Growth in early years: statistical and clinical insights

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Child growth

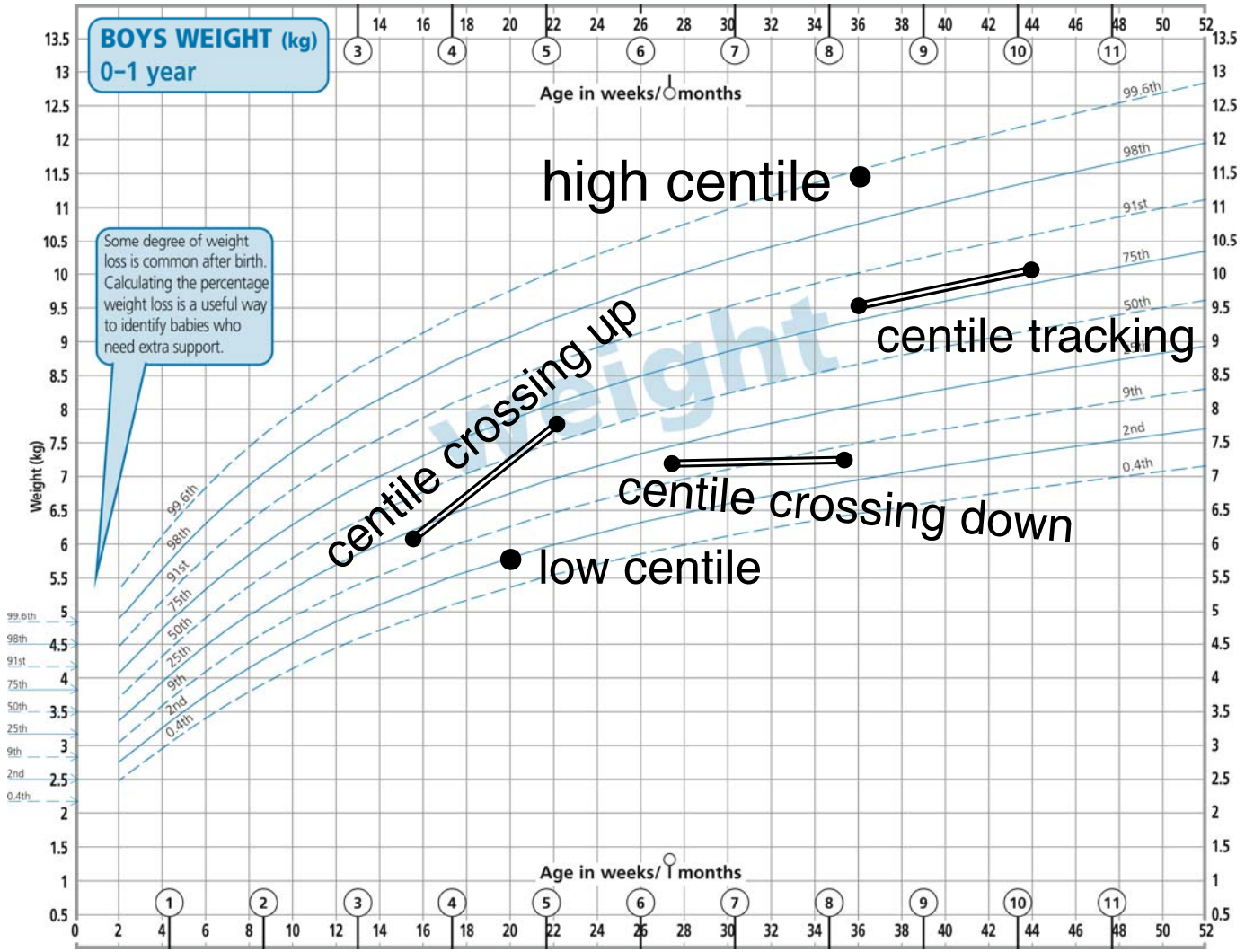
- Growth is the unique paediatric indicator of well-being, which can monitor a child for endocrine, nutritional, emotional and physical health

Ian Jefferson

How to assess growth

- Measure child
- Plot on growth chart
- Read growth chart
- Take action

Centiles and centile crossing



99.6
98
91
75
50
25
9
2
0.4

centiles

UK-WHO chart

What is a centile?

- Centile - percentage point of the frequency distribution
  - Cut-off identifies that percentage of children with measurements below it
- Examples
  - 50% of children lie below 50th centile (median)
  - 25% of children lie below 25th centile
  - 99.6% of children lie below 99.6th centile (0.4% above)
- The cut-offs vary by age, so the centiles appear as curves on the growth chart

Growth distance and velocity

- Growth chart is “road to health”
  - Current size (i.e. centile) indicates *distance* travelled
  - Centile crossing indicates *velocity* of travel

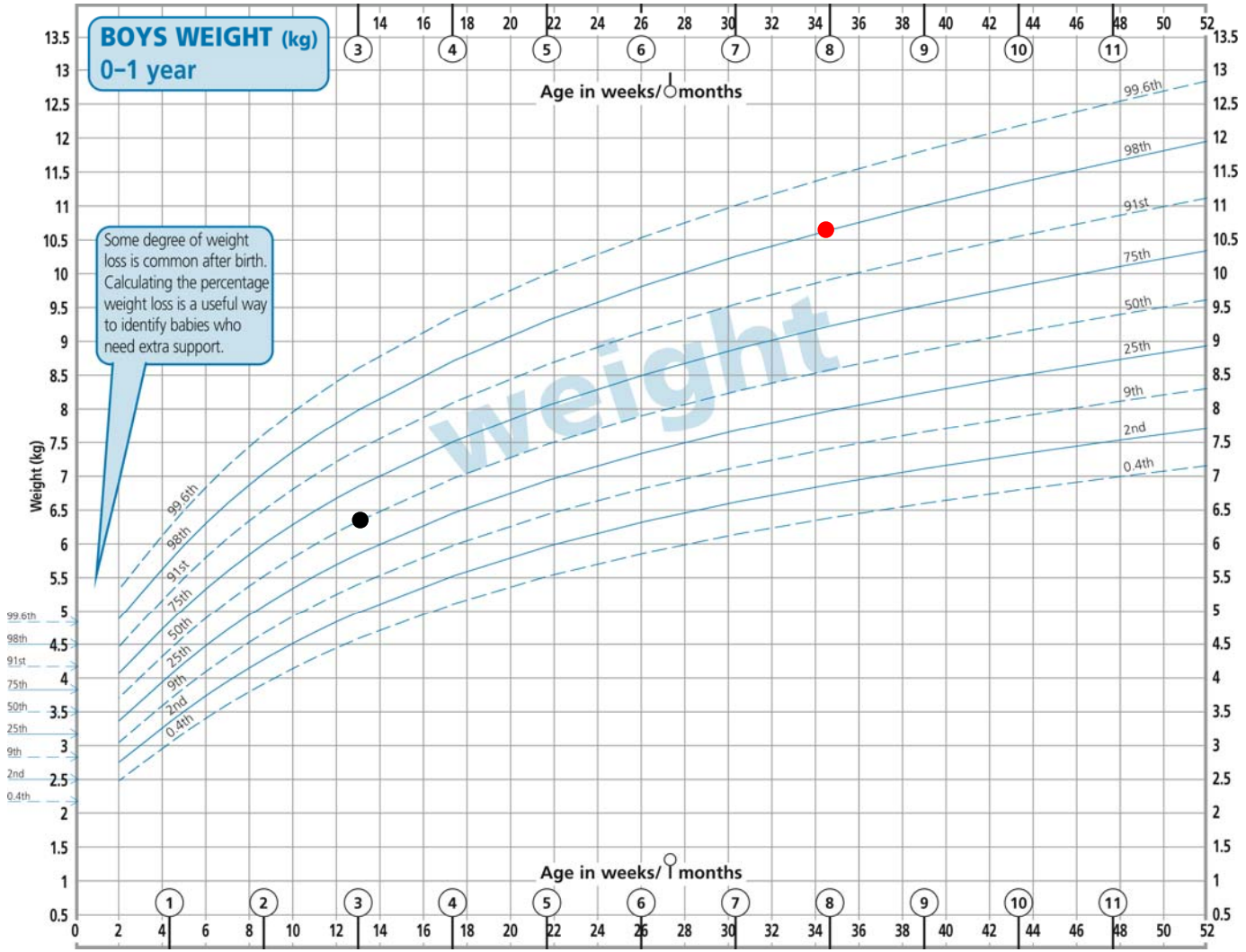
- Growth chart quantifies size/distance
  - Centile
- Growth chart *does not* quantify growth velocity
  - Centile *crossing* is uncalibrated

- *Ironic - growth chart does not measure growth…*

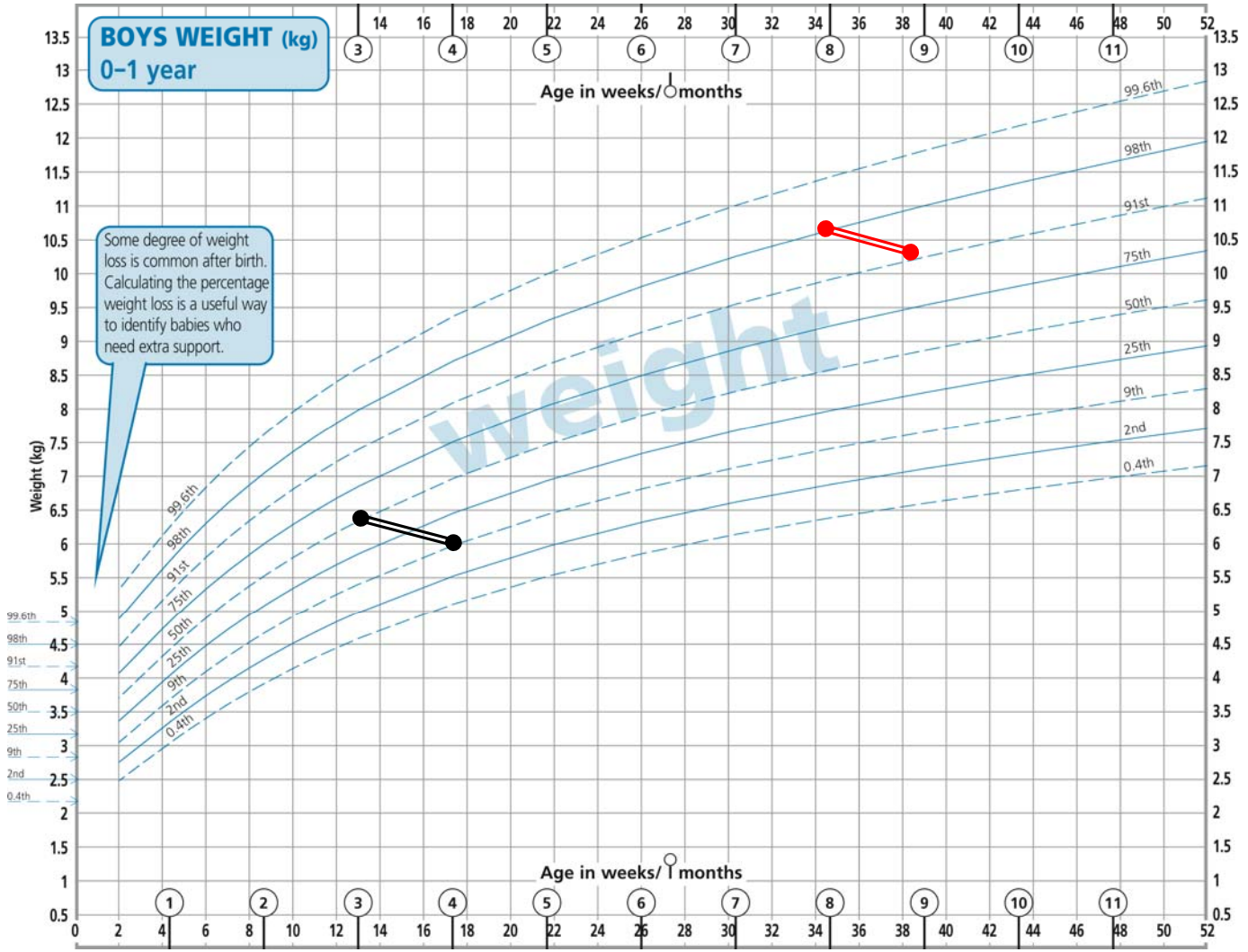
A new concept: growth acceleration

- Growth distance
  - One measurement
    - Centile
- Growth velocity
  - Two measurements
    - Centile crossing
- Growth acceleration
  - Three measurements
    - Change in centile crossing

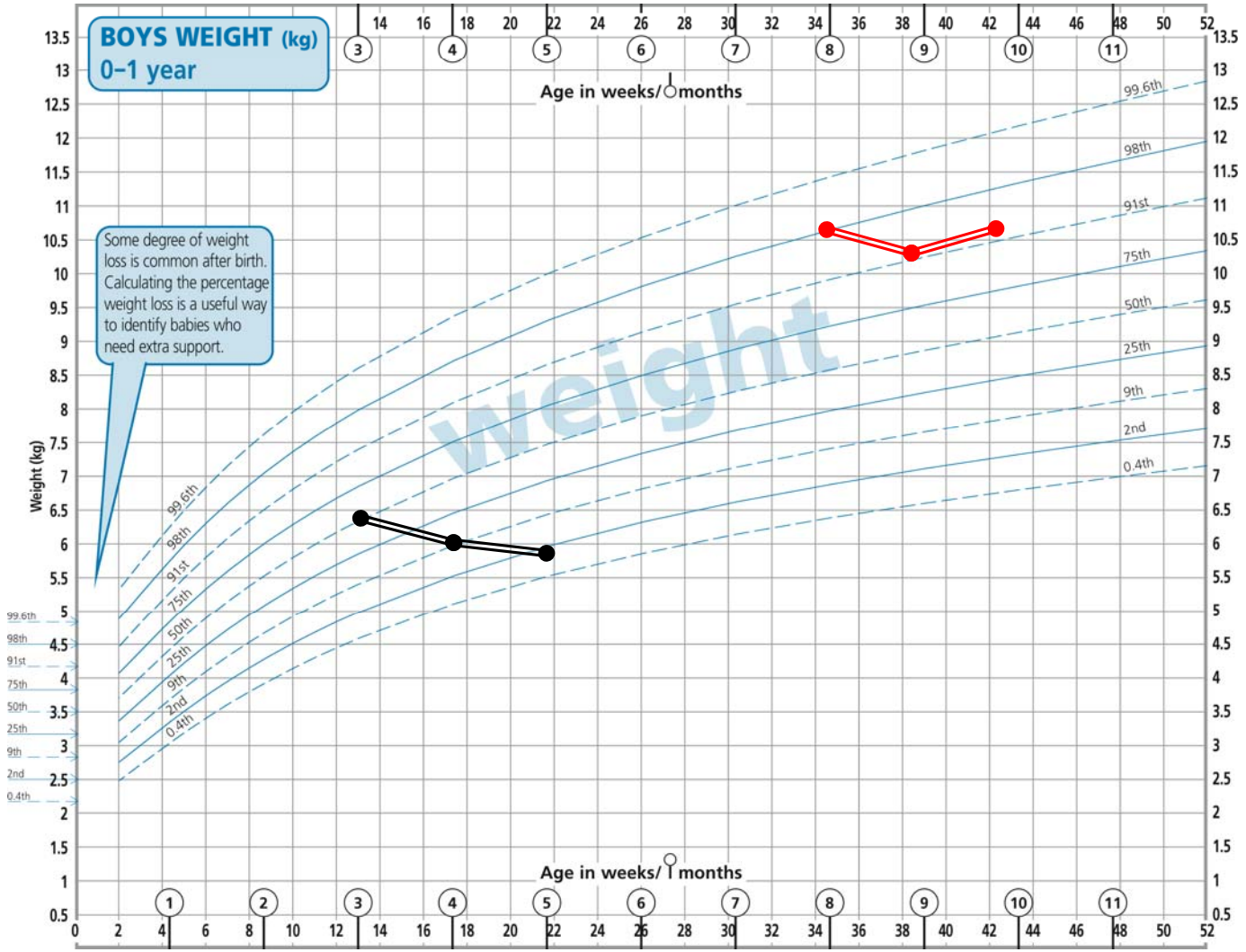
Distance - one measurement



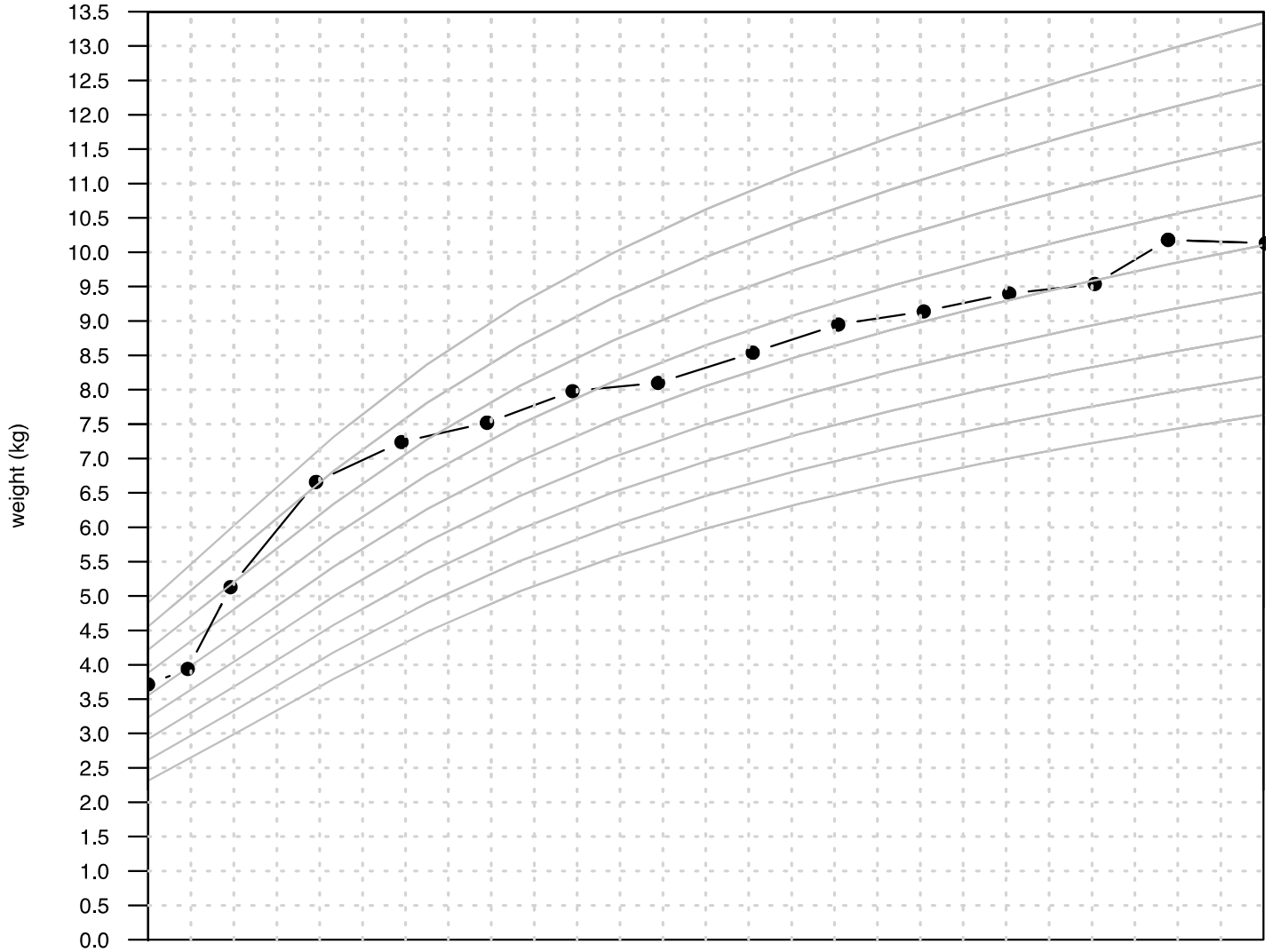
Velocity – two measurements



Acceleration – three measurements



Growth pattern – many measurements



Growth pattern – many measurements

- Modelling growth curves with SITAR
- Provides simple summary of individual growth patterns

Aims

- To show how statistics helps chart assessment for:
  1. Growth distance
  2. Growth velocity
  3. Growth acceleration
  4. Growth pattern

Growth distance

One measurement

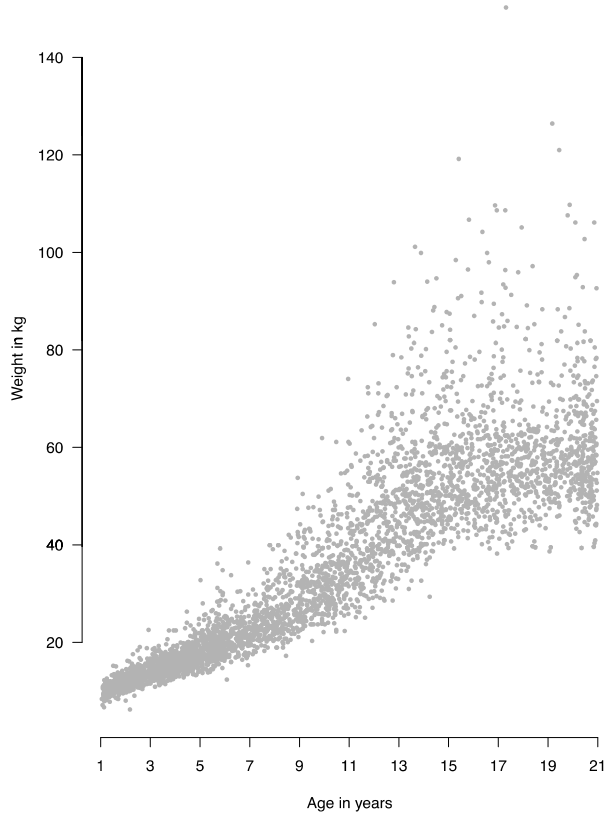
Constructing growth charts

- Growth charts designed to assess single measurements
- Compare measurement to distribution of reference measurements for age and sex
- LMS method popular way to construct growth charts
- Worked example for weight in girls

Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. Stat Med 1992;11:1305-19.

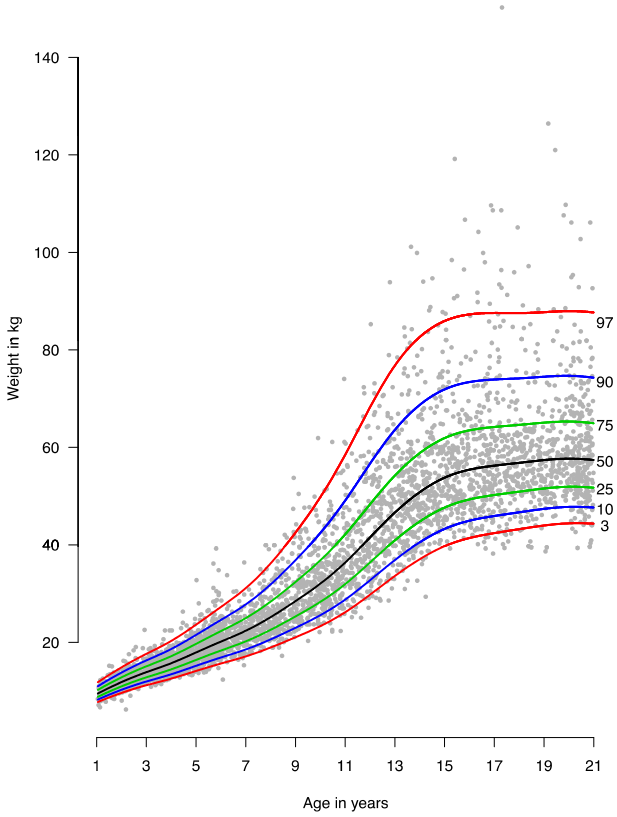
Constructing growth charts

- Weight in 4000 girls
- Age 1-21 years
- Aim: to define weight distribution at each age
  - 95% below 95th centile
  - 50% below 50th centile
  - 5% below 5th centile
  - etc



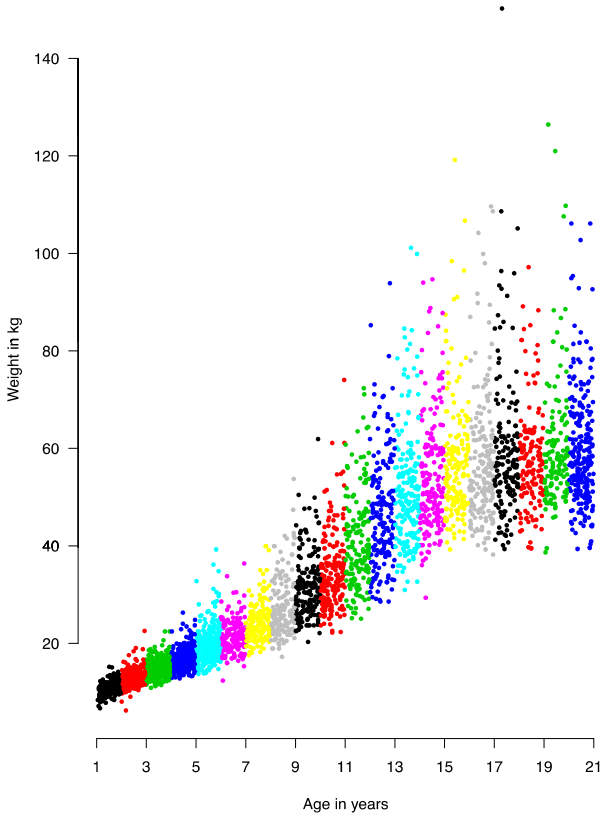
Constructing growth charts

- Weight in 4000 girls
- Age 1-21 years
- Aim: to define weight distribution at each age
- Construct smooth centile curves
  - 50% below 50th centile
  - 3% below 3rd centile
  - 97% below 97th centile
  - *etc*



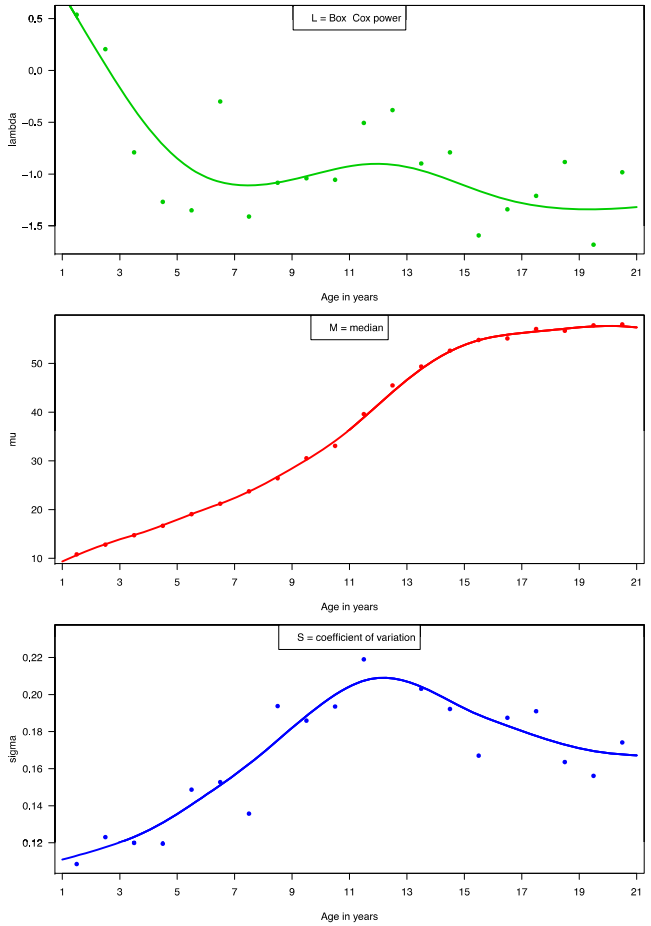
LMS method

- Cole, JRSS A (1988)
- Split into narrow age groups
- Summarise distribution in each group
  - Need to adjust for skewness
  - Raise weight to Box-Cox power λ
  - Calculate mean μ and coefficient of variation σ
- So λ μ and σ vary by age



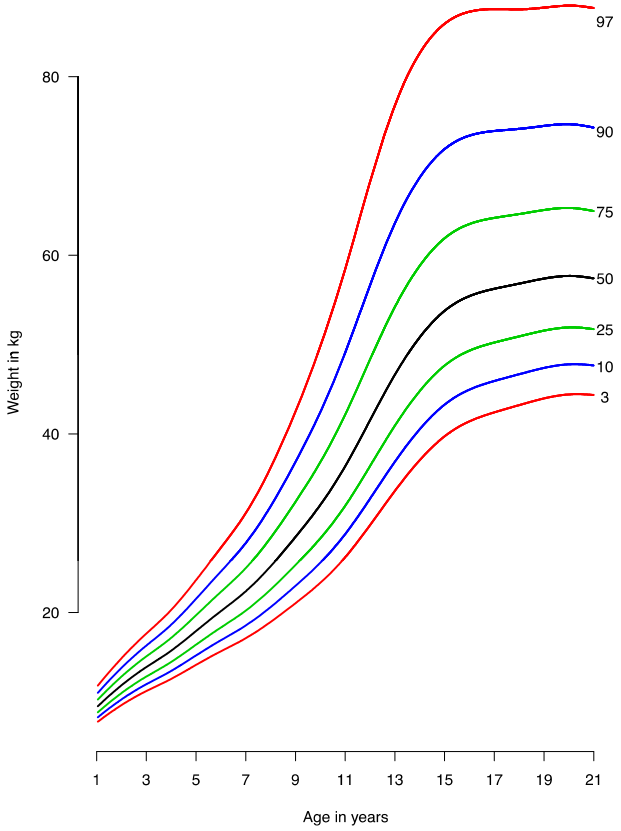
LMS method

- Plot λ μ and σ against age and fit smooth curves
  - L curve for Box-Cox power λ
  - M curve for median μ
  - S curve for coeff of variation σ
- Hence LMS method



LMS method

- Centile curves are functions of L M and S curves
  - $Centile_{100\alpha} = M(1+LSz_{\alpha})^{1/L}$
- So if L M and S curves are smooth, centiles are too



Cole-Green LMS method

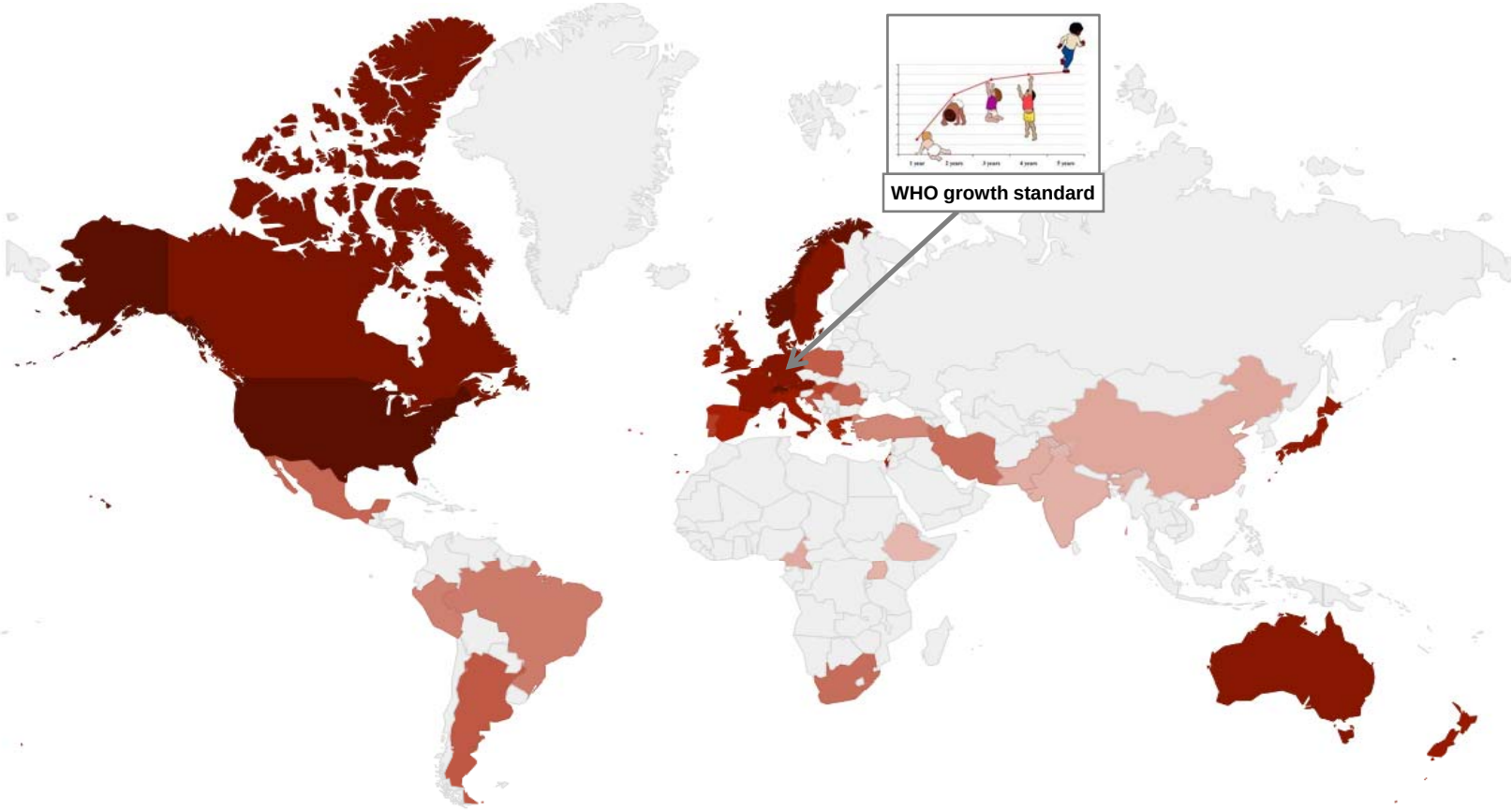
- Peter Green (1988) proposed using maximum penalized likelihood to improve LMS method

$$\sum_{i=1}^{n}\left(L(t_i)\log\left[\frac{y_i}{M(t_i)}\right]-\log S(t_i)-\frac{1}{2}\left\{\frac{[y_i/M(t_i)]^{L(t_i)}-1}{L(t_i)S(t_i)}\right\}^2\right)-\frac{1}{2}\alpha_L\int[L''(t)]^2\,dt-\frac{1}{2}\alpha_M\int[M''(t)]^2\,dt$$
$$-\frac{1}{2}\alpha_S\int[S''(t)]^2\,dt$$

- Elegantly avoids arbitrary age groupings
- See Cole & Green, Stat Med (1992)
- Now the standard method

Peter Green FRS

40 countries use LMS method



Growth velocity

Two measurements

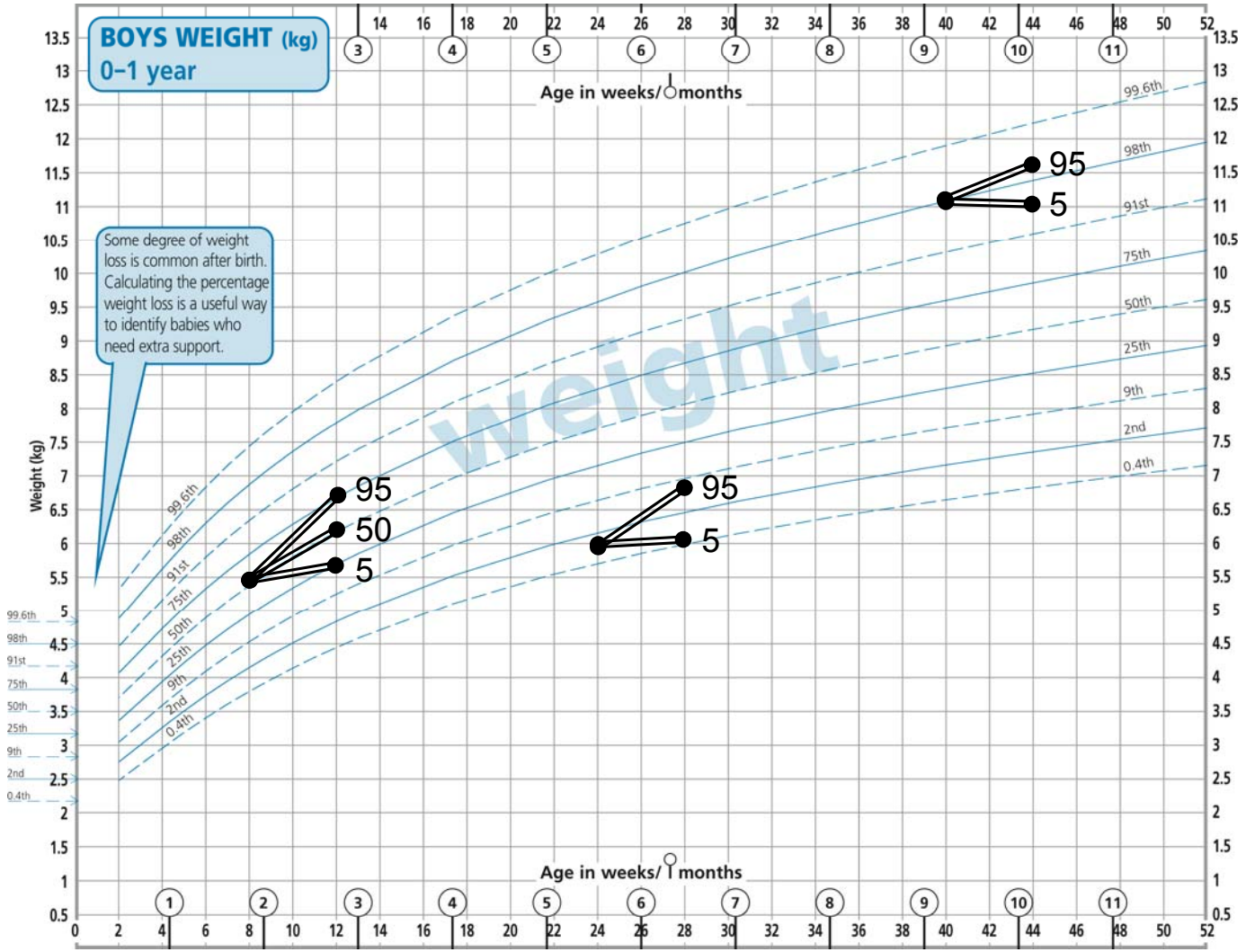
Growth velocity

- Velocity appears as centile crossing on chart
- Two problems with chart centiles
  - They assess distance not velocity
  - Light babies grow faster, heavy babies slower
    - Regression to the mean
    - So velocity depends on starting weight
- Only experience can tell if centile crossing is abnormal
- Need a way to flag abnormal centile crossing on chart

Velocity and centile crossing

- Show line on chart whose slope corresponds to 5th velocity centile over 4 weeks
- Depends on age and initial centile

Centile crossing over 4 weeks



Statistics of centile crossing

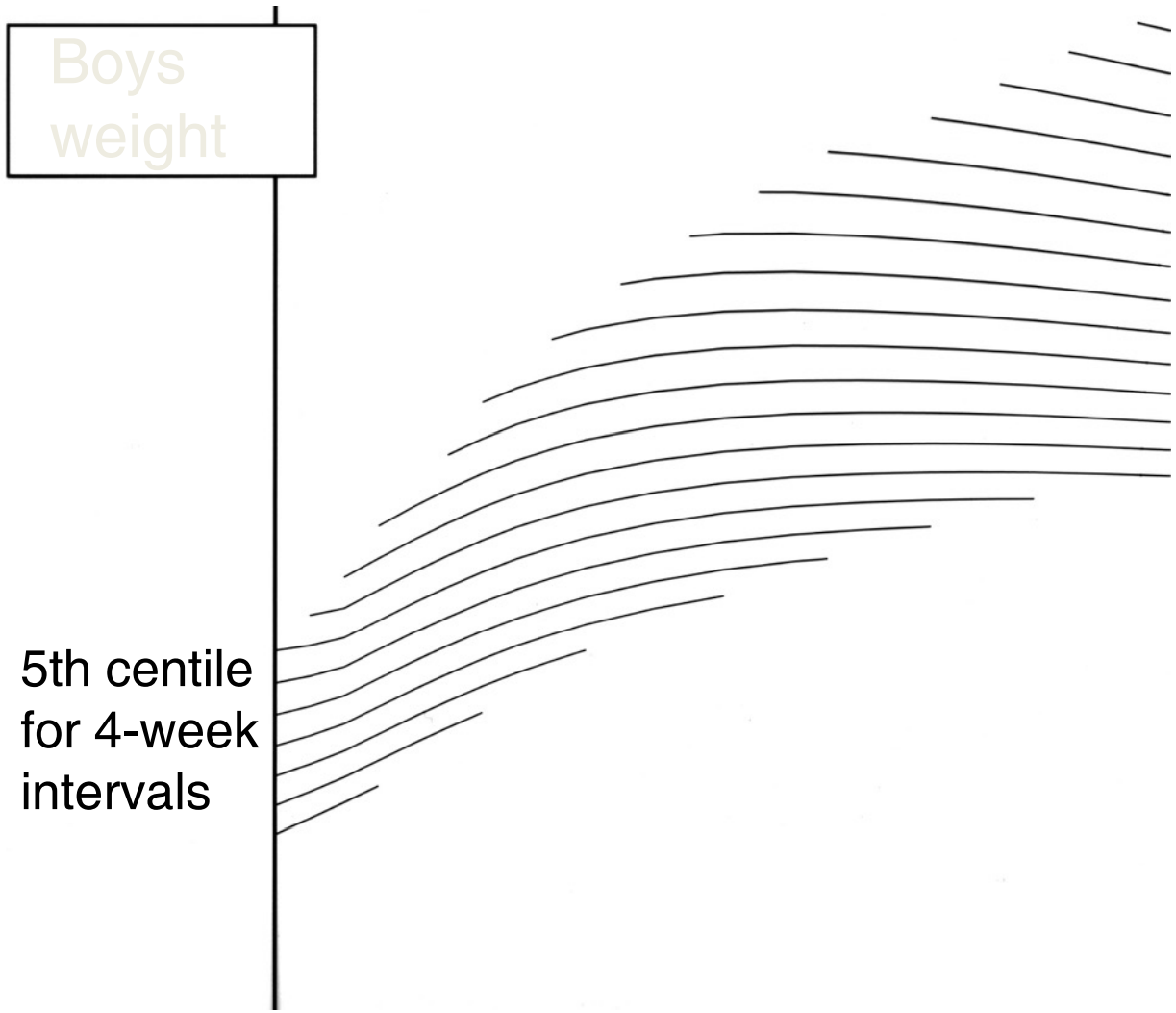
- Two weights 4 weeks apart
- Convert to z-scores z_1 and z_2
- Expected mean of z_2 is $r.z_1$
  - where r is correlation between z-scores
- SD of z_2 is $\sqrt{1-r^2}$
- So 5^{th} centile for z_2 is
  - z_2 = Mean – 1.64 SD = $r.z_1 – 1.64\sqrt{1-r^2}$
- So z_2 depends on z_1 and r

Thrive lines for growth velocity

- For ages 0-4, 4-8, 8-12 … weeks
  - calculate correlations $r_{0\text{-}4}$, $r_{4\text{-}8}$, $r_{8\text{-}12}$ etc
- Choose baseline value z_0
- Then using formula
  - $z_0 > z_4 > z_8 > z_{12}$ … defines a curve
- Call the curve a *thrive line* as it defines failure to thrive

Cole TJ. Presenting information on growth distance and conditional velocity in one chart: practical issues of chart design. Stat Med 1998;17:2697-707.

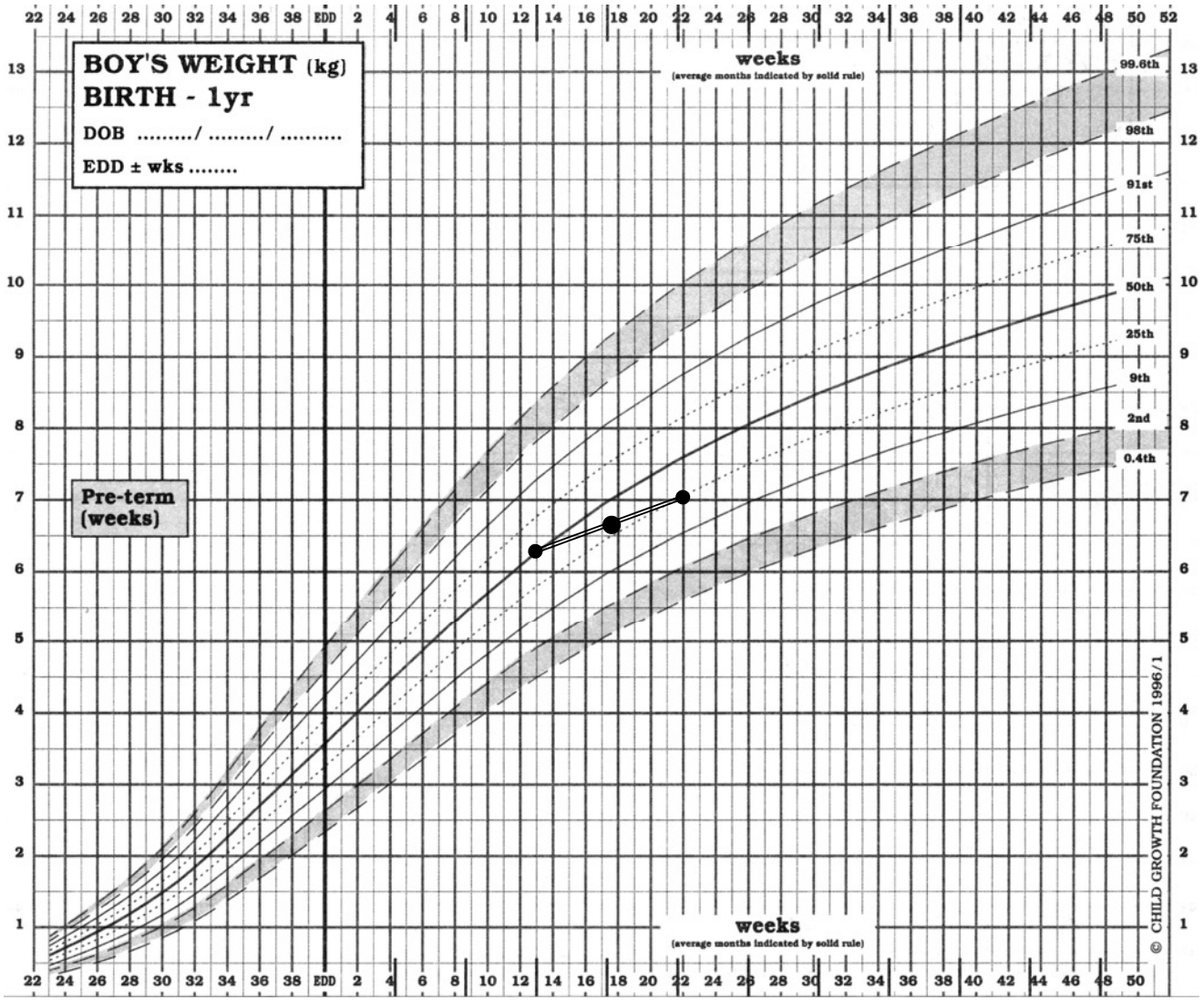
Thrive line overlay - 5th centile weight gain



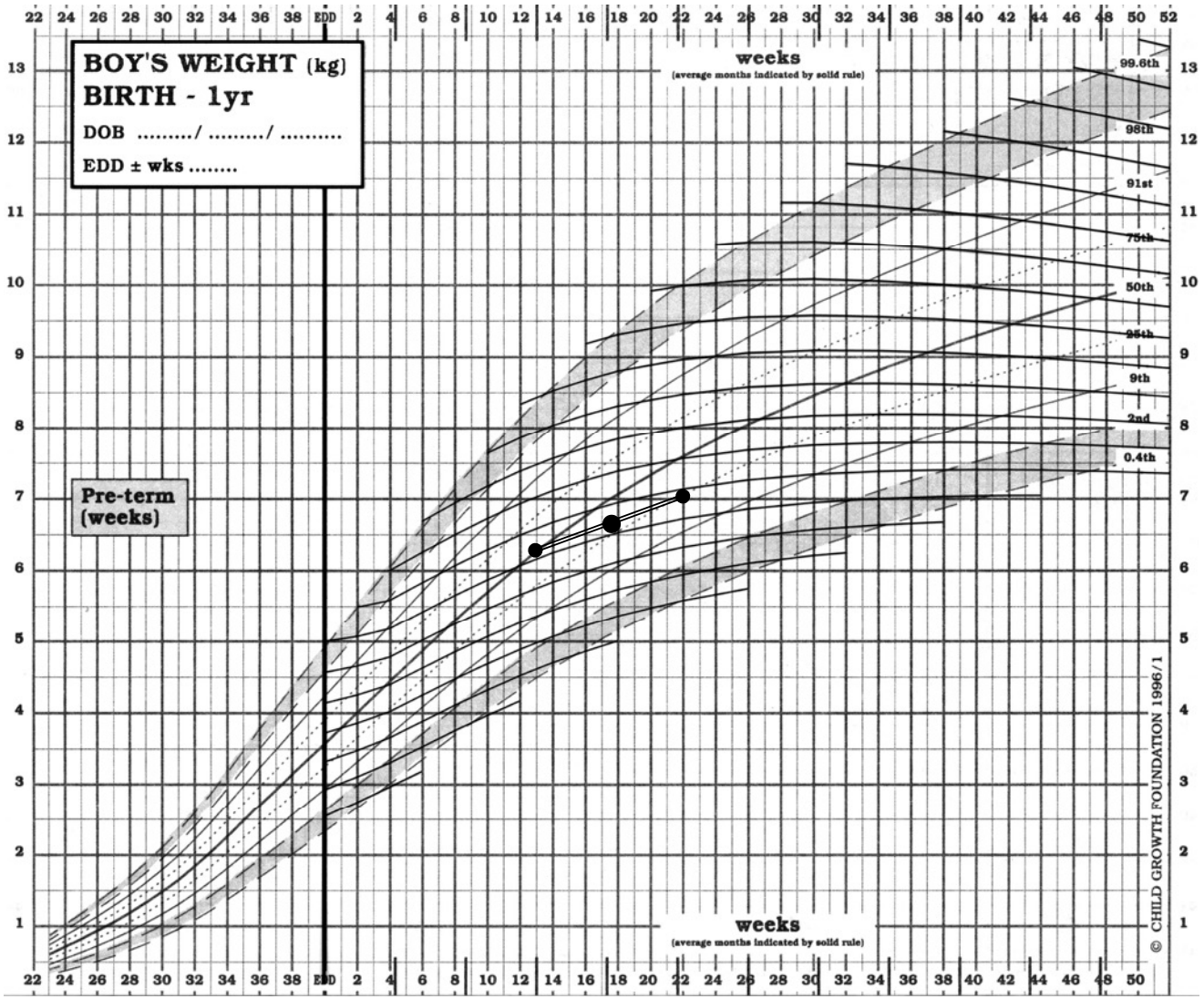
Thrive lines

- Thrive lines assess weight velocity
  - 5th velocity centile
  - Over a 4-week period
- A child's plot that tracks along the thrive lines for 4 weeks is growing on the 5th velocity centile
- Tracking for longer is worse:
  - e.g. for 8 weeks, growth < 1st velocity centile
- Thrive lines presented as plastic overlay to superimpose on chart

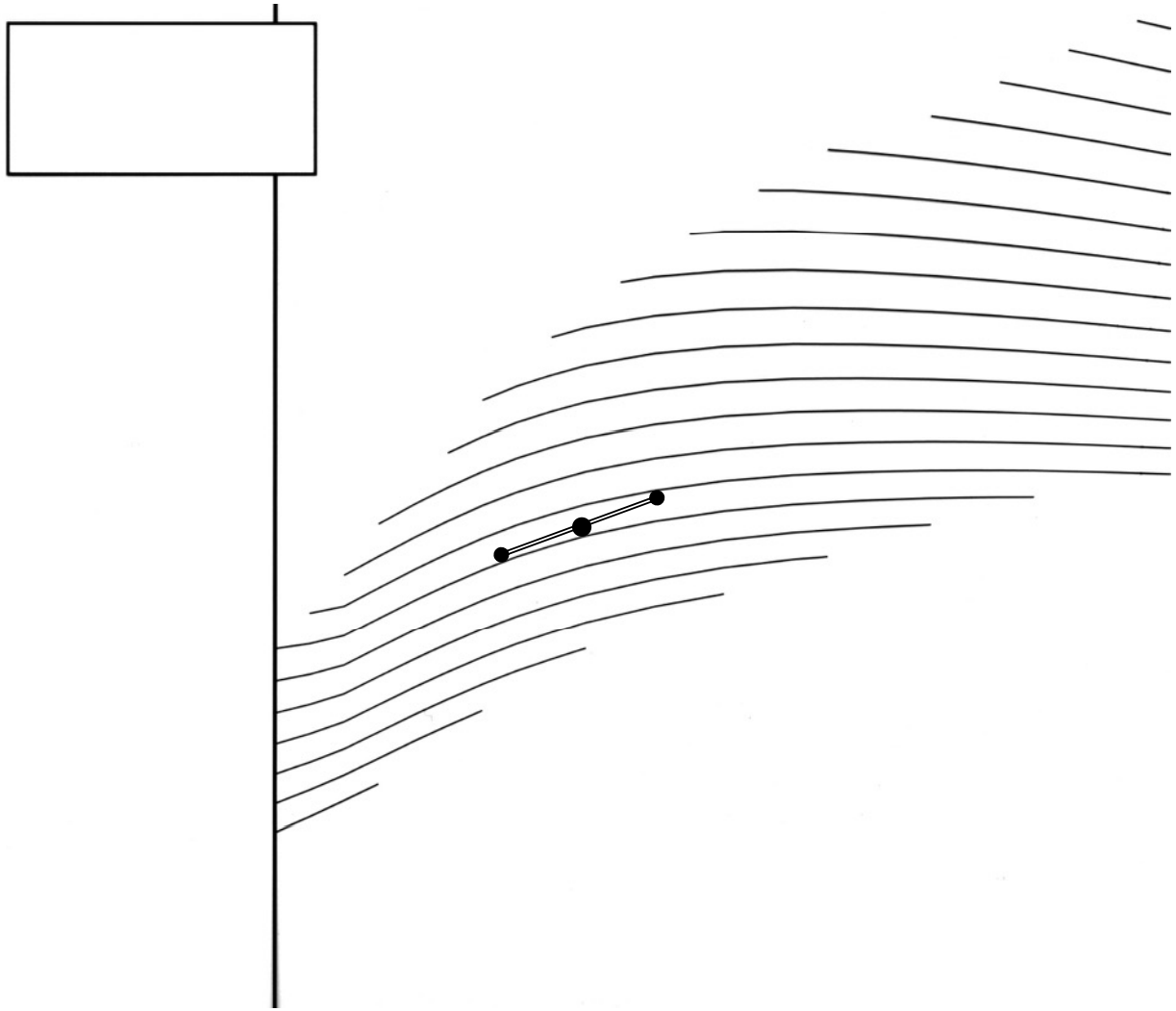
Mild centile crossing - 1 channel width over 8 weeks



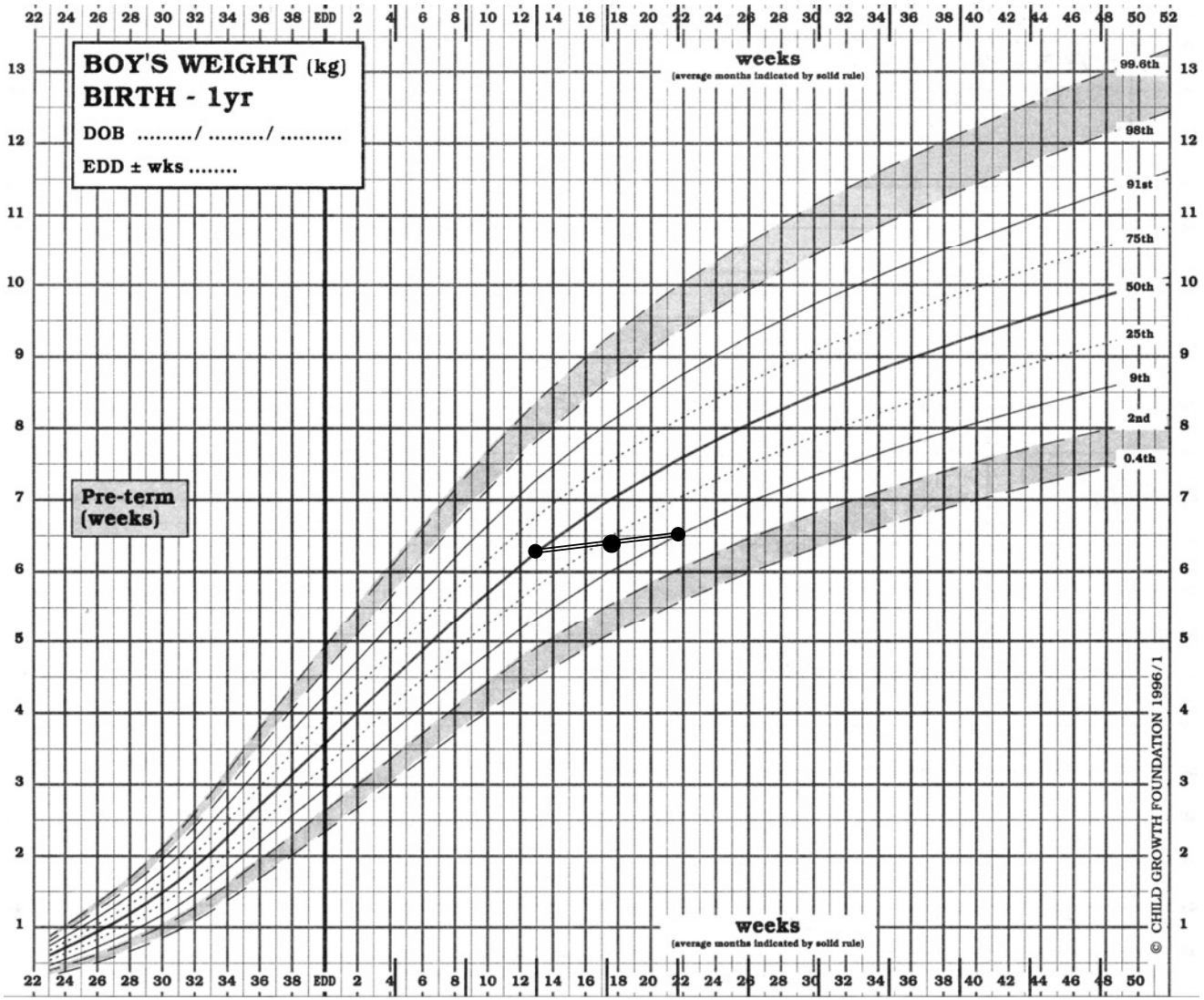
Weight gain above 5th centile



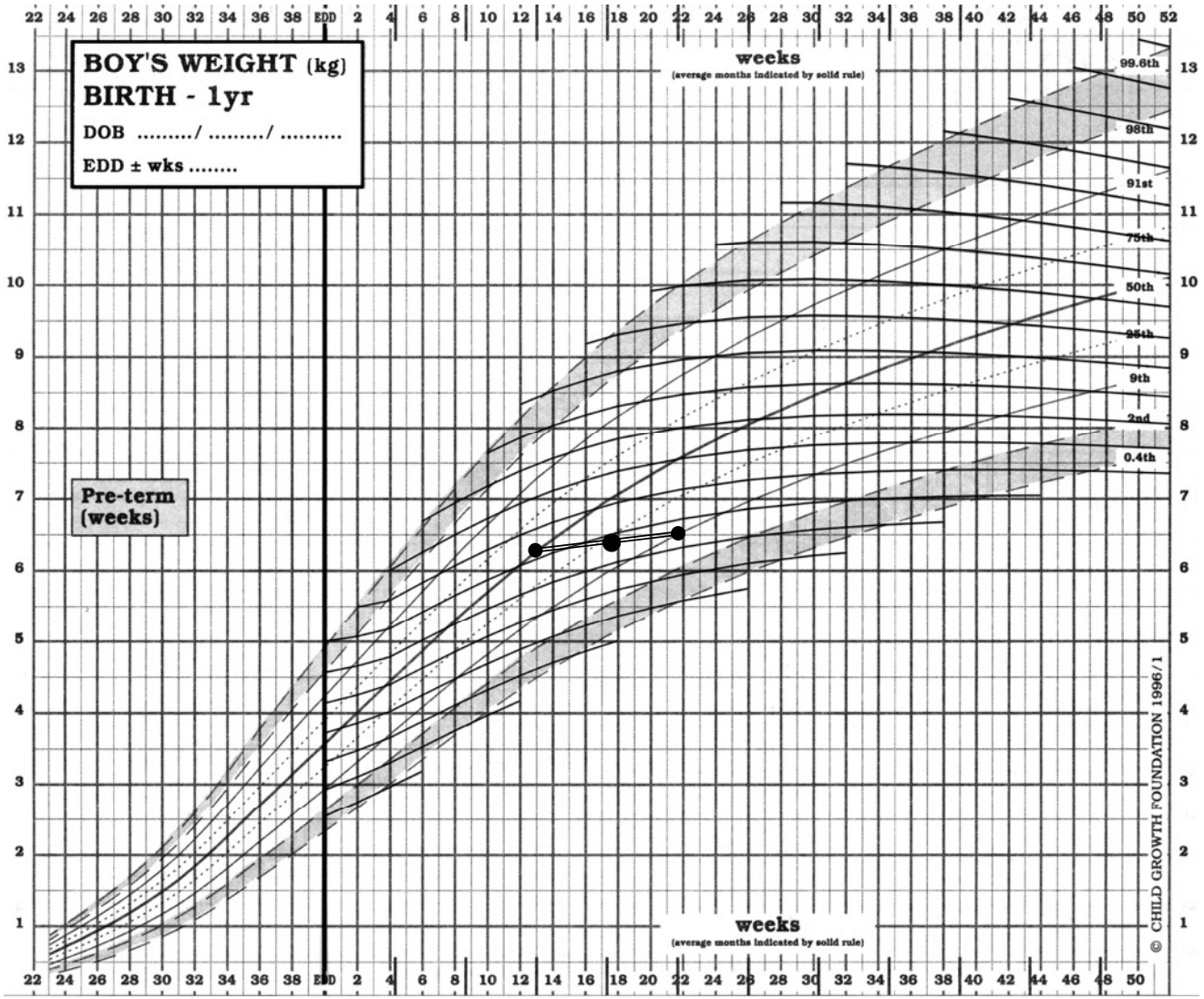
Weight gain above 5th centile



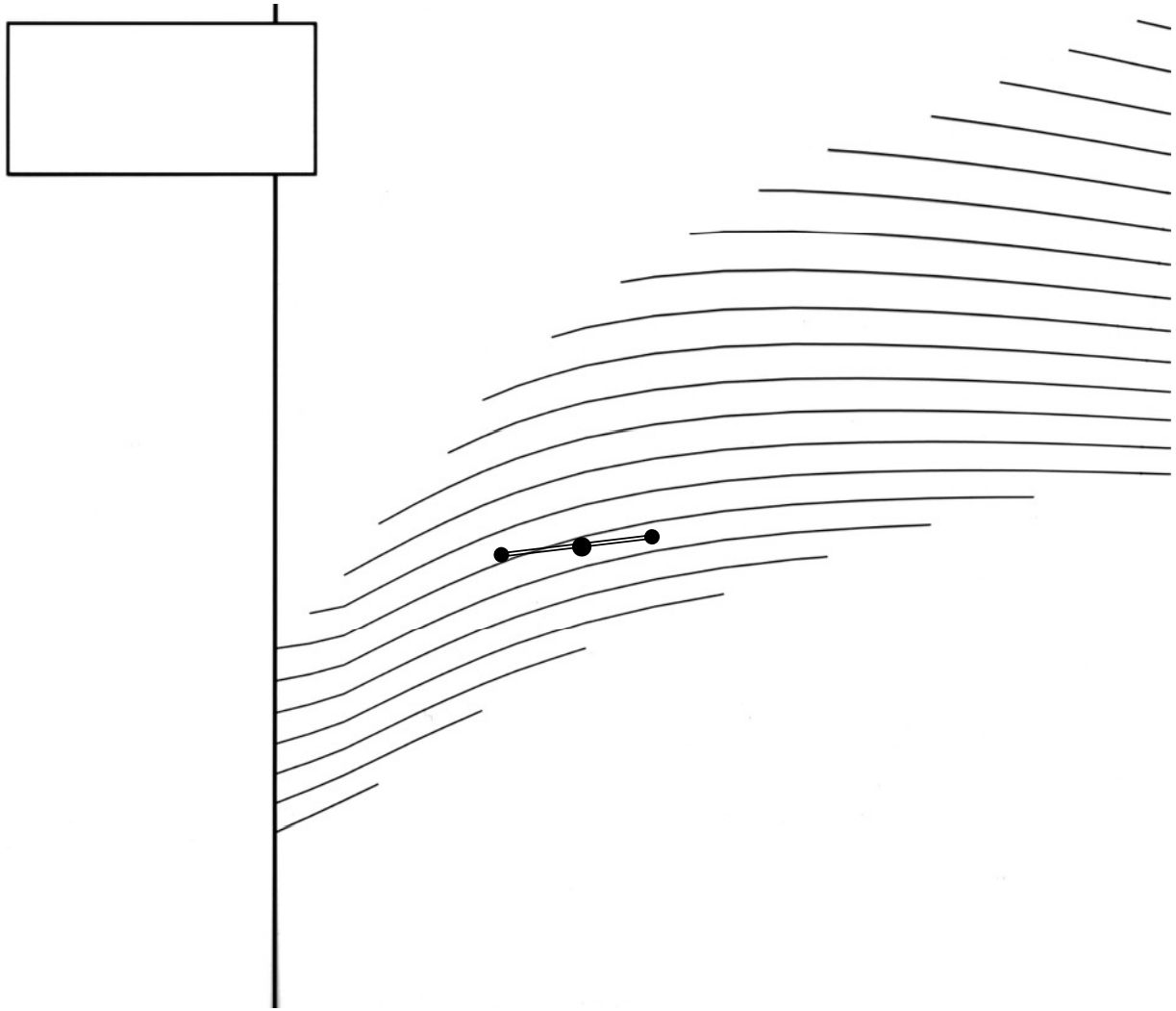
Moderate centile crossing - 2 channel widths over 8 weeks



Weight gain below 5th centile



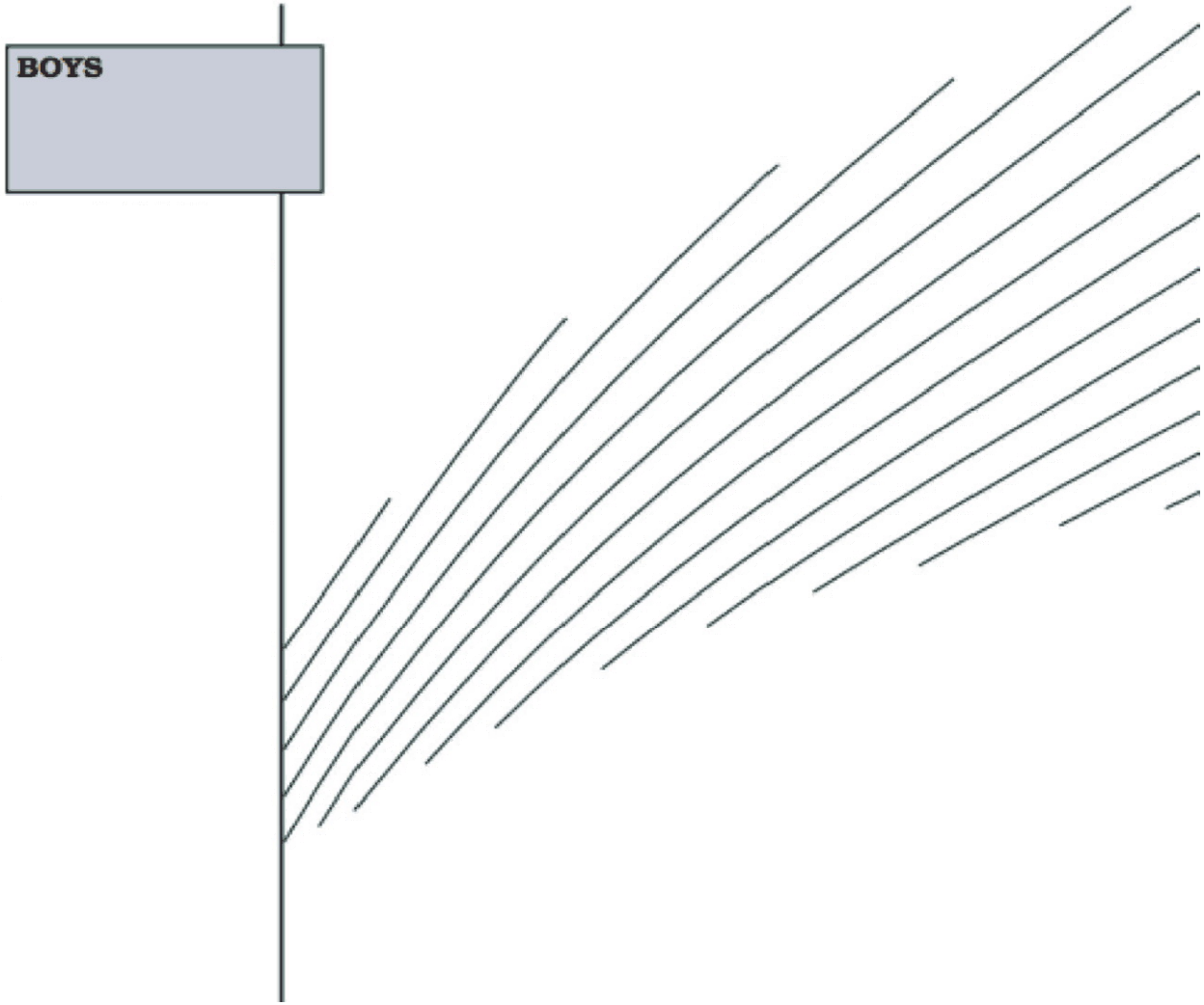
Weight gain below 5th centile

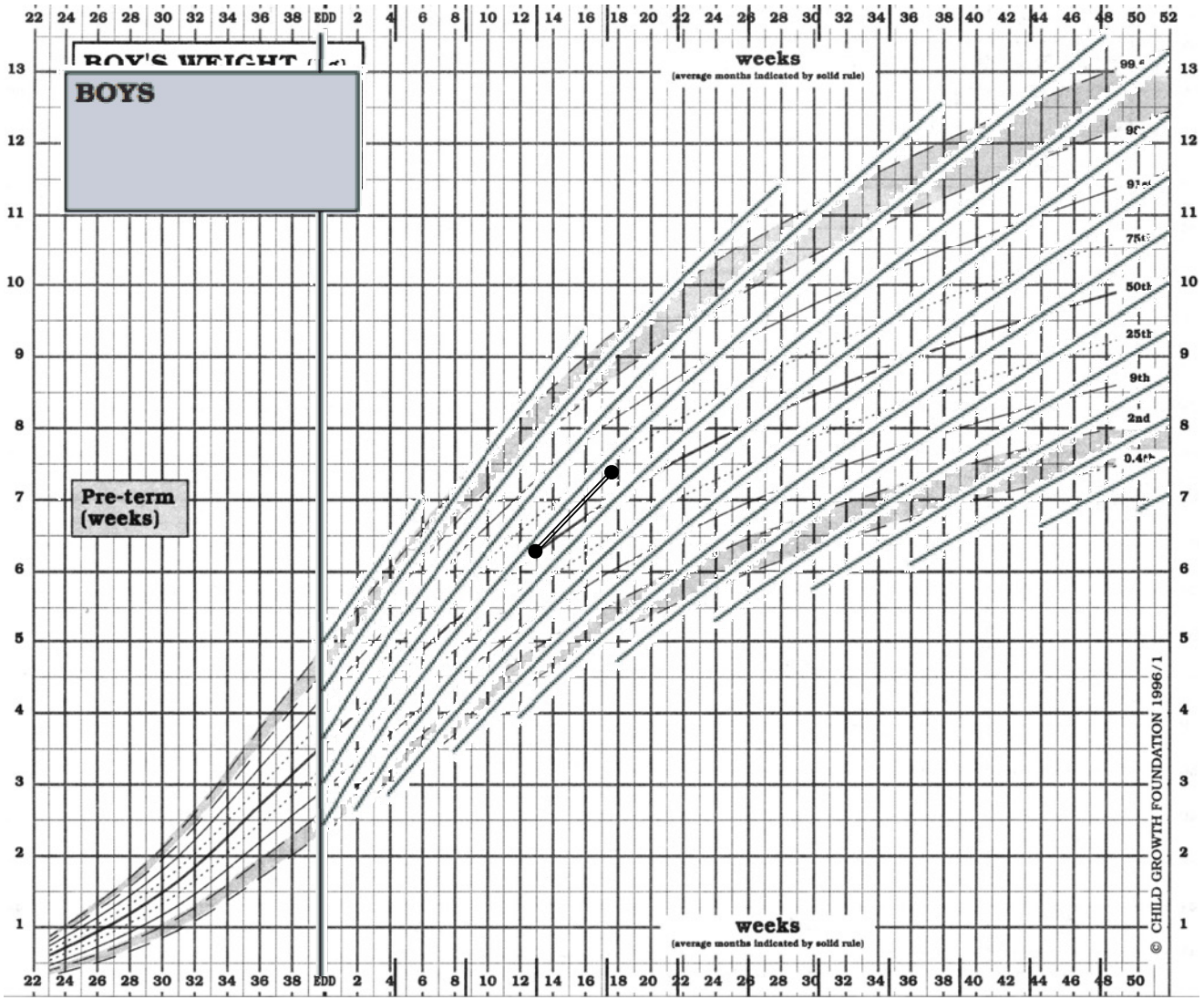


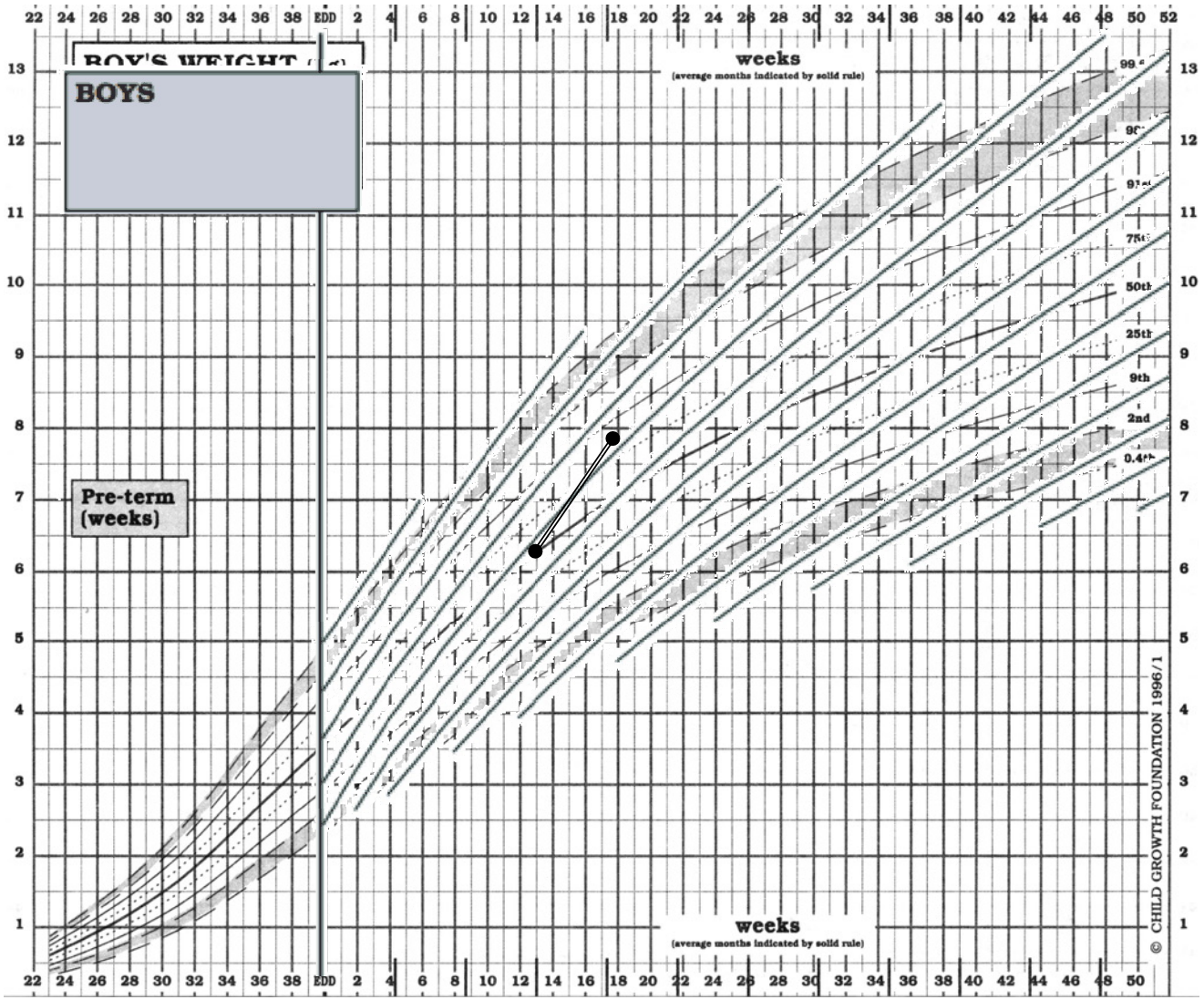
Thrive 95 lines

- Rapid infant weight gain also a concern
- Useful to identify rapid weight gain
- Hence “Thrive 95 lines”
- Define 95th centile for weight gain

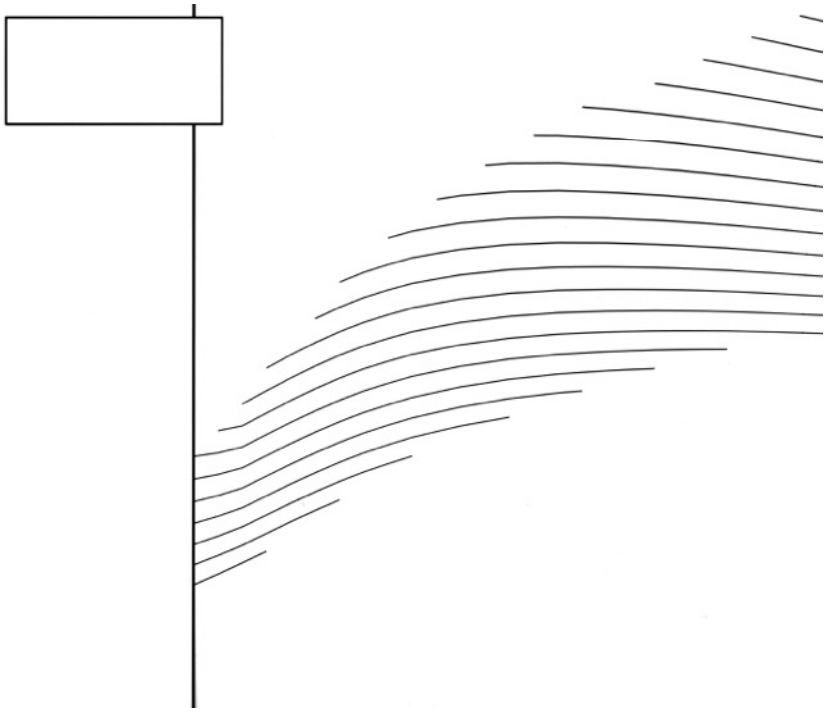
Thrive 95 lines



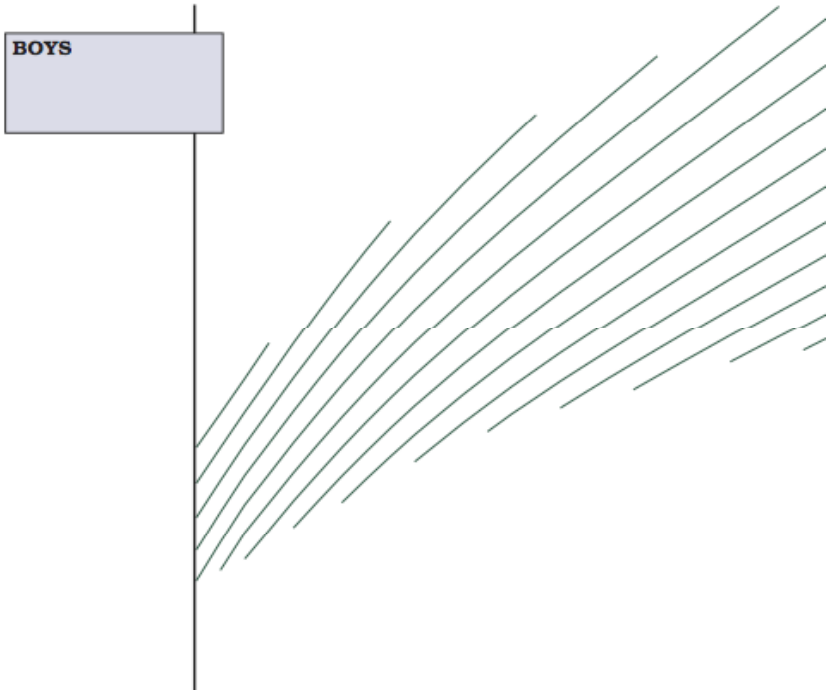

BOYS
Pre-term (weeks)
weeks
(average months indicated by solid rule)
99th
90th
75th
50th
25th
9th
2nd
0.4th
EDD
© CHILD GROWTH FOUNDATION 1996/1


BOYS
Pre-term (weeks)
weeks
(average months indicated by solid rule)
99th
90th
75th
50th
25th
9th
2nd
0.4th
EDD
© CHILD GROWTH FOUNDATION 1996/1

Thrive 5 and Thrive 95 lines



5th centile weight gain



95th centile weight gain

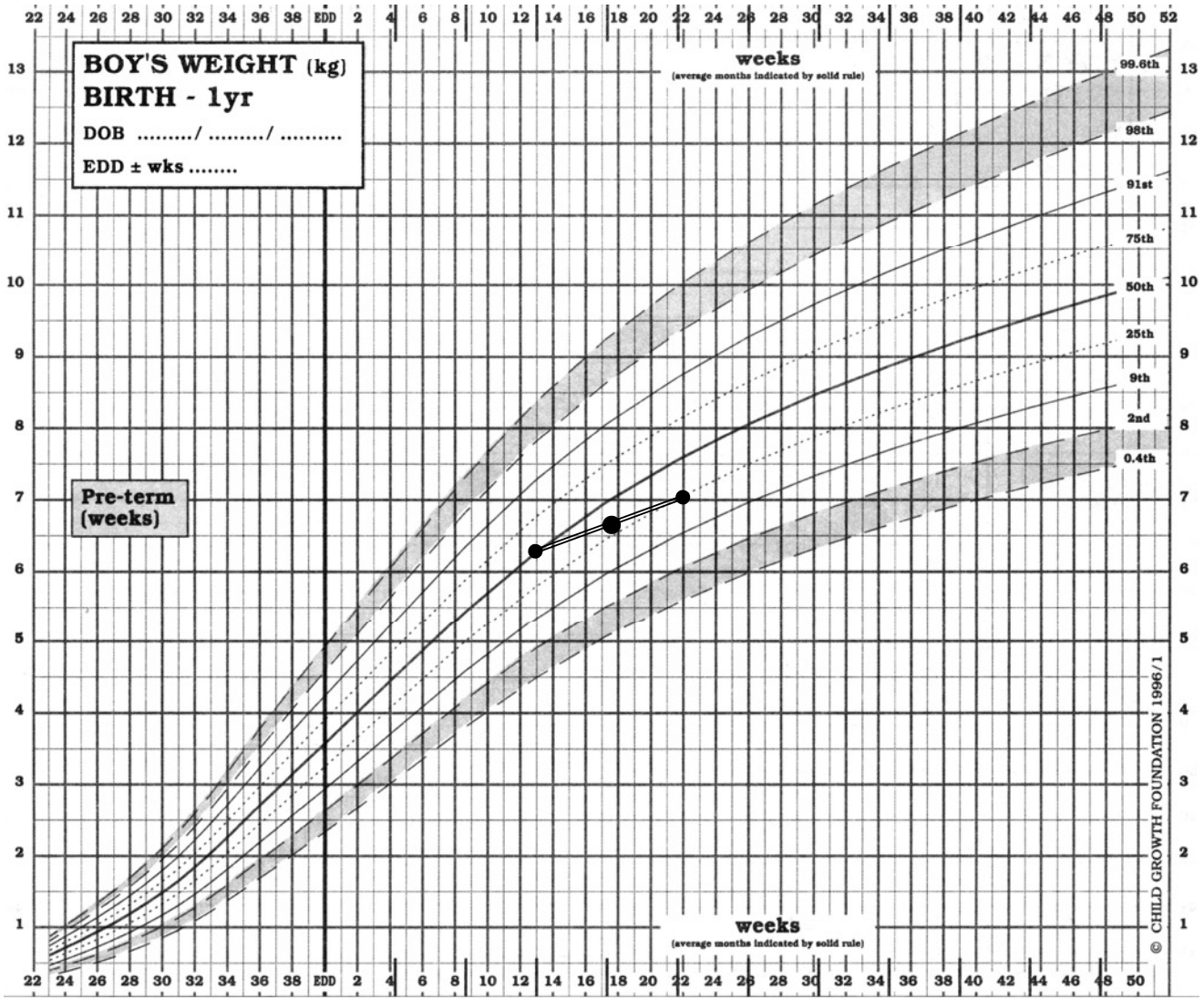
Benefit of thrive lines

- Plastic overlay designed to fit on British 1990 chart format
- Distance and velocity both assessed yet data plotted just once
  - No need for separate distance and velocity charts
- Useful addition to weight chart

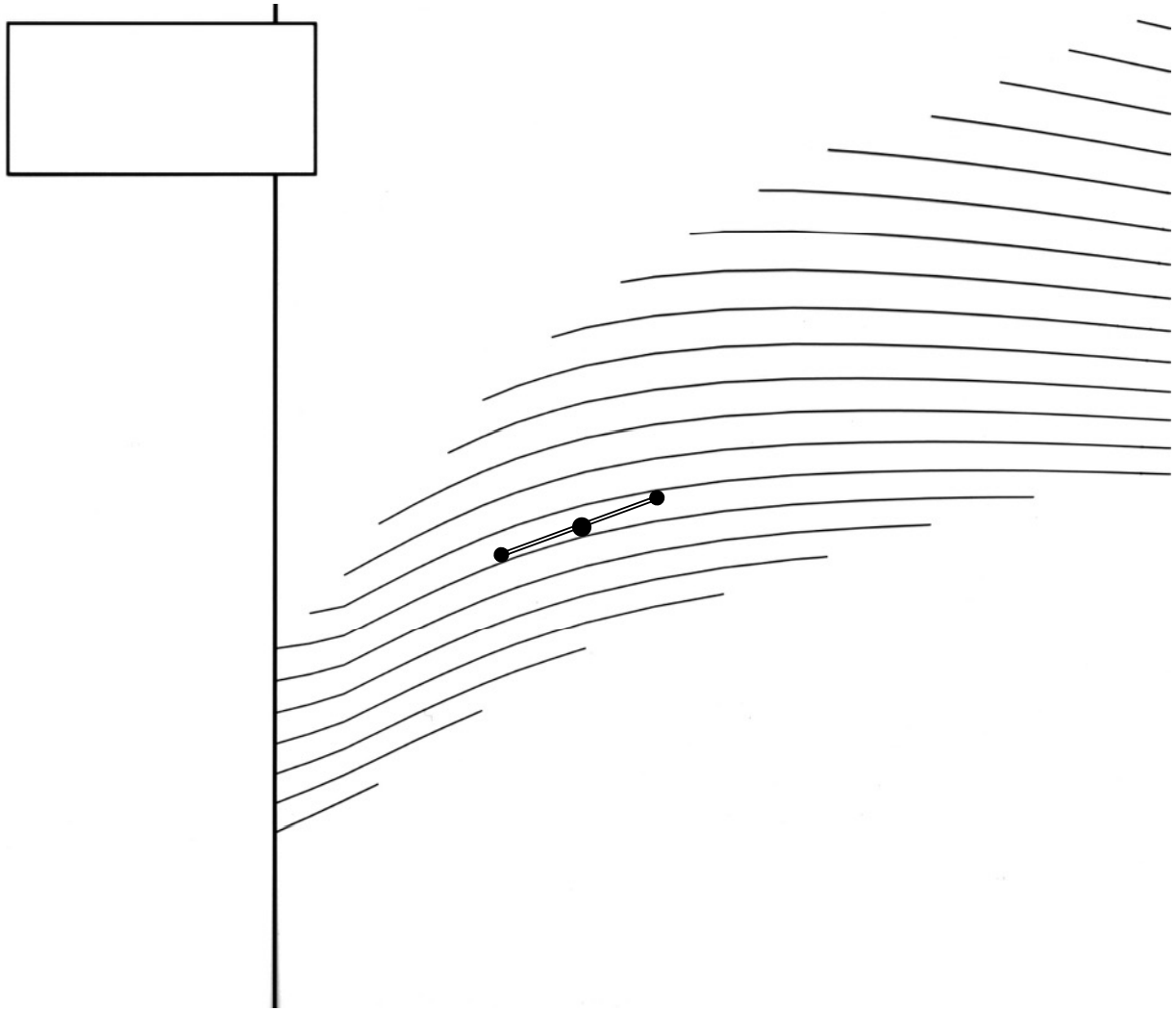
Thrive lines and electronic charts

- Now easy to add thrive lines to electronic charts
- Thrive lines can be drawn for any required velocity centile, e.g. 1st or 99th
- Switch between distance and velocity centiles

Distance centiles



Velocity centiles



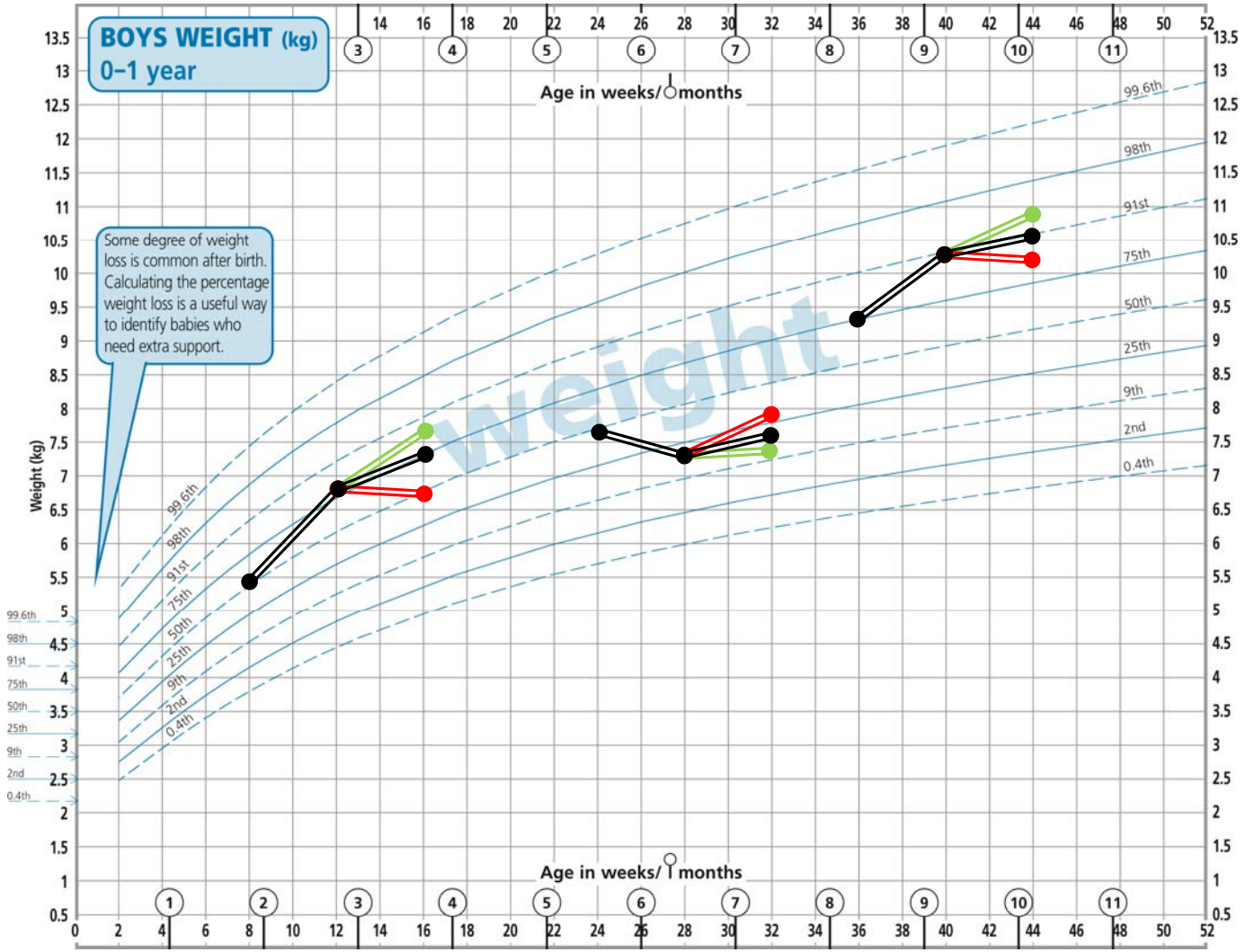
Growth acceleration

Three measurements

Question

- You observe an infant grow over 4 weeks
  - They show upward or downward centile crossing
- Ask yourself:
  - *“How will they grow over the next 4 weeks?”*
- Will they stay on the same centile?
- Will they continue to cross centiles the same way?
- Or will they cross centiles the other way?

Centile crossing over 4 weeks



Statistics of centile crossing and deviation

- As before, convert weights to z-scores
- The change in z-score over 4 weeks is *deviation*
  - e.g. from birth to 4 weeks: Deviation = $z_4 - z_0 = d_{04}$
- *Deviation* the same as *centile crossing*
- Research question: What is the correlation between successive deviations?
  - e.g. correlation between d_{04} and d_{48}

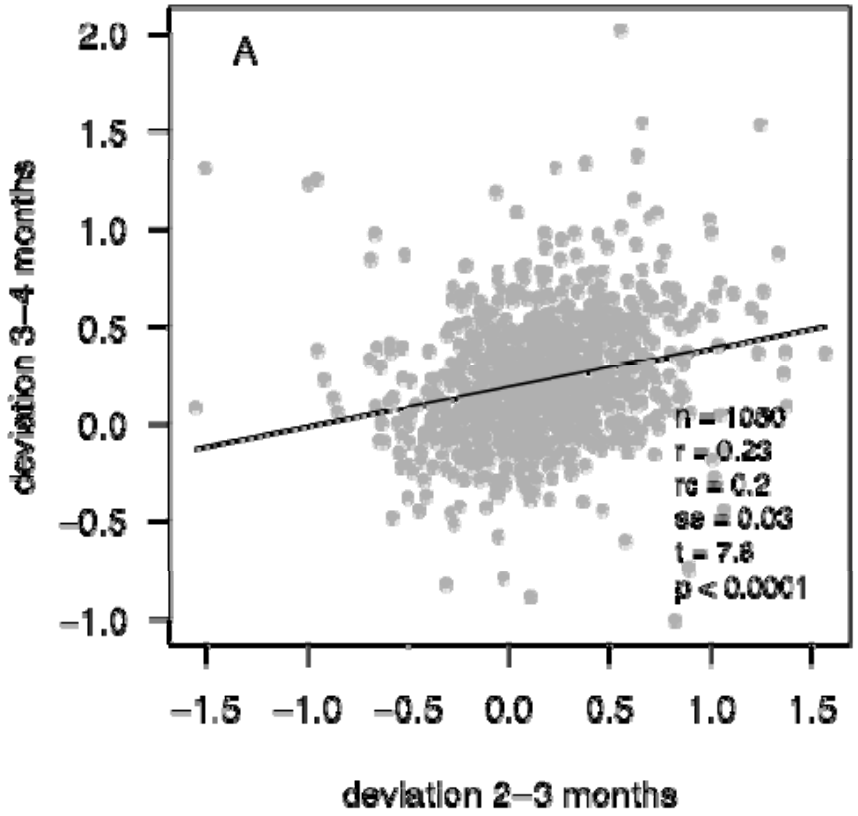
- Possible answers: zero, positive or negative

Two growth studies of Cambridge infants

- Widdowson Study (1959-65)
  - 1094 infants measured monthly from 0-12 months
  - Representative of Cambridge infants in ~1960
  - Weights obtained from child welfare clinics
- Cambridge Infant Growth Study (1984-87)
  - 255 infants measured every 4 weeks from 0-52 weeks
  - Families more selected and of higher social class
  - Infants weighed by experienced research nurse
- In brief, monthly weights in infancy

Correlation between successive deviations

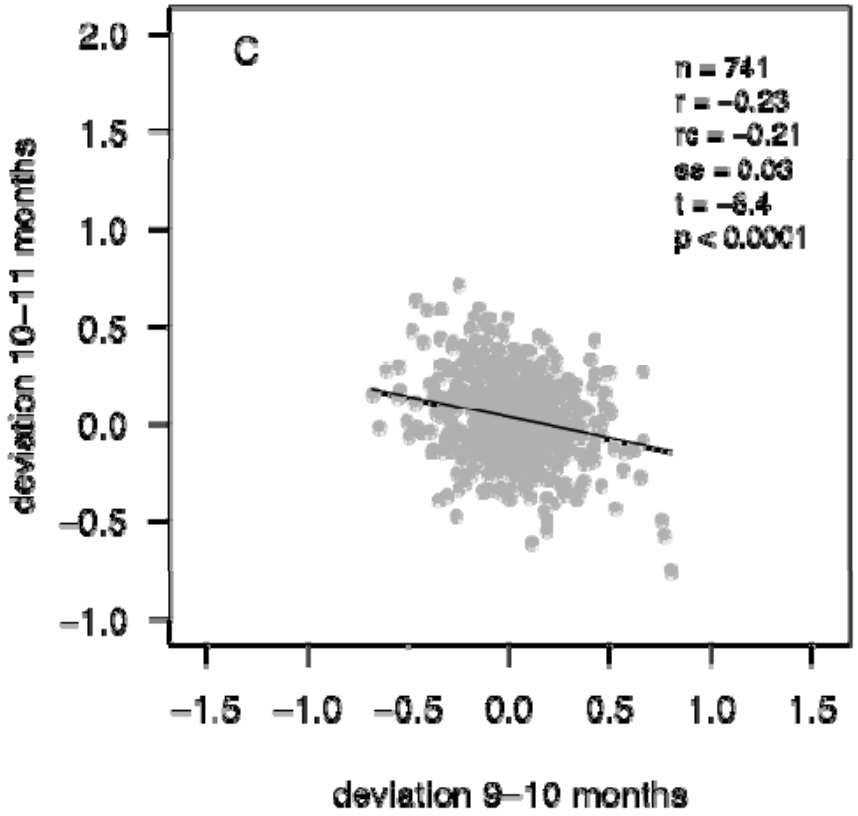
Widdowson Study



Age 3-4 months *positive correlation*

Correlation between successive deviations

Widdowson Study



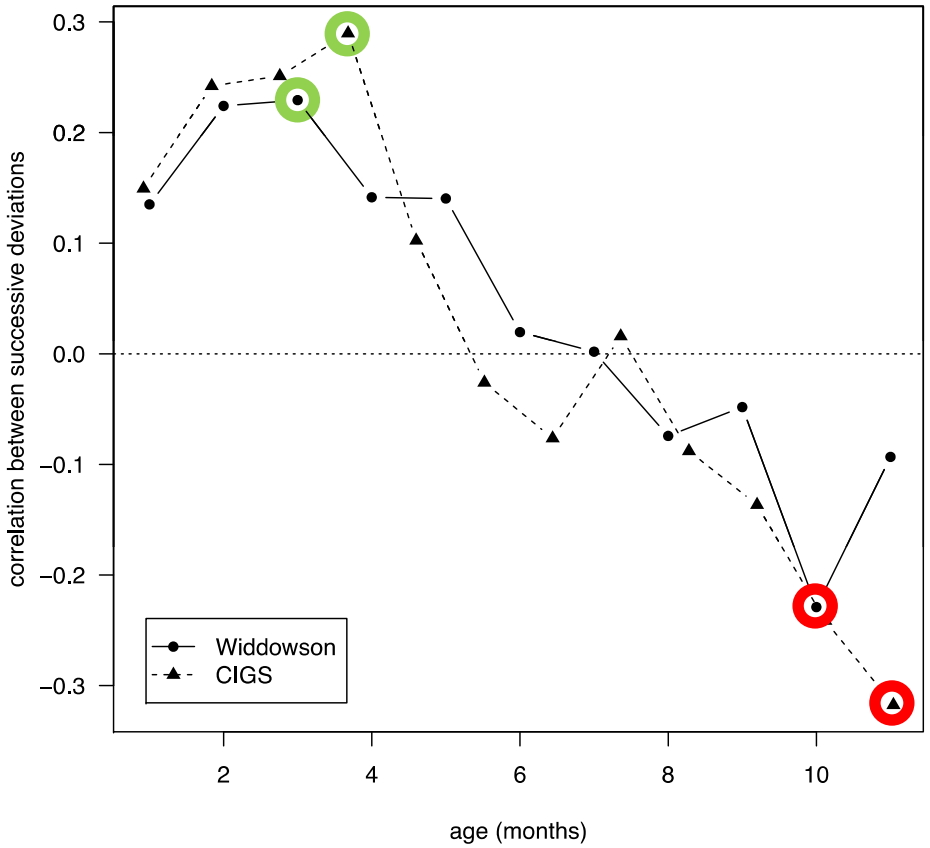
Age 10-11 months *negative correlation*

Surprise - deviations are correlated!

- At 3-4 months there is a positive correlation
  - Infants crossing centiles one month are likely to cross centiles in the *same* direction the next month
- At 10-11 months there is a negative correlation
  - Infants crossing centiles are likely to cross centiles in the *opposite* direction the next month

Cole TJ, Singhal A, Fewtrell MS, et al. Weight centile crossing in infancy: correlations between successive months show evidence of growth feedback and an infant-child growth transition. Am J Clin Nutr 2016;104:1101-9.

How does the correlation change with age?



Deviation and feedback

- Before 6 months infants crossing centiles tend to continue to cross centiles
- After 6 months they tend to cross back again
- Examples of feedback
  - Positive feedback before 6 months
  - Negative feedback after 6 months

Positive feedback

- Before 6 months, some young infants want to shift to a different centile
  - Mismatch between fetal growth and target size?
- So need to cross centiles in same direction for a time
  - But eventually reach their target
- Example of positive feedback

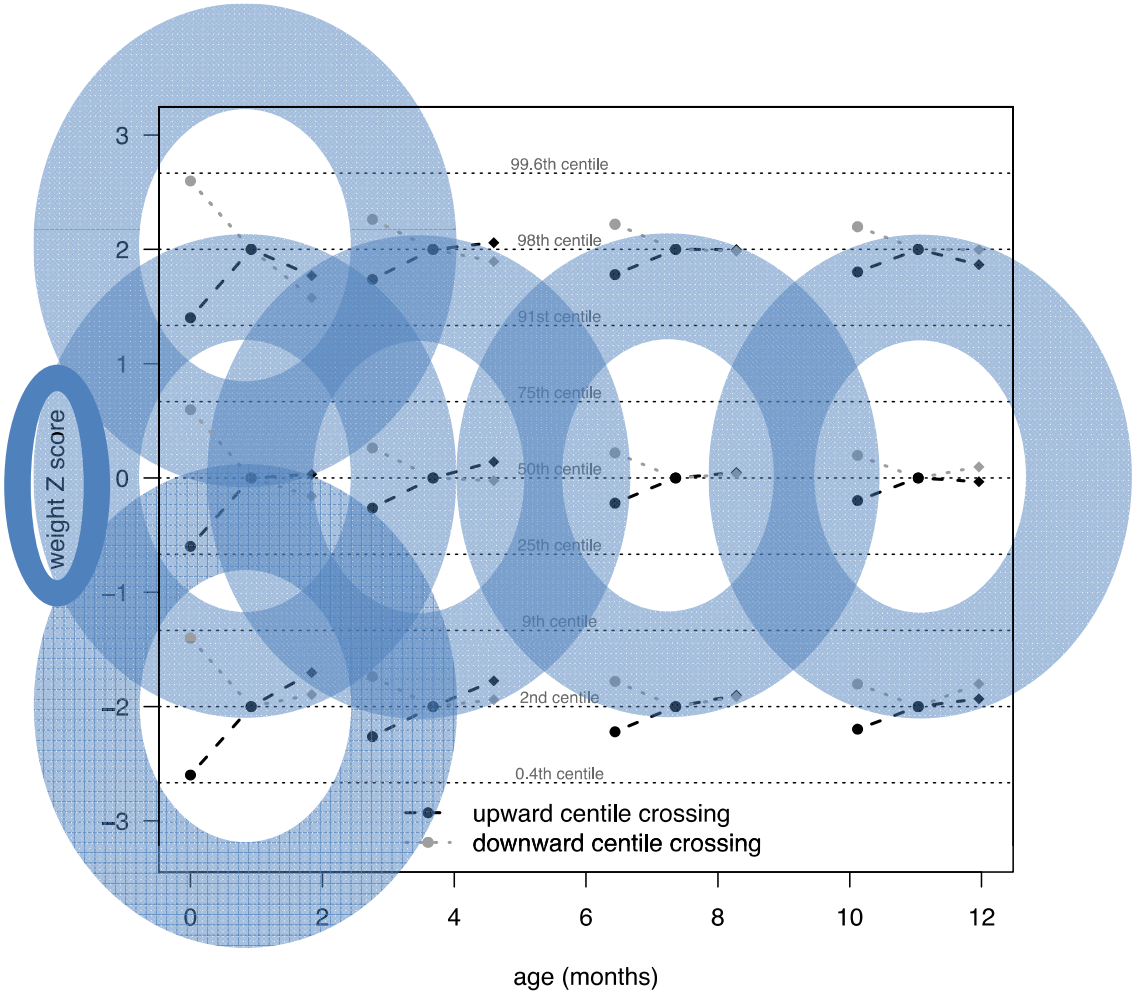
Negative feedback

- Older infants depart from growth trajectory due to some exposure
  - e.g. infection leads to downward centile crossing
- Response is to compensate the following month
  - e.g. catch-up following infection
- Example of negative feedback

Implications for chart assessment

- Centile crossing predicts centile crossing
  - But depends on age
- Early centile crossing (before 6 months)
  - Expect more centile crossing
- Late centile crossing (after 6 months)
  - Expect reverse centile crossing
- Mid-age centile crossing
  - Expect centile tracking
- Easiest to see on weight z-score scale

Growth velocity and growth assessment



Growth acceleration and feedback

- Assessment of acceleration a novel idea
- Highlights change from positive to negative feedback
- Reflects how and why centile crossing becomes less common with increasing age in infancy

Growth pattern

Many measurements

Variation in growth pattern

- Interesting to look at individual growth curves
  - To see how they differ, and how they are the same
- Here are a sample of growth curves from the Cambridge Infant Growth Study

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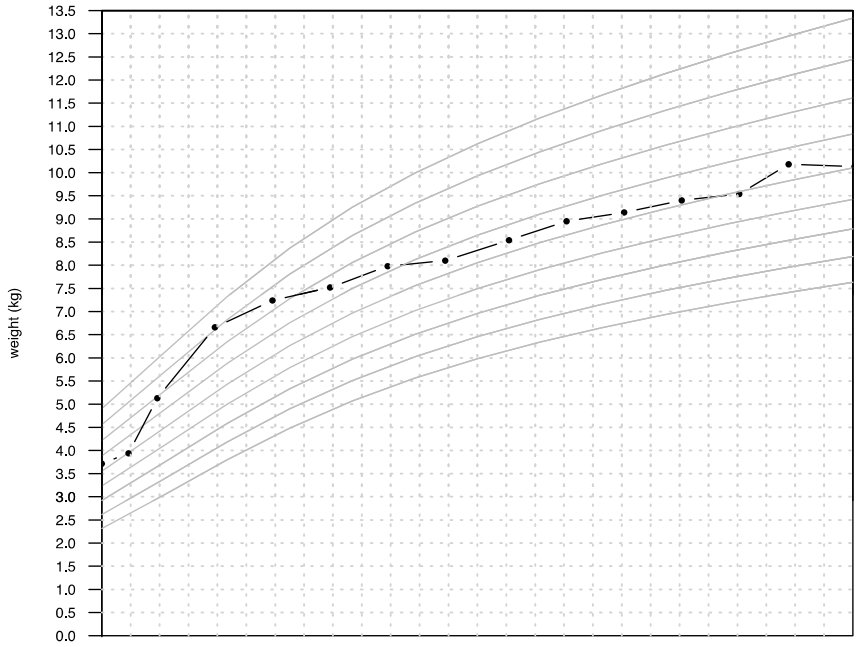
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7.5
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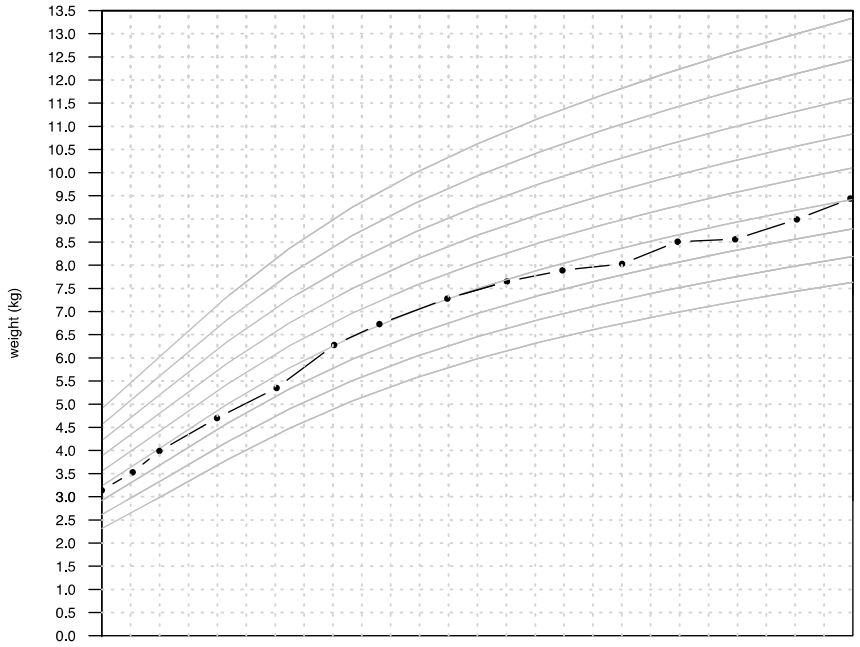
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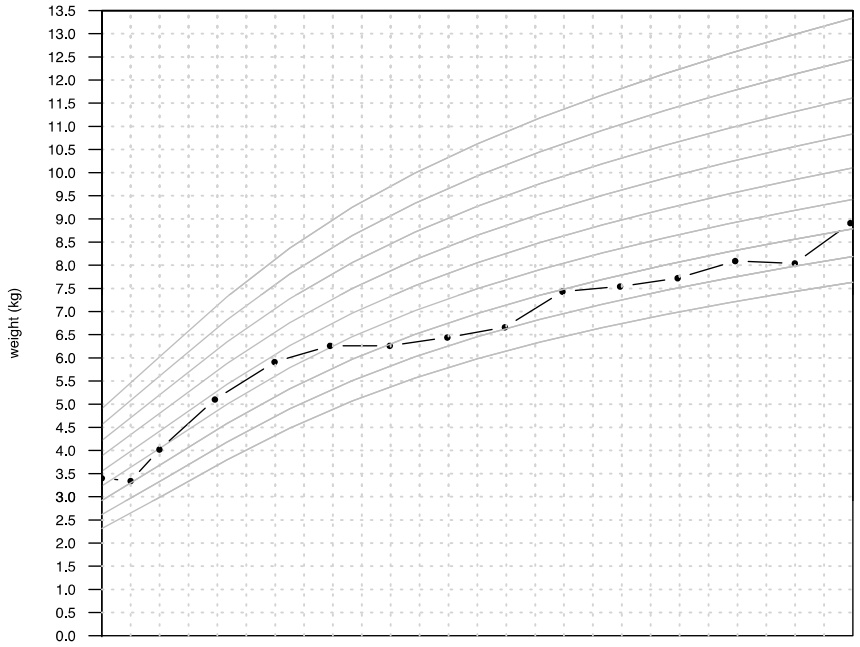
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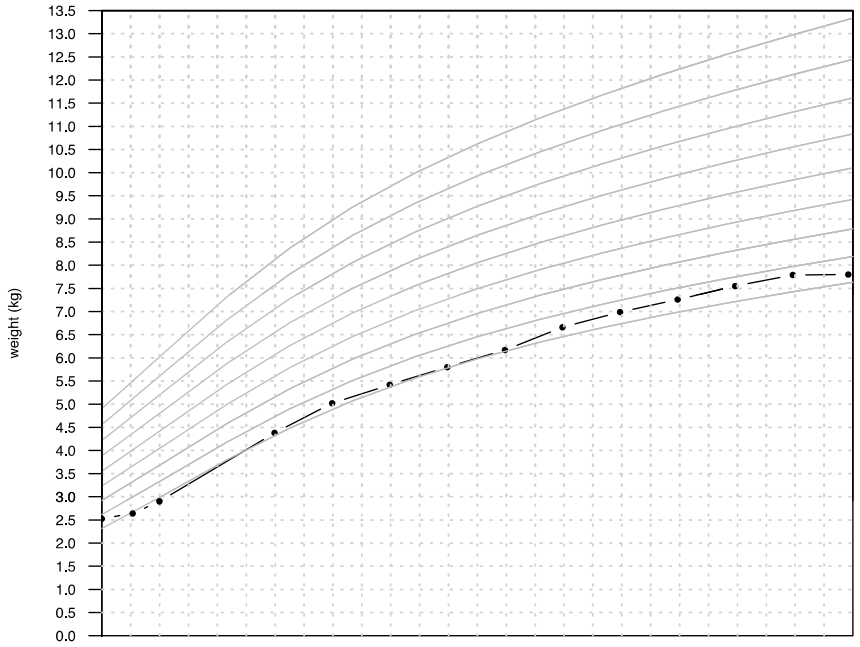
weight (kg)
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11.5
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10.5
10.0
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
3.0
2.5
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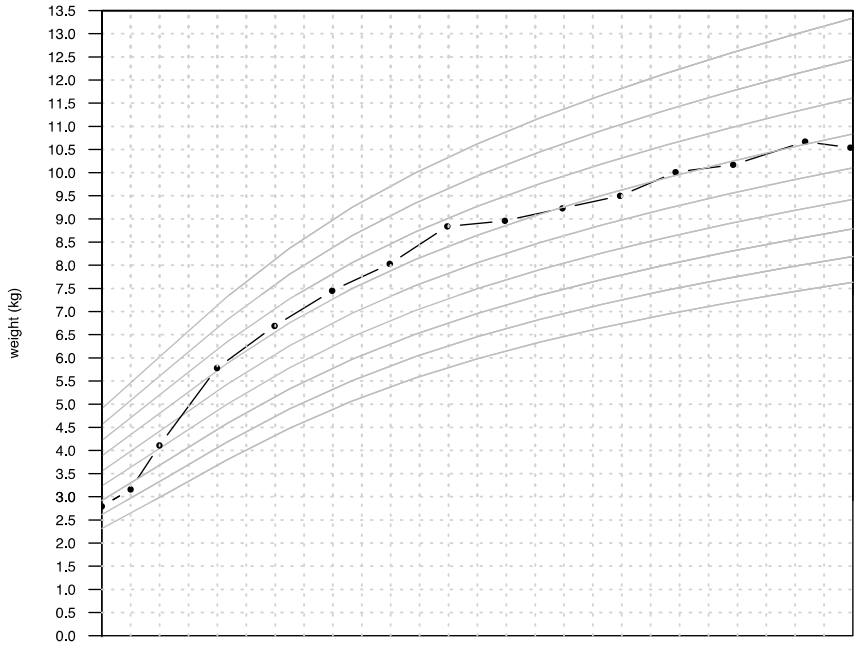
0.5
0.0

ID 1061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12.5
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11.5
11.0
10.5
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9.0
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8.0
7.5
7.0
6.5
6.0
5.5
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3.0
2.5
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1.5
1.0
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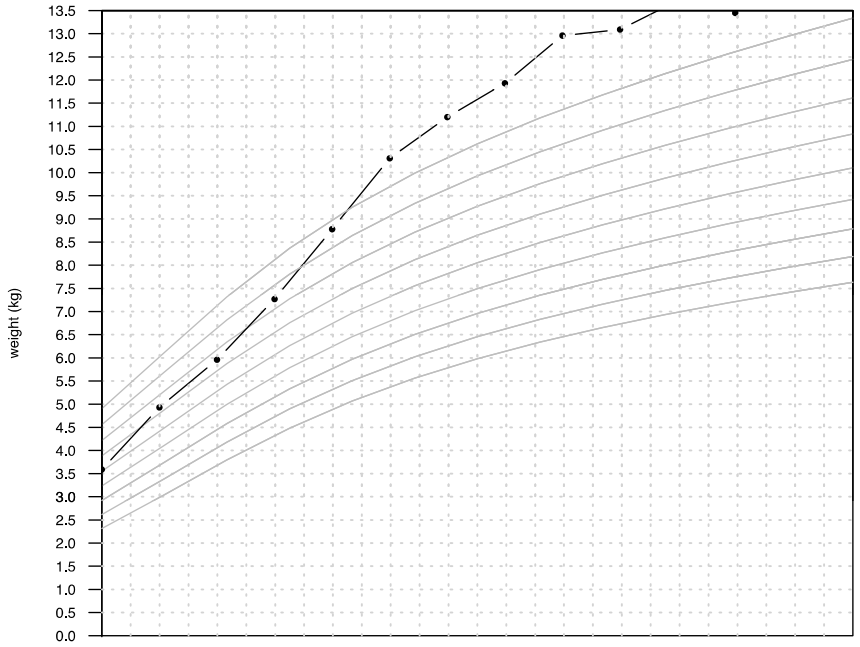
ID 1102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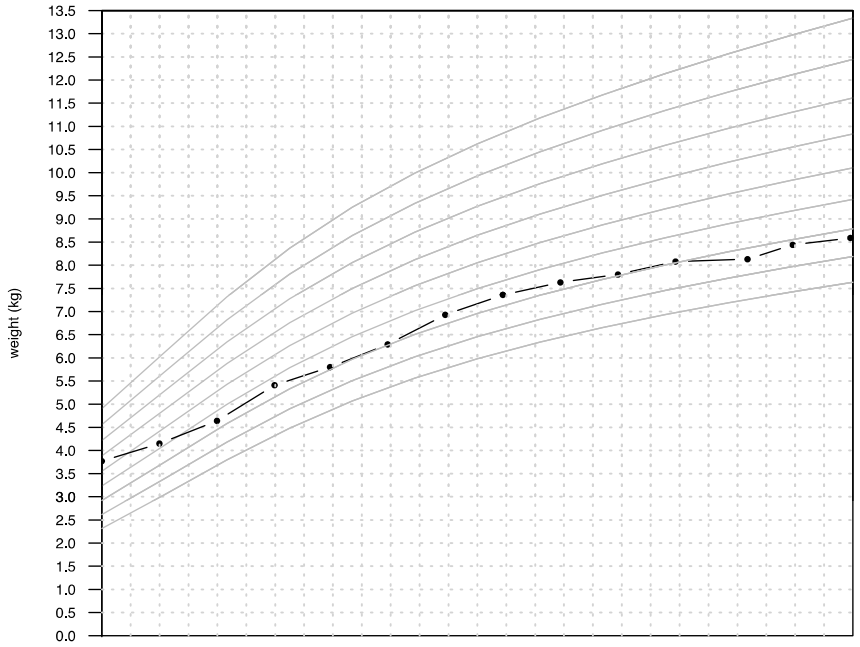
ID 1130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6.5
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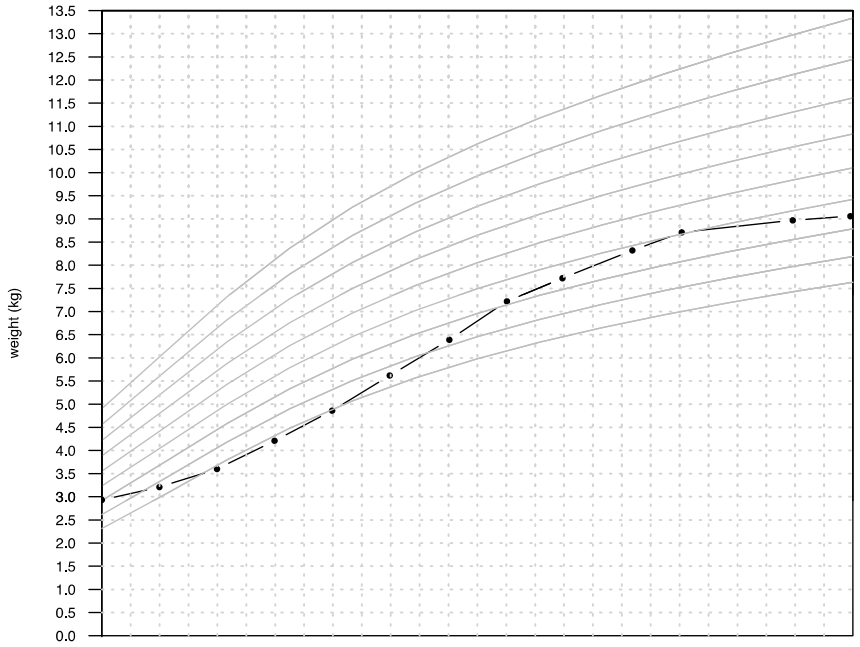
ID 1229


weight (kg)
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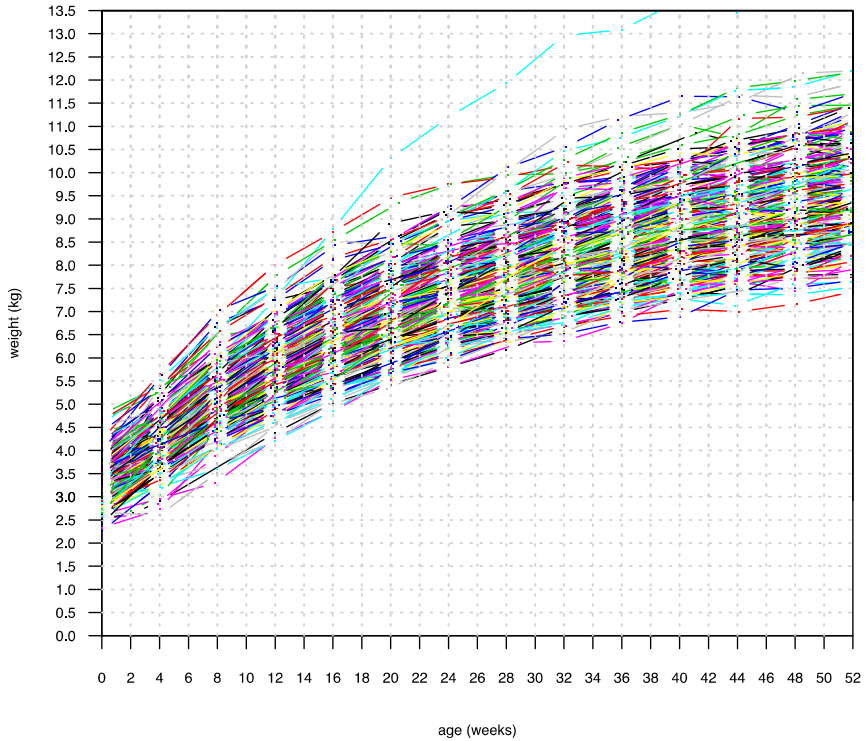
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

Summarising growth pattern

- Curves largely the same shape
  - But differing in position
    - Some high, some low
    - Some steep, some shallow
- SITAR is a growth curve model
- that adjusts each curve for being
  - high/low (size) 
  - early/late (timing) 
  - steep/shallow (intensity) 

All growth curves, colour-coded

measured every 4 weeks

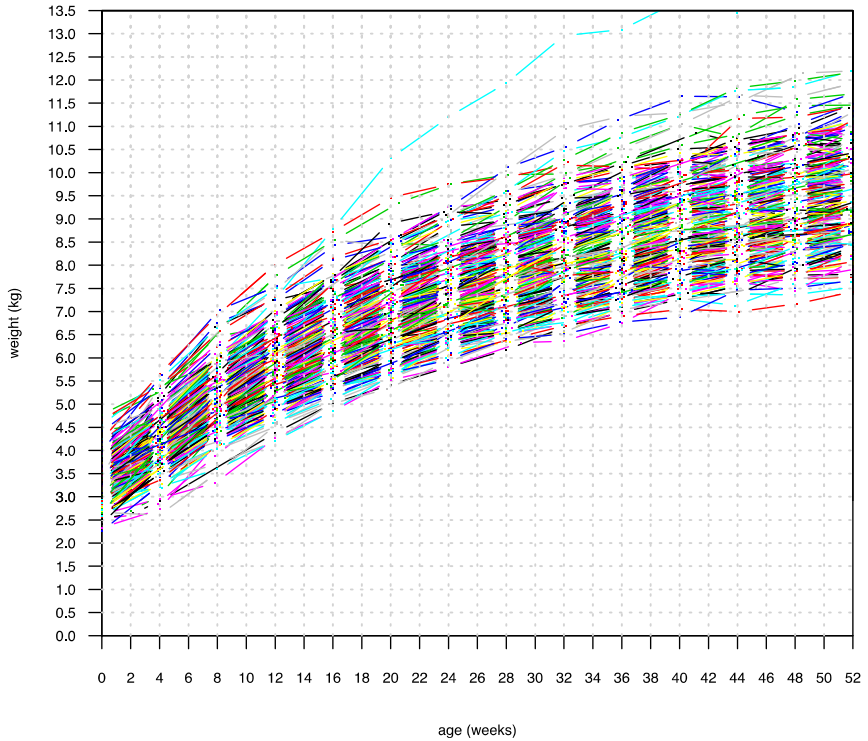


SITAR

- SITAR adjustment makes all curves like the mean curve
  - High curves shifted down, low curves up (size)
  - Steep curves made shallower, shallow steeper (intensity)
  - Early curves shifted later, late curves earlier (timing)
    - Size, timing and intensity estimated as random effects
- Net effect is to *superimpose* curves
- Then fit mean curve through superimposed curves

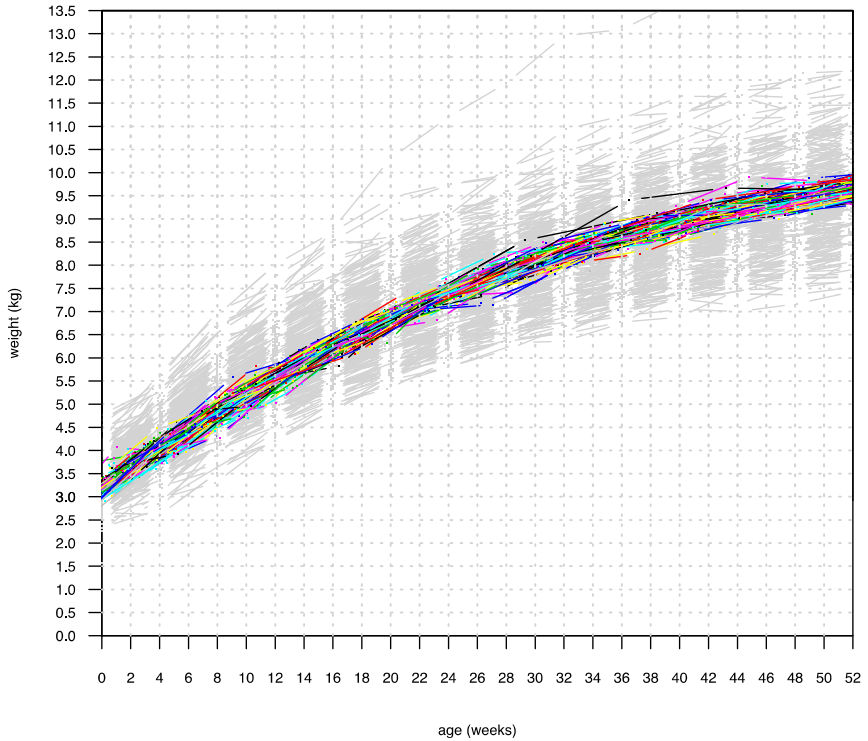
All growth curves, colour-coded

measured every 4 weeks



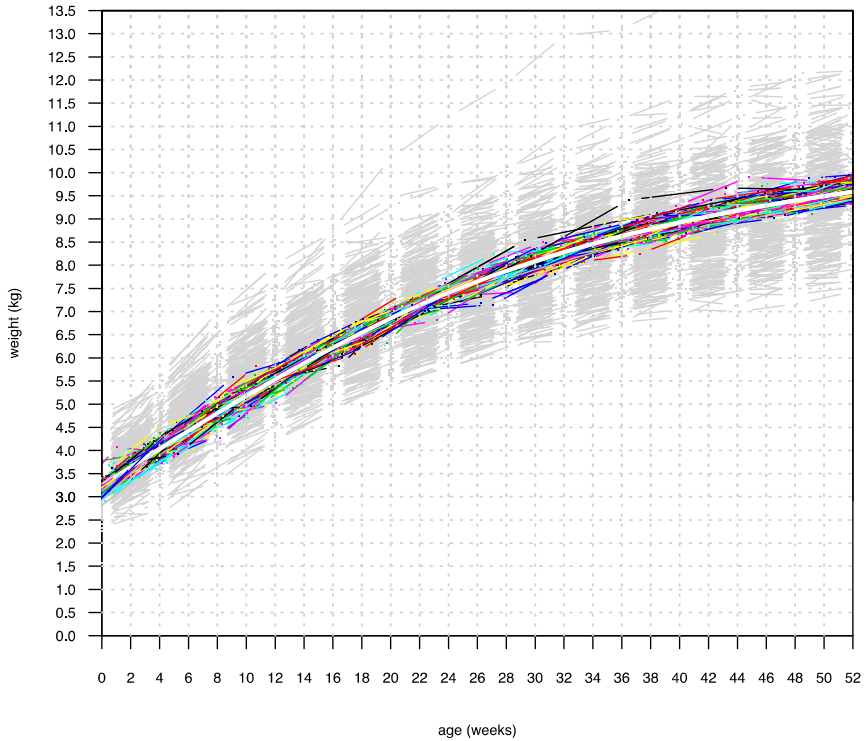
All growth curves, colour-coded

after SITAR adjustment

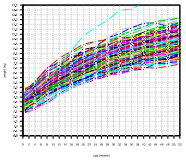
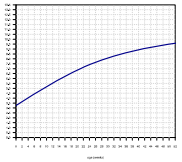
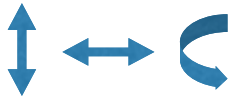


All growth curves, colour-coded

with SITAR mean curve



SITAR growth patterns

- SITAR converts growth curves: 
  - to a mean curve: 
  - and a growth pattern for each individual: 
    - size, timing, intensity
- Summary like growth distance or growth velocity

SITAR - a useful instrument for growth curve analysis.
Cole TJ, Donaldson MD, Ben-Shlomo Y. Int J Epidemiol 2010;39:1558-66.

SITAR growth patterns

- SITAR explains over 95% of variance
  - Very good fit
  - So random effects define individual growth pattern
  - Can be used as individual growth summary
    - To relate to earlier exposures or later life course
- BUT note that SITAR not useful clinically
  - It needs whole growth curve
  - Comes too late to make clinical decisions

Conclusions

- Growth summary for one, two, three and many measurements
  - Distance, velocity, acceleration and pattern
- Useful to assess growth in individuals
  - Improving decision making
- Shows how statistics can help in the assessment of growth