

Revisiting Rapid Infant Growth: Assessing Growth in Children Under Age 2

Key Evidence Gaps and Research Questions Around Defining and Measuring Rapid Infant Growth

Tim Cole, CBE FMedSci

University College London, Great Ormond Street Institute of Child Health, London, UK

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Background

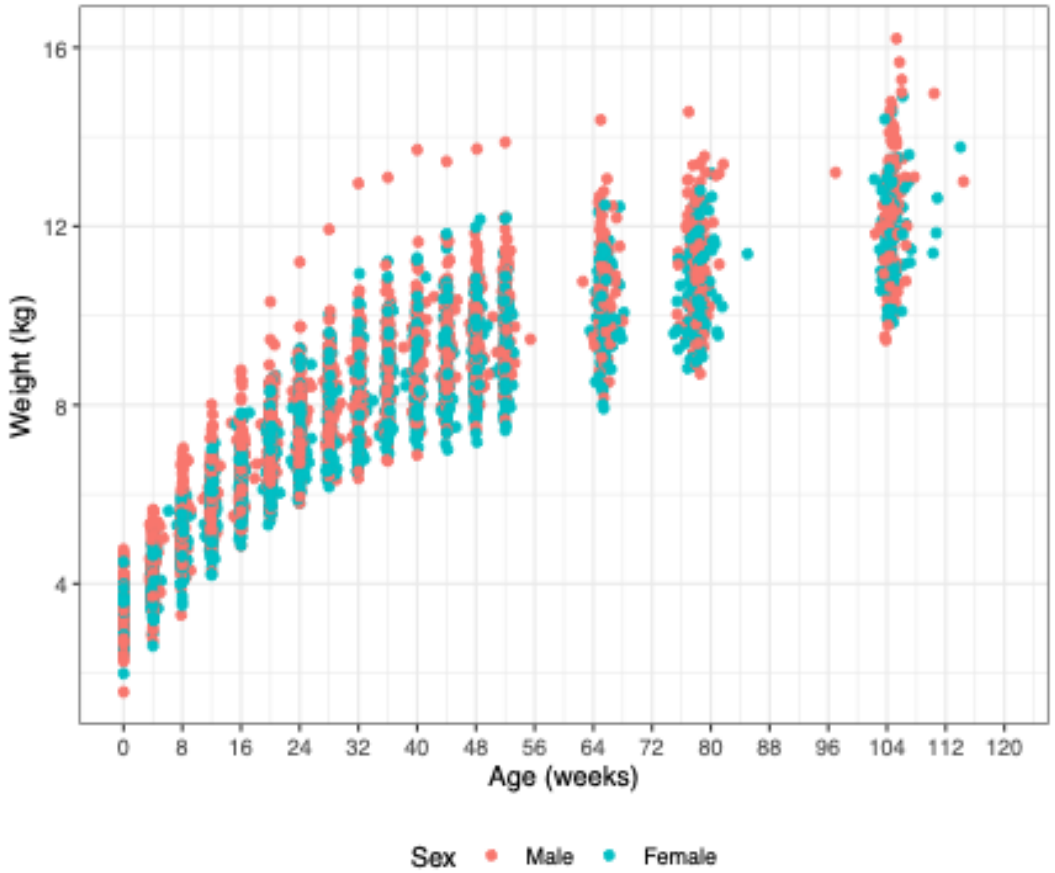
- Growth charts express weight as centile or z-score
- Essential tool for growth assessment
- Weight gain also important, where centile charts not useful
  - They assess *size* not *growth*
- Need to develop effective statistical tools to assess weight gain

Cambridge Infant Growth Study (CIGS)

- Example dataset
- 255 healthy infants from Cambridge UK recruited during 1984-87
- Seen 17 times, every 4 weeks from birth to 52 weeks then 15, 18 and 24 months
- Weight measured by experienced auxologist
- Few missing data
- Ideal dataset for exploring weight and weight change in early life

CIGS weight data

- 4181 weights
- Four-weekly to 52 weeks
- 137 boys, 118 girls
- Boys heavier than girls
- One boy gaining weight rapidly

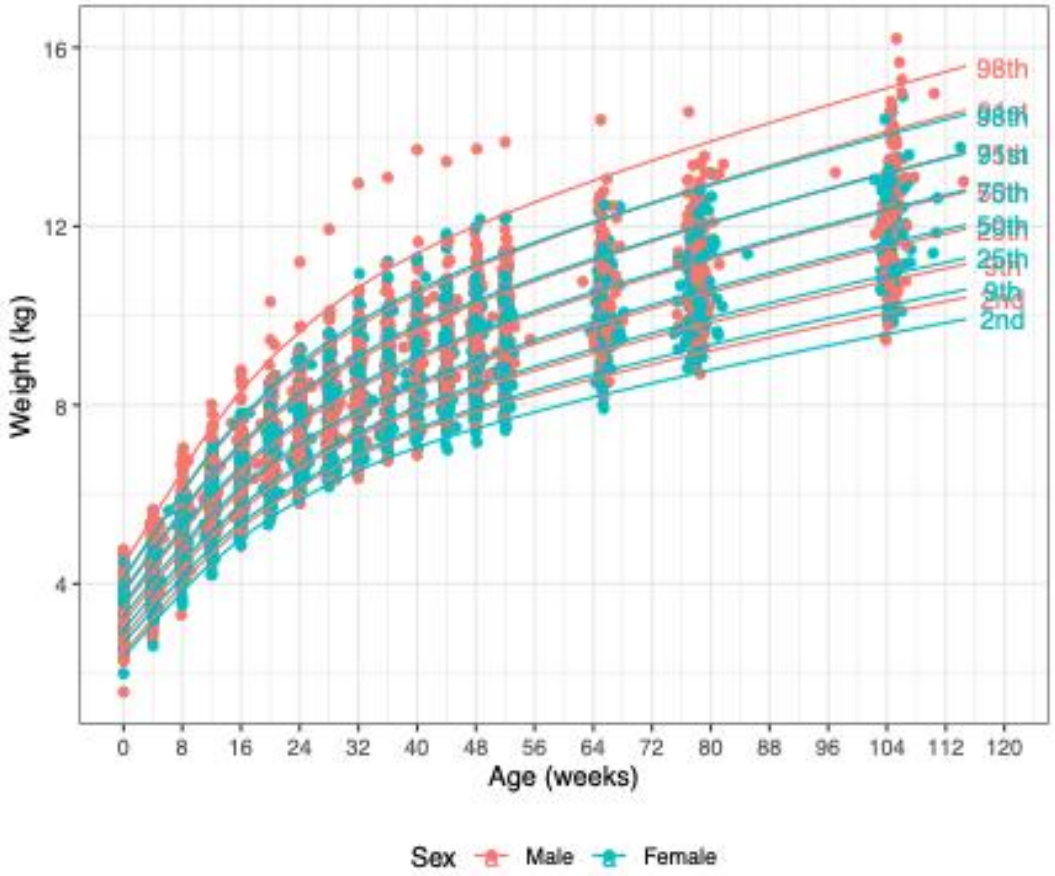


Add internal centiles

- Centiles fitted by LMS method using GAMLSS
  - Adjusted for skewness
- Seven centiles equally spaced on z-score scale, two-thirds (0.67) units apart

centile	2nd	9th	25th	50th	75th	91st	98th
z-score	-2	-4/3	-2/3	0	2/3	4/3	2

- Boys heavier than girls by one centile space



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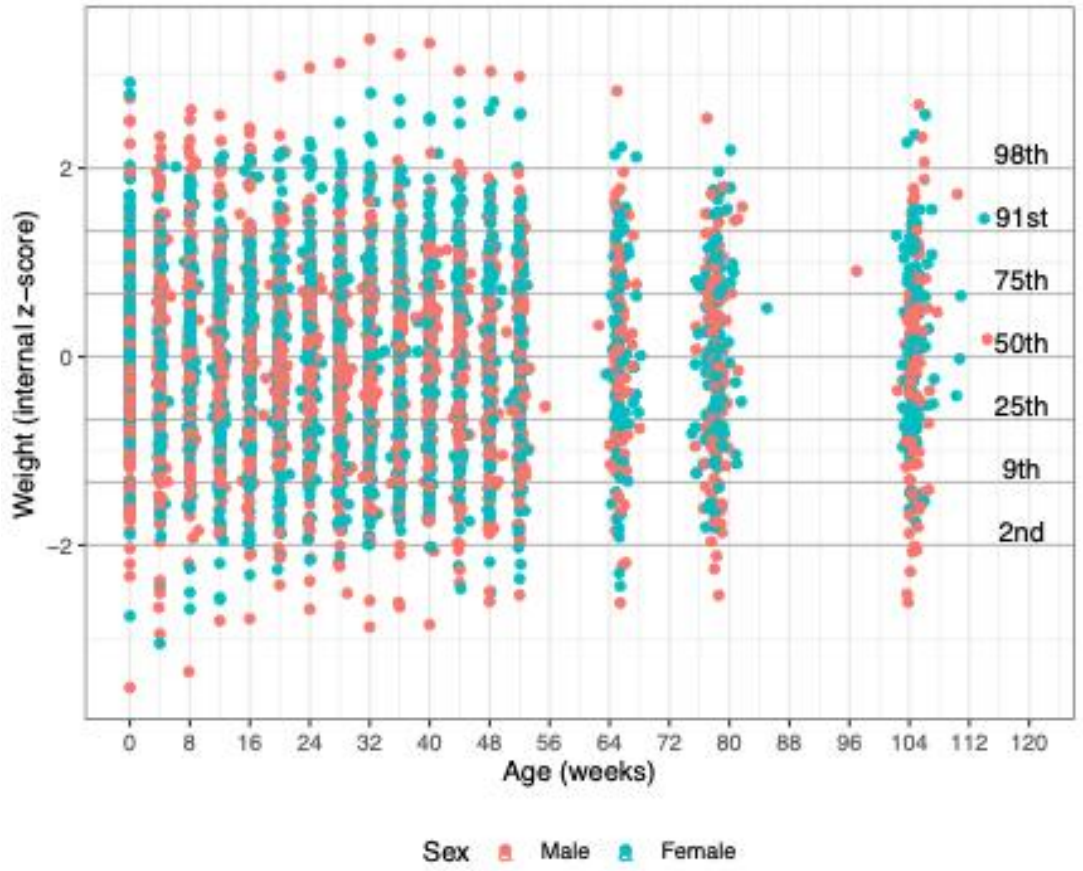
Weight z-score

- Weight z-score (Normal)
  - $Z = \frac{Weight - Mean}{SD}$

- Weight z-score (LMS)
  - $Z = \frac{\left({Weight}/{M}\right)^{L} - 1}{L\,S}$

Weight data plotted as z-scores

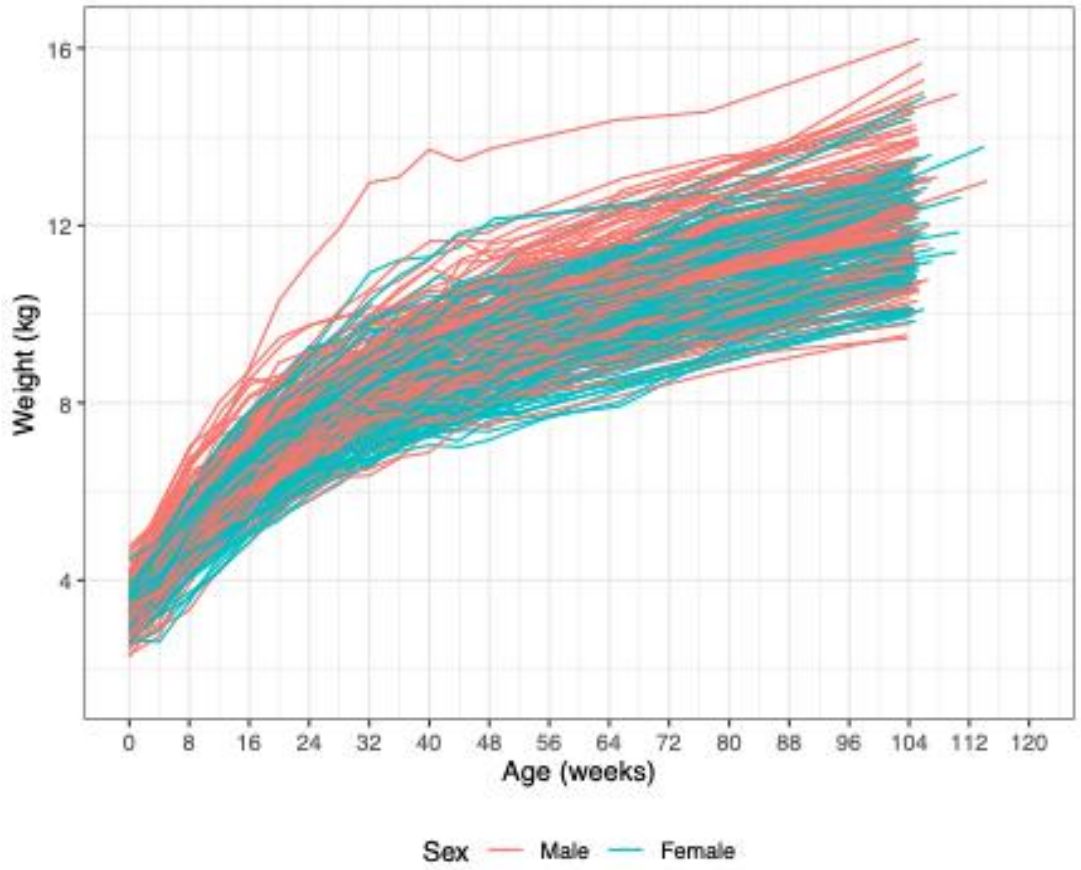
- Weight as internal z-scores
  - Mean = 0, SD = 1, no skewness
- Centiles 0.67 z-scores apart
  - Straight lines on z-score scale
- Normal growth ~ straight line



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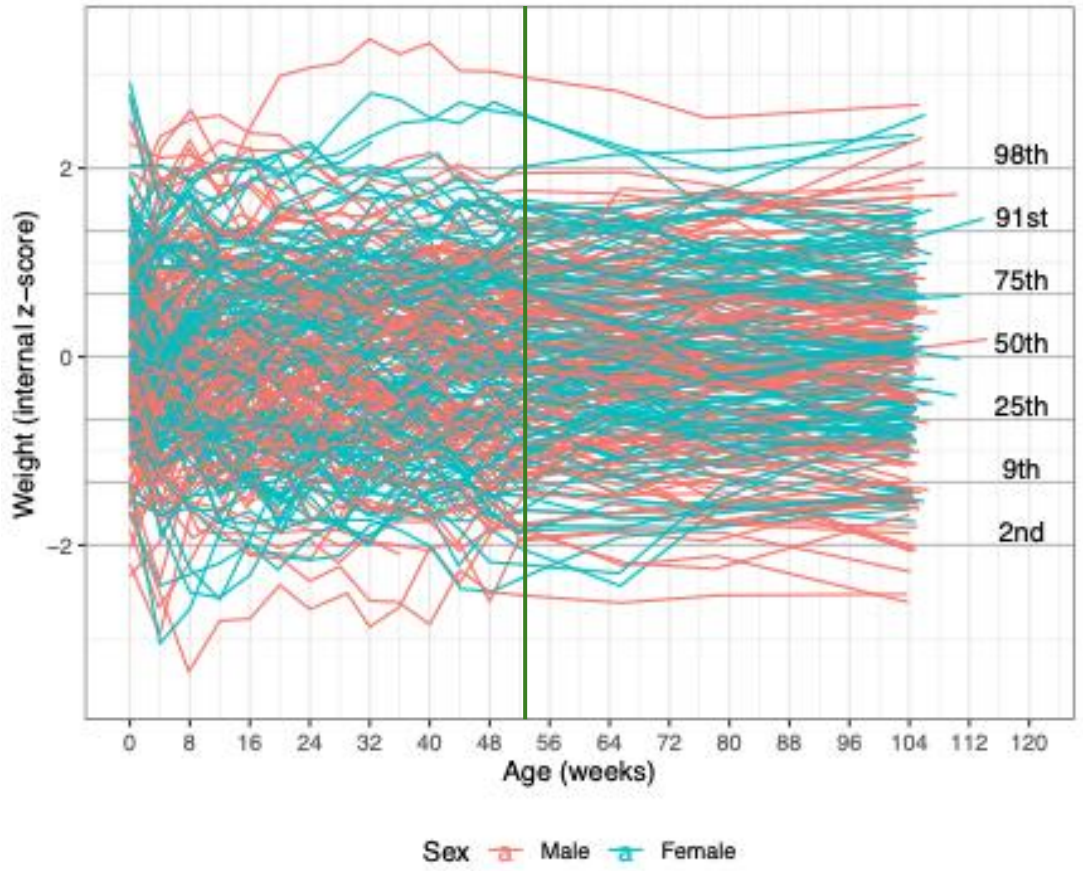
CIGS weight growth curves

- Different way to view same data
- Focuses on individual growth
  - Not population size
- Velocity is rate of weight gain
  - i.e. slope of curve
- Some centile crossing, but centile curves unhelpful for interpretation
- Easier to see on z-score scale



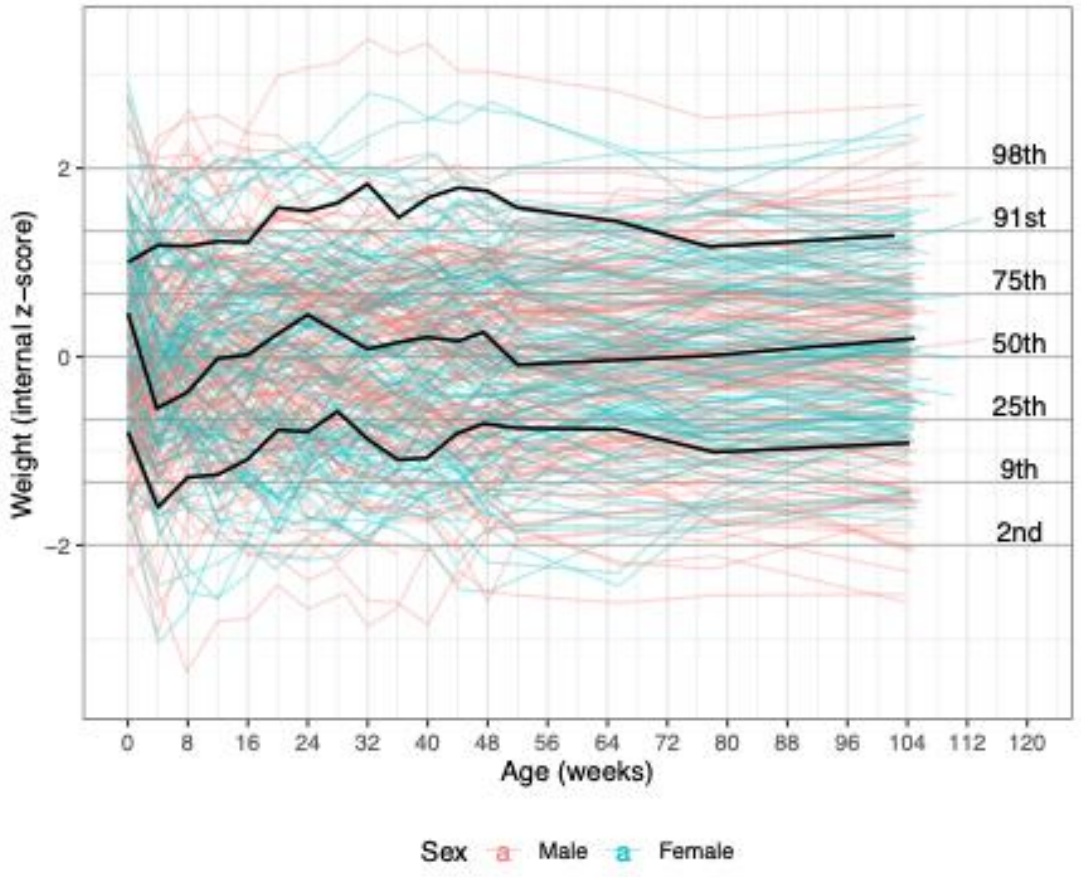
CIGS weight curves on z-score scale

- Powerful plot
- No sex differences
- Clearly shows centile crossing
- Concentrated in first year
- But how to interpret centile crossing?



CIGS weight curves on z-score scale

- Powerful plot
- No sex differences
- Clearly shows centile crossing
- Concentrated in first year
- But how to interpret centile crossing?
  - 3 examples of upward centile crossing
  - Does the degree of centile crossing raise concern?
  - What is velocity z-score?
- Centiles do not help with interpretation



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Important message

- Growth centile charts useful for assessing weight as *size*
- Not good for assessing weight as *growth* i.e. centile crossing
- Ironic that growth charts do not assess growth
- Need to assess weight growth—centile crossing, velocity, gain—in a different way
- Looking on the web gives only qualitative advice:
  - "Red flags: Watch for crossing up two or more major centile lines, or rising above the 91st to 99th centile."
- Need for quantitative methods of assessment

Quantitative methods to assess weight gain

- Three methods to consider:
  - WHO growth velocity standards (WHO 2009)
  - Rapid weight gain (Ong et al 2000)
  - Generalised conditional gain (Cole 1998)

WHO weight velocity standard (2009)

- Constructed by LMS method and GAMLSS
  - Adjusting for negative weight increments
- Variability of velocity depends on time interval as well as age
  - Velocity calculated over time intervals: of 1, 2, 3, 4 and 6 months
- Time interval needs to be tightly controlled
  - Within ±6 days for age 0-6 months
  - Within ±8 days for age 6-12 months
  - Within ±10 days for age 12-24 months

months	1	2	3	4	6
days	28	61	91	122	183

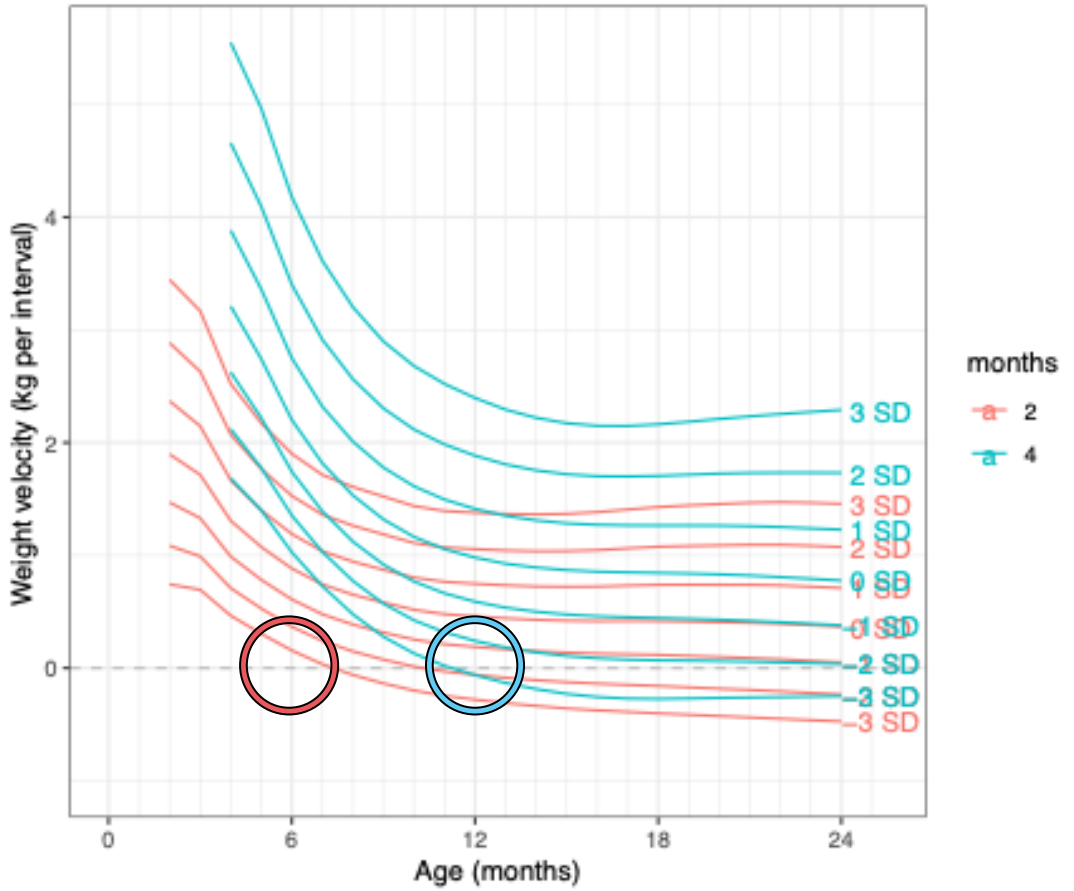
- Pro: velocity can be expressed as centile or z-score
- Con: inadmissible if time interval too long or too short
  - Major limitation
- Complicated process – not widely used
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WHO Child Growth Standards: Growth velocity based on weight, length and head circumference: methods and development. Geneva: WHO; 2009.

WHO weight velocity standard

- WHO girls weight velocity centiles for 2- and 4-month intervals
- Highlights complexity of velocity centiles
  - Depending on both age and interval
- Weight loss over 2 months very rare under age 6 months
  - And rare over 4 months under age 1 year



WHO Child Growth Standards: Growth velocity based on weight, length and head circumference: methods and development. Geneva: WHO; 2009.

"Rapid weight gain"

- Defined as weight z-score increasing by 0.67 or more over time
  - First proposed by Ong et al (2000)
- Now widely used, though crude binary index
- Also often unspecified:
  - First age of measurement
  - Second age of measurement
  - Starting weight
- So interpretation not straightforward
  - Poorly correlated with weight velocity centile

Ong KKL, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. BMJ 2000;320:967-71.

Generalised conditional gain (Cole 1998) – back to basics

- Velocity: $Vel = \left(\frac{w_2 - w_1}{t_2 - t_1}\right)$
- Assume $w_i \sim N(m_i, s_i^2)$ and require $(t_2 - t_1)$ to be constant
- Velocity z-score: $z_v = \frac{Vel - Mean\ Vel}{SD\ Vel} = \frac{(w_2 - w_1) - (m_2 - m_1)}{\sqrt{s_1^2 - 2\, r_{12}\, s_1 s_2 + s_2^2}}$
  - where r_{12} is correlation between weights at ages t_1 and t_2
- Note that $(t_2 - t_1)$ cancels out
- z_v depends on correlation but not on time interval

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

Velocity on measurement scale and z-score scale

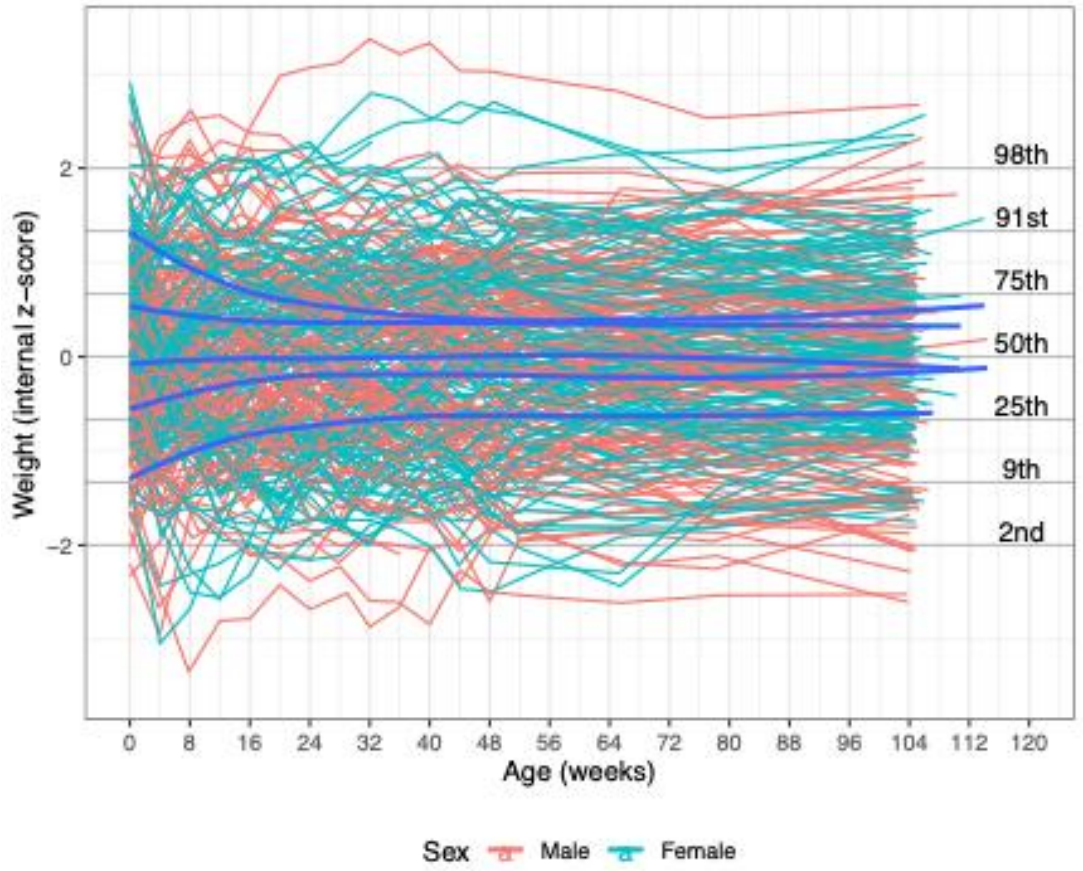
- WHO velocity standard constructed on weight scale (velocity measured as kg change over time)
- Alternative is to work on weight z-score scale (z-score change over time)
- Equates to modelling “centile crossing”
- Greatly simplifies algebra

Z-score of weight velocity based on z-scores

- Velocity z-score based on measurements
  - $z_v = \frac{Vel - Mean\ Vel}{SD\ Vel} = \frac{(w_2 - w_1) - (m_2 - m_1)}{\sqrt{s_1^2 - 2\ r_{12}\ s_1 s_2 + s_2^2}}$
- Velocity z-score based on z-scores
  - Velocity: $Vel = \left(\frac{z_2 - z_1}{t_2 - t_1}\right)$
  - Assume $z_i \sim N(0,1)$
  - $z_v = \frac{Vel - Mean\ Vel}{SD\ Vel} = \frac{(z_2 - z_1)}{\sqrt{2(1 - r_{12})}}$
- z_v depends only on correlation between z_1 and z_2 – very simple!

Unconditional versus conditional weight gain

- Expected weight gain depends on starting centile
- Heavy and light birthweight groups become less extreme over time
- “Regression to the mean”
- On average, heavier children grow more slowly
- Need to adjust z_2 for z_1 using regression
  - “conditioning on z_1”
  - Hence “conditional” weight gain



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Conditional weight gain

- Regress z_2 on z_1
  - $z_2 = a + b\, z_1 + e$
    - where $a = m_2 - b.m_1$ and $b = r_{12}\frac{s_2}{s_1}$
- But $z_i \sim N(0,1)$
    - so $a = 0$ and $b = r_{12}$
  - $z_2 = r_{12}\, z_1 + e$
    - where $var(e) = (1 - {r_{12}}^2)$
- Conditional weight gain: $z_{cv} = \frac{Vel - Mean\ Vel}{SD\ Vel} = \frac{z_2 - r_{12}\, z_1}{\sqrt{1 - {r_{12}}^2}}$
- Again z_{cv} depends only on correlation between z_1 and z_2

Unconditional and conditional weight gain

- Unconditional weight gain
  - $z_v = \frac{z_2 - z_1}{\sqrt{2(1-r_{12})}}$
- Adjusts for t_1 and t_2

- Conditional weight gain
  - $z_{cv} = \frac{z_2 - r_{12}\, z_1}{\sqrt{1-{r_{12}}^2}}$
- Adjusts for t_1, t_2 and z_1

- The two very similar when $r_{12} \sim 1$

CIGS weight correlations

Measured every 4 weeks from birth to 52 weeks

	0wk	4wk	8wk	12wk	16wk	20wk	24wk	28wk	32wk	36wk	40wk	44wk	48wk	52wk
0wk		0.78	0.63	0.55	0.50	0.47	0.44	0.42	0.40	0.41	0.38	0.38	0.37	0.37
4wk	0.78		0.91	0.83	0.75	0.67	0.62	0.58	0.56	0.54	0.51	0.49	0.47	0.47
8wk	0.63	0.91		0.94	0.88	0.80	0.74	0.69	0.67	0.64	0.61	0.59	0.57	0.56
12wk	0.55	0.83	0.94		0.96	0.90	0.85	0.81	0.77	0.73	0.70	0.68	0.66	0.65
16wk	0.50	0.75	0.88	0.96		0.96	0.92	0.88	0.85	0.81	0.78	0.76	0.74	0.73
20wk	0.47	0.67	0.80	0.90	0.96		0.97	0.94	0.91	0.87	0.83	0.82	0.79	0.78
24wk	0.44	0.62	0.74	0.85	0.92	0.97		0.97	0.95	0.91	0.89	0.86	0.84	0.83
28wk	0.42	0.58	0.69	0.81	0.88	0.94	0.97		0.97	0.95	0.92	0.90	0.89	0.87
32wk	0.40	0.56	0.67	0.77	0.85	0.91	0.95	0.97		0.98	0.96	0.94	0.92	0.91
36wk	0.41	0.54	0.64	0.73	0.81	0.87	0.91	0.95	0.98		0.98	0.96	0.95	0.93
40wk	0.38	0.51	0.61	0.70	0.78	0.83	0.89	0.92	0.96	0.98		0.97	0.96	0.95
44wk	0.38	0.49	0.59	0.68	0.76	0.82	0.86	0.90	0.94	0.96	0.97		0.98	0.97
48wk	0.37	0.47	0.57	0.66	0.74	0.79	0.84	0.89	0.92	0.95	0.96	0.98		0.97
52wk	0.37	0.47	0.56	0.65	0.73	0.78	0.83	0.87	0.91	0.93	0.95	0.97	0.97	

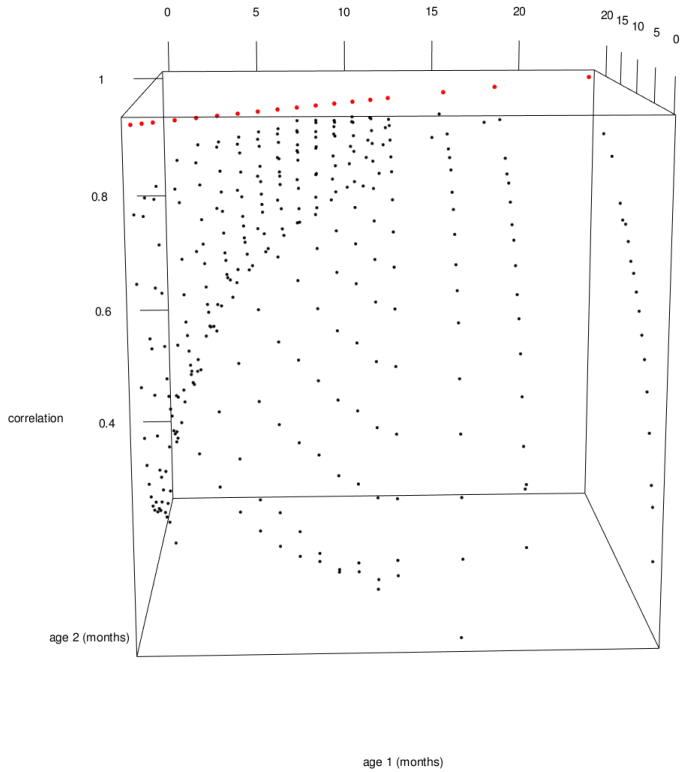
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Correlations in 3D

- Each correlation can be viewed in 3D as the vertical distance above the t_1-t_2 grid
- Join up correlations to give correlation surface
  - Result is saddle-like shape

- Illustrated with CIGS data for 0-24 months

Correlations plotted in 3D



Red points are 1's on diagonal

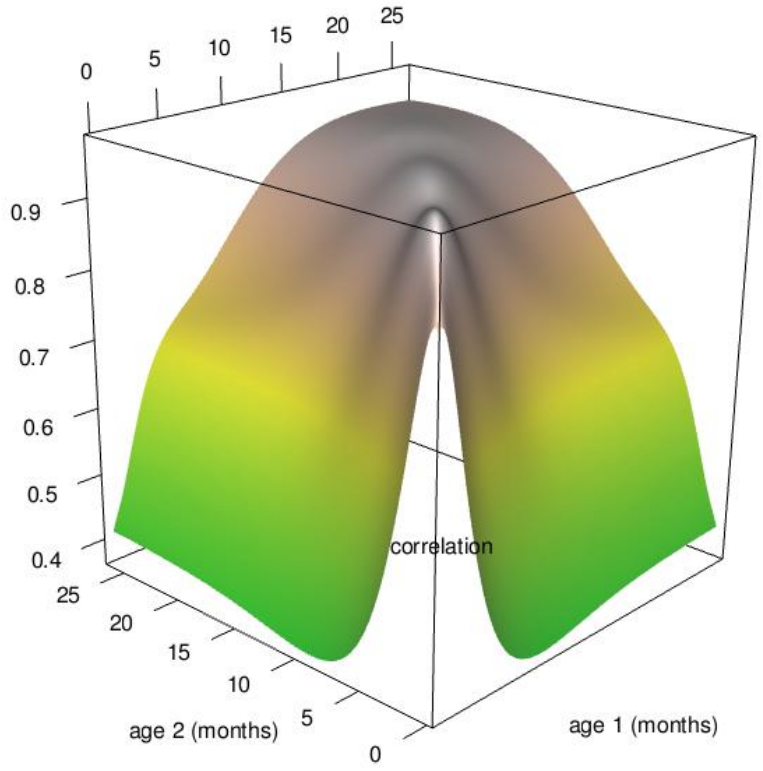
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Correlation surface

- Complex correlation pattern that depends on age and time interval
- Summarise correlation matrix as smooth 3D surface
- So can read off correlation r_{12} for *any* pair of ages (t_1, t_2)

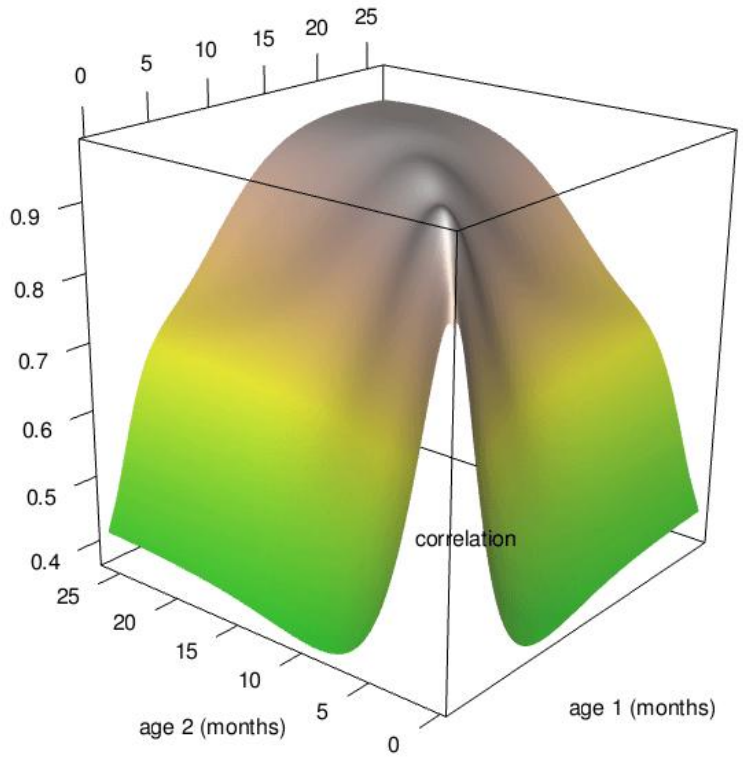
- Illustrated with CIGS data

CIGS smooth correlation surface



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CIGS smooth correlation surface



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Generalised conditional gain

- Given weight z-scores z_1 and z_2 at ages t_1 and t_2 for individual child
- Read off r_{12} at (t_1, t_2) from correlation surface
- Plug into formula: $z_{cv} = \frac{z_2 - r\, z_1}{\sqrt{1 - {r_{12}}^2}}$
- Result is conditional weight velocity z-score
  - Adjusted for t_1, t_2 and z_1
- In principle a simple and universal way to quantify weight gain
  - But requires suitable correlation surface

Conclusions

- Growth charts are useful for assessing weight but not for assessing weight gain
  - They fail to quantify the degree of centile crossing over time
- Important need for useful and accessible quantitative methods
- Three methods considered here:
- WHO growth velocity standard: gives valid z-scores but cumbersome, many exclusions, and little used in practice
- Rapid weight gain: simple to calculate but hard to interpret, and poorly correlated with weight velocity z-score
- Generalised conditional gain: conditional velocity z-score, simple to calculate, no time interval restrictions
  - Also has limitations: notably access to correlation surface
  - But has potential to be used more widely
- Extreme velocity z-scores assessed over different time intervals (e.g. 1 vs 4 months) need interpreting differently

Additional slides added post-webinar: Rapid Weight Gain as Velocity z-score

Rapid Weight Gain as Velocity z-score

- Rapid Weight Gain defined as z-score increment $\Delta z = 0.67$
  - $z_2 - z_1 = 0.67$
- Unconditional weight gain z-score
  - $z_v = \frac{z_2 - z_1}{\sqrt{2(1-r_{12})}} = \frac{0.67}{\sqrt{2(1-r_{12})}}$
  - Adjusts for t_1 and t_2
- Rapid Weight Gain as a velocity z-score depends *only* on correlation r_{12}
- Call Rapid Weight Gain velocity z-score **RWG z_v**
- See how RWG z_v varies according to r_{12}

Examples of RWG z_v over 4 weeks in infancy

Age_1	Age_2	Correlation r_{12}	RWG z_v	Velocity centile
Birth	4 weeks	0.78	1.0	85th
4 weeks	8 weeks	0.91	1.6	95th
32 weeks	36 weeks	0.98	3.4	>99.9th
48 weeks	52 weeks	0.97	2.7	99.7th

- RWG z_v over 4 weeks in infancy varies between 1.0 and 3.4 depending on the starting age
- RWG velocity centile between 85th and ≫99th
- Very important to specify starting age and time interval
- For time intervals longer than 4 weeks, z_v progressively less extreme

Rapid Weight Gain as Conditional Velocity z-score

- Rapid Weight Gain defined as z-score increment $\Delta z = 0.67$
  - $z_2 = z_1 + 0.67$
- Conditional weight gain z-score
  - $z_{cv} = \frac{z_2 - r_{12}\, z_1}{\sqrt{1 - {r_{12}}^2}} = \frac{z_2 - r_{12}\, z_1}{\sqrt{1 - {r_{12}}^2}} = \frac{z_1 + 0.67 - r_{12}\, z_1}{\sqrt{1 - {r_{12}}^2}} = \frac{0.67 + (1 - r_{12}) z_1}{\sqrt{1 - {r_{12}}^2}}$
- Adjusts for t_1, t_2 and z_1
- Rapid Weight Gain as a conditional velocity z-score depends on correlation r_{12} and z_1
- Call Rapid Weight Gain conditional velocity z-score **RWG z_{cv}**
- See how RWG z_{cv} varies according to r_{12} and z_1

Examples of $RWGz_{cv}$ over 4 weeks in infancy

Age_1 T_1	Age_2 t_2	Correlation r_{12}	RWG z_v	RWG z_{cv} for $z_1 = -1$	RWG z_{cv} for $z_1 = +1$
Birth	4 weeks	0.78	1.0	0.7	1.4
4 weeks	8 weeks	0.91	1.6	1.4	1.8
32 weeks	36 weeks	0.98	3.4	3.3	3.5
48 weeks	52 weeks	0.97	2.7	2.6	2.9

- RWG z_{cv} > RWG z_v when $z_1 > 0$
- RWG z_{cv} < RWG z_v when $z_1 < 0$
- RWG z_{cv} larger and of greater concern for heavier infants