

Supplementary material

Administration of parenteral nutrition during therapeutic hypothermia: a population level observational study using routinely collected data held in the National Neonatal Research Database

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Supplemental table 1: Extraction procedures and definitions of enteral feeding exposure variable

Variable	Data items from NNRD	Definition
Parenteral Nutrition	<p>PARENTERAL NUTRITION GROUP DEFINED AS Any of the following items entered in the <i>Daily Care Fluids and Feeding</i> during the first 3 days</p> <ul style="list-style-type: none"> Y entry for PARENTERAL NUTRITION RECEIVED INDICATOR <p>OR</p> <p>The following drug code entered in the <i>Daily care medication</i> during the first 3 days</p> <ul style="list-style-type: none"> 1010238 <i>Total parenteral nutrition</i> <p>NO PARENTERAL NUTRITION GROUP DEFINED AS All other babies not fulfilling above criteria For sensitivity analyses also extract</p> <ul style="list-style-type: none"> <i>Daily Care Fluids and Feeding</i> INTRAVENOUS INFUSION OF GLUCOSE AND ELECTROLYTE SOLUTION RECEIVED INDICATOR = Y/N 	Dichotomous (No parenteral nutrition=0; provided parenteral nutrition=1)

Supplemental table 2: Extraction procedures, definitions and classifications of background variables

Variable	Data items from NNRD	Definition(s)	Classification
Cord blood gas pH in bands	<i>Labour and Delivery Details</i> UMBILICAL CORD BLOOD pH LEVEL (ARTERIAL) <i>Or, if not recorded, use Labour and Delivery Details</i> UMBILICAL CORD BLOOD pH LEVEL (ARTERIAL)	CordpHArt: Tricotomised into bands: >7.0, 6.9-7.0, <6.9	Principal
Birth year	<i>Baby Demographics</i> YEAR AND MONTH OF BIRTH (BABY)	BirthYear: Categorical into two-year bands: 2010-2011, 2012-2013, 2014-2015, 2016-2017	Principal
Gestational age week	<i>Baby Demographics</i> GESTATION LENGTH (AT DELIVERY): Gestational weeks and days	GAweeks: Integers	Highly important
Birthweight	<i>Baby Demographics</i> BIRTH WEIGHT	Bweight: Original entries trimmed from above at 3500g and entries smaller than 1000g with a non-zero digit are multiplied by 10. Square-root transformed.	Highly important
Sex	<i>Baby Demographics</i> PERSON PHENOTYPIC SEX	Sex: Dichotomous (Male=0; Female=1)	Highly important
Emergency resuscitation drugs administered	<i>Labour and Delivery Details</i> NEONATAL RESUSCITATION METHOD Dichotomous: Y= code 17 (Adrenaline) OR 88 (any other drug) N= any other codes OR no code	ResusDrugs: Dichotomous (No=0; Yes=1)	Highly important
Instrument of delivery	<i>Labour and Delivery Details</i> DELIVERY INSTRUMENT TYPE	InstrDeliv: Dichotomised (No instrument used=0; Forceps or ventouse=1)	Highly important
Mode of delivery	<i>Labour and Delivery Details</i> MODE OF DELIVERY	Delivery: Dichotomous (Vaginal=0, Caesarean=1)	Highly important

Supplemental table 2: Extraction procedures, definitions and classifications of background variables

Variable	Data items from NNRD	Definition(s)	Classification
	Categorical: codes=1-4 AND <i>Labour and Delivery Details IN LABOUR BEFORE CAESARIAN SECTION INDICATOR=Y/N</i>		
Maternal smoking status	<i>Pregnancy Details</i> MOTHER CURRENT SMOKER AT BOOKING INDICATOR (categorical, codes 1-6)	SmokePreg: Dichotomised (Not smoking=0; Smoking during pregnancy=1) SmokePregMs: Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Maternal suspected chorioamnionitis	<i>Labour and Delivery Details</i> INTRAPARTUM ANTIBIOTICS GIVEN INDICATORS	IntrPartAntiB: Dichotomous (No intrapartum antibiotics given=0, Intrapartum antibiotics=1)	Highly important
Apgar score at 1 minute	<i>Labour and Delivery Details</i> APGAR SCORE (1 MINUTE) Continuous: 0-10	APGAR1min: Categorical (0-10) APGAR1minMs: Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Apgar score at 5 minutes	<i>Labour and Delivery Details</i> APGAR SCORE (5 MINUTE) Continuous: 0-10	APGAR5min: Categorical (0-10) APGAR5minMs: Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Umbilical cord base excess	<i>Labour and Delivery Details</i> UMBILICAL CORD BLOOD BASE EXCESS CONCENTRATION (ARTERIAL) Continuous OR if not available use <i>Labour and Delivery Details</i> UMBILICAL CORD BLOOD BASE EXCESS CONCENTRATION (VENOUS)	CordBaseExcess: Continuous (to 1 decimal place) CordBaseExcessMs: Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Admission mean blood pressure	<i>Admission Details</i> MEAN ARTERIAL BLOOD PRESSURE (ON ADMISSION TO NEONATAL CRITICAL CARE) Continuous	AdmitBP: Continuous, square-root transformed AdmitBP.Ms: Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Admission blood glucose	<i>Admission Details</i> BLOOD GLUCOSE CONCENTRATION (ON ADMISSION TO NEONATAL CRITICAL CARE) Continuous	AdmitBG: Continuous, trimmed from above at 20 AdmitBG.MS: Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Admission oxygen saturation	<i>Admission Details</i> OXYGEN SATURATION (ON	AdmitOS: Continuous, trimmed to be within the range (50, 100)	Highly important

Supplemental table 2: Extraction procedures, definitions and classifications of background variables

Variable	Data items from NNRD	Definition(s)	Classification
	ADMISSION TO NEONATAL CRITICAL CARE) Continuous	AdmitOS.Ms: Binary missing indicator created (Not missing=0; Missing=1)	
Maternal deprivation score (from lower super output area)	<i>Parents Demographics</i> POSTCODE OF USUAL ADDRESS (LSOA)	LSOAdec: Categorised into deciles (1, 2,..., 10) LSOAdecMs: Binary missing indicator created (Not missing=0; Missing=1)	Highly important
Multiplicity	<i>Labour and Delivery Details</i> BIRTH ORDER (MATERNITY SERVICES) <i>Labour and Delivery Details</i> NUMBER OF FETUSES (NOTED DURING PREGNANCY EPISODE)	MultipleBrt: Dichotomised (single birth=0; multiple births=1)	Moderately important
Maternal age	<i>Parents Demographics</i> YEAR OF BIRTH (MOTHER)	MaternalAge: Continuous (years) trimmed to be within range 17- 45	Moderately important
Maternal duration of rupture of membranes (time in hours)	<i>Labour and Delivery Details</i> RUPTURE OF MEMBRANES DATE TIME <i>or</i> RUPTURE OF MEMBRANES YEAR AND MONTH and <i>NUMBER OF MINUTES (BIRTH TO EVENT)</i> (continuous)		<i>Variable not used. (Too many missing values)</i>
Maternal disease during pregnancy	<i>Labour and Delivery Details</i> SIGNIFICANT MATERNAL PYREXIA IN LABOUR INDICATOR (Y/N) <i>Pregnancy Details</i> MATERNITY COMPLICATING MEDICAL DIAGNOSIS TYPE Dichotomous: Y=code 16 (endocrine disorder), N=any other or no code <i>Pregnancy Details</i> MATERNITY COMPLICATING MEDICAL DIAGNOSIS TYPE Dichotomous: Y=code 08 (diabetes) OR <i>Pregnancy Details</i> MATERNITY OBSTETRIC DIAGNOSIS TYPE Dichotomous: Y=code 06 (gestational diabetes mellitus) N=any other or no code	MaternalDis: Dichotomised (No diagnosis=0; At least one of pyrexia in labour, hypothyroid, diabetes=1)	Moderately important

Supplemental table 2: Extraction procedures, definitions and classifications of background variables

Variable	Data items from NNRD	Definition(s)	Classification
Maternal ethnicity	<p><i>Parents Demographics</i> ETHNIC CATEGORY (MOTHER) (categorical) Coded as: WHITE (A - British, B - Irish, C - Any other white background); MIXED (D - White and Black Caribbean, E - White and Black African, F - White and Asian, G - Any other mixed background); ASIAN OR ASIAN BRITISH (H - Indian, J - Pakistani, K - Bangladeshi, L - Any other Asian Background); BLACK OR BLACK BRITISH (M - Caribbean, N - African, P - Any other Black background); OTHER ETHNIC GROUPS (R - Chinese, S - Any other ethnic group); UNKNOWN (Z, DTA - Not stated, 99 - Not known)</p> <p>This data item is based on self-reported ethnicity as recorded in maternity notes</p>	Ethnicity: Categorised into four groups (White=1; Asian & Mixed=2; Black & Mixed=3; Other and not given=4)	Moderately important
Parity of mother (primiparous Y/N)	<p><i>Pregnancy Details</i> PREGNANCY TOTAL PREVIOUS PREGNANCIES Dichotomous: code 00=Y; code 01-29=N</p>	Primiparous: Dichotomous (Not first pregnancy=0; First pregnancy=1)	Moderately important
Chest compressions administered	<p><i>Labour and Delivery Details</i> NEONATAL RESUSCITATION METHOD Dichotomous: Code 16=Y; any other code=N</p>	ChestCompr: Dichotomous (No chest compressions applied=0; Chest compressions applied=1)	Moderately important
Intubated at resuscitation	<p><i>Labour and Delivery Details</i> NEONATAL RESUSCITATION METHOD Dichotomous: Code 15=Y; any other code=N</p>	Intubation: Dichotomous (Not intubated=0; Intubated=1)	Moderately important
Time to first spontaneous breath	<p><i>Labour and Delivery Details</i> TIME BETWEEN DELIVERY AND SPONTANEOUS RESPIRATION CODE Continuous</p>	<p>SpontRespTime: Dichotomised (≤ 5 mins=0; >5 mins=1)</p> <p>SpontRespTimeMs: Binary missing indicator created (Not missing=0; Missing=1)</p>	Moderately important
Admission heart rate	<p><i>Admission Details</i> HEART RATE (ON ADMISSION TO NEONATAL CRITICAL CARE) Continuous</p>	AdmitHR: Continuous, trimmed to be within the range 80-100	Moderately important

Supplemental table 2: Extraction procedures, definitions and classifications of background variables

Variable	Data items from NNRD	Definition(s)	Classification
		AdmitHR.Ms: Binary missing indicator created (Not missing=0; Missing=1)	
Admission temperature	<i>Admission Details</i> TEMPERATURE (ON ADMISSION TO NEONATAL CRITICAL CARE) Continuous	AdmitTempCe: Continuous, trimmed to be within 26-40 AdmitTempMs: Binary missing indicator created (Not missing=0; Missing=1)	Moderately important
Positive blood or cerebrospinal fluid culture with a recognised pathogen recorded in the first 3 days	Defined from <i>Infection Cultures (Episodic)</i> recorded up to and including day 3 <ul style="list-style-type: none"> Pure growth of pathogen from blood OR <ul style="list-style-type: none"> Pure growth of pathogen from CSF 	Infection: Dichotomous (0=No infection; 1=infection)	Moderately important
Treatment for low blood pressure with an intravenous inotrope (e.g. dopamine, noradrenaline)	<i>Daily Care Medication</i> on day 1 only <ul style="list-style-type: none"> 500098 Dopamine 500096 Dobutamine 500056 Adrenaline 500210 Noradrenaline 500116 Hydrocortisone 1010173 Milrinone Dichotomous: any of above=Y, none of above=N OR <i>Daily Care Cardiovascular</i> INOTROPE INFUSION RECEIVED INDICATOR Y/N	Inotropes: Dichotomous (Inotropes not administered=0; Inotropes administered=1)	Moderately important
Mechanical ventilation method	<i>Daily Care Respiratory</i> on day 1 only; RESPIRATORY SUPPORT MODE Dichotomous: Codes 1, 2, 3=Y; any other or no code =N	RespiSupprt: Dichotomous (Respiratory support not provided=0; Respiratory support provided=1)	Moderately important
Received inhaled nitric oxide (Y/N)	<i>Daily Care Respiratory</i> on day 1 only; NITRIC OXIDE GIVEN INDICATOR Dichotomous: Y/N	NitricOxide: Dichotomous (Nitric oxide not given=0; Nitric oxide given=1)	Moderately important
Required acute postnatal transfer, within 24 hours (Y/N)	<i>Admission Details</i> SITE CODE (OF ADMITTING NEONATAL UNIT) or ORGANISATION CODE (OF ADMITTING NEONATAL UNIT) Different from <i>Baby Demographics</i> SITE CODE (OF ACTUAL PLACE OF DELIVERY) or ORGANISATION CODE (OF ACTUAL PLACE OF DELIVERY) And	PostNTransfer: Dichotomous (No transfer=0; Transfer=1)	Moderately important

Supplemental table 2: Extraction procedures, definitions and classifications of background variables

Variable	Data items from NNRD	Definition(s)	Classification
	<i>Baby Demographics</i> EPISODE NUMBER		
Maternal occupation	<i>Parents Demographics (withheld)</i> OCCUPATION MOTHER (SNOMED CT)	MumJob: Dichotomous (No occupation=0; Any occupation=1)	Moderately important
Onset of labour	<i>Labour and Delivery Details</i> LABOUR OR DELIVERY ONSET METHOD CODE	OnsetLabour: Categorised into four groups (Not in labour=0; Spontaneous=1; Induced=2; Missing=9)	Moderately important
Time to admission	<i>Admission Details</i> CRITICAL CARE START YEAR AND MONTH and NUMBER OF MINUTES (BIRTH TO EVENT)	AdmitTime: log-transformed with zero recoded to zero	Moderately important
Presentation at delivery	<i>Labour and Delivery Details</i> PRESENTATION AT DELIVERY 1 - Breech 2 - Cephalic 3 - Transverse 8 - Other 9 - Unknown	FetusAtDelivC: Dichotomised (Cephalic=1, Not cephalic=0)	Moderately important
Blood transfusion	<i>Daily care blood transfusion</i> BLOOD TRANSFUSION PRODUCT TYPE on day 1 only	BloodTrans: Dichotomised (No=0; Yes=1)	Moderately important
Maternal or obstetric medical problem	<i>Pregnancy Details</i> MATERNITY OBSTETRIC DIAGNOSIS TYPE (CURRENT PREGNANCY) <i>Pregnancy Details</i> MATERNITY MEDICAL DIAGNOSIS TYPE (CURRENT PREGNANCY)	ProblMedic: Dichotomised (No medical problems=0; Some medical problems=1)	Moderately important

Supplemental table 3: Extraction procedures and definitions of outcome variables

Variable	Data items from NNRD	Definition
Late onset blood stream infection NNAP definition	Defined from <i>Infection Cultures (Episodic)</i> recorded after day 3 <ul style="list-style-type: none"> Pure growth of pathogen from blood OR <ul style="list-style-type: none"> Pure growth of pathogen from CSF OR <p>Either a pure growth of a skin commensal or a mixed growth with ≥ 3 clinical signs at the time of blood sampling</p>	Dichotomous (No infection=0, Infection=1)
Late onset infection, non-NNAP	5 consecutive days of antibiotic treatment defined as 5 consecutive days of any of the following (including in combination and changing during the 5 days) after day 3 <i>Daily care medication</i> <ul style="list-style-type: none"> 1010155 Benzyl Penicillin 1010158 Augmentin 1010179 Flucloxacillin 500012 Flucloxacillin 500016 Gentamicin 500072 Co-amoxiclav 500086 Co-amoxiclav 500084 Ciprofloxacin 500029 Netilmicin 500002 Amikacin 500211 Tazocin 500023 Metronidazole 500040 Vancomycin 500007 Cefotaxime 500004 Ampicillin 500009 Cefuroxime 500008 Ceftazidime 500175 Ceftriaxone 500032 Piperacillin 500206 Ofloxacin 500005 Azlocillin 1010171 Linezolid 1010271 Cefalexin 1010139 Amoxicillin 500070 Amoxicillin 500128 Meropenem 500118 Imepenenem 500145 Imipenem 500069 Ambisome (Liposomal Amphotericin) 500003 Amphotericin 1010195 Amphotericin Liposomal 	Dichotomous (No infection=0, Infection=1)
Severe NEC	Gestational age specific NEC score based on Battersby et al., JAMA Pediatrics, 2017. Data items needed: ABDOMINAL X-RAYS (EPISODIC) <ul style="list-style-type: none"> CONDITION SEEN IN ABDOMEN DURING X-RAY (NNRD field ID: XRayAppearances) ABDOMINAL X-RAY PERFORMED REASON (NNRD field ID: ClinicalFindings) TRANSFERRED FROM NEONATAL INTENSIVE CARE UNIT FOR NECROTISING ENTEROCOLITIS MANAGEMENT 	Dichotomous (No severe NEC=0, Severe NEC=1)

Supplemental table 3: Extraction procedures and definitions of outcome variables

Variable	Data items from NNRD	Definition
	<p>INDICATOR (NNRD field ID: TransferredForFurtherManagement)</p> <ul style="list-style-type: none"> LAPAROTOMY FOR NECROTISING ENTEROCOLITIS INDICATION CODE NEC CONFIRMED BY VISUAL INSPECTION DURING LAPAROTOMY (INDICATOR)HISTOLOGY CONFIRMED NECROTISING ENTEROCOLITIS FOLLOWING LAPAROTOMY INDICATOR POSTMORTEM CONFIRMED NEC CAUSE OF DEATH <p>Only available following introduction of ABDOMINAL X-RAY (EPISODIC) field</p> <ul style="list-style-type: none"> Cases identified using these data items were individually confirmed with clinicians. 	
Necrotising enterocolitis (non-UKNC definition)	<p>The following entered in the <i>Daily Care Gastrointestinal</i> on any one day during stay in a neonatal unit</p> <ul style="list-style-type: none"> Any entry (1 or 2) for TREATMENT TYPE FOR NECROTISING ENTEROCOLITIS <p>OR the following diagnostic codes</p> <ul style="list-style-type: none"> 1010683 <i>Necrotising enterocolitis – suspected</i> 10708 <i>Necrotising enterocolitis – Perforated</i> 15809 <i>Necrotizing enterocolitis</i> <p>AND</p> <p>5 or more days nil by mouth defined by the <i>Daily Care Fluids and Feeding</i> for a continuous period of 5 days</p> <ul style="list-style-type: none"> No under ENTERAL FEED TYPE GIVEN No entry under FORMULA MILK OR MILK FORTIFIER TYPE No value OR 0 for TOTAL VOLUME OF MILK RECEIVED No entry under ENTERAL FEEDING METHOD <p>WHILE ALSO RECEIVING</p> <p>5 or more days of antibiotics over the same 5 days as the baby was nil by mouth, defined as 5 consecutive days of any of the following</p> <p><i>Daily care medication</i></p> <ul style="list-style-type: none"> 1010155 Benzyl Penicillin 1010158 Augmentin 1010179 Flucloxicillin 500012 Flucloxacillin 500016 Gentamicin 500072 <i>Co-amoxiclav</i> 500086 Co-amoxiclav 500084 Ciprofloxacin 500029 Netilmicin 500002 Amikacin 500211 Tazocin 500023 Metronidazole 500040 Vancomycin 500007 Cefotaxime 500004 Ampicillin 	Dichotomous (No NEC=0, NEC=1)

Supplemental table 3: Extraction procedures and definitions of outcome variables

Variable	Data items from NNRD	Definition
	<ul style="list-style-type: none"> • 500009 Cefuroxime • 500008 Cefazidime • 500175 Ceftriaxone • 500032 Piperacillin • 500206 <i>Oflacillin</i> • 500005 Azlocillin • 1010171 Linezolid • 1010271 <i>Cefalexin</i> • 1010139 Amoxicillin • 500070 Amoxicillin • 500128 Meropenem • 500118 Imepenem • 500145 <i>Imipenem</i> • 500069 Ambisome (Liposomal Amphotericin) • 500003 Amphotericin • 1010195 Amphotericin Liposomal 	
Survival to discharge	Defined from the <i>Discharge Details</i> from final neonatal unit stay <ul style="list-style-type: none"> • DISCHARGE DESTINATION FROM NEONATAL CRITICAL CARE = 1, 2, 4, 5, 6 (NOT code 3, <i>Died</i>) 	Dichotomous (Died during neonatal stay=0, Survived until discharge =1)
Length of neonatal unit stay	Defined as the total number of days a baby received neonatal care (any level of care) from <i>Daily Care General Information</i> - LOCATIONS OF HIGHEST LEVEL OF CARE	Continuous, integers
Hypoglycaemia	Defined as any of the following <i>diagnostic codes</i> recorded at any time during an babies neonatal units stay: <ul style="list-style-type: none"> • 15771 Iatrogenic neonatal hypoglycaemia • 15773 Neonatal hypoglycaemia 	Dichotomous (No hypoglycaemia=0, Hypoglycaemia =1)
Breastfeeding at discharge	Defined from final day of neonatal care entry in <i>Daily Care Fluids and Feeding</i> of <ul style="list-style-type: none"> • ENTERAL FEED TYPE GIVEN = code 1 (Breastfeeding) OR <ul style="list-style-type: none"> • ENTERAL FEEDING METHOD = code 1 (breast) Where final day is not entered, penultimate day will be used	Dichotomous (Not suckling at the breast at discharge=0, Suckling at the breast at discharge=1)
Onset of breastfeeding	Number of days until first entry in <i>Daily Care Fluids and Feeding</i> of <ul style="list-style-type: none"> • ENTERAL FEED TYPE GIVEN = code 1 (Breastfeeding) OR <ul style="list-style-type: none"> • ENTERAL FEEDING METHOD = code 1 (breast) 	Continuous, integers
Time to first maternal breast milk feed	First day on which a baby is recorded to be receiving maternal breast milk by any route (including suckling at the breast, by bottle or nasogastric tube) defined as <i>Daily Care Fluids and Feeding</i> of <ul style="list-style-type: none"> • ENTERAL FEED TYPE GIVEN = code 1 (Breastfeeding); 2 (Mothers fresh expressed breast milk); 3 (Mothers frozen expressed breast milk); 4 (Donor expressed breast milk) OR	Continuous, integers

Supplemental table 3: Extraction procedures and definitions of outcome variables

Variable	Data items from NNRD	Definition
	<ul style="list-style-type: none"> • ENTERAL FEEDING METHOD = code 1 (breast) 	
Number of days a baby has a central venous line in situ	Defined as the number of days that has a baby has: <ul style="list-style-type: none"> • <i>Daily Care Fluids and Feeding</i> VASCULAR LINE TYPE IN SITU = code 3 (Umbilical venous line); 4 (Percutaneous central venous line ('long line')); 5 (Surgically inserted central venous line) 	Continuous, integers
Weight SDS at discharge	Defined as the following data item on the final day of neonatal care: <ul style="list-style-type: none"> • <i>Daily Care General Information</i> PERSON WEIGHT IN GRAMS If final day is not entered, the penultimate day is used	Continuous

Statistical methods: Propensity modelling

We fitted a propensity model in which the observed intervention group as the outcome is related to the background variables. The outcome variable in propensity analysis is binary, so logistic regression is applied. Since we had many background (confounding) variables, a model had to be selected from multiple candidate models. We followed the step-wise approach proposed by Imbens and Rubin¹. The background variables classified as being *highly important* were included in the model *a priori*. Models were then fitted with each of the remaining background variables added individually. The model with the largest value of the chi-squared statistic (with one degree of freedom) was adopted, if the test statistic exceeded 1.0. This procedure constitutes one cycle. In the next and following cycles, all the remaining background variables were tested similarly and the one with the largest value of the chi-squared statistic was retained. The cycles were stopped when none of the chi-squared statistics for including a covariate exceeded 1.0 and the variables included in the model at this point are referred to as the main effects.

Next interactions were selected for the propensity model. The main effects were sorted in descending order of their absolute t-ratios ($|estimate/st. error|$). For each variable A we formed a list of variables B for which the interaction $A \times B$ was an appropriate candidate for inclusion. For example, no two categories of a discrete variable could appear in an interaction. A continuous variable could be interacted with itself (the result is the quadratic transformation of the variable), but a binary variable could not. Similarly, a variable could not be interacted with its missing value indicator.

Starting with the first covariate we fitted the models with one interaction of this covariate added and selected up to two of the interactions that have the largest values of the chi-squared statistic for inclusion, subject to the condition that they exceeded 2.71 (the 10th percentile of the chi-squared distribution with 1 degree of freedom). When an interaction $A \times B$ was adopted (added to the model), the interaction $B \times A$ was removed from the list of candidate interactions, to avoid singularity in the model search that followed. After the interactions of the first covariate, the interactions of the second and successive covariates were tested and the model was expanded by the interactions found most important, subject to the constraint of including at most two interactions in each cycle.

The concluding model yielded the fitted propensities – the estimated probabilities of being assigned to the groups receiving enteral feeds, given each baby's background profile. Thus, each baby was associated with a (fitted) propensity. The set of babies in the analysis was then reduced by excluding babies with extreme propensities; first, by reducing to the subjects in the overlap of intervention and control group. That is, let the propensities in the two groups be in the respective ranges (m_1, M_1) and (m_2, M_2) . Then all subjects with propensities smaller than $m = \max(m_1, m_2)$ and greater than $M = \min(M_1, M_2)$ were excluded. Another criterion, described in Imbens and Rubin¹, was applied to reduce the sampling variance of the average treatment effect to be evaluated. It yields a positive constant $\gamma < 1$. Subjects with propensities outside the range $(\gamma, 1 - \gamma)$ were discarded from the analysis. Such reduction of the dataset by discarding subjects with extreme propensities is referred to as trimming.

Next, the entire modelling exercise, with selection of the main effects (added to the covariates selected a priori) and selection of the interactions was repeated on the reduced (trimmed) dataset. This was followed by discarding subjects with extreme propensities (fitted by the revised model). Trimming was applied after each stage of model selection.

The variables in each final propensity model have no interpretation for inference. The sole purpose of the propensity model is to facilitate a good balance of all the background variables in matched groups.

Statistical methods: Matching on propensity scores

To form matched subgroups, we first formed background groups based on unique combinations of the two principal background variables. Four birth year groups (as birth year is grouped according to two-year bands) crossed with three cord blood pH groups generate 12 background groups. We then defined propensity groups within each background group by recoding the propensities to a set of (propensity) groups separated by cutpoints. An established method splits the propensities into K groups of approximately equal size. We use $K = 10$ to form propensity score deciles. Within each background group, a baby who received parenteral nutrition was paired to a randomly drawn baby that did not receive parenteral nutrition who fell within the same propensity group. After the matching process was complete, the matched pairs of babies were reconstituted as the intervention group (received parenteral nutrition) and control group (no parenteral nutrition) and termed the *matched cohort*. Since this matching procedure involves some randomness, it was replicated 25 times to

produce 25 matched cohorts. Every subsequent analysis is conducted separately for each matched cohort and the (replicate) results are averaged to reduce the impact of the uncertainty involved in matching.

Statistical methods: Assessment of the quality of the match

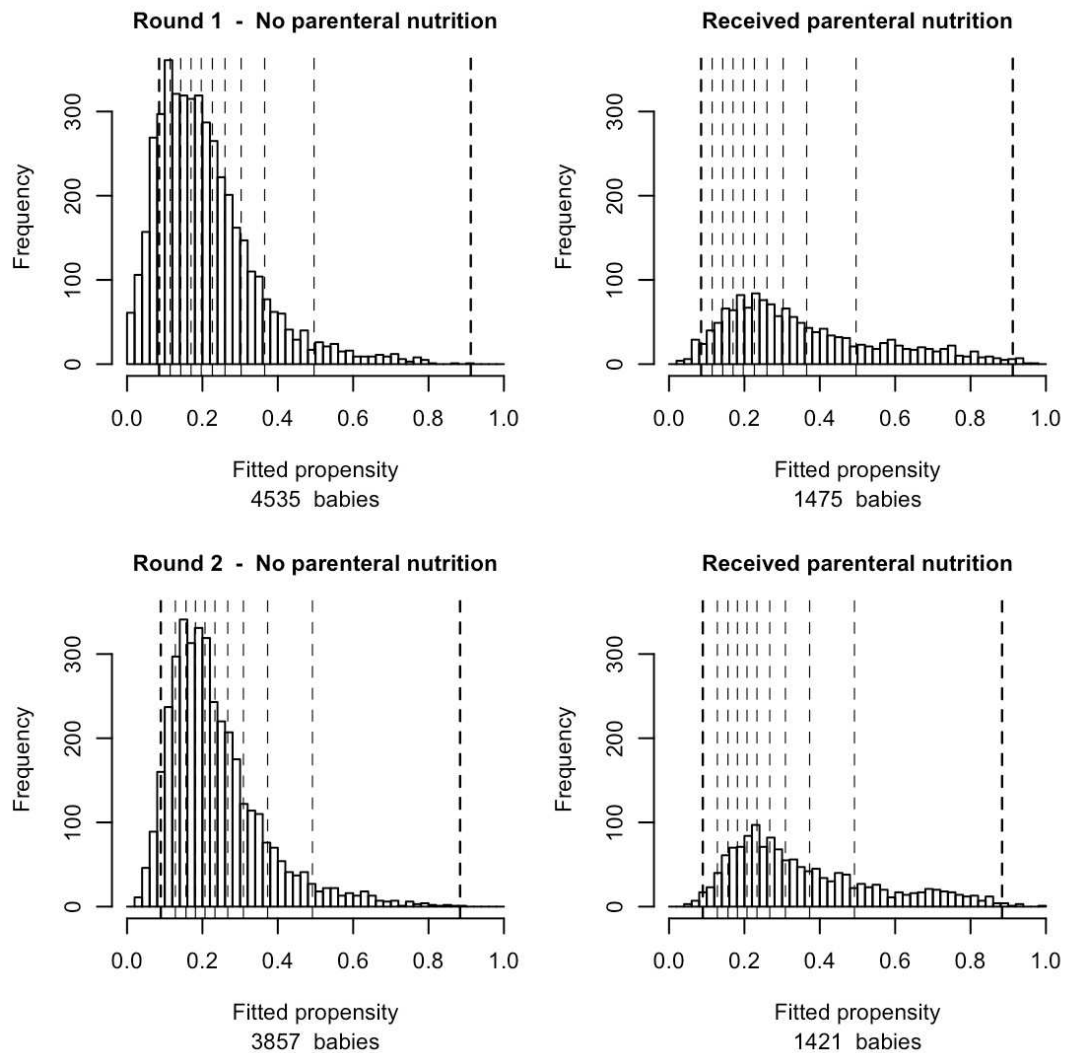
The selected (or any other) propensity model has no interpretation for inference; its sole purpose is to facilitate the formation of an exposure and control group (the matched cohorts) for analysis that is well balanced with regard to measured background variables. It was essential that no outcome variables, or more precisely, no variables that have differing potential outcomes, were involved in this stage. The motivation for this is that the background should be considered in earnest, and that this is done with no fore-knowledge of the outcomes. Accordingly, assessing the balance on all the background variables is the only relevant diagnostic for the fitted propensities.

The imbalance of an ordinal variable across two groups is defined as the difference of the within-group means divided by the standard deviation pooled across the two groups. The absolute imbalance is defined as the absolute value of the imbalance. The imbalance for a set of ordinal variables is defined as the mean of the absolute imbalances of the variables. We used this statistic as a summary or characteristic of the (overall) imbalance of two (sub-) groups. Smaller values indicate tighter balance. Imbens and Rubin¹ regard the balance of a variable as satisfactory if its absolute imbalance is smaller than 0.1. For a dataset, original or formed by matching, we report the total of the absolute imbalances and the largest and smallest imbalances. Variables that are not ordinal, that is, categorical variables, are avoided by defining indicator (dummy) variables; $H - 1$ indicators for a variable with H categories. The choice of the 'omitted' (reference) category is immaterial.

Supplemental figure 1 presents histograms of the estimated propensity scores from the final propensity model by intervention (received parenteral nutrition) and control (no parenteral nutrition) groups. There is good overlap of the propensity scores in the exposure and control groups, so many matched pairs can be formed. Data from 687 babies (11.4% of unmatched sample) were discarded due to extreme propensities.

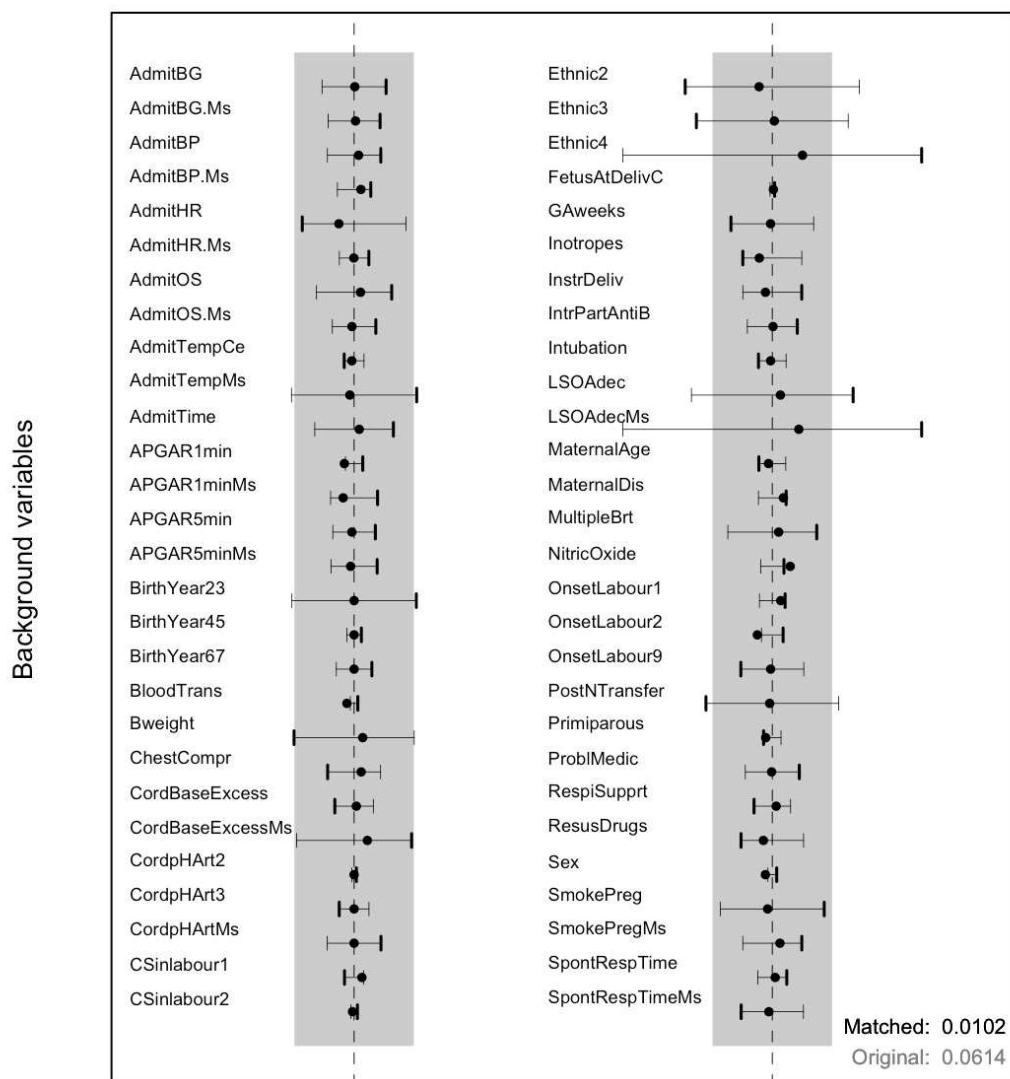
Supplemental figure 2 presents the balance plot for the background variables included in the comparison propensity model. The dashed grey line indicates perfect balance between the groups for a specific background variable. The grey shaded area indicates the acceptable limits of imbalance for any variable, equivalent to an imbalance of ≤ 0.1 in absolute value. The imbalance for a specific background variable in the unmatched cohort is depicted by the bold dash and the light dash indicates the opposite of this imbalance (imbalance multiplied by -1), which represents the same extent of imbalance. The imbalance in the matched cohort is marked by the black disc. The balances for the background variables are summarised by the mean of their absolute values. Prior to matching the mean balance is 0.061, and the balances are in the range from -0.215 to 0.563. The mean balance for the matched dataset is 0.010, and the balances are between -0.025 and 0.051. The mean balances are displayed in Supplemental figure 2.

Supplemental figure 1: Histograms of estimated propensity scores. Thick vertical dashed lines indicate trimming thresholds for extreme propensities, thin vertical dashed lines indicate propensity deciles for babies retained for analysis



Supplemental figure 2: Balance plot (1:1 matching within propensity score deciles). The grey shaded area covers the region of acceptable balances, -0.1 to 0.1

Parenteral nutrition - matching on prp deciles within background groups



Prp=propensity; AdmitBG=admission glucose; Ms= data for this item were missing; AdmitBP=admission blood pressure; AdmitHR=admission heart rate; AdmitOS=admission?; AdmitTempCe=admission temperature; AdmitTime=admission time; APGAR=Apgar score; min=minute; BloodTrans=blood transfusion on day 1; Bweight=birthweight; ChestCompr=chest compressions at resuscitation; CordBaseExcess=umbilical cord base excess; CordpHArt=Umbilical arterial pH; CSinLabour=In-labour Caesarean section; FetusAtDelivC=presentation of fetus at delivery; GAweeks=gestational age in weeks; InstrDeliv=Instrumental delivery; IntrPartAntiB=intrapartum antibiotics; LSOAdec=Lower Super Output Area decile; MaternalDis=maternal obstetric condition; MultipleBrt=multiple birth set; OnsetLabour=spontaneous/induced labour; PostNTransfer=postnatal transfer; ProbMedic=maternal medical condition in pregnancy; RespiSupprt=Received respiratory support on day of admission; ResusDrugs=received drugs during resuscitation; SmokePreg=Maternal smoking in pregnancy; SpontRespTime=time to first breath

Supplemental table 4: Estimates of the effect of receiving parenteral nutrition for binary and continuous outcomes from sensitivity analyses. Results averaged over the 25 replications of the matching procedure

Variable	Sensitivity analysis		
	Years 12-17	Intervention redefined	Inclusion of enteral nutrition on day 1 in propensity score
N	2118	2506	2502
<i>Binary outcomes: Estimate of rate difference [95% CI] (p-value)</i>			
NEC (pragmatic definition)	0.6 [0.0, 1.2] (0.04)	0.6 [0.1, 1.1] (0.02)	0.6 [0.0, 1.1] (0.03)
Late onset BSI (NNAP definition)	2.2 [-0.8, 5.3] (0.15)	1.4 [-1.4, 4.2] (0.34)	1.7 [-1.0, 4.5] (0.22)
Late onset BSI (pragmatic definition)	-0.4 [-1.2, 0.4] (0.34)	-0.2 [-0.9, 0.5] (0.62)	-0.3 [-1.0, 0.4] (0.36)
Hypoglycaemia	-1.4 [-4.0, 1.3] (0.32)	-2.1 [-4.5, 0.3] (0.08)	-2.1 [-4.6, 0.3] (0.08)
Survival at discharge	2.8 [0.9, 4.8] (0.004)	3.0 [1.2, 4.7] (<0.001)	3.8 [2.0, 5.5] (<0.001)
Breastfeeding at discharge	-0.2 [-3.7, 3.3] (0.90)	-0.1 [-3.3, 3.1] (0.96)	0.4 [-2.8, 3.5] (0.82)
<i>Continuous outcomes: mean difference [95% CI] (p-value)</i>			
Length of stay	0.5 [-0.5, 1.4] (0.32)	0.6 [-0.3, 1.6] (0.16)	1.0 [0.1, 1.9] (0.02)
First day of suckling at breast	-0.2 [-0.7, 0.3] (0.51)	0.1 [-0.4, 0.7] (0.63)	0.0 [-0.5, 0.6] (0.88)
First day of maternal milk	-0.3 [-0.5, -0.1] (0.004)	-0.2 [-0.4, -0.1] (0.01)	-0.2 [-0.4, -0.1] (0.01)
Duration of PN	0.8 [0.4, 1.2] (<0.001)	0.9 [0.5, 1.2] (<0.001)	0.9 [0.6, 1.2] (<0.001)
Duration of CV line	0.01 [-0.08, 0.10] (0.88)	0.03 [0.0, 0.1] (0.42)	0.01 [-0.07, 0.09] (0.80)
Z score of at discharge	0.5 [-0.5, 1.4] (0.32)	0.6 [-0.3, 1.6] (0.16)	1.0 [0.1, 1.9] (0.02)

Abbreviations: BSI=blood stream infection; CI=confidence interval; CV=central venous; NEC=necrotising enterocolitis; NNAP=National Neonatal Audit Programme

References

1. Imbens GW, Rubin DB. *Causal Inference for Statistics, Social, and Biomedical Science. An Introduction*. New York: Cambridge University Press; 2015

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 Birmingham Women's Hospital
 Bradford Royal Infirmary
 Broomfield Hospital, Chelmsford
 Calderdale Royal Hospital
 Chelsea & Westminster Hospital
 Chesterfield & North Derbyshire Royal Hospital
 Colchester General Hospital
 Conquest Hospital
 Countess of Chester Hospital
 Croydon University Hospital
 Cumberland Infirmary
 Darent Valley Hospital
 Darlington Memorial Hospital
 Derriford Hospital
 Diana Princess of Wales Hospital
 Doncaster Royal Infirmary
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 East Surrey Hospital
 Epsom General Hospital
 Frimley Park Hospital
 Furness General Hospital
 George Eliot Hospital
 Gloucester Royal Hospital
 Good Hope Hospital
 Great Western Hospital
 Guy's & St Thomas' Hospital
 Harrogate District Hospital
 Hereford County Hospital
 Hillingdon Hospital
 Hinchingsbrooke Hospital
 Homerton Hospital
 Hull Royal Infirmary
 Ipswich Hospital
 James Cook University Hospital
 James Paget Hospital
 Kettering General Hospital
 Kings College Hospital
 King's Mill Hospital
 Kingston Hospital
 Lancashire Women and Newborn Centre
 Leeds Neonatal Service
 Leicester General Hospital
 Leicester Royal Infirmary
 Leighton Hospital
 Lincoln County Hospital
 Lister Hospital
 Liverpool Women's Hospital
 Luton & Dunstable Hospital
 Macclesfield District General Hospital
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