Accepted: 23 January 2023 | Published Online 11 April 2023

DOI: 10.1111/1471-0528.17480

BJOG An International Journal of Obstetrics and Gynaecology

SYSTEMATIC REVIEW

Umbilical cord blood acid–base analysis at birth and long-term neurodevelopmental outcomes in children: a systematic review and meta-analysis

Hilde Tinderholt Myrhaug[1] | Anne Kaasen[1] | Aase Serine Devold Pay[1,2] | Lena Henriksen[1] | Geir Smedslund[3] | Ola Didrik Saugstad[4,5] | Ellen Blix[1]

[1]Department of Nursing and Health Promotion, Faculty of Health Sciences, Oslo Metropolitan University, Oslo, Norway

[2]Department of Obstetrics and Gynaecology, Oslo University Hospital, Oslo, Norway

[3]Division for Health Services, Norwegian Institute of Public Health, Oslo, Norway

[4]Department of Paediatric Research, University of Oslo, Nydalen, Norway

[5]Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Correspondence
H. T. Myrhaug, Department of Nursing and Health Promotion, Faculty of Health Sciences, Oslo Metropolitan University, P.O. Box 4, St. Olavs plass, 0130 Oslo, Norway.
Email: hitimy@oslomet.no

Abstract

Background: Umbilical cord blood acid–base sampling is routinely performed at many hospitals. Recent studies have questioned this practice and the association of acidosis with cerebral palsy.

Objective: To investigate the associations between the results of umbilical cord blood acid–base analysis at birth and long-term neurodevelopmental outcomes and mortality in children.

Search strategy: We searched six databases using the search strategy: umbilical cord AND outcomes.

Selection criteria: Randomised controlled trials, cohorts and case–control studies from high-income countries that investigated the association between umbilical cord blood analysis and neurodevelopmental outcomes and mortality from 1 year after birth in children born at term.

Data collection and analysis: We critically assessed the included studies, extracted data and conducted meta-analyses comparing adverse outcomes between children with and without acidosis, and the mean proportions of adverse outcomes. The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations approach.

Main results: We have very low confidence in the following findings: acidosis was associated with higher cognitive development scores compared with non-acidosis (mean difference 5.18, 95% CI 0.84–9.52; *n* = two studies). Children with acidosis also showed a tendency towards higher risk of death (relative risk [RR] 5.72, 95% CI 0.90–36.27; *n* = four studies) and CP (RR 3.40, 95% CI 0.86–13.39; *n* = four studies), although this was not statistically significant. The proportion of children with CP was 2.39/1000 across the studies, assessed as high certainty evidence.

Conclusion: Due to low certainty of evidence, the associations between umbilical cord blood gas analysis at delivery and long-term neurodevelopmental outcomes in children remains unclear.

KEYWORDS
cerebral palsy, mortality, neurodevelopmental outcomes, newborn, umbilical cord

This article includes Author Insights, a video abstract available at: https://players.brightcove.net/3806881048001/default_default/index.html?videoId=6322480161112.

1 | INTRODUCTION

Umbilical cord blood gases and acid–base measurements are used to determine fetal acidosis and assess birth asphyxia, a major cause of neonatal mortality and morbidity.[1–3] In many hospitals in high-income countries, paired cord blood gases from umbilical vein and artery are routinely collected from all newborns, including those born at term after an uncomplicated birth.[4,5] The arguments for routine testing are that cord blood gas analysis provides objective information about the baby, it is important for quality control of intrapartum care, it is important in legal cases to state whether an injury was caused by intrapartum hypoxia, and it contributes to research.[5,6] The arguments against routine testing are that the test has limited value in healthy babies and that investigating cord blood gases in all women takes time and resources.[5] In addition, obtaining blood samples may cause the collapse of vessels in the umbilical cord and thereby interfere with the baby's physiological adaptation, as it is likely to cause earlier cessation of the pulsation in the umbilical cord.[7,8] Guidelines issued by the National Institute for Clinical Excellence (NICE) and by the American College of Obstetricians and Gynecologists (ACOG) only recommend cord blood samples for blood gas analyses in cases where the baby is born in a poor condition, and do not recommend routine cord blood samples.[9,10]

Cord pH is a biomarker and is used as a surrogate endpoint for short-term and long-term morbidity in many studies.[11] Long-term morbidities after perinatal asphyxia includes neurodevelopmental conditions such as cerebral palsy (CP) and motor and cognitive development delays. To our knowledge, only one systematic review has summarised studies on associations between umbilical cord blood gas analysis and long-term neurodevelopmental outcomes in children.[3] This systematic review included a literature search from 1966 to 2008 but did not evaluate the certainty of evidence. Malin et al.[3] report an association between low pH and CP. In addition, they propose a need for future research on associations between umbilical blood cord pH across neonatal populations and fetal long-term outcomes. However, more recent single studies have questioned this assocation.[4,12–14] The purpose of this systematic review is therefore to synthesise, appraise and pool studies that investigate the associations between the results of umbilical cord blood acid–base analysis at delivery and long-term (from 1 year after birth) neurodevelopmental outcomes and mortality in children.

2 | METHODS

2.1 | Protocol and registration

This systematic review was conducted according to the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analysis).[15] The protocol was prospectively registered on PROSPERO (CRD42020216002).

2.2 | Search strategy and selection of studies

A search was conducted of the databases Ovid MEDLINE(R), Embase, Cochrane Library, Maternity & Infant Care Database (MIDIRS), Web of Science and CINAHL (EBSCO) for the period 1946 to December 2021. The search strategies combined index terms and text words relating to umbilical cord acid–base analysis and outcomes, and the search syntax was adapted to each database. The full search strategy for Ovid MEDLINE(R) is provided in Appendix S1. Relevant systematic reviews were used to identify potentially relevant studies.

Pairs of reviewers independently screened study records for eligibility by title and abstract using the Rayyan app.[16] Relevant articles were independently assessed in full text by two reviewers and included if they met the eligibility criteria. Disagreements were resolved by discussion among the authors until consensus was reached.

2.3 | Eligibility criteria

We included randomised controlled trials, cohorts and case–control studies that investigated the association between the results of umbilical cord blood acid–base analysis at delivery and long term (from 1 year after birth) neurodevelopmental outcomes and mortality in children born at term.

Study populations comprising premature infants (gestational age <37 weeks), and mortality and neurodevelopmental outcomes assessed among children <1 year of age were excluded. Only studies published in English, German or a Scandinavian language were assessed in full text. The PICO (population, intervention, comparator, outcomes) format was used to identify studies and data.

2.3.1 | Patients/population

The patients/population comprised children with a gestational age of ≥37 weeks from the following high-income areas/regions: North America, Australia, New Zealand, and Northern, Western and Central Europe[17] who have had a minimum of a 1-year follow-up.

2.3.2 | Intervention/exposure

Intervention/exposure comprised umbilical cord blood analysis at delivery, such as pH and base excess. We used the definitions of acidosis as reported in each of the included studies.

2.3.3 | Comparator(s)/control(s)

No comparator or umbilical cord blood values were defined as, for example, non-acidosis.

2.3.4 | Outcomes

The outcomes comprised neurodevelopmental outcomes (often a combination of cognitive delays, motor delays, behavioural problems, CP, blindness and/or hearing impairment) and mortality in children assessed from the 1-year follow-up.

2.4 | Data collection

HTM (the first author) extracted data on study characteristics (year of study, study design, characteristics of the study population), exposure (umbilical cord pH, base excess and/or lactic acid values) and outcome measures (neurodevelopmental outcomes and mortality). Data were cross-checked by the other authors.

2.5 | Quality assessment of studies

The quality of the studies was assessed using modified versions of the Critical Appraisal Skills Programme (CASP) checklists for cohort studies (8 items) and case control studies (7 items).[18] Studies in which all the items were checked off as 'yes' were regarded as being studies of high methodological quality (low risk of bias), whereas studies in which half or more than half of the items were assessed as 'unclear or no' were regarded as being of low methodological quality (high risk of bias).

2.6 | Strategy for data synthesis

We conducted meta-analyses when studies were sufficiently similar in terms of study design, population, exposure (pH cut-off) and outcomes, indicating a low clinical heterogeneity. The meta-analyses were conducted in R using the packages 'meta' and 'metafor'.[19,20]

For meta-analyses with one group, we used the 'metaprop' command to calculate proportions. For meta-analyses with two groups, we calculated relative risk (RR) for dichotomous outcomes using the 'rma.uni' command' and mean difference (MD) or standardised mean difference (SMD) for continuous outcomes with the 'metacont' command, both with a 95% confidence interval (CI). We used a random-effects model to account for pooling effects due to the clinical heterogeneity of the studies included. The statistical heterogeneity was described by the I^2 test.

Due to the small number of studies, it was not feasible to conduct subgroup analyses (based on pH cut-offs, mode of delivery or Apgar score) or sensitivity analyses (based on risk of bias).

2.7 | Assessment of certainty of evidence

Two authors (HTM and GS) independently assessed the certainty of evidence for the neurodevelopmental outcomes using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation).[21] They considered the risk of bias, imprecision and inconsistency of the estimates, the indirectness and magnitude of effect, the dose–response gradient, publication bias and the potential confounding factors. The certainty of evidence was subsequently classified as high, moderate, low or very low (Table S1).

2.8 | Patient and public involvement

No patients or other members of the public were involved in performing the review.

3 | RESULTS

3.1 | Literature search and study characteristics

The literature search yielded 3741 unique hits, of which 25 studies (21 cohorts[4,22–41] and 4 case–control studies),[13,42–44] were included (Figure 1). The excluded full-text articles and reasons for exclusion are shown in Table S2.

Fourteen studies[4,13,26,29–35,41–44] investigated the association between neurodevelopmental outcomes and/or mortality in term infants with umbilical cord acid–base analysis by comparing two study groups. One group included infants with low umbilical cord pH (acidosis group) and one group with normal umbilical cord pH (non-acidosis group). Eleven studies[22–25,27,28,36–40] investigated the proportion of adverse outcomes and the association between pH and adverse outcomes in one group of newborns with varying pH. The characteristics of the included studies are presented in Table 1.

Of the 25 studies, we performed quantitative syntheses based on 21 studies; four studies[34,38,40,44] were not included in these meta-analyses due to different outcome measurements or poor reporting of estimates. The forest plots showing meta-analyses from studies that include two groups are presented in Figures 2–4 and Figures S1–S3, and forest plots from one-group studies are presented in Figures S4–S7.

3.2 | Risk-of-bias assessment

We found eight of the 25 included cohort and case–control studies,[4,13,24,26,29,34,39,40] to be of high methodological quality (low risk of bias), 15/25 studies to be of moderate quality[22,23,25,27,28,30–32,36–38,41–44] and two studies[33,35] to be of low methodological quality (high risk of bias) (Tables S3 and S4). Twelve of the included studies had an unclear description, or lacked a description altogether, of whether confounding factors had been taken into consideration in the design or analysis of the studies. Given our aim, we considered this item to be the most important in reducing the risk of bias in the included studies.

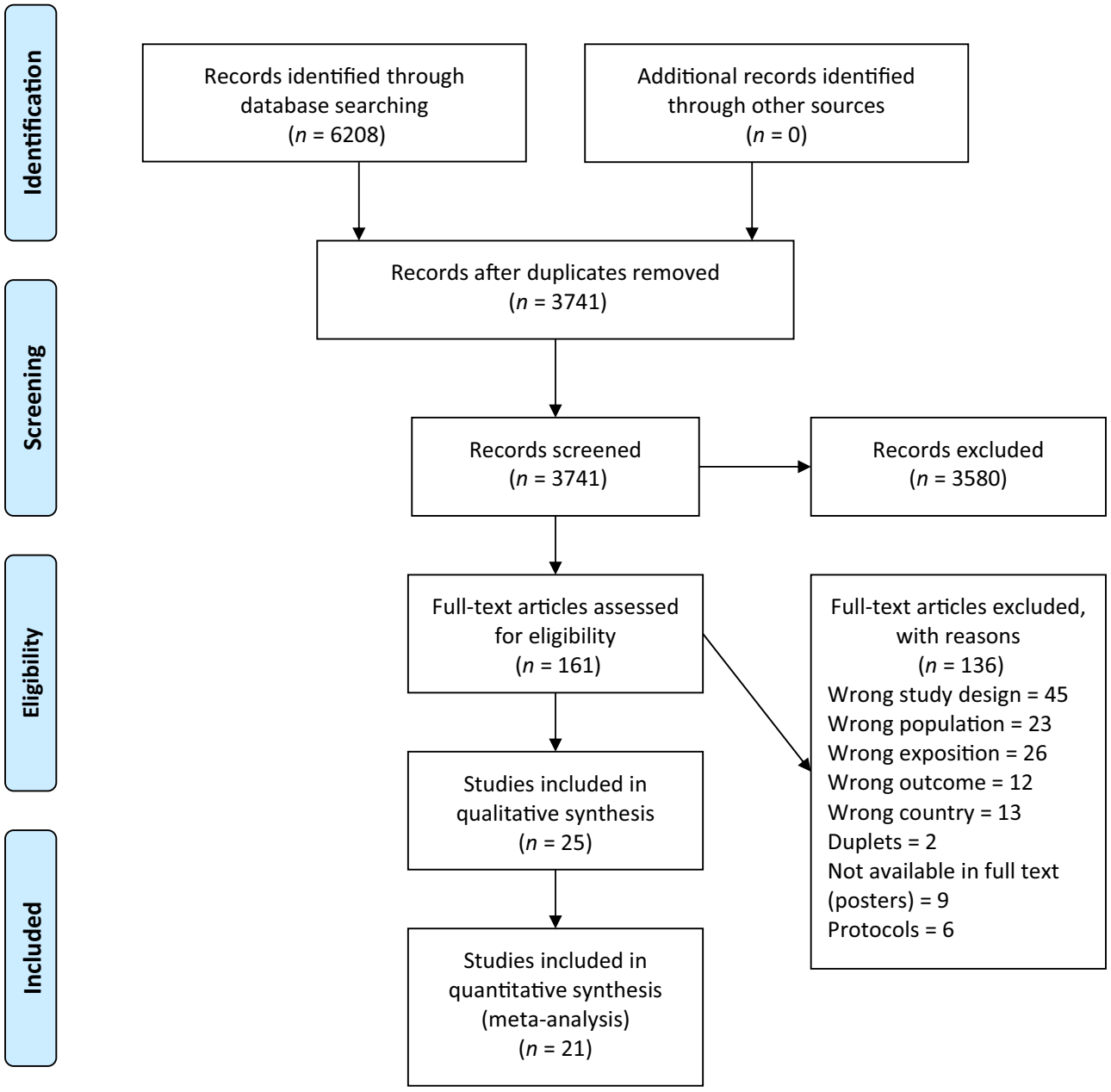

FIGURE 1 PRISMA flow diagram.[55]

3.3 | Summary of results

3.3.1 | Associations between low and normal umbilical cord pH and cognitive and motor development, CP and mortality

Two studies[33,42] assessed cognitive development using the Bayley Scale of Infants Development (BSID) at 36–42 months of age (Table 1). Infants born with acidosis had higher scores than those without acidosis (MD 5.18, 95% CI 0.84–9.52; Figure 2).

Six studies[4,29,31,33,41,42] investigated the association of cognitive development/intelligence between term children born with and without acidosis on different cognitive scales at the 2- to 18-year follow-up (Table 1). Due to different scales and different years of follow-up, we did not pool the results, but displayed the single studies' results in a forest plot (Figure S1).

A meta-analysis based on five studies[26,31,33,42,43] found an SMD of −0.16 (95% CI −0.54 to 0.23), indicating little to no differences between infants born with and without acidosis on motor development delays at the 2- to 4.5-year follow-up (Figure 3).

Four pooled studies[4,31,32,43] indicated an increased risk of CP among children born with acidosis compared with children born without (RR 3.40, 95% CI 0.86–13.39; Figure 4). However, this result was not statistically significant.

The meta-analysis of Kayani et al.[31] and Low et al.[33] showed no significant differences between the studied groups

TABLE 1 Characteristics of included studies.

Author, year (country)	Study design (methodological quality)	No. of (infants)	Umbilical cord pH	Outcome
Ahearne, 2016 (Ireland)	Cohort (moderate)	$n = 31$	pH <7.1	Mortality, neurodevelopmental outcome assessed by Bayley Scales of Infant and Toddler Development, (BSID-III) at 36–42 months
Baenziger, 1999 (Switzerland)	Cohort (moderate)	$n = 17$ (included number 2 and 10)	pH 7.12	Mortality, neurological outcome at 1 year (CP), assessed by Griffiths developmental test
Battin, 2001 (New Zealand)	RCT (High)	$N = 9$ (normothermic group)	pH 6.85 ± 0.25	Mortality, neurodevelopmental outcome assessed by BSID-II at 18 months of age, CP and hearing impairment
Beinder, 1999 (Germany)	Cohort (moderate)	$n = 25$	pH <7.0	Mortality, neurological outcome assessed by Griffith at 18 months
Dennis, 1989 (England)	Cohort (high)	$n = 192$, divided into group A–D	pH ≤7.10 or pH >7.10	Neurological development assessed by Griffith's development scale at 4.5 years
Diviney, 2015 (Ireland)	Case–control (moderate)	$n = 44$ (mild acidosis = 25, severe acidosis = 19)	pH = 7.0 ($n = 25$) pH = 7.0–7.25 ($n = 32$)	Wechsler Intelligence Scale for Children (WISC-IVUK) and Achenbach Child Behaviour Checklist (CBCL) at 7 years
Fee, 1990 (USA)	Cohort (moderate)	$n = 110$ neonates with severe acidosis	Mean pH 6.99 (± 0.06)	Neurodevelopmental outcome assessed by BSID at 12 and 24 months
Hafstrøm, 2012 (Sweden)	Case–control (High)	$n = 78$ infants with metabolic acidosis $n = 156$ control	pH median range: 6.91–6.98 pH >7.10	Neurodevelopmental categorization criteria measures at 6.5 years of age (as category 1 [no symptoms] to 5 [dead]) (See Table S5 for more categories)
Hamrik, 2003 (USA)	Cohort (moderate)	$n = 35$	pH 7.12 (6.82–7.32)	Cognitive development was assessed by BSID-II at 30 months
Handley-Derry, 1997 (Canada)	Case–control (moderate)	$n = 43$ asphyxia $n = 43$ control	Mean pH: 7.06 Mean pH: 7.12	BSID, Psychomotor Development Index assessed at 4, 6, 8 years
Hefler, 2007 (Austria)	Cohort (high)	$n = 1236$	pH <7.12 group pH ≥7.12 group	Stanine scale assessment at 18 years: overall performance, overall intelligence, technical understanding, concentration, operation accuracy, working speed, and eye-hand co-ordination
Ingemarsson, 1997 (Sweden)	Case–control (moderate)	$n = 154$ acidosis group $N = 154$ control	pH <7.05 pH >7.05	Mortality, developmental screening at age 4: assessed as attention deficits, speech problems and motor delay, CP
Julkunen, 2012 (Finland)	Cohort (moderate)	$n = 30$ asphyxia $n = 30$ control	pH <7.10 pH normal	Mortality, neurological outcome assessed at 1 year of age, by modified Griffith's scale
Kayani, 2014 (UK)	Cohort (moderate)	$n = 20$ acidosis $n = 20$ control	pH ≤7.0 pH ≥7.20	Ages and Stages Questionnaires (ASQ) (assessed: gross motor, fine motor, communication, etc.) and Health Screening Questionnaire (HSQ) (assessed: general health, hearing loss, etc.), CP at 24 months
Lavrijsen, 2005 (Nederland)	Cohort (moderate)	$n = 95$ acidosis $n = 90$ control	pH <7.0 pH >7.15	Mortality, assessed neurodevelopment by Griffith developmental scale after the first year of life, CP
Leinonen, 2019 (Finland)	Cohort (high)	$n = 404$ acidosis[a] $n = 80\,554$ control	pH <7.00 pH >7.10	Mortality, CP, epilepsy, intellectual disability, visual impairment and/or hearing impairment at 4 years
Low, 1983 (Canada)	Cohort (low)	$n = 37$ hypoxia $n = 59$ control	Mean pH: 7.20[b] Mean pH: 7.25	Neurodevelopment assessed by BSID at 12 and 24 months

TABLE 1 (Continued)

Author, year (country)	Study design (methodological quality)	No. of (infants)	Umbilical cord pH	Outcome
Mikkelsen, 2017 (Finland)	Cohort (high)	$n=9924$ $n=44131$ $n=224979$	pH <7.10 pH 7.09–7.19 pH ≥7.20	ADHD diagnosed with hyperkinetic disorder after the age of 5, according to the International Classification of Diseases (ICD-10)
Montaldo, 2020 (Italy)	Cohort (moderate)	$n=54$	Worst pH ≤1 h: 6.95 (6.86–6.98)	Neurodevelopment assessed by BSID-III at 18 and 24 months. Adverse outcome = a composite of death or moderate or severe disability
O'Sullivan, 2021 (Irland/ Sweden)	Cohort (low)	$n=43$ acidosis $n=37$ control	pH 7.05 (6.99–7.09) pH 7.28 (7.24–7.32)	Mortality, neurodevelopmental assessment at 18–36 months using BSID-III, CP
Ruth, 1988 (Finland)	Cohort (moderate)	$n=896$	pH <7.16	Mortality, cerebral palsy or delay in development (e.g. inability to sit and stand at the age of 12 months)
Schwenke, 2018 (Germany)	Cohort (moderate)	$n=573$ infants with and without AD/HD	Mean pH 7.3, SD (0.1)	A parent-reported questionnaire about the child's behaviour and different diseases was sent 10–13 years after birth
Seikku, 2016 (Finland)	Cohort (high)	$n=214465$ (GA 37^{+0}–38^{+6}) $n=859827$ (GA 39^{+0}–41^{+6})	pH <7.0, pH 7.0–7.10	Cerebral palsy (CP), epilepsy, intellectual disability, visual impairment and deafness at the age of 4 years
Svirko, 2008 (UK)	Cohort (High)	$n=563$	Mean pH 7.20 (6.86–7.37)	Intellectual function at 6–8 years of age by different tests (see Table S5)
Wildschut, 2005 (Netherlands)	Cohorts (moderate)	$n=43$	pH <7.0 ($n=7$)[c] pH ≥7.1 ($n=23$)	Motor, cognitive and behavioural functionin, e.g. assessed at 4 years by Movement Assessment Battery for Children (Movement-ABC)

[a]Not extracted data from group of pH 7.00–7.10.
[b]Umbilical artery buffer base <34 mEq/litre.
[c]Not included data 7.0 ≤ pH < 7.1 group ($n=13$).

in delayed language development (SMD −0.30, 95% CI −0.68 to 0.09; Figure S2).

We evaluated the findings relating to cognitive development (Figures 2 and S1), motor development delays (Figure 3), risk ratio of CP (Figure 4) and delayed language development (Figure S2) as having a very low certainty of evidence (Table 2).

Four studies[13,30,32,43] investigated the risk of death from the 1-year follow-up among newborn children with and without acidosis (Table 1). The meta-analysis estimate was uncertain, with a wide confidence interval for mortality (risk ratio 5.72, 95% CI 0.90–36.27; Figure S3).

Results from neurodevelopmental outcomes and mortality that are not included in meta-analyses are presented in Table S5.

3.3.2 | Associations between umbilical cord pH assessments and neurodevelopmental outcomes, and mortality in one population

Eight pooled studies[22,24,27,28,33,35,36,42] indicated a mean proportion of 0.29 (95% CI 0.12–0.49) of abnormal childhood development (≤85 score on one or all the subscales of BSID, i.e. cognitive, language and motor development) in a population of 390 children assessed by BSID I–III at 12–42 months of age (Figure S4).

Four studies[22,24,37,39] assessed the proportion of CP among 915 016 term infants by umbilical cord blood acid–base analysis. Due to the use of different CP definitions and different pH values, we did not pool the results. The unweighted proportion of CP in the studies included was 2.38/1000 (Figure S5).

Two other studies investigated the proportion of children with delayed language development[33,43] and intellectual function[40] (Table 1). The meta-analysis suggested that 12% of the 298 children had delayed language development (Figure S6).

Five other studies[22–25,36] investigated the proportion of deaths from the 1-year follow-up (Table 1). The analysis of these studies included 121 children and three events (2.5%) of deaths (Figure S7).

We found the proportion of abnormal child development (Figure S4) to have low certainty of evidence, the proportion of children with CP (Figure S5) to have high certainty of evidence and the proportion of children with delayed language development (Figure S6) to have moderate certainty of evidence (Table 3).

The results from studies that are not included in the meta-analyses are presented in Table S5.

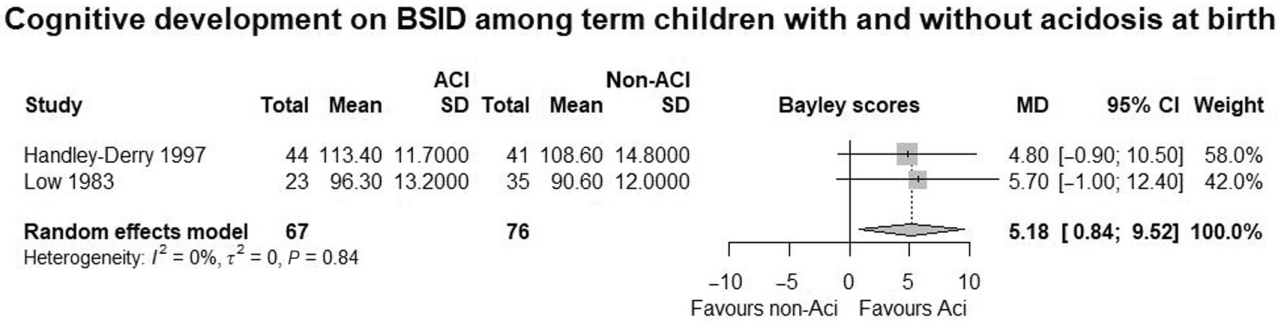

FIGURE 2 Forest plot for cognitive development on BSID among term children with and without acidosis at birth.

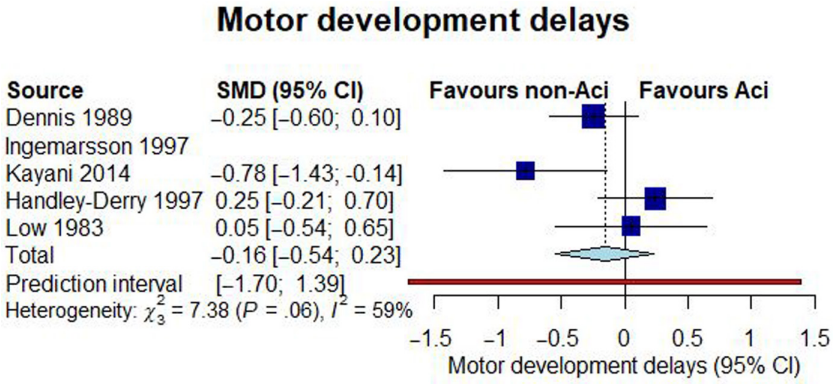

FIGURE 3 Forest plot for motor development delays among children with and without acidosis.

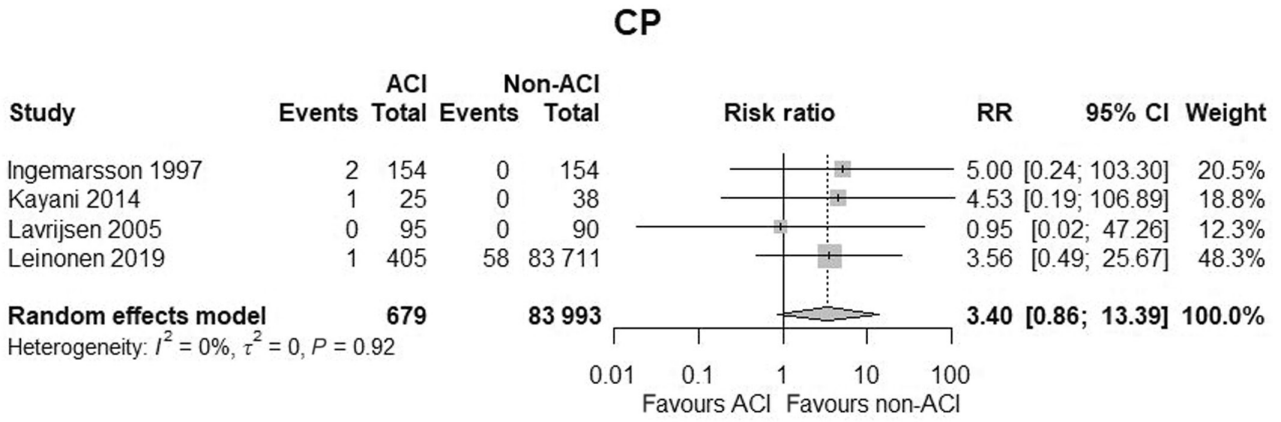

FIGURE 4 Forest plot for risk ratio of CP.

4 | DISCUSSION

4.1 | Main findings

We included 25 observational studies on associations between umbilical cord blood–acid analysis at delivery and neurodevelopmental outcomes in children from 1 year of age. Based on our GRADE evaluations, we are highly uncertain when it comes to the following findings; children born with acidosis had higher cognitive development scores than children without acidosis. However, non-significant results from the forest plots indicated both higher risk of death after 1 year of age and higher risk of CP. Due to the very low certainty of this evidence, future studies may alter the results of this systematic review.

4.2 | Strengths and limitations

The strengths of this systematic review lie in the extensive literature search, the meta-analyses and the use of GRADE. Using the GRADE approach allowed us to draw

TABLE 2 Summary of findings and certainty of evidence for associations in two study groups.

Outcomes	No. of studies	Acidosis group, *n*	Non-acidosis group, *n*	Effect size (95% CI)	Certainty of evidence
Cognitive development assessed by BSID (Figure 2)	2	67	76	MD 5.18 (0.84–9.52) Favouring acidosis group	⨁◯◯◯[a] Very low
Motor development delays (Figure 3)	5	142	165	SMD −0.16 (−0.54 to 0.23) Little to no difference	⨁◯◯◯[a,b,c] Very low
Risk ratio of CP (Figure 4)	4	4/681	58/83 993	RR 3.40 (0.86–13.39) Favouring non-acidosis group	⨁◯◯◯[c] Very low
Delayed language development (Figure S2)	2	48	60	SMD −0.30 (−0.68, 0.09) Little to no difference	⨁◯◯◯[a,c] Very low

[a]Risk of bias: Downgraded −1.
[b]Inconsistency: Downgraded −1.
[c]Imprecision: Downgraded −1.

TABLE 3 Summary of findings and certainty of evidence in one study group.

Outcome	No. of studies	No. of events (*n*)/no. of children (*N*)	Mean proportion (%) (95% CI)	Certainty of evidence
Proportion of abnormal child development at 12–42 months assessed by BSID (Figure S4)	8	136/436	0.29% (0.12–0.49)	⨁⨁◯◯[a,b] Low
Proportions of children with cerebral palsy (Figure S5)	4	2189/915 919	2.39/1000	⨁⨁⨁⨁ High
Proportion of children with delayed language development among term infants (Figure S6)	2	36/298	0.12% (0.08–0.16)	⨁⨁⨁◯[a] Moderate

[a]Risk of bias: Downgraded −1.
[b]Inconsistency: Downgraded −1.

stronger conclusions regarding our confidence in the pooled estimates.

This review has limitations. First, we could only include observational studies. Secondly, only eight of the 25 included (32%) studies had a low risk of bias. We assessed the remaining 17 studies as having an unclear to high risk of bias. This risk of bias, the imprecision and inconsistency identified in the meta-analyses, influenced our very low confidence in the pooled estimates from studies with two study groups. Thirdly, the included studies used different definitions of, for example, acidosis and CP, and employed different outcome measurement tools. The cut-off of pH for acidosis varied across the studies. Despite this variation and the heterogeneity it may represent, we decided to use the acidosis definition applied by each of the studies. In addition, the use of different outcome measures, e.g. cognitive development and time of assessment in the included studies, might introduce additional heterogeneity. Fourthly, 12 of the included studies had an unclear description or lacked descriptions of whether confounding factors had been taken into consideration. This implies that a possible effect of confounding factors cannot be excluded. Fifthly, we included only studies published in English, German or Scandinavian languages. This language restriction may have excluded other relevant studies that might have changed our results and conclusion. Sixthly, we included several studies with few participants and few events. This has an impact on the precision of our pooled results. Due to the small number of studies included in the meta-analyses, we were unable to conduct a meta-regression analysis that could identify whether umbilical cord pH assessments contribute to explaining the long-term outcome.

4.3 | Interpretation

We have very low confidence in the associations between the results of umbilical cord blood acid–base analysis at delivery and long-term neurodevelopmental outcomes in children. It is therefore unclear whether the risk of adverse long-term outcomes differed between the children who had been exposed to acidosis during delivery and those who had not.

Our meta-analysis, with very low certainty of evidence, suggests that babies with acidosis at birth performed better on their BSID test at 36–42 months of age compared with children without acidosis at birth.[33,42] The two pooled studies included children who had mild intrapartum asphyxia only, with no or only minor signs of encephalopathy (Figure 2). Another forest plot with very low certainty of evidence supports the results of higher cognitive development scores among children born with acidosis (assessed by different scales) (Figure S1). Only one of these six pooled studies[31] included children with intrapartum hypoxia events or

neurological signs consistent with birth asphyxia. This is in accordance with previous studies suggesting that babies with mild acidosis at birth but no clinical symptoms, do not have an elevated risk of adverse outcomes.[13,40,41] In fact, Svirko et al.[40] state that mild acidaemia can be neuroprotective due to the activation of NMDA-type receptors. Kro et al.[45] argue that elevated levels of pCO_2 may be beneficial for fetuses with moderate acidosis, and cord artery pCO_2 is thereby a factor that should be considered when assessing the compromised newborn. In addition, Hutchon[46] argue that beneficial outcomes could be due to delayed cord clamping. Delayed cord clamping may result in artificial lowered cord artery pH and in better outcomes for the babies, as late clamping prevents hypovolaemia and increases the oxygen-carrying capacity in the blood.[46,47] Further, delayed cord clamping per se is associated with some long-term benefits, making interpretation of long-term follow-up results that include populations with both early and delayed cord clamping difficult.[48–50] Another explanation for the BSID test result may be confounding factors, as discussed under the study's limitations.

Although not statistically significant and with very low certainty of evidence, children born with acidosis showed a tendency towards higher risk of CP in our meta-analysis. Malin et al.[3] report a moderate association between low arterial pH and CP (odds ratio 2.3, 95% CI 1.3–4.2) based on seven studies of varying quality. The pooled estimate included 1171 children with arterial cord pH <7.20. Our meta-analysis, which includes close to 85 000 children with and without acidosis, suggests the same tendency as that of Malin et al.[3]

Lee et al.[12] found that 1.8% ($n = 3/163$) cases with low cord pH were subsequently diagnosed with CP, whereas we found a percentage of only 0.6% ($n = 4/679$). This could imply that our results relating to CP may be in accordance with the observations that intrapartum events are of less importance as risk factors for CP than, for example, fetal growth restriction or birth defects.[51]

In a systematic review by Zhang et al.,[52] only babies with evidence of birth asphyxia and hypoxic ischemic encephalopathy were included. These authors found a pooled CP rate of above 20% and concluded that children with confirmed asphyxia had a higher risk of developing CP compared with healthy children. In contrast, our pooled proportion of children with CP including almost a million children, was 2.39/1000 (Figure S5). These data are extracted from studies including newborns with and without acidosis, had different cut-offs for the definitions of acidosis at birth, and had slightly different definitions of CP. This could explain why our results are somewhat higher than the overall pooled prevalence of CP, which is around 2/1000 live births (95% CI 1.98–2.25).[53] The proportions of other pooled neurodevelopmental outcomes were low across the studies.

Findings from the present systematic review support the recommendations of NICE and ACOG that collecting umbilical artery blood gas samples routinely or even in mixed populations is of limited or uncertain value in predicting long-term outcomes. In addition, routine blood gas sampling represents costs in terms of equipment and time and may influence how the birth is perceived.[5]

Malin et al.[3] found that acidosis at birth was associated with neonatal mortality. Although not statistically significant, children with acidosis at birth had a higher risk of dying after 1 year of age than did healthy children. This result must be interpreted carefully, due to the small number of events and a wide confidence interval. Nonetheless, 90% of the deaths of children suffering from birth asphyxia occurred before 18 months of age.[54] It is therefore likely that few deaths occur after 1 year from birth.

5 | CONCLUSION

No firm conclusions can be drawn regarding the association between umbilical cord pH assessments at birth and long-term neurodevelopmental outcomes in children from 1 year of age. However, our meta-analyses suggest higher scores on cognitive developmental scales and a non-significant indication of increased risk of CP and mortality among children born with acidosis compared with children born without acidosis. Due to a very low certainty of evidence, these results must be interpreted cautiously and investigated in large and well conducted cohort studies.

AUTHOR CONTRIBUTIONS

HTM: protocol development and registration, data collection, data analysis, writing of article and other (quality/risk-of-bias assessment and GRADE evaluation). AK, ASDP, LH, EB: protocol development, data collection, data analysis, writing of article and other (quality/risk-of-bias assessment). GS: data analysis, writing of article and GRADE assessment. ODS: data collection, data analysis and writing of article.

ACKNOWLEDGEMENTS

The authors would like to thank information specialists Elisabeth Karlsen and Kari Kalland at Oslo Metropolitan University who performed the literature searches.

FUNDING INFORMATION

We received no funding to conduct this review.

CONFLICT OF INTEREST STATEMENT

None declared. Completed disclosure of interest forms are available to view online as supporting information.

DATA AVAILABILITY STATEMENT

Data available in the Supporting Information to this article.

ETHICS APPROVAL

None.

REFERENCES

1. Rodríguez Fernández V, López Ramón YCCN, Marín Ortiz E, Couceiro Naveira E. Intrapartum and perinatal results associated

with different degrees of staining of meconium stained amniotic fluid. Eur J Obstet Gynecol Reprod Biol. 2018;228:65–70.
2. Blickstein I, Green T. Umbilical cord blood gases. Clin Perinatol. 2007;34(3):451–9.
3. Malin GL, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: systematic review and meta-analysis. BMJ. 2010;340:c1471.
4. Leinonen E, Gissler M, Haataja L, Andersson S, Rahkonen P, Rahkonen L, et al. Umbilical artery pH and base excess at birth are poor predictors of neurodevelopmental morbidity in early childhood. Acta Paediatr. 2019;108(10):1801–10.
5. Wiklund IE, Ahlberg M, Dahlström A, Weichselbraun M, Sjörs G. Routine testing of umbilical cord blood after normal delivery should be discontinued. Sex Reprod Healthc. 2014;5(4):165–6.
6. Xodo S, Xodo L, Berghella V. Delayed cord clamping and cord gas analysis at birth. Acta Obstet Gynecol Scand. 2018;97(1):7–12.
7. Wiberg N, Källén K, Olofsson P. Delayed umbilical cord clamping at birth has effects on arterial and venous blood gases and lactate concentrations. BJOG. 2008;115(6):697–703.
8. Boere I, Roest AA, Wallace E, Ten Harkel AD, Haak MC, Morley CJ, et al. Umbilical blood flow patterns directly after birth before delayed cord clamping. Arch Dis Child Fetal Neonatal Ed. 2015;100(2):F121–5.
9. NICE. Intrapartum care for healthy women and babies. UK: NICE; 2014 [cited 31 May 2022]. Available from: Overview | Intrapartum care for healthy women and babies | Guidance | NICE
10. Saneh H, Mendez M, Srinivasan V. Cord blood gas. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing LLC; 2021. p. 1–3.
11. Blix E, Brurberg KG, Reierth E, Reinar LM, Øian P. ST waveform analysis versus cardiotocography alone for intrapartum fetal monitoring: a systematic review and meta-analysis of randomized trials. Acta Obstet Gynecol Scand. 2016;95(1):16–27.
12. Lee J, Jung J, Park H, Kim S-Y, Kwon D, Choi S-J, et al. Umbilical cord arterial blood gas analysis in term singleton pregnancies: a retrospective analysis over 11 years. Obstet Gynecol Sci. 2020;63:293–304.
13. Hafström M, Ehnberg S, Blad S, Norén H, Renman C, Rosén KG, et al. Developmental outcome at 6.5 years after acidosis in term newborns: a population-based study. Pediatrics. 2012;129(6):e1501–7.
14. Yeh P, Emary K, Impey L. The relationship between umbilical cord arterial pH and serious adverse neonatal outcome: analysis of 51,519 consecutive validated samples. BJOG. 2012;119(7):824–31.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
16. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
17. Unaited Nations. Human Development Index: United Nations. 2020 [cited 5 October 2020]. Available from: http://hdr.undp.org/en/content/2019-human-development-index-ranking
18. CASP. CASP cheklists. 2021 [cited 20 March 2021]. Available from: CASP CHECKLISTS - CASP - Critical Appraisal Skills Programme (casp-uk.net)
19. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. 2019;22(4):153–60.
20. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36:1–48.
21. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li TPM, editors. Cochrane handbook for systematic reviews of interventions version 6.3 (updated February 2022). Cochrane; 2022 [cited 5 April 2022]. Available from: www.training.cochrane.org/handbook
22. Ahearne C, Denihan N, Walsh B, Reinke S, Kenny L, Boylan GB, et al. Early cord metabolite index and outcome in perinatal asphyxia and hypoxic-ischaemic encephalopathy. Neonatology. 2016;110:296–302.
23. Baenziger O, Moenkhoff M, Morales CG, Waldvogel K, Wolf M, Bucher HU, et al. Impaired chemical coupling of cerebral blood flow is compatible with intact neurological outcome in neonates with perinatal risk factors. Neonatology. 1998;75:9–17.
24. Battin M, Dezoete J, Gunn T, Gluckman P, Gunn A. Neurodevelopmental outcome of infants treated with head cooling and mild hypothermia after perinatal asphyxia. Pediatrics. 2001;107:480–4.
25. Beinder E, Kevecordes B, Wenzel D, Uberall M, Kandler C, Frobenius W, et al. Prediction of severe acidosis at birth in term fetuses and their neurodevelopmental outcome at 18 months of age. Geburtshilfe Frauenheilkd. 1999;59(2):70–6.
26. Dennis J, Johnson A, Mutch L, Yudkin P, Johnson P. Acid-base status at birth and neurodevelopmental outcome at four and one-half years. Am J Obstet Gynecol. 1989;161(1):213–20.
27. Fee SC, Malee K, Deddish R, Minogue JP, Socol ML. Severe acidosis and subsequent neurologic status. Am J Obstet Gynecol. 1990;162(3):802–6.
28. Hamrick SEG, Miller SP, Newton NR, Parer JT, Ferriero DM, Barkovich AJ, et al. Nucleated red blood cell counts: not associated with brain injury or outcome. Pediatr Neurol. 2003;29(4):278–83.
29. Hefler L, Tomovski C, Waibel V, Brugger C, Heim K, Reinthaller A, et al. Umbilical arterial pH levels after delivery and adult intelligence: a hospital-based study. Acta Obstet Gynecol Scand. 2007;86(11):1404–6.
30. Julkunen M, Uotila J, Eriksson K, Janas M, Luukkaala T, Tammela O. Obstetric parameters and Doppler findings in cerebral circulation as predictors of 1 year neurodevelopmental outcome in asphyxiated infants. J Perinatol. 2011;32:631–8.
31. Kayani SI, Joo Tan M, Shaw NJ, Dewhurst C, Titman A, Lancaster G, et al. Two-year outcomes for infants with low cord pH at birth. J Matern Fetal Neonatal Med. 2014;27(10):1010–4.
32. Lavrijsen S, Uiterwaal C, Stigter R, Vries L, Visser G, Groenendaal F. Severe umbilical cord acidemia and neurological outcome in preterm and full-term neonates. Biol Neonate. 2005;88:27–34.
33. Low JA, Galbraith RS, Muir DW, Killen HL, Pater EA, Karchmar EJ. Intrapartum fetal hypoxia: a study of long-term morbidity. Am J Obstet Gynecol. 1983;145(2):129–34.
34. Mikkelsen S, Olsen J, Bech B, Wu C, Liew Z, Gissler M, et al. Birth asphyxia measured by the pH value of the umbilical cord may predict an increased risk of attention deficit hyperactivity disorder. Acta Paediatr. 2017;106:944–52.
35. O'Sullivan MP, Casey S, Finder M, Ahearne C, Clarke G, Hallberg B, et al. Up-regulation of Nfat5 mRNA and Fzd4 mRNA as a marker of poor outcome in neonatal hypoxic-ischemic encephalopathy. J Pediatr. 2021;228:74–81.e2.
36. Montaldo P, Caredda E, Pugliese U, Zanfardino A, Delehaye C, Inserra E, et al. Continuous glucose monitoring profile during therapeutic hypothermia in encephalopathic infants with unfavorable outcome. Pediatr Res. 2020;88(2):218–24.
37. Ruth VJ, Raivio KO. Perinatal brain damage: predictive value of metabolic acidosis and the Apgar score. BMJ. 1988;297(6640):24–7.
38. Schwenke E, Fasching PA, Faschingbauer F, Pretscher J, Kehl S, Peretz R, et al. Predicting attention deficit hyperactivity disorder using pregnancy and birth characteristics. Arch Gynecol Obstet. 2018;298(5):889–95.
39. Seikku L, Gissler M, Andersson S, Rahkonen P, Stefanovic V, Tikkanen M, et al. Asphyxia, neurologic morbidity, and perinatal mortality in early-term and postterm birth. Pediatrics. 2016;137(6):1–11.
40. Svirko E, Mellanby J, Impey L. The association between cord pH at birth and intellectual function in childhood. Early Hum Dev. 2008;84(1):37–41.
41. Wildschut J, Feron F, Hendriksen J, Hall M, Gavilanes-Jiminez D, Hadders-Algra M, et al. Acid-base status at birth, spontaneous motor behaviour at term and 3 months and neurodevelopmental outcome at age 4 years in full-term infants. Early Hum Dev. 2005;81:535–44.
42. Handley-Derry M, Low JA, Burke SO, Waurick M, Killen H, Derrick EJ. Intrapartum fetal asphyxia and the occurrence of minor deficits in 4 to X yea' old children. Dev Med Child Neurol. 1997;39:508–14.

43. Ingemarsson I, Herbst A, Thorngren-Jerneck K. Long term outcome after umbilical artery acidaemia at term birth: influence of gender and duration of fetal heart rate abnormalities. BJOG. 1997;104(10):1123–7.
44. Diviney M, Pinnamaneni R, Murphy JF, Lynch B, Rushe H, Madigan C, et al. Neurodevelopmental outcome at seven years in term, acidotic newborns. Ir Med J. 2015;108(4):106–9.
45. Kro GA, Yli BM, Rasmussen S, Norèn H, Amer-Wåhlin I, Rosén KG, et al. Association between umbilical cord artery pCO_2 and the Apgar score; elevated levels of pCO_2 may be beneficial for neonatal vitality after moderate acidemia. Acta Obstet Gynecol Scand. 2013;92(6):662–70.
46. Hutchon DJ. What mechanism could account for a reversal of the trend for acidosis to benefit the development of the brain? Early Hum Dev. 2009;85(2):137.
47. Ashish A, Singhal N, Gautam J, Rana N, Andersson O. Effect of early versus delayed cord clamping in neonate on heart rate, breathing and oxygen saturation during first 10 minutes of birth – randomized clinical trial. Matern Health Neonatol Perinatol. 2019;5:7.
48. Bianchi A, Jacobsson B, Mol BW, FIGO Working Group for Preterm Birth. FIGO good practice recommendations on delayed umbilical cord clamping. Int J Gynecol Obstet. 2021;155(1):34–6.
49. Xodo S, Xodo L, Baccarini G, Driul L, Londero A. Does delayed cord clamping improve long-term (≥4 months) neurodevelopment in term babies? A systematic review and a meta-analysis of randomized clinical trials. Front Pediatr. 2021;9:651410.
50. Rana N, Kc A, Målqvist M, Subedi K, Andersson O. Effect of delayed cord clamping of term babies on neurodevelopment at 12 months: a randomized controlled trial. Neonatology. 2019;115(1):36–42.
51. Ellenberg J, Nelson K. The association of cerebral palsy with birth asphyxia: a definitional quagmire. Dev Med Child Neurol. 2013;55(3):210–6.
52. Zhang S, Li B, Zhang X, Zhu C, Wang X. Birth asphyxia is associated with increased risk of cerebral palsy: a meta-analysis. Front Neurol. 2020;11:704.
53. Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2013;55(6):509–19.
54. Azzopardi D, Strohm B, Marlow N, Brocklehurst P, Deierl A, Eddama O, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. N Engl J Med. 2014;371(2):140–9.
55. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed1000097

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Myrhaug HT, Kaasen A, Pay ASD, Henriksen L, Smedslund G, Saugstad OD, et al. Umbilical cord blood acid–base analysis at birth and long-term neurodevelopmental outcomes in children: a systematic review and meta-analysis. BJOG. 2023;130(10):1156–1166. https://doi.org/10.1111/1471-0528.17480