Characterizing and Forecasting Individual Weight Changes in Term Neonates

Mélanie Wilbaux PhD, S. Kasser MD, S. Wellmann MD, O. Lapaire MD, J.N. van den Anker MD, Marc Pfister MD

Pediatric Pharmacology & Pharmacometrics
Division of Neonatology, Children's Hospital Basel (UKBB)
Obstetrics and Gynecology, University Hospital Basel (USB)

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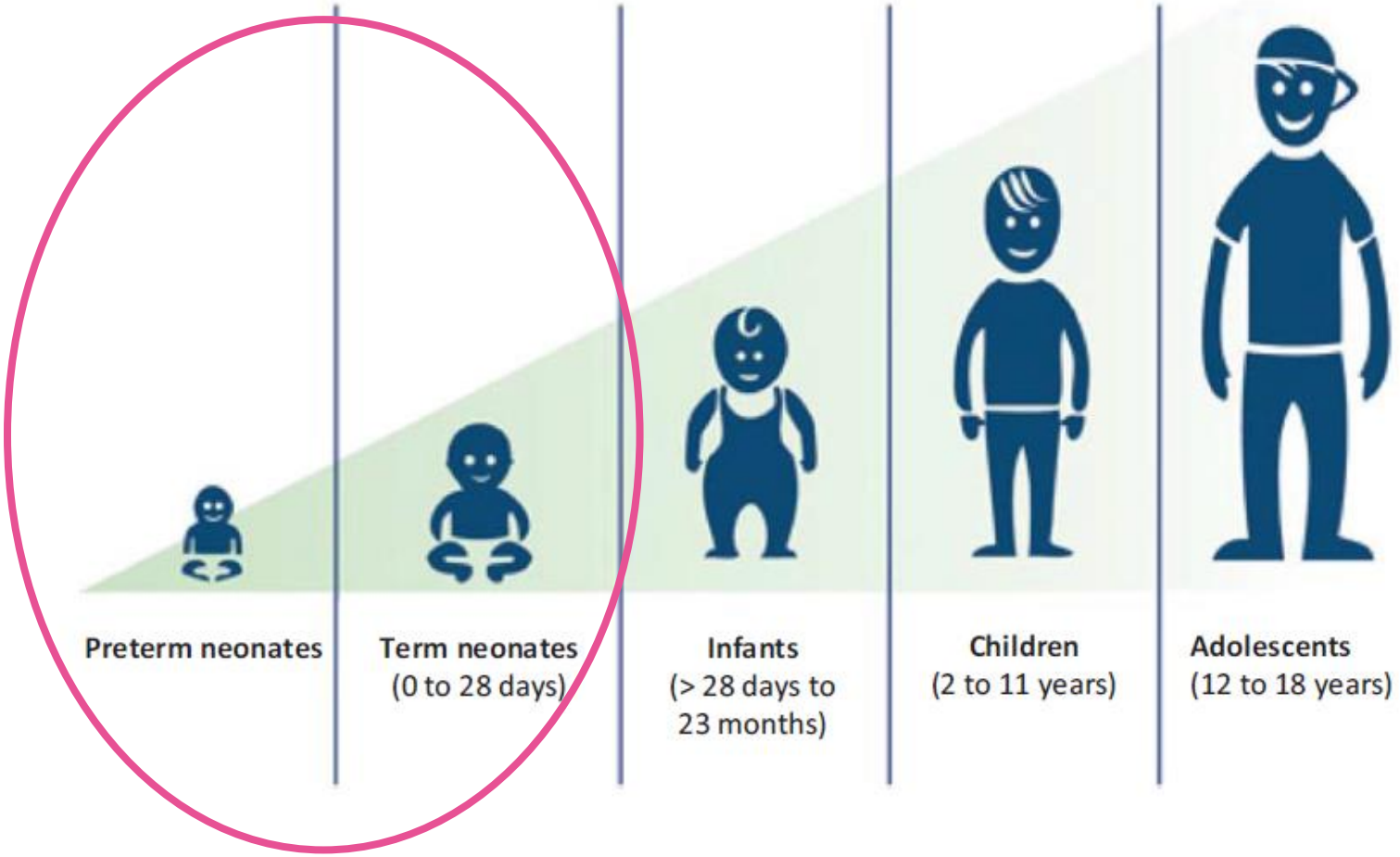
Pediatrics – A Heterogeneous Population



Rodieux F. et al. Effect of Kidney Function on Drug Kinetics and Dosing in Neonates, Infants, and Children. *Clin Pharmacokinet* 2015

Pediatrics – A Heterogeneous Population

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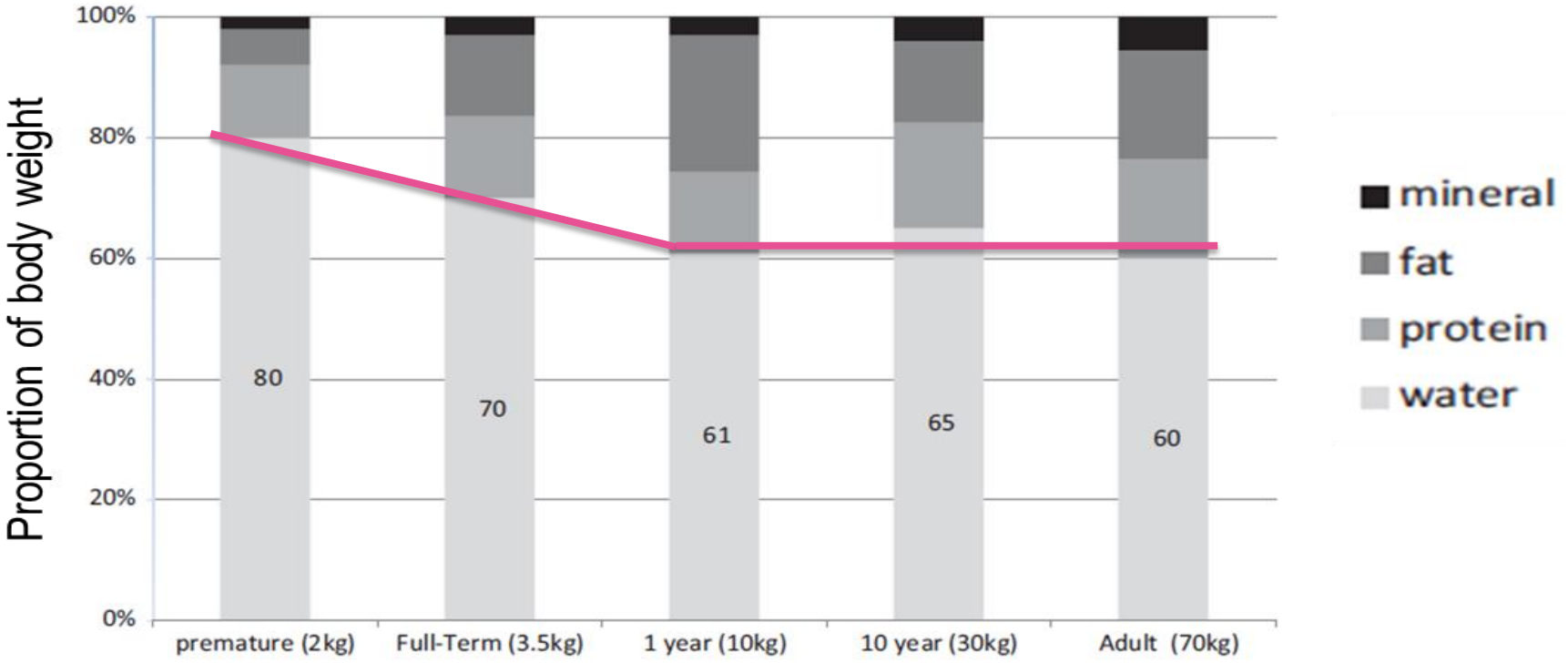
Body Composition



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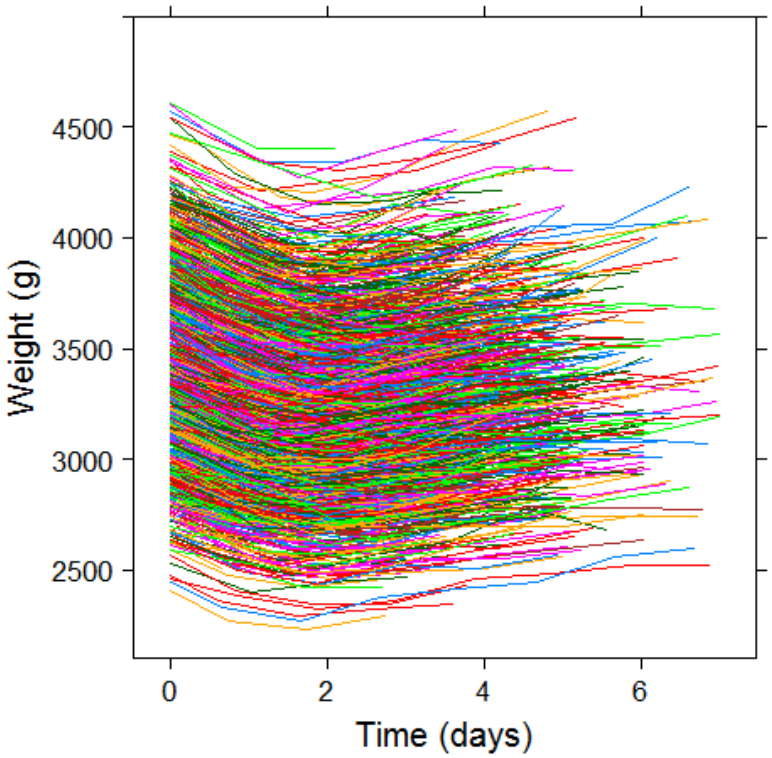
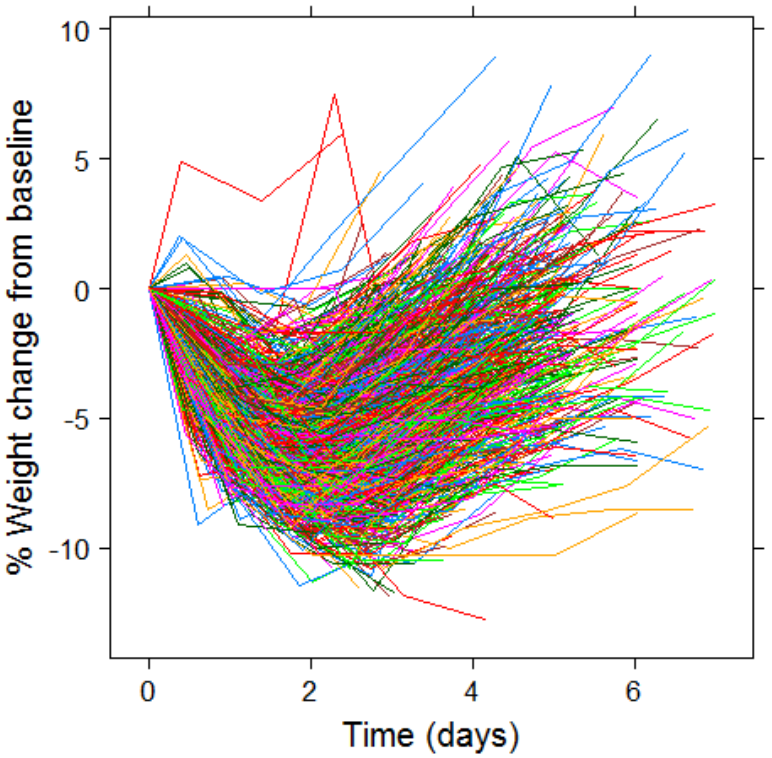
Motivation

- **Weight changes** during the first week of life in **term neonates**:





- **Excessive weight loss** (>10%) has negative effects on development and increases the risk for serious **clinical long term complications**

➢ To further **improve care of neonates** by clinicians, nurses, midwifes, and mothers

Objectives

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- **Develop** a pharmacometric model characterizing weight changes in healthy term neonates exclusively breastfed
- **Identify and quantify** effects of maternal and neonatal factors
- **Forecast** individual weight changes up to 7 days of life
- **Provide a user-friendly online monitoring tool** to support neonatologists and other caregivers

Data

- Retrospective single-center study at University Hospital of Basel & University Children's Hospital Basel: maternal and neonatal data
- A total of **1335 healthy term neonates exclusively breastfed**
- Longitudinal body weight data up to the first **7 days** of life
- **Neonatal and maternal** characteristics:

Characteristics	(%) Median [min - max]
Gender: Female / Male	50% / 50%
Delivery Mode: C-section / Vaginal Delivery	16% / 84%
Mother's Age (years)	32 [17 - 47]
Gestational Age (weeks)	40 [37 – 42]
Birth Weight (g)	3390 [2410 - 4610]

- A total of **300** additional neonates for **advanced evaluation**

Methods – Model Structure

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Development of a **pharmacometric model** by characterizing weight changes as a net balance between weight gain and weight loss rates

$$\frac{dWeight}{dt} = Kin - Kout \times Weight$$

Methods – Model Structure

Development of a **pharmacometric model** by characterizing weight changes as a net balance between weight gain and weight loss rates

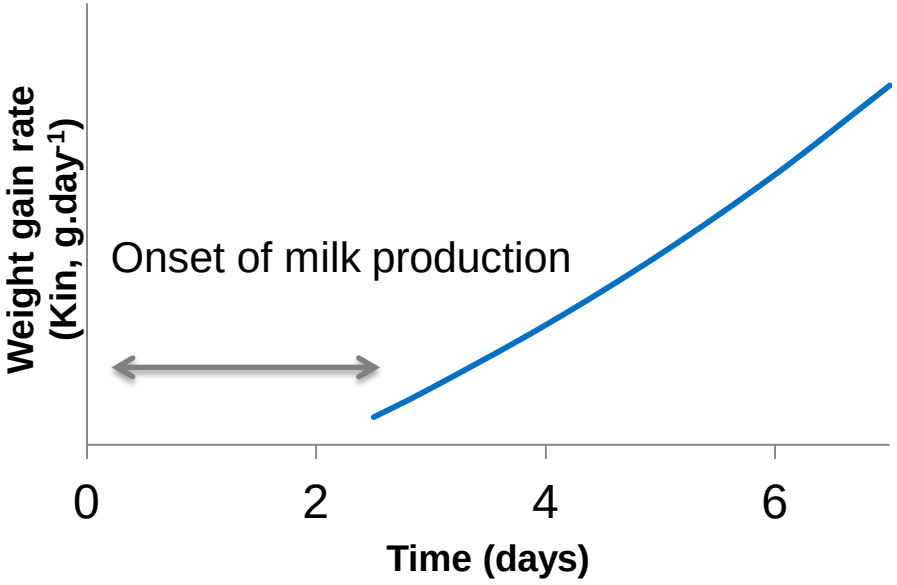
$$\frac{dWeight}{dt} = Kin(t) - Kout(t) \times Weight$$

Kin and $Kout$ describe using **time-dependent** mathematical functions

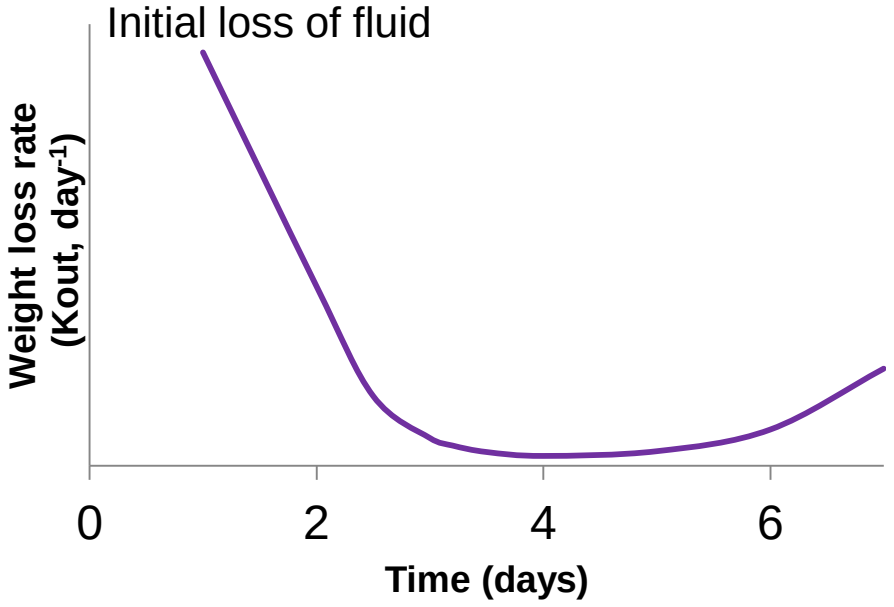
Methods – Model Development

$$\frac{dWeight}{dt} = Kin(t) - Kout(t) \times Weight$$

Kin vs. Time



Kout vs. Time



Methods – Modeling Method

- **Non-linear mixed effects modeling:**
  - NONMEM 7.3 (FOCEI algorithm)
- **Model selection & evaluation:**
  - Maximization of the likelihood
  - Standard error (SE)
  - Goodness-of-fit (GOF) plots
  - Simulation-based diagnostics (Visual predictive Check: VPC)
- **Search for covariates:**
  - Clinical relevance
  - Standard stepwise forward selection – backward deletion approach

Results - Final Model

$$\frac{dWeight}{dt} = Kin(t) - Kout(t) \times Weight$$

$$Weight(t = 0) = WT0$$

- **$Kin(t)$: Weight gain rate:**

$$IF(t < TLag):\ Kin(t) = 0$$

$$IF(t \geq TLag):\ Kin(t) = Kin_{Base} \times exp^{Kin_{PNA} \times t}$$

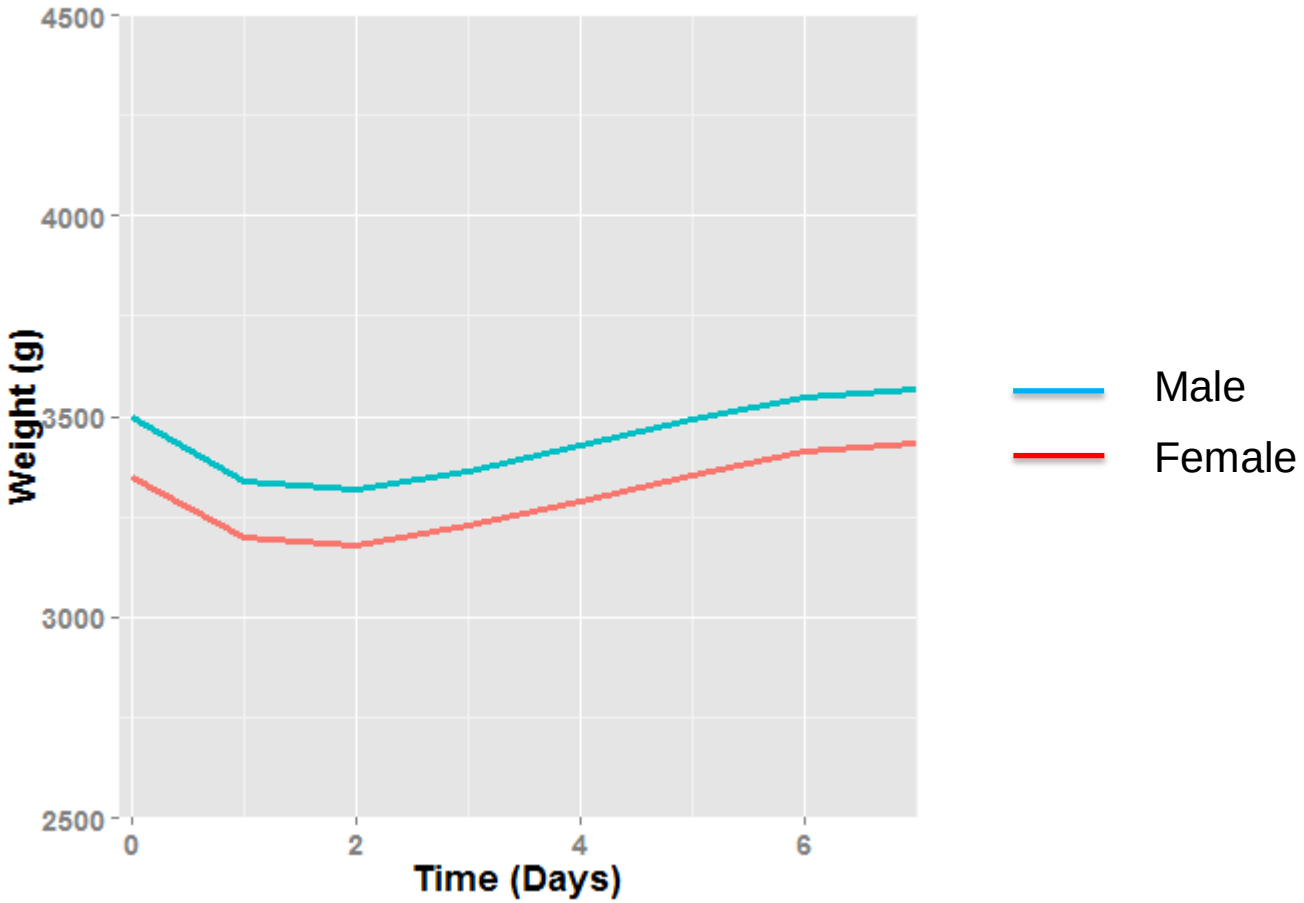
$TLag = 2\ days$ for vaginal delivery
$TLag = 3\ \ days$ for C-section

- **$Kout(t)$: Weight loss rate:**

$$Kout(t) = \underbrace{\frac{Koutmax \times t^{-H}}{T50^{-H} + t^{-H}}}_{\text{Saturable Emax with Hill coefficient}} + \underbrace{Kout_{Base} \times exp^{Kout_{PNA} \times t}}_{\text{Exponential}}$$

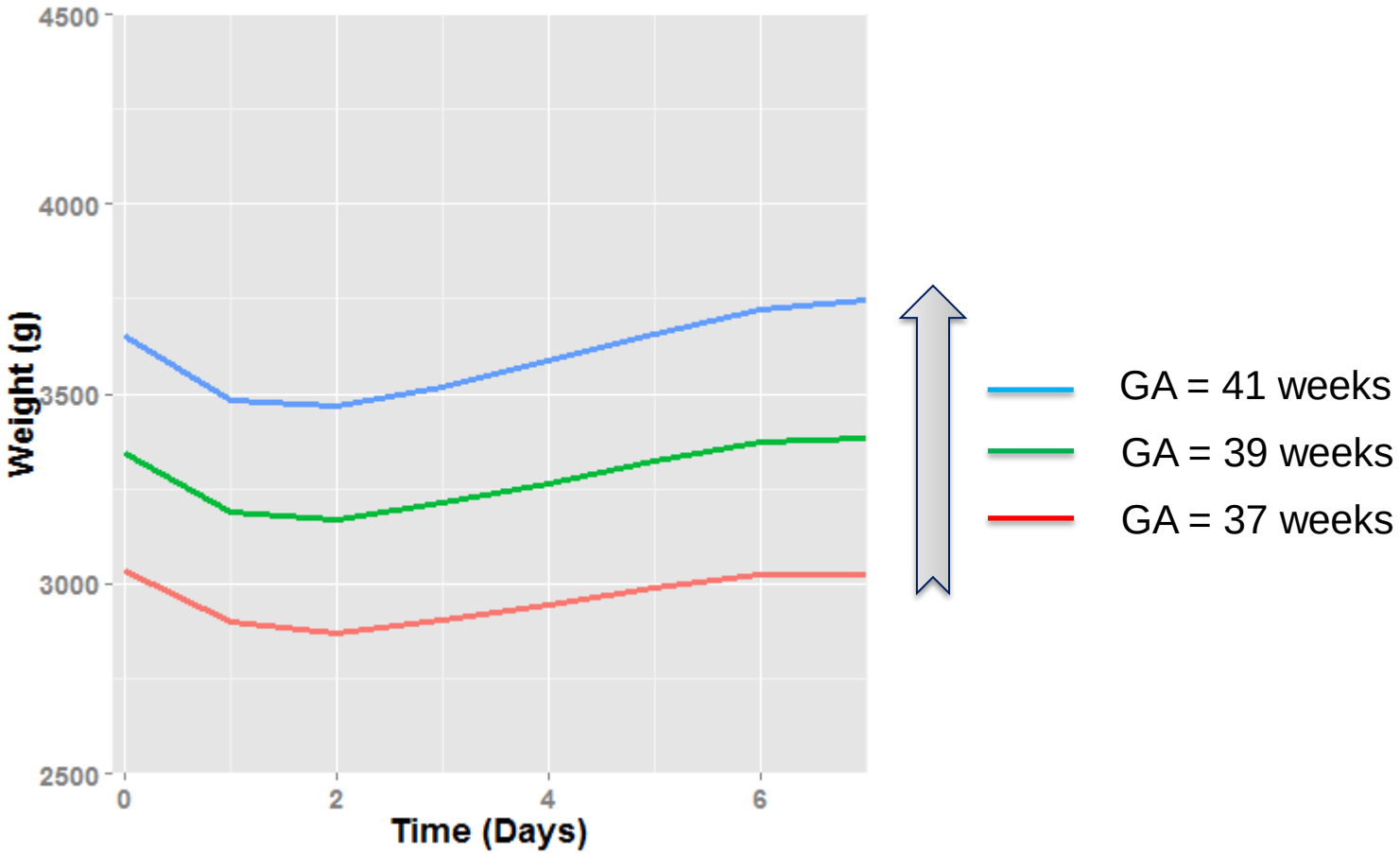
Results - Covariates

- **5 covariate – parameter relationships:**
  - **Gender** effect on $WT0$: $WT0_{Male} > WT0_{Female}$



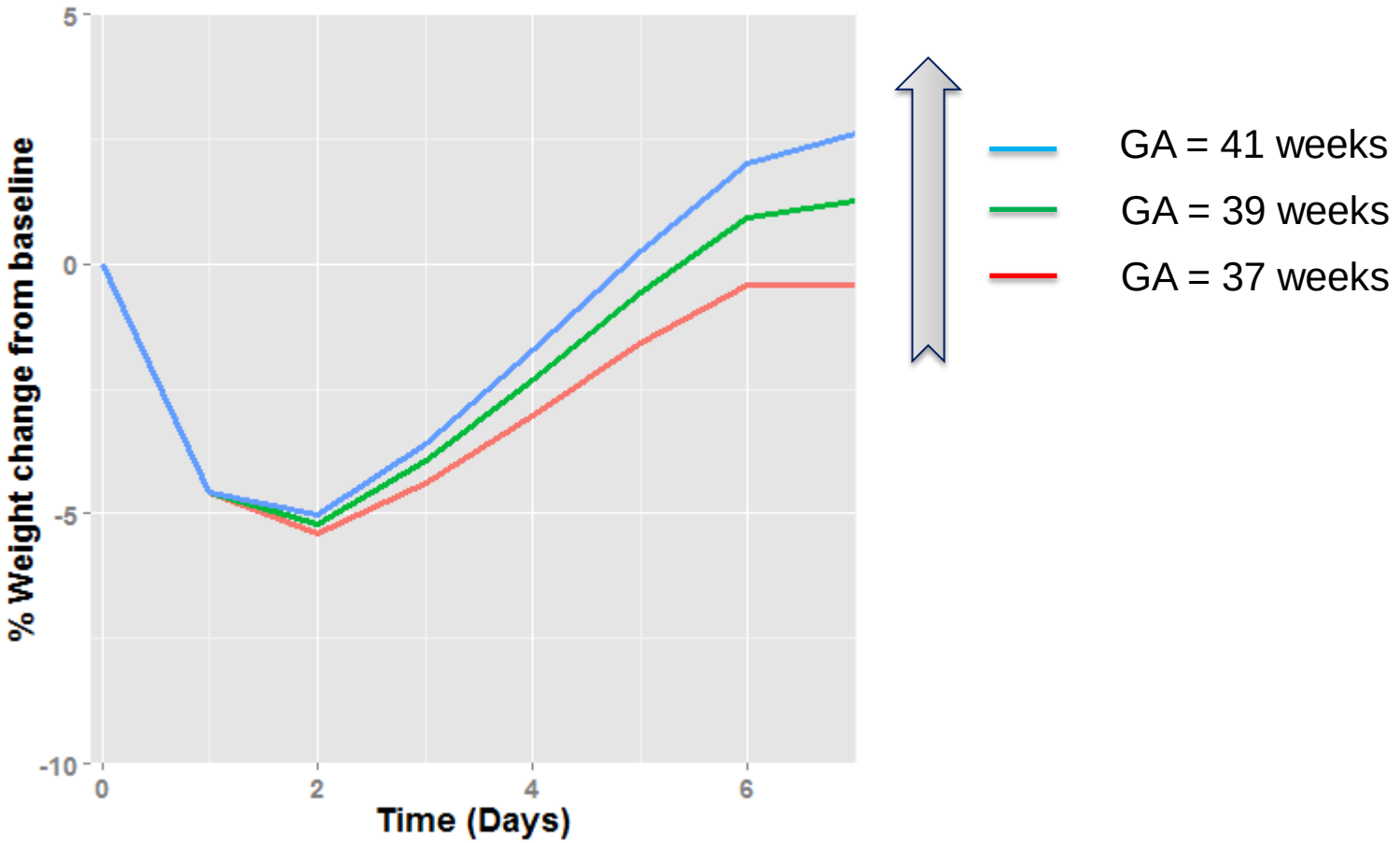
Results - Covariates

- **5 covariate – parameter relationships:**
  - Positive **GA** effect on $WT0$



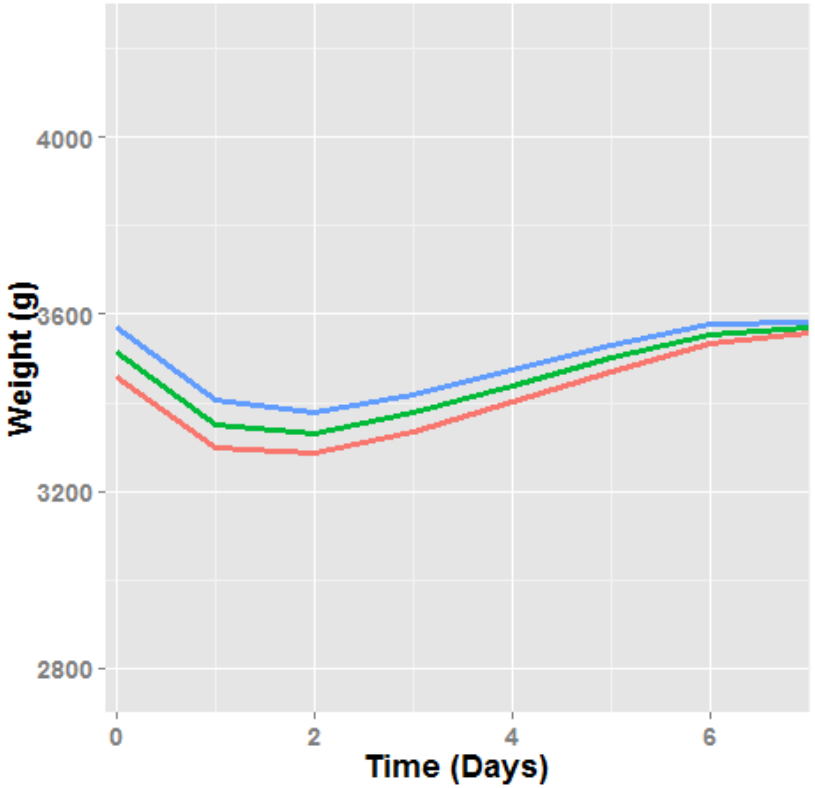
Results - Covariates

- **5 covariate – parameter relationships:**
  - Positive **GA** effect on Kin_{Base}



Results - Covariates

- **5 covariate – parameter relationships:**
  - Positive **mother age** effect on $WT0$:



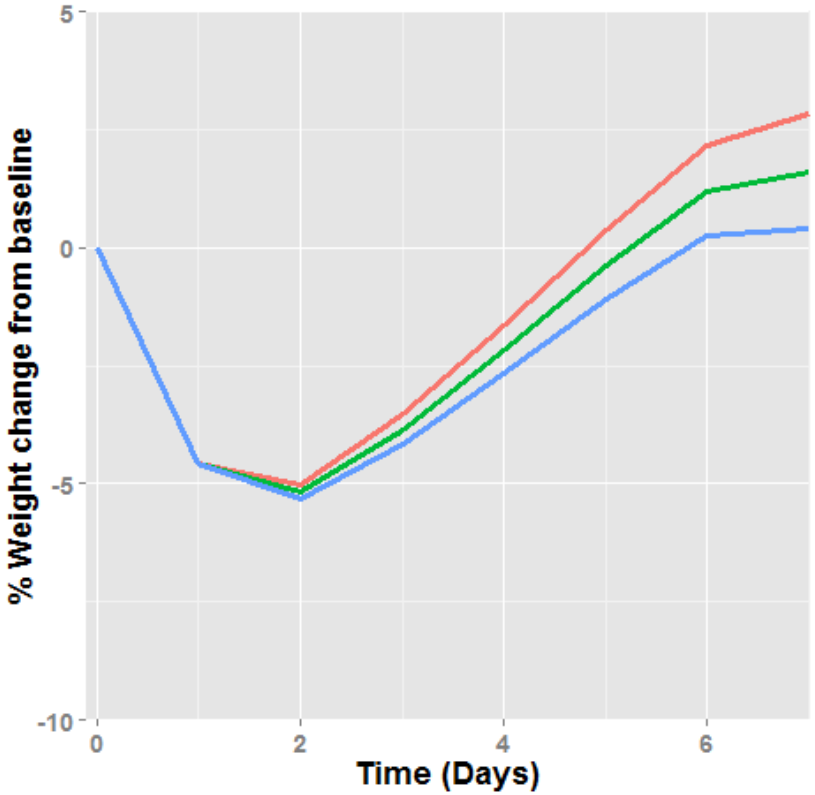
Mother age = 45 years
Mother age = 35 years
Mother age = 25 years

-> Hypothesis: age-dependent changes in mother's glucose metabolism[1]

[1] Verroken C. et al. Maternal age at childbirth is associated with glucose metabolism in adult men. Endocr Rev 2015

Results - Covariates

- **5 covariate – parameter relationships:**
  - Negative **mother age** effect on Kin_{Base}



Mother age = 25 years
Mother age = 35 years
Mother age = 45 years

-> Hypothesis: decreased milk production with mother's age [2]

[2] Nommsen-Rivers L.A. et al. Delayed onset of lactogenesis among first-time mothers is related to maternal obesity and factors associated with ineffective breastfeeding. Am J Clin Nutr 2010

Results - Goodness-of-fit Plots

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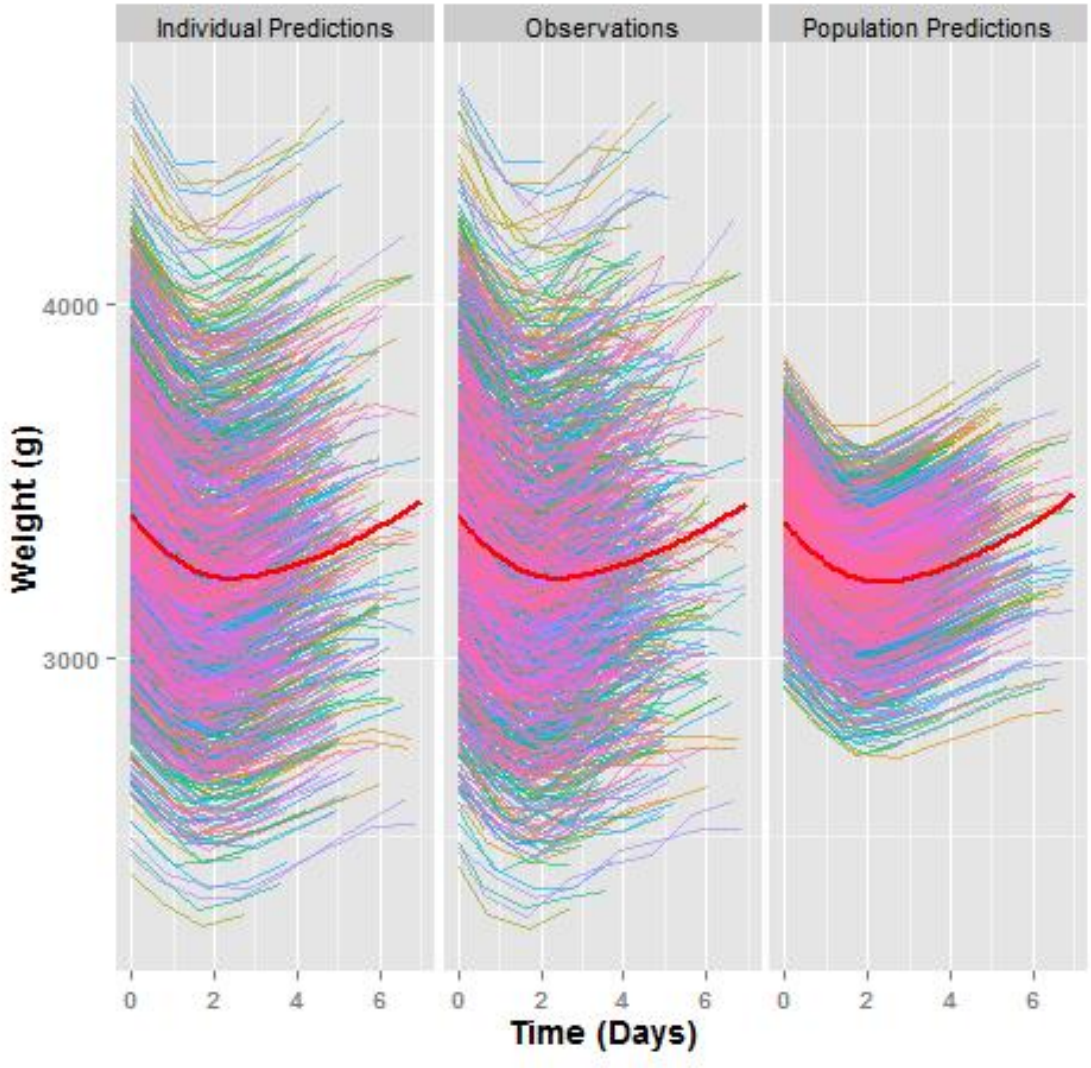
Individual Predictions, Observations and Population Predictions vs. Time



Results - Goodness-of-fit Plots

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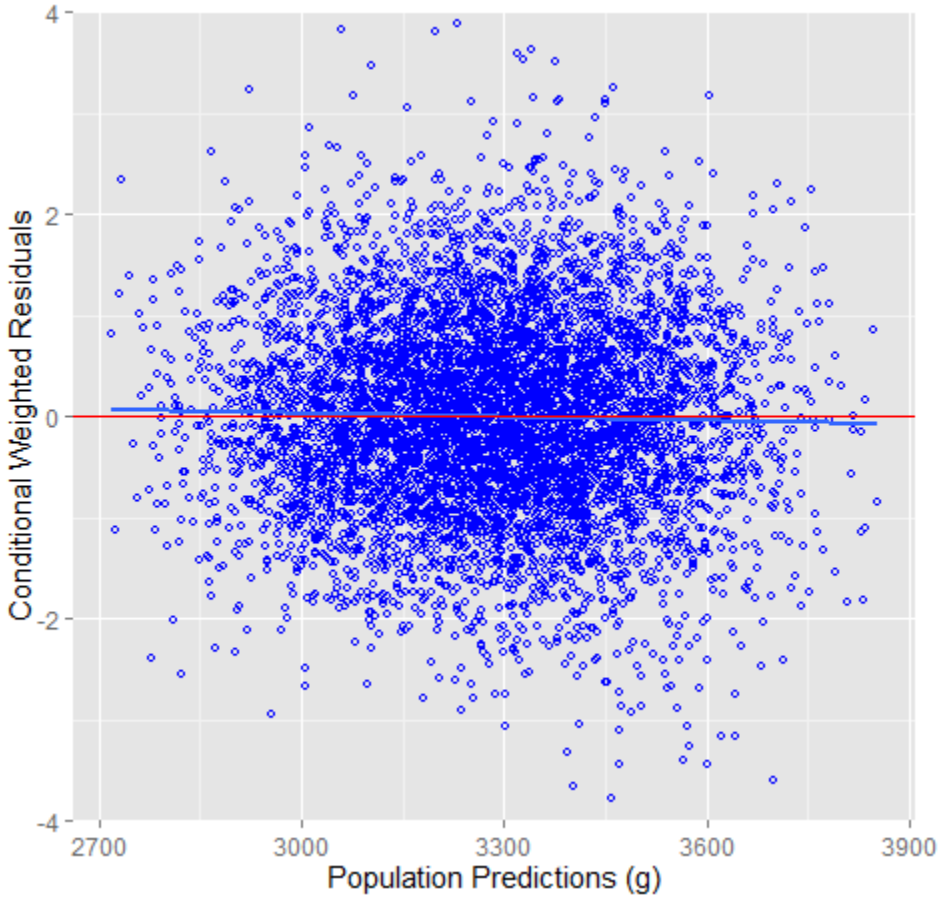
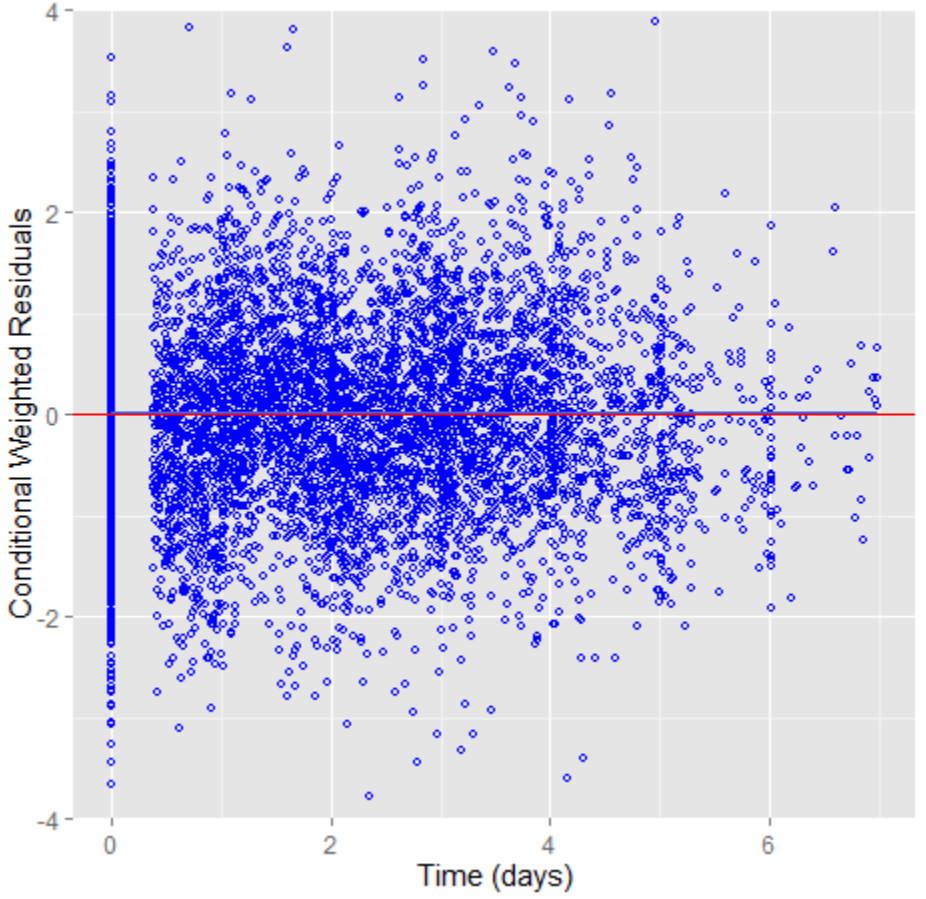
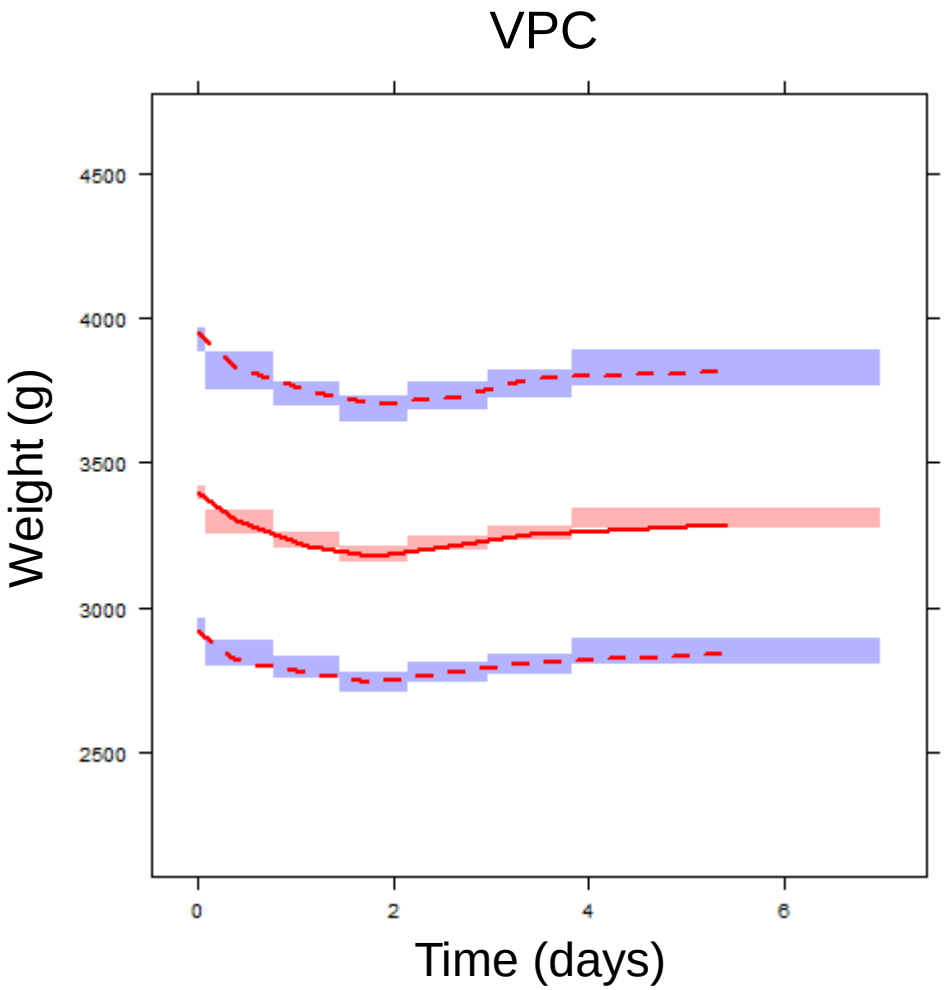
CWRES vs. Population Predictions



CWRES vs. Time



Results - Visual Predictive Check



Simulated CI (95%) of the median

Simulated CI (95%) of the 10th and 90th percentiles

Observed median

Observed percentiles (10th and 90th)

Advanced Validation: good predictive performance with accuracy (MAE=0.52%) and no bias (MPE=0.01%)

Results - Parameter Estimates

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- Typical birth weight: $WT0 = 3470\ g$
- Typical basal rate of weight gain: $Kin_{Base} = 41.51\ g.day^{-1}$; $IIV = 30\%$
- Maximum rate constant of weight loss ($Koutmax$) slowed by one-half at: $T50 = 1.9\ days$
- Variability on Kin and $WT0$ explained by covariates
- Remaining non-explained variability on $Kout$ (80%)

Clinical Application - Concept

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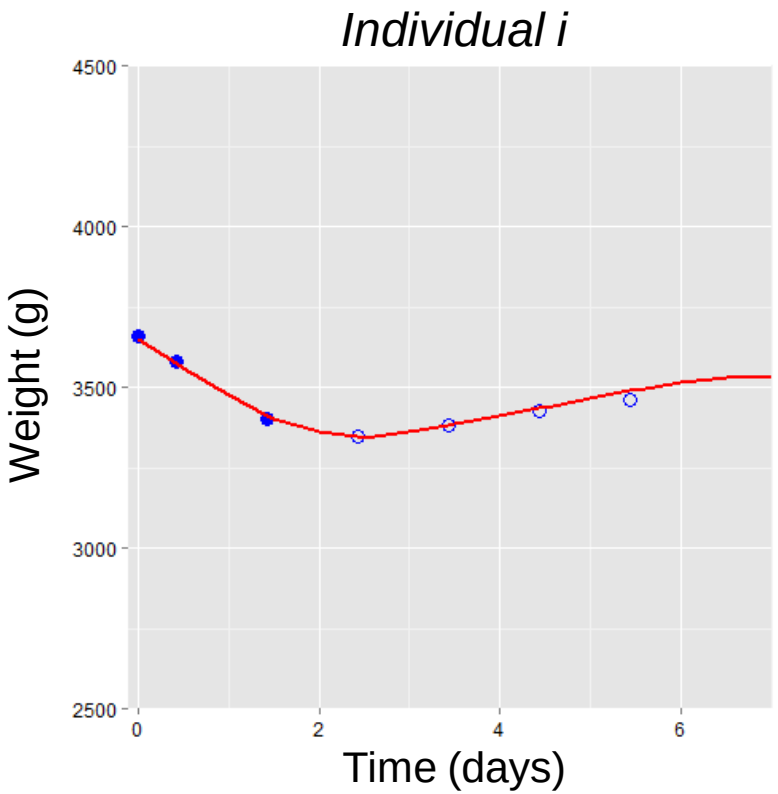
Forecast individual weight changes up to 7 days as soon as possible after birth

- Use of **3 initial weight observations** during first 48 hours of life: birth weight + 2 weight measurements
- **Apply model** to forecast individual weight changes up to 7 days

Gender

Mother Age



Gestational Age

Delivery Mode

Observations

Forecasted weight values

Clinical Application - Evaluation

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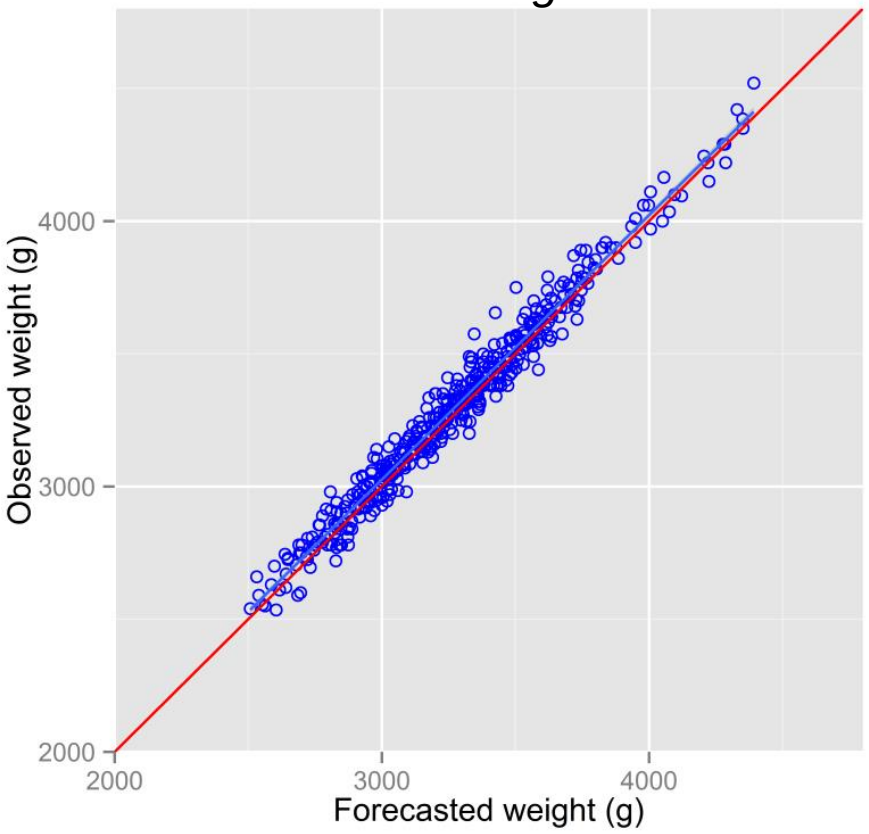
Forecast individual weight changes up to 7 days as soon as possible after birth

- Good graphical agreement:

- Predictive performance:
  - Good precision (MAE = 1.54 %)
  - No bias (MPE = -0.74 %)

Observed vs. individual forecasted weight values



NeoWeight Prediction Tool – Input

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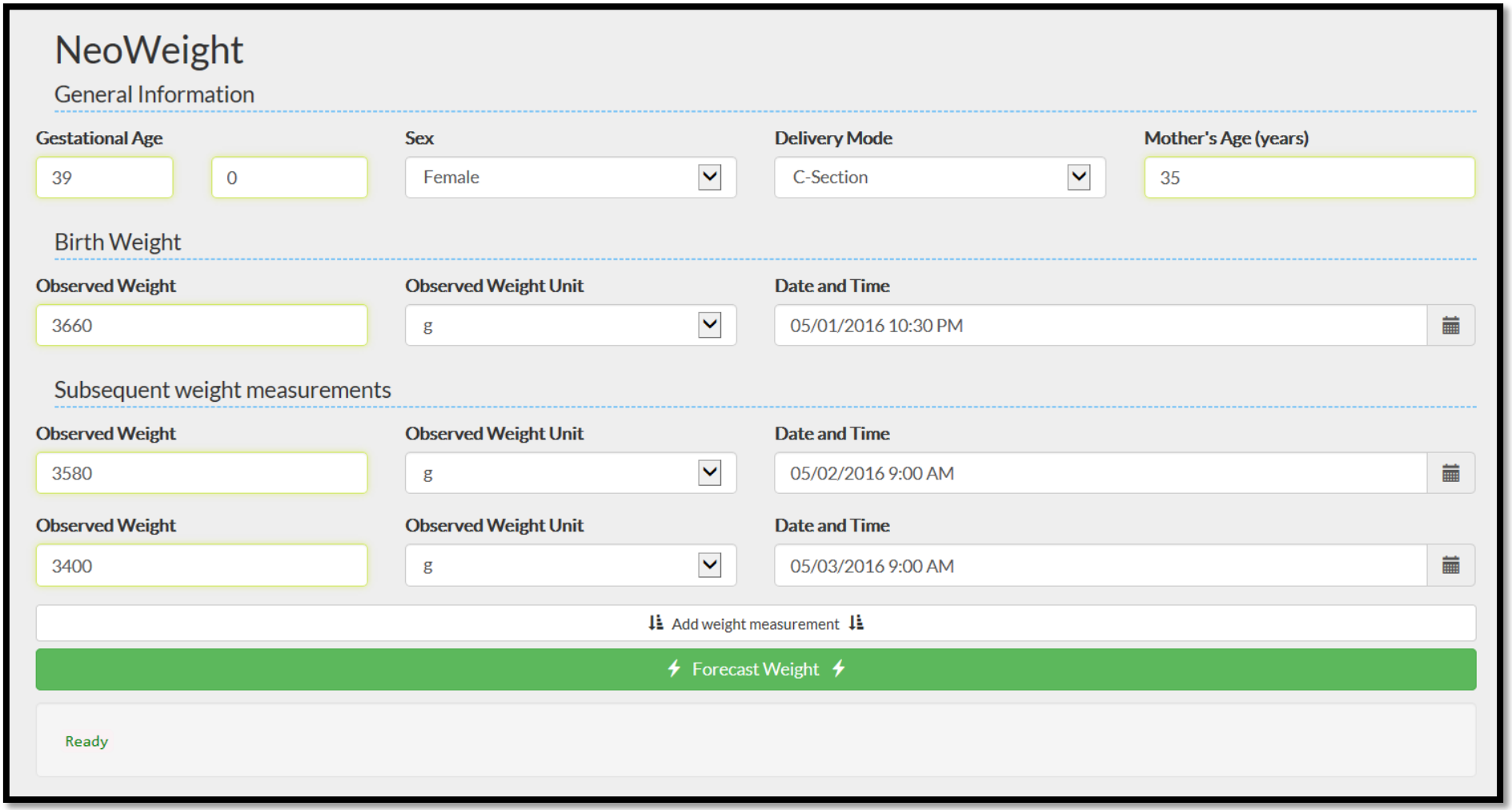
http://neoweight.mashframe.com/

Rudraya



NeoWeight Prediction Tool – Output

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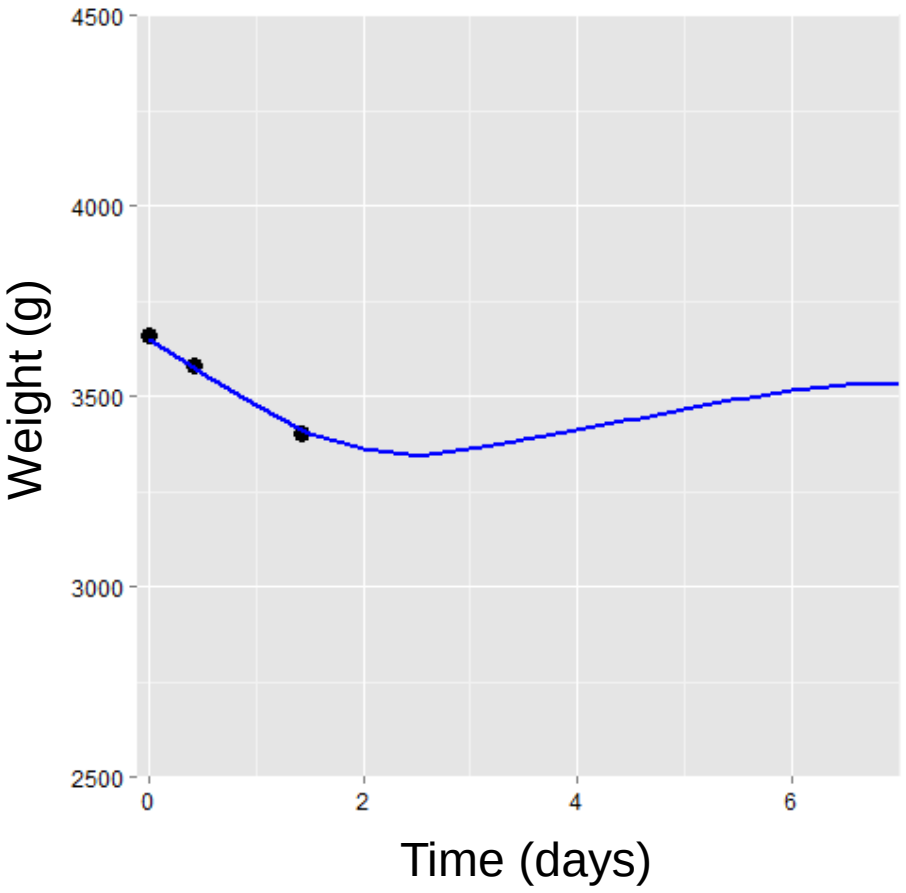

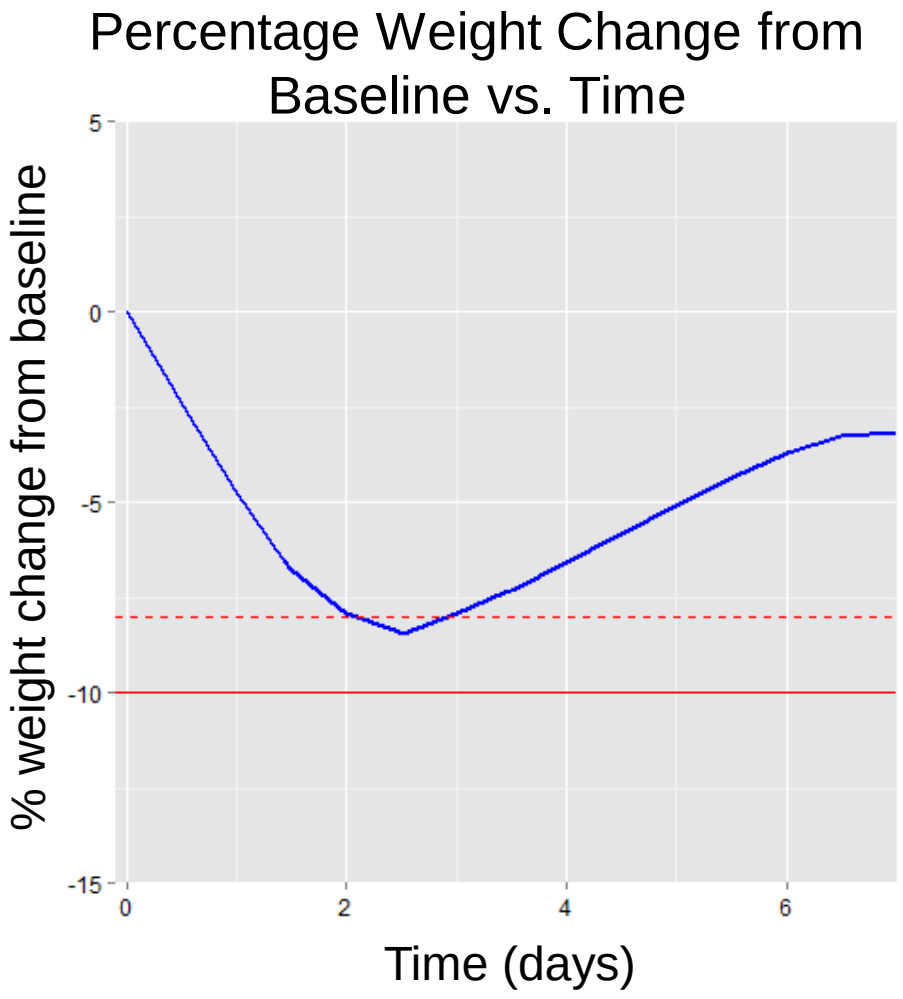

Observed weight values

Forecasted weight change

8% Weight loss

10% Weight loss

Conclusions

- **First pharmacometric model** characterizing weight changes in healthy term neonates exclusively breastfed

- **User-friendly online NeoWeight Prediction tool** allowing caregivers to:
  - **Forecast and appropriately monitor** individual weight changes
  - **Personalize and optimize** care of neonates

Outlooks – Model Expansion

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Pre-term neonates

Sick neonates

Model

Neonates with additional formula

Mother with pregnancy disorder

Data up to 60 days

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Thank you !