TITLE

Clinical Risk Factors Associated with Late-Onset Invasive Group B Streptococcal Disease: Systematic Review and Meta-analyses

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SUMMARY

We conducted systematic reviews and meta-analyses on clinical risk factors for late-onset invasive Group B streptococcal disease and found that prematurity/low birth weight and antenatal maternal colonization are major risk factors.

ABSTRACT

Background

Group B streptococcal (GBS) infection remains one of the most significant causes of late-onset sepsis and meningitis (LOGBS) among young infants. However, transmission routes and risk factors for LOGBS are not yet fully understood.

Methods

We conducted systematic reviews on clinical risk factors previously reported in the literature (prematurity, low birth weight [<2500 g], antenatal colonization, multiple-gestation pregnancy, maternal age <20 years, male infant sex, intrapartum fever, prolonged rupture of membranes) and meta-analyses to determine pooled estimates of risk.

Results

We included 27 articles, reporting 5315 cases. Prematurity (odds ratio 5.66; 95% confidence interval [4.43-7.22]), low birth weight (6.73; [4.68-9.67]), maternal colonization (2.67; [2.07-3.45]), and multiple-gestation pregnancies (8.01; [5.19-12.38]) were associated with an increased risk of LOGBS.

Conclusions

Prematurity/low birth weight and maternal colonization are major risk factors for LOGBS. Future GBS vaccine studies should try to establish the optimal time for vaccination during pregnancy to protect preterm infants.

KEYWORDS

Group B *Streptococcus*; *Streptococcus agalactiae*; risk; neonatal sepsis

INTRODUCTION

Group B streptococcus (GBS) is the leading cause of sepsis and meningitis in neonates and young infants in most countries [1].In 2015, it was estimated that there were at least 319,000 infants <90 days of age with invasive GBS disease (iGBS disease) worldwide, of whom 205,000 infants had early-onset Group B streptococcal disease (EOGBS, occurring in infants aged <7 days) and 114,000 late-onset Group B streptococcal disease (LOGBS, occurring in infants aged 7-89 days) [1]. A high proportion of LOGBS cases presents with meningitis that often results in neurodevelopmental impairment, further increasing the burden of iGBS disease [2,3]. Despite intrapartum antibiotic prophylaxis (IAP) the incidence of LOGBS has not been reduced [2,4], and is even rising in some countries [5–8]. Maternal GBS vaccination could be an effective method to prevent EOGBS and LOGBS [1]. However, compared to EOGBS, risk factors for LOGBS are less well understood and have not been systematically reviewed. Addressing this gap could help identify vaccine targetable risk factors and recognize the most vulnerable infants to inform GBS vaccine research priorities and policy decisions.

This study aimed to provide a comprehensive and systematic literature review and meta-analyses to assess the association between LOGBS and previously reported clinical and epidemiological risk factors.

METHODS

Search strategy

The review protocol was registered with the PROSPERO database (Registration number: CRD42021253749). We searched Medline, Embase and Cochrane Library databases for

studies published until 1st December 2020 with no language restrictions (full search available in Table S1). We identified additional studies by searching the reference lists of included studies and reviews.

Study selection and data collection

We included observational studies that reported risk factors for iGBS disease (case-control studies, retrospective and prospective cohort studies). The cohort studies were surveillance studies conducted to estimate the national or regional incidence of iGBS disease. Case reports, case series and reviews were excluded. We included all previously reported clinical risk factors for LOGBS and EOGBS [9]. We included studies that reported LOGBS cases (7-89 days of age at the onset of infection episode) and excluded studies with a non-representative sample (e.g., studies containing only very high-risk groups like preterm infants) or a non-appropriate comparison group (no denominator data for risk factors). We included only cases with GBS isolated from a normally sterile site (blood, CSF, joint fluid, peritoneal fluid). The most comprehensive report was included if more than one study was published on the same patients.

Two review authors (KK, HD) independently scanned the abstract, title, or both, of every record retrieved to determine which studies should be assessed further. We investigated all potentially relevant articles as full text and resolved any discrepancies through consensus. For studies that fulfilled eligibility criteria, two review authors (KK, HD) independently abstracted key data on maternal colonization in pregnancy (defined as a positive vaginal, rectal, or rectovaginal swab by culture or PCR on at least one occasion from 35 weeks of gestation until birth), maternal colonization at the time of LOGBS diagnosis, preterm birth (delivery at <37 weeks of gestation), low birth weight (LBW <2500 g), multiple-gestation

pregnancy, maternal age <20 years, infant sex, Human Immunodeficiency Virus (HIV) exposure, GBS detected in mother's breast milk at the time of LOGBS diagnosis, maternal intrapartum fever (temperature ≥38°C during labor), and prolonged rupture of membranes (PROM ≥18 hours before delivery). We used published aggregate data, not individual participant data. When the existing published data included cases isolated from non-sterile sites or with an age of onset ≥90 days, we contacted the original researchers to ask for a summary of cases that met our inclusion criteria. We collected data on the number of preterm births, LBW, multiple births, and sex ratio in the study population, either from the reports included in the articles or from the publicly available national statistics services and previously published systematic reviews that used these datasets [10–13]. For national surveillance studies, the number of live births for the whole population for that period was used as the denominator. For studies reporting cases from multi-site surveillance programmes, regional data were used as the denominator. When population data were not available for the entire duration of the study, a midpoint year was used. Due to a lack of population-wide studies on maternal GBS colonization, we used the pooled estimates of GBS colonization prevalence by country from a systematic review conducted in 2015 [14].

Quality assessment

Two review authors (KK, MM) assessed the risk of bias of each included study independently by using a modified Newcastle-Ottawa scale (NOS) (Table S2). We resolved any disagreements by consensus.

Statistical analyses

We performed a meta-analysis to calculate weighted odds ratios (OR) with 95% confidence intervals (CIs) across studies and pooled risk of LOGBS for the following parameters: (i) preterm birth, (ii) GBS colonization in pregnancy, (iii) LBW, (iv) multiple-gestation pregnancy, (v) maternal age <20 years, (vi) intrapartum fever, (vii) PROM, and (viii) infant sex. Data on HIV exposure were collected, but the synthesis of these data has recently been done [15] . Data about the other clinical risk factors (maternal colonization and isolation of GBS in breast milk at the time of LOGBS diagnosis) were disparate and could not be pooled. We summarized data with a random-effects model, using the Mantel-Haenszel method and the DerSimonian-Laird approach to estimate the variance of the distribution of true effect sizes (τ^2). We assessed between-study heterogeneity by using the I^2 statistic. Heterogeneity was further explored with subgroup analyses and meta-regression for variables where an association with a higher risk of LOGBS was found. We compared studies based on the study design, World Health Organisation (WHO) regions, high- (HIC) versus low- and middle-income countries (LMIC), presence versus absence of IAP policy, length of study, and year of publication. The subgroup pooled estimates were calculated with a mixed-effect model, without a common estimate of τ^2 across subgroups [16] . Meta-regression was performed using a mixed-effect model with continuous and categorical moderators [16] . The R^2 index was used to quantify the percentage of variation explained by the model [16] . Sensitivity analyses were performed to explore the influence of excluding studies that used a different definition of LOGBS (7 to 179 days of age) or studies that only reported sepsis or meningitis cases. We assessed publication bias by using funnel plots for analyses with more than nine included studies and tested for funnel plot asymmetry using Egger's test. We considered

Egger's test p-value less than 0.05 to implicate publication bias [17]. Statistical analyses were done with R studio (version 3.6.3) using the packages "meta", "metafor", and "dmetar" [16].

RESULTS

Study Selection

From a total of 14,468 articles identified through the literature search, we assessed 104 full manuscripts and identified 27 articles that met the inclusion criteria [2,3,5,6,18–40] (Figure 1).

Study Characteristics

We included 27 studies with a total of 5315 cases of LOGBS among 30,487,773 live births. The median incidence of LOGBS was 0.21 cases/1000 live births (range 0.06-1.18). Of the included studies, thirteen (48%) were prospective cohort studies, nine (33%) retrospective cohort studies, and five (19%) case-control studies (Table 1 and S3). Thirteen (48%) articles were from Europe, six (22%) from the Western Pacific region, five (19%) from North America, and three (11%) from Sub-Saharan Africa. Quality was moderate to high (defined as NOS score >5) for all the included studies (Table S4).

Outputs from Meta-analyses

The OR of LOGBS in preterm infants compared to those born ≥37 weeks was 5.66 (95% confidence interval [CI], 4.43-7.22), with considerable heterogeneity among the 22 studies included (I2: 92%) (Figure 2). An additional analysis was performed using birth <34 weeks as a cut-off when data were available. The OR of LOGBS for infants born <34 weeks compared to those born ≥34 weeks was 19.70 [15.25-25.45] among three studies included (I2: 0%)

(Figure S1). The OR of LOGBS in all infants with LBW compared to birth weight >2500g was 6.73 [4.68-9.67] with considerable heterogeneity among fourteen studies included (I2: 95%) (Figure 3). The OR of LOGBS in all infants born to mothers colonized with GBS antenatally compared to those born to mothers not colonized with GBS was 2.67 [2.07-3.45], with substantial heterogeneity among twelve studies included (I2: 66%) (Figure 4). The OR of LOGBS in multiple births compared to singletons was 8.01 [5.19-12.38], with considerable heterogeneity among ten studies included (I2: 72%) (Figure 5).

PROM and intrapartum fever were not associated with an increased risk of LOGBS. The OR was 1.49 [0.94-2.36] and 1.06 [0.14-8.18], respectively (Figures S2, S3). There was no difference in risk of LOGBS between male and female infants (OR: 1.02 [0.92-1.13]; I2: 20%) (Figure S4). Similarly, maternal age <20 years was not associated with an increased risk of LOGBS (OR: 1.86 [0.74-4.68]; I2: 78%) (Figure S5).

Subgroup Analyses and Meta-regression

For prematurity and LBW, studies from Africa/LMIC had lower pooled estimates than the other geographic areas and HIC (Table S5). Also, single-center studies had lower pooled estimates than multi-center or national studies, whereas comparison according to study design and IAP policy showed no significant difference (Table S5). A meta-regression analysis showed that WHO region, classification of countries based on economic resources and classification of the studies based on the number of participating sites accounted for a small to moderate proportion of heterogeneity for prematurity (R^2: 46%, 59%, 52%, respectively); and LBW (R^2: 35%, 30%, 64%), but none for colonization (R^2: 0%, 4%, 0%) and multiple gestations (R^2: 0%). A meta-regression analysis with publication year, duration of the study

and NOS score as continuous predictors showed that these factors did not influence the studies' effect size for any risk factor (R^2: 0%).

Sensitivity analyses

When we excluded studies that reported cases up to six months of age (very-late-onset GBS disease), the OR was similar to the primary analysis for prematurity (5.90 [4.58-7.60]), LBW (7.07 [4.88-10.24]), antenatal colonization (2.65 [2.02-3.48]), multiple gestation pregnancies (8.12 [5.07-12.99]), PROM (1.32 [0.82-2.12]), intrapartum fever (1.77 [0.09-34.65]), infant sex (1.01 [0.91-1.12]), and maternal age (1.29 [0.33-4.98]). Similarly, when we excluded studies that only reported sepsis or meningitis cases, the pooled estimate did not differ from the primary analysis for prematurity (5.74 [4.42-7.45]), maternal colonization (2.60 [1.94-3.49]), and infant sex (1.05 [0.94-1.17]). For the rest, primary analyses did not include studies only reporting sepsis or meningitis, therefore sensitivity analyses were not needed.

Assessment of reporting biases

Eggers' test did not indicate the presence of funnel plot asymmetry for prematurity, LBW, colonization, multiple-gestation pregnancies, and infant sex (Figure S6).

DISCUSSION

This systematic review and meta-analyses show that the risk of LOGBS is higher in preterm and LBW infants, infants born to mothers colonized with GBS in pregnancy, and multiple gestation pregnancies. Our findings are consistent with previous reviews that identified prematurity and maternal GBS colonization as risk factors for EOGBS [41] . In contrast, we did not demonstrate any association between LOGBS and other intrapartum risk factors,

such as maternal fever and PROM [41], confirming that intra-amniotic infection does not have any connection to LOGBS.

Premature and LBW infants are known to have increased susceptibility to infections due to immature immune responses, low placental antibody transfer, increased gut permeability, and the risk of nosocomial transmission during their prolonged hospitalization. Prematurity is also characterized by disturbances of microbiome development associated with frequent use of antibiotics, formula feeding and reduced contact with the maternal microbiome that might disturb the adaptation of GBS to its neonatal host environment [42]. Our sub-analysis of LOGBS risk in infants <34 weeks showed that very preterm infants are at higher risk. This is in keeping with the previous finding of increasing risk for each week of decreasing gestation [30].

In addition, our results suggest a strong association between LOGBS and maternal colonization during pregnancy. Since GBS screening results were only recorded in mothers who reached 35 weeks of pregnancy, prematurity is unlikely to have accounted for the effect of maternal GBS colonization on LOGBS risk. The transmission routes underpinning this observation, however, are not fully understood. The time infants get colonized with GBS is highly variable. Longitudinal colonization studies of mother-infant pairs showed that approximately 20-25% of infants born to mothers colonized with GBS became colonized with the same strain by two months of age, despite adequate IAP and negative GBS screening at birth [43]. It seems that GBS can persist at mucosal surfaces even after adequate therapy and cause delayed infant acquisition through nursing (e.g., via contaminated hands) and possibly breastfeeding, although the latter remains controversial [44]. It is important to note that only a small proportion of colonized infants will develop iGBS disease. There are likely

other virulence factors (e.g., adhesins) and host defences (e.g., anti-capsular polysaccharide-specific antibodies) that may modify the risk of LOGBS in the presence of maternal GBS colonization [45].

In contrast, the association of multiple-gestation pregnancies with increased risk of LOGBS is likely confounded by prematurity and LBW, although we could not adequately test this due to the use of aggregate data for this review. However, a previous review of the clinical risk factors of EOGBS showed that multiple-gestation pregnancies are not an independent risk factor, with LBW accounting for the excess risk in twins [41]. It is important to note that we compared rates of LOGBS in multiple-gestation pregnancies and singletons. Due to the use of aggregate data, we did not assess the risk of LOGBS for an infant with a twin sibling with iGBS disease (EOGBS or LOGBS), which is known to be significantly raised, since the multiples have the same mother, thus the same potential exposure to GBS colonization either vertically or horizontally [46].

Our findings might have important implications for designing GBS vaccine trials. A vaccine administered during pregnancy could substantially reduce the LOGBS disease burden through passively transferred antibodies [1]. However, to do so would require the persistence of protective concentrations of antibodies in infants until at least three months of age. Given that three-quarters of LOGBS cases occur within the first eight weeks (median 34 days, interquartile range: 20–49 days) [2], it is plausible that vaccine-induced antibodies with a half-life between 39 and 46 days [47] would protect most infants. However, optimal transfer (and persistence) of antibodies may be a particular challenge for protecting preterm/LBW infants who are at high risk of both EOGBS and LOGBS. This is because the placental transfer of IgG antibody is optimal in the third trimester of pregnancy so that

infants born prematurely may not have had a chance to receive protective concentrations. This will, however, be strongly influenced by the timing of vaccination during pregnancy. Several recent studies on maternal vaccination against pertussis support the efficacy of early vaccination in protecting preterm infants. Kent et al. showed that preterm infants whose mothers were immunised from 28 weeks had higher antibody concentrations compared to preterm infants born to unvaccinated mothers [48]. Eberhardt et al. reported higher antibody concentrations in both term and preterm infants when mothers were vaccinated in the second compared to third trimester [49]. Also, vaccine effectiveness data from the UK suggested that extending the vaccination window down to 16 weeks gestation reduced hospitalized pertussis cases in preterm infants [50]. Therefore, studies seeking to define the optimal window for GBS vaccination to protect preterm and term infants should be prioritized.

This study has some limitations. First, under-ascertainment of cases is a common problem with invasive infant disease incidence studies [1] . However, many of the included surveillance studies mitigated the problem of under-reporting by using Capture-Recapture methods to ascertain cases, where both reference laboratories and clinical surveillance data were used (Table 1). Second, most studies were from HIC; therefore, the estimated risks might not be generalizable. Subgroup analyses suggested that the OR for prematurity and LBW were lower in LMIC. This difference was driven by higher rates of LOGBS among term infants compared to HIC, whereas the incidence of disease among preterm/LBW infants was similar in LMIC and HIC. This might be explained by comorbidities such as exposure to HIV, or other clinical risk factors in early life that have not been captured in this review (e.g., malnutrition). Third, we could not adjust for multiple risk factors since we used aggregate

data. Although three case-control studies reported adjusted OR for different sets of covariates [30,36,37], we used the unadjusted OR from these studies to compare the effect sizes across all studies. Therefore, the pooled estimates are subject to possible confounding due to other factors influencing LOGBS risk. For the same reasons, it was not possible to assess the relationship between the risk of LOGBS and gestation or birth weight as continuous variables. Instead, we did a sub-analysis using a cut-off of 34 weeks that showed a higher risk in more preterm infants. We chose this threshold because it was the most common subgroup of preterm infants reported in the included studies. Limited availability of national or regional data on the prevalence of very preterm (28-32 weeks) or extremely preterm (<28 weeks) infants did not allow for further comparisons. Similarly, there were insufficient data available to perform a sub-analysis for very low birth weight (VLBW <1500g) or extremely low birth weight (ELBW <1000g) infants. Fourth, subgroup analyses and meta-regression did not provide a convincing explanation for the observed variation between the results of the studies. Finally, we did not identify enough eligible studies to estimate the risk of horizontal transmission through breast milk or non-maternal caregivers. Aside from vertical transmission risks, evidence regarding horizontal transmission risk factors to inform preventive strategies is currently limited.

CONCLUSIONS

Overall, our study shows that prematurity/low birth weight and maternal colonization with GBS are major risk factors for LOGBS. To fully understand and ultimately prevent LOGBS, we need (i) well-conducted colonization studies that use genome sequencing and include breast milk samples and specimens from other family members (not restricted to mothers), (ii) mechanistic studies of the role of virulent strains in driving LOGBS, and (iii) globally

collaborative sero-epidemiological studies of the role of maternally derived antibodies in protecting infants from GBS acquisition and LOGBS. Answering these questions would be key to developing novel strategies to control LOGBS.

NOTES

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CONFLICT OF INTEREST

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122 **Figures**

123 **Figure 1.** Data search and included studies for risk factor for LOGBS.

124 **Figure 2**. Forest Plot of Meta-analysis of risk of LOGBS for prematurity.

125 **Figure 3.** Forest Plot of Meta-analysis of risk of LOGBS for LBW.

126 **Figure 4.** Forest Plot of Meta-analysis of risk of LOGBS for antenatal GBS colonisation.

127 **Figure 5.** Forest Plot of Meta-analysis of risk of LOGBS for multiple gestation pregnancies.

128 **Tables**

129 **Table1. Characteristics of included studies**

Reference	Country	Start of data collection	End of data collection	Income	Region	Design	Setting	IAP Policy	Definition LOGBS	LOGBS clinical entity	Capture of cases
Berardi et al. 2013 [18]	Italy	2003.01	2010.12	HIC	Europe	Prospective cohort	Multi-centre	Both	>6 days <90 days	Both	CRC
Dangor et al. 2015 [3]	South Africa	2012.11	2014.02	LMIC	Africa	Case control	Multi-centre	Risk based	>6 days <90 days	Both	NA
Dangor et al. 2016 [19]	South Africa	2005	2014	LMIC	Africa	Prospective cohort	Single centre	Risk based	>6 days <90 days	Both	CRC
Fluegge et al. 2006 [20]	Germany	2001.04	2003.03	HIC	Europe	Prospective cohort	National surveillance	Both	>6 days <90 days	Both	CRC
Frigati et al. 2015 [21]	South Africa	2010.01	2011.12	LMIC	Africa	Retrospective cohort	Multi-centre	Risk based	>6 days <90 days	Both	LS
Giannoni et al. 2016 [22]	Switzerland	2011.09	2015.02	HIC	Europe	Prospective cohort	Multi-centre	Universal screening	>6 days <90 days	Only LOS	LS
Guan et al. 2018 [23]	China	2011.01	2014.12	HIC	Western Pacific	Retrospective cohort	Multi-centre	No	>6 days <90 days	Both	LS
Heath et al. 2004 [24]	UK	2000.02	2001.02	HIC	Europe	Prospective cohort	National surveillance	No	>6 days <90 days	Both	CRC

Reference	Country	Start of data collection	End of data collection	Income	Region	Design	Setting	IAP Policy	Definition LOGBS	LOGBS clinical entity	Capture of cases
Ireland et al. 2014 [25]	Australia	2002.01	2011.12	HIC	Western Pacific	Case control	Multi-centre	Policy changed during study	>2 days <90 days	Both	NA
Jordan et al. 2008 [26]	USA	2003	2005	HIC	Americas	Prospective cohort	Multi-centre	Universal screening	>6 days <90 days	Both	LS
Joubrel et al. 2015 [27]	France	2007.01	2012.12	HIC	Europe	Prospective cohort	National surveillance	Both	>6 days <90 days	Both	LS
Juncosa-Morros et al. 2014 [28]	Spain	1996	2010	HIC	Europe	Retrospective cohort	Multi-centre	Policy changed during study	>6 days <90 days	Both	LS
Ko et al. 2015 [29]	Australia	2005.07	2008.06	HIC	Western Pacific	Prospective cohort	National surveillance	Risk based	>6 days <90 days	Both	CRC
Lin et al. 2003 [30]	USA	1995.07	2000.06	HIC	Americas	Case control	Multi-centre	Risk based	>6 days <180 days	Both	NA
Matsubara et al. 2013 [31]	Japan	2004.01	2010.12	HIC	Western Pacific	Retrospective cohort	Multi-centre	Policy changed during study	>6 days <90 days	Both	CS

Reference	Country	Start of data collection	End of data collection	Income	Region	Design	Setting	IAP Policy	Definition LOGBS	LOGBS clinical entity	Capture of cases
Matsubara et al. 2017 [32]	Japan	2011.01	2015.12	HIC	Western Pacific	Retrospective cohort	Multi-centre	Policy changed during study	>6 days <90 days	Both	CS
Mynarek et al. 2020 [33]	Norway	1996	2012	HIC	Europe	Retrospective cohort	National surveillance	Risk based	>6 days <90 days	Both	CRC
Nanduri et al. 2019 [2]	USA	2006	2015	HIC	Americas	Prospective cohort	Multi-centre	Universal screening	>6 days <90 days	Both	LS
Neto et al. 2007 [34]	Portugal	2001.04	2005.03	HIC	Europe	Prospective cohort	National surveillance	Policy changed during study	>6 days <90 days	Both	CS
O'Sullivan et al. 2019 [5]	UKROI	2014.04	2015.04	HIC	Europe	Prospective cohort	National surveillance	Risk based	>6 days <90 days	Both	CRC
Óladóttir et al. 2011 [35]	Iceland	1975	2006	HIC	Europe	Retrospective cohort	National surveillance	Policy changed during study	>6 days <90 days	Both	LS
Pintye et al. 2016 [36]	USA	1992.00	2011.00	HIC	Americas	Case control	Multi-centre	Policy changed during study	>6 days <90 days	Both	NA
Romain et al. 2018 [6]	France	2001.01	2014.12	HIC	Europe	Prospective cohort	National surveillance	Both	>6 days <90 days	Only Meningitis	CRC

Reference	Country	Start of data collection	End of data collection	Income	Region	Design	Setting	IAP Policy	Definition LOGBS	LOGBS clinical entity	Capture of cases
Schuchat et al. 1990 [37]	USA	1982.01	1983.12	HIC	Americas	Retrospective cohort	Multi-centre	No	>6 days <180 days	Both	LS
Trijbels-Smeulders et al. 2007 [38]	Netherlands	1997	2001.	HIC	Europe	Prospective cohort	National surveillance	Policy changed during study	>6 days <90 days	Both	CRC
Vergadi et al. 2018 [39]	Greece	1995.01	2016.12	HIC	Europe	Retrospective cohort	Multi-centre	No	>6 days <90 days	Both	LS
Ying et al. 2019 [40]	China	2011.01	2016.12	HIC	Western Pacific	Case control	Single centre	No	>6 days <90 days	Both	NA

Abbreviations: IAP, Intrapartum Antibiotic Prophylaxis; LOGBS, Late-onset GBS disease; HIC, High Income Country; LMIC, Low-middle Income Country; LOS, Late-onset sepsis; CRC, Capture-Recapture; LS, Laboratory surveillance; CS, Clinical surveillance; USA, United States of America; UK, United Kingdom; UKROI, United Kingdom and Republic of Ireland; NA, Not Applicable.

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Figure 1

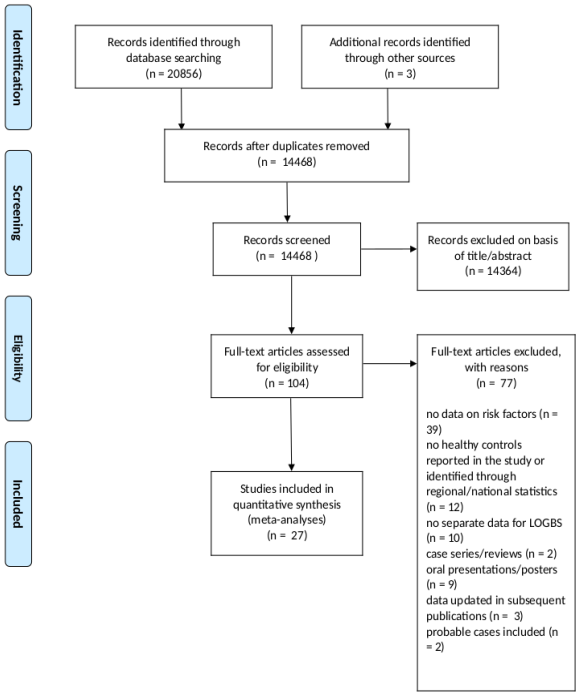

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Figure 2

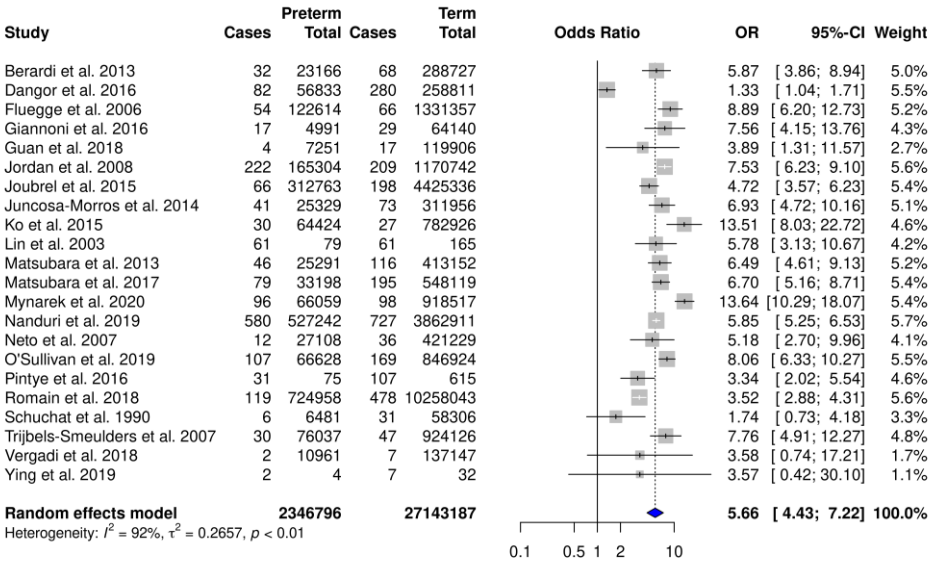

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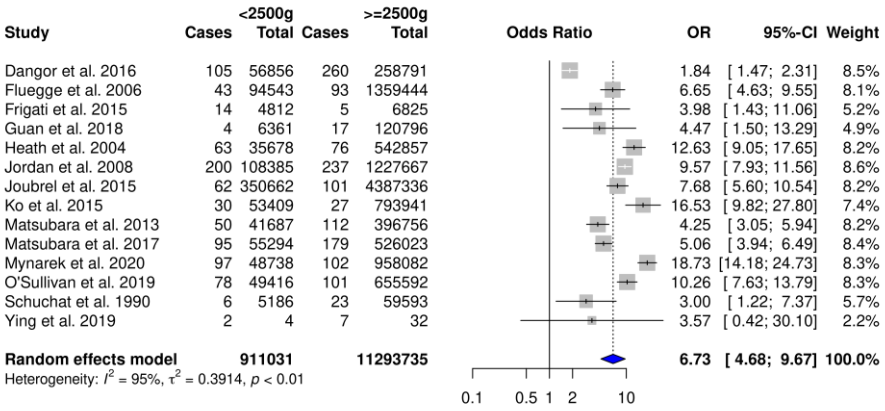
Figure 3



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140 Figure 4

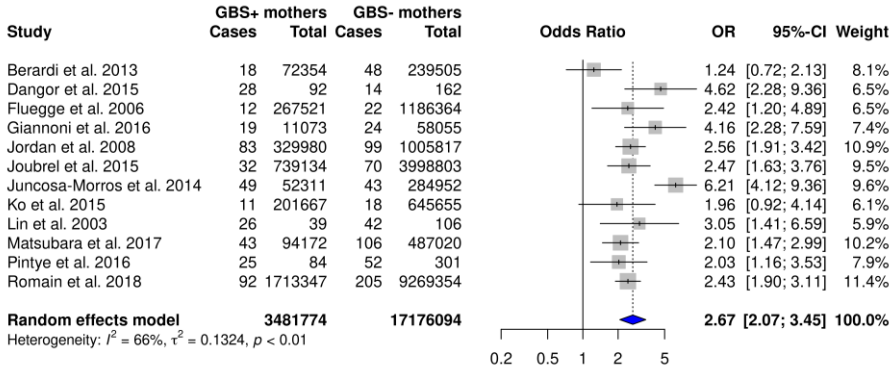

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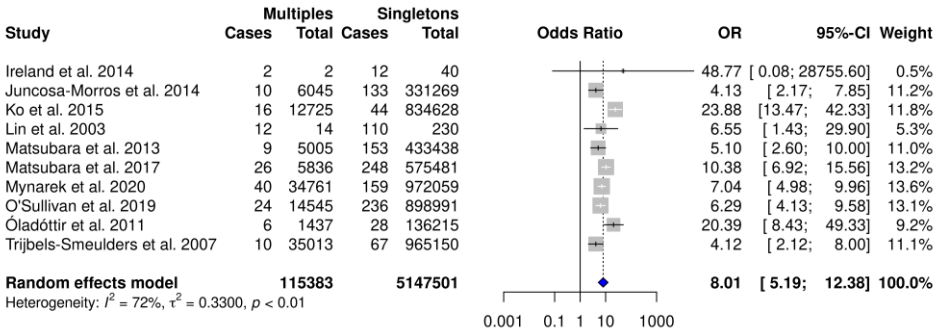
Figure 5



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