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## **Association between Early Feeding Patterns and Neonatal Outcomes in Very Preterm Infants: A Retrospective Cohort Study**

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**Short title:** Donor milk versus formula for preterm infants.

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## ABSTRACT

**Objective:** Mother's own milk (MOM) is the optimal feed for premature infants but may not always be sufficiently available. Alternative feeding includes donor human milk (DONOR), with or without fortification and preterm formula. This study evaluated the association between early feeding with exclusively or predominantly MOM (MAINLY-MOM) versus MOM supplemented with fortified DONOR (MOM+DONOR) or preterm formula (MOM+FORMULA) and in-hospital growth and neonatal morbidities.

**Methods:** This was a multicentre (n = 13 units) cohort study of infants born at < 32 weeks' gestation. Data captured at the point of care were extracted from the UK National Neonatal Research Database. The study groups were defined based on feeding patterns within the first two weeks of life using predefined cut-offs. The primary outcome was the in-hospital growth rate.

**Results:** Data from 1,272 infants were analysed. Infants fell into two groups: extremely preterm (EPT) infants and very preterm (VPT) infants, born after < 28 weeks and 28 to < 32 weeks of gestation, respectively.

Only 11 of 365 EPT infants received formula supplements, precluding a useful comparison of MOM+DONOR and MOM+FORMULA. There was no difference in median (25<sup>th</sup>–75<sup>th</sup> centile) growth velocity over the first 30 days of life between the MAINLY-MOM (n = 248) and MOM+DONOR (n = 106) groups: 10 (8–13) vs. 10 (7–13) g/kg/d.

Similarly, for VPT infants, there was no difference in growth velocities between MAINLY-MOM (n = 407), MOM+DONOR (N = 196) and MOM+FORMULA (N = 304): 11 (8–14) vs. 11 (8–14) vs. 11 (8–14) g/kg/day. Head growth did not differ (p value = 0.670). Cox-regression analysis showed no difference in time to discharge between feeding types nor any difference in major neonatal morbidities.

In both EPT and VPT infants, growth velocity from the time of regaining birth weight to discharge was significantly lower in the MAINLY-MOM group compared to the MOM+DONOR group (EPT: 12.5 [11–14.2] vs. 14 [12.3–15.9] p = 0.45, VPT 13.5 [11–15.7] vs. 14.5 [12.6–16.8] p = 0.015).

### Conclusion:

Early feeding with fortified DONOR, in comparison to formula, to supplement MOM was not associated with any differences in short-term growth, length of stay and neonatal morbidities. However, early feeding with mainly maternal milk, compared to maternal milk supplemented with donor human milk, was associated with significantly lower overall weight gain.

## INTRODUCTION

Mother's own milk (MOM) is the optimal feed for all infants, particularly preterm infants, to whom it confers many benefits, including a reduction in necrotising enterocolitis (NEC) risk when compared with formula [1]. MOM is associated with improved neurological outcomes, including better cognitive scores [2] and higher developmental scores, compared with formula feeding, independent

of social and educational confounders [3, 4]. Higher doses of MOM in the first 10 days have been associated with a significantly lower risk of NEC, sepsis and/or death (hazard ratio: 0.31, confidence interval [CI]: 0.18–0.54,  $p < 0.001$ ) compared with formula [5].

Preterm infants should receive MOM as the first choice, with consideration of donor human milk (DONOR) as an alternative if MOM is unavailable or insufficient [6]. The use of DONOR to supplement MOM in preterm infants has become common practice [7, 8], but data regarding the impact of DONOR on outcomes in contemporary neonatal care are limited. Fortification of human milk with specialised multi-nutrient human milk fortifier (HMF) is commonly practised in neonatal units [7]. A recent meta-analysis [1] compared feeding preterm infants with formula versus DONOR. It was concluded that in-hospital growth indices were higher in formula-fed infants but at the expense of increased NEC risk (risk ratio 1.87, 95% CI 1.23–2.85). The mean difference in body weight was 2.51 grams/kg/day (95% CI 1.93–3.08), in length was 1.21 cm/week (95% CI 0.77–1.65) and in head growth was 0.85 mm/week (95% CI 0.47–1.23). Out of the 12 included trials, only five recent studies practised DONOR fortification. It is unclear whether fortified DONOR improves growth and other outcomes. Furthermore, enteral feeding practices vary between centres, suggesting that outcomes may vary in differing clinical contexts.

The main objective of this cohort analysis was to compare in-hospital outcomes of early feeding (first 14 days of life) with mainly MOM, MOM supplemented with fortified DONOR and MOM supplemented with formula in very preterm (VPT) infants admitted to Scottish neonatal units using the National Neonatal Research Database (NNRD).

## **MATERIALS and METHODS**

### **Study design and subjects**

This was a multicentre ( $n = 13$  units) retrospective cohort study of infants born before 32 completed weeks of gestation and admitted to neonatal units in Scotland. Data were collected from 1,663

infants between January 2014 and July 2017, inclusive, which represented 88% of the VPT Scottish population (1,891 VPT infants were born between 2014 and 2017).

Donor milk in Scotland is provided to all neonatal units from a single national human milk bank. The milk bank adheres to the operational standards laid out in the National Institute for Health and Care Excellence Clinical Guideline “Donor milk banks: service operation” (CG93)[9]: each donor milk sample comes from a single donor rather than from pooled donors. Enteral feeding practice is broadly similar in all Scottish neonatal units (**Error! Reference source not found.**), as is the use of parenteral nutrition, which also adheres to National Institute for Health and Care Excellence guidance [10]. The HMF used are Cow & Gate nutriprem or SMA Gold Prem Breast Milk Fortifier (SMA Nutrition, Dublin).

Data were sourced from the National Neonatal Research Database (NNRD). The NNRD receives data at the point of care from all neonatal units in the UK. The patient information platform used was Badgernet ®software, with data entered by clinical staff.

## **Ethics**

The NNRD has permission to store and use patient data (Research Ethics Committee approval [REC] Reference: 16/LO/1093 and Confidentiality Advisory Group approval [CAG] Reference: ECC 8–05[f] 2010). Specific REC approval was additionally obtained for this study from the North of Scotland REC (Reference:17/NS/0052), and NHS Health Research Authority approval was obtained on 12 July 2017, along with management permission from each trust.

## **Inclusion and data management**

Data extracted from the NNRD were extensively reviewed and cleaned before extracting the study variables for analysis. The study variables recorded for the study are described in **Error! Reference source not found.** The completeness of data recording was high for most variables, with missing values not exceeding 5–10% in the majority of episodic and daily variables, respectively. Total daily milk volume intake was poorly documented (data missing for 49% of care days) and could not be

used in the analysis. Therefore, age in days rather than ml/kg/day was used to describe the time of fortification initiation. In the case of mixed feeding, information on the relative volumes of each type of milk was not available (not a standard Badgernet item). Therefore, the study groups were defined based on the number of days being fed certain types of milk. To define the study groups, the pattern of feeding for the entire stay was explored. During the first weeks of life, most infants received high amounts of MOM, while DONOR and/or formula were used mainly as supplements to MOM. Groups were thus defined according to feeding patterns within the first 14 days of life, known as the “critical phase”. Three study groups were defined, as explained in Fig. 1: exclusively/predominantly MOM-fed group (MAINLY-MOM), DONOR-supplemented MOM group (MOM+DONOR) and formula-supplemented MOM group (MOM+FORMULA). The HMF used in this cohort was bovine-based.

From a total eligible study population of 1,663, 391 infants were excluded for the following reasons: they were not fed enterally for the entire hospital stay (n = 70), there were incomplete records of their hospital stay for more than five days (n = 143) or they were fed exclusively with formula (n = 46), as the study focuses on supplementing MOM with DONOR or formula. Infants with complex feeding patterns in the first 14 days of life (n = 132) were also excluded. Further descriptions of the excluded infants are available in **Error! Reference source not found.**. Thus, 1,272 infants were included in the final analysis (Fig. 2). Infants fell into two groups: extremely preterm (EPT) and VPT, born < 28 weeks and 28 to < 32 weeks, respectively.

## Outcomes

The primary study outcome was in-hospital growth, measured as weight gain and head circumference change. Weight gain was measured over two hospitalisation periods: from birth to day 30 of life and from the time at which birth weight was regained until discharge. Growth velocity was calculated using the exponential model:  $\text{growth velocity} = (1000 \times \text{LN} [\text{WT}_n \div \text{WT}_1]) \div \text{D}_n - \text{D}_1$ , where GV = growth velocity expressed in grams per kilograms per day, W = weight in grams, D = day, 1 = beginning of time interval, n = end of time interval in days, and LN = natural log. Head

circumference growth was measured by calculating its change from admission to discharge (cm/week). The measurement of birth head circumference was considered only if it was recorded in the database within the first seven days of life. Likewise, discharge measurement was considered only if it was recorded in the database within the last seven days of the stay. Length is not routinely recorded in the database and was not assessed in this study.

The secondary outcomes were as follows: 1) confirmed NEC, defined according to the reporting of NEC as the cause of death, post-mortem confirmation of NEC, surgical resection for NEC or transfer for management of NEC in the database; 2) late onset culture-proven sepsis, defined as a positive blood culture at the age of five days or later [11]; 3) Retinopathy of prematurity (ROP), defined as positive screening outcome resulting in ROP diagnosis (if laser surgery was done for ROP, it was noted separately); and 4) bronchopulmonary dysplasia (BPD), defined by respiratory support (supplemental oxygen or any form of assisted ventilation) at the age of 36 weeks Postmenstrual age.

### **Statistical analysis**

Data were analysed using IBM-SPSS (V-25). Nonparametric data were transformed with log-10 and used in the regression models. Multiple imputation (automatic method using linear regression) was done for variables for which more than 10% of the data were missing. The imputed variables were birth head circumference (25%), mother's ethnicity (34%) and smoking during pregnancy (13%).

Chi-square tests were used to determine associations between the groups and categorical variables. For continuous variables, ANOVA or Kruskal-Wallis tests were used. Appropriate post hoc tests were performed using pairwise comparisons. The results were considered significant with p values < 0.05, and they are reported unadjusted for multiple comparisons.

### **Outcome analysis**

All analyses were performed separately for the two subgroups of EPT and VPT. For EPT infants, the outcomes were compared only for MAINLY-MOM and MOM+DONOR because of the small number of infants in the MOM+FORMULA group (n = 11).

In-hospital weight gain velocity was compared using a linear regression model. Covariates (including gestational age, timing of fortification, maternal health during pregnancy, age of first feeding, days on parenteral nutrition, neonatal unit and neonatal morbidities, including NEC, BPD, sepsis and ROP) were screened as potential confounders of weight gain velocity. This was done by entering each variable into a univariate linear regression analysis. If the variable showed a significant association with weight gain and head growth velocity, then it was included in the final multivariate model using the “Enter” method.

To investigate the interaction effect between weight gain and overall mortality/morbidity, an illness score was given to indicate the number of adverse events (zero to two or more events) that infants experienced during their hospital stay. The illness score indicates any event of mortality and/or morbidity (NEC, ROP, sepsis or BPD). The interaction effect was tested using ANOVA (**Error! Reference source not found.**).

Length of stay before discharge home was compared using Cox regression survival analysis.

## RESULTS

### Study population characteristics

The number of infants who met the inclusion criteria was 1,272. All three feeding groups had comparable clinical characteristics; however, the degree of maturity and size at birth differed.

MOM+FORMULA infants were more mature at birth than the infants in both the MOM+DONOR and MAINLY-MOM groups. For the cohort as a whole, the median (25<sup>th</sup>–75<sup>th</sup> centile) gestational age was 29 (27–31) weeks, with a range from 23–31 weeks, and birth weight was 1,240 (980–1,536) g, with a range from 400–2,490 g. Antenatal factors were similar across the three feeding groups. The

caesarean section rate was 70% in the MOM+DONOR group compared to 63% in both the MAINLY-MOM and MOM+FORMULA groups. This difference was not significant (**Error! Reference source not found.**).

All clinical characteristics were comparable for MAINLY-MOM and MOM+DONOR but different for MOM+FORMULA except for antibiotic use. Reflective of greater maturity at birth, infants in the MOM+FORMULA group had less respiratory illness and were more likely to survive (**Error! Reference source not found.**). Fortification of human milk was started earliest in the MOM+FORMULA group, followed by the MOM+DONOR group and last in the MAINLY-MOM group. The feeding patterns of the study groups throughout admission were broadly similar and can be described as follows: MOM feeding was high up to the first month. Then, MOM feeding started to decrease at the same time as formula feeding started to increase progressively (**Error! Reference source not found.**).

## **Outcomes**

### **In-hospital weight gain in EPT infants (n = 365)**

Analysis for EPT infants was done for only the MAINLY-MOM and MOM+DONOR groups, as there were just 11 infants in the MOM+FORMULA group. Feeding type in the critical phase predicted statistically different overall weight gain. Analysis of growth velocity from the time of regaining birth weight until discharge according to critical phase feed type was adjusted for birth weight and age of receiving fortifier; this was achieved by including the variables in the multivariate model using the “Enter” method. After adjustment, it remained higher in the MOM+DONOR group compared with the MAINLY-MOM group ( $p = 0.045$ ). The pattern of growth over the three hospitalisation time intervals in the MAINLY-MOM and MOM+DONOR groups was generally similar, although it was higher in MOM+DONOR than MAINLY-MOM from day 31 to 60. Growth velocity from birth to day 30 was not different between the MAINLY-MOM and MOM+DONOR groups (**Error! Reference source not found.**).

### **In-hospital weight gain in VPT infants (n = 907)**

In VPT infants, analysis of growth velocity from the time of regaining birth weight until discharge was adjusted for birth weight, age of receiving fortifier, length of hospital stay and receipt of corticosteroids (**Error! Reference source not found.**). The adjusted analysis showed a higher growth velocity in the MOM+DONOR group than in the MAINLY-MOM group ( $p = 0.015$ ).

In comparison with the MOM+FORMULA groups, growth velocity was not different in either the MAINLY-MOM ( $p = 0.338$ ) or MOM+DONOR ( $p = 0.273$ ) groups. Comparison between MAINLY-MOM and MOM+FORMULA was adjusted for birth weight, age of receiving fortifier, length of hospital stay and receipt of corticosteroids. Growth velocity from birth to day 30 was not different between the MAINLY-MOM, MOM+DONOR and MOM+FORMULA groups.

Analysis of the interaction effect between the feeding group and weight gain velocities was not affected by the change in infant illness ( $p > 0.05$ , **Error! Reference source not found.**). Illustration of mortality/morbidity score in the study sample is shown in Supplementary 6 and stratified by the level of prematurity.

### **Head growth**

Although MOM+DONOR feeding predicted a significantly higher overall growth velocity than MAINLY-MOM, this was not reflected in higher head growth in either EPT or VPT infants ( $p = 0.670$ ). Head growth in the MOM+FORMULA group did not differ significantly compared to the other groups of VPT infants ( $p = 0.670$ ).

### **Time to discharge home**

As the discharge destination was not home for all infants, with some moving to other hospitals or dying, survival analysis was conducted only for infants who were discharged home, which was the majority. In EPT infants (97% of whom were discharged home), survival analysis showed that the time to discharge home was not different between infants in the MAINLY-MOM group and infants in the MOM+DONOR group (odds ratio OR [95% CI] 0.924 [0.655–1.303],  $p = 0.652$ ). Similarly, in VPT

infants (100% of whom were discharged home), feeding type did not have an effect (MOM+DONOR and MAINLY-MOM group OR [95% CI] = 0.937 [0.777–1.130,  $p = 0.496$ ]). After adjusting for the day HMF was received, birth weight, gestational age and neonatal unit, there was no difference in the time to discharge home between infants in the MOM+FORMULA group compared to both the MAINLY-MOM and MOM+DONOR groups ( $p$  value of MAINLY-MOM versus MOM+FORMULA = 0.066, MOM+DONOR versus MOM+FORMULA = 0.118).

Secondary outcomes are presented descriptively due to the small number of cases (**Error! Reference source not found.**). There were no apparent differences between the groups for any of the morbidities.

## DISCUSSION

Evidence of the in-hospital outcomes of preterm infants fed with fortified DONOR in comparison with preterm infants fed with formula within contemporary neonatal practice is limited. The main finding of this study was that early feeding with fortified DONOR, in comparison with formula, to supplement MOM resulted in comparable weight gain, both at one month and from regaining birth weight until discharge, with no difference in major morbidities. Earlier studies using unfortified DONOR either as a sole diet or as a supplement to MOM showed DONOR to be associated with slower weight gain compared to formula [12-15]. In more recent studies, the conclusions are mixed; two observed that feeding with fortified DONOR results in growth rates similar to those associated with formula [16, 17], whereas two randomised controlled trials and two observational studies found that fortified DONOR was associated with slower weight gain than formula feeding [18-21]. The trial by Schanler et al. measured primarily NEC and infection-related outcomes, and in the study of Cristofalo et al., the sample size was calculated based on days of parenteral nutrition, with neither considering growth as the primary outcome. A possible reason for failing to see a difference in growth rates is that slow growth may initiate nutritional intervention, such as adding HMF or

increasing its concentration. More interventional studies that are powered to detect changes in growth rates are needed.

Infants in the MAINLY-MOM group had significantly lower growth rates compared with those in the MOM+DONOR group from the time birth weight was regained until discharge. It is possible that the changes in feeding patterns throughout admission might have contributed to this difference. DONOR is used mainly to initiate and establish feeding, and a switch is usually made to fortified MOM or formula after two weeks. Therefore, more infants in the MOM+DONOR group were switched to formula than infants in the MAINLY-MOM group, who remained on MOM. Formula is protein and calorie dense compared with MOM and is associated with higher growth rates [1].

The average growth rates found in this study are lower than those reported in the literature. For example, a clinical trial done by O'Connor et al. comparing fortified DONOR with preterm formula as a supplement to MOM in very low birth weight infants showed a mean weight gain of 23.9 versus 25.5 g/kg/day [22], whereas in this study, weight gain was 14.7 versus 14.5 g/kg/day from the time birth weight was regained until discharge. Potential reasons for this difference could be the variation in feeding practices. It may be that differences in fortification may impact weight gain. Many centres start fortification at lower volumes than in Scotland [7], and the difference in study design. Growth is not the only measure which should be used to assess the benefits of feeding regimens. The optimal growth rate associated with improved neurodevelopment outcomes without causing metabolic harm is not well established. Head circumference has been used as an indicator of brain growth, as it correlates well with brain size and weight [23]. In our study, head growth was not different between the study groups. This concurs with the Cochrane review that compared DONOR with formula [1]; three recent randomised controlled trials of fortified DONOR versus formula showed no difference in advantages regarding head growth (z-score = 1.04, p = 0.30). An observational study found that head growth was significantly higher in the fortified DONOR group than in the formula group (mean difference in head circumference z-score = 0.41, p = 0.03) [15].

Optimal weight gain in premature infants has also not been clearly defined [24, 25]. A growth rate higher than 18 g/k/d has been associated with improved mental and psychomotor developmental indices [26], and avoidance of growth failure has an important impact on in-hospital outcomes, such as BPD [27]. Larger randomised controlled trials designed to measure growth as a primary outcome are required to confirm the effect of fortified DONOR.

In our cohort of EPT infants, all secondary outcomes were similar between the MAINLY-MOM and MOM+DONOR groups, including NEC. A recent trial found that DONOR feeding did have a protective effect against NEC compared with formula [28]; the lack of benefit in our study could be explained by the small study numbers.

The study groups were defined based on early feeding exposure to different types of milk; it should be noted that feeding may have changed throughout the hospital stay, depending on clinical conditions, availability of MOM and growth status. This study showed variability in fortification practices, such as the time of initiation and duration of use. Fortifier was started five days later in the less mature infants (MAINLY-MOM feeding) compared with the more mature ones (MOM+FORMULA feeding). The optimal time to start fortification of human milk is not known [29]. Further research is needed to identify the best time to introduce HMF in VPT infants.

This study has several strengths. The sample size was larger than in most randomised controlled trial and observational studies, and infants came from multiple neonatal units across Scotland. The described cohort is highly representative of the VPT population born in Scotland. Data for this study were collected over three and a half consecutive years at the point of care. Data captured at the point of care are likely to be more accurate than retrospectively collected data. Overall data completeness was high and was 100% for important data, such as birth weight and gestational age. The database contained many data items that accounted for potential confounders. Clinical characteristics between the groups were comparable.

The main limitation of this study was the large proportion of missing data on total enteral milk volume, which meant that the number of days of feeding had to be substituted, which may have influenced the comparison data analysis. Another limitation was the lack of information on the percentage of each milk type in the case of mixed feeding. The study sample could have been maximised in this study if feeding data were entered in the database in a form that allowed quantification of milk volumes in mixed feeding infants. Nearly one quarter of the cohort were excluded from the study for this reason. However, the excluded infants were not clustered by birth year, nor were they smaller than the included infants. Nutritional intakes expressed as calories and protein per day were not possible to describe due to a lack of relevant data entries in the database. Recording the precise total daily enteral intake amounts in an electronic database can be difficult to achieve in a busy neonatal environment. Daily total fluid needs can also change based on the hemodynamic status of the infant. However, this finding should guide the NNRD in the optimisation of data quality for enteral intake. The interpretation of these results may be limited, as calculating energy and nutrient intake was not possible due to the nature of the available data.

## **CONCLUSION**

This study showed that in VPT, feeding with fortified DONOR in comparison to formula to supplement MOM was not associated with any differences in short-term growth, length of stay or neonatal morbidities. There was not enough data in EPT infants to compare donor milk with formula feeding. Future evaluation of feeding practices should also consider other outcomes, such as neurodevelopment.

## **Acknowledgments**

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## Statement of Ethics

This study protocol was reviewed and approved by the North of Scotland Research Ethics Committee (approval number 17/NS/0052), and NHS Health Research Authority approval was received on 12 July 2017, along with management permission from each trust. Written informed consent from the parents was not required for the study presented in this article in accordance with the North of Scotland Research Ethics Committee guidelines.

## Conflict of Interest Statement

Professor Edwards was the chair of an expert group, “Early bacterial colonisation and potential implications later in life for ILSI Europe”. Other authors have no potential conflicts of interest to disclose.

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## Author Contributions

Prof Edwards, Dr Garcia, Dr Judith Simpson and Dr Helen Mactier conceptualised and designed the study, reviewed the data analysis and reviewed and revised the manuscript. Mrs Wesam Alyahya conceptualised and designed the study, obtained ethical approvals, carried out data cleaning, conducted statistical analysis, drafted the initial manuscript and reviewed and revised the manuscript. Dr David Young reviewed the statistical analysis and the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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## Legends

### Figures

Fig. 1 Inclusion Criteria for Study Groups

Fig. 2 Inclusion and Study Groups

### Figures' footnotes

#### Figure 2 Inclusion and Study Groups

Study groups defined based on feeding pattern from birth to day 14 (MAINLY-MOM group: infants were fed predominantly/exclusively mother's own milk, MOM+DONOR group: infants were fed mother's own milk supplemented with donor human milk, MOM+FORMULA group: infants were fed mother's own milk supplemented with formula), HMF: human milk fortifier. This figure is original work.

### **Study groups cut offs**

Cut offs values denotes the percentage of feeding days with the named milk over the period from birth to day 14

<b>Exclusively/predominantly MOM fed group (MAINLY-MOM)</b>
<ul style="list-style-type: none"><li>- Receipt of MOM &gt; 90 %</li><li>- DONOR and formula &lt; 10 %</li></ul>
<b>MOM supplemented with DONOR group (DONOR+MOM)</b>
<ul style="list-style-type: none"><li>- Any amount of MOM</li><li>- DONOR <math>\geq</math> 10 %</li><li>- Formula &lt; 10 %</li></ul>
<b>MOM supplemented with formula (MOM+FORMULA)</b>
<ul style="list-style-type: none"><li>- Any amount of MOM</li><li>- DONOR &lt; 10 %</li><li>- Formula <math>\geq</math> 10 %</li></ul>

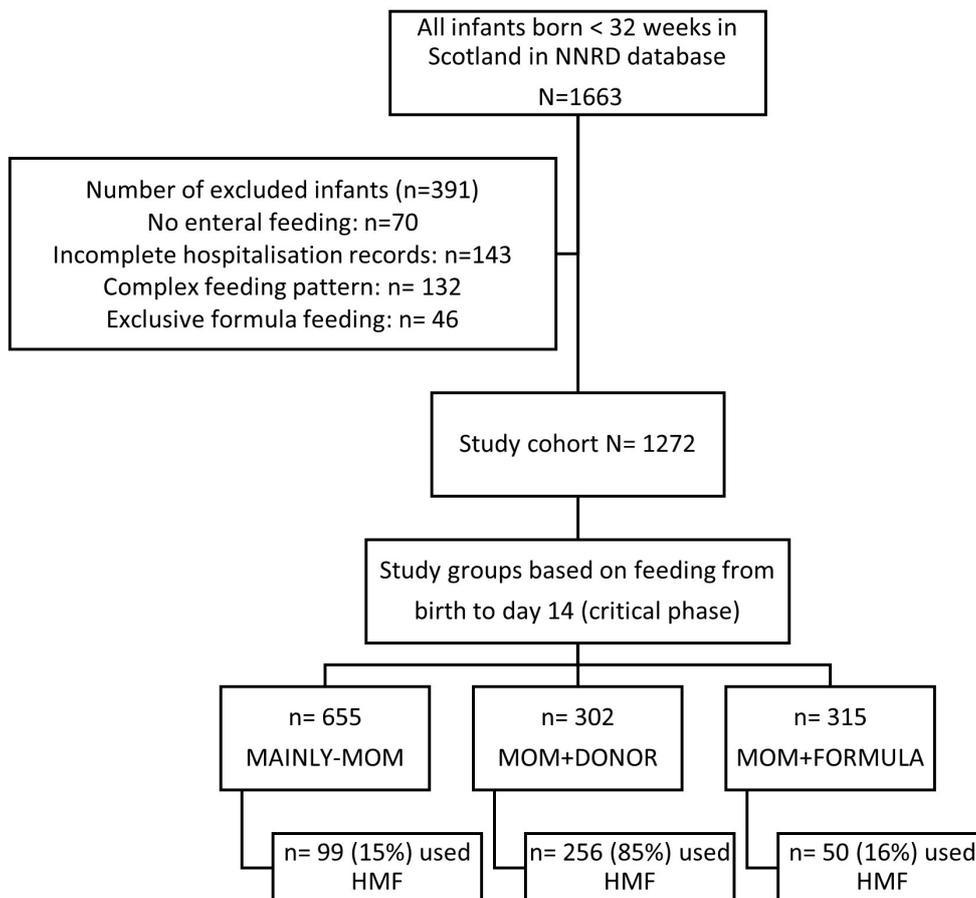
- Receipt of MOM > 90 %
- DONOR and formula < 10 %

**MOM supplemented with DONOR group (DONOR+MOM)**

- Any amount of MOM
- DONOR  $\geq$  10 %
- Formula < 10 %

**MOM supplemented with formula (MOM+FORMULA)**

- Any amount of MOM
- DONOR < 10 %
- Formula  $\geq$  10 %



**Table 1 Maternal and Infant Characteristics**

	Feeding type in the critical phase			P value <sup>1</sup>
	MAINLY-MOM (n=655)	MOM+DONOR (n= 302)	MOM+FORMULA (n=315)	
Gestational age, weeks	28 (26 - 30)	29 (27 - 30)	30 (30- 31)	<.001
Birth weight, g	1090 (860 - 1390)	1140 (920 - 1360)	1520 (1325 - 1700)	<.001
Birth head circumference, cm	26 (24 - 28)	26.5 (24.7 - 28)	28.6 (27.5 - 29.5)	<.001
Number (%)				
Male	338 (52)	144 (48)	155 (49)	0.497
Antenatal steroids	592 (90)	279 (92)	287 (91)	0.777
Caesarean section	411 (63)	212 (70)	200 (63)	0.057
White ethnicity	585 (89)	272 (90)	281 (89)	0.755
Smoking	127 (19)	61 (20)	71 (23)	0.711
Preeclampsia	57 (9)	27 (9)	23 (7)	0.710
Gestational diabetes	5 (<1)	12 (4)	7 (2)	Too few
Intrauterine growth retardation	68 (10)	40 (13)	24 (8)	0.073

Values expressed as Median (25<sup>th</sup>-75<sup>th</sup> centile) unless otherwise noted. <sup>1</sup> P value is based on chi-square for categorical variables and Kruskal-Wallis test for continuous variables. Post hoc comparisons using Mann-Whitney test showed significant differences between PREDOM-MOM and MDHM (p=0.037), MAINLY-MOM and MOM+FORMULA (p <0.002), MOM+DONOR and MOM+FORMULA (p<0.001) for gestational age. For birth weight the differences were between MAINLY-MOM and MF (p <0.001), MOM+DONOR and MOM+FORMULA (p<0.001). For head circumference the differences were between MAINLY-MOM and MOM+FORMULA (p <0.001), MOM+DONOR and MOM+FORMULA (p<0.001).

MAINLY-MOM: Predominantly/exclusively MOM group, MOM+DONOR: donor human milk supplementing mother's own milk group, MOM+FORMULA: formula supplementing mother's own milk group.

**Table 2. Clinical Characteristics and Feeding**

	Feeding type in the critical phase			P value
	MAINLY-MOM (n=655)	MOM+DONOR (n= 302)	MOM+FORMULA (n=315)	
<b>Clinical characteristics, n (%)</b>				
Surfactant given	348 (53) <sup>bc</sup>	134 (44) <sup>bc</sup>	97 (31) <sup>bc</sup>	<0.001
Discharge home	489 (75) <sup>bc</sup>	240 (79) <sup>bc</sup>	274 (87) <sup>bc</sup>	<0.001
Antibiotics	632 (96)	286 (95)	304 (97)	0.375
Diuretics	249 (38) <sup>bc</sup>	112 (37) <sup>bc</sup>	45 (14) <sup>bc</sup>	<0.001
Corticosteroids	120 (18)	57 (19)	8 (3)	Too few
Mechanical ventilation	486 (74) <sup>bc</sup>	193 (64) <sup>bc</sup>	121 (38) <sup>bc</sup>	<0.001
<b>Feeding, Median (25<sup>th</sup>-75<sup>th</sup> centile)</b>				
Age feed started, hours	30 (12 – 53) <sup>bc</sup>	29 (12 – 45) <sup>bc</sup>	19 (9 – 35) <sup>bc</sup>	<0.001
Days nil per mouth	2 (1 - 5) <sup>abc</sup>	2 (1-3) <sup>abc</sup>	1 (0 – 2) <sup>abc</sup>	<0.001
Age fortification initiated, d	18 (14 – 24) <sup>ab</sup>	15 (11-21) <sup>a</sup>	13 (9 – 18) <sup>b</sup>	<0.001
Fortification Duration, d	7 (0 – 20) <sup>abc</sup>	5 (0 – 13) <sup>abc</sup>	0 (0 – 3) <sup>abc</sup>	<0.001

P value is based on chi-square test. Superscripts are significantly different for comparisons between groups <sup>a</sup>: MAINLY-MOM versus MOM+DONOR, <sup>b</sup>:

**Table 3 Weight Gain Comparisons Across Study Groups (g/kg/day) N= 1272**

	Feeding type in the critical phase			P values		
	MAINLY-MOM	MOM+DONOR	MOM+FORMULA	MAINLY-MOM vs MOM+DONOR	MAINLY-MOM vs. MOM+FORMULA	MOM+DONOR vs. MOM+FORMULA
<b>Extremely preterm infants (n=365)</b>	(n= 248)	(n= 106)	(n= 11)			
Birth to 30 days	10 (8 – 13)	10 (7 – 13)	10 (6 – 12)	0.545	Too few	Too few
Day 31 to 60	15 (12 – 18)	17 (14 – 20)	15 (14 – 20)	-	-	-
Day 61 to discharge	12 (10 – 14)	12 (9 – 15)	Discharged by day 60	-	-	-
Regain birth weight to discharge	12.5 (11 – 14.2)	14 (12.3 – 15.9)	14 (12.3 – 16)	*0.045 <sup>a</sup>	Too few	Too few
<b>Very preterm infants (n=907)</b>	(n= 407)	(n= 196)	(n= 304)			
Birth to 30 days	11 (8 – 14)	11 (8 – 14)	11 (8 – 14)	0.341	0.518	0.512
Day 31 to 60	13 (10 – 16)	14 (12 – 17)	12 (9 – 16)	-	-	-
Day 61 to discharge	10 (8 – 13)	11 (9 – 12)	9 (8 -10)/11	-	-	-
Birth to discharge	11 (9 – 13)	12 (10 – 14)	11 (9 – 13)	-	-	-
Regain birth weight to discharge	13.5 (11 – 15.7)	14.5 (12.6– 16.8)	14.7 (11.6– 16.8)	*0.015 <sup>b</sup>	0.338 <sup>b</sup>	0.273

Values expressed as median (25<sup>th</sup>, 75th centile)/number of infants in the analysis. P value is based on linear regression analysis. <sup>a</sup> adjusted for birth weight and age of receiving fortifier. <sup>b</sup> adjusted for birth weight, age of receiving fortifier and length of hospital stay and corticosteroids use. \*: statistically significant at level 0.05.

**Table 4 Secondary Outcomes**

	Feeding type in the critical phase		
	MAINLY-MOM	MOM+DHM	MOM+FORMULA
<b>Extremely preterm infants</b>	(n= 248)	(n= 106)	(n= 11)
<b>Median (25th-75th centile)</b>			
Length of hospital stay, d	98 (76-113)	90 (71-108)	89 (56-112)
parenteral nutrition, d	16 (10 – 24)	13 (9 – 21)	10 (7 – 15)
PMA at discharge, wk.	38 (33, 41)	38(35 – 41)	38 (33 – 40)
<b>Morbidities, n (%)</b>			
Confirmed NEC	23 (9)	9 (9)	0
Bronchopulmonary dysplasia	41 (17)	13 (12)	1 (9)
Late onset Sepsis	69 (28)	29 (27)	3 (27)
ROP surgery	17 (7)	7 (7)	1 (9)
ROP diagnosis	20 (8)	9 (9)	1 (9)
<b>Very preterm infants</b>	(n= 407)	(n= 196)	(n= 304)
<b>Median (25th-75th centile)</b>			
Length of hospital stay, d	50 (40-67)	52 (40-67)	36 (28-46)
parenteral nutrition, d	9 (6 – 14)	8 (6 – 12)	6 (3 – 8)
PMA at discharge, wk.	36 (35 – 38)	37 (35 – 39)	35 (34 – 37)
<b>Morbidities, n (%)</b>			
Confirmed NEC	6 (2)	3 (2)	2 (1)
Bronchopulmonary dysplasia	18 (4)	8 (4)	4 (1)
Late onset Sepsis	45 (11)	14 (7)	17 (6)
ROP surgery	6 (2)	2 (1)	0
ROP diagnosis	4 (1)	4 (2)	1 (<1)

NEC: necrotising enterocolitis, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, PMA: postmenstrual age at discharge.