An Innovative Framework for Growth Reference in Very Preterm Infants

Explaining the making of the Postnatal Growth Charts

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Disclosure

No conflict of interest to disclose

Acknowledgement

We thank Dr. Tanis Fenton, PhD RD FDC of the University of Alberta for sharing the LMS table for the 2013 Fenton growth charts

Disclaimer

Not a presentation about optimal growth or nutrition research

Terminology

Gestational Age (GA): the age when the infant is born

- Calculated based on last menstrual period or by first-trimester ultrasound
- Due date = GA 40 weeks

Postmenstrual age (PMA): GA + day of life (DOL)

- An 9-day-old infant born at **GA 24w0d** is at **25w2d PMA**

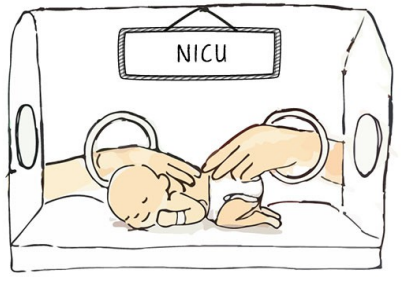
Terminology

Low Gestational Age

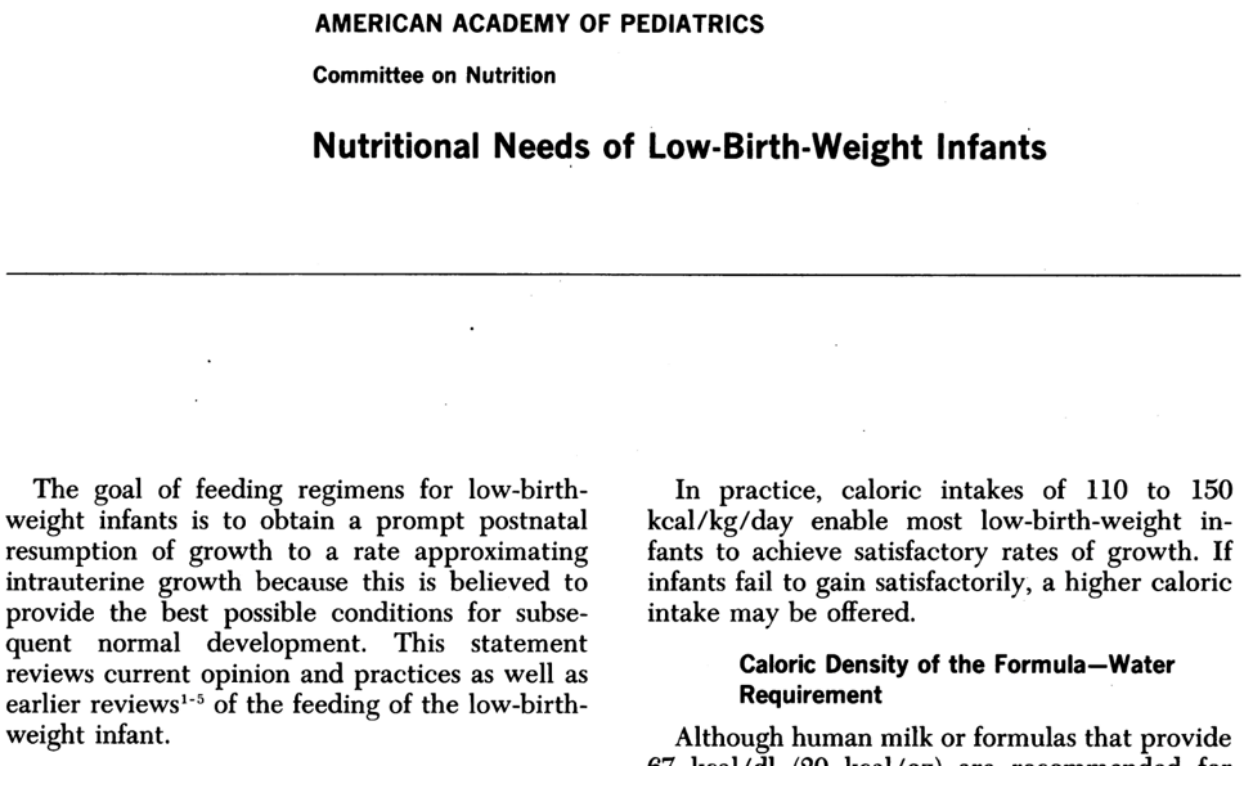
- In 2021, 3.66 million infants born alive in USA (CDC WONDER Online Database)
- 382,817 infants born < 37 weeks' gestation (preterm infants)
- 57,095 infants born < 32 weeks' gestation (very preterm infants)
  - 1.6% of total birth
  - 15% of preterm birth

Low Birth Weight (BW)

- Low birth weight infants: < 2,500g (~5lbs 8oz)
- Very low birth weight infants: < 1,500g (~3lbs 5oz)



Goal of Growth



AMERICAN ACADEMY OF PEDIATRICS

Committee on Nutrition

Nutritional Needs of Low-Birth-Weight Infants

The goal of feeding regimens for low-birth-weight infants is to obtain a prompt postnatal resumption of growth to a rate approximating intrauterine growth because this is believed to provide the best possible conditions for subsequent normal development. This statement reviews current opinion and practices as well as earlier reviews[1-5] of the feeding of the low-birth-weight infant.

In practice, caloric intakes of 110 to 150 kcal/kg/day enable most low-birth-weight infants to achieve satisfactory rates of growth. If infants fail to gain satisfactorily, a higher caloric intake may be offered.

Caloric Density of the Formula—Water Requirement

Although human milk or formulas that provide

. . . a prompt postnatal resumption of growth to a rate approximating intrauterine growth because this is believed to provide the best possible conditions for subsequent normal development. . . .

~1977 AAP

Intrauterine Growth Charts

Examples

- Lubchenco et al. : 24-42 weeks (1963, USA)
- Usher et al. : 25-42 weeks (1969, Canada)
- Fenton et al. : 22-50 weeks (2003, Canada/Sweden/Australia)
- Olsen et al. : 22-42 weeks (2010, USA)
- Fenton et al. : 22-50 weeks (2013, Germany/USA/CAN/AUS/UK/Italy)

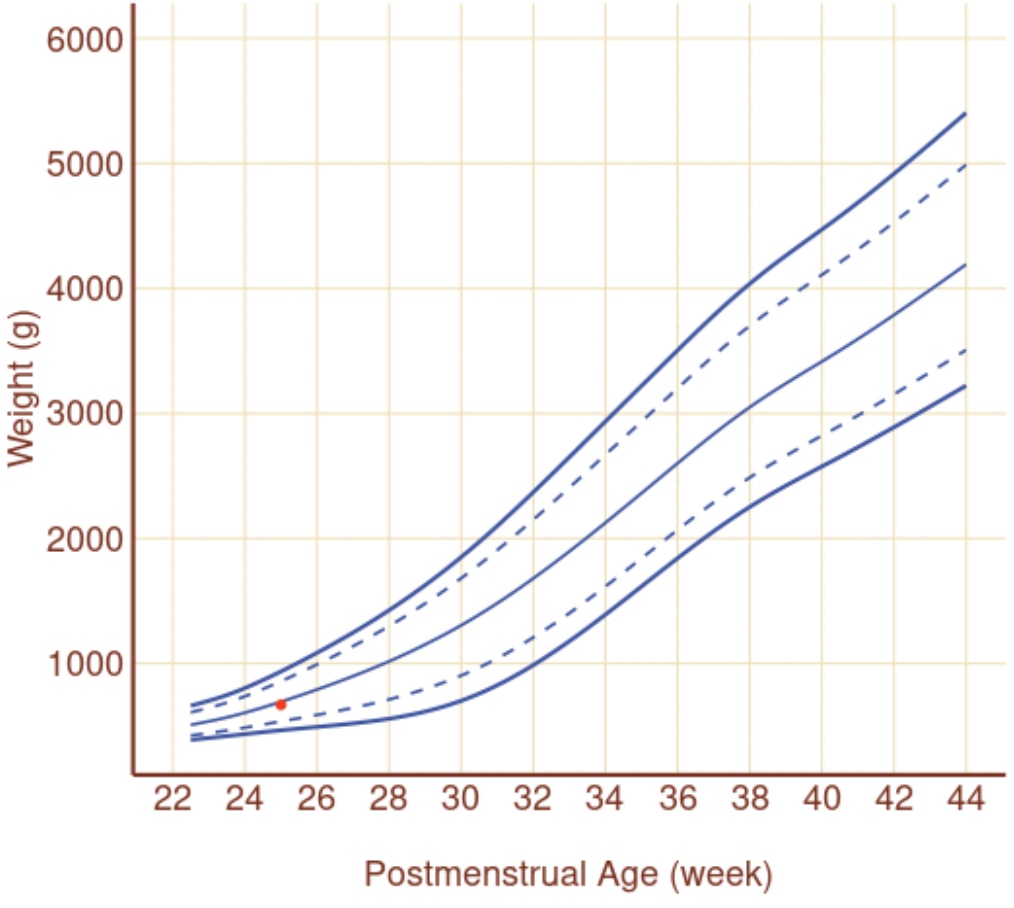


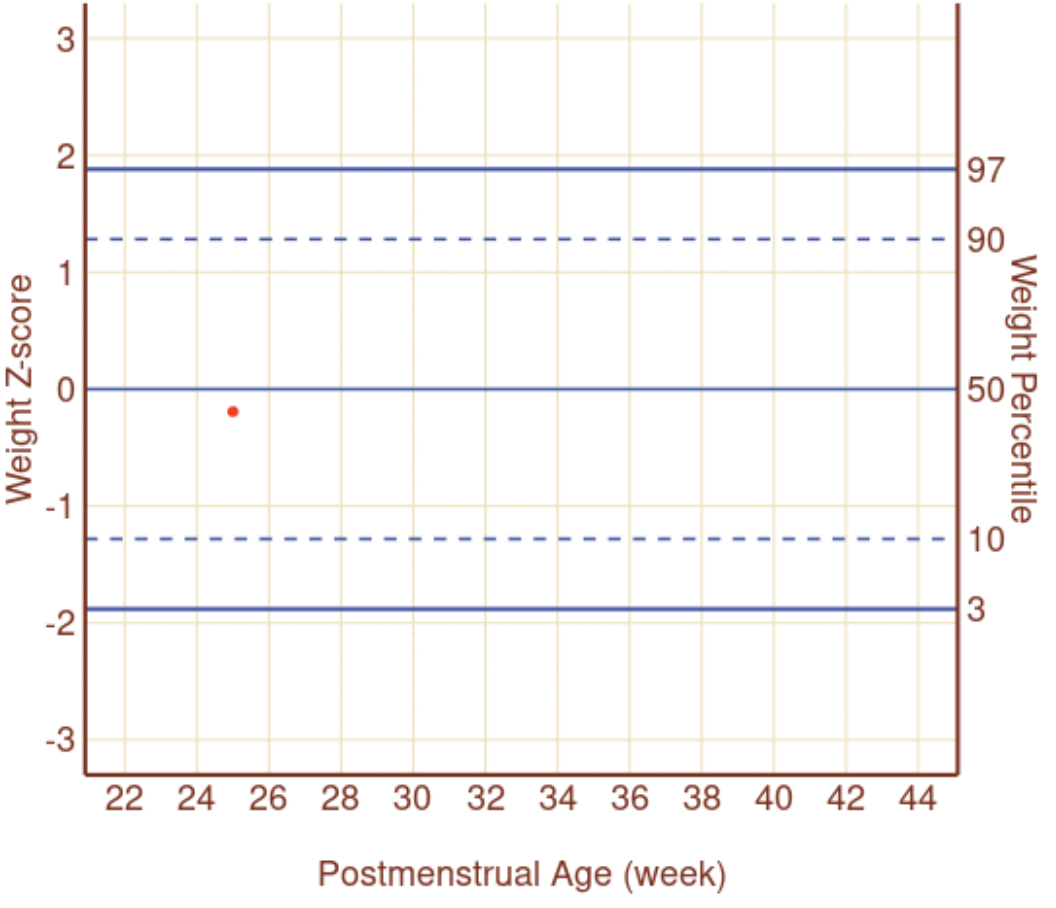
Chart Development

- Measurements at birth for each complete gestational week grouped together
- Predefined percentiles (usually 3rd, 10th, 50th, 90th, 97th) calculated, plotted, and dots connected
- Smoothing penalty applied: cubic splines (2013 Fenton)

Postnatal Growth on Fenton Charts

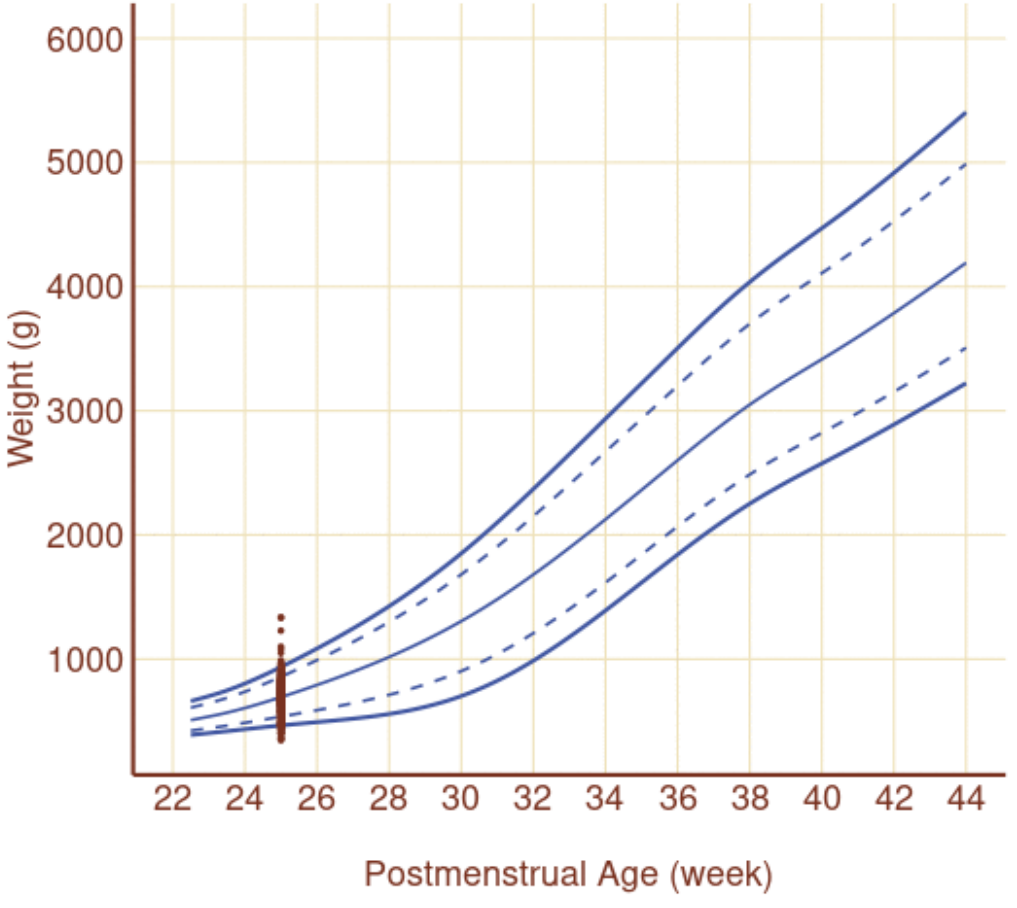
A female infant born at 25w0d

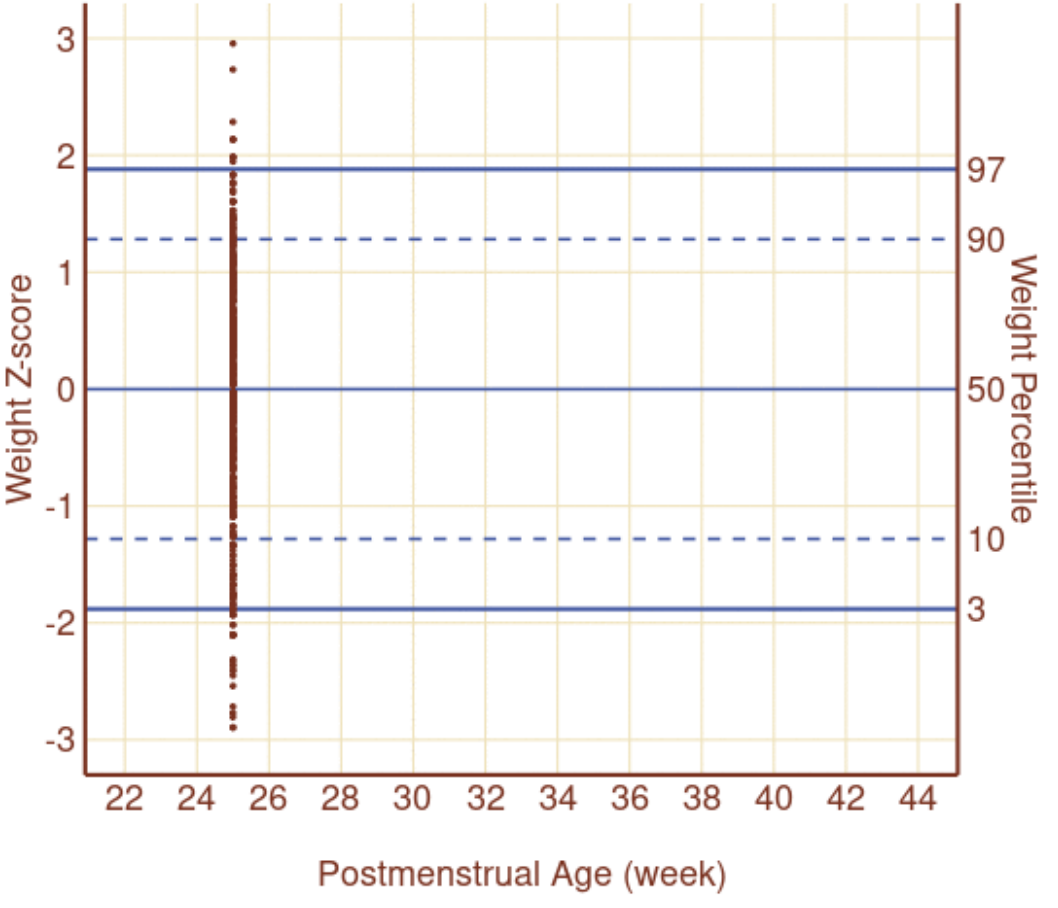




Postnatal Growth on Fenton Charts

A group of female infants born at 25w0d





Factors That may Influence Postnatal and Intrauterine Growth Trajectories

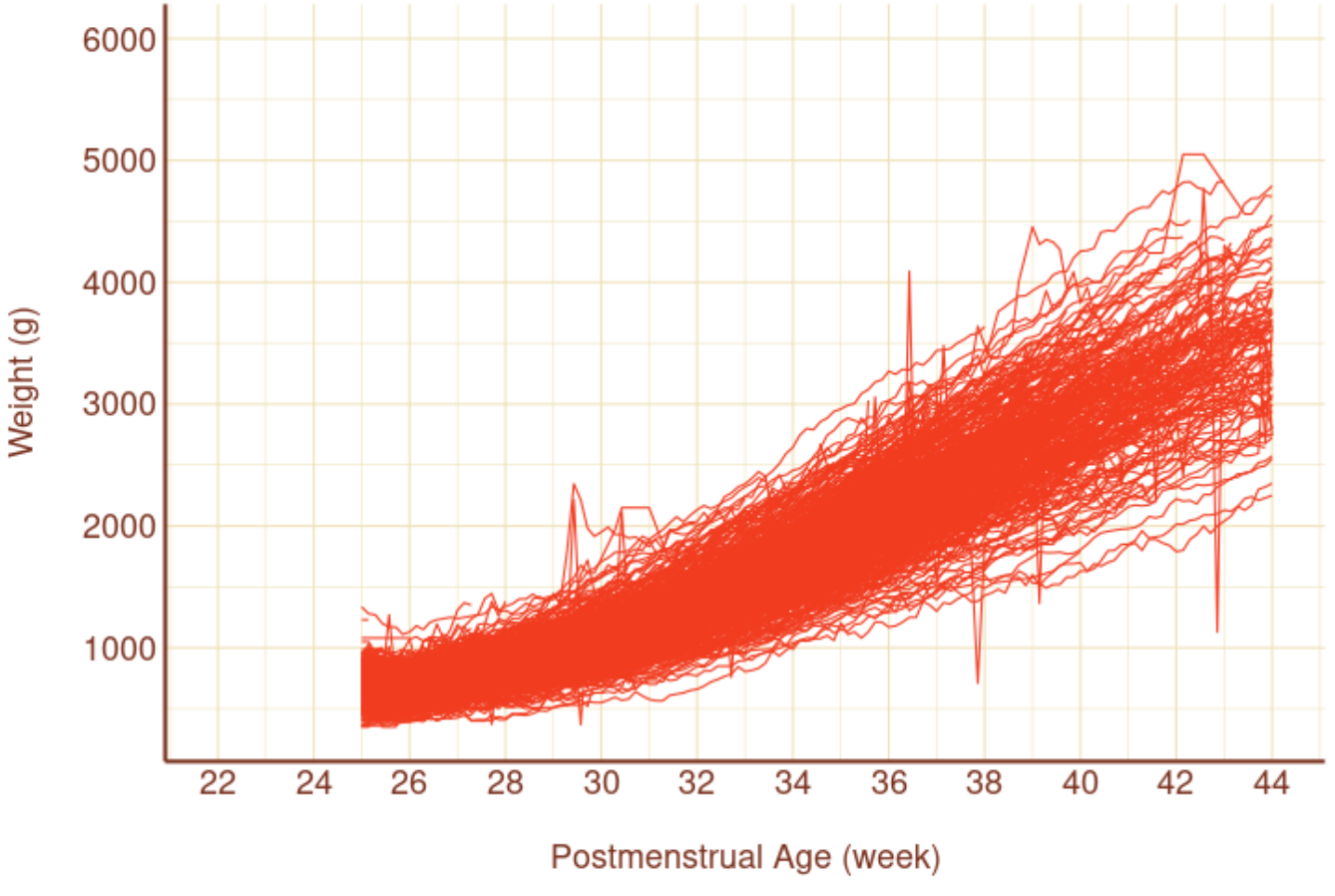
- Metabolic demand: respiratory efforts, inflammatory response, digestion/absoprtion, temperature regulation
- Metabolic supply: placental nutrition in fetuses; IV → gut nutrition postnatally
- Environment: physical confinement, oxygen tension
- Free water status: more in intrauterine life, less in extrauterine life

Postnatal Growth

≠

Intrauterine Growth

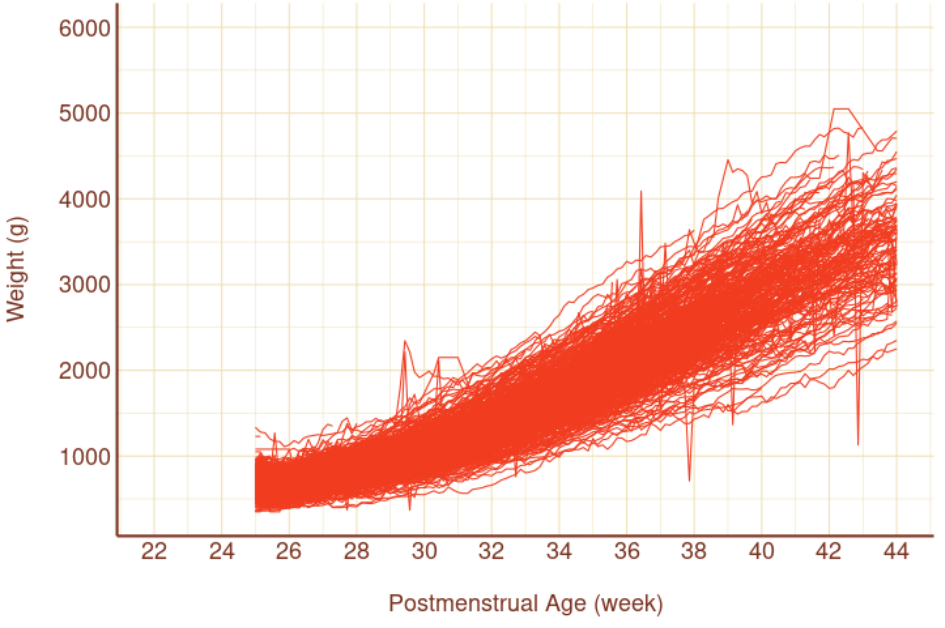
How to characterize postnatal growth so preterm infants can be compared to each other appropriately?



Longitudinal Growth Modeling & Reference Curve Development

What do we hope to achieve?

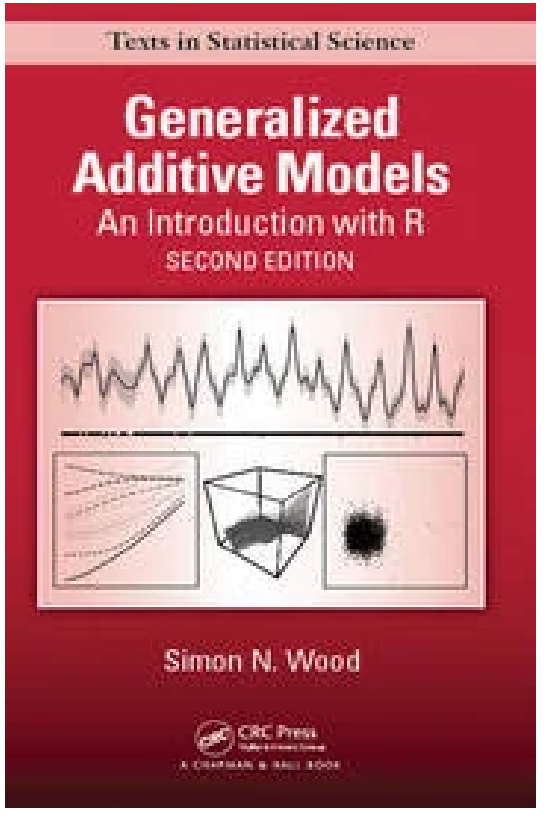
- Capture initial weight loss
- Allow variations in growth rate over time because growth rate may change over time (non-linear assumption)
- Account for variations in birth size & longitudinal growth rate among infants
- Percentile lines derived from the model



Modeling Technique of Choice

Generalized additive mixed modeling

- An extension of the Generalized Additive Modeling (GAM) technique:
  - Piecewise linear functions with smoothing penalty
  - Does not require linear assumption of the longitudinal data
  - Maximum-likelihood approach to provide unbiased estimates
  - Assume Gaussian distribution for residuals at the infant level
- Random effects to account for auto-correlations of repeated measurements



Data Source

pediatrix
Expert care for women, babies and children

- Offers newborn medical services in contracted hospitals nationwide in the US
- The network takes care of at least 20% of infants requiring intensive care of various levels
- Home-made clinical documentation and billing system, *BabySteps*
- Deidentified clinical data warehouse (CDW) for research and QI

Inclusion criteria

- Born between a GA between 22w4d to 30w3d
- Admitted to one of the Pediatrix® NICUs within 7 days of life

Exclusion criteria

- No sex assignement in the CDW
- No anthropometric data in the CDW
- Not exluding infants based on morbidity or congenital anomalies

Data Source

Total available data points (up to 44 weeks PMA of each infant)

- Total infant number: 89,218
- Weight data points: 5,478,055
- Length data points: 755,687
- Head circumference data points: 1,316,087

Grouping

- Sex: female, male
- GA by nearest GA (23w4d to 24w3d grouped as 24 weeks): 23-30 week groups

→16 models total for each measurement type

Missing Values

Assumption

- Missing due to clinical condition, not growth *per se* → treat all missings as missing-at-random (MAR)
- In other words, missing values can be explained by values from other infants of the same group
- In clinical terms, growth of infants after transfer/discharge same as growth of infants in the NICU

Handling of missing values

- Maximum likelihood-based estimates are unbiased in the presence of MAR missing values
- MAR is well tolerated by GAMM
- No imputation was performed

Outliers

- Defined as a leverage > 3X the mean leverage, and an absolute standardized residual > 2
- Assessed after models were developed

Model Formula

```
library(gamm4)
Model <- gamm4(measurement ~ s(DOL), random = ~(1+DOL|infant), data)
```

$y_{ij} = s(t_{ij}) + \mu_0 + \mu_1 \times t_{ij} + \epsilon_{ij}, i = 1, \ldots, N; j = 1, \ldots, m_i,$ where

- y_{ij} is an outcome measure for the jth measurement of infant i,
- t_{ij} is DOL for teh j_{th} measurement of infant i,
- $s(t_{ij})$ is the fixed-effect smooth function for t_{ij},
- μ_0 and μ_1 are random intercept and random slope, respectively, and
- ϵ_{ij} indicates random/measurement error.

Overfitting Examination

Concern

- Manual knot number use may lead to overfitting

Strategy

- Data split
  - 70:30 infant split using `caret::createDataPartition()`
  - Data from 70% infants used for training; remainder for validation
- Metrics
  - Root-mean-square error (RMSE)
  - Mean absolute error (MAE)
  - R-squared (RSQ)

Theory-Based Percentile Construction

$$
\begin{aligned}
Var(y) &= Var(s(t) + \mu_0 + \mu_1 \times t + \epsilon) \\
&= Var(s(t)) + Var(\mu_0) + Var(\mu_1) \times t + 2 \times Cov(\mu_0, \mu_1) \times t + Var(\epsilon) \\
&= 0 + Var(\mu_0) + Var(\mu_1) \times t + 2 \times Cov(\mu_0, \mu_1) \times t + Var(\epsilon) \\
&= Var(\mu_0) + Var(\mu_1) \times t + 2 \times Cov(\mu_0, \mu_1) \times t + Var(\epsilon)
\end{aligned}
$$

- $Var(y)$ is total variance
- $Var(s(t))$ is the variance of the fixed-effect smooth function, which is 0
- $Var(\mu_0)$ is the variance of the random intercept
- $Var(\mu_1)$ is the variance of the random slope
- $Var(Cov(\mu_0, \mu_1))$ is the variance of the covariance between random intercept and random slope
- $Var(\epsilon)$ is the variance of the error term
- t is DOL

Theory-Based Percentile Construction

$Standard\ deviation = \sqrt{Var(y)}$ under Gaussian assumption

$Standard\ deviation = f(DOL)$, may change with DOL

```
library(lme4)
vcov <- VarCorr(model$mer) %>% as.data.frame()

vcov$vcov[1] #intercept variance
vcov$vcov[2] #slope variance
vcov$vcov[3] #covariance variance
vcov$vcov[5] #error term variance
```

Computational Platform

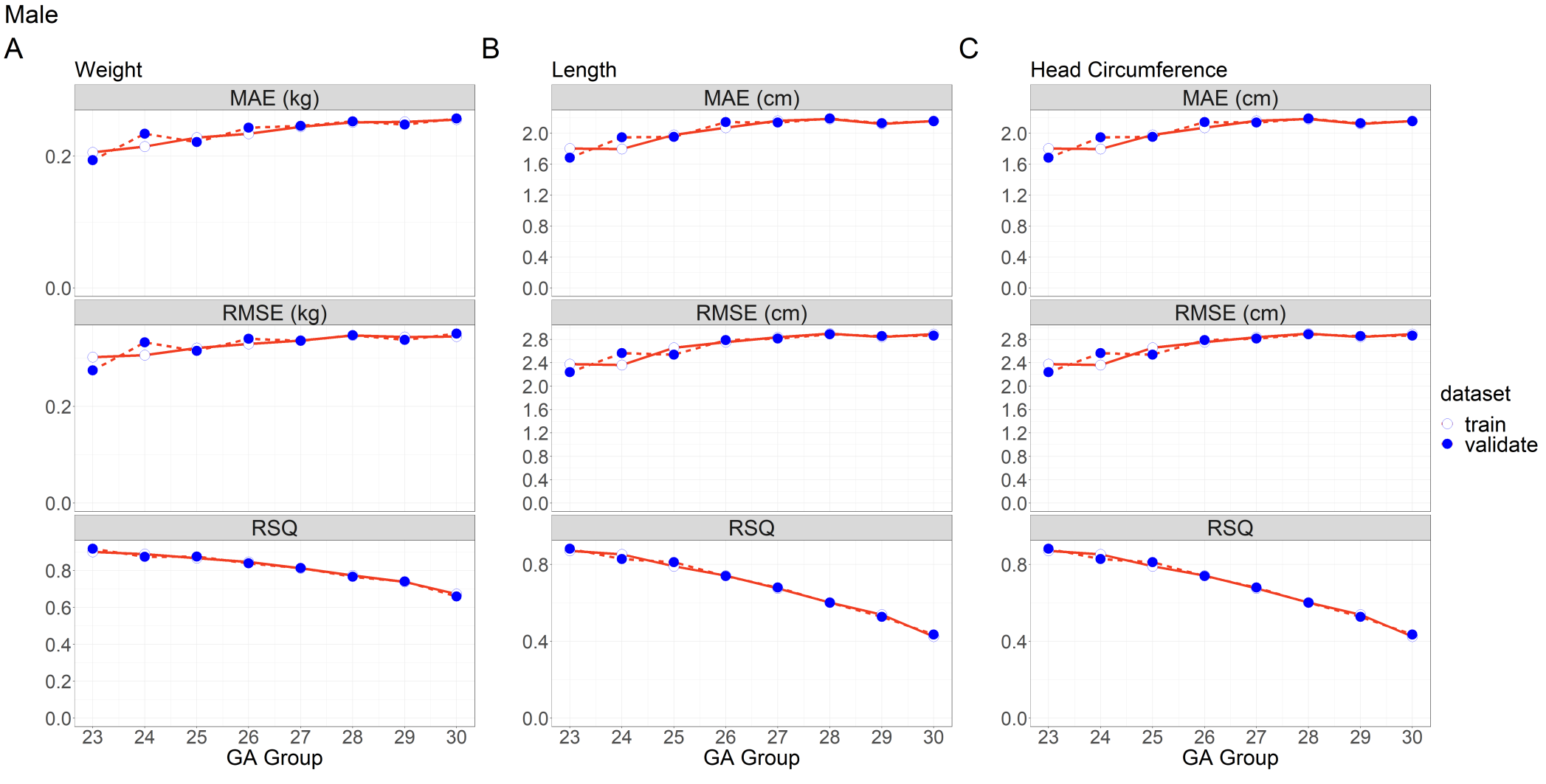
- Ubuntu 20.04 LTS
- R 4.1.1
- RStudio IDE

Demographic Summary

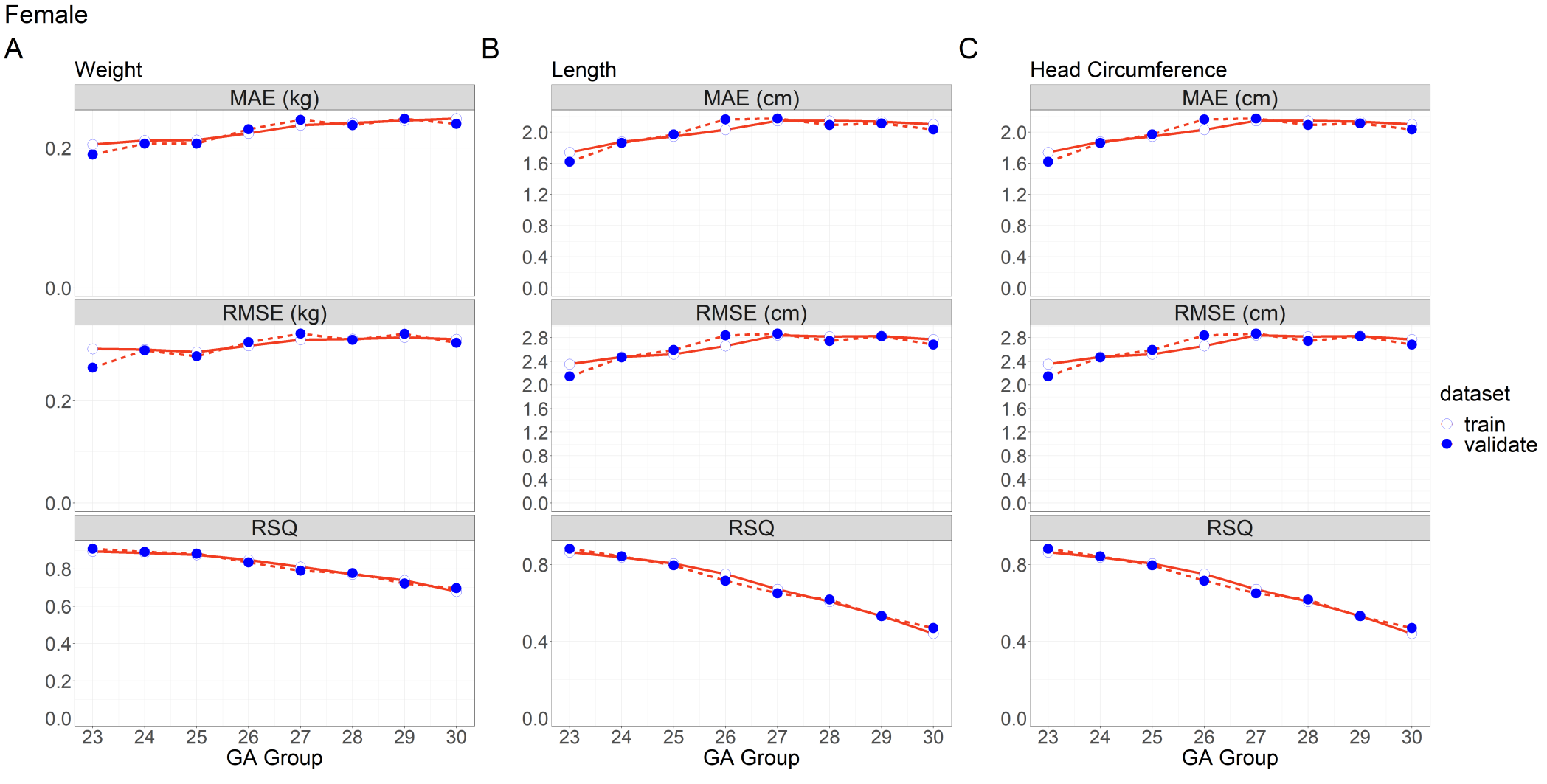
	Total	Female	Male
Number of infants	89218	41798	47420
Number of Data points			
Weight	5478055	2602008	2876047
Length	755687	358968	396719
Head Circumference	1316087	620079	696008
Race/ethnicity			
White	36628 (41%)	16930 (40%)	19698 (43%)
Black	25577 (29%)	12537 (30%)	13040 (27%)
Hispanic	17008 (19%)	7772 (19%)	9236 (19%)
Asian	2643 (3%)	1179 (3%)	1464 (3%)
Other	7362 (8%)	3380 (8%)	3982 (8%)

*Data presented are for all infants including those who were alive at NICU discharge and those who died before NICU discharge.

Overfitting Examination



Overfitting Examination



Outliers

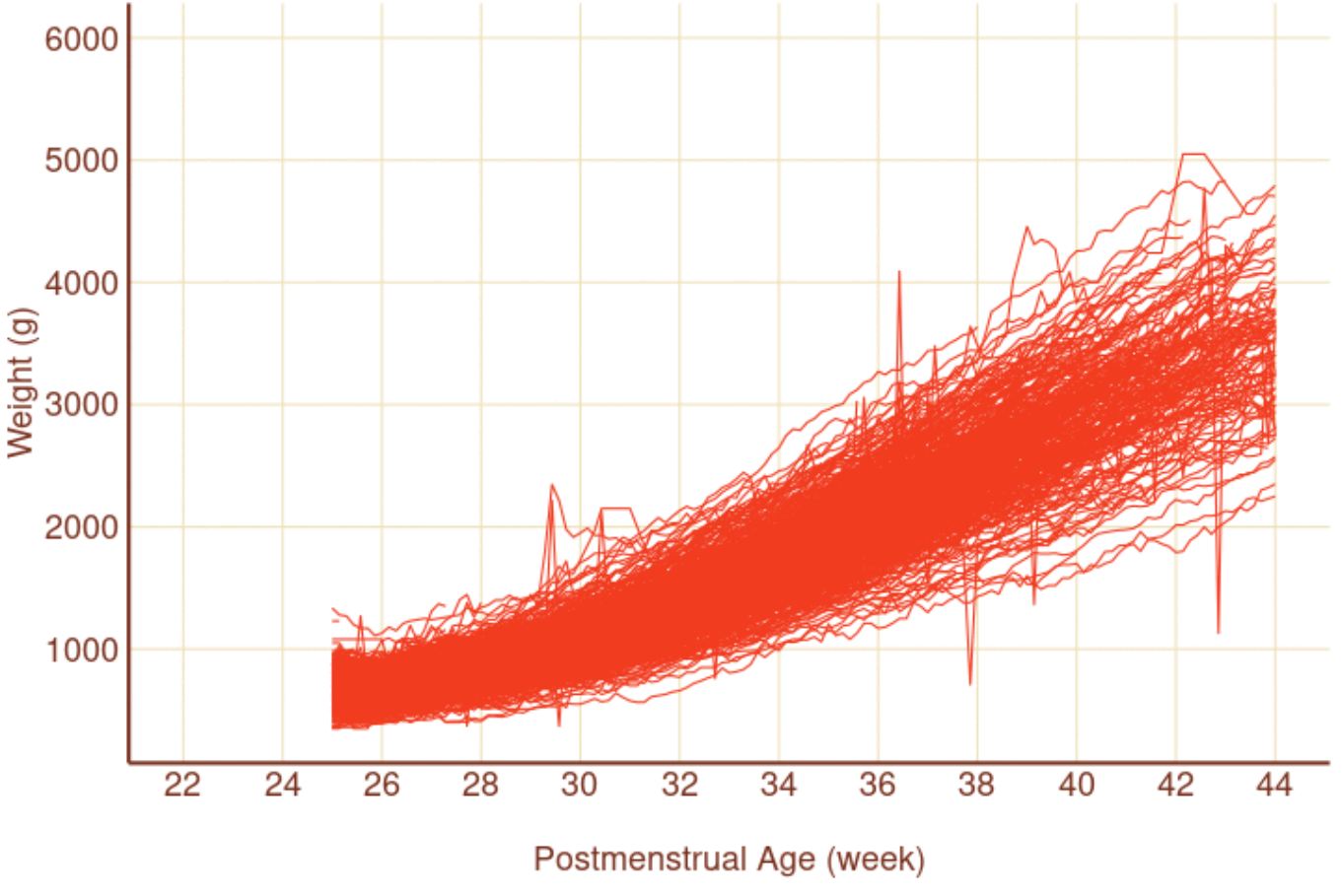
- Defined as a leverage > 3X the mean leverage, and an absolute standardized residual > 2
- None discarded for the final models

GA group	23	24	25	26	27	28	29	30
Female								
Weight	0.03%	0.04%	0.03%	0.03%	0.03%	0.03%	0.04%	0.04%
Length	0.05%	0.08%	0.06%	0.03%	0.04%	0.04%	0.02%	0.01%
Head Circumference	0.13%	0.07%	0.06%	0.08%	0.07%	0.05%	0.05%	0.03%
Male								
Weight	0.03%	0.04%	0.03%	0.04%	0.03%	0.04%	0.03%	0.02%
Length	0.09%	0.08%	0.03%	0.04%	0.05%	0.04%	0.03%	0.02%
Head Circumference	0.11%	0.07%	0.10%	0.08%	0.08%	0.06%	0.04%	0.05%

Model Estimates with Percentiles

25-week female weight growth trajectory

plotted on raw data from female infants born at 25w0d



Top to bottom:

97th percentile

90th percentile

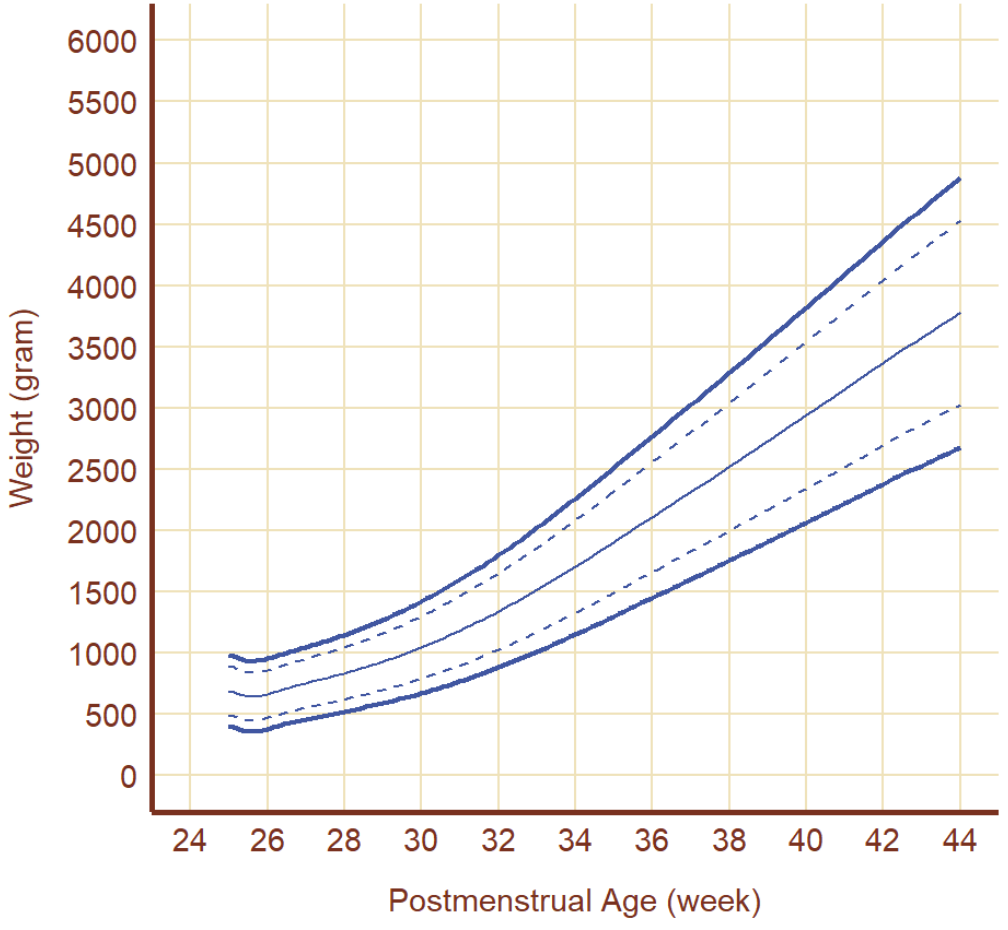
50th percentile

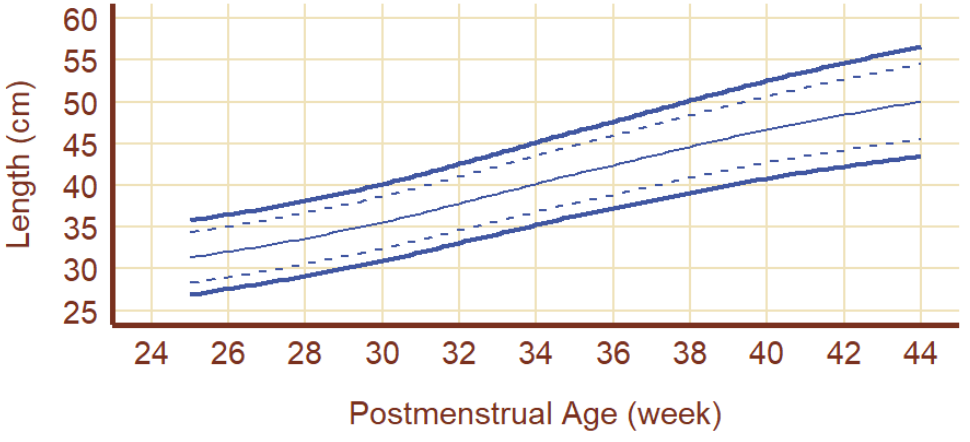
10th percentile

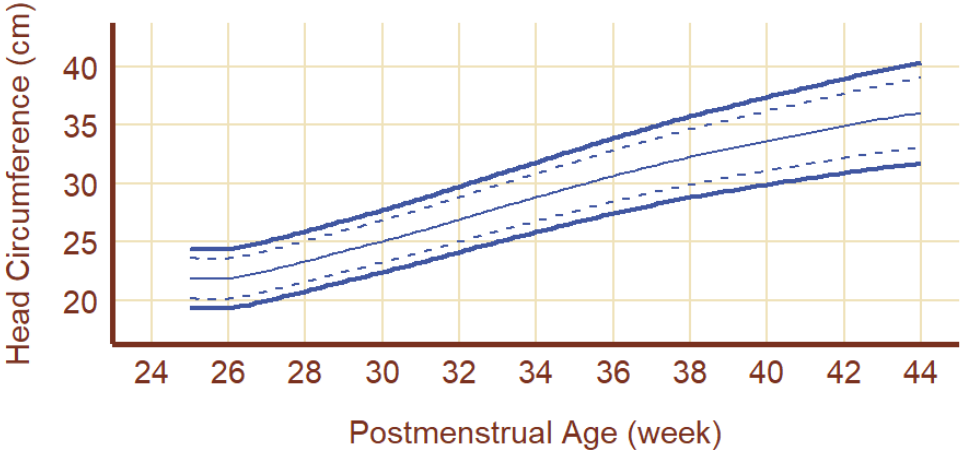
3rd percentile

Postnatal Growth Models

25-week postnatal growth for female infants



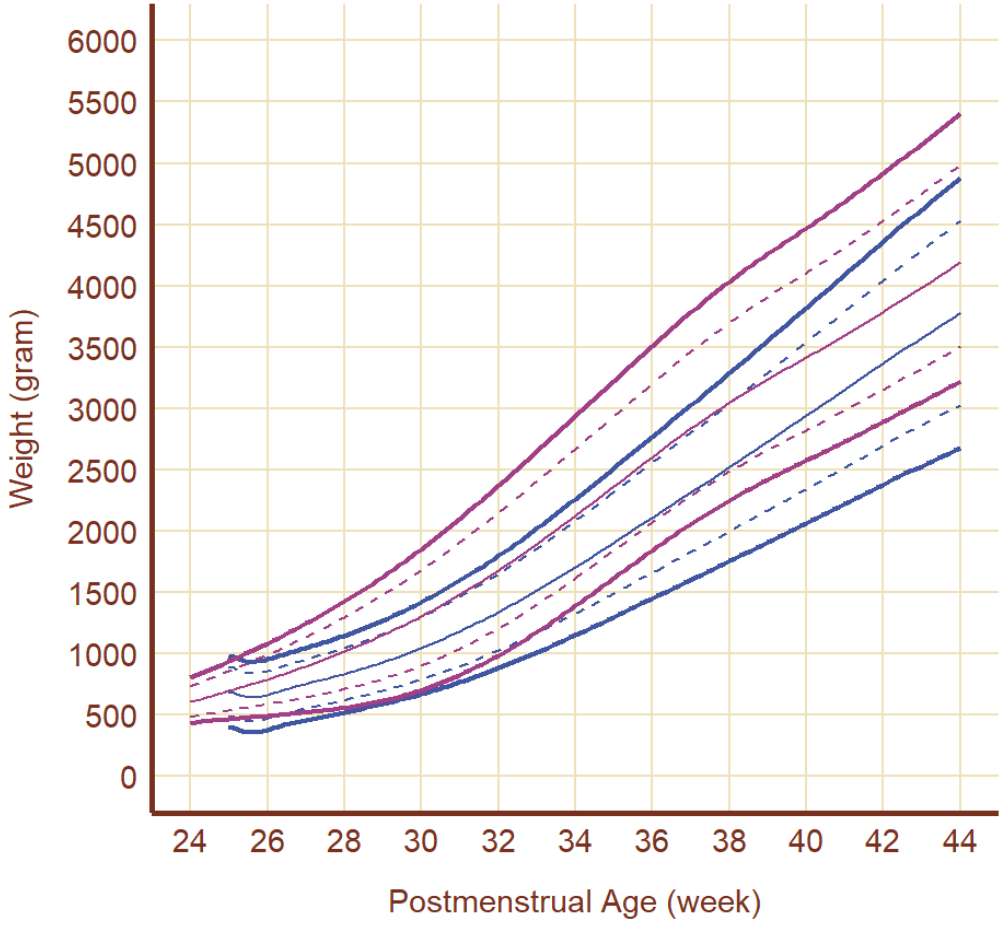


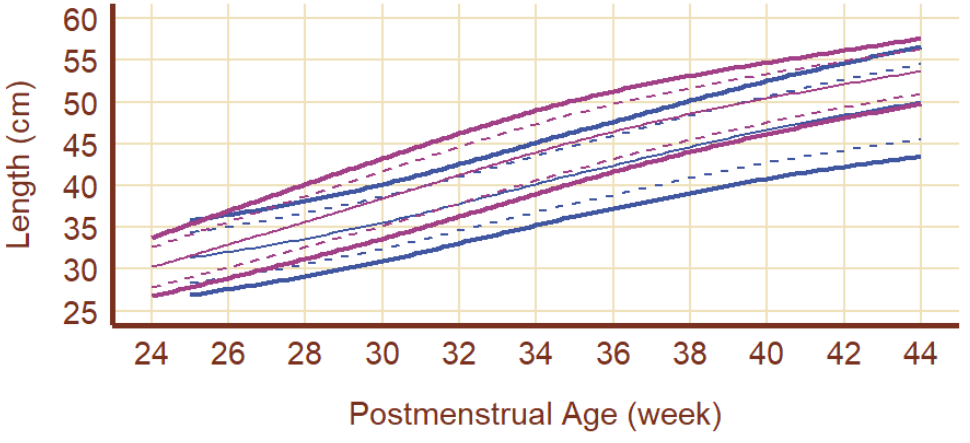


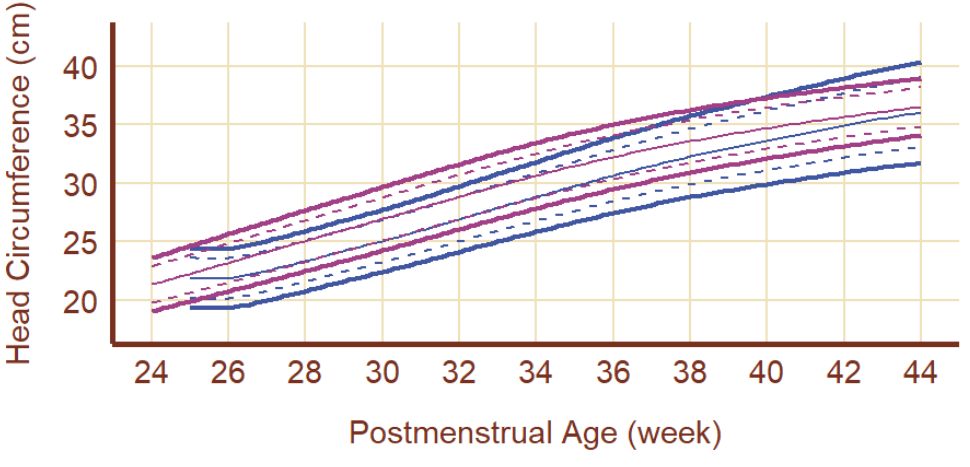
Postnatal Growth Models

25-week postnatal growth for female infants

2013 Fenton intrauterine growth charts





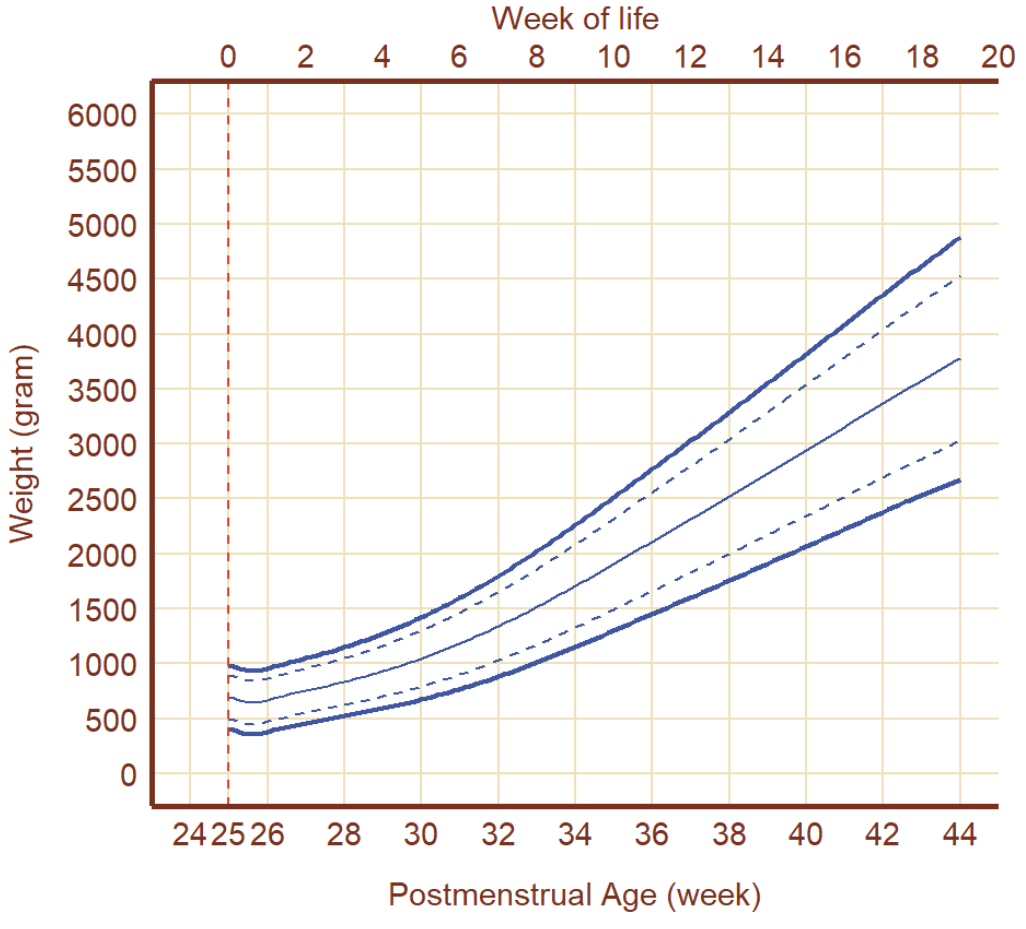


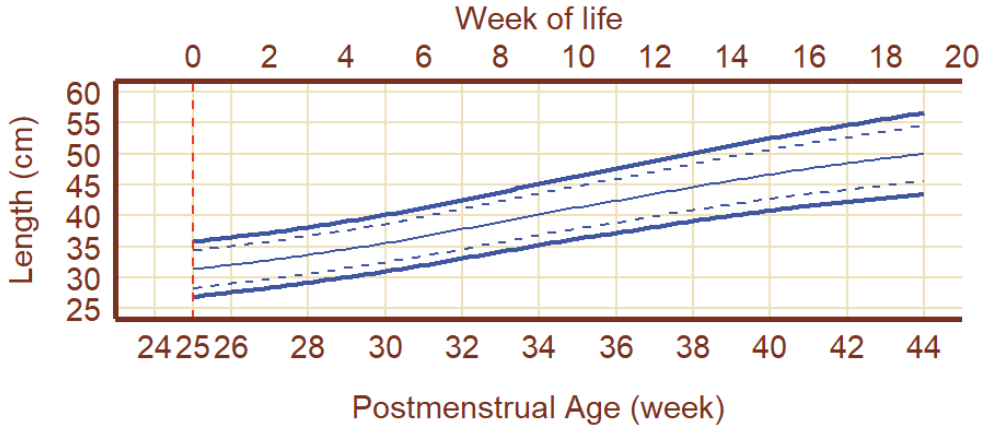
Clinical Application

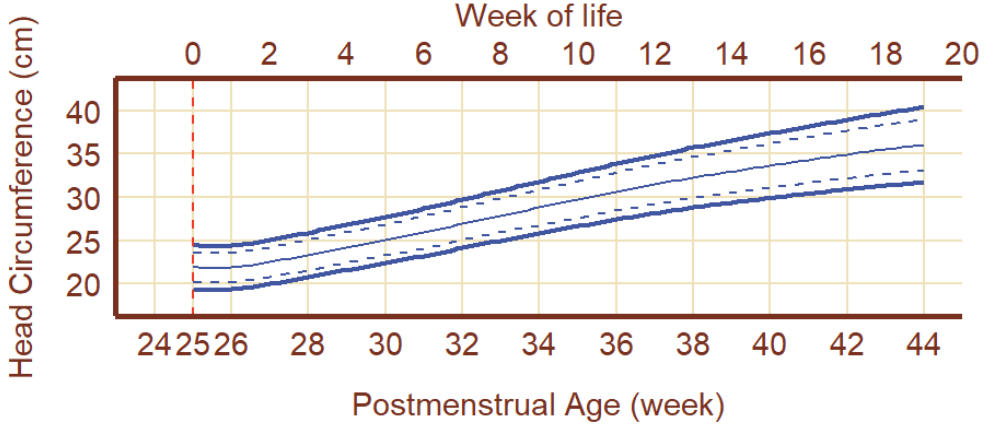
Use the postnatal growth trajectory curves on actual infants

Shift Curves on X-axis

25-week postnatal growth for female infants born at 25w0d

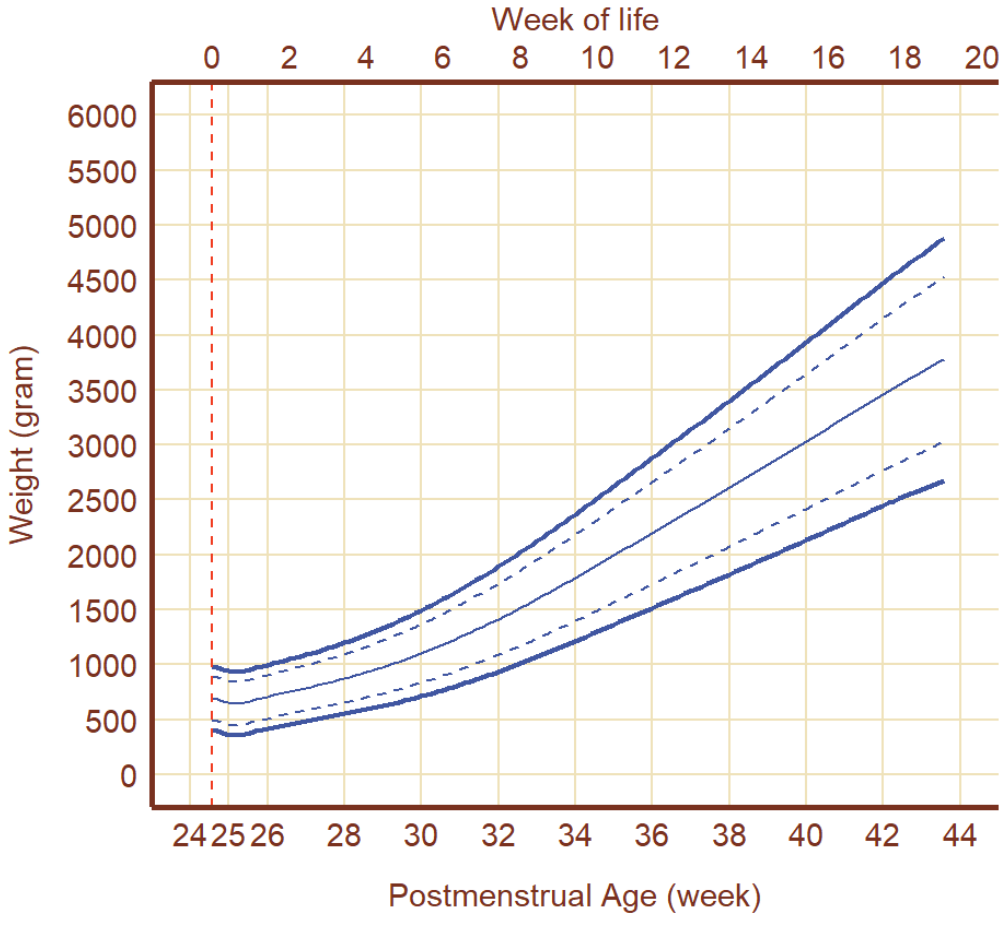


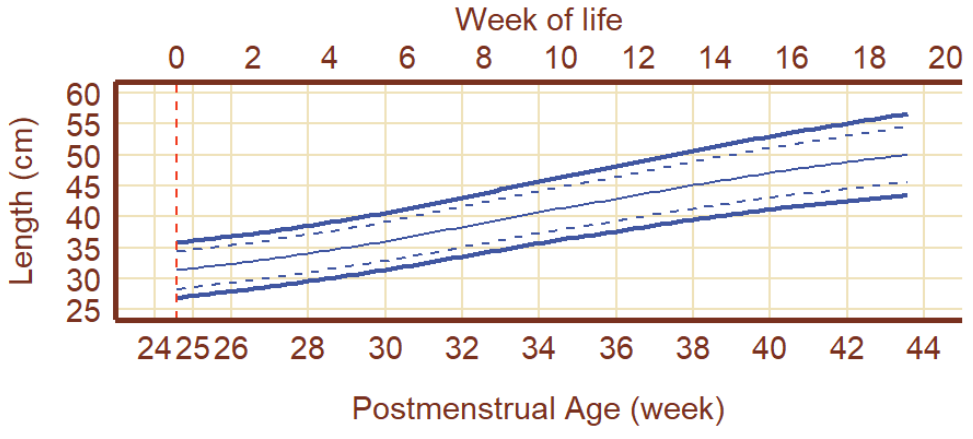


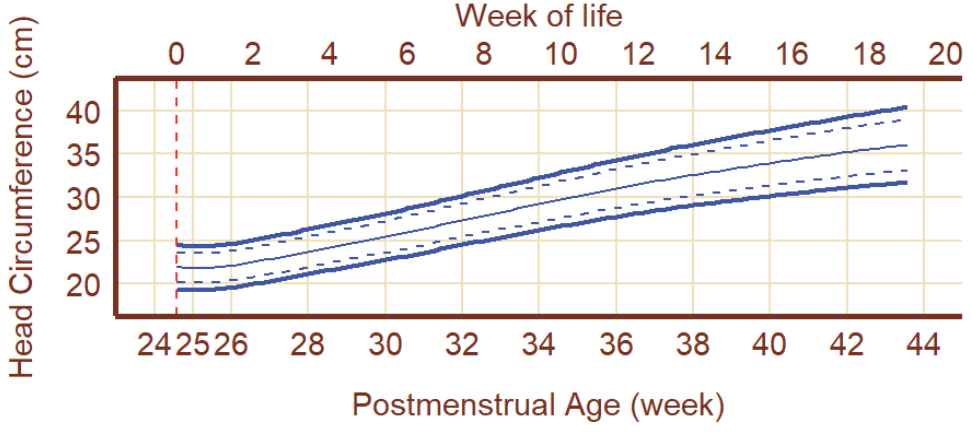


Shift Curves on X-axis

25-week postnatal growth for female infants born at 24w4d

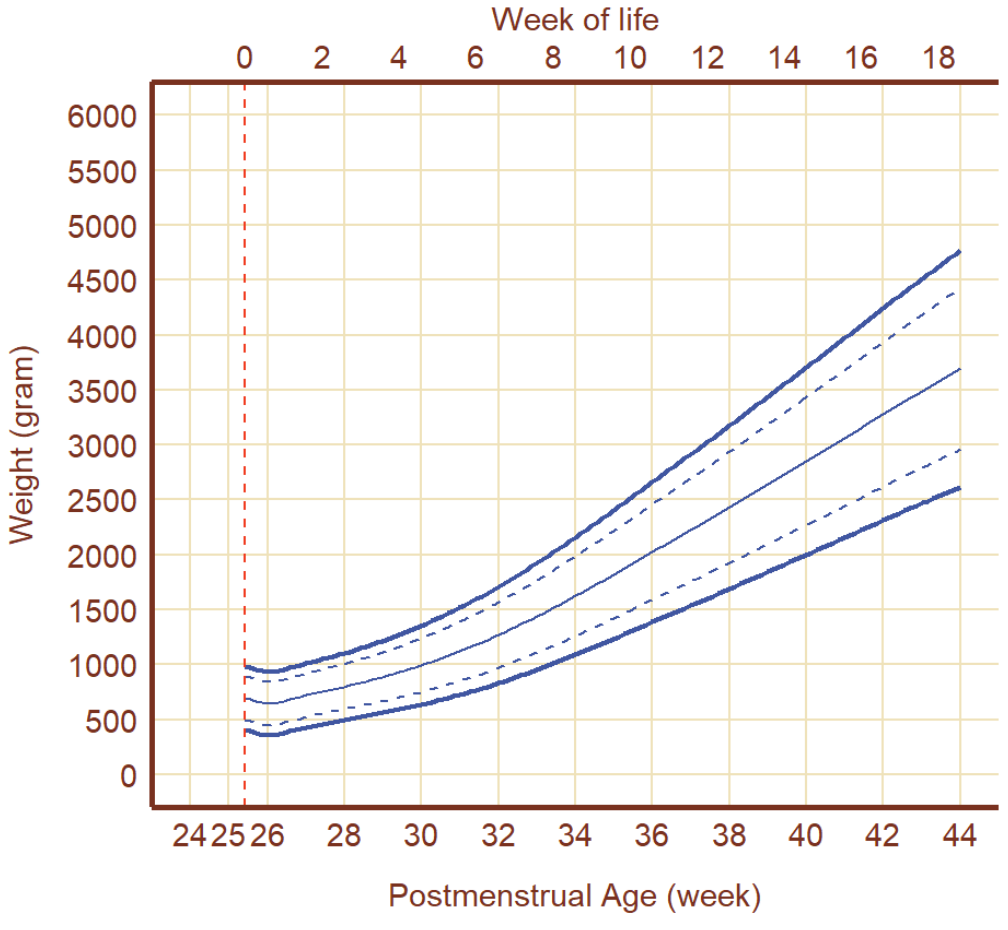


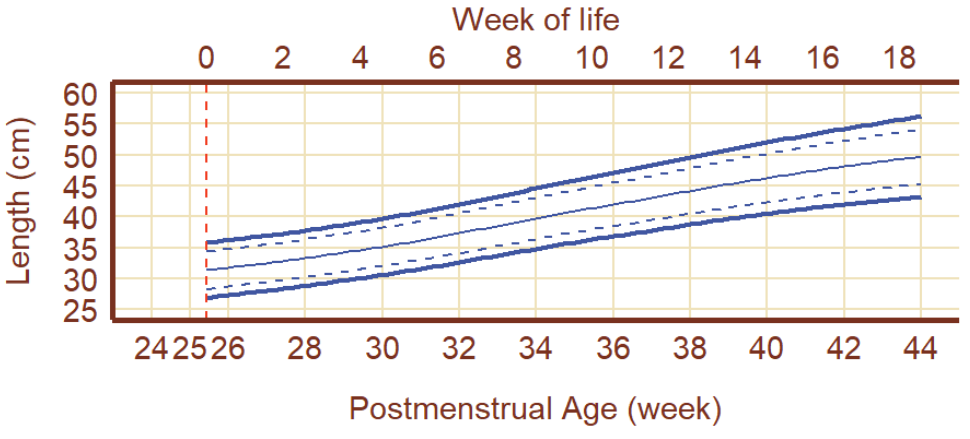


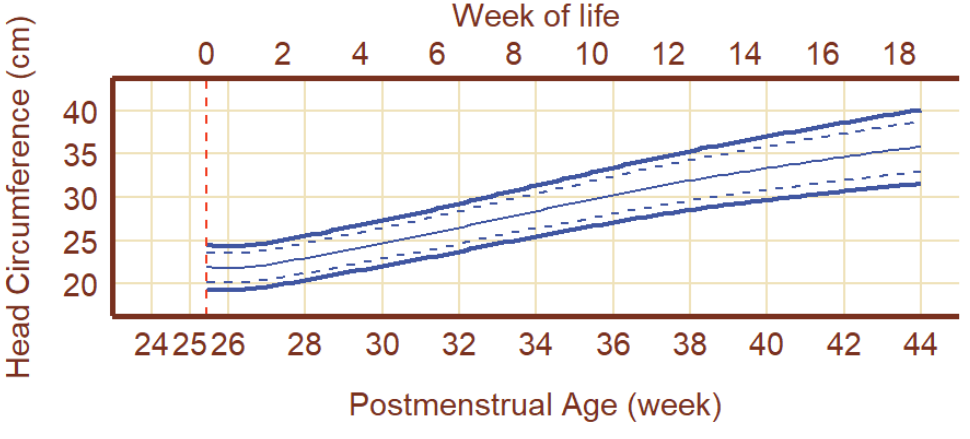


Shift Curves on X-axis

25-week postnatal growth for female infants born at 25w3d

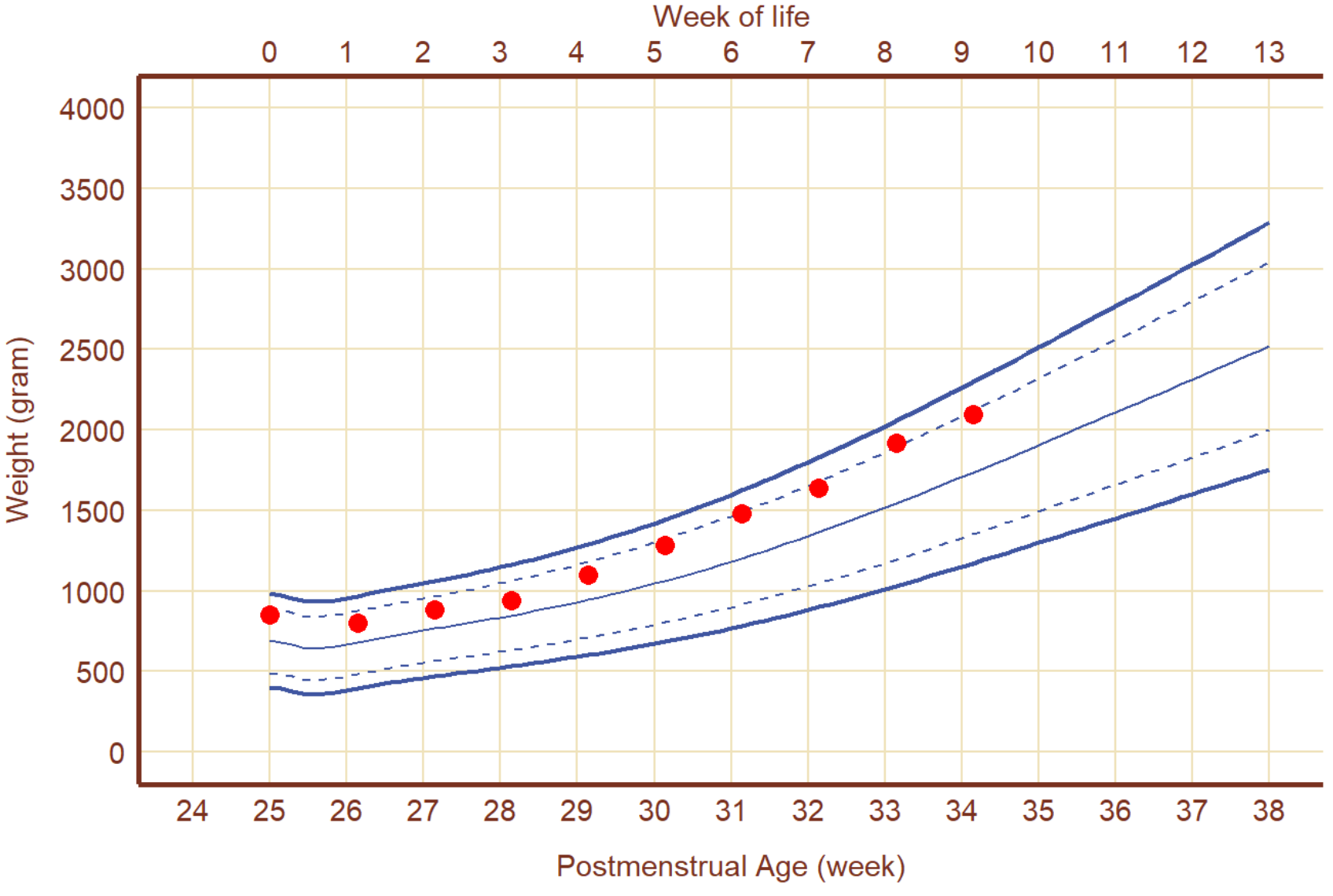




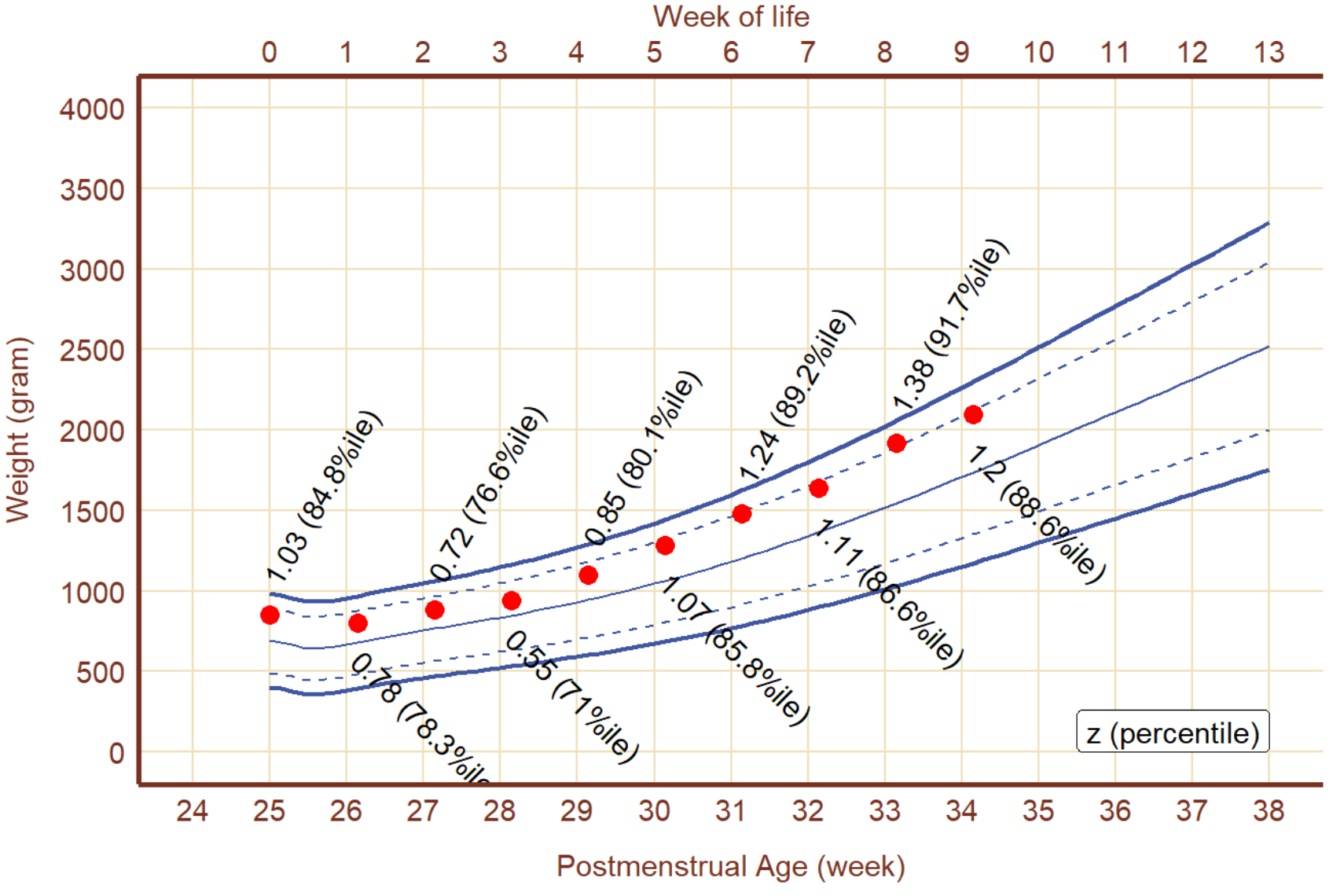


Interpret data points

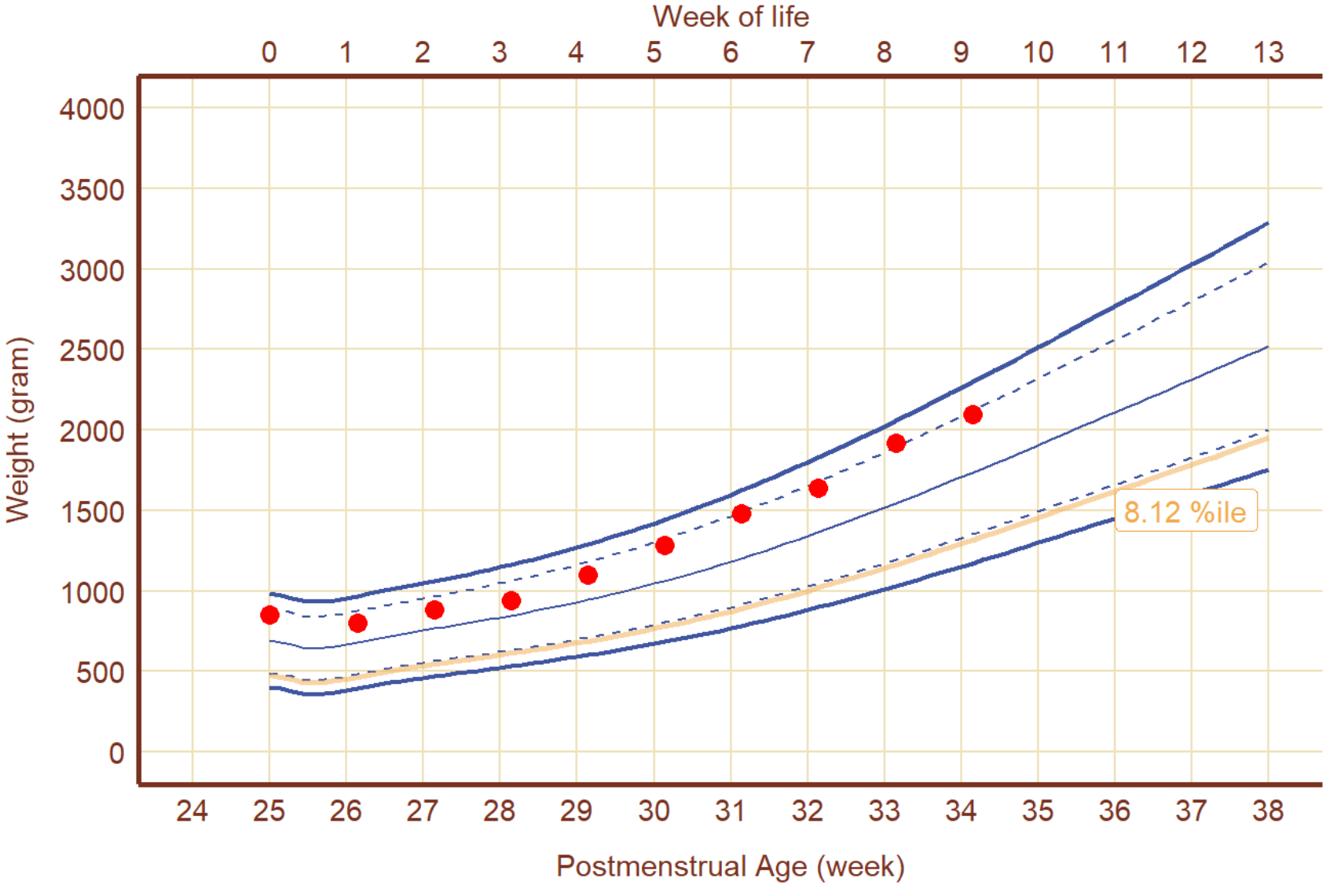
Interpreting Individual Data Points



Interpreting Individual Data Points



Trajectory Percentile



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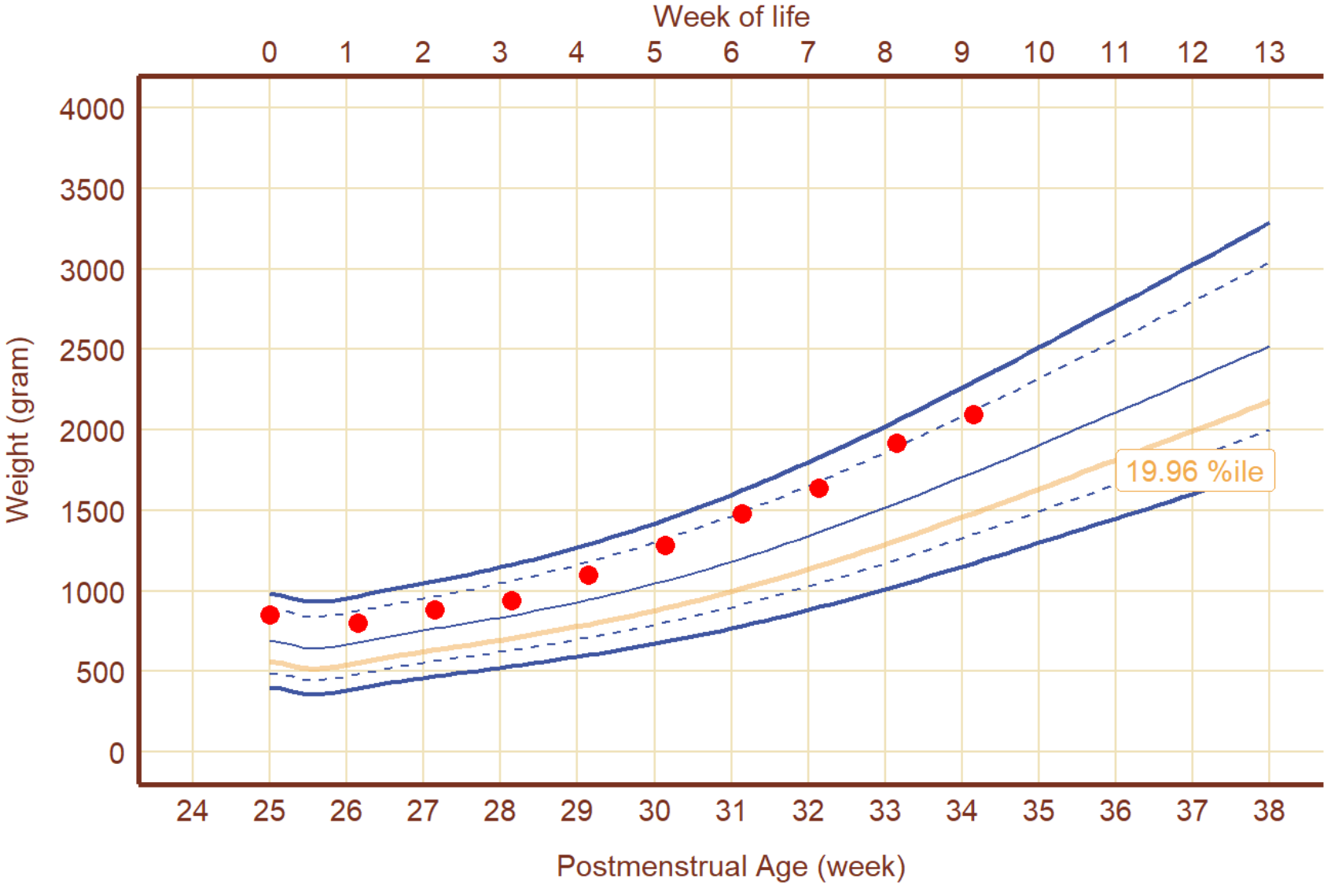
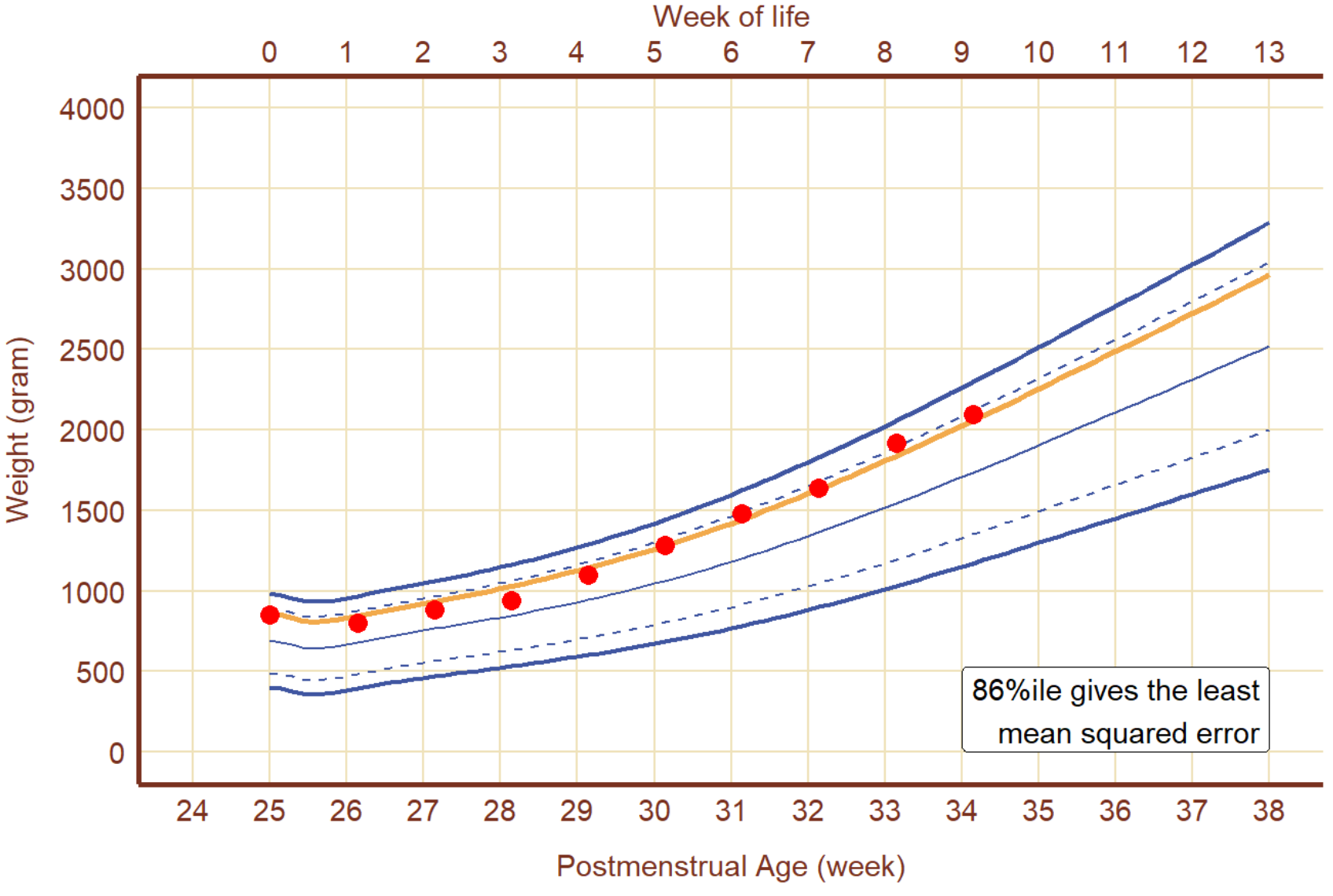
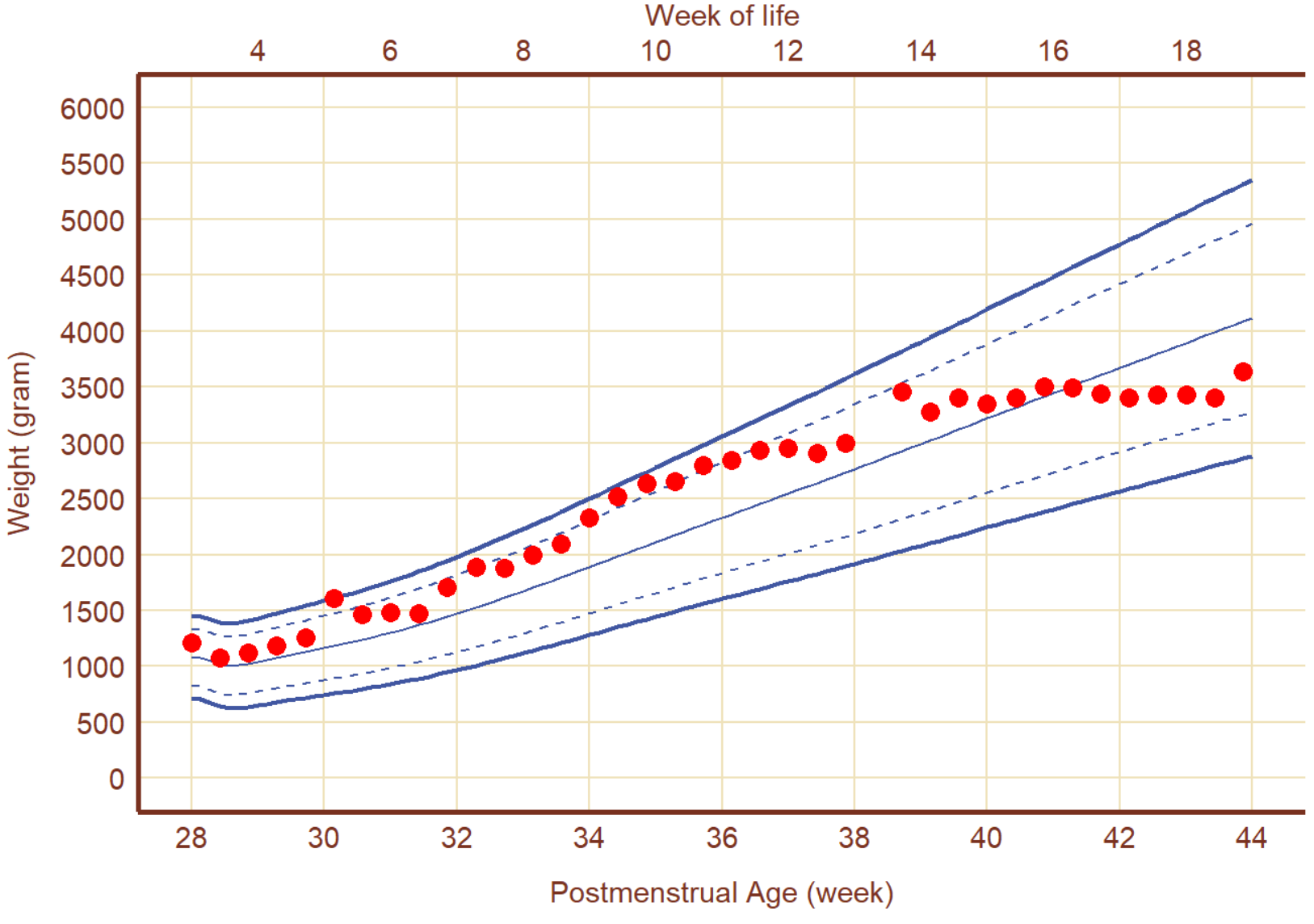


Trajectory Percentile



Trajectory Percentile from A Subset



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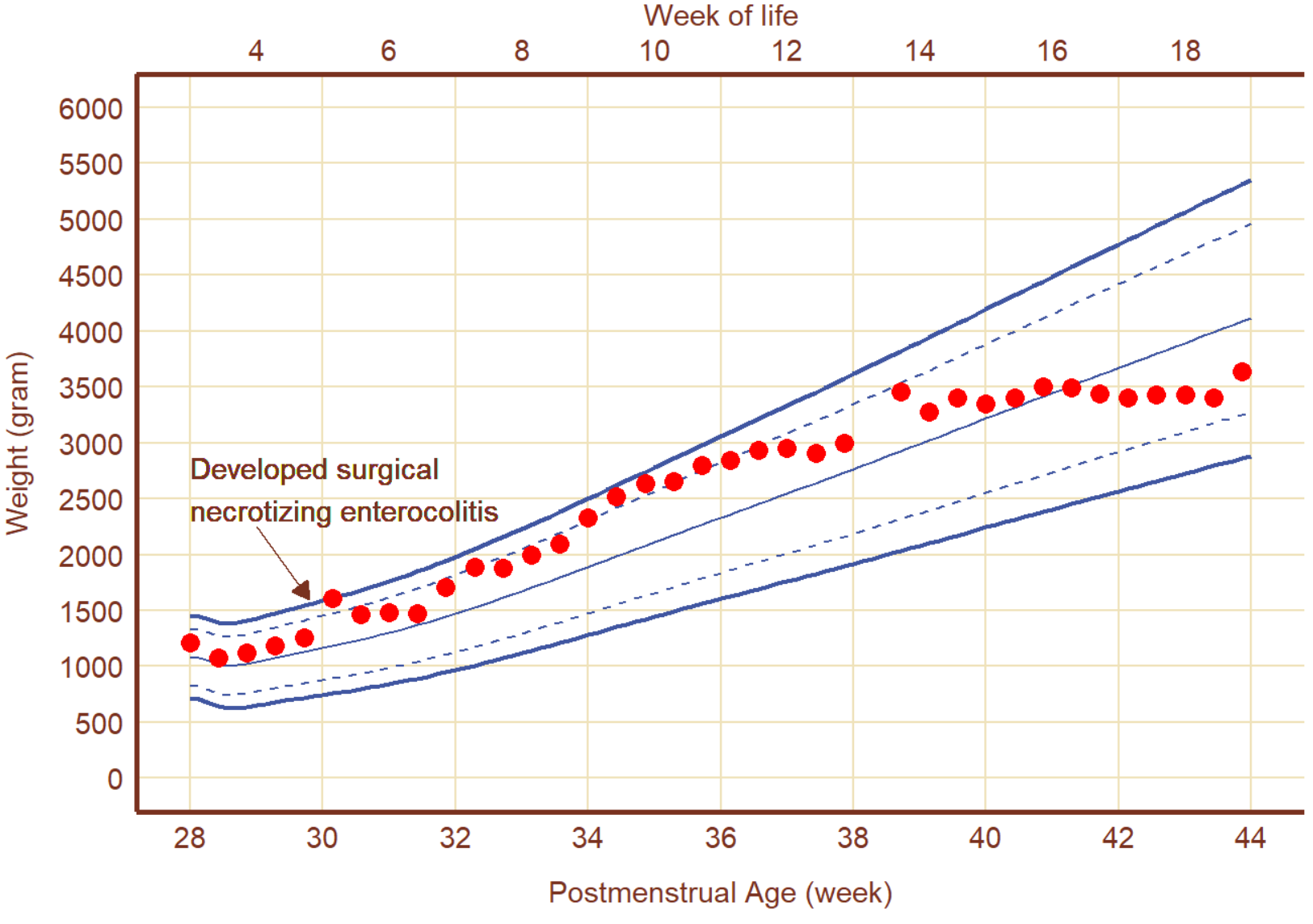

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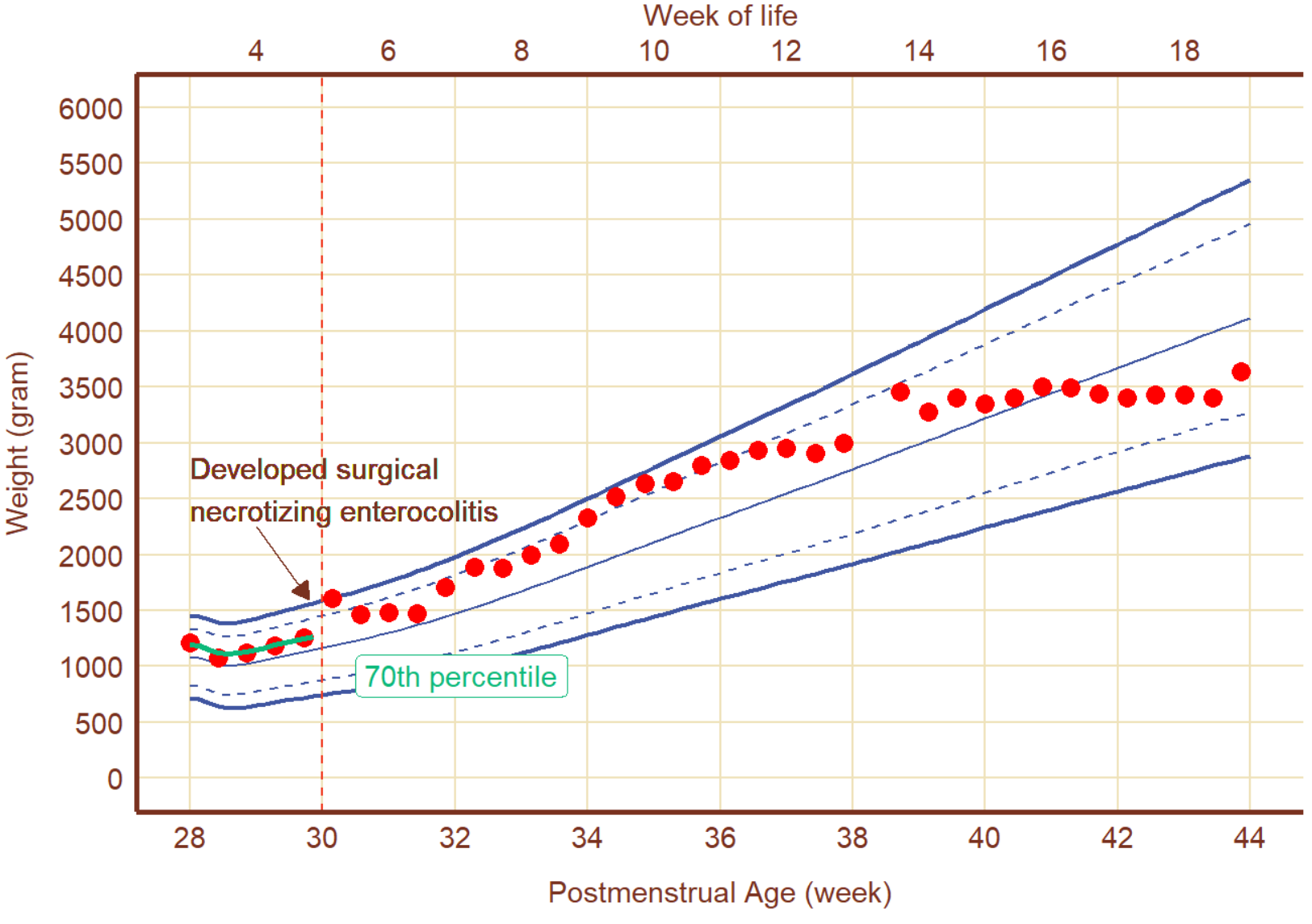

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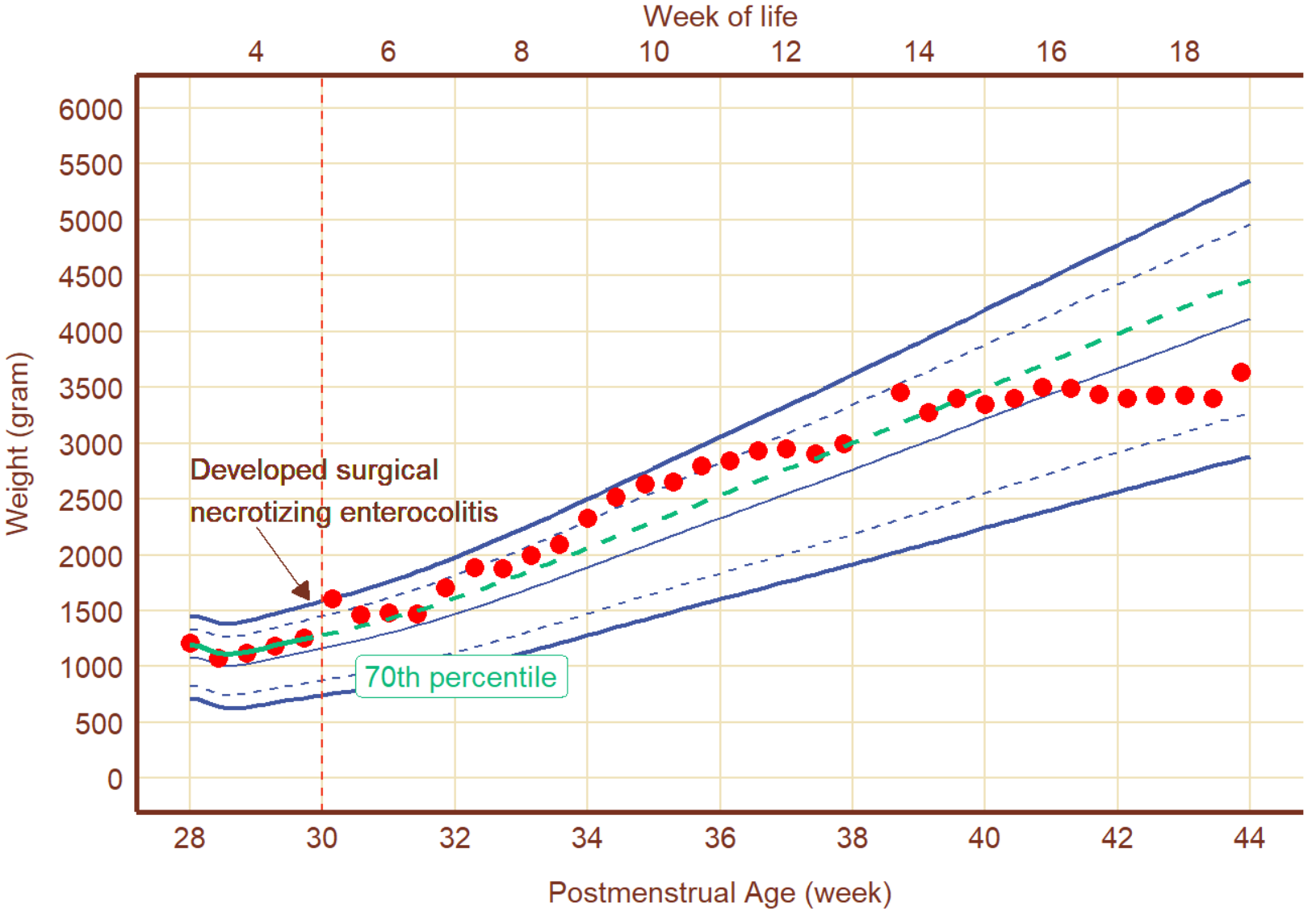
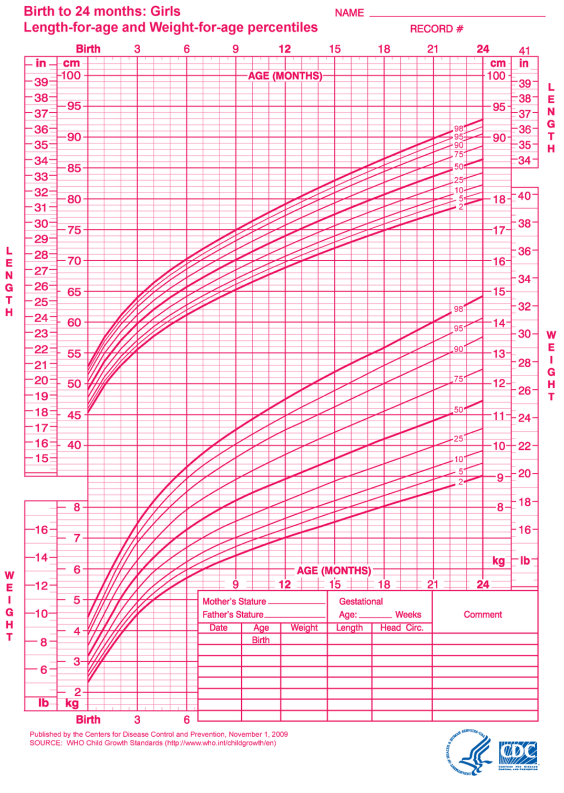


Use trajectory percentile to connect to the WHO Growth Standards

WHO Growth Standards

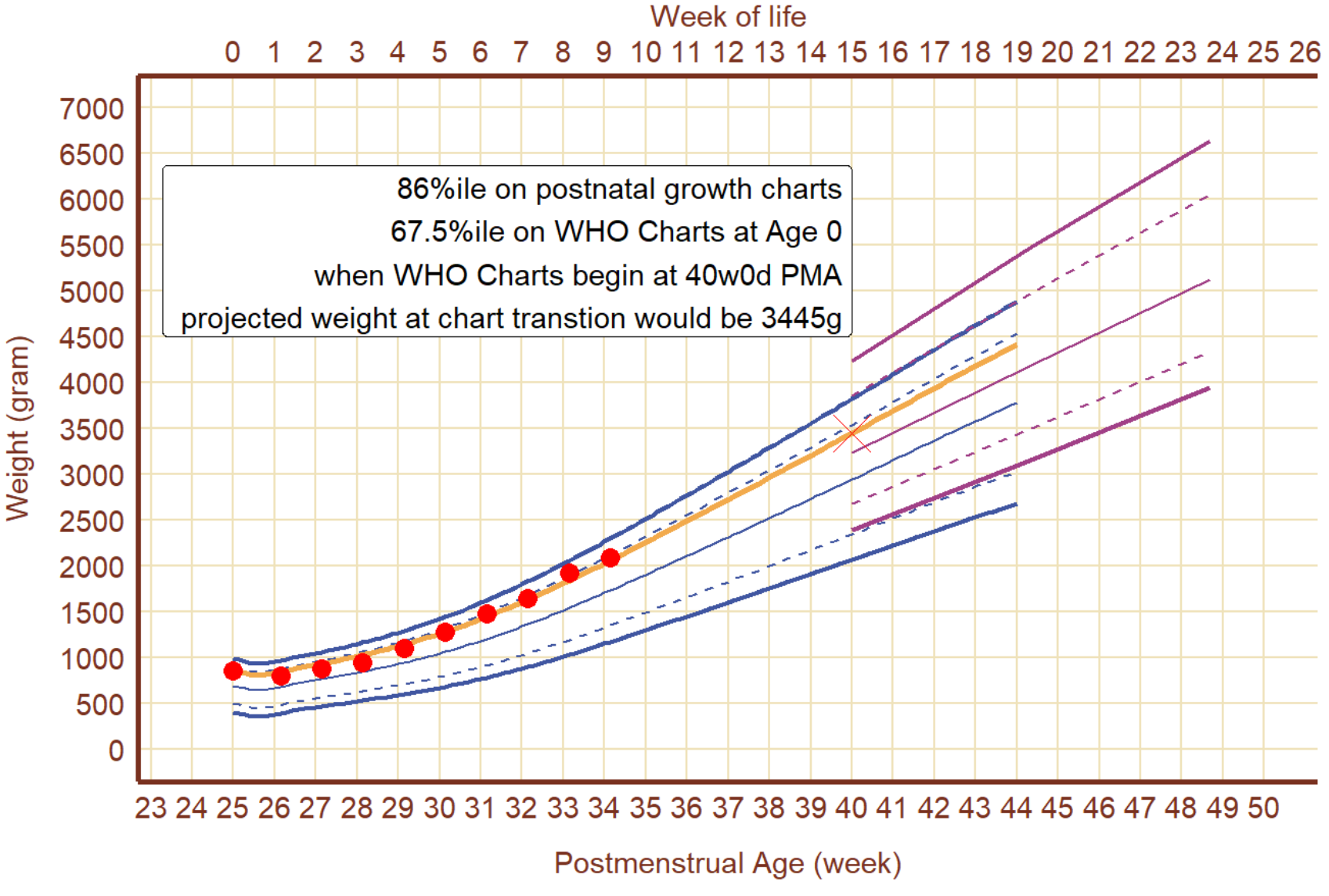
Facts about WHO Child Growth Standards:

- Growth **standards** (optimal growth), not **reference** (not necessarily optimal growth)
- Released in 2006
- Data from children born at a term GA (37w0d to 41w6d) living in environments believed to support optimal growth from six countries throughout of the world, including Brazil, Ghana, India, Norway, Oman, and the US, between July, 1997 and December, 2003.
- A longitudinal component in study design with data collection between birth and 24 months of age

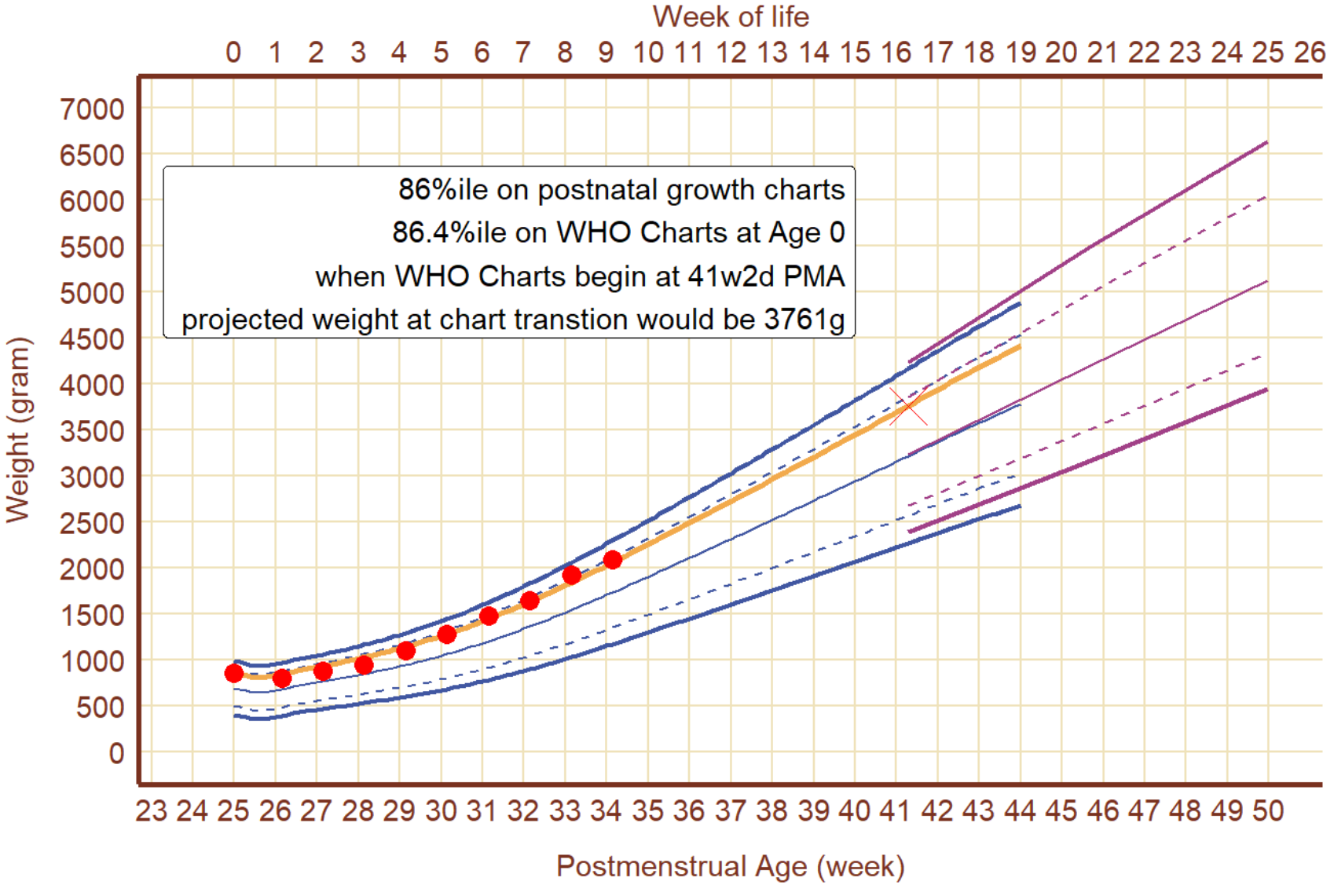


Not all infants were born on their due date (40w0d).

Connecting to WHO Growth Standards



Connecting to WHO Growth Standards



WebApp - nicugrowth.app

Goal

- Easy access and easy to use
- Avoid data entry mistakes
- Does not ask for Private Health Information

- Two pieces of info needed to render growth curves: GA, Sex
- Data table

DOL	Week	Day	Measurement	Z (%ile)
0	25	1		
1	25	2		
⋮	⋮	⋮		
132	44	0		

Quick-plotting App

Weight
Length
Head Circumference

Ediatable Data Table

- DT package

```
### ui.R
DTOutput(id="table", style="height:360px")

### server.R
rv <- reactiveValues(
        wt_table = data.frame(DOL = NA, Week = NA, Day = NA, Weight = NA, `Z (%ile)` = NA)
      )
output$table <- renderDT({
  datatable(wt_table,
            rowname=FALSE,
            selection = "none",
            editable  = list(target = "cell",
                             disable = list(columns=c(0,1,2,4))),
            options   = list(DOM = "t",
                             scrollY = "320",
                             scrollX = TRUE)
            )
})
```

Data Table Proxy

A duplicated data.frame object for manipulation

```
# copy the table in display to a proxy object
rv$wt_table_proxy <- rv$wt_table

observeEvent(input$table_cell_edit, {
  # info is a data.frame with 3 columns and 1 row
  info <- input$table_cell_edit

  # make sure to build in codes to validate datatype
  rv$wt_table_proxy[info$row, info$col] <- info$value
}

observeEvent(rv$wt_table_proxy, {
  ## data table manipulation
  ## Calculate z-score, percentile, trajectory percentile
  ## save table to database
})
```

Data Table Proxy

A duplicated data.frame object for manipulation

```
### ui.R
actionButton(id = "plot", label = "PLOT")

### server.R
observeEvent(input$plot, {
  rv$wt_table <- rv$wt_table_proxy
  # plotting
})
```

Growth Charts Plotting

- ggplot2 package

```r
# wide-form data table
ggplot(data = weightCharts, aes(x = PMA)) +
  geom_line(aes(y = percentile_3), linetype = "solid", linewidth = 1) +
  geom_line(aes(y = percentile_10), linetype = "dashed", linewidth = 0.75)
  geom_line(aes(y = percentile_50), linetype = "solid", linewidth = 0.75) +
  geom_line(aes(y = percentile_90), linetype = "dashed", linewidth = 0.75)
  geom_line(aes(y = percentile_97), linetype = "solid", linewidth = 1)

# long-form data table
ggplot(data = weightCharts_long, aes(x = PMA, y = Weight)) +
  geom_line(aes(group = percentile, linetype = type, linewidth = width))
```

Embedding WebApps in Google Sites

- Site visit log via Google Analytics
- Background & version info as static webpage
- Focusing on developing the models and the WebApps

https://nicugrowth.app

THANK YOU FOR YOUR ATTENTION!











Additional packages:

gamm4 | lme4 | DBI | DT | shinyWidgets | shinydashoard | shinyBS | kableExtra | shinycssloaders | readxl | writexl

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SUPPORTING YOUR PREEMIE'S JOURNEY
FROM NICU TO HOME