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ORIGINAL ARTICLE

Nutrition and Growth

Increased enteral lipid supplementation is not associated with weight gain in extremely preterm infants with sufficient energy intakes

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Abstract

Objectives: Practices for fortifying human milk vary among neonatal intensive care units (NICUs). It is unclear whether enteral energy intake above 140 kcal/kg/day with increased fat supplementation leads to greater weight gain in breastmilk-fed extremely preterm (EPT) infants.

Methods: Anthropometric and nutritional data were collected from clinical records for Swedish EPT infants born between gestational weeks 26 + 0 and 27 + 6. Included infants were treated at NICU A ($n = 17$) or NICU B ($n = 39$). The primary outcome was change in standard deviation (SD) scores (ΔSDS) for weight between postmenstrual weeks 29 + 0 and 34 + 0.

Results: At birth, the mean gestational age was 26.9 (±0.45 SD) weeks and the mean birthweight was 969 (±107 SD) g. Between postmenstrual weeks 29 + 0 and 33 + 6, the energy intake was significantly higher at NICU B: mean (SD) 149 (±14.9) versus 132 (±11.2) kcal/kg/day, $p \leq 0.001$. This was driven by a higher fat intake at NICU B: mean (SD) 7.97 (±1.05) versus 6.20 (±0.92) g/kg/day, $p \leq 0.001$, which in turn was explained by more liberal use of lipid supplements at NICU B. No significant differences were found in ΔSDS for weight, length or head circumference between the two NICUs.

Conclusions: Despite considerable differences in energy intake due to the use of enteral lipid supplements, our study showed no differences in ΔSDS for weight, length or head circumference. This may be due to limited fat absorption in infants already receiving adequate energy and fat, and poor absorption of fat from human donor milk.

KEYWORDS

breast milk, enteral nutrition, growth, human milk fortification

1 | INTRODUCTION

Nutrition plays a crucial role in the care of extremely preterm (EPT) infants, affecting their growth, overall illness severity and neurodevelopmental outcomes.[1–4] The most recent guidelines for enteral nutrition of preterm infants by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommend an energy intake of 115–140 kcal/kg/day.[5] This recommendation is intended to meet the needs of healthy, growing preterm infants. It is based on an assumed resting energy expenditure of 60–70 kcal/kg/day, the energy required for growth (weight gain of 17–20 g/kg/day) and the energy lost in stool. The upper recommended limit for enteral energy intake has been increased in the latest ESPGHAN recommendations, compared to 135 kcal/kg/day in their 2010 guidelines.[6] The American Society for Parenteral and Enteral

Nutrition recommends an enteral energy intake of 110–130 kcal/kg/day,[7,8] which is closer to the previous ESPGHAN guidelines.[6]

During the past two decades, much effort has been directed towards optimizing nutritional intake and avoiding malnutrition in preterm infants, thereby promoting better growth during the hospitalization.[9–11] Some preterm infants may not achieve sufficient weight gain despite receiving the recommended enteral energy intake. In these cases, increasing the energy intake is often suggested.[5] However, there is a lack of studies investigating whether an enteral energy intake above the normally recommended levels leads to better growth outcomes in this population. Also, nutritional practices are still very heterogeneous when comparing different regions, hospitals and sometimes even individual health care providers.[12] These variations can lead to inconsistencies in patient care.

Two Swedish neonatal intensive care units (NICUs) with differing practices regarding enteral energy intake in preterm infants were identified. The study utilized this 'natural experiment' to examine the association between different energy intakes and growth in EPT infants. The primary objective of the present study was to evaluate differences in weight gain in EPT infants (<28 gestational weeks) during the stable growth phase postmenstrual age (PMA) age 29–33 weeks, at the two NICUs. We hypothesized that the infants who received a higher enteral energy intake would show a greater weight gain during the study period.

What is Known?

- Nutrition plays a crucial role in the growth and neurodevelopment outcomes of infants born extremely preterm (EPT).
- Human milk fortification practices vary between hospitals in their practices and traditions.

What is New?

- No differences in growth were observed between infants treated at the two hospitals, despite a significant difference in energy intake between postmenstrual weeks 29 + 0 and 34 + 0.
- EPT infants may have limited absorption of enteral lipid supplements, especially when receiving donor human milk.

2 | METHODS

2.1 | Study population

The study population consisted of EPT infants treated at two Swedish NICUs (A and B). All live-born infants born between 26 + 0 and 27 + 6 gestational weeks + days that were treated at either of the two NICUs during the observed period between postmenstrual weeks 29 + 0 and 33 + 6 were included ($n = 74$).

The ranges of gestational age (GA) at birth and PMA for data collection, as well as exclusion criteria, were selected to achieve population-based cohorts of primarily enterally fed infants who were in the healthy growth phase.

The study included infants who were admitted to NICU A between August 2011 and April 2021, and to NICU B between September 2011 and December 2016.

The exclusion criteria were as follows: infants with chromosomal anomalies known to affect growth ($n = 1$); infants who were small for GA (SGA), defined as below −2 standard deviations (SD) in birth weight ($n = 10$), one of whom also had chromosomal anomalies known to affect growth; infants who underwent surgery for necrotizing enterocolitis ($n = 1$); and infants with parenteral fluid intake above one-third of the total fluid supply during the observed period between postmenstrual weeks 29 + 0 and 33 + 6 ($n = 8$) one of whom were also born SGA. In total, 56 infants were included in the analyses.

2.2 | Ethics

Acquisition of data from the neonatal period was approved by the Regional Ethical Review Board, Umeå University, Umeå, Sweden (Dnr 2017/294-32).

2.3 | Data collection

The study period for each patient was between postmenstrual weeks 29 + 0 and 33 + 6. Perinatal and neonatal data was retrospectively collected from clinical records and from the Swedish Neonatal Quality Register, including Apgar scores, diagnoses, neonatal morbidity and medical treatment.

Daily nutritional and anthropometric data were obtained from clinical records for the duration of the study period. Macronutrient intake from enteral fortifiers and supplements as well as from parenteral products were calculated based on product data supplied by the manufacturers.

The macronutrient content of breast milk, both mother's own milk (MOM) and donor human milk (DHM), was calculated based on breast milk analyses using mid-infrared spectrophotometry, performed every 1–2 weeks as part of the clinical routine. At NICU A, the analyses up until May 2018 were carried out at Eurofins

Steins Laboratory AB in Jönköping, Sweden, using MilkoScan 4000 (FOSS). After May 2018 at NICU A, and during the whole study period at NICU B, the analyses were done locally using MIRIS Human Milk Analyser (MIRIS AB). Clinically, the results are used for targeted fortification of breast milk. Nutrient calculations were performed using Nutrium software, which also stored the nutritional data (Nutrium AB).

Multinutrient human milk fortifiers (HMFs) were routinely used at both NICUs: Nutriprem (Nutricia®) in NICU A and PreNan FM 85 (Nestlé®) in NICU B. Separate fat, protein or carbohydrate supplements were used at the discretion of the attending physicians. The fat supplements Calogen (Nutricia®) and Liquigen (Nutricia®) were used in both NICUs. NICU B also used the protein/amino acid supplement Complete amino acid mix (Nutricia®) and energy supplements with carbohydrates Duocal (Nutricia®) and Resource Energy (Nestlé®).

All available anthropometric data was obtained from clinical records. Weights were usually measured daily, and lengths and head circumferences were measured weekly. Length was measured using a length board at NICU A and using tape measurer at NICU B. The standard Swedish growth reference for preterm infants was used to calculate SD scores (SDS).[13]

Growth was defined as change in SDS (ΔSDS) during the study period (PMA weeks 29 + 0 to 34 + 0) and was calculated for weight, length and head circumference separately. The *z*-score for weight, length and head circumference at Week 29 + 0 was subtracted from the respective *z*-score at Week 34 + 0 and the difference between the two constitutes the ΔSDS.

2.4 | Statistical analysis

Data were analysed using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp.). Parametric data were analysed using Student *T* test and nonparametric data were analysed using Mann–Whitney *U* test. A $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Population characteristics

The mean (±SD) GA at birth was 26.9 (±0.45) weeks and the mean birthweight was 969 (±107) g. There were no statistically significant baseline differences between the two NICUs in any of the baseline anthropometry variables or in GA at birth (Table 1). The mean (±SD) postnatal age at the start of the study period was 14.9 (±3.1) days and at the end of the period it was 49.9 (±3.1) days.

TABLE 1 Baseline characteristics in EPT infants born at two different NICUs in Sweden (NICU A and NICU B).

	NICU A *n* = 17 mean (SD)	NICU B *n* = 39 mean (SD)	*p*
GA at birth	26.94 (±0.60)	26.85 (±0.37)	0.495[b]
Birth weight (g)	940 (±83)	982 (±115)	0.180[b]
Birth weight (SDS)	−0.93 (±0.59)	−0.56 (±0.69)	0.065[b]
Birth length (cm)	35.4 (±1.7)	34.8 (±1.6)	0.266[b]
Birth length (SDS)	−1.10 (±1.28)	−1.41 (±1.14)	0.382[b]
Birth head circumference (cm)	25.4 (±1.0)	25.1 (±1.2)	0.370[b]
Birth head circumference (SDS)	−0.27 (±0.53)	−0.37 (±0.81)	0.634[b]
Sex, female	45%	49%	0.791[b]
Apgar at 1 min	4.53 (±2.39)[a]	5.41 (±2.38)	0.231[b]
Apgar at 5 min	6.47 (±2.23)[a]	7.33 (±1.97)	0.168[b]
Apgar at 10 min	7.73 (±2.31)[a]	8.67 (±1.40)	0.138[c]
Enteral fluid intake, mL/kg/day	157.8 (±17.89)	169.7 (±9.37)	0.002[b]
Parenteral fluid intake, mL/kg/day	6.9 (±14.19)	2.3 (±3.59)	0.061[b]
Parenteral nutrition during study period (part of fluid volume)	0.04 (±0.09)	0.01 (±0.02)	0.051[b]
Weight at week + day 29 + 0 PMA	−2.09 (±0.59)	−1.97 (±0.64)	0.488[b]

Abbreviations: EPT, extremely preterm; GA, gestational age; NICU, neonatal intensive care unit; PMA, postmenstrual age; SD, standard deviation; SDS; standard deviation score.

[a] *n* = 15 at NICU A.

[b] Student's *t* test.

[c] Mann–Whitney *U* test.

3.2 | Breast milk and nutrition

Macronutrient intakes are shown in Figure 1A. The mean energy intake during the study period was significantly higher at NICU B compared to NICU A: 149 (±14.9) versus 132 (±11.2) kcal/kg/day ($p < 0.001$). Also, the fat intake was significantly higher at NICU B: 7.97 (±1.05) versus 6.20 (±0.92) g/kg/day ($p < 0.001$). Protein and carbohydrate intakes were not significantly different between NICUs, see Figure 1A. The mean energy intake exceeded 135 kcal/kg/day in 80% at NICU B compared to 29% at NICU A ($p < 0.001$). The energy intake exceeded 160 kcal/kg/day in 28% at NICU B compared to in 6% of the infants at NICU A ($p = 0.021$).

All infants at both NICUs received multinutrient HMF during the observed period; however, more infants at the NICU B received additional fat

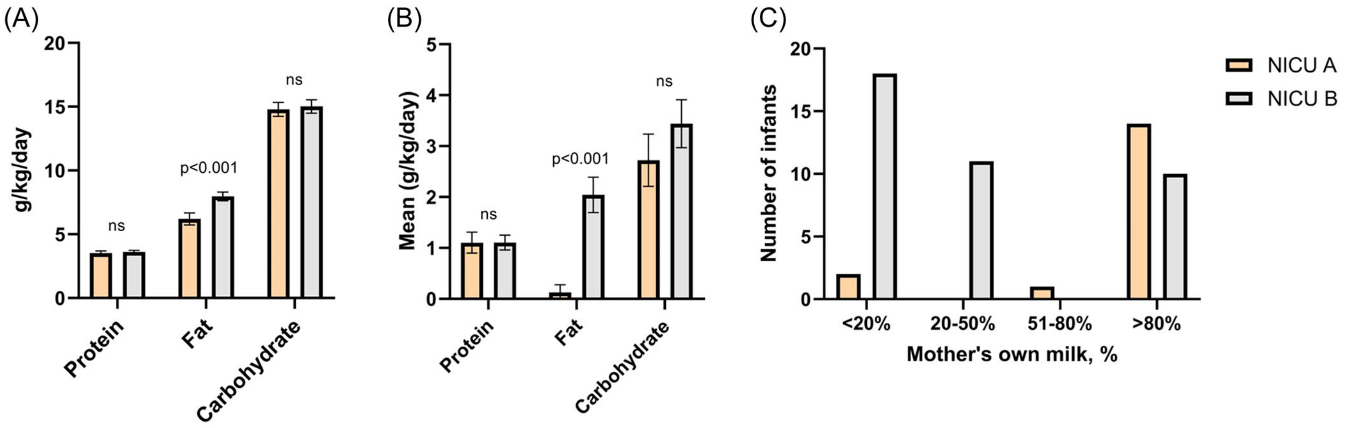

FIGURE 1 (A) Intake of enteral macronutrients during the observed period between week + day 29 + 0 to 33 + 6 PMA in extremely preterm infants at two different NICUs. (B) Macronutrients from multinutrient fortifiers and supplements during the study period between week + day 29 + 0 and 33 + 6 PMA in extremely preterm infants at two difference NICUs. (C) Percentage of given milk to extremely preterm infants that was mother's own milk during the observed period. NICU, neonatal intensive care unit; PMA, postmenstrual age.

supplements (100% at NICU B versus 24% at NICU A), resulting in a much higher intake of fat from supplements at NICU B, see Figure 1B. During the later weeks of the study period, small amounts of preterm formula was used at both NICUs. However, the energy intake from preterm formula accounted for only 0.72% of the total energy intake at both NICUs over the study period. The energy intake from parenteral nutrition accounted for 0.62% of the total energy intake at both NICUs during the study period.

MOM or DHM constituted the main diet for all infants at both NICUs during the study period. The infants at NICU A received significantly more MOM compared to the infants at NICU B (Figure 1C). The proportion of infants receiving ≥80% of their intake of breast milk as MOM was 26% at NICU B compared to 82% at NICU A ($p < 0.001$). Eleven infants received no MOM during the observed period, all treated at NICU B. There were no differences in protein or carbohydrate supplementation between the two groups receiving <50% of MOM compared with >50% of MOM (Supporting Information S1: Figure 1). However, the infants who received <50% of MOM were given significantly more fat supplements during the observed period compared to infants receiving more than 50% of MOM: 1.79 (±1.04) versus 1.06 (±1.43) g/kg/day ($p = 0.032$).

3.3 | Growth

There were no significant differences in the ΔSDS for weight, length or head circumference between NICU B and NICU A during the observed period (Table 2). Also, no significant differences in weight at Week 34 + 0 PMA was observed: 2022 (±214) g at NICU B versus 2058 (±349) g at NICU A ($p = 0.633$). There were no significant differences in the mean daily weight gain between NICU B and NICU A. NICU B had a mean daily weight gain of 17.6 (±2.6) g/kg/day, while NICU A had a mean daily weight gain of 18.3 (±3.1) g/kg/day ($p = 0.394$). There were no significant differences for length or head circumference at Week 34 + 0 PMA.

TABLE 2 Change in SDS during the observed period between PMA week + day 29 + 0 to 34 + 0.

ΔSDS	NICU A	NICU B	p[a]
Weight	0.76 (±0.46)	0.73 (±0.75)	0.875
Length	0.23 (±0.90)	−0.08 (±0.79)	0.208
Head circumference	0.48 (±0.54)	0.53 (±0.61)	0.795

Abbreviations: ΔSDS, change in standard deviation score; NICU, neonatal intensive care unit; PMA, postmenstrual age; SDS, standard deviation score.
[a]Student's *t* test.

The infants who received >50% of their breast milk as MOM, regardless of which NICU they were treated at, had a significantly higher ΔSDS in weight during the observed period: 0.96 (±0.66) versus 0.56 (±0.64), $p = 0.025$. There were no significant differences in ΔSDS for length or head circumference.

In a multivariable regression model with the dependent variable ΔSDS for weight, the percentage of MOM and the total number of days in continuous positive airway pressure (CPAP) were the only variables that were significantly associated with growth, Table 3. The model also included the variables hospital, energy intake and energy from multinutrient HMF and supplements.

3.4 | Postnatal morbidities

The infants treated at NICU A were treated significantly more days in CPAP: 27.9 (±9.5) days at NICU B in

TABLE 3 Results of the multivariable regression analysis with the ΔSDS for weight as the dependent variable.

Variable	Unstandardized coefficients		Standardized coefficient	t	p	Collinearity statistics	
	β	SE	β			Tolerance	VIF
Percentage of MOM	0.542	0.201	0.347	2.690	0.010	0.949	1.054
Days on CPAP	−0.015	0.007	−0.299	−2.314	0.025	0.949	1.054

Abbreviations: ΔSDS, change in standard deviation score; CPAP, continuous positive airway pressure; HMF, human milk fortifier; MOM, mother's own milk; SE, standard error; VIF, variance inflation factor.

Variables not included in the model: hospital, energy intake and energy from multinutrient HMF and supplements.

CPAP versus 45.5 (±11.5) days at NICU A, $p < 0.001$. The number of infants treated in mechanical ventilation at some point during the admission was 39% at NICU B and 59% at NICU A. There was no statistically significant difference in the incidence of severe bronchopulmonary dysplasia between NICU B and NICU A (2.6% vs. 0%, $p = 0.479$). No infants were treated with systemic corticosteroids at either NICU.

4 | DISCUSSION

Although infants at NICU B had a significantly higher mean energy intake of 149 kcal/kg/day compared to 132 kcal/kg/day at NICU A, there were no significant differences in ΔSDS for weight, length or head circumference between the two NICUs between Weeks 29 + 0 and 33 + 6 PMA. The difference in energy intake was driven by a higher intake of enteral fat supplements at NICU B. Infants treated at NICU B received significantly less of MOM (and thus more of DHM) than infants treated at NICU A.

The recommended energy intake from enteral nutrition at the time of the present study was 110–135 kcal/kg/day.[6] However, in the most recent ESPGHAN guidelines, the recommendation for adequate energy intake is 115–140 kcal/kg/day.[5] In cases of poor weight gain, it is suggested to increase energy intake up to 160 kcal/kg/day.[5] Infants at both NICUs met the recommended energy intake. The mean energy intake at NICU B exceeded the recommended upper limit by either 14 or 9 kcal/kg/day, depending on the version of the recommendations being compared.[5,6]

Despite the considerable difference in energy intake between the groups, there were no differences in the SDS for weight at either 29 + 0 weeks PMA or 33 + 6 weeks PMA, or in ΔSDS for weight during the observed period. This finding is noteworthy for its implications on the relationship between energy intake and weight gain. One possible explanation for this is an upper limit of fat absorption in the immature gut of these EPT infants. About half of the infants at NICU B received more than 8 g/kg/day of dietary fat, while the upper recommended limit of enteral fat intake is 8.1 g/kg/d.[5] Our results are supported by the only randomized intervention study we can identify published by Polberger et al.[14] in 1989. They studied growth rates and daily nutrient intake in four groups of very low birth weight infants that were fed varying feeding regimens. The energy intake varied from ~110 to 133 kcal/kg/day, protein intake from 2.1 to 3.6 g/kg/day and fat intake varying from 5.7 to 7.8 g/kg/day. The improved growth observed between the groups was only attributed to differing protein supplementation, whereas lipid supplementation was found to have no influence on the growth rate. The results from Polberger et al.[14] are used as the basis for the Cochrane review by Amissah et al.[15] on fat supplementation of human milk for promoting growth in preterm infants. Amissah et al.[15] concluded that the lack of high-quality evidence on the effects of fat supplementation in this population prevented them from making recommendations for practice. They also state that, to their knowledge, there are no other previous systematic reviews on this topic other than their own in 2000, which also included the same single randomized controlled trial.[16]

We found a difference between the NICUs regarding the amount of MOM that the infants received, where the infants at NICU A received more of MOM. In Sweden, MOM is not pasteurized but it is clinical practice to pasteurize all DHM, due to the risk of transmission of pathogens. During the process of pasteurization, the bile salt-stimulated lipase (BSSL) in breast milk is inactivated.[17] A Swedish study has shown that preterm infants fed pasteurized DHM had a lower absorption of fat and slower growth than infants fed MOM.[18] In the present study, this may explain why the infants at NICU B did not grow significantly better, despite the substantially higher intake of fat due to receiving more pasteurized DHM than the infants at NICU A. The study by Polberger et al.[14] only used nonpasteurized human milk, regardless of whether it was MOM or DHM.

Our results support those of Lund et al.,[19] who found statistically significant associations on weight gain and growth of head circumference with the intake of MOM, but no association between DHM and growth. Similar to our study, Lund et al.[19] examined EPT infants, but only until 32 weeks PMA. The positive effect of MOM on growth in comparison to DHM can possibly be attributed to the presence of active BSSL in MOM as well as other bioactive components in unpasteurized breast milk including hormones, insulin-like growth factor-1 and cytokines.[20,21]

The incidence of respiratory morbidity varied between the NICUs, with infants at NICU A treated more days in CPAP and mechanical ventilation. This difference between the NICUs in CPAP use may partly be explained by differences in local practice regarding CPAP, it has been shown that some parts of Sweden have more liberal CPAP use compared to other parts of Sweden.[22] Furthermore, NICU A is serving a greater geographical area and thus more likely to discharge the healthier infants to their local hospitals earlier. However, although there was a difference in respiratory morbidity incidence at NICU A and higher energy intake at NICU B, there was no significant difference in the ΔSDS for weight. Our hypothesis was that infants who received a higher energy intake would experience greater weight gain during the stable growth phase between 29 + 0 and 33 + 0 weeks PMA. If there was a difference in energy expenditure, the infants at NICU A would probably have had a higher energy expenditure, given that they received more respiratory care in CPAP and mechanical ventilation. Therefore, it is noteworthy that the infants at NICU B did not exhibit better growth than those at NICU A.

In a study published in 2021, Rochow et al.[23] compared infants receiving standard fortification with those receiving targeted fortification, with the primary outcome being weight gain during the first 21 days of the intervention. The infants were similar in PMA to the infants in our study, with a mean GA of 27.1 weeks and at the start of the intervention they were on average 30 + 4 weeks PMA. Thus, at the end of the intervention they were very similar in age to the infants included in our study. The control group in Rochow's study received 121 (±10) kcal/kg/day compared to the intervention group that received 140 (±10) kcal/kg/day, which are strikingly similar numbers to our present study. However, Rochow et al.[23] found that the infants in the intervention group had a significantly higher weight gain during the study period, 21.2 (±2.5) versus 19.3 (±2.5) g/kg/day in mean. In our present study we found no significant difference in weight gain between the two NICUs, with a mean daily weight gain of 17.6 (±2.6) at NICU B versus 18.3 (±3.1) g/kg/day at NICU A. The differences in the results compared to our study could be explained by the fact that the difference in energy intake in the Rochow study was not only due to the higher fat intake, but both carbohydrates ($p < 0.001$) and protein ($p < 0.001$) were also significantly higher in the intervention group. However, no data on the percentage of MOM versus DHM intake was presented in that study, hindering further comparisons.

The strengths of this study include high-quality data derived from hospital records and the Swedish Neonatal Quality Register. Nutritional data was collected daily for all infants during the observed period. The anthropometric measurements were carried out by trained staff in the NICUs during the standard care, with almost daily weight measurements and weekly length and head circumference measures. Although, the relatively long inclusion time and few infants included in this study, we could see significant differences in energy and fat intake between the NICUs. It was found that there was a difference in respiratory morbidity between the NICUs, which is a limitation.

5 | CONCLUSIONS

Despite considerable differences in energy intake due to the use of enteral lipid supplements, our study showed no differences in ΔSDS for weight, length, or head circumference between Week 29 + 0 and Week 33 + 6 PMA at two Swedish NICUs. A possible explanation for this discrepancy between energy intake and growth was the fact that the infants' receiving more energy and fat also received significantly less of MOM. We conclude that enteral lipid supplements may have limited absorption especially in infants receiving DHM, and that feeding of MOM to EPT infants should be promoted.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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

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