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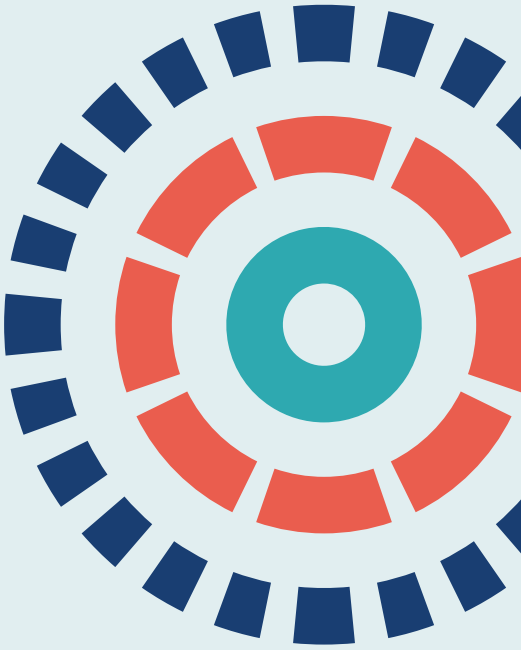

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Nutritional management in newborn babies receiving therapeutic hypothermia: two retrospective observational studies using propensity score matching

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This report

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Abstract

Nutritional management in newborn babies receiving therapeutic hypothermia: two retrospective observational studies using propensity score matching

Chris Gale,[1*] Dusha Jeyakumaran,[1] Cheryl Battersby,[1] Kayleigh Ougham,[1] Shalini Ojha,[2] Lucy Culshaw,[3] Ella Selby,[3] Jon Dorling[4] and Nicholas Longford[1]

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Background: Therapeutic hypothermia is standard of care for babies with moderate to severe hypoxic–ischaemic encephalopathy. There is limited evidence to inform provision of nutrition during hypothermia.

Objectives: To assess the association during therapeutic hypothermia between (1) enteral feeding and outcomes, such as necrotising enterocolitis and (2) parenteral nutrition and outcomes, such as late-onset bloodstream infection.

Design: A retrospective cohort study using data held in the National Neonatal Research Database and applying propensity score methodology to form matched groups for analysis.

Setting: NHS neonatal units in England, Wales and Scotland.

Participants: Babies born at ≥ 36 gestational weeks between 1 January 2010 and 31 December 2017 who received therapeutic hypothermia for 72 hours or who died during treatment.

Interventions: Enteral feeding analysis – babies who were enterally fed during therapeutic hypothermia (intervention) compared with babies who received no enteral feeds during therapeutic hypothermia (control). Parenteral nutrition analysis – babies who received parenteral nutrition during therapeutic hypothermia (intervention) compared with babies who received no parenteral nutrition during therapeutic hypothermia (control).

Outcome measures: Primary outcomes were severe and pragmatically defined necrotising enterocolitis (enteral feeding analysis) and late-onset bloodstream infection (parenteral nutrition analysis). Secondary outcomes were survival at neonatal discharge, length of neonatal stay, breastfeeding at discharge, onset of breastfeeding, time to first maternal breast milk, hypoglycaemia, number of days with a central line in situ, duration of parenteral nutrition, time to full enteral feeds and growth.

Results: A total of 6030 babies received therapeutic hypothermia. Thirty-one per cent of babies received enteral feeds and 25% received parenteral nutrition. Seven babies (0.1%) were diagnosed with severe necrotising enterocolitis, and further comparative analyses were not conducted on this outcome. A total of 3236 babies were included in the matched enteral feeding analysis. Pragmatically defined necrotising enterocolitis was rare in both groups (0.5% vs. 1.1%) and was lower in babies who

were fed during hypothermia (rate difference −0.5%, 95% confidence interval −1.0% to −0.1%; $p = 0.03$). Higher survival to discharge (96.0% vs. 90.8%, rate difference 5.2%, 95% confidence interval 3.9% to 6.6%; $p < 0.001$) and higher breastfeeding at discharge (54.6% vs. 46.7%, rate difference 8.0%, 95% confidence interval 5.1% to 10.8%; $p < 0.001$) rates were observed in enterally fed babies who also had a shorter neonatal stay (mean difference −2.2 days, 95% confidence interval −3.0 to −1.2 days). A total of 2480 babies were included in the matched parenteral nutrition analysis. Higher levels of late-onset bloodstream infection were seen in babies who received parenteral nutrition (0.3% vs. 0.9%, rate difference 0.6%, 95% confidence interval 0.1% to 1.2%; $p = 0.03$). Survival was lower in babies who did not receive parenteral nutrition (90.0% vs. 93.1%, rate difference 3.1%, 95% confidence interval 1.5% to 4.7%; $p < 0.001$).

Limitations: Propensity score methodology can address imbalances in observed confounders only. Residual confounding by unmeasured or poorly recorded variables cannot be ruled out. We did not analyse by type or volume of enteral or parenteral nutrition.

Conclusions: Necrotising enterocolitis is rare in babies receiving therapeutic hypothermia, and the introduction of enteral feeding is associated with a lower risk of pragmatically defined necrotising enterocolitis and other beneficial outcomes, including rates of higher survival and breastfeeding at discharge. Receipt of parenteral nutrition during therapeutic hypothermia is associated with a higher rate of late-onset infection but lower mortality. These results support introduction of enteral feeding during therapeutic hypothermia.

Future work: Randomised trials to assess parenteral nutrition during therapeutic hypothermia.

Trial registration: Current Controlled Trials ISRCTN474042962.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 36. See the NIHR Journals Library website for further project information.

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List of abbreviations

BSI	bloodstream infection
CI	confidence interval
HIE	hypoxic–ischaemic encephalopathy
IPW	inverse probability weighting
LSOA	lower-layer super output area
NEC	necrotising enterocolitis
NNAP	National Neonatal Audit Programme
NNRD	National Neonatal Research Database
ODN	operational delivery network
OR	odds ratio
PEPaNIC	Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit
PN	parenteral nutrition
RCT	randomised controlled trial
SD	standard deviation
UKNC	UK Neonatal Collaborative

Plain English summary

Every year, approximately 1200 babies in the UK suffer a lack of oxygen to the brain around birth. This is called hypoxic–ischaemic encephalopathy and can lead to brain injury or death. To treat hypoxic–ischaemic encephalopathy, babies receive cooling treatment in which their body temperature is lowered.

Doctors do not know the best way to give nutrition to babies receiving cooling treatment. Babies can either be fed milk into their stomach (enteral nutrition) or be given nutrients through their veins (parenteral nutrition). We compared babies who were fed milk while they were being cooled with babies from whom milk was withheld while they were being cooled to see if there was a difference in the frequency of necrotising enterocolitis, a severe gut disease. In addition, we compared babies who received parenteral nutrition while they were being cooled with babies who did not to see if there was a difference in infections. Finally, we looked at other outcomes, including survival and breastfeeding.

We used the National Neonatal Research Database, which holds de-identified (i.e. no baby can be identified) information on all babies who have received NHS neonatal care. We used a statistical approach to match babies in each group (i.e. fed babies and not fed babies) as closely as possible so that any difference in outcomes was because of different nutrition and not because of other differences.

We included > 6000 babies with hypoxic–ischaemic encephalopathy. Approximately one in three babies received milk feeds and one in four babies received parenteral nutrition during cooling. Necrotising enterocolitis was very rare.

More babies who were fed milk during cooling had good outcomes (e.g. being breastfed at discharge) and fewer had necrotising enterocolitis. Most of these babies received only a small amount of milk in the first 3 days. More babies given parenteral nutrition had infections, but also more survived.

This suggests that it is probably safe and may be beneficial to feed babies milk during cooling. More research should look at milk feeding and parenteral nutrition during cooling.

Scientific summary

Background

Therapeutic hypothermia is standard of care for babies born at ≥ 36 gestational weeks with hypoxic–ischaemic encephalopathy in high-income settings. There is limited evidence to inform provision of nutrition during therapeutic hypothermia, and nutritional practice varies widely.

Nutritional management has two main components: (1) enteral nutrition in the form of milk feeds and (2) parenteral (intravenous) nutrition. We sought to identify optimal nutritional strategies for term and near-term infants receiving therapeutic hypothermia. We examined the enteral and parenteral components independently.

Objectives

The primary objective of the enteral feeding analysis was to assess the association between milk feeding during therapeutic hypothermia and the incidence of necrotising enterocolitis.

The primary objective of the parenteral nutrition analysis was to assess the association between administering parenteral nutrition during therapeutic hypothermia and the incidence of bloodstream infection after the first 3 days.

The following secondary outcomes were also evaluated: survival at discharge from the neonatal unit, length of neonatal stay, hypoglycaemia, time to first feed with maternal breast milk, onset of breastfeeding, breastfeeding at discharge, number of days with a central line in situ and weight at neonatal discharge. The number of days parenteral nutrition was administered was examined only for the enteral comparison.

Methods

This was a retrospective, population-based cohort study using data held in the National Neonatal Research Database and applying propensity score methodology to form matched groups for analysis.

Data source

The National Neonatal Research Database holds de-identified routinely recorded clinical data from all infants admitted to NHS neonatal units in England, Scotland and Wales. A defined data extract (i.e. the Neonatal Data Set) of approximately 450 data items is extracted quarterly from neonatal electronic health records that have been completed by health professionals during routine clinical care. A patient-level data set was extracted from the National Neonatal Research Database for this analysis. Data linkage with other databases was not performed for this study.

Participants

We included babies born and admitted to NHS neonatal units in England, Scotland or Wales between 1 January 2010 and 31 December 2017 with a gestational age of $\geq 36^{+0}$ weeks$^{+\text{days}}$ at birth and who received therapeutic hypothermia for at least 3 days or died during therapeutic hypothermia.

Comparator groups

We undertook two comparisons in matched groups:

1. enteral feeding analysis [babies who were enterally fed during therapeutic hypothermia (intervention) compared with babies who received no enteral feeds during therapeutic hypothermia (control)]
2. parenteral nutrition analysis [babies who were receiving parenteral nutrition during therapeutic hypothermia (intervention) compared with babies who received no parenteral nutrition during therapeutic hypothermia (control)].

Outcomes

The primary outcome for the enteral feeding analysis was severe necrotising enterocolitis confirmed at surgery or causing death and validated with neonatal units. The primary outcome for the parenteral nutrition analysis was late-onset bloodstream infection confirmed by pure growth of a known pathogen.

Secondary outcomes were necrotising enterocolitis using a pragmatic definition (i.e. a record of necrotising enterocolitis with 5 consecutive days of antibiotics while nil by mouth), late-onset infection using a pragmatic definition (i.e. 5 consecutive days of antibiotics commenced after day 3), survival at neonatal discharge, length of neonatal stay, breastfeeding at discharge, hypoglycaemia during neonatal unit stay, onset of breastfeeding, time to first maternal breast milk feed, number of days with a central line in situ, duration of parenteral nutrition, time taken to reach full enteral feeds and weight for gestation standard deviation score at neonatal discharge.

Background variables used for matching

The following background variables were used to form matched groups for the enteral feeding and parenteral nutrition comparisons: birth year, umbilical arterial pH, birthweight, gestational age, sex, resuscitation factors, mode of delivery, maternal factors (i.e. smoking, suspected chorioamnionitis, medical and obstetric conditions), Apgar score at 1 and 5 minutes, umbilical cord blood base excess, condition at first neonatal unit admission (i.e. oxygen saturation, blood glucose concentration and mean blood pressure), maximum support needed on day 1 (i.e. respiratory, inotropic and transfusion of blood products), maternal socioeconomic decile and postnatal transfer within 24 hours.

Statistical methods

Analyses applied the potential outcomes framework and propensity score methodology. We performed 1 : 1 matching of babies who had no enteral feeds to those who were enterally fed for the enteral nutrition analysis, and of babies who received no parenteral nutrition to those who received parenteral nutrition for the parenteral nutrition analysis. Background groups were first defined using birth year (four 2-year bands) and arterial umbilical cord pH (three categories), giving 12 groups in total. Matched pairs were then formed within propensity score deciles defined separately for each background group. The matched pairs were then reconstituted as an intervention group (i.e. babies who received enteral feeds or parenteral nutrition) and a control group (i.e. babies who did not receive enteral feeds or parenteral nutrition). Their outcomes were compared using methods appropriate if the two matched groups arose in a randomised controlled trial. We undertook prespecified sensitivity analyses limited to babies born in 2012–17, when the geographical coverage was more complete, and using alternative definitions of enteral feeds or parenteral nutrition. We undertook post hoc sensitivity analyses when

parenteral nutrition or enteral feeds on day 1 were included within the propensity model for the enteral feeding and parenteral nutrition analyses, respectively.

Parent and patient involvement

The study was planned and designed by a multiprofessional investigator group that included a parent of a baby who had received therapeutic hypothermia and a parent representative. Study outcomes were chosen to reflect those prioritised as important by parents, patients and professionals, and were informed by parents and parent representatives.

Results

Between 1 January 2010 and 31 December 2017, a total of 703,911 babies were admitted to NHS neonatal units in England, Scotland and Wales, and 6030 were at ≥ 36 weeks' gestational age and treated with therapeutic hypothermia for 3 days or died during treatment. Of these babies, 31.1% received enteral feeds and 24.5% received parenteral nutrition during therapeutic hypothermia. These proportions changed only slightly over time. When enteral feeds were given during therapeutic hypothermia these were most commonly maternal breast milk.

In the total study cohort and prior to matching, seven babies (0.1%) who received therapeutic hypothermia were diagnosed with severe necrotising enterocolitis and 68 babies (1.1%) were classified as having necrotising enterocolitis when using the more pragmatic definition. Thirty babies (0.5%) had a pure growth of a recognised pathogen in a blood culture after day 3. Pragmatically defined late-onset infection was more common, with 1559 cases (25.5%). Breastfeeding at discharge was recorded for 2784 babies (46.2%) and the proportion increased over the study period. Among babies who did suckle at the breast, the first breastfeed was at a median age of 7 days (interquartile range 6–9 days), and among babies who were fed maternal breast milk the median age at first receipt of maternal breast milk was 5 days (interquartile range 4–6 days). Survival to discharge rates were high ($n = 5444$, 90.3%). The median length of stay in the neonatal unit was 11 days (interquartile range 8–16 days). Most babies ($n = 5640$, 93.6%) had a central line placed in situ for a median duration of 5 days (interquartile range 3–6 days). A total of 1208 babies (20.0%) had an episode of hypoglycaemia recorded during their neonatal stay.

For the primary enteral feeding analysis, a matched cohort of 3236 babies (1618 pairs) was formed and good balance was achieved for all recorded background variables. The incidence of severe necrotising enterocolitis was so low that comparative analyses were not undertaken. Following matching, the incidence of pragmatically defined necrotising enterocolitis was lower among babies fed ($n = 9$, 0.5%) than among those not fed ($n = 18$, 1.1%) during therapeutic hypothermia (rate difference −0.5%, 95% confidence interval −1.0% to 0.1%; $p = 0.03$). The rate of culture-positive late-onset infection was similar for babies fed ($n < 5$, 0.3%) and those not fed ($n = 8$, 0.5%) (rate difference −0.2%, 95% confidence interval −0.5% to 0.1%; $p = 0.19$). However, pragmatically defined late-onset infection was less common in babies who were fed ($n = 271$, 16.8%) than in babies who were not fed ($n = 460$, 28.4%) (rate difference −11.6%, 95% confidence interval −14.0% to −9.3%; $p < 0.001$). Survival to discharge rates were higher in babies who were fed ($n = 1552$, 96.0%) than in babies who were not fed ($n = 1465$, 90.6%) (rate difference 5.2%, 95% confidence interval 3.9% to 6.6%; $p < 0.001$), as was rates of breastfeeding at discharge [babies who were fed ($n = 883$), 54.6%; babies who were not fed ($n = 752$), 46.5%; rate difference 8.0%, 95% confidence interval 5.1% to 10.8%; $p < 0.001$]. The incidence of recorded hypoglycaemia was similar in babies fed ($n = 269$, 16.6%) and babies not fed ($n = 293$, 18.1%) (rate difference −1.5%, 95% confidence interval −3.7% to 0.6%; $p = 0.17$). The weight for gestation standard deviation score at neonatal unit discharge was also similar (babies fed −0.7 vs. babies not fed −0.6, difference 0.06, 95% confidence interval −0.01 to 0.13).

The first breastfeed was earlier, on average, for babies who were fed during therapeutic hypothermia (mean 7.3 days) than for those babies not fed (mean 8.7 days) (difference −1.4 days, 95% confidence interval −1.9 to −0.9 days; $p < 0.001$), and the first breast milk feed was earlier in babies fed (mean 3.3 days) than in those babies not fed (mean 5.4 days) (difference −2.1 days, 95% confidence interval −2.2 to −2.0 days; $p < 0.001$). The length of neonatal unit stay was shorter for babies who were fed (mean 12.7 days) than for those babies who were not fed (mean 14.8 days) (difference −2.2 days, 95% confidence interval −3.0 to −1.2 days; $p < 0.001$), as was duration of parenteral nutrition (babies fed mean 3.0 days vs. babies not fed mean 3.7 days, difference −0.7 days, 95% confidence interval −1.1 to −0.2 days; $p = 0.02$) and number of days with a central line in situ (babies fed mean 4.3 days vs. babies not fed 5.5 days, difference −1.2 days, 95% confidence interval −1.5 to −0.9 days). These findings were robust to sensitivity analyses.

For the parenteral nutrition analysis, matched cohorts consisting of 2480 babies (i.e. 1240 pairs) were formed. The two matched groups were well balanced on all of the observed background variables. Following matching, the rate of culture-positive late-onset infection was higher for babies who received parenteral nutrition ($n = 11$, 0.9%) than for those who did not ($n < 5$) (rate difference 0.6%, 95% confidence interval 0.1% to 1.2%; $p = 0.03$); however, pragmatically defined late-onset infection was seen at similar rates among those babies who received parenteral nutrition ($n = 323$, 26.1%) and those babies who received no parenteral nutrition ($n = 313$, 25.3%) (rate difference 0.8%, 95% confidence interval −2.1% to 3.6%; $p = 0.61$). The incidence of severe necrotising enterocolitis was low and comparative analyses were not undertaken for this outcome. The incidence of pragmatically defined necrotising enterocolitis was similar for babies who received parenteral nutrition (11 babies, 1.1%) and for those who did not (17 babies, 1.4%) (rate difference −0.3%, 95% confidence interval −1.0% to 0.4%; $p = 0.39$). Survival to discharge rates were higher for babies who received parenteral nutrition ($n = 1154$, 93.1%) than for those babies who did not ($n = 1116$, 90.0%) (rate difference 3.1%, 95% confidence interval 1.5% to 4.7%; $p < 0.001$). The rates of breastfeeding at discharge [parenteral nutrition, $n = 575$ (46.4%), vs. no parenteral nutrition, $n = 582$ (47.0%); rate difference −0.6%, 95% confidence interval −3.8% to 2.6%; $p = 0.71$] and recorded hypoglycaemia [parenteral nutrition, $n = 212$ (17.1%), vs. no parenteral nutrition, $n = 235$ (18.9%), rate difference −2.1%, 95% confidence interval −4.5% to 0.4%; $p = 0.10$] were similar in the two groups, as was weight for gestation standard deviation score at neonatal unit discharge (parenteral nutrition −0.6 vs. no parenteral nutrition −0.7, difference 0.02, 95% confidence interval −0.07 to 0.10; $p = 0.68$). The first breastfeed was at a similar age in babies who received parenteral nutrition (mean 8.6 days) and in those babies who did not (mean 8.4 days) (difference 0.2 days, 95% confidence interval −0.5 to 0.8 days; $p = 0.56$). In addition, age at first milk feed was similar in babies who received parenteral nutrition (mean 4.6 days) and in those babies who did not (mean 4.9 days) (difference −0.2 days, 95% confidence interval −0.4 to −0.1; $p = 0.01$). The length of neonatal unit stay was also similar for babies who received parenteral nutrition (mean 15.0 days) and for those babies who did not (mean 14.1 days) (difference 0.8 days, 95% confidence interval −0.2 to 1.8 days; $p = 0.12$). The duration of time that a baby had a central line in situ was higher in babies who received parenteral nutrition (6.0 days) than in those babies who did not (5.1 days) (difference 0.9 days, 95% confidence interval 0.5 to 1.2 days; $p < 0.001$). These findings were robust to sensitivity analyses.

Conclusions

Approximately one in three babies who receive therapeutic hypothermia in NHS neonatal units have enteral feeds introduced during hypothermia, predominantly with maternal breast milk. Necrotising enterocolitis is rare in these babies. After matching for an extensive list of background characteristics, pragmatically defined necrotising enterocolitis was diagnosed at a lower rate among babies for whom feeds were introduced during therapeutic hypothermia. Introduction of milk feeding during therapeutic hypothermia was also associated with beneficial outcomes, including shorter lengths of stay, higher rates of breastfeeding and a lower incidence of suspected infection, after matching for multiple

potential confounding factors. This was an observational study in which matched groups were formed using propensity score methodology. The study was able to address confounding related to measured factors only. Survival to discharge rates were higher for babies who were fed than for babies who were not fed during therapeutic hypothermia. This difference is unlikely to be explained by enteral feeding and, therefore, suggests residual confounding by indication, favouring babies who received milk feeds. Despite this limitation we conclude that initiating milk feeds, preferably maternal breast milk, during therapeutic hypothermia appears safe and may be beneficial.

One in four babies who received therapeutic hypothermia in NHS neonatal units received parenteral nutrition during hypothermia. Culture-positive infection was rare in this group, but after matching for multiple background characteristics it was more common in babies who received parenteral nutrition. This accords with data from a randomised controlled trial in neonates on paediatric intensive care units, in which early provision of parenteral nutrition led to a higher incidence of infection. In contrast, we found that survival until neonatal unit discharge was higher in babies who received parenteral nutrition than in those babies who did not. This may reflect residual confounding by indication, favouring babies who received parenteral nutrition. Optimal parenteral nutritional support for babies receiving therapeutic hypothermia is unknown and could not be established in this large observational study using population-level routinely recorded neonatal clinical data.

Despite the importance of longer-term developmental outcomes in this population we were unable to examine such end points in this study because population-level neurodevelopmental follow-up data in these babies were highly incomplete.

Implications for health care

- The incremental introduction of enteral feeds in term and near-term babies during therapeutic hypothermia appears safe and may be associated with benefits including higher rates of breastfeeding at discharge and shorter lengths of stay.
- Necrotising enterocolitis is rare in term and near-term babies receiving therapeutic hypothermia and may be less common in babies who were fed during therapeutic hypothermia.

Recommendations for research (listed in priority order)

- Optimal use of parenteral nutrition for term and near-term babies receiving therapeutic hypothermia is unknown. This should be examined in a randomised controlled trial comparing early with delayed provision of parenteral nutrition, which should examine both short-term outcomes, such as late-onset infection and neonatal survival, and longer-term outcomes, such as neurodevelopment.
- Given our study findings and the rarity of important outcomes such as necrotising enterocolitis, in this cohort, future randomised controlled trials to examine enteral feeding during therapeutic hypothermia are unlikely to be warranted or feasible. The optimal speed of introduction of enteral feeds or optimal choice of milk when the mother's milk is not available are not known and may benefit from further research.
- Mechanisms to obtain population-level long-term outcome data for babies who receive neonatal care, such as data linkage and national reporting, should be prioritised.

Trial registration

This trial is registered as ISRCTN474042962.

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Chapter 1 Introduction

Background

In the UK and other high-income settings, therapeutic hypothermia is standard of care for babies who are born at ≥ 36 weeks' gestational age and show signs of hypoxic–ischaemic encephalopathy (HIE).[1] Although the administration of therapeutic hypothermia itself is well defined and based on high-quality randomised controlled trials (RCTs),[2] the optimal nutritional management of babies receiving this therapy is not. There are two primary components of nutritional management: (1) enteral nutrition in the form of milk feeds and (2) intravenous or parenteral nutrition (PN).

During therapeutic hypothermia, babies can have milk feeds introduced incrementally or can have milk feeds withheld (this is the enteral component of nutritional support). Babies who receive therapeutic hypothermia in high-income countries will be commenced on intravenous fluid shortly after admission. This is because they are often unable to effectively co-ordinate sucking and swallowing, regulate fluid balance or maintain glucose metabolism. This intravenous fluid may be an intravenous dextrose solution (with electrolytes, such as sodium and potassium, as required) or PN, which contains protein, fat, carbohydrate, minerals and vitamins (this is the parenteral component of nutritional support).

The lack of high-quality evidence to inform nutritional practice during therapeutic hypothermia leads to variation in the provision of both enteral and parenteral components of nutrition. A recent UK survey of nutrition practices during therapeutic hypothermia reported that only 31% of responding units have feeding guidelines for these babies, 59% of neonatal units report routinely starting enteral feeding and 29% of neonatal units report routinely administering PN during therapeutic hypothermia.[3] International practice is also mixed. In some settings withholding enteral feeds during therapeutic hypothermia is almost universal,[4] whereas in other settings starting and incrementing milk feeds is routine practice.[5]

A key reason for withholding enteral feeds during therapeutic hypothermia is the premise that this may reduce the risk of necrotising enterocolitis (NEC).[6] NEC is seen in term and near-term babies with HIE; however, its incidence is poorly reported. NEC was reported in only 3 of the 11 RCTs that evaluated therapeutic hypothermia in HIE and only one case was documented.[7–9] Furthermore, there is no evidence that withholding or delaying milk feeds is useful in preventing NEC, even among very preterm babies at high risk of the disease.[10,11] Conversely, there is some limited evidence that enteral feeding of babies with HIE during hypothermia may be associated with lower biochemical markers of systemic inflammation,[4] and the wider benefits of maternal breast milk feeding in term babies are well described.[12]

In relation to PN support, intravenous dextrose provides sufficient hydration and energy to prevent hypoglycaemia, but does not provide the protein and fat necessary for tissue growth. It is not known how a short period of undernutrition may impact growth or the secondary and tertiary recovery phases that follow brain injury.[3,13,14] Parenteral nutrition is nutritionally superior but leads to higher rates of infection and other adverse outcomes in RCTs in paediatric and adult intensive care settings.[15,16] Moreover, PN is expensive[17] and should, therefore, be used only when likely to be beneficial.

To address this paucity of high-quality evidence we aimed to identify optimal enteral and PN strategies for term and near-term babies receiving therapeutic hypothermia. As key outcomes such as NEC are rarely reported in this population, a RCT with power sufficient to analyse such outcomes is not feasible. We therefore undertook an observational study using routinely recorded data and applying propensity score matching to form groups for comparison with near-identical distributions of background variables.

Aims and objectives

Principal research questions

We sought to test the following null hypotheses:

- There is no difference in the incidence of NEC or other clinical outcomes between babies who are enterally fed during therapeutic hypothermia and those whose feeds are withheld.
- There is no difference in the incidence of late-onset bloodstream infection (BSI) or other clinical outcomes between babies who receive PN during therapeutic hypothermia and those who receive only intravenous dextrose and electrolytes.

Primary objectives

- The primary objective of the enteral feeding analysis was to assess the effect of enteral feeding during therapeutic hypothermia on the incidence of NEC.
- The primary objective of the PN analysis was to assess the effect of administering PN during therapeutic hypothermia on the incidence of BSI after the first 3 days.

Secondary objectives

In both analyses, the secondary objectives were to assess the effects of provision of enteral feeds and PN during therapeutic hypothermia on:

- survival until discharge from the neonatal unit
- length of neonatal stay
- incidence of hypoglycaemia
- breastfeeding at discharge
- onset of breastfeeding
- time to first feed with maternal breast milk
- number of days when a central line was in situ
- weight at neonatal discharge
- number of days PN was administered (this outcome was examined for the enteral comparison only).

Chapter 2 Methods

Study design

This was a retrospective, population-based, cohort study that used existing data held in the National Neonatal Research Database (NNRD) and applied propensity score methodology.

Setting

The study used data from all designations of NHS neonatal units (i.e. special care baby units, local neonatal units and neonatal intensive care units) in England, Scotland and Wales.[18] Data were extracted for babies born between 1 January 2010 and 31 December 2017 who were admitted to neonatal units contributing to the NNRD, with follow-up data recorded until neonatal unit discharge.

Data source

The NNRD holds de-identified routinely recorded clinical data from all babies admitted to participating NHS neonatal units in England, Scotland and Wales. All NHS neonatal units in England and Wales have contributed data to the NNRD since 2012. The majority of NHS neonatal units in Scotland have contributed data to the NNRD since 2015, with all NHS units contributing as of 2019. Contributing neonatal units are known as the UK Neonatal Collaborative (UKNC). Data are extracted from point-of-care neonatal electronic health records that are completed by health professionals during routine clinical care. A defined data extract, the Neonatal Data Set, of approximately 450 data items[19] is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London and Chelsea and Westminster Hospital NHS Foundation Trust, where data are checked for internal inconsistencies and duplicates. Data items include demographic and admission items (e.g. maternal conditions, gestation and birthweight), daily items (e.g. respiratory support and feeding information), discharge items (e.g. feeding and weight at discharge) and ad hoc items (entered if and when they occur, e.g. suspected infection, ultrasound scan findings and abdominal radiographic findings). A formal comparison of NNRD data with case record forms from a multicentre RCT showed high levels of data agreement.[20]

Access to the full NNRD database population is restricted to authorised users at the Neonatal Data Analysis Unit. A patient-level data set was extracted from the NNRD for the purpose of this analysis. Data linkage with any other database was not performed for this study.

Participants

Babies were eligible for inclusion in the study if they met the following criteria:

- were born and admitted to a NHS neonatal unit between 1 January 2010 and 31 December 2017
- received care at a neonatal unit in England, Scotland and Wales that was part of the UKNC and, therefore, contributing data to the NNRD
- had a recorded gestational age of $\geq 36^{+0}$ weeks$^{+\text{days}}$ at birth
- were recorded as receiving therapeutic hypothermia for 3 consecutive days during their neonatal unit stay or died during the period of therapeutic hypothermia.

Details of data extraction procedures are provided in *Appendix 1*, *Tables 22–24*.

Data imputation

Babies who had missing data for receipt of cooling on the second day of cooling, but who were recorded as having received cooling on both the first and the last day and who did not die during cooling, had data for the second day of cooling imputed. No other data imputation was performed.

Variables

The variables used in the analysis are described in this section and are grouped as intervention, background and outcome variables. A detailed description of the data extraction procedure and any transformations or recoding applied to variables during the analysis are provided in *Appendix 1*, *Tables 22–24*.

Variables that define interventions

There were two interventions of interest:

1. provision of enteral feeds during therapeutic hypothermia for the enteral nutrition analysis
2. provision of PN during therapeutic hypothermia for the PN analysis.

Definitions of the intervention and control groups for each analysis are provided in *Table 1*.

Background variables

A variable is termed as a background variable if its values are defined prior to the assignment of the intervention variables. A large number of background variables are available within the NNRD. Background variables were reviewed by the Clinical Investigator Group (see *Appendix 2*). The background variables' relative clinical importance to the analysis was decided and variables were classified into three groups. These background variables were used to form matched groups for subsequent analysis.

TABLE 1 Definition of enteral feeding and parenteral nutrition intervention groups

Analysis	Classification of intervention groups
Enteral feeding analysis	No enteral feeds: defined as no record of receiving an enteral feed during first 3 days after birth (or up to the day of death for babies who died during therapeutic hypothermia) and having at least 1 day for which no enteral feeding was recorded. A sensitivity analysis restricting the no enteral feeding group to only those babies who were recorded as having no enteral feeding for all 3 days or up to the day of death was also conducted Enterally fed: defined as receiving milk feeds of any type (including expressed maternal breast milk, expressed donor breast milk and artificial formula), by any route of administration (including nasogastric tube, bottle and suckling at breast) and in any quantity for at least 1 day while receiving therapeutic hypothermia
PN analysis	No PN: defined as no recorded administration of PN on any day for the first 3 days after birth (or up to the day of death for those babies who died during therapeutic hypothermia) and recorded as having received intravenous dextrose (which will include different volumes and routes of administration) on at least 1 day. A sensitivity analysis restricting the no PN group to only those babies who were recorded as having no PN and receiving intravenous dextrose for all 3 days (or up to the day of death) was also conducted PN: defined as receiving PN of any type (including standard, pre-prepared bags of nutrition and individually tailored PN), by any route of administration (including peripheral intravenous cannula, percutaneous central venous catheter or umbilical venous catheter) and in any volumes, for at least 1 day during therapeutic hypothermia

The variables deemed to be of highest importance were termed principal background variables, of which there were two:

1. birth year
2. pH of arterial blood in the umbilical cord.

Highly important background variables are next in the hierarchy, of which there were 15:

1. birthweight (g)
2. gestational age (weeks)
3. sex
4. resuscitation drugs received
5. delivery instrument used (forceps or ventouse)
6. mode of delivery (vaginal or other)
7. smoking during pregnancy
8. suspected maternal chorioamnionitis
9. Apgar score at 1 minute
10. Apgar score at 5 minutes
11. umbilical cord blood base excess concentration (venous)
12. mean blood pressure at first neonatal unit admission
13. oxygen saturation at first neonatal unit admission
14. blood glucose concentration at first neonatal unit admission
15. maternal socioeconomic decile as defined using maternal lower-layer super output area (LSOA).

The remaining background variables are classified as moderately important and are listed in *Appendix 1*, *Tables 22–24*.

For variables with a considerable number of missing data, binary missing data indicators were also defined.

Outcomes

The primary outcome of interest for the enteral nutrition analyses was incidence of severe NEC. This was defined as in the UK Neonatal Collaborative NEC study.[21] Briefly, this uses daily, diagnostic, abdominal radiographic and procedural variables held on the NNRD, with subsequent verification of cases with neonatal clinical teams. Some data items used in identifying cases of the UK Neonatal Collaborative definition of severe NEC were not recorded in the NNRD prior to 2010 and, therefore, an alternative and more pragmatic definition of NEC was used as a secondary outcome (*Table 2*). We had planned to use the NEC definition described by Battersby *et al.*;[22] however, this was not possible because of many missing values for a critical component of this definition in the study cohort (i.e. abdominal radiographic findings).

The primary outcome of interest in the analysis for the PN analyses was late-onset BSI, which was defined in accordance with the Healthcare Quality Improvement Partnership National Neonatal Audit Programme (NNAP) case definition.[23] Briefly, the NNAP case definition uses NNRD data items recorded in ad hoc fields that relate to blood culture results with subsequent verification of cases with neonatal clinical teams. The annual NNAP reports demonstrate variation in the completeness of these fields at the level of neonatal units.[23] Therefore, an alternative more pragmatic definition of late-onset BSI was used as a secondary outcome.

Primary and secondary outcomes in both the enteral nutrition and the PN analyses are defined in more detail in *Table 2*.

TABLE 2 Definitions of outcome variables assessed in enteral feeding and parenteral nutrition analyses

Analysis		
Enteral feeds	**PN**	**Outcome**
✓[a]	✓	Severe NEC: a binary variable defined in accordance with the UKNC definition of Battersby *et al.*[21] This case definition uses daily diagnosis and discharge data items, and clinical and radiographic findings recorded as ad hoc data items in the NNRD. Suspected cases of severe NEC were subsequently confirmed through contact with a neonatal or paediatric clinician at the relevant unit
✓	✓	NEC (pragmatic definition): a binary variable defined as a recorded diagnosis of NEC (in daily data or diagnosis data items) in a baby who received at least 5 consecutive days of antibiotics while being kept nil by mouth
✓	✓[a]	Late-onset BSI: a binary variable defined in accordance with the NNAP case definition as pure growth of a pathogen from blood or either a pure growth of a skin commensal or a mixed growth with ≥ 3 clinical signs at the time of blood sampling, recorded > 3 days after birth. This definition uses data that are recorded as ad hoc data items in the NNRD
✓	✓	Late-onset BSI (pragmatic definition): a binary variable defined as 5 consecutive days of antibiotic treatment that commenced later than 3 days after birth
✓	✓	Survival at discharge: a binary variable indicating whether or not the baby was alive at final neonatal discharge
✓	✓	Length of stay in neonatal units: a continuous variable defined as the number of days between first admission to a neonatal unit and final discharge from a neonatal unit for surviving babies or date of death for babies who died while in neonatal care. The length of stay was analysed both as a continuous variable and as a binary variable indicating whether a baby had stayed in the unit for ≤ 14 or > 14 days
✓	✓	Hypoglycaemia: a binary variable defined as any diagnosis of hypoglycaemia recorded after therapeutic hypothermia is commenced and before the final neonatal unit discharge
✓	✓	Breastfeeding at discharge: a binary variable defined as any breastfeeding (suckling at the breast) at discharge
✓	✓	Onset of breastfeeding: a continuous variable defined as the first day on which a baby is recorded to be suckling at the breast (this does not include maternal breast milk given by bottle or nasogastric tube). Analysed as both a continuous variable and a binary variable indicating whether or not a baby began suckling at the breast within 28 days (babies who died or were discharged within 28 days without suckling at the breast were classified as not suckling at the breast within 28 days)
✓	✓	Onset of first maternal breast milk feed: a continuous variable defined as the first day when a baby is recorded to be receiving maternal breast milk by any route (including suckling at the breast, by bottle or nasogastric tube). Analysed as both a continuous variable and a binary variable indicating whether or not a baby had its first maternal breast milk feed within 28 days (babies who died or were discharged within 28 days without having a maternal breast milk feed were classified as not having a maternal breast milk feed within 28 days)
✓	✓	Number of days with a central venous line in situ: a continuous variable defined as the number of recorded days a baby has a central venous line in situ. Analysed as both a continuous variable and a binary variable indicating whether or not a baby received a central venous line
✓	✓	Growth: a continuous variable defined as the SDS or *z*-score of the weight for postmenstrual age and sex at final neonatal unit discharge
✓		Duration of PN: a continuous variable defined as the number of days that a baby was recorded to be receiving PN. Analysed as both a continuous variable and a binary variable indicating whether or not PN was received

SDS, standard deviation score.
a This outcome was the primary outcome for this analysis.

Bias

This was an observational study. The primary source of bias was deemed to be confounding owing to systemic differences in the clinical characteristics between babies receiving different nutritional interventions. For instance, babies with hypotension who receive inotropes may be more likely to have feeds withheld as well as having poorer outcomes. To overcome this bias, matching using propensity scores was implemented to form groups of babies with different enteral and parenteral nutritional interventions during therapeutic hypothermia, but who were balanced in terms of all measured background variables. The process of matching is described in detail in *Statistical methods*. This approach cannot overcome bias related to systemic differences in unmeasured confounding factors.

Study size

It was estimated that approximately 7200 babies would meet the study inclusion criteria. Pilot data extracted from the NNRD showed that in 2015 a total of 809 babies met the study inclusion criteria, of whom 37% (301/809) received enteral feeds and 29% (238/809) received PN during hypothermia. Using these rates, a sample size of 7200 babies receiving therapeutic hypothermia would be able to detect (two-sided significance 5%, power 90%) a difference of 0.7% in NEC with 2000 matched pairs (assuming that the rate of NEC is negligible in the reference treatment) and a difference of 2% in BSI with 1500 pairs (assuming rates of 1% and 3%). The difference of 0.7% for the rates of NEC (and similar figures for other outcomes) is selected for illustration and does not represent any imperative or objective in the study design.

Statistical methods

Overview

In this analysis we applied the potential outcomes framework and propensity score methodology. For each outcome variable we consider two potential outcomes for every baby: the first associated with receiving the intervention (enteral feeding or PN) and the second associated with not receiving the intervention. The subject-level treatment effect is defined as the difference in these potential outcomes for each baby. The average treatment effect in a group of subjects is defined as the mean of the subject-level treatment effects in this group. In practice, only one potential outcome per baby is observed. Therefore, no subject-level treatment effect can be evaluated or estimated. In a randomised trial, the average treatment effect can be estimated by comparing outcomes of subjects who were provided with the outcomes of subjects who were withheld the intervention since randomisation (with a large enough sample size) ensures that, on average, intervention arms will be balanced in terms of both observed and unobserved confounders. By contrast, a simple comparison of outcomes in intervention groups using observational data is likely to be a biased estimate for the average treatment effect because of the presence of confounding, for example by indication. Propensity analysis can arrange balance on observed background variables, but not on variables that are not observed.

The use of propensity scores allows us to analyse observational data so that it mimics some of the characteristics of a RCT.[24] Specifically, it establishes a balance for the observed background characteristics between babies who are provided the intervention of interest and babies from whom the intervention is withheld. The propensity score itself is defined as the probability of receiving the intervention conditional on the observed background characteristics. The propensity score plays a key role in forming two well-balanced groups: one with babies who received the intervention and one with those babies who did not.[25]

We adopt the assumption of stable unit–treatment variable assignment, according to which the outcome of each subject depends on only the treatment assigned to the subject. In principle, the outcome could depend also on the treatment assigned to other subjects, but in this study we rule out such interference. We are interested to estimate the average treatment effect in those babies who received the intervention, that is what difference in outcomes (on average) do we expect to observe if all babies who were fed were instead not fed.

Primary analysis

In the primary analyses we performed 1 : 1 matching of babies who had no enteral feeds to those enterally fed for the enteral nutrition analysis, and 1 : 1 matching of babies who received no PN to those who received PN for the PN analysis. Background groups were first defined using the principal background variables, so that babies were required to be within the same birth year group (2-year bands) and arterial cord blood pH group (i.e. < 6.9, 6.9–7.0 and > 7.0). There were 12 groups in total. Matched pairs were formed within propensity score deciles defined separately for each background group. The matched pairs were then reconstituted as an intervention group (i.e. babies who received enteral feeds or PN) and a control group (i.e. babies who did not receive enteral feeds or PN). The intervention and control groups outcomes were compared by the same method that would be appropriate if these two matched groups arose in a RCT, applying the Student's *t*-test.

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. As 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 Rubin.[26] 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 of the remaining background variables were tested similarly and the variable 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.

Interactions were then 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 (i.e. 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 to be the most important, subject to the constraint of including at most two interactions in each cycle.

The concluding model yielded the fitted propensities (i.e. the estimated probabilities of being assigned to the groups receiving enteral feeds or receiving PN, given each baby's background profile). Therefore, 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 letting the propensities in the two groups be in the ranges (m_1, M_1) and (m_2, M_2), then by excluding all subjects with propensities smaller than $m = \max(m_1, M_1)$ and greater than $M = \min(m_2, M_2)$. Another criterion, described in Imbens and Rubin,[26] was applied to reduce the sampling variance of the average treatment effect to be evaluated. It yields a positive constant of $\gamma < 1$. Subjects with propensities outside the range (γ, $1 - \gamma$) were discarded from the analysis. Such reduction of the data set by discarding subjects with extreme propensities is referred to as trimming.

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) data set. 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.

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 2-year bands) were crossed with three cord blood pH groups to 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 cut-off points. 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 enteral feeds was paired to a randomly drawn baby who did not receive enteral feeds who fell within the same propensity group. After the matching process was complete, the matched pairs of babies were reconstituted as the intervention group (i.e. received enteral feeds) and control group (i.e. received no enteral feeds) and termed the matched cohort. As 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. This process was repeated to create a matched cohort containing babies who did and did not receive PN.

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 intervention and control group (the matched cohorts) for both the enteral and the PN analyses that are 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 undertaken with no foreknowledge 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 (SD) 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 Rubin[27] regard the balance of a variable as satisfactory if its absolute imbalance is < 0.1. For a data set, original or formed by matching, we report the total of the absolute imbalances and the largest and smallest imbalances. Variables that are not ordinal (i.e. 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.

Baseline characteristics and outcomes

Baseline characteristics for the entire study cohort and for the cohorts matched for the enteral nutrition and PN analyses were tabulated, with categorical variables presented as frequencies and percentages, and continuous variables presented as means, SDs, medians and interquartile ranges. To prevent potential identification of individuals, a count of events in a particular category is presented as < 5 and the corresponding percentage is omitted when the count is < 5 (or < 10 when use of < 5 would result in potential identification).

Descriptive analyses of patterns of feeding for the entire study cohort and matched cohorts were made. These include examination of the time to first enteral feed or first administration of PN, type of milk feed provided up to 7 days after birth and variation in the rates of enteral feeding and PN provision by the neonatal operational delivery network (ODN).

The outcome variables were either binary or continuous. Dichotomous versions were defined for several continuous variables. For binary outcomes, the absolute difference in mean rates of the outcome (intervention vs. control) and the odds ratio (OR) (intervention vs. control) were estimated and the two-sided 95% confidence interval (CI) and a *p*-value were evaluated for each of them. For a continuous outcome, the absolute difference in mean rates was computed with the two-sided 95% CI and *p*-value. Results were averaged over the 25 replications. The results for matched groups (see *Table 10*) differ slightly from the results of analyses of binary outcomes (see *Table 11*) because entries in both tables entail some randomness. This randomness is ameliorated by averaging over 25 replicates, but it is not eradicated.

Prespecified sensitivity analyses

Two prespecified sensitivity analyses were conducted. The first analysis restricted the sample to babies born between 2012 and 2017. This was performed because from 2012 onwards all NHS neonatal units across England and Wales contributed data to the NNRD and, therefore, fewer missing data were expected for this period. This sensitivity analysis examined the robustness of the results to missing data. The second analysis applied a more restrictive definition of the intervention variables: only babies positively confirmed as not having received enteral feeds or PN for each day of treatment with therapeutic hypothermia were classified as being in the control groups for the enteral and parenteral analyses, respectively. This analysis examined the robustness of the results to misclassification to control groups.

In the study protocol, a further subgroup analysis was planned to exclude all babies whose first admission to neonatal care was from a postnatal ward to exclude babies for whom therapeutic hypothermia was administered following postnatal collapse. This was not undertaken because of the small number of babies admitted from a postnatal ward in the entire cohort.

Post hoc sensitivity analyses

Two post hoc sensitivity analyses were conducted:

1. Receipt of PN on the first day of life was added as a highly important background variable to the propensity model for the enteral nutrition analysis.
2. Receipt of enteral feeds on the first day of life was added as a highly important background variable to the propensity model for the PN analysis.

These post hoc analyses were undertaken following advice of the Clinical Investigator Group and with the agreement of the Study Steering Committee. The intention of these sensitivity analyses was to examine the impact of nutritional practice on the first day as an additional background (matching) variable.

Alternative methods for matching on the propensity score and background variables

We refer to the statistical methods detailed thus far as the preliminary method of analysis. We explored the robustness of results to alternative matching methods at three stages of the matching process (see *Figure 1*). In the preliminary analysis, babies in the intervention group were matched on a 1 : 1 basis to those in the control group. Inverse probability weighting (IPW) is an alternative to matching. In IPW a matched cohort is formed by applying to the babies the reciprocal of the probability of receiving the treatment that was actually received. The weights assigned to babies who received and did not receive enteral feeds and the estimated average effect of being enterally fed and not fed are as follows.

Enterally fed weight:

$$W_i = \frac{1}{PS_i}. \tag{1}$$

Estimated average effect of receiving enteral feeds:

$$\mu_F = \frac{1}{N}\sum_{i=1}^{N} W_i T_i Y_i. \tag{2}$$

Not enterally fed weight:

$$W_i = \frac{1}{(1 - PS_i)}. \tag{3}$$

Estimated average effect of not being enterally fed:

$$\mu_{NF} = \frac{1}{N}\sum_{i=1}^{N} W_i (1 - T_i) Y_i, \tag{4}$$

where PS_i is the fitted propensity for baby i, T_i is a binary indicator of the treatment received ($T_i = 1$ indicates that a baby received enteral feeds) and Y_i is the outcome for subject i. Treatment effects are calculated by the method appropriate for the type of outcome variable (continuous or binary). The standard errors are estimated by the weighted versions of the formulae for random samples.

In the preliminary analysis, propensity score deciles were formed within each background group so that thresholds between deciles varied across the 12 principal background groups. We implemented two alternatives. First, we formed propensity groups prior to forming background groups so that thresholds were common to all the background groups. Second, we ignored background groups altogether and matched only on the propensity groups. In addition to forming propensity groups by splitting into deciles, we also implemented an adaptive method proposed by Imbens and Rubin.[28] Propensities were repeatedly split by the within-group median propensities of provisional propensity groups until the subjects in each group were well balanced on (i.e. had similar means of) the propensities. This method is called adaptive splitting.

In summary, in addition to the preliminary analysis (*Figure 1*, analysis A) we conducted 11 further analyses (see *Figure 1*, analyses B–L), implementing alternative methods of propensity and background matching in the primary analysis and all three sensitivity analyses.

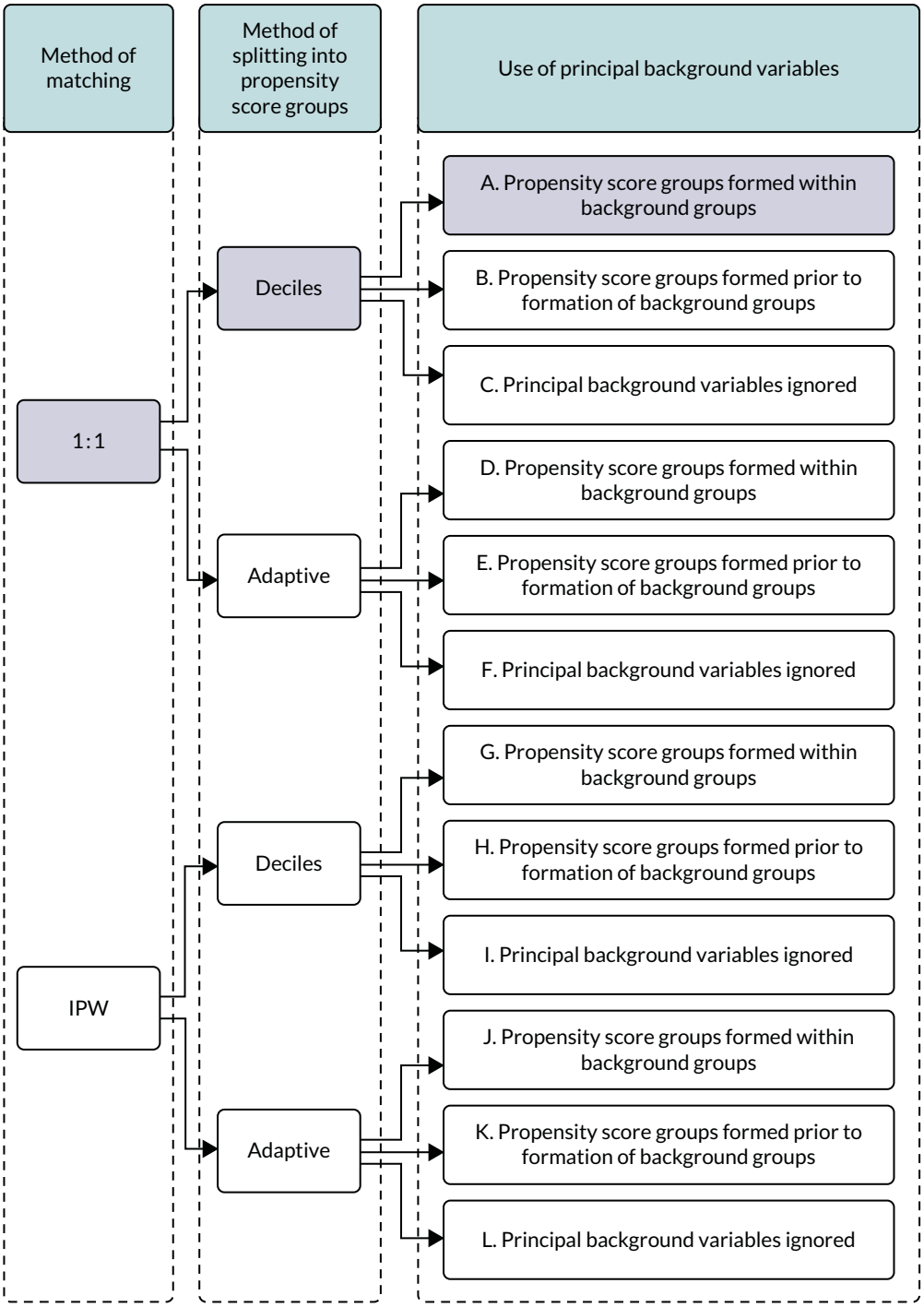

FIGURE 1 Alternative methods of matching on the propensity scores and principal background groups. The preliminary method of analysis is shaded in purple.

Chapter 3 Parent and patient involvement

Background

Involvement of parents, patients and the public in research can be defined as research being carried out 'with' parents, patients and the public, rather than 'to' or 'for' them.[29] High-quality parent, patient and public involvement in research is considered best practice and is associated with tangible benefits, including higher enrolment in clinical trials.[30] Parents and parent representatives were involved in this study at all stages from conception through to dissemination.

Aim

To gain meaningful parent perspectives into the design, analysis, interpretation and dissemination of this study.

Objectives

Objective 1
To ensure that the views of parents with experience of having a baby who received therapeutic hypothermia are incorporated in the design of the study.

Objective 2
To ensure that the views of parents are represented in the meetings of the Study Steering Committee.

Objective 3
To ensure that study results are disseminated using a parent-centred approach and in plain English.

Methods

The study was planned and designed by a multiprofessional investigator group that included a parent who had experienced having a baby who received therapeutic hypothermia (author ES). The investigator group also included a representative (author LC) from the national charity Bliss (a charity for babies born prematurely or who are sick) (London, UK) to represent parents more widely and to support ES in contributing to the study. ES and LC contributed to the design, planning, analysis, interpretation and dissemination stages of the study.

A further parent who had experienced having a baby who received therapeutic hypothermia was recruited to join the Study Steering Committee as an independent member through social media channels of the national charity Bliss [i.e. Facebook (URL: www.facebook.com; Facebook, Inc., Menlo Park, CA, USA); Twitter, (URL: www.twitter.com; Twitter, Inc., San Francisco, CA, USA); and Instagram, (URL: www.instagram.com; Instagram, Inc., Menlo Park, CA, USA).

The parent co-investigator, parent Study Steering Committee member and parent representatives were strongly encouraged to actively contribute to discussions, investigator group and steering group meetings.

Parents were informed about the study through the website of the national charity Bliss (*Figure 2*). Parents were informed that data about their babies were collected by neonatal staff and were

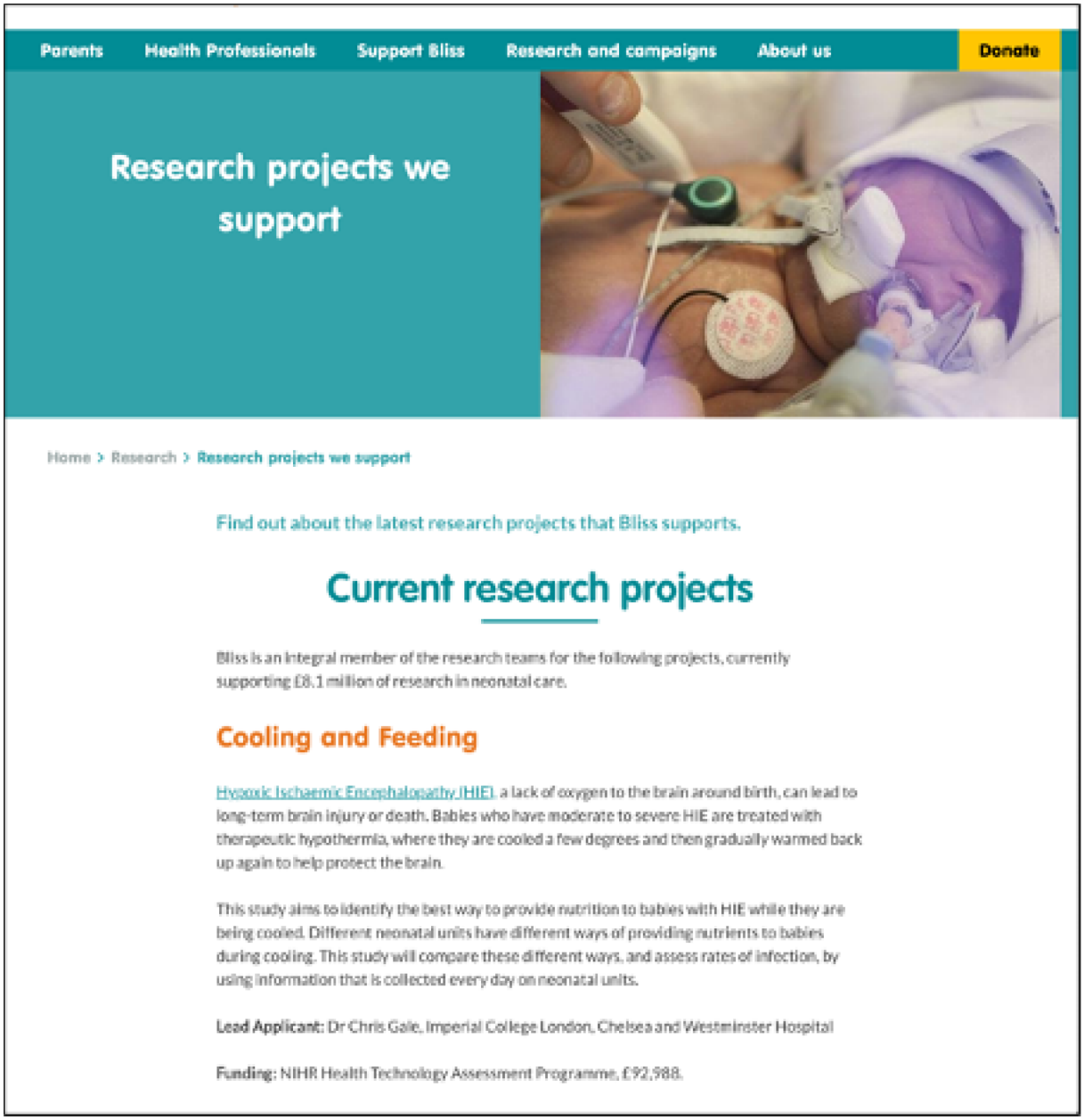

FIGURE 2 Bliss webpage informing parents about the study. URL: www.bliss.org.uk/research-campaigns/research/current-research (accessed 29 October 2019). Reproduced with permission from Bliss.

added to the NNRD to improve neonatal care through research, using posters and leaflets on all NHS neonatal units [URL: www.imperial.ac.uk/neonatal-data-analysis-unit/about-us/for-parents-and-carers/ (accessed 24 July 2020)].

Results

Parents influenced the study design and, specifically, the choice of outcomes in several ways. The primary outcome for the enteral nutrition comparison is NEC and the primary outcome for the PN comparison is late-onset infection. Prevention of these outcomes was identified as the third and second most important treatment uncertainties, respectively, by parents, patients and professionals in a James Lind Alliance Priority Setting Partnership related to neonatal care.[31,32]

A parent (ES) and a parent representative (Bliss) identified that 'breastfeeding' as a binary outcome was not sufficient to capture the different aspects of breastfeeding that may be important to parents of babies who are receiving therapeutic hypothermia. The following outcomes were included in the study as a direct result of this:

- First maternal breast milk feed, defined as the first day when a baby is recorded as receiving maternal breast milk by any route, including suckling at the breast, by bottle or by nasogastric tube.
- Onset of breastfeeding, defined as the first day when a baby is recorded as suckling at the breast. This does not include maternal breast milk given by bottle or nasogastric tube.
- Breastfeeding at discharge, defined as any breastfeeding (i.e. suckling at the breast) at discharge.

Both a parent and a parent representative were actively involved in study oversight and were present at all Study Steering Committee meetings.

A parent and a parent representative contributed to the analysis of study results and drafting of study publications, including this report.

Planned dissemination

Parent-centred plain English summaries of key study results are being co-designed by parents, parent representatives and the study statistician (DJ) to facilitate dissemination of the study results to parents. These will be made freely available online through the Bliss [URL: www.bliss.org.uk (accessed 24 July 2020)] and NNRD [URL: www.imperial.ac.uk/neonatal-data-analysis-unit/ (accessed 24 July 2020)] websites and will be publicised through the Bliss and study team social media channels.

Discussion

Parents and parent representatives were actively involved in this study from its outset. Meaningful parent involvement was achieved, and this translated into the inclusion of outcomes relevant to parents. These outcomes included different aspects of breastmilk feeding, such as first administration of breast milk and first feed at the breast, recognising the different value and importance of these events to parents. Parent and parent representative involvement has also been essential for development of effective plain English research summaries. This study uses data held in the NNRD. Parents have been extensively involved in the development of the NNRD and have expressed strong support for sharing health data for research.[33]

The strengths of the study include involvement of a parent who had experienced having a baby who received therapeutic hypothermia from study inception with parallel involvement of a parent representative charity to provide further parent representation and support for the parent co-investigator (ES). This enabled the parent co-investigator (ES) to gain experience and expertise in study design and to contribute meaningfully. Having the same parent co-investigator throughout the study also provided continuity in relation to the parent perspective and input.

The limitations include the challenge of involving parents in a retrospective observational study in which the choice of study outcomes was limited by available data. A further limitation is that we did not involve ex-neonatal patients who experienced therapeutic hypothermia in the neonatal period. This was challenging because of the neonatal patient population and because the treatment of interest, therapeutic hypothermia, became standard of care only 10 years ago.

Parent involvement in this study led to beneficial changes in the design of the study and in the outcomes analysed.

Chapter 4 Results

Participants

A total of 703,911 babies were recorded as having been admitted to a NHS neonatal unit in England, Scotland or Wales between 1 January 2010 and 31 December 2017. Of these babies, 6033 were ≥ 36 weeks' gestational age and recorded as being treated with therapeutic hypothermia for HIE for 6 days or as having died during treatment. After exclusion of babies with missing data for sex or missing feeding data on all days when they were recorded as receiving therapeutic hypothermia, the enteral nutrition and PN cohorts comprised 5847 and 6010 babies, respectively (*Figure 3*).

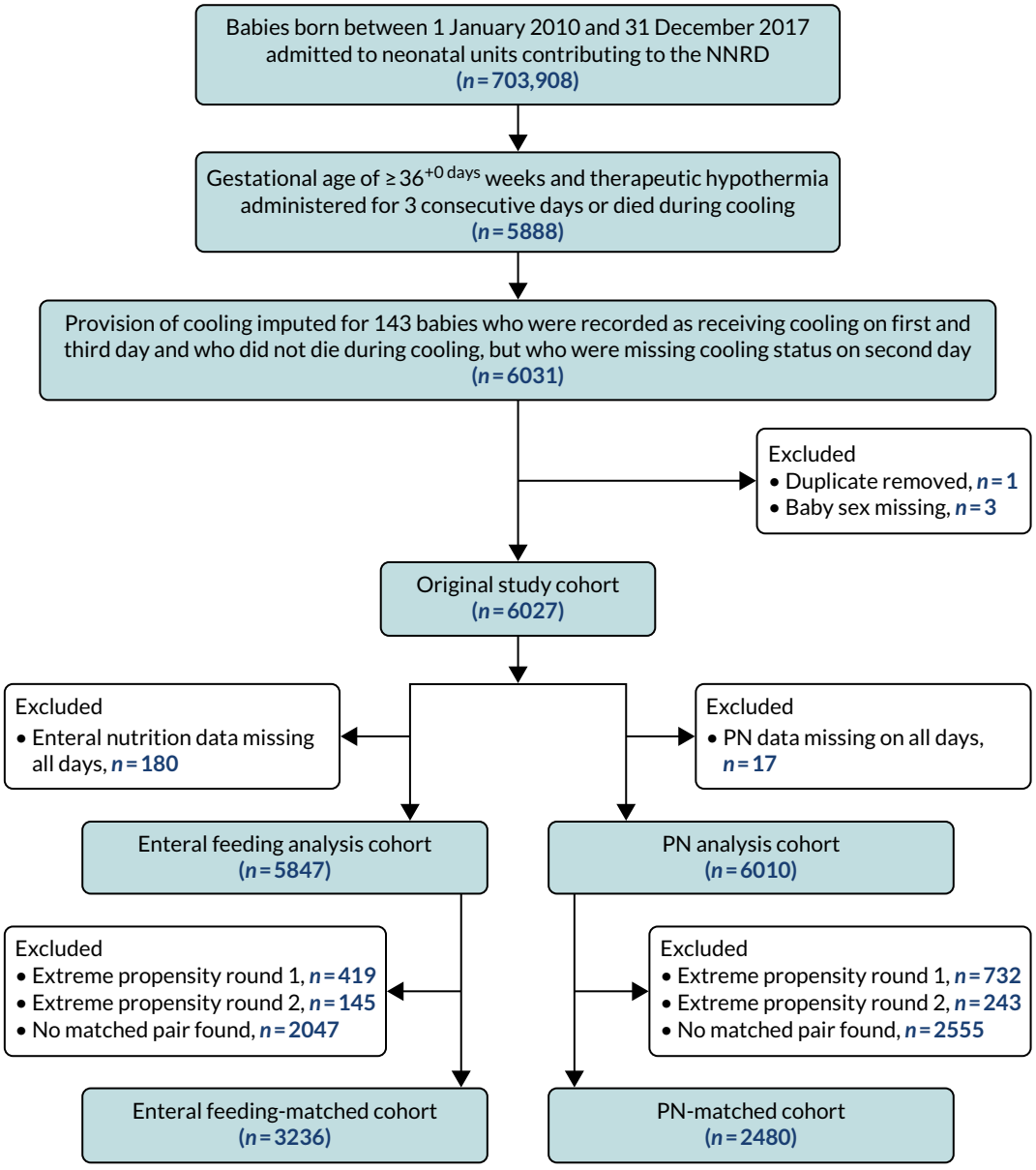

FIGURE 3 Participant flow through study for the primary analysis.

In the primary analysis, propensity score matching created matched cohorts of 3236 babies (i.e. 1618 pairs) for the enteral feeding analysis and 2480 babies (i.e. 1240 pairs) for the PN analysis. These cohorts were smaller than the sample sizes estimated in the protocol of 2000 matched pairs for the enteral nutrition analysis and 1500 matched pairs for the PN analysis.

Descriptive analyses: original study cohort

Background variables

Tables 3 and *4* report selected background variables used in the analyses summarised by year of birth. Annual summary data for other background variables used in the analyses are presented in *Appendix 3*, *Tables 25–27*.

TABLE 3 Background variables in the entire study cohort by year of birth

Variable	Year								All years
	2010	2011	2012	2013	2014	2015	2016	2017	
Total number of babies	474	678	686	815	871	859	819	825	6027
Male									
n	246	369	379	421	481	496	464	472	3328
%	51.9	54.4	55.2	51.7	55.2	57.7	56.7	57.2	55.2
Multiple birth									
n	21	24	23	29	22	22	24	15	180
%	4.4	3.5	3.4	3.6	2.5	2.6	2.9	1.8	3
Gestational age at birth (weeks)									
Mean	39.4	39.4	39.4	39.4	39.4	39.3	39.3	39.4	39.4
SD	1.6	1.6	1.6	1.5	1.5	1.6	1.5	1.5	1.6
Birthweight (g)									
Mean	3403	3360	3397	3348	3347	3394	3345	3398	3372
SD	669	628	641	614	603	603	627	594	619
Caesarean delivery									
n	221	324	297	385	410	361	369	375	2742
%	46.6	47.8	43.3	47.2	47.1	42	45.1	45.5	45.5
Maternal age (years)									
Median	30	31	30	30	30	31	31	30	31
Lower quartile	25	26.8	26	26	26	27	27	26	26
Upper quartile	34	35	34	34	35	35	34	34	35
Maternal suspected chorioamnionitis									
n	51	73	76	83	105	78	90	98	654
%	10.8	10.8	11.1	10.2	12.1	9.1	11	11.9	10.9
Smoking in pregnancy									
n	63	92	82	110	112	96	106	73	734
%	13.3	13.6	12	13.5	12.9	11.2	12.9	8.8	12.2
Missing, *n*	78	92	97	89	124	124	107	137	848
%	16.5	13.6	14.1	10.9	14.2	14.4	13.1	16.6	14.1

TABLE 3 Background variables in the entire study cohort by year of birth (*continued*)

Variable	Year								All years
	2010	2011	2012	2013	2014	2015	2016	2017	
Ethnicity (maternal) (%)									
White	77.0	74.2	71.9	66.3	63.7	59.7	57.0	55.8	64.6
Asian and mixed	7.8	10.0	11.2	11.0	10.7	8.4	10.9	10.5	10.2
Black and mixed	7.8	8.1	6.9	6.7	7.1	6.5	5.5	6.1	6.8
Other	6.7	5.6	4.8	4.7	3.0	6.1	5.1	5.7	5.1
Maternal diabetes[a]									
n	8	18	18	40	36	39	49	48	256
%	1.7	2.7	2.6	4.9	4.1	4.5	6	5.8	4.2
Deprivation score (LSOA) (%)									
Deciles 1 or 2 (most deprived)	27.9	25	27.2	26.8	26.8	23.8	28.7	28.6	26.8
Primiparous[a]									
n	272	402	389	433	494	414	370	436	3210
%	57.4	59.3	56.7	53.1	56.7	48.2	45.2	52.8	53.3

a Data were collected via a checkbox indicating presence of condition. Therefore, it is not possible to distinguish between missing data and presence of no condition.

TABLE 4 Birth and resuscitation variables for the entire study cohort by year of birth

Variable	Year								All years
	2010	2011	2012	2013	2014	2015	2016	2017	
Total number of babies	474	678	686	815	871	859	819	825	6027
Cord blood gas pH: arterial									
> 7.0, *n*	123	196	216	254	290	289	245	283	1896
%	25.9	28.9	31.5	31.2	33.3	33.6	29.9	34.3	31.5
6.9–7.0, *n*	85	109	111	143	158	134	129	139	1008
%	17.9	16.1	16.2	17.5	18.1	15.6	15.8	16.8	16.7
< 6.9, *n*	136	168	179	207	180	180	174	156	1380
%	28.7	24.8	26.1	25.4	20.7	21	21.2	18.9	22.9
Missing, *n*	130	205	180	211	243	256	271	247	1743
%	27.4	30.2	26.2	25.9	27.9	29.8	33.1	29.9	28.9
Apgar score at 1 minute									
0 or 1, *n*	228	321	321	367	376	400	364	372	2749
%	48.1	47.3	46.8	45	43.2	46.6	44.4	45.1	45.6
2–4, *n*	174	246	227	291	332	289	274	267	2100
%	36.7	36.3	33.1	35.7	38.1	33.6	33.5	32.4	34.8
5–7, *n*	27	41	57	69	58	60	67	85	464

continued

TABLE 4 Birth and resuscitation variables for the entire study cohort by year of birth (*continued*)

Variable	Year								All years
	2010	2011	2012	2013	2014	2015	2016	2017	
%	5.7	6.0	8.3	8.5	6.7	7.0	8.2	10.3	7.7
8–10, *n*	6	18	32	31	36	29	41	27	220
%	1.3	2.7	4.7	3.8	4.1	3.4	5.0	3.3	3.7
Missing, *n*	39	52	49	57	69	81	73	74	494
%	8.2	7.7	7.1	7.0	7.9	9.4	8.9	9.0	8.2
Apgar score at 5 minutes									
0 or 1, *n*	93	134	118	126	114	127	130	112	954
%	19.6	19.8	17.2	15.5	13.1	14.8	15.9	13.6	15.8
2–4, *n*	187	261	239	317	345	310	302	308	2269
%	39.5	38.5	34.8	38.9	39.6	36.1	36.9	37.3	37.6
5–7, *n*	129	187	210	246	266	270	252	251	1811
%	27.2	27.6	30.6	30.2	30.5	31.4	30.8	30.4	30
8–10, *n*	24	44	66	72	81	69	71	79	506
%	5.1	6.5	9.6	8.8	9.3	8	8.7	9.6	8.4
Missing, *n*	41	52	53	54	65	83	64	75	487
%	8.6	7.7	7.7	6.6	7.5	9.7	7.8	9.1	8.1
Received chest compressions at resuscitation[a]									
n	202	298	289	286	292	313	300	253	2233
%	42.6	44	42.1	35.1	33.5	36.4	36.6	30.7	37
Received resuscitation drugs[a]									
n	103	128	124	117	105	118	130	102	927
%	21.7	18.9	18.1	14.4	12.1	13.7	15.9	12.4	15.4
Intubated at resuscitation[a]									
n	328	471	462	517	548	555	512	473	3866
%	69.2	69.5	67.3	63.4	62.9	64.6	62.5	57.3	64.1
Time to first spontaneous breath									
> 5 minutes, *n*	279	401	412	493	531	509	494	483	3602
%	58.9	59.1	60.1	60.5	61	59.3	60.3	58.5	59.8
Missing, *n*	144	195	186	191	195	213	200	190	1514
%	30.4	28.8	27.1	23.4	22.4	24.8	24.4	23	25.1
Time to admission (minutes)									
Median	30	30	30	30	30	30	31	30	30
Lower quartile	20.2	19	20	20	20	21	22	21	20
Upper quartile	49.8	46	45	44	42	43	45	43	44

TABLE 4 Birth and resuscitation variables for the entire study cohort by year of birth (*continued*)

Variable	Year								All years
	2010	2011	2012	2013	2014	2015	2016	2017	
Temperature on admission (°C)									
Mean	35.8	35.7	35.8	35.9	35.9	35.8	35.9	36	35.9
SD	1.3	1.3	1.3	1.2	1.2	1.3	1.2	1.3	1.3
Transfusion of any blood products on day of admission									
n	79	103	107	131	95	120	110	118	863
%	16.7	15.2	15.6	16.1	10.9	14.0	13.4	14.3	14.3
Mechanical ventilation on day of admission									
n	375	535	534	613	679	655	637	613	4641
%	79.1	78.9	77.8	75.2	78	76.3	77.8	74.3	77
Early-onset infection (in the first 3 days, defined using NNAP definition)									
n	1	2	5	10	14	7	10	6	55
%	0.2	0.3	0.7	1.2	1.6	0.8	1.2	0.7	0.9
Admitted to neonatal unit from postnatal ward									
n	< 5	< 5	< 5	9	9	5	7	10	46
%				1.1	1.0	0.6	0.9	1.2	0.8
Postnatal transfer to another neonatal unit within the first 48 hours									
n	213	338	319	397	387	415	419	374	2862
%	44.9	49.9	46.5	48.7	44.4	48.3	51.2	45.3	47.5

a Data were collected via a checkbox, so it is not possible to distinguish between missing data and presence of no condition.

In the entire study cohort, 55.2% of babies were male. The babies had a mean gestational age at birth of 39.4 weeks, 26.8% of mothers lived in areas considered to be the most deprived (i.e. within deciles 1 or 2 of the deprivation score) and this was the first birth for 53.3% of mothers.

Nutritional interventions

Table 5 displays the annual rates of enteral feeding and administration of PN for the study cohort. Approximately 31% of babies were recorded as having received enteral feeds during their treatment with therapeutic hypothermia. There was no evidence of a (linear) trend in the proportion of babies being enterally fed over the study period (chi-squared test for trend $p = 0.24$). Over the study period, approximately 25% of babies treated with therapeutic hypothermia were recorded as having received PN during hypothermia. There was strong evidence ($p = 0.003$) of an increasing (linear) trend in the proportion of babies who received PN over the study period, although the magnitude of the slope was small (slope = 0.007), indicating that the increase in PN use over the study period was small.

Outcomes in the unmatched cohort

The annual number of incidences of outcomes in the whole study cohort is summarised in *Tables 6* and *7*. Counts and rates for binary outcomes are presented in *Table 6*. Median and quartiles for the continuous outcome variables, and the counts and rates for their dichotomised versions (which are defined for all continuous outcomes except for weight *z*-score at discharge), are presented in *Table 7*.

TABLE 5 Intervention variables for the entire study cohort by year of birth

	Year								
Nutritional intervention	2010	2011	2012	2013	2014	2015	2016	2017	All years
Total number of babies	474	678	686	815	871	859	819	825	6027
Received enteral feeds during therapeutic hypothermia									
n	132	209	220	234	244	298	268	267	1872
%	27.8	30.8	32.1	28.7	28	34.7	32.7	32.4	31.1
Missing, *n*	29	56	16	21	17	18	9	14	180
%	6.1	8.3	2.3	2.6	2.0	2.1	1.1	1.7	3.0
Received PN during therapeutic hypothermia									
n	73	138	179	239	218	211	225	192	1475
%	15.4	20.4	26.1	29.3	25	24.6	27.5	23.3	24.5
Missing, *n*	1	2	2	0	0	7	1	4	17
%	0.2	0.3	0.3	0	0	0.8	0.1	0.5	0.3

TABLE 6 Binary outcome variables for the entire study cohort by year of birth

	Year								
Variable	2010	2011	2012	2013	2014	2015	2016	2017	All years
Total number of babies	474	678	686	815	871	859	819	825	6027
Severe NEC									
n	0	< 5	< 5	< 5	< 5	< 5	0	< 5	7
%	0						0		0.1
NEC (pragmatic definition)									
n	10	< 10	11	14	< 10	10	< 10	< 10	68
%	2.1		1.6	1.7		1.2			1.1
Late-onset infection (NNAP definition)									
n	< 5	0	< 5	< 5	< 5	< 5	6	11	30
%		0					0.7	1.3	0.5
Late-onset infection (pragmatic definition)									
n	134	191	182	208	237	209	177	221	1559
%	28.3	28.2	26.5	25.5	27.2	24.3	21.6	26.8	25.9
Survival to neonatal discharge									
n	408	603	609	720	802	788	745	766	5441
%	86.1	88.9	88.8	88.3	92.1	91.7	91	92.8	90.3
Missing, *n*	1	2	2	0	0	0	0	1	6
%	0.2	0.3	0.3	0	0	0	0	0.1	0.1

TABLE 6 Binary outcome variables for the entire study cohort by year of birth (*continued*)

Variable	Year								All years
	2010	2011	2012	2013	2014	2015	2016	2017	
Hypoglycaemia									
n	97	145	122	169	183	171	155	166	1208
%	20.5	21.4	17.8	20.7	21	19.9	18.9	20.1	20
Breastfeeding at discharge									
n	185	310	305	359	410	411	401	403	2784
%	39	45.7	44.5	44	47.1	47.8	49	48.8	46.2
Had a central venous line									
n	450	635	625	754	826	810	764	776	5640
%	94.9	93.7	91.1	92.5	94.8	94.3	93.3	94.1	93.6

TABLE 7 Continuous outcome variables for the entire study cohort by year of birth

Variable	Year								All years
	2010	2011	2012	2013	2014	2015	2016	2017	
Total number of babies	475	678	686	815	871	861	820	825	6031
Length of stay (days)									
Median	11	11	11	11	11	11	10	11	11
Lower quartile	8	8	8	8	8	8	8	8	8
Upper quartile	18	17	16	16	16	16	15	15	16
Missing, *n*	1	0	0	0	0	0	0	0	1
%	0.2	0	0	0	0	0	0	0	0
> 14 days, *n*	163	220	197	254	272	262	212	228	1808
%	34.4	32.4	28.7	31.2	31.2	30.5	25.9	27.6	30
Time to suckling at breast (days) in babies who breastfed									
≤ 28 days, *n*	271	406	407	496	541	518	498	490	3627
%	57.2	59.9	59.3	60.9	62.1	60.3	60.8	59.4	60.2
Median	7	7	7	7	7	7	7	7	7
Lower quartile	6	6	5	6	6	6	6	6	6
Upper quartile	10	10	9	9	10	9	9	9	9
Missing, *n*	201	266	275	311	325	340	314	330	2362
%	42.4	39.2	40.1	38.2	37.3	39.6	38.3	40	39.2
Time to receiving mother's milk (days)									
≤ 28 days, *n*	374	552	561	653	727	709	676	674	4926
%	78.9	81.4	81.8	80.1	83.5	82.5	82.5	81.7	81.7
Median	5	5	5	5	5	5	5	5	5
Lower quartile	4	4	4	4	4	3	3	3	4

continued

TABLE 7 Continuous outcome variables for the entire study cohort by year of birth (*continued*)

Variable	Year								All years
	2010	2011	2012	2013	2014	2015	2016	2017	
Upper quartile	6	6	6	6	6	6	5	5	6
Missing, *n*	100	125	125	161	144	149	143	150	1097
%	21.1	18.4	18.2	19.8	16.5	17.3	17.5	18.2	18.2
Received PN									
n	157	263	274	372	378	340	349	309	2442
%	33.1	38.8	39.9	45.6	43.4	39.6	42.6	37.5	40.5
Duration of PN (days)									
Median	4	3	3	3	3	3	3	3	3
Lower quartile	3	2	2	2	2	2	2	2	2
Upper quartile	5	5	4	4	4	4	5	4	4
Central venous line duration (days)									
Median	5	5	5	5	5	5	5	5	5
Lower quartile	4	3	3	3	4	3	3	4	3
Upper quartile	7	6	6	6	6	6	6	6	6
Weight *z*-score at discharge									
Mean	−0.6	−0.7	−0.5	−0.6	−0.7	−0.5	−0.6	−0.5	−0.6
SD	1.3	1.3	1.3	1.7	1.2	1.2	1.2	1.2	1.2
Median	−0.6	−0.8	−0.6	−0.7	−0.7	−0.6	−0.6	−0.6	−0.6
Lower quartile	−1.4	−1.5	−1.4	−1.5	−1.5	−1.3	−1.4	−1.3	−1.4
Upper quartile	0.2	0.1	0.2	0.1	0.2	0.2	0.2	0.2	0.2
Missing, *n*	1	1	0	0	0	0	7	0	12
%	0.2	0.1	0	0	0	0	0.9	0	0.2

Seven babies (0.1%) who received therapeutic hypothermia were diagnosed with severe NEC over the 8-year study period. When the more pragmatic definition of NEC was applied (i.e. any recorded diagnosis of NEC concurrent with 5 days of antibiotics and 5 days nil by mouth), 68 babies (1.1%) were classified as having NEC over the study period. There were no detectable (linear) trends in the annual incidence rates of either severe or pragmatically defined NEC.

The incidence of NNAP-defined late-onset infection was low. Thirty babies (0.5%) had a pure growth of a recognised pathogen in a blood culture after day 3. The incidence of the more pragmatically defined late-onset infection (i.e. 5 concurrent days of antibiotic treatment) was substantially higher, with 25.9% of babies ($n = 1559$) receiving therapeutic hypothermia having late-onset infection by this measure. Survival to discharge rates from the neonatal unit were high (90.3%) and there was strong evidence (chi-squared test for trend $p < 0.001$) of an increase in the rates of survival over the study period.

Just under half of babies were breastfeeding at discharge (46.2%). This proportion increased over the study period. Among the babies who did suckle at the breast, the first breastfeed was at a median age of 7 days. In babies who were fed maternal breast milk, the median age at first receiving maternal breast milk (by any route of administration) was 5 days. The median length of stay in the neonatal unit was 11 days (interquartile range 8–16 days).

Enteral feeding analyses

Overview

In this section, we present matched-group analyses comparing different approaches with enteral feeding (i.e. starting enteral feeds compared with not starting enteral feeds during therapeutic hypothermia). First, we present summary data for selected background variables within the unmatched groups by approach to feeding. Second, we present summary background data by approach to feeding for the matched subgroups and summaries of the quality of the match. The main results of the primary analyses are the estimates and CIs for the treatment effects for each outcome.

To better describe feeding within the study cohort, exploratory analyses were conducted into the type of enteral feeding provided to babies and time to receipt of first enteral feed in the unmatched and matched cohorts. We also present regional variation in the provision of enteral feeds during therapeutic hypothermia.

Primary analysis

Background variables in unmatched and matched cohorts

Tables 8 and *9* (see also *Appendix 4*, *Tables 28–31*) present the background characteristics of babies recorded as having received enteral feeds during therapeutic hypothermia and babies for whom enteral feeds were recorded as being withheld, before and after matching. There are clear differences between unmatched cohorts of babies who received and babies who did not receive enteral feeds. Higher proportions of babies were delivered by caesarean section and to mothers living in the most deprived LSOAs in the withheld enteral feeds group. Babies who did not receive enteral feeds during therapeutic hypothermia also received more intensive medical care at resuscitation and on the first day of their life. After matching, differences in baseline characteristics between babies who received enteral feeds and babies from whom enteral feeds were withheld were markedly reduced (see *Tables 8* and *9*), as intended.

Quality of the match for enteral feeding analysis

Figure 4 presents histograms of the estimated propensity scores from the final enteral feeding propensity model by intervention (i.e. received enteral feeds) and control (i.e. no enteral feeds) groups. There is good overlap of the propensity scores in the intervention and control groups and so many matched pairs can be formed. Data from 574 babies (9.8% of total sample) were discarded because of extreme propensities.

TABLE 8 Background variables, by enteral feeding intervention groups, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enterally fed	No enteral feeds	Enterally fed
Total number of babies	3975	1872	1618	1618
Male				
n	2173	1055	903	903
%	54.7	56.4	55.8	55.8
Multiple birth				
n	116	61	48	54
%	2.9	3.3	3.0	3.3

continued

TABLE 8 Background variables, by enteral feeding intervention groups, for unmatched and matched cohorts (*continued*)

Variable	Cohort			
	Unmatched		Matched	
	No enteral feeds	Enterally fed	No enteral feeds	Enterally fed
Gestational age at birth (weeks)				
Mean	39.3	39.5	39.5	39.5
SD	1.6	1.5	1.5	1.5
Birthweight (g)				
Mean	3358	3395	3403	3386
SD	621	636	625	633
Caesarean delivery				
n	1921	738	649	638
%	50.6	41.2	41.9	41.1
Maternal age (years)				
Median	30	31	31	31
Lower quartile	26	27	26.9	26.5
Upper quartile	34	35	35	35
Maternal suspected chorioamnionitis				
n	406	240	202	187
%	12.6	15.2	15.2	13.7
Smoking in pregnancy				
n	524	191	159	169
%	15.4	11.7	11.3	12
Missing, *n*	566	244	207	205
%	16.6	15	14.7	14.5
Ethnicity (maternal) (%)				
White	65.4	63.3	74.5	74.9
Asian and mixed	10.0	10.7	12.5	12.2
Black and mixed	7	6.4	7.0	7.5
Other and missing	17.6	19.6	6.0	5.5
Maternal diabetes[a]				
n	171	75	66	60
%	4.3	4.0	4.1	3.7
Deprivation score (LSOA) (%)				
In deciles 1 or 2 (most deprived)	29.4	21.0	23.1	21.6
Primiparous[a]				
n	2107	991	857	844
%	53	52.9	53	52.2

a Data are collected via a check box indicating presence of condition. Therefore, it is not possible to distinguish between missing data and presence of no condition.

Note

The results were averaged over 25 matched replications.

TABLE 9 Neonatal clinical characteristics, by enteral feeding intervention groups, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enterally fed	No enteral feeds	Enterally fed
Total number of babies	3975	1872	1618	1618
Cord blood gas pH: arterial				
> 7.0, *n*	1240	613	536	536
%	44.1	45.4	46	46
6.9–7.0, *n*	661	318	262	262
%	23.5	23.5	22.5	22.5
< 6.9, *n*	913	420	368	368
%	32.4	31.1	31.6	31.6
Missing, *n*	1161	521	452	452
%	29.2	27.8	27.9	27.9
Apgar score at 1 minute				
0 or 1, *n*	1886	778	720	687
%	47.4	41.6	44.5	42.5
2–4, *n*	1311	731	604	632
%	33.0	39.0	37.3	39.1
5–7, *n*	304	154	130	129
%	7.6	8.2	8	7.9
8–10, *n*	135	76	60	61
%	3.4	4.1	3.7	3.8
Missing, *n*	339	133	104	109
%	8.5	7.1	6.4	6.8
Apgar score at 5 minutes				
0 or 1, *n*	695	223	231	198
%	17.5	11.9	14.3	12.2
2–4, *n*	1476	736	650	648
%	37.1	39.3	40.2	40
5–7, *n*	1140	623	490	537
%	28.7	33.3	30.3	33.2
8–10, *n*	324	166	147	132
%	8.2	8.9	9.1	8.2
Missing, *n*	340	124	100	103
%	8.6	6.6	6.2	6.4
Received chest compressions at resuscitation[a]				
n	1555	608	560	532
%	39.1	32.5	34.6	32.9

continued

TABLE 9 Neonatal clinical characteristics, by enteral feeding intervention groups, for unmatched and matched cohorts (*continued*)

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enterally fed	No enteral feeds	Enterally fed
Received resuscitation drugs[a]				
n	683	209	191	183
%	17.2	11.2	11.8	11.3
Intubated at resuscitation[a]				
n	2619	1126	1020	995
%	65.9	60.1	63	61.5
Time to first spontaneous breath				
> 5 minutes, *n*	2369	1128	985	985
%	59.6	60.3	60.9	60.9
Missing, *n*	1011	452	383	387
%	25.4	24.1	23.7	23.9
Temperature (°C)				
Mean	35.9	36.0	36	35.9
SD	1.3	1.2	1.2	1.2
Transfusion of any blood products on day of admission				
n	641	196	180	172
%	16.1	10.5	11.1	10.6
Mechanical ventilation on day of admission				
n	3176	1335	1196	1189
%	83.1	73.4	77.6	75.3
Inhaled nitric oxide on day of admission				
n	201	57	56	51
%	5.3	3.2	3.7	3.3
Treatment with inotropes on day of admission				
n	1099	320	295	288
%	29.0	17.9	19.3	18.5
Early-onset infection (in the first 3 days, defined using NNAP's definition)				
n	44	11	16	11
%	1.1	0.6	1.0	0.7
Admission from postnatal ward				
n	30	14	14	11
%	0.8	0.7	0.9	0.7
Postnatal transfer to another neonatal unit within the first 48 hours				
n	1908	913	790	796
%	48.0	48.8	48.8	49.2

a Data are collected via a check box indicating presence of condition. Therefore, it is not possible to distinguish between missing data and presence of no condition.

Note
The results were averaged over 25 matched replications.

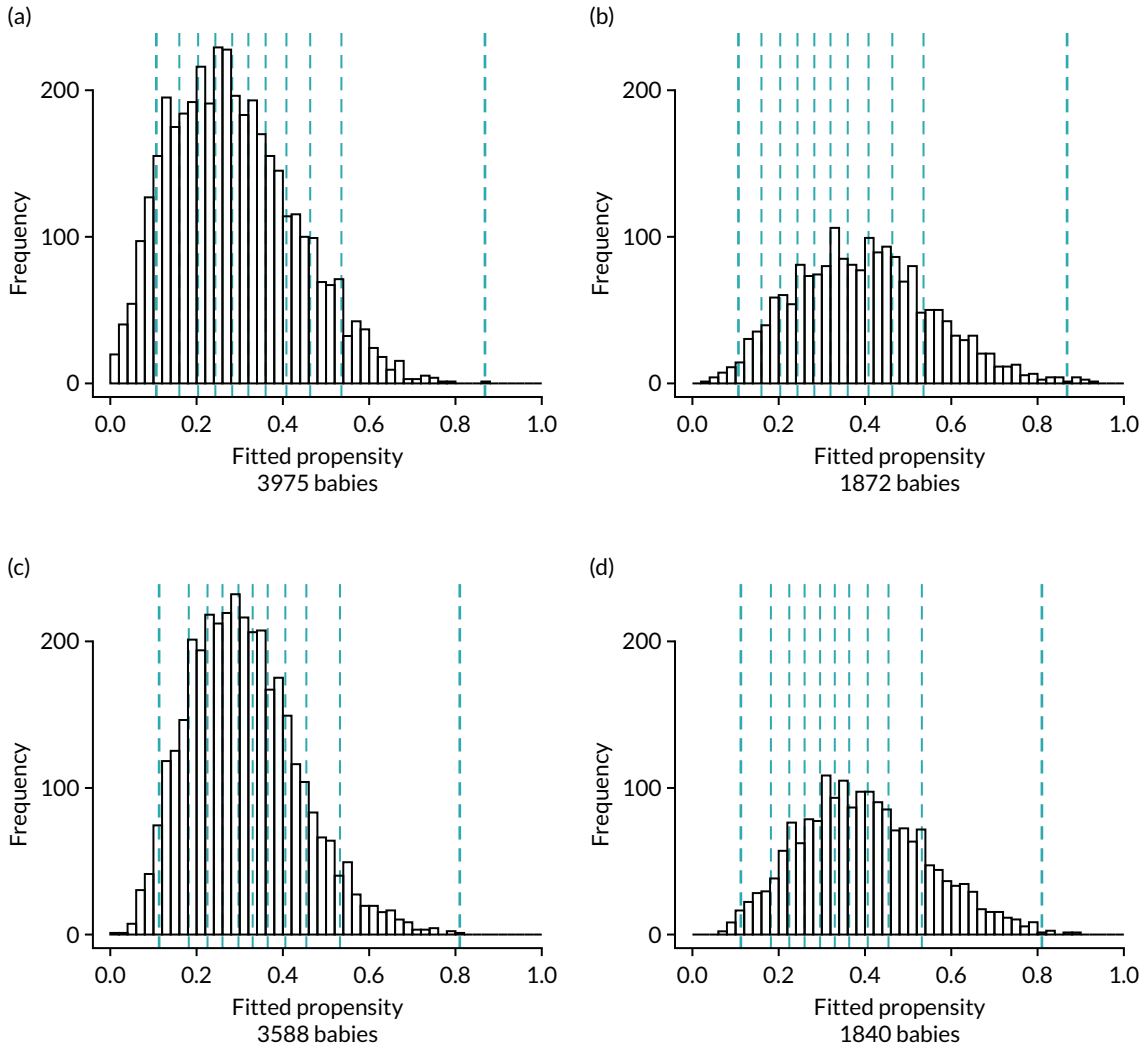

FIGURE 4 Histograms of estimated propensity scores for primary enteral feeding analysis. Thick vertical dashed lines indicate trimming thresholds for extreme propensities, thin vertical dashed lines indicate propensity deciles for babies retained for the analysis. (a) Round 1, no enteral feeds; (b) round 1, received enteral feeds; (c) round 2, no enteral feeds; and (d) round 2, received enteral feeds.

Figure 5 presents the balance plot for the background variables included in the final enteral nutrition comparison propensity model. The dashed black line indicates perfect balance between the enteral nutrition for a specific background variable. The shaded area indicates the acceptable limits of imbalance for any variable, equivalent to an imbalance of ≤ 0.01 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 0.064 and the balances are between −0.248 and 0.188. The mean balance for the matched data set is 0.0090 and the balances are between −0.037 and 0.029. The mean balances are displayed in *Figure 5*.

The balance plot (see *Figure 5*) demonstrates that several variables in the unmatched cohort exhibited large imbalances between the babies who were provided enteral feeds and the babies from whom enteral feeds were withheld. For example, unacceptable levels of imbalance (imbalance of > 0.1 in absolute value) between the two groups existed in the proportion of babies receiving respiratory

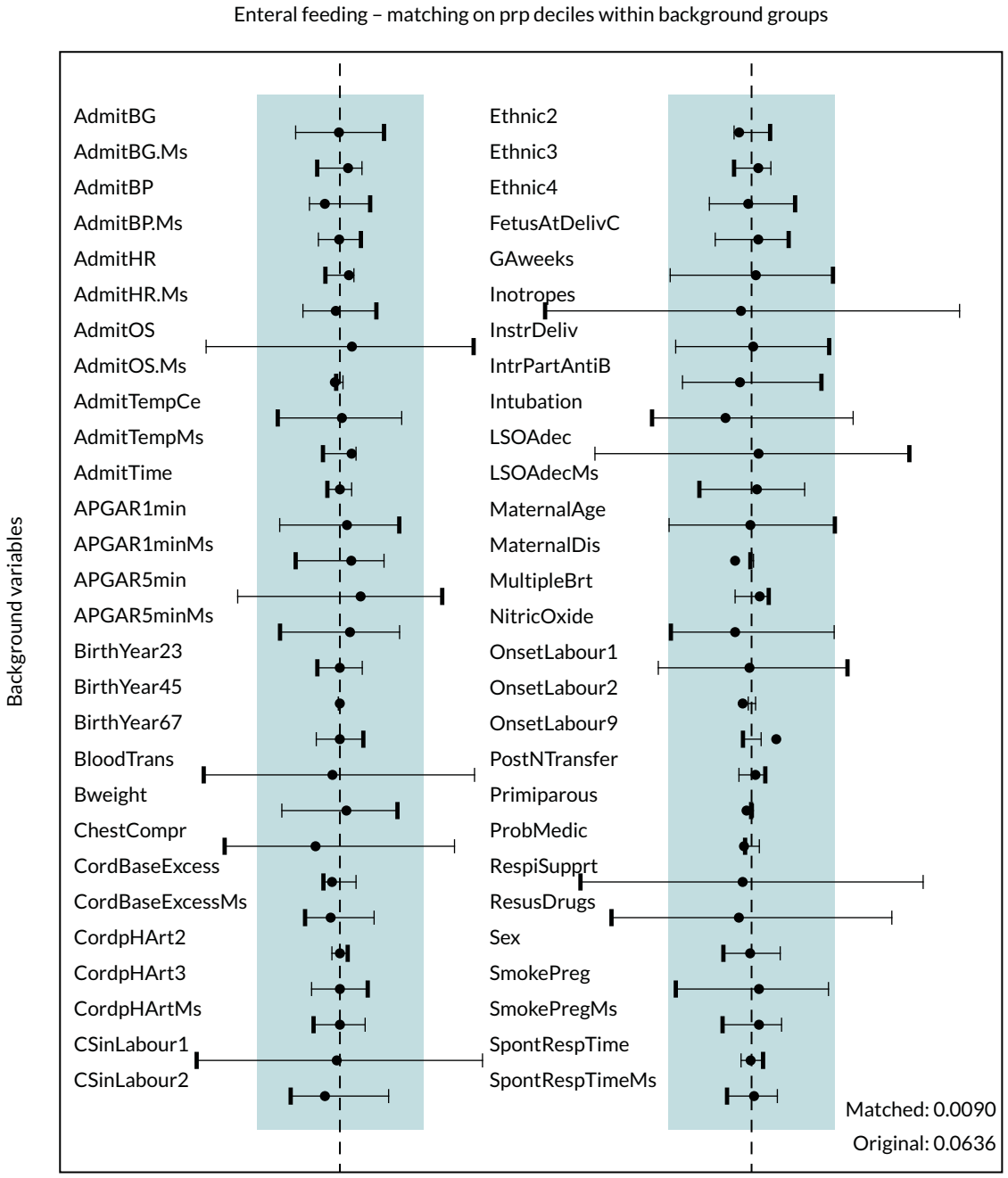

FIGURE 5 Balance plot for primary analysis of the effect of enteral feeding (1 : 1 matching within propensity score deciles). The dashed black line indicates perfect balance for a specific background variable. The shaded area indicates the acceptable limits of imbalance for any variable, equivalent to 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. Mean balances are displayed in the bottom right of the figure. AdmitBG, admission glucose; AdmitBP, admission blood pressure; AdmitHR, admission heart rate; AdmitOS, oxygen saturation on admission; AdmitTempCe, admission temperature; AdmitTime, admission time; BloodTrans, blood transfusion on day 1; Bweight, birthweight; ChestCompr, chest compressions at resuscitation; CordBaseExcess, umbilical cord base excess; CordpHArt, umbilical cord arterial pH; CsinLabour, in-labour caesarean; FetusAtDelivC, presentation of fetus at delivery; GAweeks, gestational age in weeks; InstrDeliv, instrumental delivery; IntrPartAntiB, intrapartum antibiotics; LSOAdec, LSOA decile; MaternalDis, maternal obstetric condition; Ms, data for this item were missing; MulipleBrt, multiple birth set; OnsetLabour, spontaneous/induced labour; PostNTransfer, postnatal transfer; ProbMedic, maternal medical condition in pregnancy; prp, propensity; RespiSupprt, received respiratory support on day of admission; ResusDrugs, received drugs during resuscitation; SmokePreg, maternal smoking in pregnancy; SpontRespTime, time to first breath.

support (see *Figure 5*, RespiSupprt) and the proportion of babies receiving blood transfusions (see *Figure 5*, BloodTrans). However, after the process of matching all background variables showed acceptable levels of imbalance and in the vast majority of cases the balance was much improved when compared with the unmatched cohort.

Results for outcomes in enteral feeding matched comparisons

The outcomes in babies who were enterally fed during therapeutic hypothermia and in babies who were not fed are presented in *Table 10*, in unmatched and matched cohorts. *Tables 11* and *12* present the results for binary and continuous outcome variables, respectively. The results for dichotomised outcome variables can be found in *Appendix 5*, *Table 32*.

The incidence of severe NEC was so low that cases were potentially identifiable and, therefore, counts of < 5 were used in *Tables 10* and *11*. Owing to the small numbers of cases in both babies who were fed and babies from whom feeds were withheld, no further analyses were undertaken for severe NEC. Although it was rare in both groups, following matching the incidence of pragmatically defined NEC was lower in babies fed than in babies not fed during therapeutic hypothermia (0.5% and 1.1%, respectively; $p = 0.03$) (see *Tables 10* and *11*).

TABLE 10 Outcome variables, by enteral feeding intervention groups, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enterally fed	No enteral feeds	Enterally fed
Total number of babies	3975	1872	1618	1618
Severe NEC				
n	< 5	< 5	< 5	< 5
NEC (pragmatic definition)				
n	54	11	18	9
%	1.4	0.6	1.1	0.6
Late-onset infection (NNAP definition)				
n	25	5	8	< 5
%	0.6	0.3	0.5	
Late-onset infection (pragmatic definition)				
n	1193	321	460	271
%	30.0	17.1	28.4	16.8
Survival at discharge				
n	3498	1794	1465	1552
%	88.1	95.9	90.6	96.0
Hypoglycaemia				
n	846	316	293	269
%	21.3	16.9	18.1	16.6

continued

TABLE 10 Outcome variables, by enteral feeding intervention groups, for unmatched and matched cohorts (*continued*)

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enterally fed	No enteral feeds	Enterally fed
Breastfeeding at discharge				
n	1690	1029	752	883
%	42.5	55.0	46.5	54.6
Onset of breastfeeding (days)				
Median	7	6	7	6
Lower quartile	6	5	6	5
Upper quartile	10	8	9.4	8
Missing, *n*	1735	544	626	477
%	43.6	29.1	38.7	29.5
≤ 28 days, *n*	2211	1320	982	1133
%	55.6	70.5	60.7	70.0
Time to first mother's milk (days)				
Median	5	3	5	3
Lower quartile	5	2	5	2
Upper quartile	6	4	6	4
Missing, *n*	832	221	294	197
%	20.9	11.8	18.2	12.2
≤ 28 days, *n*	3140	1650	1324	1420
%	79.0	88.1	81.8	87.8
Received PN				
n	1689	683	674	596
%	42.5	36.5	41.6	36.8
Duration of PN (days)				
Median	3	3	3	3
Lower quartile	2	2	2	2
Upper quartile	5	3	5	3
Had a central venous line				
n	3832	1637	1546	1417
%	96.4	87.4	95.5	87.6
Days of central venous line in situ				
Median	5	4	5	4
Lower quartile	4	3	4	3
Upper quartile	7	5	6	5

TABLE 10 Outcome variables, by enteral feeding intervention groups, for unmatched and matched cohorts (*continued*)

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enterally fed	No enteral feeds	Enterally fed
Weight *z*-score at discharge				
Median	−0.7	−0.6	−0.6	−0.7
Lower quartile	−1.5	−1.3	−1.4	−1.4
Upper quartile	0.1	0.2	0.2	0.1
Missing, *n*	2	9	4	8
%	0.1	0.5	0.1	0.3
Length of stay (days)				
Median	11	10	11	10
Lower quartile	8	7	8	7
Upper quartile	17	13	16	13
> 14 days, *n*	1351	392	484	344
%	34.0	21.0	29.9	21.3

Note
The results were averaged over 25 matched replications.

TABLE 11 Analysis of binary outcome variables for babies provided with enteral feeds vs. babies for whom enteral feeds were withheld

	Intervention, % (95% CI)				
Variable	No enteral feeds rate	Enterally fed rate	Rate difference, % (95% CI)	OR estimate (95% CI)	*p*-value
Total number of babies	1618	1618			
Severe NEC	n/a	n/a	n/a	n/a	n/a
NEC (pragmatic definition)	1.1 (0.7 to 1.4)	0.5 (0.2 to 0.9)	−0.5 (−1.0 to −0.1)	0.50 (0.22 to 1.12)	0.03
Late-onset infection (NNAP definition)	0.5 (0.2 to 0.7)	0.3 (0.04 to 0.4)	−0.2 (−0.5 to 0.1)	0.55 (0.17 to 1.80)	0.19
Late-onset infection (pragmatic definition)	28.4 (26.7 to 30.0)	16.7 (15.0 to 184)	−11.6 (−14.0 to −9.3)	0.51 (0.43 to 0.60)	< 0.001
Hypoglycaemia	18.1 (16.7 to 19.5)	16.6 (15.0 to 18.3)	−1.5 (−3.7 to 0.6)	0.90 (0.75 to 1.08)	0.17
Survival at discharge	90.8 (89.7 to 91.8)	96.0 (95.0 to 96.8)	5.2 (3.9 to 6.6)	2.42 (1.80 to 3.26)	< 0.001
Breastfeeding at discharge	46.7 (44.8 to 48.5)	54.6 (52.4 to 56.8)	8.0 (5.1 to 10.8)	1.38 (1.20 to 1.58)	< 0.001

n/a, not analysed.
Note
Results averaged over the 25 replications of the matching procedure.

TABLE 12 Analysis of continuous outcome variables for babies provided with enteral feeds vs. babies for whom enteral feeds were withheld

Variable	Intervention		Difference (95% CI)	*p*-value
	No enteral feeds	Enterally fed		
Total number of babies	1618	1618		
Length of stay (days) (95% CI)	14.8 (14.2 to 15.5)	12.7 (12.0 to 13.3)	−2.2 (−3.0 to −1.2)	< 0.001
First day suckling at breast (95% CI)	8.7 (8.4 to 9.0)	7.3 (6.9 to 7.7)	−1.4 (−1.9 to −0.9)	< 0.001
First day of maternal milk 95% CI)	5.4 (5.4 to 5.5)	3.3 (3.2 to 3.4)	−2.1 (−2.2 to −2.0)	< 0.001
Duration of PN (days) (95% CI)	3.7 (3.5 to 3.8)	3.0 (2.7 to 3.4)	−0.7 (−1.1 to −0.2)	0.02
Duration of central venous line in situ (days) (95% CI)	5.5 (5.3 to 5.7)	4.3 (4.1 to 4.5)	−1.2 (−1.5 to −0.9)	< 0.001
Weight *z*-score (95% CI)	−0.60 (−0.65 to −0.55)	−0.54 (−0.59 to −0.48)	0.06 (−0.01 to 0.13)	0.11

Note
Results averaged over the 25 replications of the matching procedure.

Late-onset infection, as defined using the NNAP definition, was rare and, after matching the incidence, was similar between babies fed and babies not fed during therapeutic hypothermia. We found no evidence ($p = 0.19$) of a difference in the rates of NNAP-defined late-onset infection between babies who received enteral feeds and babies from whom enteral feeds were withheld. However, when defined using the more pragmatic definition, there was strong evidence ($p < 0.001$) that the risk of late-onset infection was lower in babies who were provided with enteral feeds. Babies who were provided with enteral feeds were estimated to have approximately half the odds of having pragmatically defined late-onset infection than babies from whom enteral feeds were withheld (OR 0.51, 95% CI 0.43 to 0.60) (see *Table 11*).

We found strong evidence ($p < 0.001$) of a higher survival rate in babies who were fed during therapeutic hypothermia in the matched comparison, in addition to higher rates of breastfeeding at discharge ($p < 0.001$) (see *Tables 10* and *11*). In matched comparisons, babies who received enteral feeds during therapeutic hypothermia had a mean length of stay of 2.2 days (95% CI 1.2 to 3.0 days) shorter than those babies who were not fed ($p < 0.001$) and a mean duration of central line placement in situ that was 1.2 days (95% CI 0.9 to 1.5 days) shorter than those who were not fed ($p < 0.001$) (see *Table 12*). Similar patterns were observed in matched comparisons for the dichotomised versions of the continuous outcomes. The odds of a baby staying in the neonatal unit for > 14 days was reduced by an estimated 37% in babies fed compared with those from whom enteral feeds were withheld (OR 0.63, 95% CI 0.54 to 0.74; $p < 0.001$) (see *Appendix 5*, *Table 32*).

Sensitivity analyses

The reduction of the time period of interest to years of birth (i.e. 2012–17), omitting the first 2 years of the study period, resulted in a reduction in the number of matched pairs to 1300. Excluding babies who were not actively recorded as receiving no enteral feeds reduced the matched cohort to 1453 pairs and adding receipt of PN on the first day of life resulted in a matched cohort of 1644 pairs. Results of the three sensitivity analyses were consistent with the corresponding results of the primary analysis (*Table 13*; see also *Appendix 6*, *Table 33*).

TABLE 13 Estimates of the effect of receiving enteral feeds for binary and continuous outcomes from sensitivity analyses

	Sensitivity analysis		
Variable	**Years 2012–17**	**Intervention redefined**	**Inclusion of PN in PSM**
Binary outcomes: estimate of rate difference (95% CI) [*p*-value]			
NEC (pragmatic definition)	−0.7 (−1.3 to −0.1) [0.03]	−0.6 (−1.2 to −0.1) [0.07]	−0.5 (−1.0 to −0.0) [0.15]
Late-onset BSI (NNAP definition)	−0.4 (−0.8 to −0.003) [0.05]	−0.3 (−0.7 to 0.1) [0.22]	−0.3 (−0.6 to −0.0) [0.15]
Late-onset BSI (pragmatic definition)	−11.1 (−13.7 to −8.4) [< 0.001]	−11.3 (−13.9 to −8.7) [< 0.001]	−11.4 (−13.8 to −9.1) [< 0.001]
Hypoglycaemia	−1.3 (−3.7 to 1.2) [0.31]	−0.5 (−2.8 to 1.9) [0.83]	−1.1 (−3.3 to 1.1) [0.52]
Survival at discharge	4.8 (3.3 to 6.3) [< 0.001]	4.4 (2.9 to 5.9) [< 0.001]	4.5 (3.2 to 5.8) [< 0.001]
Breastfeeding at discharge	8.3 (5.0 to 11.5) [< 0.001]	6.5 (3.4 to 9.6) [0.003]	7.9 (5.0 to 10.7) [< 0.001]
Continuous outcomes: mean difference (95% CI) [*p*-value]			
Length of stay (days)	−2.3 (−3.4 to −1.3) [< 0.001]	−2.0 (−2.9 to −1.1) [< 0.001]	−2.0 (−2.8 to −1.1) [< 0.001]
First day of suckling at breast	−1.3 (−1.9 to −0.7) [< 0.001]	−1.2 (−1.8 to −0.6) [< 0.001]	−1.4 (−1.9 to −0.9) [< 0.001]
First day of maternal milk	−2.2 (−2.3 to −2.0) [< 0.001]	−2.1 (−2.3 to −2.0) [< 0.001]	−2.1 (−2.2 to −2.0) [< 0.001]
Duration of PN (days)	−0.7 (−1.2 to −0.2) [0.02]	−0.7 (−1.2 to −0.2) [0.02]	−0.6 (−1.0 to −0.2) [0.01]
Duration of central venous line in situ (days)	−1.3 (−1.6 to −1.0) [< 0.001]	−1.2 (−1.4 to −1.0) [< 0.001]	−1.1 (−1.4 to −0.9) [< 0.001]
Weight *z*-score at discharge	0.09 (0.01 to 0.17) [0.06]	0.08 (0.00 to 0.16) [0.13]	0.07 (0.00 to 0.15) [0.12]

PSM, propensity score model.
Note
The results were averaged over the 25 replications of the matching procedure.

Babies admitted from the postnatal ward

A subgroup analysis was planned to exclude all babies whose first admission to neonatal care was from a postnatal ward to exclude babies to whom therapeutic hypothermia was administered following postnatal collapse rather than following resuscitation at birth. Only 46 babies in the entire cohort were admitted from a postnatal ward and, therefore, this sensitivity analysis was not conducted. The number of babies admitted from the postnatal ward by enteral feeding group is similar before and after matching (see *Table 9*).

Influence of alternative matching methods

The results were found to be consistent across all alternative methods of matching on the propensity groups and principal background variables (see *Appendix 7*, *Figure 9*).

Patterns of enteral feeding

Details of the types of milk that babies received during therapeutic hypothermia and up to day 7, in both matched and unmatched cohorts, are shown in *Figure 6*. In both cohorts, the most common enteral feed type was mother's breast milk. There were a substantial number of missing data on the type of milk provided to babies on the first day of life.

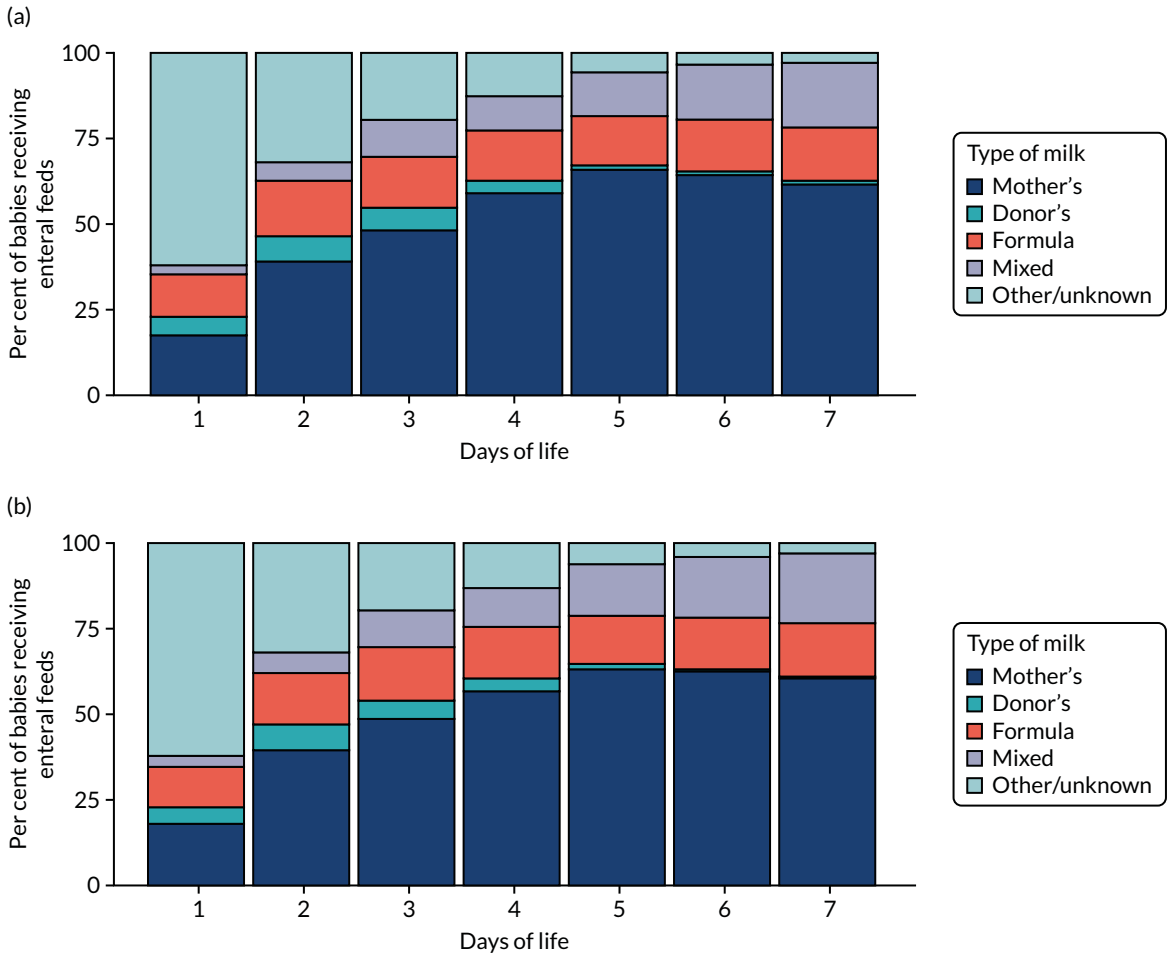

FIGURE 6 Type of enteral feeds provided up to 7 days of life for babies treated with therapeutic hypothermia, in (a) unmatched and (b) matched cohorts, as a proportion of babies who received enteral feeds.

In the unmatched cohort the median time to first enteral feed was 5 days after birth, with the probability of being enterally fed reaching 80% at 6 days after birth.

The highest rates of enteral feeding were in the North West London ODN and South East Coast ODN (89% and 59% of babies treated with therapeutic hypothermia, respectively). The lowest rates of enteral feeding during therapeutic hypothermia were in West Midlands (12%), East Midlands (13%) and Wales (13%) (*Table 14*).

Parenteral nutrition analysis

Overview

In this section we present matched analyses comparing different approaches to PN (i.e. administering PN vs. not administering PN during therapeutic hypothermia). We present summary data for selected background variables within the unmatched groups and summary background data by use of PN for the matched subgroups, and data describing the quality of the match. The main results of the primary analyses are presented as estimates and CIs for the treatment effects for each outcome.

TABLE 14 Provision of enteral feeding during therapeutic hypothermia by neonatal ODN

	Provision of enteral feeds			
	No		Yes	
ODN	*n*	%	*n*	%
East Midlands	313	86.9	47	13.1
East of England	369	68.0	174	32.0
North Central and East London	324	72.5	123	27.5
North West	521	81.8	116	18.2
North West London	25	11.0	203	89.0
Northern	157	69.5	69	30.5
South East Coast	228	41.0	328	59.0
South West	314	62.6	188	37.5
South London	253	66.1	130	33.9
Thames Valley and Wessex	361	63.9	204	36.1
West Midlands	492	88.0	67	12.0
Yorkshire and the Humber	290	70.7	120	29.3
Isle of Man	< 5		< 5	
Scotland	121	63.0	71	37.0
Wales	194	86.6	30	13.4
Total	3962	67.9	1870	32.1

Note
Seventeen babies were treated at units that could not be assigned to a relevant ODN and a further 181 babies were missing information on enteral feeding status.

Primary analysis

Background variables in unmatched and matched cohorts

Tables 15 and *16* (see also *Appendix 8*, *Tables 34–37*) present the background characteristics of babies recorded as having received PN during therapeutic hypothermia and those babies who were not recorded as receiving PN, before and after matching. Prior to matching, the characteristics of babies who received PN were similar to those who did not receive PN, although the latter tended to have higher proportions of mothers from areas of deprivation. After matching, differences in baseline characteristics between babies who received PN and babies who did not receive PN were reduced (see *Tables 15* and *16*).

TABLE 15 Background variables, by parenteral nutrition intervention groups, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Total number of babies	4535	1475	1240	1240
Male				
n	2507	810	652	664
%	55.3	54.9	52.6	53.5

continued

TABLE 15 Background variables, by parenteral nutrition intervention groups, for unmatched and matched cohorts (*continued*)

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Multiple birth				
n	121	58	42	45
%	2.7	3.9	3.4	3.6
Gestational age at birth (weeks)				
Mean	39.4	39.29	39.4	39.4
SD	1.55	1.6	1.6	1.6
Birthweight (g)				
Mean	3385	3321	3330	3328
SD	621	631	609	628
Caesarean delivery				
n	2066	667	545	549
%	47.7	47.1	45.9	46.1
Maternal age (years)				
Median	30	31	30	31
Lower quartile	26	26	26	26
Upper quartile	35	34	34	34
Maternal suspected chorioamnionitis				
n	479	175	147	150
%	12.8	14.5	14.5	14.6
Smoking in pregnancy				
n	520	211	175	176
%	13.3	16.9	16.6	16.8
Ethnicity (maternal) (%)				
White	65.7	61.4	80.8	79.9
Asian and mixed	11.2	6.8	7.9	7.5
Black and mixed	7.5	4.3	4.3	5
Other and missing	15.5	27.5	6.9	7.6
Maternal diabetes[a]				
n	191	65	49	53
%	4.2	4.4	4.0	4.3
Deprivation score (LSOA) (%)				
In deciles 1 or 2 (most deprived)	27.9	22.3	23.9	21.7
Primiparous[a]				
n	2425	778	669	671
%	53.5	52.7	54	54.1

a Data are collected via a checkbox indicating presence of condition. Therefore, it is not possible to distinguish between missing data and presence of no condition.

Note

The results were averaged over 25 matched replications.

TABLE 16 Neonatal clinical characteristics, by parenteral nutrition intervention groups, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Total number of babies	4535	1475	1240	1240
Cord blood gas pH: arterial				
> 7.0, *n*	1439	451	396	396
%	44.4	44.0	45.3	45.3
6.9–7.0, *n*	756	248	198	198
%	23.3	24.2	22.7	22.7
< 6.9, *n*	1049	326	280	280
%	32.3	31.8	32.0	32.0
Missing, *n*	1291	450	366	366
%	28.5	30.5	29.5	29.5
Apgar score at 1 minute				
0 or 1, *n*	2062	679	553	562
%	45.5	46.0	44.6	45.3
2–4, *n*	1601	494	429	415
%	35.3	33.5	34.6	33.5
5–7, *n*	347	116	99	99
%	7.7	7.9	8	8
8–10, *n*	165	53	47	49
%	3.6	3.6	3.7	4.0
Missing, *n*	360	133	113	115
%	7.9	9.0	9.1	9.3
Apgar score at 5 minutes				
0 or 1, *n*	730	218	188	182
%	16.1	14.8	15.1	14.7
2–4, *n*	1704	563	450	470
%	37.6	38.2	36.2	37.9
5–7, *n*	1372	433	389	362
%	30.3	29.4	31.3	29.2
8–10, *n*	374	130	107	116
%	8.2	8.8	8.6	9.4
Missing, *n*	355	131	107	109
%	7.8	8.9	8.6	8.8
Received chest compressions at resuscitation[a]				
n	1705	523	431	427
%	37.6	35.5	34.8	34.4
Received resuscitation drugs[a]				
n	719	206	176	172
%	15.9	14.0	14.2	13.9

continued

TABLE 16 Neonatal clinical characteristics, by parenteral nutrition intervention groups, for unmatched and matched cohorts (*continued*)

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Intubated at resuscitation[a]				
n	2925	935	784	783
%	64.5	63.4	63.2	63.1
Time to first spontaneous breath				
6 (> 5 minutes) , *n*	2701	896	757	758
%	59.6	60.7	61	61.1
Missing, *n*	1160	344	283	284
%	25.6	23.3	22.8	22.9
Time to admission (minutes)				
Median	30	30	30	29
Lower quartile	20	20	21	20
Upper quartile	44	45	45	44
Temperature (°C)				
Mean	35.9	35.9	35.9	35.9
SD	1.3	1.2	1.3	1.2
Transfusion of any blood products on day of admission				
n	648	214	195	187
%	14.3	14.5	15.8	15.1
Mechanical ventilation on day of admission				
n	3508	1122	951	956
%	80.2	79.5	79.6	80.2
Inhaled nitric oxide on day of admission				
n	197	70	50	58
%	4.5	5.0	4.2	4.9
Treatment with inotropes on day of admission				
n	1126	335	295	287
%	26.0	23.9	25.0	24.2
Early-onset infection (in the first 3 days, defined using NNAP definition)				
n	37	18	9	14
%	0.8	1.2	0.7	1.1
Admission from postnatal ward				
n	32	12	11	11
%	0.7	0.8	0.9	0.9
Postnatal transfer to another neonatal unit within the first 48 hours				
n	2219	640	546	549
%	48.9	43.4	44.0	44.2

a Data are collected via a checkbox indicating presence of condition. Therefore, it is not possible to distinguish between missing data and presence of no condition.

Note

The results were averaged over 25 matched replications.

Quality of the match of parenteral nutrition analysis

Figure 7 presents the estimated propensity scores from the primary PN comparison propensity model by intervention (i.e. received PN) and control (i.e. did not receive PN) groups. The fitted propensities for the two treatment groups have good overlap. Data from 687 babies (11.4% of unmatched sample) were discarded because of extreme propensities.

Figure 8 presents the balance plot for the background variables included in the primary propensity model for the PN comparison. As previously, the dashed black line indicates perfect balance between the PN analysis groups for each specific background variable. The shaded area indicates the acceptable limits of imbalance for the variables, from −0.1 to 0.1. The imbalance for a specific background variable in the unmatched cohort is marked by a bold dash and the light dash indicates this imbalance by −1 to facilitate comparison to imbalance in the matched cohort, which itself 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 data set is 0.010 and the balances are between −0.025 and 0.051. The mean balances are displayed in *Figure 8*.

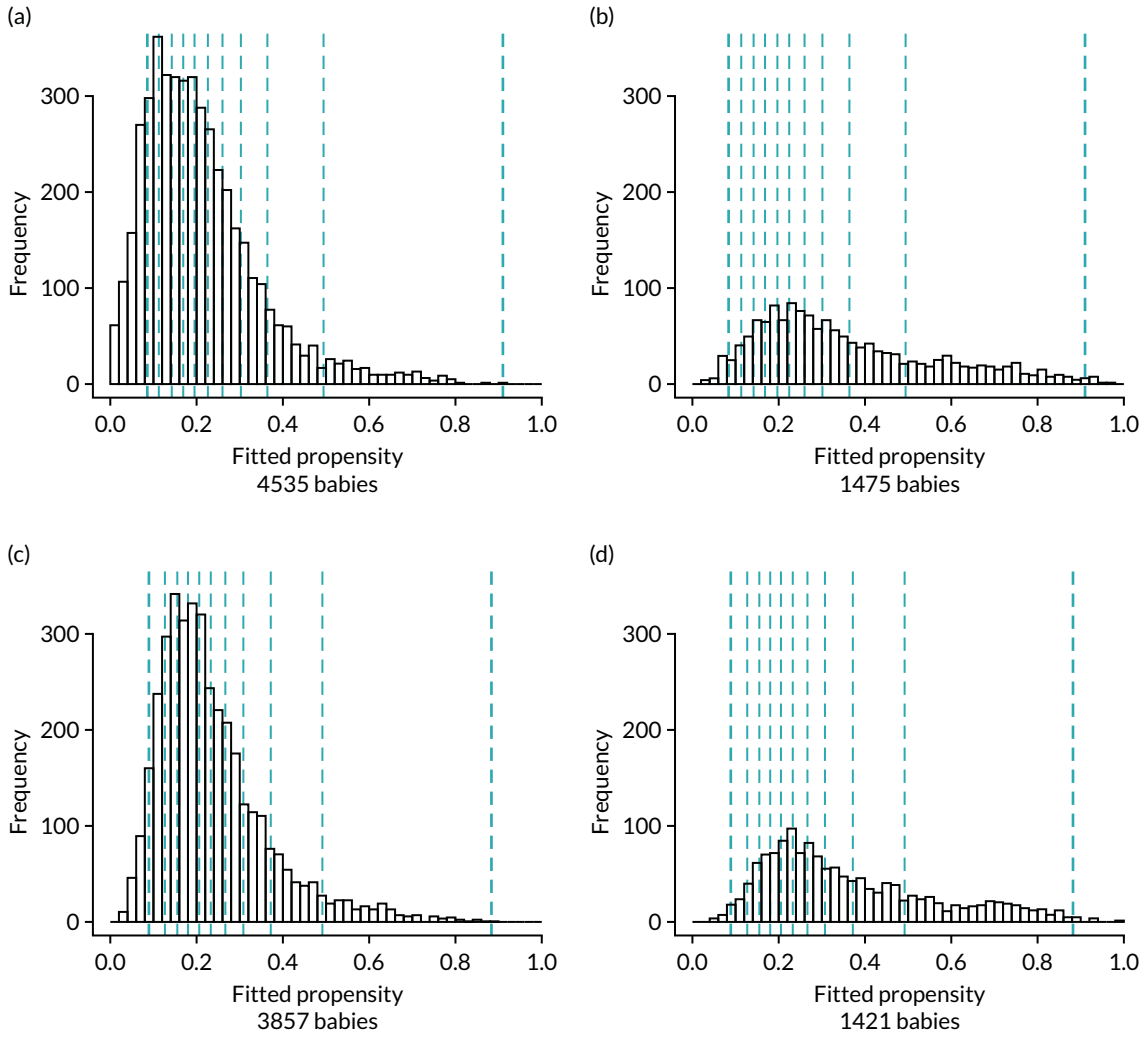

FIGURE 7 Histograms of estimated propensity scores for primary parenteral nutrition analysis. Thick vertical dashed lines indicate trimming thresholds for extreme propensities and thin vertical dashed lines indicate propensity deciles for babies retained for analysis. (a) Round 1, no parental nutrition; (b) round 1, received parental nutrition; (c) round 2, no parental nutrition; and (d) round 2, received parental nutrition.

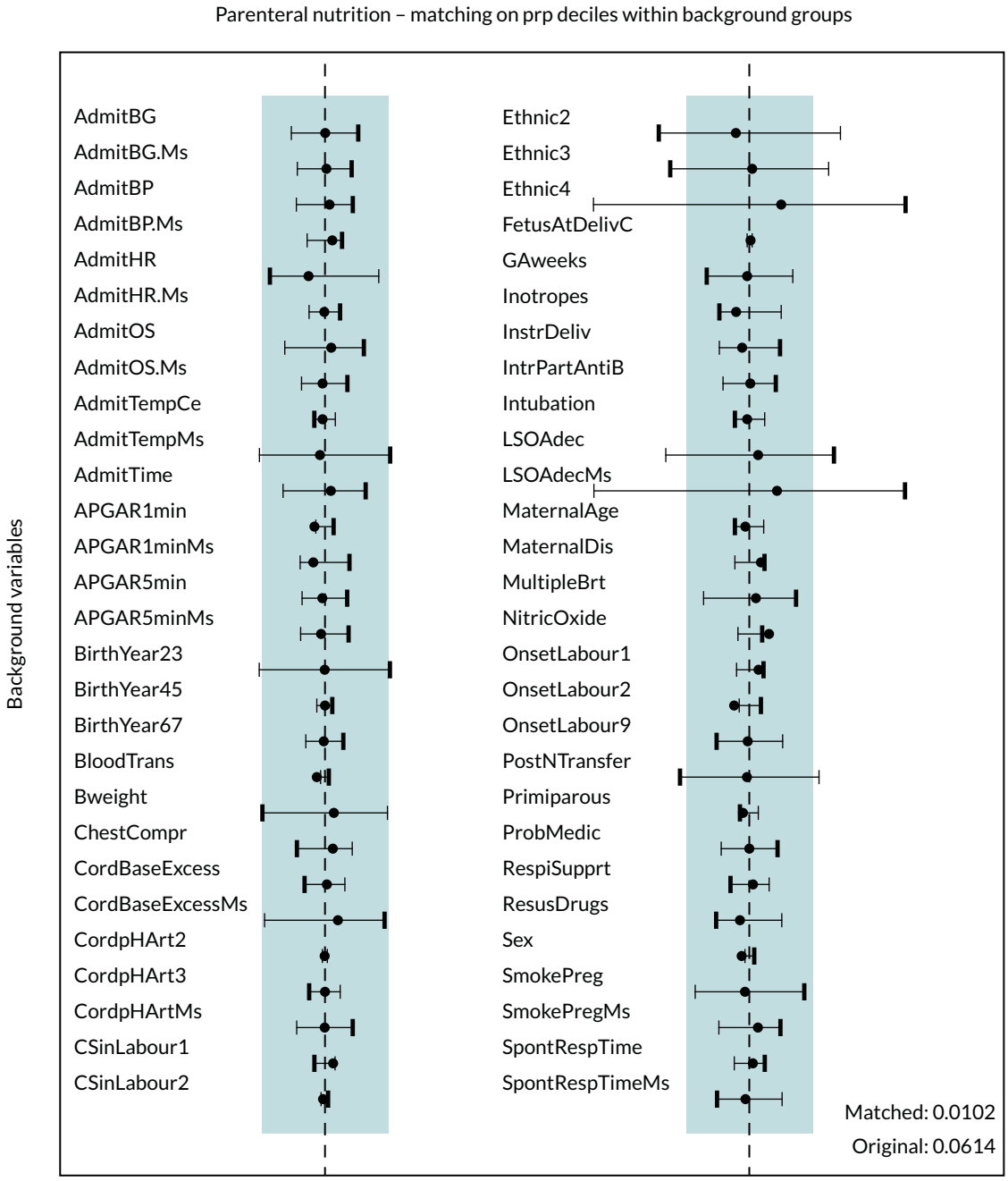

FIGURE 8 Balance plot for primary analysis of the effect of parenteral nutrition (1 : 1 matching within propensity score deciles). The dashed black line indicates perfect balance for a specific background variable. The shaded area indicates the acceptable limits of imbalance for any variable, equivalent 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 (multiplied by −1), which represents the same extent of imbalance. The imbalance in the matched cohort is marked by the black disc. Mean balances are displayed in the bottom right of the figure. AdmitBG, admission glucose; AdmitBP, admission blood pressure; AdmitHR, admission heart rate; AdmitOS, oxygen saturation on admission; AdmitTempCe, admission temperature; AdmitTime, admission time; BloodTrans, blood transfusion on day 1; Bweight, birthweight; ChestCompr, chest compressions at resuscitation; CordBaseExcess, umbilical cord base excess; CordpHArt, umbilical cord arterial pH; CsinLabour, in-labour caesarean; FetusAtDelivC, presentation of fetus at delivery; GAweeks, gestational age in weeks; InstrDeliv, instrumental delivery; IntrPartAntiB, intrapartum antibiotics; LSOAdec, LSOA decile; MaternalDis, maternal obstetric condition; Ms, data for this item were missing; MulipleBrt, multiple birth set; OnsetLabour, spontaneous/induced labour; PostNTransfer, postnatal transfer; ProbMedic, maternal medical condition in pregnancy; prp, propensity; RespiSupprt, received respiratory support on day of admission; ResusDrugs, received drugs during resuscitation; SmokePreg, maternal smoking in pregnancy; SpontRespTime, time to first breath.

The balance plot shows that several variables in the unmatched cohort exhibited large imbalances between the two treatment groups. For example, unacceptable levels of imbalance (i.e. an imbalance of > 0.1 in absolute value) were present for ethnicity other or not given, and missing deprivation score. After matching, all background variables showed acceptable levels of imbalance. Several variables, including sex and proportion of babies delivered by caesarean section, demonstrated slightly greater imbalances after matching. The balance plot confirms that these imbalances are not substantial and that all variables included in the propensity model have acceptable levels of imbalance after matching.

Results for outcomes in parenteral nutrition matched comparisons

Outcomes for babies who received PN during therapeutic hypothermia and babies who did not are presented in *Table 17*, in unmatched and matched cohorts. *Tables 18* and *19* present the results for binary and continuous outcome variables. The results for dichotomised outcome variables can be found in *Appendix 9*, *Table 38*.

TABLE 17 Outcome variables, by parenteral nutrition intervention groups, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Total number of babies	4538	1476	1240	1240
Late-onset infection (NNAP definition)				
n	16	14	< 5	11
%	0.4	0.9		0.9
Late-onset infection (pragmatic definition)				
n	1175	383	313	323
%	25.9	26.0	25.3	26.1
Severe NEC				
n	6	< 5	7	< 5
%	0.1		0.6	
NEC (pragmatic definition)				
n	52	16	17	13
%	1.1	1.1	1.4	1.1
Survival at discharge				
n	4056	1374	1116	1154
%	89.5	93.2	90.0	93.1
Hypoglycaemia				
n	946	258	235	212
%	20.9	17.5	18.9	17.1
Breastfeeding at discharge				
n	2110	670	582	575
%	46.5	45.4	47.0	46.4

continued

TABLE 17 Outcome variables, by parenteral nutrition intervention groups, for unmatched and matched cohorts (*continued*)

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Onset of breastfeeding (days)				
Median	7	7	7	7
Lower quartile	6	6	6	6
Upper quartile	9	9	9	9
Missing, *n*	1774	576	488	474
%	39.1	39.1	39.3	38.2
≤ 28 days, *n*	2735	888	744	757
%	60.3	60.2	60.0	61.0
Time to first mother's milk (days)				
Median	5	5	5	5
Lower quartile	4	3	4	3
Upper quartile	6	5	6	5
Missing, *n*	868	223	235	182
%	19.1	15.1	18.9	14.7
≤ 28 days, *n*	3665	1250	1005	1057
%	80.8	84.7	81.1	85.2
Had a central venous line				
n	4184	1441	1145	1213
%	92.3	97.7	92.3	97.9
Days of central venous line in situ				
Median	5	5	5	5
Lower quartile	3	4	3	4
Upper quartile	6	7	6	7
Weight *z*-score at discharge				
Median	−0.6	−0.7	−0.7	−0.6
Lower quartile	−1.4	−1.4	−1.4	−1.4
Upper quartile	0.2	0.1	0.1	0.2
Missing, *n*	9	2	8	4
%	0.2	0.1	0.2	0.2
Length of stay (days)				
Median	11	10	10	11
Lower quartile	8	7	8	8
Upper quartile	17	13	16	16
> 14 days, *n*	1338	466	361	382
%	29.5	31.6	29.1	30.8

Note
The results were averaged over 25 matched replications.

TABLE 18 Analysis of binary outcome variables for babies provided with parenteral nutrition vs. babies from whom parenteral nutrition was withheld

Variable	Intervention, % (95% CI)		Rate difference, % (95% CI)	OR estimate (95% CI)	*p*-value
	No PN rate	PN rate			
Total number of babies	1240	1240			
Late-onset infection (NNAP definition)	0.3 (0.1 to 0.5)	0.9 (0.4 to 1.4)	0.6 (0.1 to 1.2)	3.04 (0.95 to 9.76)	0.03[a]
Late-onset infection (pragmatic definition)	25.3 (23.6 to 27.1)	26.1 (23.8 to 28.3)	0.8 (−2.1 to 3.6)	1.04 (0.87 to 1.25)	0.61
Severe NEC	n/a	n/a	n/a	n/a	n/a
NEC (pragmatic definition)	1.4 (0.9 to 1.9)	1.1 (0.6 to 1.6)	−0.3 (−1.0 to 0.4)	0.77 (0.38 to 1.58)	0.39
Hypoglycaemia	19.0 (17.5 to 20.6)	17.0 (15.1 to 18.9)	−2.1 (−4.5 to 0.4)	0.87 (0.71 to 1.07)	0.10
Survival at discharge	89.9 (88.7 to 91.1)	93.2 (91.8 to 94.5)	3.1 (1.5 to 4.7)	1.50 (1.17 to 2.01)	< 0.001
Breastfeeding at discharge	47.0 (45.1 to 48.9)	46.4 (43.9 to 48.9)	−0.6 (−3.8 to 2.6)	0.98 (0.83 to 1.14)	0.71

n/a, not analysed.
a This *p*-value is common to the OR and to the difference in rates. Overlap of the CI cannot be taken for significance because it involves two intervals, both with a 5% margin.
Note
The data were for results averaged over 25 matched replications.

TABLE 19 Analysis of continuous outcome variables for babies provided with parenteral nutrition vs. babies from whom parenteral nutrition was withheld

Variable	Intervention		Difference (95% CI)	*p*-value
	No PN	PN		
Total number of babies	1240	1240		
Length of stay (days) (95% CI)	14.1 (13.6 to 14.7)	15.0 (14.1 to 15.8)	0.8 (−0.2 to 1.8)	0.12
Onset of breastfeeding (days) (95% CI)	8.4 (8.0 to 8.7)	8.6 (8.0 to 9.1)	0.2 (−0.5 to 0.8)	0.56
First maternal milk (days) (95% CI)	4.9 (4.8 to 4.9)	4.6 (4.5 to 4.8)	−0.2 (−0.4 to −0.1)	0.01
Duration of central venous line in situ (days) (95% CI)	5.1 (5.0 to 5.3)	6.0 (5.7 to 6.3)	0.9 (0.5 to 1.2)	< 0.001
Weight *z*-score (95% CI)	−0.66 (−0.71 to −0.61)	−0.65 (−0.71 to −0.58)	0.02 (−0.07 to 0.10)	0.68

Note
The data were for results averaged over 25 matched replications.

Although late-onset infection defined using the NNAP definition was rare, there was some evidence ($p = 0.03$) of increased late-onset infection in babies who were provided PN compared with babies from whom PN was withheld during therapeutic hypothermia (risk difference 0.6%, 95% CI 0.1% to 1.2%). Late-onset infection defined using the more pragmatic definition was more common, but we found no evidence of a difference ($p = 0.61$) in incidence between babies who did and did not receive PN during therapeutic hypothermia (see *Table 18*). Mortality was lower among babies who received PN during therapeutic hypothermia in the matched comparison. There was no evidence of differences between matched groups in the incidence of hypoglycaemia, pragmatically defined NEC or breastfeeding at discharge. The incidence of severe NEC was so low that cases were potentially identifiable and, therefore, counts of < 5 were used and comparative analyses after matching were not undertaken for this comparison.

After matching, length of stay, time to first breastfeed, time to first feed with maternal breast milk and weight at discharge were all similar between babies who received PN during therapeutic hypothermia and those who did not (see *Table 19*). Although there was a statistically significant difference in time to first feed with maternal breast milk, this difference of 0.2 days (95% CI 0.1 to 0.4 days) was not considered clinically important. Babies who did not receive PN had a shorter duration with a central line in situ, with a mean difference of approximately 1 day ($p < 0.001$).

Similar patterns were observed in matched comparisons when continuous outcomes were dichotomised. Babies who did not receive PN had a lower rate of any central line insertion than babies who received PN (92.4% vs. 97.9%; $p < 0.001$) (see *Appendix 9*, *Table 38*).

Sensitivity analyses

The reduction of the time period of interest to years 2012–17, omitting the first 2 years of the study period, resulted in a sample for the matched cohort of 1059 pairs, excluding babies who were not actively recorded as receiving no PN resulted in a matched cohort of 1253 pairs, and adding receipt of enteral nutrition on the first day of life resulted in a matched cohort of 1251 pairs. Results of the three sensitivity analyses were largely consistent with the corresponding results of the primary analysis (*Table 20*; see also *Appendix 10*, *Table 39*).

TABLE 20 Estimates of the effect of parenteral nutrition provision for binary and continuous outcomes from the sensitivity analyses

	Sensitivity analysis		
Variable	**Years 2012–17**	**Intervention redefined**	**Inclusion of enteral feeds on day 1 in PSM**
Total number of babies	2118	2506	2502
Binary outcomes: estimate of rate difference (95% CI) [*p*-value]			
Late-onset infection (NNAP definition)	0.6 (0.0 to 1.2) [0.04]	0.6 (0.1 to 1.1) [0.02]	0.6 (0.0 to 1.1) [0.03]
Late-onset infection (pragmatic definition)	2.2 (−0.8 to 5.3) [0.15]	1.4 (−1.4 to 4.2) [0.34]	1.7 (−1.0 to 4.5) [0.22]
NEC (pragmatic definition)	−0.4 (−1.2 to 0.4) [0.34]	−0.2 (−0.9 to 0.5) [0.62]	−0.3 (−1.0 to 0.4) [0.36]
Hypoglycaemia	−1.4 (−4.0 to 1.3) [0.32]	−2.1 (−4.5 to 0.3) [0.08]	−2.1 (−4.6 to 0.3) [0.08]
Survival at discharge	2.8 (0.9 to 4.8) [0.004]	3.0 (1.2 to 4.7) [< 0.001]	3.8 (2.0 to 5.5) [< 0.001]
Breastfeeding at discharge	−0.2 (−3.7 to 3.3) [0.90]	−0.1 (−3.3 to 3.1) [0.96]	0.4 (−2.8 to 3.5) [0.82]
Continuous outcomes: estimate of mean difference (95% CI) [*p*-value]			
Length of stay (days)	0.5 (−0.5 to 1.4) [0.32]	0.6 (−0.3 to 1.6) [0.16]	1.0 (0.1 to 1.9) [0.02]
First day suckling at breast (days)	−0.2 (−0.7 to 0.3) [0.51]	0.1 (−0.4 to 0.7) [0.63]	0.0 (−0.5 to 0.6) [0.88]
First day of mother's milk (days)	−0.3 (−0.5 to −0.1) [0.004]	−0.2 (−0.4 to −0.1) [0.01]	−0.2 (−0.4 to −0.1) [0.01]
Duration of central venous line in situ (days)	0.8 (0.4 to 1.2) [< 0.001]	0.9 (0.5 to 1.2) [< 0.001]	0.9 (0.6 to 1.2) [< 0.001]
Weight *z*-score	0.01 (−0.08 to 0.10) [0.88]	0.03 (0.0 to 0.1) [0.42]	0.01 (−0.07 to 0.09) [0.80]

PSM, propensity score model.
Note
The results are based on averages over 25 matched replications.

Babies admitted from the postnatal ward

In the study protocol, a subgroup analysis was planned to exclude all babies whose first admission to neonatal care was from a postnatal ward to exclude cases for whom therapeutic hypothermia was administered following postnatal collapse. Only 46 babies in the entire cohort were admitted from a postnatal ward and, therefore, this sensitivity analysis was not conducted. The distribution of babies admitted from the postnatal ward by PN groups before and after matching is shown in *Table 16*.

Influence of alternative matching methods

The results were found to be consistent across all alternative methods of matching on the propensity groups and principal background variables (see *Appendix 11*, *Figure 12*).

Patterns of parenteral nutrition provision

The highest rates of PN were in neonatal ODNs in Scotland and Wales (79% and 61% of babies treated with therapeutic hypothermia, respectively) and the lowest rates were in the North West ODN and Yorkshire and the Humber ODNs (9% and 7%, respectively) (*Table 21*).

TABLE 21 Provision of parenteral nutrition during therapeutic hypothermia by neonatal ODN in the entire study cohort

	Provision of PN			
	No		Yes	
ODN	*n*	%	*n*	%
East Midlands	282	77.9	80	22.1
East of England	479	87.9	66	12.1
North Central and East London	351	76.8	106	23.2
North West	209	91.3	20	8.7
North West London	540	84.1	102	15.9
Northern	182	78.8	49	21.2
South East Coast	417	74.1	146	25.9
South West	430	78.6	117	21.4
South London	332	84.9	59	15.1
Thames Valley and Wessex	270	47.2	302	52.8
West Midlands	472	84.0	90	16.0
Yorkshire and the Humber	428	93.3	31	6.8
Isle of Man	< 5		< 5	
Scotland	44	21.2	164	78.9
Wales	89	39.0	139	61.0
Total	4525	75.5	1471	24.5

Note
Seventeen babies were treated at units that could not be assigned to a relevant ODN and a further 17 babies were missing information regarding PN status.

Chapter 5 Discussion

Key results

In this large, UK population-based cohort of term and near-term infants treated with therapeutic hypothermia, we identify widespread variation in nutritional practice, with sizable minorities of babies receiving milk feeds and/or PN during hypothermia. We demonstrate that severe NEC, using a robust and validated definition, is rare in this population, with an incidence of < 1 per 1000 babies. Late-onset, culture-positive BSI is also rare in these infants, occurring in approximately 5 per 1000 infants.

To identify optimal nutritional management we undertook comparative analyses using matched groups that were balanced on multiple potentially confounding background variables and followed a pre-registered protocol.[34] We found that severe NEC, defined using a validated case definition,[21] was comparatively rare whether or not babies were fed during therapeutic hypothermia. We used a more pragmatic definition of NEC to identify potential cases that were not fatal and did not require surgery, and, although NEC defined in this way was rare, it was somewhat more common in babies for whom feeds were witheld during therapeutic hypothermia. Introduction of feeds during therapeutic hypothermia was associated with benefit across multiple other outcomes in matched analyses, including earlier initiation of breastfeeding and higher rates at discharge, lower rates of pragmatically defined late-onset infection, shorter lengths of stay and higher survival to neonatal unit discharge. When feeds were introduced they were predominantly maternal breast milk and tended to be started later in the course of therapeutic hypothermia. Based on the consistent benefit associated with introduction of milk feeding during hypothermia, we conclude that initiating milk feeds, preferably with maternal breast milk, during therapeutic hypothermia is safe and may be beneficial.

Matched analyses comparing babies who received PN during therapeutic hypothermia with those who did not found more mixed results. Although culture-positive infection was rare in both groups, it was more common in babies who received PN. Conversely, survival to discharge rates were higher in babies who received PN. Results for other outcomes, such as breastfeeding outcomes and length of stay, were similar between babies who received PN and those who did not, with the exception of central line duration, which was longer in babies who received PN. The apparent survival benefit seen in babies who received PN is contrary to RCT data from neonates being cared for on paediatric intensive care units.[35] This result may reflect residual confounding by indication, favouring babies who received PN.

Putative benefits from administering PN to infants during therapeutic hypothermia include improved brain growth and repair, potentially leading to improved neurodevelopment.[36] In this study we were unable to examine later neurodevelopmental outcomes because of high incompleteness of such data within currently available routine databases. Therefore, we were unable to evaluate a key potential benefit of administering PN in this group. Conclusions from this study are uncertain in relation to provision of PN during therapeutic hypothermia, and are consistent with both potential benefits and potential harms from this practice. We are unable to identify an optimal approach to PN during therapeutic hypothermia using currently available routinely recorded neonatal data and recommend further prospective interventional research that captures longer-term neurodevelopmental outcomes.

Results in context

This study involved > 6000 infants who received therapeutic hypothermia and reports population-level data from all babies admitted to NHS neonatal care in England, Scotland and Wales (neonatal intensive care such as therapeutic hypothermia is not undertaken at non-NHS units in the UK). To the best of

our knowledge, this is the largest and most comprehensive cohort of such babies. For comparison, the most recent Cochrane review[2] in this area identified 11 trials and 1505 infants in total. NEC is one of the most feared complications of neonatal care[6] and is well described in case studies and single-centre series in babies with HIE.[37,38] There has been a paucity of robust incidence data because studies have hitherto been limited by small size and the use of subjective definitions of NEC. By applying a validated definition of severe NEC with confirmation of cases to large-scale population data,[21] we have produced robust incidence rates for rare but important outcomes (e.g. NEC and late-onset infection) in babies receiving therapeutic hypothermia.

Using routinely recorded national data we have accurately described current nutritional practice in the UK for babies receiving therapeutic hypothermia, in contrast to previous studies that have relied on surveys that report intention rather than actual practice.[3] We find that feeding during therapeutic hypothermia occurs less commonly in practice (i.e. 31% of babies) than would be suggested by the most recent survey[3] (in which 59% of responding neonatal units reported feeding during hypothermia). Furthermore, and in contrast to surveys of UK practice that suggest that enteral feeding is becoming more common during hypothermia (i.e. 29% of units in 2010[6] vs. 59% of units in 2016[3]), we found that the proportion of babies for whom enteral feeds were introduced (31%) remained stable over the 8-year period 2010–17. These findings may be explained by incomplete survey coverage or simply reflect the difference between reported and actual practice. We note that the rate of PN administration seen in this study (i.e. 25%) more closely mirrors that seen in the most recent UK survey[3] (i.e. 29%).

Our finding that the introduction of enteral feeding during therapeutic hypothermia is safe and may be associated with benefits such as a lower risk of pragmatically defined NEC, earlier initiation of breastfeeding, higher rates of breastfeeding at discharge and shorter lengths of stay is supported by the limited data from previous studies.[4,5] A retrospective case–control study[4] of 34 infants in the USA compared minimal enteral nutrition with withholding feeds during therapeutic hypothermia, and found that the duration of PN and hospital stay was shorter in the enteral feeding group. This study did not adjust for illness severity and there were some differences between groups, for example in relation to clinical staging of encephalopathy.[4] This suggests that confounding by indication (whereby infants who are more sick have their feeds withheld) may in part explain these results. Another small retrospective study[5] compared 34 babies cared for at a unit in the UK in which feeds are commonly withheld with 51 babies cared for in Sweden where feeds are commonly initiated during hypothermia.[5] In keeping with our data, this study also found that feeding during hypothermia was safe, with no complications noted in either group. In addition, rates of breastfeeding at discharge were higher among babies cared for in Sweden where enteral feeds were started during hypothermia. The degree to which this is explained by cultural and social differences between countries, rather than initiation of treatment, is unclear. Our study adds considerably to the existing literature through the very large population-level nature of the cohort and by application of statistically robust approaches to deal with potential confounding in comparative analyses.

In the UK and other high-income settings, infants who receive therapeutic hypothermia receive some form of intravenous fluid to maintain hydration and blood glucose concentration. This can be in the form of intravenous fluid or PN. We find that the use of PN is associated with a higher incidence of culture-positive BSI, but also with lower mortality prior to neonatal discharge. This latter finding is counter to adult and paediatric intensive care trials that demonstrated clinical benefits from later compared with early initiation of PN.[15,16] Although similar trials have not been undertaken in neonatal intensive care units or among infants receiving therapeutic hypothermia, the paediatric intensive care-based PEPaNIC (Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit) trial[15] randomised 209 infants in the neonatal period (< 28 days) to early (i.e. < 24 hours after admission) or late (i.e. > 7 days after admission) commencement of PN. Pre-planned secondary analysis of these infants found lower rates of infection in babies recruited at < 1 week of age and randomised to receive early PN,[35] in keeping with our study. This secondary neonatal analysis found similar mortality between early and late PN groups, but mortality was low in both trial arms and, therefore, the trial lacked

power to detect a clinically important difference. The PEPaNIC trial[15] also found higher rates of hypoglycaemia in neonates randomised to late PN, which is not confirmed in our study. This may be explained by how data are held in the NNRD, whereby diagnoses (such as hypoglycaemia) are not recorded in a way that is attributable to a particular day of stay, but are attributed to an 'episode' of care on a particular neonatal unit. As a result, we were unable to determine whether or not hypoglycaemic episodes occurred during the period of therapeutic hypothermia. We were unable to identify further studies that examined the use of PN in babies receiving therapeutic hypothermia. The conflicting findings seen both in this study and when considered with the of the PEPaNIC trial[15] indicate that further research is required to identify the role of PN in these babies. We note that supplemental nutrition following brain injury has shown promise in a small pilot trial,[36] supporting a potential role of early nutrition in optimising longer-term neurodevelopmental outcomes and highlighting the importance of such outcomes in any future research.

Strengths and limitations

The main aim of this study was to identify optimal approaches to nutrition through comparative analyses of babies fed milk and those not fed milk, and between babies who received PN and babies who did not. Although we did not undertake a randomised trial, we applied multiple approaches to limit bias. We utilised the comprehensive range of background data items held in the Neonatal Data Set[19] and available within the NNRD to form matched groups, balanced on all measured potential confounders by matching on key background factors and on propensity score. To prevent outcome switching or data dredging, we followed a detailed pre-registered protocol that specified exposures, background factors and outcomes, and the data items used to define them, as well as the matching process to be applied.[34] The use of routinely recorded data reduced the risk of ascertainment bias, as data collection occurred well in advance of study conception. Furthermore, we applied prespecified sensitivity analyses to examine whether or not data quality and definitions of the nutritional exposures influenced results, and post hoc sensitivity analyses to determine whether or not different approaches to matching influenced the findings. Finally, primary results were robust to sensitivity analyses. By using existing data we were able to include a large number of infants and to examine rare outcomes, such as pragmatically defined NEC and culture-positive BSI. The sample size was several times larger than in all previous randomised trials of therapeutic hypothermia combined.[2] A further strength of this study was the considerably lower level of resources required to undertake it. The study was funded at < 10% of the cost of contemporaneous National Institute for Health Research-funded neonatal clinical trials and reported over a shorter time frame.

The most important limitation of this study stems from the non-randomised design used (i.e. the matching approach applied in this study was able to account for only measured confounders). Although we utilised a wide range of background and day 1 clinical data items to form matched groups, and the statistical measures of balance indicated that acceptable balance had been obtained, we cannot exclude the possibility that clinically relevant factors may have differed by small but clinically relevant degrees between the groups, or that there were important differences in unmeasured factors between the comparator groups. In matched analyses we found higher survival to neonatal unit discharge in babies who were fed during therapeutic hypothermia. This difference in survival is unlikely to be caused by enteral feeding during therapeutic hypothermia and suggests that residual confounding is present in the enteral comparison. This is supported by background data indicating that, although the proportion of babies receiving inotropes on the first day was more balanced after matching, a potentially clinically relevant difference remained (see *Table 9*). Furthermore, there may be other additional markers of 'sickness' that are discernible to clinicians and influence decision-making around enteral feeding, but are not captured in the extensive data items held in the NNRD. Such residual and unmeasured confounding by indication may overestimate the benefit associated with enteral feeding, and results should be interpreted accordingly. However, in the light of the low rate of adverse outcomes seen in

both fed and non-fed infants, and the consistent benefit seen across outcomes favouring fed infants, we conclude that initiating milk feeds, preferably with maternal breast milk, during therapeutic hypothermia is safe and may be beneficial.

Similar residual or unmeasured confounding by indication may be present in the comparative analyses of PN. This study found a higher level of survival among babies treated with PN, despite higher levels of culture-positive late-onset BSI, a finding that is counter to randomised trials of early compared with late PN in adults. Such confounding is, again, likely to overestimate the benefit of early PN in this population of infants. Given the more mixed results of the PN analyses, which were consistent with both benefit and harm from early administration of PN, we suggest further randomised evaluations of early PN in this group.

Other limitations include the smaller than planned numbers of infant pairs that were able to be included in the matched analyses (i.e. 1618 pairs were analysed for the enteral nutrition analysis and 1240 pairs for the PN analysis vs. estimated samples of 2000 matched pairs and 1500 matched pairs, respectively). The planned numbers of pairs were selected for illustration only and did not represent an imperative or objective of the study design. Consequently, the lower than planned achieved number of pairs should not be interpreted as indicating that the study is underpowered. These matched groups were still considerably larger than in previous trials[2] and are able to detect small but clinically relevant differences of 1.0% in NEC and 2.5% in the incidence of late-onset infection. As with any study that utilises routinely recorded data, data completeness and accuracy are dependent on the health-care professionals who enter the data and may be variable between sites. The NNRD is formed from data entered as part of a baby's clinical care record and data are used for multiple purposes, including national audit and determining neonatal unit activity for purposes such as funding and staffing. Furthermore, the data held in the NNRD have been validated against those data recorded in case record forms of a multicentre trial,[39] which demonstrated a high degree of data agreement (> 95%) for multiple background and outcome variables,[10] including key data items for this study, such as receipt of enteral feeds and presence of central line in situ. This validation study did not examine other key data items used in this study, such as receipt of therapeutic hypothermia, administration of PN or type of enteral feed (for which considerable missing data were found on day 1; see *Figure 6*), and, therefore, data quality for such items is less well known. For these reasons, we do not consider incomplete and inaccurate data to be a major problem in this study. Given the retrospective nature of this study and the routine nature of data collection, there is no reason for poor data quality to be more common in one comparative arm than another and, therefore, any incompleteness or inaccurate data would be expected to lead to imprecision in all estimates, rather than any systematic bias. We also acknowledge that cases of both severe and pragmatic NEC may have been missed when suspected NEC occurred in infants with severe encephalopathy and a decision to provide palliative care had been made. When NEC was felt to contribute to the infant death then this would have been recorded on the death certificate (and hence in the severe NEC definition) and so the incidence of such missed cases is likely to be very low. Finally, limitations in the data available within the NNRD meant that we were unable to examine the relationship between volume of feeds, including very small-volume or 'trophic feeds', and outcomes in this study.

Interpretation

The incremental introduction of enteral feeds in term and near-term babies during therapeutic hypothermia appears safe and may be associated with benefits including higher rates of breastfeeding at discharge and shorter lengths of stay.

Necrotising enterocolitis is rare in term and near-term babies receiving therapeutic hypothermia and may be less common in babies fed during therapeutic hypothermia.

Optimal parenteral nutritional support for babies receiving therapeutic hypothermia could not be established.

Generalisability

This study used data from all babies who were ≥ 36 gestational weeks of age and who were recorded as receiving therapeutic hypothermia in NHS neonatal units, over a contemporary 8-year period. As ongoing neonatal intensive care is not undertaken outside NHS units, this population-level study is highly generalisable to current neonatal care in the UK and other high-income health-care systems. We did not limit the study to infants who met National Institute for Health and Care Excellence guidance for therapeutic hypothermia and, therefore, the analysed population included infants who were treated for mild HIE and other conditions (e.g. postnatal collapse). As such babies are increasingly treated with therapeutic hypothermia in the UK[40] and internationally, the results of this study are therefore generalisable to current clinical practice, where 'therapeutic creep' is widespread in relation to hypothermia treatment.

We did not include preterm babies earlier than 36 gestational weeks of age in this study because of the specifications laid out by the funder when commissioning this research. More preterm infants have higher rates of feed intolerance than term infants and the results of this study may not be generalisable to these more preterm babies receiving therapeutic hypothermia. A number of infants who received therapeutic hypothermia were not able to be matched (see *Figure 3*). This occurred because for babies with certain background profile one or the other nutritional management was selected almost exclusively by clinical staff. Consequently, the results of this study are generalisable to the range of infants described by the matched cohorts, rather than the wider population of all infants who received therapeutic hypothermia.

Recommendations/implications for future research

- Optimal PN for babies receiving therapeutic hypothermia is unknown. This should be examined in a RCT comparing early with delayed provision of PN, which should examine both short-term outcomes, such as late-onset infection and neonatal survival, and longer-term outcomes, such as neurodevelopment.
- Future RCTs to examine enteral feeding during therapeutic hypothermia are unlikely to be warranted or feasible. The optimal speed of introduction of enteral feeds or optimal choice of milk when mothers' milk is not available are not known and may benefit from further research.
- Mechanisms to obtain population-level, long-term outcome data for babies who receive neonatal care generally and babies who are treated with hypothermia specifically, such as data linkage and national routine reporting, should be prioritised.

Chapter 6 Conclusions

Necrotising enterocolitis is rare in babies receiving therapeutic hypothermia and may be less common in babies fed during therapeutic hypothermia. Introduction of enteral feeds is associated with a lower risk of pragmatically defined NEC and other beneficial outcomes, including higher rates of survival and breastfeeding at discharge. Receipt of PN during therapeutic hypothermia is associated with higher rates of late-onset infection, but lower rates of mortality. Residual confounding may partially explain these findings. Further research should focus on identifying optimal PN for babies receiving therapeutic hypothermia. Commencing enteral feeding during therapeutic hypothermia appears to be safe and may be beneficial.

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Contributions of authors

Chris Gale (https://orcid.org/0000-0003-0707-876X) (Reader in Neonatal Medicine and Consultant Neonatologist) conceived, designed and planned the study. He contributed to planning data extraction and analysis, interpretation of results and wrote the first and final draft of the study report.

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Cheryl Battersby (https://orcid.org/0000-0002-2898-553X) (Senior Clinical Lecturer in Neonatal Medicine and Consultant Neonatologist) conceived, designed and planned the study. She contributed to planning data extraction and analysis, undertook data extraction, interpreted the results, and contributed to and approved the final report.

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Shalini Ojha (https://orcid.org/0000-0001-5668-4227) (Clinical Associate Professor in Neonatal Medicine and Consultant Neonatologist) conceived, designed and planned the study. She contributed to the analysis and interpretation of the results. She contributed to and approved the final report.

Lucy Culshaw (https://orcid.org/0000-0002-4542-2659) (Senior Research Engagement Officer at Bliss) contributed to the planning of the study and interpretation of results. She led parent involvement in the study, and contributed to and approved the final report.

Ella Selby (https://orcid.org/0000-0002-1125-7712) (parent with experience of having a baby that needed therapeutic hypothermia) contributed to the planning of the study and interpretation of results. She led parent involvement in the study, and contributed to and approved the final report.

Jon Dorling (https://orcid.org/0000-0002-1691-3221) (Professor of Paediatrics and Division Head of Neonatal-Perinatal Medicine) conceived, designed and planned the study. He contributed to the analysis and interpretation of the results. He contributed to and approved the final report.

Nicholas Longford (https://orcid.org/0000-0003-4129-9726) (Senior Statistician) conceived, designed and planned the study. He led the analysis and undertook matching. He contributed to the interpretation of the results. He contributed to and approved the final report.

Publications

Battersby C, Longford N, Patel M, Selby E, Ojha S, Dorling J, Gale C. Study protocol: optimising newborn nutrition during and after neonatal therapeutic hypothermia in the United Kingdom: observational study of routinely collected data using propensity matching. *BMJ Open* 2018;**8**:e026739.

Ojha S, Dorling J, Battersby C, Longford N, Gale C. Optimising nutrition during therapeutic hypothermia. *Arch Dis Child Fetal Neonatal Ed* 2019;**104**:F230–1.

Gale C, Longford NT, Jeyakumaran D, Ougham K, Battersby C, Ojha S, Dorling J. Feeding during neonatal therapeutic hypothermia, assessed using routinely collected National Neonatal Research Database data: a retrospective, UK population-based cohort study. *Lancet Child Adolesc Health* 2021;**5**:408–16.

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Data-sharing statement

Data are available through the NNRD with relevant approvals. More information is available at URL: www.imperial.ac.uk/neonatal-data-analysis-unit/neonatal-data-analysis-unit/utilising-the-national-neonatal-research-database/. All data requests should be submitted to the corresponding author for consideration.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Variable definitions and extractions

TABLE 22 Extraction procedures and definitions of enteral feeding and parenteral nutrition intervention variables

Variable	Data items from the NNRD	Definition
Enteral feeding	ENTERAL FEEDING GROUP DEFINED AS Any of the following items entered in the *Daily Care Fluids and Feeding* during the first 3 days Any entry (1–6) under ENTERAL FEED TYPE GIVEN OR any entry (0–88) under FORMULA MILK OR MILK FORTIFIER TYPE OR any value > 0 for TOTAL VOLUME OF MILK RECEIVED OR any entry (1–8) under ENTERAL FEEDING METHOD NO ENTERAL FEEDING GROUP DEFINED AS All other babies not fulfilling above criteria	Dichotomous (no enteral feeds = 0; provided enteral feeds = 1)
PN	PARENTERAL NUTRITION GROUP DEFINED AS Any of the following items entered in the *Daily Care Fluids and Feeding* during the first 3 days Y entry for PARENTERAL NUTRITION RECEIVED INDICATOR OR The following drug code entered in the *Daily care medication* during the first 3 days 1010238 *Total parenteral nutrition* NO PARENTERAL NUTRITION GROUP DEFINED AS All other babies not fulfilling above criteria For sensitivity analyses also extract *Daily Care Fluids and Feeding* INTRAVENOUS INFUSION OF GLUCOSE AND ELECTROLYTE SOLUTION RECEIVED INDICATOR = Y/N	Dichotomous (no parenteral nutrition = 0; provided parenteral nutrition = 1)

TABLE 23 Extraction procedures, definitions and classifications of background variables

Variable	Data items from the NNRD	Definition(s)	Classification
Cord blood gas pH in bands	Labour and delivery details UMBILICAL CORD BLOOD pH LEVEL (ARTERIAL) Or, if not recorded, use Labour and delivery details UMBILICAL CORD BLOOD pH LEVEL (ARTERIAL)	*CordpHArt*: trichotomised into bands: > 7.0, 6.9–7.0 and < 6.9	Principal
Birth year	Baby demographics YEAR AND MONTH OF BIRTH (BABY)	*BirthYear*: categorised into 2-year bands: 2010–11, 2012–13, 2014–15 and 2016–17	Principal
Gestational age week	Baby demographics GESTATION LENGTH (AT DELIVERY): gestational weeks and days	*GAweeks*: integers	Highly important
Birthweight	Baby demographics BIRTH WEIGHT	*Bweight*: original entries trimmed from above at 3500 g and entries smaller than 1000 g with a non-zero digit are multiplied by 10. Square-root transformed	Highly important
Sex	Baby demographics PERSON PHENOTYPIC SEX	*Sex*: dichotomous (male = 0; female = 1)	Highly important
Emergency resuscitation drugs administered	Labour and delivery details 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	Labour and Delivery Details DELIVERY INSTRUMENT TYPE	*InstrDeliv*: dichotomised (no instrument used = 0; forceps or ventouse = 1)	Highly important
Mode of delivery	Labour and Delivery Details MODE OF DELIVERY Categorical: codes = 1–4 AND Labour and Delivery Details IN LABOUR BEFORE CAESARIAN SECTION INDICATOR = Y/N	*Delivery*: dichotomous (vaginal = 0, caesarean = 1)	Highly important
Maternal smoking status	Pregnancy Details 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	Labour and delivery details INTRAPARTUM ANTIBIOTICS GIVEN INDICATORS	*IntrPartAntiB:* dichotomous (no intrapartum antibiotics given = 0, intrapartum antibiotics = 1)	Highly important
Apgar score at 1 minute	Labour and delivery details APGAR SCORE (1 MINUTE) Continuous: 0–10	*APGAR1min*: categorical (0–10) *APGAR1minMs*: binary missing indicator created (not missing = 0; missing = 1)	Highly important

TABLE 23 Extraction procedures, definitions and classifications of background variables (*continued*)

Variable	Data items from the NNRD	Definition(s)	Classification
Apgar score at 5 minutes	Labour and delivery details 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	Labour and delivery details UMBILICAL CORD BLOOD BASE EXCESS CONCENTRATION (ARTERIAL) Continuous OR if not available use Labour and delivery details UMBILICAL CORD BLOOD BASE EXCESS CONCENTRATION (VENOUS)	*CordBaseExcess*: continuous (to one decimal place) *CordBaseExcessMs*: binary missing indicator created (not missing = 0; missing = 1)	Highly important
Admission mean blood pressure	Admission details 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 concentration	Admission details 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	Admission details OXYGEN SATURATION (ON ADMISSION TO NEONATAL CRITICAL CARE) Continuous	*AdmitOS*: continuous, trimmed to be within the range (50, 100) *AdmitOS.Ms*: binary missing indicator created (not missing = 0; missing = 1)	Highly important
Maternal deprivation score (from LSOA)	Parents demographics 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	Labour and delivery details BIRTH ORDER (MATERNITY SERVICES) Labour and delivery details NUMBER OF FETUSES (NOTED DURING PREGNANCY EPISODE)	*MultipleBrt*: dichotomised (single birth = 0; multiple births = 1)	Moderately important
Maternal age	Parents demographics YEAR OF BIRTH (MOTHER)	*MaternalAge*: continuous (years) trimmed to be within range 17–45 years	Moderately important
Maternal duration of rupture of membranes (time in hours)	Labour and delivery details RUPTURE OF MEMBRANES DATE TIME or RUPTURE OF MEMBRANES YEAR AND MONTH and NUMBER OF MINUTES (BIRTH TO EVENT) Continuous		Variable not used (too many missing values)

continued

TABLE 23 Extraction procedures, definitions and classifications of background variables (*continued*)

Variable	Data items from the NNRD	Definition(s)	Classification
Maternal disease during pregnancy	Labour and delivery details SIGNIFICANT MATERNAL PYREXIA IN LABOUR INDICATOR (Y/N) Pregnancy details MATERNITY COMPLICATING MEDICAL DIAGNOSIS TYPE Dichotomous: Y = code 16 (endocrine disorder), N = any other or no code Pregnancy details MATERNITY COMPLICATING MEDICAL DIAGNOSIS TYPE Dichotomous: Y = code 08 (diabetes) OR Pregnancy details 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, hypothyroidism, diabetes = 1)	Moderately important
Maternal ethnicity	Parents demographics 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) This data item is based on self-reported ethnicity as recorded in maternity notes	*Ethnicity*: categorised into four groups (white = 1; Asian and mixed = 2; black and mixed = 3; other and not given = 4)	Moderately important
Parity of mother (primiparous Y/N)	Pregnancy details PREGNANCY TOTAL PREVIOUS PREGNANCIES Dichotomous: code 00 = Y; code 01-29 = N	*Primiparous*: dichotomous (not first pregnancy = 0; first pregnancy = 1)	Moderately important

TABLE 23 Extraction procedures, definitions and classifications of background variables (*continued*)

Variable	Data items from the NNRD	Definition(s)	Classification
Chest compressions administered	Labour and delivery details NEONATAL RESUSCITATION METHOD Dichotomous: code 16 = Y; any other code = N	*ChestCompr*: dichotomous (no chest compressions applied = 0; chest compressions applied = 1)	Moderately important
Intubated at resuscitation	Labour and delivery details NEONATAL RESUSCITATION METHOD Dichotomous: code 15 = Y; any other code = N	*Intubation*: dichotomous (not intubated = 0; intubated = 1)	Moderately important
Time to first spontaneous breath	Labour and delivery details TIME BETWEEN DELIVERY AND SPONTANEOUS RESPIRATION CODE Continuous	*SpontRespTime*: dichotomised (≤ 5 minutes = 0; > 5 minutes = 1) *SpontRespTimeMs*: binary missing indicator created (not missing = 0; missing = 1)	Moderately important
Admission heart rate	Admission details HEART RATE (ON ADMISSION TO NEONATAL CRITICAL CARE) Continuous	*AdmitHR*: continuous, trimmed to be within the range 80–100 b.p.m. *AdmitHR.Ms*: binary missing indicator created (not missing = 0; missing = 1)	Moderately important
Admission temperature	Admission details TEMPERATURE (ON ADMISSION TO NEONATAL CRITICAL CARE) Continuous	*AdmitTempCe*: continuous, trimmed to be within 26–40 °C *AdmitTempMs*: binary missing indicator created (not missing = 0; missing = 1)	Moderately important
Positive blood or CSF culture with a recognised pathogen recorded in the first 3 days	Defined from infection cultures (episodic) recorded up to and including day 3 • Pure growth of pathogen from blood OR • 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)	Daily care medication on day 1 only • 500098 dopamine • 500096 dobutamine • 500056 adrenaline • 500210 noradrenaline • 500116 hydrocortisone • 1010173 milrinone Dichotomous: any of above = Y, none of above = N OR Daily care cardiovascular INOTROPE INFUSION RECEIVED INDICATOR Y/N	*Inotropes*: dichotomous (inotropes not administered = 0; inotropes administered = 1)	Moderately important

continued

TABLE 23 Extraction procedures, definitions and classifications of background variables (*continued*)

Variable	Data items from the NNRD	Definition(s)	Classification
Mechanical ventilation method	Daily care respiratory 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)	Daily care respiratory 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)	Admission details SITE CODE (OF ADMITTING NEONATAL UNIT) or ORGANISATION CODE (OF ADMITTING NEONATAL UNIT) Different from Baby demographics SITE CODE (OF ACTUAL PLACE OF DELIVERY) or ORGANISATION CODE (OF ACTUAL PLACE OF DELIVERY) And Baby demographics EPISODE NUMBER	*PostNTransfer*: dichotomous (no transfer = 0; transfer = 1)	Moderately important
Maternal occupation	Parents demographics (withheld) OCCUPATION MOTHER (SNOMED CT)	*MumJob*: dichotomous (no occupation = 0; any occupation = 1)	Moderately important
Onset of labour	Labour and delivery details 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	Admission details 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	Labour and delivery details PRESENTATION AT DELIVERY 1 – breech 2 – cephalic 3 – transverse 8 – other 9 – unknown	*FetusAtDelivC*: dichotomised (cephalic = 1, not cephalic = 0)	Moderately important
Blood transfusion	Daily care blood transfusion BLOOD TRANSFUSION PRODUCT TYPE On day 1 only	*BloodTrans*: dichotomised (no = 0; yes = 1)	Moderately important
Maternal or obstetric medical problem	Pregnancy details MATERNITY OBSTETRIC DIAGNOSIS TYPE (CURRENT PREGNANCY) Pregnancy details MATERNITY MEDICAL DIAGNOSIS TYPE (CURRENT PREGNANCY)	*ProblMedic*: dichotomised (no medical problems = 0; some medical problems = 1)	Moderately important

b.p.m., beats per minute; CSF cerebrospinal fluid.

TABLE 24 Extraction procedures and definitions of outcome variables

Variable	Data items from NNRD	Definition
Severe NEC	Gestational age-specific NEC score based on Battersby *et al.*[21] Data items needed: ABDOMINAL X-RAYS (EPISODIC) • 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 INDICATOR (NNRD field ID: TransferredForFurtheManagement) • 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 Only available following introduction of ABDOMINAL X-RAY (EPISODIC) field Cases identified using these data items were individually confirmed with clinicians	Dichotomous (no severe NEC = 0; severe NEC = 1)
NEC (non-UKNC definition)	The following entered in the daily care gastrointestinal on any 1 day during stay in a neonatal unit • Any entry (1 or 2) for TREATMENT TYPE FOR NECROTISING ENTEROCOLITIS OR the following diagnostic codes: • 1010683 necrotising enterocolitis – suspected • 10708 necrotising enterocolitis – perforated • 15809 necrotising enterocolitis AND 5 or more days nil by mouth defined by the daily care fluids and feeding for a continuous period of 5 days • 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 WHILE ALSO RECEIVING 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 Daily care medication: • 1010155 benzylpenicillin • 1010158 augmentin • 1010179 flucloxicillin	Dichotomous (no NEC = 0; NEC = 1)

continued

TABLE 24 Extraction procedures and definitions of outcome variables (*continued*)

Variable	Data items from NNRD	Definition
	• 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 oflacillin • 500005 azlocillin • 1010171 linezolid • 1010271 cefalexin • 1010139 amoxicillin • 500070 amoxicillin • 500128 meropenem • 500118 imepenem • 500145 imipenem • 500069 ambisome (liposomal amphotericin) • 500003 amphotericin • 1010195 amphotericin (liposomal)	
Late-onset BSI (NNAP definition)	Defined from infection cultures (episodic) recorded after day 3 • Pure growth of pathogen from blood OR • Pure growth of pathogen from CSF OR • Either a pure growth of a skin commensal or a mixed growth with ≥ 3 clinical signs at the time of blood sampling	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 Daily care medication: • 1010155 benzylpenicillin • 1010158 augmentin • 1010179 flucloxicillin • 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	Dichotomous (no infection = 0; infection = 1)

TABLE 24 Extraction procedures and definitions of outcome variables (*continued*)

Variable	Data items from NNRD	Definition
	• 500008 ceftazidime • 500175 ceftriaxone • 500032 piperacillin • 500206 oflacillin • 500005 azlocillin • 1010171 linezolid • 1010271 cefalexin • 1010139 amoxicillin • 500070 amoxicillin • 500128 meropenem • 500118 imepenem • 500145 imipenem • 500069 ambisome (liposomal amphotericin) • 500003 amphotericin • 1010195 amphotericin (liposomal)	
Survival to discharge	Defined from the discharge details from final neonatal unit stay • DISCHARGE DESTINATION FROM NEONATAL CRITICAL CARE = 1, 2, 4, 5, 6 (NOT code 3, died)	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 daily care general information – LOCATIONS OF HIGHEST LEVEL OF CARE	Continuous, integers
Hypoglycaemia	Defined as any of the following diagnostic codes recorded at any time during an babies neonatal units stay: • 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 daily care fluids and feeding of • ENTERAL FEED TYPE GIVEN = code 1 (breastfeeding) OR • 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 daily care fluids and feeding of • ENTERAL FEED TYPE GIVEN = code 1 (breastfeeding) OR • 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 Daily Care Fluids and Feeding of • 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 • ENTERAL FEEDING METHOD = code 1 (breast)	Continuous, integers

continued

TABLE 24 Extraction procedures and definitions of outcome variables (*continued*)

Variable	Data items from NNRD	Definition
Duration of parenteral nutrition	Defined as the number of days UNTIL a baby has: • Daily Care Fluids and Feeding PARENTERAL NUTRITION RECEIVED INDICATOR = N AND • The following drug code NOT entered in the daily care medication: 1010238 total parenteral nutrition This outcome will be analysed only for the ENTERAL FEEDING COMPARISON	Continuous, integers
Number of days a baby has a central venous line in situ	Defined as the number of days that has a baby has: • Daily Care Fluids and Feeding 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: • Daily care general information PERSON WEIGHT IN GRAMS If final day is not entered, the penultimate day is used	Continuous

CSF, cerebrospinal fluid; SDS, standard deviation score.

Appendix 2 Study oversight committees

Clinical Investigator Group members

- Chris Gale (Chairperson), Reader in Neonatal Medicine and Consultant Neonatologist, Imperial College London and Chelsea and Westminster Hospital NHS Foundation Trust, London, UK.
- Nicholas Longford, Senior Statistician, Imperial College London, London, UK.
- Cheryl Battersby, Clinical Senior Lecturer in Neonatal Medicine and Consultant Neonatologist, Imperial College London and Chelsea and Westminster Hospital NHS Foundation Trust, London, UK.
- Jon Dorling, Professor of Neonatal Medicine, IWK Health Centre, Halifax, NS, Canada.
- Shalini Ojha, Clinical Associate Professor in Neonatal Medicine, University of Nottingham, Nottingham, UK.
- Lucy Culshaw, Senior Research Engagement Officer, Bliss, London, UK. (Prior to March 2019 this role was held by Mehali Patel, Research Engagement Officer, Bliss, London, UK.)
- Ella Selby, mother of child who received therapeutic hypothermia as a baby.

Study Steering Group members

- David Odd (Independent chairperson), Senior Clinical Lecturer in Neonatal Medicine and Consultant Neonatologist, University of Bristol and North Bristol NHS Trust, Bristol, UK.
- Louise Linsell (Independent), Senior Medical Statistician, Clinical Trials Unit, National Perinatal Epidemiology Unit, University of Oxford, Oxford, UK.
- James Carpenter (Independent), Professor of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK.
- Carol Rhodes (Independent), mother of child who received therapeutic hypothermia as a baby.
- Chris Gale (Non-independent), Reader in Neonatal Medicine and Consultant Neonatologist, Imperial College London and Chelsea and Westminster Hospital NHS Foundation Trust, London, UK.

Appendix 3 Annual summary data for remaining background variables

TABLE 25 Background variables for the entire study cohort by year of birth

Variable	Year								All years
	2010	2011	2012	2013	2014	2015	2016	2017	
Total number of babies	474	678	686	815	871	859	819	825	6027
Place of birth: England									
n	459	647	635	728	763	747	701	718	5398
%	96.8	95.4	92.6	89.3	87.6	87.0	85.6	87.0	89.6
Birth length (cm)									
Mean	50.7	51.8	50.8	49.8	51.3	51.7	50.9	49.4	50.8
SD	3.4	4.0	4.4	3.8	4.6	4.9	3.7	5.9	4.4
Median	51	52	51	50	52	53	51	50	51
Lower quartile	49.1	50.9	48	47	48	51	48.2	48	48
Upper quartile	51.9	54	54.6	52	54	54	53.4	53.8	54
Missing, *n*	454	642	651	770	821	825	785	794	5742
%	95.8	94.7	94.9	94.5	94.3	96.0	95.8	96.2	95.3
Birth head circumference (cm)									
Mean	34.8	34.7	34.8	34.7	34.6	34.5	34.6	34.4	34.6
SD	2.0	1.7	1.7	1.8	1.8	2.4	2.1	2.6	2.0
Median	35	35	35	34.6	34.7	34.8	34.5	34.5	34.8
Lower quartile	33.7	33.7	33.6	33.5	33.5	33.5	33.5	33.5	33.5
Upper quartile	36.0	36.0	36.0	36.0	35.8	35.8	36	35.7	36
Missing, *n*	219	276	303	422	525	570	529	518	3362
%	46.2	40.7	44.2	51.8	60.3	66.4	64.6	62.8	55.8
Maternal pyrexia									
n	26	35	40	32	58	36	30	51	308
%	5.5	5.2	5.8	3.9	6.7	4.2	3.7	6.2	5.1
Missing, *n*	86	107	109	121	128	153	146	168	1018
%	18.1	15.8	15.9	14.8	14.7	17.8	17.8	20.4	16.9
Maternal diabetes[a]									
n	8	18	18	40	36	39	49	48	256
%	1.7	2.7	2.6	4.9	4.1	4.5	6.0	5.8	4.2
Maternal hypothyroidism[a,b]									
n				6	17	17	10	15	65
%				0.7	2.0	2.0	1.2	1.8	1.1

continued

TABLE 25 Background variables for the entire study cohort by year of birth (*continued*)

Variable	Year								All years
	2010	2011	2012	2013	2014	2015	2016	2017	
Maternal obstetric diagnosis[a]									
n	240	361	385	421	394	391	367	359	2918
%	50.6	53.2	56.1	51.7	45.2	45.5	44.8	43.5	48.4
Maternal medical diagnosis[a]									
n		11	59	223	392	466	431	424	2006
%		1.6	8.6	27.4	45.0	54.2	52.6	51.4	33.3

a Data are collected via a checkbox indicating presence of condition. Therefore, it is not possible to distinguish between missing data and absence of the condition.
b Not collected in years 2010–12.

TABLE 26 Resuscitation variables for the entire study cohort by year of birth

Variable	Year								All years
	2010	2011	2012	2013	2014	2015	2016	2017	
Total number of babies	475	678	686	815	871	861	820	825	6031
Umbilical cord base excess									
Median	−14.6	−13.7	−13.0	−13.8	−12.5	−12.9	−12.1	−12.4	−13.0
Lower quartile	−19.3	−18.6	−17.3	−17.8	−16.7	−17.0	−16.8	−16.5	−17.4
Upper quartile	−8.5	−8.0	−8.9	−9.1	−8.1	−8.1	−7.8	−7.6	−8.2
Missing, *n*	148	219	225	260	310	325	348	313	2148
%	31.2	32.3	32.8	31.9	35.6	37.8	42.5	37.9	35.6
Time to first spontaneous breath									
0 (< 1 minute), *n*	0	0	0	0	0	0	0	0	0
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1 (1–1.5 minutes), *n*	4	8	19	21	17	26	20	24	139
%	0.8	1.2	2.8	2.6	2.0	3.0	2.4	2.9	2.3
2 (1.6–2 minutes), *n*	6	10	14	18	13	17	20	24	122
%	1.3	1.5	2.0	2.2	1.5	2.0	2.4	2.9	2.0
3 (2.1–3 minutes), *n*	16	17	16	40	36	36	31	36	228
%	3.4	2.5	2.3	4.9	4.1	4.2	3.8	4.4	3.8
4 (3.1–4 minutes), *n*	12	24	18	25	45	20	24	34	202
%	2.5	3.5	2.6	3.1	5.2	2.3	2.9	4.1	3.4
5 (4.1–5 minutes), *n*	13	23	21	27	34	38	30	34	220
%	2.7	3.4	3.1	3.3	3.9	4.4	3.7	4.1	3.7
6 (> 5 minutes)	279	401	412	493	531	509	494	483	3602
%	58.9	59.1	60.1	60.5	61.0	59.3	60.3	58.5	59.8
Missing, *n*	144	195	186	191	195	213	200	190	1514
%	30.4	28.8	27.1	23.4	22.4	24.8	24.4	23.0	25.1

TABLE 27 Neonatal variables for the entire study cohort by year of birth

Variable	Year								All years
	2010	2011	2012	2013	2014	2015	2016	2017	
Total number of babies	475	678	686	815	871	861	820	825	6031
Blood glucose concentration at admission (mmol/l)									
Median	5.9	5.8	5.9	5.7	5.6	5.5	5.5	5.3	5.6
Lower quartile	3.5	3.5	3.8	3.7	3.7	3.7	3.7	3.4	3.6
Upper quartile	8.1	8.1	8.1	7.8	7.8	7.4	7.4	7.3	7.7
Missing, *n*	108	124	131	137	154	178	155	156	1143
%	22.8	18.3	19.1	16.8	17.7	20.7	18.9	18.9	19.0
Heart rate (b.p.m.)									
Median	140	144	142	144	145	145	144	145	144
Lower quartile	127	130	128	130	130	130	130	132	130
Upper quartile	155	159	155.5	160	160	160	158	160	159
Missing, *n*	73	79	67	42	53	66	51	57	488
%	15.4	11.7	9.8	5.2	6.1	7.7	6.2	6.9	8.1
Oxygen saturation (mmHg)									
Median	96	96	97	96	97	97	97	98	97
Lower quartile	90	91	92	92	92	93	93	93	92
Upper quartile	99	99	100	99	100	100	100	100	100
Missing, *n*	86	78	79	50	63	77	75	67	575
%	18.1	11.5	11.5	6.1	7.2	9.0	9.2	8.1	9.5
Temperature (°C)									
Mean	35.8	35.7	35.8	35.9	35.9	35.8	35.9	36	35.9
SD	1.3	1.3	1.3	1.2	1.2	1.3	1.2	1.3	1.3
Median	36.2	36.0	36.1	36.2	36.2	36.2	36.2	36.4	36.2
Lower quartile	35.4	35.1	35.2	35.5	35.6	35.5	35.6	35.8	35.5
Upper quartile	36.6	36.6	36.6	36.7	36.7	36.6	36.7	36.8	36.7
Missing, *n*	11	7	26	38	39	46	35	39	241
%	2.3	1.0	3.8	4.7	4.5	5.4	4.3	4.7	4.0
Inhaled nitric oxide on day of admission									
n	17	31	34	37	38	39	31	40	267
%	3.6	4.6	5.0	4.5	4.4	4.5	3.8	4.8	4.4
Missing, *n*	30	46	32	42	36	38	31	35	290
%	6.3	6.8	4.7	5.2	4.1	4.4	3.8	4.2	4.8
Treatment for low blood pressure on day of admission									
n	153	191	184	200	203	173	195	164	1463
%	32.3	28.2	26.8	24.5	23.3	20.1	23.8	19.9	24.3
Missing, *n*	30	46	31	38	36	40	31	32	284
%	6.3	6.8	4.5	4.7	4.1	4.7	3.8	3.9	4.7

b.p.m., beats per minute.

Appendix 4 Background variables by enteral feeding status in unmatched and matched cohorts

TABLE 28 Background variables, by enteral feeding intervention groups, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enteral feeds	No enteral feeds	Enteral feeds
Total number of babies	3975	1872	1618	1618
Male				
n	2173	1055	903	903
%	54.7	56.4	55.8	55.8
Missing, *n*	0	0	0	0
Multiple birth				
n	116	61	48	54
%	2.9	3.3	3	3.3
Missing, *n*	0	1	0	1
%	0	0.1	0	0.1
Gestational age at birth (weeks)				
Median	40	40	40	40
Lower quartile	38	38.8	38.8	38.3
Upper quartile	41	41	41	41
Missing, *n*	0	0	0	0
Birthweight (g)				
Median	3340	3390	3400	3372.1
Lower quartile	2940	2984.5	2988.5	2987.6
Upper quartile	3748.5	3796.2	3792.3	3787.2
Missing, *n*	0	0	0	0
Birth length (cm)				
Median	51.0	51.0	51.9	51.0
Lower quartile	48.0	48.4	49.5	48.2
Upper quartile	54.0	54.0	54.0	54.0
Missing, *n*	3764	1800	1528.6	1555.4
%	94.7	96.2	94.5	96.1

continued

TABLE 28 Background variables, by enteral feeding intervention groups, for unmatched and matched cohorts (*continued*)

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enteral feeds	No enteral feeds	Enteral feeds
Birth head circumference (cm)				
Median	34.6	35.0	34.9	35.0
Lower quartile	33.5	33.6	33.5	33.6
Upper quartile	36.0	36.0	36.0	35.9
Missing, *n*	2300	967	906	828
%	57.9	51.7	56.0	51.2
Caesarean delivery				
n	1921	738	649	638
%	50.6	41.2	41.9	41.1
Missing, *n*	178	80	70	68
%	4.7	4.5	4.5	4.4
Cord blood gas pH: arterial				
> 7.0, *n*	1240	613	536	536
%	44.1	45.4	46.0	46.0
6.9–7.0, *n*	661	318	262	262
%	23.5	23.5	22.5	22.5
< 6.9, *n*	913	420	368	368
%	32.4	31.1	31.6	31.6
Missing, *n*	1161	521	452	452
%	29.2	27.8	27.9	27.9

Note
The results were averaged over 25 matched replications.

TABLE 29 Maternal variables, by enteral feeding intervention groups, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enteral feeds	No enteral feeds	Enteral feeds
Total number of babies	3975	1872	1618	1618
Maternal age (years)				
Median	30	31	31	31
Lower quartile	26	27	26.9	26.5
Upper quartile	34	35	35	35
Missing, *n*	38	21	15	18.2
%	1.0	1.1	0.9	1.1

TABLE 29 Maternal variables, by enteral feeding intervention groups, for unmatched and matched cohorts (*continued*)

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enteral feeds	No enteral feeds	Enteral feeds
Maternal pyrexia				
n	205	98	91	78.7
%	6.3	6.1	6.7	5.7
Missing, *n*	708	266	261.5	224.9
%	21.7	16.6	19.3	16.1
Maternal suspected chorioamnionitis				
n	406	240	202	187
%	12.6	15.2	15.2	13.7
Missing, *n*	757	288	283	247
%	23.5	18.2	21.2	18.0
Smoking in pregnancy				
n	524	191	159	169
%	15.4	11.7	11.3	12.0
Missing, *n*	566	244	207	205
%	16.6	15.0	14.7	14.5
Deprivation score (LSOA)				
Median	4	5	5	4
Lower quartile	2	3	2	2
Upper quartile	7	8	7	7
Missing, *n*	515	204	379	374
%	13.0	10.9	11.7	13.4
Maternal hypothyroidism[a,b]				
n	40	24	18	21
%	1.0	1.3	1.1	1.3
Maternal diabetes[a]				
n	171	75	66	60
%	4.3	4.0	4.1	3.7
Maternal obstetric diagnosis[a]				
n	1921	916	837	798
%	48.3	48.9	51.7	49.3
Maternal medical diagnosis[a]				
n	1328	644	569	554
%	33.4	34.4	35.2	34.3
Primiparous[a]				
n	2107	991	857	844
%	53.0	52.9	53.0	52.2

a Data were collected via a checkbox indicating presence of condition. Therefore, it is not possible to distinguish between missing data and absence of the condition.
b Not collected in years 2010–12.
Note
The results were averaged over 25 matched replications.

TABLE 30 Resuscitation variables, by enteral feeding intervention groups, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enteral feeds	No enteral feeds	Enteral feeds
Total number of babies	3975	1872	1618	1618
Apgar score at 1 minute				
Median	1	2	2	2
Lower quartile	1	1	1	1
Upper quartile	3	3	3	3
Missing, *n*	339	133	104	109
%	8.5	7.1	6.4	6.8
Apgar score at 5 minutes				
Median	4	4	4	4
Lower quartile	2	3	3	3
Upper quartile	6	6	6	6
Missing, *n*	340	124	100	103
%	8.6	6.6	6.2	6.4
Chest compressions[a]				
n	1555	608	560	532
%	39.1	32.5	34.6	32.9
Emergency resuscitation drugs[a]				
n	683	209	191	183
%	17.2	11.2	11.8	11.3
Intubated at resuscitation[a]				
n	2619	1126	1020	995
%	65.9	60.1	63.0	61.5
Umbilical cord base excess				
Median	−13	−12.7	−12.9	−12.7
Lower quartile	−17.5	−17.1	−17	−17.1
Upper quartile	−8.4	−8.1	−8.2	−8.1
Missing, *n*	1433	638	564.3	557
%	36.1	34.1	34.9	34.4
Time to first spontaneous breath				
0–5 minutes, *n*	595	292	250	246
%	15.0	15.6	15.5	15.2
> 5 minutes, *n*	2369	1128	985	985
%	59.6	60.3	60.9	60.9
Missing, *n*	1011	452	383	387
%	25.4	24.1	23.7	23.9

a Data were collected via a checkbox indicating presence of condition. Therefore, it is not possible to distinguish between missing data and presence of no condition.

Note

The results were averaged over 25 matched replications.

TABLE 31 Neonatal variables, by enteral feeding intervention groups, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enteral feeds	No enteral feeds	Enteral feeds
Total number of babies	3975	1872	1607	1607
Time to admission (minutes)				
Median	30	30	29	30
Lower quartile	20	20	20	20
Upper quartile	44	43	43	43
Missing, *n*	0	0	0	0
Blood glucose concentration at admission (mmol/l)				
Median	5.6	5.6	5.8	5.6
Lower quartile	3.4	4.0	3.8	4.0
Upper quartile	7.8	7.7	7.8	7.7
Missing, *n*	766	341	281	287
%	19.3	18.2	17.3	17.7
Heart rate (b.p.m.)				
Median	145	144	144	144
Lower quartile	130	130	130	130
Upper quartile	160	158	160	158
Missing, *n*	301	164	124	124
%	7.6	8.8	7.7	7.6
Oxygen saturation (mmHg)				
Median	96	97	97	97
Lower quartile	92	93	93	93
Upper quartile	99	100	100	100
Missing, *n*	374	174	140	143
%	9.4	9.3	8.7	8.8
Temperature (°C)				
Median	36.2	36.3	36.1	36.2
Lower quartile	35.4	35.6	35.3	35.6
Upper quartile	36.6	36.7	36.6	36.7
Missing, *n*	164	70	114	127
%	4.1	3.7	3.5	4.6
Mechanical ventilation on day of admission				
n	3176	1335	1196	1189
%	83.1	73.4	77.6	75.3
Missing, *n*	155	53	76	40
%	4.1	2.9	4.9	2.5

continued

TABLE 31 Neonatal variables, by enteral feeding intervention groups, for unmatched and matched cohorts (*continued*)

	Cohort			
	Unmatched		Matched	
Variable	No enteral feeds	Enteral feeds	No enteral feeds	Enteral feeds
Inhaled nitric oxide on day of admission				
n	201	57	56	51
%	5.3	3.2	3.7	3.3
Missing, *n*	184	81	92	64
%	4.9	4.5	6.0	4.1
Treatment with inotropes on day of admission				
n	1099	320	295	288
%	29	17.9	19.3	18.5
Missing, *n*	180	80	90	63
%	4.7	4.5	5.9	4.0
Infection in the first 3 days (NNAP)[a]				
n	44	11	16	11
%	1.1	0.6	1	0.7
Postnatal transfer (acute)				
n	1908	913	790	796
%	48.0	48.8	48.8	49.2
Missing, *n*	0	0	0	0

b.p.m., beats per minute.

a Data were collected via a checkbox indicating presence of condition. Therefore, it is not possible to distinguish between missing data and presence of no condition.

Note

The results were averaged over 25 matched replications.

Appendix 5 Primary analysis of dichotomous outcome variables in enteral feeding comparison

TABLE 32 Analysis of dichotomised outcome variables for babies provided with enteral feeding vs. babies from whom enteral feeding was withheld

Variable	Intervention		Rate difference, % (95% CI)	OR (95% CI)	*p*-value
	No enteral feeds rate	Enterally fed rate			
Total number of babies	1618	1618			
Length of stay (> 14 days), % (95% CI)	30.0 (28.3 to 31.7)	21.2 (19.4 to 23.0)	−8.8 (−11.2 to −6.3)	0.63 (0.54 to 0.74)	< 0.001
First day suckling at breast (≤ 28 days), % (95% CI)	60.6 (58.8 to 62.4)	70.1 (68.0 to 72.1)	9.4 (6.7 to 12.1)	1.52 (1.31 to 1.76)	< 0.001
First day of maternal milk (≤ 28 days), % (95% CI)	81.8 (80.4 to 83.2)	87.7 (86.2 to 89.2)	5.9 (3.9 to 8.0)	1.59 (1.31 to 1.93)	< 0.001
Had a central venous line in situ, % (95% CI)	95.6 (94.8 to 96.4)	87.5 (86.1 to 89.0)	−8.1 (−9.7 to −6.4)	0.32 (0.25 to 0.43)	< 0.001
Received PN, % (95% CI)	41.7 (39.9 to 43.6)	36.8 (34.7 to 39.0)	−4.9 (−7.7 to −2.1)	0.81 (0.71 to 0.94)	0.36

Note
The results were averaged over 25 matched replications.

Appendix 6 Sensitivity analyses of dichotomous outcome variables in enteral feeding comparison

TABLE 33 Estimates of the effect of enteral feeding for dichotomous outcomes from sensitivity analyses

	Sensitivity analysis, estimate of rate difference (95% CI) [*p*-value]		
Outcome	**Years 2012–17**	**Intervention redefined**	**Inclusion of PN in PSM**
Length of stay (> 14 days)	−8.6 (−11.4 to −5.9) [< 0.001]	−9.9 (−12.6 to −7.1) [< 0.001]	−9.0 (−11.5 to −6.6) [< 0.001]
First day suckling at breast (≤ 28 days)	10.5 (7.5 to 13.6) [< 0.001]	9.3 (6.4 to 12.2) [< 0.001]	9.5 (6.8 to 12.2) [< 0.001]
First day of maternal milk (≤ 28 days)	7.1 (4.8 to 9.3) [< 0.001]	5.6 (3.3 to 7.8) [< 0.001]	6.6 (4.6 to 8.6) [< 0.001]
Had a central venous line in situ	−7.1 (−8.8 to −5.3) [< 0.001]	−7.7 (−9.4 to −6.0) [< 0.001]	−7.9 (−9.5 to −6.3) [< 0.001]
Received PN	−2.0 (−5.2 to 1.2) [0.32]	−5.2 (−8.2 to −2.2) [0.006]	−4.6 (−7.4 to −1.8) [0.02]

PSM, propensity score model.
Note
The results were averaged over 25 matched replications.

Appendix 7 Results for alternative methods of matching on the propensity score and background variables in enteral feeding analysis

The consistency of results using alternative methods of matching on the propensity groups and principal background variables was explored and is presented using jail plots for each outcome of interest (*Figures 9–11*). Each of the six plots presents the results for a single outcome of interest [i.e. plot (a) presents the results for the outcome of pragmatically defined NEC]. Each plot contains 48 vertical segments that connect the lower and upper 95% CIs for the estimate of the treatment effect (i.e. rate difference for binary variables and mean difference for continuous variables). The estimate of the treatment effect is represented by a black disc. The 48 estimates and CIs are grouped into four sets of 12. Each of these four groups represents a set of analyses: (1) the primary analysis, (2) restricting to years 2012–17, (3) implementing a more restrictive definition of the enteral feeding intervention groups and (4) including receipt of PN on the first day in the propensity model. Within each group, the preliminary method of analysis is presented in bold, and is followed by the 11 alternative methods of analysis that are ordered as in *Figure 1*. For all outcomes, there was a high level of consistency between treatment effect estimates across all methods of analysis.

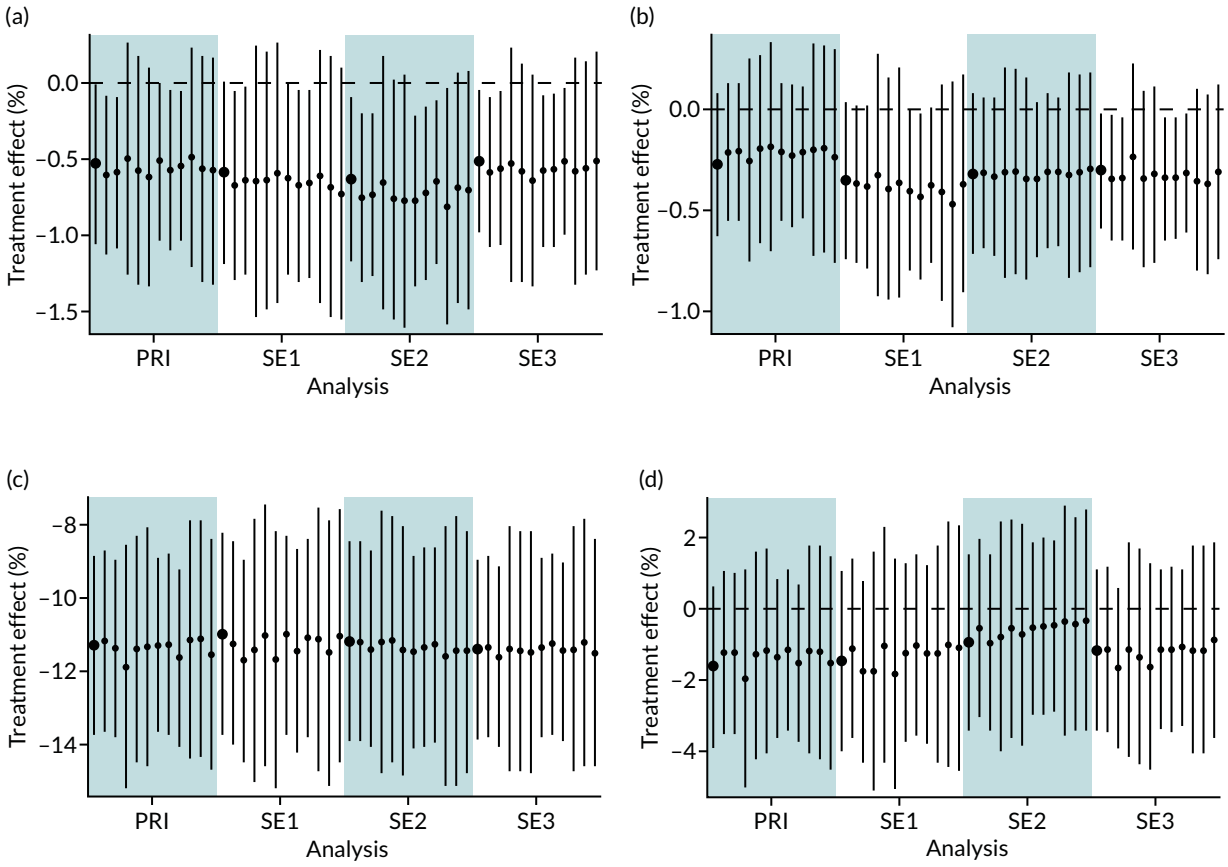

FIGURE 9 Jail plots of binary outcomes for enteral feeding analyses. (a) NEC (pragmatic definition); (b) late infection (NNAP); (c) late infection (pragmatic definition); (d) survival till discharge; (e) hypoglycaemia; and (f) breastfeeding at discharge. PRI, primary analyses; SE1, sensitivity analysis 1 (reduction to years 2012–17); SE2, sensitivity analysis 2 (redefining enteral feeding variable); SE3, sensitivity analysis 3 (adding receipt of PN on first day of life to propensity model). (*continued*)

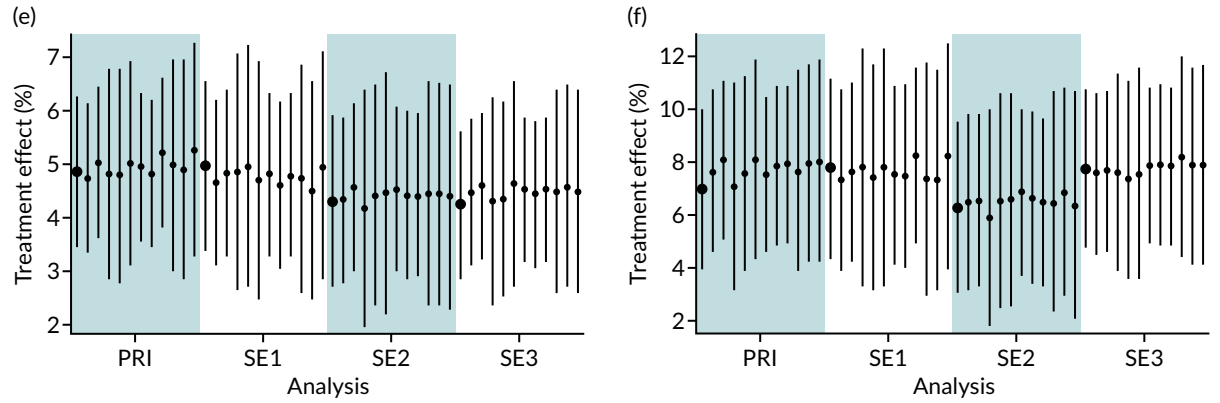

FIGURE 9 Jail plots of binary outcomes for enteral feeding analyses. (a) NEC (pragmatic definition); (b) late infection (NNAP); (c) late infection (pragmatic definition); (d) survival till discharge; (e) hypoglycaemia; and (f) breastfeeding at discharge. PRI, primary analyses; SE1, sensitivity analysis 1 (reduction to years 2012–17); SE2, sensitivity analysis 2 (redefining enteral feeding variable); SE3, sensitivity analysis 3 (adding receipt of PN on first day of life to propensity model).

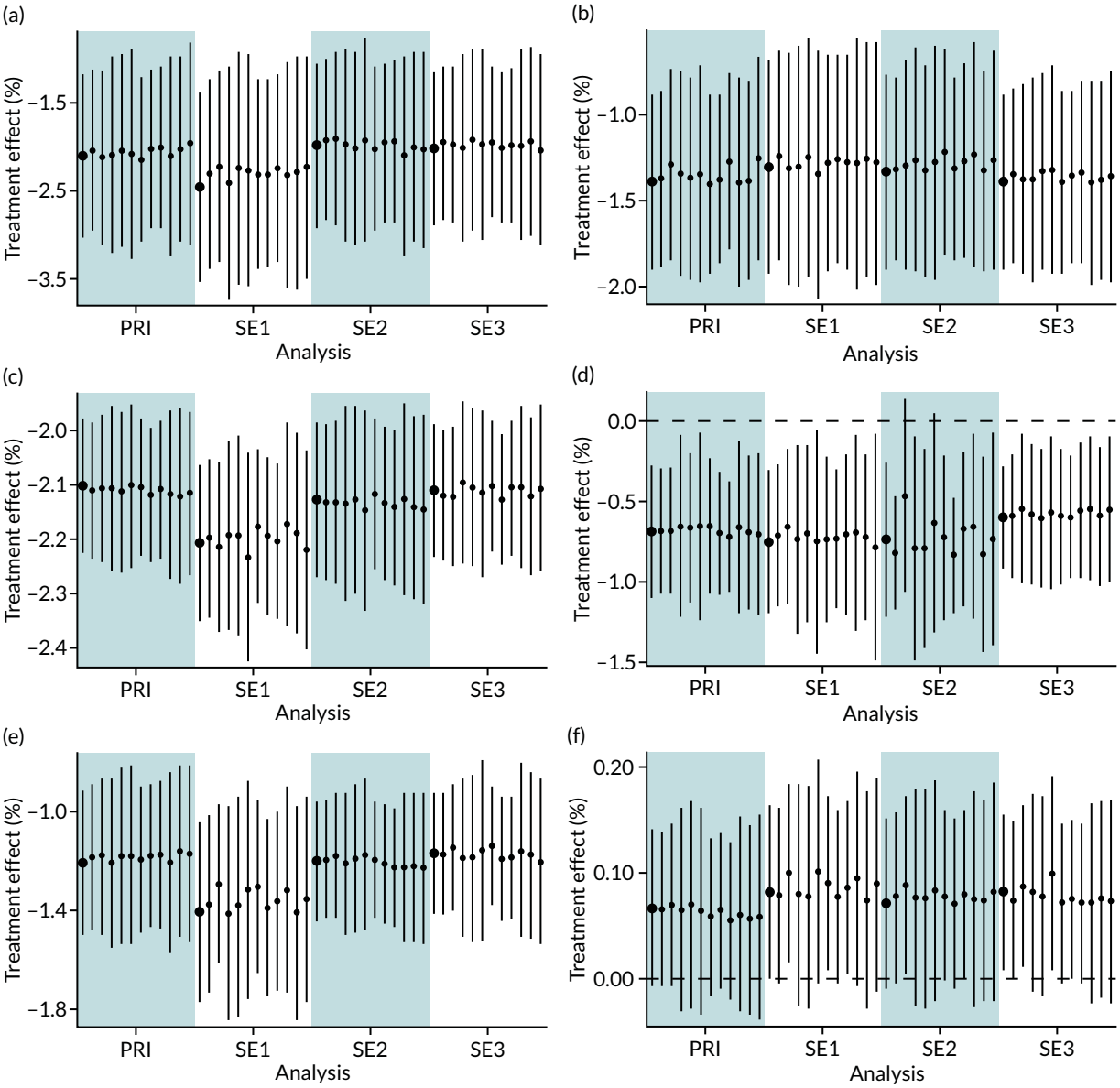

FIGURE 10 Jail plots of continuous outcomes for enteral feeding analyses. (a) Length of stay; (b) first day of suckling at breast; (c) first day of maternal milk; (d) first day of PN; (e) duration of central venous line; and (f) *z*-score of weight at discharge. PRI, primary analyses; SE1, sensitivity analysis 1 (reduction to years 2012–17); SE2, sensitivity analysis 2 (redefining enteral feeding variable); and SE3, sensitivity analysis 3 (adding receipt of PN on first day of life to propensity model).

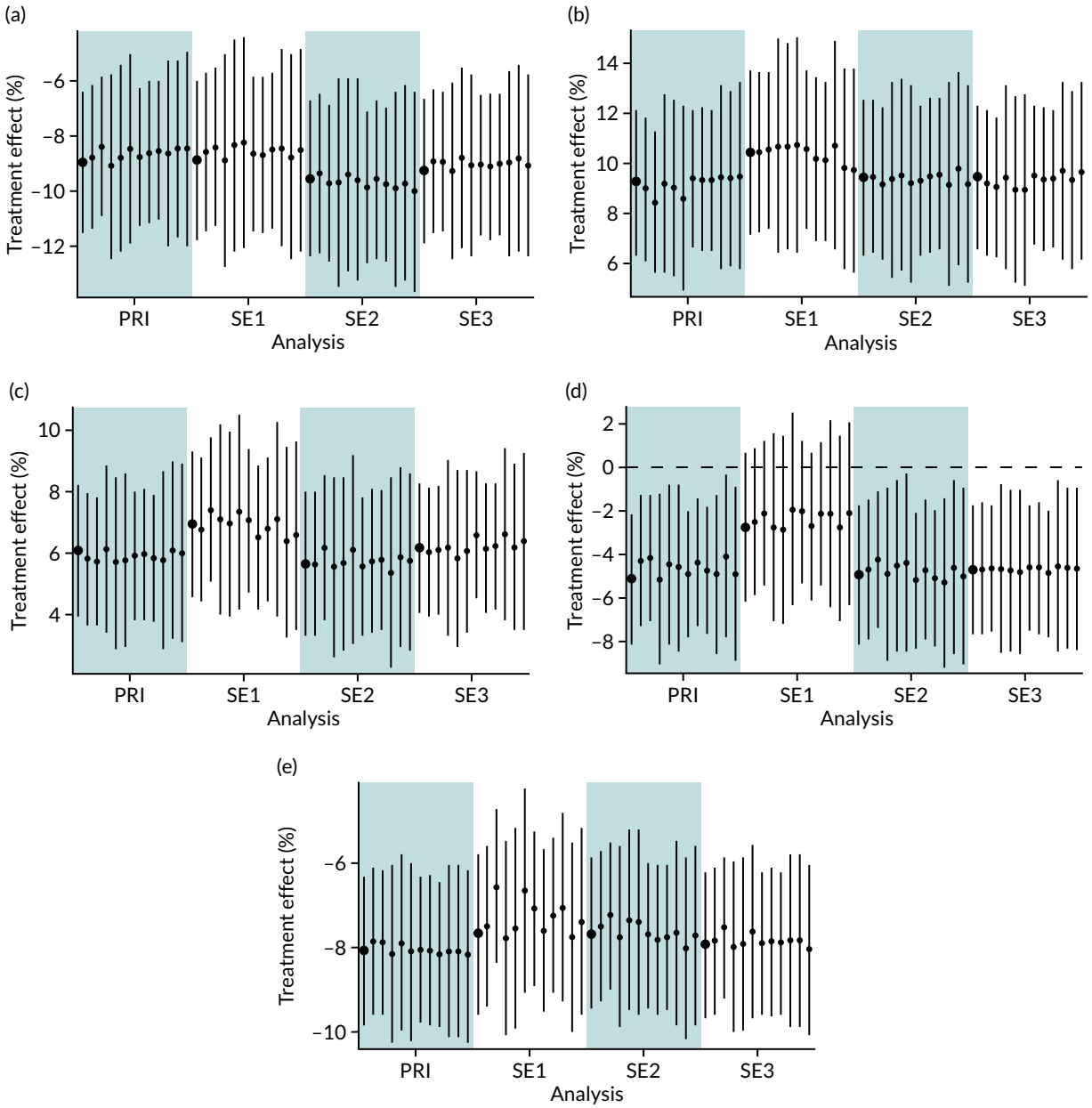

FIGURE 11 Jail plots of dichotomous outcomes for enteral feeding analyses. (a) Length of stay > 14 days; (b) first time suckling at breast < 29 days; (c) first day of maternal milk < 29 days; (d) any parental nutrition; and (e) central venous line on at least 1 day. PRI, primary analyses; SE1, sensitivity analysis 1 (reduction to years 2012–17); SE2, sensitivity analysis 2 (redefining enteral feeding variable); SE3, sensitivity analysis 3 (adding receipt of PN on first day of life to propensity model).

Appendix 8 Background variables by parenteral nutrition status in unmatched and matched cohorts

TABLE 34 Background variables, by parenteral nutrition intervention groups, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Total number of babies	4535	1475	1240	1240
Male				
n	2507	810	652	664
%	55.3	54.9	52.6	53.5
Missing, *n*	0	0	0	0
Multiple birth				
n	121	58	42	45
%	2.7	3.9	3.4	3.6
Missing, *n*	0	1	0	1
%	0	0.1	0	0.1
Gestational age at birth (weeks)				
Median	40	40	40	40
Lower quartile	38	38	38	38
Upper quartile	41	40	41	41
Missing, *n*	0	0	0	0
Birthweight (g)				
Median	3365	3300	3309	3319
Lower quartile	2971	2909	2906	2916
Upper quartile	3780	3716	3729	3719
Missing, *n*	0	0	0	0
Birth length (cm)				
Median	51.0	51.0	51.4	51.6
Lower quartile	48.0	49.0	48.3	49.1
Upper quartile	54.0	53.8	54.0	54.0
Missing, *n*	4317	1405	1182	1184
%	95.2	95.3	51.4	51.6

continued

TABLE 34 Background variables, by parenteral nutrition intervention groups, for unmatched and matched cohorts (*continued*)

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Birth head circumference (cm)				
Median	34.9	34.5	34.7	34.5
Lower quartile	33.5	33.5	33.5	33.5
Upper quartile	36.0	35.8	35.9	35.7
Missing, *n*	2526	826	686	704
%	55.7	56.0	55.3	56.8
Caesarean delivery				
n	2066	667	545	549
%	47.7	47.1	45.9	46.1
Missing, *n*	208	58	51	49
%	4.8	4.1	4.3	4.1
Cord blood gas: arterial pH				
> 7.0, *n*	1439	451	396	396
%	44.4	44.0	45.3	45.3
6.9–7.0, *n*	756	248	198	198
%	23.3	24.2	22.7	22.7
< 6.9, *n*	1049	326	280	280
%	32.3	31.8	32.0	32.0
Missing, *n*	1291	450	366	366
%	28.5	30.5	29.5	29.5

Note
The results were averaged over 25 matched replications.

TABLE 35 Maternal variables, by parenteral nutrition status, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Total number of babies	4535	1475	1240	1240
Maternal age (years)				
Median	30	31	30	31
Lower quartile	26	26	26	26
Upper quartile	35	34	34	34
Missing, *n*	39	27	19	21
%	0.9	1.8	1.5	1.7

TABLE 35 Maternal variables, by parenteral nutrition status, for unmatched and matched cohorts (*continued*)

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Maternal pyrexia				
n	228	80	61	69
%	6.1	6.5	5.9	6.5
Missing, *n*	767	240	204	190
%	20.4	19.4	19.7	18.1
Maternal suspected chorioamnionitis				
n	479	175	147	150
%	12.8	14.5	14.5	14.6
Missing, *n*	804	269	224	212
%	21.5	22.3	22.1	20.7
Smoking in pregnancy				
n	520	211	175	176
%	13.3	16.9	16.6	16.8
Missing, *n*	620	227	187	189
%	15.8	18.2	17.8	18.0
Deprivation score (LSOA)				
Median	4	5	4	4.5
Lower quartile	2	3	2	2
Upper quartile	7	8	7	7
Missing, *n*	364	385	425	328
%	8	26.1	12	13.2
Maternal hypothyroidism[a,b]				
n	50	15	14.3	12.8
%	1.1	1.0	1.2	1.0
Maternal diabetes[a]				
n	191	65	49	53
%	4.2	4.4	4.0	4.3
Maternal obstetric diagnosis[a]				
n	2196	720	585	623
%	48.4	48.8	47.2	50.2
Maternal medical diagnosis[a]				
n	1456	544	429	449
%	32.1	36.9	34.6	36.2
Primiparous[a]				
n	2425	778	669	671
%	53.5	52.7	54.0	54.1

a Data were collected via a checkbox indicating presence of condition. Therefore, it is not possible to distinguish between missing data and presence of no condition.
b Not collected in years 2010–12.
Note
The results were averaged over 25 matched replications.

TABLE 36 Resuscitation variables, by parenteral nutrition status, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Total number of babies	4535	1475	1240	1240
Apgar score at 1 minute				
Median	2	1	2	2
Lower quartile	1	1	1	1
Upper quartile	3	3	3	3
Missing, *n*	360	133	113	115
%	7.9	9.0	9.1	9.3
Apgar score at 5 minutes				
Median	4	4	4	4
Lower quartile	2	3	3	3
Upper quartile	6	6	6	6
Missing, *n*	355	131	107	109
%	7.8	8.9	8.6	8.8
Received chest compressions[a]				
n	1705	523	431	427
%	37.6	35.5	34.8	34.4
Received emergency resuscitation drugs[a]				
n	719	206	176	172
%	15.9	14.0	14.2	13.9
Intubated at resuscitation[a]				
n	2925	935	784	783
%	64.5	63.4	63.2	63.1
Umbilical cord base excess (mmol/l)				
Median	−13	−12.7	−12.9	−12.5
Lower quartile	−17.4	−17.4	−17.4	−17.3
Upper quartile	−8.2	−8.3	−8.2	−8.2
Missing, *n*	1562	576	463	468
%	34.4	39.1	37.3	37.7
Time to first spontaneous breath				
0–5 minutes, *n*	674	235	200	198
%	14.9	15.9	16.1	16.0
> 5 minutes, *n*	2701	896	757	758
%	59.6	60.7	61.0	61.1
Missing, *n*	1160	344	283	284
%	25.6	23.3	22.8	22.9

a Data were collected via a checkbox indicating presence of condition. Therefore, it is not possible to distinguish between missing data and presence of no condition.

Note

The results were averaged over 25 matched replications.

TABLE 37 Neonatal variables, by parenteral nutrition status, for unmatched and matched cohorts

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Total number of babies	4535	1475	1240	1240
Time to admission (minutes)				
Median	30	30	30	29
Lower quartile	20	20	21	20
Upper quartile	44	45	45	44
Missing, *n*	0	0	0	0
Blood glucose concentration at admission (mmol/l)				
Median	5.6	5.6	5.8	5.6
Lower quartile	3.6	3.8	3.8	3.9
Upper quartile	7.7	8.0	7.7	8.0
Missing, *n*	836	297	241	242
%	18.4	20.1	19.4	19.5
Heart rate (b.p.m.)				
Median	145	143	144	144
Lower quartile	130	128	129	130
Upper quartile	160	157	158	157
Missing, *n*	354	125	99	101
%	7.8	8.5	7.9	8.1
Oxygen saturation (mmHg)				
Median	97	97	97	97
Lower quartile	92	93	93	92
Upper quartile	100	100	100	100
Missing, *n*	416	151	117	118
%	9.2	10.2	9.4	9.5
Temperature (°C)				
Median	36.2	36.2	36.2	36.2
Lower quartile	35.4	35.5	35.5	35.4
Upper quartile	36.7	36.6	36.7	36.6
Missing, *n*	159	82	146	95
%	3.5	5.6	4.1	3.8
Mechanical ventilation				
n	3508	1122	951	956
%	80.2	79.5	79.6	80.2
Missing, *n*	161	63	46	49
%	3.7	4.5	3.9	4.1

continued

TABLE 37 Neonatal variables, by parenteral nutrition status, for unmatched and matched cohorts (*continued*)

	Cohort			
	Unmatched		Matched	
Variable	No PN	PN	No PN	PN
Inhaled nitric oxide				
n	197	70	50	58
%	4.5	5	4.2	4.9
Missing, *n*	204	71	59	56
%	4.7	5.1	5.0	4.7
Treatment for low blood pressure				
n	1126	335	295	287
%	26	23.9	25	24.2
Missing, *n*	198	71	57	56
%	4.6	5.1	4.8	4.7
Infection in the first 3 days (NNAP)[a]				
n	37	18	9	14
%	0.8	1.2	0.7	1.1
Postnatal transfer (acute)				
n	2219	640	546	549
%	48.9	43.4	44	44.2
Missing, *n*	0	0	0	0

b.p.m., beats per minute.
a Data were collected via a checkbox indicating presence of condition. Therefore, it is not possible to distinguish between missing data and presence of no condition.
Note
The results were averaged over 25 matched replications.

Appendix 9 Primary analysis of dichotomous outcome variables in parenteral nutrition comparison

TABLE 38 Analysis of dichotomised outcome variables for babies provided with parenteral nutrition vs. babies from whom parenteral nutrition was withheld

Variable	Intervention		Rate difference, % (95% CI)	OR (95% CI)	*p*-value
	No PN rate	PN rate			
Total number of babies	1240	1240			
Length of stay (> 14 days), % (95% CI)	29.2 (27.4 to 31.0)	30.9 (28.5 to 33.2)	1.7 (−1.3 to 4.6)	1.08 (0.91 to 1.28)	0.27
First day suckling at breast (≤ 28 days), % (95% CI)	59.8 (57.9 to 61.8)	61.1 (58.6 to 63.5)	1.2 (−1.9 to 4.4)	1.05 (0.90 to 1.24)	0.44
First day of maternal milk (≤ 28 days), % (95% CI)	80.8 (79.3 to 82.4)	85.3 (83.5 to 87.0)	4.4 (2.1 to 6.8)	137 (1.11 to 1.69)	< 0.001
Days of central venous line in situ (> 0 days), % (95% CI)	92.4 (91.4 to 93.4)	97.9 (97.2 to 98.6)	5.5 (4.3 to 6.8)	3.85 (2.48 to 5.97)	< 0.001

Note
The results were averaged over 25 matched replications.

Appendix 10 Sensitivity analyses of dichotomous outcome variables in parenteral nutrition comparison

TABLE 39 Estimates of the effect of parenteral nutrition for dichotomous outcomes from sensitivity analyses

	Sensitivity analysis, estimate of rate difference (95% CI) [*p*-value]		
Outcome	**Years 2012–17**	**Intervention redefined**	**Inclusion of enteral feeds on day 1 in PSM**
Length of stay (> 14 days)	2.5 (–0.7 to 5.7) [0.13]	1.9 (–1.0 to 4.9) [0.20]	2.5 (–0.4 to 5.5) [0.09]
First day suckling at breast (≤ 28 days)	0.8 (–2.7 to 4.2) [0.66]	1.3 (–1.8 to 4.4) [0.40]	2.2 (–0.9 to 5.4) [0.16]
First day of maternal milk (≤ 28 days)	3.3 (0.6 to 5.9) [0.02]	4.4 (2.0 to 6.8) [< 0.001]	4.9 (2.5 to 7.3) [< 0.001]
Days of central venous line in situ (> 0 days)	4.8 (3.5 to 6.2) [< 0.001]	5.7 (4.5 to 7.0) [< 0.001]	5.6 (4.3 to 6.8) [< 0.001]

PSM, propensity score model.
Note
The results were averaged over 25 matched replications.

Appendix 11 Results for alternative methods for matching on the propensity score and background variables in the parenteral nutrition comparison

The consistency of the results using alternative methods of matching on the propensity groups and principal background variables was explored and is presented using jail plots for each outcome of interest (*Figures 12–14*). Each of the six plots presents the results for a single outcome of interest [i.e. plot (a) presents the results for the outcome of pragmatically defined NEC]. Each plot contains 48 vertical segments that connects the lower and upper 95% CIs for the estimate of the treatment effect (i.e. rate difference for binary variables and mean difference for continuous variables). The estimate of the treatment effect is represented by the black disc. The 48 estimates and CIs are grouped into four groups of 12. Each of the four groups represents a set of analyses: (1) the primary analysis, (2) restricting to years 2012–17, (3) implementing a more restrictive definition of the PN intervention groups, and (4) including receipt of enteral feeds on the first day in the propensity model. Within each group, the preliminary method of analysis is presented in bold and is followed by the 11 alternative methods of analysis that are ordered as in *Figure 1*. For all outcomes, there was a high level of consistency between treatment effect estimates across all methods of analysis.

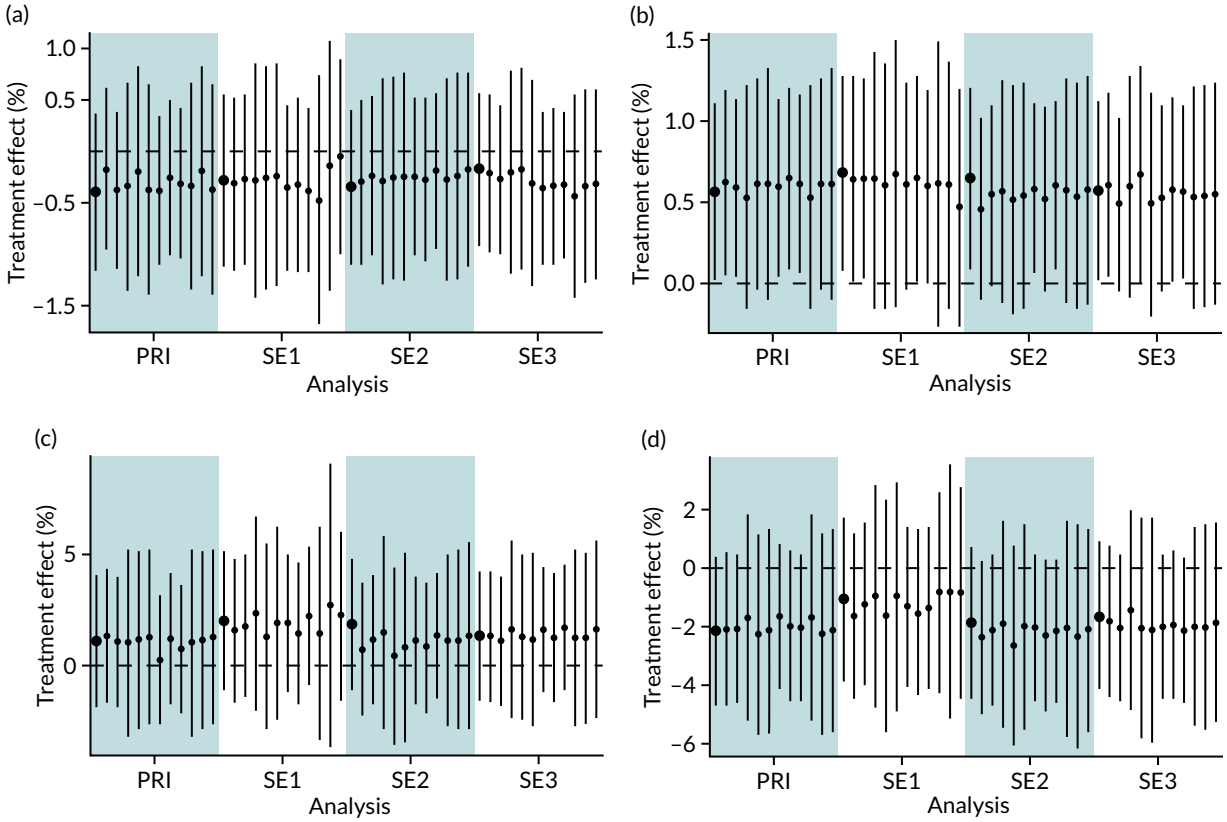

FIGURE 12 Jail plots of binary outcomes for parenteral nutrition analyses. (a) NEC (pragmatic definition); (b) late infection (NNAP); (c) late infection (pragmatic definition); (d) survival till discharge; (e) hypoglycaemia; and (f) breastfeeding at discharge. PRI, primary analyses; SE1, sensitivity analysis 1 (reduction to years 2012–17); SE2, sensitivity analysis 2 (redefining PN variable); SE3, sensitivity analysis 3 (adding receipt of enteral feeds on first day of life to propensity model). (*continued*)

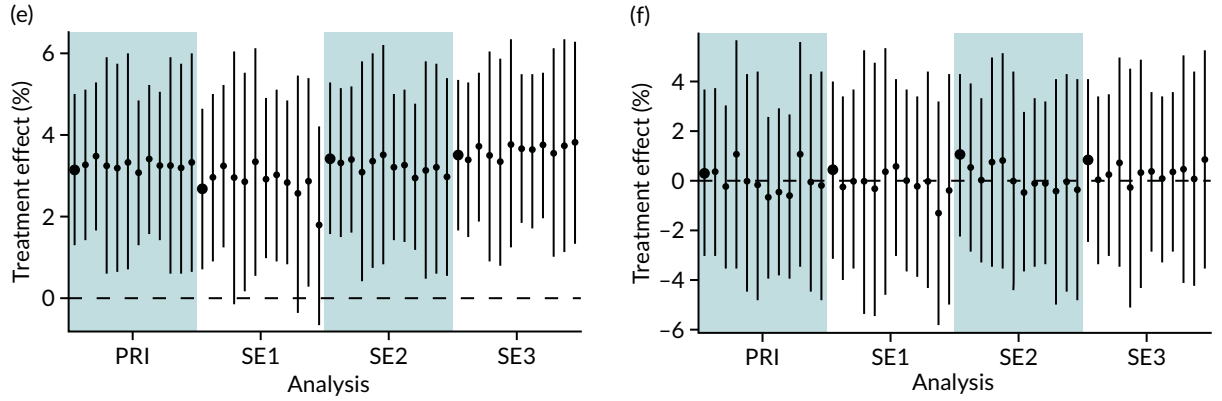

FIGURE 12 Jail plots of binary outcomes for parenteral nutrition analyses. (a) NEC (pragmatic definition); (b) late infection (NNAP); (c) late infection (pragmatic definition); (d) survival till discharge; (e) hypoglycaemia; and (f) breastfeeding at discharge. PRI, primary analyses; SE1, sensitivity analysis 1 (reduction to years 2012–17); SE2, sensitivity analysis 2 (redefining PN variable); SE3, sensitivity analysis 3 (adding receipt of enteral feeds on first day of life to propensity model).

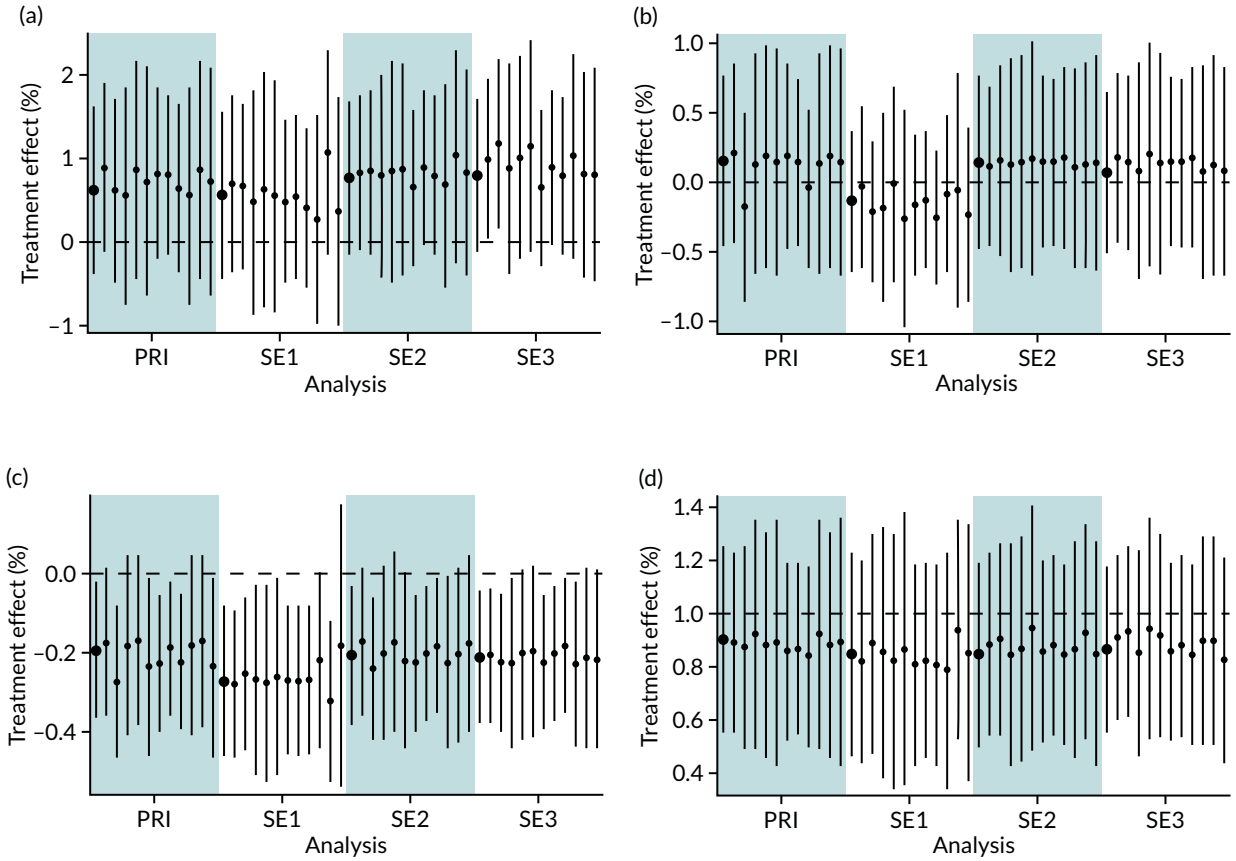

FIGURE 13 Jail plots of continuous outcomes for parenteral nutrition analyses. (a) Length of stay; (b) first day of suckling at breast; (c) first day of maternal milk; (d) duration of central venous line in situ; and (e) *z*-score of weight at discharge. PRI, primary analyses; SE1, sensitivity analysis 1 (reduction to years 2012–17); SE2, sensitivity analysis 2 (redefining PN variable); SE3, sensitivity analysis 3 (adding receipt of enteral feeds on first day of life to propensity model). (*continued*)

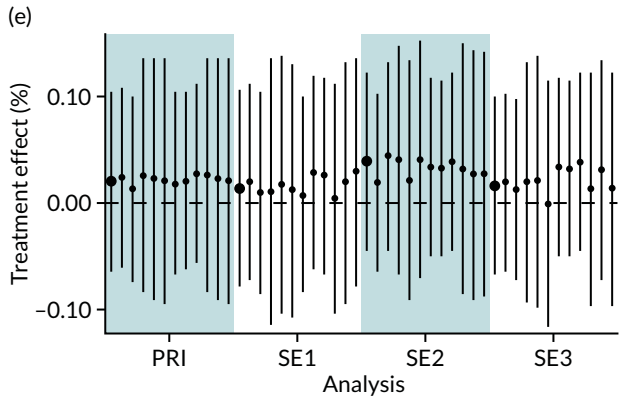

FIGURE 13 Jail plots of continuous outcomes for parenteral nutrition analyses. (a) Length of stay; (b) first day of suckling at breast; (c) first day of maternal milk; (d) duration of central venous line in situ; and (e) *z*-score of weight at discharge. PRI, primary analyses; SE1, sensitivity analysis 1 (reduction to years 2012–17); SE2, sensitivity analysis 2 (redefining PN variable); SE3, sensitivity analysis 3 (adding receipt of enteral feeds on first day of life to propensity model).

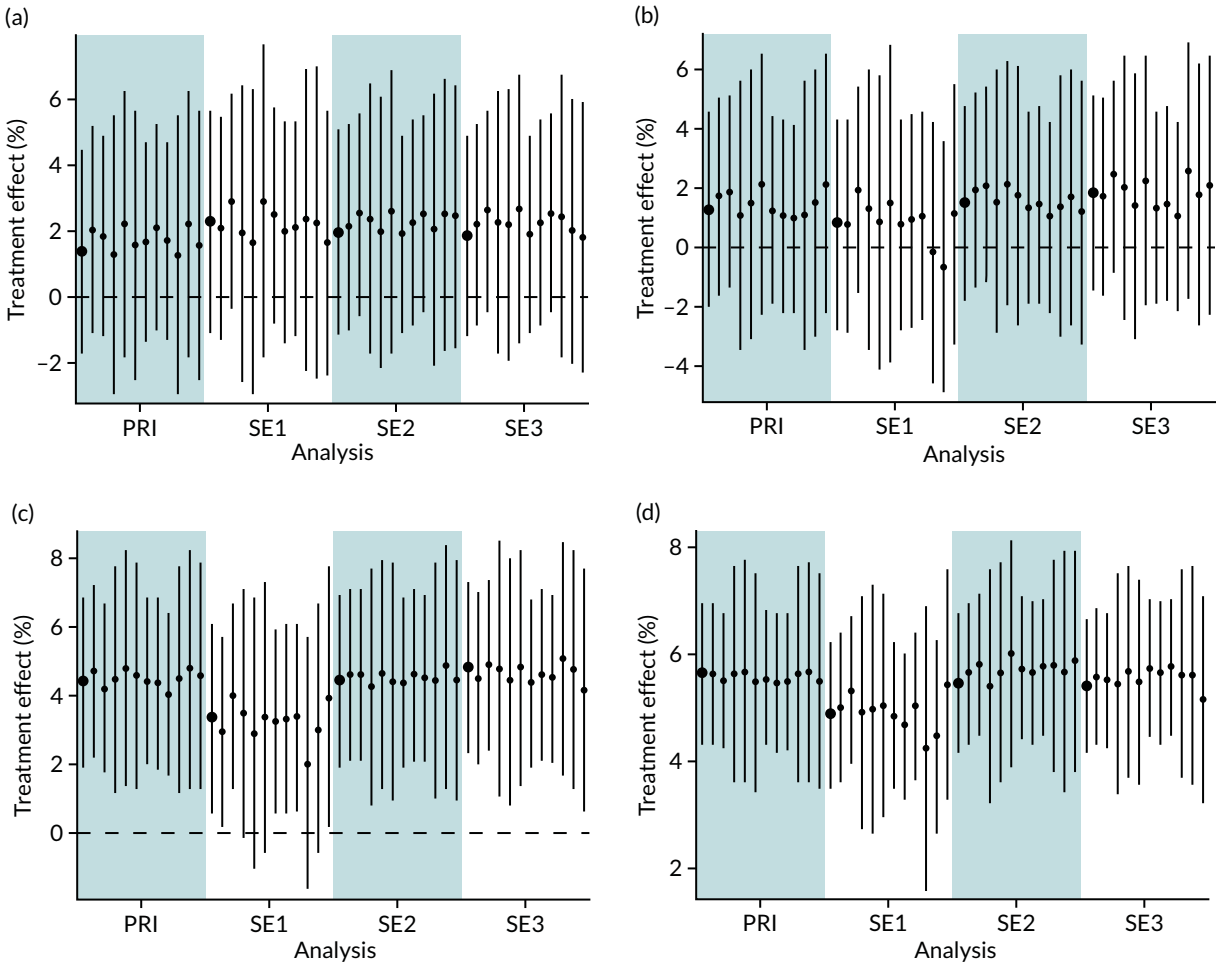

FIGURE 14 Jail plots of dichotomous outcomes for parenteral nutrition analyses. (a) Length of stay > 14 days; (b) first time suckling at breast < 29 days; (c) first day of maternal milk < 29 days; and (d) central venous line in situ on at least 1 day. PRI, primary analyses; SE1, sensitivity analysis 1 (reduction to years 2012–17); SE2, sensitivity analysis 2 (redefining PN variable); SE3, sensitivity analysis 3 (adding receipt of enteral feeds on first day of life to propensity model).

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