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Original article

Personalized weight change prediction in the first week of life

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SUMMARY

Background & aims: Almost all neonates show physiological weight loss and consecutive weight gain after birth. The resulting weight change profiles are highly variable as they depend on multiple neonatal and maternal factors. This limits the value of weight nomograms for the early identification of neonates at risk for excessive weight loss and related morbidities. The objective of this study was to characterize weight changes and the effect of supplemental feeding in late preterm and term neonates during the first week of life, to identify and quantify neonatal and maternal influencing factors, and to provide an educational online prediction tool.
Methods: Longitudinal weight data from 3638 healthy term and late preterm neonates were prospectively recorded up to 7 days of life. Two-thirds (n = 2425) were randomized to develop a semi-mechanistic model characterizing weight change as a balance between time-dependent rates of weight gain and weight loss. The dose-dependent effect of supplemental feeding on weight gain was characterized. A population analysis applying nonlinear mixed-effects modeling was performed using NONMEM 7.3. The model was evaluated on the remaining third of neonates (n = 1213).
Results: Key population characteristics (median [range]) of the whole sample were gestational age 39.9 [34.4–42.4] weeks, birth weight 3400 [1980–5580] g, maternal age 32 [15–51] years, cesarean section 26%, and girls 50%. The model demonstrated good predictive performance (bias 0.01%, precision 0.56%), and is able to accurately predict individual weight change (bias 0.15%, precision 1.43%) and the dose-dependent effects of supplemental feeding up to 1 week after birth based on weight measurements during the first 3 days of life, including birth weight, and the following characteristics: gestational age, gender, delivery mode, type of feeding, maternal age, and parity.
Conclusions: We present the first mathematical model not only to describe weight change in term and late preterm neonates but also to provide an educational online tool for personalized weight prediction in the first week of life.

Abbreviations: CI, confidence interval; DoseFM, dose of formula milk; DosePM, dose of pumped breast milk; GA, gestational age; H, Hill coefficient; IIV, inter-individual variability; $Kin_{Add.FM}$, additional weight gain dependent on the daily dose of formula milk; $Kin_{Add.PM}$, additional weight gain dependent on the daily dose of pumped breast milk; Kin_{Base}, basal rate of weight gain; Kin_{PNA}, shape of the time-dependent weight gain rate; Kin(t), time-dependent rate of weight gain; Kout(t), time-dependent rate constant of weight loss; $Kout_{max}$, maximum rate constant of weight loss; MAPE, mean absolute percentage error; MPE, mean percentage error; PNA, postnatal age; RSE, relative standard error; t, time; T50, time at which Kout equals 50% of $Kout_{max}$; TLag, delay before start of time-dependent increase in weight gain rate; VPC, visual predictive check; WT0, birth weight.

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1. Introduction

Nutrition and growth are inextricably linked, especially in neonates. The point at which food intake exceeds postnatal fluid and fat loss marks the weight loss nadir and the onset of weight gain [1,2]. Excessive weight loss, usually defined as >10% birth weight (WT0), increases the risk of serious clinical complications such as exaggerated jaundice and hypernatremia [3,4]. Therefore, neonates at high risk of excessive weight loss need to be identified early to assure appropriate monitoring and optimal personalized care. Weight loss nomograms compare and interpret weight values to the distribution in a reference population of breast- or formula-fed neonates delivered vaginally or by cesarean section [5,6]. However, they only estimate the risk of observing excessive weight loss in a given neonate and do not predict weight change, which is the product of weight loss and weight gain. Whereas maximum weight loss usually occurs within the first few days after birth subsequent weight gain might be complicated especially in infants born preterm owing to increased rates of readmission [7]. To overcome this limitation, we developed and published a mathematical model that characterizes physiological weight change in exclusively breastfed healthy term neonates [8]. We applied pharmacometric and population analysis in a nonlinear mixed-effects model based on the simultaneous incorporation of all available longitudinal data from a population of interest comprising different observations derived from different individuals [9]. This approach not only estimates the average weight change profile in the population of interest but also characterizes interindividual variability, itself dependent at least in part on certain neonatal and maternal factors influencing initial weight loss and weight gain. Based on identified factors, such as delivery mode and gestational age (GA), defined as the time elapsing between day 1 of the last normal menstrual period and the day of delivery, and on the three initial weight observations, we developed a model that accurately predicted individual weight changes up to 1 week after birth. However, this initial model was limited to the population from which it was developed: exclusively breastfed healthy term newborns.

The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding given its medical and neurodevelopmental advantages for infants and mothers [10]. But in practice, breastfed neonates are frequently supplemented with formula milk for various reasons, such as difficulties in breastfeeding, increased risk of disease (preterm neonates, low birth weight, increasing weight loss), and uncertainty by mothers or caregivers [11]. Supplemental feeding during the first days of life is challenging as it may complicate breastfeeding and shorten breastfeeding duration [12]. Thus, understanding the effects of supplemental feeding and clinical factors on postnatal weight change and providing an educational online tool to predict individual risk may help to reassure caregivers and mothers and raise breastfeeding rates.

Our aims were (i) to characterize the effect of formula feeding on weight change in "healthy" neonates during the first week of life, by expanding the existing semi-mechanistic model; (ii) to identify and quantify effects of neonatal and maternal factors on weight loss and gain; (iii) to predict individual weight change and the effect of supplemental feeding up to 1 week after birth; and (iv) to provide an online tool to support caregivers in evaluating supplemental feeding to further personalize and optimize care during the first week of life.

2. Subjects and methods

2.1. Neonatal and maternal data

Following approval by the local ethics committee (EKZN 2015-050), we performed a retrospective study of prospectively recorded maternal and neonatal data for two complete birth years, 2009 and 2010, at the University Hospital of Basel. We collected a total of 4196 live born term and late preterm neonates with GA >34 weeks. We did not include multiple births and newborns transferred to a neonatal ward as our objective was to describe weight changes in "healthy" neonates. We also did not include neonates with aberrant weight profiles (no initial weight loss) and neonates with only one observation, to avoid any convergence issue in parameter estimation of our model.

The following characteristics were recorded and included in our analyses: (i) neonatal factors at birth: gender, birth weight (baseline), GA, length, head circumference, umbilical cord arterial pH, Apgar 5 min; (ii) follow-up characteristics: daily weight, time of follow up (days), maximum weight loss (nadir) and time of nadir, type of feeding, additional fluid intake in L/day (pumped breast milk or formula milk); and maternal characteristics: BMI before pregnancy, parity, gestational diabetes, age at infant's birth, peripartum blood loss, delivery mode, anesthesia.

We classified newborns into five groups based on first explorations of weight profiles: (i) exclusively breastfed; (ii) mainly breastfed, receiving $\leq$2 doses of formula during the entire observation period; (iii) exclusively formula-fed; (iv) breastfed with supplemental formula; and (v) breastfed with supplemental formula and pumped breast milk. High-risk reasons for supplementation in the latter two groups comprised gestational diabetic mother, preterm birth, low birth weight (<2500 g), and high weight loss (>10%).

Two-thirds of eligible neonates, gathered in a so-called learning dataset, were randomly selected to enhance and expand the published mathematical model [8]. The remaining third, the evaluation dataset, was used for advanced evaluation of the final expanded model.

2.2. Model development

We had already developed a semi-mechanistic model to characterize longitudinal weight data in term neonates exclusively breastfed during their first week of life [8]. A semi-mechanistic model can be defined as a compartmental model with minimal physiological components described using mathematical equations.

In our previously developed model, physiological weight changes in neonates were described by a turnover model, where the observed effect (change in weight) is considered as a dynamic process, with the net baseline effect being a balance between the apparent rate of "production" of the effect and rate of "removal" of the effect. In our case, the weight change is a function of the balance between the rates of weight gain [Kin(t)] and weight loss [Kout(t)] (Fig. 1) [8,13]. For example, if the input rate Kin(t), increases and/or the output rate Kout(t) decreases, the net balance is positive and thus the weight increases.

Based on known neonatal physiology, we assumed that the rates Kin(t) and Kout(t) vary over time, i.e. with increasing postnatal age (PNA). The rate of weight gain Kin(t) increases with time after an initial delay caused by the time to onset of maternal milk production, itself dependent on the delivery mode [5,6]: Kin(t) starts to increase 2 days after vaginal delivery, as opposed to 3 days after non-vaginal delivery, i.e. cesarean section [5,6]. The rate of weight loss Kout(t) decreases during the first 2–3 days of life, due to initial redistribution and fluid and fat loss.

We enhanced and expanded this existing model by incorporating multiple new components: (i) dose-dependent effects of supplemental feeding (formula and pumped breast milk) on weight gain; (ii) differences in weight dynamics between various neonatal populations; and (iii) covariate effects on parameters related to the initial weight loss.

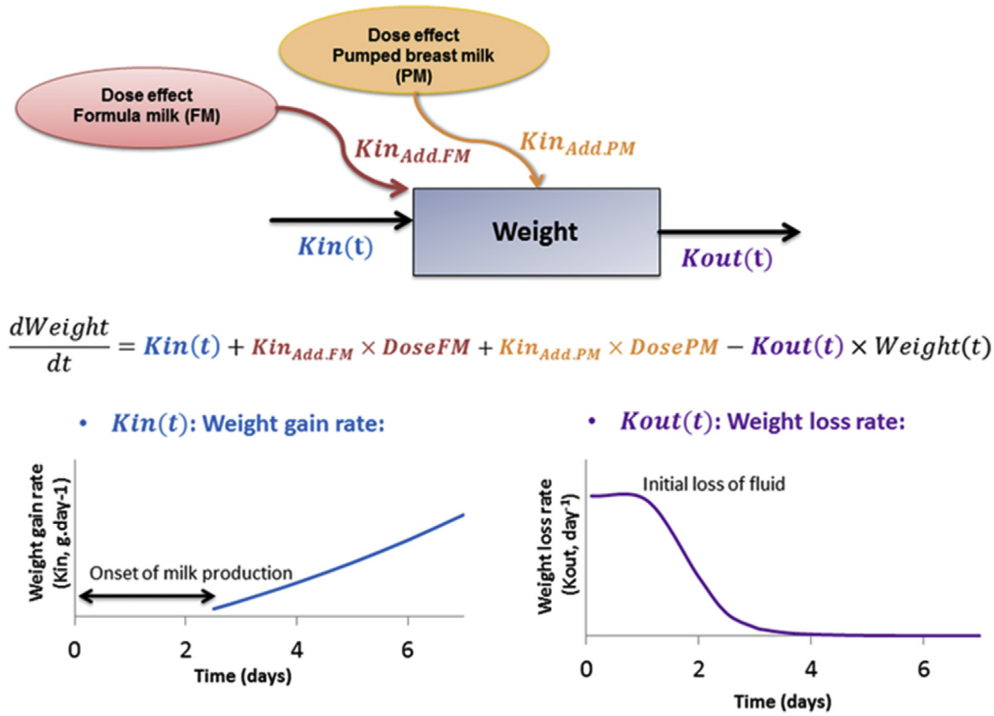

Fig. 1. Concept of the semi-mechanistic model describing physiological postnatal weight changes and dose effects of formula and pumped breast milk in "healthy" neonates. The postnatal weight change is a function of the time-dependent rates of weight gain and weight loss, Kin(t) and Kout(t) respectively. $Kin_{Add.FM}$ and $Kin_{Add.PM}$ are the additional weight gains depending on the daily doses of formula milk (DoseFM) and pumped breast milk (DosePM).

We tested various functions of direct and indirect dose effect, such as linear or saturable mathematical functions, to characterize supplemental feeding effects on weight changes during the first week of life.

Model parameters were estimated using a nonlinear mixed-effects modeling approach, also called population approach (Online Supporting Material 1) [9]. It is based on the simultaneous analysis of all available longitudinal weight data from all neonates, considering the fact that different observations are derived from different individuals. Thus, this approach permits the estimation and prediction of an average weight change profile, and also the characterization of the variability between individuals, called inter-individual variability. It also allows distinguishing the residual variability that includes for example measurement errors in weight values.

We applied a 3-step approach to develop the expanded model: (i) we began by estimating model parameters independently for each of the five groups and compared parameter estimates between the groups; (ii) then, we pooled the groups, re-estimated all parameters and tested population effects as covariate on each parameter identified as different in the first step. For that, we used a standard forward selection–backward deletion. We tried to explain these population effects by neonatal and maternal characteristics, which showed different inter-group distributions; (iii) finally, we tested the remaining covariates on clinically relevant parameters using standard stepwise forward –backward approach.

The tested covariate-parameter (Param) relationships for categorical covariate COV_{Cat} with two possible conditions (0 or 1) was $Param = TV_{Param} \times (1 + \theta \times COV_{Cat})$, and for continuous covariate COV_{Cont} was $Param = TV_{Param} \times (1 + \theta \times (COV_{Cont} - median(COV_{Cont})))$, with TV_{Param} the typical parameter value (Param) for a neonate with a covariate equal to the reference value ($COV_{Cat=}0$ or $COV_{Cont} = median(COV_{Cont})$), and Θ the estimated parameter describing the magnitude of the covariate-parameter relationships.

2.3. Model evaluation

We evaluated the final expanded model using three methods: (i) basic internal evaluation, (ii) simulation-based evaluation of predictive performance, and (iii) advanced evaluation on data from the evaluation dataset, i.e. data not used for model expansion [14].

Basic internal evaluation was performed based on established statistical criteria such as maximum likelihood, precision of parameter estimates (relative standard error [RSE]), and classical goodness-of-fit plots such as predicted versus observed weight change [14].

Predictive performance was tested by plotting visual predictive check (VPC) [14,15], involving 500 dataset simulations using parameter estimates of the final model. Simulated 10th, median and 90^{th} percentiles and their 95% confidence intervals (CI) were compared with observations.

We applied the final expanded model to predict individual weight changes in neonates from the evaluation dataset. Classical goodness-of-fit plots and VPCs were generated. Predictive performance of the final model was also numerically evaluated by calculating mean percentage error (MPE) to assess prediction bias, and mean absolute percentage error (MAPE) and root mean squared error (RMSE) to estimate prediction accuracy (Online Supporting Material 2) [16].

2.4. Model application

We applied the final expanded and validated model to predict individual weight changes during the first week of life based on initial weight observations up to 3 days after birth from the evaluation dataset. For that, the maximum *a posteriori* Bayesian method was utilized (Online Supporting Material 1) [17]. We assessed predictive performance by comparing predicted with observed weights using MPE, MAPE and RMSE calculations (Online Supporting Material 2) [16].

We developed a user-friendly online tool to predict individual weight profiles in the first week of life.

2.5. Computing process

We used NONMEM® 7.3 (NONlinear Mixed Effects Modeling, ICON Development Solutions, Ellicott City, MD, USA; www.iconplc.com) software to estimate model parameters using the population approach [18,19]. Parameter estimations were achieved by maximizing data likelihood using the first-order conditional estimation (FOCE) algorithm with interaction [18]. Evaluation of the remaining covariates from the last modeling step was performed after selection of the clinically relevant relationships using the Stepwise Covariate Model (SCM) from the Perl speaks NONMEM (PsN) toolbox [19,20]. Data handling, plots and numerical criteria calculations were performed in R [21].

3. Results

3.1. Maternal and neonatal data

We excluded 558 of the 4196 screened neonates due to transfer to a neonatal ward (n = 269), multiple birth (n = 148), too few weight observations (n = 119), and aberrant weight profiles (n = 22), leaving a total of 3638 "healthy" neonates for inclusion in our analysis.

Longitudinal weight data were obtained from 5 [2–8] measurements per neonate (Supplemental Fig. 1, Online Supporting Material 3). In our analysis, time 0 corresponds to the time of birth. Key individual characteristics of the whole sample, including learning (n = 2425) and evaluation dataset (n = 1213), were as follows: GA 39.86 [34.43–42.43] weeks, birth weight 3400 [1980–5580] g, maternal age 32 [15–51] years, girls 50%, and cesarean section 26%. Daily doses of formula and pumped breast milk, reported in mL/day, were converted to L/day for our analysis. Individual daily doses varied with time, e.g. increasing with weight loss and decreasing with weight gain (Online Supporting Material 4 – Supplemental Fig. 2).

Data were split into two datasets: the learning dataset comprising 2425 neonates used to expand the model, and the evaluation dataset comprising 1213 neonates used to evaluate the predictive performance of the model. Individual characteristics from the learning dataset are summarized in Table 1, and were similar to those from the evaluation dataset (Online Supporting Material 5, Supplemental Table 1).

The five groups of "healthy" term and late preterm neonates from the learning dataset (N = 2425) were as follows: (i) exclusively breastfed n = 887 (37%); (ii) mainly breastfed n = 496 (20%); (iii) exclusively formula-fed n = 46 (2%); (iv) formula-supplemented n = 187 (8%); and (v) formula- and pumped breast milk-supplemented n = 809 (33%).

Table 1 comprises the learning dataset and shows differences between the five groups in the distribution of some characteristics. The time of follow up is longer in neonates supplemented with formula milk ± pumped breast milk. The maximum weight loss is lower in exclusively formula-fed neonates. The time of maximal weight loss is also longer in supplemented with formula milk and pumped breast milk. The Apgar score at 5 min shows that exclusively breastfed and exclusively formula-fed neonates were born more healthy than the other populations. The delivery mode also differs between groups, with more cesarean-sections in exclusively formula-fed neonates. More spinal anesthesia were observed in the groups of exclusively formula-fed, formula-supplemented and formula- and pumped breast milk-supplemented neonates. Finally, more primiparity status are observed in formula- and pumped breast milk-supplemented neonates. The respective data of the evaluation data set are gathered in Supplemental materials, Supplemental Table 1.

3.2. Final structural model

In the final expanded model, weight gain rate Kin(t) was modeled as an exponential function of time. We assumed that Kin(t) starts to increase with a delay (TLag) of 2 days after vaginal delivery and 3 days after cesarean section [5,6]. Weight loss rate Kout(t) was modeled as a saturable decreasing Emax function with a Hill coefficient. In our previous model, Kout(t) increased after the initial decrease, but parameters were difficult to identify, so we kept only the first decrease [8]. We added two additional weight gains ($Kin_{Add.FM}$ and $Kin_{Add.PM}$) linearly dependent on daily doses of formula milk (DoseFM) and pumped breast milk (DosePM) (Fig. 1). The following equations describe the model's structural components:

$$\frac{dWeight}{dt} = Kin(t) + Kin_{Add.FM} \times DoseFM + Kin_{Add.PM} \times DosePM - Kout(t) \times Weight(t)$$

where:

$$Kin(t) = 0 \quad if \;\; t < TLag$$

$$Kin(t) = Kin_{Base} \times exp^{Kin_{PNA} \times t} \quad if \;\; t \geq TLag$$

$$Kout(t) = \frac{Kout_{max} \times t^{-H}}{T50^{-H} + t^{-H}}$$

$$Weight(0) = WT0$$

Kin(t) (g day^{-1}) and Kout(t) (day^{-1}) are time-dependent rates of weight gain and weight loss; t is the time corresponding to the PNA (day). $Kin_{Add.FM}$ and $Kin_{Add.PM}$ (g L^{-1}) are the additional weight gains dependent on the daily doses of formula and pumped breast milk (*DoseFM* and *DosePM*, (L day^{-1}). TLag (day) corresponds to the delay before the start of the time-dependent increase in weight gain rate, set to 2 and 3 days after vaginal and cesarean delivery [5,6]. Kin_{Base} (g day^{-1}) is the basal rate of weight gain and Kin_{PNA} (day^{-1}) the shape of the time-dependent weight gain rate. $Kout_{max}$ (day^{-1}) is the maximum rate of weight loss, T50 (day) the time at which Kout is equal to 50% of $Kout_{max}$, while H (*dimensionless*) is the Hill coefficient determining the steepness of the time-dependent rate constant of weight loss. The initial condition at time 0, birth weight, was estimated with the parameter WT0 (g), as standard in pharmacometric modeling [22]. Kin(t) was set at 0 for the exclusively formula-fed group to evaluate the effect of formula milk only.

Interindividual variability (IIV) was estimated for Kin_{Base}, H, T50, and WT0. It was fixed at 10% for TLag. The data did not support estimation of IIV for Kin_{PNA} or $Kout_{max}$ (set at 0). For the population approach, log-normal parameter distributions were assumed, and an additive error model was used to reflect residual variability, including measurement errors in weight values.

3.3. Population and covariate effects on the final model

Pooling of all data from the five groups revealed a population effect on the following parameters: Kin_{Base}, Kin_{PNA}, H, T50, WT0, and WT0 IIV. The population effect on Kin_{PNA} was replaced by the effect of GA as higher GA values were associated with faster weight gain rates. The population effect on WT0 was replaced by the

Table 1
Learning dataset characteristics stratified by population group.

Characteristics	Exclusively breastfed	Mainly breastfed	Exclusively formula-fed	Formula-supplemented	Formula- & pumped breast milk- supplemented
Neonates (n)	887 (37%)	496 (20%)	46 (2%)	187 (8%)	809 (33%)
Observations (n)	4175	2484	250	1042	4744
Follow-up (days)	3.6 [0.4–7.0]	3.8 [0.7–7.0]	4.1 [1.1–6.8]	4.4 [1.5–7.0]	4.8 [1.0–7.0]
Observations per neonate (n)	5 [2–8]	5 [2–8]	5 [2–8]	6 [3–8]	6 [2–8]
Birth weight (g)	3400 [2480–4610]	3490 [2480–4940]	3332 [2240–4520]	3470 [2120–4865]	3350 [1980–5230]
Max weight loss from baseline (%)	6.3 [12.8–0.0]	6.8 [13.0–0.6]	5.2 [10.0–0.6]	7.1 [13.3–1.6]	7.0 [15.7–0.7]
Time of nadir (days)	1.8 [0.0–4.2]	2.0 [0.4–5.0]	2.0 [0.9–5.4]	2.3 [0.4–4.8]	2.4 [0.5–6.3]
Gestational age (weeks)	39.86 [37.00–42.14]	40.14 [35.14–42.14]	39.07 [34.71–41.71]	40.00 [35.43–42.14]	39.71 [34.43–42.43]
Umbilical cord arterial pH	7.28 [7.04–7.48] NA: 100	7.27 [7.02–7.48] NA: 61	7.31 [7.00–7.37] NA: 4	7.27 [7.02–7.49] NA: 16	7.27 [7.02–7.42] NA: 83
Mother's age (years)	31 [17–44]	31 [16–45] NA: 1	33 [15–47]	32 [19–44]	31 [16–46]
Mother's BMI (kg.m-2)	27 [19–46] NA: 97	28 [20–51] NA: 71	28 [21–45] NA: 5	28 [21–51] NA: 23	28 [17–56] NA: 109
Mother's blood loss (mL)	350 [40–2000] NA: 11	400 [100–2500] NA: 15	500 [200–2000] NA: 2	500 [200–5000] NA: 4	450 [40–2900] NA: 23
Formula milk (mL/day)	0	0 [0–113]	57 [0.0–220]	15 [0–165]	5 [0–184]
Pumped breast milk (mL/day)	0	0	0	0	0 [0–40]
Gender					
Female	436 (49%)	267 (54%)	25 (54%)	103 (55%)	395 (49%)
Male	451 (51%)	229 (46%)	21 (46%)	84 (45%)	414 (51%)
Apgar 5					
<=8	63 (7%)	66 (13%)	2 (4%)	27 (14%)	112 (14%)
>8	823 (93%) NA: 1	429 (87%) NA: 1	44 (96%)	160 (86%)	696 (86%) NA: 1
Delivery					
ECS	77 (9%)	57 (12%)	14 (31%)	31 (17%)	121 (15%)
N-ECS	55 (6%)	50 (10%)	7 (15%)	47 (25%)	150 (19%)
Vaginal	755 (85%)	389 (78%)	25 (54%)	109 (58%)	538 (66%)
Anesth					
None	416 (47%)	178 (36%)	10 (22%)	42 (22%)	161 (20%)
Spinal	463 (52%) NA: 8	292 (59%) NA: 26	32 (70%) NA: 4	141 (75%) NA: 4	595 (73%) NA: 53
Parity					
1	309 (35%)	226 (46%)	10 (22%)	111 (59%)	588 (73%)
>1	578 (65%)	268 (54%) NA: 2	36 (78%)	76 (41%)	217 (27%) NA: 4
GDM					
No	887 (100%)	481 (97%)	41 (89%)	173 (93%)	772 (95%)
Yes	0 (0%)	14 (3%) NA: 1	5 (11%)	14 (7%)	37 (5%)

Data are presented as median [minimum - maximum] or number of subjects (%).
NA: not available; Max: maximum; Apgar 5: Apgar score at 5 min; ECS: Elective Cesarean section; N-ECS: None-ECS; Anesth: Anesthesia; GDM, gestational diabetes mellitus.

effects of gender, GA and parity as male newborns, high GA values and multiparity were associated with higher birth weight.

Given the available data, none of the tested covariates explained the population effects on Kin_{Base}, H, T50, and IIV WT0.

Additional linear covariate-parameter relationships were found to be significant. Maternal age had a negative effect on basal weight gain rate Kin_{Base}. Elective cesarean section, relatively high maternal age and nulliparity were linked to higher, longer and steeper weight loss.

We performed model-based simulations of a typical neonate to illustrate the effect and magnitude of key covariates on weight change in the first week of life (Fig. 2).

Compared to the initial model [8], the new enhanced model includes some covariate effects on the weight loss rate constant ($Kout_{max}$ and T50). In addition, the effect of maternal age on birth weight in the initial model was better explained in the enhanced model by an effect of parity. Finally, GA effect on weight gain rate was included in the parameter Kin_{PNA} instead of Kin_{Base}.

3.4. Interpretation of the final model parameters

Table 2 shows the estimated population average ("typical") parameters of the final model with their corresponding IIV and covariate effects. RSE values for all parameters indicate acceptable estimate precision.

Estimated population average birth weight (WT0) was 3243 g. Estimated typical basal weight gain rate Kin_{Base} differed between groups: (i) exclusively breastfed: $45.14{\circ}g{\circ}day^{-1}$; (ii) mainly breastfed: $39.66{\circ}g{\circ}day^{-1}$; (iii) exclusively formula-fed: set at 0; (iv) formula-supplemented: $33.27{\circ}g{\circ}day^{-1}$; and (v) formula- and pumped breast milk-supplemented: $28.25{\circ}g{\circ}day^{-1}$.

Typical time achieving 50% of the maximum rate constant of weight loss ($Kout_{max}$) in breastfed (groups i, ii, iv and v) and exclusively formula-fed neonates (group iii) was estimated to be within 2.2 days and 1.6 days (T50), respectively.

One liter per day (1 L day^{-1}) of formula or pumped breast milk was estimated to increase the weight gain rate by $51.08{\circ}g{\circ}day^{-1}$ and $27.25{\circ}g{\circ}day^{-1}$, respectively.

3.5. Final model evaluation

According to classical goodness-of-fit plots, weight changes were adequately fitted by the final, expanded model and there was no apparent bias (Online Supporting Material 6). Consistent with this finding, VPC (Fig. 3) showed matching observations and simulations, thus confirming satisfactory predictive performance. VPCs

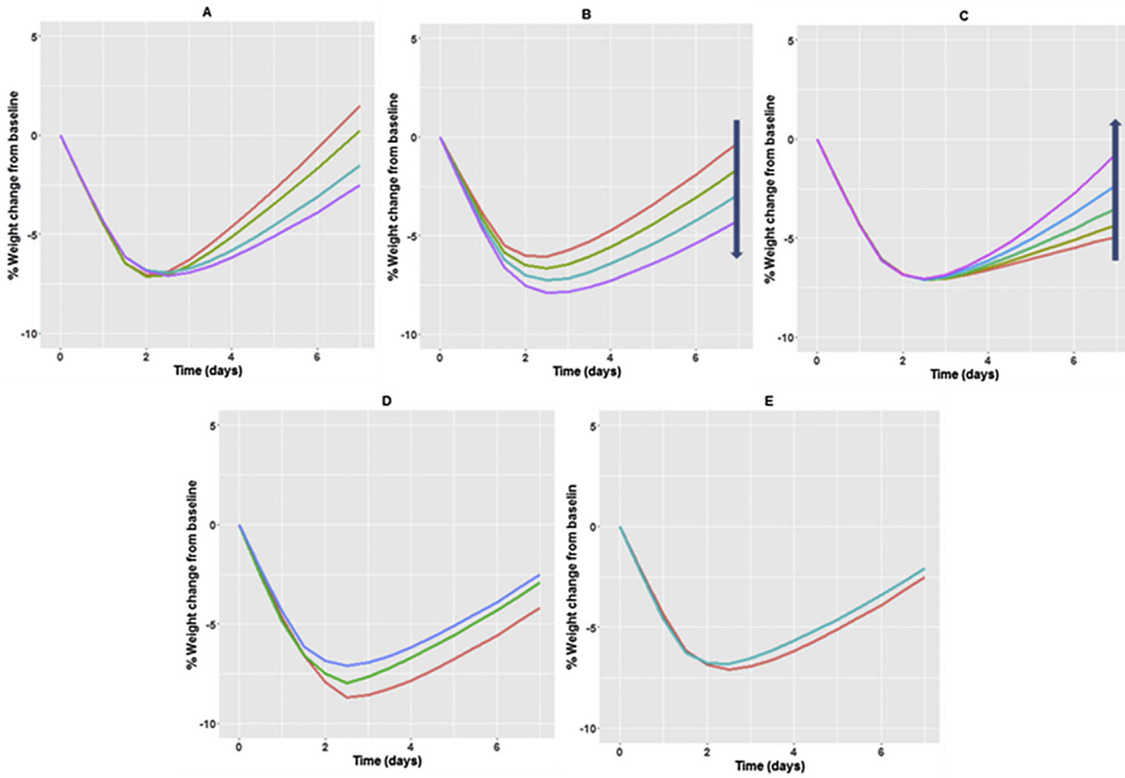

Fig. 2. Model-based simulations of a typical neonate to illustrate covariate effects on weight changes during the first week of life. All plots represent the percent weight change from baseline (%) by time. A typical neonate is considered to have the following characteristics: girl exclusively breastfed with a gestational ag of 39.7 weeks, born from a first-time mother of 32 years old. Only the neonatal or maternal factor of interest changes in these plots. **A:** Feeding effects on weight changes. The red, yellow, blue and purple curves correspond to simulated typical neonates exclusively breastfed, mainly breastfed (supplemental formula maximum 2 times), breastfed with supplemental formula milk, breastfed with supplemental formula and pumped breast milk, respectively. Of note, a simulated neonate exclusively formula fed is not represented in this plot to avoid any misleading. **B:** Mother age effects on weight changes. The red, green, blue and purples curves correspond to simulated typical neonates with mother age values of 15, 25, 35 and 45 years old. **C:** Gestational age effects on weight gain rates. The red, yellow, green, blue and purples curves correspond to simulated typical neonates with gestational ages of 34, 36, 36 and 42 weeks. **D:** Delivery mode effects on weight changes. The red, green and blue curves correspond to simulated typical neonates delivered by elective cesarean section, non-elective cesarean section and vaginally delivered, respectively. **E:** Parity effects on weight loss rates. The red curve corresponds to a simulated typical neonate born as a first child. The blue curve is a simulated neonate born as a second or more children.

stratified by population groups also showed good performance (not shown). The final, expanded model was applied to the evaluation dataset and validated by classical goodness-of-fit plots and VPC (not shown). Numerical results from advanced model evaluation demonstrated accurate prediction of individual weight profiles with acceptable precision (MAPE [95% CI]: 0.56% [0.55–0.57%], RMSE = 24 g) and limited bias (MPE [95% CI]: −0.01% [−0.03–0.01%]).

3.6. Model application

Using weight observations from the first 3 days of life for each neonate we applied the final, expanded model to predict individual weight change up to 1 week of life.

Altogether 2073 weight observations were available after 3 days from 986 neonates, of whom 0.3%, 45.5% and 54.2% had 2, 3 and 4 weight measurements before 3 days.

Observed weight data plotted against predicted values after the first 3 days of life showed good graphical agreement (Fig. 4). Consistent with this finding, the precision of predicted values was acceptable (MAPE [95% CI]: 1.43% [1.38–1.49%], RMSE = 62 g) and bias was limited (MPE [95% CI]: 0.15% [0.07–0.23%]), with a mean error magnitude between observed and predicted weights of only 46.2 g [95% CI: 44.4–47.9 g], or 1.43%.

Model-based predictions of individual weight change profiles based on weight measurements after the first 2 days also showed acceptable accuracy (MAPE [95% CI]: 1.75% [1.70–1.80%], RMSE = 73 g) and limited bias (MPE [95% CI]: 0.24% [0.16–0.32%]).

A user-friendly online tool, called "neoweight", has been developed and is available at the following link: http://neoweight.mashframe.com.

4. Discussion

In this study we enhanced and expanded our existing semi-mechanistic weight change model [8] by prospectively recording longitudinal weight data from 3638 "healthy" term and late preterm neonates. The results show that the expanded model not only accurately describes individual weight change but also provides early prediction of individual weight profiles and effects of supplemental feeding on weight change up to 1 week after birth in different groups, whether exclusively breastfed, exclusively formula-fed, or formula-supplemented.

Our hospital promotes breastfeeding and uses formula or pumped breast milk only to supplement newborns at high disease risk. Our previous model used data from exclusively breastfed neonates [8]. The present study addressed different groups of neonates and found population effects on key model parameters. We evaluated the effects of several key neonatal and maternal factors based on their clinical relevance. We identified GA, gender, delivery mode, parity and maternal age as key predictors of individual weight change in the first week of life. As expected, birth weight

Table 2
Parameter estimates of the final model.

Parameter (unit)	Estimate	RSE estimate (%)	IIV (% CV)	RSE IIV (%)	Covariates
$Kin_{Add.FM}$ (g L^{-1})	51.08	17	0 FIX	–	–
$Kin_{Add.PM}$ (g L^{-1})	27.25	36	0 FIX	–	–
Kin_{Base} Group (i) (g day^{-1})	45.14	5	37	6	Mother age: 5 years increase in mother age decreases Kin_{Base} by 6%
Kin_{Base} Group (ii) (g day^{-1})	39.66	5			
Kin_{Base} Group (iv) (g day^{-1})	33.27	7			
Kin_{Base} Group (v) (g day^{-1})	28.25	5			
Kin_{PNA} (day^{-1})	0.068	15	0 FIX	–	GA: 1 week increase in GA increases Kin_{PNA} by 48%
TLag (day) C-section	3 FIX	–	10 FIX	–	No
TLag (day) vaginal delivery	2 FIX	–	10 FIX	–	No
$Kout_{max}$ (day^{-1})	0.046	1	0 FIX	–	Delivery mode: - elective cesarean section: +9% - non-elective cesarean section: +14% Mother age: 5 years increase in mother age decreases $Kout_{max}$ by 10% Parity: multiparity +6%
H (*dimensionless*) Groups (i) and (ii)	−6.47	4	59	5	No
H (*dimensionless*) Groups (iii), (iv) and (v)	−4.38	4			
T50 (day) Groups (i), (ii), (iv) and (v)	2.20	1	20	2	Parity: multiparity −12%
T50 (day) Group (iii)	1.62	3			Delivery mode: non elective cesarean section: −16%
WT0 (g)	3243	1	10/12/13*	2/3/2*	GA: 1 week increase in GA increases WT0 by 5% Parity: multiparity +4% Gender: male +4%

A typical neonate is considered to have the following characteristics: girl exclusively breastfed with a gestational age of 39.7 weeks, born from a first-time mother of 32 years old. CV: coefficient of variation; FIX: fixed parameter; IIV: inter-individual variability; RSE: relative standard error; GA: gestational age; Groups (i): exclusively breastfed; (ii): mainly breastfed; (iii): exclusively formula-fed; (iv); formula-supplemented; (v): formula and pumped breast milk-supplemented; *: WT0 IIV and RSE in groups (i–v), respectively.

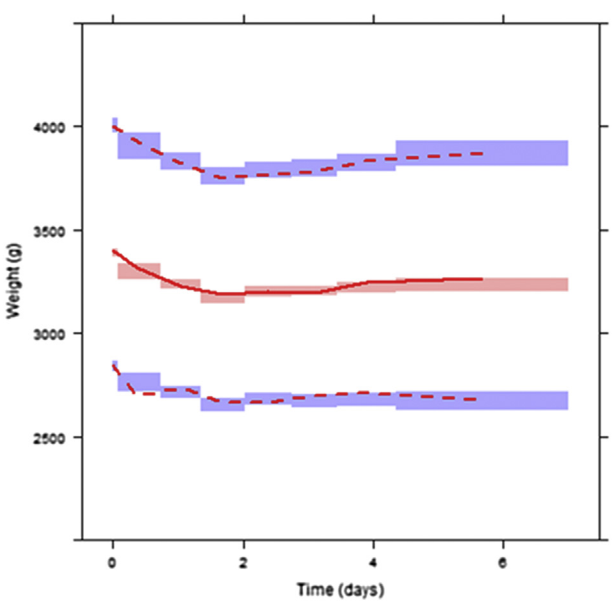

Fig. 3. Visual Predictive Check (VPC) to evaluate the predictive performance of the final model. Weight values are plotted against time. Red and blue areas correspond to the simulated confidence interval (95%) of the median and the 10th and 90th percentiles. The red curves are the observed median (dashed) and 10th and 90th percentiles. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

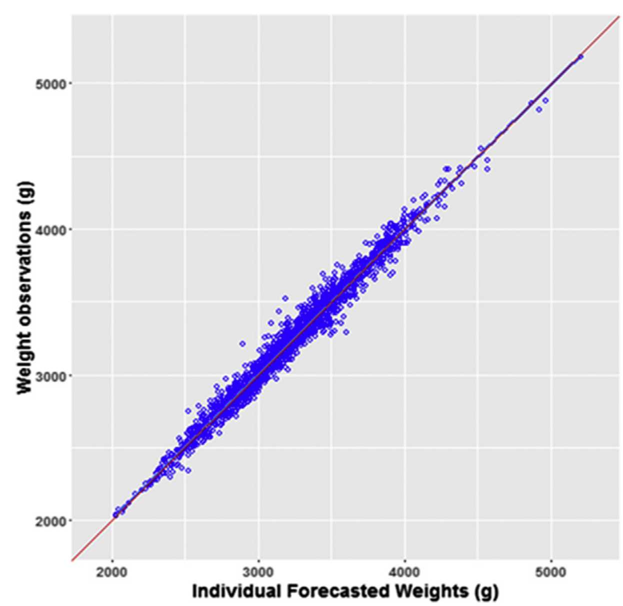

Fig. 4. Forecasted versus observed weight values in neonates from the evaluation dataset. The weight measurements of the first 3 days were used to forecast individual weight change up to 7 days. Only points after 3 days are plotted.

increases with increasing GA and boys weigh more than girls at birth [23,24]. Birth weight also increases with parity probably due to the inherent biological differences between nulliparous and multiparous mothers, such as the greater uteroplacental blood flow in multiparous mothers [25]. Weight gain is faster in neonates with increasing GA [23,24]. Interestingly, we found that the rate of weight gain decreases with increasing maternal age, while higher weight loss is observed in the first 3–4 days of life. This finding may be explained by the decrease and delay in milk production with increasing maternal age [26,27]. We also found that primiparity was associated with higher and longer initial weight loss as compared to multiparity, probably due to biological differences and lack of breastfeeding experience. An effect of delivery mode on weight loss rate was also significant, with higher, longer and steeper weight loss for elective cesarean section compared to non-elective cesarean section and vaginal delivery [28].

Compared to our initial model [8], the effects of delivery mode, parity and maternal age on weight loss parameters in the expanded model explain some of the variability in initial weight loss and weight gain. In addition, the effect of maternal age on birth weight observed in the initial model is now better explained in the expanded model by an effect of parity [25].

Other groups have developed weight nomograms but these fail to account either for weight change dynamics or for complexity when multiple risk factors are involved [6,29,30]. Our expanded semi-mechanistic model accounts for multiple key neonatal and maternal factors and can be applied to predict not just a reference weight loss and gain curve from various neonatal populations but also individual weight change up to 1 week after birth from weight measurements in the first 3 days of life. Pediatricians, neonatologists, midwives, other caregivers and parents can use this tool for the early prediction and monitoring of individual weight change, enabling them to further personalize feeding and treatment strategies in order to promote breastfeeding and avoid the clinical complications of excessive weight loss.

However our analysis presents some limitations. The number of weight measurements is influenced by the clinical status of the newborn, with more data collected in less "healthy" neonates. The numbers of exclusively formula-fed and formula supplemented neonates are small compared to the other groups. It should be noted that application of our model, at the current stage, is limited to "healthy" term and late preterm neonates and may not be used to project weight change in sick newborns or preterm neonates requiring intensive care therapy. Further validations are required using additional data from other centers as weight change profiles may differ between countries. Finally, prospective studies are needed to assess the potential clinical benefits of model-based optimization of personalized feeding strategies over current feeding practices in the first week of life.

In conclusion, we present the first mathematical model characterizing postnatal weight change and the effects of supplemental feeding in the first week of life in "healthy" term and late preterm neonates. We have also developed a user-friendly educational online tool to encourage breastfeeding, facilitate personalized care and monitoring, and support caregiver decision-making in supplemental formula feeding.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.04.001.

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