Rehospitalisation Risk Factors and Rates in Preterm Babies: A Systematic Review and Meta-Analysis

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Research Article

Keywords: Prematurity, Neonatology, Rehospitalisation, Epidemiology, Systematic review, Meta-analysis

Posted Date: January 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-136833/v1

Abstract

Objective: To systematically review evidence of risk factors and rates for rehospitalisations within one month of discharge for babies born at <37 weeks gestation.

Design: Systematic review and meta-analysis

Data Sources: PubMed (including MEDLINE and life science journals), Web of Science and reference lists of included articles.

Study Selection: Inclusion criteria were studies published in English or French between 01 January 2000 to 31 March 2019, recruiting from the year 2000 onwards evaluating risk factors for rehospitalisation within one month of discharge in preterm babies. Two reviewers independently selected relevant studies, extracted study details, baseline characteristics and results of risk factor analyses.

Results: Across 14 included studies, five studied babies of <37 weeks gestation, seven studied late preterm babies (34-36 weeks gestation), and two studied very to moderate preterm babies (<34 weeks gestation). Important risk factors were low birth weight, respiratory morbidity, male sex and lower socioeconomic status in <37 week babies, and shorter length of stay among late preterm babies. Pooled rehospitalisation rates were 4.3% (95% CI 1.9-9.7) in <37 week babies and 6.6% (95% CI 3.2-13.4) in late preterm babies. There was high heterogeneity in risk factors included in analyses and studies often lacked clarity on variable measurement and confounder adjustment.

Conclusion: We found evidence for clinical and socioeconomic risk factors, high heterogeneity and important limitations. Limitations included a lack of breadth in both the gestational age ranges and risk factors studied, as well as lack of clarity around variable measurement and confounder adjustment

Introduction

Babies born at < 37 completed weeks gestation are more vulnerable than full-term babies. Outcomes in preterm babies are closely linked to gestational age (GA) at delivery[1], and babies born before 32 weeks, and particularly those before 27 weeks gestation, experience the greatest risk of short and long term mortality and morbidity.[2–6] Advances in care have improved outcomes among preterm babies[7, 8], although this increased survival has at times been accompanied by more being discharged with serious morbidities[8–10].

Rehospitalisations temporally close to discharge can provide insight into care and discharge quality.[11, 12] Measures of rehospitalisation are used as indicators of quality and utilisation by health systems such as Medicaid in the United States[13, 14] and the National Health Service in the United Kingdom[15]. Early rehospitalisations are burdensome and costly, particularly among vulnerable preterm populations.[16, 17]

There has been significant amounts of research into risk factors for early rehospitalisation in preterm babies, but to the best of our knowledge there are no systematic reviews of risk factors for early rehospitalisation. Improving our understanding of rehospitalisation risk factors could inform clinical, discharge and policy decisions. We sought to review the evidence pertaining to the risk factors for, and likelihood of, early rehospitalisation among preterm babies. Our primary objective was to conduct a systematic review of risk factors for early rehospitalisation in preterm babies, with a secondary objective of analysing rates of early rehospitalisation across the included studies.

Methods

A systematic review and meta-analysis of risk factors for rehospitalisation (within one month of discharge) in babies born at < 37 weeks gestation was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[18] (Online supplemental1) Two reviewers (RAR and ASM) independently conducted study selection, data extraction and quality assessment. Disagreements were resolved through further discussion or referral to a third author (BK). The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO); CRD42018086549.

Databases and search strategy

PubMed (including MEDLINE and life science journals), Web of Science and reference lists of included articles were searched for studies published between January 01, 2000 and March 31, 2019. Search terms for titles and abstracts included: ('preterm', 'premature', 'near term', 'neonate', 'gestation', 'birth weight') and ('readmission', 'rehospitalisation', 'readmitted') and ('risk factor', 'risk', 'determinant', 'cause', 'variables'). Medical Subject Headings (MeSH) and wildcard terms were included when available. The search strategy and term were developed in consultation with a systematic review expert. Full details are provided in Online supplemental 2.

Inclusion and exclusion criteria

We included observational and experimental studies published in English or French, as well as abstracts. Study populations were either exclusively preterm (babies born at < 37 weeks GA) or – in studies including both full-term and preterm babies in their samples – included an analysis of a sample subset, containing preterm babies only. Included studies investigated risk factors for rehospitalisations occurring within a maximum of one

month of discharge. We excluded studies recruiting patients before the year 2000, those with only full-terms (≥ 37 weeks GA) or where the preterm population could not be distinguished, and those investigating interventions specific to their local environment.

Data extraction

Study characteristics (concerning design, sampling and analyses) and descriptive statistics were extracted from eligible articles. All data relating to rehospitalisation risk factor analyses were extracted. Rates of early rehospitalisation were also extracted from all included studies. In cases where rate data were not provided in articles, data were requested directly from authors.

Quality assessment

Quality of analyses relating to the identification of risk factors for rehospitalisation were independently evaluated by both reviewers using the relevant tools from the Critical Appraisal Skills Programme (CASP).[19]

Analysis

Due to heterogeneity an overall meta-analysis of risk factors was not possible and a narrative synthesis was performed instead. The synthesis was grouped according to the GA categories studied. Studies were grouped into logical categories whilst also maximising the number of studies in each. Groupings were defined in this study as: (1) all preterm babies (studies of < 37 weeks GA); (2) late preterm babies (studies of 34–36 weeks GA); (3) very to moderate preterm babies (studies of < 34 weeks GA or very low birth weight (VLBW) babies).

Two meta-analyses of rehospitalisation rates were performed: the first related to studies of all preterm babies (< 37 weeks GA) and the second focussed on studies of babies born at 34–36 weeks gestation; insufficient data were available for other GA groupings. Studies investigating rehospitalisation within follow-up periods significantly shorter than one month (15 or 7 days for example) were insufficient in number to be included in a separate meta-analysis. Study rates were combined using a random effects model and presented in forest plots. The pooled proportion was estimated using logit transformation with the inverse variance method. Heterogeneity between studies was assessed using the I^2 test statistic.[20]

All analyses used R version 3.4.2[21] and the 'meta' package[22].

Results

Description of included studies

The initial search returned 1,580 records, 169 underwent full text review, with 156 excluded. Thirteen records met inclusion criteria and the manual search of reference lists for included articles identified one additional study[14]. Full details can be found in Fig. 1. Extracted study details are presented in Table 1 and population characteristics in Online supplemental 3. Details of quality assessment are shown in Table 2 and Online supplemental 4.

Table 1
Details of design, recruitment and analysis extracted from included studies.

Study (country)	Design (period of inclusion as reported)	Eligible gestational ages (weeks)	Rehospitalisation type (follow-up)	Statistic(s)	Method for selecting independent variables	Additional inclusion/exclusion details	Routine data use
Donohue et al, 2009 (USA)	Prospective cohort (2004–2006)	Very low birth weight	Any (2-week)	Odds ratio/t-test	Not clear	Included: very low birth weight babies cared for in the 2 regional-referral neonatal intensive care units during 2004–2006 were enrolled in the study after stabilisation. Excluded: babies with complex congenital anomalies, those transferred for speciality consultation only, or those whose parents did not have legal custody or speak English.	No: extraction from medical records and parental interviews.
Harron et al, 2017 (UK)	Retrospective cohort (April 2005 – February 2014)	≥ 34 (≥ 39; 37–38; 34–36)	Unplanned (30-day)	Risk ratio/t-test	Review of the literature	Included: singleton births ≥ 34 completed weeks gestation, who were not admitted for neonatal intensive care, and who did not have congenital anomalies. Analyses were further restricted to babies with a newborn length of stay of ≤ 5 days and to hospitals with > 100 births per year.	Yes. National Health Service, Hospital Episode Statistics (HES).
Jensen et al, 2018 (USA)	Retrospective cohort (January 01, 2010 – November 16, 2016)	< 37	Any (30-day)	Odds ratio	Maternal/infant characteristics associated with car seat tolerance screening (CSTS) failure at $p \leq 0.2$ in bi-variable testing were included in initial regression model. Variables associated with CSTS failure at $p < 0.05$ in multi-variable modelling were retained in final model	Included: <37 week gestational age babies born on or after January 1, 2010, and underwent pre-discharge CSTS in a NICU before November 16, 2016. Excluded: babies diagnosed with cyanotic congenital heart disease and/or structural abnormalities of the airway.	Yes. Optum neonatal database (Eden Prairie, Minnesota). The Optum Corporation provides neonatal care management services for multiple private, government, and self-insured employer health plans throughout the United States.
Mallick et al, 2019 (India)	Prospective cohort-single centre (November 2011 – June 2015)	34-<37	Any-not clear (1-month)	Risk ratio	Not clear	Included: all live inborn late preterm babies were included after informed consent was obtained from any one of the parents. Excluded: major congenital malformation and large-for-age late preterms.	No: hospital study

Study (country)	Design (period of inclusion as reported)	Eligible gestational ages (weeks)	Rehospitalisation type (follow-up)	Statistic(s)	Method for selecting independent variables	Additional inclusion/exclusion details	Routine data use
McLaurin et al, 2008 (USA)	Retrospective cohort (2004)	late preterm: 33–36; full-term: ≥37	Any (15-day)	t-test	Not clear	Included: study subjects were identified from newborn diagnosis related group (DRG) codes (385–391) on the birth admission claim. Late-preterm babies were identified when their birth admission included either a DRG code for prematurity (386–388) or a DRG code during birth admission for neonate (385 and 390) and a diagnosis code for gestational age 33–36 weeks (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 765.27–8) reported on any claim during the first year of life. Excluded: babies not associated with an employer group that contributed prescription drug claims data to the MarketScan databases or if they had a capitated insurance plan. Babies from multiple births were excluded if they did not have distinct enrollment identification numbers.	Yes: MedStat MarketScan Commercial Claims and Encounters database.
Moyer et al, 2013 (USA)	Matched case-control (January 01, 2009 – December 31, 2009)	34-<37	Any-not clear (28-day)	Odds ratio	Covariates deemed to be empirically or statistically important ($p < 0.2$) was used to develop parsimonious multi-variable logistic regression model	Included: all late-preterm babies rehospitalised within 28 days of birth (case subjects) were identified through manual chart review for each study hospital. A control population of non-readmitted late-preterm babies for each hospital was then chosen by using birth certificate data provided by the Ohio Department of Health. Cases were then matched to a sample of control infants who were not readmitted within 28 days.	No: extraction from maternal and infant birth hospitalisation records as well as rehospitalisation records – manual chart review; Also birth certificate data to identify controls.

Study (country)	Design (period of inclusion as reported)	Eligible gestational ages (weeks)	Rehospitalisation type (follow-up)	Statistic(s)	Method for selecting independent variables	Additional inclusion/exclusion details	Routine data use
Oltman et al, 2018 (USA)	Retrospective cohort (2005–2011)	34–36	Any-not clear (7-day)	Risk ratio	Not clear	Included: all singleton live births in California between 2005 and 2011 with gestational ages from 34 to 36 completed weeks and a discharge within 3 days of birth.	Yes: all data included was obtained from linked birth cohort from the California Office of Statewide Health Planning and Development and the California Newborn Screening program.
Regenbogen et al, 2018 (USA)	Retrospective cohort (2003–2014)	< 37	Any-not clear (30-day)	Odds ratio/t-test	Model eligible variables included as possible apnea predictors included reflux, gestational age, birth weight, race, health region, and the sub-group of the most prevalent co-morbidities and complications.	Included: preterm live singleton births. Excluded: babies with unknown gender, missing gestational age, > 36w gestational age, multiple birth records and non-matching records.	Yes: New York State Statewide Planning and Research Cooperative System hospital claims database.
Samra et al, 2013 (USA)	Prospective cohort (April 2010 – August 2010)	34-<37	Any-not clear (1-month)	Not clear	Not clear	Included: late-preterm mother-baby dyads admitted to 1 of 3 level III NICUs in a Midwestern, predominately rural state between April and August 2010, English-speaking mothers and their biologically born late preterm babies with no known congenital anomalies or chromosomal abnormalities. Mothers of twins were asked to participate in the study on behalf of one twin. Excluded: mothers that mailed their questionnaires 6 to 8 weeks postmark the 1-month data collection point were excluded from the analysis because of this long lapse in time.	No: the 75-item McPhee Knowledge of Infant Development Inventory (KIDI) and The 10-item White-Traut Competence in Preterm Infant Care (CPIC) questionnaire was used to measure maternal knowledge and competence in preterm infant care. The 48-item CPIC questionnaire was developed by White-Traut to assess self efficacy expectations and confidence in mothers of preterm babies.

Study (country)	Design (period of inclusion as reported)	Eligible gestational ages (weeks)	Rehospitalisation type (follow-up)	Statistic(s)	Method for selecting independent variables	Additional inclusion/exclusion details	Routine data use
Schell et al, 2016 (USA)	Retrospective cohort-single centre (2008–2009)	< 37	Any (30-day)	Odds ratio	Selection of risk factors for the model was based on empirical knowledge obtained through published investigations, physiological plausibility and $p \leq 0.2$ from the unadjusted bivariate analysis of associations between risk factors and rehospitalisation	Included: babies admitted to and discharged from the Maria Fareri Children's Hospital, Westchester Medical Center, Valhalla, NY, USA in 2008 and 2009. Rehospitalisation requiring admission for at least one night. Excluded: babies who died or were transferred out of the NICU, full-term babies (≥ 37 weeks), those whose medical records were missing and those rehospitalised at other institutions within 6 months of discharge.	No: medical record review and also phone survey.
Soni et al, 2016 (India)	Retrospective cohort-single centre (February 01, 2014 – January 31, 2015)	< 34	Any (4-week)	Not clear	None	Included: ex-preterm babies (< 34 weeks gestational age at birth) discharged home from our NICU between February 01, 2014 to January 31, 2015. Excluded: babies discharged against medical advice or those that died.	No: hospital study

Study (country)	Design (period of inclusion as reported)	Eligible gestational ages (weeks)	Rehospitalisation type (follow-up)	Statistic(s)	Method for selecting independent variables	Additional inclusion/exclusion details	Routine data use
Tseng et al, 2010 (Taiwan)	Retrospective cohort (2000–2002)	Babies with a primary or secondary diagnosis of disorders relating to short GA and unspecified LBW	Unplanned (15/31-day)	Hazard ratio	Cox proportional hazard model was used to identify the significant predictors for the occurrence of rehospitalisation, and to assess the potential interactions of gestational age with various significant predictors for rehospitalisation.	Included: babies (i) born on or after January 01, 2000; and (ii) first hospitalisation after birth occurring between 2000 and 2002 with a primary or secondary diagnosis of disorders relating to short GA and unspecified LBW (ICD-9-CM code: 765). Excluded: if one or more of the following criteria occurred in the first lifetime hospitalisation: (i) birthweight < 500 g (n = 112); (ii) in-hospital mortality (n = 1267), or unclassified (n = 4878). The purpose of excluding births < 500 g was to avoid possible implausible birthweight. Also, all infants from the 112 live births with a birthweight < 500 g noted in the national health insurance claims were also not eligible for inclusion because 93 of them died in hospital, and nine had a length of stay > 365 days.	Yes: data retrieved from Taiwan's national health insurance database.
Young et al, 2013 (USA)	Retrospective cohort (2000–2010)	late preterm: 34–36; early preterm: 37–38; term: 39–42	Any (28 day)	t-test	None	Included: all newborns with gestational ages between 34–42 weeks who were discharged alive between 2000 and 2010. Excluded: Newborns who stayed > 24 hours in or were discharged from a NICU were excluded.	Yes: used the Intermountain Healthcare Enterprise Data Warehouse, a large vertically integrated health care system that includes hospitals in Utah and Idaho.

Study (country)	Design (period of inclusion as reported)	Eligible gestational ages (weeks)	Rehospitalisation type (follow-up)	Statistic(s)	Method for selecting independent variables	Additional inclusion/exclusion details	Routine data use
Zhang et al 2018 (China)	Randomised control trial (June 2014 – September 2016)	< 37	Any-not clear (1-week/month)	t-test	Intervention versus standard care	Included: parents of babies born < 37 weeks gestation. Parents were included if they were able to commit spending a minimum of 4 hours per day with their babies between office hours to enable attendance at medical rounds and education sessions. Excluded: parents of babies with: 1) major life threatening congenital anomaly; 2) critical illness and unlikely to survive; and 3) respiratory support (continuous positive airway pressure, mechanical ventilation, high frequency oscillatory or jet ventilation, extracorporeal membrane oxygenation). Parents were excluded if they have health, family, social, or language issues that might limit their integration and collaboration with the healthcare team.	No: RCT study

Table 2
Synthesis of quality assessment by gestational age (weeks) (GA) grouping of each study.

GA grouping (N. studies)	Synthesis
< 37w (Five[23,25,26,30,35])	Of the four cohort studies, Jensen et al[23] Regenbogen et al[25], Schell et al[26] and Tseng et al[30] lacked clarity relating to the measurement of exposures. In studies that used health system or insurance databases[23,25,30] details of how data were extracted, coded and extent of validation were not provided. Two studies did not clearly define how GA was established or measured[26,30] In addition, Jensen et al[23] acknowledged that testing for their key risk factor of car seat tolerance screening may vary widely between centres and they assumed that initial screenings were all performed in an infant car seat. Further lack of clarity over the identification, selection and, inclusion of confounders was present in Jensen et al[23], Regenbogen et al[25] and Tseng et al[30]. Zhang et al's randomised control trial[35] also had an increased risk of bias as it recruited from a single Chinese neonatal intensive care, had a small sample and could not blind clinicians to the intervention.
34-36w (Six[14,27,29,32–34])/ 33-36w (One[24])	Three of the seven studies[27,32,33] provided unclear information concerning the measurement of exposures. Three[14,24,33] did not adjust for confounding while three[24,33,34] controlled for confounding in only a limited fashion. Samra et[32] al and Oltman et al[27] in particular provide insufficient detail of the selection of and adjustment for confounders. A majority of studies did not report details of loss to follow-up and missingness. Only Samra et al[32] presented analyses of the role of loss to follow-up in their study while only Harron et al[29] conducted sensitivity analyses regarding missingness.
< 34w (Two[28,30])/ VLBW (One[31])	There were multiple limitations with the three studies included. Two[28,31] had small samples (below 250 babies) and established the outcome using interviews which are vulnerable to recall bias. Soni et al[28] did not control for confounding while Tseng et al[31] and Donohue et al[31] provide insufficient detail concerning selection and adjusted for a limited range of variables. Two studies[28,31] failed to detail missingness in their samples.

Design and study population

Nine studies used retrospective cohort design[14, 23–30], three were prospective studies[31–33], one was a case-control study[34]and another was experimental[35]. Most studies were conducted in the USA[14, 23–27, 31, 32, 34] while the remainder were based in India[28, 33], United Kingdom[29], China[35] and Taiwan[30]. Half of the studies used national or regional health system or insurance databases[14, 23–25, 27, 29, 30] and others used either multiple[31, 32, 34] or single hospitals.[26, 28, 33, 35] Populations of 34–36[14, 27, 29, 32–34]/33–36 week GA babies[24] were most frequently studied, followed by < 37 weeks GA[23, 25, 26, 30, 35], 28–36 weeks GA[30] and VLBW[31]. Sample sizes ranged from to 28[32] to 103,469[25]. See Table 1 for full details.

Outcome

Two studies[29, 30] focussed on unplanned rehospitalisations while twelve studies considered either any rehospitalisation (both planned and unplanned) or did not stipulate. Eleven studies used a follow-up period of approximately one month and four used shorter periods of 15 days or below[24, 27, 30, 31]

Potential explanatory variables

There was substantial heterogeneity in the variables included in analyses (Online supplemental 5, 6 & 7). A variable quantifying categories of GA was included by two studies[25, 30], birth weight by four[25, 26, 30, 31, 34], and small for gestational age (SGA) by two[31, 33]. Nine studies[23, 25–28, 30, 31, 33, 34] included a measure of clinical sequelae and morbidities and ten included care and treatment variables[14, 23–26, 29–31, 34, 35]. Finally, demographic and socio-economic variables were used in five studies[25–27, 30, 31] while maternal variables were included in two[26, 31].

Risk factors for early rehospitalisation

Five studies addressed rehospitalisations babies of < 37 weeks GA[23, 25, 26, 30, 35] and seven investigated either 34–36[14, 27, 29, 32–34] or 33–36 week GA babies[24]. An additional three studies studied either < 34 week GA[28, 30] or VLBW babies[31]. A narrative synthesis of risk factors is shown in Table 3, and all relevant data in Online supplemental 5,6 & 7.

Table 3
Narrative synthesis of risk factor analyses by gestational age (weeks) (GA) grouping of each study. RH = rehospitalisation within one month or less of discharge, as defined in each study.

GA grouping (N. studies)	Risk factor type	Synthesis
< 37w (Five[23,25,26,30,35])	Growth	All three studies including growth variables in analysis identified sub-optimal birth weight as a risk factor for RH.[25,26,30]
	Treatment & care	Tseng et al[30] found treatment in a regional hospital (versus a medical centre) was a risk factor for RH. Zhang et al's randomised control trial[35] identified lower rates of 1-week and 1-month RH in babies receiving family-centred care compared to standard care. Neither Schell et al[26] nor Jensen et al[23] found treatment and care to be associated with RH.
	Morbidities	Four studies investigated the role of morbidities.[23,25,26,30] Tseng et al[30] found congenital abnormality and lung disease increased RH, while Regenbogen et al[25] reported an increased rate of RH in babies with apnea versus those without.
	Maternal	Only Schell et al[26] studied maternal variables, concluding that chronic maternal conditions were not associated with RH.
	Socio-demographic	Tseng et al[30] and Regenbogen et al[25] found males had a higher risk of RH. For proxies of socio-economic status, Regenbogen et al and Schell et al[26] found being on Medicaid or Medicare versus commercial cover to be a risk factor. Similarly, Tseng et al found lower insurance premium costs were associated with increased RH risk. Of the three studies[25,26,31] that included a race variable, only Regenbogen et al found it played a role in RH.
34-36w (Six[14,27,29,32–34])/ 33-36w (One[24])	Growth	Mallick et al[33] found being SGA was a risk factor for one-month RH while conversely, Moyer et al[34] found that increasing birthweight raised the risk of hyperbilirubinemia RH.
	Treatment & care	All four studies investigating length of stay found that shorter rather than longer length of stay increased RH risk.[14,24,29,34]
	Morbidities	Oltman et al[27] found preterm babies with high levels of certain metabolites C16:1, C14:1 and C3, and high tyrosine to ornithine ratios had an increased risk of RH.
	Maternal	No studies investigating this population of preterm babies included maternal variables in their analyses.
	Socio-demographic	No studies found an effect from demographic and environmental variables.
< 34w (Two[28,30])/ VLBW (One[31])	Growth	Donohue et al[31] found being SGA was a risk factor for RH. Birth weight was not associated with RH.
	Treatment & care	Transfer to community hospital (versus no transfer) was associated with an increased risk of RH by Donohue et al[31].
	Morbidities	Tseng et al[30] found congenital abnormality and lung disease were risk factors for RH. Donohue et al[31] did not find chronic lung disease, severe intraventricular haemorrhage or necrotising enterocolitis to be associated with RH.
	Maternal	Donohue et al[31] found no association between maternal education or age with 2-week RH.
	Socio-demographic	Only Donohue et al[31] investigated demographic and environmental variables, finding no association between any such variables (including race) and RH.

Meta-analysis of early rehospitalisation rates

We included four studies[23, 25, 26, 30] of < 37 week and five studies[14, 26, 29, 32, 33] of 34–36 week GA babies in two separate meta-analyses. Cross-study heterogeneity was 100%; the pooled rates of rehospitalisation within 31-days were 4.3% (95% CI 1.9–9.7) in < 37 week babies and 6.6% (95% CI 3.2–13.4) for late preterms. Results are shown in Fig. 2 and a synthesis in Online supplemental 8.

Discussion

In this systematic review of the literature on risk factors for, and likelihood of, early rehospitalisation in preterm babies we found 14, albeit heterogeneous articles. These articles were heterogeneous in terms of populations, gestational ages and risk factors in analyses. Several large studies found that sub-optimal birth weight, respiratory morbidities, being male and lower socioeconomic status were risk factors for rehospitalisation among babies of < 37 week gestation. There was also consistent evidence that shorter length of stay increased the risk of rehospitalisation in late preterm babies, though this evidence was of limited quality due to inadequate control for confounders and poor reporting of missingness and loss to follow-up. Evidence pertaining to babies born at < 34 weeks gestation was less abundant, comprising predominantly

small samples with limited detail concerning confounder adjustment and missing data. Meta-analysis of rehospitalisation rates is difficult to interpret given marked heterogeneity between studies.

Evidence for risk factors of early rehospitalisation

In preterm babies as a whole, lower birth weight was consistently a risk factor for rehospitalisation[25, 26, 30]. This finding was most likely in part due to the fact that birth weight is correlated with gestational age, which is a key determinant of physiological immaturity and outcome in newborns. Conversely, Schell et al[26] found that being SGA was associated with a lower risk of rehospitalisation, perhaps indicating that babies benefit from the more intensive management potentially afforded to SGA babies. Evidence of a role for respiratory morbidity (apnea[25] and lung disease[30]) in rehospitalisation was shown in two large studies, was unsurprising given the strong association between lower gestational age and respiratory system immaturity.[4, 36] Two studies[25, 26] found Medicaid recipients had an increased rehospitalisation risk and Tseng et al[30] found lower insurance premium payments increased risk. These findings regarding contextual factors related to socioeconomic status are supported by the literature[37–39] and present challenges for clinicians, as such factors may not b e possible to influence. Being male was a risk factor for rehospitalisation among preterm babies (< 37 weeks gestation) in a US[25] and Taiwanese[30] study, reflecting the well established male disadvantage[40, 41], likely accounted for by physiological, hormonal and developmental factors.[41]

Among late preterm babies, multiple studies[14, 24, 29, 34] found shorter length of stay to be a risk factor. However, the failure of three of the studies[14, 24, 29] to adjust for environmental factors such as socioeconomic status or maternal variables hinders interpretation of these results.

Rates of early rehospitalisation

The pooled rate of rehospitalisation within 31-days was 4.3% in < 37 week babies and 6.6% for late preterms. Differences in populations, methodology and clinical practice may account for some of the variations across studies. The highest rates came from studies from Taiwan[30] and India[33] respectively, whilst the lowest rates were seen in US studies[14, 23]. This disparity could in part be explained by differences in discharge criteria, preparation of families, and follow-up between regions. The lower rate seen in Young et al[14] versus Harron et al[29] is somewhat surprising as Harron et al[29] considered only unplanned rehospitalisations while Young et al[14] considered all rehospitalisations, including planned admissions for surgery or investigations. Despite this, the discrepancy might be explained by more conservative discharge practices in the United States. Establishing whether differences in rate were due to divergence in sample risk profiles was not possible as the reporting of relevant baseline characteristics was not comprehensive in Harron et al[29], Mallick et al[33] nor Young et al[14]. Moreover, we also acknowledge that the use of interview to ascertain rehospitalisation status by several studies[26, 28, 31–33] could have introduced recall bias, leading studies such as Mallick et al[33] to underestimate rehospitalisation rates.

Strengths and limitations of the eligible studies

Almost all studies recruited over a period of at least one year, thus limiting the influence of seasonality on outcome measures. Multiple studies used large samples, recruited from regional or national databases – thus improving representativeness – and used statistical methods that facilitated adjustment and produced useful measures to quantify effect sizes.

There were many limitations across the studies. Recruitment from single centres and corresponding small sample sizes was relatively common, that could have resulted in limited power to detect associations with potential risk factors[20] and a higher likelihood that samples were not representative of the underlying populations. Many studies used electronic health data, insurance databases or medical records. These are vulnerable to biases related to missing data and systematic measurement error. As such, it is important that such administrative data are validated[42], yet only Harron et al[29] used data that was clearly routinely validated[43]. Other studies used interviews to establish the outcome and these are vulnerable to recall and social-desirability bias, as well as misunderstanding of questions on behalf of the interviewee.

Insufficient adjustment for confounders or effect modifiers affected over half[14, 23, 24, 27–29, 32, 33] of the fourteen studies and gestational age, birth weight and socioeconomic status were too infrequently adjusted for in particular. The processes used to select confounders was rarely described in the studies. This made comparison across studies challenging and reduced the likelihood that measures were quantifying the true or even the same effect. Under half of the studies reported the proportion of loss to follow-up[25, 28, 30–33], and just one[32] compared eligible babies to those lost to follow-up. Fewer than half of studies reported details of missing data[24–26, 29, 30] or conducted relevant analyses[26, 29]. Consequently, it was difficult to establish the potential role of attrition bias.

Strengths and limitations of this review

This systematic review provides novel results, synthesising the scientific literature as it relates to risk factors for, and the likelihood of, early rehospitalisation in samples of preterm babies. We followed PRISMA guidelines[18], and the development of the search strategy was made in consultation with an expert in systematic reviews. We consulted multiple large databases, included abstracts, and conducted additional reference searches. We believe our exclusion of studies of specific local interventions and pre-year 2000 populations ensured the broad relevance and generalisability of this review to modern standards of neonatal care, across contexts. Our use of the CASP tools is an added strength given its comprehensive scope and lack of reliance upon potentially arbitrary and reductive aggregate article scores.[20]

We acknowledge that we may have missed some studies given our inclusion of only English and French articles. In addition, heterogeneity in GA categories complicated synthesis of study findings and the size of the evidence-base data related to each GA category. Categorisation of GA in the literature and this review's synthesis could be deemed arbitrary as the effects of prematurity are likely present on a continuum. Study heterogeneity made pooling of risk factor effects impractical and meant we could not effectively assess publication bias. We also assumed that studies using follow-up periods of 31 days or less were measuring the same outcome. Though most studies used a follow-up of approximately one month, we acknowledge that babies rehospitalised within one week may have different risk factor profiles, complicating interpretation of this review.

Conclusions

Among babies of < 37 weeks gestation, sub-optimal birth weight respiratory morbidities, being male and lower socioeconomic status were associated with early rehospitalisation. Shorter length of stay was a consistent risk factor for early rehospitalisation in studies of late preterm babies. This review also highlights a lack of high quality research and substantial heterogeneity among studies addressing late (34–36 weeks GA) and very to moderate preterm (< 34 weeks GA) babies in particular. However, despite limitations in the literature, there is little to suggest that clinicians are not broadly managing the discharge and follow-up of preterm babies effectively. Future research should consider wider ranges of gestational age (particularly < 34 weeks gestation) and risk factors, while adjusting more comprehensively for confounding. Strengthening the evidence-base on early rehospitalisation could improve clinical decision making, thus reducing healthcare burdens and improving outcomes for preterm babies.

Abbreviations

aHR – adjusted hazard ratio

aOR – adjusted odds ratio

CASP – Critical Appraisal Skills Programme

CI – confidence interval

CLD – chronic lung disease

CSTS – car seat tolerance screening

HES – Hospital Episode Statistics

GA – gestational age

ICD – International Classification of Diseases

IVH – intraventricular haemorrhage

LOS – length of stay

MeSH – Medical Subject Headings

NEC – necrotising enterocolitis

NT$ – New Taiwanese Dollar

NICU – neonatal intensive care unit

PMA – post-menstrual age

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PROSPERO – International Prospective Register of Systematic Reviews

RCT – randomised control trial

RF – risk factor

RH – rehospitalisation

SD – Standard deviation

SGA – small for gestational age

VLBW – very low birth weight

Declarations

Ethics approval and consent to participate

Not applicable. Systematic review and meta-analysis study design.

Consent for publication

Not applicable.

Availability of data and materials

All the data collected in this study are are provided in either the main article or supplementary materials.

Competing interests

The authors declare that they have no competing interests.

Funding

Robert A. Reed has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 665850. Andrei S. Morgan has received funding from the Fondation pour la Recherche Médicale (reference SPF20160936356).

Author's contributions

Robert A. Reed and Dr Andrei S. Morgan conceptualized and designed the study, collected data, carried out the initial analyses and drafted, reviewed and revised the manuscript. Dr Babak Khoshnood, Dr Pierre-Yves Ancel and Dr Jennifer Zeitlin conceptualized and designed the study and drafted, reviewed and revised the manuscript. Dr Agnès Dechartres designed the study and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Acknowledgments

We would like to thank the authors of included studies that responded to requests for additional data.

References

1. Purisch SE, Gyamfi-Bannerman C. Epidemiology of preterm birth. *Semin Perinatol* 2017;**41**:387–91. doi:10.1053/j.semperi.2017.07.009
2. Larroque B, Ancel P-Y, Marret S, *et al.* Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study. *Lancet Lond Engl* 2008;**371**:813–20. doi:10.1016/S0140-6736(08)60380-3
3. Zeitlin J, Draper ES, Kollée L, *et al.* Differences in Rates and Short-term Outcome of Live Births Before 32 Weeks of Gestation in Europe in 2003: Results From the MOSAIC Cohort. *Pediatrics* 2008;**121**:e936–44. doi:10.1542/peds.2007-1620
4. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *The Lancet* 2008;**371**:261–9. doi:10.1016/S0140-6736(08)60136-1
5. Ancel P-Y, Goffinet F, Kuhn P, *et al.* Survival and Morbidity of Preterm Children Born at 22 Through 34 Weeks' Gestation in France in 2011: Results of the EPIPAGE-2 Cohort Study. *JAMA Pediatr* 2015;**169**:230–8. doi:10.1001/jamapediatrics.2014.3351
6. Glass HC, Costarino AT, Stayer SA, *et al.* Outcomes for Extremely Premature Infants. *Anesth Analg* 2015;**120**:1337–51. doi:10.1213/ANE.0000000000000705
7. Iams JD, Romero R, Culhane JF, *et al.* Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. *Lancet* 2008;**371**:164–75. doi:10.1016/S0140-6736(08)60108-7
8. Stoll BJ, Hansen NI, Bell EF, *et al.* Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. *JAMA* 2015;**314**:1039–51. doi:10.1001/jama.2015.10244
9. MANUCK TA, RICE MM, BAILIT JL, *et al.* Preterm Neonatal Morbidity and Mortality by Gestational Age: A Contemporary Cohort. *Am J Obstet Gynecol* 2016;**215**:103.e1-103.e14. doi:10.1016/j.ajog.2016.01.004
10. Eichenwald EC, Stark AR. Management and outcomes of very low birth weight. *N Engl J Med* 2008;**358**:1700–11. doi:10.1056/NEJMra0707601

11. Escobar GJ, Clark RH, Greene JD. Short-term outcomes of infants born at 35 and 36 weeks gestation: we need to ask more questions. *Semin Perinatol* 2006;**30**:28–33. doi:10.1053/j.semperi.2006.01.005
12. Goldfield NI, McCullough EC, Hughes JS, *et al.* Identifying potentially preventable readmissions. *Health Care Financ Rev* 2008;**30**:75–91.
13. Kangovi S, Grande D. Hospital readmissions--not just a measure of quality. *JAMA* 2011;**306**:1796–7. doi:10.1001/jama.2011.1562
14. Young PC, Korgenski K, Buchi KF. Early readmission of newborns in a large health care system. *Pediatrics* 2013;**131**:e1538-1544. doi:10.1542/peds.2012-2634
15. Ali AM, Bottle A. How do we interpret readmission rates? *BMJ* 2018;**362**:k3104. doi:10.1136/bmj.k3104
16. Underwood MA, Danielsen B, Gilbert WM. Cost, causes and rates of rehospitalization of preterm infants. *J Perinatol Off J Calif Perinat Assoc* 2007;**27**:614–9. doi:10.1038/sj.jp.7211801
17. Barradas DT, Wasserman MP, Daniel-Robinson L, *et al.* Hospital Utilization and Costs Among Preterm Infants by Payer: Nationwide Inpatient Sample, 2009. *Matern Child Health J* 2016;**20**:808–18. doi:10.1007/s10995-015-1911-y
18. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535. doi:10.1136/bmj.b2535
19. CASP checklist. Crit. Apprais. Ski. Programme. 2018.https://casp-uk.net/casp-tools-checklists/ (accessed 8 Aug 2019).
20. Higgins J, Green S. Quality scales and Cochrane reviews. In: *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration 2011.
21. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: : R Foundation for Statistical Computing 2013. http://www.R-project.org/
22. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 2019;**22**:153–60. doi:10.1136/ebmental-2019-300117
23. Jensen EA, Foglia EE, Dysart KC, *et al.* Car Seat Tolerance Screening in the Neonatal Intensive Care Unit: Failure Rates, Risk Factors, and Adverse Outcomes. *J Pediatr* 2018;**194**:60-66.e1. doi:10.1016/j.jpeds.2017.11.010
24. McLaurin KK, Hall CB, Jackson EA, *et al.* Persistence of Morbidity and Cost Differences Between Late-Preterm and Term Infants During the First Year of Life. *Pediatrics* 2009;**123**:653–9. doi:10.1542/peds.2008-1439
25. Regenbogen E, Zhang S, Yang J, *et al.* Epidemiological trends among preterm infants with apnea. A twelve-year database review. *Int J Pediatr Otorhinolaryngol* 2018;**107**:86–92. doi:10.1016/j.ijporl.2018.01.036
26. Schell S, Kase JS, Parvez B, *et al.* Maturational, comorbid, maternal and discharge domain impact on preterm rehospitalizations: a comparison of planned and unplanned rehospitalizations. *J Perinatol Off J Calif Perinat Assoc* 2016;**36**:317–24. doi:10.1038/jp.2015.194
27. Oltman SP, Amsalu R, Rogers EE, *et al.* Identification of Independent Metabolic Risk Profiles for 7-Day Readmission of Late Preterm Infants Using Machine Learning. San Diego:
28. Soni A, Kadam S, Pandit A, *et al.* Early Discharge of Preterm Infants- An Indian Perspective. *J Clin Diagn Res JCDR* 2016;**10**:SC21–3. doi:10.7860/JCDR/2016/21176.9110
29. Harron K, Gilbert R, Cromwell D, *et al.* Newborn Length of Stay and Risk of Readmission. *Paediatr Perinat Epidemiol* 2017;**31**:221–32. doi:10.1111/ppe.12359
30. Tseng Y-H, Chen C-W, Huang H-L, *et al.* Incidence of and predictors for short-term readmission among preterm low-birthweight infants. *Pediatr Int Off J Jpn Pediatr Soc* 2010;**52**:711–7. doi:10.1111/j.1442-200X.2010.03129.x
31. Donohue PK, Hussey-Gardner B, Sulpar LJ, *et al.* Convalescent care of infants in the neonatal intensive care unit in community hospitals: risk or benefit? *Pediatrics* 2009;**124**:105–11. doi:10.1542/peds.2008-0880
32. Samra HA, McGrath JM, Wey H, *et al.* The influence of geographic isolation on late preterm infant and mother outcomes. *Adv Neonatal Care Off J Natl Assoc Neonatal Nurses* 2013;**13**:205–15. doi:10.1097/ANC.0b013e318285fd58
33. Mallick AK, Venkatnarayan K, Thapar RK, *et al.* Morbidity Patterns of Late Preterm Babies Born Small for Gestation. *Indian J Pediatr* 2019;**86**:578–83. doi:10.1007/s12098-019-02925-4
34. Moyer LB, Goyal NK, Meinzen-Derr J, *et al.* Factors associated with readmission in late-preterm infants: a matched case-control study. *Hosp Pediatr* 2014;**4**:298–304. doi:10.1542/hpeds.2013-0120
35. Zhang R, Huang R-W, Gao X-R, *et al.* Involvement of Parents in the Care of Preterm Infants: A Pilot Study Evaluating a Family-Centered Care Intervention in a Chinese Neonatal ICU. *Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc* 2018;**19**:741–7. doi:10.1097/PCC.0000000000001586
36. Colin AA, McEvoy C, Castile RG. Respiratory Morbidity and Lung Function in Preterm Infants of 32 to 36 Weeks' Gestational Age. *Pediatrics* 2010;**126**:115–28. doi:10.1542/peds.2009-1381
37. Laugier O, Garcia P, Boucékine M, *et al.* Influence of Socioeconomic Context on the Rehospitalization Rates of Infants Born Preterm. *J Pediatr* 2017;**190**:174-179.e1. doi:10.1016/j.jpeds.2017.08.001

38. Ambalavanan N, Carlo WA, McDonald SA, *et al.* Identification of Extremely Premature Infants at High Risk of Rehospitalization. *Pediatrics* 2011;**128**:e1216–25. doi:10.1542/peds.2011-1142
39. Morris BH, Gard CC, Kennedy K, *et al.* Rehospitalization of extremely low birth weight (ELBW) infants: are there racial/ethnic disparities? *J Perinatol Off J Calif Perinat Assoc* 2005;**25**:656–63. doi:10.1038/sj.jp.7211361
40. Liptzin DR, Landau LI, Taussig LM. Sex and the lung: Observations, hypotheses, and future directions. *Pediatr Pulmonol* 2015;**50**:1159–69. doi:10.1002/ppul.23178
41. Townsel CD, Emmer SF, Campbell WA, *et al.* Gender Differences in Respiratory Morbidity and Mortality of Preterm Neonates. *Front Pediatr* 2017;**5**. doi:10.3389/fped.2017.00006
42. van Walraven C, Bennett C, Forster AJ. Administrative database research infrequently used validated diagnostic or procedural codes. *J Clin Epidemiol* 2011;**64**:1054–9. doi:10.1016/j.jclinepi.2011.01.001
43. The processing cycle and HES data quality. NHS Digit. https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics/the-processing-cycle-and-hes-data-quality (accessed 13 Jan 2020).

Figures

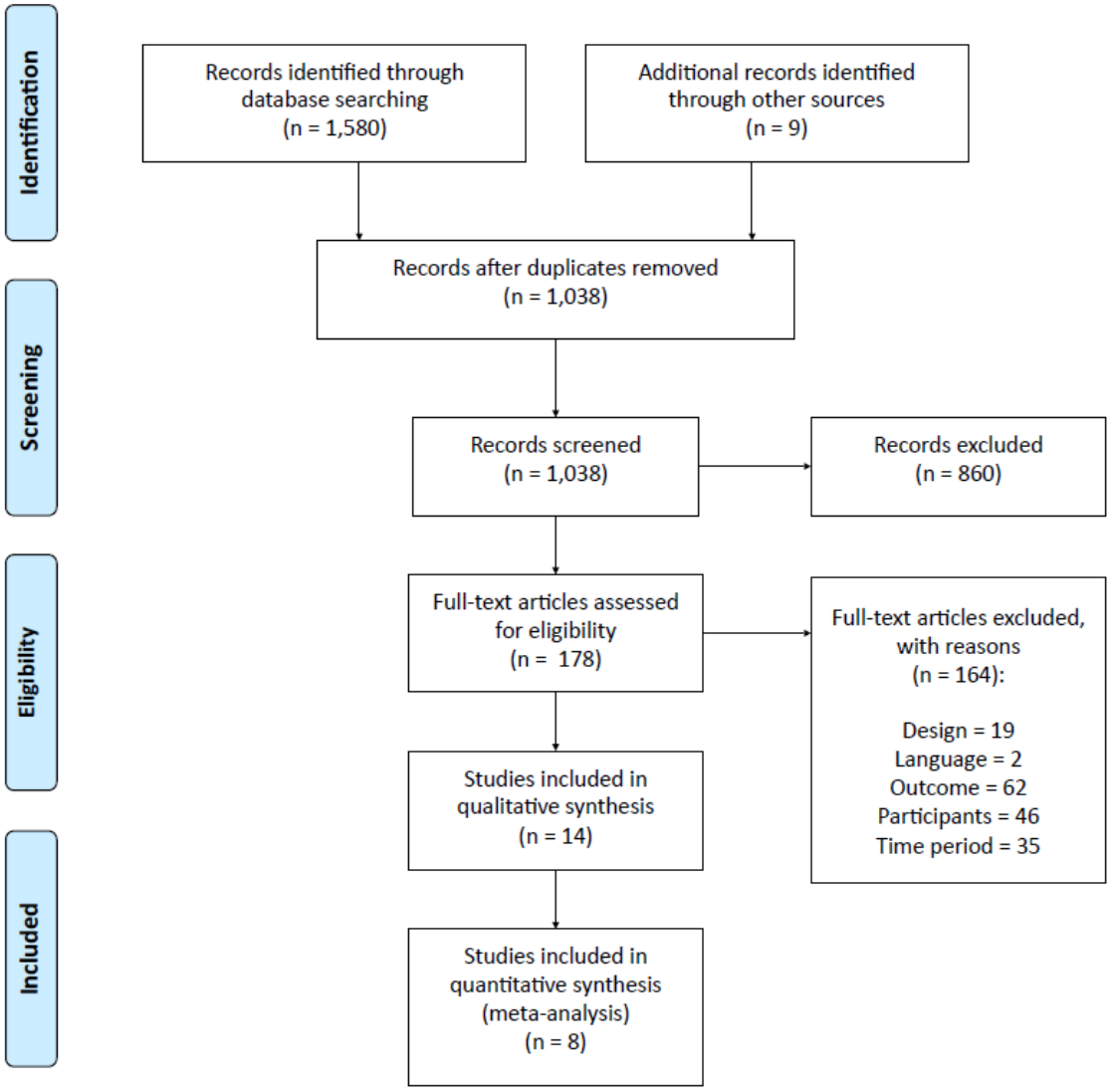
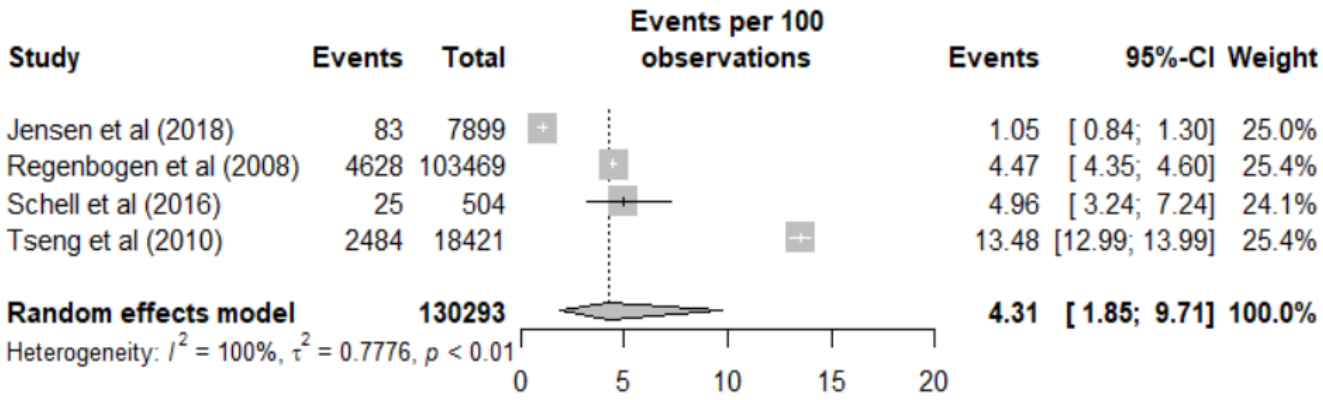


Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of study selection.

(a)



(b)

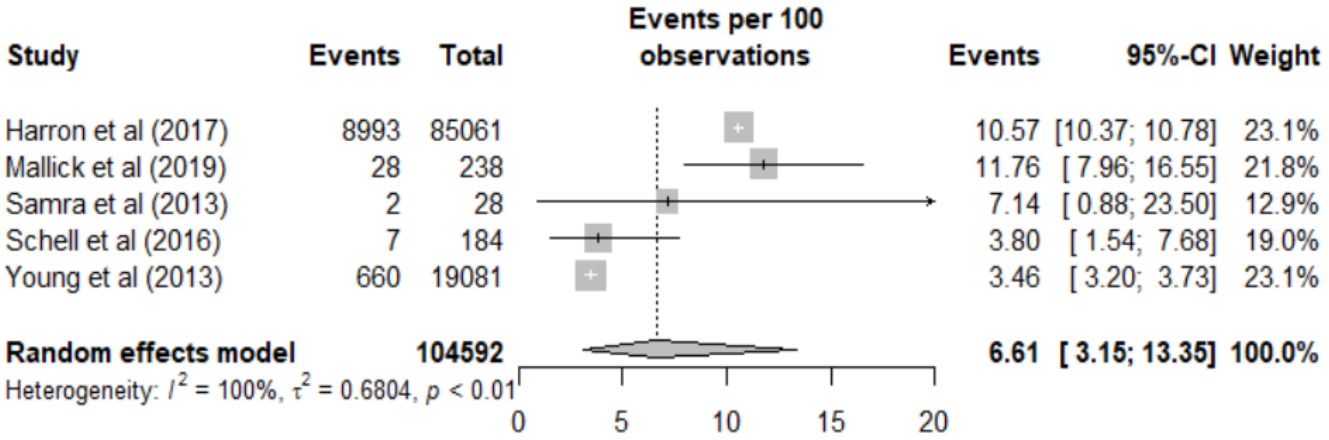


Figure 2

Forest plots for random effects meta-analysis of rehospitalisation rates in (a) four studies using samples of preterm babies born at <37 weeks gestation and (b) five studies using samples of babies born at 34 to <37 weeks gestation; CI= confidence interval.

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