What is Normal Pre- and Postnatal Growth?

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Developmental Origins of Adiposity and Long-Term Health
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How do / should children grow?

Standards of **Size** for Age

- Fetal period
- Birth to 2 years
- 5 to 19

Goal: Optimal Growth
Growth Charts: Design, Construction and Function
Size for Age

Step 1. Measure children

Step 2. Data Analysis: Descriptive Statistics of Size By Age

Step 3. Curve-Fit Descriptive Statistics Across Age

Step 4. Size for Age Growth Chart

Weight for Age

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What Can Growth Charts Tell Us?

**SIZE**  Who is relatively **Tall** & small

<table>
<thead>
<tr>
<th></th>
<th>Male, 6 months</th>
<th>Female, 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW</td>
<td>3860 g</td>
<td>3068 g</td>
</tr>
<tr>
<td>MH</td>
<td>1.62 m</td>
<td>1.52 m</td>
</tr>
<tr>
<td>99%</td>
<td>74 cm</td>
<td>49%</td>
</tr>
<tr>
<td>58%</td>
<td>8100 grams</td>
<td>21%</td>
</tr>
</tbody>
</table>

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Can Growth Charts Do More? Chart our Course?

Implications:

Big kids at birth remain big and grow like “big kids”

Little kids at birth remain little and grow like “little kids”

Mean length from birth through 2 y illustrated as smoothed percentile curves and corresponding empirical observations.
A few dots don’t make a line, they make a few dots

• Growth charts tell us how big children are relative to one another
• Growth charts are useful clinically and for public and community health
• Individual children need not follow a percentile line
• Individuals ‘cross percentiles’ (regression to the mean & biology)
• Percentile crossing can be predictive but need not be; can be useful to rule-in, but cannot rule-out subtler processes that have phenotypic signals we have yet to recognize
Catch-Up, Catch-Down & Non-Constant Growth

Percentages of children who crossed major percentiles in height-for-age, from the California CHDS. A, Proportions of children who did not cross a major percentile (0), caught up 1 major percentile (+1), caught up ≥2 major percentiles (+2), caught down 1 major perceile (-1) and caught down more than 2 major percentiles (-2).

Zuguo Mei et al. Pediatrics 2004;113:e617-e627
Growth Chart ‘Percentile Crossing’ First 5 years

Healthy Child Growth Need Not Track Along Percentiles

Mei et al., 2004 Shifts in Percentiles of Growth During Early Childhood: Analysis of Longitudinal Data From the California Child Health and Development Study

Pediatrics 113:e617-e627; 10,844 children, 44,296 height and weight measurements first 60 months

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How Do We Know How Humans Grow? (Change through time): Sampling Effects

(a) 14 day intervals

(b) 7 day intervals

(c) 5 day intervals

(d) 3 day intervals
Any single measurement is a snapshot in time
Measuring growth requires the accumulation of many of those snapshots.
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Measuring growth requires the accumulation of many of those snapshots, and the process between each snapshot cannot be inferred in the absence of actual data particularly because individuals can follow different patterns of growth.
Growth Variability Among Individuals

Example: Birth to Nine Months
Signal to Noise Sampling: Growth is Saltatory

Variable amplitude daily saltations separated by variable durations of no significant growth

Daily length growth first 630 days

Total length growth 29.7 centimeters: 54 daily growth saltations

Declining velocity: Growth is less common
Weekly weight gain & length growth relationships: concordant increases = “fueling up”

Non-random coincidence between weight gain & length growth (p<0.001) suggests coupled process

Saltatory Growth Dynamics

• Growth is a discrete event: Time specificity, discontinuous
• Variable Amplitude and Frequency within and between individuals
• Each growth saltation is a sensitive window for size accrual

'Super Tonio' lies behind another newborn in Jesus Kumate Rodriguez hospital. Photograph: Elizabeth Ruiz/EPA
How children *Grow*: More Rapidly at some developmental ages

“Velocity Curve of Human Linear Growth”

“Critical Periods” or “Sensitive Windows” of Growth in Development

- First 1000 days
- Adolescence

The Human Growth Curve Reflects Dynamic Changes in Saltatory Growth

*Timing:*

*Timing where, what, how?*

It is likely that a perturbation at the time of maximal growth of a tissue would have more impact on the final size of that tissue than when it is growing more slowly and when its growth is nearing completion (Duggleby and Jackson 2001).
Length Growth Rate First Two Years

Period of rapid growth
With a Growth rate decline across time,
Hence individuals grow ‘less’

http://www.who.int/childgrowth/standards/l_velocity_2_mo_p_girls/en/
How, exactly, do we grow taller?

• ‘Hydraulic Lift’ at the end of long bones
• Requires the right cells, matrix and materials
Bone Elongation Drives Height Growth: Cell Action of Chondrocytes

1. Differentiation: Chondrocytes from Mesenchymal Stem Cells

2. Mitosis: Chondrocyte Numbers Increase
   ~10 % Height Growth

3. Chondrocytes Increase Volume: Hydraulic effect elongating the bone
   ~60 % Height Growth

3-dimensional reconstruction of the proximal tibial growth plate

Wilsman et al., 1998
Driver of increasing height:
Chondrocytic Hypertrophy

Chondrocytes in the cell cycle phase

Hypertrophic Chondrocytes near the chondro-osseous junction

Wilsman et al., 1998
Growth Plate Microenvironmental Regulatory Opportunities during Chondrogenesis

Vitamin D Protein Glucocorticoids

Regulate Production

Chondrogenesis Cascade

Chondrocyte Secreted Factors

Modulate Expression

Matrix Molecules

Alters Phenotype

epigenetic and microRNA mediated mechanisms

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Michigami et al., 2013 Cell Mol Life Sci 70:4213
Vitamin D₃ Metabolism and Effects the Growth Plate

- Resting Zone
- Proliferative Zone
- Post-Mitotic, Pre-Hypertrophic Zone
- Hypertrophic Zone
- Ossification Zone

Vitamin D Metabolic Pathway

1. **Vitamin D₃**
   - Diet
   - Sun

2. **25(OH)D₃**
   - Liver

3. **1,25(OH)₂D₃**
   - Kidney

4. **24,25(OH)₂D₃**
   - Kidney

Bone
Ethanol reduces tibial length

1> Reduced diaphyseal length

2> Altered histology proximal epiphysis

PF Paired Feed controls for ethanol in terms of calories
Fasting and the growth plate: Is Catch-Up Possible?

Recovery: Weight and bone elongation increased. Is the bone quality the same?

Growth rate depends on the age of the donor epiphyseal plate and is independent of the age of the recipient.

Bone Growth is a Complex System
Summary of regionalized gene expression in the growth plate

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Receptors</th>
<th>Transcription factors</th>
<th>Structural proteins</th>
<th>Other</th>
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<tbody>
<tr>
<td>Fgf9/18</td>
<td>PTHrP</td>
<td>EGFR/TGFβ</td>
<td>RANKL</td>
<td></td>
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<tr>
<td>CNP</td>
<td>Fgfr1</td>
<td>Ihh</td>
<td>VEGFA</td>
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<tr>
<td></td>
<td>Fgfr2</td>
<td></td>
<td></td>
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</tr>
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<td></td>
<td>Fgfr3</td>
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<td></td>
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<td>Me12cid</td>
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<tr>
<td>Sik3</td>
<td>ROS</td>
<td></td>
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</tbody>
</table>

Limiting Factor: Chondrocytic Cell Number (Cell recruitment on top, 10%)
But GROWTH primarily comes from VOLUMETRIC INCREASE (60%)
To Build a Skeleton Clad with Muscle and Invested with Fat...

Cell Fate Decisions....
To maximize height growth, Maximize bone cells

Chondrocyte, Osteoblast versus Adipocyte Differentiation

MSC Niche

↑ Wnt signaling

↑ β-catenin signaling

Adipocytes
↓ Differentiation

Osteoblasts
↑ Differentiation

↑ Bone mineralization

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Metabolic Effects of Trading Bone for Fat: Loss of Beneficial Osteocalcin Effects

Karsenty and Ferron (2012)
In many ways, laying down of fat is a failure of skeletal growth.

Gain Weight or Height?
Fat vs Bone Cell Commitment

Chen et al., 2016 Cell Death & Differentiation
Critical Periods: Limited Time Frames for Development

Heart
- Prenatal Day 18: Cardiac progenitor cells
- Prenatal Day 20-35: Heart tube elongation during looping and myocardium accretion
- Prenatal Week 8: Heart partitioned into 4 chambers
- Prenatal Week 38-40: 70% of cardiomyocytes are terminally differentiated

Kidneys
- Prenatal Week 3: Intermediate mesoderm
- Prenatal Week 4-8: Metanephric mesenchymal cells
- Prenatal Week 9-36: Contact between uterine bud and metanephric blastema
- Postnatal Week 14-Year 2: Adult Kidney; disappearance of fetal lobulation, volume increase, adaptation glomerular filtration rate and blood flow value

Lung
- Prenatal Week 3-4: Epithelial cells form the trachea
- Prenatal Week 17: Formation of airways and bronchioles complete
- Prenatal Week 17-27: Formation of alveoli
- Prenatal Week 36-Postnatal Year 22: Multiplication of alveoli, Alveoli and bronchioles expand in size
Critical Period of Fat Development: 14th-28th week of Gestation

14 Weeks

Blood vessels proliferate and signal areas where fat cells will organize

Appearance of primitive fat lobules; visible fat storage

28 weeks

Development of mesenchymal lobules or pre-adipocytes without lipid droplets

Definitive Fat Lobules

Undifferentiated Fat Tissue

Poissonnet et al., 1983
Fat Cell Development In Utero

It is said that...deposition of body fat begins around 25 weeks of gestation

Martin et al., 1998
Maternal Diabetic Effects: Third trimester Short and Plump patterns emerge

- Limbs: Short, Plump
- Length Growth Declines Relative to Limb Perimeter

Femur length

Thigh perimeter

Lampl & Jeanty 2005 *AJHB*
Ethnic variability: Body Composition Development
Early fat, late lean phenotype

Non-Hispanic Caucasian

African-American

© M Lampl 2013
Lampl et al., 2012 Am J Hum Biol 24:640; Data: Roberto Romero & colleagues, PRB, NICHD
Skinny-Fat South Asian Phenotype

By 8 weeks of age South Asians tend to have more FM and, therefore, less FFM than European infants.

The Y files: John Yudkin (L) and Chittaranjan Yajnik (R) share the same body mass index, but Yajnik's body harbors significantly more fat. Reprinted with permission from Elsevier (The Lancet, 363, 157−163)

doi:10.1038/nm0404-325

News Feature: Asia's big problem

Stanfield et al, Int Epidemiol 2012;41:1409–1418
**Skinny-Fat: Prenatal Origins**

South Asians: Lower BW, PI
Higher Skinfolds (Triceps and Subscapular)
Across BW Quartiles

Newborn body composition by maternal AUC glucose tertiles
By age 2, obese children had achieved adult non-obese values for cell size (0.4-0.7 ug lipid/cell), Knittle et al, 1979
Critical Size & Recruitment

Critical Size

Mature Adipocyte

Hypertrophy

Hyperplasia

Distensibility

Stem Cell

myocyte

osteocyte

chondrocyte

adipocyte

Pre-Adipocyte

IGF-1
GC
PGI₂

MacDougald et al., 2002 Trends in Endo Metab 13:5-11
Adipogenesis Moderators: maternal obesity, exposure to a high energy diet in utero, and particular nutrients (i.e. vitamin A, D, folic acid, b12) alter cell signaling pathways or the recruitment of key transcription factors.
Nutrigenomic regulation of Adipogenesis

Retinoic acid affects progenitor cells and mature adipocytes differently due to the stage-specific expression of related transcription factors.
Epigenetic Priming of an inflammatory Response in Adipocyte Precursors: Glucose Exposure

Rønningen et al., 2015
Why does any of this matter? The Case of FUFs & *GUMS

Developmental Origins of Adiposity and Long-Term Health

CLAIM

“clinically proven nutrition to help kids grow”

Promoting Healthy Growth\(^1\) or Feeding Obesity\(^2\)?

Claims rely on ideas of What is & Is Not “Healthy Growth”

- Weight Gain
- Percentile Crossing
- Z-score Channeling
- Catch-up Growth
- Sizes approaching the median
- 0.67 criteria: ~ for inclusion, not exclusion

- clinically shown to help kids ages 3-4 grow out of at-risk weight-for-height percentiles.\(^{*\dagger}\)
- \(^{\dagger}\) (in the 5th – 25th weight-for-height percentiles)

\(^*\)Suthutvoravut et al., Ann Nutr Metab 2015; 67:119-132

\(^{1}\)Hyunh et al. J Hum Nutr Diet. 2015,28:623-635.

What is normal pre- and postnatal growth?

- Individuals Grow: Individual level biology
- Increase in skeletal dimensions
- Increase in body mass, not merely weight
- Differences age, sex & ethnicity
- Embody socio-cultural aspects
- Healthy children do cross percentiles
- Handy summaries may be neither sensitive nor specific
- Optimal growth is a strategy, not a state
Diagrammatic representation of the fetal circulation, showing umbilical venous supply to the fetal liver and the ductus venosus

Maternal Smoking Effects:
Altered limb proportions

Ratio of arm / leg length

- Longer arms
- Shorter legs
- Proportional differences

Lampl et al., 2003 AJHB
Mechanism for developmental timing and adaptation

- HIF upregulation of IGF in fetal sheep [Schnell et al., 2003]
- Bone growth continued at the expense of soft tissue
Fitted 3rd, 50th, and 97th smoothed percentile curves (dashed blue lines) for BL according to gestational age showing empirical values for each week of gestation (open red circles) and the actual observations (closed gray circles).

33 to 43 gestational weeks of age
Normal Growth: High Variability is the Strategy

Conclusion: The concordance of perinatal mortality and SGA rates when based on ethnic-specific standards, and their discordance when based on a single standard, strongly suggests that the observed ethnic differences in fetal growth are physiologic, rather than pathologic, and make a strong case for ethnic-specific standards.

United States Fetal Growth Standards

No sex differences
No ethnic differences

BMC Pregnancy and Childbirth 2008, 8:1

Empirical Evidence for Human Variability
Descriptive, Public Health, Clinical & Basic Science

- Children are of different sizes at the same age
- Children grow differently
- Growth is a variable system by which one cell makes it to adulthood
- Investigative perspectives vary: What’s the question?
  - Global, community interests vs clinical interests
- The Optimal Growth Vision: Are we looking in the right direction? Is everyone else pathological? Or is this how biology works....

Willie 4 feet 11
Wilt 7 feet 1
(6 ft by 10 yrs)
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