Importance of characterizing growth trajectories

Matthew W. Gillman

EN Power of Programming
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Thanks to...

Faculty, Trainees, & Staff

Obesity Prevention Program
Department of Population Medicine
Harvard Medical School/Harvard Pilgrim Health Care Institute
EarlyNutrition
2013 Growth Trajectory Workshop

- How approaches relate to each other
- Choosing an approach
  - For different objectives/applications
    - Are some useful across different goals?
  - Theoretically, practically
Today

• Growth trajectories
  – Why we care
    • Determinants
    • Outcomes
    • Prediction
  – Meanings/definitions
Growth Trajectory Analysis
Uses in epidemiology/clinical epidemiology

• What causes the patterns (etiology)
• What do the patterns predict (outcomes)
• Identify individuals at high risk (prediction)
• Some observed, some modeled
• Models typically assess
  – Within-individual change over time, and
  – Between-individual differences in patterns
Growth Trajectory Analysis
Uses in epidemiology/clinical epidemiology

• Etiology
  – What causes the patterns
    • How different are they for different people?
    • Can we put people into categories?
    • Why are patterns different for different people or in different categories?
  – Can we identify inflection points (= critical periods?)
    • To discover drivers of these
Example

Energy intake and weight gain in rats
Differential food access during nursing permanently programs body size

21 days: Weights 14g, 60g

75 days: Weights 86g, 230g

Widdowson and McCance, 1960
Food restriction during weeks 0-3 results in sustained lower body weight.

Widdowson and McCance, 1963
Timing is important

Later food restriction (weeks 9-12) – rats quickly regain and perhaps overshoot body weight

Widdowson and McCance, 1963
Example

Gestational diabetes (GDM) and offspring obesity
Higher maternal glucose level associated with higher weight at birth

“Fuel-mediated teratogenesis\textsuperscript{1}”

\textsuperscript{1}Freinkel 1980
Higher maternal glucose level associated with higher weight at birth

“Fuel-mediated teratogenesis”\(^1\)

- “Dubreil and Anderodias were the first to point out the association of maternal diabetes with hypertrophy and increase in the number of islets of Langerhans in the fetus.”\(^2\)

\(^1\)Freinkel 1980

\(^2\)CR Soc Biol 1920; 23:1491
Higher maternal glucose level associated with higher weight at birth

“Fuel-mediated teratogenesis”

- “Dubreil and Anderodias were the first to point out the association of maternal diabetes with hypertrophy and increase in the number of islets of Langerhans in the fetus.”


Freinkel 1980

CRM Soc Biol 1920; 23:1491

Higher maternal glucose level (or GDM) associated with higher weight (and adiposity) at birth.
To what extent does gestational diabetes cause obesity and metabolic dysfunction in the growing child?
The 3 studies of GDM and offspring BMI adjusted for maternal BMI

<table>
<thead>
<tr>
<th>Study or subgroup (first author, year, ref.)</th>
<th>Mean difference</th>
<th>SE</th>
<th>Weight</th>
<th>Mean difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lawlor, 2009 [27]</td>
<td>0.01</td>
<td>0.32</td>
<td>11.9</td>
<td>0.01 (0.62, 0.64)</td>
<td>11.9</td>
</tr>
<tr>
<td>Lindsay, 2010 [15]</td>
<td>0.34</td>
<td>0.193</td>
<td>32.6</td>
<td>0.34 (−0.04, 0.72)</td>
<td>32.6</td>
</tr>
<tr>
<td>Wright, 2009 [46]</td>
<td>−0.08</td>
<td>0.148</td>
<td>55.5</td>
<td>−0.08 (−0.37, 0.21)</td>
<td>55.5</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.07</td>
<td>0.15, 0.28</td>
<td>100.0</td>
<td>0.07 (−0.15, 0.28)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

0.23 [ 0.06, 0.40] before to 0.07 [ −0.15, 0.28] after maternal BMI adjustment

GDM predicts slower weight-for-length gain in early infancy

GDM not associated with 3-year BMI (but does predict sum of skinfolds and BP)

Effect of treatment of GDM on offspring BMI

Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes

Caroline A. Croxh...
No effect of intervention on BMI at age 4-5 y

<table>
<thead>
<tr>
<th></th>
<th>Intervention group (n = 100)</th>
<th>Routine care control group (n = 111)</th>
<th>Unadjusted Treatment Effect</th>
<th>Adjusted Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI z-score</td>
<td>0.51 (1.18)</td>
<td>0.41 (1.38)</td>
<td>0.10 (-0.25, 0.45)</td>
<td>0.11 (-0.24, 0.46)</td>
</tr>
<tr>
<td><strong>No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt; 85th percentile</td>
<td>32 (32.0)</td>
<td>32 (28.8)</td>
<td>1.11 (0.74, 1.67)</td>
<td>1.09 (0.73, 1.64)</td>
</tr>
</tbody>
</table>

Gillman et al., Diabetes Care 2010;33:964-8
Association of GDM with offspring BMI at 7 y but not at 3 or 4 y
National Collaborative Perinatal Project

<table>
<thead>
<tr>
<th>BMI at age...</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 y (N ~10K)</td>
<td>-0.04</td>
<td>-0.56, 0.48</td>
</tr>
<tr>
<td>4 y (N ~12K)</td>
<td>0.14</td>
<td>-0.45, 0.73</td>
</tr>
<tr>
<td>7 y (N ~23K)</td>
<td>0.49</td>
<td>0.30, 0.68</td>
</tr>
</tbody>
</table>

Adjusted for maternal age, maternal pregnancy BMI, pregnancy weight gain, family income

[GDM < 2%]
Offspring of Mothers with DM
Weight index higher at birth & later childhood

FIG. 3. Symmetry index (SI) (mean ± SEM) in offspring of diabetic mothers from birth to 8 yr of age. SI is greater than expected (1.0) at all ages except 12 mo (P < 0.05). Data points are means ± SE.
Growth Curve Modeling
Getting Our Terms Straight

• Growth
  – Weight?
  – Length?
  – Weight-for-length (WFL, BMI, PI)?
  – Something we don’t measure well?
    • Adiposity? Fat distribution?
    • Lean mass?
Getting Our Terms Straight

• “Catch-up growth”
  – Weight?
  – Length?
  – Weight-for-length (WFL, BMI, PI)?
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Getting Our Terms Straight

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  – Weight-for-length (WFL, BMI, PI)?
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Catch-up and catch-down growth in 1st 6 months

Luo & Karlberg
2000
“Catch-up Growth”

• Expunge
  – Conflates weight with length
  – Has positive valence
  – Ignores that babies born large also have long-term adverse health consequences
  – Implies that we don’t (can’t?) know its drivers
Getting Our Terms Straight

• Linear
  – Growth in length
  – Causal reasoning (no feedback loops)
  – In regression ("model is linear")
    • Outcome is Normal
    • Shape of exposure-outcome ass’n is a straight line
    • Terms in model are added, not multiplied
    • Parameters are not complex, e.g., not exponentiated
Getting Our Terms Straight

• Model
  – ?
Getting Our Terms Straight

• Model
  – Heuristic
  – Directed acyclic graph of causality
  – Statistical representation of “truth,” based on observations

• Are all models “latent?”
Cacophony of Names

- Growth
- Trajectory
- Growth Curve
- Latent
- Hierarchical
- Fractional polynomial

- Random
  - Intercept
  - Coefficient
  - Intercept/Slope

- Variance Component
- Structural equation
All models are wrong, but some are useful.

--G. Box
Growth Curve Modeling for BMI

• More complex
  – Model BMI

• Simpler
  – Model length/height and weight separately
  – Calculate BMI at given age
Fractional polynomial model of BMI

Showing characteristics from the trajectory of a hypothetical child

Goal is characterization, but not classification

Age (year)

BMI

SAS output

CHILDID=991619

AUC

Infancy peak (Age\textsubscript{IP}, BMI\textsubscript{IP})

Adiposity rebound (Age\textsubscript{AR}, BMI\textsubscript{AR})

Velocity\textsubscript{1}

Velocity\textsubscript{2}

Velocity\textsubscript{3}

7 years (BMI\textsubscript{7 y})

Birth (BMI\textsubscript{birth})

BMI (kg/m\textsuperscript{2})
Weight growth curves according to maternal glucose tolerance status

N. Regnault in preparation
Weight growth curves according to maternal glucose tolerance status

...do same for length
then calculate BMI for any age of interest

N. Regnault  in preparation
Insights

• GDM associated with higher BMI at birth
  – Boys: remained through school age
  – Girls: declined in 1\textsuperscript{st} year (and maybe after)
    • Sex-specific prenatal partitioning of energy?

• IGT showed curvilinear pattern with age
  – Boys & girls: similar magnitude/age @ nadir
    • Critical period? Timing/identity of “2\textsuperscript{nd} hit?”
  – Boys: did not rise beyond normal glu tol
  – Girls: steep rise; associated with higher BMI by school age
Could “2\textsuperscript{nd} hit” be at onset of puberty?

Changes in total body fat mass (in kg) for GDM offspring (n = 47) and non-GDM offspring (n = 163) across Tanner stage

Davis et al., J Pediatr 2012; epub ahead of print
Growth Trajectories to Quantify Effects at Different Periods

Adjusted models include all potential confounding factors and earlier growth trajectory estimates for post-natal growth

<table>
<thead>
<tr>
<th>Table 3 Associations between pre-natal and post-natal growth trajectories (z-scores) through 5 years of age and teacher SDQ scores at age 6.5 years</th>
</tr>
</thead>
</table>

| Total difficulties | Length/Height trajectory |
| --- | --- | --- |
| At birth | Unadjusted | Adjusted<sup>a</sup> |
| Gain from 0 to 3 months | $-0.29 (-0.40, -0.17)$ | $-0.21 (-0.33, -0.08)$ |
| Gain from 3 to 12 months | $-0.05 (-0.17, 0.07)$ | $-0.07 (-0.21, 0.06)$ |
| Gain from 1 to 5 years | $0.01 (-0.10, 0.12)$ | $-0.11 (-0.25, 0.03)$ |
| Gain from 0 to 3 months | $-0.10 (-0.20, -0.002)$ | $0.01 (-0.12, 0.15)$ |

Adjusted<sup>a</sup>

Adjusted models include all potential confounding factors and earlier growth trajectory estimates for post-natal growth


Length/height (cm/year)

- 0–3 months: 36.0 (6.21)
- 3–12 months: 21.54 (1.95)
- 1–5 years: 8.88 (0.80)
Growth Trajectory Analysis
Uses in epidemiology/clinical epidemiology

• Outcomes
  – What do the patterns predict
  – Is it useful to classify (put into groups)
    • Individuals
    • Characteristics
  – How feasible is it
Example

Early infancy weight-for-length gain and later obesity
CDC’s WFL growth charts

Length for age

Weight for age

Weight for length
Crossing Percentiles

- Major growth percentiles defined by CDC
Crossing Percentiles

- Major growth percentiles defined by CDC
- Upward crossing 2 lines – Important early?
% Children Who Crossed Major WFL Percentiles in 1st 2 years

<table>
<thead>
<tr>
<th>Age-Period (Months)</th>
<th>Number of Upward Percentiles Crossed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0</td>
</tr>
<tr>
<td>1 to 6</td>
<td>17%</td>
</tr>
<tr>
<td>6 to 12</td>
<td>31%</td>
</tr>
<tr>
<td>12 to 18</td>
<td>35%</td>
</tr>
<tr>
<td>18 to 24</td>
<td>45%</td>
</tr>
</tbody>
</table>

Taveras et al, Arch Ped Adol Med 2011; N = 22,178
Probability of later obesity highest with upward crossing in 1st 6 mos

Percent obese at age 5 y

Starting Weight-for-Length Percentile

- <25
- 25-<50
- 50-<75
- 75-<90

1-6 mos
6-12 mos
12-18 mos
18-24 mos

Probability of later obesity highest with upward crossing in 1st 6 mos
Example

Comparing gains in length v. WFL for Obesity v. neurodevelopment in Term v. preterm infants
**Infant Growth Tradeoffs**

By gest age, fetal size, growth type, outcome

<table>
<thead>
<tr>
<th></th>
<th>Healthy AGA full term</th>
<th>Preterm</th>
<th>Full term SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linear growth</td>
<td>Gain in WFL</td>
<td>Linear growth</td>
</tr>
<tr>
<td>Obesity/cardiometabolic risk</td>
<td>?</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Neurodevelopment</td>
<td>↔</td>
<td>↔</td>
<td>+</td>
</tr>
</tbody>
</table>

WFL = weight-for-length
↔ = no association + = positive association ? = insufficient evidence

*Gain in weight-for-length during NICU hospitalization associated with better neurodevelopment; weight-for-length gain after NICU discharge appears less important

Growth Trajectory Analysis
Uses in epidemiology/clinical epidemiology

• Prediction
  – Identify individuals at high risk
  • High bar
Growth Trajectory Analysis

Conclusions

- Define use
  - Determinants, outcomes, prediction
- Choose method appropriate to question
  - Balance between
    - Complex—more accuracy, precision
    - Simple—more tractable, ?useful
- Future
  - Need taxonomy, pros/cons of each approach
  - Use for measures other than anthropometry
No effect of intervention on BMI at age 4-5 y

• Doubtful
  – Selection bias
  – Chance neonatal findings of ACHOIS

• Possible
  – GDM not severe enough to show effects
  – Postnatal lifestyle overwhelms

• Intriguing
  – Latent period
  – BMI ≠ adiposity
<table>
<thead>
<tr>
<th></th>
<th>2 years of age</th>
<th></th>
<th>8 years of age</th>
<th></th>
<th>11 years of age</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted OR (95% CI)</td>
<td>P value</td>
<td>Adjusted OR (95% CI)</td>
<td>P value</td>
<td>Adjusted OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>n</td>
<td>215</td>
<td></td>
<td>89</td>
<td></td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Maternal BMI in early pregnancy ≥30 kg/m²</td>
<td>2.6 (1.04–6.4)</td>
<td>0.04</td>
<td>5.1 (1.4–18.6)</td>
<td>0.014</td>
<td>7.0 (1.8–27.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Birth size LGA</td>
<td>5.4 (2.3–12.4)</td>
<td>0.0001</td>
<td>3.5 (1.0–12.1)</td>
<td>0.05</td>
<td>3.7 (0.9–16.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy</td>
<td>2.2 (0.6–8.3)</td>
<td>0.3</td>
<td>0.7 (0.1–6.5)</td>
<td>0.7</td>
<td>22.7 (1.9–278)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Variables included in the multivariate analysis: maternal BMI before pregnancy, birth size, and maternal smoking during pregnancy. LGA, large for gestational age.
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Length/Height (cm/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 months</td>
<td>36.0 (6.21)</td>
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<td>8.88 (0.80)</td>
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</table>
Metabolic Programming of MEST DNA Methylation by Intrauterine Exposure to Gestational Diabetes Mellitus

Nady El Hajj,1 Galyna Pliushch,1 Eberhard Schneider,1 Marcus Dittrich,2 Tobias Müller,2 Michael Korenkov,3 Melanie Aretz,4 Ulrich Zechner,5 Harald Lehnen,4 and Thomas Haaf1
Diabetes during pregnancy associated with higher BMI in Swedish sibs at age 18 y

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Within-brother</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean BMI difference, kg/m² (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (Y v. N)</td>
<td>0.46 (0.21, 0.72)</td>
<td>1.23 (0.11, 2.36)</td>
</tr>
<tr>
<td>Early preg BMI (per kg/m²)</td>
<td>0.30 (0.29, 0.30)</td>
<td>-0.04 (-0.07, -0.01)</td>
</tr>
</tbody>
</table>

147,000 Swedish men; 46,000 with a brother in the cohort

Lawlor et al., Circulation 2011, 123:258-265
Diabetes Increasing Rapidly Worldwide
### After-term growth & school age BP

**1980s cohort of ex-premies**

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP at 8 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight gain</strong></td>
<td><strong>mmHg per z-score growth</strong></td>
</tr>
<tr>
<td>Term to 4 months</td>
<td>1.0 (0.2, 1.7)</td>
</tr>
<tr>
<td>4 to 12 months</td>
<td>0.1 (-0.8, 1.1)</td>
</tr>
<tr>
<td><strong>Linear growth</strong></td>
<td></td>
</tr>
<tr>
<td>Term to 4 months</td>
<td>1.2 (0.4, 1.9)</td>
</tr>
<tr>
<td>4 to 12 months</td>
<td>-0.4 (-1.3, 0.5)</td>
</tr>
<tr>
<td><strong>Weight-for-length gain</strong></td>
<td></td>
</tr>
<tr>
<td>Term to 4 months</td>
<td>0.1 (-0.5, 0.7)</td>
</tr>
<tr>
<td>4 to 12 months</td>
<td>0.8 (0.1, 1.4)</td>
</tr>
</tbody>
</table>

*Estimates adjusted for child and maternal factors*

n=911 participants <2500g and <37 weeks

Belfort et al. *Pediatrics* 2010
BMI gain before and after term: neurodevelopment at 18 months
2000s cohort

<table>
<thead>
<tr>
<th>Bayley-II</th>
<th>Week 1 to term</th>
<th>Term to 4 months</th>
<th>4 to 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Points per z-score BMI gain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental development index</td>
<td>1.7 (0.4, 3.1)</td>
<td>-0.1 (-1.5, 1.3)</td>
<td>0.8 (-0.8, 2.4)</td>
</tr>
<tr>
<td></td>
<td>p=0.01</td>
<td>p=0. 9</td>
<td>p=0.3</td>
</tr>
<tr>
<td>Psychomotor development index</td>
<td>2.5 (1.2, 3.9)</td>
<td>1.2 (-0.2, 2.5)</td>
<td>0.9 (-0.8, 2.6)</td>
</tr>
<tr>
<td></td>
<td>p=0.0003</td>
<td>p=0.09</td>
<td>p=0.3</td>
</tr>
</tbody>
</table>

Estimates adjusted for child and maternal factors

n=613 participants <33 weeks

Belfort et al. Pediatrics 2011