nested case control; RC, retrospective cohort; CS, cross-sectional.

[b] See Appendix 2 for list of confounder definitions.

[c] UY, AR, PE, CO, HN, PY, SV, CL, BO, CR, PA, DO, NI, BR, EC, MX, BS, BZ, VE.

[d] Calculated from the paper.

Table 4

Included studies of low birthweight and inter-pregnancy intervals (IPIs)

Source	Study type[a] Country	Exposed IPI (No.) *Unexposed IPI*	Low birthweight definition (g)	Variables controlled[b]	Crude OR [95% CI]	Adjusted OR [95% CI]
Middle/low-income country						
Cecatti *et al.* 2008[45]	CS BR	<6 months (1038) *18–23 months*	<2500	SES (2,3), Drug/ale use (5), Infant char (26), Mat body comp (13), QoC (83), Pg hx (10, 78, 95, 122), Paternal age (51)	1.68 [1.29, 2.17]	1.74 [1.18, 2.55]
		6–11 months (1919)			1.13 [0.88, 1.44]	1.07 [0.74, 1.55]
Conde-Agudelo *et al.* 2005[25]	RC Multiple countries[C]	<6 months (34 888) 18–23 *months*	<2500	SES (2, 3), Mat body comp (59, 81), QoC (80, 82, 83), Pg hx (10, 69), Paternal age (51) Setting (8, 9)	2.44 [2.35, 2.53][d]	1.88 [1.78, 1.90]
			<1500		2.88 [2.66, 3.11][d]	2.01 [1.73, 2.31]
		6–11 months (165 438)	<2500		1.17 [1.14, 1.21][d]	1.15 [1.10, 1.21]
			<1500		6.89 [6.46, 7.34][d]	1.23 [1.12, 1.35]
Jafari *et al.* 2010[40]	PC IL	<12 months (199) ≥*12 months*	<2500	SES (2, 36, 50, 52), Infant char (26), Mat body comp (13, 14, 17, 59, 60, 61), QoC (7), Pg hx (10, 68), Parental age (51), Setting (9)	2.86 [1.83, 4.45]	3.26 [1.53, 6.93]
High-income country						
Basso *et al.* 1998[29]	RC DK	<4 months *24–36 months*	<2500	SES (96, 97), Infant char (26), Pg hx (10), Parental age (51)	3.0 [1.6, 5.73]	0.97 [0.41, 2.31]
		4.01–8 months			1.78 [1.08, 2.92]	0.86 [0.45, 1.64]
		8.01–12 months (559: 0–8 months IPI)			1.15 [0.72, 1.82]	0.97 [0.54, 1.73]
Zhu and Le 2003[39]	RC US	<6 months (52 712) *18–23 months*	<2500	Class (1), SES (2, 53), Drug/ale use (5, 6), QoC (7), Pg hx (64, 69), Paternal age (51)	2.20 [2.11, 2.32][d]	First-second birth pair: 1.4 [1.3, 1.5] Second-third birth pairs: 1.5 [1.3, 1.6] Third-fourth birth pairs: 1.2 [1.1, 1.4] Fourth-fifth birth pairs: 1.3 [1.1, 1.6]
		6–11 months (97 278)			1.29 [1.23, 1.35][d]	First-second birth pair: 1.1 [1.0, 1.1] Second-third birth pairs: 1.1 [1.0, 1.2] Third-fourth birth pairs: 1.0 [0.9, 1.2]

Source	Study type[a] Country	Exposed IPI (No.) *Unexposed IPI*	Low birthweight definition (g)	Variables controlled[b]	Crude OR [95% CI]	Adjusted OR [95% CI]
						Fourth-fifth birth pairs: 1.0 [0.9, 1.3]
Zhu *et al*. 1999[33]	RC US	0–5 months (9311) *18–23 months*	<2500	Class (1), SES (2, 3), Drug/ale use (5, 6), Mat body comp (14, 17, 47), QoC (83, 90), Pg hx (24, 62, 63, 69, 119), Paternal age (51), Setting (33)	2.14 [1.93, 2.37][d]	1.4 [1.3, 1.6]
		6–11 months (23 700)			1.31 [1.19, 1.43][d]	1.1 [1.0, 1.2]

BR, Brazil; UY, Uruguay; AR, Argentina; PE, Peru; CO, Colombia; HN, Honduras; PY, Paraguay; SV, EI Salvador; CL, Chile; BO, Bolivia; CR, Costa Rica; PA, Panama; DO, Dominican Republic; NI, Nicaragua; EC, Ecuador; MX, Mexico; BS, Bahamas; BZ, Belize; VE, Venezuela; IL, Israel; DK, Demark; US, United States.

[a] CS, cross-sectional; RC, retrospective cohort; PC, prospective cohort.

[b] See Appendix 2 for confounder definitions.

[C] UY, AR, PE, CO, HN, PY, SV, CL, BO, CR, PA, DO, NI, BR, EC, MX, BS, BZ, VE.

[d] Calculated from the paper.

Table 5

Included studies of maternal morbidities/mortality and inter-pregnancy intervals (IPIs)

Source	Study type[a] Country	Exposed IPI (No.) *Unexposed IPI*	Maternal morbidity definition	Variables controlled[b]	Crude OR [95% CI]	Adjusted OR [95% CI]
Middle/low-income country						
Cecatti *et al.* 2008[45]	CS BR	<6 m (1038) *18–23 m*	*Premature rupture of membranes:* rupture of the membranes before the onset of labour	SES (2, 3), Drug/alc use (5), Infant char (26), Mat body comp (13), QoC (83), Pg hx (10, 78, 85, 122), Parental age (51)	**<6 m:** 0.87 [0.67, 1.13]	**<6 m:** 0.98 [0.70, 1.37]
		6–11 m (1919)			**6–11 m:** 0.90 [0.72, 1.13]	**6–11 m:** 1.04 [0.78, 1.40]
			Hypertensive disorders: the diagnosis of diastolic blood pressure above 90 mmHg during pregnancy or post-partum period due to any cause		**<6 m:** 1.08 [0.80, 1.47]	**<6 m:** 1.36 [0.91, 2.04]
					6–11 m: 0.94 [0.72, 1.24]	**6–11 m:** 1.0 [0.69, 1.46]
			Haemorrhage: a peripartum abnormal vaginal bleeding registered in medical records		**<6 m:** 1.42 [0.87, 2.32]	**<6 m:** 1.01 [0.48, 2.14]
					6–11 m: 0.90 [0.56, 1.45]	**6–11 m:** 1.08 [0.57, 2.06]
			Maternal infection: any systemic infectious disease diagnosed during pregnancy and puerperium		**<6 m:** 1.12 [0.79, 1.60]	**<6 m:** 1.39 [0.89, 2.17]
					6–11 m: 1.00 [0.73, 1.37]	**6–11 m:** 1.08 [0.57, 2.06]
Conde-Agudelo *et al.* 2000[46]	RC Multi-country[c]	0–5 m (12 704) *18–23 m*	*Preeclampsia:* ICD-10 code O14	SES (2, 3), Drug/alc use (5), Mat body comp (59, 81), Pg hx (24, 77, 78, 113, 121), QoC (83, 90), Parental age (45), Setting (8, 9)	**0–5 m:** 1 [0.90, 1.11][d]	**0–5 m:** 1.00 [0.93, 1.07]
		6–11 m (63 415)			**6–11 m:** 0.94 [0.88, 1.0][d]	**6–11 m:** 0.98 [0.88, 1.08]
			Eclampsia: ICD-10 code O15		**0–5 m:** 1.08 [0.62, 1.89][d]	**0–5 m:** 1.12 [0.63, 2.29]
					6–11 m: 0.91 [0.64, 1.28][d]	**6–11 m:** 1.04 [0.68, 1.43]
			Third-trimester bleeding: included placenta previa with haemorrhage, ICD-10 code O44.1, and placental abruption, ICD-10 code O45		**0–5 m:** 1.74 [1.50, 2.02][d]	**0–5 m:** 1.73 [1.42, 2.24]
					6–11 m: 1.09 [0.98, 1.21][d]	**6–11 m:** 1.03

Source	Study type[a] Country	Exposed IPI (No.) *Unexposed IPI*	Maternal morbidity definition	Variables controlled[b]	Crude OR [95% CI]	Adjusted OR [95% CI]
						[0.91, 1.16]
			Premature rupture of membranes: ICD-10 code O42		**0–5 m:** 1.83 [1.71, 1.96][d]	**0–5 m:** 1.72 [1.53, 1.93]
					6–11 m: 1.06 [1.01, 1.11][d]	**6–11 m:** 1.04 [0.96, 1.12]
			Post-partum haemorrhage: ICD-10 code O72		**0–5 m:** 0.92 [0.85, 1.01][d]	**0–5 m:** 0.94 [0.76, 1.13]
					6–11 m: 1.02 [0.97, 1.07][d]	**6–11 m:** 0.96 [0.87, 1.06]
			Puerperal endometritis: ICD-10 code O85		**0–5 m:** 1.29 [1.18, 1.41][d]	**0–5 m:** 1.33 [1.22, 1.45]
					6–11 m: 1.05 [0.99, 1.11][d]	**6–11 m:** 1.04 [0.94, 1.14]
			Maternal death: the death of a woman while she was pregnant or within 42 days after delivery from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes		**0–5 m:** 2.55 [1.26, 5.16][d]	**0–5 m:** 2.54 [1.22, 5.38]
					6–11 m: 1.19 [0.68, 2.08][d]	**6–11 m:** 1.11 [0.53, 2.28]
Rahman *et al*. 2009[47]	RC BD	<12 m (9906) *24–59 m*	*Maternal mortality:* death of a woman during pregnancy or within 42 days of pregnancy outcome from any cause related to or aggravated by the pregnancy or its management, but not from accidently or incidental causes	SES (2, 76), Pg hx (10, 63, 85), Parental age (51), Setting (123)	OR = 1.17 [*P* > 0.05, no CI provided]	OR = 1.14 [*P* > 0.05, no CI provided]
Razzaque *et al*. 2005[48]	RC BD	<6 m (412) *27–50 m*	*Proteinuria* (laboratory test)	SES (2, 75, 76), Pg hx (10, 85), Paternal age (51)	1.14 [CI not calculable][d,e]	1.20 [*P* > 0.10, no CI provided]
			High blood pressure: diastolic of 90 mmHg or more, instrument based		2.0 [CI not calculable][d,e]	1.66 [*P* < 0.10, no CI provided]
			Bleeding (clinical definition)		1.83 [CI not calculable][d,e]	0.95 [*P* > 0.10, no CI provided]
			Premature rupture of membranes (clinical definition)		2.46 [CI not calculable][d,e]	1.94 [*P* > 0.10, no CI provided]
			Pre-eclampsia: the presence of any two of oedema, protein-uria		2.40 [CI not calculable][d,e]	2.19 [*P* < 0.05, no

Source	Study type[a] Country	Exposed IPI (No.) *Unexposed IPI*	Maternal morbidity definition	Variables controlled[b]	Crude OR [95% CI]	Adjusted OR [95% CI]
			or high blood pressure; no measurement specified			CI provided]
High-income country						
Stamilio *et al*. 2007	RC US	*Multivariable model:* 0–5 m (286) *18–59 m* 6–11 m (1109) *Crude model:* <6 m ≥*6 m*	*Uterine rupture:* uterine scar separation determined at laparotomy that was preceded by a non-reassuring foetal heart rate pattern, maternal signs or symptoms of acute blood loss, or haemoperitoneum (this definition excluded asymptomatic uterine dehiscence)	Class (1), SES (37), Drug/alc use (5), Infant char (26), Mat body comp (108), QoC (80), Pg hx (10, 78, 122, 123), Parental age (51)	**<6 m vs. ≥6 m:** 3.09 [1.53, 6.27][e]	**0–5 m:** 3.05 [1.36, 6.87] **6–11 m:** 1.18 [0.60, 2.33]
			Composite morbidity: uterine rupture; bladder, ureter or bowel injury; and uterine artery laceration (patients were categorised as having morbidity if they had one or more of the events)		**<6 m vs. ≥6 m:** 1.94 [1.10, 3.42][e]	**0–5 m:** 1.92 [1.01, 3.62] **6–11 m:** 0.93 [0.57, 1.52]

ICD-10, International Classification of Diseases, 10th Revision.

AR, Argentina; BR, Brazil; PE, Peru; CO, Colombia; HN, Honduras; PY, Paraguay; SV, EI Salvador; CL, Chile; BO, Bolivia; CR, Costa Rica; PA, Panama; DO, Dominican Republic; NI, Nicaragua; EC, Ecuador; MX, Mexico; BS, Bahamas; VE, Venezuela; BD, Bangladesh; UY, Uruguay; US, United States.

[a] CS, cross-sectional; RC, retrospective cohort.

[b] See Appendix 2 for confounder definitions.

[c] UY, AR, PE, CO, HN, PY, SV, CL, BO, CR, PA, DO, NI, BR, EC, MX, BS, VE.

[d] Calculated manually by the authors of the systematic review.

[e] Risk ratio.

Table 6

Included studies of maternal anaemia and inter-pregnancy intervals (IPIs)

Source	Study type[a] Country	Exposed IPI (No.) *Unexposed IPI*	Outcome definition	When outcomes was measured	Variables controlled[b]	Crude OR [95% CI]	Adjusted OR [95% CI]
Middle/low-income country							
Conde-Agudelo *et al*. 2000[46]	CS Multi-country[c]	0–5 m (12 704) *18–23 m* 6–11 m (63 415)	*Anaemia:* ICD-10 code O99.0	Data entered during antenatal visits	SES (2, 3), Drug/alc use (5), Mat body comp (81), QoC (80, 83, 90), Pg hx (24, 77, 78, 121), Paternal age (51), Setting (8, 9)	1.32 [1.30, 1.34][d] 1.07 [1.05, 1.09][d]	1.30 [1.18, 1.43] 1.03 [0.95, 1.12]
Razzaque *et al*. 2005[48]	RC BD	<6 m (412) *27–50 m*	*Anaemia:* clinical	The last antenatal care visit during the third trimester	SES (2, 75, 76), Pg hx (10, 85), Paternal age (51)	1.00 [CI not calculable][d,e]	1.03 [*P* > 0.10, no CI provided]
High-income country							
Singh *et al*. 1998[50]	CS SG	<3 m[f] 3–5 m[f] 6–11 m[f] 12–17 m[f] 18–23 m[f]	*Anaemia:* <11 g/dl	At delivery	Class (1), SES (4), Mat body comp (60, 86, 87), QoC (90), Pg hx (10), Paternal age (51)	<3 m 23.3%[f] 3–5 m 21.4%[f] 6–11 m 20.2%[f] 12–17 m 20.2%[f] 18–23 m 13.8%[f]	Found no significant associations between anaemia and mean birth interval

ICD-10, International Classification of Diseases, 10th Revision.

UY, Uruguay; AR, Argentina; PE, Peru; Co, Colombia; HN, Honduras; PY, Paraguay; SV, EI Salvador; CL, Chile; BO, Bolivia; CR, Costa Rica; PA, Panama; DO, Dominican Republic; NI, Nicaragua; BR, Brazil; EC, Ecuador; MX, Mexico; BS, Bahamas; VE, Venezuela; BD, Bangladesh; SG, Singapore.

[a] CS, cross-sectional; RC, retrospective cohort.

[b] See Appendix 2 for confounder definitions.

[c] UY, AR, PE, CO, HN, PY, SV, CL, BO, CR, PA, DO, NI, BR, EC, MX, BS, VE.

[d] Calculated from the paper.

[e] Risk ratio.

[f] Did not specify how many women were in each IPI group.

Table 7

Quality assessment of studies of inter-pregnancy interval (IPI) on pregnancy outcomes

Quality assessment				Directness	Summary of findings	
No. of studies	**Design**	**Limitations**	**Consistency**	**Generalisability to population of interest**	**No. exposed**	**Effect estimate**
Infant morbidity and mortality Stillbirth – Moderate						
Three	Retrospective cohort	Imprecision; not population based; misclassification bias	Moderate	Moderate (2/3 studies in low-income countries)	287 227	1.35 [1.07, 1.71]*
Early neonatal death – Moderate						
Three	Retrospective cohort	Imprecision; not population based; misclassification bias	Moderate	Low (1/3 studies included many low-income countries)	105 042	1.29 [1.02, 1.64]*
Preterm birth – Moderate						
Twelve	Retrospective cohort; nested case-control; cross-sectional	Misclassification bias; uncontrolled confounders; not population based	Moderate	Moderate (4/12 in middle-income countries)	493 565	N/A
Five (<6 months IPI and extreme preterm birth)	Retrospective cohort	Not population based	Moderate	Low (1/5 studies in middle/low-income countries)	115 412	1.58 [1.40, 1.78]****
Six (<6 months IPI and all or moderate preterm birth)	Retrospective cohort	Imprecision; not population based	Moderate	Low (1/6 studies in middle/low-income countries)	126 863	1.41 [1.20, 1.65]****
Five (>6 months IPI and extreme preterm birth)	Retrospective cohort	Not population based	Low	Low (1/5 studies in middle/low-income countries)	321195	1.23 [1.03, 1.46]*
Five (>6 months IPI and all or moderate preterm birth)	Retrospective cohort	Not population based	Low	Low (1/5 studies in middle/low-income countries)	321195	1.09 [1.01, 1.18]*
Low birthweight – Moderate						
Six	Case–control; descriptive prospective study; retrospective cohort	Misclassification bias; hospital-based; selection bias; not population based	Low	Moderate (3/6 in middle/low-income countries)	387 042	N/A
Five (<6 months IPI and <2500g)	Retrospective cohort	Selection bias; not population based; misclassification bias	Low	Moderate (2/5 in middle/low-income countries)	98 508	1.44 [1.30, 1.61]****
One (<6 months IPI and <1500g)	Retrospective cohort	Not population based	N/A	Moderate (1 study included many low-income countries)	34 888	N/A
Five (>6 months IPI and <2500g)	Retrospective cohort	Selection bias; not population based; misclassification bias	Low	Moderate (2/5 in middle/low-income countries)	288 894	1.12 [1.08, 1.17]****
One (>6 months IPI and <1500g)	Retrospective cohort	Not population based	N/A	Moderate (1 study included many low-income countries)	165 438	N/A
Maternal morbidity and mortality – Low						

Quality assessment				Directness	Summary of findings	
No. of studies	**Design**	**Limitations**	**Consistency**	**Generalisability to population of interest**	**No. exposed**	**Effect estimate**
Five	Retrospective cohort; cross-sectional	Possible misclassification of IPI; hospital-based; imprecision; recall bias	Low; N/A	High (8/9 studies in middle/low-income countries)	90 789	N/A
Maternal nutritional status Anaemia – Low						
Three	Cross-sectional; retrospective cohort	Different exposure group definitions; different times of measurement; different outcome definitions	Low	Moderate (2 in middle/low-income countries)	13 116[a]	N/A
Pre-pregnancy weight – Very Low						
One	Prospective cohort	Misclassification bias	N/A	Moderate (study in middle-income country)	N/A[a]	N/A

[a] Short birth interval group size not reported.

* $P < 0.05$,

** $P < 0.01$,

*** $P < 0.001$,

**** $P < 0.0001$.

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