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Supplementary appendix 9

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary Appendix
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Table 1. Haematological, biochemical, and clinical support at 24 hours

	Hypothermia group		Control group		Difference (95% CI)	p-value
	n	Summary	n	Summary		
Haemoglobin, g per dL	195	16·2 ± 2·5	201	16·2 ± 2·2	0·0 (-0·5, 0·5)	0·95
Hb <12 per dL	195	8 (4·1%)	201	6 (3·0%)	1·1% (-2·5%, 4·8%)	0·55
White blood cells per µL	193	20000 [15100, 26100]	196	21200 [15600, 28000]	-900 (-2610, 1000)	0·38
WBC <5000 or >15,000	193	148 (76·7%)	196	160 (81·6%)	-4·9% (-13·0%, 3·1%)	0·23
Platelets, 105 per µL	195	2·2 ± 0·7	200	2·3 ± 0·8	-0·1 (-0·2, 0·1)	0·50
Platelets <100 000 per µL	195	10 (5·1%)	200	10 (5·0%)	0·1% (-4·2%, 4·5%)	0·95
CRP >10 mg per L	179	23 (12·9%)	178	19 (10·7%)	2·2% (-4·5%, 8·9%)	0·52
pH	184	7·22 ± 0·15	186	7·26 ± 0·15	-0·03 (-0·06, 0·00)	0·05
pCO2, mm of Hg	183	34·6 ± 17·6	183	33·0 ± 13·3	1·5 (-1·7, 4·7)	0·35
Base excess (mEq/L)	174	-12·5 ± 6·4	170	-11·6 ± 6·1	-0·9 (-2·2, 0·4)	0·18
Lowest blood sugar, mg per dL	182	89 ± 38	180	85 ± 26	4 (-2, 11)	0·21
Blood sugar <40 mg per dl	182	6 (3·3%)	180	3 (1·7%)	1·6% (-1·6%, 4·8%)	0·32
Highest blood sugar, mg per dL	167	139 ± 87	175	115 ± 38	25 (10, 39)	<0·001
Blood sugar >125 mg per dL	167	65 (38·9%)	175	54 (30·9%)	8·1% (-2·0%, 18·1%)	0·12
Prothrombin time, seconds	152	19·2 [16·5, 24·6]	157	18·5 [15·9, 23·0]	0·9 (-0·3, 2·0)	0·17
Activated partial thromboplastin time, seconds	133	45·1 [36·0, 58·0]	131	42·3 [33·5, 58·0]	2·4 (-1·9, 7·0)	0·26
International normalised ratio (INR)	98	1·5 [1·2, 2·0]	111	1·4 [1·2, 1·8]	0·1 (-0·1, 0·2)	0·27
INR > 1·2	98	71 (72·5%)	111	84 (75·7%)	-3·2% (-15·1%, 8·7%)	0·59
Inotropes (any)	202	140 (69·3%)	206	114 (55·3%)	14·0% (4·7%, 23·3%)	0·004
Dopamine	202	69 (34·2%)	206	51 (24·8%)	9·4% (0·6%, 18·2%)	0·04
Dobutamine	202	124 (61·4%)	206	106 (51·5%)	9·9% (0·4%, 19·5%)	0·04
Adrenaline	202	21 (10·4%)	206	14 (6·8%)	3·6% (-1·8%, 9·0%)	0·19
Noradrenaline	202	2 (1·0%)	206	1 (0·5%)	0·5% (-1·1%, 2·2%)	0·55
Other	202	7 (3·5%)	206	4 (1·9%)	1·5% (-1·6%, 4·7%)	0·34
Breathing support						
None	202	39 (19·3%)	206	59 (28·6%)	-9·3% (-17·5%, -1·1%)	0·03
Oxygen	202	52 (25·7%)	206	42 (20·4%)	5·4% (-2·8%, 13·5%)	0·20
CPAP	202	3 (1·5%)	206	7 (3·4%)	-1·9% (-4·9%, 1·1%)	0·21
Invasive ventilation	202	108 (53·5%)	206	98 (47·6%)	5·9% (-3·8%, 15·6%)	0·23
Sedation (any)	202	65 (32·2%)	206	44 (21·4%)	10·8% (2·3%, 19·4%)	0·01
Chloral hydrate	202	10 (5·0%)	206	0 (0·0%)	5·0% (2·0%, 7·9%)	0·001
Fentanyl	202	33 (16·3%)	206	25 (12·1%)	4·2% (-2·6%, 11·0%)	0·22
Morphine	202	18 (8·9%)	206	12 (5·8%)	3·1% (-2·0%, 8·2%)	0·23
Other	202	6 (3·0%)	206	10 (4·9%)	-1·9% (5·6%, 1·9%)	0·33
Anticonvulsants (any)	202	167 (82·7%)	206	173 (84·0%)	-1·3% (-8·5%, 5·9%)	0·72
Phenobarbitone	202	165 (81·7%)	206	172 (83·5%)	-1·8% (-9·2%, 5·5%)	0·63
Phenytoin	202	15 (7·4%)	260	23 (11·2%)	-3·7% (-9·4%, 1·9%)	0·19
Levetiracetam	202	13 (6·4%)	206	15 (7·3%)	-0·8% (-5·7%, 4·1%)	0·75
Midazolam	202	6 (3·0%)	206	11 (5·3%)	-2·4% (-6·2%, 1·5%)	0·23
Others	202	3 (1·5%)	206	5 (2·4%)	-0·9% (-3·6%, 1·7%)	0·49
Sedation and/or anti-convulsant (any)	202	176 (87·1%)	206	177 (85·9%)	1·2% (-5·4%, 7·8%)	0·72
Clinical seizures	202	176 (87·1%)	206	185 (89·8%)	-2·7% (-8·9%, 3·5%)	0·40
Antibiotics	201	176 (87·6%)	206	181 (87·9%)	-0·3% (-6·7%, 6·1%)	0·93
Fluids therapy						
IVF	202	188 (93·1%)	206	180 (87·4%)	5·7% (0·0%, 11·4%)	0·05
IVF and NG feeds	202	14 (6·9%)	206	24 (11·7%)	-4·7% (-10·3%, 0·9%)	0·10
NG feeds	202	0 (0·0%)	206	2 (1·0%)	-1·0% (-2·3%, 0·4%)	0·16
Cup feeds	202	0 (0·0%)	260	0 (0·0%)	-	-

Data are mean ± standard deviation, median [inter-quartile range] plus median change (95% confidence intervals), or number (percentage) plus risk difference (95% confidence intervals). The laboratory data are based on the worst value during the first 24 hours after birth and were analysed at standard laboratory conditions without any temperature correction. Seizures are based on the number of babies who had clinical seizures during the first 24 after birth.

WBC: white blood cell count; CRP: C-reactive protein; pCO2: partial pressure of carbon dioxide; CPAP: continuous positive airway pressure; IVF: intravenous fluids; NG: Nasogastric feeds

Table 2. Haematological, biochemical, and clinical support at 48 hours

	Hypothermia group		Control group		Difference (95% CI)	p-value
	n	Summary	n	Summary		
Haemoglobin, g per dL	97	15·4 ± 2·6	59	14·9 ± 2·6	0·5 (-0·3, 1·4)	0·22
Hb <12 per dL	97	8 (8·3%)	59	6 (10·2%)	-1·9% (-11·4%, 7·5%)	0·68
White blood cells per µL	95	15200 [10700, 19200]	58	18865 [12800, 25000]	-3565 (-6520, -600)	0·01
WBC <5000 or >15,000	95	53 (55·8%)	58	43 (74·1%)	-18·3% (-33·4%, -3·3%)	0·02
Platelets, 105 per µL	96	1·7 ± 0·8	59	1·7 ± 0·7	0·0 (-0·2, 0·3)	0·89
Platelets <100 000 per µL	96	17 (17·7%)	59	7 (11·9%)	5·8% (-5·4%, 17·1%)	0·33
CRP >10 mg per L	56	16 (28·6%)	39	12 (30·8%)	-2·2% (-20·9%, 16·5%)	0·82
pH	119	7·29 ± 0·12	86	7·34 ± 0·11	-0·05 (-0·08, -0·02)	0·003
pCO2, mm of Hg	119	31·1 ± 10·9	86	29·5 ± 9·8	1·7 (-1·3, 4·6)	0·26
Base excess (mEq/L)	114	-10·4 ± 6·2	79	-8·6 ± 4·7	-1·8 (-3·4, -0·1)	0·03
Lowest blood sugar, mg per dL	162	88 ± 28	162	87 ± 25	1 (-5, 7)	0·75
Blood sugar <40 mg per dl	162	3 (1·9%)	162	0 (0·0%)	1·9% (-0·2%, 3·9%)	0·08
Highest blood sugar, mg per dL	153	136 ± 91	151	111 ± 34	25 (10, 41)	0·002
Blood sugar >125 mg per dL	153	58 (37·9%)	151	33 (21·9%)	16·1% (5·9%, 26·2%)	0·002
Prothrombin time, seconds	48	18·4 [15·6, 22·7]	29	15·9 [14·0, 18·5]	2·3 (0·4, 4·5)	0·03
Activated partial thromboplastin time, seconds	37	42·0 [38·9, 55·3]	24	42·0 [34·5, 54·0]	2·1 (-4·9, 11·1)	0·53
International normalised ratio	27	1·7 [1·3, 2·0]	14	1·3 [1·1, 1·5]	0·3 (0·1, 0·6)	0·03
Haemoglobin, g per dL	27	22 (81·5%)	14	8 (57·1%)	24·3% (-5·4%, 54·1%)	0·10
Inotropes (any)	193	142 (73·6%)	199	102 (51·3%)	22·3% (13·0%, 31·6%)	<0·001
Dopamine	193	76 (39·4%)	199	43 (21·6%)	17·8% (8·8%, 26·7%)	<0·001
Dobutamine	193	132 (68·4%)	199	93 (46·7%)	21·7% (12·1%, 31·2%)	<0·001
Adrenaline	193	27 (14·0%)	199	21 (10·6%)	3·4% (-3·1%, 9·9%)	0·30
Noradrenaline	193	5 (2·6%)	199	3 (1·5%)	1·1% (-1·7%, 3·9%)	0·45
Other	193	4 (2·1%)	199	5 (2·5%)	-0·4% (-3·4%, 2·5%)	0·77
Breathing support						
None	193	59 (30·6%)	199	83 (41·7%)	-11·1% (-20·6%, -1·7%)	0·02
Oxygen	193	34 (16·8%)	199	25 (12·1%)	4·7% (-2·1%, 11·5%)	0·18
CPAP	193	3 (1·5%)	199	7 (3·4%)	-1·9% (-4·9%, 1·1%)	0·21
Invasive ventilation	193	97 (48·0%)	199	85 (41·3%)	6·8% (-2·9%, 16·4%)	0·17
Sedation (any)	193	69 (35·8%)	199	46 (23·1%)	12·6% (3·7%, 21·6%)	0·006
Chloral hydrate	193	10 (5·2%)	199	0 (0·0%)	5·2% (2·1%, 8·3%)	0·001
Fentanyl	193	35 (18·1%)	199	25 (12·6%)	5·6% (-1·6%, 12·7%)	0·13
Morphine	193	15 (7·8%)	199	9 (4·5%)	3·2% (-1·5%, 8·0%)	0·18
Other	193	10 (5·2%)	199	14 (7·0%)	-1·9% (-6·6%, 2·9%)	0·44
Anticonvulsants (any)	193	155 (80·3%)	199	169 (84·9%)	-4·6% (-12·1%, 2·9%)	0·23
Phenobarbitone	193	149 (77·2%)	199	166 (83·4%)	-6·2% (-14·1%, 1·6%)	0·12
Phenytoin	193	18 (9·3%)	199	39 (18·1%)	-8·8% (-15·5%, -2·0%)	0·01
Levetiracetam	193	20 (10·4%)	199	18 (9·1%)	1·3% (-4·5%, 7·2%)	0·66
Midazolam	193	8 (4·2%)	199	8 (4·0%)	0·1% (-3·8%, 4·0%)	0·95
Others	193	1 (0·5%)	199	4 (2·0%)	-1·5% (-3·7%, 0·7%)	0·19
Sedation and/or anti-convulsant (any)	193	161 (83·4%)	206	175 (87·9%)	-4·5% (-11·4%, 2·4%)	0·20
Clinical seizures	192	34 (17·7%)	199	49 (24·6%)	-6·9% (-15·0%, 1·1%)	0·09
Antibiotics	191	176 (92·2%)	176	176 (88·4%)	3·7% (-2·2%, 9·6%)	0·22
Fluids therapy						
IVF	193	152 (78·8%)	199	138 (69·4%)	9·4% (0·8%, 18·0%)	0·03
IVF and NG feeds	193	41 (21·2%)	199	54 (27·1%)	-5·9% (-14·3%, 2·6%)	0·17
NG feeds	193	0 (0·0%)	199	7 (3·5%)	-3·5% (-6·1%, -1·0%)	0·009
Cup feeds	193	0 (0·0%)	199	1 (0·5%)	-0·5% (-1·5%, 0·5%)	0·32

Data are mean (standard deviation), median [inter-quartile range] plus median change (95% confidence intervals), or number (percentage) plus risk difference (95% confidence intervals). The laboratory data are based on the worst value between 24 to 48 hours after birth and were analysed at standard laboratory conditions without any temperature correction. Seizures are based on the number of babies who had clinical seizures between 24 to 48 hours after birth.

WBC: white blood cell count; CRP: C-reactive protein; pCO2: partial pressure of carbon dioxide; CPAP: continuous positive airway pressure; IVF: intravenous fluids; NG: Nasogastric feeds

Table 3. Haematological, biochemical, and clinical support at 72 hours

	Hypothermia group		Control group		Difference (95% CI)	p-value
	n	Summary	n	Summary		
Haemoglobin, g per dL	79	14·5 ± 2·7	62	14·7 ± 2·1	-0·2 (-1·1, 0·6)	0·61
Hb <12 per dL	79	13 (16·5%)	62	4 (6·5%)	10·0% (-0·2%, 20·2%)	0·07
White blood cells per µL	79	10500 [7860, 15470]	62	12450 [9300, 16300]	-2000 (-3800, -200)	0·03
WBC <5000 or >15,000	79	30 (38·0%)	62	24 (38·7%)	-0·7% (-16·9%, 15·4%)	0·93
Platelets, 105 per µL	79	1·4 ± 0·8	62	1·7 ± 0·7	-0·3 (-0·5, 0·0)	0·03
Platelets <100 000 per µL	79	18 (22·8%)	62	10 (16·1%)	6·7% (-6·4%, 19·7%)	0·33
CRP >10 mg per L	38	17 (44·7%)	37	13 (35·1%)	9·6% (-12·5%, 31·7%)	0·40
pH	89	7·32 ± 0·09	68	7·36 ± 0·09	-0·04 (-0·07, -0·01)	0·005
pCO2, mm of Hg	89	31·8 ± 10·8	68	33·3 ± 10·3	-1·5 (-4·9, 1·9)	0·37
Base excess (mEq/L)	84	-8·7 ± 5·5	65	-6·2 ± 3·8	-2·5 (-4·1, -0·9)	0·002
Lowest blood sugar, mg per dL	152	83 ± 22	146	84 ± 21	-1 (-6, 4)	0·78
Blood sugar <40 mg per dl	152	2 (1·3%)	146	1 (0·7%)	0·6% (-1·6%, 2·9%)	0·59
Highest blood sugar, mg per dL	138	115 ± 45	135	102 ± 23	13 (4, 22)	0·003
Blood sugar >125 mg per dL	138	31 (22·5%)	135	15 (11·1%)	11·4% (2·6%, 20·1%)	0·01
Prothrombin time, seconds	34	17·5 [15·0, 23·2]	21	15·0 [13·5, 16·6]	2·5 (0·6, 4·9)	0·01
Activated partial thromboplastin time, seconds	31	42·9 [38·8, 49·3]	20	41·6 [33·1, 44·4]	3·4 (-2·0, 9·2)	0·23
International normalised ratio	15	1·4 [1·2, 2·3]	8	1·4 [1·2, 1·5]	0·2 (-0·1, 0·8)	0·37
Haemoglobin, g per dL	15	11 (73·3%)	8	6 (75·0%)	-1·7% (-39·1%, 35·8%)	0·93
Inotropes (any)	182	122 (67·0%)	189	72 (38·1%)	28·9% (19·2%, 38·7%)	<0·001
Dopamine	182	59 (32·4%)	189	33 (17·5%)	15·0% (6·3%, 23·3%)	<0·001
Dobutamine	182	111 (61·0%)	189	67 (35·5%)	25·5% (15·7%, 35·4%)	<0·001
Adrenaline	182	28 (15·4%)	189	12 (6·4%)	9·0% (2·7%, 15·3%)	0·005
Noradrenaline	182	7 (3·9%)	189	2 (1·1%)	2·8% (-0·4%, 5·9%)	0·08
Other	182	6 (3·3%)	189	6 (3·2%)	0·1% (-3·5%, 3·7%)	0·95
Breathing support						
None	182	72 (39·6%)	189	92 (48·7%)	-9·1% (-19·2%, 0·9%)	0·08
Oxygen	182	22 (12·1%)	189	25 (13·2%)	-1·1% (-7·9%, 5·6%)	0·74
CPAP	182	8 (4·4%)	189	10 (5·3%)	-0·9% (-5·3%, 3·5%)	0·69
Invasive ventilation	182	80 (44·0%)	189	62 (32·8%)	11·2% (1·3%, 21·0%)	0·03
Sedation (any)	182	59 (32·4%)	189	27 (14·3%)	18·1% (9·7%, 26·6%)	<0·001
Chloral hydrate	182	12 (6·6%)	189	0 (0·0%)	6·6% (3·0%, 10·2%)	<0·001
Fentanyl	182	28 (15·4%)	189	16 (8·5%)	6·9% (0·3%, 13·5%)	0·04
Morphine	182	11 (6·0%)	189	4 (2·1%)	3·9% (-0·1%, 8·0%)	0·06
Other	182	9 (5·0%)	189	10 (5·3%)	-0·3% (-4·8%, 4·1%)	0·88
Anticonvulsants (any)	182	149 (81·9%)	189	152 (80·4%)	1·4% (-6·5%, 9·4%)	0·72
Phenobarbitone	182	145 (79·7%)	189	149 (78·8%)	0·8% (-7·4%, 9·1%)	0·84
Phenytoin	182	19 (10·4%)	189	27 (14·3%)	-3·8% (-10·5%, 2·8%)	0·26
Levetiracetam	182	14 (7·7%)	189	19 (10·1%)	-2·4% (-8·1%, 3·4%)	0·42
Midazolam	182	5 (2·8%)	189	6 (3·2%)	-0·4% (-3·9%, 3·0%)	0·81
Others	182	0 (0·0%)	189	1 (0·5%)	-0·5% (-1·6%, 0·5%)	0·33
Sedation and/or anti-convulsant (any)	182	154 (84·6%)	189	157 (83·1%)	1·5% (-5·9%, 9·0%)	0·69
Clinical seizures	181	11 (6·1%)	188	12 (6·4%)	-0·3% (-5·2%, 4·6%)	0·90
Antibiotics	181	171 (94·5%)	189	164 (86·8%)	7·7% (1·8%, 13·5%)	0·01
Fluids therapy						
IVF	182	129 (70·9%)	188	98 (52·1%)	18·8% (9·0%, 28·5%)	<0·001
IVF and NG feeds	182	53 (29·1%)	188	72 (38·3%)	-9·2% (-18·7%, 0·4%)	0·06
NG feeds	182	0 (0·0%)	188	14 (7·5%)	-7·5% (-11·2%, -3·7%)	<0·001
Cup feeds	182	0 (0·0%)	188	6 (2·9%)	-2·9% (-5·2%, -0·6%)	0·01

Data are mean (standard deviation), median [inter-quartile range] plus median change (95% confidence intervals), or number (percentage) plus risk difference (95% confidence intervals). The laboratory data are based on the worst value between 48 to 72 hours after birth and were analysed at standard laboratory conditions without any temperature correction. Seizures are based on the number of babies who had clinical seizures between 48 to 72 hours after birth.

WBC: white blood cell count; CRP: C-reactive protein; pCO2: partial pressure of carbon dioxide; CPAP: continuous positive airway pressure; IVF: intravenous fluids; NG: Nasogastric feeds

Table 4. Haematological, biochemical, and clinical support at 96 hours

	Hypothermia group		Control group		Difference (95% CI)	p-value
	n	Summary	n	Summary		
Haemoglobin, g per dL	83	14·3 ± 2·6	54	14·0 ± 2·3	0·3 (-0·6, 1·2)	0·48
Hb <12 per dL	83	14 (16·9%)	54	7 (13·0%)	3·9% (-8·1%, 16·0%)	0·54
White blood cells per µL	81	9500 [6500, 12500]	53	11500 [7300, 14100]	-1500 (-3210, 200)	0·08
WBC <5000 or >15,000	81	19 (23·5%)	53	13 (24·5%)	-1·1% (-15·9%, 13·7%)	0·89
Platelets, 105 per µL	81	1·4 ± 0·8	55	1·6 ± 1·1	-0·2 (-0·5, 0·1)	0·20
Platelets <100 000 per µL	81	25 (30·9%)	55	17 (30·9%)	0·0% (-15·9%, 15·8%)	0·99
CRP >10 mg per L	43	19 (44·2%)	40	19 (47·5%)	-3·3% (-24·8%, 18·1%)	0·76
pH	77	7·32 ± 0·09	54	7·34 ± 0·09	-0·02 (-0·05, 0·01)	0·21
pCO2, mm of Hg	77	36·4 ± 13·1	55	34·6 ± 10·2	1·7 (-2·5, 5·9)	0·42
Base excess (mEq/L)	71	-6·2 ± 6·1	50	-5·3 ± 5·3	-1·0 (-3·1, 1·2)	0·37
Lowest blood sugar, mg per dL	131	83 ± 20	125	83 ± 21	-1 (-6, 5)	0·83
Blood sugar <40 mg per dl	131	1 (0·8%)	125	1 (0·8%)	0·0% (-2·2%, 2·1%)	0·97
Highest blood sugar, mg per dL	117	105 ± 27	111	102 ± 21	3 (-4, 9)	0·44
Blood sugar >125 mg per dL	117	18 (15·4%)	111	11 (9·9%)	5·5% (-3·1%, 14·1%)	0·21
Prothrombin time, seconds	30	16·9 [14·4, 20·9]	17	14·0 [12·6, 16·3]	2·7 (0·4, 5·1)	0·03
Activated partial thromboplastin time, seconds	24	57·6 [43·9, 87·7]	18	36·8 [30·4, 44·0]	18·2 (7·0, 32·9)	0·004
International normalised ratio	22	1·6 [1·3, 2·0]	11	1·1 [1·1, 1·3]	0·3 (0·0, 0·6)	0·04
Haemoglobin, g per dL	22	17 (77·3%)	11	4 (36·4%)	40·9% (7·5%, 74·3%)	0·02
Inotropes (any)	170	90 (52·9%)	184	50 (27·2%)	25·8% (15·9%, 35·6%)	<0·001
Dopamine	170	49 (28·8%)	184	27 (14·7%)	14·1% (5·6%, 22·3%)	0·001
Dobutamine	170	78 (45·9%)	184	45 (24·5%)	21·4% (11·7%, 31·2%)	<0·001
Adrenaline	170	18 (10·6%)	184	13 (7·1%)	3·5% (-2·4%, 9·4%)	0·24
Noradrenaline	170	2 (1·2%)	184	2 (1·1%)	0·1% (-2·1%, 2·3%)	0·94
Other	170	6 (3·5%)	184	5 (2·7%)	0·8% (-2·8%, 4·4%)	0·66
Breathing support						
None	170	74 (43·5%)	183	103 (56·3%)	-12·8% (-23·1%, -2·4%)	0·02
Oxygen	170	19 (11·2%)	183	18 (9·8%)	1·3% (-5·1%, 7·7%)	0·68
CPAP	170	14 (8·2%)	183	9 (4·9%)	3·3% (-1·9%, 8·5%)	0·21
Invasive ventilation	170	63 (37·1%)	183	53 (29·0%)	8·1% (-1·7%, 17·9%)	0·11
Sedation (any)	170	32 (18·8%)	184	24 (13·0%)	5·8% (-1·8%, 13·4%)	0·14
Chloral hydrate	170	4 (2·4%)	184	1 (0·5%)	1·8% (-0·7%, 4·3%)	0·15
Fentanyl	170	23 (13·5%)	184	16 (8·7%)	4·8% (-1·7%, 11·4%)	0·15
Morphine	170	3 (1·2%)	184	6 (0·5%)	0·6% (-1·3%, 2·6%)	0·52
Other	170	10 (1·8%)	184	14 (3·3%)	-1·5% (-4·7%, 1·7%)	0·37
Anticonvulsants (any)	170	131 (77·1%)	184	145 (78·8%)	-1·7% (-10·4%, 6·9%)	0·69
Phenobarbitone	170	128 (75·3%)	184	140 (76·1%)	-0·8% (-9·7%, 8·2%)	0·86
Phenytoin	170	16 (9·4%)	184	23 (12·5%)	-3·1% (-9·6%, 3·4%)	0·35
Levetiracetam	170	18 (10·6%)	184	17 (9·2%)	1·3% (-4·9%, 7·6%)	0·67
Midazolam	170	1 (0·6%)	184	4 (2·2%)	-1·6% (-4·0%, 0·8%)	0·21
Others	170	1 (0·6%)	184	2 (1·1%)	-0·5% (-2·4%, 1·4%)	0·61
Sedation and/or anti-convulsant (any)	170	138 (81·2%)	184	149 (81·0%)	0·2% (-8·0%, 8·4%)	0·96
Clinical seizures	170	4 (2·4%)	184	3 (1·6%)	0·7% (-2·2%, 3·6%)	0·63
Antibiotics	169	153 (90·5%)	155	155 (84·2%)	6·3% (-0·5%, 13·2%)	0·08
Fluids therapy						
IVF	170	87 (51·2%)	184	71 (38·6%)	12·6% (2·3%, 22·9%)	0·02
IVF and NG feeds	170	75 (44·1%)	184	77 (41·9%)	2·3% (-8·1%, 12·6%)	0·67
NG feeds	170	5 (2·9%)	184	29 (15·8%)	-12·8% (-18·7%, -7·0%)	<0·001
Cup feeds	170	3 (1·8%)	184	9 (4·9%)	-3·1% (-6·8%, 0·6%)	0·10

Data are mean (standard deviation), median [inter-quartile range] plus median change (95% confidence intervals), or number (percentage) plus risk difference (95% confidence intervals). The laboratory data are based on the worst value between 72 to 96 hours after birth and were analysed at standard laboratory conditions without any temperature correction. Seizures are based on the number of babies who had clinical seizures between 72 to 96 hours after birth.

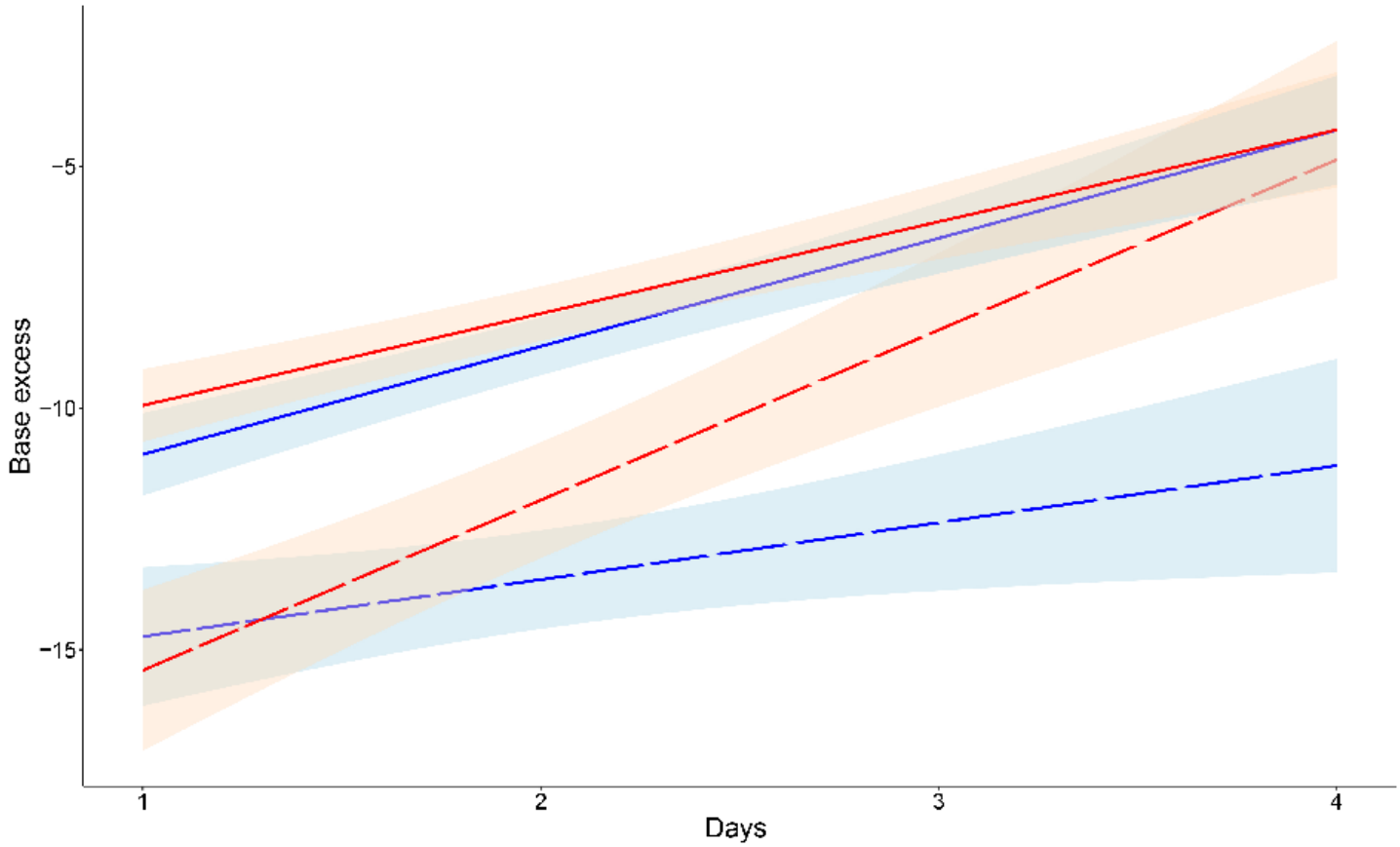
WBC: white blood cell count; CRP: C-reactive protein; pCO2: partial pressure of carbon dioxide; CPAP: continuous positive airway pressure; IVF: intravenous fluids; NG: Nasogastric feeds

Table 5. Severity of cerebral lesions seen on MRI in cooled and non-cooled infants

	Hypothermia group (n=122)	Control group (n=145)	Odds Ratio (95% CI)	p
Basal ganglia and thalami				
0	96 (78·7%)	108(74·5%)	0·80 (0·45-1·41)	0·44
1	7 (5·8%)	10 (6·9%)		
2	10 (8·1%)	15(10·4%)		
3	9 (7·4%)	12(8·2%)		
Posterior limb of internal capsule				
Normal	101 (82·8%)	112 (77·2 %)	0·70 (0·38-1·28)	0·25
Equivocal	5 (4·1%)	6 (4·1%)		
Abnormal	16 (13·1%)	27 (18·6%)		
White matter				
Normal	22 (18·0%)	33(22·8%)	1·00 (0·64-1·57)	0·98
1	30 (24·6%)	28 (19·3%)		
2	58(47·5%)	66 (45·5%)		
3	12 (9·8%)	18 (12·4%)		
Cortex				
0	91 (74·6%)	99 (68·3%)	0·74 (0·43-1·25)	0·26
1	19 (15·6%)	26 (17·9%)		
2	3(2·5%)	9 (6·2%)		
3	9 (7·4%)	11 (7·6%)		
Basal ganglia/thalami (>0) AND white matter (>0) OR cortical (>0) injury	23 (18·9%)	33 (22·8%)	0·79 (0·43-1·43)	0·44

Data are number (%) or Odds ratio (OR) (95% Confidence interval: CI).
*Odds ratio for MRI abnormalities score in cooled relative to non-cooled infants from ordinal logistic regression analysis.
Basal ganglia and thalamic score: 0=normal, 1=mild (focal abnormal signal intensity), 2=moderate (multifocal abnormal signal intensity), 3=severe (widespread abnormal signal intensity).
White matter score: 0=normal, 1=mild (exaggerated long T1 and long T2 in periventricular white matter only), 2=moderate (long T1 and long T2 extending out to subcortical white matter and /or focal punctate lesions or focal area of infarction), 3=severe widespread abnormalities including overt infarction, haemorrhage, and long T1 and long T2.
Cortical involvement was scored as the presence of abnormal signal intensity, usually decreased T1 or cortical highlighting. 0=normal, 1=mild (1–2 sites involved), 2=moderate (3 sites involved), 3=severe (more than 3 sites involved).

Figure 1. Change in base excess



Mean (95% confidence interval) base excess (mEq/L) in the hypothermia (blue line) and control group (red line). The worst base excess for each 24 hour period was fitted using a linear regression model. Continuous line indicates survivors and broken line indicates non-survivors.

Figure 2. Proportion of infants with mild or no encephalopathy in the hypothermic (blue) and control (red) groups.

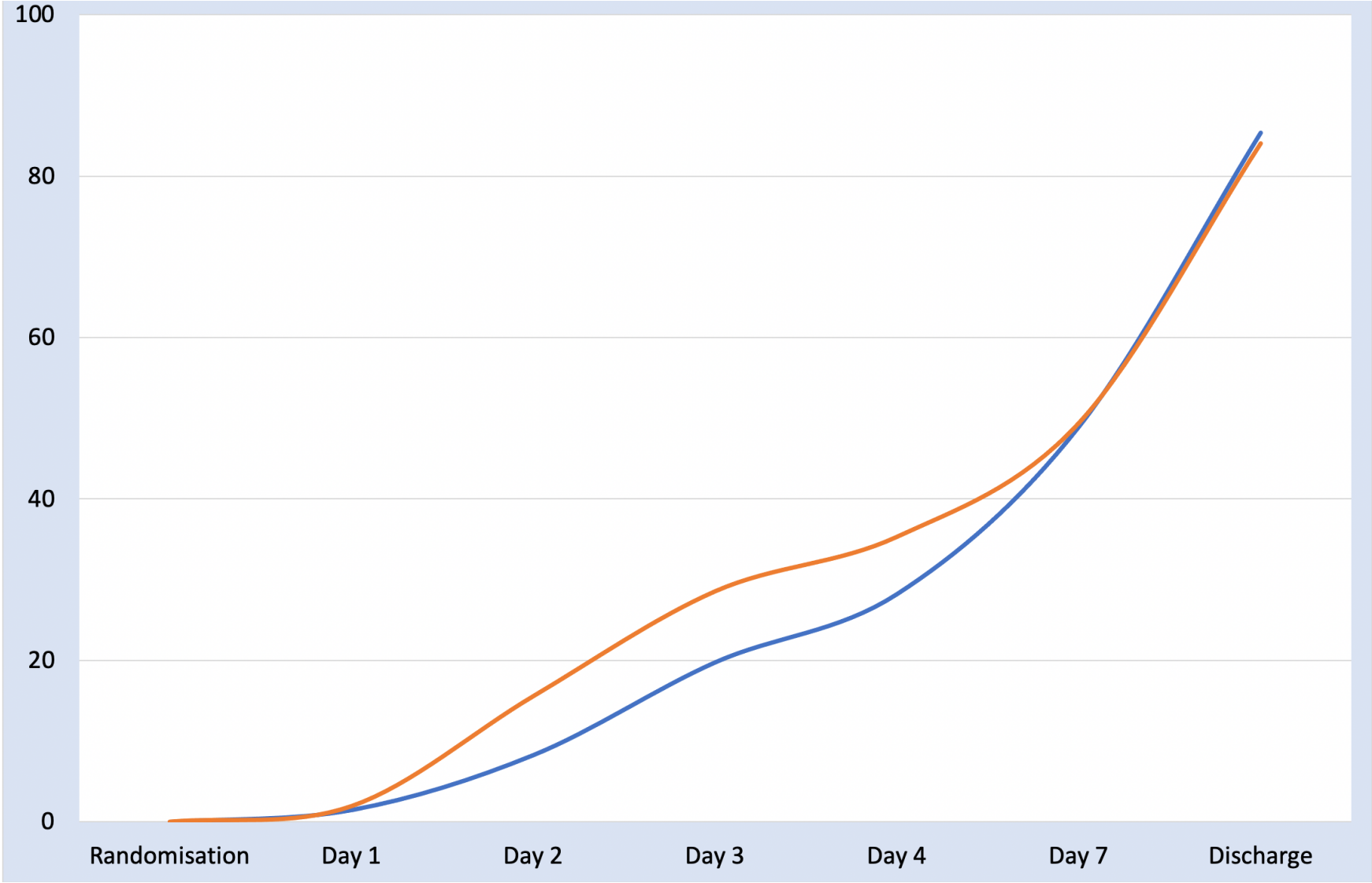
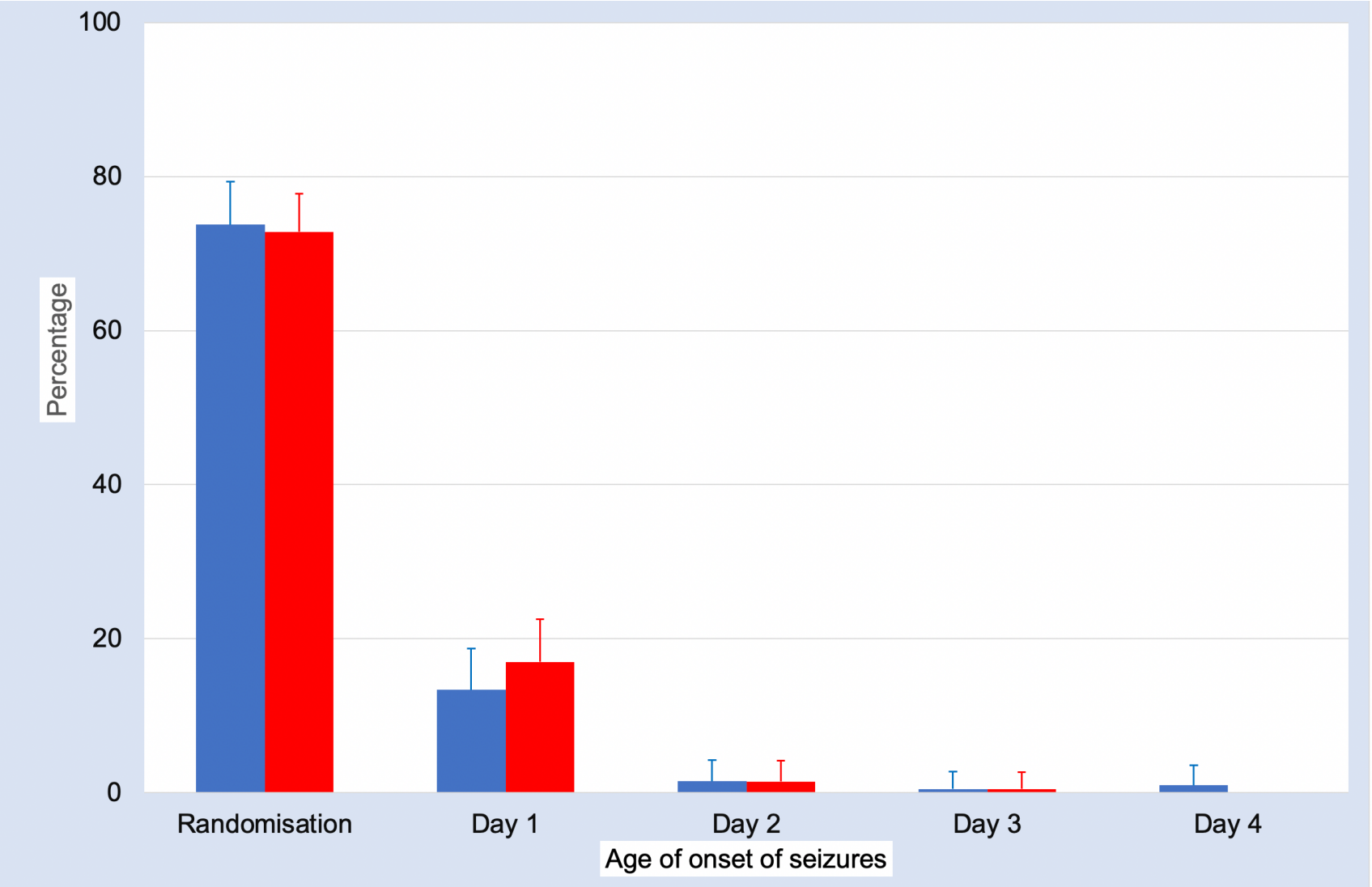
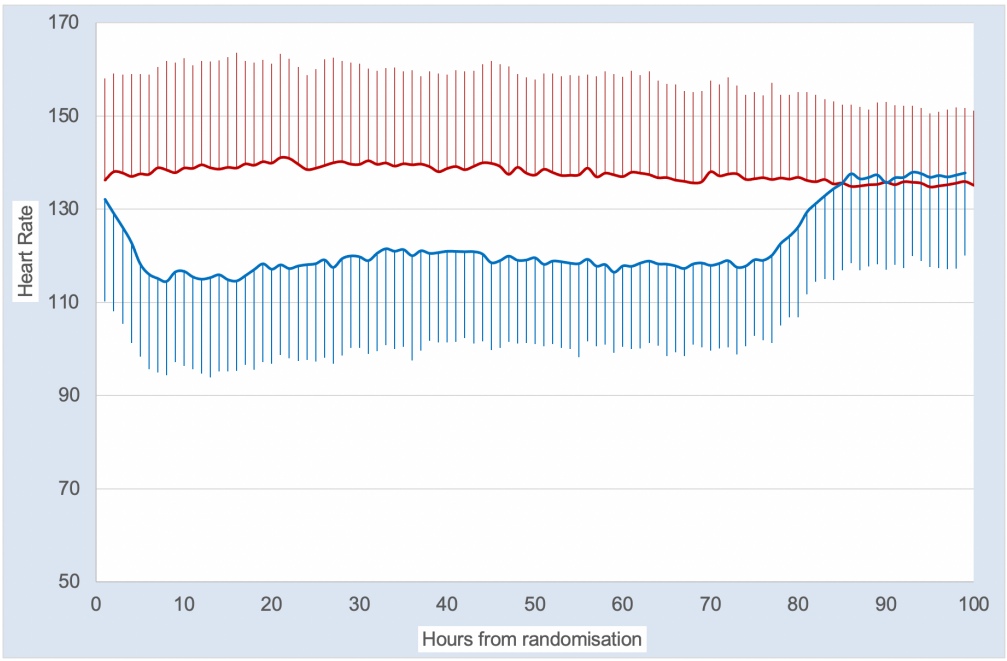


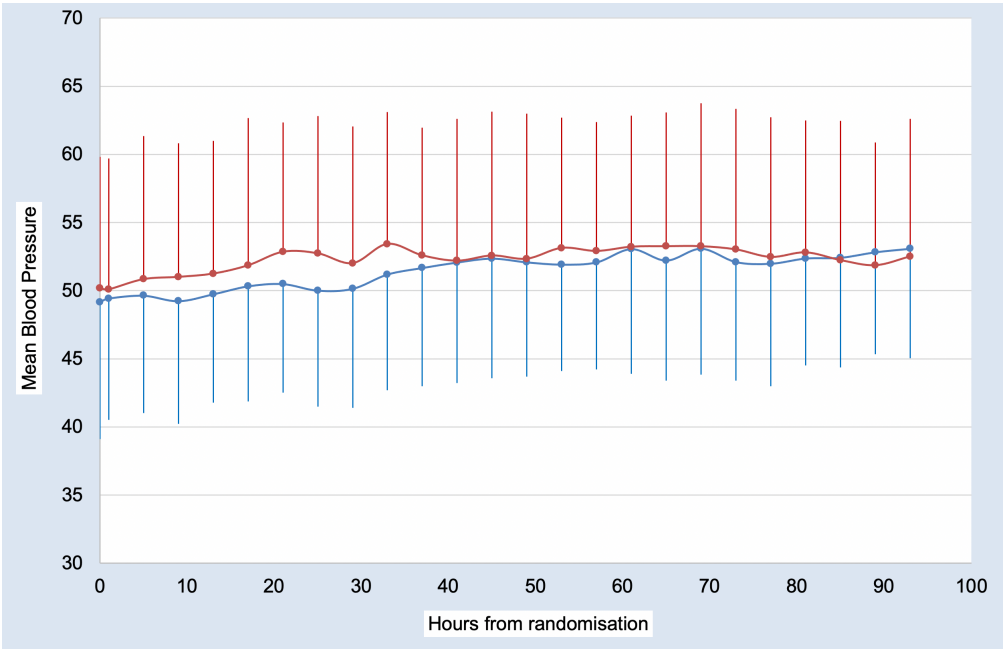
Figure 3. Age of onset of seizures.



Error bars indicate 95% confidence intervals in the hypothermic (blue) and control (red) group.

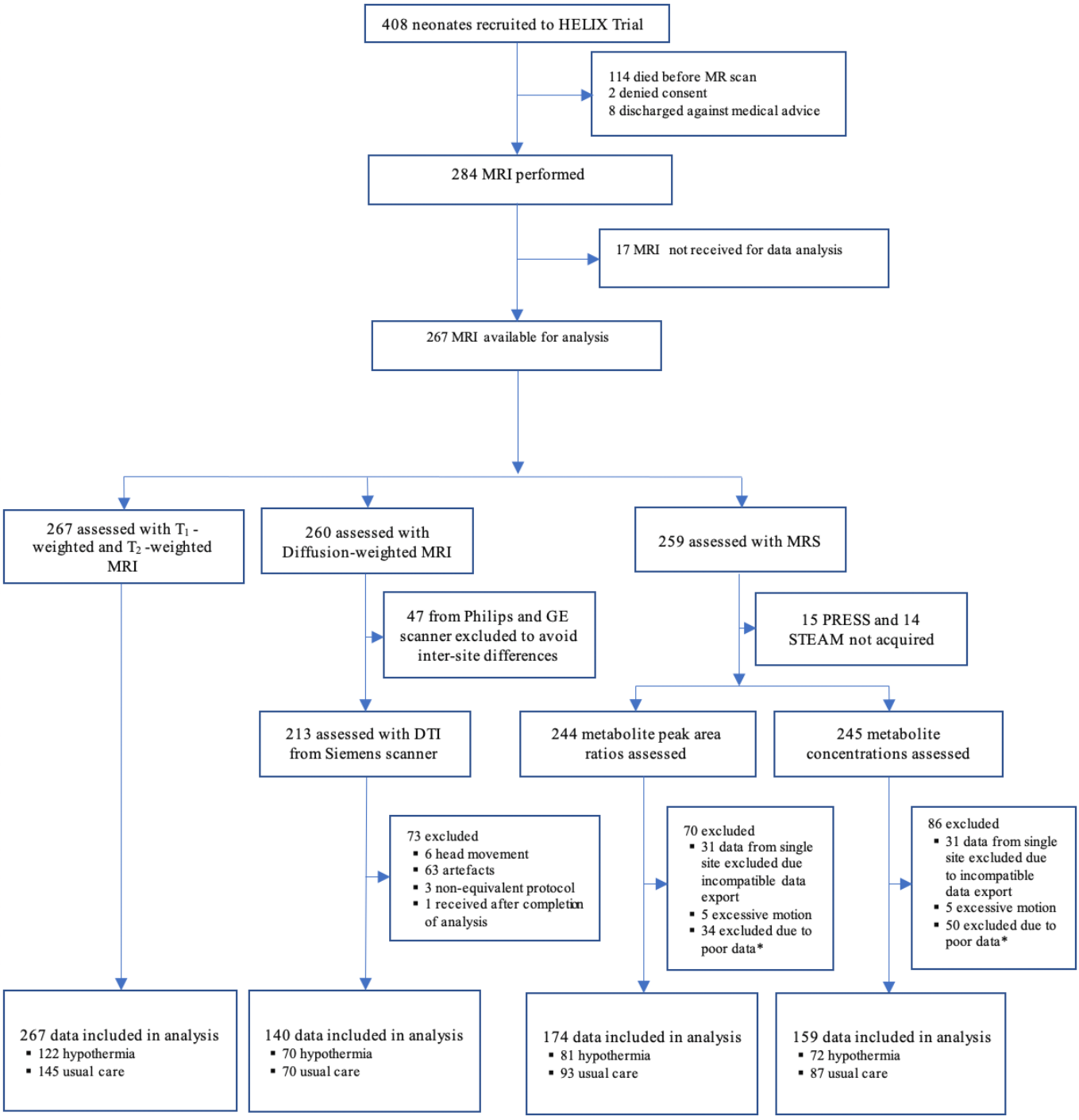
Figure 4. Heart rate and blood pressure of the hypothermia and control groups





Mean (standard deviation) of hourly heart rate (middle panel) and 4 hourly non-invasive blood pressure (bottom panel) in the hypothermia group (blue) and control group (red).

Figure 5. Flow chart of the MR data analysis



*Rejection criteria for MR spectroscopy included data artefacts, wild baseline, bad shimming, and poor eddy current correction.

Figure 6. MRS analysis

In-vivo MR Spectroscopy Data Acquisition Protocol:

Table S1: PRESS Protocol: Peak Area Ratios (PARs) estimation

Step	TE (ms)	TR (ms)	Water suppression	Phase cycling	Sub-spectra	Dummy scans	Centre frequency (ppm)	Acquisition time (min:sec)
1	288	2290	On	8	16	1	2·01	6:43
2	288	2290	Off	8	1	1	4·67	0:21

Table S2: STEAM Protocol: tNAA concentration estimation

Step	TE (ms)	TM (ms)	TR (ms)	Water suppression	Phase cycling	Sub-spectra	Dummy scans	Centre frequency (ppm)	Acquisition time (min:sec)
1	20	20	1500	On	4	24	1	2·01	3:00
2	20	20	1500	Off	4	1	1	4·67	0:12
3	20	20	3500	On	4	20	1	2·01	5:50
4	20	20	3500	Off	4	1	1	4·67	0:18
OR									
3	20	20	5000	On	4	20	1	2·01	8:20
4	20	20	5000	Off	4	1	1	4·67	0:40
5	20	20	9030	Off	1	1	1	4·67	0:18
6	40	20	9040	Off	1	1	1	4·67	0:18
7	80	20	9060	Off	1	1	1	4·67	0:18
8	140	20	9090	Off	1	1	1	4·67	0:18
9	220	20	9130	Off	1	1	1	4·67	0:18
10	300	20	9170	Off	1	1	1	4·67	0:18

Quality assurance:
The inter-site variation in MRS measurements was quantified across all scanners using a spherical phantom containing a buffered solution of 10mM N-acetylaspartate (NAA) and 10mM lactate (Lac). *In vivo* quality assurance included the visual assessment of motion from imaging before and after MRS; protocol adherence; manual rejection of motion corrupted sub-spectra; automated spectral corrections for both frequency and phase; and the rejection of spectra with linewidths outside the normal distribution of the full dataset.

Representative *in-vivo* spectra:

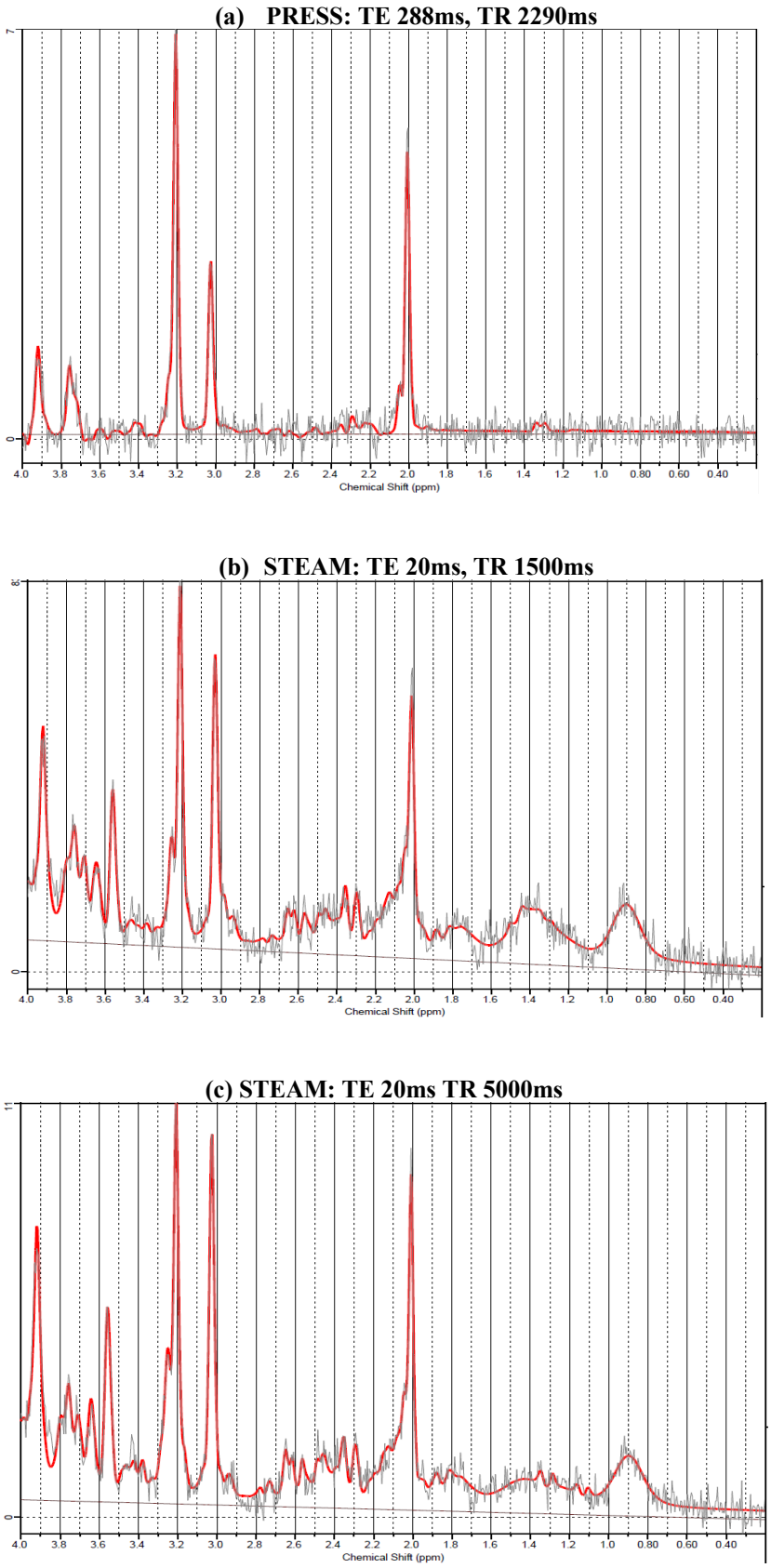


Figure S1: Spectra collected according to the protocol, with the LCModel fit overlaid (in red). (a) The PRESS TE 288ms, TR 2290ms acquisition protocol for peak area ration (Lac/NAA, NAA/Cr, NAA/Cho) incorporated the T_1 or T_2 relaxation effects in the observed metabolites. (b) STEAM TE 20ms TR 1500ms (c) STEAM TE 20ms TR 5000ms data acquired on the same participant for the tNAA concentration estimation.

Analysis:

MR spectroscopy data was first analysed in LCModel (Provencher, 2001) with the basis set, optimised for the timings of the Philips implementation and with ideal RF pulses. This was then repeated in LCModel with the STEAM protocol, generating a basis set with the same 1Hz Gaussian lineshape in VeSPA-Simulate (Soher et al., 2011), and including the same list of metabolites (with NAA, NAAG, Cho, Cr and PCr methyl peaks). From the STEAM series, the same relaxivity corrections were applied to the metabolite signals, and water signals.

All water suppressed spectra were analysed using LCModel (v6·3-1J), with basis sets simulated using VeSPA (v0·9·11) with ideal RF pulses according to the PRESS (TE = 288 ms) and STEAM (TE = 20 ms) sequence timings employed by each vendor for each acquisition (personal communication). The following metabolites were included in the simulations and analyses: acetate (Act), alanine (Ala), ascorbate (Asc), betaine (Bet), aspartate (Asp), choline (Cho), phosphocholine (PCh), glycerophosphocholine (GPC), creatine (Cr), phosphocreatine (PCr), gamma-aminobutyric acid (GABA), glucose (Glc), glutamate (Glu), glutamine (Gln), glutathione (GSH), glycine (Glyc), lactate (Lac), myo-inositol (mIns), N-acetylaspartate (NAA), N-acetylaspartyl glutamate (NAAG), phosphoethanolamine (PE), propylene glycol (PGC), scyllo-inositol (Scyllo), taurine (Tau), and threonine (Thr).

Specific LCModel control parameters were, for PRESS (TE=288 ms):

NSIMUL=0
NCOMBI=17
CHCOMB(17)='Lac+Thr'
PPMST=4·0(default)
PPMEND=0·2 (default)

And for STEAM (TE=20 ms):

NSIMUL=11
NCOMBI=17
CHCOMB(17)='Lac+Thr'
PPMST=4·0 (default)
PPMEND=0·2 (default)

The methyl peaks of NAA, NAAG, choline (Cho), phosphocreatine (PCr), and creatine (Cr) were separated from other groups in the basis spectra to allow quantification of individual relaxation rates. NAA+NAAG methyl peaks at ~2·0ppm were combined and referred to as 'NAA', and PCr+Cr methyl peaks at ~3·0ppm were combined and referred to as 'Cr' due to strong covariance. Lac+Thr were combined and referred to as 'Lac' due to strong covariance. A single peak was used to fit the choline signal at ~3·2ppm and referred to as 'Cho'. Water unsuppressed signals were quantified using HLSVD.

NAA/Cho, NAA/Cr and Lac/NAA were all derived from the LCModel fitted results of first water suppressed PRESS acquisition only (TR/TE=2290ms/288ms) (Figure S1a). [tNAA] was calculated from the fitted NAA methyl singlets through two STEAM experiments (TE=20 ms; TM= 20ms, TR=1500; 5000 (or 3500 ms) acquired for T1 and T2 corrections) (Figure S1 b and c), comparing the relaxation corrected NAA signal to the relaxation corrected unsuppressed water signal. This process is outlined in the following Figure S2:

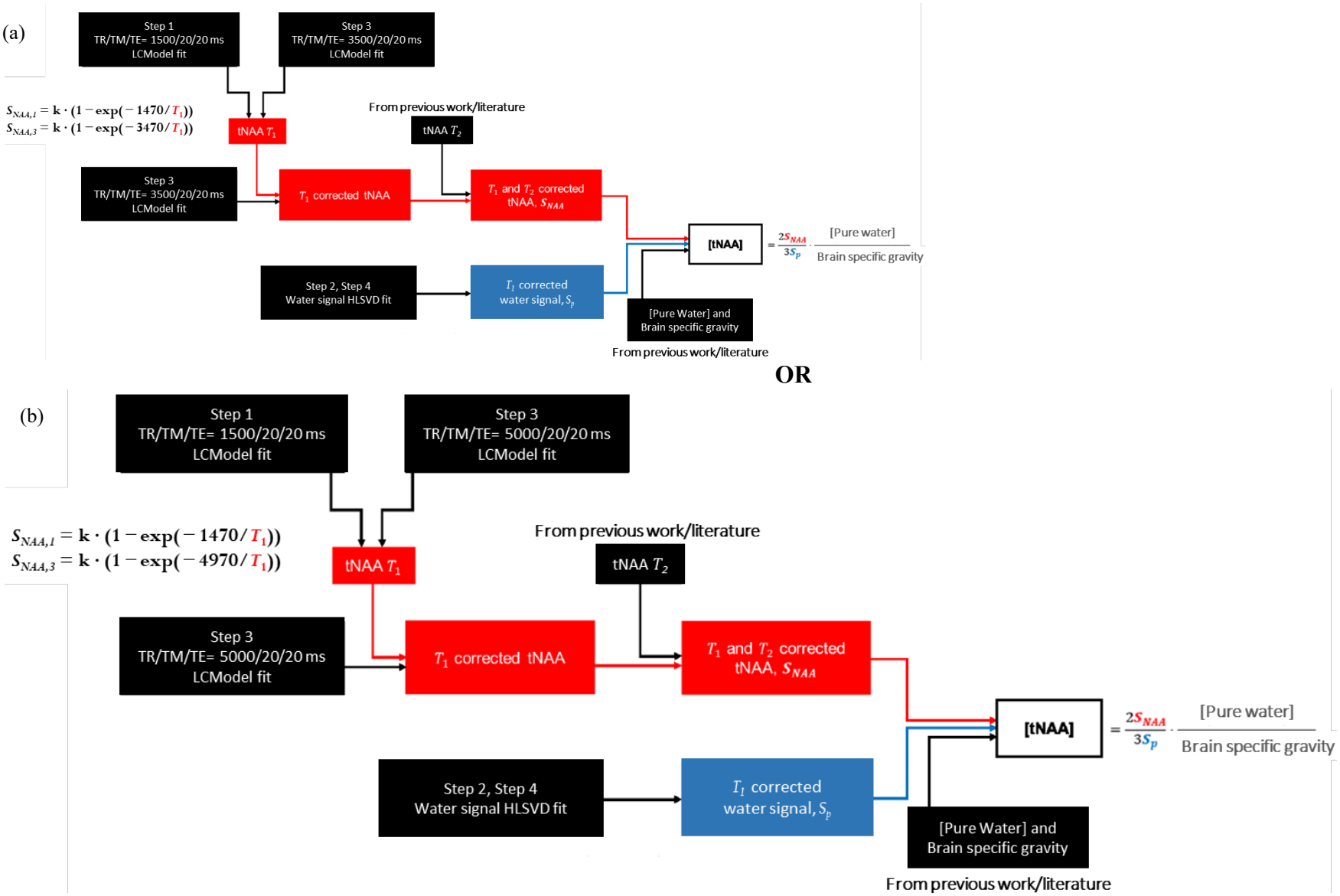


Figure S2: Calculation steps to derive thalamic NAA concentration, [NAA], from the data collected in the various steps of the STEAM protocol (a) TE/TM/TR = 20/20/3500 ms, (b) TE/TM/TR = 20/20/5000 ms. Black boxes show the input data, either obtained from the LCModel/HLSVD fits or reference values. Red boxes and text denote calculated quantities from the NAA resonance, and blue boxes and text denote calculated quantities from the water signal. Equations accompany the different calculation steps. $S_{NAA,step}$ denotes the NAA signal intensity in the corresponding protocol step, with the relaxation corrected intensities for NAA and parenchyma water given by S_{NAA} and S_p respectively.

STEAM PROTOCOL SELECTION:

Two-Point Saturation Recovery STEAM: To accurately measure changes in the parenchyma water concentration, *T*2 relaxometry of the water signal was performed using saturation recovery experiment. *In-vivo* experiments, were optimised with two-point saturation recovery by choosing an appropriate pair of TRs for accurate and precise measurement of metabolite concentrations. A pair of TRs sufficiently long to ensure near fully recovered Lip/MM signals (i.e. TR≥1500ms) were used.

Choice of acquisition scheme for tNAA concentration: This protocol comprises 10 separate STEAM acquisitions in the same $15\times15\times15mm^3$ thalamic voxel. In this study scan duration (approximately 13 minutes) for NAA concentration estimation is significantly shorter than in the PRESS protocol (~25 min) for the previous MARBLE study.

In the present two-point saturation recovery STEAM protocol (Table S2), steps 1 and 3 comprise a two-point *T*1 relaxometry experiment with TR 1500ms and 5000ms (or 3500ms) for each metabolite, allowing the calculation of fully *T*1 relaxed signal intensities. The short TE of 20ms ensures that differential *T*2 decay effects between metabolites and water are minimised. Steps 2 and 4 allow eddy current correction of steps 1 and 3, and can be combined to determine the fully *T*1 relaxed brain water signal under the same phase cycling scheme as steps 1 and 3.

Although STEAM acquisitions provide a lower inherent signal-to-noise ratio than PRESS, they are less susceptible to chemical shift displacement artefacts, and can achieve a shorter TE to minimise variation due to the variance *T*2 relaxation effects. Though, the use of a short TE complicates the fitting of key metabolites due to overlapping with broader resonances from lipids and macromolecules, their short *T*1 ensures that they are fully relaxed throughout the present experiment. The estimates of the NAA concentration and *T*1 of acetate were in agreement between PRESS (used in our earlier MARBLE study) and present STEAM protocols. Within normal variation and mild pathology, the PRESS and STEAM protocols are comparable in their measurements of [tNAA] in the neonatal brain, although STEAM tends to overestimate this.

Optimising Two-Point Saturation Recovery: Initial few STEAM acquisitions (total 07 included in analysis) were taken with TR =1500 ms and 3500ms. The protocol was further optimised by increasing TR from 3500ms to 5000ms. By increasing the TR of the second acquisition in the two-point saturation recovery experiment, the estimates of fully relaxed signals and *T*1s are less biased and more precise, which is a desirable property for robust estimation of metabolite concentrations. With the longer TR at 3500ms, estimates from the two acquisitions were sensitive to the signal to noise ratio, however, with 5000ms, fully *T*1 relaxed signal intensities are largely independent of the error at the shorter TR. In the proposed STEAM protocol, the Lip/MM resonances are fully relaxed due to *T*1 effects throughout the experiment. A TR of 5000ms was also observed as a reasonable balance of signal-to-noise ratio efficiency and overall fitting accuracy, while also allowing effective post-hoc motion correction on the collected sub-spectra.

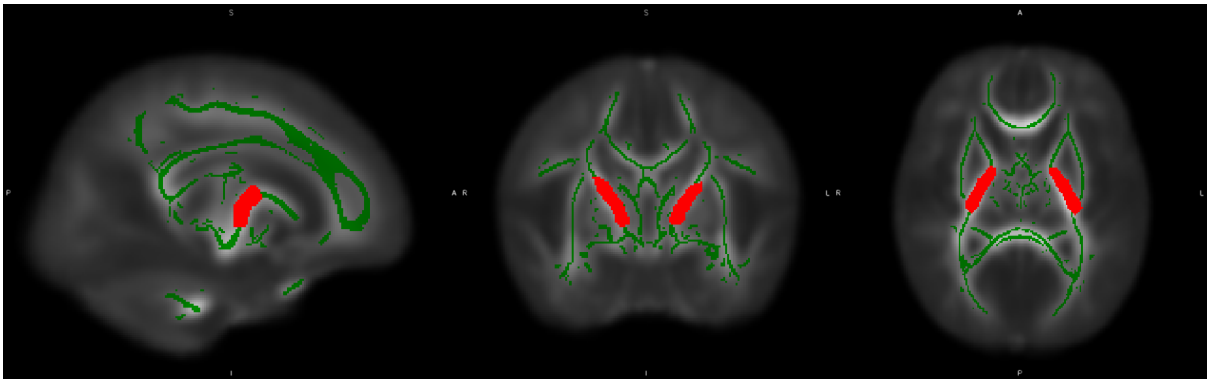
Figure 7. DTI analysis

DTI data acquisition protocol:
DTI acquisition in 30 diffusion gradient directions were carried out using 2D spin-echo echo-planar imaging with 31 total images per slice (30 b = 750 s/mm^2 and 1 b = 0 s/mm^2), TE = 79 ms, 1·95×1·95×2 mm^3 voxel size and parallel imaging acceleration factor of 2·0.

Quality assurance and processing:
Data was assessed for excessive motion and acquisition artefacts, both before and after isolating the brain signal and undertaking corrections for eddy currents and motion using FSL.

Diffusion tensors were then calculated in FSL, and datasets of sufficient quality were spatially normalised to skull stripped JHU_neonate_SS_fass FA map. Major white matter tracts were selected by thresholding according to fractional anisotropy (FA > 0·15) and skeletonised using FSL.

To select a region of interest in the posterior limbs of the internal capsule, a binarized mask was extracted using JHU neonatal brain atlas and placed over mean FA map, as shown below:



Mean FA skeleton thresholded to include only major white matter tracts (green). Binarized mask at PLICs are shown overlaid (red)

The mean FA and standard deviation within this region of interest was then used for assessing prognostic accuracy.

Tract-based spatial statistics (FSL) was then used to examine relationships between FA values in Hypothermia vs control study groups, estimated across all of the major white matter tracts included in the mean skeleton. These analyses were corrected for multiple comparisons using threshold-free cluster enhancement.

Figure 8. Effect of hypothermia on mortality at hospital discharge: Subgroup analysis based on place of delivery.

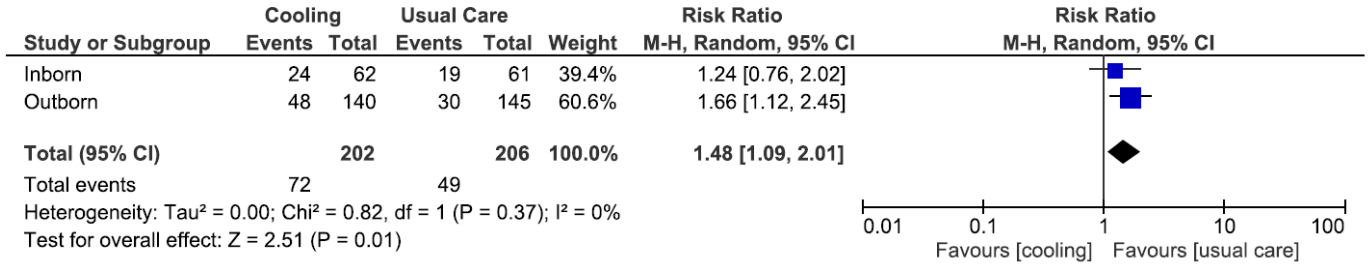


Figure 9. Effect of hypothermia on mortality at hospital discharge: Subgroup analysis based on birth weight.

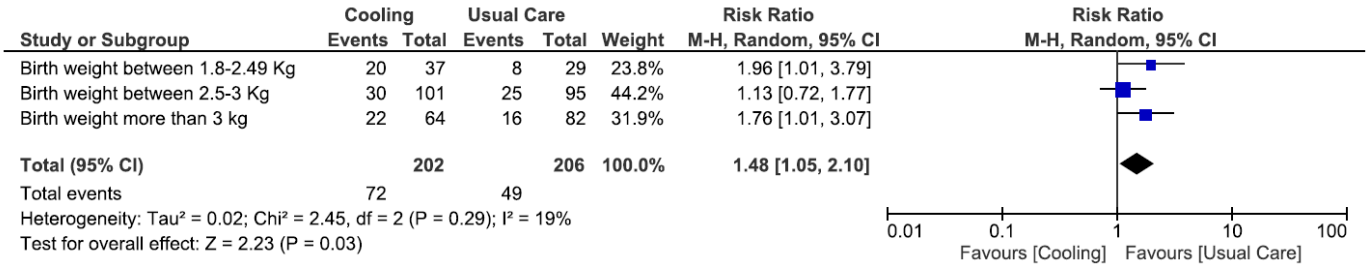
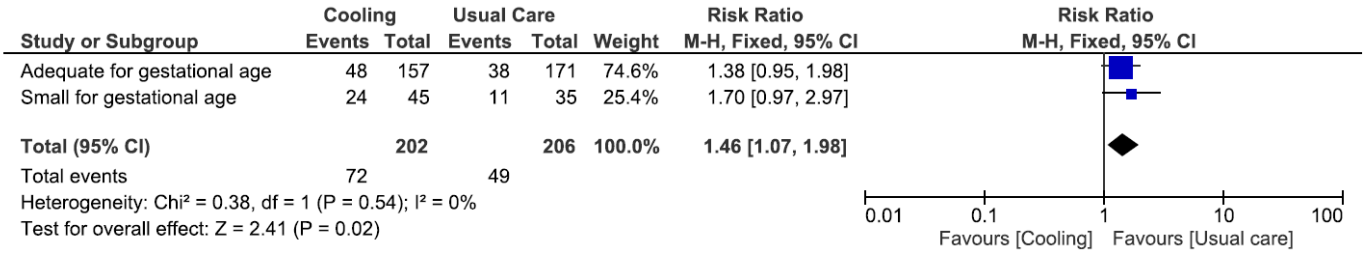


Figure 10. Effect of hypothermia on mortality at hospital discharge: Subgroup analysis based on growth restriction



Small for gestational age was defined as birth weight less than 2 standard deviations on the World Health Organisation growth chart

Figure 11. Effect of hypothermia on mortality at hospital discharge: Subgroup analysis based on co-existent sepsis.

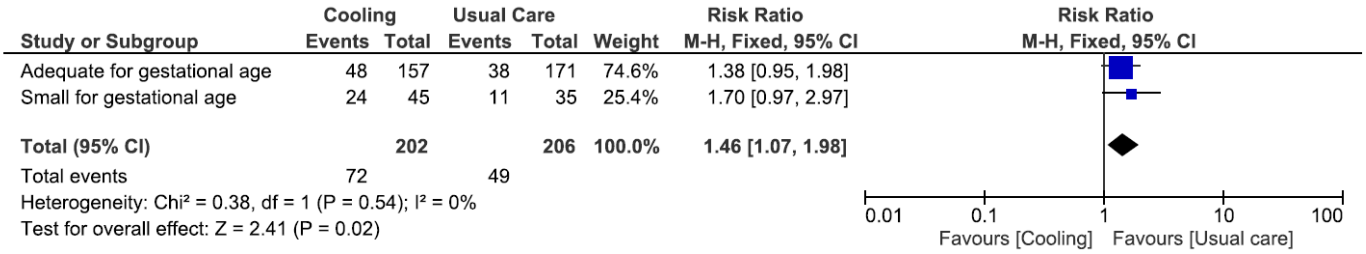


Figure 12. Effect of hypothermia on mortality at hospital discharge: Subgroup analysis based on perinatal sentinel events

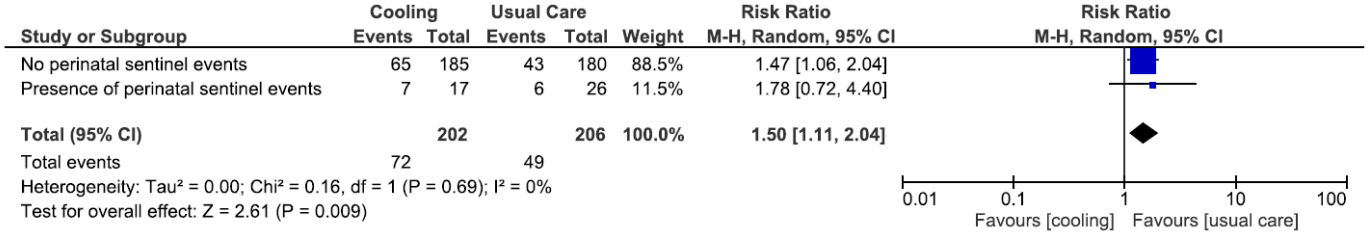


Figure 13. Effect of hypothermia on mortality at hospital discharge: Subgroup analysis based on socio-demographic index of the region.

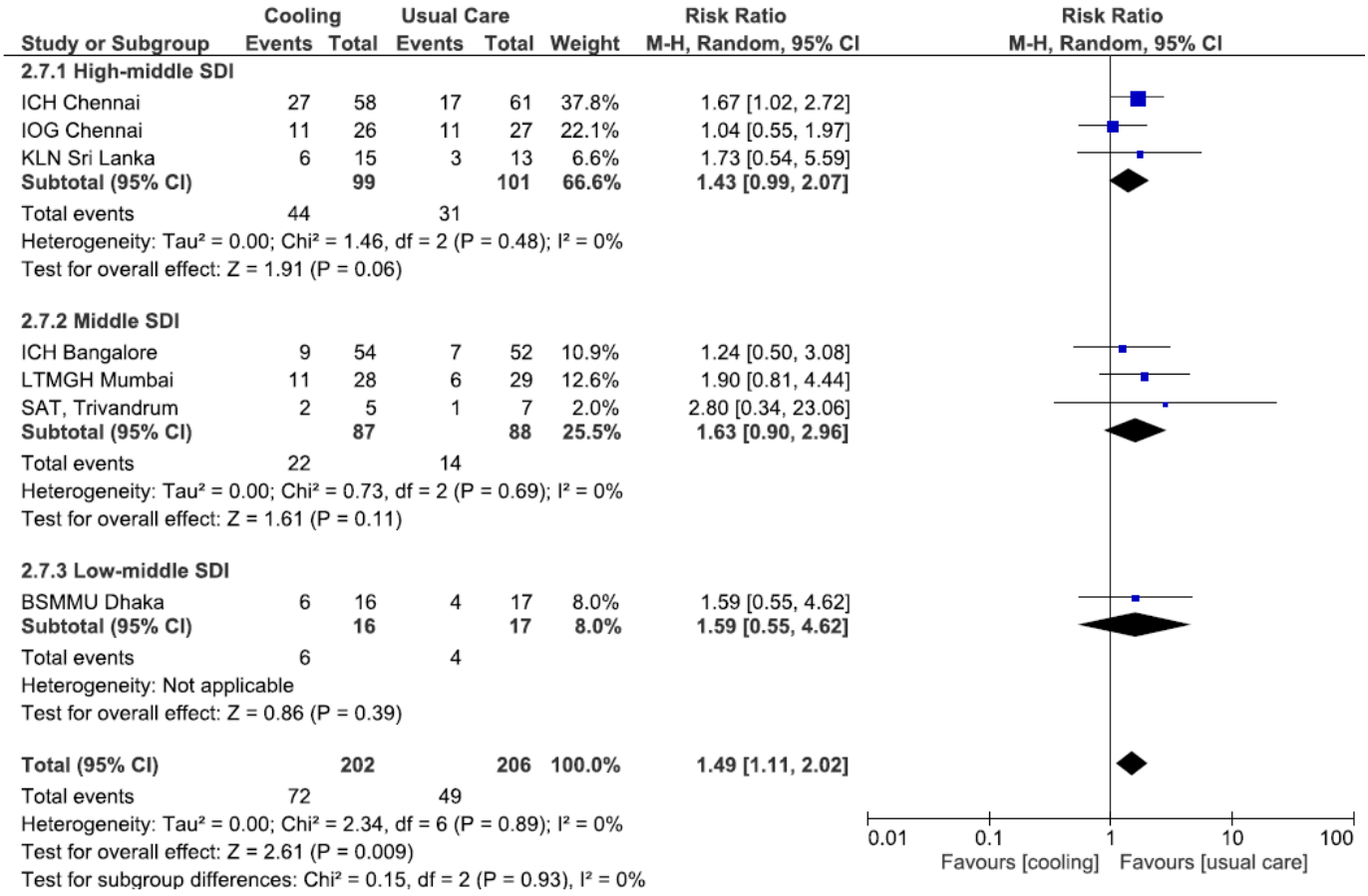


Figure 14. Effect of hypothermia on mortality at hospital discharge: Subgroup analysis based on neonatal mortality rate of the region

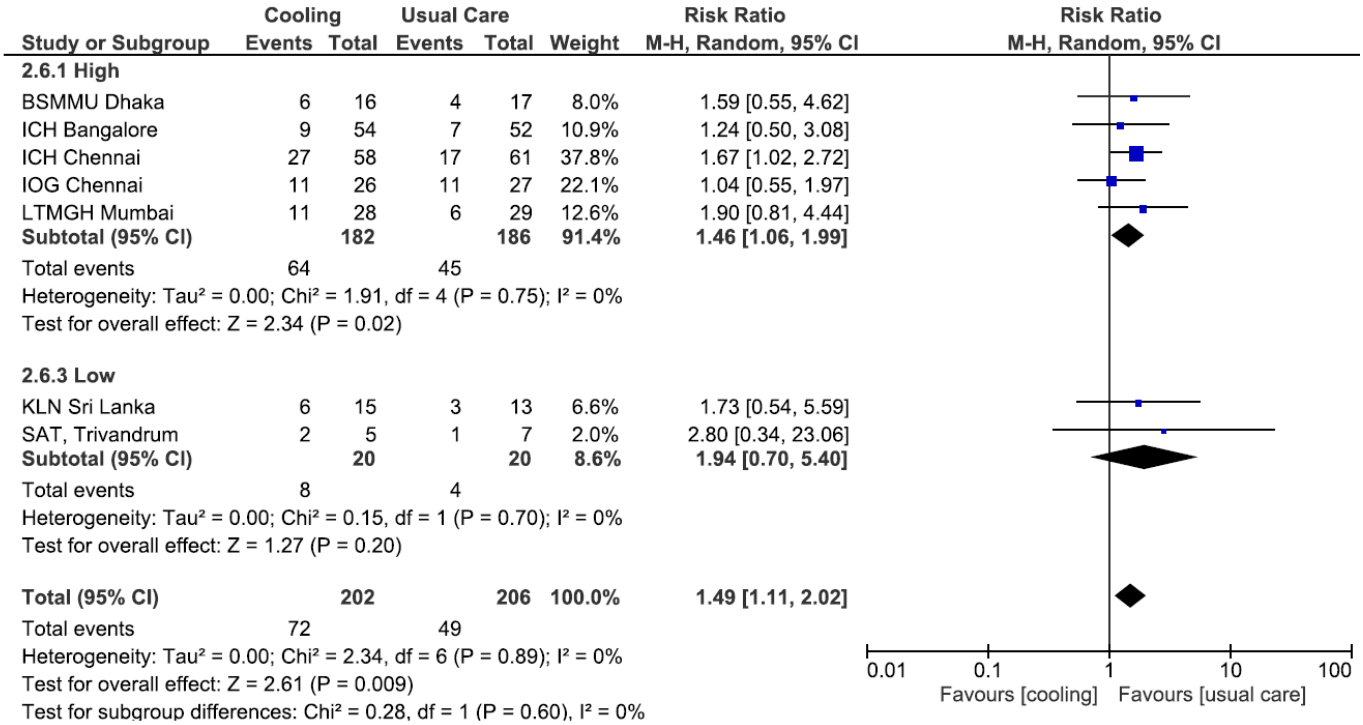


Figure 15. Effect of hypothermia on death or disability at 18 months: Subgroup analysis based on place of delivery.

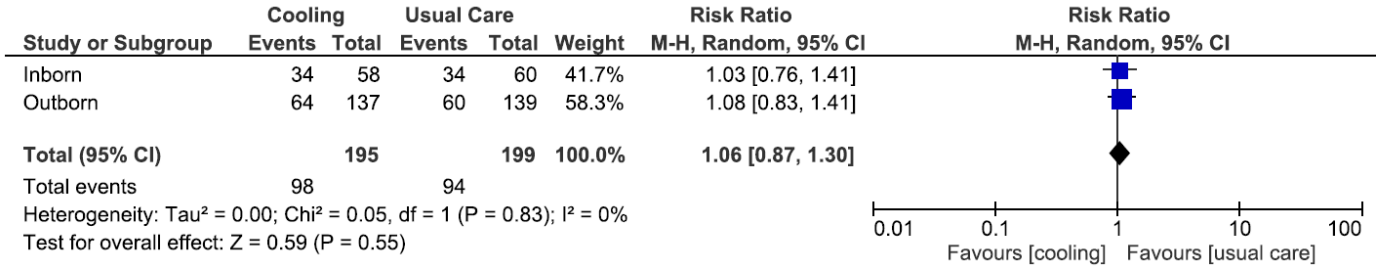


Figure 16. Effect of hypothermia on death or disability at 18 months: Subgroup analysis based on birth weight.

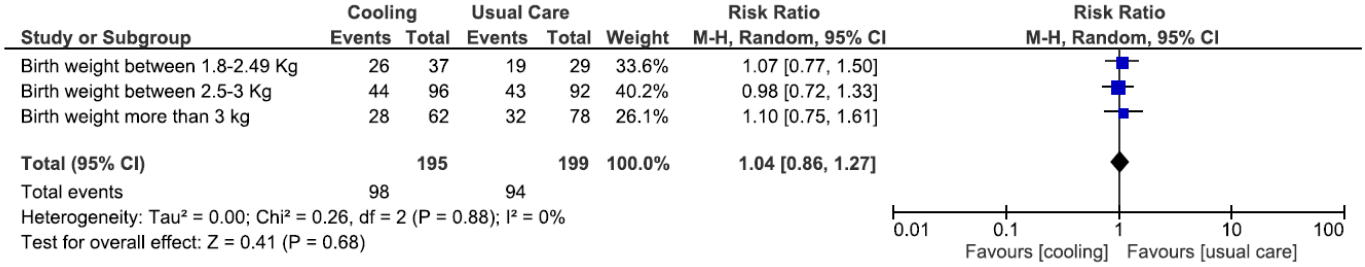
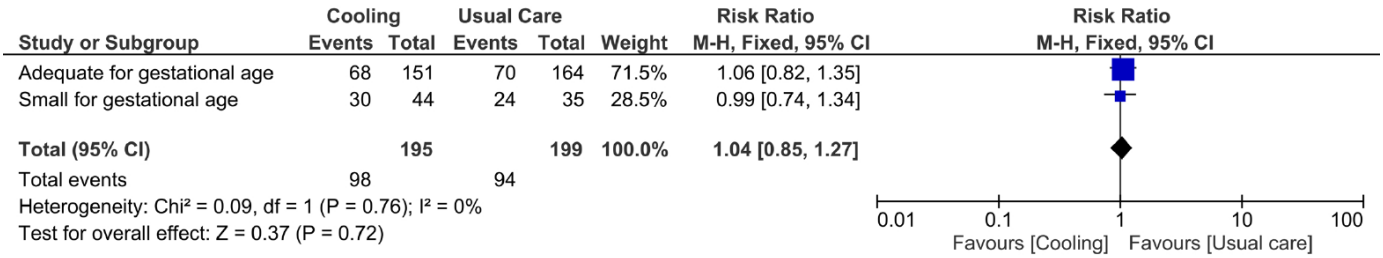


Figure 17. Effect of hypothermia on death or disability at 18 months: Subgroup analysis based on growth restriction



Small for gestational age was defined as birth weight less than 2 standard deviations on the World Health Organisation growth chart

Figure 18. Effect of hypothermia on death or disability at 18 months: Subgroup analysis based on co-existent sepsis.

Figure 19. Effect of hypothermia on death or disability at 18 months: Subgroup analysis based on perinatal sentinel events

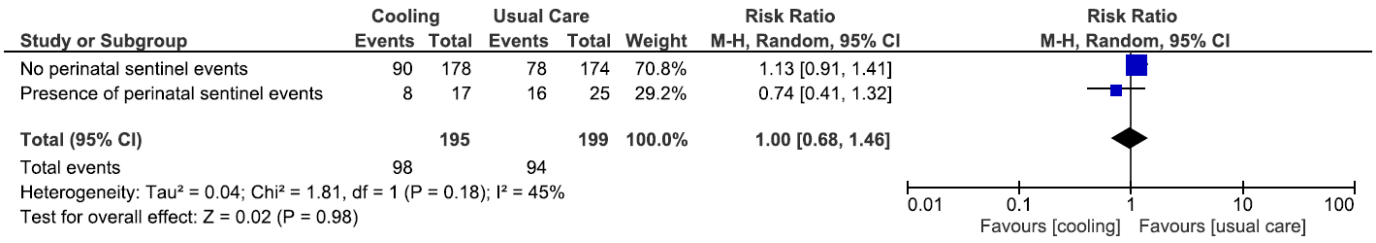


Figure 20. Effect of hypothermia on death or disability at 18 months: Subgroup analysis based on socio-demographic index (SDI) of the region.

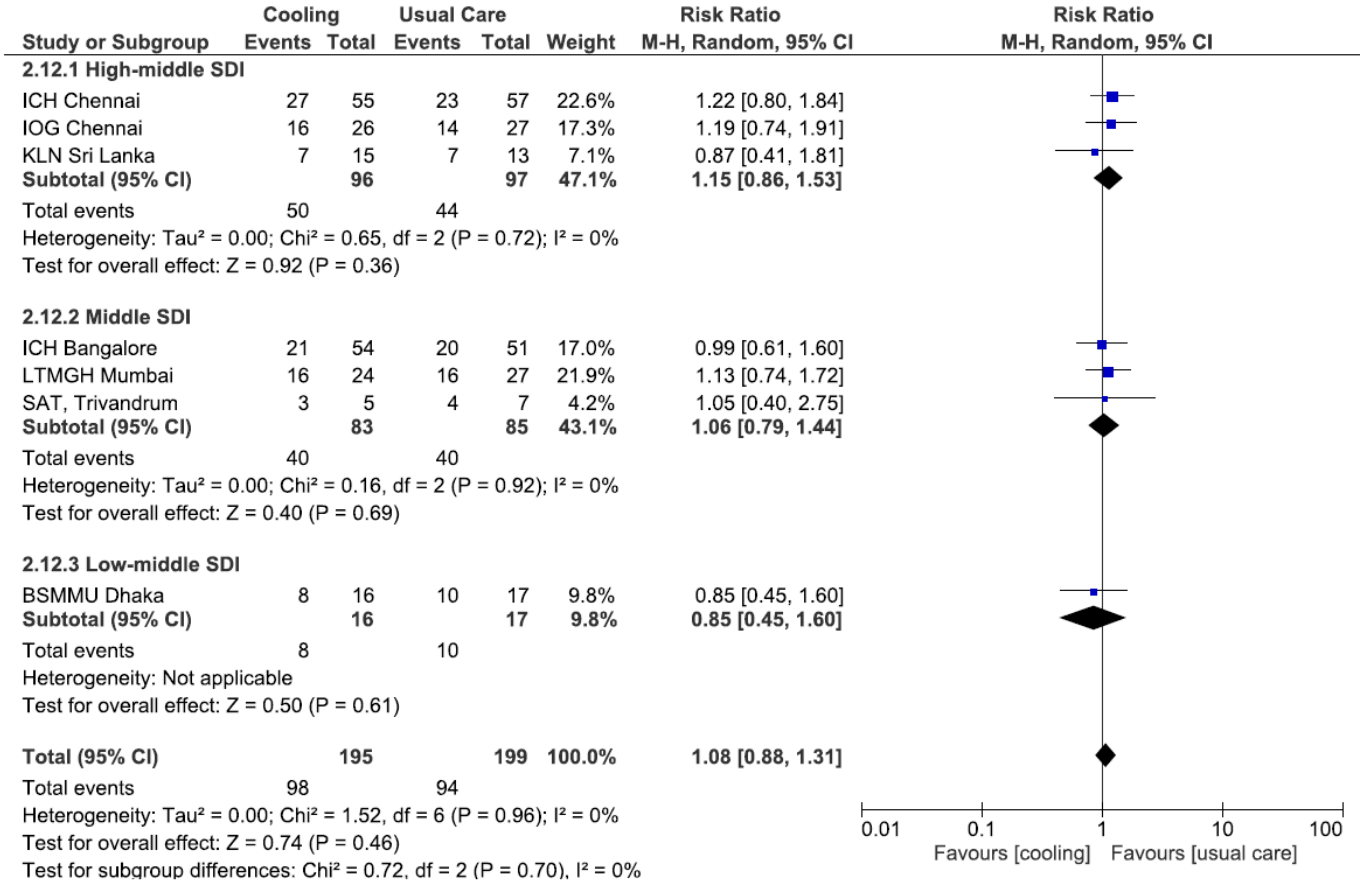
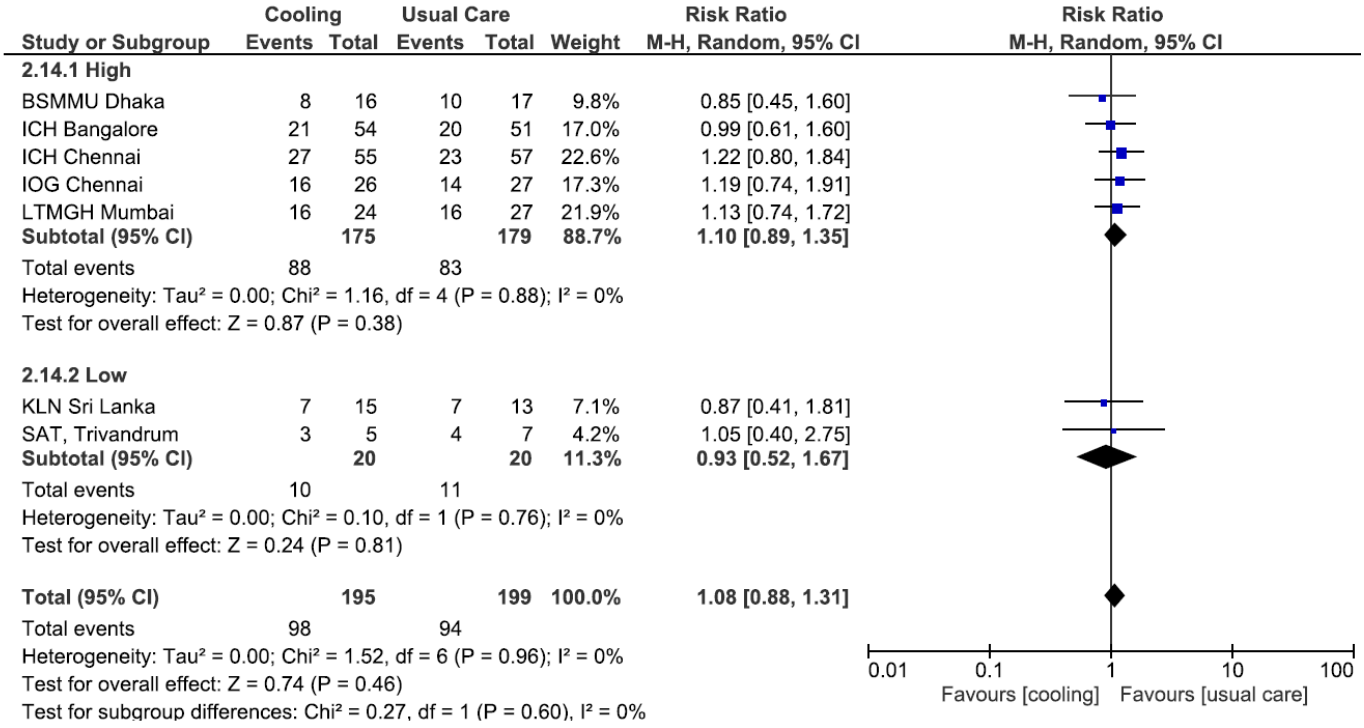
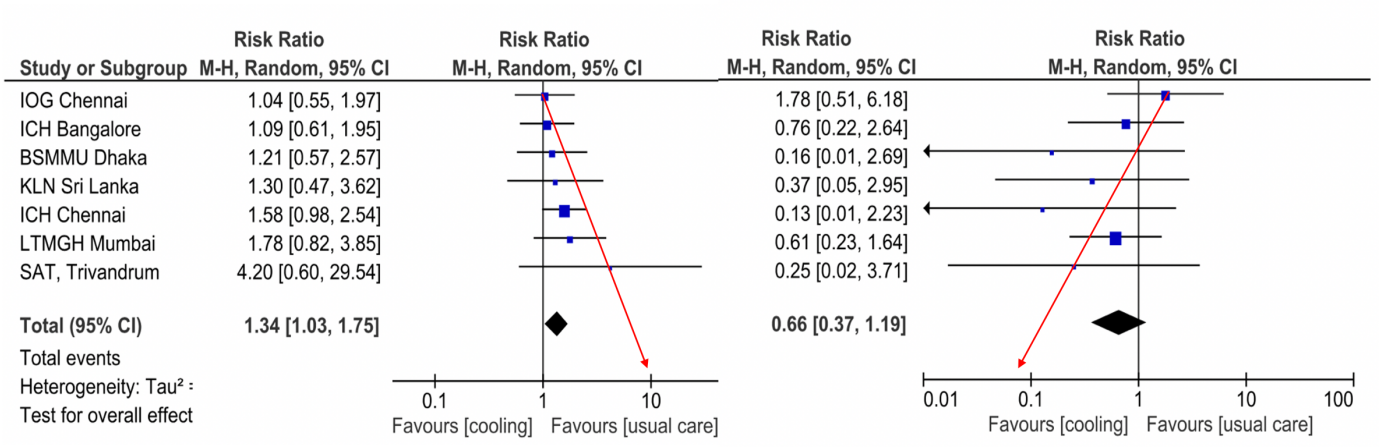


Figure 21. Effect of hypothermia on death or disability at 18 months: Subgroup analysis based on neonatal mortality rate of the region



High neonatal mortality: 10 to 20 per 1000 live births; Low neonatal mortality <10 per 1000 live birth

Figure 22. Relation of neonatal mortality (left forest plot) and moderate or severe disability (right forest plot) and therapeutic hypothermia.



The centres are arranged in the order of increasing mortality in the left panel. The centers with higher mortality appears to have lower rates of disability.