Outcomes in relation to early parenteral nutrition use in preterm neonates born between 30 and 33 weeks' gestation: a propensity score matched observational study

James William Harrison Webbe, Nicholas Longford, Cheryl Battersby, Kayleigh Oughham, Sabita N Uthaya, Neena Modi, Chris Gale

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2021-321643).

Neonatal Medicine, Imperial College London, London, UK

Correspondence to
Dr James William Harrison Webbe, Section of Neonatal Medicine, Imperial College London, London, SW10 9NH, UK; j.webbe@imperial.ac.uk

Received 17 January 2021
Accepted 6 August 2021
Published Online First 21 September 2021

ABSTRACT

Objective To evaluate whether in preterm neonates parenteral nutrition use in the first 7 postnatal days, compared with no parenteral nutrition use, is associated with differences in survival and other important morbidities. Randomised trials in critically ill older children show that harms, such as nosocomial infection, outweigh benefits of early parenteral nutrition administration; there is a paucity of similar data in neonates.

Design Retrospective cohort study using propensity matching including 35 maternal, infant and organisational factors to minimise bias and confounding.

Setting National, population-level clinical data obtained for all National Health Service neonatal units in England and Wales.

Patients Preterm neonates born between 30^{+0} and 32^{+6} weeks^{+days}.

Interventions The exposure was parenteral nutrition administered in the first 7 days of postnatal life; the comparator was no parenteral nutrition.

Main outcome measures The primary outcome was survival to discharge from neonatal care. Secondary outcomes comprised the neonatal core outcome set.

Results 16 292 neonates were compared in propensity score matched analyses. Compared with matched neonates not given parenteral nutrition in the first postnatal week, neonates who received parenteral nutrition had higher survival at discharge (absolute rate increase 0.91%; 95% CI 0.53% to 1.30%), but higher rates of necrotising enterocolitis (absolute rate increase 4.6%), bronchopulmonary dysplasia (absolute rate increase 3.9%), late-onset sepsis (absolute rate increase 1.5%) and need for surgical procedures (absolute rate increase 0.92%).

Conclusions In neonates born between 30^{+0} and 32^{+6} weeks' gestation, those given parenteral nutrition in the first postnatal week had a higher rate of survival but higher rates of important neonatal morbidities. Clinician equipoise in this area should be resolved by prospective randomised trials.

Trial registration number NCT03767634.

What is already known on this topic?

- Preterm neonates are among the highest users of parenteral nutrition.
- Randomised trials in critically ill older children show that harms, such as nosocomial infection, outweigh benefits of early parenteral nutrition administration.
- There is a paucity of similar randomised trial data in neonates.

What this study adds?

- Early parenteral nutrition use is associated with higher survival but higher morbidity.
- Trials focused on important outcomes are needed to determine which neonates benefit from early parenteral nutrition.

INTRODUCTION

Preterm birth abruptly ends the transplacental transfer of nutrients that support fetal growth. Preterm neonates have limited stores of energy, protein and other nutrients, and have difficulty tolerating adequate milk volumes immediately after birth.[1] Recognising this, preterm neonates are commonly given parenteral nutrition (PN) until enteral feeding is fully established. Neonatal PN was first described in 1968[2] and since then it has become widely used,[3] but the evidence is sparse. Specifically, the impact of administration of early compared with late initiation of PN has not been evaluated in randomised controlled neonatal trials powered for clinically meaningful endpoints.[4] Consequently, meta-analyses have not provided reliable recommendations for clinical practice.[5–7]

PN has known detrimental effects, in particular increased risk of bloodstream infection.[8] Recent evidence from large randomised controlled trials showed use of PN in critically unwell adults[9] and children[10] during the first week of admission to an intensive care unit led to worse outcomes when compared with delayed PN administration. Furthermore, a subgroup analysis of the paediatric population limited to term neonates showed increased rates of nosocomial infection with early PN use.[11] These studies highlight the uncertainty around the risks and benefits of PN administration in the early postnatal period. Additionally, the neonatal population is heterogeneous and the balance of risks and

► http://dx.doi.org/10.1136/fetalneonatal-2021-322383
► http://dx.doi.org/10.1136/fetalneonatal-2021-323072

To cite: Webbe JWH, Longford N, Battersby C, *et al*. *Arch Dis Child Fetal Neonatal Ed* 2022;**107**:F131–F136.

benefits is likely to vary according to gestational age and growth restriction. Thus, despite the limited evidence base and enduring uncertainty, the early initiation of PN in more preterm neonates is widely practised[12] and advised in national practice guidance[13]; therefore, conducting a randomised trial may be difficult in this population due to a lack of equipoise.[4]

Recognising these challenges, we undertook an observational study using population-level, routinely recorded clinical data. We selected preterm neonates born between 30^{+0} and 32^{+6} gestational weeks because routine early initiation of PN was not universally indicated in UK national guidance over the study period (January 2012–December 2017) for these infants, and hence nutritional practice varied. We used propensity scores to form matched comparator groups. The use of population-level data ensured this study was powered for clinically important outcomes.

OBJECTIVE

To evaluate if there was any difference in survival and other important neonatal outcomes in preterm neonates born between 30^{+0} and 32^{+6} weeks' gestation who did or did not receive PN in the first 7 postnatal days.

METHODS

We undertook a retrospective cohort study using quality-assured, routinely recorded neonatal clinical data available in a national database. We applied propensity score methodology to form matched subgroups of neonates with similar background characteristics, exposed to different PN strategies to compare their outcomes. We prospectively registered this study and published the study protocol.[14] All UK National Health Service (NHS) neonatal units in England and Wales agreed to the use of their data. A list of contributing neonatal units and their UK Neonatal Collaborative lead clinicians is provided (online supplemental etable 8).

Patients

We used de-identified data held in the National Neonatal Research Database (NNRD)[15] from all NHS neonatal units in England and Wales from 2012 onwards. The NNRD holds quality-assured, curated data sourced through extractions from point-of-care electronic health records completed by health professionals during clinical care.[16] The quality and completeness of the data held in the NNRD have been shown to be satisfactory for research[17] and no additional data cleaning was undertaken.

Study population

We used data from all neonates born between 30^{+0} and 32^{+6} weeks' gestational age between 1 January 2012 and 31 December 2017 and admitted to a neonatal unit in England and Wales. We excluded neonates with major congenital gastrointestinal malformations, life-limiting conditions or congenital conditions requiring surgery in the neonatal period (defined in online supplemental etable 1): they do not receive standard neonatal nutritional care and were expected to have different outcomes. We also excluded neonates in whom key background data (birth weight or gestational age) or primary outcome data were missing.

Intervention

The intervention was PN administered at any point in the first 7 days of postnatal life. This threshold was based on the previous randomised trials in adult and paediatric intensive care populations.[9 10] We defined the 'PN' group as infants who received PN in any volume, of any type (standardised or tailor-made), by any route (peripheral intravenous cannula or central venous catheter) for any duration during the first 7 postnatal days. The comparator group—the 'No PN' group—comprised eligible neonates not recorded to have received any PN in the first 7 days.

Outcomes

The primary outcome was survival to discharge from neonatal care; secondary outcomes were other components of the neonatal core outcomes set[18] and growth (online supplemental etable 2). Neonatal core outcomes are those considered essential for neonatal research by former patients, parents, clinicians and researchers.[19] Growth was included as a widely cited justification for administering PN to neonates to improve growth and theoretically optimise long-term outcomes.[20] As measures for the core outcomes have not been defined, established definitions were used (online supplemental etable 2). The following core outcome set components were not reported as relevant data are not captured in the NNRD: quality of life, gross motor ability and cognitive ability. After the prespecified analyses showed opposing effects of PN on mortality and morbidity, post-hoc analyses investigating the effect of PN on death or each secondary outcome were undertaken to explore whether any increased morbidity seen in a treatment group was solely due to increased survival.

Statistical analysis

We calculated that 12 000 neonates were required in each group to have 90% power to detect an absolute difference in survival to discharge of 1.3% (two-sided significance of 5%); the expected difference was calculated using a baseline mortality rate of 3.4%[21] and an OR of 0.73 for early versus late PN suggested by previous research.[10]

To minimise bias by confounding, we used propensity matching with logistic regression. Infants were initially matched on gestational week at birth (three groups) and whether or not they were small for gestational age defined as <10th centile for gestational age at birth (two groups) as these were identified a priori as critically important variables. Within the six groups this created, further matching was then undertaken using propensity score (split by decile). The propensity score included maternal, infant and organisational factors. Infant factors were those occurring at birth and on the first postnatal day, preceding the decision to administer PN (online supplemental file etable 3). We then identified pairs of matched neonates who differed on exposure to PN. We calculated absolute risk differences and ORs for the prespecified, dichotomous outcomes for the two groups. We used the Holm-Bonferroni method[22] when analysing secondary outcomes to avoid erroneous inferences due to multiple comparisons.

To minimise the risk confounding due to hidden bias affecting the findings, we undertook a planned sensitivity analysis. We constructed a dichotomous variable and calculated the magnitude of imbalance between the two groups required to stack the odds against the superior treatment option; we then compared this with the imbalance in observed background variables to assess whether it was plausible such as an unobserved variable existed.[23] This models a 'worst-case' scenario in which an unobserved background variable provided an alternative explanation for the significant differences in outcomes between the two groups.

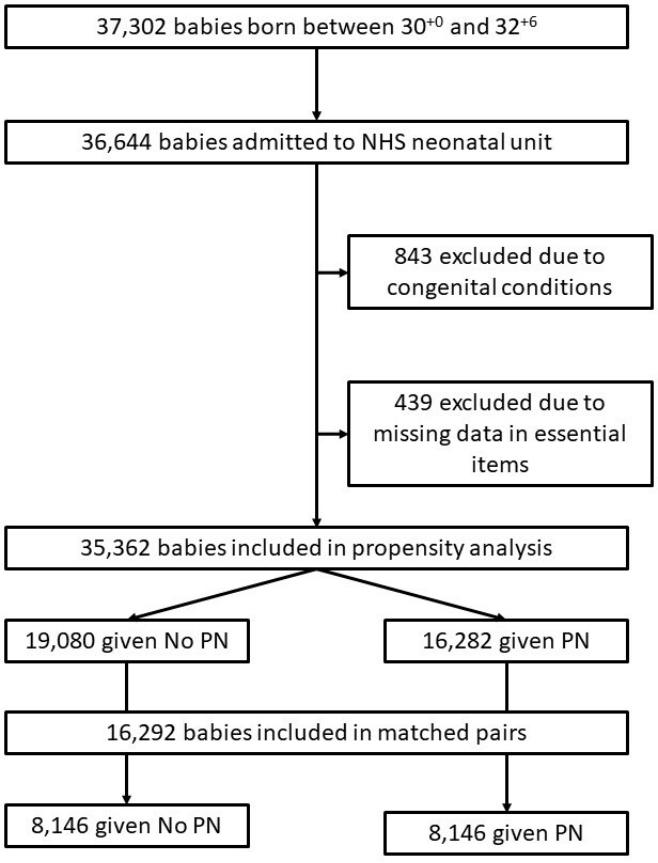

Figure 1 Participant flow for the primary analysis. NHS, National Health Service; PN, parenteral nutrition.

Table 1 Key background characteristics of neonates

	Entire cohort		Matched cohort	
	No PN group (N=19 080)	PN group (N=16 282)	No PN group (N=8146)	PN group (N=8146)
Gestational age (weeks), mean (SD)	31.5 (0.7)	30.9 (0.8)	31.2 (0.8)	31.2 (0.8)
Birth weight (kg), mean (SD)	1.74 (0.28)	1.47 (0.32)	1.67 (0.28)	1.59 (0.29)
Birth weight Z-score, mean (SD)	0.12 (0.95)	−0.16 (1.0)	0.01 (0.91)	−0.05 (0.88)
Proportion small for gestational age, n (%)	834 (4.4)	3773 (23.2)	710 (8.7)	715 (8.8)
Female, n (%)	8787 (46.1)	7424 (45.6)	3664 (45.0)	3733 (45.8)
Maternal factors				
Maternal age, mean (SD)	30.5 (6.3)	30.7 (6.3)	30.8 (6.3)	30.8 (6.2)
Maternal complications of pregnancy*, n (%)	14 025 (73.5)	12 234 (75.1)	6055 (74.3)	6177 (75.8)
Complete course of antenatal steroids, n (%)	3312 (18.2)	2515 (16.1)	1328 (17.0)	1324 (17.0)
Infant factors after birth				
Apgar score at 5 min, median (IQR)	9 (8–10)	9 (8–9)	9 (8–10)	9 (8–10)
Intubation during resuscitation, n (%)	1730 (9.1)	3275 (20.1)	1175 (14.4)	1180 (14.5)
Infant factors on first day				
Admission temperature, mean (SD)	36.7 (0.6)	36.7 (0.6)	36.8 (0.6)	36.8 (0.6)
Admission heart rate, mean (SD)	156 (18.0)	157 (18.2)	157 (18.0)	157 (18.1)
Admission oxygen saturation, mean (SD)	93.4 (7.8)	93.6 (7.6)	93.3 (7.8)	93.3 (7.8)
Ventilated on first day, n (%)	2833 (14.9)	5364 (33.1)	1932 (23.8)	1979 (24.4)
Inotropes on first day, n (%)	186 (1.0)	658 (4.1)	128 (1.6)	149 (1.8)
Treated for infection on first day, n (%)	8487 (44.5)	7795 (47.9)	3837 (47.1)	3843 (47.2)
Enteral feeding on first day, n (%)	14 401 (75.5)	8593 (52.8)	4570 (56.1)	4555 (55.9)
Organisational factors				
Born in level 3 unit (NICU), n (%)	7963 (41.7)	7294 (44.8)	3525 (43.3)	3463 (42.5)
Transferred on first day, n (%)	810 (4.2)	1112 (6.8)	450 (5.5)	464 (5.7)

*'Maternal complications of pregnancy' includes gestational hypertension, pre-eclampsia, diabetes, gestational diabetes, prolonged rupture of membranes or suspected chorioamnionitis.
NICU, neonatal intensive care unit; PN, parenteral nutrition.

Deviations from protocol

Two deviations from the published protocol occurred. The first related to the use of data from neonates born in Scotland: this required authorisation from the Scottish Public Benefit and Privacy Panel,[24] which we did not obtain in sufficient time. Therefore, we completed the project using data from neonates born in England and Wales. The second involved post-hoc analyses of the effect of PN on composite outcomes, combining death or each secondary outcome, as described above: this was the only analysis that was not prespecified.

RESULTS

Over the study period, there were 37 302 births in this cohort: 36 644 neonates were admitted to an NHS neonatal unit in England or Wales.

We excluded 843 neonates due to congenital conditions, 439 due to missing data, leaving 35 362 included in the propensity score analysis with 8146 matched pairs (figure 1).

In the cohort before matching, 16 282 neonates received PN in the first 7 days and 19 080 did not. The population given PN had a lower gestational age and lower birth weight. They also had higher rates of interventions after birth (table 1). After matching, no major differences were seen: the 8146 pairs were well matched on all background variables (table 1, online supplemental etable 4 and efigure 1).

The survival rate for the cohort before matching was 98.6%. After matching, the PN group had a higher rate of survival (98.9% vs 98.0%; absolute rate difference 0.91%, 95% CI 0.53% to 1.30%). The PN group had higher rates of bronchopulmonary dysplasia, late-onset sepsis, necrotising enterocolitis and need for surgical procedures after correcting for multiple comparisons (table 2). The largest effects associated with PN were a 4.6% higher rate of necrotising enterocolitis (absolute rate: 8.1% vs 3.5%: 95% CI for difference 3.9% to 5.3%) and a 3.9% higher rate of bronchopulmonary dysplasia (absolute rate: 7.7% vs 3.8%: 95% CI for difference 3.2% to 4.7%). The PN group had a lower weight at discharge with an absolute difference in mean Z-score of 0.12 (95% CI 0.10 to 0.15). We undertook post-hoc analyses to examine the association between PN use and a composite of death or each morbidity separately. The PN group had a higher proportion of neonates with 'death or bronchopulmonary dysplasia' (absolute rate: 8.5% vs 5.8%) and 'death or necrotising enterocolitis' (absolute rate: 8.7% vs 5.6%) (online supplemental etable 1).

For several outcomes, there were large amounts of missing data (table 2). This was an issue for the 2-year outcome components impaired ability to walk, blindness or visual impairment, and deafness or hearing impairment, where over 85% of data were missing. In addition, as discharge head circumference data

Table 2 Neonatal outcomes

	Entire cohort				Matched cohort					
	No PN group (N=19 080)		PN group (N=16 282)		No PN group (N=8146)		PN group (N=8146)			
		Missing data		Missing data		Missing data		Missing data	Treatment effect (95% CI)	P value
Survival, n (%)	18 838 (98.7)	0	16 059 (98.6)	0	7987 (98.0)	0	8057 (98.9)	0	0.91 (0.53 to 1.30)	<0.001*
Secondary outcomes: outcomes during admission										
Brain injury on imaging, n (%)	88 (0.5)	0†	182 (1.1)	0†	48 (0.59)	0†	73 (0.90)	0†	0.31 (0.05 to 0.57)	0.02
Bronchopulmonary dysplasia, n (%)	525 (2.8)	354	1923 (12.0)	234	302 (3.8)	198	619 (7.7)	106	3.9 (3.2 to 4.7)	<0.001*
Late-onset sepsis, n (%)	108 (0.6)	0†	441 (2.7)	0†	59 (0.73)	0†	179 (2.2)	0†	1.5 (1.1 to 1.8)	<0.001*
Necrotising enterocolitis, n (%)	521 (2.7)	0†	1518 (9.3)	0†	285 (3.5)	0†	660 (8.1)	0†	4.6 (3.9 to 5.3)	<0.001*
Need for surgical procedures, n (%)	123 (0.6)	0†	358 (2.2)	0†	69 (0.85)	0†	147 (1.8)	0†	0.92 (0.57 to 1.3)	<0.001*
Retinopathy of prematurity, n (%)	410 (4.9)	10 728	879 (6.9)	3504	272 (5.3)	3007	297 (5.4)	2642	0.12 (−0.73 to 0.97)	0.78
Seizures, n (%)	107 (0.6)	14	214 (1.3)	37	81 (0.99)	3	114 (1.4)	8	0.39 (0.06 to 0.72)	0.02
Weight Z-score, mean (SD)	0.12 (0.95)	245	−0.16 (1.0)	170	0.073 (0.98)	134	−0.024 (0.96)	77	−0.12 (−0.10 to −0.15)	<0.001*
Secondary outcomes: outcomes at 2 years										
Impaired ability to walk, n (%)	62 (3.9)	17 481	127 (4.4)	13 371	41 (4.1)	7157	44 (3.8)	6994	−0.25 (−1.9 to 1.4)	0.77
Blindness or visual impairment, n (%)	91 (5.8)	17 516	178 (6.2)	13 414	54 (5.5)	7173	73 (6.4)	7009	0.83 (−1.2 to 2.9)	0.42
Deafness or hearing impairment, n (%)	23 (1.5)	17 530	56 (2.0)	13 436	13 (1.4)	7183	19 (1.7)	7022	0.31 (−0.76 to 1.4)	0.57

*Indicates a statistically significant result (p<0.05). Secondary outcomes corrected for multiple comparisons using Holm-Bonferroni method.
†Amount of missing data uncertain as absence of data interpreted as absence of outcome.
PN, parenteral nutrition.

were almost universally missing: this outcome was not analysed. Due to the format in which data are entered into the electronic patient record for the outcomes brain injury on imaging, late-onset sepsis, necrotising enterocolitis and need for surgical procedures, absence of a response was assumed to be lack of the condition: it is not possible to know how much data were missing.

The sensitivity analysis showed the magnitude of imbalance required for an unrecorded background variable to account for the differences found (online supplemental etable 5) was only exceeded by a minority of the background variables before matching (online supplemental etable 6).

DISCUSSION

In this matched observational study of neonates born between 30^{+0} and 32^{+6} weeks' gestation, those given PN during the first postnatal week had higher survival compared with neonates not given PN. However, neonates given PN had higher rates of bronchopulmonary dysplasia, late-onset sepsis, necrotising enterocolitis and need for surgical procedures. They also had a lower weight for gestation SD score at discharge.

The finding of higher survival in neonates given PN in the first postnatal week contrasts with the results of a randomised trial in critically unwell older children[10] and the subsequent subgroup analysis of term neonates,[11] where no difference in mortality was found. Similar randomised data for preterm neonates are not available, but our finding should be interpreted with caution as in this observational study, residual confounding cannot be excluded.[25] It remains possible clinicians withheld PN from very ill babies, even though the study cohorts were well matched on all recorded variables. There are plausible biological mechanisms that could explain the higher survival in neonates given PN. Nutritional deficits are common in the first postnatal week, particularly in more preterm infants, and this period is also when the majority of neonatal deaths occur.[26] Early PN initiation is intended to decrease catabolism which may, in this period, be crucial for survival. The difference in survival is small in absolute terms (0.9%), but given the mortality in this population equates to a 50% reduction in relative risk of mortality and thus warrants further investigation.

We also find neonates given PN have higher rates of important neonatal morbidities, particularly bronchopulmonary dysplasia and necrotising enterocolitis. Harmful effects are plausible, such as systemic pro-inflammatory changes triggered by PN proposed as a mechanism causing bronchopulmonary dysplasia[27] and necrotising enterocolitis.[24] PN use soon after an insult such as preterm birth may impair tissue healing by directly inhibiting autophagy.[28] Neonates given PN also had a lower weight for gestation SD score at discharge. This is in keeping with previous meta-analyses which have failed to find consistent evidence that

PN use increases growth.[5 6] Administration of PN might also influence clinician decision around enteral feeding and reduce milk intake. Lack of enteral substrate exacerbates the risk of necrotising enterocolitis.[29 30]

A strength of this work is that we followed prespecified analyses which were detailed in the prospectively published protocol. A further strength is that by combining propensity score matching and the extensive background data held in the NNRD on both the neonates and their mothers,[17 30] we generated two well-matched cohorts, approximating the effect of prospective randomisation and minimising the risk of confounding. The database used enabled us to study a complete population of size sufficient for analyses of associations of PN and rare outcomes. Previous PN trials in neonates have been powered for short-term surrogate outcomes, and the lack of data on clinically meaningful outcomes has prevented Cochrane reviews from making recommendations for practice.[5–7] We limited the risk of false discovery associated with multiple comparisons[31] by using the Holm-Bonferroni method.

The major limitation of this comparative study is that the intervention was not randomly assigned: confounding is a possibility[32] as other elements of care were not standardised or equally balanced as in a rigorous randomised controlled trial. We undertook a sensitivity analysis to explore whether confounding due to an unmeasured variable was possible as propensity score matching only balances measured variables. This showed the magnitude of imbalance required in a hypothetical missing variable was similar to the imbalance seen in variables like the Apgar score at 5 min or whether a neonate was transferred. Another limitation relates to missing data in the matched babies: we were able to quantify the degree of missingness for some data items, for other items it was not possible. For the 2-year outcomes, over 85% of data were missing, meaning no firm conclusions could be drawn. For other outcomes, it is not known how much data were missing and comparison with published data is difficult due to differences in how populations and outcomes are defined. Analyses of the NNRD show a rate of brain injury comparable with other published reports,[33] and data for outcomes including necrotising enterocolitis and sepsis are used for national audit and benchmarking.[34]

The overall findings that PN use is associated with higher survival, but also with higher rates of important neonatal morbidities, reflect the complex effects this intervention has in preterm neonates. The balance of risk to benefit is likely to vary by gestation and degree of growth restriction: to show how these balance in vivo prospective, randomised controlled trials adequately powered for important neonatal outcomes in relevant subgroups should be undertaken.[35] Previously, it was felt that further randomised trials would not be possible due to lack of clinician equipoise,[4] but our results show such research is essential.

CONCLUSION

In this matched study of neonates born between 30^{+0} and 32^{+6} weeks' gestation, those given PN in the first postnatal week had a higher rate of survival but also higher rates of necrotising enterocolitis, sepsis and bronchopulmonary dysplasia. This study provides evidence of important uncertainty around the benefits and risks of PN which should be addressed in prospective randomised trials.

Twitter Cheryl Battersby @DrCBattersby, Neena Modi @NeenaModi1 and Chris Gale @DrCGale

Acknowledgements We wish to thank Angela Richard-Löndt and Laura Noakes, parents of preterm infants, for their support in developing this research project and BLISS for their input and support in disseminating this research. We wish also to acknowledge and thank all neonatal teams for contributing to the National Neonatal Research Database.

Contributors JWHW, NM and CG conceived this project. JWHW, NL, SNU and CG planned the statistical analyses. Data were extracted from the NNRD by KO and checked by CB. Data analysis was undertaken by JWHW and NL. The first draft of the manuscript was written by JWHW and revised by CG. NL, CB, KO, SNU and NM edited and reviewed the manuscript. It was approved by JWHW, NL, CB, KO, SNU, NM and CG.

Funding The NNRD is funded and maintained from awards to NM. These include costs for data transfer, storage, cleaning, merging, administration and regulatory approvals. The extraction of study data from the NNRD and analysis for this study was funded through a Mason Medical Research Fellowship awarded to JWHW. CG was funded by the UK Medical Research Council (MRC) through a Clinician Scientist Fellowship award.

Disclaimer The MRC and Mason Medical Research Foundation were not involved in the design of the study, collection, analysis, and interpretation of data or in writing the manuscript.

Competing interests JWHW has received support from Chiesi Pharmaceuticals to attend an educational conference and has received a research grant from Mason Medical Research Foundation. SNU has received funding from the National Institute of Health Research, the Department of Health and Prolacta Life Sciences. SNU has been on the Advisory Board of Fresenius Kabi and received honoraria and travel expenses for speaking at study days organised by Fresenius Kabi. SNU is a member of the National Institute for Health and Care Excellence Parenteral Nutrition Guideline Development Committee. NM is the Chief Investigator for the National Neonatal Research Database and Director of the Neonatal Data Analysis Unit at Imperial College London. In the last 5 years, NM has served on the Board of Trustees of the Royal College of Paediatrics and Child Health, David Harvey Trust, Medical Women's Federation and Medact; and is a member of the Nestle Scientific Advisory Board. NM has received research grants from the British Heart Foundation, Medical Research Council, National Institute of Health Research, Westminster Research Fund, Collaboration for Leadership in Applied Health and Care Northwest London, Healthcare Quality Improvement Partnership, Bliss, Prolacta Life Sciences, Chiesi, Shire and HCA International; travel and accommodation expenses from Nutricia, Prolacta, Nestle and Chiesi; honoraria from Ferring Pharmaceuticals and Alexion Pharmaceuticals for contributions to expert advisory boards, and Chiesi for contributing to a lecture programme. CG is part of an international team developing reporting guidance (a CONSORT extension) for clinical trials using cohorts and routinely collected health data. He has received support from Chiesi Pharmaceuticals to attend an educational conference; in the past 5 years he has been an investigator on received research grants from Medical Research Council, National Institute of Health Research, Canadian Institute of Health Research, Department of Health in England, Mason Medical Research Foundation, Westminster Medical School Research Trust and Chiesi Pharmaceuticals, and has been an unremunerated member of the Neonatal Data Analysis Unit Board, which oversees the NNRD.

Patient consent for publication Not applicable.

Ethics approval This study only used de-identified data from the NNRD. The NNRD is a UK Research Ethics Committee-approved (REC Reference: 16/LO/1093) and Confidentiality Advisory Group-approved (ECC 8-05(f/2010)) national data asset. All data were stored on NHS servers. Parents can opt out of their baby's data being held within the NNRD. Study-specific REC approval and Health Research Authority and Health and Care Research Wales approval was obtained (18/NI/0214). Approval for inclusion of data from their centres in this study was obtained from all English and Welsh neonatal units. A list of all contributing neonatal units and their UK Neonatal Collaborative lead clinicians is provided (online supplemental table 8).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The NNRD is a national Data Asset discoverable through the Health Data Research UK Alliance Innovation Gateway (https://www.healthdatagateway.org/) and is available for use by external investigators. Data from this study is available from the Neonatal Data Analysis Unit upon reasonable request.

ORCID iDs
James William Harrison Webbe http://orcid.org/0000-0001-8546-3212
Sabita N Uthaya http://orcid.org/0000-0002-6112-2277
Neena Modi http://orcid.org/0000-0002-2093-0681
Chris Gale http://orcid.org/0000-0003-0707-876X

REFERENCES

1 Fanaro S. Feeding intolerance in the preterm infant. *Early Hum Dev* 2013;89 Suppl 2:S13–20.
2 Wilmore DW, Dudrick SJ. Growth and development of an infant receiving all nutrients exclusively by vein. *JAMA* 1968;203:860–4.
3 Christensen RD, Henry E, Wiedmeier SE, *et al*. Identifying patients, on the first day of life, at high-risk of developing parenteral nutrition-associated liver disease. *J Perinatol* 2007;27:284–90.
4 Moyses HE, Johnson MJ, Leaf AA, *et al*. Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis. *Am J Clin Nutr* 2013;97:816–26.
5 Simmer K, Rao SC. Early introduction of lipids to parenterally-fed preterm infants. *Cochrane Database Syst Rev* 2005;2:CD005256.
6 Trivedi A, Sinn JKH. Early versus late administration of amino acids in preterm infants receiving parenteral nutrition. *Cochrane Database Syst Rev* 2013;7:CD008771.
7 Moon K, Athalye-Jape GK, Rao U, *et al*. Early versus late parenteral nutrition for critically ill term and late preterm infants. *Cochrane Database Syst Rev* 2020;4:CD013141.
8 Zingg W, Tomaske M, Martin M. Risk of parenteral nutrition in neonates--an overview. *Nutrients* 2012;4:1490–503.
9 Casaer MP, Mesotten D, Hermans G, *et al*. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011;365:506–17.
10 Fivez T, Kerklaan D, Mesotten D, *et al*. Early versus late parenteral nutrition in critically ill children. *N Engl J Med* 2016;374:1111–22.
11 van Puffelen E, Vanhorebeek I, Joosten KFM, *et al*. Early versus late parenteral nutrition in critically ill, term neonates: a preplanned secondary subgroup analysis of the PEPaNIC multicentre, randomised controlled trial. *Lancet Child Adolesc Health* 2018;2:505–15.
12 Mason DG, Puntis JWL, McCormick K, *et al*. Parenteral nutrition for neonates and children: a mixed bag. *Arch Dis Child* 2011;96:209–10.
13 NICE. Neonatal parenteral nutrition: NICE guideline [NG154]. In: *Excellence NIfHaC, eds*, 2020.
14 Webbe J, Longford N, Uthaya S, *et al*. Outcomes following early parenteral nutrition use in preterm neonates: protocol for an observational study. *BMJ Open* 2019;9:e029065.
15 Gale C, Morris I, Neonatal Data Analysis Unit (NDAU) Steering Board. The UK national neonatal research database: using neonatal data for research, quality improvement and more. *Arch Dis Child Educ Pract Ed* 2016;101:216–8.
16 Spencer A, Modi N. National neonatal data to support specialist care and improve infant outcomes. *Arch Dis Child Fetal Neonatal Ed* 2013;98:F175–80.
17 Battersby C, Statnikov Y, Santhakumaran S, *et al*. The United Kingdom national neonatal research database: a validation study. *PLoS One* 2018;13:e0201815.
18 Webbe J, Brunton G, Ali S, *et al*. Developing, implementing and disseminating a core outcome set for neonatal medicine. *BMJ Paediatr Open* 2017;1:e000048.
19 Webbe JWH, Duffy JMN, Afonso E, *et al*. Core outcomes in neonatology: development of a core outcome set for neonatal research. *Arch Dis Child Fetal Neonatal Ed* 2020;105:425–31.
20 Ziegler EE, Thureen PJ, Carlson SJ. Aggressive nutrition of the very low birthweight infant. *Clin Perinatol* 2002;29:225–44.
21 Manktelow BN, Smith LK, Prunet C. *MBRRACE-UK perinatal surveillance report: UK perinatal deaths for births from January to December 2015*. Leicester: The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester, 2017.
22 Holm S. A simple sequentially Rejective multiple test procedure. *Scand J Stat* 1979;6:65–70.
23 Rosenbaum PR, Rubin DB. Assessing sensitivity to an unobserved binary covariate in an observational study with binary outcome. *J R Stat Soc Series B Stat Methodol* 1983;45:212–8.
24 Bjornvad CR, Thymann T, Deutz NE, *et al*. Enteral feeding induces diet-dependent mucosal dysfunction, bacterial proliferation, and necrotizing enterocolitis in preterm pigs on parenteral nutrition. *Am J Physiol Gastrointest Liver Physiol* 2008;295:G1092–103.
25 Wang MTM, Bolland MJ, Grey A. Reporting of limitations of observational research. *JAMA Intern Med* 2015;175:1571–2.
26 Seaton SE, Barker L, Draper ES, *et al*. Estimating neonatal length of stay for babies born very preterm. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F182–6.
27 Cooke RW. Factors associated with chronic lung disease in preterm infants. *Arch Dis Child* 1991;66:776–9.
28 Gunst J. Recovery from critical illness-induced organ failure: the role of autophagy. *Crit Care* 2017;21:209.
29 Neu J. Gastrointestinal development and meeting the nutritional needs of premature infants. *Am J Clin Nutr* 2007;85:629S–34.
30 Battersby C, Longford N, Mandalia S, *et al*. Incidence and enteral feed antecedents of severe neonatal necrotising enterocolitis across neonatal networks in England, 2012-13: a whole-population surveillance study. *Lancet Gastroenterol Hepatol* 2017;2:43–51.
31 SS Y, K A. Deming, data and observational studies. *Signif* 2011;8:116–20.
32 Bosco JLF, Silliman RA, Thwin SS, *et al*. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J Clin Epidemiol* 2010;63:64–74.
33 Gale C, Statnikov Y, Jawad S, *et al*. Neonatal brain injuries in England: population-based incidence derived from routinely recorded clinical data held in the National neonatal research database. *Arch Dis Child Fetal Neonatal Ed* 2018;103:F301–6.
34 RCPCH. *National Neonatal Audit Programme (NNAP) 2019 annual report on 2018 data*. London, 2019.
35 Prasad V, Cifu A, Ioannidis JPA. Reversals of established medical practices: evidence to abandon SHIP. *JAMA* 2012;307:37–8.