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Physiological adjustment to postnatal growth trajectories in healthy preterm infants

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BACKGROUND: International guidelines suggest that growth of preterm infants should match intrauterine rates. However, the trajectory for extrauterine growth may deviate from the birth percentile due to an irreversible, physiological loss of extracellular fluid during postnatal adaptation to extrauterine conditions. To which "new" physiological growth trajectory preterm infants should adjust to after completed postnatal adaptation is unknown. This study analyzes the postnatal growth trajectories of healthy preterm infants using prospective criteria defining minimal support, as a model for physiological adaptation.

METHODS: International, multi-center, longitudinal, observational study at five neonatal intensive care units (NICUs). Daily weights until day of life (DoL) 21 of infants with undisturbed postnatal adaptation were analyzed (gestational ages: (i) 25–29 wk, (ii) 30–34 wk).

RESULTS: 981 out of 3,703 admitted infants included. Maximum weight loss was 11% (i) and 7% (ii) by DoL 5, birth weight regained by DoL 15 (i) and 13 (ii). Infants transitioned to growth trajectories parallel to Fenton chart percentiles, 0.8 z-scores below their birth percentiles. The new trajectory after completed postnatal adaptation could be predicted for DoL 21 with $R^2 = 0.96$.

CONCLUSION: This study provides a robust estimate for physiological growth trajectories of infants after undisturbed postnatal adaptation. In the future, the concept of a target postnatal trajectory during NICU care may be useful.

Improved survival rates of very-low-birth-weight (<1,500 g birth weight) infants have shifted the focus of neonatal care onto improving postnatal growth and nutrition, aiming to achieve growth rates that optimize later health outcomes (1). Pediatric societies in North America and Europe have recommended that postnatal growth of preterm infants match the *in utero* growth rates of fetuses that remain *in utero* until full-term (2–4). These recommendations gain importance in light of the Developmental Origins of Health and Disease (DOHaD) hypothesis (5). The DOHaD concept suggests that suboptimal growth of a fetus or a newborn infant can impact the early onset of adult metabolic and cardiovascular diseases. *In utero*, the growth rate of an individual fetus is determined by its genetic potential and modified by "environmental" factors such as maternal nutrition, body composition, pathologies, or altitude above sea level. After birth, growth patterns of preterm infants are under external control by neonatal staff who modify the infants' nutrient intake. **Figure 1** shows three hypothetical postnatal trajectories for a given preterm infant (27 wk of gestation, birth weight 1,000 g). It is of interest to note that these trajectories have similar slopes and hence not dramatically different growth rates. However, postnatal adjustment to different percentiles during the phase of stable growth will lead to different body compositions—potentially affecting later health outcomes.

The current evidence for optimal postnatal growth trajectories is scarce. Most published postnatal growth patterns for preterm infants were established by studying neonatal intensive care unit (NICU) cohorts, which inevitably consist of a mix of sick and more healthy infants (6–10). The resulting growth pattern will therefore not reflect the true potential of postnatal growth for healthy preterm infants. Two factors cause postnatal trajectories to deviate further from the ones *in utero*; (i) postnatal adaptation to extrauterine life initiates a one-time, irreversible contraction of extracellular water space during the first days of life (11–16). This physiological contraction and subsequent weight loss makes it reasonable to assume that there will be a permanent offset of postnatal growth trajectories when compared to intrauterine trajectories. (ii) The abrupt lapse of placental supply causes a transient nutritional deficit, which further offsets postnatal growth curves. Delayed nutritional support, slow postnatal enteral feeding advancement, prolonged use of parenteral nutrition, repeated bouts of feeding intolerance, and/or providing nutrition that does not provide the optimal composition and nutrients needed for

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Received 31 August 2015; accepted 12 November 2015; advance online publication 9 March 2016. doi:10.1038/pr.2016.15

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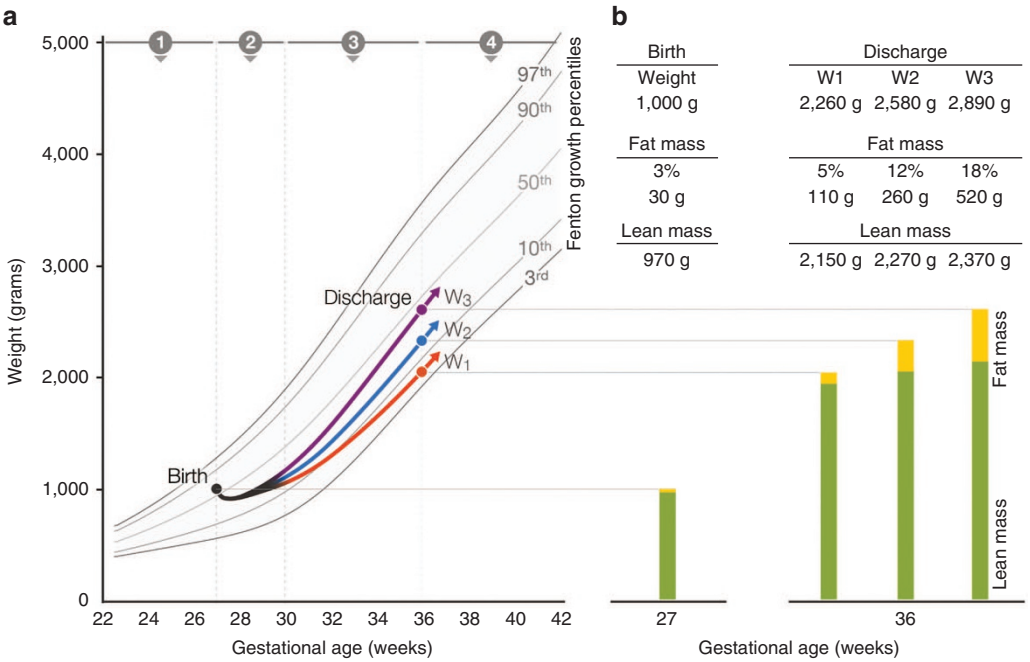

Figure 1. Growth trajectory (**a**) and body composition (**b**) of three extremely low-birth-weight infants. Early adjustment of postnatal growth trajectories affects weight and body composition at discharge. The infants transition to different hypothetical growth trajectories, but have similar growth rates after postnatal adaption: (i) intrauterine growth, (ii) preterm birth and postnatal adjustment of growth trajectories, (iii) percentile-parallel growth (17 g/kg/d), and (iv) term age with different DOHaD risk profiles due to different body compositions (22,26,32,33).

high growth rates in preterm infants can aggravate this deficit. The impact seems to be center-specific (1,6,17–20).

Preterm infants with undisturbed postnatal adaptation who are not exposed to growth-affecting conditions may represent the most appropriate model to study physiological postnatal weight loss and early weight gain in order to determine which postnatal growth trajectory preterm infants best adapt to.

It was therefore the aim of the current study to analyze a cohort of preterm infants from 25 to 34 gestational weeks who are characterized by absence of maternal and neonatal pathologies, as well as minimal clinical interventions including little or no respiratory support during the first 21 DoL.

RESULTS

In total, 3,703 preterm infants with gestational age 25–34 wk were admitted to the five centers during the study period, of which 981 (26%) met the inclusion criteria. **Table 1** presents the number of screened and included subjects stratified by perinatal center. **Table 2** presents perinatal characteristics of all included infants stratified by gestational age at birth. There were no differences between mean birth weights of included and screened infants indicating for each gestational age that our inclusion/exclusion criteria did not introduce a selection bias for birth weight or fetal growth pattern. Further, the centers followed similar clinical guidelines regarding nutrition, respiratory support, surfactant therapy, and treatment of apnea of prematurity with caffeine citrate.

In total, 17,379 day-specific weight measurements were recorded from day of birth to DoL 21. For each gestational age category, **Table 3** shows DoL with the lowest postnatal weight, percent difference of the lowest postnatal weight to birth weight, as well as DoL when birth weight was regained. Average percent postnatal weight loss was higher in more immature infants. Birth weight was regained on average 2 d earlier in infants of 30–34 wk gestation compared to infants of 25–29 wk gestation.

Independent of gestational age, infants showed similar postnatal trajectories with minimal crossing of percentiles after the weight loss nadir (**Figure 2**). The period of initial weight loss lasted on average between 4 and 6 d (**Table 3**). During the period of growth that follows completed postnatal adaptation, the new extrauterine growth trajectories adapted to a growth percentile consistently below the *in utero* percentile (at birth) with an average z-score difference between −0.7 and −0.8 (**Figure 3**, **Table 4**). Similarly, the 10th, 25th, 75th, and 90th percentiles followed a pattern parallel to that of the median trajectory.

It is of interest to note that the dynamics of initial weight loss (until DoL 7) seemed to be similar across all gestational age groups, although younger infants experienced a slightly higher z-score loss (**Figure 3**).

Average birth weight and gestational age of analyzed infants with gestational ages of 25–29 wk were similar between centers. Weights and z-scores at DoL 7, 14, and 21 did not differ significantly between the centers (**Table 5**).

Nonparametric bootstrapping on multiple linear regression models predicted weight and z-scores accurately at DoL 7, 14, and 21 when birth weight and gestational age at birth were included as independent variables (**Tables 6** and **7**). The Akaike Information Criterion ratios which assessed the impact

Table 1. Selection of study participants

		MUMC Canada	UHH Germany	UHG Germany	SMH Canada	SJH Canada	
Center	GA	Level III			Level II		Total
Screened	Total	1,633	888	449	403	330	3,703
	25–29	461	194	137			792
	30–34	1,172	694	312	403	330	2,911
Included and analyzed	Total	185	344	100	140	212	981
	25–29	107	58	65			230
	30–34	78	286	35	140	212	751

UHG, University Hospital of Greifswald; UHH, University Hospital of Heidelberg; MUMC, McMaster University Medical Centre; GA, gestational age.

Table 2. Subject characteristics at birth by completed weeks of gestational age

Gestational age (weeks)	*N* (*n* male)	Birth weight (g)	Multiple birth (%)	C-section rate (%)	SGA (%)	LGA (%)	Ratio of mean birth weight: included vs. screened
25.6 ± 0.2	10 (3)	760 ± 90	20	90	0	0	1.01
26.4 ± 0.3	37 (20)	840 ± 160	14	78	14	5	0.99
27.5 ± 0.3	40 (19)	990 ± 180	40	85	5	3	1.02
28.4 ± 0.3	68 (43)	1,130 ± 190	38	79	4	6	1.02
29.4 ± 0.3	75 (37)	1,240 ± 240	37	87	11	3	0.96
30.5 ± 0.3	37 (21)	1,420 ± 250	43	51	8	3	0.98
31.5 ± 0.3	77 (40)	1,670 ± 300	29	52	5	8	1.03
32.4 ± 0.3	145 (86)	1,800 ± 290	39	70	5	3	1.00
33.5 ± 0.3	195 (117)	1,980 ± 340	28	50	13	3	0.99
34.4 ± 0.3	297 (165)	2,180 ± 300	37	46	9	1	0.96

LGA, large for gestational age; SGA, small for gestational age.

Table 3. Characteristics of postnatal weight changes and nutrition

GA	DoL with lowest postnatal weight	Average percent postnatal weight loss	DoL when birth weight was regained	DoL start enteral feeding	DoL when 120 ml/kg/d enteral feeding
25	6 (4, 6)	12 ± 3	18 (17; 21)	3 (1; 8)	13 (9; 25)
26	5 (4, 6)	11 ± 5	16 (13; 19)	3 (2; 5)	12 (10; 15)
27	5 (4, 6)	13 ± 4	16 (14; 20)	3 (2; 4)	11 (10;` 16)
28	5 (4, 6)	12 ± 5	15 (13; 19)	3 (2; 5)	12 (9; 15)
29	5 (4, 6)	9 ± 5	15 (11; 17)	3 (1; 4)	11 (8; 14)
30	4 (4, 5)	9 ± 3	13 (11; 17)	2 (2)	8 (6; 10)
31	5 (4, 6)	9 ± 4	13 (10; 16)	2 (2; 3)	7 (5; 8)
32	5 (4, 5)	8 ± 3	13 (10; 16)	2 (1; 3)	6 (5; 8)
33	4 (3, 5)	6 ± 3	12 (10; 15)	2 (1; 2)	5 (4; 7)
34	5 (4, 6)	7 ± 3	14 (11; 16)	1 (1; 2)	5 (4; 6)

Data show mean ± SD (or median and interquartile range).
GA, gestational age.
Percent postnatal weight loss = (birth weight−lowest postnatal weight)/birth weight × 100.

of additional covariates such as gender, center, and mode of delivery were close to 1, which indicated that the simplest model only including birth weight or z-score and gestational age was appropriate to predict weight or z-score at DoL 7, 14, and 21 (21). For both age groups, time to reach full enteral feedings was different between the centers ($P < 0.001$).

Residual analysis (**Figure 4**) confirmed that the described model did not introduce differences between observed and predicted weight z-scores. This indicated that the level of precision was high for predictive weight and z-score models at DoL 7, 14, and 21. The models' correlation and accuracy for days 7, 14, and 21 were high (**Tables 6** and **7**). Weight was predicted

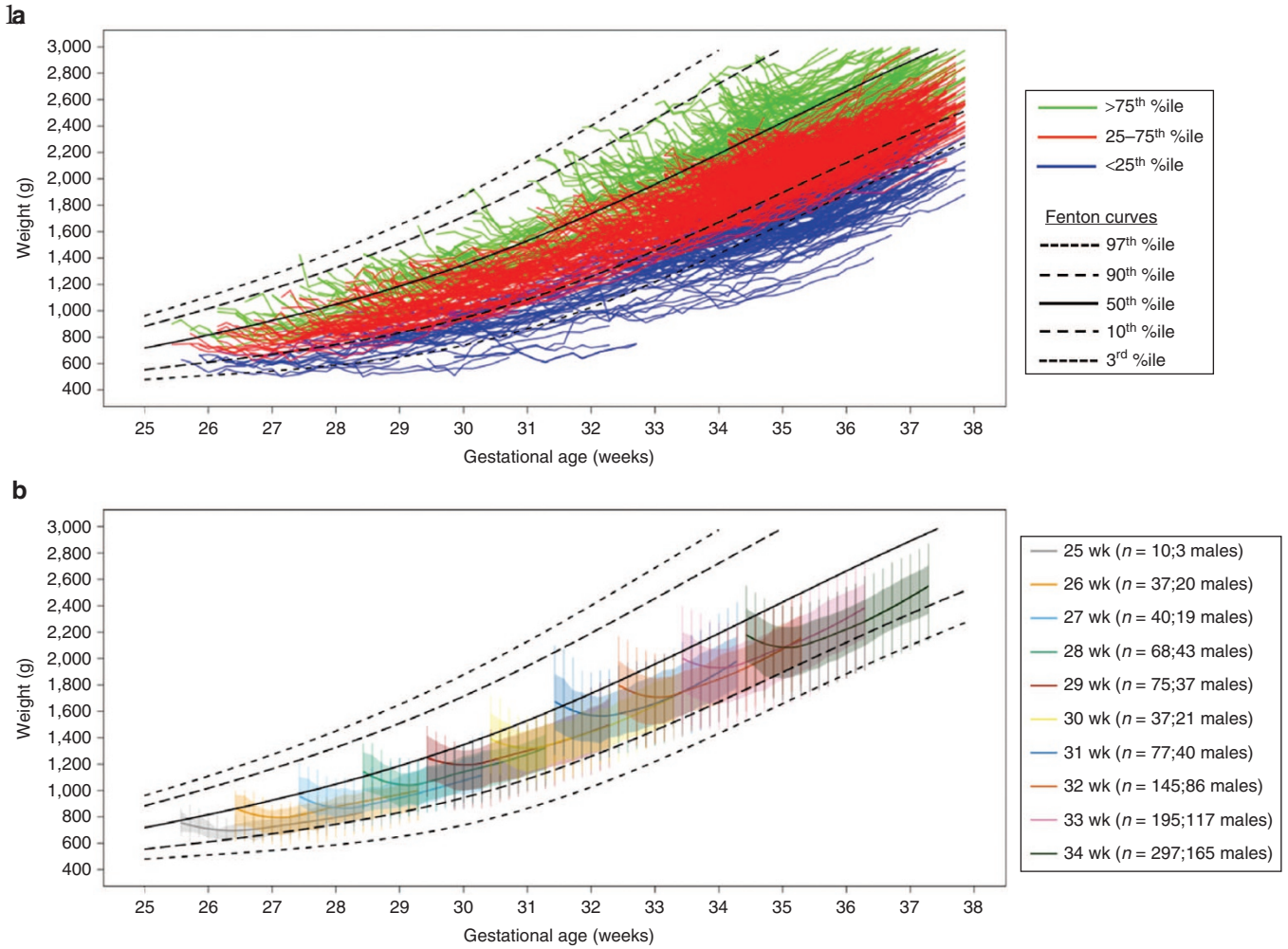

Figure 2. Patterns of adaptational weight change in healthy preterm infants during the first 21 postnatal days, superimposed on Fenton charts (3rd, 10th, 50th, 90th, and 97th percentiles) (26). (**a**) Individual trajectories color-coded for birth weight quartiles (blue <25th, orange 25–50th, red 50–75th, green >75th percentiles). (**b**) Median, interquartile ranges (shaded) and range of 10th to 90th percentiles for each week of gestation. Trajectories were plotted using the average gestational age (34).

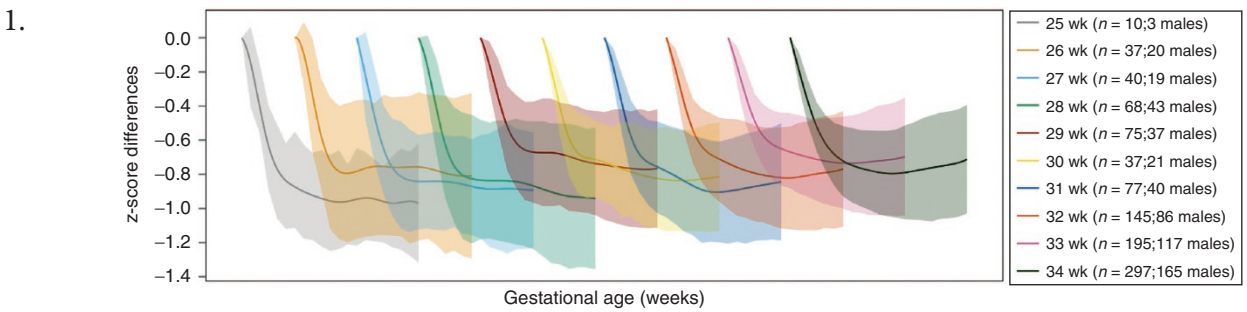

Figure 3. Z-scores of postnatal weight changes for infants born at each week of gestation; the solid line represents the mean; the shaded area ±1 SD.

for DoL 14 and 21 with R^2 = 0.97 and 0.96, and z-score predicted with R^2 = 0.86 and 0.81, respectively.

DISCUSSION

In this international multi-center study, we found a selected group of healthy preterm infants adjusted their extrauterine growth trajectories to −0.8 z-scores below their intrauterine percentile after completed postnatal adaptation. This effect was independent from hospital center and feeding regimes. Our approach is comparable to the one used to establish the WHO growth charts of breast-fed infants. In both studies, selected healthy populations with undisturbed physiological conditions

Table 4. Demographics, nutrition, and growth stratified by completed weeks of gestational age

GA (weeks)	FEF (day of life)	Weight (g) at DoL			z-score at day of life			
		7	14	21	1	7	14	21
25	13 (9; 25)	710 ± 90	770 ± 110	850 ± 90	0 ± 0.6	−0.8 ± 0.4	−0.9 ± 0.4	−1 ± 0.3
26	12 (10; 15)	770 ± 130	870 ± 140	970 ± 150	−0.1 ± 0.9	−0.9 ± 0.6	−0.9 ± 0.5	−0.9 ± 0.5
27	11 (10; 16)	900 ± 170	1,010 ± 190	1,140 ± 220	0.1 ± 0.8	−0.8 ± 0.6	−0.8 ± 0.6	−0.8 ± 0.6
28	12 (9; 16)	1,030 ± 160	1,160 ± 180	1,300 ± 190	0.1 ± 0.8	−0.7 ± 0.5	−0.8 ± 0.5	−0.8 ± 0.5
29	11 (8; 14)	1,170 ± 230	1,320 ± 240	1,500 ± 280	0 ± 0.8	−0.7 ± 0.7	−0.8 ± 0.7	−0.8 ± 0.8
30	8 (6; 10)	1,330 ± 230	1,490 ± 230	1,700 ± 250	0 ± 0.8	−0.7 ± 0.7	−0.9 ± 0.6	−0.8 ± 0.6
31	7 (5; 8)	1,570 ± 270	1,730 ± 290	1,980 ± 310	0.1 ± 0.8	−0.6 ± 0.7	−0.8 ± 0.7	−0.7 ± 0.7
32	6 (5; 8)	1,710 ± 250	1,890 ± 270	2,150 ± 290	−0.1 ± 0.8	−0.8 ± 0.6	−0.9 ± 0.6	−0.9 ± 0.7
33	5 (4; 7)	1,910 ± 310	2,110 ± 320	2,360 ± 330	−0.2 ± 0.8	−0.9 ± 0.7	−1 ± 0.8	−0.9 ± 0.8
34	5 (4; 6)	2,080 ± 270	2,280 ± 270	2,530 ± 310	−0.3 ± 0.7	−1 ± 0.7	−1.1 ± 0.7	−1 ± 0.7

Data presented as mean ± SD or median (interquartile range).
FEF, full enteral feeding; GA, gestational age.

Table 5. Demographics, nutrition and growth stratified by center and gestational age at birth (25–29 and 30–34 wk)

Center	*N*	Birth weight (g)	GA (weeks)	FEF (DOL)	Weight (g) at			z-score at			
					DoL 7	DoL 14	DoL 21	DoL 1	DoL 7	DoL 14	DoL 21
25–29 wk											
MUMC	107	1,100 ± 230	28.2 ± 1.1	12 (10; 14)	990 ± 200	1,120 ± 230	1,260 ± 260	0.1 ± 0.8	−0.8 ± 0.6	−0.8 ± 0.6	−0.9 ± 0.6
UHH	58	1,070 ± 260	28.3 ± 1.3	13 (12; 17)	1,000 ± 260	1,120 ± 280	1,260 ± 300	−0.1 ± 0.8	−0.8 ± 0.6	−0.9 ± 0.6	−0.9 ± 0.5
UHG	65	1,050 ± 270	27.9 ± 1.4	9 (8; 12)	1,000 ± 270	1,130 ± 300	1,280 ± 360	0 ± 0.8	−0.6 ± 0.7	−0.7 ± 0.6	−0.7 ± 0.7
All	230	1,080 ± 250	28.1 ± 1.2	12 (9; 14)**	1,000 ± 230	1,120 ± 260	1,260 ± 300	0 ± 0.8	−0.8 ± 0.6	−0.8 ± 0.6	−0.8 ± 0.6
30–34 wk											
MUMC	78	1,830 ± 400	32.8 ± 1.4	4 (3; 7)	1,730 ± 370	1,900 ± 380	2,120 ± 400	−0.3 ± 0.9	−1.0 ± 0.8	−1.1 ± 0.8	−1.1 ± 0.8
UHH	286	1,940 ± 390	33.3 ± 1.2	6 (5; 7)	1,860 ± 350	2,060 ± 370	2,320 ± 380	−0.3 ± 0.8	−1.0 ± 0.7	−1.0 ± 0.7	−0.9 ± 0.7
UHG	35	2,090 ± 310	33.9 ± 0.8	6 (6; 7)	2,100 ± 310	2,310 ± 340	2,610 ± 340	−0.2 ± 0.6	−0.6 ± 0.6	−0.7 ± 0.6	−0.5 ± 0.6
SMH	140	1,920 ± 340	33.2 ± 1.2	7 (5; 9)	1,830 ± 320	2,010 ± 340	2,260 ± 410	−0.2 ± 0.7	−0.9 ± 0.6	−1.0 ± 0.6	−1.0 ± 0.7
SJH	212	2,050 ± 360	33.4 ± 1.1	4 (4; 5)	1,940 ± 330	2,120 ± 340	2,360 ± 350	0 ± 0.8	−0.8 ± 0.7	−0.9 ± 0.7	−0.9 ± 0.7
All	751	1,960 ± 380	33.3 ± 1.2	5 (4; 7)**	1,880 ± 350	2,070 ± 360	2,310 ± 390	−0.2 ± 0.8	−0.9 ± 0.7	−1.0 ± 0.7	−0.9 ± 0.7

Data show mean and SD or median and interquartile range; ** indicates $P < 0.001$ for ANOVA.
FEF, full enteral feeding (≥120 ml/kg/d); GA, gestational age; MUMC, McMaster University Medical Centre; SJH, St. Joseph's Healthcare, Hamilton; SMH, St. Michael's Hospital, Toronto; UHG, University Hospital of Greifswald; UHH, University Hospital of Heidelberg.

Table 6. Multiple regression model optimized with bootstrapping algorithm to predict body weight at DoL 7, 14, or 21 using birth weight (g) and GA (complete weeks) as covariates

Weight at DoL	Intercept (a)	Coefficient for birth weight (b)	Coefficient for GA at birth (c)	Standard error of residuals (g)	R^2	*P* value
7	−530 (−610; −450)	0.86 (0.85; 0.88)	21.6 (18.3; 24.9)	72 (68; 75)	0.98 (0.98; 0.98)	$< 2.2 \times 10^{-16}$
14	−750 (−850; −640)	0.87 (0.85; 0.89)	33.4 (29.2; 37.7)	93 (88; 98)	0.97 (0.97; 0.97)	$< 2.2 \times 10^{-16}$
21	−970 (−1,110; −840)	0.90 (0.87; 0.92)	46.3 (40.9; 51.7)	120 (115; 127)	0.96 (0.95; 0.96)	$< 2.2 \times 10^{-16}$

Weight at DoL = a + (b × birth weight) + (c × GA at birth).
DoL, day of life; GA, gestational age.

were studied. The aim of our study was to observe how preterm infants with minimal influence of peri- and neonatal diseases adapt to their postnatal growth trajectory. This approach has the potential to serve as a reference model for how preterm infants naturally transition from fetal to neonatal growth trajectories.

Growth trajectories after completed postnatal adaptation were found to be surprisingly consistent through all gestational ages from 25 to 34 wk. Growth trajectories expressed either as means or as z-score differences followed parallel courses for all gestational age groups. Previous studies in preterm and

Table 7. Multiple regression model optimized with bootstrapping algorithm to predict z-score at DoL 7, 14, or 21 using z-scores at birth and GA (complete weeks) as covariates

z-score at DoL	Intercept (a)	Coefficient for z-score (b)	Coefficient for GA at birth (c)	Standard error of residuals (g)	R^2	*P* value
7	−0.85 (−1.01; −0.69)	0.80 (0.78; 0.81)	0.003 (−0.002; 0.008)	0.20 (0.19; 0.21)	0.91 (0.90; 0.92)	$< 2.2 \times 10^{-16}$
14	−0.77 (−0.97; −0.57)	0.78 (0.76; 0.80)	−0.002 (−0.008; 0.005)	0.24 (0.23; 0.26)	0.87 (0.86; 0.88)	$< 2.2 \times 10^{-16}$
21	−1.26 (−1.50; −1.03)	0.78 (0.76; 0.81)	0.015 (0.008; 0.022)	0.30 (0.29; 0.32)	0.81 (0.79; 0.83)	$< 2.2 \times 10^{-16}$

z-score at DoL = a + (b × z-score at birth) + (c × GA at birth).
DoL, day of life; GA, gestational age.

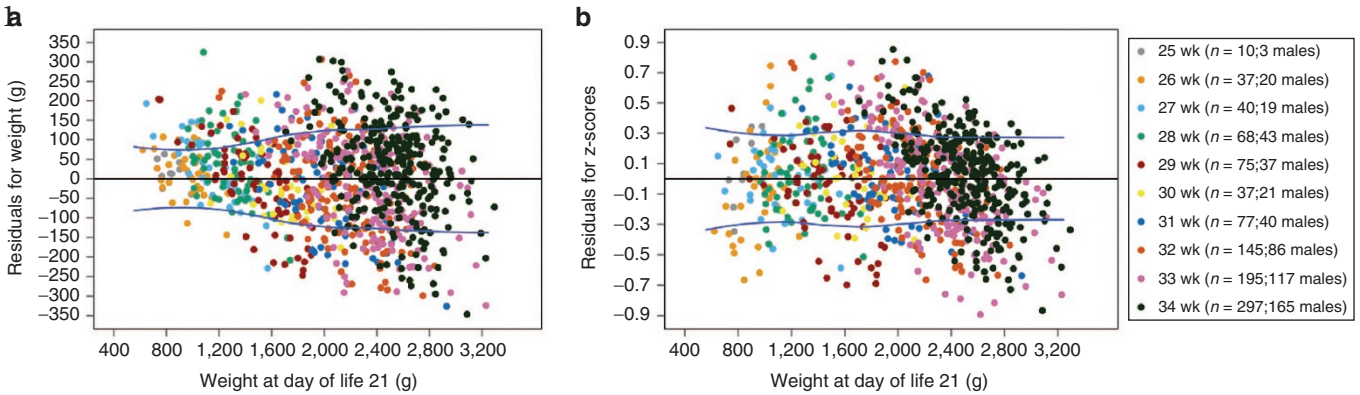

Figure 4. Residuals for all infants of predicted weight (**a**) and z-score (**b**) at DoL 21; data shown as absolute differences (predicted—measured: black) and SDs (blue).

term infants using tracer technology showed that after birth, extracellular fluid space irreversibly contracts by one third (13,16,21). Assuming an extracellular fluid volume of 35–40% of body water as well as a contraction factor of 30–35%, this extracellular fluid reduction translates into 10–14% of body water that is physiologically lost. Depending on the infant's fat mass (typically 5–8% for very preterm infants, 15–25% for term infants), this will result in a weight loss of 6–13% with a proportionally higher loss in the more immature population (16,22). The postnatal trajectories observed in our study population correspond with these figures. The contradictory observation that more immature infants have a higher percent weight loss, but an unchanged z-score shift can be explained by the fact that the relative distance between z-scores varies with gestational age and is larger at lower gestational ages. This is illustrated by comparing the difference between the 50th and 3rd percentiles divided by 50th percentile weight for distinct gestational age ranges. At 24 wk, this difference is 32%, at 28–30 wk up to 44%, then decreasing to 28% at 36 wk. Consequently, the relative distance between z-score intervals differs by a factor of up to 1.3. Therefore, the higher relative weight loss in very preterm born infants still translates into similar z-scores when compared to more mature infants with a lower percentage of weight loss.

In this group of healthy preterm infants, it can be assumed that physiological nutritional deficits during postnatal adaptation had only a minimum impact on growth. After birth, in addition to extracellular fluid loss, newborn infants are normally subjected to a cumulative nutritional deficit because of interruption of placento-umbilical supply, time needed to introduce enteral feeds and—in cases of sick infants—increased postnatal nutritional needs due to neonatal diseases. In our study group, introduction of enteral feeds was usually completed after 4 (32–34 wk of gestation) and 10 d (<27 wk of gestation) while the infant was supported by partial parenteral nutrition. These infants were selected because they did not have diseases associated with delays in nutritional intake and growth and were nourished by parenteral and enteral nutrition according to protocols.

Our finding that there was no difference in weight loss between centers despite minor differences in feeding practice and fluid management suggests that our careful selection identified a consistent sample between centers. It can be speculated that there is a physiological set point in healthy infants for extracellular volume after completed postnatal adaptation. Further, it can be theorized that kidneys of healthy infants may compensate for the minor differences in fluid intake and that these small differences did not impact adjustment of weight.

In contrast to our findings, most published studies report that postnatal growth trajectories of preterm infants increasingly divert from intrauterine reference curves (6,7,10,23). This discrepancy is caused by several factors. In our study, we were strictly focusing on postnatal adaptation of healthy preterm infants whereas the quoted studies included complete NICU cohorts with a mix of healthy and sick infants. Interestingly, three of those publications report growth curves that are similar to our curves (7,8,10). Ehrenkranz *et al.* presented a re-analysis of growth trajectories of a previously published preterm population (multicenter study of $n = 1{,}660$ infants with birth weight of 501–1,500 g during 1994–95) that

was divided into subjects with and without major morbidities (24). Infants without major morbidities had higher weight gain and trajectories that were less diverging from intrauterine curves. Across all gestational ages, the healthier infants in the study of Ehrenkranz *et al.* adapted in a similar pattern to infants from our study, however with larger z-score differences to their birth percentile. Different from our study, inclusion criteria for infants were not as narrow and there was no control for maternal disease such as chorioamnionitis or diabetes mellitus, or neonatal factors such as nutrition and need for respiratory support. Furthermore, the authors classified mostly typical neonatal morbidities such as bronchopulmonary dysplasia, etc. that evolve during hospital stay and were assessing the long term course, up to 54 postmenstrual weeks. It is of interest to note that Dr. Ehrenkranz's study is one of the first to reveal that growth of preterm infants can come close to intrauterine growth rates if infants were not exposed to neonatal complications during their NICU stay (23). In another study (multicenter design, n = 5,009 infants with gestational age <32 wk from 2006–2011), Cole *et al.* were able to show a similar trend for growth rates. Average growth trajectories were superior to those achieved by infants in the Ehrenkranz study, but nonetheless inferior to our presented data. Cole's study was performed 15 y after the Ehrenkranz study and included healthy and sick infants. The improved growth rates, however, may reflect advances in neonatal care during the last decade, such as reduced length of mechanical ventilation, earlier start of nutrition, less late onset sepsis, and fewer exposures to other iatrogenic complications. This temporal change toward improved growth due to advances in neonatal intensive care suggests that our approach to look at healthy infants as a role model and reference for neonatal growth rates is an appropriate approach for considering what healthy growth should be for preterm infants.

Contrary to findings made by our study and others, it is of interest to note that in Dr. Cole's study the more immature infants initially did not lose weight as part of the postnatal adaptation but instead showed a steady weight gain already during the first week of life. The exact reason for this observation is unclear, but it may be hypothesized that the low gestational age and weight category predominantly included sick infants, which may have retained water due to disease processes such as capillary leak, which is frequently part of a fetal inflammatory response syndrome (25). Infants with such characteristics would have been excluded from our study.

In a third study (multicenter design, n = 977 infants, gestational age 23–31 wk from 2001 to 2010), growth curves were established for a larger cohort of preterm infants up to the age of 10 wk post-term and were compared with the Fetal-Infant Growth Reference (an intrauterine meta-analysis until 40 wk of gestational age) and the World Health Organization Growth Standard (10,26,27). Similar to what we observed in our study, the authors observed that preterm infants had an initial weight loss during the first weeks of life, which was observed as a downward shift of growth trajectories on the Fetal-Infant Growth Reference. After reaching 42 wk of gestational age,

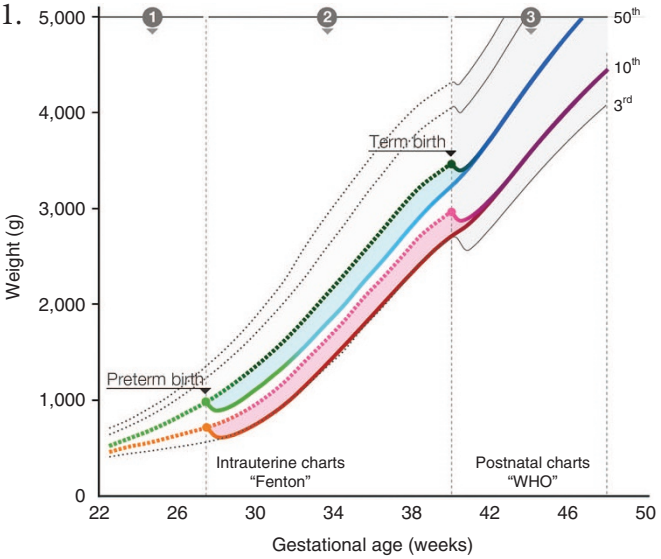

Figure 5. Postnatal offset of growth trajectories. Illustration of the concept of "premature contraction of water spaces" leading to temporary shift of growth trajectories projected on Fenton (22–40 wk) and WHO Growth Standard (40–48 wk) curves (10,27). Courses of two hypothetical infants are illustrated: dotted and solid lines represent intrauterine and postnatal growth trajectories, respectively: (i) intrauterine growth along 50th and 10th percentile; (ii) preterm birth at 50th and 10th percentile and physiological deviation of postnatal growth trajectories due to premature contraction of water spaces, preterm infants then continue to grow on a trajectory parallel to its peer remaining *in utero*; (iii) peers remaining *in utero* experience contraction of water spaces at term thereby shifting their growth trajectory to that of their preterm born counterparts. Growth trajectories of preterm and term infants coincide after 42 wk.

however, when the WHO Growth Standard is usually applied for growth monitoring, these infants reapproached their birth percentiles. Thus the downward shift on the percentile curves was a temporary offset, and some catch-up occurred as the preterm infants continued to grow steadily through the phase of the term infants' post-birth weight loss (10,28). In other words, preterm infants seem to experience an offset in postnatal growth trajectories due to the fluid loss of the postnatal adaptation. For term infants, this shift is not shown in currently available growth curves, as the custom is to smooth over this transition. For preterm infants, however, the shift becomes more noteworthy because the growth charts based on intrauterine growth do not incorporate this postnatal adaptation. Further, the timing of this adaptation varies by their gestational age at the time of birth. Our analysis of healthy preterm infants, in combination with the Fenton Fetal-Infant Growth Reference nicely illustrates that preterm infants shift their postnatal trajectory by −0.8 z-scores, then grow parallel to their intrauterine curves with growth rates (expressed in z-scores) similar to those *in utero*. In the future, we are interested in analyzing whether the infant's birth percentile is reachieved between 42 and 44 wk of gestation (**Figure 5**). In other words, this observed postnatal offset might be a temporary phenomenon under normal physiology, sufficient nutrition and normal environmental conditions. Intrauterine growth charts developed based on birth size, such as those by Fenton, allow health

practitioners to evaluate whether infants are growing at rates similar to intrauterine rates, the recommended growth rates, after the postnatal adaptation phase (2–4).

In this study, we have chosen an observation period of 21 d to investigate postnatal growth trajectory adaptation of healthy preterm infants of various gestational ages. The rationale for this design was to investigate how healthy undisturbed preterm infants physiologically adjust their growth trajectory. We assumed a priori that the offset of growth trajectories due to postnatal adaptation is achieved after 7–10 d and data from the third week of life would be needed to justify the course of the growth trajectory. We further assumed that more than 21 d observation period is not needed because healthy preterm infants would have settled on and would follow a new growth trajectory analogous to intrauterine counterparts during subsequent gestational ages. Our results show that there is no significant or important difference in z-score difference for DoL 14 and 21. This result may confirm that postnatal adjustment of growth trajectories is completed by the third week of life in healthy preterm infants of various gestational ages.

Our study has several strengths: (i) The multi-center approach used in this study reduced biases introduced by only including a single hospital center and allowed for comparison of study population characteristics, nutritional strategies, and growth trends across hospital centers. (ii) A selected subset of the most healthy preterm infants was chosen for the study, ensuring that conditions which may impair growth such as sepsis, delayed nutrition, respiratory insufficiency, and neonatal or maternal morbidities did not confound the results. (iii) The results of the study were very consistent amongst infants of all gestational ages. This consistency applies not only to the trajectories of means and/or medians, but also to the corresponding standard deviations and quartiles, which confirms the quality of the model. The superimposition of all day 10-to-21 trajectories eventually seems to create a new set of percentiles for healthy postnatal growth. (iv) The postnatal weights could be predicted for individual infants with a precision range of 30–50 g compared to the actual weight across all analyzed gestational ages.

Our study has some limitations: (i) Although the total sample size was large, with almost 1,000 infants included in this study, the number of infants in some of the lower gestational age groups was small. Nonetheless, between 10 and 40 infants per week for the gestational age range from 25 to 27 wk might still be appropriate to support the validity of the underlying principle for postnatal adaptation, given the consistency of our findings across gestational ages. (ii) This study does not provide a new set of postnatal growth percentiles. However, the study investigates the physiological reaction of transitioning from a fetal to extrauterine environment in healthy preterm infants in the absence of other confounding factors. (iii) The study was a short term observational study and no biomarker or body composition markers were measured. (iv) This study does not provide outcome data such as body fat percentage, lean mass percentage and neurodevelopment to determine whether these healthy infants who maintained growth trajectories at a z-score difference of −0.8 achieved comparable outcomes to term-born counterparts.

Conclusion

Our study presents postnatal weight change trajectories for a selected healthy group of preterm infants, 25–34 wk gestational age, with little to no clinical interventions required. Although a considerable number of preterm infants treated in the NICU are sick and fail to thrive, these data may provide target trajectories for extrauterine growth after completed postnatal adaptation. Current growth charts based on simple cross-sectional birth weight data do not reflect the normal postnatal adaptation, but can still be used to assess whether infants grow at rates similar to intrauterine rates. Our study is an important step toward understanding how preterm infants should grow. However, the results need to be further validated before they can be introduced as a tool for clinical decision-making. Ideally, the data set would be supplemented by a longer duration of growth monitoring, along with associations between growth patterns, length, head circumference, body composition, biomarkers, and health outcomes in later childhood and adulthood.

METHODS

Study Design

This longitudinal, multi-center, observational study was performed in the NICUs of five academic hospitals in Canada and Germany. Approval was obtained from the Research Ethics Boards at all five hospitals (Canada: McMaster University Medical Centre, Hamilton (MUMC), St. Joseph's Healthcare, Hamilton (SJH), and St. Michael's Hospital, Toronto (SMH); Germany: University Hospital of Greifswald (UHG), and University Hospital of Heidelberg (UHH) in Germany). The need for parental consent was waived because of retrospective analysis of pseudonymized data.

MUMC, UHG, and UHH are level III NICUs providing the full spectrum of neonatal intensive care. S.J.H. and S.M.H. are classified as advanced level II, providing care for preterm infants ≥32 gestational weeks, including nasal continuous positive airway pressure (nCPAP) and short-term ventilation. Data was extracted from medical records by trained personnel.

Study Subjects

All preterm infants $\geq 25^{0}/_{7}$ and $\leq 34^{6}/_{7}$ gestational weeks (estimated according to Naegele's rule and sonographic assessment) admitted to one of the five participating NICUs within the first 24 h of life during the period of January 2008 until December 2012 were screened for eligibility. Using local admission databases and a set of prospectively defined criteria (see next paragraph), infants were identified who required minimal medical intervention.

Infants were excluded if there was maternal substance abuse, diabetes mellitus, or histological chorioamnionitis or if the infants had major malformations, severe gastrointestinal disorders (like neuronal intestinal dysplasia, malrotation, volvulus, intususception, etc.) or chromosomal aberrations. Infants also were excluded if one of the following events occurred within the 21-d study period: nosocomial sepsis confirmed by positive blood culture results, necrotizing enterocolitis stage ≥2a, ileus, intraventricular hemorrhage ≥2, or periventricular leukomalacia. Additionally, infants with uncertain gestational age or less than 14 d of postnatal growth data were also excluded.

Further exclusion criteria for infants between 30 to $34^{6}/_{7}$ gestational weeks were: any need for mechanical ventilation, nCPAP therapy beyond day 3 of life, FiO_2 ≥0.3 between 6 to 72 h of life and >0.21 after 72 h, or enteral feeding of ≤120 ml/kg/d after day 10 of life. Exclusion criteria for infants born between 24 to $29^{6}/_{7}$ gestational weeks were: any

need for mechanical ventilation after day 3 of life or $FiO_2 > 0.3$ within the study period (i.e., the first 21 d). There were no exclusion criteria with respect to nCPAP or enteral feeding volumes for the more premature infants. As well, infants receiving surfactant or caffeine were not excluded. Infants with respiratory distress usually received surfactant when exceeding $FiO_2 \geq 0.4$ while on nCPAP or when mechanically ventilated. Treatment of apnoea of prematurity was usually done with caffeine citrate (loading dose: 20 mg/kg, maintenance dose: 10 mg/kg). Table 1 shows admitted and included subjects for all study sites.

Nutritional Regime

All NICUs were operating based on the written local guidelines for enteral and parenteral nutrition. The common policy for all infants was to start enteral feedings as soon as tolerated, preferably with breast milk with daily increment rates of 12–35 ml/kg/d. At full enteral feeding, breast milk for very-low-birth-weight infants was routinely fortified. Fortifier was introduced under direction of the attending physician using half recommended dosage for 2 d followed by recommended dosage. For infants with a birth weight below 1,250 g the following schedules applied: infants treated at MUMC received trophic feeds for 1–3 d according to birth weight. Infants at UHG were fed 25% maltodextrin for the first two feeds within the first 24 h. Subsequently, enteral feeds were introduced by daily increments of 12–25 ml/kg/d (6). At UHH, enteral feeding was started 2 h after birth and enteral feeding was started with either maltodextrin given until passage of the first meconium or breast milk (colostrum). At MUMC, UHG, and UHH parenteral nutrition was usually started on day 1, with glucose (4–6 mg/kg/min) and protein (1.5 g/kg/d). At UHG, lipids were started on day 1 (at 1.5 g/kg/d) and at UHH and MUMC lipids were started on day 2. From day 2 onward, parenteral nutrition was continuously increased targeting an intake of 10–12 mg/kg/min for glucose, 3.5 g/kg/d for protein, and 2.5–3.5 g/kg/d for lipids (UHH 1.5–2.5 g/kg/d).

Statistical Analyses

Body weight measurements were abstracted for the first 21 d of life.

Nonskewed data was summarized using mean and standard deviation. Skewed data was presented as median, first, and third quartile. Shapiro-Wilk test was used to test for normality of distributions. The data were compared for differences between centers using ANOVA, Student *t*-test, Kruskal-Wallis test, and Mann-Whitney *U*-tests, at the 0.05 significance level. This analysis was performed using the R software package for statistical analysis, version 3.1.0 (2014-04-10). Figures were drawn by ggplot2 Version 0.9.3.1. Median growth curve and z-score difference curves were smoothed using the Loess method (26,29).

Imputation

Statistical analysis was performed using a complete set of daily weights until day 21. 9.3% of single data points were unavailable during the NICU stay and were imputed using exponential interpolation between the two adjacent data points. 6.3% of data points were missing after week 2 due to transfer or discharge. They were imputed using a linear regression model that applied gestational age and birth weight specific growth rates calculated for DoL 8 to 21, obtained from infants with complete data sets (30).

Predictive Model

Multiple regression analysis with a nonparametric bootstrapping optimization algorithm to predict body weight or z-score at DoL 7, 14, or 21 was modeled using gestational age at birth and birth weight or z-score as covariates (26,31).

ACKNOWLEDGMENT

The authors would like to thank Erin. M. Warkentin, BHSc (Hons), MScBMC, CMI Candidate for drawing Figures 1 and 5.

STATEMENT OF AUTHORSHIP

N.R., C.F.: Developed study design, abstracted data, analyzed and interpreted the data, wrote the manuscript. P.R.: Wrote research ethics protocol, abstracted data, helped with data analysis, drafted parts of manuscript. K.L.: Imputation, predictive model, data analysis. T.R.F.: Helped to interpret the data and wrote the manuscript. E.L.: Manuscript editing and helped to interpret the results. S.G., A.J., S.L.: Data abstraction. S.S., D.C., M.H., J.P.: Recruitment of patients, manuscript editing and scientific discussion.

STATEMENT OF FINANCIAL SUPPORT

Christoph Fusch is Inaugural Holder of Hamilton Health Sciences Foundation—Jack Sinclair Chair of Neonatology at McMaster University, Faculty of Health Sciences and provided fund for expenses of this study.

Disclosure: The authors have no financial relationships relevant to this article to disclose. The authors have no conflicts of interest to disclose.

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