INTRODUCTION

Sodium constitutes the major determinant of extracellular fluid volume and is thereby a key component of fluid homeostasis. During the first postnatal days, a physiologic contraction of extracellular fluid with negative fluid and sodium balances occurs. The contraction of extracellular fluid is associated with early postnatal weight loss and, according to the European guidelines, a 7%–10% weight loss is suggested to be adequate in very low birthweight (VLBW, birthweight <1500 g) infants.

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Abstract

Aim: To describe sodium and potassium intake, their sources and plasma concentrations, and the association between intake and morbidity in very-low-birthweight (VLBW, <1500 g) infants during the first week of life.

Methods: This retrospective cohort study comprised 951 VLBW infants born at <32 weeks. Infants were divided into three groups according to gestational age: 23–26 (n = 275), 27–29 (n = 433) and 30–31 (n = 243) weeks. Data on fluid management and laboratory findings were acquired from an electronic patient information system.

Results: The median sodium intake was highest in the 23–26 week group, peaking at 6.4 mmol/kg/day. A significant proportion of sodium derived from intravascular flushes; it reached 27% on day 1 in the 23–26 week group. High cumulative sodium intake in the first postnatal week was associated with weight gain from birth to day 8 in the 23–26 week group. High intake of sodium associated with an increased risk of surgically ligated patent ductus arteriosus (PDA), bronchopulmonary dysplasia and intraventricular haemorrhage, whereas low intake of potassium associated with an increased risk of PDA.

Conclusion: Sodium intake in the most premature infants exceeded recommendations during the first postnatal week. Saline flushes accounted for a significant proportion of the sodium load.

KEYWORDS
infant, premature, infant, very-low-birthweight, water-electrolyte balance, weight loss
fluid intake and insufficient early postnatal weight loss have been associated with increased risk of complications, such as patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD) and necrotising enterocolitis (NEC).\(^4\)–\(^6\) Due to renal and adrenal immaturity and high insensible water loss, preterm infants are at risk of both hypo- and hypernatraemia.\(^7\)–\(^8\) In preterm neonates, chronic hyponatraemia has been associated with impaired growth and adverse neurodevelopmental outcomes.\(^8\)–\(^9\) In previous studies, hypernatraemia and increasing intake of sodium in the first days of life have appeared to increase the risk of intraventricular haemorrhage (IVH) in VLBW infants.\(^10\)–\(^11\) Sodium intake, rather than fluid volume, has been suggested to be the major regulator of plasma sodium concentration in extremely low birthweight (ELBW, birthweight <1000 g) infants.\(^12\)

Potassium is the most abundant cation in intracellular fluid and plays an important role in many intracellular functions, including protein synthesis and cell growth. Potassium is vital for growth, and infants and growing children typically maintain a positive potassium balance.\(^13\) Even though earlier studies indicate that ELBW infants are prone to hyperkalaemia during the first few days of life, it has been reported that those born small for gestational age and managed with currently recommended early parenteral nutrition are at high risk of early hypokalaemia.\(^14\)–\(^15\)

There are few studies on the actual sodium and potassium intake of VLBW infants in the first days of life. The objective of this study was to describe the sodium and potassium intake and their sources in VLBW infants during the first week in neonatal intensive care and to examine the association between electrolyte intake, plasma electrolyte concentrations and morbidity using recent, detailed data on a large cohort of VLBW infants. We hypothesised that VLBW infants have high sodium intake associated with hypernatraemia and inadequate early postnatal weight loss.

2 | PATIENTS AND METHODS

2.1 | Study design, subjects, and diagnoses

This study was conducted as part of the Big Data – Tiny Infants research project. We retrospectively identified all infants with a birthweight below 1500 g admitted to the tertiary care neonatal intensive care unit (NICU) of the Helsinki University Children’s Hospital between January 1, 2005, and December 31, 2013. The inclusion criteria were birthweight below 1500 g, gestational age (GA) below 32 weeks, admission to the NICU during the first 24 h of life, no gastrointestinal or other major malformations or chromosomal abnormalities, and spending at least one full 24-h period in the NICU. This cohort of VLBW infants was otherwise previously described in our report on the fluid intake in VLBW infants,\(^16\) but for the purposes of this study, infants with acute kidney failure and severe uraemia were excluded from the analyses.

Clinical characteristics and diagnoses, except for sepsis, were retrieved from the Finnish Medical Birth Register Data on Premature Infants, a nationwide register administered by The National Institute of Health and Welfare, Finland. A detailed description of the Medical Birth Register data used has been provided previously.\(^16\) Due to missing register data, clinical characteristics of 17 infants were acquired manually from medical records. GA was determined from the first day of the last menstrual period and, in 86% of the cases, it was confirmed by ultrasonography at 11+0/7 – 13+6/7 weeks of gestation (i.e., the timing of the first-trimester screening ultrasonography in Finland), and for the rest of the cases, the ultrasound was performed outside of this time frame. A birthweight Z-score of <−2 standard deviations on the Finnish growth charts was considered small for gestational age (SGA).\(^17\) PDA was diagnosed by ultrasound and considered clinically significant if a pharmacological and/or surgical intervention was needed. Pharmacological treatment of PDA was active during the earlier years of our study period and with changing clinical practices the incidence of clinically significant PDA markedly decreased during the years. Thus, only surgically treated PDAs were considered as a PDA in the analyses. The grading of IVHs was determined according to Papile classification.\(^18\) BPD was defined as a need for supplemental oxygen at 36-weeks postmenstrual age.\(^19\) NEC was defined according to modified Bell’s staging criteria as Bell stage II or higher. The diagnosis of sepsis required a positive blood culture in combination with a C-reactive protein level > 10 mg/L on the day the positive blood culture sample was drawn or on the two succeeding days.\(^20\)

2.2 | Electrolytes and postnatal weight change

Intake of sodium and potassium was studied during the first seven postnatal days. All parenteral and enteral preparations given to each infant were acquired retrospectively from the NICU’s electronic patient information system, Centricity Critical Care Clinisoft (GE Healthcare, Chicago, IL). Electrolyte intake was calculated from manufacturer information and published electrolyte content.\(^21\) The sodium content in blood products equalled the sodium content of the additives; information on the blood product additives was obtained from the Finnish Red Cross. Since potassium content in stored blood increases over time, the potassium content in blood products is highly variable and therefore, the potassium from blood
products was not included in the analyses. Instead, the correlation between the amount of red blood cells given and succeeding plasma potassium concentration was studied.

The data from the NICU’s patient information system contained detailed, time-stamped records of all preparations given and their routes of administration, thus enabling us to analyse the different sources of sodium and potassium intake. Daily sodium and potassium intake were calculated over successive 24-h periods, each starting at 14.00 hours, with this point in time determined by the NICU’s clinical practice. The period from birth until the first 14.00 hours was regarded as day zero, and subsequently, only full 24-h periods were included in the analyses. Electrolyte intake was adjusted by dividing the amount by birthweight, and throughout the paper, electrolyte intake is given in mmol/kg birthweight/day. To study the association between electrolyte and fluid intake, we also calculated fluid intake (mL/kg birthweight/day) over successive 24-h periods. To study the postnatal weight change, daily weight measurements were obtained until day 8 of life. Weight change from birth was calculated as (weight measured on a given day – birthweight)/birthweight. We calculated the cumulative sodium intake during the first week of life for the infants with complete data and examined its correlation to the weight change from birth to day 8. When examining the association between electrolyte intake and morbidity, we calculated the cumulative electrolyte intakes during the first two days of life for PDA, IVH, BPD and NEC, as well as the cumulative intake during the first week of life for BPD and NEC. These differing periods of analysis were chosen, since PDA and IVH usually occur already during the first days of life, whereas BPD and NEC are typically diagnosed later. For the analyses regarding morbidity, we included only infants with complete data from the first week of life (n = 610).

The first available plasma sodium and potassium measurements for each 24-h period were analysed. The first plasma electrolyte concentration of each day was considered to reflect the electrolyte intake of the previous day; thus, plasma sodium and potassium concentration was analysed during postnatal days 2–8. Hyponatraemia was defined as a plasma sodium concentration of <135 mmol/L, and hypernatraemia as a concentration of higher than 145 mmol/L. Hypokalaemia was defined as a plasma potassium concentration of <3.3 mmol/L, and hyperkalaemia as a concentration of higher than 5.2 mmol/L, these definitions arising from the reference values of the laboratory operating in our hospital.

### 2.3 Clinical practice

The nutritional practices in our unit followed the European guidelines on parenteral and enteral nutrition.3,23–25 If necessary, Ringer’s solution, fresh frozen plasma, 4%–5% albumin solution, and sterile water were used as volume expanders. For flushing medications and arterial or venous lines, saline solutions of 0.225%, 0.45%, and 0.9% and 5% glucose solution were used. The sources of sodium intake were defined as follows: (1) parenteral nutrition, (2) enteral nutrition, (3) saline flushes, (4) volume expanders, and (5) others. The group others contained blood products (excl. fresh frozen plasma), 20% albumin solution, sodium bicarbonate and other buffer solutions and sodium chloride concentrate not administered as part of parenteral nutrition (PN). The sources of potassium intake were defined as follows: (1) parenteral nutrition, (2) enteral nutrition, and (3) others, containing Ringer’s solution, albumin solutions and potassium concentrates not administered as part of PN.

### 2.4 Statistics

Descriptive data are presented as numbers and percentages or medians and interquartile ranges (IQR), where appropriate. The chi-square test and Fisher’s exact test were adopted for categorical data. Due to skewed distributions, sodium and potassium intake data are presented as medians and interquartile ranges. The non-parametric Kruskal–Wallis test and Mann–Whitney U test, with Bonferroni correction to correct for multiple comparisons, were applied for the analysis of electrolyte intake data. Plasma electrolyte concentration, which shows normal distribution, is presented using means and standard deviations, and one-way analysis of variance with Bonferroni correction was applied for analysis. To examine the strength of the linear relationship between electrolyte and water intake, and electrolyte intake and plasma electrolyte concentration, as well as the cumulative sodium intake during the first week of life and postnatal weight change on day 8, Pearson’s correlation was applied. In box plots, whiskers are shown according to the style of Tukey presenting the largest and smallest values no further than 1.5 times the IQR from the hinge. Associations between electrolyte intake and morbidities were calculated using logistic regression. Separate models were fitted for sodium and potassium, and the models were adjusted for GA and SGA status. Model fit was assessed, and the linearity assumption was met. These data are presented as adjusted odds ratios (OR) and 95% confidence intervals (CI). Logistic regression was used to examine the associations between electrolyte disturbances and morbidities. A p-value of <0.05 was considered statistically significant. Statistical analyses were conducted, and figures were drawn using R4.3.2 statistical software (R Foundation for Statistical Computing).

### 3 Results

During the study period, a total of 1227 VLBW infants were admitted to the NICU of the Helsinki University Children’s Hospital. Based on the exclusion criteria shown in Figure 1, 276 infants were excluded. For the analyses, the final study cohort of 951 infants was divided into three groups according to gestational age at birth: 23–26 weeks (n = 275), 27–29 weeks (n = 433) and 30–31 weeks (n = 243). The clinical characteristics of the study groups are presented in Table 1. Towards the end of the first postnatal week, the group sizes decreased due to transfers to other hospitals or due to mortality. On day seven, 737 infants were still in the NICU (Table 1).
3.1 Sodium and potassium intake and their sources

The total daily sodium and potassium intake during the first week of life is shown in Figure 2. Infants in the 23–26 week group had higher sodium intake and lower potassium intake during the first postnatal week compared with the other two groups (Figure 2). The median sodium intake in the 23–26 week group remained relatively stable throughout the first week of life (median sodium intake 6.3 mmol/kg/day on both days 1 and 7), whereas in the 30–31 week group, the intake increased towards the end of the week from a median of 3.2 mmol/kg/day on day 1 to 4.8 mmol/kg/day on day 7 (Figure 2A). The median potassium intake increased in all the study groups towards the end of the first week: in the 23–26 week group from 0.7 mmol/kg/day on day 1 to 2.0 mmol/kg/day on day 7, in the 27–29 week group from 0.8 to 2.2 mmol/kg/day, and in the 30–31 week group from 1.0 to 2.4 mmol/kg/day (Figure 2B).

Volume expanders constituted a considerable source of sodium intake in the 23–26 week group during the first three days, with the highest median intake from volume expanders being 1.8 mmol/kg/day (28% of total intake) on day 1 (Figure 3A). On the other hand, saline solutions used for flushing medications and arterial or venous lines constituted a significant proportion of sodium intake in all the study groups throughout the first week of life (Figure 3A), even though hypotonic saline solutions were preferred over 0.9% saline as flushes. Hypotonic solutions constituted 90% of all flush volumes given (54% for 0.45% NaCl and 36% for 0.225% NaCl), whereas the proportions of 0.9% saline and 5% glucose were 6% and 4%, respectively. On day 1, the 23–26 week group received a median of 1.7 mmol/kg/day sodium (27% of total intake) from flushes. In the 23–26 week group, sodium intake from nutrition constituted less than a half of the total sodium intake on days 1–4 (the proportions were 17%, 29%, 36% and 41% on days 1–4, respectively). From day 2 onwards, parenteral nutrition accounted for the largest single source of sodium intake in all the study groups (Figure 3A).

Potassium intake derived almost exclusively from nutrition, parenteral nutrition constituting the largest source of potassium intake in the 23–26 and 27–29 week groups, and the role of enteral nutrition strengthening in the 30–31 week group towards the end of the week (Figure 3B).

3.2 Plasma electrolyte concentration

The mean plasma sodium and potassium concentration and the incidences of electrolyte disturbances are presented in Table S1.

Plasma sodium concentration was significantly higher in the 23–26 week group compared with the other two groups during the first days of life, with the incidence of hypernatraemia peaking at 32.3% on day 2 in this group (Table S1). We did not detect any significant correlation between the first available plasma sodium measurement for each 24-h period and the sodium intake of the previous...
We detected a weak positive correlation between potassium intake and hypokalaemia during the first week of life in all the study groups (R 0.65 in the 30–31 week group; 0.62 in the 27–29 week group and 0.55 in the 23–26 week group; Figure S1D). When examining the association between potassium and fluid intake, a moderate positive linear correlation was detected only in the 30–31 week group (R 0.51), whereas the correlations in the 27–29 week and the 23–26 week groups were weaker (Figure S1F).

Figure 4 shows the association between cumulative sodium intake during the first week of life and the percent change in weight from birth to day 8. Only infants with complete data from the first week of life were analysed (n = 610). In the 23–26 week group, there was a positive correlation between cumulative sodium intake and weight change (R 0.45), whereas in the 27–29 and 30–31 week groups the correlations were weaker (Figure 4). Among the 610 infants, there were 30 infants with a marked weight gain from birth exceeding +20% on day 8. Median water and sodium intake during the first week of life was higher in these infants, peaking at 188 mL/kg/day (IQR 163–211) on day 6 for water and at 8.1 mmol/kg/day (IQR 4.5–9.7) on day 4 for sodium, compared with the other 580 infants with complete data from the first week of life (p < 0.001 for water and p < 0.05 for sodium; data not shown). The 30 infants with marked weight gain had a lower birthweight and higher morbidity and neonatal mortality than other infants with complete data (see Table S2 for clinical characteristics of infants with complete data). Daily percent change in weight from birthweight during the first week of life for infants with complete data is presented in Figure S2.

3.3 Electrolyte and fluid intake and postnatal weight change

We found a positive linear correlation between sodium and fluid intake during the first week of life in all the study groups (R 0.65 in the 23–26 week group, 0.62 in the 27–29 week group and 0.55 in the 30–31 week group; Figure S1D). When examining the association between potassium and fluid intake, a moderate positive linear correlation was detected only in the 30–31 week group (R 0.51), whereas the correlations in the 27–29 week and the 23–26 week groups were weaker (Figure S1F).

Table 1 shows the correlation between potassium and fluid intake, with the fluid intake of the previous day (Figure S1B). The plasma sodium concentration correlated neither with the fluid intake of the previous day (Figure S1B) nor of the same day (Figure S1C). Median total fluid intakes in the 23–26 week, 27–29 week and 30–31 week groups varied from 151, 121 and 116 mL/kg/d on day 1 to peak intakes of 176 mL/kg/day on day 3, 147 mL/kg/day on day 4 for sodium, compared with the other 580 infants with complete data from the first week of life (p < 0.05 for sodium; data not shown). The 30 infants with marked weight gain had a lower birthweight and higher morbidity and neonatal mortality than other infants with complete data (see Table S2 for clinical characteristics of infants with complete data). Daily percent change in weight from birthweight during the first week of life for infants with complete data is presented in Figure S2.

### Table 1 Clinical characteristics.

<table>
<thead>
<tr>
<th>GA 23–26 weeks (n = 275)</th>
<th>GA 27–29 weeks (n = 433)</th>
<th>GA 30–31 weeks (n = 243)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>138 (50.2)</td>
<td>234 (54.0)</td>
<td>107 (44.0)</td>
</tr>
<tr>
<td>Birthweight (g), median (min–max)</td>
<td>760 (375–1200)</td>
<td>1110 (400–1495)</td>
<td>1285 (650–1495)</td>
</tr>
<tr>
<td>Small for gestational age, n (%)</td>
<td>31 (11.3)</td>
<td>64 (14.8)</td>
<td>91 (37.4)</td>
</tr>
<tr>
<td>Caesarean section, n (%)</td>
<td>151 (54.9)</td>
<td>305 (70.4)</td>
<td>180 (74.1)</td>
</tr>
<tr>
<td>Apgar score &lt;7 at 5 min, n (%)</td>
<td>139 (50.5)</td>
<td>157 (36.3)</td>
<td>49 (20.2)</td>
</tr>
<tr>
<td>Maternal pre-eclampsia, n (%)</td>
<td>35 (12.7)</td>
<td>112 (25.9)</td>
<td>100 (41.2)</td>
</tr>
<tr>
<td>Antenatal corticosteroid given, n (%)</td>
<td>258 (93.8)</td>
<td>410 (94.7)</td>
<td>237 (97.5)</td>
</tr>
<tr>
<td>Surfactant given, n (%)</td>
<td>274 (99.6)</td>
<td>355 (82.0)</td>
<td>98 (40.3)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (day), median (IQR)</td>
<td>19.0 (7.0–39.0)</td>
<td>3.0 (0.9–7.0)</td>
<td>2.0 (0.4–3.3)</td>
</tr>
<tr>
<td>Central venous catheter, n (%)</td>
<td>250 (90.9)</td>
<td>269 (62.1)</td>
<td>58 (23.9)</td>
</tr>
<tr>
<td>Patent ductus arteriosus, surgically treated, n (%)</td>
<td>96 (34.9)</td>
<td>38 (8.8)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Culture-positive sepsis during the first week of life, n (%)</td>
<td>11 (4.0)</td>
<td>15 (3.5)</td>
<td>9 (3.7)</td>
</tr>
<tr>
<td>Death during the first postnatal week, n (%)</td>
<td>26 (9.5)</td>
<td>7 (1.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stayed in the NICU for the first postnatal week, n (%)</td>
<td>250 (91)</td>
<td>367 (85)</td>
<td>120 (49)</td>
</tr>
</tbody>
</table>

Note: Statistical tests: a: Chi-square test, b: Kruskal–Wallis test, c: Fisher’s exact test.

Abbreviations: NICU, neonatal intensive care unit; NS, not significant.
Electrolyte intake and morbidity

The association between cumulative electrolyte intake during the first two days of life and morbidity is shown in Figure 5. Only surgically ligated PDA was considered as a PDA in these analyses since pharmacological treatment of PDA was active during the earlier years of our study period and with changing clinical practices, the incidence of either pharmacologically or surgically treated PDA markedly decreased during the years from 66% to 30%, whereas the incidence of surgically ligated PDA varied between 4% and 13% without any rising or declining trend during the study period. Higher cumulative sodium intake during the first two days of life was associated with an increased risk of surgically ligated PDA (OR 1.15), IVH (OR 1.11) and BPD (OR 1.09), when adjusting for GA and SGA status (Figure 5). Adjusting for cumulative fluid intake during the first two days of life using residuals had a minor effect on the results: the odds ratios for surgically ligated PDA, IVH and BPD were 1.17 (95% CI 1.10–1.25, \(p<0.001\)), 1.14 (95% CI 1.06–1.24, \(p<0.001\)) and

**FIGURE 2** Daily total sodium (A) and potassium (B) intake in the first week of life in three gestational age groups. The ESPGHAN recommendation (2018) on sodium and potassium intake during the first week of life shown as highlighted areas. (A) The asterisk (*) marks a statistically significant difference between infants in the 23–26 week and 27–29 week groups (\(p<0.001\)) and infants in the 23–26 week and 30–31 week groups (\(p<0.001\)). (B) There were * statistically significant differences between the 23–26 week and 30–31 week groups (on days 1–4 and 7 \(p<0.001\), on day 5 \(p<0.01\) and on day 6 \(p<0.05\)).
Cumulative sodium intake during the first week of life (mmol/kg/week) was associated with an increased risk of BPD (OR 1.04, 95% CI 1.02–1.05, \( p < 0.001 \)). There was no statistically significant association between sodium intake and the risk of NEC.

Higher cumulative potassium intake during the first two days of life was associated with a decreased risk of surgically ligated PDA (OR 0.73), with each 1 mmol/kg increase in potassium intake decreasing the risk of PDA by 27%, when adjusting for GA and SGA status. Cumulative potassium intake during the first two days of life was not significantly associated with the risk of IVH, BPD or NEC. Higher cumulative potassium intake during the first week of life (mmol/kg/week) was associated with a slightly lower risk of BPD (OR 0.94, 95% CI 0.88–0.99, \( p = 0.03 \)).
3.5 | Plasma electrolyte concentration and morbidity

Neither hyponatraemia (P-Na < 135 mmol/L) nor hypernatraemia (P-Na > 145 mmol/L) measured at least once during the first two days of life was associated statistically significantly with the risk of surgically ligated PDA, IVH, BPD or NEC.

Hypokalaemia (P-K < 3.3 mmol/L) measured at least once during the first two days of life was associated with increased risk of BPD (OR 1.60, 95% CI 1.06–2.44, \( p < 0.05 \)). Hypokalaemia did not affect the risk of surgically ligated PDA, IVH or NEC. Hyperkalaemia (P-K > 5.2 mmol/L) during the first 2 days of life was not significantly associated with the risk of surgically ligated PDA, BPD, IVH or NEC.

4 | DISCUSSION

In this large cohort of VLBW infants, we demonstrated that the cumulative sodium intake during the first week of life was positively correlated with the percent weight change from birthweight to postnatal day 8. High sodium intake during the first week of life may thus hinder early postnatal weight loss and lead to increased morbidity. In our data, higher cumulative sodium intake in the first days of life was associated with significantly increased risks of surgically treated PDA, IVH and BPD.

Our finding is in parallel with the randomised controlled trial by Hartnoll et al. suggesting that early sodium supplementation reduces maximum postnatal weight loss. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines suggest that, in VLBW infants, a 7%–10% weight loss is adequate. In our data, maximum postnatal weight loss remained modest in all the study groups, the medians ranging from −1.5% to −2.9%. Weight accretion during the first week of life does not usually reflect actual growth, but rather is a sign of oedema. During the immediate postnatal period in VLBW infants, an initial relative oliguria lasting for hours to days is followed by a diuretic phase characterised by a high fractional excretion of sodium. Due to a restricted renal glomerular filtration rate together with an immature renin-angiotensin-aldosterone system, preterm infants have limited ability to tolerate high sodium and water loads. Renal glomerular and tubular function have been shown to be significantly affected by gestational age at birth with the most premature infants having the lowest creatinine clearance. Accordingly, in our data, the positive correlation between cumulative sodium intake and weight change from birth during the first week of life was strongest in the most premature group. Failure to achieve physiological contraction of extracellular fluid during the first days of life has been associated

\[
R = 0.45, p < 0.001 \\
R = 0.34, p < 0.001 \\
R = 0.37, p < 0.001
\]
with an increased risk of symptomatic patent ductus arteriosus and necrotising enterocolitis.\textsuperscript{4–6}

We found that increasing cumulative sodium intake during the first two days of life was associated with an increased risk of surgically ligated PDA, IVH and BPD, with each 1 mmol/kg increase in sodium intake increasing the risk by 15%, 11% and 9%, respectively. This independent effect of sodium intake remained, when adjusting for fluid intake. We found no association between the cumulative sodium intake and the risk of NEC. In accordance with our results, Eibensteiner et al. demonstrated in a retrospective study of 90 ELBW infants, that each mmol of sodium intake during the first postnatal week was associated with a 45% higher risk of BPD and a 31% higher risk of IVH grade III or IV. They found no statistically significant association for PDA. However, these analyses were unadjusted.\textsuperscript{30}

Our study found that the actual sodium intake in VLBW infants was high during the first week of life, especially in infants born at GA 23–26 week. Throughout the entire week, sodium intake in this most premature study group was practically twice the maximum intake of 3 mmol/kg/day recommended during the study period of years 2005–2013.\textsuperscript{23} The European guidelines on paediatric parenteral nutrition were revised in 2018.\textsuperscript{25} For VLBW infants, the new guidelines recommend a sodium supply of 0–2 mmol/kg/day during the first two postnatal days, 0–5 mmol/kg/day on day 3 and 2–5 mmol/kg/day thereafter.\textsuperscript{3} The sodium intake in the most premature group of our study exceeded these revised guidelines as well, even though the recommended supplies are more liberal from day 3 onwards. The high sodium intake observed in the extremely preterm infants of our cohort supports the findings by Eibensteiner et al.\textsuperscript{30} Compared with our findings, they reported an even higher median sodium supply of 11.3 mmol/kg/day (IQR 9.3–14.1) during the first week.\textsuperscript{30}

During the first two postnatal days, median sodium intake exceeded the new guidelines in all our study groups. Several studies suggest that sodium supplementation should be limited in this vulnerable period of adaptation.\textsuperscript{2,26,28} In a trial by Shaffer and Meade assessing sodium balance and extracellular volume regulation in VLBW infants, twenty infants were randomly assigned to receive either 1 or 3 mmol/kg/day sodium during the first 10 postnatal days.\textsuperscript{2} In this study, administration of larger quantities of sodium appeared to increase the risk of hypernatraemia despite increased sodium excretion.\textsuperscript{2} In a randomised study by Costarino et al., 17 VLBW infants were assigned either to receive no sodium supplementation or to receive supplemental sodium of 3–4 mmol/kg/day after the first day of life for 5 days thereafter. Sodium restriction was associated with a decreased incidence of hypernatraemia and bronchopulmonary dysplasia, and the authors concluded that sodium intake during the first 3–5 days of life should be restricted.\textsuperscript{28} In a recent retrospective case–control study of 140 extremely preterm (GA < 27 week) infants by Späth et al.,\textsuperscript{31} a higher early sodium supply until postnatal day 2 was associated with an increased risk of severe intraventricular haemorrhage. A similar association was found in our data of VLBW infants: a higher sodium intake during the first two days of life was

**Figure 5** Association between sodium (Na) and potassium (K) intake during the first 2 days of life and morbidity, logistic regression adjusted for gestational age and small for gestational age status. BPD, bronchopulmonary dysplasia; CI, confidence interval; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; OR, odds ratio; PDA, patent ductus arteriosus.
associated with an increased risk of IVH even in the absence of hypernatraemia.

Particularly interesting clinically was our finding that a significant proportion of sodium intake throughout the first week of life came from saline solutions used for flushing medications and arterial or venous lines. On the first postnatal day, over half of the total sodium intake in all the study groups derived from these saline flushes together with volume expanders. The sodium intake from these hidden sources, which is easily overlooked while prescribing fluids and electrolyte supplies in clinical practice, contributes significantly to the excessive sodium load observed during the first two postnatal days. Similar inadvertent sodium load in ELBW infants was reported by Eibensteiner et al. In their study, 0.9% saline was used for flushing antibiotics and arterial lines. The authors contemplated replacing 0.9% saline with hypotonic solutions and 5% glucose and presented two sodium replacement models resulting in a decrease in sodium intake of 3.2–4.0 mmol during the first postnatal day. Even though in our study hypotonic saline solutions (0.45% and 0.225%) were preferred over 0.9% saline, sodium intake from hidden sources remained high. To further reduce the sodium load from flushes, 5% glucose solution might be preferred, if applicable.

In our data, we could not demonstrate a correlation between sodium intake and plasma sodium concentration. Instead, there was a positive correlation between sodium and fluid intake. This correlation between sodium and fluid intake was explored as a basis for the morbidity analyses since we wanted to separate the independent effects of sodium and fluid intake. In the most premature group of our study, the fluid intake in the first three days of life markedly exceeded the recommendations, largely due to a considerable amount of fluid deriving from volume expanders and flush solutions. In volume expanders and flush solutions, sodium and fluid are delivered simultaneously. The provision of fluid closely linked with sodium supply might dilute the effect of sodium load on plasma sodium concentration. Furthermore, it has been suggested that in the presence of increased intake of sodium, physicians tend to prescribe more parenteral fluids to compensate for the increasing plasma sodium concentration. In contrast to our results, Eibensteiner et al. reported that a 1 mmol/kg increase of sodium intake was associated with an average increase in serum sodium of 0.05 mmol/L on the following day during the first two weeks of life in ELBW infants. Also, in an observational study of 592 extremely preterm infants by Späth et al., sodium supply during days 4–9 after birth correlated positively with plasma sodium concentration at postnatal age of 10 days.

We observed that potassium intake fell below recommendations during postnatal days 4 and 5 in the 23–26 week and 27–29 week groups. The European guidelines recommend a potassium supply of 0–3 mmol/kg/day during the first three postnatal days, 2–3 mmol/kg/day during days 4 and 5, and 1–3 mmol/kg/day thereafter in VLBW infants. Parenteral potassium supplementation should be initiated before serum concentration decreases below the reference values. A recent review on the electrolyte management of preterm infants recommended providing potassium supplementation once serum potassium concentration is below 4 mmol/L. Postnatal days 1–3 have been described as a vulnerable period for hyperkalaemia especially in ELBW infants, with the predisposition shifting to hypokalaemia after the onset of diuresis. In accordance with previous studies, the incidence of hyperkalaemia in our data was highest in the most premature group during the first three days of life. However, our data did not demonstrate an increasing tendency to hypokalaemia in VLBW infants towards the end of the first week of life. In our data, the positive correlation between potassium and fluid intake was stronger in the 30–31 week group compared with the more premature groups, probably suggesting that more mature infants receive potassium supplementation more freely as part of enteral feeds, while clinicians tend to be wary of adding potassium to parenteral nutrition due to concern for hyperkalaemia. Potassium is vital for various intracellular functions and growth, and efforts should be made to provide sufficient potassium supply after the onset of diuresis. In our data, higher potassium intake during the first days of life decreased the risk of PDA and BPD, which is, to our knowledge, a novel finding and needs further research in prospective settings. The mechanism mediating the effect of potassium is not possible to evaluate based on the present data. However, a hypothesis is that hypokalaemia might turn the smooth muscle cells of ductus arteriosus less excitable for contraction and thus hinder the closure of ductus arteriosus.

A strength of our study is the detailed data on the actual sodium and potassium intake of a large cohort of VLBW infants treated with current neonatological practices. The data enabled us to examine the sources of electrolyte intake separately and thus to identify hidden sources of sodium intake. Recent studies on sodium intake in preterm infants have focused on extremely low birthweight and extremely preterm infants. Our cohort of 951 infants consisted of 394 infants born with birthweight of less than 1000 g and 557 infants with birthweight of 1000–1499 g, enabling us to examine the electrolyte intake not only in the ELBW infants but in all VLBW infants. Furthermore, our study population covered a wide range of gestational ages at birth from 23 to 31 weeks.

The retrospective nature of our study is associated with some limitations. Not all the infants stayed in the NICU for the entire study period. Since the healthiest infants were transferred to lower-level units, a selection bias is possible. There were also some missing data due to software updates. In the analyses, we included only full 24-h periods, each starting at 14.00 hours, a point in time determined by our NICU’s clinical practice. This implies that the first hours of life were not always included, and the infants were of slightly different ages during the same 24-h periods. Unfortunately, we did not have reliable data on diuresis or urine sodium and potassium concentration. Since the ESPGHAN guideline on paediatric parenteral nutrition was revised in 2018, there have been some changes to NICU practices concerning fluid management after our study period. However, these new guidelines contained minor changes to the fluid intake recommendations, and the sodium intake in the most premature infants of our cohort exceeded also the new, more liberal guidelines.
5 | CONCLUSION

During the first week of life, sodium intake in the most premature infants exceeded the European guidelines. High sodium intake hinders physiological early postnatal weight loss and associates with increased morbidity. Sodium from saline flushes constituted a substantial proportion of sodium intake during the first week of life, an observation that should be considered in clinical practice.

AUTHOR CONTRIBUTIONS
Paulina M. Mäkelä: Conceptualization; writing – original draft; methodology; validation; visualization; software; formal analysis; data curation. Lotta Immeli: Writing – review and editing; data curation. Markus Leskinen: Data curation; writing – review and editing. Olli-Pekka Rinta-Koski: Data curation; writing – review and editing. Reijo Sund: Methodology; validation; writing – review and editing. Sture Andersson: Conceptualization; funding acquisition; writing – review and editing; supervision; project administration. Päivi Luukkainen: Supervision; writing – review and editing; conceptualization.

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CONFLICT OF INTEREST STATEMENT
The authors have no conflicts of interest to disclose.

ETHICAL APPROVAL
The study protocol was approved by the Ethics Committee of the Helsinki University Hospital. As all the data obtained were pseudonymized, informed consent was waived.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.