

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Effects of Hypothermia for Perinatal Asphyxia on Childhood Outcomes – The TOBY Children Study

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1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Table S1: Demographic/clinical characteristics at trial entry and 18 month outcomes of children with and without at 6-7 years outcomes

	6-7 year outcomes available (n=280)			6-7 year outcomes not available (n=45)	P-value ^a
	Hypothermia group (n=145)	Control group (n=135)	Overall (n=280)		
Demographic and clinical characteristics at trial entry					
Male sex, n (%):	91 (63)	74 (55)	165 (59)	24 (53)	0.48
Gestational age (weeks):					
Median {IQR}	40.3 {39.3 – 41.3}	40.1 {39.0 – 41.1}	40.2 {39.0 – 41.1}	40.0 {37.7 – 41.1}	0.20
Missing	16	16	32	1	
Birth weight (grams):					
Median {IQR}	3467 {3053 – 3883}	3351 {3060 – 3700}	3428 {3055 – 3790}	3142 {2740 – 3790}	0.05
Missing	1	1	2	0	
Head circumference (cm):					
Median {IQR}	35.0 {34.0 – 36.0}	35.0 {34.0 – 36.0}	35.0 {34.0 – 36.0}	34.9 {33.0 – 35.6}	0.24
Missing	37	37	74	11	
Age at randomisation, n (%):					
< 4 hours	45 (31)	52 (39)	97 (35)	8 (18)	0.03
4-6 hours	100 (69)	83 (61)	183 (65)	37 (82)	
Maternal pyrexia during labour, n (%):					
Missing	10 (7)	9 (7)	19 (7)	1 (2)	0.25
Missing	2	4	6	2	
Delivery complications, n (%):					
Missing	102 (71)	98 (74)	200 (72)	34 (76)	0.67
Missing	2	2	4	0	
Apgar score ≤5 at 10 minutes, n (%):					
Missing	98 (84)	88 (78)	186 (81)	29 (76)	0.51
Missing	28	22	50	7	
Resuscitation required at 10 minutes of age, n (%):					
Missing	132 (92)	124 (93)	256 (92)	44 (98)	0.17
Missing	1	1	2	0	
Clinical seizures, n (%):					
Missing	84 (60)	66 (51)	150 (55)	25 (58)	0.73
Missing	4	5	9	2	
Temperature at randomization, (°C):					
Mean [SD]	36.6 [1.1]	36.4 [1.2]	36.5 [1.1]	36.9 [1.0]	0.04
Missing	0	2	2	0	

Abnormality on aEEG at randomization, n (%): Moderate Severe	62 (43) 83 (57)	57 (42) 78 (58)	119 (42.5) 161 (57.5)	13 (29) 32 (71)	0.08
Outcomes at 18 months	n=103	n=91	n=194	n=43	
Severe neurodevelopmental disability, n (%): Missing	25 (24) 0	32 (35) 0	57 (29) 0	17 (41) 2	0.13
Survival without neurological abnormality, n (%):	65/145 (45)	41/135 (30)	106/280 (38)	10/43 (22)	0.06
Multiple neurodevelopmental disabilities, n (%): Missing	15 (15) 2	24 (27) 2	39 (21) 4	15 (36) 1	0.04
BSID-II Mental Developmental Index score, n (%): <70 70-84 ≥85 Missing	22 (22) 5 (5) 73 (73) 3	29 (33) 7 (8) 52 (59) 3	51 (27) 12 (6) 125 (66) 6	15 (41) 6 (16) 16 (43) 6	0.10 0.01
BSID-II Psychomotor Developmental Index score, n (%): <70 70-84 ≥85 Missing	22 (22) 8 (8) 69 (70) 4	28 (33) 9 (10) 49 (57) 5	50 (27) 17 (9) 118 (64) 9	14 (37) 6 (16) 18 (47) 5	0.22 0.06
Gross Motor Function Classification System (GMFCS), n (%): No abnormality 1-2 3-5	75 (73) 10 (10) 18 (17)	53 (58) 11 (12) 27 (30)	128 (66) 21 (11) 45 (23)	20 (47) 8 (19) 15 (35)	0.02 0.11
Cerebral palsy, n (%):	26 (25)	36 (40)	62 (32)	19 (44)	0.13
Hearing loss not corrected by aids, n (%): Missing	3 (3) 5	5 (6) 7	8 (4) 12	3 (8) 3	0.41
No useful vision, n (%): Missing	6 (6) 1	8 (9) 2	14 (7) 3	6 (14) 1	0.15
Seizures requiring anticonvulsant therapy at time of assessment, n (%): Missing	9 (9) 4	10 (11) 1	19 (10) 5	9 (21) 0	0.05

^aThe P-value is for the comparison between the total participants (n=280) and the non-participants (n=45)

IQR = Interquartile Range; aEEG = amplitude-integrated electroencephalography

Table S2: Demographic/clinical characteristics at trial entry and 18 month outcomes of children with and without at 6-7 years outcomes by treatment group

	6-7 year outcomes available (n=280)		6-7 year outcomes not available (n=45)	
	Hypothermia group (n=145)	Control group (n=135)	Hypothermia group (n=18)	Control group (n=27)
Demographic and clinical characteristics at trial entry				
Male sex, n (%):	91 (63)	74 (55)	8 (44)	13 (48)
Gestational age (weeks):				
Median {IQR}	40.3 {39.3 – 41.3}	40.1 {39.0 – 41.1}	39.9 {37.7 – 41.3}	40.1 {37.7 – 41.7}
Missing	16	16	0	1
Birth weight (grams):				
Median {IQR}	3467 {3053 – 3883}	3351 {3060 – 3700}	2925 {2700 – 3600}	3220 {2780 – 3860}
Missing	1	1	0	0
Head circumference (cm):				
Median {IQR}	35.0 {34.0 – 36.0}	35.0 {34.0 – 36.0}	34.1 {32.5 – 35.5}	35.1 {33.5 – 35.7}
Missing	37	37	4	7
Age at randomisation, n (%):				
< 4 hours	45 (31)	52 (39)	3 (17)	5 (19)
4-6 hours	100 (69)	83 (61)	15 (83)	22 (81)
Maternal pyrexia during labour, n (%):				
Missing	10 (7)	9 (7)	0 (0)	1 (4)
	2	4	0	2
Delivery complications, n (%):				
Missing	102 (71)	98 (74)	13 (72)	21 (78)
	2	2	0	0
Apgar score ≤5 at 10 minutes, n (%):				
Missing	98 (84)	88 (78)	12 (80)	17 (74)
	28	22	3	4
Resuscitation required at 10 minutes of age, n (%):				
Missing	132 (92)	124 (93)	17 (94)	27 (100)
	1	1	0	0
Clinical seizures, n (%):				
Missing	84 (60)	66 (51)	8 (47)	17 (65)
	4	5	1	1
Temperature at randomization, (°C):				
Mean [SD]	36.6 [1.1]	36.4 [1.2]	36.9 [0.8]	36.9 [1.1]
Missing	0	2	0	0
Abnormality on aEEG at randomization, n (%):				
Moderate	62 (43)	57 (42)	3 (17)	10 (37)

Severe	83 (57)	78 (58)	15 (83)	17 (63)
Outcomes at 18 months	n=103	n=91	n=17	n=26
Severe neurodevelopmental disability, n (%): Missing	25 (24) 0	32 (35) 0	7 (41) 0	10 (42) 2
Survival without neurological abnormality, n (%):	65/145 (45)	41/135 (30)	6/17 (35)	4/26 (15)
Multiple neurodevelopmental disabilities, n (%): Missing	15 (15) 2	24 (27) 2	6 (35) 0	9 (36) 1
BSID-II Mental Developmental Index score, n (%): <70 70-84 ≥85 Missing	22 (22) 5 (5) 73 (73) 3	29 (33) 7 (8) 52 (59) 3	6 (40) 1 (7) 8 (53) 2	9 (41) 5 (23) 8 (36) 4
BSID-II Psychomotor Developmental Index score, n (%): <70 70-84 ≥85 Missing	22 (22) 8 (8) 69 (70) 4	28 (33) 9 (10) 49 (57) 5	5 (33) 1 (7) 9 (60) 2	9 (39) 5 (22) 9 (39) 3
Gross Motor Function Classification System (GMFCS), n (%): No abnormality 1-2 3-5	75 (73) 10 (10) 18 (17)	53 (58) 11 (12) 27 (30)	10 (59) 1 (6) 6 (35)	10 (38) 7 (27) 9 (35)
Cerebral palsy, n (%):	26 (25)	36 (40)	7 (41)	12 (46)
Hearing loss not corrected by aids, n (%): Missing	3 (3) 5	5 (6) 7	1 (6) 1	2 (8) 2
No useful vision, n (%): Missing	6 (6) 1	8 (9) 2	2 (12) 0	4 (16) 1
Seizures requiring anticonvulsant therapy at time of assessment, n (%): Missing	9 (9) 4	10 (11) 1	3 (18) 0	6 (23) 0

2. SOCIO ECONOMIC STATUS

Table S3: Summary of Socio Economic Status

	Hypothermia group N=98	Control group N=86
Mother's Highest Qualification, N (%)		
Vocational qualification NVQ or CSE	6 (7)	4 (6)
O Level GCSE or Scottish Standards	10 (12)	9 (13)
BTEC A Levels or Scottish Highers	16 (20)	15 (21)
Diploma or HND	10 (12)	12 (17)
University degree	10 (12)	8 (11)
Postgraduate university degree	20 (24)	12 (17)
Other qualification	10 (12)	9 (13)
None	0 (0)	2 (3)
Missing	16	15
Mother's Employment, N (%)		
Employed	46 (57)	28 (39)
Self-Employed	4 (5)	8 (11)
Unemployed	10 (12)	15 (21)
Other	21 (26)	20 (28)
Missing	17	15
Parents' Home, N (%)		
Owner (mortgage)	59 (70)	48 (65)
Council rented	8 (10)	12 (16)
Private rented (furnished)	2 (2)	3 (4)
Private rented (unfurnished)	11 (13)	5 (7)
Housing society or co-operative	1 (1)	3 (4)
Other	3 (4)	3 (4)
Missing	14	12

Table S4: Index of Multiple Deprivation (IMD) at 6-7 year follow-up for surviving children

IMD^a	Hypothermia group (N=98)	Control group (N=86)	Mean Difference (95% CI)	P-value
Mean (SD)	19.5 (16.3)	23.9 (18.1)	-4.5 (-10.3 to 1.4)	0.13
Missing, N	35	24		

^aHigh IMD scores imply greater deprivation

3. SENSITIVITY ANALYSIS

Table S5: Children included in sensitivity analysis

	Hypothermia group	Control group	Total
Lost to follow up at 6-7 years	18	27	45

Missing IQ at 6-7 years	0	3	3
Total missing primary outcome at 6-7 years	18	30	48
MDI score available at 18 months	15	24	39
Missing MDI at 18 months	3	6	9
Total Included in Sensitivity analysis	160	156	316

Table S6: Sensitivity analysis imputing 18 month MDI scores for missing IQ

Primary outcome (all children with IQ score at 6-7 years or MDI at 18 months)	Hypothermia group (n=160)	Control group (n=156)	Effect measure (95% CI)	P-value
Survival with IQ \geq 85 (WPPSI-III) at age 6-7 years, n (%):	83/160 (51.9%)	62/156 (39.7%)	1.31 (1.02 to 1.67)	0.03

Table S7: Sensitivity analysis imputing missing IQ as IQ<85

Primary outcome (Missing IQ imputed as <85)	Hypothermia group (n=145)	Control group (n=135)	Effect measure (95% CI)	P-value
Survival with IQ \geq 85 (WPPSI-III) at age 6-7 years, n (%):	72/145 (49.7%)	49/135 (36.3%)	1.37 (1.04 to 1.80)	0.03

Table S8: Education adjusted analysis (survivors)

Adjusted for mother's education level (Diploma & above or below), survivors only	Hypothermia group (n=82)	Control group (n=71)	Relative Risk (95% CI)	P-value
IQ \geq 85 (WPPSI-III) at age 6-7 years n (%)			1.27 (1.02 to 1.57)	

4. OTHER OUTCOMES

Table S9: Survival without neurologic abnormality

	Hypothermia group	Control group	Relative risk (95% CI)	P-value
Survival without neurologic abnormality	65/145 (44.8%)	37/132 (28.0%)	1.60 (1.15 to 2.22)	0.004

Table S10: Growth

Growth Standard Deviation Scores (SDS)^a	Hypothermia group (n=98)	Control group (n=86)	Relative risk (95% CI)	P-value
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Weight SDS: Mean [SD]	0.6 (1.7)	0.3 (1.3)	0.3 (-0.2 to 0.8)	0.26
Missing	29	29		
Height SDS: Mean [SD]	0.6 (1.6)	0.5 (1.5)	0.2 (-0.3 to 0.7)	0.46
Missing	16	21		
Head circumference: SDS: Mean [SD]	-1.1 (1.7)	-1.5 (1.8)	0.4 (-0.2 to 0.9)	0.22
Missing	15	18		

^a Calculated using The British 1990 growth reference (revised September 1996). The Standard Deviation Scores (SDS) indicate how far a baby is from the population mean weight and head circumference for babies of the same age and sex. So for example, babies with a SDS of -2 or below compare approximately with the bottom 2% of the reference population.

Table S11: Health Utility Index: HUI3 and HUI2 means, SD and mean differences (UK only, total n=124)

HUI version	Hypothermia group			Control group			Mean differences (95% confidence intervals) and p-values	P=value
	n	Mean	SD	n	Mean	SD		
HUI3	65	0.752	0.397	59	0.659	0.454	0.093 (-0.058 to 0.245)	0.23
HUI2	64	0.832	0.259	60	0.757	0.299	0.075 (-0.025 to 0.174)	0.14

Table S12: Parent and teacher report of behavioral outcomes and abilities

	Hypothermia group (n=98)	Control group (n=86)	Effect measure (95% CI)	P-value
Parent report				
Strengths and Difficulties score (SDQ) ^a :				
Mean [SD]	8.0 [6.9]	9.9 [6.9]	2 (-4 to 0)	0.12
Median {IQR}	7 {3-10}	8 (5-14)		
Missing	24	25		
ADHD Rating Scale IV (DuPaul) ^b :				
Mean [SD]	10.1 [11.5]	12.6 [11.4]	-2 (-6 to 1)	0.12
Median {IQR}	7 {2-15}	11 {3-20}		
Missing	30	30		
Teacher report				

Strengths and Difficulties score (SDQ) ^a :				
Mean [SD]	6.7 [6.5]	7.4 [5.1]	-1 (-3 to 1)	0.18
Median {IQR}	6 {2-10}	6 {3-11}		
Missing	31	27		
ADHD Rating Scale IV (DuPaul) ^b :				
Mean [SD]	9.8 [11.1]	11.3 [10.0]	-2 (-6 to 1)	0.23
Median {IQR}	6 {1-15}	9 {4-19}		
Missing	35	30		
Special Educational Needs (SEN), n (%):				
Attends a special school	10 (14.1)	11 (17.2)	0.82 (0.37 to 1.80)	0.64
Missing	27	22		
Attends a mainstream school with academic or behavioural SEN	19 (31.2)	24 (46.2)	0.67 (0.42 to 1.08)	0.12
Use of SEN resources	21 (34.4)	24 (46.2)	0.75 (0.47 to 1.17)	0.25
Statement of SEN	5 (8.2)	14 (26.9)	0.30 (0.12 to 0.79)	0.01
Missing	37	34		
Academic achievement score ^c :				
Mean [SD]	33.6 (11.6)	30.2 (10.0)	3.4 (-0.8 to 7.7)	0.11
Median {IQR}	36 {29-39}	34 {23-37}		
Missing	44	36		

^a The SDQ ranges from 0 to 40. A score of 0 indicates no difficulties or behavioural problems.

^b The ADHD Rating Scale IV ranges from 0 to 54. A score of 0 indicates no problems with attention and hyperactivity.

^c The academic achievement score ranges from 12 to 60 (12 academic subjects scoring from 0-very below average to 5-very above average).

A score of 12 indicates very below average for all 12 subjects.

5. MEMBERS OF THE TOBY CHILDREN STUDY GROUP

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