Serial Assessment of Fat and Fat-free Mass Accretion in Very Preterm Infants: A Randomized Trial

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Abstract

Background: Clinicians could modify dietary interventions during early infancy by monitoring fat and fat-free mass accretion in very preterm infants.

Methods: Preterm infants were randomly assigned to either having reports on infant body composition available to the clinicians caring for them (intervention group) or not having reports available (control group). All infants underwent serial assessments of body composition by air-displacement plethysmography before 32 weeks of postmenstrual age (PMA) and at 36 weeks PMA. The primary outcome was percent body fat (%BF) at 3 months of corrected age (CA).

Results: Fifty infants were randomized (median gestational age: 30 weeks; mean ± SD birth weight: 1387 ± 283 g). The mean %BF increased from 7 ± 4 before 32 weeks PMA to 20 ± 5 at 3 months CA. The differences in mean %BF between the intervention group and the control group were not statistically significant at 36 weeks PMA (14.5 vs. 13.6) or 3 months CA (20.8 vs. 19.4). Feeding practices and anthropometric measurements during hospitalization did not differ between groups.

Conclusions: Serial assessments of body composition in both intervention and control groups showed consistent increments in %BF. However, providing this information to clinicians did not influence nutritional practices or growth.

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INTRODUCTION

Clinicians in the neonatal unit have the ability to effectively control all external sources of nutrition in the immediate neonatal period. However, having this type of control has not led to significant reductions in postnatal growth failure at 36 weeks of postmenstrual age (PMA). Postnatal growth failure (weight $< 10^{th}$ percentile) occurs in up to 60% (1–3) of the nearly 80,000 infants born preterm at 32 weeks of gestation or less every year in the United States (4).

To prevent postnatal growth failure, clinicians often prescribe high-calorie diets to promote weight gain between 15 and 20 g/kg/d in preterm infants (5). This nutritional practice is common across neonatal units, but the practice of assessing the effects of weight gain on body composition using air-displacement plethysmography (ADP) is not. A comprehensive evaluation of postnatal growth with infant body composition could help guide dietary interventions for infants at high risk of excessive weight gain and rapid body fat accretion that may ultimately increase the risk of obesity and long-term related morbidities (6–9). Currently, assessment of body composition is neither part of the usual care of preterm infants in neonatal units nor part of screening programs to monitor body composition of infants with a history of prematurity in follow-up clinics.

We hypothesized that, by monitoring fat and fat-free mass accretion before and after hospital discharge in very preterm infants (28 to 32 weeks of gestation), clinicians could modify dietary interventions in early infancy, promote fat-free mass (FFM) accretion, and prevent excessive fat mass (FM) accretion (10, 11). The specific aims of this pilot trial were to evaluate the feasibility of serial assessments of body composition in the routine care of preterm infants and to determine if providing information on body composition to clinicians could guide dietary interventions and improve growth outcomes of preterm infants.

SUBJECTS AND METHODS

Trial design

This study was a parallel-group randomized controlled trial in which preterm infants were randomly assigned to either intervention or control group with a 1:1 allocation ratio. The study protocol was approved by the University of Alabama at Birmingham (UAB) Institutional Review Board (IRB).

Participants

Very preterm infants with gestational ages between 28 and 32 weeks of gestation admitted to the neonatal unit at the UAB hospital located in Birmingham, Alabama were included. Infants with gastrointestinal malformations, central nervous system malformations, or terminal illness needing to limit or withhold support were excluded.

Randomization, allocation concealment, and masking

Prior to randomization, written parental consent was obtained within the first week after birth. A computer-generated, random-block sequence was used to randomize study participants. Numbered, opaque, sealed envelopes were opened in sequential order to

allocate the study intervention. Twin infants were randomized individually. The study intervention was not masked.

Interventions

All infants underwent serial assessments of body composition during their stay in the neonatal unit. The first assessment was performed between birth and 32 weeks of postmenstrual age (PMA), and the subsequent assessment was performed at 36 weeks PMA or hospital discharge, whichever occurred first. Infants randomly assigned to the intervention group had the information about infant body composition available for the clinicians caring for them (including reference data). Infants randomly assigned to the control group had this information about infant body composition collected, but it was not available for the clinicians caring for them.

Primary and secondary outcomes

The primary outcome was percent body fat (%BF) estimated by ADP at 3 months of corrected age (CA). Other pre-specified secondary outcomes were FM, FFM, and %BF at 36 weeks PMA or hospital discharge (whichever occurred first), postnatal growth failure (below 10th percentile) at 36 weeks PMA or discharge, weight gain (g/kg/d) from birth to 36 weeks PMA estimated by using the exponential method (12), and anthropometric measurements at 36 weeks PMA (weight, head circumference, and length).

Study procedures

For infants in the intervention group, written reports were prepared 1 to 4 days after the assessment date and presented to front-line clinicians (i.e., residents or nurse practitioners) caring for the infant. Clinicians were instructed to discuss the body composition report during multidisciplinary rounds in subsequent days. Weight, length, %BF, and percentile values were included in the report. Information on FFM was not included.

Only infants who did not require intravenous fluids or respiratory support had ADP assessments of body composition. Serial assessments of infant body composition were performed with the PeaPod® (Life Measurement Instruments, Concord, CA) (13). For inpatient assessments, nursery staff and parents, if present, transported the infant from the neonatal unit to the exam room within the same building where the PeaPod® is located. For outpatient assessments at 3 months of age, a follow-up visit was scheduled prior to discharge from the hospital.

Control or monitoring of co-interventions

Clinical care and decisions about nutritional practices were conducted at the discretion of the attending neonatologist. During the trial, enteral nutrition was initiated at 20–30 ml/kg/d for 1 to 3 days and then advanced by 20–30 ml/kg/d until full enteral nutrition was established (>150 ml/kg/d). Bovine-based fortifiers were added to human milk when enteral nutrition reached 100 to 120 ml/kg/d. If the supply of human milk was insufficient to advance enteral nutrition, 24 kcal/oz preterm formula was prescribed. Donor milk was not offered. Enteral nutrition was discussed daily during family-centered rounds and weekly during multidisciplinary rounds that included a registered dietitian.

Sample size

A sample size of 46 patients was considered necessary to detect a 3-point difference in %BF between groups with SD of 3.6, 0.05 level of significance, and 80% power. In anticipation of a loss to follow-up rate close to 10%, 2 patients were added to each group and the sample size was increased to 50.

Statistical methods

This trial recorded core data on nutrition, as recommended by consensus groups (12, 14). For analysis of the primary outcome, an unadjusted t-test comparison of the mean %BF between control and intervention groups was performed. A similar approach was used for secondary outcomes. Descriptive data was expressed as the mean (SD) or number (percentage) of observations. A pre-specified MANOVA analysis was performed to determine within subject and between subjects variability in the repeated measures model. The primary statistical analyses were performed using JMP software, version 14.1 (SAS Institute Inc., Cary, NC).

RESULTS

Fifty very preterm infants were randomized (Figure 1). The mean ± SD birth weight was 1387 ± 283 g, and the median gestational age was 30 weeks (IQR: 30 – 32 weeks). A set of triplets born at 28 weeks of gestation who needed non-invasive respiratory support during the first weeks after birth were not assessed by 32 weeks PMA. The number of infants without a body composition assessment at 36 weeks PMA did not differ between groups. Nine infants were not assessed at 36 weeks PMA or discharge due to an unexpected, 6-week long, maintenance problem with the PeaPod®. Sociodemographic characteristics did not differ between groups (Table 1). Approximately one-third of the infants included (16 of 50) were the product of multiple gestations (3 sets of twins, 2 sets of triplets, and 1 set of quadruples). Most infants received mother's milk as primary source of nutrition during the first weeks after birth and achieved enteral feeding volumes > 120 ml/kg/day by postnatal day 8.

Between birth and 32 weeks PMA, 45 of 50 infants had a body composition assessment. Three of these infants had a weight of less than 1000 g at the time of assessment. The median postnatal age at the first assessment was 12 d (IQR: 10 – 14 d), around 32 weeks PMA. At 36 weeks PMA or hospital discharge (whichever occurred first), 35 of 50 infants had a body composition assessment. The median postnatal age at the second assessment was 35 d (IQR: 28 – 40 d), around 36 weeks PMA. At 3 months CA, 25 of 50 infants had a body composition assessment. The mean %BF between birth and 32 weeks PMA was 6.7 ± 3.6, the mean %BF at 36 weeks PMA was 14.2 ± 3.7, and the mean %BF at 3 months CA was 19.9 ± 4.8. Mean differences in %BF between the intervention group and the control group were not statistically significant at 36 weeks PMA (+0.9 favoring the intervention group; 95% CI: −1.7 – 3.5; p=0.49) or 3 months CA (+1.5 favoring the intervention group; 95% CI: −2.6 – 5.5; p=0.46) (Figure 2). In a MANOVA analysis, neither variability between subjects (p=0.26) nor variability within subjects (p=0.89) explained the effects observed across the repeated measurements of %BF. The correlation between %BF at 36 weeks PMA and %BF

at 3 months CA was low (r=0.32). Significant differences in FFM accretion between groups were not found. BF, FM, and FFM *z* scores at 3 months CA or 52 weeks PMA were closer to sex-specific reference values available for preterm infants of the same postnatal age (i.e. 3 months CA) (15) and they did not differ significantly between groups (Figure 3).

Around the time of the first body composition assessment, the median caloric intake was 113 cal/kg/d (IQR: 105 – 125 cal/kg/d) and the median protein intake was 1.7 g/kg/d (IQR: 1.5 – 4 g/kg/d). These median values did not differ significantly between groups. By the time of the second body composition assessment, the median protein intake increased by 1 g/kg/d (IQR: 0 – 2.7 g/kg/d) and the median caloric intake increased by 6 cal/kg/d (IQR: 0 – 22 cal/kg/d) in both groups. There were no significant differences in these increments between groups.

After comparing baseline characteristics between infants with missing data and infants with complete data for the outcome of %BF at 3 months CA, we determined that black infants were less likely to return for follow-up (35% vs. 63%; p=0.05) and that only 7 of 16 infants who were the product of multiple gestations returned for follow-up assessments at 3 months CA.

Feeding practices and growth outcomes during hospitalization did not differ between groups (Table 2). The median postnatal age at discharge was 48 d (IQR: 36 – 59 d), around 37 weeks PMA. No harms or unintended effects of the study intervention were found. Of 23 infants that required respiratory support during the first weeks after birth, 11 were supported with non-invasive ventilation, 9 were supported with mechanical ventilation, and 3 were supported with supplemental oxygen only. None of the infants received postnatal steroid treatment. Similarly, no episodes of culture-proven sepsis were documented. One case of stage 1 necrotizing enterocolitis and one case of grade 1 intraventricular hemorrhage were reported. No other serious events occurred before discharge.

DISCUSSION

This randomized pilot trial that compared the current standard of care with the practice of monitoring changes in infant body composition from birth to hospital discharge in very preterm infants (28 to 32 weeks of gestation) failed to identify the impact of serial assessments of body composition during the hospital stay on infant weight gain, nutritional practices, growth outcomes, and infant body composition at 3 months CA.

The negative results of this pilot trial need a careful interpretation. By not including the body composition reports in the electronic medical records (EMRs), we limited the clinicians' ability to access and review the results during rounds. Also, we did not standardize the reporting on changes in body composition during rounds. Moreover, we did not include specific dietary recommendations in the reports, and the dietitian assigned to the unit was unaware of the allocated intervention and, therefore, unable to provide dietary recommendations according to changes in body composition during multidisciplinary rounds. The 3 to 4-week interval between assessments could also explain the negative results reported in this trial. A trial with body composition assessments at more frequent intervals

and standardized reporting of both FM and FFM gains in the EMR system could be more supportive of our conclusions.

Our hypothesis was based on an improved understanding of the interaction between dietary interventions, infant weight gain, and body fat accretion. Preventing postnatal growth failure with diets that promote excessive weight gain in developing infants (5) might increase susceptibility to early metabolic reprogramming of adverse health outcomes (16–18) including hypertension, insulin resistance (19), and disproportionate increase of body fat (17, 20). Cohort studies that followed preterm infants from birth to adulthood reported higher blood pressure values, higher rates of insulin resistance, and higher body fat in adults born preterm compared to term controls (9, 21). Increased body fat in preterm infants has also been documented at term CA and during early infancy (22), a critical period for infant development. The definition of excessive weight gain depends on the target growth. If the nutritional goal is to prevent postnatal growth failure and achieve growth patterns similar to the ones observed in fetuses of the same gestational age, a weight gain of 15 to 20 g/kg/d can be considered adequate and a weight gain >20 g/kg/d can be considered excessive (23). Conversely, if the nutritional goal is to achieve growth patterns similar to the ones observed in healthy preterm infants, a weight gain > 15 g/kg/d may be unnecessary and, therefore, considered excessive (24). One half of the preterm infants included in our trial had postnatal growth failure at 36 weeks PMA and most experienced weight gain below recommended targets (i.e., 15 g/kg/d). Under these circumstances, detecting disproportionate increase of body fat among preterm infants is more challenging. Many would argue that insufficient weight gain could potentially affect neurodevelopment of preterm infants. However, several randomized trials of dietary interventions that prevented growth failure through adequate weight gain failed to identify benefits on neurodevelopment (17, 25–27). These findings demand caution with the assumption that promoting brain development through weight gain outweighs the risk of potential long-term metabolic dysfunction. Although we could not determine whether weight gain of 15 to 20 g/kg/d increases body fat accretion in preterm infants, we provide preliminary information on body composition outcomes in early infancy, a high-priority field of nutrition research. Because the collective nutritional goal for preterm infants in many neonatal units is to promote adequate weight gain between 15 to 20 g/kg/d that some may consider excessive, a future trial comparing specific targets of weight gain could help elucidate the effects of excessive weight gain on body composition of preterm infants.

We chose very preterm infants as the ideal study population for this trial because their risk for adverse health outcomes is moderate (6, 9), their need for supplemental oxygen after birth is usually resolved by postnatal day 7, and their diets between birth and hospital discharge are strictly controlled for more than 30 days. This trial confirmed most of these assumptions. The majority of infants stayed in the hospital for more than 30 days and 90% of them had their first assessment of body composition by postnatal day 10.

We selected infant body composition at 3 months of age as the primary outcome of the trial because at this age non-invasive methods to assess body fat are available, follow-up rates are usually high, physical activity and other risk factors for overweight and obesity are generally inconsequential, and measurements of body fat accretion are strongly correlated with

measurements at 2 years of age. Recent studies suggest that changes in body composition after hospital discharge could be an important tool to analyze long-term health risks of excessive weight gain during early development (28). We confirmed that %BF assessed within the first month after birth in preterm infants is significantly higher than %BF assessed within the first few days after birth in term infants (15). We also confirmed that by 52 weeks PMA, the differences in body composition between term and preterm infants are minimal (29, 30). However, the implications of these early and transient differences in body fat accretion remain unknown.

Serial assessment of infant body composition using ADP in a randomized clinical trial is one of the strengths of this trial. Currently, ADP is the less invasive method to assess infant body composition (13, 31). With ADP, reference values of adiposity expressed as %BF at different gestational ages have been determined (22, 32). They range from 6% at 30 weeks of gestation to 9.5% at 37 weeks of gestation (15, 32). Others have used low-accuracy methods to assess infant body composition (22) and have suggested that weight data can predict FFM and FM (33). However, several studies that measured body composition with ADP have concluded that anthropometric data cannot predict neonatal adiposity (34, 35).

Another strength of this trial is that we calculated the sample size needed using our institutional data of %BF among preterm infants. Because the average difference in %BF between term and preterm infants is usually 3% (22), we estimated that a 3% absolute difference between groups would be clinically meaningful. Although we selected %BF as the primary outcome of this trial, we recognize that other outcomes of body composition in early infancy (i.e., FFM accretion) may also be critical and superior to traditional growth outcomes associated with long-term health. FFM accretion as a result of weight gain has been linked with improved neurodevelopment (36). Body mass index (BMI) is widely accepted to define obesity in many populations. However, in early infancy, BMI has poor predictive accuracy for childhood obesity and a weak correlation with body fat. Because high BMI correlates with high FFM and BMI explain only up to 43% of the variation in FM among term infants (35, 37), reducing BMI to prevent obesity in early infancy is not currently recommended (38). Body fat accretion as a result of excessive weight gain might have a stronger correlation with overweight and other adverse health outcomes at school age (39).

The main limitations of the study were the single-center study design, the higher than expected loss to follow-up, the small sample size, and the lack of information on other anthropometric measurements such as skin folds and thigh/arm circumferences. Our nutritional practices may differ from nutritional practices in other units. Others have reported that preterm infants can have mean %BF values as high as 17% at 36 weeks PMA. The large amount of breast milk feeding observed during the trial could explain the lower mean %BF values reported. We showed that access to body composition data did not influence decisions on dietary interventions in our unit. However, others may implement more dietary interventions based on changes in body composition. Likewise, our respiratory practices that allowed ADP assessments soon after birth in very preterm infants likely differ from those observed in other units. Only a few studies have validated ADP assessments before 32 weeks PMA. Our follow-up rates at 3 months CA among very preterm infants were lower than our

follow-up rates at 24 months among extremely preterm infants (approximately 80% at our institution). Our small sample size affected the precision of our estimates and reduced the external validity of our results, but our maximized efforts to improve the accuracy of our results increased their internal validity.

While incorporating longitudinal assessment of infant body composition into current practices of neonatal care is innovative, more research is still needed to determine if monitoring changes in body composition could reduce the risk of overweight and obesity in very preterm infants. Future studies promoting weight gain with hospital-based nutritional interventions should report data on infant body composition. Reports of qualitative and quantitative outcomes of growth will determine if close monitoring of body composition during infancy can guide clinical decision-making and define patient-specific nutritional support that balances neurodevelopmental benefit and metabolic risk.

In summary, our results indicate that assessing body composition at intervals defined by ongoing clinical research (i.e., birth to 32 weeks and 36 weeks or discharge) neither reduces variability in nutritional practices nor minimizes the risk of excessive body fat accretion in preterm infants. These results suggest that assessments of body composition at more frequent intervals may be needed to make meaningful changes to dietary interventions and thus affect body composition in infancy.

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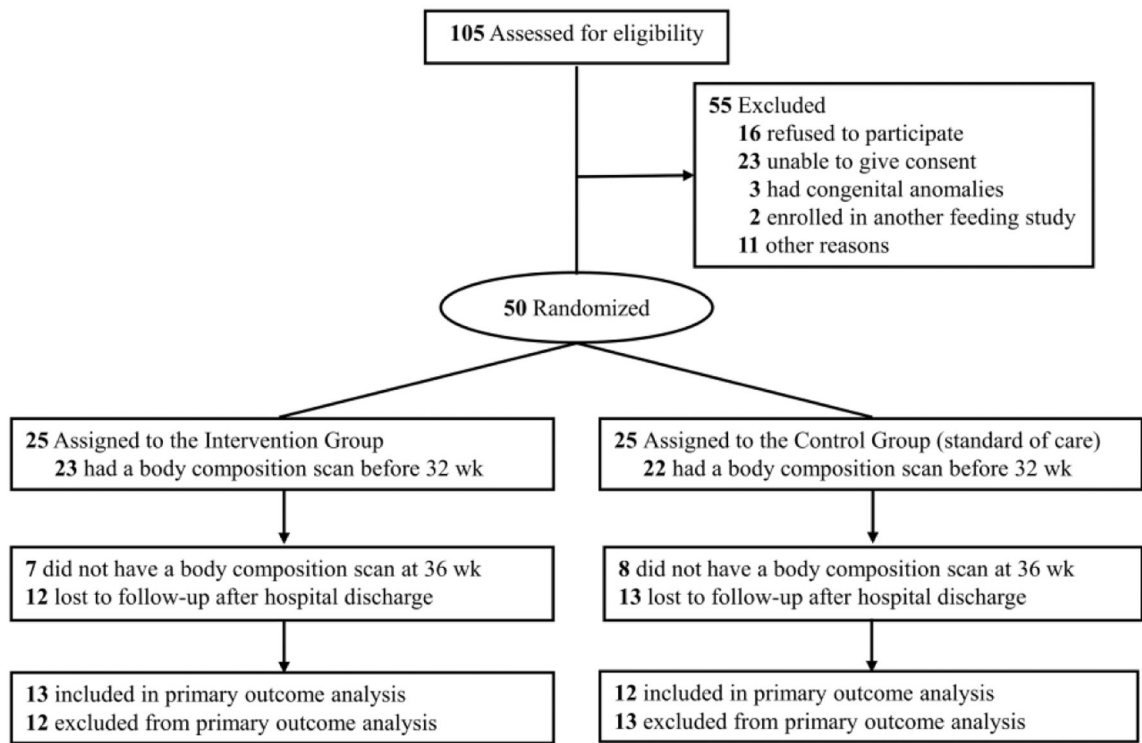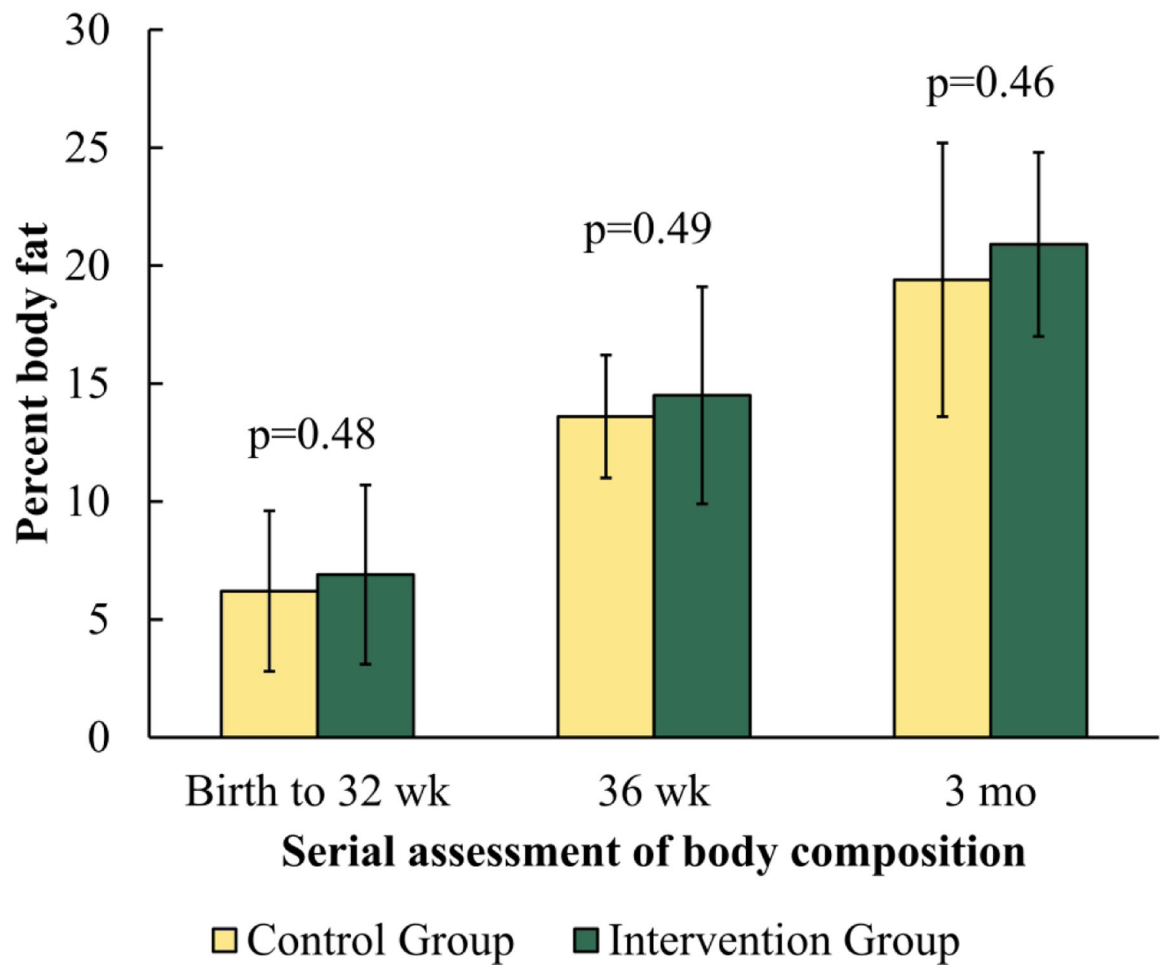
Figure 1.
Flow diagram

Figure 2.
Serial assessment of body fat accretion in very preterm infants

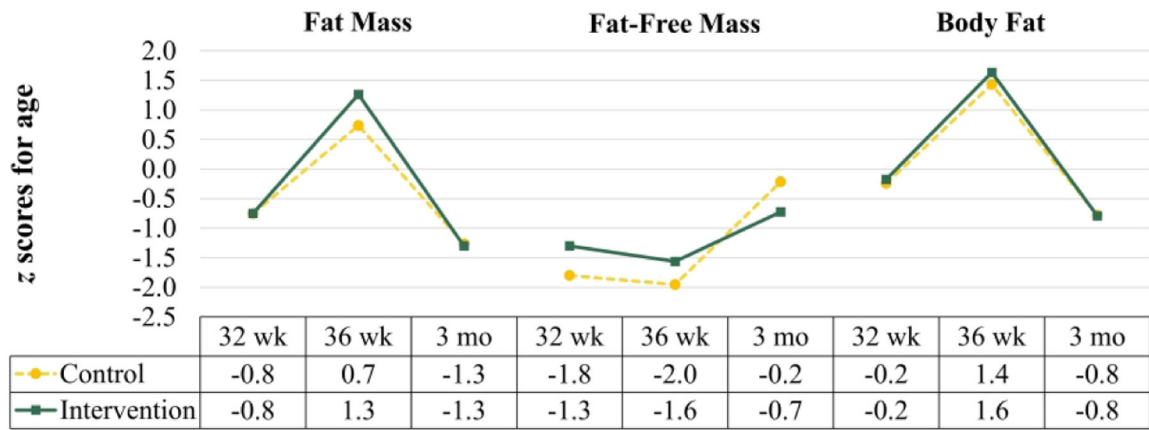|	Fat Mass			Fat-Free Mass			Body Fat		
	32 wk	36 wk	3 mo	32 wk	36 wk	3 mo	32 wk	36 wk	3 mo
Control	-0.8	0.7	-1.3	-1.8	-2.0	-0.2	-0.2	1.4	-0.8
Intervention	-0.8	1.3	-1.3	-1.3	-1.6	-0.7	-0.2	1.6	-0.8

Figure 3. Changes in body composition z scores between birth and 3 months corrected age*
* Differences between groups were not statistically significant

Table 1.

Baseline characteristics [*]

	Intervention group (n = 25)	Control group (n = 25)
Demographic characteristics		
Birth weight in grams, median (IQR)	1423 ± 295	1353 ± 273
Gestational age in weeks, median (IQR)	31(30–32)	30 (30–32)
Weight-for-age z score at birth[1], mean ± SD	−0.16 ± 0.77	−0.38 ± 0.84
Weight <10th percentile at birth[1], n (%)	3 (12)	5 (20)
Male, n (%)	15 (60)	11 (44)
Black race, n (%)	11 (44)	12 (48)
Exposure to a full course (2 doses) of antenatal steroids, n (%)	22 (88)	22 (88)
Vaginal delivery, n (%)	10 (40)	6 (24)
Postnatal age when enteral feeding was initiated in days, median (IQR)	3 (2–4)	3 (2–4)
Postnatal age when > 120 ml/kg of enteral feeding was achieved in days, median (IQR)	8 (7 – 9)	8 (7 – 9)
Proportion of intake as mother's milk (>80%) at postnatal day 7, n (%)	17 (68)	16 (70)
Duration of parenteral nutrition in days, median (IQR)	6 (0–7)	5 (0–7)

[*] Differences between groups were not statistically significant

[1] z scores were estimated with the Fenton 2013 growth curves.

Table 2.

Study outcomes

Outcomes	Intervention group (n = 25)	Control group (n = 25)	p
Nutritional outcomes			
Proportion of intake as mother's milk (>80%) at 36 weeks, n (%)	8 (32)	10 (40)	0.56
Feeding volume at 36 weeks in ml/kg/d, mean ± SD	161 ± 21	164 ± 27	0.63
Caloric intake at 36 weeks in cal/kg/d, median (IQR)	120 (105 – 135)	125 (112 – 138)	0.47
Protein intake at 36 weeks in g/kg/d, median (IQR)	4.0 (1.8 – 4.5)	4.0 (3.2 – 4.4)	0.83
Growth rate from birth to 36 weeks in g/kg/d, mean ± SD	12 ± 4	12 ± 3	0.51
Anthropometric outcomes[1]			
Weight-for-age z score at 36 weeks, mean ± SD	−1.1 ± 0.9	−1.3 ± 1.0	0.37
Length-for-age z score at 36 weeks, mean ± SD	−1.1 ± 1.1	−1.3 ± 1.1	0.99
Head circumference-for-age z score at 36 weeks, mean ± SD	−0.8 ± 0.8	−0.8 ± 1.4	0.97
Postnatal growth failure at 36 weeks (weight <10th percentile), n (%)	11 (40)	14 (56)	0.40
Difference between weight z score at birth and weight z score at 36 weeks, mean ± SD	−0.9 ± 0.6	−1.0 ± 0.6	0.90
Body composition outcomes at 36 weeks PMA	n = 18	n= 17	
Postnatal age at assessment in days, median (IQR)	35 (29 – 48)	32 (28 – 37)	0.12
Fat mass in g, mean ± SD	315 ± 133	282 ± 87	0.39
Fat-free mass in g, mean ± SD	1802 ± 216	1763 ± 245	0.62
% Body fat, mean ± SD	14 ± 5	14 ± 3	0.49
Body composition outcomes at 3 months CA	n = 13	n= 12	
Postmenstrual age at assessment in weeks, median (IQR)	54 (53 – 55)	53 (52 – 56)	0.60
Fat mass in g, mean ± SD	1050 ± 306	1089 ± 427	0.79
Fat-free mass in g, mean ± SD	3913 ± 366	4286 ± 545	0.06
% Body fat, mean ± SD	21 ± 4	19 ± 6	0.46

[1] z scores were estimated with the Fenton 2013 growth curves.