Outcomes of neonatal hypoxic-ischaemic encephalopathy in centres with and without active therapeutic hypothermia: a nationwide propensity score-matched analysis

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ABSTRACT

Objective

Therapeutic hypothermia (TH) for neonatal hypoxic-ischaemic encephalopathy (HIE), delivered mainly in tertiary cooling centres (CCs), reduces mortality and neurodisability. It is unknown if birth in a non-cooling centre (non-CC), without active TH, impacts short-term outcomes.

Design

Retrospective cohort study using National Neonatal Research Database and propensity score-matching.

Setting

UK neonatal units.

Patients

Infants ≥36 weeks gestational age with moderate or severe HIE admitted 2011-2016.

Interventions

Birth in non-CC compared to CC.

Main outcome measures

Primary outcome was survival to discharge without recorded seizures. Secondary outcomes were recorded seizures, mortality and temperature on arrival at CCs following transfer.

Results

5059 infants were included with 2364 (46.7%) born in non-CCs. Birth in a CC was associated with improved survival without seizures (35.1% vs 31.8%; OR 1.15, 95% CI 1.02-1.31; p=0.02), fewer seizures (60.7% vs 64.6%; OR 0.84, 95% CI 0.75-0.95, p=0.007) and similar mortality (15.8% vs 14.4%; OR 1.11, 95% CI 0.93-1.31, p=0.20) compared with birth in a non-CC. Matched infants from level 2 centres only had

similar results, and birth in CCs was associated with greater seizure-free survival compared to non-CCs. Following transfer from a non-CC to a CC (n=2027), 1362 (67.1%) infants arrived with a recorded optimal therapeutic temperature but only 259 (12.7%) of these arrived within six hours of birth.

Conclusions

Almost half of UK infants with HIE were born in a non-CC, which was associated with suboptimal hypothermic treatment and reduced seizure-free survival. Provision of active TH in non-CC hospitals prior to upward transfer warrants consideration.

INTRODUCTION

Moderate or severe hypoxic ischaemic encephalopathy (HIE) is the leading cause of mortality and neurodisability in infants ≥36 weeks gestational age (GA) affecting an estimated 1.5 - 2.0/1000 births.[1 2] Active therapeutic hypothermia (TH) commenced within the first six hours post insult is safe [3 4] and significantly improves survival and neurodisability. [5 6] Active TH for moderate/severe HIE has been successfully established within regional cooling centres (CCs), [7] that are mainly tertiary neonatal centres in the UK. Infants born in non-cooling centres (non-CCs), typically non-tertiary centres where equipment to undertake active TH is not available, are usually passively cooled prior to upward transfer to a regional CC. Although many neonatal transport teams use active TH during transportation,[8] their availability, despatch time and travelling distance can delay achieving target temperature for babies in non-CCs with delays beyond six hours of age could reduce the benefits of TH.[9] Furthermore, early TH (<3 hours of age) has been associated with better neurodevelopmental outcomes [9 10] although not universally.[11 12]

High seizure burden in HIE, based on their number, frequency and treatment required, is associated with more severe brain injury and adverse neurodevelopmental outcomes [13-18] and this may be independent of HIE severity.[15 19] Furthermore, studies have suggested that TH for HIE suppresses and reduces the overall burden of seizures,[6 13 20 21] leading some to conclude that seizures exacerbate the underlying brain injury and is potentially one of the mechanisms by which TH protects the brain.[21 22] Parents of infants with seizures associated with HIE have more mental health problems with symptoms of anxiety and depression.[23]

Centralisation of CCs has resulted in many infants requiring transportation soon after their insult and potentially during a period of increased susceptibility to secondary brain injury. It is unclear if the transport of newborns with HIE impacts on their outcomes.[24] No study has explored the impact of a nationwide approach to centralised TH for infants with HIE and the impact on outcomes.

The primary aim of this study was to evaluate the relationship between birth in a non-CC and seizure-free survival to discharge in infants ≥36 weeks GA with moderate/severe HIE. The secondary aims were to compare mortality, seizures only and admission temperatures for infants transported to a CC.

METHODS

Study Population

We performed a retrospective cohort study using the validated UK National Neonatal Research Database (NNRD).[25] The NNRD contains prospectively recorded demographic and clinical data. It uses a designated approved dataset (National Neonatal Data Set) within the NHS Data Dictionary with all data items searchable [26] and approved by the Standardised Committee for Care Information. Anonymised data is cleaned prior to entry into the database; erroneous entries are amended by the Neonatal Data Analysis Unit.

Data Collection

Data were extracted on all infants 36 to 42 weeks' GA, admitted to neonatal units in the UK between 2011 and 2016, with a diagnosis of moderate/severe HIE and underwent TH. Infants who died within the first 48 hours of life with moderate/severe

HIE but did not undergo TH, were also included within the study population. Infants were identified using data fields from the NNRD (Supplementary Table 1); the most severe grade of HIE recorded was allocated for each infant. Infants were excluded if their birth weight was >2 standard deviations above the 99.6th weight centile (to avoid erroneous data, n=5), those born in private hospitals or with missing birth hospital codes. Identification of CCs and their date of active TH commencement, was cross-checked using the TOBY trial register [5] and via direct communication with centres.

Outcomes

The primary outcome was seizure-free survival to neonatal discharge in infants ≥36 weeks GA with moderate/severe HIE. Seizures were as recorded by the attending clinical team within the database. Secondary outcomes were mortality, seizures alone, anticonvulsant use and admission temperature from time of birth to arrival at a CC following transfer.

Statistical Analysis

Clinical variables between infants born in non-CCs and CCs were compared using chi-squared test for categorical data and Mann-Whitney U test for non-normally distributed data.

Propensity score-matching was used to provide balanced groups of infants matched on demographic and clinical covariates within treatment groups.[27 28] Propensity score analysis entailed fitting a logistic regression model using a priori variables followed

by a stepwise process and evaluation of potential interactions to determine covariates to include in the propensity score model (Supplementary eMethods). Balancing of the groups post-matching was evaluated by the standardised difference and mean bias between control and treatment groups (Supplementary eMethods, Supplementary Fig. 1 and Table 1).[29 30] Matched groups of infants from non-CC and CC were identified and the effect of birth in a CC on outcomes was described using odd ratios.[31] Data were statistically analysed using Stata SE (StataCorp, Version 16).

Sensitivity Analyses

We performed two further paired, matched analyses between infants born in level 2 non-CCs and CCs and between infants born in a non-CC and CC but excluding those born either at home or in midwife led units. The propensity matching methodology was undertaken as previously described (Supplementary eMethods, Supplementary Figure 2 and 3). These additional analyses were performed to evaluate the reliability of our findings by minimising potential bias through differences in intrapartum and early neonatal care between different level centres.

RESULTS

Population

There were 5120 infants ≥36 weeks GA admitted to UK neonatal units with moderate/severe HIE and treated with TH. An additional 127 infants with moderate/severe HIE died within the first 48 hours of life without TH treatment were also included. In total, 188 infants were excluded (Supplementary Figure 1) leaving 5059 infants for analysis. Prior to matching, 2364 (46.7%) infants were born in a non-

CC (Table 1). In the unmatched groups, 65.4% of infants in the non-CC group were born in level 2 units; 71.9% of CC infants were born in a level 3 unit.

Propensity matched groups

Propensity score-matching (Supplementary Figure 2) yielded a total of 4330 infants (n=2165/group, Table 1). Infants born in a CC had significantly higher rates of seizure-free survival prior to discharge compared to infants born in a non-CC (35.1% vs 31.8%; OR 1.15, 95% CI 1.02–1.31; p=0.02) and significantly lower odds of recorded seizures overall (60.7% vs 64.6%; OR 0.84, 95% CI 0.75-0.95; p=0.007). Mortality prior to discharge was similar between the groups (Table 2).

In matched infants, 76.2% (n=2068) of infants recorded as having seizures received anticonvulsant medication, 27.1% of these infants received escalation of treatment with additional anticonvulsant agents but there was no difference between groups (Table 2). Compared to CC infants, those born in a non-CC received similar amounts of cardiorespiratory support but did require a longer length of hospital stay (Table 2).

Level 2 births only

Propensity score-matching yielded 1392 infants (n=696/group, Table 3 and 4, Supplementary Figure 3). Matched infants born in a level 2 CC had significantly higher seizure-free survival (38.8% vs 32.3%; OR 1.33, 95% CI 1.06-1.65; p=0.01), less recorded seizures (57.6% vs 63.9%; OR 0.77, 95% CI 0.61-0.95; p=0.02), and fewer anticonvulsants compared to infants born in level 2 non-CC. Mortality was not significantly different between the groups.

Admission temperature following transfer

2027 infants (85.7%) transferred from a non-CC to a CC had an admission temperature recorded after arrival. Of these, 259 (12.7%) had an admission temperature within the optimal therapeutic range of 33.5 +/- 0.5 ^{o}C[32] before six hours of age (Figure 1 and Supplementary Table 2). Overall, 1362 (67.1%) of infants arrived at the CC following transfer with an admission temperature within target range (Supplementary Table 2). There was no significant difference between time of admission for infants who arrived with their temperature within and outside of optimal therapeutic range (7 hours 40 minutes vs 7 hours 44 minutes, p=0.77). Following transfer to a level 3 centre, infants born in a level 2 CC were significantly more likely to arrive with a temperature in therapeutic range compared to those born in a level 2 non-CC (78.3% vs 67.4% respectively, OR 0.57; 95% CI 0.43-0.76, p<0.001) and were less likely to be over-cooled (<33^{o}C) on arrival (8.1% vs 14.9%, OR 0.51; 95% CI 0.34-0.76, P<0.001) (Table 4, Figure 1 and Supplementary Table 3).

DISCUSSION

In the UK, the management of HIE with active TH remains mostly in centralised centres within geographical networks and therefore is not currently available in every birthing hospital. This nationwide UK study, of over 5,000 infants with HIE, evaluated the relationship between birth in a non-CC and important short-term outcomes using propensity-score matched groups. We found almost half of infants were born in non-CCs and were less likely to survive without seizures at discharge compared to those born in CCs. This association appears to be driven by a higher rate of recorded seizures in non-CC infants as the mortality rates were similar. Importantly, the association remained significant when comparing only infants born in level 2 centres and following exclusion of those born at home or midwifery led units.

There is increasing evidence that seizures, and the seizure burden relating to HIE, can have an additive effect on the initial brain injury, independent of HIE severity.[15-17] [22] [33] Neonatal seizures occur in 50-60% of infants with HIE[34] and are associated with an increased risk of adverse neurodevelopment outcome, cerebral palsy and epilepsy compared to those without seizures.[35] We found fewer recorded seizures in those with access to immediate active TH in CCs supporting evidence from several smaller studies [21] [36] and a systematic review which found a borderline risk reduction of seizures.[6] There was no increase in the use of anticonvulsants between the groups in the main analysis; the subgroup of level 2 non-CC births were exposed to more treatment with multiple anticonvulsants, some potentially neurotoxic with adverse additive effects on long-term neurodevelopment.[37]

Specialist neonatal transport teams transferred 53.1% of infants with HIE during the study period at a time when many transport services transitioned from mainly passive cooling to active, servo-controlled TH.[38] Only 12.7% of infants transferred to a CC had an admission temperature within the optimal therapeutic range by six hours of age. A further 48.3% arrived between 6-12 hours of age in target range. There could be delay in deciding to initiate TH in some of the infants which could account for those in the normothermic range. Brain injury following hypoxic-ischaemic injury is progressive consisting of primary, latent and secondary phase.[39] The latent period is considered the optimal time for TH through reduction of cellular injury,[40] [41] although TH commenced within the late latent phase resulted in reduced cell survival compared to earlier use.[9] Furthermore, TH commenced after the latent phase post seizure activity did not improve cell survival.[42] It is plausible that these

infants only receive partial protection from TH through passive cooling, which is more likely to occur during the late latent phase or beyond and result in decreased dampening of excitatory neurotransmitters.[9] Studies have suggested this reduction in excitatory transmitter release, along with alterations in neuronal membrane potentials as a result of TH, could contribute to the potential of this treatment to directly reduce epileptiform activity, either alone or synergistically with other agents[43] [44]. This could also support our findings that infants born in a CC with immediate access to TH had fewer reported seizures.

Comparing infants born in level 2 centres, a greater proportion of CC infants arrived with a temperature in optimal range compared with non-CC infants, with more over-cooled in the latter group. Immediate access to active TH not only reduces the risk of complications associated with over-cooling or potential lack of neuroprotection due to under-cooling, but also mitigates the time critical burden placed on the transport team to commence TH within six hours of birth. This could explain the later admission time to tertiary CCs of infants born within level 2 centres CCs.

The transport process itself exposes the infant to noxious stimuli which could contribute to on-going brain injury.[45] Preterm infants transferred in early life have an increased risk of brain injury.[46] It is unclear if exposure to significant levels of vibration and noise during inter-hospital transport, beyond that deemed safe for healthy adults, is a contributory mechanism to the additional seizures identified in this study.

Strengths and limitations

This study is one of the largest population studies in the TH era utilising routinely recorded patient data from over 180 centres, overcoming single-centre study weakness and allowing variation in management across a national healthcare service. The use of robust propensity matching with well-balanced groups is also a significant strength, especially as undertaking a clinical trial of this nature may not be ethical or feasible. The large dataset has allowed identification of fewer infants recorded as having seizures that may not have been possible with smaller studies. The main limitation of our study is the use of seizures as a proxy of brain injury due to the lack of neuroimaging results or long-term follow-up as these are not universally recorded in the NNRD dataset. However, previous work has demonstrated an association with seizures, MRI findings and later development.[36 47] Another limitation is the lack of details on seizure diagnostic criteria or alternative aetiology, such as hypoglycaemia, fetal and neonatal drug exposure, as these are not recorded in sufficient detail within the database. Diagnosis of seizures were determined and coded by the attending clinical team and could be either clinical or electrical in nature. We did try to mitigate this by reporting the use of anticonvulsant therapy.

We could not account for differences in antenatal or neonatal care within the model which may be different between non-CCs and CCs, although sub-analysis of level 2 births only minimised bias due to variation in clinical practice. Criteria for TH in infants with HIE are clearly defined by national guidance [32] but the database had significant numbers of missing data such as 10 minute Apgar and cord/admission pH values. We therefore assumed if the diagnostic classification was recorded and an infant underwent TH they met the criteria for treatment. We also acknowledge the database does not allow differentiation of equipment used by transport teams nor the

exact time that target temperatures are achieved, which could be before admission to the CC.

CONCLUSION

This study demonstrates that almost half of infants with moderate/severe HIE in the UK are born in non-CCs and are less likely to have seizure-free survival compared to infants born in CCs, even when comparing level 2 centre births only. Furthermore, many infants transferred to CCs have admission temperatures outside the optimal TH time and temperature windows. The disparity of immediate access to active TH, a treatment known to reduce mortality and disability, could delay optimal therapy and impact on outcomes. With the increasing recognition of the relative safety of TH,[6] consideration should be given for training, equipping and supporting non-CCs with active TH, minimising delays in initiating and achieving optimal target temperature prior to upward transfer to a specialised CC. Further work is also required to explore any potential adverse effects of inter-hospital transport on infants at risk of brain injury and suitable mitigation strategies.

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to the Neonatal Data Analysis Unit (NDAU) to form the National Neonatal Research Database (NNRD). Don Sharkey had full access to all the data in the study and takes full responsibility for the integrity of the data and accuracy of the data analysis. We are grateful to all the families that agreed to the inclusion of their baby's data in the NNRD, the health professionals who recorded data and the NDAU team.

Authors' contributions

LJS and DS made substantial contributions to the concept, planning, design of the study and acquisition of data. AM and DS collated access to TH data. LJS and DS analysed and interpreted the data with support from Professor C Coupland (acknowledgement). All authors assisted in drafting and editing the manuscript. All authors approved the final version for publication.

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Competing interests

The authors have no conflict of interest. The sponsor had no involvement in the conduct of this study.

Ethics approval

The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by London – City and East Research Ethics Committee (REC: 17/LO/1822).

Data availability statement

All data were extracted and supplied by the NDAU and are available from the corresponding author on reasonable request and with permission of the study team and NDAU.

What is already known on this topic –

- Hypoxic ischaemic encephalopathy (HIE) remains the leading cause of mortality and neurodisability in term infants
- Active therapeutic hypothermia commenced within the first six hours post hypoxic insult is safe and significantly improves survival and severe neurodisability
- Infants who subsequently develop seizures secondary to HIE have worse neurodevelopmental outcomes, independent of HIE severity

What this study adds –

- Infants with moderate or severe HIE who are born in centres without immediate access to active therapeutic hypothermia are less likely to survive without seizures
- Infants who are transferred into cooling centres frequently arrive beyond the optimal six hour therapeutic window and with temperatures outside of treatment range.
- Infants transferred to tertiary cooling centres from level 2 centres with active therapeutic hypothermia are more likely to arrive in target temperature range

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Table 1. Demographic and clinical variables of infants ≥36 weeks gestational age with moderate or severe hypoxic ischaemic encephalopathy both pre- and post-propensity score-matching

	Unmatched infants				Propensity score-matched infants			
Variables	**Born in non-CC n=2364[a]**	**Born in CC n=2695[a]**	**SMD**	***p* Value[b]**	**Born in non-CC n=2165[a]**	**Born in CC n=2165[a]**	**SMD**	***p* Value[b]**
Gender (Male)	1354 (57.3)	1417 (52.6)	-0.095	0.002	1203 (55.6)	1225 (56.6)	0.020	0.49
Birthweight (grams)	3340 (2957-3760)	3332 (2940-3750)	0.014	0.70	3340 (2944-3760)	3340 (2970-3775)	-0.018	0.23
Gestation (weeks)	40 (38-41)	40 (38-41)	-0.015	0.47	40 (38-41)	40 (38-41)	-0.006	0.85
Birth year	2014 (2012-2015)	2014 (2012-2015)	-0.089	0.02	2014 (2012-2015)	2014 (2012-2015)	0.026	0.40
Pre-eclampsia	113 (4.8)	120 (4.5)	0.016	0.58	98 (4.5)	97 (4.5)	0.003	0.92
Maternal infection	555 (23.5)	559 (20.7)	0.066	0.02	480 (22.2)	480 (22.2)	0.000	0.99
Mode of delivery[c]								
Em CS no labour	405 (17.1)	449 (16.7)	0.013	0.66	375 (17.3)	357 (16.5)	0.022	0.48
Em CS in labour	682 (28.9)	787 (29.2)	-0.008	0.78	639 (29.5)	630 (29.1)	0.008	0.80
El CS no labour	20 (0.9)	28 (1.0)	-0.020	0.48	21 (0.95)	18 (0.81)	0.014	0.64
El CS in labour	7 (0.3)	6 (0.2)	0.014	0.61	7 (0.33)	6 (0.27)	0.011	0.72
Instrumental	358 (15.1)	514 (19.1)	-0.104	<0.001	355 (16.4)	310 (14.3)	0.060	0.05
Missing	100 (4.2)	84 (3.1)	0.059	0.04	80 (3.7)	74 (3.4)	0.014	0.65
Presentation								
Cephalic	1833 (77.5)	2206 (81.9)	-0.107	<0.001	1753 (81.0)	1734 (80.1)	0.022	0.47
Breech	154 (6.5)	205 (7.6)	-0.043	0.13	142 (6.6)	162 (7.5)	-0.036	0.20
Transverse	11 (0.5)	12 (0.5)	0.003	0.91	11 (0.62)	11 (0.5)	0.003	0.92
Other	20 (0.9)	17 (0.6)	0.025	0.37	15 (0.7)	15 (0.68)	0.004	0.90
Missing	346 (14.6)	255 (9.5)	0.160	<0.001	244 (11.3)	244 (11.3)	0.000	1.00
Intra-partum events	276 (11.7)	349 (13.0)	-0.039	0.17	265 (12.2)	257 (11.9)	0.011	0.72
Significant resuscitation	1364 (57.7)	1703 (63.2)	-0.112	<0.001	1312 (60.6)	1278 (59.0)	0.033	0.28

Table 1. (continued)

	Unmatched infants				Propensity score-matched infants			
Variables	**Born in non-CC n=2364[a]**	**Born in CC n=2695[a]**	**SMD**	***p* Value[b]**	**Born in non-CC n=2165[a]**	**Born in CC n=2165[a]**	**SMD**	***p* Value[b]**
Apgar at 5 minutes	4 (2-5)	4 (2-6)	-0.010	0.56	4 (2-5)	4 (2-6)	-0.003	0.72
Grade of HIE								
Grade 2	811 (34.3)	1068 (39.6)	0.110	<0.001	779 (36.0)	760 (35.1)	-0.018	0.55
Grade 3	1553 (65.7)	1627 (60.4)			1386 (64.0)	1405 (64.9)		
Place of birth level[d]								
Level 1	670 (28.3)	0	-		615 (28.4)	0	-	-
Level 2	1546 (65.4)	701 (26.0)	0.861	<0.001	1425 (65.8)	566 (26.2)	0.868	<0.001
Level 3	18 (0.8)	1938 (71.9)	-2.198	<0.001	16 (0.8)	1551 (71.6)	-2.183	<0.001
Home	96 (4.1)	56 (2.1)	0.094	<0.001	82 (3.8)	48 (2.2)	0.094	0.002
Midwife led unit	34 (1.4)	0	-		27 (1.2)	0	-	-
Interhospital transfers[d]								
L1-L3 Transfer	632 (26.7)	0	0.854	<0.001	578 (26.7)	0	-	<0.001
L2-L3 Transfer	1386 (58.6)	452 (16.8)	0.957	<0.001	1283 (59.3)	358 (16.5)	0.981	<0.001

CC, Cooling Centre; SMD, Standardised mean difference; NVD, Normal vaginal delivery; Em CS, Emergency caesarean section; El CS, Elective caesarean section; HIE, Hypoxic Ischaemic encephalopathy; L2, level 2; L3, Level 3

[a] Data are n (%) or median (interquartile range).

[b] Categorical data analysed using chi squared test; non normally distributed continuous data analysed using Mann-Whitney U test; matched data by paired t-test for continuous data or McNemar's test or extensions thereof for binary and categorical data

[c] Compared to baseline – NVD

[d] Variables not included in propensity score matching

Table 2. Outcomes of infants with moderate or severe hypoxic ischaemic encephalopathy who were born in either a non-cooling or cooling centre after propensity score matching

Outcome variable	Born in non-CC n = 2165[a]	Born in CC n = 2165[a]	Odds Ratio (95% CI)	*p* Value
Survival without seizures	693 (31.8)	764 (35.1)	1.15 (1.02-1.31)	0.02
Seizures	1399 (64.6)	1314 (60.7)	0.84 (0.75-0.95)	0.007
Death	312 (14.4)	343 (15.8)	1.11 (0.93-1.31)	0.20
Day of death (Hours)				
< 24	65 (3.0)	81 (3.7)	-	0.06
24 -72	87 (4.0)	116 (5.4)	1.08 (0.70-1.66)	
> 72	160 (7.4)	145 (6.7)	0.72 (0.49-1.08)	
Anticonvulsants[b,c]				
None	349 (25.0)	296 (22.5)	-	-
1 drug	668 (47.3)	663 (50.5)	1.17 (0.96-1.42)	0.10
≥2 drugs	382 (27.2)	355 (27.0)	1.09 (0.88-1.36)	0.40
Respiratory support[b]				
Ventilated	1454 (67.2)	1515 (70.0)	1.15 (0.94-1.42)	0.17
HFOV	388 (17.9)	340 (15.7)	0.97 (0.76-1.24)	0.81
CPAP	95 (4.4)	104 (4.8)	1.21 (0.85-1.72)	0.28
Hypotension	983 (45.4)	982 (45.4)	0.99 (0.88-1.12)	0.96
PPHN	260 (12.0)	236 (10.9)	0.90 (0.74-1.08)	0.25
Nitric Oxide	214 (9.9)	236 (10.1)	1.02 (0.84-1.25)	0.79
Length of stay (days)	11.3 (7.3-18.9)	10.0 (6.5-16.4)	0.14 (0.05-0.36)	<0.001

CC, Cooling Centre, 95% CI, 95% Confidence interval, HFOV, High Frequency Oscillatory Ventilation; CPAP, Continuous positive airway pressure; PPHN, Persistent pulmonary Hypertension;

[a] Data are n (%) or median (interquartile range)

[b] Compared to baseline – No anticonvulsant/No respiratory support

[c] Data are n (%) of infants with seizures

Table 3. Demographic and clinical variables of infants with moderate or severe hypoxic ischaemic encephalopathy born in level 2 centres post propensity score-matching

	Unmatched infants				Propensity score matched infants			
Variables	**Born in non-CC n = 1546[a]**	**Born in CC n = 701[a]**	**SMD**	***p* Value[b]**	**Born in non-CC n = 696[a]**	**Born in CC n = 696[a]**	**SMD**	***p* Value[b]**
Gender (Male)	877 (56.7)	373 (53.2)	-0.070	0.12	366 (52.6)	373 (53.6)	0.020	0.71
Birthweight (grams)	3332 (2929-3760)	3370 (2960-3730)	-0.033	0.42	3372 (3004 – 3764)	3370 (2953 – 3730)	0.036	0.50
Gestation (weeks)	40 (38–41)	40 (38-41)	-0.047	0.28	40 (39–41)	40 (38–41)	0.032	0.56
Birth year	2014 (2012-2015)	2014 (2012-2015)	-0.134	0.003	2014 (2013–2015)	2014 (2012–2015)	0.010	0.86
Pre-eclampsia	71 (4.6)	38 (5.4)	-0.040	0.40	31 (4.5)	38 (5.5)	-0.046	0.39
Maternal Infection	383 (24.8)	173 (24.7)	0.002	0.96	176 (25.3)	172 (24.7)	0.013	0.80
Mode of delivery[c]:								
Em CS no labour	263 (17.0)	118 (16.8)	0.005	0.92	115 (16.5)	118 (17.0)	-0.012	0.83
Em CS in labour	494 (32.0)	205 (29.2)	0.059	0.20	200 (28.7)	205 (29.5)	-0.016	0.77
El CS no labour	13 (0.8)	7 (1.0)	-0.017	0.71	7 (1.0)	6 (0.9)	0.015	0.78
El CS in labour	6 (0.4)	3 (0.4)	-0.006	0.89	4 (0.6)	3 (0.4)	0.020	0.71
Instrumental	240 (15.5)	144 (20.5)	-0.131	0.003	137 (19.7)	140 (20.1)	-0.011	0.84
Missing	57 (3.7)	19 (2.7)	0.055	0.24	28 (4.0)	19 (2.7)	0.072	0.18
Presentation:								
Cephalic	1231 (79.6)	586 (83.6)	-0.103	0.03	588 (84.5)	582 (83.6)	0.024	0.66
Breech	84 (5.4)	42 (6.0)	-0.024	0.59	34 (4.9)	41 (5.9)	-0.044	0.41
Transverse lie	10 (0.7)	4 (0.6)	0.010	0.83	4 (0.6)	4 (0.6)	0.000	1.00
Other	11 (0.7)	5 (0.7)	-0.000	1.00	3 (0.4)	5 (0.7)	-0.038	0.48
Missing	210 (13.6)	64 (9.1)	0.141	0.003	67 (9.6)	64 (9.2)	0.015	0.78
Intra-partum events	187 (12.1)	89 (12.7)	-0.018	0.69	93 (13.4)	89 (12.8)	0.017	0.75
Significant Resuscitation	935 (60.50	434 (61.9)	-0.029	0.52	440 (63.2)	432 (62.1)	0.023	0.66
Apgar at 5 minutes	4 (2-5)	4 (2-6)	-0.070	0.09	4 (3 – 6)	4 (2 – 6)	0.018	0.74
Grade of HIE								
Grade 2	521 (33.7)	243 (34.7)	0.020	0.66	236 (33.9)	240 (34.5)	0.012	0.82
Grade 3	1025 (66.3)	458 (65.3)			460 (66.1)	456 (65.5)		

CC, Cooling centre; SMD, Standardised Mean Difference; NVD, Normal vaginal delivery; Em CS, Emergency caesarean section; El CS, Elective caesarean section; HIE, Hypoxic Ischaemic Encephalopathy

[a] Data are n (%) or median (interquartile)

[b] Categorical data analysed using chi squared test; non normally distributed continuous data analysed using Mann-Whitney U test; matched data by paired t-test for continuous data or McNemar's test or extensions thereof for binary and categorical data

[c] Compared to baseline - Normal Vaginal delivery

Table 4. Outcomes of infants with moderate or severe hypoxic ischaemic encephalopathy who were born in either a level 2 non-cooling or cooling centre after propensity score-matching

Outcome variable	Born in non-CC n = 696[a]	Born in CC n = 696[a]	Odds Ratio (95%CI)	*p* Value
Survival without seizures	225 (32.3)	270 (38.8)	1.33 (1.06-1.65)	0.01
Seizures	445 (63.9)	401 (57.6)	0.77 (0.61-0.95)	0.02
Death	105 (15.1)	90 (12.9)	0.84 (0.62-1.13)	0.25
Day of death (Hours)				
<= 24	25 (3.6)	22 (3.2)	-	0.84
24 -72	28 (4.0)	27 (3.9)	1.10 (0.50-2.40)	
> 72	52 (7.5)	41 (5.9)	0.90 (0.44-1.82)	
Anticonvulsants[b,c]				
None	97 (21.8)	116 (28.9)	-	-
1 drug	222 (49.9)	206 (51.4)	0.90 (0.71-1.13)	0.67
≥2 drugs	126 (28.3)	79 (19.7)	0.57 (0.42-0.78)	<0.01
Respiratory support[b]				
Ventilated	493 (70.8)	454 (65.2)	0.92 (0.64-1.32)	0.66
HFOV	108 (15.5)	145 (20.8)	1.34 (0.88-2.04)	0.17
CPAP	29 (4.2)	30 (4.3)	1.03 (0.56-1.91)	0.91
Hypotension	326 (46.8)	303 (43.5)	0.88 (0.71-1.08)	0.22
PPHN	97 (13.9)	95 (13.8)	0.98 (0.72-1.32)	0.88
Nitric Oxide	66 (9.5)	67 (9.6)	1.01 (0.71-1.45)	0.93
Transferred L2-L3	615 (88.4)	449 (64.5)	0.24 (0.18-0.32)	<0.001
Length of stay (days)	10.6 (7.0-17.5)	10.5 (6.8-17.7)	0.55 (0.13-2.40)	0.41

CC, Cooling Centre; 95% CI, 95% Confidence Interval; HFOV, High Frequency Oscillatory Ventilation; CPAP, Continuous positive airway pressure; PPHN, Persistent pulmonary Hypertension;

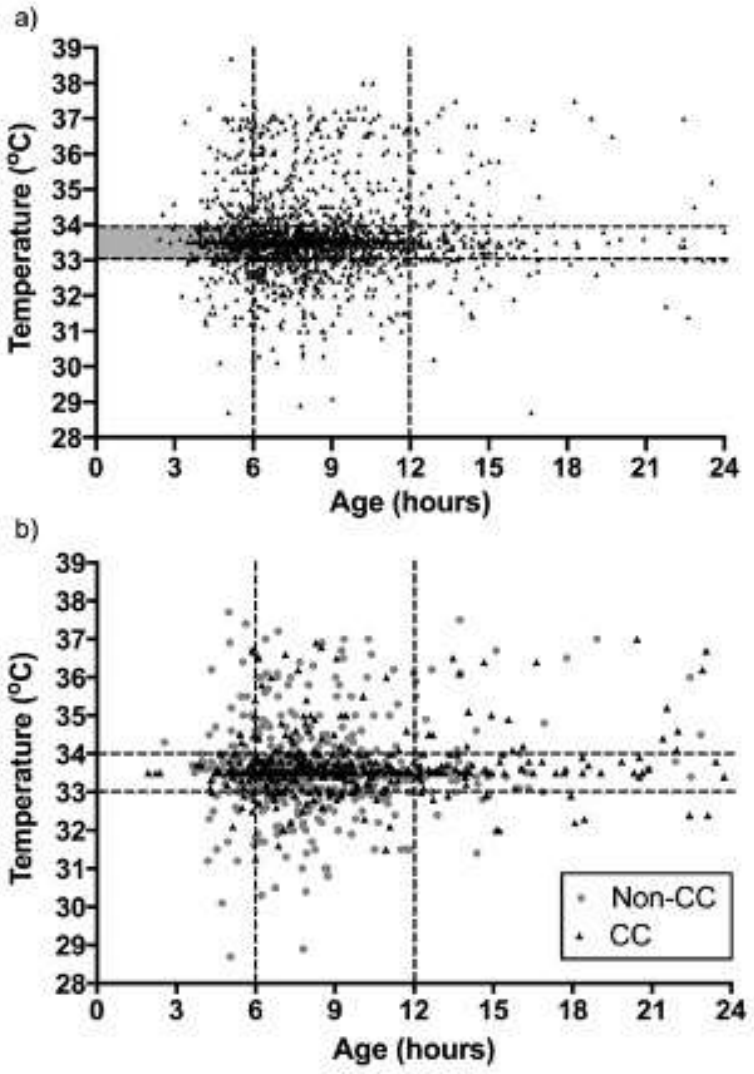
[a] Data are n (%)

[b] Compared to baseline - No anticonvulsants/No respiratory support

[c] Data are n (%) of infants with seizures

FIGURE LEGENDS

Figure 1. Admission temperature and arrival time following transfer to a cooling centre of infants ≥36 weeks gestational age with moderate or severe HIE a) who were born in a non-cooling hospital (n=2027) (shaded area optimal temperature in the six hour optimal therapeutic window), b) who were born level 2 centres with immediate access to active TH or non-CC and transferred to a level 3 CC.



Supplementary Online Content

Outcomes of neonatal hypoxic-ischaemic encephalopathy in centres with and without active therapeutic hypothermia: a nationwide propensity score-matched analysis

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Content:

Supplementary Table 1. Description of data fields used for determining covariates and outcomes from the National Neonatal Research Database

Principle Diagnosis at Discharge database entries for HIE Grading
<u>Severe HIE:</u> - HIE Grade 3 - Severe Neonatal Encephalopathy - Hypoxic ischaemic brain damage ; Severe - Severe perinatal asphyxia (with 1 minute Apgar <4) - Severe Neonatal Encephalopathy - Gr.3 - Hypoxic Ischaemic Encephalopathy (Gr 3) - Severe Neonatal Encephalopathy – Grade 3 HIE <u>Moderate HIE:</u> - HIE Grade 2 - Moderate Neonatal Encephalopathy - Hypoxic ischaemic brain damage ; Moderate - Moderate perinatal asphyxia (with 1 minute Apgar 4-7) - Moderate Neonatal Encephalopathy - Gr.2 - Hypoxic Ischaemic Encephalopathy (Gr 2) - Moderate Neonatal Encephalopathy - Grade 2 HIE <u>Mild HIE:</u> - HIE Grade 1 - Mild Neonatal Encephalopathy - Hypoxic ischaemic brain damage ; Mild - Mild perinatal asphyxia (with 1 minute Apgar >7) - Mild Neonatal Encephalopathy - Gr.1 - Hypoxic Ischaemic Encephalopathy (Gr 1) - Mild Neonatal Encephalopathy - Grade 1 HIE - Very mild perinatal asphyxia - clinically normal by 24 hours <u>Unspecified</u> - Birth Asphyxia - Anoxic Brain Damage <u>Therapeutic Hypothermia</u> - Therapeutic Hypothermia - Therapeutic Hypothermia (whole body cooling) - Hypothermia Therapeutic
Principle procedures during stay entries for identification of Therapeutic Hypothermia
<u>Therapeutic Hypothermia</u> - Therapeutic Hypothermia - Therapeutic Hypothermia (whole body cooling) - Hypothermia Therapeutic
Demographic and Clinical Variables

- Gender
- Birthweight
- Gestation in weeks
- Year of Birth
- Onset of Labour
- Presentation of fetus
- Mode of Delivery
- Methods of resuscitation
- Apgar score at 5 minutes
- Nulliparity determined from data field “Number of previous pregnancies”
- Meconium stained liquor
- Maternal Infection determined from data fields “Maternal pyrexia in labour” and “Problems during pregnancy with mother” (maternal UTI /chorioamnionitis/prolonged rupture of membranes)
- Hypotension determined from data fields “Inotropes given”, “Daily drugs”, “Principal diagnosis at discharge”
- Place of birth NHS hospital code
- Place of birth NHS hospital level
- Nitric oxide determined from data fields “Pulmonary vasodilator” and “Principle diagnosis at discharge”
- Persistent pulmonary hypotension determined from data fields “Principle diagnosis at discharge”
- Pre-eclampsia determined from data field problems during pregnancy with mother
- Gestational Diabetes determined from data field “Problems during pregnancy with mother”
- Acute intrapartum events determined from data fields “Problems (obstetric) during pregnancy with mother” (Reduced fetal movements/placental abruption/cord problems/shoulder dystocia) and “Principle diagnosis on discharge”
- Significant resuscitation determined from data field “Methods of resuscitation” (cardiac compressions/intubation/adrenaline/other drugs)
- Respiratory Support device (No support/CPAP/Ventilated/HFOV)

Outcome Variables

- Death determined from Destination at Discharge data field. If an infant was discharge “home”, “ward” or “Foster Care” the infants was coded as surviving.
- Seizures determined from “Convulsions today” and “Principle diagnosis at discharge data fields”. Infants were also coded as having seizures if they received anticonvulsants in the “Daily Drugs” data field.
- Number of anticonvulsants determined from “Daily Drugs” data field
- Admission temperature
- Time of admission temperature
- Admission time to neonatal unit
- Length of stay determined from Admission time and Time of discharge data fields

HIE, Hypoxic Ischaemic Encephalopathy; UTI, Urinary Tract Infection; NHS, National Health Service; CPAP, Continuous positive airway pressure; HFOV, High frequency oscillatory ventilation

eMethods

Propensity Score Matching

Propensity score analysis entailed fitting a logistic regression model using a stepwise process and evaluation of potential interactions to determine variables to include in the propensity score. For variables with missing data values were either imputed using Markov chain Monte Carlo method (1) or a separate category was defined indicating non-response. Initially, a priori background variables (gender, gestation, birthweight and birth year) were selected for inclusion into the logistic regression model regardless of their statistical association with the outcome. This baseline model was fitted with addition of one other background variable at a time. The variable with the greatest t ratio was included in the model if >1.0. This process was repeated, until t ratios for all remaining variables were smaller than 1.0. Following this analysis 13 covariates were included. These were:

- Gender
- Birthweight
- Gestation in weeks
- Birth year
- Nulliparity
- Pre-eclampsia
- Maternal infection
- Mode of delivery
- Presentation at birth
- Acute intrapartum events
- Significant resuscitation at birth
- Apgar score at 5 minutes
- Grade of HIE

Interactions

Interactions were determined for inclusion into model by ranking the variables in the concluding model by their t ratio and expanding this model by one second-order term at a time. The interaction term was included in the model if t ratio was greater than 2.71, which corresponds to nominal statistical significance at 10% level. No interactions reached this level in our analysis (2).

Propensity scores were estimated using logistic regression based on the selected background variables. A matched sample of untreated and treated infants was created through matching on the logit of the propensity score with caliper width set at 0.05. The propensity strata were trimmed by excluding infants with extreme propensities to minimise residual confounding. A nearest neighbour 1:1 matching algorithm with no replacement was used to form pairs of infants in the CC and non-CC group (3).

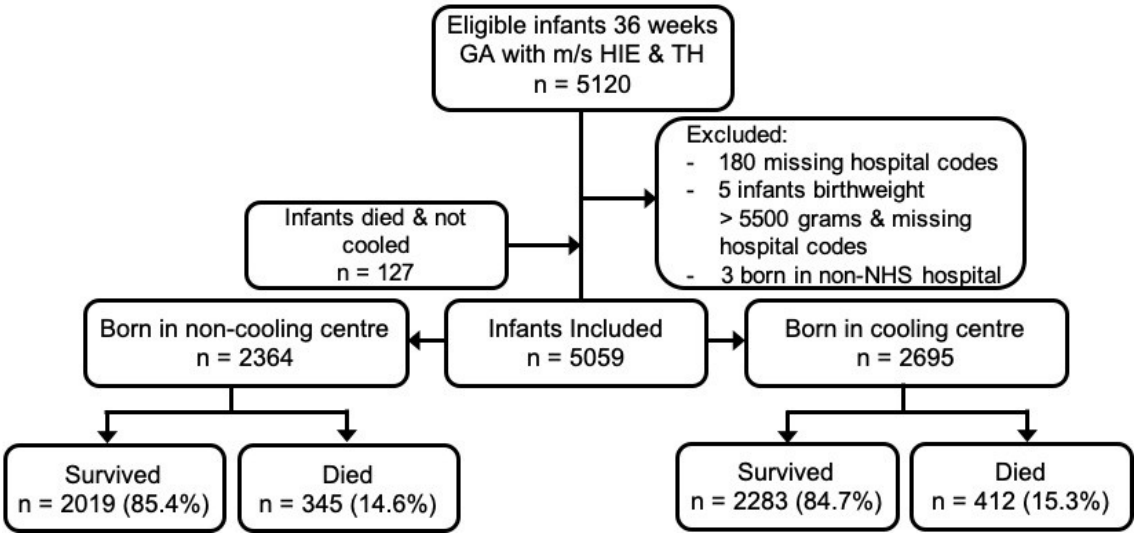
Assessment of balance

The matching process was evaluated by division of the propensity score into an optimal number of blocks and assessing the within-block equality of means of covariates across the treatment groups. The propensity distribution density was evaluated between control and treated groups both pre and post matching. (Supplementary Figure 2). Additionally, standardised percentage bias for each covariate (formulae as detailed by Rosenbaum and Rubin) after matching was calculated. A covariate was considered balanced if the standardised differences were between -0.2 and 0.2 and standardised mean bias was <5% (4) (5)(Supplementary Figure 2). The resulting model was well balanced with no covariate with a mean bias of >5% and overall mean bias 1.7 with no significant difference between the group (p=0.75).

Sensitivity analyses

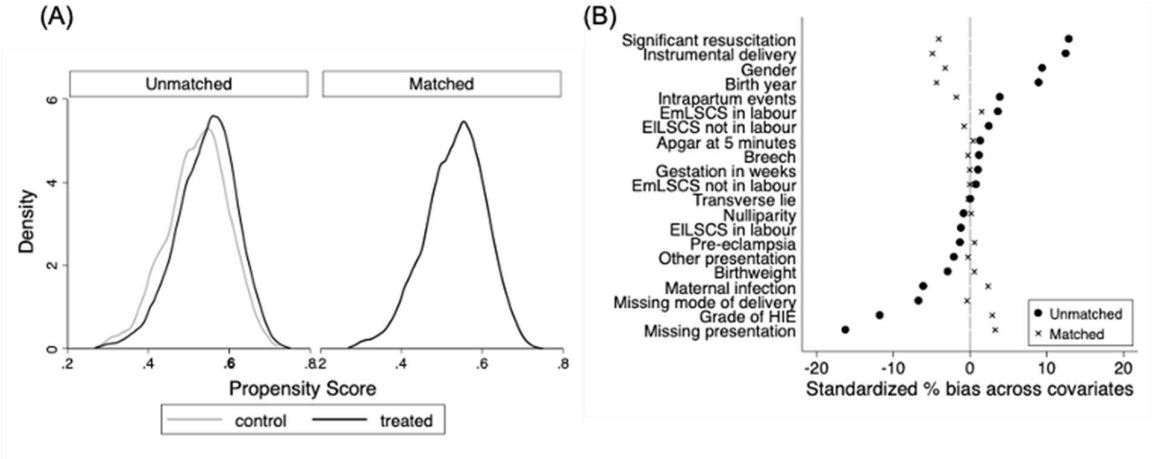
Sensitivity analyses were performed between infants born in level 2 non-cooling and cooling centres and between infants born in non-cooling and cooling centres but excluding infants born at home and midwife led units to mitigate potential bias. Further propensity score matching and assessment of balance was undertaken using the above described methodology for these subgroups of infants. Evaluation of model balance is demonstrated in Supplementary Figure 3 and 4.

Supplementary Figure 1. Flowchart of study participants demonstrating the number of infants ≥36 weeks gestational age with moderate or severe hypoxic ischaemic encephalopathy admitted to neonatal units in the UK managed with therapeutic hypothermia



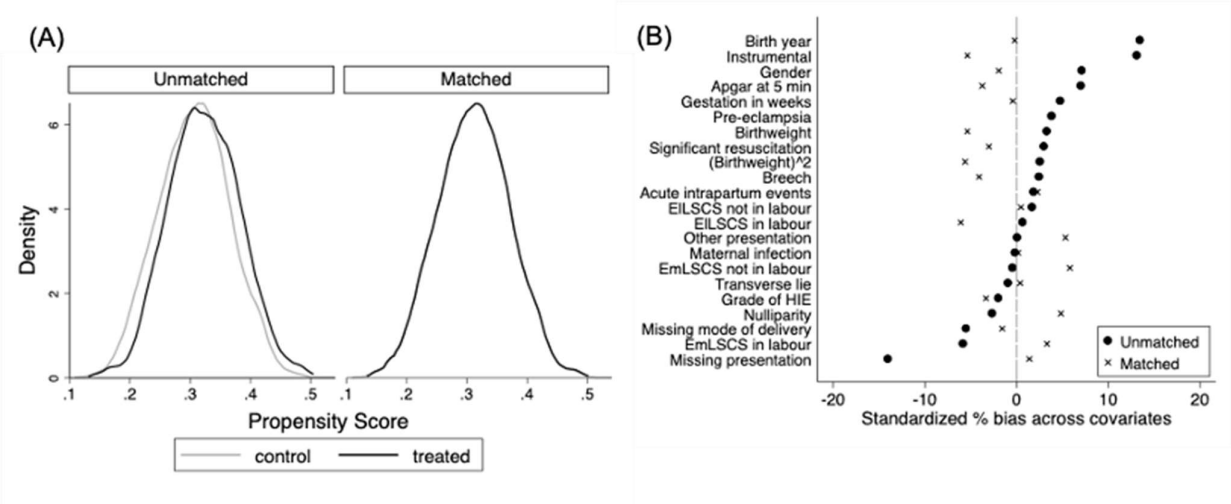
GA, Gestational age; m/s HIE, moderate or severe hypoxic ischaemic encephalopathy; TH, therapeutic hypothermia; NHS, National Health Service

Supplementary Figure 2. Propensity score distribution (A) and Standardised Bias (B) for infants born in non-cooling centres (control) and those born in cooling centres (treated) both before and after propensity score-matching



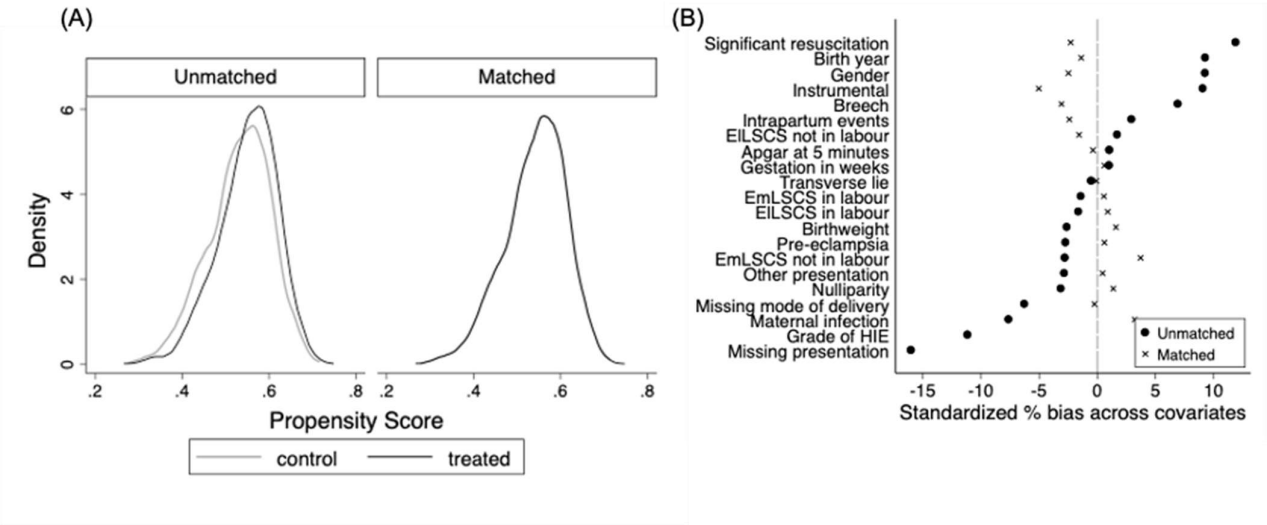
EmLSCS, Emergency caesarean section; ElLSCS, Elective caesarean section; APGAR, Appearance, Pulse, Grimace, Activity and Respiration score; HIE, Hypoxic ischaemic encephalopathy

Supplementary Figure 3. Propensity score distribution (A) and Standardised Bias (B) for infants born in level 2 non-cooling centres (control) and those born in cooling centres (treated) both before and after propensity score matching



EmLSCS, Emergency caesarean section; EILSCS, Elective caesarean section; APGAR, Appearance, Pulse, Grimace, Activity and Respiration score; HIE, Hypoxic ischaemic encephalopathy

Supplementary Figure 4. Propensity score distribution (A) and Standardised Bias (B) between infants born in a non-cooling centre (control) and those born in a cooling centre (treated) both before and after propensity score-matching excluding those born at home or in midwife led units



EmLSCS, Emergency caesarean section; EILSCS, Elective caesarean section; APGAR, Appearance, Pulse, Grimace, Activity and Respiration score; HIE, Hypoxic ischaemic encephalopathy

Supplementary Table 2. Admission temperature and arrival time following transfer to a cooling centre of infants ≥36 weeks gestational age with moderate or severe HIE who were born in a non-cooling hospital (n=2027).

		Age at Admission		
		<6 Hours	**6-12 Hours**	**>12 Hours**
Temperature	**>34ºC**	4.2% (n = 86)	11.9% (n = 242)	2.4% (n = 48)
	33-34ºC	12.7% (n = 259)	48.3% (n = 979)	6.1% (n = 124)
	<33ºC	2.5% (n = 52)	10.3% (n = 209)	1.3% (n = 27)

Supplementary Table 3. Admission temperature and arrival time following transfer to a level 3 cooling centre for infants ≥36 weeks gestational age with moderate or severe HIE who were born level 2 centres with immediate access to active therapeutic hypothermia or non-cooling centre.

		Age at Admission					
		Non-cooling centre (n = 611)			Cooling centre (n = 443)		
		< 6 Hours	**6 - 12 Hours**	**>12 Hours**	**< 6 Hours**	**6 - 12 Hours**	**> 12 Hours**
Temperature	**> 34ºC**	3.6 (n = 22)	11.6 (n = 71)	2.5 (n = 15)	1.1 (n = 5)	8.1 (n = 36)	4.3 (n = 19)
	33-34ºC	12.9 (n = 79)	49.3 (n = 301)	5.2 (n = 32)	9.9 (n = 44)	55.3 (n = 245)	13.1 (n = 58)
	<33ºC	2.3 (n = 14)	11.9 (n = 73)	0.7 (n = 4)	1.1 (n = 5)	4.7 (n = 21)	2.3 (n = 10)

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