Characterizing and Forecasting Individual Weight Changes in Term Neonates

Mélanie Wilbaux, PhD1,*, Severin Kasser, MD2,*, Sven Wellmann, MD2, Olav Lapaire, MD3, Johannes N. van den Anker, MD, PhD1,4, and Marc Pfister, MD1

Objectives To develop a mathematical, semimechanistic model characterizing physiological weight changes in term neonates, identify and quantify key maternal and neonatal factors influencing weight changes, and provide an online tool to forecast individual weight changes during the first week of life.

Study design Longitudinal weight data from 1335 healthy term neonates exclusively breastfed up to 1 week of life were available. A semimechanistic model was developed to characterize weight changes applying nonlinear mixed-effects modeling. Covariate testing was performed by applying a standard stepwise forward selection-backward deletion approach. The developed model was externally evaluated on 300 additional neonates collected in the same center.

Results Weight changes during first week of life were described as a function of a changing net balance between time-dependent rates of weight gain and weight loss. Males had higher birth weights (WT0) than females. Gestational age had a positive effect on WT0 and weight gain rate, whereas mother’s age had a positive effect on WT0 and a negative effect on weight gain rate. The developed model showed good predictive performance when externally validated (bias = 0.011%, precision = 0.52%) and was able to accurately forecast individual weight changes up to 1 week with only 3 initial weight measurements (bias = −0.74%, precision = 1.54%).

Conclusions This semimechanistic model characterizes weight changes in healthy breastfed neonates during first week of life. We provide a user-friendly online tool allowing caregivers to forecast and monitor individual weight changes. We plan to validate this model with data from other centers and expand it with data from preterm neonates. (J Pediatr 2016;173:101-7)

As part of normal physiology, newborns lose body fluid and fat during the first days of life. Once food intake outweighs the initial loss of fluid and fat, the nadir of weight loss is achieved and weight gain follows. Multiple maternal and neonatal factors influence weight changes during the first week of life. In a subgroup of newborns, an imbalance of fluid and fat loss and weight gain results in an excessive weight loss, usually defined as ≥10% of birth weight, which increases the risk for serious clinical complications such as exaggerated jaundice and hypernatremia. In past years, hospital stays of mother-infant dyads shortened significantly, resulting in an increase of newborn readmissions mainly because of jaundice, dehydration, and feeding difficulties. Therefore the American Academy of Pediatrics announced recently that a shortened hospital stay of less than 48 hours after delivery for healthy term newborns may be accommodated but that it is not appropriate for every mother and newborn.

To identify newborns at increased risk for excessive weight loss, a first-day weight loss ≥5% was identified as a warning sign, and weight loss charts were established for breastfed newborns. To account for important confounders, such charts were published for newborns delivered vaginally and for those born by cesarean delivery. However, the impact of other possible confounders such as sex remains unclear. Weight loss charts are a good first step to guide caregivers and may set the frame for further research identifying the percent weight loss at which intervention (eg, formula feeding) should be initiated to prevent clinical complications, but they do not allow for individual forecasting of weight changes in neonates.

<table>
<thead>
<tr>
<th>IIV</th>
<th>Interindividual variability</th>
<th>KoutPNA</th>
<th>Shape of time-Kout positive relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kin</td>
<td>Time-dependent rate of weight gain</td>
<td>MAE</td>
<td>Mean absolute prediction error</td>
</tr>
<tr>
<td>KinPNA</td>
<td>Shape of the time-dependent weight gain curve</td>
<td>MPE</td>
<td>Mean prediction error</td>
</tr>
<tr>
<td>Kout</td>
<td>Time-dependent rate constant of weight loss</td>
<td>PNA</td>
<td>Postnatal age</td>
</tr>
<tr>
<td>Koutmax</td>
<td>Maximum rate of weight loss constant</td>
<td>T50</td>
<td>Time at which Kout is equal to 50% of Koutmax</td>
</tr>
<tr>
<td>Koutbase</td>
<td>Basal increase of Kout</td>
<td>TLag</td>
<td>Delay before the start of the weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VPC</td>
<td>Visual predictive check</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WT0</td>
<td>Birth weight</td>
</tr>
</tbody>
</table>

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Individual prediction can be obtained with the use of pharmacometrics, an emerging science of developing and applying mathematical and statistical methods for characterizing, understanding, and predicting pharmacokinetics of medicines, biomarkers, and clinical responses over time.\textsuperscript{18,19} Introduced by Sheiner et al\textsuperscript{20} in the 1970s, the population approach, or nonlinear mixed-effects modeling, is based on a simultaneous analysis of all data from a study population while taking into account that different observations are derived from different individuals. Such analyses permit us to estimate average population parameters, characterize intersubject and intrasubject variability, and identify and quantify key factors that influence parameters and their variability.

To overcome the main limitations of weight loss charts, this study performed a multimodal approach targeting the following goals: (1) to develop a semimechanistic model that characterizes physiological weight loss and weight gain during the first week of life in healthy term neonates exclusively breastfed; (2) to identify and quantify effects of maternal and neonatal factors on weight changes; (3) to forecast individual weight changes during the first week of life; and (4) to provide a user-friendly online monitoring tool to support pediatricians, neonatologists, midwives, and other caregivers.

**Methods**

A retrospective, single-center study of prospectively recorded maternal and neonatal data from healthy term newborns exclusively breastfed was performed at the University Hospital of Basel and approved by the local ethics committee (EKZN 2015-050). Two complete birth years (2009 and 2010) including 4128 term neonates were screened. To describe natural weight changes, newborns were excluded if they received any formula feeding at any time during individual study participation and if they were transferred to a neonatal ward. For mathematical modeling purpose, neonates without initial weight loss and with only 1 observation were excluded. Finally, only singleton neonates were included. A total of 300 additional healthy term newborns exclusively breastfed (external dataset) were collected in the same center from an additional birth year (2011) for external evaluation of the developed model.

A semimechanistic model, defined as a compartmental model with minimal physiological components, was built to describe longitudinal weight data from neonates during their first week of life. Physiological weight changes during the first week of life were described with a turnover model, characterizing weight change as a function of a changing net balance between rates of weight gain (input rate) and weight loss (output rate) (Figure 1).\textsuperscript{21} If the input rate is greater than the output rate, the net balance is positive and body weight increases. On the other hand, if the input rate is smaller than the output rate, body weight decreases. As input and output rates change over time, they were described with time-dependent mathematical functions.

Previous studies showed that the rate of weight gain (input rate) increases 2 days after vaginal delivery, whereas it increases 3 days after cesarean delivery.\textsuperscript{2,3} As a result of initial loss of fluid and fat, the rate of weight loss (output rate) is maximal at birth and decreases during the first 2-3 days of life before increasing with increasing input rate. To define structural components of the semimechanistic model, different time-dependent mathematical functions were tested for the rates of weight gain and weight loss: linear, exponential, saturable Emax (sigmoid functions plateauing at maximum weight gain or weight loss rates), and different combinations of these functions (plots illustrating evaluated mathematical functions in Figure 2; available at www.jpeds.com).

To estimate population average parameters and their intersubject and intrasubject variability, a population analysis was performed using a nonlinear mixed-effects modeling approach, analyzing data from all individuals simultaneously (Appendix 1; available at www.jpeds.com).\textsuperscript{20} Once structural and statistical components of the model were developed, maternal and neonatal characteristics, called covariates in modeling analysis, were tested applying a standard stepwise forward selection-backward deletion approach. The goal of such tests was to identify covariate effects that explain (at least in part) intersubject variability of model parameters.

Evaluation of the final model was performed by applying rigorous statistical criteria and methods. First, prespecified criteria such as maximization of the likelihood, precision of parameter estimation (relative SEs), and classical goodness-of-fit plots, such as predicted vs observed weight changes were used to evaluate models.\textsuperscript{22} Second, the model’s predictive performance was tested using the visual predictive check (VPC) method.\textsuperscript{22,23} To obtain VPC, 100 simulations of the data were performed with parameters estimates from the final model. Simulated 10th, median, and 90th percentiles and their 95% CIs were compared with observed values. Third, the final model was applied to predict individual weight changes in neonates of the external dataset (ie, data not used in the model development process). Classical goodness-of-fit plots and VPC were generated based on this external dataset. Further, the predictive performance of the final model was numerically externally evaluated by calculating mean prediction error (MPE) to assess prediction bias and mean absolute prediction error (MAE) to estimate prediction accuracy (Appendix 2; available at www.jpeds.com).

From the external dataset, the 3 initial weight observations (birth weight and 2 additional time points) for each neonate were retained. The final model and its parameter estimates were applied to these data to forecast individual weight changes up to 1 week of life. The maximum a posteriori Bayesian method was used (Appendix 1) to predict...
individual weight change curves. Individual weight predictions were graphically compared with observed weight values and the predictive performance was numerically evaluated with MPE and MAE calculations.

A user-friendly online tool was developed to forecast individual weight profiles during first week of life, based on only 3 initial weight measurements.

The software packages NONMEM 7.3 (ICON Development Solutions, Ellicott City, Maryland) and Perl-speaks-NONMEM (PsN) were used to fit individual weight data to the semimechanistic model. Estimations were made by maximizing the likelihood of the data, with the first-order conditional estimation algorithm with interaction. The covariate model was developed with the PsN’s scm program. Data handling, graphical representations, and numerical criteria calculations were performed in R. The python programming language was used to build the web server implementation.

![Weight change for one neonate](image)

\[
\frac{d\text{Weight}}{dt} = K_{\text{in}}(t) - K_{\text{out}}(t) \times \text{Weight}
\]

![Weight gain rate vs Time](image)

![Weight loss rate vs Time](image)

**Figure 1.** Example of one neonate to illustrate the developed model describing weight changes during the first week of life as a function of changing net balance between the time-dependent rates of weight gain (K_{\text{in}}) and weight loss (K_{\text{out}}\times\text{Weight}).
Results

From 4128 screened neonates, a total of 1335 healthy term neonates exclusively breastfed were included in this analysis. Excluded newborns comprised of 2430 neonates with formula feeding, 24 neonates with only 1 observed weight, 267 neonates that were transferred to a neonatal ward, and 72 multiples.

Longitudinal weight data with a median (minimum-maximum) of 3270 g (2235-4610 g) up to 7 days of life were available from 662 female and 673 male neonates. A median (range) of 5 (2-11) weight observations per subject was available. The individuals’ weight change profiles are provided in Figure 3 (available at www.jpeds.com). The external analysis dataset was comprised of data from 300 neonates, with a median weight of 3305 g (2430-4590 g) and comparable characteristics with that of original analysis data used for model development process. Key characteristics of neonates in both analysis datasets are given in Table I.

In the final model, the weight change was described as a function of a changing net balance between the time-dependent rates of weight gain (input rate) and weight loss (output rate). The input rate was modeled as an exponential function of time started to increase with a delay of 2 days after vaginal delivery and 3 days after cesarean delivery (delay before the start of the weight gain [TLag]). The output rate was modeled with 2 components: a saturable decreasing Emax function to describe changing output rate during the first 2-3 days of life followed by an exponential time-dependent increase in output rate to describe increasing output with increasing input over time. The structural components of the model were described with the following equations:

\[
\frac{d\text{Weight}}{dt} = \text{Kin}(t) - \text{Kout}(t) \times \text{Weight}
\]

With:

\[
\text{Kin}(t) = 0 \text{ if } t < \text{TLag}
\]

\[
\text{Kin}(t) = \frac{\text{Kin}_{\text{Base}} \times \exp^{\text{Kin}_{\text{PNA}} \times t}}{\text{C}^0} \text{ if } t \geq \text{TLag}
\]

\[
\text{Kout}(t) = \frac{\text{Kout}_{\text{max}}}{\text{C}^0} \times t^{-\text{H}} + \frac{\text{Kout}_{\text{Base}} \times \exp^{\text{Kout}_{\text{PNA}} \times t}}{\text{C}^0}
\]

\[
\text{Weight}(0) = \text{WT}_0
\]

Time-dependent rate of weight gain (Kin, g·day$^{-1}$) and time-dependent rate constant of weight loss (Kout, day$^{-1}$) are the input rate and output rate, respectively; t is the time, corresponding to the postnatal age (PNA) (day); TLag (day) corresponds to the TLag, set to 2 and 3 days after vaginal delivery and cesarean delivery, respectively. Kin$_{\text{Base}}$ (g·day$^{-1}$) is the basal input rate and Kin$_{\text{PNA}}$ (day$^{-1}$) the shape of the time-dependent weight gain curve. Kout$_{\text{max}}$ was modeled with 2 components: a saturable decreasing Emax function to describe changing output rate during the first 2-3 days of life followed by an exponential time-dependent increase in output rate to describe increasing output with increasing input over time. The structural components of the model were described with the following equations:

\[
\frac{d\text{Weight}}{dt} = \text{Kin}(t) - \text{Kout}(t) \times \text{Weight}
\]

With:

\[
\text{Kin}(t) = 0 \text{ if } t < \text{TLag}
\]

\[
\text{Kin}(t) = \frac{\text{Kin}_{\text{Base}} \times \exp^{\text{Kin}_{\text{PNA}} \times t}}{\text{C}^0} \text{ if } t \geq \text{TLag}
\]

\[
\text{Kout}(t) = \frac{\text{Kout}_{\text{max}}}{\text{C}^0} \times t^{-\text{H}} + \frac{\text{Kout}_{\text{Base}} \times \exp^{\text{Kout}_{\text{PNA}} \times t}}{\text{C}^0}
\]

\[
\text{Weight}(0) = \text{WT}_0
\]

Table I. Neonatal characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data used for model building</th>
<th>External dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of neonates</td>
<td>1335 (6351 observations)</td>
<td>300 (1323 observations)</td>
</tr>
<tr>
<td>Time of follow-up (d)</td>
<td>3.7 (0.4-7.0)</td>
<td>3.4 (0.4-7.1)</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>3270 (2235-4610)</td>
<td>3305 (2430-4590)</td>
</tr>
<tr>
<td>Number of weight observations</td>
<td>5 (2-11)</td>
<td>4 (2-8)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3390 (2410-4610)</td>
<td>3420 (2630-4590)</td>
</tr>
<tr>
<td>Percentage weight changes from baseline (%)</td>
<td>$-3.7 \text{ (} -12.8 \text{ to } 12.9 \text{)}$</td>
<td>$-3.9 \text{ (} -12.3 \text{ to } 6.2 \text{)}$</td>
</tr>
<tr>
<td>GA (wk)</td>
<td>39.9 (37.0-42.1)</td>
<td>39.9 (37.0-41.9)</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>50 (44-57)</td>
<td>50 (39-55)</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>35 (30-43)</td>
<td>35 (31-39)</td>
</tr>
<tr>
<td>Umbilical cord arterial pH</td>
<td>7.3 (7.0-7.5)</td>
<td>7.3 (7.1-7.5)</td>
</tr>
<tr>
<td>Umbilical cord venous pH</td>
<td>7.4 (7.1-7.8)$^*$</td>
<td>7.4 (7.2-7.6)$^*$</td>
</tr>
<tr>
<td>Mother’s age (y)</td>
<td>32 (17-47)</td>
<td>31 (19-45)</td>
</tr>
<tr>
<td>Mother’s BMI (kg·m$^{-2}$)</td>
<td>27 (19-46)$^*$</td>
<td>-</td>
</tr>
<tr>
<td>Mother’s blood loss (mL)</td>
<td>400 (40-2200)$^*$</td>
<td>-</td>
</tr>
<tr>
<td>Parity</td>
<td>2 (1-8)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>None/Regional anesthesia</td>
<td>-</td>
</tr>
<tr>
<td>Sex</td>
<td>619 (46%)/703 (53%)$^*$</td>
<td>-</td>
</tr>
<tr>
<td>Apgar at 5 min &lt;9/≥9</td>
<td>662 (50%)/673 (50%)</td>
<td>140 (47%)/160 (53%)</td>
</tr>
<tr>
<td>Delivery mode</td>
<td>100 (7%)/1234 (92%)$^*$</td>
<td>37 (12%)/263 (88%)</td>
</tr>
<tr>
<td>Vaginal/cesarean</td>
<td>1126 (84%)/209 (16%)</td>
<td>249 (83%)/51 (17%)</td>
</tr>
<tr>
<td>Nationality</td>
<td>Switzerland</td>
<td>667 (50%)</td>
</tr>
<tr>
<td>Europe</td>
<td>456 (34%)</td>
<td>126 (42%)</td>
</tr>
<tr>
<td>Other</td>
<td>199 (16%)</td>
<td>39 (14%)</td>
</tr>
</tbody>
</table>

BMI, body mass index; GA, gestational age.
Data are presented as median (minimum-maximum) or number of subjects (%).
*Approximately 10% of missing values.
†Approximately 1% of missing values.
‡BMI measured before pregnancy.
(day\(^{-1}\)) is the maximum output rate constant, T50 (day) the time at which Kout is equal to 50% of Kout\(_{\text{max}}\), and the Hill coefficient (dimensionless) determining the steepness of the Kout-time relationship. Kout\(_{\text{Base}}\) (day\(^{-1}\)) is the basal increase of Kout. Kout\(_{\text{PNA}}\) (day\(^{-1}\)) is the shape of the increase of Kout.

The initial condition at time 0 was estimated with the parameter birth weight (WT0) (g), as commonly done in pharmacometric modeling.\(^{30}\) Interindividual variability (IIV) was estimated on Kin\(_{\text{Base}}\), T50, Kout\(_{\text{Base}}\), and WT0. IIV was fixed at 10% on Kout\(_{\text{max}}\) and TLag. The data did not support estimation of IIV on Kin\(_{\text{PNA}}\), Hill coefficient, and Kout\(_{\text{PNA}}\) (fixed to 0). For the population approach, log-normal parameter distributions within the study population were assumed, and an additive error model was used to reflect residual variability, including measurement errors, in body weight values.

As a result of the stepwise forward-backward covariate search, 5 linear covariate-parameter relationships were found to be significant. Male newborns have higher birth weight (WT0) values than female newborns. Gestational age has a positive effect on birth weight and basal rate of weight gain (Kin\(_{\text{Base}}\)). Maternal age has a positive effect on birth weight, and it has a negative effect on basal rate of weight gain. Estimates for key parameters and their IIV from the final model are provided in Table II (available at www.jpeds.com). The typical basal rate of weight gain (Kin\(_{\text{Base}}\)) was estimated at 41.51 g・day\(^{-1}\). The maximum rate constant of weight loss (Kout\(_{\text{max}}\)) was estimated to be slowed by one-half at a typical age of 1.9 days. The typical birth weight (WT0) was estimated at 3470 g. Relative SE of population average parameters and corresponding IIV values, representative of estimation precision, were all less than 33%.

According to goodness-of-fit plots, weight changes were adequately fitted by the final model (Figures 4 and 5; available at www.jpeds.com). The VPC in Figure 6 shows that observations are in agreement with simulations, which is consistent with good predictive performance of the model. The final model was externally validated according to goodness-of-fit plots and VPC (Figure 7; available at www.jpeds.com). Results from external validation demonstrated good predictive performance with accuracy (MAE, 95% CI 0.52% [0.49%-0.54%]) and no bias (MPE 95% CI 0.01% [-0.026% to 0.047%]). In other words, the median error magnitude between predicted weight and observed value at a given time was equal to 13.5 g (first quartile = 6.6 g; third quartile = 23.7 g). The worst case scenarios in these data were an underprediction of −97.1 g and an overprediction of 95.6 g.

Observed weight data from the external dataset plotted against forecasted values after 3 initial weight measurements showed good agreement (Figure 8). Further statistical review of model-based predictions indicated that forecasting of individual weight change profiles was with acceptable precision (MAE: 1.54% [1.42%-1.65%]) and without bias (MPE: −0.74% [−0.91% to −0.57%]). The median error magnitude between forecasted observed weight at a given time was equal to 42.6 g (first quartile = 20.0 g; third quartile = 71.0 g). The worst-case scenarios were an

![Figure 6. Visual Predictive Check to internally evaluate the predictive performance of the model. Weight values are plotted against time. Blue and red areas correspond to the simulated 95% CI of the median, 10th and 90th percentiles. The red curves are the observed median (dashed), 10th and 90th percentiles.](image)

![Figure 8. Forecasted vs observed weight in term neonates from the external dataset. The first 3 observed weight values were used to forecast individual weight change up to 7 days. Only points after the first 3 observations are plotted. The red line is the identity line and the blue line corresponds to a regression of all points.](image)
Randomly selected individual weight change profiles are provided in Figure 9 (available at www.jpeds.com). The median (minimum-maximum) time corresponding to the third observation is 1.86 (1.38-3.11) days.

We also explored model-based predictions of individual weight change profiles based on 2 weight measurements (birth weight and 1 additional time point on day 1 or 2) with a median (minimum-maximum) time corresponding to the second observation of 0.85 (0.38-2.11) days. Predictions of weight change profiles were accurate (MAE: 1.95% [1.85%-2.06%]) and showed limited bias (MPE: −1.16% [-1.32% to −1.00%]) (Figure 10; available at www.jpeds.com). However, for a subgroup of neonates, without any specific characteristics, predictions were much better forecasted using 3 observations (Figure 11; available at www.jpeds.com).

A user-friendly online NeoWeight Prediction tool was developed. This NeoWeight Prediction tool forecasts individual weight change profiles during first week of life, based on 3 weight measurements during first 2 days of life and key neonate characteristics. The NeoWeight Prediction tool can be found at http://neoweight.mashframe.com/ (Appendix 3; available at www.jpeds.com).

### Discussion

Multiple maternal and neonatal factors influence weight change in neonates. It is critical to identify neonates that are at risk for excessive weight loss during the first days of life, as a decrease in weight ≥10% of birth weight is associated with rehospitalizations because of serious clinical complications such as jaundice and hypernatremia. We developed a semimechanistic model that: (1) characterizes weight changes during the first week of life; (2) accounts for key covariate effects such as sex, gestational age, and mother’s age; and (3) can be used to early forecast and monitor individual weight changes during the first week of life. In contrast to previously reported, empirical models, the pharmacometric, semimechanistic model reported here: (1) characterizes weight changes with mathematical functions and parameters that have physiological meanings; (2) accounts for effects of key maternal and neonatal factors on model parameters; (3) quantifies both intersubject and intra-subject variability; and (4) forecasts individual weight change profiles up to 1 week of life. Further, the weight change model was applied on 300 additional healthy exclusively breastfed term neonates that were not used in the model development process. Our model accurately describes individual weight change profiles and is able to project weight curve until 1 week of life in these neonates.

From our evaluated maternal and neonatal factors (Table 1), we identified gestational age, sex, and mother’s age as key predictors. First, birth weight increases with increasing gestational age, and boys weigh more than girls at birth. Second, the basal rate of weight gain depends on gestational age. Third, birth weight increases with increasing age of mother at childbirth. This is consistent with a recent report indicating a positive correlation between mother’s age and baby’s birth weight as a result of age-dependent changes in mother’s glucose metabolism. Interestingly, we found that the basal rate of weight gain decreases with increasing maternal age. This finding may be explained by previous reports that milk production decreases with maternal age. Finally, we set the time to start of weight gain to 2 days for vaginal delivered neonates and 3 days for those born by cesarean delivery to account for different onset of milk production in these 2 populations.

Weight charts have been recently developed by other groups. They are useful to compare weight of an individual with expected weight range given the delivery mode. However, they cannot be used to project individual weight changes in neonates. Further, development of charts based on individual characteristics becomes complex as multiple maternal and neonatal factors influence weight change during the first week of life. For this reason, we developed a semimechanistic model accounting for key maternal and neonatal factors that can be applied to predict not just a reference curve from a population of neonates but also individual weight change during the first week of life. We provide a user-friendly online NeoWeight Prediction tool that permits to project individual weight curves with birth weight and only 2 weight measurements. Pediatricians, neonotologists, midwifes, and other caregivers can use this NeoWeight Prediction tool to forecast and monitor early weight changes and personalize treatment to avoid excessive weight loss and associated clinical complications, including prolonged hospitalization or readmission to the hospital.

It should be noted that our model is based on data from healthy term neonates who were exclusively breastfed, as our primary goal was to investigate the natural course of postnatal weight change. Median (20th percentile-80th percentile) maximum weight loss was −6.25% (−7.79% to −4.70%) in our analysis data set (Figure 12; available at www.jpeds.com). For this reason, application of this initial model is limited to a healthy term neonatal population. It cannot be used to project weight changes in preterm infants, sick newborns, or neonates with additional formula-based feeding because of excessive weight loss, and the next step will be to expand the current model with data from these populations. In addition, the external evaluation was performed on data from one center, which could limit the generalizability of our model. Additional data from other centers are needed to fine-tune and validate the model as weight changes profiles may differ between countries (eg, neonates from the US may not have the same weight change profiles as neonates in Europe). Prospective studies are also warranted to assess the potential clinical benefits of a model-based personalized, optimized feeding strategy vs current feeding practices of neonates during the first week of life.

In conclusion, this semimechanistic model characterizes physiological weight changes in healthy breastfed neonates and quantifies effects of key maternal and neonatal factors...
on weight change profiles during the first week of life. A user-friendly online NeoWeight Prediction tool (http://neoweight.mashframe.com/) allows caregivers to forecast and monitor individual weight changes to further personalize and optimize care of neonates. The next step will be to evaluate and expand this model with data from other centers and other populations such as preterm neonates. We are grateful to Chiara De Angelis (San Gerardo Hospital, Monza, Italy), Hanna Rickenbacher, and Noemi Klarer (both from University of Basel Children’s Hospital, Basel, Switzerland) for developing the online NeoWeight Prediction tool.

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References

The population analysis was performed using the nonlinear mixed effects modeling approach: a 1-stage analysis that simultaneously estimates fixed effect parameters, interindividual variability (IIV), and random residual error. The \( j \)th observation in the \( i \)th individual, \( y_{i,j} \), can be described by:

\[
y_{i,j} = f(\theta_i, x_{i,j}, z_i) + g(\theta_i, x_{i,j}, z_i) \times \epsilon_{i,j}
\]

\( f \) is the function of the structural model. \( g \) is the function for the error model. \( \theta_i \) is the vector of model parameters for the \( i \)th individual. \( x_{i,j} \) are the design variables for the \( j \)th observation in the \( i \)th individual. \( z_i \) corresponds to the covariates in subject \( i \). \( \epsilon_{i,j} \) is the residual error for the \( j \)th observation in the \( i \)th individual and is assumed to be normally distributed with mean 0 and unit variance \( \sigma^2 \):

\[
\epsilon_{i,j} \sim N(0, \sigma^2)
\]

The second level of variability characterizes differences between individuals. IIV is usually modeled with the vector of individual parameters \( q_i \) as a function of the vector of fixed effects, \( m \), of individual covariates, \( Z_i \), and the vector of individual random effects, \( h_i \):

\[
q_i = h(m, z_i, h_i)
\]

\( h_i \) is assumed to be normally distributed with mean 0 and unit variance \( \Omega \):

\[
h_i \sim N(0, \Omega)
\]

Thereby, 3 parameters have to be estimated:

- the fixed effect vector: \( \theta_i \)
- the random effect parameter quantifying the residual unknown variability: \( \sigma^2 \)
- the random effect parameter quantifying the IIV: \( \Omega \)

Different statistical models were tested for the IIV and the residual error model.

**The Search of Covariates**

The search for covariates able to reduce the unexplained variability of model parameters used a stepwise forward selection-backward deletion approach. The parameter-covariate relations tested for continuous and categorical covariates were not included and included as a linear function of the covariate \( (1 + THETA \times COV_{continuous}) \times Parameter \).

**Selection Criteria**

The criteria used for selection of the best model during model building and for inclusion of covariates were the objective function value (OFV) for nested models and the Akaike information criterion (AIC) for nonnested models:

\[
OFV = -2 \times \log(L)
\]

\( L \) is the likelihood of the data to the model.

\[
AIC = -2 \times \log(L) + 2 \times k
\]

\( L \) is the likelihood and \( k \) is the number of parameters. For both criteria, a lower value corresponds to a better fit. For the comparison of nested models, the difference in OFVs can be compared with a \( \chi^2 \) distribution.

**The Maximum a Posteriori Bayesian Method**

The maximum a posteriori Bayesian method uses a point estimate of the mode of parameters’ posterior density, corresponding to the product of the prior (model structure and population parameters’ log-normal distributions) and the likelihood (residual error model).

**Appendix 2**

The mean prediction error (MPE) and mean absolute prediction error (MAE) were computed to evaluate bias and precision of the predictions:

- MPE (%):
  \[
  MPE = \frac{1}{n} \sum \left( \frac{Pred - Obs}{Obs} \right) \times 100
  \]

- MAE (%):
  \[
  MAE = \frac{1}{n} \sum \left( \frac{|Pred - Obs|}{Obs} \right) \times 100
  \]

n is the number of observations.

**Appendix 3**

The Figures illustrate how to use the NeoWeight Prediction tool. A, Request login credentials (Register button). B, Log in with username and password. C, Click on “Apps” and “NeoWeight”. D, Input neonate’s characteristics and weight observations. E, Click on “Forecast Weight” to F, generate graphs showing projected weight change and the critical limits of 8%-10%.
Appendix Figure 1. NeoWeight Prediction tool interface. (Continues)
### NeoWeight

**General Information**

<table>
<thead>
<tr>
<th>Gestational Age (weeks)</th>
<th>Sex</th>
<th>Delivery Mode</th>
<th>Mother's Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>41.25</td>
<td>Male</td>
<td>Vaginal</td>
<td>25</td>
</tr>
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</table>

**Birth Weight**

<table>
<thead>
<tr>
<th>Observed Weight</th>
<th>Observed Weight Unit</th>
<th>Time after birth</th>
<th>Time Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>2955</td>
<td>kg</td>
<td>0.0</td>
<td>Days</td>
</tr>
</tbody>
</table>

**Subsequent weight measurements**

<table>
<thead>
<tr>
<th>Observed Weight</th>
<th>Observed Weight Unit</th>
<th>Time after birth</th>
<th>Time Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>2205</td>
<td>kg</td>
<td>0.5</td>
<td>Days</td>
</tr>
<tr>
<td>2715</td>
<td>kg</td>
<td>1.47</td>
<td>Days</td>
</tr>
</tbody>
</table>

**Forecast Weight**

### Absolute Weight Time Plot

- **Predicted Weight Change**
- **Observed Weights**

### Percent Weight Change Time Plot

- **Predicted Weight Change**
- **Observed Weights**
- **8% Weight Loss**
- **10% Weight Loss**

**Sourcing Information for the app**

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Appendix Figure 2. Example of a male newborn with a gestational age of 41.85 weeks vaginal delivered from a mother 25 years of age. He had a birth weight of 2955 g and 2 weight observations: 2885 g at 0.5 days and 2765 g at 1.47 days. Graphs show that the newborn will rapidly gain a lot of weight and will not need any intervention.
Appendix Figure 3. Example of a female newborn with a gestational age of 40.85 weeks delivered by cesarean delivery from a mother 33 years of age. She had a birth weight of 4280 g and 2 weight observations: 4190 g at 0.6 days and 4000 g at 1.6 days. Graphs show that the newborn will continue to lose weight close to −8% and will gain weight without returning to birth weight at 7 days. This neonate may need to be followed more carefully compared with the previous newborn and may need additional interventions such as formula feeding.
Figure 2. Evaluated mathematical functions to describe time-dependent rates of weight gain and weight loss. *Blue curves* represent a positive relationship and *black dashed lines* a negative relationship between weight gain rate or weight loss rate and time. The last plot represents a sigmoidal Emax model with different values of Hill coefficient: the *blue* and *black curves* have higher values of Hill coefficient compared with the *red curve*.

Figure 3. All individuals’ profiles of weight changes. Each *curve* corresponds to 1 neonate.

Figure 4. Model internal evaluation. Individual observations were plotted against individual predictions.
Figure 5. Individual profiles. Weights are plotted against time for different neonates. Grey dots correspond to the observed values. Red curves are the individual predicted profiles and blue dashed curves the population predicted profiles.
Figure 7. External evaluation. A, Observations vs individual predictions. B, Visual Predictive Check. Weight values are plotted against time. Blue and red areas correspond to the simulated 95% CI of the median, 10th and 90th percentiles. The red curves are the observed median (dashed), 10th and 90th percentiles.

Figure 9. Example of weight changes forecast based on 3 initial observations. Percentage weight changes were plotted against time for 2 subjects from the external dataset, A, newborn and B, another newborn. Blue dots are the observations. The red curve correspond to the weight changes predictions using 3 initial observations. Horizontal dashed lines correspond to the limit of 5%-10% of weight loss.
Figure 10. Forecasted vs observed weight after 2 initial observations from the external dataset. The first 2 observed weight values were used to forecast individual weight change up to 7 days. Only points after the first 2 observations are plotted.

Figure 11. Example of weight changes forecast. Percentage weight changes were plotted against time for 2 subjects. Blue dots are the observations. The red curve correspond to the weight changes predictions using 2 initial observations, the blue curve using 3 initial observations. Horizontal dashed lines correspond to the limit of 5%-10% of weight loss. A, Observations are better predicted using 3 initial values. B, Observations are equally predicted using 2 or 3 initial values.
Figure 12. Distribution of maximum weight loss in the dataset used for model building.

Table II. Parameter estimates

<table>
<thead>
<tr>
<th>Parameters (unit)</th>
<th>Estimates</th>
<th>RSE estimate (%)</th>
<th>IIV (%CV)</th>
<th>RSE IIV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KinBase (g day⁻¹)</td>
<td>41.51</td>
<td>8.3</td>
<td>29</td>
<td>7.2</td>
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<tr>
<td>KinPNA (day⁻¹)</td>
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<tr>
<td>TLag cesarean delivery (day)</td>
<td>3 FIX</td>
<td>-</td>
<td>10 FIX</td>
<td>-</td>
</tr>
<tr>
<td>TLag vaginal delivery (day)</td>
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<td>-</td>
<td>10 FIX</td>
<td>-</td>
</tr>
<tr>
<td>Kout, max (day⁻¹)</td>
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<td>1.3</td>
<td>10 FIX</td>
<td>-</td>
</tr>
<tr>
<td>H</td>
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<td>-</td>
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<td>T50 (day)</td>
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<td>21</td>
<td>3.5</td>
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<td>-</td>
</tr>
<tr>
<td>W0 (g)</td>
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<td>0.4</td>
<td>10</td>
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<td>GA effect on KinBase</td>
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<tr>
<td>GA effect on W0</td>
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<td>Sex effect on W0</td>
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<td>Mother’s age effect on W0</td>
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<td>Residual error (g)</td>
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<td>3.2</td>
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<td>-</td>
</tr>
</tbody>
</table>

CV, coefficient of variation; FIX, fixed parameter; GA, gestational age; H, Hill coefficient; RSE, relative standard error.