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Review Article

OBSTETRIC ANAESTHESIA

Epidural analgesia, intrapartum hyperthermia, and neonatal brain injury: a systematic review and meta-analysis

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Abstract

Background: Epidural analgesia is associated with intrapartum hyperthermia, and chorioamnionitis is associated with neonatal brain injury. However, it is not known if epidural hyperthermia is associated with neonatal brain injury. This systematic review and meta-analysis investigated three questions: (1) does epidural analgesia cause intrapartum hyperthermia, (2) is intrapartum hyperthermia associated with neonatal brain injury, and (3) is epidural-induced hyperthermia associated with neonatal brain injury?

Methods: PubMed, ISI Web of Knowledge, The Cochrane Library, and Embase were searched from inception to January 2020 using Medical Subject Headings (MeSH) terms relating to epidural analgesia, hyperthermia, labour, and neonatal brain injury. Studies were reviewed independently for inclusion and quality by two authors (Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach). Two meta-analyses were performed using the Mantel–Haenszel fixed effect method to generate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Forty-one studies were included for Question 1 (646 296 participants), 36 for Question 2 (11 866 021 participants), and two studies for Question 3 (297 113 participants). When the mode of analgesia was randomised, epidural analgesia was associated with intrapartum hyperthermia (OR: 4.21; 95% CI: 3.48–5.09). There was an association between intrapartum hyperthermia and neonatal brain injury (OR: 2.79; 95% CI: 2.54–2.3.06). It was not possible to quantify the association between epidural-induced hyperthermia and neonatal brain injury.

Conclusions: Epidural analgesia is a cause of intrapartum hyperthermia, and intrapartum hyperthermia of any cause is associated with neonatal brain injury. Further work is required to establish if epidural-induced hyperthermia is a cause of neonatal brain injury.

Keywords: cerebral palsy; epidural analgesia; fever; hyperthermia; labour; neonatal brain injury; neonatal encephalopathy; thermoregulation

Editor's key points

- The authors performed a systematic review and meta-analysis of the evidence linking epidural analgesia, intrapartum hyperthermia, and neonatal brain injury.
- The evidence suggests that epidural analgesia is a cause of intrapartum hyperthermia. Although intrapartum hyperthermia is associated with an increase in the risk of neonatal brain injury, the association with epidural-induced hyperthermia is not clear.
- Further evidence is needed to allow us to determine whether epidural-induced hyperthermia is an independent risk factor for neonatal brain injury.

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Neonatal brain injury is a devastating condition with lifelong consequences for the individual, their families, and healthcare organisations. Its prevalence in England is approximately 5 per 1000 live births.[1] It is difficult to estimate the total financial burden, but an indication may be derived from the amounts awarded as a result of medical litigation. In 2012, an analysis of maternity claims by the National Health Service Litigation Authority reported that the value of claims for the period 2000–10 was £1.26 billion.[2] The term 'neonatal brain injury' refers to a spectrum of disease that includes neonatal encephalopathy and cerebral palsy.[3]

The aetiology of neonatal brain injury is multifactorial.[4] Although the terms 'neonatal brain injury' and 'birth asphyxia' are sometimes used synonymously, overt evidence of intrapartum hypoxia is present in less than 20% of cases of cerebral palsy.[5] In contrast, chorioamnionitis is present in up to 31% of cases and is associated with a 2.1-fold increased risk of cerebral palsy.[6,7] However, in many studies, the diagnosis of chorioamnionitis is made clinically: elevated maternal temperature (hyperthermia) with or without other features of infection, such as tachycardia (maternal or fetal), leucocytosis, or foul-smelling vaginal discharge.[6] During the intrapartum period, clinical parameters have poor sensitivity for the prediction of microbiologically proven infection, and so it is not clear if the increased risk of brain injury is confined to parturients with infection or if intrapartum hyperthermia of any cause is detrimental to the neonatal brain.[8]

Intrapartum hyperthermia may be secondary to intrapartum infection or epidural analgesia (epidural hyperthermia). The most common form of intrapartum infection is bacterial genito-urinary tract infection, which has an incidence of 4%.[9] Epidural hyperthermia, also known as epidural-related fever, refers to the situation in which a parturient who has an epidural for labour analgesia develops an elevated body temperature.[10] It was first reported in 1989 that epidural analgesia increases the risk of intrapartum hyperthermia, and over the ensuing 30 yr, this association has been extensively studied.[11,12] However, it remains a somewhat enigmatic condition, and the underlying mechanism remains unclear. Previous systematic reviews have demonstrated that epidural analgesia does not increase the risk of intrapartum infection and that it is not selected by parturients with a greater risk of intrapartum infection (selection bias).[11,12] Consequently, the most likely explanation is that epidural hyperthermia is a distinct condition secondary to either cholinergic sympathetic blockade, immunomodulation, or both.[13–15]

The increasing evidence linking intrapartum hyperthermia and neonatal brain injury, and the recognition of epidural hyperthermia as a distinct condition have raised the question of whether epidural-induced hyperthermia is an independent risk factor for neonatal brain injury, distinct from the established risk factor of intrapartum infection.[16,17] Currently, no systematic reviews have sought to investigate this question. The aims of this systematic review and meta-analysis were to investigate if there is (1) a causal link between epidural analgesia and intrapartum hyperthermia, (2) an association between intrapartum hyperthermia (of any cause, rather than chorioamnionitis) and neonatal brain injury, and (3) an association between epidural-induced hyperthermia and neonatal brain injury. Meta-analyses were performed to assess the strength of these links and to provide estimates of the effect sizes.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was prospectively registered on the PROSPERO register (CRD42020164144).[18,19]

Literature search

PubMed, ISI Web of Knowledge, The Cochrane Library, and Embase were searched electronically in January 2020 by two independent reviewers (SM and JK) using separate Medical Subject Headings (MeSH) terms (Table 1). To investigate a causal link between epidural analgesia and intrapartum hyperthermia (study Question 1), the MeSH terms for epidural analgesia, hyperthermia, labour, and types of study were combined with the Boolean operator 'AND'. To investigate the association between intrapartum hyperthermia (of any cause) and neonatal brain injury (study Question 2), the MeSH terms for hyperthermia, labour, neonatal brain injury, and types of study were combined. To investigate the association between epidural hyperthermia and neonatal brain injury (study Question 3), all MeSH terms were combined with the Boolean operator 'AND'. All databases were searched from inception until the search date (January 13, 2020). Included study designs were peer-reviewed RCTs and prospective and retrospective cohort and case–control studies. Participant inclusion criteria were human females who were pregnant and underwent labour for delivery of a neonate. Included exposures and outcomes were epidural analgesia, intrapartum hyperthermia (temperature ≥37.5°C), and neonatal brain injury. Non-English language papers were excluded. A full description of the

Table 1 Medical Subject Headings (MeSH) terms for electronic database search.

Hyperthermia
fever* OR hyperthermia* OR chorioamnionitis OR temperature OR sepsis OR infection OR septicaemia
Terms for epidural analgesia
epidural OR combined spinal epidural OR CSE OR neuraxial block OR neuraxial blockade
Labour
labour* OR labor OR intrapartum
Adverse neurological neonatal outcomes
neonatal brain injury OR neonatal neurological outcome OR cerebral palsy OR neonatal encephalopathy OR neonatal seizures OR therapeutic hypothermia
Types of study
retrospective OR prospective OR randomised OR randomised controlled OR observational OR cohort studies OR RCT OR randomised* OR cohort OR case-control

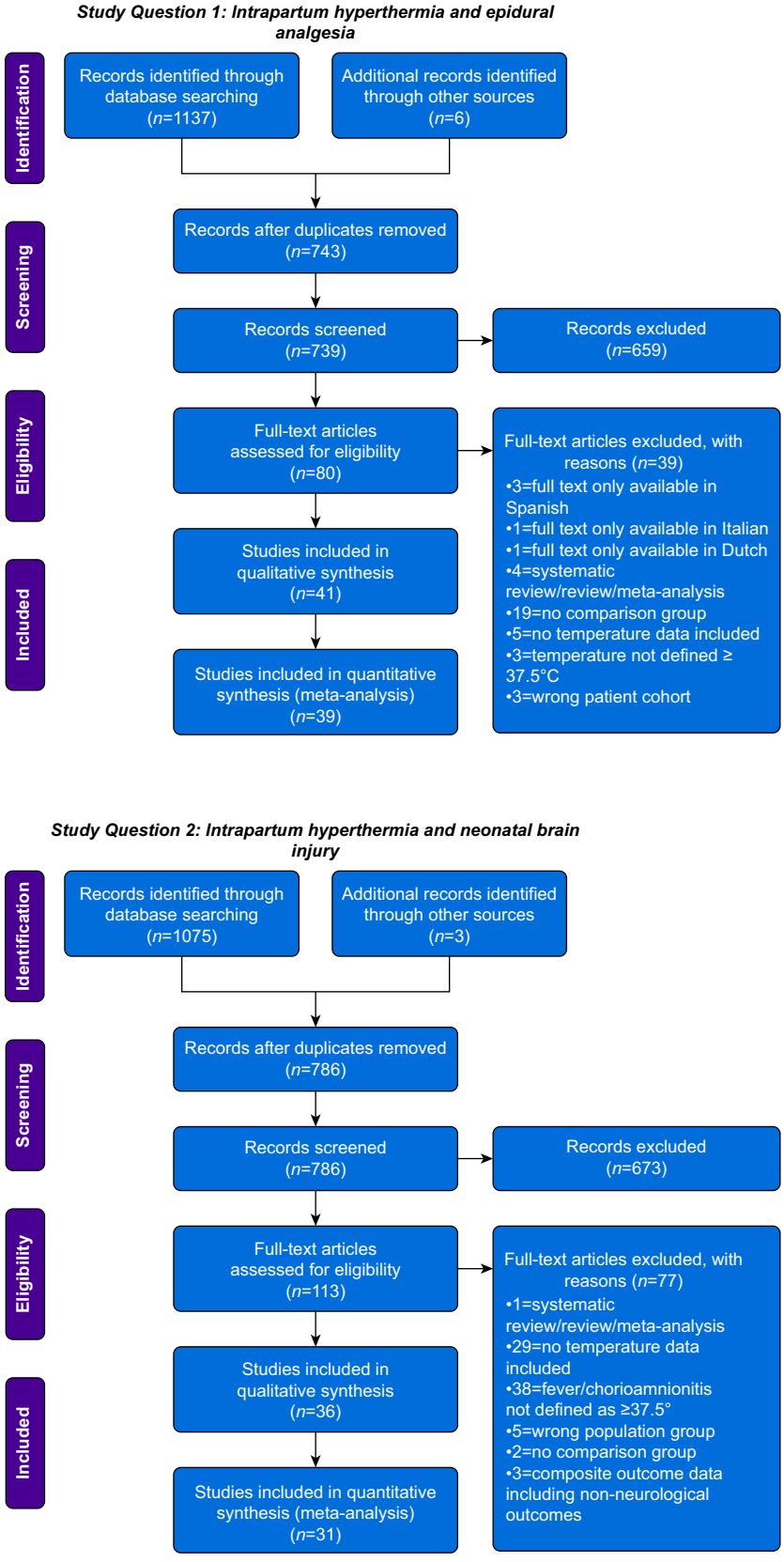


Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for each study question.

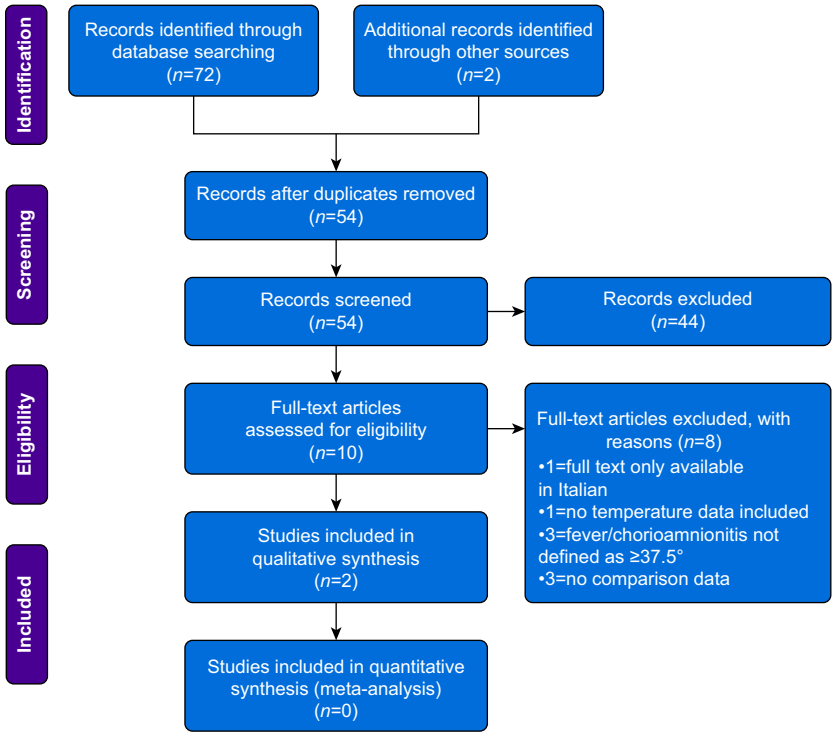


Fig 1. (continued).

inclusion and exclusion criteria is found in Supplementary Table 1.

Titles were uploaded to a reference manager software (EndNote X7; Clarivate Analytics, Boston, MA, USA) and duplicates were removed. All titles were searched and reviewed by two independent authors (SM and JK). Full-text articles were obtained for those titles that fulfilled the inclusion and exclusion criteria. Reference lists of included studies were also screened for any additional studies. After review of abstracts, full-text articles were reviewed to ensure they met the inclusion criteria. If any clarification was required about a study, authors were contacted via e-mail; if no response was obtained from the author(s) within 1 month, their study was excluded from the analysis. Any disagreements regarding inclusion were reviewed by a third independent author (CJM), who made the final decision.

Data extraction and analysis

Data were extracted independently by two authors (SM and JK). Extracted parameters included study design, number of participants, gestation at the time of delivery, neonate birth weight, study exposures, and study outcomes. All data extraction was reviewed by a third author (CJM).

Two meta-analyses were performed using Review Manager 5.3 (The Cochrane Collaboration, London, UK). Data were extracted for study Questions 1 and 2; it was not possible to perform a meta-analysis for study Question 3, as only two studies were included. Studies were excluded from the meta-analysis if there was no comparison group, the outcome data were already included in another study (to prevent double counting of data), or no event data were available. For the meta-analysis, only adverse neurological neonatal outcomes that had a long-term effect on the child were included (early-onset seizures; neonatal encephalopathy; *Bayley Scales of Infant Development*, 2nd Edn. (BSID-II) score; and radiological and clinical diagnoses of cerebral palsy).[20] A hierarchy of outcome significance was used to determine which outcome to extract in the case of a study including two or more outcomes (early-onset seizures < neonatal encephalopathy < BSID-II score < radiological cerebral palsy < clinical cerebral palsy); the outcome with the most significant long-term significance was included.

Forest plots were generated and overall odds or risk ratios with 95% confidence intervals (CIs) were calculated using the Mantel–Haenszel fixed effect method. Statistical significance was defined as a P-value <0.05. An I^2 statistic was calculated as a measure of statistical heterogeneity and classified as per the Cochrane Handbook: 0–40% non-significant, 30–60% moderate heterogeneity, 50–90% substantial heterogeneity, and 75–100% considerable heterogeneity.[21] Funnel plots were generated to assess publication bias for any analysis including 10 or more studies. Egger's regression test was performed to quantitatively assess the presence of funnel plot asymmetry. Two pre-specified subgroup analyses were performed. For study Question 1, only RCTs were included. For study Question 2, only studies where the exposure was intrapartum hyperthermia alone were included, rather than hyperthermia as a

Table 2 Summary of study characteristics. BSID-II, *Bayley Scales of Infant Development*, 2nd Edn.; BW, birth weight; CSE, combined spinal–epidural; HIE, hypoxic–ischaemic encephalopathy; IVH, intraventricular haemorrhage; PCA, patient-controlled analgesia; PVL, periventricular leucomalacia. *Retrospective and prospective design. †Included in 'epidural analgesia and intrapartum hyperthermia' meta-analysis. ‡Stratified into term and preterm deliveries. ¶Included in 'epidural analgesia and intrapartum hyperthermia' and 'intrapartum hyperthermia and neonatal brain injury' meta-analyses.

Reference (publication year)	Sample	Study design	Exposure	Outcome	Gestation/BW
Epidural analgesia and intrapartum hyperthermia					
Abramovici and colleagues[24] (2014)	1785	Cohort (RCT: 2° analysis)	Epidural *vs* no epidural	Clinical chorioamnionitis	All deliveries
Agakidis and colleagues[25] (2011)	960	Retrospective cohort	Epidural *vs* no epidural	Hyperthermia (>38°C)	Full term
Baheri and colleagues[26] (2013)	180	Prospective cohort	Epidural *vs* no analgesia	Hyperthermia (>37.5°C)	Full term
Burgess and colleagues[27] (2017)	360	Retrospective cohort	Epidural *vs* no epidural	Hyperthermia (>38°C)	36–42 weeks
Curtin and colleagues[28] (2015)	641	Retrospective cohort	Epidural *vs* no epidural	Hyperthermia (>38°C)	≥37 weeks
Dashe and colleagues[29] (1999)	149	Prospective cohort	Epidural *vs* pethidine	Hyperthermia (>38°C)	≥2500 g
del Arroyo and colleagues[14] (2019)	53	Prospective cohort	Epidural *vs* other analgesia	Hyperthermia (≥38°C)	≥37 weeks
de Orange and colleagues[30] (2011)	72	RCT	CSE *vs* non-pharmacological	Hyperthermia (>38°C)	Full term
Douma and colleagues[31] (2015)	116	RCT	Epidural *vs* remifentanil PCA	Hyperthermia (>38°C)	37–42 weeks
Evron and colleagues[32] (2007)	56	RCT	Epidural *vs* pethidine PCA	Hyperthermia (>37.5°C)	Full term
Evron and colleagues[33] (2008)	213	RCT	Epidural *vs* remifentanil PCA	Hyperthermia (>38°C)	Full term
Freeman and colleagues[34] (2015)	1358	RCT	Epidural *vs* remifentanil PCA	Hyperthermia (>38°C)	>32 weeks
Fusi and colleagues[10] (1989)	40	Prospective cohort	Epidural *vs* pethidine	Hyperthermia (>37.5°C)	>36 weeks
Goetzl and colleagues[35] (2001)	1109	Cohort (RCT: 2° analysis)	Epidural *vs* no epidural	Hyperthermia (>37.5°C)	Full term
Gross and colleagues[36] (2002)	1233	Cohort (RCT: 2° analysis)	Epidural *vs* no epidural	Hyperthermia (>38°C)	Full term
Herbst and colleagues[37] (1995)	3109	Retrospective case–control	Epidural *vs* no epidural	Hyperthermia (>38°C)	Full term
Kaul and colleagues[38] (2001)	1177	Retrospective cohort	Epidural *vs* no epidural	Hyperthermia (>38°C)	All deliveries
Lieberman and colleagues[39] (1999)	1233	Cohort (RCT: 2° analysis)	Epidural *vs* no epidural	Hyperthermia (>37.5°C)	Full term
Logtenberg and colleagues[40] (2017)	409	RCT	Epidural *vs* remifentanil PCA	Hyperthermia (>38°C)	>32 weeks
Lucas and colleagues[41] (2001)	736	RCT	Epidural *vs* pethidine PCA	Hyperthermia (≥38°C)	All deliveries
Maayan-Metzger and colleagues[42] (2006)	320	Case–control	Epidural *vs* no epidural	Hyperthermia (>37.8°C)	>35 weeks
Mark and colleagues[43] (2000)	16 226	Retrospective cohort	Epidural *vs* no epidural	Clinical chorioamnionitis (>37.8°C)	All deliveries
Mayer and colleagues[44] (1997)	287	Retrospective cohort	Epidural *vs* i.v. opioid	Hyperthermia (>37.8°C)	Full term
Nafisi[45] (2006)	395	RCT	Epidural *vs* i.v. pethidine	Hyperthermia (≥38°C)	All deliveries
Philip and colleagues[46] (1999)	715	RCT: 2° analysis	Epidural *vs* pethidine PCA	Hyperthermia (>38°C)	Full term
Ploeckinger and colleagues[47] (1995)	7317	Retrospective cohort	Epidural *vs* no epidural	Hyperthermia (>38°C)	All deliveries
Ramin and colleagues[48] (1995)	1330	RCT	Epidural *vs* pethidine	Hyperthermia (>38°C)	Full term
Reilly and Oppenheimer[49] (2005)	16 505	Case–control	Epidural *vs* no epidural	Hyperthermia (>37.5 [×2] or 38 [×1]°C)	≥37 weeks
Riley and colleagues[50] (2011)	200	Cohort (RCT: 2° analysis)	Epidural or CSE *vs* no epidural	Hyperthermia (>38°C)	≥37 weeks
Sharma and colleagues[51] (1997)	715	RCT	Epidural *vs* pethidine PCA	Hyperthermia (>38°C)	Full term
Sharma and colleagues[52] (2002)	459	RCT	Epidural *vs* i.v. pethidine	Hyperthermia (≥38°C)	Full term
Sweed and colleagues[53] (2011)	60	RCT	Epidural *vs* CSE *vs* i.v. pethidine	Hyperthermia (≥38°C)	Full term
Vinson and colleagues[54] (1993)	81	Cohort*	Epidural *vs* no epidural	Hyperthermia (>37.5°C)	Full term

Continued

Table 2 Continued

Reference (publication year)	Sample	Study design	Exposure	Outcome	Gestation/BW
Wassen and colleagues[55] (2014)	906	Case–control	Epidural *vs* no epidural	Hyperthermia (>38°C)	37–42 weeks
White and colleagues[56] (2017)	261 457	Retrospective cohort	Epidural *vs* no epidural	Hyperthermia (>38°C)	≥37 weeks
Yin and Hu[57] (2019)	506	Retrospective cohort	Epidural *vs* no epidural	Hyperthermia (>37.5°C)	≥37 weeks
Intrapartum hyperthermia and neonatal brain injury					
Alexander and colleagues[58] (1999)	101 170	Retrospective cohort	Clinical chorioamnionitis	Early-onset seizures	≥2500 g
Ashwal and colleagues[59] (2018)†	927	Retrospective cohort	Hyperthermia (>38°C)	Early-onset seizures	37–42 weeks
Badawi and colleagues[60] (1998)	564	Case–control	Hyperthermia (>37.5°C)	Neonatal encephalopathy	Full term
Bauer and colleagues[61] (2009)	339	Case–control	Hyperthermia (>38°C)	PVL	26–35 weeks
Blume and colleagues[62] (2008)	6390	Case–control	Hyperthermia (>38°C)	Neonatal encephalopathy	≥37 weeks
Dammann and colleagues[63] (2003)	294	Prospective cohort	Hyperthermia (>38.5°C)	Cerebral palsy	<37 weeks and <1500 g
Dior and colleagues[64] (2014)	42 601	Retrospective cohort	Hyperthermia (>37°C)	HIE or seizures	≥37 weeks and <5000 g
Dior and colleagues[65] (2016)†	43 560	Retrospective cohort	Hyperthermia (>38°C)	HIE or seizures	≥37 weeks and <5000 g
Edwards and colleagues[66] (2018)	1944	Cohort (RCT: 2° analysis)	Clinical chorioamnionitis	Cerebral palsy at 2 yr	24–31 weeks
Ghi and colleagues[67] (2010)	72	Case–control	Hyperthermia (>38°C)	Neonatal encephalopathy	≥37 weeks
Greenwood and colleagues[68] (2005)	881	Case–control	Hyperthermia (≥38°C)	Cerebral palsy	All deliveries‡
Grether and Nelson[69] (1997)	475	Case–control	Hyperthermia (>38°C)	Cerebral palsy	>2500 g
Haar and Gyamfi-Bannerman[70] (2016)	1574	Cohort (RCT: 2° analysis)	Clinical chorioamnionitis	BSID-II score at 2 yr old	High-risk preterm
Hayes and colleagues[71] (2013)	735	Case–control	Hyperthermia (>38°C)	Neonatal encephalopathy	≥36 weeks
Impey and colleagues[72] (2001)	4915	Prospective cohort	Hyperthermia (>37.5°C)	Neonatal encephalopathy	36–41 weeks
Impey and colleagues[73] (2008)	8299	Cohort (RCT: 2° analysis)	Hyperthermia (>37.5°C)	Neonatal encephalopathy	37–41 weeks
Jacobsson and colleagues[74] (2002)	444	Case–control	Hyperthermia (>38°C)	Cerebral palsy	<37 weeks
Kaukola and colleagues[75] (2006)	53	Prospective cohort	Hyperthermia (>37.8°C)	PVL or IVH	<32 weeks
Lieberman and colleagues[17] (2000)	190	Case–control	Hyperthermia (>38°C)	Early-onset seizures	≥37 weeks and ≥2500 g
Lieberman and colleagues[76] (2000)†	1218	Cohort (RCT: 2° analysis)	Hyperthermia (>38°C)	Early-onset seizure	Full term
Linder and colleagues[77] (2003)	105	Case–control	Clinical chorioamnionitis	IVH	<1500 g
Martinez-Biarge and colleagues[78] (2016)	723	Case–control	Hyperthermia (>38°C)	HIE	≥35 weeks
Matsuda and colleagues[79] (2000)	192	Case–control	Clinical chorioamnionitis	Cerebral palsy	26–30 weeks
Nasef and colleagues[80] (2013)	274	Retrospective cohort	Clinical chorioamnionitis	Cerebral palsy	<30 weeks
Nelson and colleagues[81] (2014)	86 371	Retrospective cohort	Clinical chorioamnionitis	Neonatal encephalopathy	≥36 weeks
Petrova and colleagues[82] (2001)	11 246 042	Retrospective cohort	Hyperthermia (>38°C)	Early-onset seizures	All deliveries
Redline and O'Riordan[83] (2000)	216	Case–control	Hyperthermia (>38 [×2] or 38.5 [×1]°C)	Cerebral palsy	≥37 weeks
Rouse and colleagues[84] (2004)	16 650	Prospective cohort	Hyperthermia (≥37.8°C)	HIE	≥37 weeks
Sameshima and Ikenoue[85] (2007)	230	Retrospective cohort	Clinical chorioamnionitis	Cerebral palsy	22–32 weeks
Schlapbach and colleagues[86] (2010)	99	Retrospective cohort	Clinical chorioamnionitis	BSID-II score at 2 yr old	25–32 weeks
Shalak and colleagues[87] (2005)	51	Case–control	Clinical chorioamnionitis	Neonatal encephalopathy	≥36 weeks
Spinillo and colleagues[88] (1998)	349	Retrospective cohort	Clinical chorioamnionitis	PVL	25–33 weeks

Continued

Table 2 Continued

Reference (publication year)	Sample	Study design	Exposure	Outcome	Gestation/BW
Takahashi and colleagues[89] (2005)	180	Retrospective cohort	Clinical chorioamnionitis	Cerebral palsy	22–33 weeks
Wilson-Costello and colleagues[7] (1998)	144	Case–control	Clinical chorioamnionitis	Cerebral palsy	<1500 g
Epidural hyperthermia and neonatal brain injury					
Greenwell and colleagues[16] (2012)¶	2784	Retrospective cohort	Hyperthermia (>37.5°C)	Early-onset seizures	≥37 weeks and ≥2500 g
Törnell and colleagues[90] (2015)¶	294 329	Retrospective cohort	Hyperthermia (>38°C)	Neonatal encephalopathy	37–42 weeks

factor in a clinical diagnosis of chorioamnionitis. Additionally, as preterm birth and low birth weight are major factors in the development of neonatal brain injury, for Question 2, a second subgroup analysis divided studies into term/normal-birth-weight neonates *vs* preterm/low-birth-weight neonates.

Quality assessment

Two authors (SM and JK) independently assessed the methodological quality of each selected article using Cochrane's risk-of-bias tool.[22] For RCTs, the risk-of-bias tool evaluates the risk of selection bias, performance bias, detection bias, attrition, and reporting bias, and for observational studies, it evaluates the risk of confounding, selection bias, performance bias, detection bias, attrition, and reporting bias. Each study was rated as having either a 'low', 'unclear', or 'high' risk of bias. A third author (CJM) was the final independent assessor for any disagreements.

Two authors (SM and JK) independently assessed the quality of evidence for each study question (including subgroup analyses) using Cochrane's Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[23] According to GRADE methodology, the baseline quality rating for RCTs is 'high' and for observational studies is 'low'. Six quality assessment criteria (risk of bias, inconsistency, indirectness, imprecision, publication bias, and others) were used to judge evidence quality, after which the ratings were either downgraded or upgraded. Evidence was downgraded one or two levels in the presence of a serious or very serious concern, respectively.

Results

The literature search and study selection procedure are summarised in Figure 1. After removing duplicates, 739 records were screened for study Question 1 (epidural analgesia and intrapartum hyperthermia), 786 for Question 2 (intrapartum hyperthermia and neonatal brain injury), and 54 for Question 3 (epidural hyperthermia and adverse neonatal neurological outcome). After reviewing full texts, a total of 41 studies were included for Question 1 (39 for meta-analysis), 36 for Question 2 (31 for meta-analysis), and 2 for Question 3. The study characteristics are summarised in Table 2. Full descriptions of study characteristics and risk of bias are presented in Supplementary Tables 2 and 3 and Supplementary Figure 1.

Study Question 1: epidural analgesia and intrapartum hyperthermia

Of the 41 studies included, 13 were RCTs, with the remaining studies being observational studies (Table 2). This resulted in a total of 646 296 parturients being included. Twenty-five studies included singleton pregnancies at full term (≥37 weeks) in healthy women (Table 2). All study populations were hospital based. Epidural protocols varied between the studies, including the use of combined spinal–epidurals, the drugs administered, and the method of drug administration; where available, protocols are detailed in Supplementary Table 2a. The study of Fusi and colleagues[10] was not included in the meta-analysis because there was only a graphical representation of their results. The study of Lieberman and colleagues[39] was excluded because of duplication of data from Goetzl and colleagues.[35]

For the 39 studies included in the meta-analysis, those with an epidural had an overall odds ratio of 5.26 (95% CI: 4.98–5.56) of developing intrapartum hyperthermia, although there was considerable statistical heterogeneity (I^2=76%; Fig. 2a). On subgroup analysis of the 13 RCTs, this association remained, with an odds ratio of 4.21 (95% CI: 3.49–5.09) and non-significant statistical heterogeneity (I^2=23%; Fig. 2b). Funnel plots for study Question 1 can be found in Supplementary Figure 3. There was no evidence of funnel plot asymmetry in the meta-analysis as a whole (P=0.70) or in the RCT subgroup analysis (P=0.24). The GRADE quality of evidence for study Question 1 as a whole was low (Supplementary Table 4). The GRADE quality was downgraded one level for the high risk of bias and one level for considerable inconsistency, but upgraded two levels for the very large magnitude of effect. For the RCT subgroup, the GRADE quality was high (Supplementary Table 4). The GRADE quality was downgraded one level for the high risk of bias, but upgraded one level for the large magnitude of effect. The high risk of bias was attributable to lack of blinding and attrition.

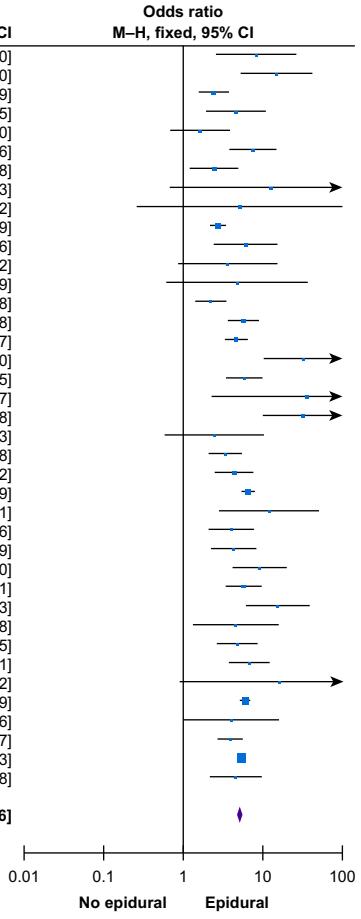
Study Question 2: intrapartum hyperthermia and neonatal brain injury

Thirty-six studies were included for this study question; eight were prospective observational studies, with the remainder being retrospective observational studies (Table 2). A total of 11 866 021 subjects were included. Adverse neonatal outcomes varied significantly between studies and included short-term outcomes, such as Apgar scores, neonatal ICU admission, early-onset seizures, and neonatal encephalopathy and the long-term outcome: cerebral palsy. Supplementary Table 2b provides a narrative account of the outcome measures. Definitions for hyperthermia also varied significantly between studies (≥37.5°C up to >38.5°C), including the method of temperature measurement (Table 2; Supplementary Table 2b). Clinical chorioamnionitis, the composite of hyperthermia and at least one additional clinical sign, was the exposure in 13

a

Study or subgroup	Epidural Events	Epidural Total	No epidural Events	No epidural Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Abramovici and colleagues 2014	118	1491	3	294	0.3	8.34 [2.63, 26.40]
Agakidis and colleagues 2011	54	480	4	480	0.2	15.08 [5.42, 42.00]
Ashwal and colleagues 2018	277	759	32	168	2.1	2.44 [1 .62, 3.69]
Baheri and colleagues 2013	28	90	8	90	0.4	4.63 [1.97, 10.85]
Burgess and colleagues 2017	46	291	7	68	0.6	1.64 [0.70, 3.80]
Curtin and colleagues 2015	180	487	11	154	0.7	7.62 [4.02, 14.46]
Dashe and colleagues 1999	37	80	18	69	0.7	2.44 [1.22, 4.88]
de Orange and colleagues 2011	5	35	0	35	0.0	12.80 [0.68, 241.03]
del Arroyo and colleagues 2019	5	38	0	15	0.0	5.09 [0.26, 97.92]
Dior and colleagues 2016	792	27 631	167	15 929	13.2	2.79 [2.35, 3.29]
Douma and colleagues 2015	18	49	8	91	0.2	6.02 [2.38, 15.26]
Evron and colleagues 2007	9	29	3	27	0.1	3.60 [0.86, 15.12]
Evron and colleagues 2008	15	148	1	44	0.1	4.85 [0.62, 37.79]
Freeman and colleagues 2015	55	347	35	447	1.6	2.22 [1.41, 3.48]
Goetzl and colleagues 2001	149	613	26	496	1.4	5.80 [3.75, 8.98]
Greenwell and colleagues 2012	1246	2784	62	425	3.8	4.74 [3.59, 6.27]
Gross and colleagues 2002	123	736	3	497	0.2	33.04 [10.45, 104.50]
Herbst and colleagues 1995	44	72	639	3037	0.7	5.90 [3.64, 9.55]
Kaul and colleagues 2001	61	922	0	255	0.0	36.48 [2.25, 591.87]
Lieberman and colleagues 2000	120	724	3	494	0.2	32.52 [10.28, 102.88]
Logtenberg and colleagues 2017	6	60	3	69	0.2	2.44 [0.58, 10.23]
Lucas and colleagues 2001	76	372	26	366	1.3	3.36 [2.09, 5.38]
Maayan-Metzger and colleagues 2006	310	567	20	93	1.0	4.40 [2.61, 7.42]
Mark and colleagues 2000	1194	8603	185	7623	10.8	6.48 [5.53, 7.59]
Mayer and colleagues 1997	39	191	2	96	0.1	12.06 [2.85, 51.11]
Nafisi 2006	43	197	13	198	0.6	3.97 [2.06, 7.66]
Philip and colleagues 1999	54	358	14	357	0.8	4.35 [2.37, 7.99]
Ploeckinger and colleagues 1995	17	1056	11	6261	0.2	9.30 [4.34, 19.90]
Ramin and colleagues 1995	98	432	21	437	1.0	5.81 [3.55, 9.51]
Reilly and Oppenheimer 2005	156	10 999	5	5484	0.4	15.77 [6.47, 38.43]
Riley and colleagues 2011	34	150	3	50	0.2	4.59 [1.34, 15.68]
Sharma and colleagues 1997	58	243	16	259	0.8	4.76 [2.65, 8.55]
Sharma and colleagues 2002	75	226	16	233	0.7	6.74 [3.78, 12.01]
Sweed and colleagues 2011	11	40	0	20	0.0	15.98 [0.89, 286.72]
Törnell and colleagues 2015	1838	129 451	395	164 878	21.9	6.00 [5.38, 6.69]
Vinson and colleagues 1993	11	41	3	36	0.1	4.03 [1.03, 15.86]
Wassen and colleagues 2014	172	453	61	453	2.4	3.93 [2.83, 5.47]
White and colleagues 2017	3782	173 324	362	88 133	30.0	5.41 [4.85, 6.03]
Yin and Hu 2019	93	371	9	135	0.6	4.68 [2.29, 9.58]
Total (95% CI)		**364 940**		**298 296**	**100.0**	**5.26 [4.98, 5.56]**
Total events	11 449		2195			

Heterogeneity: χ^2=156.22, df=38 (P<0.00001); I^2=76%
Test for overall effect: Z=59.02 (P<0.00001)



b

Study or subgroup	Epidural Events	Epidural Total	No epidural Events	No epidural Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
de Orange and colleagues 2011	5	35	0	35	0.4	12.80 [0.68, 241.03]
Douma and colleagues 2015	18	49	8	91	3.0	6.02 [2.38, 15.26]
Evron and colleagues 2007	9	29	3	27	1.8	3.60 [0.86, 15.12]
Evron and colleagues 2008	15	148	1	44	1.2	4.85 [0.62, 37.79]
Freeman and colleagues 2015	55	347	35	447	21.9	2.22 [1.41, 3.48]
Logtenberg and colleagues 2017	6	60	3	69	2.1	2.44 [0.58, 10.23]
Lucas and colleagues 2001	76	372	26	366	17.7	3.36 [2.09, 5.38]
Nafisi 2006	43	197	13	198	8.6	3.97 [2.06, 7.66]
Philip and colleagues 1999	54	358	14	357	10.1	4.35 [2.37, 7.99]
Ramin and colleagues 1995	98	432	21	437	13.7	5.81 [3.55, 9.51]
Sharma and colleagues 1997	58	243	16	259	10.0	4.76 [2.65, 8.55]
Sharma and colleagues 2002	75	226	16	233	9.0	6.74 [3.78, 12.01]
Sweed and colleagues 2011	11	40	0	20	0.4	15.98 [0.89, 286.72]
Total (95% CI)		**2536**		**2583**	**100**	**4.21 [3.48, 5.09]**
Total events	523		156			

Heterogeneity: χ^2=15.65, df=12 (P=0.21); I^2=23%
Test for overall effect: Z=14.83 (P<0.00001)

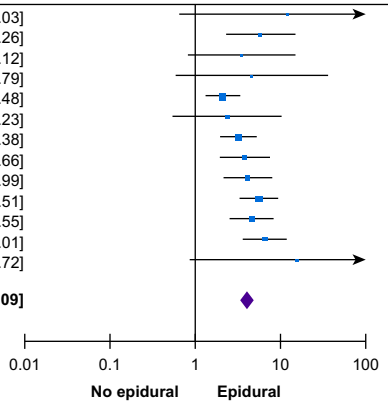


Fig 2. Meta-analysis of study Question 1: epidural analgesia and intrapartum hyperthermia. (a) RCTs and observational studies. (b) RCTs only (where mode of analgesia was randomised). Events: intrapartum hyperthermia. CI, confidence interval; M–H, Mantel–Haenszel.

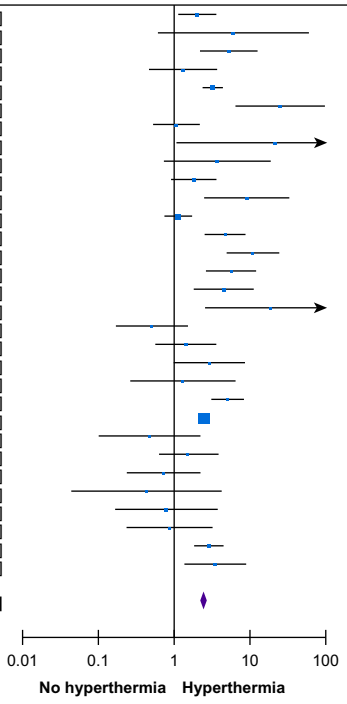
studies.[7,58,70,75,77,79,80,85–88,91] Fifteen studies included only neonates born at term or a weight >2500 g; 14 studies included only preterm neonates or those born at a low birth weight. Novak and colleagues[91] included any neonate who required therapeutic hypothermia on arrival to neonatal intensive care, and Sameshima and Ikenoue[85] included singleton pregnancies diagnosed with cerebral palsy at the age of 2.

Five studies were excluded from the meta-analysis: three had no control data,[75,85,91] one had no data on long-term adverse outcomes,[64] and one had only odds ratio data

a

Study or subgroup	Hyperthermia Events	Hyperthermia Total	No hyperthermia Events	No hyperthermia Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Alexander and colleagues 1999	14	5144	127	96 026	2.6	2.06 [1.19, 3.58]
Ashwal and colleagues 2018	3	309	1	618	0.1	6.05 [0 .63, 58.39]
Badawi and colleagues 1998	18	27	146	537	0.9	5.36 [2.35, 12.19]
Bauer and colleagues 2009	6	18	87	318	1.3	1.33 [0.48, 3.65]
Blume and colleagues 2008	89	234	971	6156	9.0	3.28 [2.50, 4.31]
Dammann and colleagues 2003	11	14	36	280	0.1	24.85 [6.61, 93.38]
Edwards and colleagues 2018	10	201	68	1505	3.1	1.11 [0.56, 2.19]
Ghi and colleagues 2010	4	4	20	68	0.1	21.29 [1.10, 413.80]
Greenwell and colleagues 2012	6	1246	2	1538	0.4	3.72 [0.75, 18.44]
Greenwood and colleagues 2005	16	41	212	825	2.5	1.85 [0.97, 3.53]
Grether and Nelson 1997	5	10	41	414	0.2	9.10 [2.53, 32.75]
Haar and Gyamfi-Bannerman 2016	37	194	233	1380	9.4	1.16 [0.79, 1.70]
Hayes and colleagues 2013	37	55	198	662	2.0	4.82 [2.68, 8.67]
Impey and colleagues 2008	11	571	14	7728	0.4	10.82 [4.89, 23.95]
Jacobsson and colleagues 2002	13	38	34	404	0.8	5.66 [2.66, 12.06]
Lieberman and colleagues 1999	12	26	26	164	0.8	4.55 [1.89, 10.94]
Lieberman and colleagues 2000	2	61	2	1095	0.0	18.53 [2.56, 133.83]
Linder and colleagues 2003	6	25	30	80	2.2	0.53 [0.19, 1.46]
Martinez-Biarge and colleagues 2016	17	24	388	620	1.7	1.45 [0.59, 3.55]
Matsuda and colleagues 2000	6	25	16	167	0.6	2.98 [1.04, 8.54]
Nasef and colleagues 2013	2	33	11	241	0.5	1.35 [0 .29, 6.37]
Nelson and colleagues 2014	26	5710	72	80 661	1.9	5.12 [3.27, 8.02]
Petrova and colleagues 2001	305	179 480	7525	11 066 562	48.7	2.50 [2.23, 2.81]
Redline and colleagues 2000	2	19	38	197	1.2	0.49 [0.11, 2.22]
Rouse and colleagues 2004	6	1965	29	14 685	1.4	1.55 [0.64, 3.73]
Schlapbach and colleagues 2010	8	33	10	33	1.5	0.74 [0.25, 2.19]
Shalak and colleagues 2005	1	6	14	45	0.6	0.44 [0.05, 4.15]
Spinillo and colleagues 1998	2	12	67	337	0.8	0.81 [0.17, 3.77]
Takahashi and colleagues 2005	3	20	27	160	1.0	0.87 [0.24, 3.17]
Törnell and colleagues 2015	21	2231	949	292 098	2.9	2.92 [1.89, 4.50]
Wilson-Costello and colleagues 1998	22	30	50	114	1.1	3.52 [1.45, 8.57]
Total (95% CI)		**197 806**		**11 575 718**	**100.0**	**2.48 [2.28, 2.70]**
Total events	721		11 444			

Heterogeneity: χ^2=116.57, df=30 (P<0.00001); I^2=74%
Test for overall effect: Z=20.73 (P<0.00001)



b

Study or subgroup	Hyperthermia Events	Hyperthermia Total	No hyperthermia Events	No hyperthermia Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Ashwal and colleagues 2018	3	309	1	618	0.2	6.05 [0.63, 58.39]
Badawi and colleagues 1998	18	27	146	537	1.3	5.36 [2.35, 12.19]
Bauer and colleagues 2009	6	18	87	318	1.7	1.33 [0.48, 3.65]
Blume and colleagues 2008	89	234	971	6156	12.0	3.28 [2.50, 4.31]
Dammann and colleagues 2003	11	14	36	280	0.2	24.85 [6.61, 93.38]
Ghi and colleagues 2010	4	4	20	68	0.1	21.29 [1.10, 413.80]
Greenwell and colleagues 2012	6	1246	2	1538	0.5	3.72 [0.75, 18.44]
Greenwood and colleagues 2005	16	41	212	825	3.3	1.85 [0.97, 3.53]
Grether and Nelson 1997	5	10	41	414	0.3	9.10 [2.53, 32.75]
Hayes and colleagues 2013	37	55	198	662	2.7	4.82 [2.68, 8.67]
Impey and colleagues 2008	11	571	14	7728	0.5	10.82 [4.89, 23.95]
Jacobsson and colleagues 2002	13	38	34	404	1.0	5.66 [2.66, 12.06]
Lieberman and colleagues 1999	12	26	26	164	1.0	4.55 [1.89, 10.94]
Lieberman and colleagues 2000	2	61	2	1095	0.1	18.53 [2.56, 133.83]
Martinez-Biarge and colleagues 2016	17	24	388	620	2.3	1.45 [0.59, 3.55]
Petrova and colleagues 2001	305	179 480	7525	11 066 562	65.4	2.50 [2.23, 2.81]
Redline and colleagues 2000	2	19	38	197	1.6	0.49 [0.11, 2.22]
Rouse and colleagues 2004	6	1965	29	14 685	1.9	1.55 [0.64, 3.73]
Törnell and colleagues 2015	21	2231	949	2 92 098	3.9	2.92 [1.89, 4.50]
Total (95% CI)		**186 373**		**11 394 969**	**100.0**	**2.79 [2.54, 3.06]**
Total events	584		10 719			

Heterogeneity: χ^2=58.46, df=18 (P<0.00001); I^2=69%
Test for overall effect: Z=21.55 (P<0.00001)

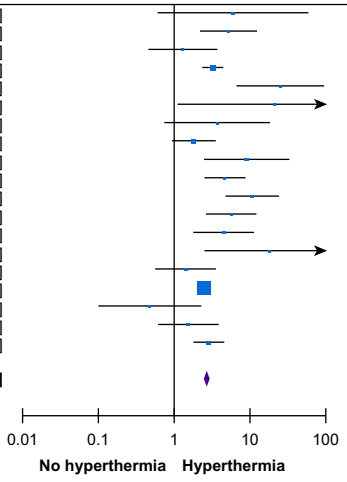


Fig 3. Meta-analysis of study Question 2: intrapartum hyperthermia and neonatal brain injury. (a) All studies. (b) Studies where hyperthermia alone was the exposure. (c) Studies of neonates born at ≥37 weeks' gestation. (d) Studies of neonates born at <37 weeks' gestation. Events: neonatal brain injury. CI, confidence interval; M–H, Mantel–Haenszel.

available,[65] and the study of Impey and colleagues[72,73] was excluded to prevent double counting of data. In the remaining 31 studies, intrapartum hyperthermia was associated with adverse neonatal neurological outcome (odds ratio: 2.48; 95% CI: 2.28–2.70), although substantial statistical heterogeneity was present (I^2=74%; Fig. 3a). When studies that used clinical chorioamnionitis as the exposure were excluded, the association remained (19 studies; odds ratio: 2.79; 95% CI: 2.54–3.06; Fig. 3b). Subgroup analysis revealed that this association was present in both term (12 studies; odds ratio: 3.38; 95% CI: 2.79–4.10) and preterm (13 studies; odds ratio: 1.63; 95% CI: 1.32–2.02; Fig. 3c and d) neonates. Funnel plots for each analysis are presented in Supplementary Figure 4. There was no evidence of funnel plot asymmetry in the meta-analysis as

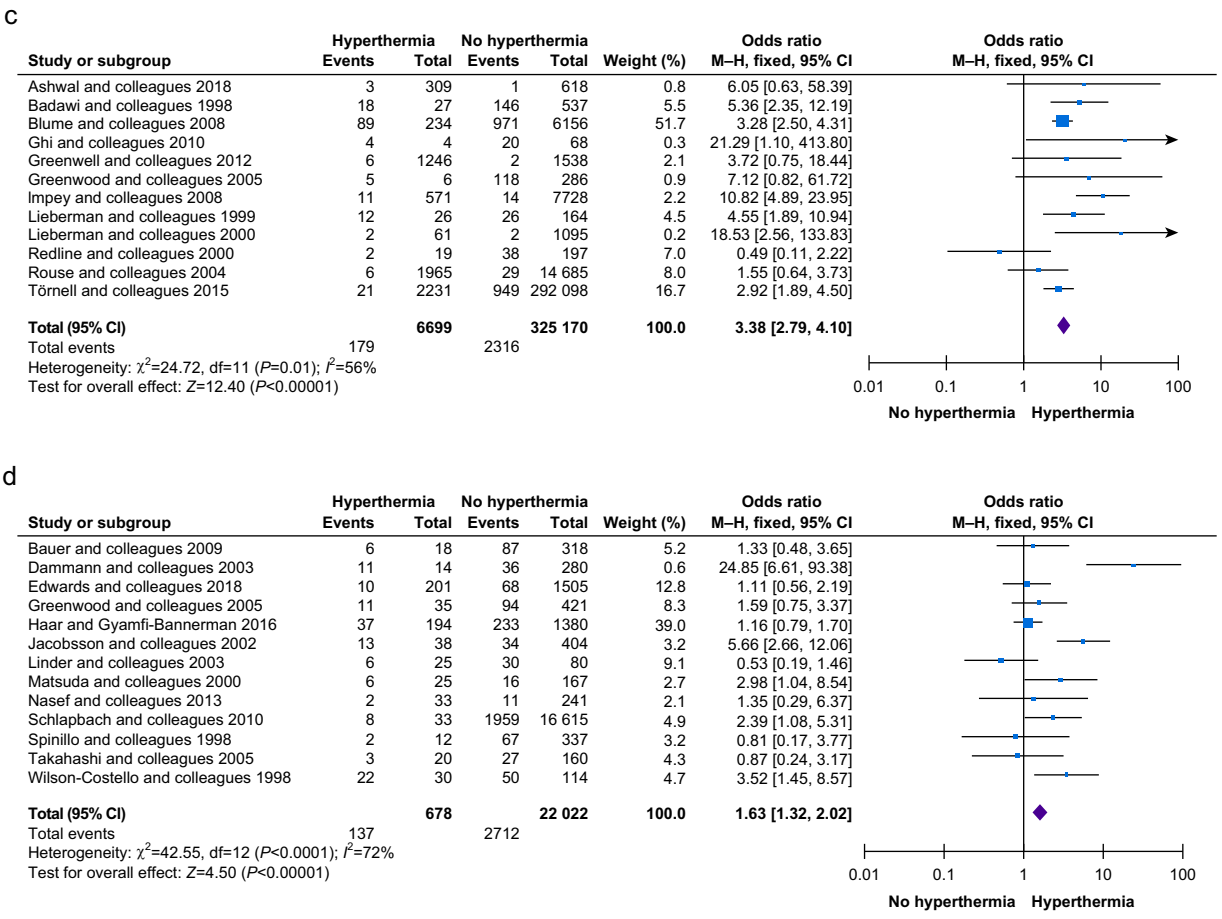


Fig 3. (continued)

a whole (P=0.76) or in the subgroup analyses of term (P=0.33) or preterm (P=0.19) deliveries. However, funnel plot asymmetry was present in the subgroup analysis of studies in which hyperthermia alone was the exposure (P=0.0009). The GRADE quality of evidence for study Question 2 as a whole and the term subgroup was low (Supplementary Table 4). For both questions, the GRADE quality was downgraded one level for inconsistency, but upgraded one level for the large magnitude of effect. For the hyperthermia and preterm subgroups, the GRADE quality was very low (Supplementary Table 4). For the hyperthermia subgroup, the GRADE quality was downgraded one level for substantial inconsistency and one level for publication bias, but upgraded one level for the large magnitude of effect. For the preterm subgroup, the GRADE quality was downgraded one level for the high risk of bias and one level for substantial inconsistency.

Study Question 3: epidural-induced hyperthermia and neonatal brain injury

Two studies were included for this study question, both retrospective cohort studies (Supplementary Table 2c) and both of low quality (Supplementary Table 3c; Supplementary Fig. 1c). Because of the low number of studies and diversity in outcome measures, a meta-analysis could not be performed. A total of 297 113 subjects were included. Greenwell and colleagues[16] showed that early-onset neonatal seizures were increased in patients with an epidural and a temperature >38.3°C (P=0.008). Törnell and colleagues[90] did not perform a subgroup analysis of parturients with epidural analgesia, but did demonstrate that, when intrapartum temperature is adjusted for, epidural analgesia is not associated with a diagnosis of neonatal encephalopathy (odds ratio: 1.11; 95% CI: 0.96–1.29). The GRADE quality of evidence for study Question 3 was very low (Supplementary Table 4). The GRADE quality was downgraded one level because of the high risk of bias and one level because of the low event rate (imprecision), but upgraded one level for the presence of a dose–response gradient.

Discussion

This systematic review and meta-analysis reviewed the evidence linking (1) epidural analgesia and intrapartum hyperthermia, (2) intrapartum hyperthermia (all cause) and

neonatal brain injury, and (3) epidural-induced hyperthermia and neonatal brain injury. The results demonstrate (1) a causal link between epidural analgesia and intrapartum hyperthermia, (2) an association between intrapartum hyperthermia (all cause) and neonatal brain injury, and (3) insufficient evidence to formally evaluate the link between epidural hyperthermia and neonatal brain injury.

Study Question 1: epidural analgesia and intrapartum hyperthermia

The overall odds ratio of 5.26 for the association between epidural analgesia and intrapartum hyperthermia is strong, especially considering the large pooled sample size of 644 969 parturients. This strong association (odds ratio: 4.21) remained in the subgroup analysis of RCTs. This fits with other reviews of this nature, which reported risk ratios between 2.51 and 3.54.[11 12] Additionally, this study finds that, since the previous systematic review, the GRADE quality of evidence supporting a causal link between epidural analgesia and intrapartum hyperthermia has increased to high.[11]

The RCT subgroup analysis demonstrates a causal link between epidural analgesia and intrapartum hyperthermia. Epidural hyperthermia is not therefore a consequence of selection bias, that is, it is not the result of parturients with a greater risk of intrapartum hyperthermia selecting epidural analgesia. Although this causal link is biologically plausible, the underlying mechanism(s) remains unclear. A potential explanation is that epidural analgesia increases the risk of intrapartum infection, but a previous systematic review indicates that this is unlikely.[11] The most plausible explanation is that epidural hyperthermia is a distinct condition resulting from either cholinergic sympathetic blockade, immunomodulation, or both.[13–15] The cholinergic blockade mechanism is that epidural local anaesthetic blocks the sympathetic pathways responsible for the control of sweating and active vasodilation, and thus, parturients' cutaneous heat loss is limited.[13] The immunomodulation mechanism is that the local anaesthetic either stimulates the release of interleukin-6, and thus induces activity in the pro-pyrogenic inflammatory pathway or inhibits the release of interleukin-1 receptor antagonist, and thus reduces the activity in the anti-pyrogenic inflammatory pathway, or both.[14,15] Although not a primary focus, this systematic review found no evidence favouring one mechanism.

Study Question 2: intrapartum hyperthermia and neonatal brain injury

This meta-analysis includes more than 11 million parturients and found a strong association between intrapartum hyperthermia and adverse neonatal neurological outcome (odds ratio: 2.48). This association remained when studies that investigated clinical chorioamnionitis were excluded (odds ratio: 2.79). Previous systematic reviews have demonstrated an association between clinical chorioamnionitis and the development of cerebral palsy.[6,92,93] However, this systematic review is the first to find an association between intrapartum hyperthermia of any cause and neonatal brain injury.

Two mechanisms have been proposed that may account for the association between intrapartum hyperthermia and neonatal brain injury: the cytokine hypothesis and the energy failure hypothesis, neither of which is fully proven.[6] The cytokine hypothesis is that intrauterine infection induces an inflammatory response in the fetus, which is neurotoxic.[6] The energy failure hypothesis is that, after an intrapartum insult, hyperthermia exacerbates neuronal injury by increasing the intracellular energy deficit.[94] Energy failure is the principle that underpins the use of therapeutic hypothermia to treat neonates with encephalopathy caused by birth asphyxia (hypoxic–ischaemic encephalopathy).[95] Superficially, at least the cytokine hypothesis appears disease-specific to chorioamnionitis, whereas the energy deficit hypothesis seems applicable to intrapartum hyperthermia of any cause. However, the proposed immunomodulation mechanism of epidural hyperthermia may link with the cytokine hypothesis.[14,15] The diagnosis of clinical chorioamnionitis requires intrapartum hyperthermia in addition to other clinical signs of infection, such as tachycardia (maternal and fetal), tachypnoea, leucocytosis, and foul-smelling vaginal discharge.[96] However, of these symptoms, only foul-smelling vaginal discharge cannot be attributed to the hyperthermia itself.[97] Previous meta-analyses found that, whilst there is often an association between clinical chorioamnionitis and cerebral palsy, this is not seen to the same extent with histological chorioamnionitis.[6,92,93] This hints that it is the hyperthermia itself, rather than the underlying disease process, that has the greater impact on neonatal neurological outcome. The finding in the present meta-analysis that intrapartum hyperthermia of any cause is associated with neonatal brain injury adds weight to this argument.

Gestational age at delivery is the greatest factor in the development of neonatal brain injury. However, this systematic review demonstrates that intrapartum hyperthermia has an impact on neonatal neurological outcome that is independent of gestational age. The aetiology of brain injury in premature neonates differs to that of their term counterparts.[1] The most common form of brain injury in premature neonates is intracerebral haemorrhage caused by the fragility of immature blood vessels, whereas in term neonates, brain injury is most commonly secondary to birth asphyxia and is associated with damage to watershed areas of the brain, the basal ganglia, and the thalamus.[1,98] Consequently, it should not be assumed that intrapartum hyperthermia has a similar impact on neurological outcome in both term and preterm neonates. The subgroup analysis in the present systematic review reveals that intrapartum hyperthermia increases the risk of neonatal brain injury in both term and preterm neonates. Superficially, at least it also appears to indicate that intrapartum hyperthermia has a greater impact in term neonates (odds ratio: 3.38) than in preterm neonates (odds ratio: 1.63). This result aligns with two previous meta-analyses, which investigated clinical chorioamnionitis and cerebral palsy in term and preterm neonates and demonstrated a higher risk ratio for term neonates.[6,92] However, it should be noted that in the present meta-analysis, the absolute risk increase was greater in preterm neonates than term neonates: +4.4% and +0.6%, respectively. This disparity is attributable to the difference in the baseline incidence of brain injury in the two populations: in comparison to term neonates, the risk of neonatal brain injury is approximately 7.5-fold greater in preterm neonates.[1] Therefore, it can be concluded that the impact of intrapartum hyperthermia upon neurological outcome is at least as great in preterm neonates as their term counterparts.

Study Question 3: epidural-induced hyperthermia and neonatal brain injury

This investigation is the first to systematically review the evidence linking epidural hyperthermia and neonatal brain injury. It finds that, at present, there is insufficient evidence to answer this question. Only two studies met the inclusion criteria for this question and the GRADE quality of evidence was very low. Greenwell and colleagues[16] showed that epidural hyperthermia increases the risk of early-onset seizures (odds ratio: 6.5), but the total number of events was low (eight). Törnell and colleagues[90] found an association between intrapartum hyperthermia of any cause and neonatal encephalopathy (odds ratio: 1.97), but they did not consider the impact of epidural hyperthermia and non-epidural-related intrapartum hyperthermia separately. Further research is required to address this knowledge gap.

Limitations

The results of this systematic review and meta-analysis are limited by the quality of the individual studies. However, given the nature of the study questions, higher-quality study designs are unrealistic. Study Question 1 (epidural analgesia and intrapartum hyperthermia) contains 13 unblinded RCTs. To blind subjects in this situation is impossible, and it would be unethical to prevent parturients from changing their minds about epidural use. That Evron and colleagues[33] and Nafisi[45] managed no patient non-adherence and that de Orange and colleagues[30] only had one participant not follow the protocol in each arm of the study is remarkable. It is not possible to control whether or not a parturient develops intrapartum hyperthermia, and therefore multicentre prospective observational study designs are the optimal method of investigating study Questions 2 (intrapartum hyperthermia and neonatal brain injury) and 3 (epidural hyperthermia and neonatal brain injury). Although observational study designs are inherently at risk of selection bias, in the majority of studies, potential confounders were identified and adjusted for. Detection bias and attrition bias are also inherent risks. Detection bias is likely present in the majority of studies, as the method of temperature measurement was often unclear and observers were only blinded in one study.[7] It is unclear to what extent attrition bias is present, as missing data were not reported in the majority of studies. However, loss to long-term follow-up was reported as 22% in one study and 20% in another.[80,85]

Considerable statistical heterogeneity was present in the meta-analysis of study Question 1 and substantial statistical heterogeneity in the meta-analysis of study Question 2. The likely sources of this heterogeneity are the definition of intrapartum hyperthermia, maternal characteristics, gestational age, and the form of neonatal brain injury. The definition of intrapartum hyperthermia ranged from >37.0 to >38.5°C.[64,83] This lack of consistency is likely caused by geographical and temporal variations in the definition of intrapartum hyperthermia.[96,99] Clinical chorioamnionitis was the exposure or outcome in 15 studies (Table 2). However, this is unlikely to have been a significant factor, as there was little reduction in statistical heterogeneity in the subgroup analysis of studies, where hyperthermia alone was the exposure (Fig. 3b). The non-significant statistical heterogeneity in the subgroup meta-analysis of RCTs for study Question 1 suggests that variation in maternal characteristics was a significant factor. For example, parity may influence the incidence of hyperthermia via its impact on the duration of labour and thus the risk of epidural hyperthermia.[100] Variation in epidural protocols was noted between studies, but it is unclear if this was a source of statistical heterogeneity. The choice of epidural local anaesthetic has been shown to have at most a small effect on incidence of intrapartum hyperthermia, and it is unclear if the method of epidural drug delivery has an impact.[101–104] Neonatal brain injury is more common and has a different aetiology in preterm infants, and therefore the gestational age of the individual study populations is likely to have been a contributor.[1] The reduced statistical heterogeneity in the subgroup analysis of term deliveries may also reflect the more homogeneous aetiology of neonatal brain injury at term.[1] The forms of neonatal brain injury reported include clinical diagnoses, such as neonatal encephalopathy and cerebral palsy, and radiological diagnoses, such as intraventricular haemorrhage and periventricular leucomalacia. This variation in part reflects the different methods of diagnosing and classifying brain injury at the time of birth, during the neonatal period, and later in childhood. However, they are distinct conditions, and so this variation is a likely source of statistical heterogeneity.

The funnel plot (Supplementary Fig. 4b) shows asymmetry. The major source of this asymmetry is the study design of two outlying studies, both of which are case–control studies of neonatal brain injury with a small number of cases of intrapartum hyperthermia.[63,67] Such study designs are prone to overestimation of the effect size.[105] However, this asymmetry is unlikely to affect the results of this subgroup analysis, as the two outlying studies comprise only 0.3% of the model. It is also possible that there is publication bias within this subgroup. Potential sources are inclusion of English language studies only and a lack of a grey literature search.[105]

Clinical implications

This systematic review and meta-analysis evaluates the evidence pertaining to an important clinical question: does epidural hyperthermia increase the risk of neonatal brain injury? It finds that, currently, there is insufficient evidence to answer this question. However, the findings that epidural analgesia is a cause of intrapartum hyperthermia and that intrapartum hyperthermia of any cause is associated with neonatal brain injury highlight the need for further investigation. Although chorioamnionitis is a risk factor for neonatal brain injury, it cannot be assumed that epidural hyperthermia has a similar impact on the neonatal brain.[6] Study Question 1 demonstrates that chorioamnionitis and epidural hyperthermia are distinct conditions, and it is not known if the mechanism by which chorioamnionitis increases the risk of neonatal brain injury is common to both conditions.[6,94] In contrast, it is well recognised that epidural analgesia has many benefits, including being the most effective form of labour analgesia, reducing the need for general anaesthesia and improving outcome in high-risk parturients.[12,106,107] Consequently, if unnecessary harm is to be avoided, it is crucial that the association between epidural hyperthermia and neonatal brain injury is investigated with high-quality research, before any changes in clinical practice. Given the nature of the question, it is likely that prospective multicentre observational studies are the optimum approach. However, mechanistic studies may also prove

informative. For example, developing a technique to accurately differentiate epidural-induced hyperthermia from intrapartum infection will help elucidate the true relationship between epidural-induced hyperthermia and neonatal neurological outcome.

Conclusion

This systematic review and meta-analysis shows a causal link between epidural analgesia and intrapartum hyperthermia. It also reveals a strong association between intrapartum hyperthermia of any cause, not simply chorioamnionitis, and the development of neonatal brain injury. However, there was insufficient evidence to evaluate the link between epidural-induced hyperthermia and neonatal brain injury. Consequently, further research is required to determine whether or not epidural-induced hyperthermia is a modifiable risk factor for neonatal brain injury.

Authors' contributions

Study design: SM, CJM
Literature search: SM, JK
Data collection: SM, JK
Quality review: all authors
Statistical analysis: SM
Manuscript preparation: SM, CJM
Manuscript revision: all authors

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Declarations of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.09.046.

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