Outcomes 8 years after preterm birth

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2019

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)
Ruys, C. A. (2019). *Outcomes 8 years after preterm birth: the effect of nutrition after discharge*.

Chapter 3

Follow-up of a randomized trial on postdischarge nutrition in pretermborn children at age 8 years

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Am J Clin Nutr. 2017;106(2):549-558

ABSTRACT

Background Early nutritional interventions may modulate health risks in preterm infants. Previously, we showed that preterm infants fed an isocaloric protein- and mineral-enriched postdischarge formula (PDF) from term age to 6 months corrected age (CA), gained more lean mass compared to those fed term formula (TF). Long-term follow-up of randomized nutritional trials is important to test the hypothesis that short-term positive effects on health are sustainable.

Objective The aim of this follow-up study was to compare body size, body composition, and metabolic health at age 8 years in preterm-born children who were randomly assigned to receive either PDF or TF from term age until 6 months CA.

Design A total of 79 of 152 children (52%) from the original randomized controlled trial were enrolled for follow-up at age 8 years. Weight, height, and head circumference were measured by using standard methods. Body composition, including fat mass, lean mass, bone mineral content, and bone mineral density, was determined by dual-energy X-ray absorptiometry. Blood pressure was measured in the supine position by using an automatic device. Metabolic variables, including glucose, insulin, insulin-like growth factor 1, triglycerides, cholesterol, cortisol, and leptin were measured after an overnight fast. Nutritional habits at age 8 years were assessed by using a 3-day nutritional diary.

Results At age 8 years, no differences were found in body size, body composition, bone variables, and metabolic health variables when comparing children fed PDF with those fed TF. Adjustment for known and possible confounders did not change these results.

Conclusion In this follow-up study in preterm-born children, we showed that the favorable effects of PDF at 6 months CA either were not maintained or could not be confirmed because of attrition at the age of 8 years. We suggest that future research should focus on nutritional interventions in the pre- and postdischarge period as a continuum rather than as separate entities.

INTRODUCTION

Preterm birth has been associated with adverse outcomes such as neurodevelopmental impairment and (precursors of) the metabolic syndrome.[1-3] Therefore, research in preterm infants is focused not only on survival but to a great extent on improving health in later life. Many preterm-born infants are underweight at discharge or term age, and subsequent catch-up growth may seem desirable.[4] However, excessive catch-up growth, especially in weight, although beneficial for neurodevelopment, has been associated with an increased risk of developing cardiometabolic disease.[5,6]

Dietary adjustments in early life are aimed at the achievement of balanced, healthy catch-up growth,[7,8] although the optimal nutrition for the period after hospital discharge has remained a much-debated subject. Not only the exact timing of nutritional intervention but also the composition of the formulas used are profoundly heterogeneous among the studies conducted thus far. Nevertheless, a recent systematic review on the effects of postdischarge formula (PDF) suggested that nutrient-enriched formulas may have short-term advantages, such as improved growth and greater accretion of lean mass (LM) than standard term formula (TF).[9] Accordingly, we demonstrated that infants randomly assigned to an isocaloric protein-and mineral-enriched PDF from term age until 6 months corrected age (CA) showed increases in LM accretion and bone mineral content (BMC) at 6 months CA compared with infants fed TF.[10] Furthermore, Roggero et al.[11] described beneficial effects of a nutrient-enriched formula compared with a standard TF on gain in head circumference and LM in the first 6 months of life in preterm infants born with an appropriate size for their gestational age.[11]

Little is known about the sustainability of these short-term beneficial effects of PDF, or the chances of adverse consequences of feeding preterm infants a protein-enriched formula during 6 months after term age. Some randomized trials and observational studies found that PDF was associated with improved growth, body composition, and bone variables at ages ≤ 24 months.[12-15] However, to our knowledge, no studies have reported on the long-term effects of PDF. Because it has been suggested that early nutrition may permanently alter health risks,[16,17] long-term follow-up of nutritional intervention studies seems necessary.

The aim of the present study was to investigate whether an isocaloric protein- and mineral-enriched PDF, compared with TF and human milk (HM), given to infants born preterm between term age and 6 months CA would lead to alterations in body composition, bone mineralization, and metabolic health variables at age 8 years. We hypothesized that the differences found at 6 months CA would persist, without increasing the risks of adverse consequences, at age 8 years.

METHODS

Original trial

In this article, we describe the follow-up at age 8 years of our randomized controlled trial (RCT) called 'Study Towards the Effects of Postdischarge nutrition on growth and body composition of infants born ≤ 32 weeks gestation and/or ≤ 1500 g birth weight' (STEP). The participants of the STEP-study were included between January 2003 and March 2006. In this RCT, infants fed formula were randomly assigned at term age to receive either an isocaloric protein- and mineral-enriched PDF (n = 54) or standard TF (n = 48). An additional control group of HM-fed infants was also included (n = 50). The study formula was continued until 6 months CA. The composition of PDF compared with the TF (per 100 mL) was as follows: energy, 67 compared with 67 kcal; protein, 1.70 compared with 1.47 g; carbohydrates, 7.0 compared with 7.2 g; fat, 3.5 compared with 3.5 g; calcium, 65 compared with 50 mg; and vitamin D, 38 compared with 30 μg.

Both parents and researchers were blinded to the allocation. Blinding was maintained until analyses at 6 months CA were performed. At term age and at 3 and 6 months CA, anthropometric measurements were performed and blood was drawn for the determination of bone markers, lipid status, iron status, glucose, and insulin. At term age and at 6 months CA, body composition was measured with dual-energy X-ray absorptiometry (DXA). Further details of the study are described elsewhere.[10]

Study protocol of follow-up

For the follow-up study (STEP-2 study) at 8 years we approached all parents of participants who were included in the STEP-study. Exclusion criteria were as follows: incomplete follow-up until 24 months CA, severe physical impairment, or conditions known to affect growth or body composition.

The primary objective of the follow-up study was to compare body size, body composition, and metabolic health at age 8 years between preterm-born children fed either PDF or TF from term age to 6 months CA. The secondary objective was to compare body size, body composition, and metabolic health at age 8 years between preterm-born children fed HM and those fed either PDF or TF.

Children were seen at our outpatient clinic. Anthropometric measurements were performed; weight was measured to the nearest 0.05 kg with an electronic scale (Seca) and standing height was measured to the nearest 0.1 cm using a digital stadiometer (DGI 250D; De Grood). Head, waist, and hip circumference were measured 3 times with a nonstretchable measuring tape to the nearest 0.1 cm, and the mean values were calculated.

A DXA-scan (Hologic Discovery 4500 A, whole-body scan; Hologic Inc.) was performed and analyzed by using Apex version 13.3.3 software. This provided information on whole-body LM (kg), fat mass (FM; kg), bone area (BA; cm^2), BMC (g), and bone mineral density (BMD; g/cm^2). As suggested by Van Itallie et al.,[18] we also reported FM and LM normalized for height: FM index (FMI) = $FM/height^2$, and LM index (LMI) = $LM/height^2$.

After 15 min of rest in supine position, blood pressure (BP) was measured 6 times during 30 min. The measurements were performed on the non-dominant arm with an automatic device (Dinamap) by using an appropriate cuff for the upper arm circumference. Systolic and diastolic BP (SBP and DBP, respectively) were reported by the device, and mean arterial pressure (MAP) was calculated as [(DBP x 2) + SBP]/3. Means for SBP, DBP and MAP were calculated from the 6 measurements. Absolute values were converted to percentiles adjusted for sex, age and height.[19] A blood sample was obtained after an overnight fast. EMLA (lidocaine/prilocaine) cream (AstraZeneca) was applied ≥ 30 min before the insertion of an intravenous cannula.

To assess nutritional habits at age 8 years, parents and children were asked to fill in a 3-day nutritional diary. During 2 weekdays and 1 weekend day, all meals, snacks, and beverages were recorded as precisely as possible. These data were entered in a digital nutrient-calculating tool on the 'The Netherlands Nutrition Centre' website,[20] which calculated daily intakes of energy, fat, protein, carbohydrates, and various micronutrients.

Education level and ethnicity were self-reported by parents. Education level was categorized as neither of the parents, 1 parent, or both parents having completed higher education. Ethnicity was categorized as white when both parents were from white origin.

The study protocol was approved by the Ethics Committee of VU University Medical Center, Amsterdam. All parents of subjects gave written informed consent. This trial was registered at www.trialregister.nl as NTR 2972 (follow-up study [STEP-2 (Study Towards the Effects of Postdischarge nutrition 2)]) and NTR 55 [original randomized controlled trial (STEP)].

Laboratory analysis

The following variables were analyzed on an automated Modular analytics (Roche diagnostics) immediately after blood was obtained: glucose (mmol/L), triglycerides (mmol/L), total cholesterol (mmol/L), high-density-lipoprotein- (HDL) cholesterol (mmol/L), calcium (mmol/L), phosphate (mmol/L), magnesium (mmol/L), free thyroxine (fT4; pmol/L) and thyroid-stimulating hormone (TSH) (mIU/L). Low-density-lipoprotein-(LDL) cholesterol (mmol/L), was calculated by using the Friedewald formula.[21]

For the following analyses, plasma was stored at -80°C and thawed once, just before analysis. Insulin (pmol/L), C-peptide (nmol/L) and cortisol (nmol/L) were measured using immunoassays (Luminescence; Advia Centaur XP, Siemens Medical Solutions Diagnostics). The interassay CV ranges were 7–8%, 5–7%, and 6–7%, respectively. The lower detection limits were 10 pmol/L, 0.03 nmol/L and 30 nmol/L, respectively. Leptin (mg/L) was measured by radioimmunoassay (Linco Research Inc.), with an interassay CV of 6% and a lower detection limit of 0.5 μg/L.

Adrenocorticotropic hormone (ACTH; pmol/L) and insulin-like growth factor I (IGF-I; nmol/L) were measured by chemiluminescence immunoassay (Liaison Diasorin S.p.A.). The interassay CV was 6% for ACTH, and ranged from 7.4 to 16% for IGF-I. The lower detection limits were 1.1 pmol/L and 3.2 nmol/L, respectively. IGF binding protein 3 (IGF-BP3; mg/L) was measured by using a noncompetitive immunoassay (ELISA; DRG International Inc.). The interassay CV ranged from 9 to 17%, and the lower detection limit was 0.4 mg/L. 25-Hydroxycholecalciferol (pmol/L) was measured by HPLC separation with tandem mass spectrometry detection.[22] The interassay CV ranged from 6 to 8%, and the lower detection limit was 4 nmol/L.

HOMA-IR was calculated from fasting glucose and insulin concentrations as [glucose (mmol/L) x insulin (mIU/L)]/22.5. All laboratory tests were performed by the Department of Clinical Chemistry and the Endocrine Laboratory of VU University Medical Center, Amsterdam.

Statistics

We aimed to study 37 participants per feeding group, which would allow us to detect a difference (mean ± SD) in growth variable SD scores (SDSs) of 0.5 ± 0.7, a 3.5 ± 0.5% difference in fat percentage, or both, with a power of 80% and an α of 0.05.

Auxologic data were converted to SDSs on the basis of Dutch reference data.[23] Groups were compared on an intention to treat basis. Normally distributed outcome data (reported as means ± SDs) were analyzed by using (multivariable) regression analysis to compare the PDF to the TF group and the HM group to the PDF and TF groups. Skewed data (reported as medians and 25^{th}–75^{th} percentile IQRs) were natural ln-transformed and subsequently analyzed by using (multivariable) linear regression analysis. Variables that were unequally distributed among the feeding groups ($P < 0.05$) were considered as possible confounders and were included in the regression analyses as covariates. This was the case for GA, birth weight (BW) and parental educational level (**Table 3.1**). Because previous studies suggested beneficial effects of PDF specifically for boys and infants born small for gestational age (SGA), the regression analyses were also adjusted for sex and SGA status (BW and/or birth length ≤ -2 SDS). Analyses with FM, LM, and bone variables were additionally adjusted for weight and height. Analyses with BMC were also adjusted for BA.

To explore the impact of early weight changes on the effect of the intervention on the outcomes at age 8 years, we performed 2 types of post hoc analyses, considering the following: 1) weight loss from birth to term age (≥ 1 compared with < 1 SDS), and 2) weight gain from term age to 6 months CA (≥ 0.67 compared with < 0.67 SDS). First, we added an interaction term (feeding group x weight loss or gain) to the regression equation. Second, if the interaction term was significant, we performed analyses stratified by weight loss or gain.

Significance was reached at a P value < 0.05. Statistical analysis was performed with IBM SPSS Statistics, version 22.

RESULTS

Of the 152 children who completed the original trial, 21 were excluded on the basis of the exclusion criteria. A total of 131 parents and children were approached for follow-up, and 52 declined to participate or could not be traced. Seventy-nine children were included for follow-up (from March 2011 to April 2014) at age 8 years: 33 from the original PDF group, 21 from the original TF group, and 25 from the original HM group (**Figure 3.1**). Exclusions and nonparticipants were equally distributed among the feeding groups (chi-square test, overall P = 0.341; PDF compared with TF P = 0.190). Baseline characteristics were not different between participants and nonparticipants as a group (**Table 3.1**). Furthermore, we compared weight, length, and head circumference SDSs at birth, term age, and at 3, 6, 12, and 24 months CA between participants and nonparticipants and found no significant differences at any of the time points (data not shown). However, within nonparticipants, FMI and FM% were lower in the PDF than in the TF group at 6 months CA (P = 0.045 and 0.028, respectively), whereas within participants, no differences between the PDF and TF group in FM or FMI, LM or LMI, and FM% at 6 months CA were found.

Table 3.1. Characteristics of children that participated vs. children that did not participate in the follow-up of the nutritional RCT 'STEP-study'[1]

	Participants of follow-up (*n* = 79)			Nonparticipants (*n* = 52)			
	PDF	TF	HM	PDF	TF	HM	*P* value[2]
n	33	21	25	15	21	16	79 vs. 52
Perinatal characteristics							
BW,[3] g	1382 ± 321	1328 ± 212	1211 ± 328	1245 ± 247	1370 ± 261	1422 ± 348	0.498
SDS	-0.4 ± 0.9	-0.2 ± 0.9	-0.4 ± 1.2	-0.6 ± 1.0	-0.3 ± 0.8	-0.1 ± 1.0	0.871
BL, cm	38.7 ± 3.0	37.6 ± 2.8	37.5 ± 3.4	37.1 ± 2.7	38.3 ± 3.0	37.5 ± 3.3	0.563
SDS	-0.8 ± 1.2	-1.1 ± 1.1	-0.5 ± 1.5	-1.3 ± 1.2	-0.9 ± 1.1	-1.1 ± 1.0	0.155
Birth HC, cm	27.8 ± 1.7	28.0 ± 1.7	27.1 ± 2.1	27.4 ± 2.1	27.8 ± 1.8	27.7 ± 1.9	0.838
SDS	-0.4 ± 0.9	0.03 ± 0.9	0.03 ± 1.5	-0.4 ± 1.2	-0.2 ± 0.9	-0.2 ± 0.9	0.563
BW and/or BL ≤ -2 SDS, *n* (%)	7 (21.2)	5 (23.8)	5 (20.0)	4 (26.7)	5 (23.8)	4 (25.0)	0.507
Gestational age,[4] wk	31 [30;32]	31 [29;32]	30 [29;31]	30 [30;31]	31 [30;32]	30 [30;31]	0.834
NTISS score	19.2 ± 8.1	23.2 ± 7.2	24.2 ± 6.9	22.6 ± 6.5	20.1 ± 7.7	22.1 ± 7.1	0.738
6 months CA							
Weight, kg	7.3 ± 0.9	7.4 ± 1.4	7.0 ± 0.9	7.2 ± 1.0	7.5 ± 1.1	7.3 ± 1.0	0.457
SDS	-0.4 ± 1.1	-0.4 ± 1.4	-0.7 ± 1.2	-0.5 ± 1.2	-0.2 ± 1.3	-0.4 ± 1.0	0.395
Length, cm	66.7 ± 2.0	66.7 ± 3.2	65.8 ± 3.2	66.9 ± 2.8	66.6 ± 3.4	65.9 ± 2.4	0.898
SDS	-0.2 ± 0.8	-0.3 ± 1.3	-0.5 ± 1.3	-0.1 ± 1.1	-0.3 ± 1.3	-0.5 ± 0.8	0.843
FM, kg	1.9 ± 0.6	2.1 ± 0.8	1.8 ± 0.6	1.7 ± 0.6	2.2 ± 0.9	2.1 ± 0.8	0.328
LM, kg	5.9 ± 0.6	5.7 ± 0.7	5.5 ± 0.6	5.9 ± 0.5	5.6 ± 0.5	5.6 ± 0.8	0.792

Demographic characteristics							
Male, *n* (%)	17 (51.5)	13 (61.9)	10 (40)	7 (46.7)	11 (52.4)	8 (50)	0.943
Age at follow-up, years	8.0 [7.6;8.2]	8.0 [7.7;8.3]	7.8 [7.5;8.3]	-	-	-	-
Education level of parents (higher education),[5] *n* (%)							
Neither parent	21 (63.6)	13 (61.9)	7 (28.0)	9 (60.0)	10 (47.6)	4 (25.0)	0.632
1 parent	5 (15.2)	7 (33.3)	3 (12.0)	1 (6.7)	9 (42.9)	3 (18.8)	-
2 parents	6 (18.2)	1 (4.8)	15 (60.0)	4 (26.7)	2 (9.5)	9 (56.3)	-
Both parents are white, *n* (%)	24 (72.7)	17 (81.0)	21 (84.0)	12 (80.0)	15 (71.4)	12 (75.0)	0.643

[1] Values are means ± SDs or medians [25th ;75th IQRs] unless otherwise indicated. BL, birth length; BW, birth weight; CA, corrected age; FM, fat mass; HC, head circumference; HM, human milk; LM, lean mass; NTISS, Neonatal Therapeutic Intervention Scoring System; PDF, postdischarge formula; SDS, SD score; STEP, Study Towards the Effects of Postdischarge nutrition; TF, term formula.
[2] Participants compared with nonparticipants, derived by using unpaired *t* test, chi-square test, or Mann-Whitney *U* test as appropriate.
[3,4] Only participants of the follow-up – PDF compared with HM: [3] $P = 0.034$, [4] $P = 0.019$.
[5] Only participants of the follow-up – TF compared with HM and PDF compared with HM: $P < 0.05$. Higher education = higher vocational education or university.

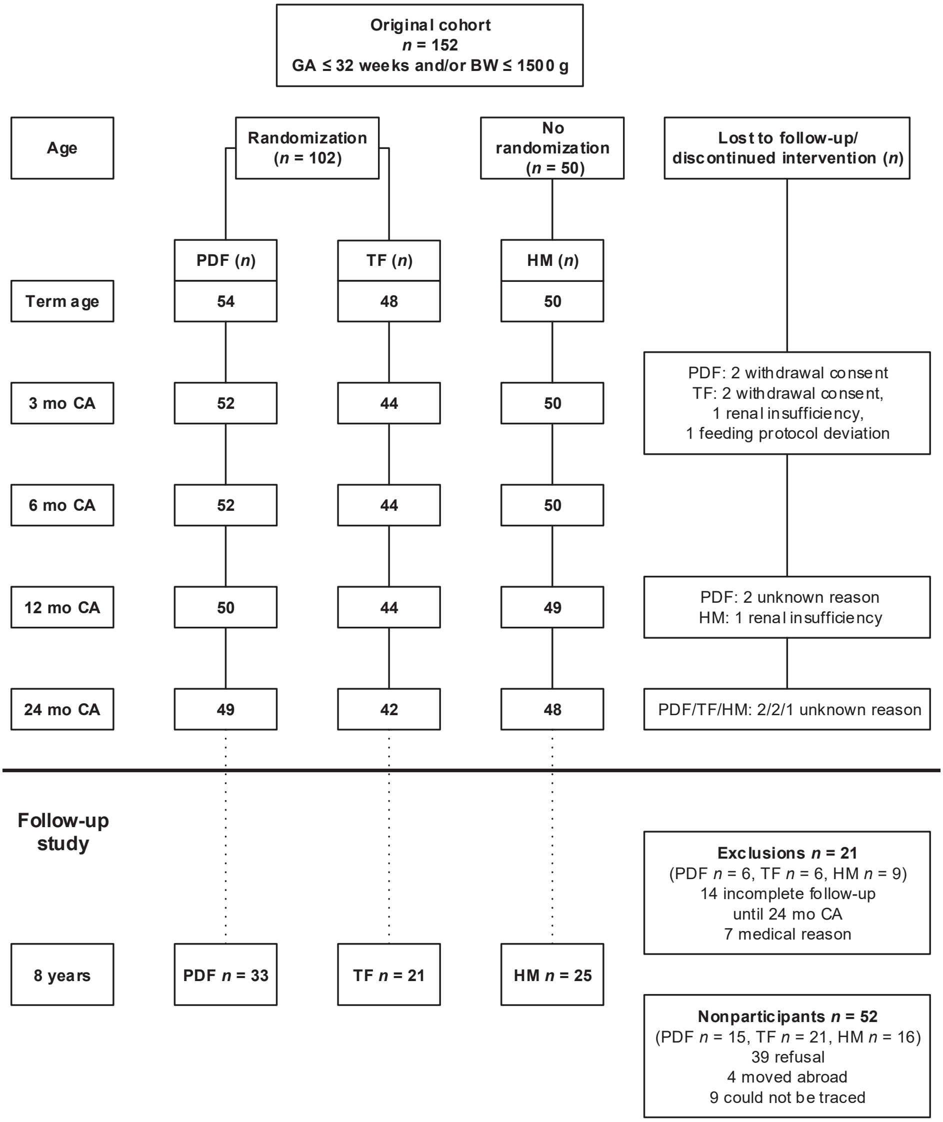

Figure 3.1. Flow chart of the study population.
BW, birth weight; CA, corrected age; GA, gestational age; HM, human milk; PDF, postdischarge formula; TF, term formula.

Primary outcomes

Growth variables measured at birth, term age, and at 3, 6, 12 and 24 months CA and 8 years were compared according to type of feeding. No differences between the groups were found at any of the time points (**Figure 3.2**).

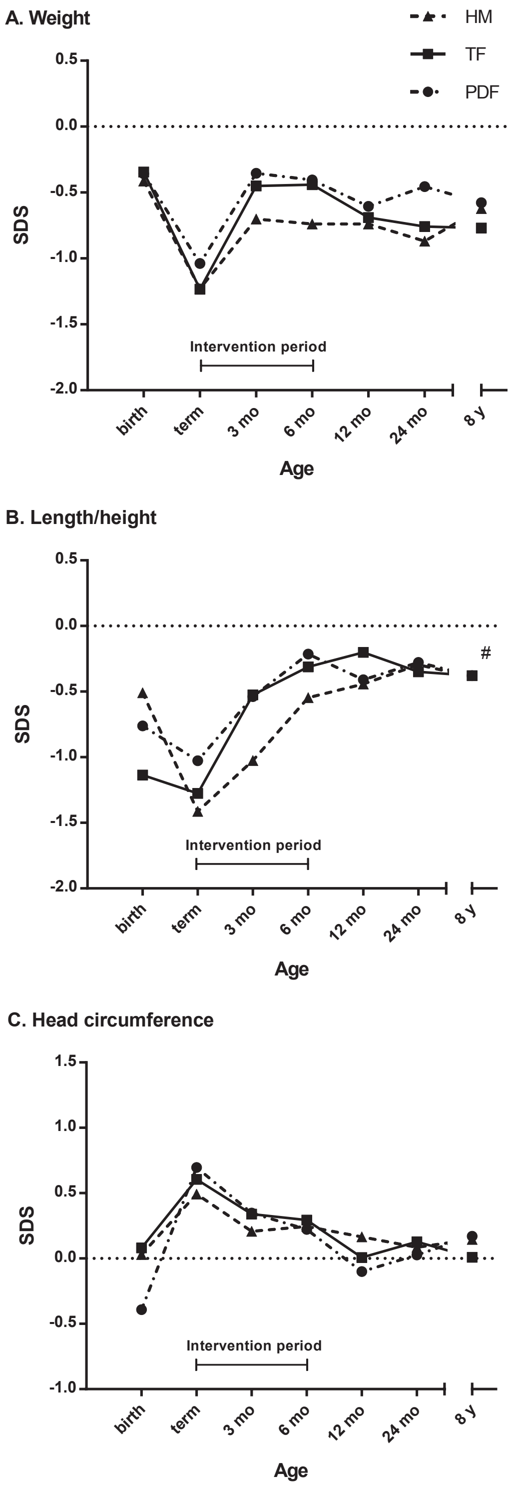

Figure 3.2. Weight (A), length and height (B) and head circumference (C) SDSs according to type of infant feeding.
Groups (*n* = 33, 21, and 25 for PDF, TF and HM groups, respectively) were compared using linear regression analyses and no significant differences were found at any of the time points (all *P* > 0.10). Horizontal dotted lines indicate the reference population mean.
At age 8 years, the means of the 3 feeding groups overlap. HM, human milk; PDF, postdischarge formula; SDS, SD score; TF, term formula.

Both body size and body composition at 8 years were not different between the children fed PDF or TF from term age until 6 months CA (**Table 3.2**). Adjustment of the regression analyses with FM and LM for weight and height, did not change these results (data not shown).

Table 3.2. Comparison of anthropometric parameters and body composition at age 8 years according to type of infant feeding, using linear regression analysis[1]

	Feeding groups			*P* value		
	PDF	TF	HM	PDF vs. TF	TF vs. HM	PDF vs. HM
Anthropometric parameters						
n	33	21	25			
Weight, kg	26.3 ± 4.3	25.7 ± 5.7	25.5 ± 3.9	0.651	0.870	0.510
SDS	-0.6 ± 1.2	-0.8 ± 1.4	-0.6 ± 1.0	0.556	0.667	0.888
SDS for height	-0.3 ± 1.0	-0.8 ± 1.3	-0.5 ± 1.1	0.127	0.427	0.465
Height, cm	129.5 ± 5.6	130.2 ± 6.6	129.0 ± 4.6	0.654	0.474	0.743
SDS	-0.4 ± 0.9	-0.4 ± 0.9	-0.4 ± 0.8	0.994	0.966	0.968
BMI, kg/m^2	15.6 ± 1.9	15.0 ± 2.0	15.3 ± 1.9	0.252	0.626	0.506
SDS	-0.3 ± 1.0	-0.8 ± 1.3	-0.6 ± 1.1	0.144	0.507	0.421
Head circumference, cm	52.3 ± 1.7	52.2 ± 2.6	52.2 ± 1.5	0.794	0.997	0.780
SDS	0.17 ± 1.03	0.17 ± 1.41	0.15 ± 0.81	0.593	0.669	0.932
Waist circumference, cm	57.3 ± 4.8	56.6 ± 6.6	57.1 ± 6.0	0.650	0.743	0.911
SDS	0.15 ± 0.91	-0.14 ± 1.3	0.09 ± 1.1	0.334	0.473	0.826
Hip circumference, cm	62.8 ± 4.6	62.0 ± 6.9	62.3 ±4.2	0.589	0.707	0.862
SDS	-0.39 ± 0.84	-0.61 ± 1.15	-0.47 ± 0.69	0.378	0.744	0.590
Waist-hip ratio	0.91 ± 0.05	0.91 ± 0.06	0.92 ± 0.05	0.979	0.755	0.798
SDS	0.80 ± 0.98	0.78 ± 1.13	0.92 ± 0.91	0.945	0.644	0.632
DXA body composition						
n	31	20	24			
FM, kg	7.2 ± 2.4	6.6 ± 2.4	6.9 ± 2.3	0.389	0.692	0.638
Fat, %	26.2 ± 5.2	25.0 ± 4.7	25.9 ± 5.3	0.408	0.539	0.850
FMI,[2] kg/m^2	4.0 [3.3;5.1]	3.6 [2.9;4.7]	3.7 [3.2;5.1]	0.263	0.542	0.612
LM, kg	18.9 ± 2.8	18.4 ± 3.8	18.2 ± 1.9	0.493	0.792	0.310
LMI, kg/m^2	11.2 ± 1.1	10.8 ± 1.3	10.8 ± 0.7	0.219	0.903	0.197
Δ FM (6 months CA to 8 years), kg	5.2 ± 2.3	4.7 ± 2.0	5.0 ± 2.2	0.411	0.615	0.755
Δ LM (6 months CA to 8 years), kg	13.1 ± 2.6	12.7 ± 3.4	12.6 ± 1.7	0.524	0.936	0.448

[1] Values are means ± SDs or medians [25th ;75th IQRs] unless otherwise indicated. Unadjusted *P* values are reported. CA, corrected age; DXA, dual-energy X-ray absorptiometry; FM, fat mass; FMI, fat mass index; HM, human milk; LM, lean mass; LMI, lean mass index; PDF, postdischarge formula; SDS, SD score adjusted for age unless indicated otherwise; TF, term formula; Δ, gain in FM/LM between 6 months corrected age and 8 years.
[2] FMI was ln-transformed before use in linear regression analysis.

Bone variables, including serum calcium, phosphate, vitamin D, and magnesium, were compared between the formula groups and no significant differences were found (**Table 3.3**). For BMC, BA was added to the regression model, but this had no effect on the association between feeding group and BMC. No differences were found in metabolic health variables between PDF- and TF-fed children (**Table 3.4**). Adjustment for the potential confounding variables GA, BW, and education level of the parents or sex and SGA-status did not lead to significant differences between the 2 formula groups (data not shown), with the exception of ACTH [β (95% CI): 0.32 (0.03, 0.61) (*P* = 0.031) and 0.33 (0.01, 0.66) (*P* = 0.043), respectively, for ln-transformed variable].

Table 3.3. Comparison of bone variables at age 8 years according to type of infant feeding by using linear regression analysis [1]

	Feeding groups			*P* value		
	PDF	TF	HM	PDF vs. TF	TF vs. HM	PDF vs. HM
DXA bone parameters						
n	31	20	24			
BA, cm^2	1226.0 ± 67.0	1212.8 ± 76.3	1213.5 ± 65.5	0.503	0.974	0.502
BMC, g	909.4 ± 99.6	896.4 ± 129.2	870.1 ± 74.3	0.655	0.395	0.156
BMD, g/cm^2	0.74 ± 0.055	0.74 ± 0.064	0.72 ± 0.037	0.774	0.220	0.095
Serum bone parameters						
n	23	16	18			
Calcium, mmol/l	2.32 ± 0.07	2.28 ± 0.14	2.33 ± 0.08	0.165	0.145	0.874
Phosphate, mmol/l	1.44 ± 0.11	1.40 ± 0.10	1.44 ± 0.14	0.348	0.291	0.854
25(OH)D_3, pmol/l	89.9 ± 28.7	92.6 ± 28.1	80.1 ± 25.6	0.279	0.201	0.767
Magnesium, mmol/l	0.82 ± 0.05	0.81 ± 0.07	0.81 ± 0.04	0.611	0.964	0.565

[1] Values are means ± SDs unless otherwise indicated. Unadjusted P values are reported. BA, bone area; BMC, bone mineral content; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; HM, human milk; PDF, postdischarge formula; TF, term formula; 25(OH)D_3, 25-hydroxycholecalciferol.

Secondary outcomes

When comparing the HM group with the PDF and TF groups, no differences were found in body size, body composition, bone variables, blood pressure, or metabolic health variables (**Table 3.2–3.4**), with the exception of lower HDL cholesterol in the TF group than in the HM group [β (95% CI) -0.23 (-0.40, -0.06) (*P* = 0.010), for ln-transformed variable].

After adjustment for GA, BW, and education level of parents, glucose was significantly different between the PDF and HM groups [β (95% CI) -0.34 (-0.67, -0.01) (*P* = 0.044)]. Thyroid-stimulating hormone was lower in both the PDF and TF groups than in the HM

Table 3.4. Comparison of blood pressure and other metabolic health variables at age 8 years according to type of infant feeding by using linear regression analysis[1]

	Feeding groups			*P* value		
	PDF	TF	HM	PDF vs. TF	TF vs. HM	PDF vs. HM
Blood pressure						
n	33	21	25			
SBP, mmHg	106 [99;108]	105 [101;110]	107 [101;110]	0.294	0.511	0.763
Percentile [2]	70 [56;79]	65 [59;76]	74 [59;84]	0.161	0.511	0.521
DBP, mmHg	60 ± 7	59 ± 5	61 ± 6	0.505	0.211	0.486
Percentile [2]	54 ± 22	48 ± 16	57 ± 20	0.517	0.133	0.283
MAP, mmHg	75 ± 7	74 ± 5	76 ± 5	0.396	0.253	0.682
Laboratory parameters						
n	23	16	18			
Glucose, mmol/l	4.7 ± 0.5	4.8 ± 0.3	4.9 ± 0.4	0.360	0.740	0.194
Insulin, pmol/l	30 [20;39]	17 [15;36]	27.5 [18;40]	0.393	0.350	0.891
C-peptide, nmol/l	0.21 ± 0.08	0.22 ± 0.09	0.21 ± 0.06	0.643	0.717	0.933
HOMA-IR	1.04 ± 0.5	1.14 ± 1.0	1.12 ± 0.6	0.662	0.937	0.713
Triglycerides, mmol/l	0.5 [0.4;0.7]	0.4 [0.3;0.5]	0.4 [0.4;0.5]	0.069	0.691	0.125
HDL-cholesterol, mmol/l	1.7 [1.3;1.8]	1.5 [1.3;1.6]	1.8 [1.4;2.2]	0.140	0.010	0.172
LDL-cholesterol, mmol/l	2.2 ± 0.5	2.3 ± 0.5	1.9 ± 0.7	0.432	0.080	0.251
IGF-I, nmol/l	23.8 ± 9.2	21.1 ± 5.7	22.8 ± 6.3	0.267	0.501	0.688
IGF-BP3, mg/l	2.7 ± 0.6	2.6 ± 0.5	2.8 ± 0.6	0.305	0.151	0.615
Leptin, µg/l	3.5 [2.2;4.8]	2.9 [2.1;5.4]	3.6 [2.6;4.2]	0.749	0.751	0.988
ACTH, pmol/l	2.9 [2.1;3.9]	2.6 [1.7;3.2]	2.4 [1.8;3.6]	0.072	0.674	0.162
Cortisol, nmol/l	227 [174;385]	189 [167;259]	201 [163;249]	0.356	0.514	0.110
fT4 (pmol/l)	17.0 ± 1.6	17.8 ± 1.9	17.1 ± 1.8	0.201	0.286	0.855
TSH, µIU/l	2.3 [1.8;3.1]	2.5 [1.5;4.0]	3.3 [2.5;4.8]	0.783	0.074	0.084

[1] Values are means ± SDs or medians [25th;75th IQRs] unless otherwise indicated. Unadjusted *P* values are reported. For skewed data, ln-transformed variables were used. ACTH, adrenocorticotropic hormone; DBP, diastolic blood pressure; fT4, free thyroxine; HM, human milk; IGF-I, insulin-like growth factor I; IGF-BP3, IGF-binding protein 3; MAP, mean arterial pressure; PDF, postdischarge formula; SBP, systolic blood pressure; TF, term formula; TSH, thyroid-stimulating hormone.
[2] Percentiles for SBP and DBP were adjusted for sex, age, and height.

group [β (95% CI) -0.40 (-0.79, -0.02) (*P* = 0.042) and -0.43 (-0.84, -0.01) (*P* = 0.045), respectively, for ln-transformed variable]. Adjustment for sex and SGA status did not result in significant differences (data not shown), with the exception of lower HDL cholesterol in TF-fed children than in HM-fed children [β (95% CI) -0.25 (-0.42, -0.07) (*P* = 0.007), for ln-transformed variable]. Furthermore, TF- compared with HM-fed children showed a trend toward higher LDL cholesterol [β (95% CI) 0.43 (-0.02, 0.88) (*P* = 0.058)].

On the basis of the 3-day nutritional diaries we compared the mean daily intakes of energy (kcal), (saturated) fat (g), protein (g), carbohydrates (g), fibers (g) and salt (g) at age 8 years between the feeding groups. No significant differences were found for any of the nutrients ($P > 0.10$; data not shown).

Post hoc analyses considering early weight changes

There was no interaction between the type of feeding and weight loss from birth to term age when assessing the effect of feeding type on our outcome variables (all $P > 0.10$). An interaction was found between the type of feeding (PDF compared with TF) and weight gain from term age to 6 months CA on anthropometric measurements (weight, $P = 0.071$;

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Table 3.5. Post hoc analyses at age 8 years for the subgroup with weight gain < 0.67 SDS between term age and 6 months CA according to type of infant feeding[1]

			PDF vs. TF	
	PDF	TF	β (95% CI)	*P* value
Weight (kg)	25.6 ± 5.0	22.7 ± 4.3	2.85 (-0.54, 6.24)	0.097
SDS	-0.7 ± 1.1	-1.5 ± 1.2	0.85 (0.03, 1.67)	0.043
SDS for height	-0.3 ± 1.0	-1.6 ± 1.2	1.31 (0.45, 2.17)	0.004
Height (cm)	127.7 ±5.9	127.8 ± 6.4	-0.56 (-4.36, 4.25)	0.979
SDS	-0.6 ± 0.9	-0.7 ± 0.8	0.02 (-0.65, 0.68)	0.962
BMI (kg/m^2)	15.± 2.1	13.8 ± 1.6	1.76 (0.27, 3.26)	0.022
SDS	-0.4 ± 1.0	-1.6 ± 1.2	1.25 (0.44, 2.06)	0.003
Head circumference (cm)	52.0 ± 1.4	50.7 ± 2.4	1.28 (0.01, 2.54)	0.048
SDS	-0.1 ± 0.7	-0.7 ± 1.3	0.70 (0.02, 1.38)	0.044
Waist circumference (cm)	56.4 ± 5.6	52.2 ± 4.8	4.21 (-0.12, 8.53)	0.056
SDS	-0.1 ± 1.0	-1.0 ± 1.1	0.99 (0.19, 1.79)	0.017
Hip circumference (cm)	62.6 ± 4.9	58.8 ± 4.1	3.86 (0.30, 7.43)	0.034
SDS	-0.4 ± 0.9	-1.1 ± 0.8	0.78 (0.15, 1.40)	0.017
Waist/hip ratio	0.9 ± 0.05	0.9 ± 0.04	0.01 (-0.02, 0.05)	0.468
SDS	0.5 ± 1.0	0.4 ± 0.7	0.12 (-0.55, 0.79)	0.721
Fat mass (kg)	6.9 ± 2.5	5.4 ± 1.4	1.50 (-0.20, 3.19)	0.082
Fat mass index Ln (kg/m^2) [2]	4.1 ± 1.3	3.3 ± 0.7	0.22 (0.00, 0.43)	0.050
Lean mass (kg)	18.5 ± 3.2	16.8 ± 3.4	1.66 (-0.59, 3.91)	0.144
Lean mass index (kg/m^2)	11.2 ± 1.3	10.2 ± 1.2	0.98 (0.10, 1.86)	0.031
BA (cm^2)	1221 ± 63	1177 ± 58	43.61 (-4.99, 92.21)	0.077
BMC (g)	908 ± 98	836 ± 93	71.57 (1.98, 141.16)	0.044
BMD (g/cm^2)	0.74 ± 0.06	0.71 ± 0.05	0.03 (-0.01, 0.07)	0.092

[1] Values are means ± SDs unless otherwise indicated. PDF ($n = 20$) was compared to TF ($n = 11$) by using linear regression analysis, with unadjusted *P* values. BA, bone area; BMC, bone mineral content; BMD, bone mineral density; CA, corrected age; PDF, postdischarge formula; SDS, SD score adjusted for age (unless indicated otherwise); TF, term formula.
[2] Fat mass index was ln-transformed before use in linear regression analysis.

weight SDS, $P = 0.006$; head circumference, $P = 0.028$) and DXA bone variables (BA, $P = 0.092$; BMC, $P = 0.023$; BMD, $P = 0.031$). In addition, an interaction was found between the type of feeding (TF compared with HM) and weight gain from term age to 6 months CA on anthropometric measurements (weight, $P = 0.022$; weight SDS, $P = 0.006$; head circumference, $P = 0.003$; head circumference SDS, $P = 0.005$), body composition (FM, $P = 0.066$; LM, $P = 0.041$), DXA bone variables (BA, $P = 0.054$; BMC, $P = 0.046$), and BP (mean MAP, $P = 0.068$; mean DBP, $P = 0.061$). There was no evidence for an interaction between feeding type (PDF compared with HM) and weight gain from term age to 6 months CA on outcomes, with the exception of head circumference SDS ($P = 0.073$). Within the group of children with a weight gain ≥ 0.67 SDS ($n = 34$), there were no significant differences between the PDF and TF groups, nor between the PDF and HM groups. Children from the TF group had a larger waist circumference than those in the HM group. Furthermore, they showed a tendency toward increases in head circumference ($P = 0.050$), LM ($P = 0.068$), LMI ($P = 0.057$), BMC ($P = 0.059$), and BMD ($P = 0.053$) (data not shown). Within the group of children with a weight gain < 0.67 SDS ($n = 45$), there were no significant differences between the PDF and HM groups (data not shown). Compared with children fed TF, children fed PDF showed a higher weight-for-age SDS; weight-for-height SDS; BMI (SDS); head, waist, and hip circumferences (including SDSs); LMI; and BMC (**Table 3.5**). When comparing TF and HM, weight, BMI, head, waist, and hip circumferences (including SDSs), and DBP and DBP percentile, were lower in the TF group (data not shown).

DISCUSSION

In our follow-up study of postdischarge nutrition in infants born preterm, we found no differences in body size, body composition, bone variables, BP, or metabolic health variables at age 8 years between children fed PDF or TF between term age and 6 months CA. Furthermore, there were no differences between children fed HM or formula from term age to 6 months CA.

There may be several possible explanations for the lack of association between type of feeding and outcomes at age 8 years. First, our sample was probably too small to detect significant differences between treatment arms. Second, the timing of the intervention might have been too late to exert persistent effects on body composition. The growth trajectories of our study population from birth to age 8 years showed that postnatal growth restriction between birth and term age was considerable in our cohort. In addition, as shown before, our study population had a much lower protein intake in the early postnatal (predischarge) period, compared with another cohort in which the current European

Society for Pediatrics Gastroenterology, Hepatology, and Nutrition guideline was followed.[24] According to this guideline, a protein intake of 3.5–4.5 g · kg^{-1} · d^{-1} is recommended immediately after preterm birth.[25] Together with protein, a balanced parenteral supply of energy and lipids as soon as possible after birth should be pursued.[26] There is no doubt that this approach substantially reduces the extent of postnatal growth restriction,[27,28] and, as a consequence, the need for catch-up. Altogether, this emphasizes the importance of an adequate early nutritional supply to accomplish adequate postnatal growth and healthy neurocognitive and metabolic development.[29] Third, because the differences at 6 months CA were small, the children's diet and their individual lifestyles after the intervention might have attenuated the potential benefits of PDF.

Previously, (short-term) benefits of nutrient-enriched PDF have been reported, particularly for boys and infants born SGA.[9] Adding sex and SGA status to our regression models did not result in significant differences between the formula groups. The presumed benefits on body size, body composition, bone variables, and metabolic health could not be tested separately for boys and infants born SGA in our population due to the small sample sizes of the subgroups. The post hoc analyses might imply an advantage of PDF in children with a weight gain < 0.67 SDS between term age and 6 months CA, albeit not for every outcome, but the impact on long-term health remains unknown. Moreover, because subgroups were very small, these results should be interpreted with caution.

Although, to our knowledge, no long-term follow-up studies with PDF as a nutritional intervention specifically have been published, follow-up data of early postnatal nutrition for preterm infants in a broader context are available. Similar to our results, short-term effects were found that did not persist into childhood. Two parallel randomized trials of predischarge diet (banked breast milk compared with preterm formula, preterm compared with term formula supplemented to own mother's milk) showed enhanced neonatal growth in preterm formula fed infants. However, no differences in growth or skinfold thickness at ages 9 and 18 months, nor at 7.5–8 years were observed.[30] Furthermore, there was no effect of early diet on bone mass, FMI, and LMI at ages 8–12 years,[31,32] nor on peak bone mass at age 20 years.[33] In contrast to our findings at age 8 years, a positive effect of an HM-rich diet was found on whole-body BA and BMC at age 20 years.[33] We did not find such a positive effect of HM; however, HM-fed children received a considerable amount of TF after 3 months CA because of insufficiently available HM. Moreover, our follow-up was at age 8 years instead of age 20 years.

Both short- and long-term benefits of HM for (preterm) infants have been described, notably decreased risks of developing obesity and type 2 diabetes,[34] higher whole-body bone mass and BMC,[35] and higher intelligence quotient.[36] In our study, such benefits were not found, even though the parents of infants receiving HM were more often highly educated. Parental educational level (as a proxy for socioeconomic status) has been associated with quality of diet[37,38] and metabolic health, possibly through the degree of physical activity in children.[39] The few small differences found between the HM group and the formula groups may be explained merely by chance.

In our study, we measured a set of outcomes that has previously been associated with cardiometabolic disease risk.[3,40] Although there is no consensus on a pediatric definition of metabolic syndrome, Ford and Li[41] suggested that, with appropriate adjustments, criteria for adults could be extrapolated to children. Common components for the diagnosis of metabolic syndrome include fasting levels of triglycerides, HDL-cholesterol, and glucose; waist circumference; and BP. Ramírez-Vélez et al.[42] compared 4 different definitions of metabolic syndrome in a large cohort of children and adolescents aged 9–17 years, and found that its incidence varied considerably with the definition used. Overall, our cohort of preterm-born children did not fulfill any of these definitions at age 8 years. In particular, children fed PDF did not have a higher BP or a more harmful cardiometabolic profile. On the basis of these results, we have no reason to believe that PDF has an adverse effect on metabolic health at age 8 years.

Strengths and limitations

The main strength of our study is that it comprises a long-term follow-up of an early nutritional randomized trial. An important limitation of our study, as in many follow-up studies, is attrition, which may introduce selection bias and limits the statistical power of the study. However, participants of the follow-up study were representative of the original cohort, because baseline characteristics were not different between participants and nonparticipants, although, when comparing body composition at 6 months CA (the primary outcome of the original RCT) between the intervention groups, we were able to reproduce our previous observation that showed that PDF decreased FM at 6 months CA among nonparticipants, but not among participants. Therefore, it could be possible that if all former subjects had participated in the follow-up, our results at age 8 years would have been different. In addition, the numbers of nonparticipants were not statistically different between the feeding groups, although in absolute numbers a higher percentage of the original PDF group was seen for follow-up at age 8 years (61% of the PDF group compared with 44% of the TF group). This may overestimate the effect of PDF on outcomes at 8 years; nevertheless we did not observe any differences. As stated recently by the European Society for Pediatrics Gastroenterology, Hepatology, and Nutrition Early Nutrition Research Working Group, despite the almost inevitable cohort attrition, long-term follow-up of early nutrition RCTs is necessary.[43] Another limitation is the generalizability of our results to current neonatal intensive care unit populations, who are born even more prematurely.

Although early nutrition is a key factor for growth, body composition, and metabolism, it is certainly not the only one. Considering the complex interactions between endocrine factors, such as IGF-I, and nutrition, we hypothesize that introducing a protein-, but not calorie-enriched nutrition (i.e., PDF) already before discharge might prevent excessive fat accretion and its accompanying long term health risks. The terms 'postdischarge nutrition' or PDF may become obsolete when the rather arbitrary division of the postnatal period in pre- and postdischarge with regard to nutrition is abandoned.

Conclusion

In conclusion, this long-term follow-up study of a nutritional intervention RCT during the postdischarge phase of preterm infants showed that the beneficial effects of PDF at 6 months CA were either not maintained or could not be confirmed due to attrition at the age of 8 years. However, we do not know whether the previous positive effects might be of influence later in life. A combination of optimal nutritional support before and after hospital discharge of preterm infants, might result in a more physiologic growth pattern (i.e., less early postnatal growth restriction and catch-up growth thereafter). Therefore, we suggest that future research focuses on nutritional interventions in the pre- and postdischarge period as a continuum rather than as separate entities. Consistent with recent recommendations, parenteral or enteral nutrition should be started immediately after birth and increased rapidly to reduce the extent of postnatal growth restriction. As soon as an adequate growth rate (i.e., similar to the intrauterine norm) is achieved, energy and protein needs should be re-evaluated, and irrespective of whether the child is still admitted, a switch to a 'postdischarge formula composition' may be considered for the prevention of excessive catch-up growth while still supporting neurodevelopment.

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