

## Supplementary Online Content

Trends in the Incidence and Management of Hypoxic-Ischaemic Encephalopathy in the Therapeutic Hypothermia Era: A national population study

Shibley LJ<sup>1</sup>, Gale C<sup>2</sup>, Sharkey D<sup>1</sup>

<sup>1</sup> Division of Child Health and Obstetrics and Gynaecology, School of Medicine, University of Nottingham, UK

<sup>2</sup> Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London, Chelsea and Westminster Hospital campus, London, UK

### Corresponding Author:

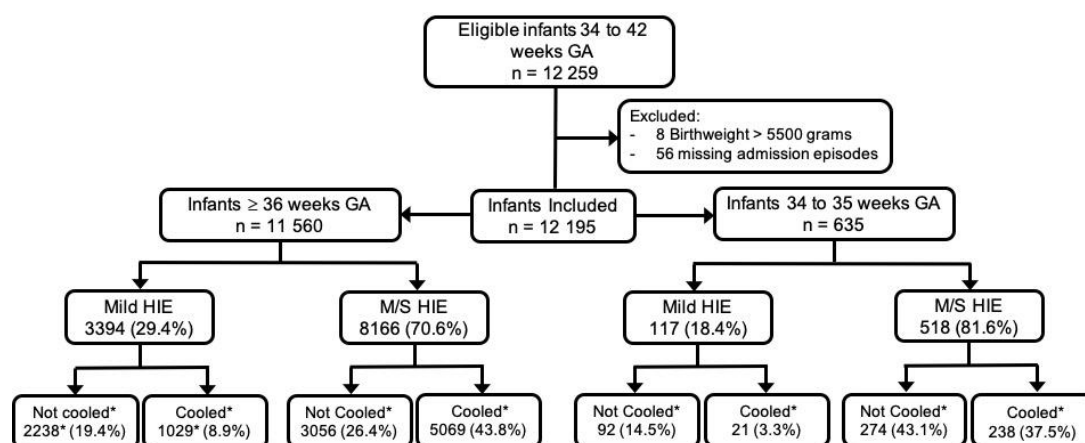
Dr Don Sharkey, Academic Child Health, E floor, East Block, University Hospital, Derby Rd, Nottingham, NG72UH, UK. Don.Sharkey@nottingham.ac.uk. Tel no. +44 1158230611.

### Content:

<b>Supplementary Figure 1</b> Flowchart of study participants demonstrating included/excluded infants and rate of hypoxic ischaemic encephalopathy for each gestational subgroup	1
<b>Supplementary Table 1</b> National Neonatal Research Database Hypoxic-Ischaemic Encephalopathy and Therapeutic Hypothermia identifiers	2
<b>Supplementary Table 2</b> Comparison of antenatal and delivery characteristics between epochs (2011-13 and 2014-16) for infants $\geq 36$ weeks gestational age with moderate/severe hypoxic ischaemic encephalopathy who died without therapeutic hypothermia	3
<b>Supplementary Table 3</b> Comparison of antenatal and delivery characteristics between epoch 1 (2011-13) and 2 (2014-16) for infants $\geq 36$ weeks gestational age with moderate/severe hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia	4
<b>Supplementary Table 4</b> Comparison of antenatal and delivery characteristics between epoch 1 (2011-13) and 2 (2014-16) for infants $\geq 36$ weeks gestational age with mild hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia	5
<b>Supplementary Table 5</b> Comparison of antenatal and delivery characteristics between infants $\geq 36$ weeks with moderate/severe and mild hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia	6
<b>Supplementary Table 6</b> Incidence rates for the whole study population by gestational age for any grade of hypoxic ischaemic encephalopathy (HIE),	6

moderate/severe HIE and mortality with moderate/severe HIE	
<b>Supplementary Table 7</b> Comparison of antenatal and delivery characteristics between epoch 1 (2011-13) and 2 (2014-16) for infants 34 to 35 weeks with hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia	7

**Supplementary Figure 1.** Flowchart of study participants demonstrating included/excluded infants and rate of hypoxic ischaemic encephalopathy for each gestational subgroup



\* Therapeutic hypothermia data not available for all infants within each subgroup  
GA, gestation age; m/s moderate/severe; HIE, Hypoxic Ischaemic encephalopathy

**Supplementary Table 1.** National Neonatal Research Database Hypoxic Ischaemic Encephalopathy and Therapeutic Hypothermia data identifiers

<b>Principal Diagnosis at Discharge database entry</b>
<p><u>Severe HIE :</u></p> <ul style="list-style-type: none"> <li>- HIE Grade 3 - Severe Neonatal Encephalopathy</li> <li>- Hypoxic ischaemic brain damage ; Severe</li> <li>- Severe perinatal asphyxia (with 1 minute Apgar &lt;4)</li> <li>- Severe Neonatal Encephalopathy - Gr.3</li> <li>- Hypoxic Ischaemic Encephalopathy (Gr 3)</li> <li>- Severe Neonatal Encephalopathy – Grade 3 HIE</li> </ul> <p><u>Moderate HIE:</u></p> <ul style="list-style-type: none"> <li>- HIE Grade 2 - Moderate Neonatal Encephalopathy</li> <li>- Hypoxic ischaemic brain damage ; Moderate</li> <li>- Moderate perinatal asphyxia (with 1 minute Apgar 4-7)</li> <li>- Moderate Neonatal Encephalopathy - Gr.2</li> <li>- Hypoxic Ischaemic Encephalopathy (Gr 2)</li> <li>- Moderate Neonatal Encephalopathy - Grade 2 HIE</li> </ul> <p><u>Mild HIE:</u></p> <ul style="list-style-type: none"> <li>- HIE Grade 1 - Mild Neonatal Encephalopathy</li> <li>- Hypoxic ischaemic brain damage ; Mild</li> <li>- Mild perinatal asphyxia (with 1 minute Apgar &gt;7)</li> <li>- Mild Neonatal Encephalopathy - Gr.1</li> <li>- Hypoxic Ischaemic Encephalopathy (Gr 1)</li> <li>- Mild Neonatal Encephalopathy - Grade 1 HIE</li> <li>- Very mild perinatal asphyxia - clinically normal by 24 hours</li> </ul> <p><u>Unspecified</u></p> <ul style="list-style-type: none"> <li>- Birth Asphyxia</li> <li>- Anoxic Brain Damage</li> </ul> <p><u>Therapeutic Hypothermia</u></p> <ul style="list-style-type: none"> <li>- Therapeutic Hypothermia</li> <li>- Therapeutic Hypothermia (whole body cooling)</li> <li>- Hypothermia Therapeutic</li> </ul>
<b>Principal procedures during stay</b>
<p><u>Therapeutic Hypothermia</u></p> <ul style="list-style-type: none"> <li>- Therapeutic Hypothermia</li> <li>- Therapeutic Hypothermia (whole body cooling)</li> <li>- Hypothermia Therapeutic</li> </ul>

**Supplementary Table 2.** Comparison of antenatal and delivery characteristics between epochs (2011-13 and 2014-16) for infants  $\geq 36$  weeks gestational age with moderate/severe hypoxic ischaemic encephalopathy who died without therapeutic hypothermia

Variables	Number of infants (n=120)*	Missing n (%)
<b><u>Antenatal Characteristics</u></b>		
Diabetes mellitus	0	0
Gestational diabetes	4 (3.3)	0
Preeclampsia	2 (1.7)	0
Risk factors of early infection <sup>a</sup>	22 (18.3)	0
<b><u>Delivery Characteristics</u></b>		
Gender (male)	61 (50.8)	0
Gestational age (weeks)	39 (37 - 40)	0
Birth weight (grams)	3252 (2840 - 3576)	0
> 98 <sup>th</sup> Centile	3 (2.5)	0
Intrapartum events <sup>b</sup>	13 (10.8)	0
Apgar 1 minute	2 (0 - 5)	9 (7.5)
Apgar 5 minute	5 (1 - 8)	9 (7.5)
Significant resuscitation <sup>c</sup>	58 (38.1)	0
Venous Cord pH	7.23 (7.09 - 7.32)	55 (45.8)
Day of death (days)	0.7 (0.37 - 2.0)	0

\* Data are n (%) or median (interquartile range)

<sup>a</sup> Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection

<sup>b</sup> Cord prolapse, shoulder dystocia, abruption, reduced fetal movements

<sup>c</sup> Chest compressions, intubation, drugs

Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic

**Supplementary Table 3.** Comparison of antenatal and delivery characteristics between epoch 1 (2011-13) and 2 (2014-16) for infants  $\geq 36$  weeks gestational age with moderate/severe hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia

Variables	Infants $\geq 36$ weeks GA with moderate/severe HIE and TH				p value**
	Epoch 1 (n=2286)*	Missing n (%)	Epoch 2 (n=2783)*	Missing n (%)	
Diabetes mellitus	13 (0.6)	0	46 (1.7)	0	<0.001
Gestational diabetes	63 (2.8)	0	123 (4.4)	0	0.002
Preeclampsia	111 (4.9)	0	122 (4.3)	0	0.43
Risk factors of early infection <sup>a</sup>	384 (16.8)	0	732 (26.3)	0	<0.001
<b>Delivery Characteristics</b>					
Gender (male)	1244 (54.4)	0	1528 (54.9)	0	0.70
Gestational age (weeks)	40 (38 – 41)	0	40 (38 – 41)	0	0.04
Birth weight (grams)	3355 (2958 – 3760)	0	3330 (2940 – 3750)	0	0.29
> 98 <sup>th</sup> Centile	131 (5.7)	0	158 (5.6)	0	0.94
Intrapartum events <sup>b</sup>	278 (12.2)	0	351 (12.6)	0	0.63
Apgar 1 minute	1 (0 – 3)	156 (6.8)	1 (1 – 3)	209 (7.5)	0.37
Apgar 5 minute	4 (2 – 6)	159 (7.0)	4 (2 – 6)	198 (7.1)	0.03
Significant resuscitation <sup>c</sup>	1136 (51.9)	0	1934 (71.3)	0	<0.001
Venous Cord pH	7.11 (6.93 – 7.25)	698 (30.5)	7.13 (6.97 – 7.26)	803 (28.8)	0.009

GA, Gestational age; HIE, Hypoxic-ischaemic encephalopathy; TH, Therapeutic hypothermia

\* Data are n (%) or median (interquartile range)

\*\* Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test

<sup>a</sup> Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection

<sup>b</sup> Cord prolapse, shoulder dystocia, abruption, reduced fetal movements

<sup>c</sup> Chest compressions, intubation, drugs

Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic

**Supplementary Table 4.** Comparison of antenatal and delivery characteristics between epoch 1 (2011-13) and 2 (2014-16) for infants  $\geq 36$  weeks gestational age with mild hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia

Variables	Infants $\geq 36$ weeks GA with mild HIE and TH				p value**
	Epoch 1 (n=426)*	Missing n (%)	Epoch 2 (n=603)*	Missing n (%)	
<b>Antenatal Characteristics</b>					
Diabetes mellitus	1 (0.2)	0	6 (1.0)	0	0.14
Gestational diabetes	8 (1.9)	0	18 (3.0)	0	0.27
Preeclampsia	10 (2.3)	0	23 (3.8)	0	0.19
Risk factors of early infection <sup>a</sup>	69 (16.2)	0	142 (23.5)	0	0.004
<b>Delivery Characteristics</b>					
Gender (male)	243 (57.0)	0	347 (57.5)	0	0.85
Gestational age (weeks)	40 (39 – 41)	0	40 (39 – 41)	0	0.60
Birth weight (grams)	3405 (2970 – 3760)	0	3330 (2950 – 3705)	0	0.10
> 98 <sup>th</sup> Centile	16 (3.8)	0	17 (2.8)	0	0.40
Intrapartum events <sup>b</sup>	37 (8.7)	0	52 (8.6)	0	0.97
Apgar 1 minute	2 (1 – 4)	38 (8.9)	3 (1 – 5)	58 (9.6)	0.02
Apgar 5 minute	5 (4 – 7)	40 (9.4)	6 (4 – 7)	50 (8.3)	0.04
Significant resuscitation <sup>c</sup>	163 (38.3)	0	270 (44.8)	0	0.04
Venous Cord pH	7.14	120 (28.2)	7.14	161 (26.7)	0.78

---

(6.98 – 7.25)

(6.99 – 7.25)

---

GA, Gestational age; HIE, Hypoxic-ischaemic encephalopathy; TH, Therapeutic hypothermia

\* Data are n(%) or median (interquartile range)

\*\* Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test

<sup>a</sup> Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection

<sup>b</sup> Cord prolapse, shoulder dystocia, abruption, reduced fetal movements

<sup>c</sup> Chest compressions, intubation, drugs

Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic



**Supplementary Table 5.** Comparison of antenatal and delivery characteristics between infants  $\geq 36$  weeks with moderate/severe and mild hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia

Variables	Infants $\geq 36$ weeks GA with M/S versus mild HIE and TH				p value**
	M/S HIE (n=5069)*	Missing n (%)	Mild HIE (n=1029)*	Missing n (%)	
<b>Antenatal Characteristics</b>					
Diabetes mellitus	59 (1.2)	0	7 (0.7)	0	0.17
Gestational diabetes	186 (3.7)	0	26 (2.5)	0	0.07
Preeclampsia	233 (4.6)	0	33 (3.2)	0	0.05
Risk factors of early infection <sup>a</sup>	1116 (22.0)	0	211 (20.5)	0	0.28
<b>Delivery Characteristics</b>					
Gender (male)	2772 (54.7)	0	590 (57.3)	0	0.12
Gestational age (weeks)	40 (38 – 41)	0	40 (39 – 41)	0	<0.001
Birth weight (grams)	3340 (2950 – 3760)	0	3360 (2965 – 3740)	0	0.98
> 98 <sup>th</sup> Centile	289 (5.7)	0	33 (3.2)	0	0.001
Intrapartum events <sup>b</sup>	629 (12.4)	0	89 (8.6)	0	0.001
Apgar 1 minute	1 (0 - 3)	365 (7.2)	3 (1 – 5)	96 (9.3)	<0.001
Apgar 5 minute	4 (2 – 6)	357 (7.0)	5 (4 – 7)	90 (8.7)	<0.001
Significant resuscitation <sup>c</sup>	3070 (60.6)	0	433 (42.1)	0	<0.001
Venous Cord pH	7.13 (6.96 – 7.25)	1501 (29.6)	7.14 (6.99 – 7.25)	281 (27.3)	0.06

GA, Gestational age; m/s, moderate/severe; HIE, Hypoxic-ischaemic encephalopathy; TH, Therapeutic hypothermia

\* Data are n (%) or median (interquartile range)

\*\* Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test

<sup>a</sup> Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection

<sup>b</sup> Cord prolapse, shoulder dystocia, abruption, reduced fetal movements

<sup>c</sup> Chest compressions, intubation, drugs

Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic

**Supplementary Table 6.** Incidence rates for the whole study population by gestational age for any grade of hypoxic ischaemic encephalopathy (HIE), moderate/severe HIE and mortality with moderate/severe HIE

<b>Gestation (weeks)</b>	<b>Any grade HIE (n=12195)</b>	<b>Rate per 1000 live births</b>	<b>M/S HIE &amp; TH (n=5307)</b>	<b>Rate per 1000 live births</b>	<b>Died &amp; M/S HIE (n=843)</b>	<b>Rate per 1000 live births</b>
<b>34</b>	255	6.22	76	1.85	41	1.00
<b>35</b>	380	6.31	162	2.69	40	0.66
<b>36</b>	615	5.04	319	2.61	66	0.54
<b>37</b>	977	3.50	483	1.73	81	0.29
<b>38</b>	1344	2.38	612	1.09	109	0.19
<b>39</b>	1989	1.97	858	0.85	129	0.13
<b>40</b>	3319	2.94	1456	1.29	212	0.19
<b>41</b>	2837	3.63	1163	1.51	144	0.18
<b>42</b>	479	3.49	178	1.34	21	0.15
<b>Total</b>						
<b>34-35 weeks</b>	635	6.27	238	2.35	81	0.80
<b>≥36 weeks</b>	11560	3.03	5069	1.26	762	0.19

M/S, moderate/severe; TH, Therapeutic Hypothermia

**Supplementary Table 7.** Comparison of antenatal and delivery characteristics

between epoch 1 (2011-13) and 2 (2014-16) for infants 34 to 35 weeks with hypoxic ischaemic encephalopathy undergoing therapeutic hypothermia

Variables	Infants 34 to 35 weeks GA with HIE and TH				p value**
	Epoch 1 (n=103)*	Missing n (%)	Epoch 2 (n=156)*	Missing n (%)	
<b>Antenatal Characteristics</b>					
Diabetes mellitus	1 (1.0)	0	10 (6.4)	0	0.03
Gestational diabetes	6 (5.8)	0	14 (9.0)	0	0.35
Preeclampsia	8 (7.8)	0	17 (10.9)	0	0.40
Risk factors of early infection <sup>a</sup>	24 (23.3)	0	40 (25.6)	0	0.67
<b>Delivery Characteristics</b>					
Gender (male)	60 (58.3)	0	92 (59.0)	0	0.91
Gestational age (weeks)	35 (34 – 35)	0	35 (34 – 35)	0	0.38
Birth weight (grams)	2275 (2030 - 2650)	0	2370 (2122 – 2640)	0	0.14
> 98 <sup>th</sup> Centile	6 (5.8)	0	12 (7.7)	0	0.56
Intrapartum events <sup>b</sup>	21 (20.4)	0	37 (23.7)	0	0.53
Apgar 1 minute	1 (0 – 3)	7 (6.8)	1 (0 – 3)	8 (5.1)	0.79
Apgar 5 minute	4 (1 – 5)	8 (7.8)	3 (1 – 6)	8 (5.1)	0.64
Significant resuscitation <sup>c</sup>	56 (54.4)	0	119 (76.3)	0	<0.001
Venous Cord pH	7.03 (6.85 – 7.23)	40 (38.8)	7.08 (6.85 – 7.26)	60 (38.5)	0.56

GA, Gestational age; HIE, Hypoxic-ischaemic encephalopathy; TH, Therapeutic hypothermia

\* Data are n(%) or median (interquartile range)

\*\* Categorical data analysed using Chi Squared test; Non-normally distributed continuous data analysed using Mann U Whitney test

<sup>a</sup> Maternal fever, Chorioamnionitis, prolonged rupture of membranes, urinary tract infection

<sup>b</sup> Cord prolapse, shoulder dystocia, abruption, reduced fetal movements

<sup>c</sup> Chest compressions, intubation, drugs

Data items diabetes mellitus, gestational diabetes, preeclampsia, risk factors for sepsis, intrapartum events and significant resuscitation variables are collected using a tick box, so not possible to accurately determine missing data from absence of a characteristic