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Lean tissue deficit in preterm infants persists up to 4 months of age: results from a Swedish longitudinal study.

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Short title: Body composition in preterm infants.

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Abbreviations:

FM - fat mass

FFM - fat free mass

%BF – percentage body fat

FMI - fat mass index

FFMI - fat free mass index

1. Abstract

Background: At term-equivalent age, infants born premature are shorter, lighter and have more adipose tissue compared to term counterparts. Little is known on whether the differences in body composition persist in later age.

Methods: We prospectively recruited 33 preterm infants (<32 weeks gestational age, mean gestational age 28.1 weeks) and 69 term controls. Anthropometry and body composition (air displacement plethysmography) were monitored up to 4 months of age. Nutrient intakes from preterm infants were collected from clinical records.

Results: At 4 months of age preterm infants were lighter and shorter than term controls (mean weight-for-age z-score: -0.9 vs 0.1, p=0.002; mean length-for-age z-score: -1.4 vs 0.2, p=0.002). The significantly greater percentage of total body fat seen in preterms at term-equivalent age [20.2% vs 11.7%, p<0.0001)] was no longer observed at 4 months. A deficit of fat free mass persisted until 4 months of age (fat free mass at term equivalent age: 2.71 vs 3.18 kg, p<0.0001; at 4 months: 4.3 vs 4.78 kg, p<0.0001). The fat mass index (FMI) and fat free mass index (FFMI) (taking length into account) did not differ between the groups. Nutrition had little effect on body composition. Higher protein intake at week 2 was a negative predictor of fat free mass at discharge.

Conclusions: At 4 months corrected age, preterm infants were both lighter and shorter than term controls and the absolute FFM deficit remained until this age. Little effect of nutrition on body composition was observed.

2. Introduction

Extremely preterm infants at term-equivalent age are lighter, shorter and have smaller head circumference than their term counterparts.[1] This suboptimal growth is attributed both to neonatal morbidity and to insufficient early postnatal nutrients supply. The latter is still challenging in spite of advances in neonatal care [2]. Not only quantitative growth, but also body composition is different in preterm- compared to term infants. A meta-analysis of eight studies (733 infants) showed that preterm infants at term-equivalent age had greater percentage total body fat (mean difference 3%, p=0.003), less fat mass (FM, -50g, p=0.03), and much less fat-free mass

(FFM, -460g, p<0.0001) than those born full-term.[3] This data show that the difference in body weight between preterm infants at term-equivalent age and infants born at term, can be substantially attributed to a difference in lean tissue. It is unclear whether the differences in body composition seen at term-equivalent age persist until later age.

Premature birth has been associated with higher risk for hypertension and decreased insulin sensitivity later in life.[4] Growth pattern is of great interest in this context since rapid growth has been associated with insulin resistance, hypertension and obesity, but at the same time with improved neurodevelopment in preterm infants.[4,5] Emerging evidence suggests that lean tissue rather than fat mass is a benchmark for optimal growth in preterm infants, possibly reflecting metabolic activity, later risk of non-communicable diseases and neurodevelopmental outcome.[6-8]

The role of nutrition in quantitative and qualitative growth is undeniable. Research under the last decade has given special attention to protein intakes. Several studies have shown that higher intakes of protein during hospitalization is associated to higher gain of FFM, also after discharge.[6,9,10] In very preterm infants, higher protein intake increased weight velocity and lean mass accretion comparable to that of term infants.[11] However, evidence is still scarce on how body composition changes in very preterm infants and how early nutrition affects it.

We prospectively assessed growth and changes in body composition in premature infants born before 32 weeks of gestation, compared to term healthy controls up to 4 months of age. Additionally, the associations with growth and early postnatal nutrition, particularly energy and protein intakes, were explored.

3. Materials and methods

Participants and setting

This was a prospective longitudinal study conducted in a tertiary care hospital in Umeå, Sweden. We recruited premature infants (< 32 weeks gestation or birth weight < 2000g) and full-term healthy controls (37-41 weeks gestation, birth weight 2500-4500 g).

Body composition and anthropometry

We assessed body composition by means of air displacement pletysmography (PeaPod Infant Body Composition System, COSMED Ltd, Concord, California, USA). In brief, the method is based on measuring body mass and volume (air displaced by the infant body placed in the chamber) and applying standard densitometric model to FM, FFM, and percentage of FM. The method was validated in infants. [12] In order to correct for length, we calculated FMI (FM/square length) and FFMI (FFM/square length). Body composition in preterms was determined at achieving clinical stability, at discharge, at term-equivalent age, and at 4 months; in term controls at 7 to 14 days after birth, and at 4 months. Infants had no clothes or diaper on during examination. Length was taken with an infantometer (Seca 416, Seca Medical Measuring Systems, Germany) and weight with digital infant scale (Seca 727). Head circumference was measured with a plastic tape (Seca 212). The measurements precision was up to 1 mm or 1g. Additionally, we retrospectively retrieved the data routinely collected at the neonatal intensive care unit (weight daily, length and head circumference weekly).

Nutrient intakes

Data on nutrients intake in preterm infants were collected retrospectively from clinical records, and double-checked (AC, IO). We used Nutrium™ software, a graphical interface for clinical and research setting (www.nutrium.se). We recorded intakes of energy and macronutrients with exclusion of transfused blood products. For simplicity, we added all enteral and parenteral nutrition. We counted amino acids as protein. Mother's own milk was analyzed with mid-infrared spectrophotometry (Eurofins Steins Laboratory AB, Jönköping, Sweden). For donor milk, we used a standard assumed nutrient content for early and mature donated breastmilk (< 28 days and > 28 days, respectively).[13] Mother's own breastmilk was analyzed on a weekly basis. Intakes were calculated daily up to 28 days, and weekly up to 10 weeks or until discharge. We used the intakes recommended by European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) as reference.[14] When breastfeeding was initiated, nutrient intake was no longer possible to calculate but feeding mode was noted until 4 months. Thus, we present nutrient intakes for the first 4 weeks of life only.

Statistics

To enable detection of a difference in body fat mass of 2 % between the groups, based on the assumption of 9% in term infants and SD 4%, with the power of 80% and α=0.05, the calculated sample size was 160 infants (80 per group).[15] However, recruitment had to be ceased before achieving this number (see Results). Post-hoc power analysis accounting for unequal samples sizes showed that we had a power of 100% to detect the observed difference in body fat percentage. We used independent sample t-test to compare means between the groups. We investigated factors potentially associated with body composition (anthropometry, growth, nutrition) by univariate regression, and adjusted for gestational age and birth weight z-score. Due to small number of infants recruited, we did not explore the associations in a multivariate regression models.

4. Results

We included 33 preterm infants and 69 term controls. The main reason for not achieving the target sample size for premature infants (n=80) were logistic difficulties due to renovation of the hospital premises. These made us perform the body composition examination away from neonatal unit, which required transportation of infants in unfavorable (though safe) conditions. Birth characteristics and morbidity are presented in **Table 1**.

Growth

Growth over time is presented in **Figure 1**. The most premature infants (< 27 weeks) experienced extrauterine growth restriction during the initial 5 weeks of life, followed by catch-up growth. In infants => 27 weeks of gestation, growth restriction period was shorter and the rebound in z-scores occurred sooner. At birth, preterm infants had significantly lower z-scores for weight and length compared to controls. The difference in weight z-scores vanished at term-equivalent age but reappeared at the age of 4 months (**Table 2**). Length z-scores were significantly lower in preterms both at term-equivalent age and at 4 months. Head circumference z-scores were similar in both groups.

Nutrition

Mean intakes of macronutrients in the preterm infants are shown in T**able 3**. From week 1 energy and protein intakes increased. At week 2 mean energy intake was within recommended intake of 115-135 kcal/kg/d and protein intake close to recommended range of 4-4.5 gram/kg/d (**Table 3**).[14] [16] Almost all preterm infants received breastmilk from week 1 and rates were still high at 4 months. Feeding mode in term infants is presented in **Table 1**.

Body composition

See **Table 2** and **Figure 2** for body composition parameters over time. At term-equivalent age, preterm infants compared to term peers, had significantly greater percentage of body fat, and lower FFM. While the difference in adiposity was no longer significant at 4 months of age, the premature infants compared with term controls still had significantly less lean tissue (FFM). When body length was taken into account and the results were analyzed as FMI and FFMI, significant differences were found at term-equivalent age, but no longer at 4 months (**Table 2**).

Determinants of body composition at discharge

Results of univariate regression analysis are presented in **Table 4**. In brief, **adiposity** (fat mass and percentage of body fat) was negatively associated with gestational age, and **lean tissue** was positively associated with antenatal growth (defined as anthropometry z-scores at birth), and initial postnatal growth. Greater adiposity was positively associated with the pace of later growth (gain in weight and length after 4 weeks of age) but no effect on growth during this late period was seen on lean tissue accretion. We have seen little association of nutritional intakes and later body composition (carbohydrates and fat intakes not show). Surprisingly, higher protein intake, and protein/energy index were negative predictors of FFM at discharge. After adjusting for gestational age and birth weight z-scores, most of these associations were no longer significant. However, protein intake at week 2 was still a negative predictor of FFM (data not presented).

5. Discussion

Premature infants in the current study experienced moderate to severe growth restriction during the initial 5 weeks of life, the more immature the infant the greater the severity. This was followed by catch-up growth seen between discharge and 4 months corrected age when almost half of infants was still fed human milk. Preterm infants at achieving term-equivalent age were shorter, had greater adiposity and less lean tissue, compared to healthy term controls. At 4 months, body weight of preterm infants was significantly lower, and they remained shorter. The absolute difference of FFM in grams was still observed during this period but there was no remaining difference in FFMI. In addition, our results show that velocity of growth after 4 weeks of age was associated with more adiposity. Higher protein intake was associated to less FFM at discharge.

Our findings on more adiposity and less lean tissue in preterm infants at discharge and at term-equivalent age, are in accordance with those reported by other authors. In a meta-analysis of eight studies, preterm infants at term-equivalent age had greater percentage of body fat, less FM and much less FFM, compared to term peers.[3] There is less research on how body composition changes after discharge. Existing data suggest that differences between preterm and term infants resolve by late infancy. [8,17] Similar to our findings, Ramel et al.[9] observed that the lower FFM and higher adiposity in preterm infants at term corrected age were no longer significant at 3 to 4 month of age.[9] Whether these early transient alterations in body composition have impact on later health is not yet fully understood.

Altered body composition in premature infants is likely to be caused by a range of exposures that modulate partitioning of nutrients to build up fat and lean tissue. Appropriate growth is affected by availability of nutrients, mode of supply (enteral/parenteral), co-morbidity, and hormonal influences.[18] Physiologically, adipose tissue accretion is rapid after birth due to sudden shift from intra- to extrauterine environment. Continuous nutrients delivery via the placenta is replaced by intermittent enteral, high-fat feeding. Fat is gathered as energy store and to reduce heat loss. [8] This follows both premature and term birth. This phenomenon of rapid adipose tissue accretion can be clearly seen by comparing at-discharge body composition in our cohort (mean postmenstrual age 36.8 weeks, %BF 20, FM 0.7 kg, FFM 2,7 kg) with the recent body composition curves for premature infants at the corresponding gestational age, examined shortly after birth (%BF 9, FM 0.23 kg, FFM 2,25 kg).[19] If we consider accretion of adipose tissue an adaptive physiological process following birth, then the current recommendation to mimic both growth and body composition in preterm infants so they are the same as in normal fetus of the same age, might be debatable. [14]

The great majority of preterm infants in our study were fed breastmilk, which may have contributed to high adiposity seen at term-equivalent age. Breastfed, compared to formula fed, infants were shown to have less FFM at the age of 3 to 6 months of age, but lower adiposity at 12 months.[20] It has been postulated that considering higher adiposity at this early age as a determinant for later risk for adiposity may be inappropriate.[20] FFM may be a better prognostic marker for metabolic and neurologic outcomes of preterm infants than is FM.[6] Changes of FFM are a marker of protein accretion and organ development. Thus, pace of growth during the first months of postnatal life is critical for later development. [5,9] Results recently published by Ramel et al. have shown that the gains in FFM, not FM were positively associated to later neurodevelopment.[7]

In this cohort of preterm infants, protein intake was higher compared to our earlier findings (below requirements only at week 1). [2] In general, the effect of early postnatal nutrition on body composition was surprisingly small (**Table 4**). This might be due to the little variation in nutrient intakes observed and other factors affecting growth such as hormonal profile and prematurity-related morbidity (**Table 1**). Adjusting for these factors in the present study was not possible due to small sample size.

Surprisingly, higher protein intake was associated with less lean tissue accretion at discharge. This finding stands in contradiction to other studies pointing out that higher energy and protein intakes improve FFM gains in premature infants.[6,9,21,22] We speculate that our unexpected finding is the effect of restricted growth followed by increasing energy and protein supply rather than the effect of protein *per se*.

The main strength of our study are the early, pre-discharge measurements of body composition and the long follow up. To date, there has been very little data on the body composition in preterm infants shortly after birth, and limited data are available on long-term body composition determination in premature infants. [19,23] We provide the data for the time of achieving clinical stability (mean postmenstrual age of 33.3 weeks). Another strength was the partly-prospective nutrition and growth data collection. Control group consisted of healthy full-term infants measured after one week of age to avoid bias related to high body water at birth and weight loss thereafter.

The most important limitation is the small sample size. While we were able to show the difference for the main outcome (percentage body fat) between term- and preterm infants , conclusions regarding observations within preterm group e.g. associations of nutritional intakes and body composition, should be drawn with great cautionespecially taking the unexpected finding of adverse association of protein intakes and lean tissue accretion. The choice of air displacement plethysmography as a method to determine body composition might also be considered as not optimal. Even though reproducibility of the results is reasonable, accuracy in preterm infants might be modest.[24] Despite these concerns, PeaPod has been considered a valuable tool with a broad clinical research application and it is indeed used by many research groups enabling comparing of research results.

CONCLUSIONS

The current study showed that preterm infants when achieving term-equivalent age, were lighter, shorter, had more adiposity (% BF, FM) and less lean tissue (FFM) compared to their term peers. At 4 months of age, body weight and length, as well as FFM were still lower than in term infants. Antenatal and early postnatal growth had a positive association with more favorable body composition (less adiposity, more lean tissue). Surprisingly, we observed little effect of macronutrient intakes measured during the first 4 weeks of life on body composition. The unexpected finding of higher protein intake being a predictor of having less lean tissue at discharge, may be interpreted as an effect of postnatal growth restriction (and higher protein intake in these who experienced it) rather than the effect of protein *per se*.

Our results add to the existing literature supporting closer monitoring of body composition in infants born premature. Nutrition is one of the crucial factors in the process of acquiring body composition promoting better health outcome.

Statement of Ethics and Disclosure Statement

Bioethical Committee of Umeå approved the study protocol (2010-6031, 2010-03-02). Parents have given their written informed consent at study entry. The PeaPod study was funded through the regional agreement between Umeå University and Västerbotten County Council on cooperation in the field of Medicine, Odontology and Health (ALF), Oskar Foundation, the Swedish Research Council (Vetenskapsrådet, grant # 2016-02095) and The Västerbotten County Council (ALF grant). None of the authors has any conflicts of interest to disclose.

REFERENCES

1 Wood NS CK, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR; EPICure Study Group: The EPICure study: growth and associated problems in children born 25 weeks of gestational age or less. Arch Dis Child Fetal Neonatal Ed 2003;88:F492-F500.

2 Stoltz Sjostrom E, Ohlund I, Ahlsson F, Engstrom E, Fellman V, Hellstrom A, Kallen K, Norman M, Olhager E, Serenius F, Domellof M: Nutrient intakes independently affect growth in extremely preterm infants: results from a population-based study. Acta Paediatr 2013;102:1067-1074.

3 Johnson MJ, Wootton SA, Leaf AA, Jackson AA: Preterm birth and body composition at term equivalent age: a systematic review and meta-analysis. Pediatrics 2012;130:e640-649.

4 Lapillonne A, Griffin IJ: Feeding preterm infants today for later metabolic and cardiovascular outcomes. J Pediatr 2013;162:S7-16.

5 Belfort MB, Gillman MW, Buka SL, Casey PH, McCormick MC: Preterm infant linear growth and adiposity gain: trade-offs for later weight status and intelligence quotient. J Pediatr 2013;163:1564-1569 e1562.

6 Simon L, Frondas-Chauty A, Senterre T, Flamant C, Darmaun D, Roze JC: Determinants of body composition in preterm infants at the time of hospital discharge. Am J Clin Nutr 2014;100:98-104.

7 Ramel SE, Gray HL, Christiansen E, Boys C, Georgieff MK, Demerath EW: Greater Early Gains in Fat-Free Mass, but Not Fat Mass, Are Associated with Improved Neurodevelopment at 1 Year Corrected Age for Prematurity in Very Low Birth Weight Preterm Infants. J Pediatr 2016;173:108-115.

8 Griffin IJ, Cooke RJ: Development of whole body adiposity in preterm infants. Early Hum Dev 2012;88 Suppl 1:S19-24.

9 Ramel SE, Gray HL, Ode KL, Younge N, Georgieff MK, Demerath EW: Body composition changes in preterm infants following hospital discharge: comparison with term infants. J Pediatr Gastroenterol Nutr 2011;53:333-338.

10 Costa-Orvay JA F-AJ, Romera G, Closa-Monasterolo R, Carbonell-Estrany X: The effects of varying protein and energy intakes on the growth and body composition of very low birth weight infants. Nutrition Journal 2011;10:140.

11 Tremblay G, Boudreau C, Belanger S, St-Onge O, Pronovost E, Simonyan D, Marc I: Body Composition in Very Preterm Infants: Role of Neonatal Characteristics and Nutrition in Achieving Growth Similar to Term Infants. Neonatology 2017;111:214-221.

12 Urlando A, Dempster P, Aitkens S: A new air displacement plethysmograph for the measurement of body composition in infants. Pediatr Res 2003;53:486-492.

13 Stoltz Sjostrom E, Ohlund I, Tornevi A, Domellof M: Intake and macronutrient content of human milk given to extremely preterm infants. J Hum Lact 2014;30:442-449.

14 Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, Domellof M, Embleton ND, Fusch C, Genzel-Boroviczeny O, Goulet O, Kalhan SC, Kolacek S, Koletzko B, Lapillonne A, Mihatsch W, Moreno L, Neu J, Poindexter B, Puntis J, Putet G, Rigo J, Riskin A, Salle B, Sauer P, Shamir R, Szajewska H, Thureen P, Turck D, van Goudoever JB, Ziegler EE, Nutrition ECo: Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr 2010;50:85-91.

15 Roggero P, Gianni ML, Amato O, Orsi A, Piemontese P, Morlacchi L, Mosca F: Is term newborn body composition being achieved postnatally in preterm infants? Early Hum Dev 2009;85:349-352.

16 Vård för extremt för tidigt födda barn. En vägledning för vård av barn födda före 28 fullgångna graviditetsveckor. Socialstyrelsen: National Board of Health and Welfare, Sweden (September 2014) 2014

17 Giannì ML MS, Roggero P, Amato O, Piemontese P, Orsi A, Vegni C, Puricelli V, Mosca F: Regional fat distribution in children born preterm evaluated at school age. Journal of Pediatric Gastroenterology and Nutrition 2008;46:232-235.

18 Hellström A LD, Hansen-Pupp I, Hallberg B, Löfqvist C, van Marter L, van Weissenbruch M, Ramenghi LA, Beardsall K, Dunger D, Hård AL, Smith LEH.: Insulin-like growth factor 1 has multisystem effects on foetal and preterm infant development. Acta Paediatrica 2015;105:576-586.

19 Demerath EW, Johnson W, Davern BA, Anderson CG, Shenberger JS, Misra S, Ramel SE: New body composition reference charts for preterm infants. Am J Clin Nutr 2017;105:70-77.

20 Gale C, Logan KM, Santhakumaran S, Parkinson JR, Hyde MJ, Modi N: Effect of breastfeeding compared with formula feeding on infant body composition: a systematic review and meta-analysis. Am J Clin Nutr 2012;95:656-669.

21 Loe IM, Lee ES, Luna B, Feldman HM: Behavior problems of 9-16 year old preterm children: biological, sociodemographic, and intellectual contributions. Early Hum Dev 2011;87:247-252.

22 Rochow N, Fusch G, Muhlinghaus A, Niesytto C, Straube S, Utzig N, Fusch C: A nutritional program to improve outcome of very low birth weight infants. Clin Nutr 2012;31:124-131.

23 Lapillonne A BP, Claris O, Chatelain PG, Delmas PD, Salle BL: Body composition in appropriate and in small for gestational age infants. Acta Pediatrica 1997;86:196-200.

24 Mazahery H, von Hurst PR, McKinlay CJD, Cormack BE, Conlon CA: Air displacement plethysmography (pea pod) in full-term and pre-term infants: a comprehensive review of accuracy, reproducibility, and practical challenges. Matern Health Neonatol Perinatol 2018;4:12.

Legend to figures:

Figure 1. Growth in preterm infants born at the gestational age. A. Gestational age <= 27 weeks. B. Gestational age > 27 weeks. (TEA: term-equivalent age; 4 mo: 4 months)

Figure 2. Body composition overtime in preterm and term infants. A.% body fat. B. Fat free mass and fat mass. (* significant difference, $p<0.05$)

Table 1. Characteristics of the preterm infants (N=33).

PREMATURE INFANTS (N=33)		
Birth characteristics	n/N	Proportion (%)
Male	12/33	36
Twins	8/33	22
Gestational age <= 27 weeks	13/33	39
SGA (<-2 SD)	6/33	18
	n	Mean (SD)
Gestational age (weeks)	33	28.1 (2.6)
Birth weight (g)	33	1136 (406)
Birth length (cm)	29	36.7 (4.2)
Birth head circumference (cm)	27	26 (2.8)
Postmenstrual age (weeks)		
• at achieving clinical stability	22	33.3 (1.7)
• at discharge	28	36.8 (0.8)
• at term equivalent age	27	40.8 (0.7)
• 4 months	21	55 (0.7)
Morbidity / interventions	n/N	Proportion (%)
ROP, retinopathy of prematurity	8/31	24
NEC, necrotizing enterocolitis	0/33	-
RDS, respiratory distress syndrome	22/33	67
Mechanical ventilation	10/33	40
• 5 - 8 days	4	
• 11 – 14 days	3	
• 19 - 21 days	3	
Requiring oxygen		
• at 28 weeks postmenstrual age	9/33	27
• at 36 weeks postmenstrual age	5/33	15
IVH grade I	8/32	25
IVH grade II	1/32	3
PDA requiring surgery	2/33	6
PDA pharmacologic treatment	8/33	24
TERM CONTROLS (N=68)		
Birth characteristics	n	Mean (SD) / %
Male (%)	69	52%
Gestational age (weeks, SD)*	69	40 (1.0)
Birth weight (g)	61	3509 (474)
Birth length (cm)	59	50.6 (1.9)
Birth head circumference (cm)	43	34.9 (1.3)
Feeding mode	TEA (n=67)	4 months (n=62)
• Exclusive breastfeeding: n (%)	49 (71)	45 (65)
• Mixed feeding: n (%)	17 (24.5)*	6 (9)
• Formula feeding: n (%)	1 (1.5)	11 (16)

SD: standard deviation; IVH: intraventricular hemorrhage; PDA: patent ductus arteriosus; SGA: small for gestational age (birth weight <-2SD); TEA: term-equivalent age.

Table 2. Anthropometry and body composition in premature infants compared to healthy term controls. Data presented as means (SD) and mean difference (MD).

	Term equivalent age			
	Term (N=68)	Preterm (N=26)	MD	p
Weight (grams)	3617 (477)	3405 (401)	212	0.045
Weight (z-score)	-0.76 (0.88)	-0.87 (0.89)	0.1	0.509
Length (cm)	52.7 (1.7)	49.0 (2.0)	2.9	<0.0001
Length (z-score)	-0.41 (0.93)	-1.8 (1.1)	1.4	<0.0001
Head circumference (cm)	35.6 (1.1)	35.0 (1.4)	0.58	0.035
Head circumference (z-score)	0.22 (4.7)	-0.46 (0.98)	0.68	0.464
Total body fat (%)	11.67 (3.98)	20.17 (3.56)	-8.49	<0.0001
FM (kg)	0.431 (0.186)	0.695 (0.181)	-0.264	<0.0001
FFM (kg)	3.18 (0.361)	2.715 (0.277)	0.464	<0.0001
FMI (kg/m^2)	1.5 (0.6)	2.8 (0.6)	-1.29	<0.0001
FFMI (kg/m^2)	11.7 (0.7)	11.2 (0.6)	0.45	0.012
	4 months (N=25)			
	Term (N=65)	Preterm (N=25)	MD	p
Weight (grams)	6430 (1092)	5896 (765)	543	0.011
Weight (z-score)	0.06 (0.97)	-0.73 (1.0)	0.8	0.001
Length (cm)	62.5 (2.0)	59.2 (2.3)	3.2	<0.0001
Length (z-score)	0.29 (1.0)	-1.31 (1.0)	1.6	<0.0001
Head circumference (cm)	41.0 (1.6)	40.5 (1.5)	0.5	0.165
Head circumference (z-score)	-0.17 (0.86)	-0.34 (1.0)	0.1	0.451
Total body fat (%)	26.41 (4.38)	26.51 (3.97)	-0.09	0.924
FM (kg)	1.735 (0.411)	1.582 (0.397)	0.153	0.113
FFM (kg)	4.781 (0.476)	4.3 (0.44)	0.472	<0.0001
FMI (kg/m^2)	4.4 (1.0)	4.4 (0.9)	-0.1	0.93
FFMI (kg/m^2)	12.2 (0.7)	12.2 (0.7)	-0.4	0.82

Independent sample t-test.

Table 3. Macronutrients intake and feeding mode in preterm infants. Values presented as means (SD) or percentage.

	Week 1 n=32	Week 2 n=32	Week 3 n=32	Week 4 n=32	Disch. n=22	TEA n=24	4 mo n=25
Energy (kcal/kg/d)	84.5 (9.1)	124.4 (13.4)	131.3 (12.6)	134.2 (19.1)	-	-	-
Protein (g/kg/d)	3.1 (0.3)	3.7 (0.3)	3.8 (0.4)	3.9 (0.3)	-	-	-
PE index (g/100 kcal)	3.2 (0.4)	3.0 (0.3)	2.8 (0.2)	2.8 (0.3)	-	-	-
Carbohydrates (g/kg/d)	11.2 (1.6)	13.8 (1.4)	14.4 (1.6)	14.6 (2.0)	-	-	-
Lipids (g/kg/d)	3.1 (0.6)	5.7 (0.9)	6.2 (0.9)	6.4 (1.4)	-	-	-
Mothers own milk [n (%)]	75	96	100	96	20(90%)	17 (70%)	11 (44%)
Donated milk [n (%)]	53	68	68	78	-	-	-
Excl. breastfed [n (%)]					12 (54%)	10 (41%)	10 (40%)

PE index: protein to energy index; Disch.: discharge; TEA: term-equivalent age.

Table 4. Univariate regression models assessing baseline characteristics, growth, and nutrition as predictors of body composition in preterm infants at discharge.

Univariate predictor	% BODY FAT B unst	R2	p	FAT MASS (g) B unst	R2	p	FAT FREE MASS (kg) B unst	R2	p
Gestational age	-1.083	0.387	0.001	-39	0.422	<0,0001	-16	0.028	0.426
Female gender	-2.487	0.081	0.168	-61	0.041	0.332	140	0.089	0.149
Birth W z-score	0.456	0.017	0.531	42	0.126	0.082	154	0.682	<0.0001
Birth L z-score	-0.251	0.005	0.752	24	0.044	0.346	182	0.697	<0.0001
Birth HC z-score	0.718	0.024	0.502	53	0.128	0.112	180	0.394	0.002
W z-score discharge	1.976	0.152	0.054	100	0.332	0.003	215	0.621	<0.0001
HC z-score discharge	-1.322	0.079	0.173	-14	0.008	0.672	0,155	0,374	0,001
W z-score TEA	0.727	0.024	0.458	51	0.1	0.142	166	0.433	0.001
L z-score discharge	-0.469	0.014	0.571	14	0.01	0.629	163	0.594	<0.0001
L z-score TEA	-0.473	0.013	0.601	16	0.012	0.612	159	0.528	<0.0001
HC z-score discharge	-1.322	0.079	0.173	-14	0.008	0.672	155	0.374	0.001
HC z-score TEA	-1.368	0.08	0.192	-10	0.003	0.791	181	0.492	<0.0001
Delta W z-score birth – 2 weeks	-0.441	0.003	0.78	-0.052	0.04	0.339	-0.210	0.27	0.008
Delta W z-score birth – 4 weeks	-2.489	0.263	0.009	-0.01	0.363	0.001	-0.102	0.152	0.054
Delta W z-score 4 weeks - discharge	3.591	0.518	<.0001	0.116	0.456	<.0001	-0.004	<.0001	0.947
Delta L z-score birth – 2 weeks	-3.421	0.307	0.011	-0.098	0.242	0.028	0.017	0.02	0.851
Delta L z-score birth – 4 weeks	-2.474	0.341	0.007	-0.075	0.314	0.010	0.001	<.0001	0.99
Delta L z-score 4 weeks - discharge	3.773	0.412	0.001	0.12	0.35	0.003	-0.008	0.001	0.909
Delta HC z-score birth – 2 weeks	-3.299	0.154	0.108	-0.111	0.17	0.089	-0.072	0.02	0.578
Delta HC z-score birth – 4 weeks	-3.144	0.47	<.0001	-0.103	0.503	<.0001	-0.034	0.014	0.597
Energy days 0-3 (kcal/kg)	0.22	0.141	0.065	5	0.057	0.251	-11	0.105	0.115
Protein day 0-3 (g/kg)	4.25	0.241	0.013	122	0.186	0.042	-70	0.023	0.473
PE index day 0-3 (g/100 kcal)	3.32	0.175	0.037	106	0.151	0.055	-12	0.001	0.892
Energy week 1	0.05	0.013	0.587	<0.0001	<0.0001	0.967	-9	0.131	0.076
Protein week 1	4,16	0.222	0.017	113	0.138	0.067	-109	0.053	0.268
PE index week 1	5.36	0.293	0.005	17	0.249	0.011	-30	0.003	0.786
Energy week 2	-0.08	0.021	0.23	-4	0.1	0.124	-5	0.091	0.143
Protein week 2	2.33	0.047	0.296	3	<0.0001	0.965	-37	0.411	0.001
PE index week 2	7.69	0.269	0.008	184	0.131	0.075	-296	0.138	0.068
Energy total week 1 to 4	0.098	0.041	0.345	1	0.007	0.688	-10	0.154	0.058
Protein total week 1 to 4	3.8	0.109	0.115	61	0.023	0.476	-334	0.281	0.008
PE index total week 1 to 4	5.13	0.071	0.207	89	0.018	0.535	-365	0.120	0.097

W: weight; L: length; HC: head circumference; TEA: term-equivalent age; PE index: protein to energy index.

Figure 1A

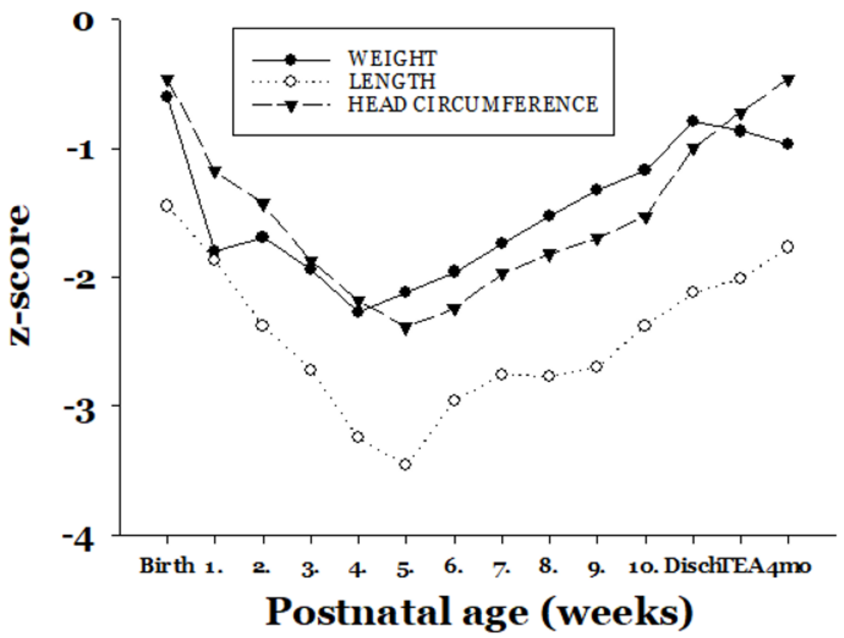

Figure 1B

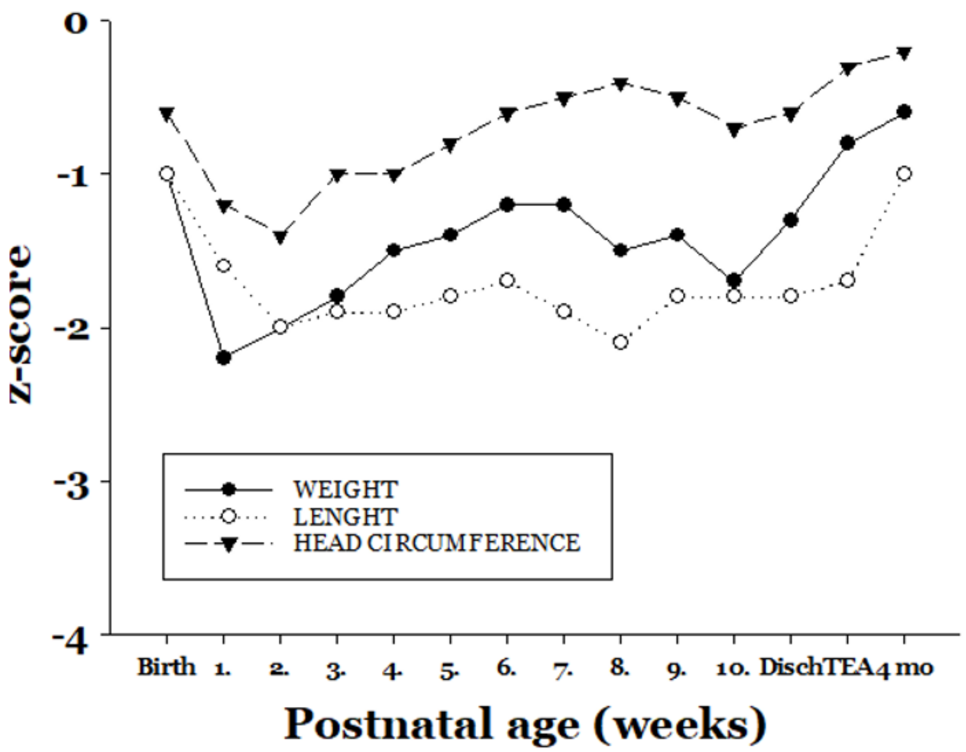

Figure 2A_Percentage of body fat in preterms vs term infants

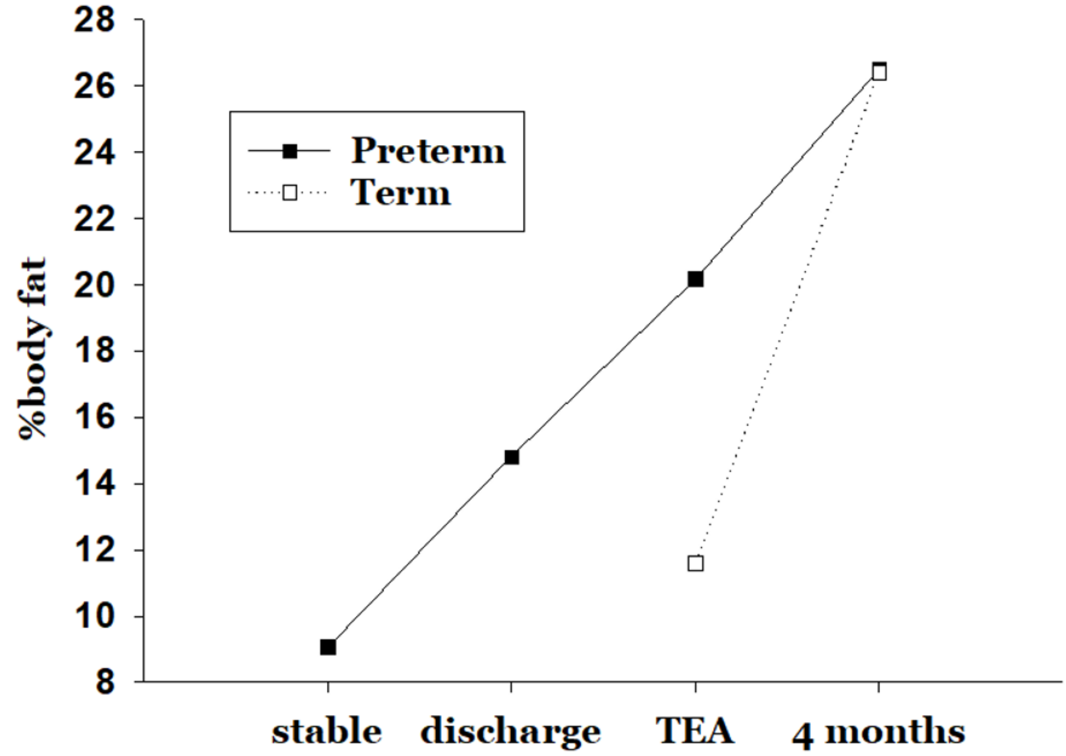

Figure 2B_Fat free mass and fat mass in preterms vs term infants