Title: Risk of stillbirth, preterm delivery and fetal growth restriction following exposure in previous birth: systematic review and meta-analysis

Running title: The impact of previous adverse birth outcomes

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Abstract

Background: Little is known about the risk of non-recurrent adverse birth outcomes.

Objectives: To evaluate the risk of stillbirth, preterm birth (PTB), and small-for-gestational age (SGA) as a proxy for fetal growth restriction (FGR) following exposure to one or more of these factors in previous birth.

Search Strategy: We searched MEDLINE, EMBASE, Maternity and Infant Care, and Global Health from inception to 30 November 2016.

Selection Criteria: Studies were included if they investigated the association between stillbirth, PTB, or SGA (as proxy for FGR) in two subsequent births.

Data Collection and Analysis: Meta-analysis and pooled association presented as odds ratios (OR) and adjusted OR.

Main results: Of the 3,399 studies identified, 17 met the inclusion criteria. A PTB or SGA (as proxy for FGR) infant increased the risk of subsequent stillbirth (pooled OR 1.70; 95% CI 1.34-2.16) and (pooled OR 1.98; 95% CI 1.70-2.31), respectively. A combination of exposures, such as preterm SGA (as proxy for FGR) birth, doubled the risk of subsequent stillbirth (pooled OR 4.47; 95% CI 2.58-7.76). The risk of stillbirth also varied with prematurity increasing three-fold following PTB <34 weeks (pooled OR 2.98; 95% CI 2.05-4.34) and six-fold following preterm SGA (as proxy for FGR) <34 weeks (pooled OR 6.00; 95 CI 3.43-10.49). Previous stillbirth increased the risk of PTB (pooled OR 2.82; 95% CI 2.31-3.45), and subsequent SGA (as proxy for FGR) (pooled OR 1.39; 95% CI 1.10-1.76).

Conclusion: The risk of stillbirth, PTB, or SGA (as proxy for FGR) was moderately elevated in women who previously experienced a single exposure, but increased two-to-three-fold when two prior adverse outcomes were combined. Clinical guidelines should consider the interrelationship of stillbirth, PTB and SGA and that each condition is an independent risk factor for the other conditions.

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Keywords: stillbirth; preterm birth; growth restriction; systematic review; meta-analysis; pregnancy

Tweetable Abstract: Risk of adverse birth outcomes in next pregnancy increases with the combined number of previous adverse events.

Introduction

Stillbirth, preterm birth (PTB) and small-for-gestational age (SGA) (as proxy for fetal growth restriction (FGR)) continue to be major public health problems, despite improvements in healthcare. They are the leading cause of infant morbidity and mortality.[1-3] Globally, around 2.6 million infants are stillborn each year.[2] It is estimated that almost 15 million infants are born preterm[4] and at least 32 million infants SGA (as proxy for FGR).[5] Those who survive are at increased risk of long-term developmental and health complications.[6]

Recurrence of adverse birth outcomes (stillbirth, PTB and SGA (as proxy for FGR)) from one pregnancy to the next has been widely acknowledged.[7-10] A recent meta-analysis of 16 studies investigating recurrence of stillbirth reported a fourth-fold increase in the relative risk.[7] Women with PTB in the first birth have a 2.5 to 10.6-fold increased risk of recurrence,[11, 12] and the risk of recurrence is nearly 14 times greater for PTB <34 weeks of gestation.[13] Women who experienced SGA (and its proxy FGR) in the previous pregnancy have at least an eight-fold increased risk of recurrence.[8]

Traditionally, stillbirth, PTB, and SGA (as proxy for FGR) have been viewed as separate entities. However, they can be observed together and their aetiology can be partially attributed to common antecedents (i.e. placental insufficiency).[14, 15] SGA (as proxy for FGR) is a common cause of preventable stillbirth, accounting for up to 50%,[16, 17] and many preterm infants are growth-restricted.[18]

The association between these adverse birth outcomes implies that they might inform risk of non-recurrent adverse outcomes in subsequent pregnancies. However, relatively little attention has been directed to the investigation of potential adverse outcomes of subsequent pregnancy, apart from the risk of recurrence.[7] Hence, each of these adverse birth outcomes could be markers of predisposition to subsequent other adverse outcomes as well as to recurrence.[8, 10] Identifying at-risk pregnancies may provide an opportunity to target interventions to prevent adverse outcomes in multiparous pregnancies.

The aim of this study was to undertake a systematic review and meta-analysis of current evidence to determine the non-recurrent risk of stillbirth, PTB, and SGA (as proxy for FGR) following exposure to these birth outcomes in the previous pregnancy.

Methods

Search strategy

We conducted a systematic review and meta-analysis adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[19] We searched MEDLINE, EMBASE, Maternity and Infant Care, and Global Health through Ovid from inception to 30 November 2016, using consistent search terms (Appendix S1).

Eligibility criteria

Eligible studies included peer-reviewed articles that reported non-recurrent risk of adverse birth outcomes following exposure to one or more of these in the previous pregnancy. Adverse birth outcomes comprised stillbirth, commonly defined as fetal death from 20 weeks' gestation; PTB with birth <37 completed weeks of gestation; and SGA (as proxy for FGR) defined as infant birthweight for gestational age and sex below the 10th percentile. We used the term "non-recurrent risk" for cross-outcome measures, such as preterm birth in the first pregnancy and stillbirth in the next as opposed to "recurrent risk" for recurrence of each condition. Studies were restricted to singletons births with gestation >20 weeks. Two authors (EM, AR) independently screened the titles and abstracts of identified articles before performing a full-text review.

Quality assessment

The quality of the selected studies was independently assessed (EM and AR) using the Newcastle-Ottawa Quality Assessment Scale.[20] Cohort studies were assessed according to 1) selection (representative exposed and non-exposed cohorts, reliable ascertainment of exposure, and outcome was set at the start of the study); 2) comparability (accounted for risk factors); and 3) outcome (appropriate assessment, sufficient and adequate follow-up). Studies could score up to nine, being the highest quality.

Data extraction

For each study, data were extracted on sample size, study design, data source, location, study period, exposure, outcome measure of interest, adjustment or matching variables, effect size and variability of the effect (EM).

Statistical analysis

We estimated pooled effect sizes by applying random-effects meta-analysis with the inverse variance method, which accounts for both heterogeneity within and between studies and appropriately weights the estimates by the inverse of the standard error of the log odds ratio.[21, 22] We calculated pooled odds ratios (OR) from all studies that provided adjusted odds ratios or hazard ratios.[23] We estimated pooled effect sizes for unadjusted estimates (informative for risk assessment) as well as adjusted estimates (informative for causal assessment) to verify findings. The unadjusted effect sizes were calculated using the raw counts of births. Data were analysed in STATA, version 12.1 (College Station, Texas, USA).

Heterogeneity and publication bias. We reported the I^2 statistic as a measure of heterogeneity between studies.[24] We also conducted sensitivity analyses to investigate potential sources of heterogeneity in our data by restricting analyses to studies: 1) with ≥8 points on the Newcastle-Ottawa Quality Assessment; and 2) from high income settings. Egger's weighted regression test was used to assess publication bias.[25]

RESULTS

Study selection

We identified 960 MEDLINE, 1,683 EMBASE, 550 Infant Care, and 206 Global Health citations (Figure 1). After removal of duplicates, there were 1,891 citations, further exclusion of 1,752 citations based on the title and abstract left 139 articles for full-text review. Additionally, we searched reference lists of these 139 articles and conducted an internet search and identified three additional citations. Of those, 17 studies fulfilled the eligibility criteria (Table S1), while 125 studies were excluded (Table S2).

Study characteristics

The 17 studies included in the systematic review consisted of 14 retrospective and 3 prospective cohort studies (Table S1). Studies were published between 1994 and 2013, with combined data spanning 1967 to 2013. Three of the studies were from North America;[13, 26, 27] 8 from Europe;[28-35] 2 from Australia;[36, 37] 1 from Asia;[38] 1 from Latin America;[39] 1 from the Middle East;[40] and 1 from Africa, Asia and Latin America combined.[41]

Eleven studies investigated stillbirth from a range of gestational ages, including ≥20 weeks (n=8),[13, 26, 27, 29, 34, 36-38] ≥22 weeks (n=3),[30, 33, 41] or later (≥23 weeks, ≥24 weeks, or ≥28 weeks).[28, 31, 35, 40] One study did not describe the gestational week from which stillbirth was recorded.[32] Although PTB <37 weeks gestation was used by most studies (n=13),[13, 26-29, 31, 32, 35-39, 41] seven investigated PTB <34 weeks (n=2),[13, 29] <33 weeks (n=2),[27, 30] and <32 weeks gestation (n=3).[35, 36, 38] Five studies classified sub-groups of gestational age: moderate PTB (32-36 weeks, 33-36 weeks and 34-36 weeks);[26, 30, 33-35] very PTB (28-32 weeks and 29-33 weeks);[26, 33, 34] and extremely PTB (20-27 weeks, 20-28 weeks, and 22-27 weeks).[26, 33, 34] For the five studies that did not report odds ratios for PTB, we used the counts for sub-categories of PTB to estimate odds ratios.[26, 30, 33-35] Seven studies defined SGA (as proxy for FGR) <10th percentile,[26, 27, 31, 33, 37, 40, 41] while 3 others used birthweight 2 standard deviations (SD) below the mean.[32, 34, 35]

With the exception of two studies,[30, 40] all studies controlled for one or more covariates (Tables S3-S5), either by adjustment, clustering or matching, using a range of sociodemographic, pregnancy complications and other risk factors. The most commonly adjusted variables were maternal age, marital status and mother's level of education (among sociodemographic factors); gestational diabetes, pre-eclampsia and hypertensive diseases (among pregnancy complications); and inter-pregnancy interval, mother's smoking status, BMI, parity and year of subsequent delivery.

Effects of previous birth outcomes on risk of stillbirth

Results from individual studies, including frequency, unadjusted and adjusted odds ratios for previous adverse birth outcomes followed by stillbirth (Table S6), preterm stillbirth (Tables S7-S8), SGA (as proxy for FGR) stillbirth (Table S9), PTB (Tables S10-S14), preterm SGA (as proxy for FGR) birth (Table S15), or SGA (as proxy for FGR) birth (Table S16), in subsequent pregnancy are presented in the supplementary material.

In the unadjusted analysis, the pooled odds ratio of stillbirth following PTB was 1.70 (95% CI 1.34-2.16). The association varied by prematurity (Table 1), with the pooled odd ratio of stillbirth following moderate PTB 1.39 (95% CI 1.08-1.79), following PTB <34 weeks, 2.98 (95% CI 2.05-4.34), and following extreme PTB 2.85 (95% CI 0.77-10.48) (Table 1). The pooled odds ratio of stillbirth after SGA (as proxy for FGR) birth was 1.98 (95% CI 1.70-2.31). The association was stronger for more severe SGA (as proxy for FGR) birth <2SD (OR 2.55; 95% CI 2.05-3.17) and weaker for SGA (as proxy for FGR) birth <10^{th} percentile (pooled OR 1.83; 95% CI 1.63-2.06). The odds of stillbirth doubled if the previous SGA (as proxy for FGR) birth was also preterm (pooled OR 4.47; 95% CI 2.58-7.76), or moderate preterm (OR 3.99; 95% CI 2.53-6.30), and six times higher for SGA (as proxy for FGR) birth <34 weeks (pooled OR 6.00; 95% CI 3.43-10.49) (Table 1). The odds of stillbirth were greater if the previous preterm SGA (as proxy for FGR) birth was more severe <2SD (OR 5.08; 95%

CI 3.58-7.20) than if the previous preterm SGA (as proxy for FGR) birth was <10th percentile (pooled OR 4.28; 95% CI 1.85-9.90). The odds of stillbirth were also greater for previous preterm SGA (as proxy for FGR) <34 weeks and <2SD (OR 8.05; 95% CI 4.72-13.71) than for previous preterm SGA (as proxy for FGR) <34 weeks and <10th percentile (OR 4.55; 95% CI 2.77-7.48). The unadjusted pooled odds ratio of preterm stillbirth after previous PTB was 2.70 (95% CI 2.41-3.03), and the pooled odds more than doubled for PTB <34 weeks (OR 4.94; 95% CI 4.06-6.01) (data not shown). Similarly, the unadjusted odds for SGA (as proxy for FGR) stillbirth after PTB was 2.91 (95% CI 2.05-4.13), and the effect increased nine-fold after PTB <34 weeks (OR 8.90; 95% CI 5.08-15.62) (Table S9). Previous SGA (as proxy for FGR) birth resulted in greater effect with the odds of SGA (as proxy for FGR) stillbirth 12.63 (95% CI 7.67-20.79), and this odds doubled following SGA (as proxy for FGR) birth <34 weeks (OR 24.95; 95% CI 12.73-48.91) (Table S9).

Effects of previous birth outcomes on risk of preterm birth

In the unadjusted analysis, the pooled odds of PTB after stillbirth was OR 2.82 (95% CI 2.31-3.45), and the effect varied with the extent of prematurity from pooled OR 2.42 (95% CI 1.80-3.45) for risk of moderate PTB to OR 9.88 (95% CI 6.29-15.50) for risk of extreme PTB (Table 2). In unadjusted analysis, the odds ratio of PTB after SGA (as proxy for FGR) birth was 2.7 (95% CI 2.0-3.7) (Table S10).

Effects of previous birth outcomes on risk of SGA (as proxy for FGR)

The pooled unadjusted odds ratio of SGA (as proxy for FGR) birth alone after PTB was 1.66 (95% CI 1.53-1.81), and this effect moderately varied with the extent of prematurity from OR 1.60 (95% CI 1.46-1.75) after moderate PTB to OR 2.14 (95% CI 1.41-3.26) after extreme PTB (Table S16). The pooled odds ratio of SGA (as proxy for FGR) after stillbirth was 1.39 (95% CI: 1.10-1.76), and the effect slightly increased for the odds of preterm SGA (as proxy for FGR) birth OR 1.74 (95% CI 1.14-2.65) (Table 2).

Adjusted analyses

Effects on risk of stillbirth were only slightly attenuated and largely consistent with unadjusted analyses. The pooled adjusted odds ratios of stillbirth were 2.05 (95% CI 1.18-3.55) after PTB, 1.85 (95% CI 1.42-2.40) after SGA (as proxy for FGR), and 4.51 (95% CI 2.94-6.91) after preterm SGA (as proxy for FGR) < 34 weeks (Table 1).

Effects of previous stillbirth on risk of adverse pregnancy outcomes were generally attenuated yet largely consistent after adjustment. The adjusted effects of previous stillbirth were pooled OR 2.27 (95% CI 1.90-2.72) for the risk of PTB, pooled OR 1.90 (95% CI 1.16-3.10) for the risk of moderate PTB, and OR 4.20 (95% CI 1.78-9.90) for the risk of extreme PTB (Table 2). The odds of SGA (as proxy for FGR) was also similar after adjustment.

Heterogeneity and publication bias

The I^2 statistics varied from 0% to 88% for unadjusted, and 0% to 72% for adjusted pooled estimates (Tables 1 and 2). Heterogeneity attenuated slightly after adjustment for the odds of stillbirth after PTB or SGA (as proxy for FGR), but remained moderate (≥70%) (Table 1). Heterogeneity for the odds of PTB after stillbirth was sensitive to inclusion of specific studies; dropping one study (Study ID=1) increased the heterogeneity from 0% to 48% for the unadjusted pooled odds ratio of PTB after stillbirth.

Evaluation of Egger's regression intercepts demonstrated that there was insufficient statistical evidence of publication bias for studies investigating the risk of stillbirth after PTB (n=6) [Egger's regression intercept: -1.32 (95% CI -6.25-3.61), p-value=0.499] and the risk of PTB after stillbirth (n=6) [Egger's regression intercept: -2.70 (95% CI -7.64-2.23), p-value=0.203].

Quality and sensitivity analyses

Of the 17 studies included, quality ranged from 5 to 9 (median: 9). Fourteen out of 17 (82%) studies were fit for the purpose of our study, with quality scores of ≥8 (Table S1). A sensitivity analysis of the 14 studies that scored ≥8 showed little change in the risk estimates as did a sensitivity analysis of 13 studies from high income settings (USA, Finland, Denmark, Norway, Sweden, Scotland, Italy, Australia, and Israel) (results not shown).

Discussion

Main findings

We found consistent evidence for a moderate increase in the likelihood of stillbirth, PTB or SGA (as proxy for FGR) in women who previously experienced a single adverse birth outcome, which doubled with increasing severity of the exposure, and increased two-to-three-fold in some cases when two exposures were combined. Although recurrence of stillbirth, PTB and SGA (as proxy for FGR) is widely acknowledged,[7-10] cross-outcome risks between successive pregnancies are much less well-understood. To our knowledge, this is the first study to synthesise the current body of knowledge on risk of stillbirth, PTB and SGA (as proxy for FGR) to ascertain the effect of *exposure* to these in the previous pregnancy.

Strengths and Limitations

A major strength of this review was that we employed a comprehensive, well-described and replicable search strategy. Two independent reviewers examined the titles and abstract and conducted full-text review. The studies included large populations of women from high to low income countries and from diverse settings. We were able to evaluate the effect of multiple exposures and outcomes. Additional to unadjusted pooled estimates, we also calculated pooled adjusted effect sizes and confirmed that the effects were largely consistent before and after adjustment. We also performed two sets of sensitivity analyses, within higher quality studies or high income countries and both made little change to the

pooled effect sizes, thus confirming the robustness of our findings. There was insufficient statistical evidence of publication bias of the reviewed studies based on Egger's test.

We were able to calculate heterogeneity in only a few instances, as estimating heterogeneity for fewer than three studies is not meaningful. Since the observed heterogeneity in the pooled estimates between studies ranged from none (for stillbirth as an exposure) to substantial, the findings need to be interpreted with caution. Only 17 studies were included in this review, thus demonstrating a lack of research investigating adverse birth outcomes followed by non-recurrent adverse outcomes in the next pregnancy. Most studies investigated the risk of stillbirth after PTB or the risk of PTB after stillbirth, with only few studies focusing on the relative risk of SGA (as proxy for FGR), and fewer still on investigating the interaction between different adverse pregnancy outcomes. There were minor differences in the definition of stillbirth, PTB categories, which may have either overestimated or underestimated the relative risk. Of the few studies investigating SGA (as proxy for FGR), most used the standard definition of $<10^{th}$ percentile.[3,8,9,11,13,14,17] There were not enough studies using a more severe cut-off point of SGA (as proxy for FGR) <2SD to be included separately in any of the pooled analyses. However, for comparison, we have reported odds separately for the two cut-off points in addition to their combined odds. SGA is only a proxy for FGR. Ten studies did not differentiate between spontaneous and medically indicated PTB,[4-6,9-11,13,14,16,17] with only three studies focussing on spontaneous PTB,[3,12,15] and one study on medically indicated PTB,[1] while another one on preeclampsia-related PTB.[2] One study reported odds of PTB following stillbirth for all PTB and then separately for spontaneous PTB, with slightly higher odds for spontaneous PTB.[36] Another limitation was that the cause of stillbirth was unknown for most studies, and no study stratified the risk by the cause of stillbirth. Stillbirth is the end point of multiple processes, including placental dysfunction. There are a number of stillbirth classification schemes in use that assign cause of death and/or factors contributing to stillbirth.[41-43] Common causes or factors associated with stillbirth include congenital malformations, infection, hypoxia, fetal growth disorders and PTB, and by identifying the cause of stillbirth, targeting interventions could be applied.[45]

Interpretation

Our finding that women who experienced PTB or SGA (as proxy for FGR) have at least a 1.7-fold increased risk of subsequent stillbirth suggests that adverse (non-recurrent) birth outcomes are equally (if not more) important risk factors for stillbirth as other behavioural or demographic factors, such as smoking during pregnancy (pooled OR 1.47), primaparity (pooled adjusted OR 1.42),[46] advanced maternal age (>35 years) (pooled adjusted OR 1.65) or maternal obesity (BMI >30kg/m^2 pooled adjusted OR 1.63).[46] The effect increased by prematurity with previous PTB <34 weeks associated with a three-fold greater risk of stillbirth. This risk is comparable to the risk of stillbirth associated with mother's medical conditions, such as pre-existing hypertension (adjusted OR 2.58) or pre-existing diabetes (adjusted OR 2.90),[46] and may have been attributable to some of these conditions. Similarly, the effect of SGA (as proxy for FGR) increased with severity and was greater for a cut-off point of 2 SD than for the 10th percentile.

A more pronounced four-fold increase in the risk of stillbirth was observed when previous adverse birth outcomes were combined, which is comparable to the risk reported for recurrent stillbirth (OR 4.77 or 3.38 after adjustment).[7] However, the risk of stillbirth was higher still when the combination of adverse birth outcomes involved increased prematurity. SGA (as proxy for FGR) birth <34 weeks was one of the strongest risk factors for stillbirth (pooled OR 6.00 or 4.51 after adjustment) or SGA (as proxy for FGR) birth <34 weeks which was more severe <2SD (OR 8.05 or 5.00 after adjustment). However, the greatest risk observed was the effect of combined preterm SGA (as proxy for FGR) birth on SGA (as proxy for FGR) stillbirth which increased the odds by 15, this was, however, based on a single study of more than 400,000 women.[35] Thus, confirmation is required. Nevertheless, these results highlight that the likelihood of adverse birth outcomes following a previous event is strong and that these are not random events and are at increased-risk, and require routine monitoring in subsequent pregnancies.

Stillbirth as an exposure in the previous pregnancy was associated with a nearly three-fold increase in the odds of PTB and ten-fold risk for extremely PTB. However, this was based on just a single study and more research is needed to confirm.[26] Similarly, only one study considered SGA (as proxy for FGR) as an exposure for subsequent PTB, and findings were similar to previous exposure to stillbirth.[32]

Exposure to stillbirth in the previous pregnancy led to a modest increased in the odds of SGA (as proxy for FGR), which stands in stark contrast of the six-fold increase reported by the Royal College of Obstetricians and Gynaecologists (RCOG) clinical guideline no.31 (accessed 28 February 2017).[47] This guideline references an Australian case-control study of infants born to women in a socio-economically disadvantaged region, with no indication of the number of stillbirths or whether stillbirths referred to previous pregnancy or any prior history of stillbirth.[48] More research is required to provide conclusive evidence regarding the risk of SGA (as proxy for FGR) after previous stillbirth, as the three studies that were included in our review reported odds ranging from 1.00 to 1.51, all considerably less than that cited in the RCOG guideline.[47]

Our results highlight the importance of identifying the underlying pathophysiology that may be driving the increased risk of adverse birth outcomes, particularly as congenital anomalies, maternal conditions such as preeclampsia and potential placental dysfunction are some of the leading causes of stillbirth and are also strongly associated with PTB and SGA (as proxy for FGR).[14,15] Targeted interventions to mitigate this underlying mechanism in multiparous pregnancies could significantly improve perinatal health.

Most of the increases in the odds of adverse birth outcomes we identified were greater than OR 2.0. An OR of 2 is used by the RCOG to identify women at risk of SGA (as proxy for FGR), who require extra monitoring with serial ultrasound and assessment with umbilical artery Doppler from 26-28 weeks.[47] Identifying women at high risk of adverse birth outcomes may enable interventions to reduce the risk

in subsequent births.[49] This may include aspirin to reduce the risk of preeclampsia, SGA (as proxy for FGR), PTB and stillbirth.[50] In addition, cervical ultrasound surveillance to predict PTB may enable intervention with progesterone or cerclage,[51] or ultrasound surveillance of fetal growth to detect SGA (as proxy for FGR) and enable intervention by planned birth.[47] Induction of labour, which has also been shown to be associated with a reduction in perinatal deaths compared to conservative management post-dates may also be considered,[52] especially where the background risk of stillbirth is high.[45]

Conclusions

Stillbirth, PTB and SGA (as proxy for FGR) are strongly interrelated and each condition predisposes to the other outcomes in the next pregnancy. It is important for health providers to be aware of the risk involved for women with a history of adverse birth outcomes and to offer appropriate antenatal care.

Disclosure of interests

None declared.

Contribution to authorship

EM had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. GP conceived the idea of the systematic review. EM and AR developed the search strategy. EM was responsible for data collection, data extraction and analysis of the data. EM and AR carried out independent reviews of abstract and full-text articles and quality assessments. AR, NN and GP contributed to the interpretation of the data. EM developed the first draft of the manuscript, and AR, NN, CRG, HL, RS, AS, TL, and GP critically revised the manuscript for important intellectual content. All authors approved the final version.

Details of ethical approval

Not applicable.

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Supporting Information

Additional Supporting Information can be found in the online version of this article:

Appendix S1. The search strategy.

Table S1. Characteristics of included studies.

Table S2. List of excluded studies.

Table S3. Socio-demographic variables controlled by adjustment, matching or restriction for each of the reviewed studies by study number.

Table S4. Pregnancy complications controlled by adjustment, matching or restriction for each of the reviewed studies by study number.

Table S5. Risk factors controlled by adjustment, matching or restriction for each of the reviewed studies by study number.

Table S6. Previous adverse pregnancy outcomes followed by stillbirth.

Table S7. Previous adverse pregnancy outcomes followed by preterm stillbirth.

Table S8. Previous adverse pregnancy outcomes followed by extreme preterm stillbirth.

Table S9. Previous adverse pregnancy outcomes followed by SGA stillbirth.

Table S10. Previous adverse pregnancy outcomes followed by PTB.

Table S11. Previous adverse pregnancy outcomes followed by moderate PTB.

Table S12. Previous adverse pregnancy outcomes followed by PTB (<34 weeks).

Table S13. Previous adverse pregnancy outcomes followed by very PTB.

Table S14. Previous adverse pregnancy outcomes followed by extreme PTB.

Table S15. Previous adverse pregnancy outcomes followed by preterm SGA birth.

Table S16. Previous adverse pregnancy outcomes followed by SGA birth.

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Figure 1: Flowchart of study selection.

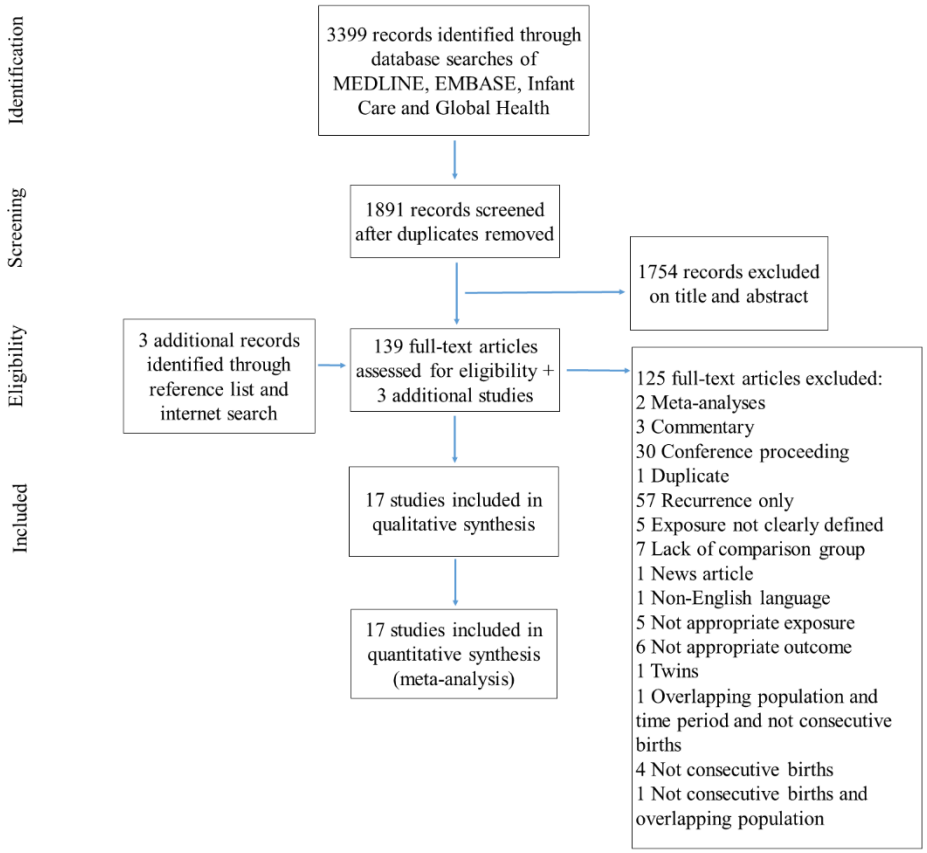

Table 1: Pooled effects of adverse birth outcomes (exposure) on subsequent risk of stillbirth.

Adverse birth outcomes (Exposure)**	Study ID*	Number of stillbirths with		Unadjusted OR (95% CI)	I^2	Adjusted OR (95% CI)	I^2
		Previous exposure	No previous exposure				
PTB	[10, 11, 13-16]	545/83,560	5,893/1,570,004	1.70 (1.34-2.16)	78.3%	2.05 (1.18-3.55)	70.7%
Moderate PTB	[13, 15, 16]	344/62,621	5,181/1,389,644	1.39 (1.08-1.79)	75.7%	1.10 (0.84-1.46)	-
PTB <34 weeks	[13, 15, 16]	131/10,421	5,181/1,389,644	2.98 (2.05-4.34)	63.6%	-	-
Very PTB	[13, 15]	73/5,867	4,233/1,007,447	2.46(1.50-4.06)	-	1.62 (0.73-3.61)	-
Extreme PTB	[13, 15]	32/1,807	4,233/1,007,447	2.85 (0.77-10.48)	-	0.64 (0.09-4.54)	-
SGA (10^{th} percentile + <2 SD)	[11, 13, 14, 16, 17]	987/129,244	5,795/1,473,438	1.98 (1.70-2.31)	71.9%	1.85 (1.42-2.40)	72.4%
SGA (10^{th} percentile)	[11, 13, 14, 17]	898/111,862	4,840/1,081,757	1.83 (1.63-2.06)	45.4%	1.85 (1.42-2.40)	72.4%
SGA (<2 SD)	[16]	89/14,382	955/391,681	2.55 (2.05-3.17)	-	-	-
PTB SGA (10^{th} percentile + 2< SD)	[13, 14, 16, 17]	152/8,851	5,098/1,300,332	4.47 (2.58-7.76)	88.0%	3.15 (1.89-5.25)	-
PTB SGA (10^{th} percentile)	[13, 14, 17]	119/6,125	4,206/929,791	4.28 (1.85-9.90)	92.0%	3.15 (1.89-5.25)	-
PTB SGA (<2 SD)	[16]	33/2,726	892/370,541	5.08 (3.58-7.20)	-	-	-
Moderate SGA PTB	[16]	19/1,991	892/370,541	3.99 (2.53-6.30)	-	3.40 (2.06-5.60)	-
PTB SGA (10^{th} percentile + 2< SD) <34 weeks	[16, 17]	30/1,551	2,461/729,007	6.00 (3.43-10.49)	-	4.51 (2.94-6.91)	-
PTB SGA (10^{th} percentile) <34 weeks	[17]	16/816	1,569/358,466	4.55 (2.77-7.48)	-	4.20 (2.42-7.30)	-
PTB SGA (<2SD) <34 weeks	[16]	14/735	892/370,541	8.05 (4.72-13.71)	-	5.00 (2.55-9.80)	-

*Studies included only in unadjusted analyses: PTB [13, 15, 16], Moderate PTB [13, 16], PTB< 34 weeks [13, 15, 16], Very PTB [13], Extreme PTB [13], SGA [13, 16], Preterm SGA birth [13, 16].

**OR: Odds ratio; CI: Confidence interval; PTB: Preterm birth; SGA: Small-for-gestational age; SD: Standard deviation.

Table 2: Pooled effects of stillbirth in the previous pregnancy on risk of adverse pregnancy outcomes.

Adverse birth outcome (Outcome)**	Study ID*	Number of adverse birth outcomes with		Unadjusted OR (95% CI)	I^2	Adjusted OR (95% CI)	I^2
		Previous stillbirth	No previous stillbirth				
PTB***	[1-7]	278/1,615	10,737/152,605	2.82 (2.31-3.45)	47.8%	2.27 (1.90-2.72)	0.0%
Moderate PTB	[3, 6]	73/642	5,354/103,510	2.42 (1.80-3.26)	-	1.90 (1.16-3.10)	-
PTB <34 weeks***	[1, 3-7]	78/1,523	3,221/140,787	2.64 (1.17-5.95)	86.4%	4.32 (2.33-8.02)	-
Very PTB	[3]	25/373	1,064/70,942	4.72 (3.13-7.11)	-	3.20 (1.47-6.97)	-
Extreme PTB	[3]	21/373	426/70,942	9.88 (6.29-15.50)	-	4.20 (1.78-9.90)	-
SGA	[2, 3, 8]	133/1,334	6,456/69,837	1.39 (1.10-1.76)	0.0%	1.31 (0.97-1.77)	-
Preterm SGA birth	[9]	23/1,211	630/57,273	1.74 (1.14-2.65)	-	1.38 (0.89-2.15)	-

*Study included only in unadjusted analyses: PTB [6], Moderate PTB [6], PTB <34 weeks [3-7], SGA [8].

**OR: Odds ratio; CI: Confidence interval; PTB: Preterm birth; SGA: Small-for-gestational age.

***Study included only in adjusted analyses: PTB [1], PTB <34 weeks [1].