

BMJ Open Impact of regionalisation and case-volume on neonatal and perinatal mortality: an umbrella review

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ABSTRACT

Objective This umbrella review summarises and critically appraises the evidence on the effects of regulated or high-volume perinatal care on outcome among very low birth weight/very preterm infants born in countries with neonatal mortality <5/1000 births.

Intervention/exposition Perinatal regionalisation, centralisation, case-volume.

Primary outcomes Death.

Secondary outcomes Disability, discomfort, disease, dissatisfaction.

Methods On 29 November 2019 a systematic search in MEDLINE and Embase was performed and supplemented by hand search. Relevant systematic reviews (SRs) were critically appraised with A MeaSurement Tool to Assess systematic Reviews 2.

Results The literature search revealed 508 hits and three SRs were included. Effects of perinatal regionalisation were assessed in three (34 studies) and case-volume in one SR (6 studies). Centralisation has not been evaluated. The included SRs reported effects on 'death' (eg, neonatal), 'disability' (eg, mental status), 'discomfort' (eg, maternal sensitivity) and 'disease' (eg, intraventricular haemorrhages). 'Dissatisfactions' were not reported. The critical appraisal showed a heterogeneous quality ranging from moderate to critically low. A pooled effect estimate was reported once and showed a significant favour of perinatal regionalisation in terms of neonatal mortality (OR 1.60, 95% CI 1.33–1.92). The qualitative evidence synthesis of the two SRs without pooled estimate suggests superiority of perinatal regionalisation in terms of different mortality and non-mortality outcomes. In one SR, contradictory results of lower neonatal mortality rates were reported in hospitals with higher birth volumes.

Conclusions Regionalised perinatal care seems to be a crucial care strategy to improve the survival of very low birth weight and preterm births. To overcome the low and critically low methodological quality and to consider additional clinical and patient-reported results that were not addressed by the SRs included, we recommend an updated SR. In the long term, an international, uniformly conceived and defined perinatal database could help to provide evidence-based recommendations on optimal strategies to regionalise perinatal care.

PROSPERO registration number CRD42018094835.

Strengths and limitations of this study

- To our knowledge this is the first umbrella review to synthesise and critically appraise present systematic reviews with and without pooled estimate to the effects of perinatal regionalisation in very low birth weight or very preterm birth cohorts.
- A systematic and comprehensive procedure was applied to find all published studies on this topic.
- An a priori protocol was registered.
- Evidence presented based solely on articles written in English or German.
- Heterogeneous quality of included reviews limits valid conclusions in terms of effectiveness of perinatal regionalisation programmes.

INTRODUCTION

Preterm birth and/or low birth weight are among the leading causes for child and infant mortality across high-income and middle-income countries and the main reason of disability adjusted life years,¹ despite of a decreased mortality due to very low birth weight (VLBW) or very preterm (VPT) birth in the past decades.² Preterm birth and low birth weight infants represent a highly vulnerable group with serious risks for death or severe morbidities.³ Different interventions to improve the physical, psychological and social outcomes of low birth weight and preterm infants range from medical treatments (eg, caffeine), psychosocial interventions (eg, parental empowerment) to political requirements like perinatal regionalisation.^{4–6}

The terms perinatal regionalisation and centralisation are often used interchangeably but both healthcare concepts have to be carefully distinguished. *Perinatal regionalisation* however, is a care strategy usually enforced by law. *Centralisation* is defined as a non-enforced concentration of care in well-experienced and equipped, usually large clinics.⁷ Depending on the case complexity, newborns are transferred to different levels of

care, starting with basic care in well newborn nurseries, followed by special care nurseries and neonatal intensive care units that usually provide highest level of care.

The aim of perinatal regionalisation is to improve newborn and maternal outcomes based on a risk-appropriate and specialised care.⁸ The forms, mechanisms and intensity of perinatal regionalisation programmes can differ and range from financial incentives and hospital (coordination, legislative requirements), geographical or patient characteristics.⁹

In different countries (eg, Germany, Finland, Norway, USA), neonatal care is provided at different levels of care, with well-defined technical and personal requirements. Otherwise, the centre is not allowed to provide this complex care.^{10 11}

Despite the potential benefit of perinatal regionalisation and minimal case-volume on perinatal and neonatal mortality and morbidity, there is still great controversy to implement these strategies. Opponents argue with potential difficulties (eg, in-utero transport) due to a subsequently reduced number of hospitals providing neonatal care.¹²

Thus, the present umbrella review aims to synthesise and critically appraise the current evidence concerning the association between both perinatal regionalisation, centralisation and case-volume on perinatal and post-natal death and morbidity to provide recommendations for healthcare regulations.

METHODS

In addition to a synthesis and critical appraisal of the existing systematic reviews (SRs), a further objective was to identify research gaps regarding possible populations, interventions or outcomes in order to make

recommendations for the need of an updated SR. This prospectively registered¹³ umbrella review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.¹⁴

Patient and public involvement

Since this is an SR and no patient-related primary data were collected, there was no involvement of patients or the public.

Inclusion and exclusion criteria

As presented in [table 1](#), articles were included if they met our predefined inclusion criteria.¹⁵ Eligible articles were published as a systematic review or meta-analysis in English or German until 29 November 2019. To be defined as SR, the following contents had to be reported according to the PRISMA statement¹⁴:

- ▶ A clear research question (details of the population, intervention and outcome).
- ▶ A search strategy.
- ▶ Study selection criteria.
- ▶ Some form of a (critical) appraisal of the studies included. While tools for the critical appraisal of the methodological study quality help to identify and understand the strengths and weaknesses of a study, reporting guidelines define a minimum amount of information necessary to ensure a clear and transparent process in conducting the study.¹⁶

Furthermore, relevant SRs had to include studies of (national) healthcare settings with a neonatal mortality <5/1000 births according to the child mortality report of 2017 to be able to analyse a comparable study population.¹⁵

Table 1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	VLBW (<1500 g) or VPT (<32 weeks' GA) born/treated in a national setting with neonatal mortality <5/1000 according to the UN child mortality report 2017 ¹⁵	No report of birth weight or GA
Interventions/expositions	Perinatal regionalisation, high case-volume, centralisation	No analysis of perinatal regionalisation, case-volume or centralisation
Comparisons	Low case-volume, perinatal deregionalisation/decentralisation	No comparison against other case-volumes/perinatal deregionalisation/centralisation
Outcomes	Primary: neonatal or perinatal mortality Secondary/explorative: other outcomes according to Donabedians '5 D's' (death, disease, disability, patient-reported dissatisfaction and discomfort) ⁴⁴ with focus on caesarean delivery rates; neonatal/maternal birth complications; readmissions; developmental delays	No measurement of mortality
Study types	Aggregated evidence presented as systematic review or meta-analysis	Study protocols, evidence presented by individual clinical or observational studies
Languages	German or English	Other languages than English or German

GA, gestational age; UN, United Nations; VLBW, very low birth weight; VPT, very preterm.

Literature search and study selection procedure

Based on a priori defined eligible criteria, a comprehensive search was conducted for relevant SRs in MEDLINE and Embase (via Ovid interface) published up to 29 November 2019 using different search terms like 'very low birth weight', 'perinatal', 'neonatal', 'volume', 'size' and 'regionalisation'. The detailed search strategy is outlined in online supplemental file 1. The search strategy included a combination of free text words and database-specific subject headings (eg, infant mortality/Perinatal Care). For 'systematic reviews' the search strategy proposed by the Scottish Intercollegiate Guidelines Network (SIGN) were applied.¹⁷ Additionally, a manual search by screening reference lists of included and full-text-screened articles was performed to identify further potentially relevant reviews. Two authors (FW and AB) independently screened titles/abstracts and full texts for eligibility. Disagreements were resolved by discussion and, if needed, by consulting a third reviewer (SD).

Data extraction

A predefined data extraction form in Excel was used including characteristics of the included reviews (eg, population/setting, number and types of included studies, definition of intervention) and outcomes (eg, label and definition) and study results (pooled estimate or descriptive). Data were extracted by one reviewer (FW) and verified by another reviewer (DBK) with discrepancies resolved by consensus between both reviewers.

Assessment of methodological quality of included reviews

The established instrument 'A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2) guideline, V.2' was used to assess the quality of the SRs. Due to the complexity of perinatal regionalisation as an intervention, we expected reviews that included both randomised and non-randomised study designs. Therefore 'A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2) guideline, V.2' facilitates the evaluation of reviews of both randomised and non-randomised study designs.

AMSTAR 2 contains 16 items which cover contents regarding transparent and prospectively registered inclusion criteria (items 1–3), search strategy (item 4), methods of study selection (items 5, 7), data extraction (item 6), quality appraisal (items 9, 13), reporting of study details and funding (items 8, 10), methods for quantitative synthesis (items 11, 12, 15) and funding (item 16). AMSTAR 2 focuses on 'critical weaknesses' and 'critical flaws' to provide a rating for overall confidence ('high', 'moderate', 'low', 'critically low') and is not intended to generate an overall score. Online supplemental file 2 contains detailed methodological explanations and definitions in the context of the application of the AMSTAR 2 checklist. Two reviewers (FW and DBK) conducted the quality assessment of included SRs independently. A third reviewer (SD) arbitrated discrepancies.

Data synthesis

Results and characteristics of included reviews were summarised in tabular format, organised according to intervention/exposition and outcomes.

RESULTS

In total 508 records were identified and 3 SRs^{18–20} were included for this umbrella review (figure 1). During the full-text screening, four articles were excluded.^{21–24} One review lacked a reporting guideline or a quality appraisal of its included studies²² and three did not evaluate an intervention²⁴ or evaluated irrelevant interventions like performance-based incentives²¹ or different therapy and emergency approaches.²³

Objectives and characteristics of included SRs

The included SRs were published between 2010 and 2014 and included 43 publications encompassing 40 different studies, which cover a study period starting in 1979 and ending in 2008 with study types varying from controlled before–after studies, retrospective cohort studies to randomised controlled trials. As presented in table 2, the studies were conducted in the USA (27/40), different European countries (8/40), Canada (4/40) and USA/Europe (1/40). Every review included the assessment of neonatal mortality, which was defined solely in one SR as death within 28 days of life.²⁰ One SR conducted a pooled estimate²⁰ and two SRs reported results descriptively.^{18 19} A quality appraisal of the studies included was performed by two SRs using either the risk of bias assessment of the Cochrane's Effective Practice and Organisation of Care group^{18 25} or an own quality assessment providing overall results of 'insufficient', 'adequate' and 'high' quality evidence without items applied.²⁰ One SR reported the application of the reporting guideline of the Meta-analysis Of Observational Studies in Epidemiology study group²⁶ without providing results.¹⁹

As illustrated in table 2 and more detailed in online supplemental file 3, all three SRs reported outcome-effects for perinatal regionalisation^{18–20} and one additionally reported size/volume-outcome relationships.¹⁹ The effects of perinatal centralisation were neither reported in any of the reviews nor conceptually distinguished from perinatal regionalisation. Rashidian *et al* descriptively summarised effects of perinatal regionalisation and focused on perinatal outcomes and process-outcomes of neonatal care in controlled or uncontrolled experimental or quasi-experimental study designs. The intervention, perinatal regionalisation, had to include 'formal levels of care and a referral arrangement between hospitals in a specified region or territory'. These inclusion criteria were fulfilled by eight studies published between 1979 and 2007.¹⁸

Neogi *et al* descriptively summarised the effects of perinatal regionalisation programmes and other factors like unit size and case-volume on neonatal and perinatal mortality compared with standard care/small units in six studies published between 1983 and 2007. The

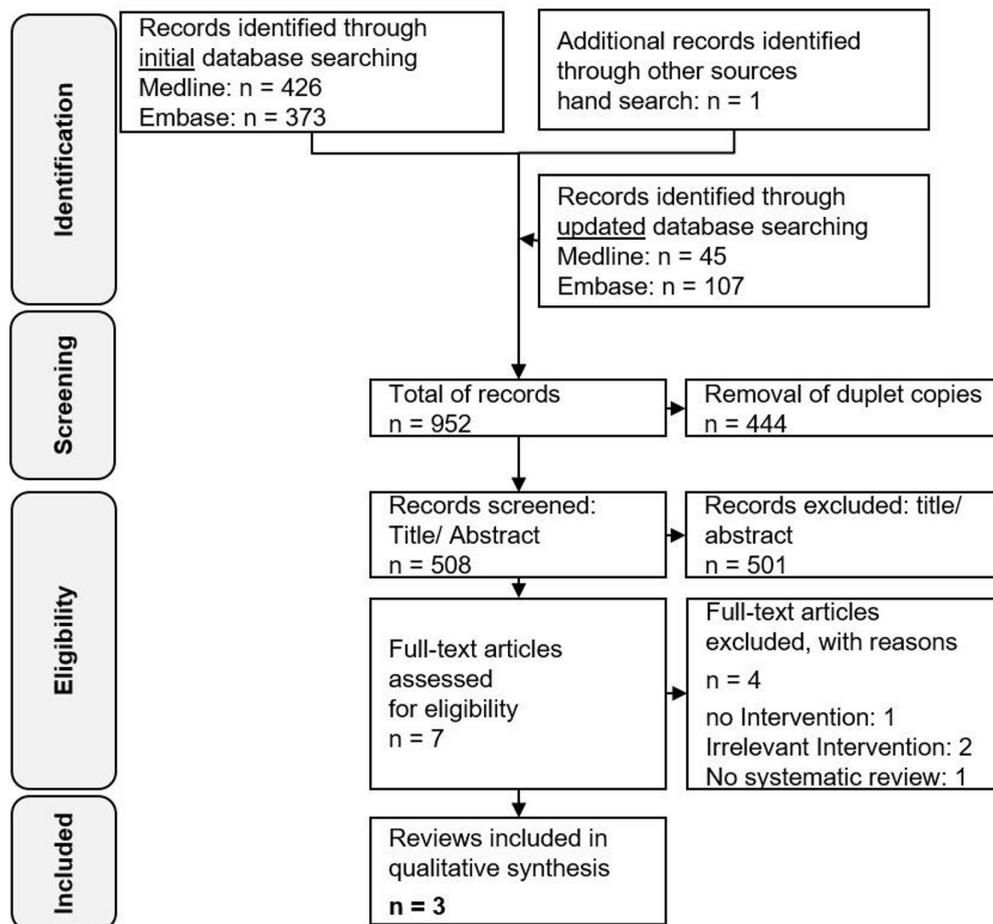


Figure 1 Flowchart of the review selection process.

volume-thresholds in the reported studies varied in terms of definition of the population (low-risk vs high risk) and thresholds (2000 annual births vs 3000 annual births). Perinatal regionalisation was evaluated in 17 studies and defined as a regionally coordinated and cooperative system in which maternal and perinatal care is designed according to the structural and procedural capabilities of the hospitals carrying it out.¹⁹ Due to lack of reporting, detailed results were only provided for 13 studies. The authors of this umbrella review additionally extracted the remaining four studies.^{27–30}

Lasswell *et al* quantitatively analysed the effects of perinatal regionalisation and focused on neonatal mortality of live-born VLBW (≤ 1500 g) or VPT (≤ 32 weeks' gestational age) neonates born after 1975. Lasswell *et al* defined perinatal regionalisation according to level-based system issued by the March of Dimes.²⁰ The model 'Improving the Outcome of Pregnancy' starts with basic, uncomplicated care of healthy neonates/infants (level I) to care for ill infants in level II and care for serious complications (eg, VLBW) and illnesses around the birth in level III.³¹ Included study types were randomised controlled trials, case-control studies and prospective or retrospective cohort studies. Twelve studies met inclusion criteria for the meta-analysis and were published between 1982 and 2008.²⁰

Given the slightly different inclusion criteria of the three SRs, there is minimal overlap of studies that were included in more than one review. As illustrated in figure 2, two studies were analysed for the outcome neonatal mortality in multiple reviews. Bode *et al*³² was included in all three^{18–20} and Cifuentes *et al*²⁸ in two SRs.^{19 20}

Effects of perinatal regionalisation and case-volume on neonatal and perinatal mortality and secondary outcomes

Table 3 summarises the effects of perinatal regionalisation and/or case-volume on neonatal and perinatal outcomes in the single study results (n/N) per SR.

Neonatal mortality

Rashidian *et al* reported on seven studies in which mortality decreased significantly (3/7) and non-significantly (4/7) after the implementation of perinatal regionalisation.¹⁸ Neogi *et al* reported that neonatal mortality of low and VLBW infants decreased significantly (4/10) and non-significantly (6/10) after perinatal regionalisation. For units with higher annual birth rates significantly (3/6) and non-significantly (3/6) lower neonatal mortality rates of VLBW and VPT infants were reported in comparison to units with smaller numbers of birth. Definition of 'higher birth rates' varied between 1000 and 3000 births per year in the different studies.¹⁹

Table 2 Characteristics of included SRs

Ref.	Year	Population	Intervention/ exposition	Comparison	Outcomes	Included studies			Critical appraisal of study or reporting quality	
						Σ	Designs	Published		Setting
SR without meta-analysis										
Rashidian <i>et al</i> ¹⁸	2014	Term and preterm birth	Perinatal regionalisation	Historical or concurrent control groups, comprised of usual care services (ie, no perinatal regionalisation)	Mortality (neonatal, perinatal, maternal), morbidit, birth weight, stillbirth, place of delivery	8	3 ITS 1 CBA 4 BA	1979–2007	6 USA 1 FR 1 CA	Risk of bias criteria for EPOC reviews
Neogi <i>et al</i> ¹⁹	2012	Term and preterm birth	Perinatal regionalisation	Not born in level III centres	Neonatal and perinatal mortality	17*	1 PC 2 BA 14 RC	1979–2001	13 USA 2 CA 1 UK 1 POR	MOOSE guidelines (no results provided)
SR with meta-analysis										
Lasswell <i>et al</i> ²⁰	2010	Liveborn VLBW (≤1500g), VPT (≤32 weeks' GA) born ≥1976	Perinatal regionalisation	Births at facilities with lower designated level of care, regardless of subsequent transfer	Neonatal mortality or pre-discharge/ in-hospital mortality	12	9 RC 1 PC 1 C-C 1 RCT	1982–2008	8 USA 1 USA and EU 1 CA 1 SWE 1 NL	Unreferenced own quality assessment (no results provided)

*The review authors reported the results of 13 studies; for four studies, the authors of this umbrella review extracted these missing results.

†Categorised by authors of the present umbrella review due to a lack of described study designs.

BA, before-after; CA, Canada; CBA, controlled before-after; C-C, case-control; EPOC, Cochrane's Effective Practice and Organisation of Care; EU, Europe; FR, France; GA, gestational age; GER, Germany; ITS, interrupted time series; MOOSE, Meta-analysis Of Observational Studies in Epidemiology; NL, Netherlands; NO, Norway; PC, prospective cohort; POR, Portugal; RC, retrospective cohort; RCT, randomised controlled trial; SR, systematic review; SWE, Sweden; VLBW, very low birth weight; VPT, very preterm.

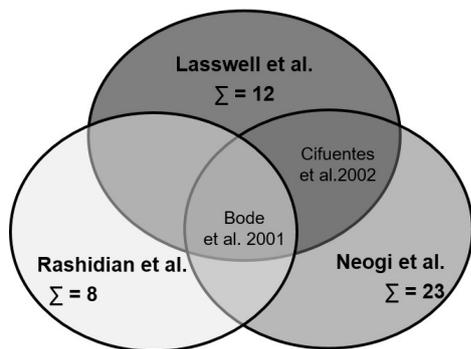


Figure 2 Multiple included primary studies.

Lasswell *et al* performed a pooled estimate (meta-analysis) and reported significantly decreased ORs in neonatal mortality for VLBW (OR 1.60 (95% CI: 1.33–1.92)), extremely low birth weight (OR 1.80 (95% CI: 1.31–2.46)) and VPT infants (OR 1.42 (95% CI: 1.06–1.88)) treated and born in highly equipped and well-staffed perinatal care centres.²⁰

Perinatal mortality

Rashidian *et al* reported a non-significant/descriptive decrease of perinatal mortality in three studies after implementing perinatal regionalisation programmes.¹⁸

Other types of mortality

For other types of mortality (fetal/stillbirth, 1-year mortality, unspecified, outborn), both significant and non-significant reductions were reported in two SRs.^{18 19} In three studies results of fetal, outborn and unspecified infant mortality could not be interpreted due to a lack of provided values and multiple inter-group comparisons.¹⁹

Other clinical outcomes

After implementing perinatal regionalisation, the incidence of possible ‘disease’-outcomes and perinatal complications like intraventricular haemorrhage (1/1) and low 5-min Apgar Score (2/2) decreased significantly. The rate of low birth weight deliveries decreased either significantly (2/3) and non-significantly (1/3). Maternal sensitivity as a possible outcome of ‘discomfort’ increased significantly in one study. Motor development and mental status of the infant at an age of 1 year as a possible outcome of ‘disability’ improved non-significantly in one study.¹⁸ The secondary outcome ‘dissatisfaction’ has not been reported in any systematic review.

Critical appraisal

As shown in table 4, the quality of the included reviews appeared to be heterogeneous (more details can be found in online supplemental file 4). Complete or partial complete information for most of the AMSTAR 2³³ items has been considered by Rashidian *et al* (9/12, ‘moderate confidence’) and Lasswell *et al* (11/16 ‘low confidence’).^{18 20} Neogi *et al* lacked information concerning review methods in summary (3/12, ‘critically low confidence’).¹⁹ The majority of reviews did not

provide complete Population, Intervention, Comparison, Outcome Study-based inclusion and exclusion criteria, a priori published protocols, justifications for exclusions of studies or provide transparent risk of bias assessments. The SR of Neogi *et al* unveiled inconsistencies in both the provided quality appraisals, extracted results and review methods. The lacking information in both the reporting quality of the included studies and five critical domains (items 2, 4, 7, 9, 13) led to two critical flaws and to a ‘critically low confidence’. The authors were contacted once about the inconsistencies described, but did not reply. The meta-analysis of Lasswell *et al* with a low confidence level included ‘adequate and high-quality’ studies without providing either detailed results or the instrument itself that was used for the quality appraisal.²⁰ This led to a lack of understanding for the quality rating itself and the reasons why studies were included for or excluded from the pooled estimate. This critical flaw and the insufficient information in three critical domains (items 7, 9 and 11) led to a ‘low confidence’ rating.

DISCUSSION

Main findings

Three SRs^{18–20} were included after the electronic and manual search of 508 titles and abstracts. These three reviews included 43 publications encompassing 40 different studies. Due to the slightly varying inclusion criteria of the included reviews, two studies were examined in several included reviews.^{28 32} As focused, the SRs mostly reported on neonatal mortality and different other mortality outcomes (eg, perinatal, infant, outborn). One SR reported results for different non-mortality outcomes like low birth weight or maternal sensitivity.¹⁸ Both the meta-analysis²⁰ and the qualitatively summarised SRs^{18 19} showed that neonatal mortality and other mortality outcomes decreased in the course of perinatal regionalisation and higher case-volumes. In addition, one review reported benefits associated with perinatal regionalisation for the outcomes intraventricular haemorrhage, low 5-minute Apgar score, low birth weight and maternal sensitivity.¹⁸

The methodological quality appeared to be heterogeneous between the three SRs with moderate, low and critically low confidence. This means that two out of three SRs did not meet the methodological criteria to give an accurate and careful umbrella review of the evidence presented. In particular, the non-transparent reporting on the results of the quality assessment limits traceability to such an extent that the results of one SR with²⁰ and one SR without a pooled estimate¹⁹ do not appear trustworthy. Since the reviews’ publication date (2010–2014), more studies were published recently, showing the continuous importance of this topic for both research and perinatal care. Results of several studies indicate that perinatal regionalisation, avoidance of postnatal transfer and particularly high-volume care led to decreased mortality and

Table 3 Effects of perinatal regionalisation/high case-volumes on birth outcomes

Ref.	Intervention/exposure	Reported outcomes	Studies per outcome	Design	Results
SRs without meta-analysis					
Rashidian <i>et al</i> ¹⁸	Perinatal regionalisation	Neonatal mortality	7	3× ITS, 1× CBA, 3× BA	Significant decrease: 1× ITS, 2× BA Non-significant decrease: 2× ITS, 1× CBA, 1× BA
		Perinatal mortality	3	2× ITS, 1× BA	Non-significant decrease: 1× ITS, 1× BA
		Fetal mortality	2	1× ITS, 1× BA	Significant decrease: 1× BA Non-significant descriptive decrease: 1× ITS
		Stillbirth	2	1× ITS, 1× BA	Non-significant decrease: 1× ITS, 1× BA
		Intraventricular haemorrhage	1	1× BA	Significant decrease: 1× BA
		Infant mortality	1	1× ITS	Significant decrease: 1× ITS
		Low 5-min Apgar Score	2	2× BA	Significant decrease: 2× BA
		Low birth weight	3	1× ITS, 2× CBA	Significant decrease: 2× BA Non-significant decrease: 1× ITS
		Motor development, mental status	1	1× BA	Non-significant increase: 1× BA
		Maternal sensitivity	1	1× BA	Significant increase: 1× BA
Neogi <i>et al</i> ¹⁹	Perinatal regionalisation	Neonatal mortality	8+2	7±2× RC, 1× BA	Significant decrease: 3±1× RC Non-significant decrease: 4±1× RC, 1× BA
		Fetal mortality/stillbirth	2	2× RC	No difference: 1× RC not interpretable: 1× RC
		Unspecified infant mortality	2+2	2±2× RC	Descriptive decrease in 2±1× RC not interpretable in ±1× RC
		Outborn mortality	1	1× PC	Not interpretable in 1× PC
Neogi <i>et al</i> ¹⁹	Unit size/ case-volume	Neonatal mortality	6	6× RC	Significant decrease in higher care-volumes: 3× RC Non-significant decrease in higher care-volumes: 3× RC
SRs with meta-analysis					
Lasswell <i>et al</i> ²⁰	Perinatal regionalisation	Neonatal mortality: VLBW	9	7× RC, 1× PC, 1× C-C	Pooled estimate significantly higher when born in lower level hospitals: adjusted OR 1.60; (95% CI, 1.33–1.92)
		Neonatal mortality: ELBW	5	4× RC, 1× C-C	Pooled estimate significantly higher when born in lower level hospitals: adjusted OR 1.80; (95% CI, 1.31–2.46)
		Neonatal mortality: VPT	3	2× RC, 1× RCT	Pooled estimate significantly higher when born in lower level hospitals: adjusted OR 1.42; (95% CI, 1.06–1.88)

(±...) study were extracted by authors of the present umbrella review.

BA, before–after; CBA, controlled before–after; C–C, case–control ; CI, confidence interval

; ELBW, extremely low birth weight; ITS, interrupted time series; OR, odds ratio

; PR, perinatal regionalisation; RC, retrospective cohort; RCT, randomised controlled trial; SRs, systematic reviews; VLBW, very low birth weight; VPT, very preterm.

**Table 4** Critical appraisal of included SRs (short version)¹⁸

Quality criteria	Rashidian <i>et al</i> ¹⁸	Neogi <i>et al</i> ¹⁹	Lasswell <i>et al</i> ²⁰
1. Did the research questions and inclusion criteria for the review include the components of PICO?	NO	NO	YES
2. <i>Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?</i>	Partial YES	NO	Partial YES
3. Did the review authors explain their selection of the study designs for inclusion in the review?	NO	NO	NO
4. <i>Did the review authors use a comprehensive literature search strategy?</i>	Partial YES	NO	Partial YES
5. Did the review authors perform study selection in duplicate?	YES	YES	NO
6. Did the review authors perform data extraction in duplicate?	YES	NO	YES
7. <i>Did the review authors provide a list of excluded studies and justify the exclusions?</i>	YES	NO	NO
8. Did the review authors describe the included studies in adequate detail?	YES	Partial YES	Partial YES
9. <i>Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?</i>	Includes NRSI: YES	Not provided: NO	Includes NRSI and RCTs: NO
10. Did the review authors report on the sources of funding for the studies included in the review?	NO	NO	NO
11. Meta-analysis performed?	NO	NO	YES
(a) <i>If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results for RCTs?</i>	N/A	N/A	NO
(b) <i>If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results for NRSI?</i>	N/A	N/A	NO
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A	N/A	YES
13. <i>Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?</i>	YES	NO	YES
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N/A	N/A	YES
15. <i>If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?</i>	N/A	N/A	YES
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	YES	YES	YES
Summary by authors: complete or partially fulfilled items (N=16 or 12, resp.)	9/12	3/12	11/16
Insufficient information in critical domains	1/7	5/7	3/7
Critical flaw* (insufficient information in item 9; insufficient information in items 1–4 and 7)	None	2	1
Overall confidence	Moderate	Critically low	Low

*Items written in italic are critical for an overall confidence rating.

N/A, not applicable; NRSI, non-randomised studies of interventions; PICO, Population, Intervention, Comparison, Outcome; RCT, randomised controlled trial; RoB, risk of bias; SRs, systematic reviews.

morbidity outcomes of (very) low birth weight and preterm births.^{34–36} The results for (very) low birth weight and (very) preterm birth led to the question whether regionalisation/case-volume could improve the outcome of low-risk births as well. The impact of case-volume and/or perinatal regionalisation on neonatal and/or maternal outcomes after healthy pregnancy is in the focus of current research but shows inconsistent results.^{37–39} Therefore, an updated SR seems to be necessary to overcome the methodological

limitations in already published SRs and to include additional clinical and patient-reported outcomes.

In addition, an assessment of regionalisation or volume effects must take into account both the national individual design of healthcare (eg, neonatal transport) and methodological differences in study design (eg, different definitions of neonatal mortality).^{40–42} Additionally, a specific international perinatal database (eg, European Union) could help to describe homogeneous settings,

study populations, outcomes and care-volumes for low-risk as well as high-risk births.

Strengths and limitations

One strength of this umbrella review is the clear and replicable method used to select appropriate SRs to answer the research question. In addition to the comprehensive search strategy, screenings of reference lists and citations of potentially relevant SRs were performed to capture all available evidence. Two independent reviewers performed screening of potentially relevant SRs, data extraction and critical appraisal by using a standardised checklist of all SRs included.³³

However, the global approach of an umbrella review leads to methodological weaknesses.⁴³ The analysis relied on information that were given in the included SRs. Given the results of our critical appraisal of all three reviews, the presented evidence synthesis of this umbrella review suffers from heterogeneous reporting and low respectively critically low methodological quality in two SRs. For example, in the meta-analysis of Lasswell *et al.*,²⁰ it was not possible to understand the study selection for the pooled estimate. Neither the (self-conceptualised) quality rating and its validity nor detailed results per study were illustrated. In consequence, we do not know if the pooled evidence has the 'high quality' as reported by Lasswell *et al.*²⁰

It has to be taken into consideration that perinatal regionalisation programmes are designed differently with basic similarities (level-based care) and heterogeneous additional mechanisms (eg, financial incentives).⁹ Neither the included SRs broadly described the interventions with detailed frameworks, structures and requirements nor did they distinguish perinatal regionalisation and perinatal centralisation. In the SR of Neogi *et al* different volume-thresholds of 'large' and 'small' hospitals were described, which is strongly limiting comparability. Additionally, the included studies cover a time span of 29 years in which the setting and the birth care changed fundamentally.

Implications for policy and research

The three included reviews analysed primarily data on neonatal mortality and reported an improved survival due to perinatal regionalisation/high case-volume care of VLBW and VPT infants. Whereas the available evidence favours perinatal regionalisation programmes and high-volume settings, an updated meta-analysis of recent studies would help to overcome the questionable quality of two SRs and would provide data on additional clinical and patient-reported outcomes. In a long-term perspective, the development and implementation of a specific international perinatal database that consider both care and patient context with the goal to overcome differences in the definition of thresholds, population and outcomes would help to establish a sustainable comparability between results of future studies and local policies of perinatal care.

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