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A triple-chamber parenteral nutrition solution was associated with improved protein intake in very low birthweight infants

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Short title: Nutrition of very low birthweight infants

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Abstract

Aim

We evaluated the nutrient intakes of very low birthweight (VLBW) infants weighing less than 1500g and tested the hypothesis that using a triple-chamber parenteral nutrition (PN) solution, containing lipids, glucose and amino acids, would improve protein intake.

Methods

This retrospective cohort study comprised 953 VLBW infants born in 2005-2013 at a gestational age of less than 32+0/7 weeks and admitted to the neonatal care unit at Helsinki Children's Hospital, Finland. The infants were divided into four groups according their birth year and PN regime. Nutrient intakes were obtained from computerised medication administration records.

Results

In 2012-2013, when a triple-chamber PN solution was used, infants were more likely to reach the target parenteral protein intake of 3.5g/kg/d, and reach it 3-7 days earlier, compared with infants who received individual PN or standard two-in-one PN solutions in 2005-2011. In addition, infants in the triple-chamber group had the highest median energy intake (90kcal/kg/d) during the first week. They also had higher median protein intakes in weeks one, two and three (3.1, 3.4 and 3.7g/kg/d) than infants born in 2005-2011 ($p<0.05$).

Conclusion

Using a triple-chamber PN solution was associated with improved protein intake and the protein target was more likely to be achieved.

Keywords

Energy intake, Enteral nutrition, Parenteral nutrition, Protein intake, Very low birthweight infants

Keynotes

- The provision of sufficient nutrition for very low birthweight (VLBW) infants is challenging. A better understanding is needed on how to optimise their nutritional intakes.
- The early protein intake of VLBW infants improved during the period when a triple-chamber parenteral nutrition solution was used.

- Computerised medication administration records contain precise data on actual nutritional intakes, and offer possibilities to study nutrition in a large cohort of patients.

INTRODUCTION

Ideally, a preterm infant should grow at a similar rate, and attain a similar body composition, as a fetus of a similar gestational age. However, providing optimal nutritional support for very low birthweight (VLBW) infants is challenging and postnatal growth restriction is common (1). In Europe, the guidelines for parenteral and enteral nutrition of preterm infants were issued in 2005 and 2010 (2,3), respectively, and the guidelines for parenteral nutrition (PN) were updated in 2018 (4,5). Despite the long-standing availability of nutritional guidelines for VLBW infants, a better understanding is needed on how these recommendations have translated into actual intakes.

The neonatal intensive care unit (NICU) of the Helsinki Children's Hospital, Finland, has followed the European guidelines (2,3). However, PN practices have varied markedly during different time periods. Individual parenteral nutrition, standard two-in-one PN solutions containing amino acids and glucose and a commercially available triple-chamber solution containing amino acids, glucose and lipids, have all been used. Our aim was to evaluate the actual nutrition of VLBW infants admitted to the Helsinki Children's Hospital NICU during 2005–2013 and to compare the nutritional intakes with current recommendations. We hypothesised that the use of a triple-chamber PN solution would improve the nutrient intake of VLBW infants.

MATERIALS AND METHODS

Design

This study was conducted as part of the Big Data – Tiny Infants research project. Nutritional data from VLBW infants admitted to the NICU of the Helsinki Children's Hospital were obtained from the electronic patient information system, Centricity Critical Care Clinisoft (GE Healthcare). These data were linked to the Finnish Medical Birth Register data on premature infants, managed by the National Institute for Health and Welfare, Finland, which includes prenatal and neonatal information on all infants born in Finland with a birthweight of less than 1501g or a gestational age of less than 32+0/7 weeks. A description of the Register is provided in Table S1. The Register authority and the Ethics Committee of the Helsinki University Hospital approved the study protocol. All the data analysed were anonymised and no consent was required.

Subjects and nutritional practices

We focused on 1227 infants with a registered birthweight of less than 1500g who were admitted to the NICU of the Helsinki Children's Hospital in 2005–2013. The exclusion criteria for the study cohort are shown in Figure 1. Gestational age was determined from the first day of the last menstrual period and confirmed by ultrasonography in 86% of cases. Being small for gestational age was defined as a birthweight Z-score of less than -2 standard deviations on the Finnish growth charts (6).

Throughout the study period, the nutrition prescription practice remained the same and we followed local PN guidelines that were similar to the European PN guidelines published in 2005 (2). However, the implementation of the PN varied during the study period and the infants were divided into four subgroups according to their year of birth and the PN regime used (Table 1). PN was started immediately after birth. In 2005–2007 infants received a standard two-in-one PN solution, which was replaced by individual parenteral solutions by three days of age. In both 2008–2009 and 2010-2011, four different standard two-in-one PN solutions were used, which were prepared by the in-hospital pharmacy or were commercial products. In 2012–2013, a commercially available triple-chamber PN solution called Numeta G13E (Baxter S.A Lessines, Belgium) was used. The energy and protein content of the different PN solutions varied between 50–91kcal/100ml and 2.2–3.9g/100ml, respectively. The triple-chamber PN solution had the highest energy and protein content. If needed, supplementary protein could be added. Table S2 provides a detailed description of the standard parenteral solutions. Throughout the study period, parenteral lipids were initiated within the first two postnatal days.

Enteral nutrition was started during the first day of life with minimal amounts of the mother's own milk or donor human milk, and the amount was gradually increased by 10–20ml/kg/d, according to tolerance. A breast milk fortifier (Nutriprem BMF in 2005–2009 or Nutrilon BMF in 2010–2013, Nutricia Medical Oy, Turku, Finland) was added when enteral intake was at least 100ml/kg/d. Enteral nutrition was prescribed in a similar way to PN, with a computerised order entry system. The amount of milk and fortifier was calculated based on the individual needs of the infant. Before 2010, our local guidelines contained an enteral protein intake target of up to 4g/kg/d. After that, we followed the European guidelines published in 2010.

Nutrition

The actual daily nutrient intake was obtained from the electronic patient information system. The system includes a computerised order entry system and computerised medication administration records, which contain detailed information of all preparations given to each infant: name of the

preparation, amount given and the time and route of administration. After selecting preparations containing any macronutrients or micronutrients, we had a total of 2.05 million records. The nutrient content of each record was calculated using the manufacturers' product information. For human milk, the following composition was applied: 67.7kcal/100ml, 1.4g/100ml and 3.2g/100ml for energy, protein and fat, respectively (7). Next, the daily nutrient intake for each 24-hour period was computed, starting at 2pm each day. This time was based on our NICU's clinical practice. Finally, the daily intake was adjusted by weight. Birthweight was used for the first seven days and after that we used the recorded weight of the respective day.

All of the data were screened for possible errors and outliers before the analyses,. Of the 2.05 million records, we detected 19 records that clearly deviated, 60–800 times, from other similar observations. These were regarded as outliers and removed. In addition, we removed days with a total calorie intake of less than 20kcal/kg/d. These were caused by missing recordings, which were due to software updates of the electronic patient information system. This corresponded to 667 recordings (0.03%) and 69 24-hour periods (0.25%). Because we only wanted to analyse full 24-hour periods, the last day of each infant's stay was excluded.

Statistics

The data are presented as medians and interquartile ranges or numbers and percentages as appropriate and the 95% confidence intervals (CI) for the medians were calculated using bootstrapping. Categorical data were analysed by chi-square tests or the Fisher´s exact test. Skewed continuous data were analysed by the Kruskal–Wallis test, and, where appropriate, the Mann-Whitney U test with Bonferroni correction was used for pairwise comparisons. In addition, we defined the first time points when the energy and protein intakes reached the recommended levels of 110kcal/kg/d and 3.5g/kg/d, respectively, for each infant. Alternatively we used the time until the end of follow up, which was 28 days, if no event was observed before that. To compare this time-to-event outcome between the subgroups, Kaplan–Meier curves with log-rank tests and median survival times were estimated. Cox regression models, adjusted for gestational age, gender, being small for gestational age and having a central venous catheter, were also applied, with robust standard errors. Statistical analyses were executed using R software (R Foundation for Statistical Computing, Vienna, Austria). Significance was set at $p < 0.05$.

RESULTS

After exclusions, 953 infants were analysed, after they had been divided into four groups according to their year of birth and the PN regime they received (Table 1). The groups were similar in gestational age and birthweight. Infants born in 2005–2007 had the longest duration of stay and the longest duration of invasive ventilation. The incidence of postnatal morbidities was similar between the groups, except for respiratory distress syndrome, patent ductus arteriosus and sepsis (Table S3).

The total and parenteral energy and protein intakes during the first four postnatal weeks are presented in Figures 2 and 3, respectively.
The first week was mostly a PN phase and the median proportion of parenteral nutrient intake varied between 75–90%. The second week was a transition phase from parenteral to enteral nutrition and the median proportion of parenteral nutrient intake varied between 45–72%. During the third and fourth weeks the nutrition was mainly administered enterally.

According to the guidelines (2,3) that were in place during the study period, the target energy intakes were set at 110 and 120kcal/kg/d for parenteral and enteral intake, respectively (Figure 2). The infants born in 2012–2013 had the highest total median energy intake during the first week. The median (95%CI) energy intakes during the first week for infants born in 2005–2007, 2008–2009, 2010–2011 and 2012–2013 were 87 (85.5 - 88.6), 89 (87.9 - 90.4), 87 (85.1 - 87.7) and 90 (88.0 - 91.2) kcal/kg/d, respectively ($p<0.05$). Table S4 provides detailed information on the relevant pairwise comparisons. Furthermore, the total median energy intake reached the parenteral target level during the second week in all groups and the target enteral level during the third week in all groups, excluding the infants born in 2010–2011. According to the 2018 updated parenteral guidelines (4), the total median energy intake reached the recommended intake, of over 90kcal/kg/d, during the first week in all study groups.

Figure 3 shows the protein intake of the study groups. According to the guidelines (2, 3), the target intakes were set at 3.5 and 4.0 g/kg/d for parenteral and enteral intake, respectively. The total median protein intake did not reach the target parenteral intake during the first two weeks in any of the groups. However, infants born in 2012–2013 were closest to the target and had a higher protein intake during the first two weeks compared with the other groups. The median (95%CI) protein intake during the first week for infants born in 2005–2007, 2008–2009, 2010–2011 and 2012–2013 was 2.8 (2.8 - 2.8), 2.5 (2.5 - 2.6), 2.5 (2.4 - 2.5) and 3.1 (3.1 - 3.2) g/kg/d

respectively (p<0.01) (Table S4). The median (95%CI) protein intake during the second week for infants born in the same years was 3.3 (3.2 - 3.3), 3.1 (3.0 - 3.1) , 3.0 (2.9 - 3.0) and 3.4 (3.3 - 3.4) g/kg/d respectively (p<0.01) (Table S4). These data were compared with the updated European parenteral guidelines (5), which recommend that the parenteral protein intake from postnatal day two onwards should be between 2.5 and 3.5 g/kg/d. This showed that only infants born in 2012–2013 reached this target on day two, whereas infants born in 2005–2011 reached it on either day three or day four.

The total median protein intake did not reach the target enteral intake of 4.0g/kg/d during the third and fourth week in any of the groups (Figure 3). However, infants born in 2012–2013 were closest to this target (p<0.05) (Table S4). Furthermore, 92% of those infants born in 2012–2013 and followed for the whole 28-day study period, reached the target enteral protein intake compared with 74%, 77% and 84% of infants born in 2005–2007, 2008–2009 and 2010–2011, respectively (p=0.02).

The cumulative probabilities of reaching the target parenteral energy and protein intakes, of 110kcal/kg/d and 3.5g/kg/d respectively, are presented in Figure 4. The target parenteral energy intake was reached by the eighth day of life in all groups, and, in the adjusted Cox model, the cumulative probability of reaching this target was similar in infants born in 2012–2013 compared with infants born in 2005–2011 (data not shown). However, infants born in 2012–2013 reached the target parenteral protein intake on the fifth day of life (median), which was three to seven days earlier than infants born in 2005–2011. Furthermore, in the adjusted Cox proportional hazard model, they were more likely to reach the target parenteral protein intake during the first four postnatal weeks: the hazard ratios (95% CI) were 0.52 (0.41 - 0.66), 0.29 (0.22 - 0.37) and 0.34 (0.26 - 0.43) for infants born in 2005–2007, 2008–2009 and 2010–2011, respectively. The same analyses were also performed in the subpopulation of infants who stayed in the NICU for the whole 28-day study period, with similar results (data not shown).

DISCUSSION

The current study demonstrates that the protein intake of this cohort of VLBW infants improved in 2012-2013 when a commercially available triple-chamber PN solution was used instead of standard two-in-one PN solutions or individual solutions. Infants born in 2012–2013 had a higher median protein intake during the first three postnatal weeks compared with infants born in 2005–

2011. In addition, the target parenteral protein intake of 3.5g/kg/d was more likely to be reached during 2012-2013, and 3–7 days earlier, than in 2005–2011.

During the 2005–2013 study period, we followed the European paediatric PN guidelines issued in 2005 (2). According to these guidelines, we were aiming at an energy intake of 110kcal/kg/d and a protein intake of 3.5g/kg/d. During the first two postnatal weeks, in the PN phase, the total median protein intake did not reach the target level in any of the groups. However, energy intake was more in line with the recommendations; the target parenteral energy intake was reached during the second postnatal week in all groups, except for infants born in 2010–2011.

On the other hand, the most recent PN guidelines released in 2018 (4, 5), provide more moderate targets of 90–120kcal/kg/d and 2.5–3.5g/kg/d for energy and protein intake, respectively. If we apply these updated guidelines to our data, the median protein intake was above 2.5g/kg/d from day two onwards among the infants born in 2012–2013, whereas infants born in 2005–2011 reached this level one to two days later. We believe that during the PN phase, in an optimal setting, the variation (interquartile range) of the actual parenteral protein intake should be somewhere between 2.5–3.5g/kg/d. It seems that infants born in 2012–2013 were closest to this goal (Figure 3B). The total median energy intakes were between 48 and 67kcal/kg/d on the first postnatal day and gradually increased to 90kcal/kg/d on day four or five in all study groups.

Another factor that could have contributed to the improved protein intake of the infants born in 2012–2013 could have been the more prevalent use of central venous catheters in 2012–2013, which enabled the use of more concentrated PN solutions. When the use of central venous catheters was included as a confounding factor in the Cox model, we still found better protein intake in 2012–2013 than 2005–2011. Also, the ready-to-use triple-chamber PN solutions with the option to add extra protein was possibly easier to use by less experienced doctors. Otherwise, the clinical characteristics of the four groups were mainly similar and the groups were comparable. There were variations in the prevalence of respiratory distress syndrome, patent ductus arteriosus and time on invasive ventilation between the study periods. However, we believe that this could have been due to changes in clinical practice and did not necessarily reflect the severity of these illnesses.

In line with our results, others have reported an association between improved nutrient intake and the use of standard PN solutions (8, 9). A French prospective observational study of 107 infants born before 33 weeks of gestational age reported improved energy and protein intake during the

first postnatal week, when standardised PN solutions were used instead of individual PN solutions (8). A Swedish retrospective observational study of 118 VLBW infants reported improved energy and protein intake during the first postnatal week when a more concentrated, commercially available PN solution was used instead of a pharmacy-prepared all-in-one PN (9). Similarly to our study, they used computerised assisted prescriptions. The use of a computer-aided nutrition calculation programme or a computerised physician order entry for PN has been shown to improve the nutritional intake of very premature infants (10,11). Furthermore, our data support the updated European guidelines, where standard PN solutions are recommended instead of individual solutions. The guidelines also state that '*the combination of computerised prescription and the use of multi-chamber PN bags solutions may enhance the ability to rely on standardised PN with minimal usage of individualised prescriptions*' (12).

In this study, the nutrient intakes of 953 VLBW infants were obtained from computerised medication administration records and more than two million entries were analysed. To our knowledge, using computerised medication administration records and big data to analyse preterm infants' nutrient intakes, instead of manually collected data, is a novel approach and adds to the accuracy of the data (13,14).

Since the release of the European guidelines in 2005 and 2010, the nutrient intakes and adherence to the nutritional guidelines for VLBW infants have been studied in smaller cohorts using medical records (15-18). Several authors have also studied nutritional practices in different hospitals (19,20). However, since feeding intolerance and metabolic disturbances are common among VLBW infants, there might be significant discrepancies between perceived and actual intakes, due to, for example, withholding enteral feeds or alterations in the PN prescribed. Therefore, it is crucial to document the actual nutrient intake instead of the prescribed nutrition.

A strength of our study was the large cohort of VLBW infants with comprehensive and accurate data on their nutritional intake. However, a limiting factor was the retrospective study design and a lack of randomisation. In addition, not all the 953 VLBW infants were followed for the whole four-week study period. Nonetheless, the results remained the same even when we analysed the subgroup of infants whose length of stay was at least 28 days. It is also important to recognise that the recommendations do not necessarily correspond to an individual infant's actual nutritional requirements. Despite, this, it is essential to pay attention to how well the premature infants' nutritional intakes meet the guidelines when they are in the NICU. According to surveys, wide

variations in clinical practices exist and the level of compliance with current guidelines remains unclear (19).

CONCLUSION

We found that the median protein intake of VLBW infants improved during the time when commercially available triple-chamber PN solutions were used instead of standard two-in-one PN solutions or individual PN solutions. Our findings support the recently published European paediatric PN guidelines. The recommended nutrient intakes for VLBW infants could be achieved by combining computerised PN prescriptions and the use of multi-chamber PN solutions.

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CONFLICTS OF INTEREST

Lotta Immeli has received a lecture fee from Baxter Healthcare. The other authors have no conflicts of interest to declare.

ABBREVIATIONS

VLBW, very low birthweight; PN, parenteral nutrition; NICU, neonatal intensive care unit; CI, confidence interval

Table S1: Information contained in the small preterm infants data provided by the Medical Birth Register for Finland

Table S2: Composition, per 100ml, of the standard parenteral nutrition solutions

Table S3: Clinical characteristics of the study population

Table S4: Comparison of total energy and protein intake during the first four weeks between infants born in 2005-2007, 2008-2009, 2010-2011 and 2012-2013. Reported as p values, medians and 95% confidence intervals (CI) for medians.

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Figure legends

Figure 1. Flowchart of the study cohort

Figure 2. The total (2A) and parenteral (2B) energy intake during the first four postnatal weeks in very low birthweight infants according to the year of birth. Data for the first seven days are presented separately and after that for seven-day periods as medians, 95% confidence intervals for medians (notch) and first and third quartiles. Blue dashed lines represent the target intakes of 110kcal/kg/d and 120kcal/kg/d for parenteral and enteral intake, respectively (2,3) and the dark dashed line represents the new minimum target parenteral intake of 90kcal/kg/d (4). * statistically significant difference of $p<0.05$ in energy intake during first or second week in 2012–2013 compared with 2005–2007 and 2010–2011; ** statistically significant difference of $p<0.05$ for 2012–2013 compared with 2010–2011; *** statistically significant difference of $p<0.05$ for 2012–2013 compared with 2005–2007, 2008–2009, 2010–2011. Based on pairwise Mann–Whitney U tests with Bonferroni corrections (Table S4).

Figure 3. The total (3A) and parenteral (3B) protein intake during the first four postnatal weeks in very low birthweight infants according to the year of birth. Data for the first seven days are presented separately and after that for seven-day periods as median, 95% confidence interval for medians (notch), and first and third quartiles. Blue dashed lines represent the target intakes of 3.5g/kg/d and 4.0g/kg/d for parenteral and enteral intake, respectively (2,3) and the dark dashed line the new minimum target parenteral intake of 2.5g/kg/d (5). * statistically significant difference in protein intake during the first, second and third postnatal week in 2012–2013 compared with 2005–2007, 2008–2009 and 2010–2011, $p<0.05$ (Mann–Whitney U test with Bonferroni corrections, Table S4).

Figure 4. The cumulative probability of reaching the recommended parenteral energy and protein intakes. Stratified according to the year of birth. Dashed line represents the median "survival" line. Tick marks indicate censored subjects. *statistically significant difference of $p<0.01$, 2012–2013 set as the reference stratum (Cox proportional hazard model, adjusting for gestational age, gender, being small for gestational age and having a central venous catheter).

Table 1. Clinical characteristics of the study population.

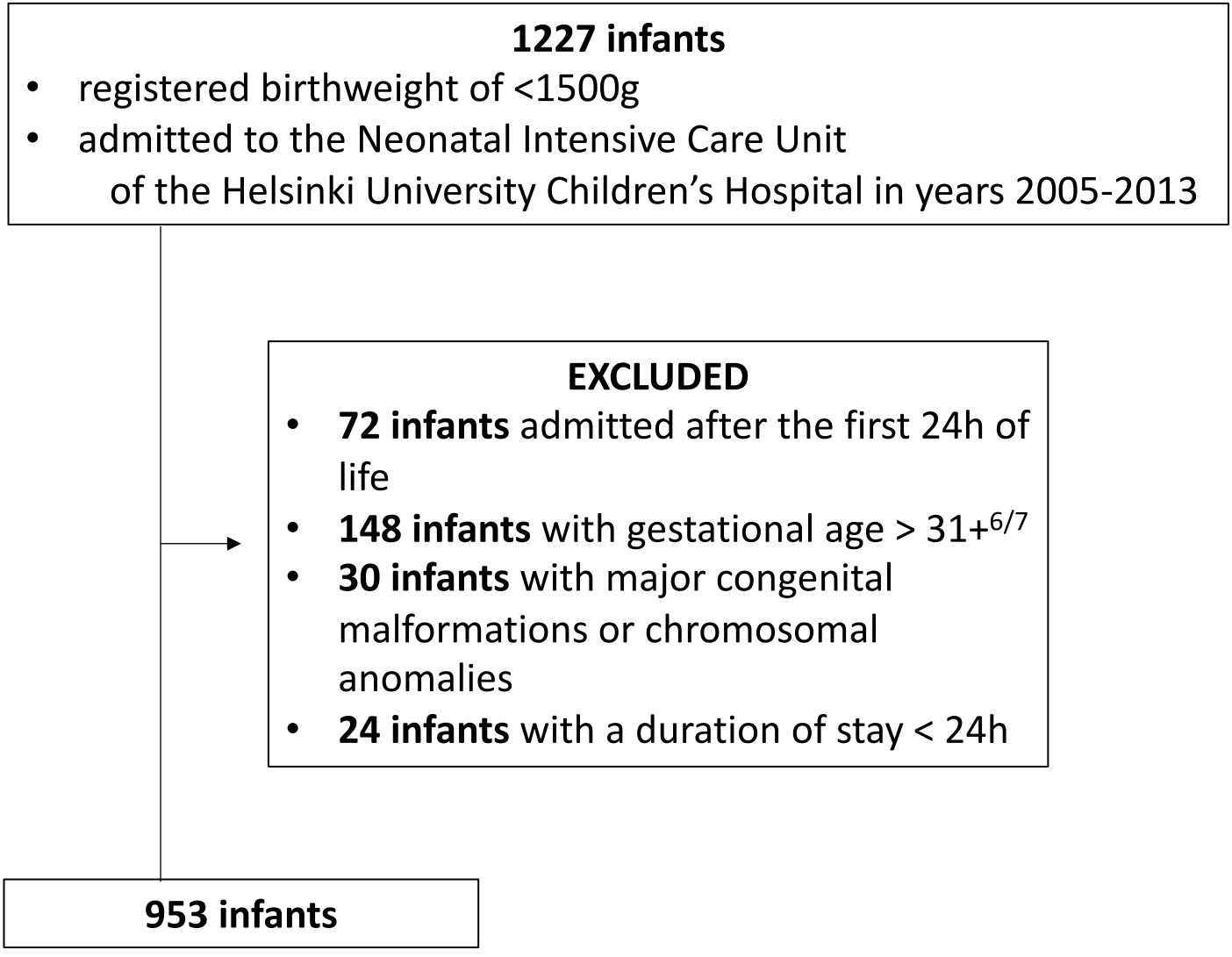
	Total Cohort (N=953)	2005-2007 (n=278)	2008-2009 (n=246)	2010-2011 (n=239)	2012-2013 (n=190)	p-value
Parenteral nutrition (PN) regime		Individual solutions	2-in-1 PN solutions + lipids	2-in-1 PN solutions + lipids	3-chamber PN solution	
Gestational age, week, median (IQR)	28.4 (26.6, 30.0)	28.6 (26.7, 30.1)	28.2 (26.4, 29.7)	28.4 (26.5, 30.0)	28.3 (26.3, 29.4)	0.2[c]
Extremely premature GA<28w, n (%)	415 (43.5)	108 (38.8)	114 (46.3)	105 (43.9)	88 (46.3)	0.3[a]
Birthweight, kg, median (IQR)	1.06 (0.8, 1.3)	1.08 (0.8, 1.3)	1.06 (0.8, 1.3)	1.07 (0.8, 1.3)	1.06 (0.8, 1.2)	0.7[c]
Birthweight <1kg, n (%)	396 (41.6)	106 (38.1)	106 (43.1)	101 (42.3)	83 (43.7)	0.6[a]
Small for gestational age, n (%)	167 (17.5)	56 (20.1)	35 (14.2)	42 (17.6)	34 (17.9)	0.4[a]
Male, n (%)	480 (50.4)	141 (50.7)	116 (47.2)	127 (53.1)	96 (50.5)	0.6[a]
Number of days on ventilator, median (IQR)	5 (1, 17)	7 (2, 24.5)	3 (0.7, 10)	5 (2, 22)	5 (1, 14)	<0.01[c]
Central venous catheter, n (%)^	579 (60.8)[M]	166 (59.7)[m]	135 (54.9)[m]	138 (57.7)[m]	140 (73.7)[m]	0.03[a]
Died before 28d of life, n (%)	53 (5.6)	10 (3.6)	14 (5.7)	18 (7.5)	11 (5.8)	0.5[b]
Length of stay, days, median (IQR)	17 (8, 43)	24.5 (10, 50.8)	13 (7, 41.5)	14 (8, 39.5)	18 (9, 31)	<0.01[c]

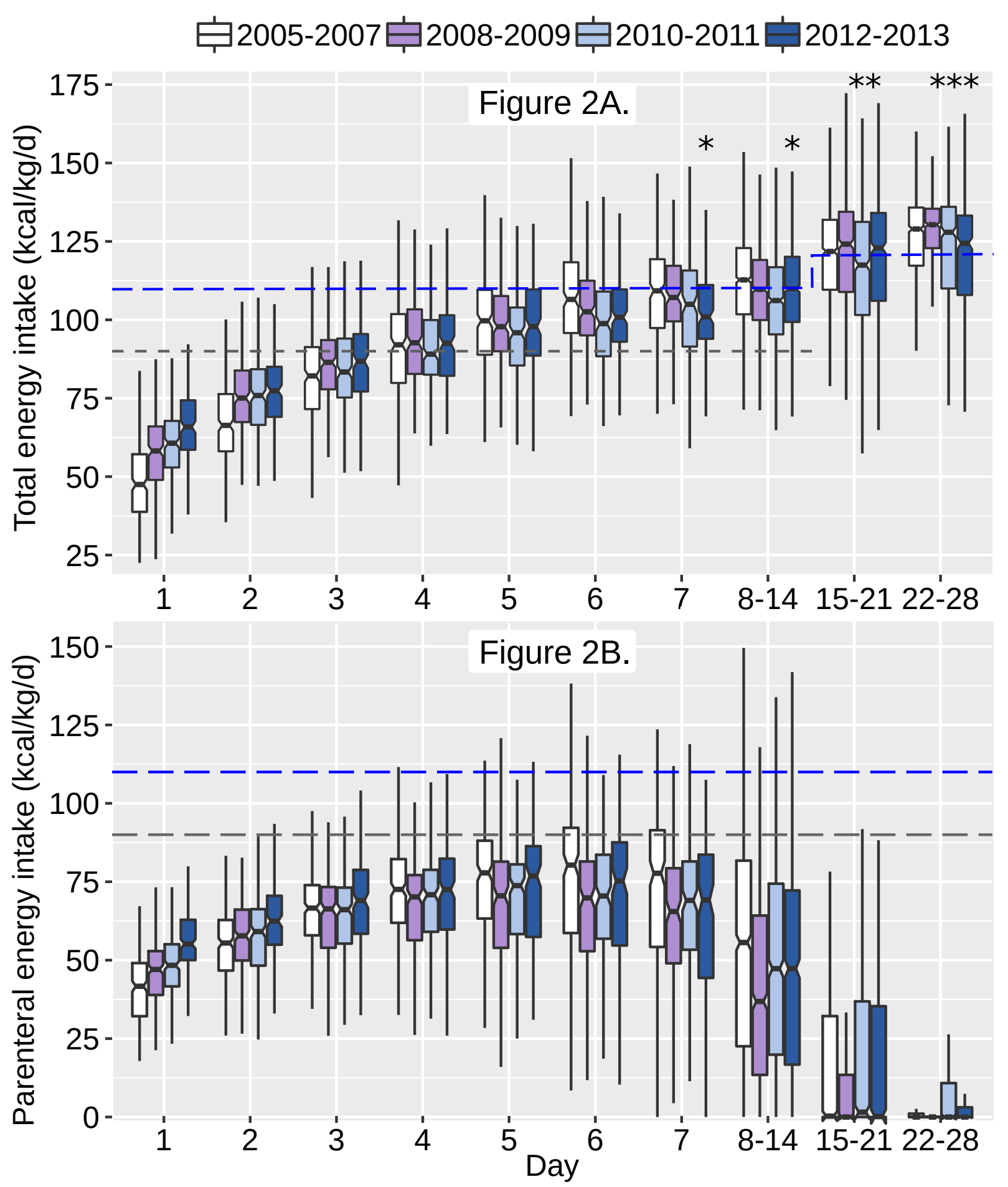
Continuous data are presented as median and interquartile range (IQR) and categorical data as number (n) and %.

Small for gestational age is defined as birthweight Z-score < -2 standard deviations[9]

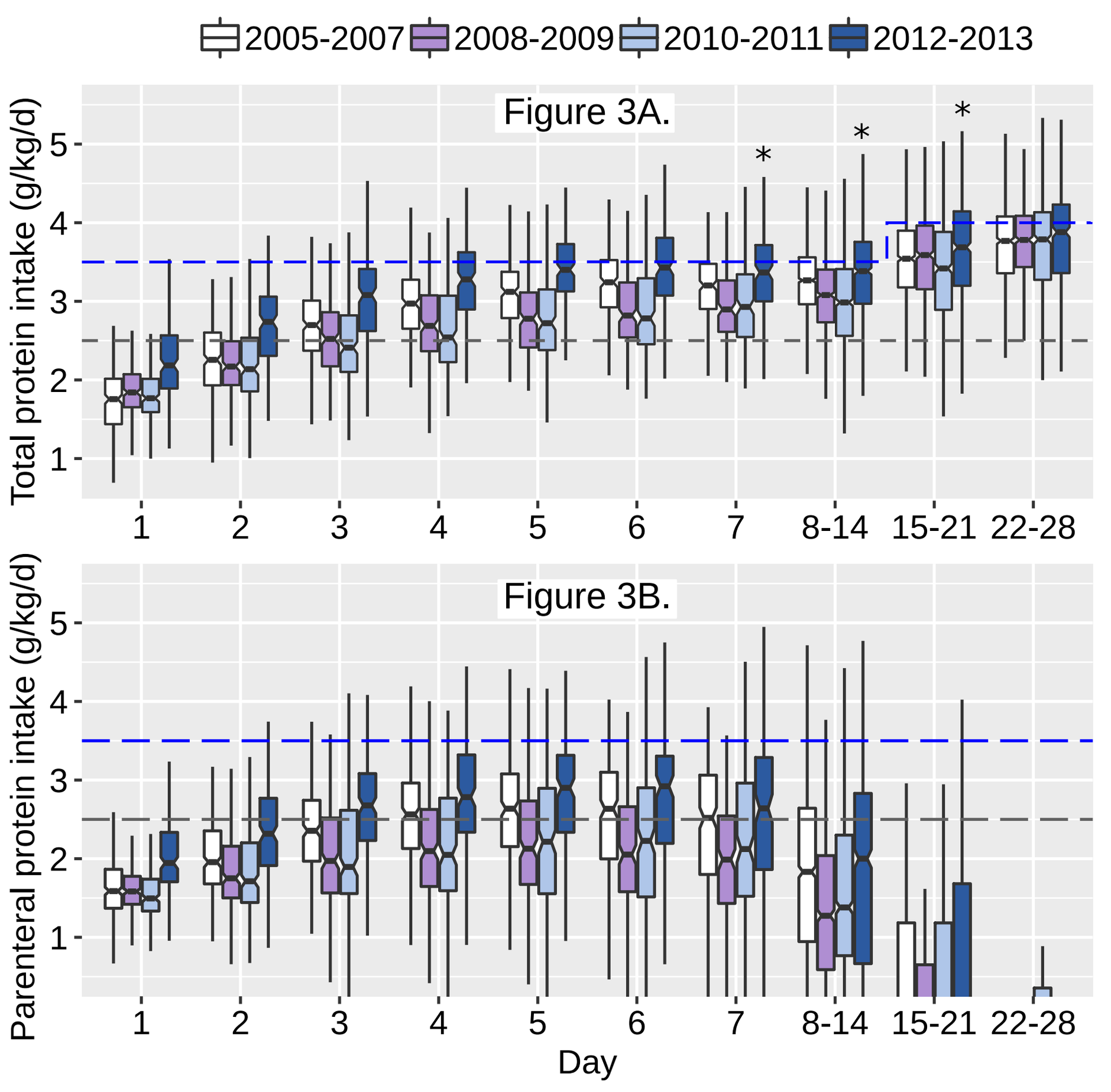
a = Chi-squared test, b = Fisher's test, c = Kruskal–Wallis test. M = missing data >5, m = missing data ≤5

^the local guideline was similar throughout the study period

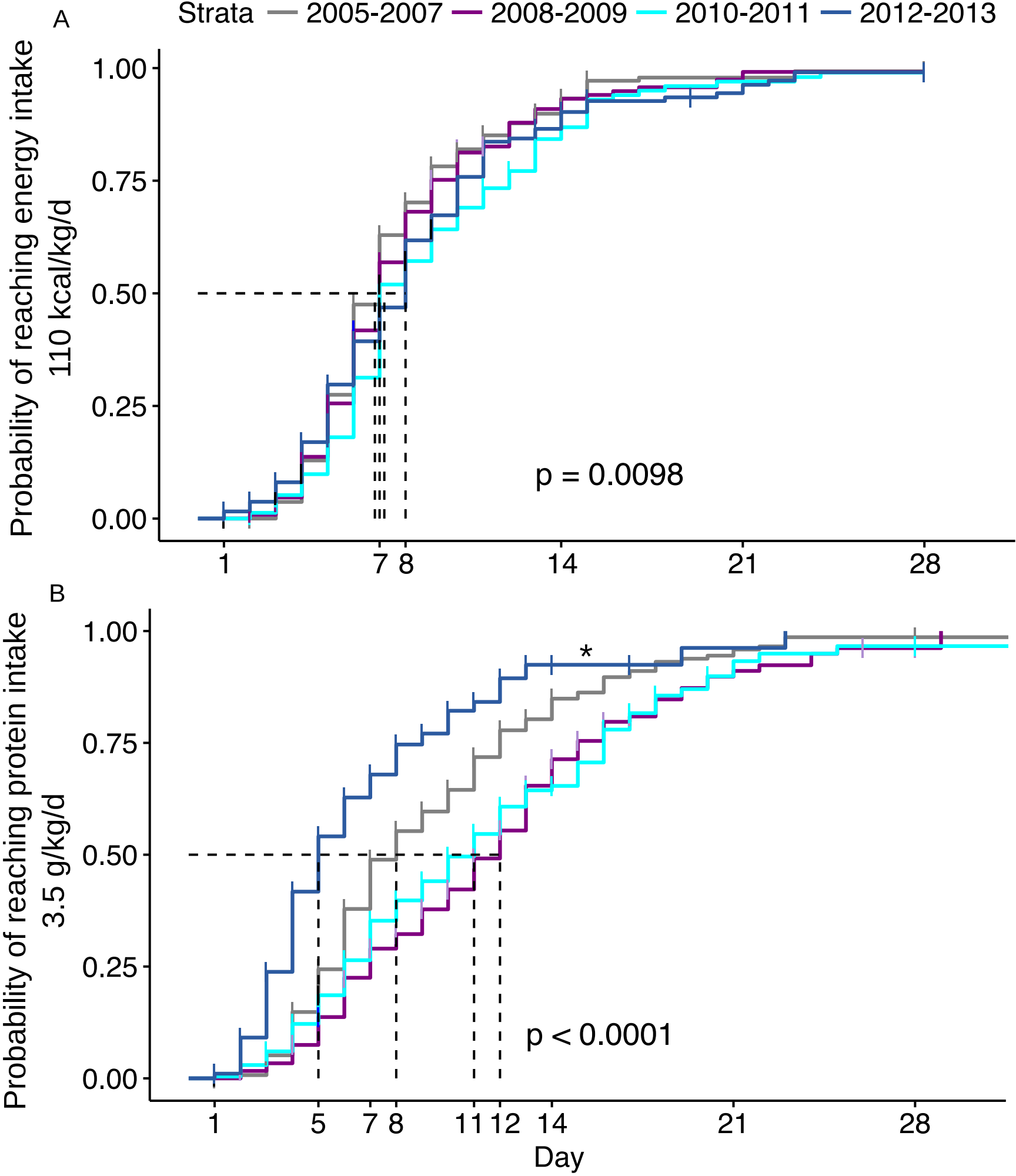

1227 infants
• registered birthweight of <1500g
• admitted to the Neonatal Intensive Care Unit of the Helsinki University Children's Hospital in years 2005-2013
EXCLUDED
• 72 infants admitted after the first 24h of life
• 148 infants with gestational age > 31+6/7
• 30 infants with major congenital malformations or chromosomal anomalies
• 24 infants with a duration of stay < 24h
953 infants



Number of patients: D1-2=953, D7=738, D14=519, D21=410, D28=344



Number of patients: D1-2=953, D7=738, D14=519, D21=410, D28=344


A
Strata
2005-2007
2008-2009
2010-2011
2012-2013
Probability of reaching energy intake
110 kcal/kg/d
1.00
0.75
0.50
0.25
0.00
p = 0.0098
1
7
8
14
21
28
B
Probability of reaching protein intake
3.5 g/kg/d
1.00
0.75
0.50
0.25
0.00
*
p < 0.0001
1
5
7
8
11
12
14
21
28
Day