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Effect of early nutritional intake on long-term growth and bone mineralization of former very low birth weight infants

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ABSTRACT

Background: Preterm infants are at risk for impaired bone mineralization and growth in length later in life due to inadequate nutritional intake in the early postnatal period.
Objective: To investigate whether increased nutritional supplementation of calcium, phosphate and protein in Very Low Birth Weight (VLBW) infants during the first 14 days after birth was associated with improvement in length and bone development until 9–10 years of age.
Design: Observational follow-up study of VLBW infants (birth weight < 1500 g or gestational age < 32 weeks) born in two consecutive years (eligible infants: 2004 n: 63 and 2005: n: 66). Cohort 2005 received higher intake of calcium, phosphate and protein with parenteral nutrition compared to Cohort 2004. Anthropometric data were collected during standard follow-up visits until five years, and additionally at 9–10 years of age including measurements of bone mineral content, bone mineral density of the whole body and lumbar spine determined by dual-energy X-ray absorptiometry. Long-term growth trajectories of both cohorts were evaluated separately for participants born appropriate (AGA) and small for gestational age (SGA), stratified by gender. Multivariate linear regression was used to examine the effect of nutritional intake and clinical covariates on length and bone mineralization.
Results: Both cohorts achieved a catch-up in length to SDS within the normal range by 6 months (length SDS: estimated mean (95% confidence interval (CI): 6 months: Cohort 2004: −0.7 (−1.1, −0.3) Cohort 2005: −0.5 (−0.8, −0.2)). Bone mineral content and density were within the normal range and not different between the cohorts. SGA children achieved a catch-up in length at 5 years with bone mineralization comparable to AGA children. Only for girls birth weight was significantly associated with length SDS (per gram: β 0.001; 95% CI (0.000, 0.003); $p = 0.03$) There was no evidence of an association between early nutritional intake and bone mineralization.
Conclusion: Children born as appropriate or small for gestational age preterm infants are able to catch up in length after the postnatal period, and achieve a normal length and bone mineralization at age nine–ten years. An improvement of calcium and phosphate intake during the first 14 days after birth was not associated with improvement in length and bone development.
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1. Introduction

Achieving growth and development comparable to healthy term born infants has been a challenge for the treatment of preterm born infants for many decades [1]. As the survival of Very Low Birth Weight (VLBW) infants has increased significantly during the last years, it is important to evaluate their long-term outcomes, especially since recommendations and policies with regard to nutritional intake have been changed to improve postnatal growth [2–4].

Abbreviations: AGA, appropriate for gestational age; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; BW, birth weight; DEXA, dual energy X-ray absorptiometry; GA, gestational age; LS, Lumbar spine scan; SDS, standard deviation score; TCA, term corrected age; SGA, small for gestational age; VLBW, Very Low Birth Weight infants; WB, Whole body scan.

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While early cohort studies demonstrated that VLBW infants experienced a significant growth retardation during the early postnatal period without catch-up to the initial birth percentile, more recent studies showed that improvement of early nutritional intake diminishes the cumulative nutritional deficit and thereby may prevent growth retardation [5–7]. Growth and skeletal development seem to be closely related [8–10]. Adequate bone mineralization is necessary for optimal development of the bones [11–13]. Given the difficulties associated with meeting the nutritional needs of VLBW infants and to provide sufficient nutritional supply of minerals, VLBW infants are especially at risk of impaired bone mineral content [14–17]. While early studies showed that exclusive feeding of human milk in preterm infants leads to deficiencies of calcium and phosphate, it is nowadays generally recommended to fortify human milk with additional minerals, protein and vitamins [18–20]. Furthermore, parenteral supplementation of calcium and phosphate has been improved through the inclusion of organic phosphate in parenteral nutrition (PN) [21].

Only a few studies have evaluated long-term bone development of VLBW children until childhood and adolescence [22–30]. Their findings were diverse but most of the studies showed that these former preterm infants remained smaller later in life, some with lower bone mineralization, others with low mineralization but normal in proportion to their small body size. Several studies found impaired bone mineral content in boys compared to girls [22,31]. Despite the low content of minerals, human milk seemed to have a positive effect on bone development [32,33]. All of the participants of these studies received diets that provided nutrients markedly below the current recommendations and therefore the results may not be representative for the population of preterm infants treated nowadays. A more recent randomized trial in VLBW infants found a positive effect of post- discharge feeding on BMC in comparison to human milk and term formula at the corrected age of 6 months, irrespective of gain in weight and length [34].

Previously we reported the short-term outcome results for two consecutive year-cohorts of VLBW infants that differed with regard to the nutritional intake during the first two weeks of life [35]. The second cohort received a higher intake of protein, energy as well as calcium and phosphate and this was associated with improved weight gain during the early postnatal period and at the corrected age of two years there was a tendency of improved growth in length. A secondary analysis revealed that this was mainly based on improvement in boys. Small for gestational age (SGA) infants had a higher postnatal weight gain than appropriate for gestational age (AGA) born infants [35]. For the current study we describe the long-term growth in length for the surviving infants of the original cohorts and analyze the effect of the postnatal nutritional intake on length and bone mineralization at the of age 9 to 10 years. We hypothesized that increased nutritional intake would lead to improved length and bone mineralization.

2. Methods

2.1. Study population and design

This observational follow-up study evaluated the long-term outcomes of growth and bone mineralization of a previously described prospective cohort study that was conducted in 2004 and 2005, in order to evaluate changes in the composition of parenteral nutrition (PN) [35,36]. Surviving participants of both cohorts who were eligible for the standard follow-up schedule provided to VLBW infants born prior to 32 weeks of gestation, or those with a birth weight below 1500 g were included in the study. (Eligible children: Cohort 2004: $n = 63$; Cohort 2005: $n = 66$). These children were invited for an additional outpatient clinic visit that included an evaluation of bone mineralization by dual energy X-ray absorptiometry (DEXA). The parents of all participants provided written informed consent for the additional investigation. The study was approved by the local ethics committee (2013/594) and registered within the Dutch Trial Registry (NTR = TC4842).

In accordance with the standard follow-up program, growth and general health status were recorded at the corrected ages of six months, and 1, 2 and 5 years. For the current study, we extended the follow-up by inviting children who were previously seen during the national follow-up program to return for further testing around the ages of nine and 10 years.

2.2. Nutritional protocol

The 2004 and 2005 cohorts included preterm infants admitted to the level III neonatal intensive care unit (Radboud University Medical Center, The Netherlands) on the first day of life after it was estimated that parenteral nutrition would be needed for at least 5 days. Infants with major congenital malformations or asphyxia were excluded. The nutritional protocols for the two cohorts primarily differed in terms of the parenteral nutritional intake with higher amounts of protein, calcium and phosphate provided to the 2005 Cohort. (Table 1) Following the recommendation of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition the 2005 PN provided 3 mmol per kg per day of calcium and 1.92 mmol per kg per day of glycerophosphate [4,37]. According to the nutritional protocol of 2005, full PN was achieved four days following birth, while the maximum amount of PN in Cohort 2004 was achieved later, at day six. For both cohorts, enteral feeding was started on the first day of life and human milk was enriched with a commercially available fortifier (HMF) (Nutrilon Nenatal BMF, Nutricia, Zoetermeer, The Netherlands) from an intake of 50 ml per day onwards. HMF added 1.6 mmol/dL of calcium and 1.95 mmol/dL of phosphate. If human milk was not available, infants received a preterm formula (Nutrilon Nenatal Start, Nutricia, Zoetermeer, The Netherlands). The formula contained 2.5 mmol per dL of calcium and 1.6 mmol per dL of phosphate and 200 IE per dL of Vitamin D. The full nutritional protocol has previously been described in detail [35,36]. No major changes in clinical practice occurred and all infants received nutrition according to standard institutional protocols.

2.3. Anthropometric measurements and questionnaire

At the last visit length and weight were determined, and the health condition evaluated using a questionnaire. We specifically focused on morbidities and the use of medication that could have affected growth and bone mineralization, for example corticosteroids, asthma and fractures. For the preceding follow-up visits anthropometric measurements

Table 1
Parenteral nutritional intake.

		D0	D1	D2	D3	D4	D5	D6
2004	Fluid ml/kg/d	60	80	100	120	140	160	180
	CH g/kg/d	4.9	5.9	6.8	7.8	8.83	11.7	13.7
	AA g/kg/d	0.5	1	1.5	2	2.25	2.5	2.5
	Lipids g/kg/d	0.5	1	1.5	2	2.5	3	3
	EQ kcal/kg/d	26	37	47	57	67	86	92
	Ca mmol/kg/d	0.17	0.17	0.33	0.50	0.66	0.83	1.08
	P mmol/kg/d	0.04	0.04	0.08	0.12	0.16	0.20	0.26
2005	Fluid ml/kg/d	80	100	125	150	150	150	150–180
	CH g/kg/d	8	9.6	11.7	13.8	13.8	13.8	13.8–16.8
	AA g/kg/d	0.75	1.5	2.25	3	3	3	3
	Lipids g/kg/d	–	1	2	3	3	3	3
	EQ kcal/kg/d	35	53	74	94	94	94	94–106
	Ca mmol/kg/d	0.75	1.5	2.25	3.00	3.00	3.00	3.00
	P mmol/kg/d	0.48	0.96	1.44	1.92	1.92	1.92	1.92

Standard protocol for parenteral nutrition of Cohort 2004 and Cohort 2005 with different standardized parenteral solutions. CH: carbohydrates; AA: amino acid; EQ: energy quotient. Ca: calcium; P: phosphateThe parenteral nutrition consisted of two standard prepared components, a mixture of amino acids/glucose/minerals and lipid emulsion plus vitamins. Amino acid solutions and lipid emulsion: Cohort 2004: Aminovenos N paed 10% (Fresenius Kabi), Intralipid 20% (Fresenius Kabi), Ca gluconate 10% (Braun Melsungen), Potassium phosphate (Braun melsungen) Cohort 2005: Primene (Clintec, Brussels), Intralipid 30% (Fresenius Kabi) Ca gluconate 10% (Braun Melsungen), Sodium-glycerophosphate (Glycophos; Fresenius Kabi).

were collected either from the patient charts or requested from the local paediatric out-patient clinics specifically for measurements at term corrected age (TCA). Body weight was measured to the nearest 0.1 kg using an electronic digital scale (SECA MOD701) and body height to the nearest 0.1 cm by a wall-tapered height meter (SECA MOD240).

2.4. Dual energy X-ray absorptiometry

Bone mineralization of the whole body and lumbar spine (L1-L4) was evaluated using dual energy X-ray absorptiometry (QDR Discovery A 85606, Hologic, Inc., USA) (DEXA). The measurements of this DEXA-scan were analyzed using the APEX system software version 13.3. The DEXA estimated the bone mass at the measurement site as Bone Mineral Content (BMC) in grams. Bone Mineral Density (BMD) is an aerial measurement and was recorded as grams per square centimeter. BMC and BMD were measured for the Whole Body (WB) and the Lumbar Spine (LS). For both sites, the BMD standard deviation scores (SDS) were calculated. The SDS of the WB were based on the reference data of the National Health and Nutrition Examination Survey (NHANES 2008) [38], while the SDS of the LS were based on reference data from the Bone Mineral Density in Childhood Study (BMDCS) [39]

2.5. Data handling

Patient characteristics including growth, clinical course and intake of all nutrients via both parenteral nutrition and enteral feeding were recorded daily for the first two weeks, and then weekly until week five, as described previously [35]. The amounts of daily intake of all nutrients

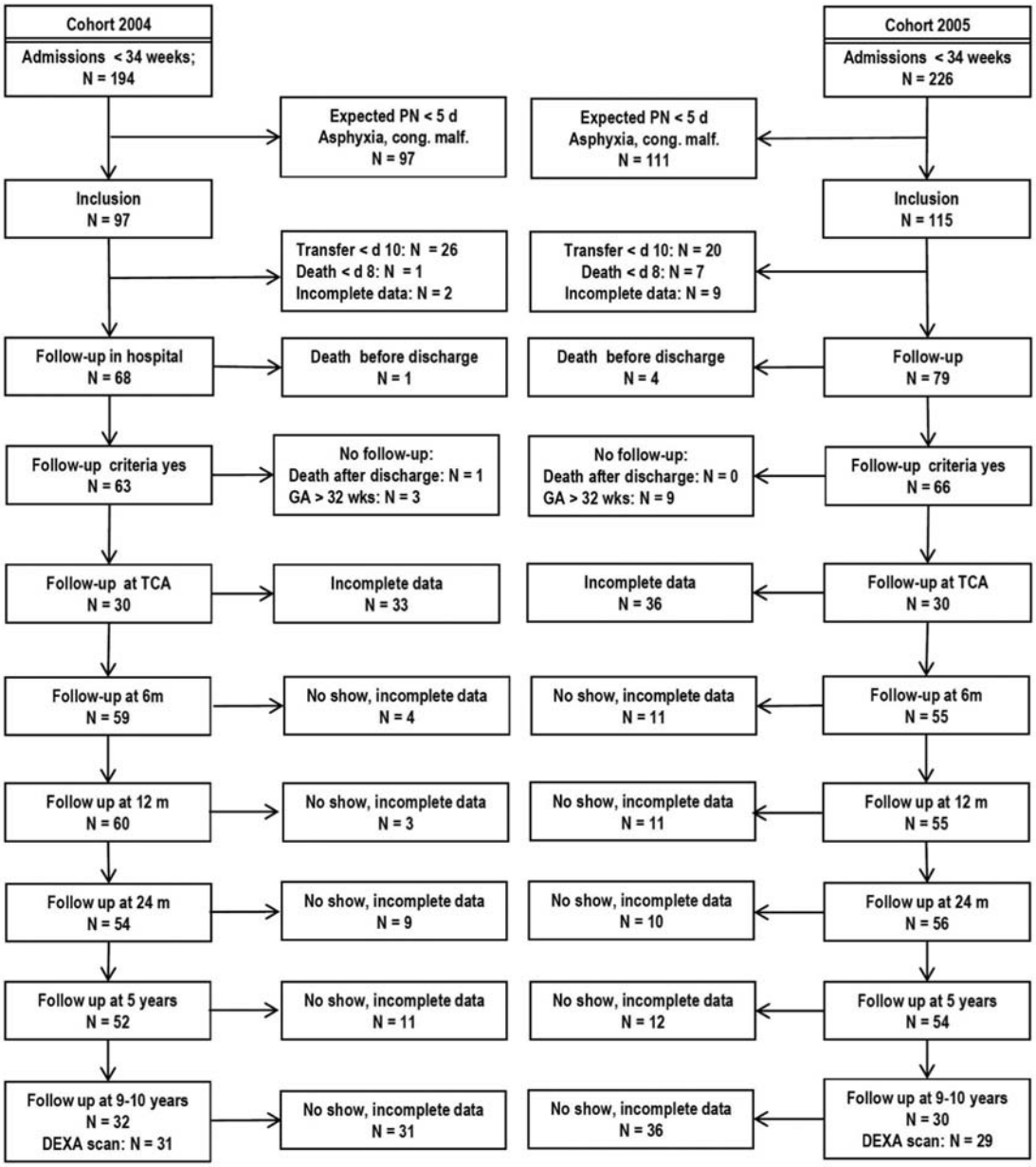

Fig. 1. Consort diagram. Legend: N: number of patients; TCA: Term corrected age; 6 m: six months, 12 m: 12 months, 24 m; 24 months, incomplete data: missing data with regard to weight or length.

were calculated for each patient. From term age onwards the SDS were calculated for length and BMI using the Dutch reference of the nationwide growth study [40,41]. A birth weight below the 10th percentile of the Dutch reference curves for birth weight by gestational age was defined as small for gestational age (SGA). A birth weight above the 10th percentile was defined as appropriate for gestational age (AGA) [42]. Differences in patient characteristics between responders and non-responders at corrected age of 5 years and at nine to 10 years are presented in the Supplementary materials. (Table 5a, Table 5b, Table 6a, Table 6b).

2.6. Statistical analysis

The required sample size was not estimated for the current study as the study involved the follow-up of surviving children who were included in the original two cohorts and fulfilled the criteria for standard follow-up. The average length at each time point was estimated separately for the 2004 and 2005 cohorts, as well as for the subgroups of SGA/AGA at birth and gender within the cohorts. Age related differences in growth and bone mineralization were accounted for by using age and gender specific standard deviation scores. Associations between nutritional intake and the outcomes of length SDS, whole body and lumbar spine BMD and BMD SDS at 9–10 years of age were examined using multivariable linear regression for all eligible children and separately for boys and girls. As potential confounders of cohort, sex, gestational age, birth weight, SGA/AGA status, and use of corticosteroids at 5 years of age were included as covariates in the analyses. Models were also conducted for males and females combined.

Not all children who were eligible for follow-up had data collected at each time point (Fig. 1). Missing data were handled using multiple imputation. We generated 100 imputed datasets using the method of chained equations. [43]. The imputation model included length at each time point, BMD and BMD SDS measurements for whole body and lumbar spine, and the full set of nutrition variables and potential confounders included in the regression models. All estimates were obtained by averaging results across the 100 imputed datasets with inferences under multiple imputation obtained using Rubin's rules [44]. Statistical analyses were conducted using Stata Corp (2015). Stata Statistical Software: Release 14. StataCorp LP,: College Station, TX and IBM SPSS statistics, version 22 for Windows (IBM SPSS Inc., IL, USA).

Table 2
Patient characteristics at 9–10 years.

	Cohort 2004	Cohort 2005
Numbers	32	30
Sex (boy/girl), n	18/14	15/15
Exact age, years	10.3 (0.3)	9.5 (0.3)*
Postnatal characteristics		
Gestational age, weeks,	29.4 (1.9)	29.4 (1.4)
Appropriate/small for gestational age, n	29/3	27/3
Birth weight, grams	1182 (254)	1160 (328)
Birth weight SDS	0.2 (1.0)	0.04 (1.1)
GV week 1–5, gram/kg/day	8.6 (2.6)	11.1 (2.8)*
Nutrition		
PN days, median (IQR)	26.0 (14.0–38.8)	10 (8.0–16.0)*
Phosphate, mmol/kg/14 days	16.0 (8.8)	35.7 (9.3)*
Calcium, mmol/kg/14 days	22.6 (10.1)	40.9 (7.4)*
Protein, grams/kg/14 days	35.3 (7.7)	41.6 (6.2)*
Energy, kcal/kg/14 days	1185 (238)	1403 (205)*
Growth		
Weight, kg	32.2 (5.6)	30.2 (5.5)
Length, cm	141 (6)	137 (5)*
BMI	16.1 (2.2)	16.0 (2.5)
SDS length	−0.6 (0.9)	−0.5 (0.7)
SDS BMI	−0.4 (1.2)	−0.2 (1.2)

Data presented as mean (SD); SDS: standard deviation score; GV: growth velocity from postnatal week 1 until week 5 according to Patel's formula [58]; PN days: number of days of parenteral nutrition; BMI: body mass index.
* p-value <0.01.

3. Results

3.1. Cohort description

3.1.1. Recruitment

Fig. 1 presents the number of children for whom length could be measured. Two infants in the 2004 cohort and four infants in the 2005 cohort had died before discharge, while three and nine infants of the respective cohorts did not fulfill the criteria for the follow-up program, thus 63 and 66 children of 2004 and 2005 respectively were eligible for the current analysis. Since the national follow up program aimed at the evaluation of health care and had a more scientific character, participation was voluntary, thereby not all parents followed the invitation and a varying number of children were seen over the time period. At term corrected age, measurements of length were available for about half of the participant sample. At the age of five years, 52 (83%) and 54 (82%) children were seen in the 2004 and 2005 cohorts respectively. Finally, at 9–10 years of age, growth was evaluated for 32 and 30 children, and bone mineralization in 31 and 29 children (49 and 43%) of the 2004 and 2005 cohorts respectively.

3.1.2. Characteristics and morbidity

Table 2 presents the characteristics of the children of both cohorts seen at 9–10 years of age. The postnatal characteristics of the children were similar between the cohorts. However, SGA born children of both cohorts had a higher gestational age at birth and a significantly lower birth weight compared to their respective AGA group. Cohort 2005 also had a significant higher weight gain during the first five weeks. With the exception of AGA/SGA status, patient characteristics of those who responded to the invitation for further follow-up at 9–10 years were similar to those for the full cohort. Comparisons of the characteristics of responders and non-responders at five years of age, and at 9–10 years are provided in Tables 5a and 5b and tables 6a and 6b in the Supplementary materials.

In agreement with the original full sample postnatal cohorts, children of Cohort 2005 seen at the follow-up, had received a significant higher amount of calcium, phosphate, protein and energy during the first 14 days of life, with a shorter duration of parenteral nutrition, compared to cohort 2004. (Table 2) AGA born children of Cohort 2005 also had a greater weight gain during the first five weeks of life compared to children of Cohort 2004, which was significant for the AGA boys, while all SGA infants demonstrated the highest weight gain [35,45]. Since children of both cohorts differed by one year of age at the last visit, the mean length and BMI of cohort 2004 were higher. For both groups the respective SDS were within the normal range for the Dutch reference population. More than one third of the children in both cohorts reported bronchial hyper reactivity including the use of medication, while 22% in Cohort 2004 and 14% Cohort 2005 reported to have had at least one incident with bone fractures. These incidences and the use of other medication were similar between both cohorts. None of the children received growth hormone therapy.

3.2. Length and bone mineralization

3.2.1. Longitudinal development of length and BMI

Fig. 2 presents the estimation of change in length SDS from TCA until 9–10 years after multiple imputation. Both cohorts were severely growth retarded by the time they had reached term corrected age (TCA) (SDS length: estimated mean (95% CI) TCA: Cohort 2004 versus Cohort 2005: −3.0 (−3.8, −2.2) vs. −3.0 (−3.7, −2.2)). Both cohorts showed a catch-up in length within the first 6 months with an improvement in mean SDS up to the normal range for the reference population (SDS length: estimated mean (95% CI) 6 months: Cohort 2004: −0.7

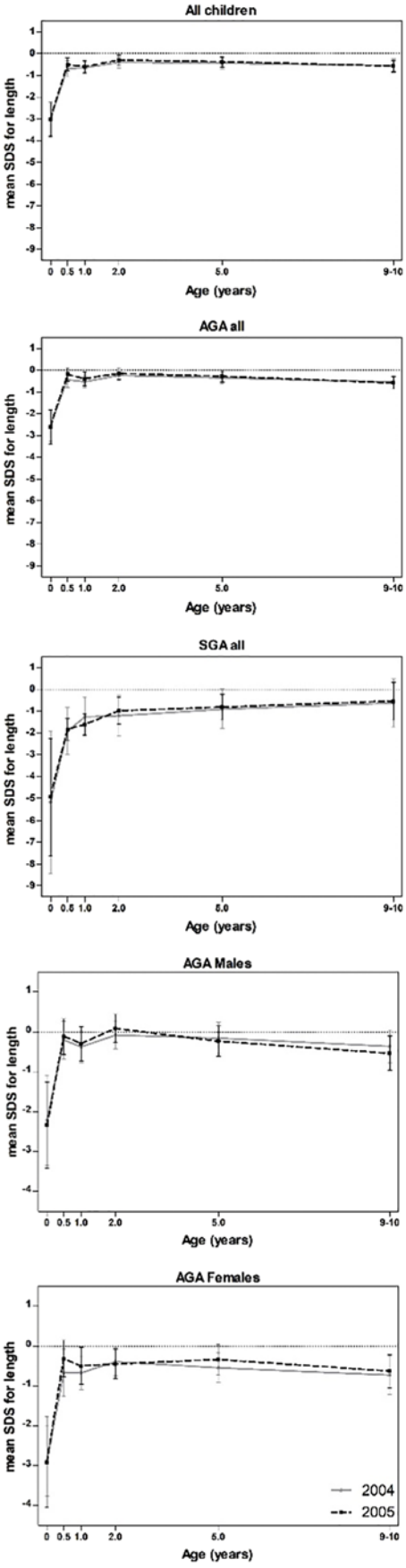

Fig. 2. Follow up in length SDS. Legend: Follow up of length SDS, by cohort and AGA/SGA status. AGA: appropriate for gestational age at birth; SGA: small for gestational age at birth; SDS: standard deviation scores; bars represent estimates of the mean and 95% confidence intervals; Zero reflects term corrected age; The analysis represents the full sample of children who were eligible for standard follow up.

Table 3
Bone mineralization at 9–10 years.

	Boys		Girls	
Appropriate for gestational age				
	2004 ($n = 17$)	2005 ($n = 12$)	2004 ($n = 11$)	2005 ($n = 14$)
Exact age, years	10.3 (0.3)	9.5 (0.26)	10.5 (0.3)	9.5 (0.3)
Whole body				
BMC g	1208.8 (156.1)	1042.7 (117.6)	1103.7 (132.1)	1096.4 (146.7)
BMD g/cm^2	0.882 (0.06)	0.831 (0.05)	0.843 (0.07)	0.834 (0.07)
BMD SDS	0.73 (1.09)	0.19 (0.84)	−0.2 (1.0)	0.49 (0.95)
Lumbar spine				
BMC g	25.6 (4.9)	22.3 (3.5)	25.1 (4.5)	24.1 (4.0)
BMD g/cm^2	0.606 (0.08)	0.548 (0.09)	0.608 (0.06)	0.616 (0.09)
BMD SDS	0.06 (0.08)	−0.64 (1.31)	−0.37 (0.74)	0.17 (1.15)
Small for gestational age				
	2004 ($n = 0$)	2005 ($n = 2$)	2004 ($n = 3$)	2005 ($n = 1$)
Exact age, years		9.7 (0.16)	10.2 (0.37)	9.6
Whole body				
BMC g		1106.0 (32.9)	1173.2 (151.9)	1159.0
BMD g/cm^2		0.829 (0.033)	0.857 (0.08)	0.874
BMD SDS		0.05 (0.63)	0.40 (0.98)	1.00
Lumbar spine				
BMC g		23.5 (2.1)	26.7	25.8
BMD g/cm^2		0.574 (0.047)	0.677 (0.04)	0.722
BMD SDS		−0.25 (0.64)	0.67 (0.23)	1.5

Data presented as mean (SD); SDS: standard deviation score; BMC: bone mineral content; BMD: bone mineral density.

(−1.1, −0.3) Cohort 2005: −0.5 (−0.8, −0.2)). Children of Cohort 2005 seemed to have slightly improved length SDS compared to Cohort 2004 until the age of two years. This was more pronounced for the group of children born as AGA and specifically for the AGA girls at five years. The group of AGA boys of Cohort 2005 showed a decrease in length SDS from two years onwards and remained below the SDS of AGA boys of Cohort 2004. The SGA groups did not achieve a normal length at corrected age of six months but in contrast to AGA children continuously improved their SDS for length until the end of the observational period reaching the normal range for the reference population.

BMI developed in the same manner as the length with a major catch-up during the first six months. There were no differences seen between both cohorts or among subgroups of AGA and SGA children. For the group of SGA children SDS BMI developed within the same range as SDS length with mean lower values.

3.2.2. Bone development

The results of the Whole Body (WB) and Lumbar spine (LS) scan for the sub-groups of both cohorts are presented in Table 3. Comparing the total cohorts, the mean bone mineral content (BMC) of both, WB and LS, tended to be higher for Cohort 2004 ($n = 31$), which is likely to be related to the average younger age and lower weight of Cohort 2005 ($n = 29$). The mean whole body BMC of Cohort 2004 was on average 90.0 g higher compared to Cohort 2005 (95% confidence interval (CI): (8.1, 161.8); p-value = 0.015). The mean whole body BMD only differed by 0.032 g/cm^2 (95% CI: (0.00, 0.06); p-value = 0.049). The mean lumbar spine BMC and BMD were only slightly higher for Cohort 2004

compared to 2005 respectively, with 2.1 g (95% CI: (0.05, 4.3); *p*-value = 0.045) and 0.026 g/cm^2(95% CI: (−0.02,0.07); *p*-value = 0.230). While the differences for the lumbar spine were relatively small, the more relevant age dependent mean BMD SDS for both measurement sites were similar between both cohorts and within the normal range for the reference population (2004 versus 2005: mean WB BMD SDS 0.43 vs. 0.35 (mean diff: 0.08; 95% CI: (−0.43, 0.58); *p*-value = 0.75); mean LS BMD SDS −0.036 vs. −0.15 (mean diff: 0.11; 95% CI: (−0.48, 0.71); *p*-value = 0.70).

The evaluation of subgroups of children (Table 3) showed that the lower bone mineral content (WB and LS) of Cohort 2005 was specifically associated with a lower mean BMC of AGA boys of 2005, while in contrast the mean BMC of AGA girls of 2005 nearly attained the same amount as the respective subgroup of 2004. Thus, of Cohort 2005, girls had a non-significant higher BMC than boys despite a comparable body weight. This was also seen for the BMD. The subgroup of SGA girls was found to have the highest BMC and BMD compared to all other subgroups.

3.2.3. The effect of early nutrition on length and bone mineralization

Table 4 presents the results of the adjusted associations between nutritional intake during the first 14 days of life, clinical characteristics and length SDS and BMD and BMD SDS for whole body and lumbar spine, separately for boys and girls. For the total eligible group, there was some evidence that birth weight was associated with length, with a 1 g increase associated with 0.001 SDS increase in length (95% CI: 0.0002, 0.002; *p*-value 0.046), (Table 4a, Supplementary material). This was mainly based on the association between birth weight and length for girls with 0.001 SDS increase in length (95% CI: 0.000, 0.003; *p*-value 0.03). For boys as well as for girls, there was no evidence of an association between length at nine to 10 years of age and nutritional intake of the first 14 days or any of the potential confounders.

For the total group as well as both sexes, there was no evidence that mean BMD of the whole body and lumbar spine and BMD SDS was associated with nutritional intake or any of the other clinical characteristics that were measured.

4. Discussion

Our evaluation of two cohorts of VLBW infants suggested that growth retardation achieved in the postnatal period returned to a normal range length within the first 6 months. At nine to 10 years the mean bone mass SDS measured for Whole Body and Lumbar Spine was within the normal range and seemed not related to nutritional

Table 4
Effect of nutritional intake and clinical characteristics on length and bone mineralization.

	Boys ($n = 63$)			Girls ($n = 66$)		
SDS length at 9–10 years	β	95% CI	*p*-value	β	95% CI	*p*-value
Cohort 2005 (vs. 2004)	−0.195	(−1.091, 0.701)	0.662	−0.421	(−1.310, 0.468)	0.341
Phosphate mmol/kg/14 days	0.007	(−0.040, 0.054)	0.768	0.029	(−0.016, 0.075)	0.201
Calcium mmol/kg/14 days	−0.015	(−0.071, 0.041)	0.597	−0.003	(−0.060, 0.053)	0.900
Protein grams/kg/14 days	0.007	(−0.056, 0.070)	0.832	−0.008	(−0.066,0.051)	0.796
Gestational age, weeks	0.089	(−0.137, 0.316)	0.430	−0.009	(−0.217, 0.199)	0.932
Birth weight, grams	0.001	(−0.001, 0.002)	0.378	0.001	(0.000, 0.003)	**0.030**
Small for gestational age	−0.053	(−1.237, 1.130)	0.928	0.490	(−0.626, 1.606)	0.379
Any corticosteroids (5 years)	−0.387	(−1.133, 0.359)	0.297	0.020	(−1.156, 1.196)	0.972
Whole body BMD	β	95% CI	*p*-value	β	95% CI	*p*-value
Cohort 2005 (vs. 2004)	−0.028	(−0.107, 0.050)	0.459	−0.059	(−0.146, 0.027)	0.169
Phosphate mmol/kg/14 days	0.001	(−0.004, 0.005)	0.732	0.003	(−0.002, 0.008)	0.256
Calcium mmol/kg/14 days	−0.002	−0.007, 0.003)	0.438	−0.002	(−0.008, 0.005)	0.558
Protein grams/kg/14 days	0.001	(−0.005, 0.008)	0.611	0.000	(−0.006, 0.006)	0.953
Gestational age, weeks	0.008	(−0.012, 0.028)	0.399	0.008	(−0.012, 0.029)	0.402
Birth weight, grams	0.000	(0.000,0.000)	0.352	0.000	(0.000, 0.000)	0.208
Small for gestational age	−0.012	(−0.115, 0.090)	0.808	0.006	(−0.099, 0.110)	0.911
Any corticosteroids (5 years)	−0.007	(−0.070, 0.056)	0.808	0.025	(−0.055, 0.106)	0.529
Whole body SDS	β	95% CI	*p*-value	β	95% CI	*p*-value
Cohort 2005 (vs. 2004)	−0.253	(−1.476, 0.969)	0.672	−0.444	(−1.767,0.878)	0.493
Phosphate mmol/kg/14 days	0.007	(−0.056, 0.070)	0.823	0.033	(−0.039, 0.105)	0.350
Calcium mmol/kg/14 days	−0.019	(−0.100, 0.062)	0.627	−0.015	(−0.110, 0.079)	0.734
Protein grams/kg/14 days	0.016	(−0.076, 0.108)	0.717	−0.004	(−0.094, 0.087)	0.935
Gestational age, weeks	0.163	−0.147, 0.472)	0.291	0.123	(−0.182, 0.427)	0.414
Birth weight, grams	0.001	(−0.001, 0.003)	0.373	0.001	(−0.001, 0.003)	0.156
Small for gestational age	−0.272	(−1.840, 1.296)	0.723	0.177	(−1.385, 1.740)	0.817
Any corticosteroids (5 years)	−0.139	(−1.119, 0.842)	0.722	0.412	(−0.873, 1.697)	0.520
Lumbar spine BMD	β	95% CI	*p*-value	β	95% CI	*p*-value
Cohort 2005 (vs. 2004)	−0.044	(−0.156,0.067)	0.418	−0.078	(−0.187, 0.032)	0.155
Phosphate mmol/kg/14 days	0.000	(−0.006, 0.006)	0.992	0.004	(−0.003, 0.011)	0.236
Calcium mmol/kg/14 days	−0.002	(−0.010, 0.007)	0.690	−0.001	(−0.011, 0.008)	0.763
Protein grams/kg/14 days	0.003	(−0.006, 0.012)	0.472	−0.002	(−0.010, 0.007)	0.669
Gestational age, weeks	0.009	(−0.019, 0.036)	0.522	0.015	(−0.013, 0.043)	0.276
Birth weight, grams	0.000	(0.000, 0.000)	0.896	0.000	(0.000, 0.000)	0.948
Small for gestational age	0.021	(−0.115, 0.157)	0.751	0.019	(−0.121, 0.160)	0.777
Any corticosteroids (5 years)	−0.029	(−0.115, 0.157)	0.751	0.022	(−0.106, 0.151)	0.728
Lumbar spine SDS	β	95% CI	*p*-value	β	95% CI	*p*-value
Cohort 2005 (vs. 2004)	−0.451	(−2.067, 1.164)	0.567	−0.624	(−2.195, 0.946)	0.419
Phosphate mmol/kg/14 days	−0.003	(−0.089, 0.083)	0.941	0.045	(−0.050, 0.140)	0.336
Calcium mmol/kg/14 days	−0.016	(−0.136, 0.103)	0.772	−0.014	(−0.149, 0.121)	0.818
Protein grams/kg/14 days	0.042	(−0.088, 0.172)	0.499	−0.021	(−0.146, 0.103)	0.718
Gestational age, weeks	0.139	(−0.263, 0.541)	0.487	0.179	(−0.208, 0.565)	0.347
Birth weight, grams	0.000	(−0.002, 0.002)	0.820	0.000	(−0.002, 0.002)	0.923
Small for gestational age	0.267	(−1.690, 2.224)	0.782	0.333	(−1.634, 2.300)	0.728
Any corticosteroids (5 years)	−0.485	(−1.717, 0.746)	0.424	0.239	(−1.456, 1.935)	0.776

Multivariable linear regression with adjustment for the potential confounders: cohort, gestational age, birth weight, AGA/SGA status, and use of corticosteroids at 5 years of age, SDS: standard deviation score; BMD: bone mineral density (g/cm^2).

intake. Only birth weight appeared to be associated with length at 9–10 years of age for girls.

While a number of previous studies found a decreased length and bone mass in former preterm infants, both cohorts in our study had SDS for length, and BMD SDS for whole body and lumbar spine within the normal range for age [29–31,46]. Several studies pointed at the positive effect of human milk on bone mineralization despite the low mineral content [27,28]. >90% of all infants in both cohorts received own mother's milk. For Cohort 2004 the use of human milk may have compensated for the low parenteral mineral intake [35].

Although both cohorts had achieved mean SDS for length and BMI within the normal range for the reference population, this was still below the initial SDS for weight at birth. Any long-term effect of early nutrition in our study may be questioned, as in both cohorts a substantial growth retardation was observed by the time infants were discharged. Besides postnatal illness, this phenomenon can be explained by the fact that fortification of human milk at levels that were used >10 years ago did not prevent nutritional deficits. A considerable number of infants of both cohorts never achieved the recommended enteral intake [4,35]. It is possible that further improvement of early postnatal nutritional intake may have prevented postnatal growth retardation and consecutively may have led to childhood growth SDS equivalent to growth at birth.

In contrast to our hypothesis, the significant different nutritional intake did not lead to a higher bone mass. The results from the linear regression showed no effect of mineral intake on bone mineralization, neither for boys nor for girls. The nutritional increment of calcium, phosphate in combination with more protein may not have been adequate for bone development. Recently, studies demonstrated that high protein intake may be related to hypophosphatemia indicating an increased need for phosphate supplementation [47,48]. Despite the significant increased amount of phosphate supplementation, Cohort 2005 had hypophosphatemia during the first week of life [36]. This may have been the result of an imbalanced nutritional intake of amino acids and phosphate [49]. On the other hand the mean BMD SDS was within the normal range of the reference population for both cohorts. As mentioned above this may have been the positive effect of human milk, but it may also indicate that preterm infants have the capability for catch-up for bone mineralization. Follow up studies of a randomized trial in preterm infants evaluating post-discharge feeding showed that higher nutritional intake positively affected BMC at six months corrected age, while this was not maintained until the age of eight years suggesting a catch up in children who received a lower mineral intake in the post-discharge period [34,50].

A varying number of children could not be evaluated at the standard follow up visits, leading to lower numbers of patients than originally eligible and thereby questioning the representativeness of the current data. Patient characteristics of the responders to follow up at five and nine to 10 years were comparable to the respective original cohorts and characteristics of non-responders differed only slightly compared to responders. We used multiple imputation to reduce the potential for bias from due to missing data and thus calculated estimates for the total eligible cohorts (2004: $n = 63$; 2005: $n = 66$). This narrowed the differences between the groups but the results based on analyses using observed data and those from multiple imputation were generally consistent. The original postnatal evaluation of growth revealed a significant higher weight gain until week 5 for AGA infants of Cohort 2005, mainly based on improved growth in boys [35,45]. The same group of boys of 2005 seemed to deteriorate with regard to length from two years of age onwards in contrast to the respective AGA girls and AGA boys of 2004. This was in contrast to the early reported Dutch follow up study of VLBW infants where boys showed a significant improved catch-up between 5 and 10 years compared to girls [51]. The repeated use of inhaled corticosteroids has been shown to negatively affect linear growth and bone mineralization [52–54]. Further, an increasing obstructive airway disease from childhood into adolescence has been demonstrated in follow up studies of VLBW infants [55]. While a considerable number of children of both cohorts reported bronchial hyperreactivity, for the current study corticosteroid use seemed not to affect length and bone mineralization. Nevertheless, we cannot exclude effects of childhood morbidities that were not accounted for in the current analysis.

The Dutch nationwide prospective study found stunting of SGA children at 10 years of age, while a 20 year follow up of SGA preterm born young adults found lower SDS for height and lumbar spine bone mineralization [51,56]. In contrast, our SGA children of both cohorts demonstrated the highest growth velocity during the first 5 postnatal weeks, had a lower decline in SDS for weight compared to AGA infants at TCA, and continuously improved growth with a full catch-up in height at the last visit at age nine to 10 years [35]. Bone mineral density of the whole body and lumbar spine were higher than the respective AGA groups. According to the multivariate regression analysis being SGA did not significantly affect SDS for length and BMD. It has been suggested that SGA infants are not able to compensate the intra-uterine incomplete bone mineral accretion in the postnatal period, we speculate that the first postnatal weeks may represent the critical window for SGA infants to start the catch-up growth and thereby indicating the need for sufficiency of nutritional intake directly after birth [57].

This study has several limitations. First, the patients were not randomly assigned to a treatment, but recruited over two consecutive time periods. However, nutritional protocols and data collection were standardized, patient characteristics were comparable even for the follow-up. For the last visit we were unable to invite all children at the same age which led to age dependent differences in growth and bone mineralization. We accounted for these differences by using age dependent standard deviation scores for comparisons. The major limitation of this study was the fact that the power calculation was not performed for differences in bone development or morbidities in childhood. We tried to overcome a considerable loss of follow up by evaluating characteristics of responders and non-responders to evaluate the representativeness of the children seen at follow up and used the method of multiple imputation. The latter may even be seen as a strength of this study since the few recent studies that evaluated long-term bone mineralization in former preterm infants mostly evaluated lower numbers of patients. However, unknown morbidities during the childhood period and individual lifestyles that were not accounted for may have biased the results.

5. Conclusions

Children born preterm as appropriate or small for gestational age are able to catch up in length after the postnatal period, and achieve a normal length and bone mineralization. An improvement of calcium and phosphate intake during the first 14 days of life was not associated with improvement in length and bone development.

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VC and MvdP were equally responsible for designing the study, data acquisition, analyzing and interpreting the data, and writing of the manuscript; LR performed the statistical analyses and contributed to the interpretation of the data and review of the manuscript; KS was responsible for data acquisition, interpreting of the data and reviewing of the manuscript, MG supervised the design, interpretation of the data and reviewing the manuscript, J.B.v.G. contributed in designing

the study, interpretation of the data and review of the manuscript; and A.v.H. supervised the design, analyses and interpretation of the data, and writing of the manuscript. All authors listed on the manuscript have seen and approved the manuscript and take full responsibility for the manuscript.

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Appendix A. Supplementary data

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