What is Normal Pre- and Postnatal Growth?

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The Power of Programming 2016
Developmental Origins of Adiposity and Long-Term Health
Munich, Germany
13-15 October 2016

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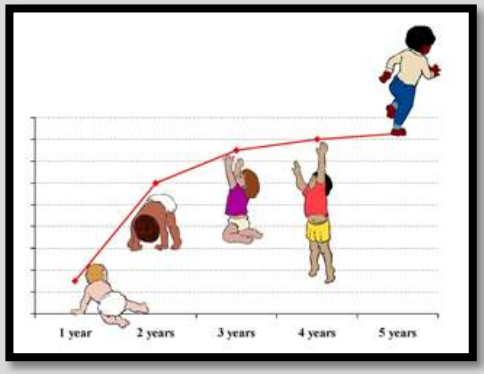
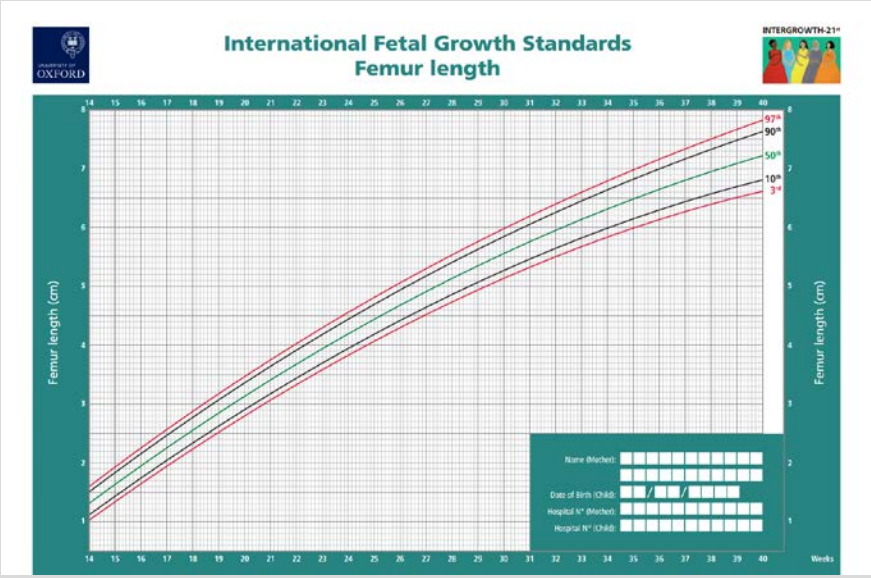
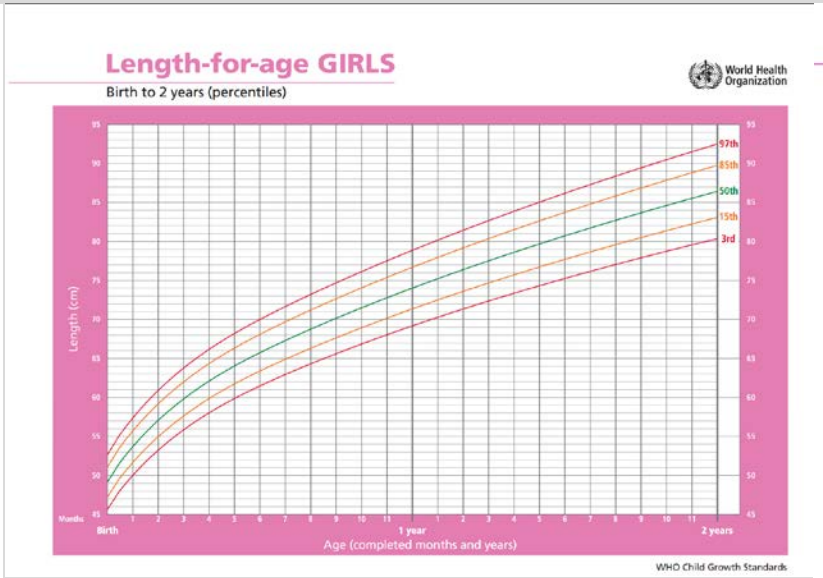
How do / should children grow?



Standards of ***Size*** for Age



Fetal period



Birth to 2 years

5 to 19

Goal: Optimal Growth

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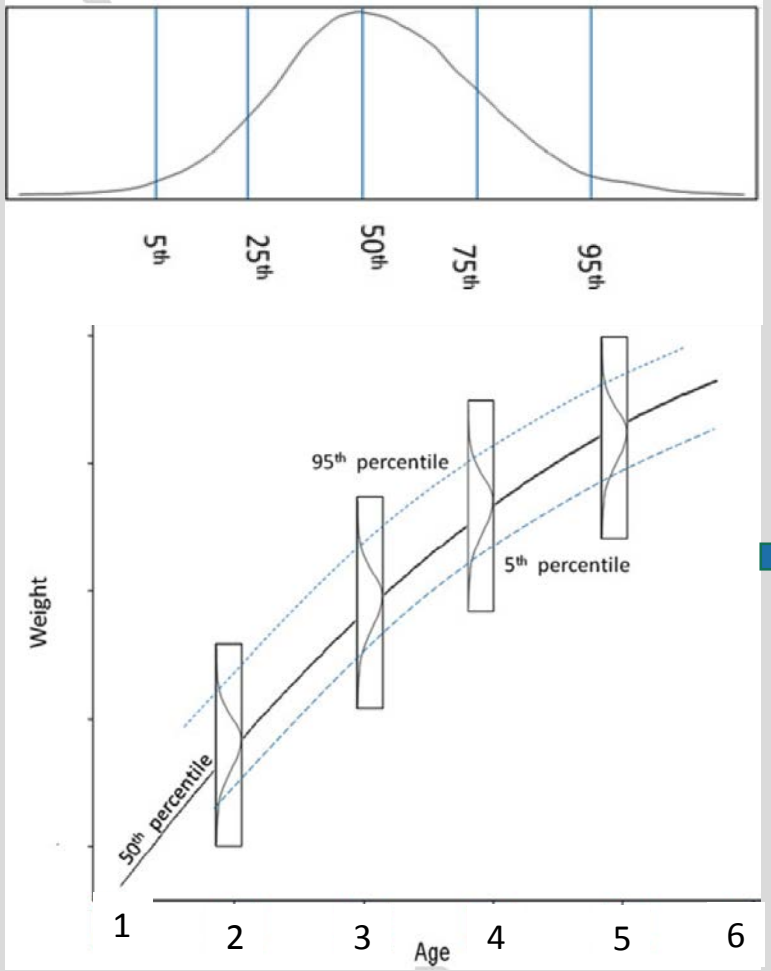
Growth Charts: Design, Construction and Function

Size for Age

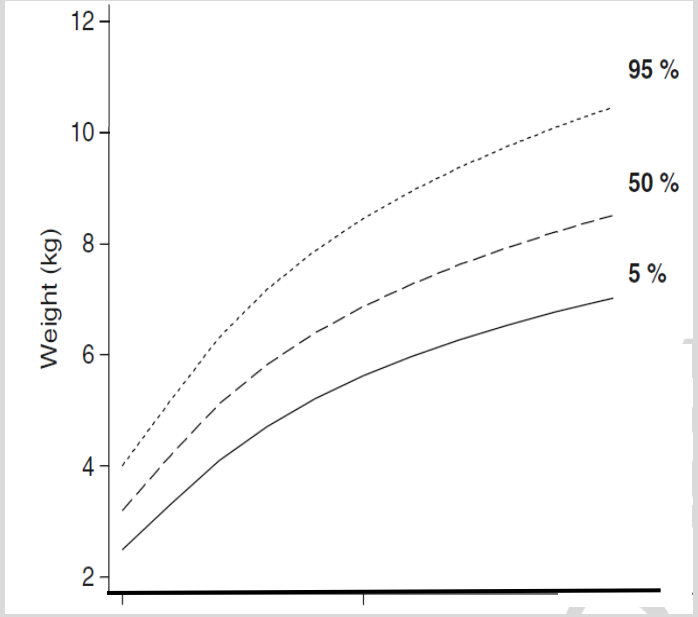
Step 2. Data Analysis: Descriptive Statistics of Size By Age

Step 1. Measure children



Step 3. Curve-Fit Descriptive Statistics Across Age

Weight for Age



Age

Step 4. Size for Age Growth Chart

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What Can Growth Charts Tell Us?

SIZE Who is relatively Tall & small

BW 3860 g

MH 1.62 m

BW 3068 g

MH 1.52 m

Male, 6 months		Female, 12 months
99%	74 cm	49%
58%	8100 grams	21%

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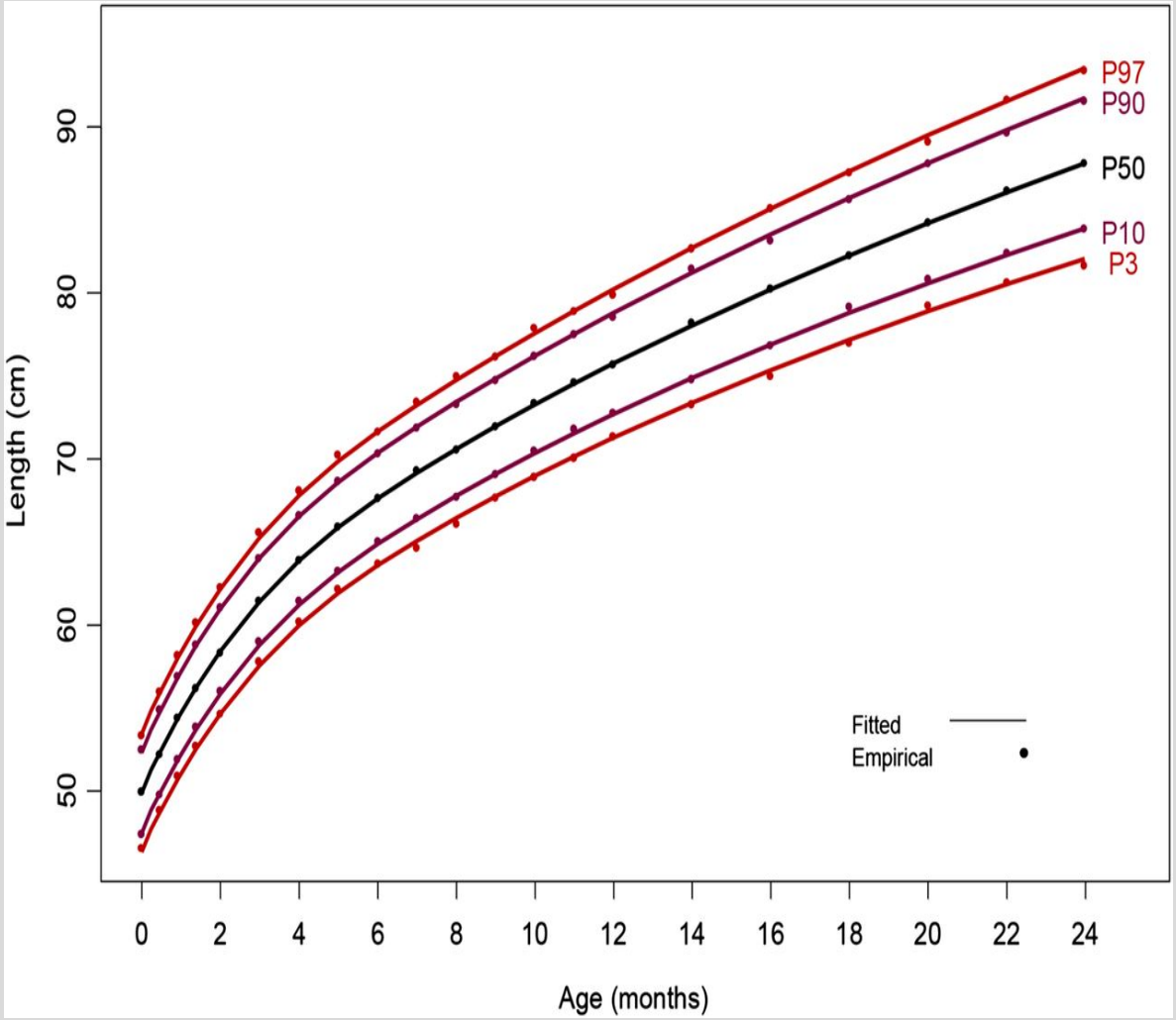
Can Growth Charts Do More? Chart our Course?

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.

Cutberto Garza Adv Nutr 2015;6:383-390
Advances in Nutrition
AN INTERNATIONAL REVIEW JOURNAL

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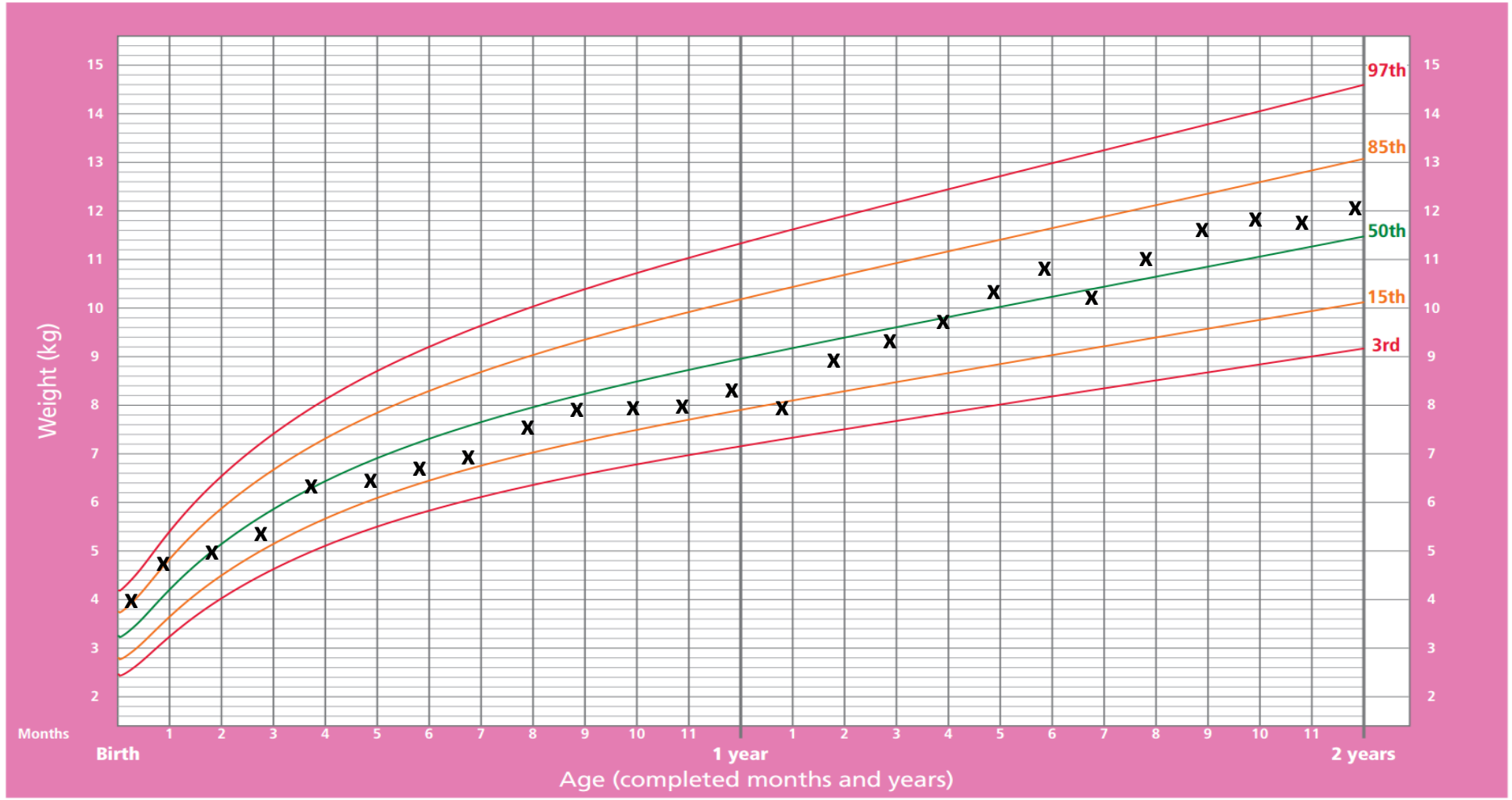
Weight-for-age GIRLS

Birth to 2 years (percentiles)

World Health Organization



WHO Child Growth Standards

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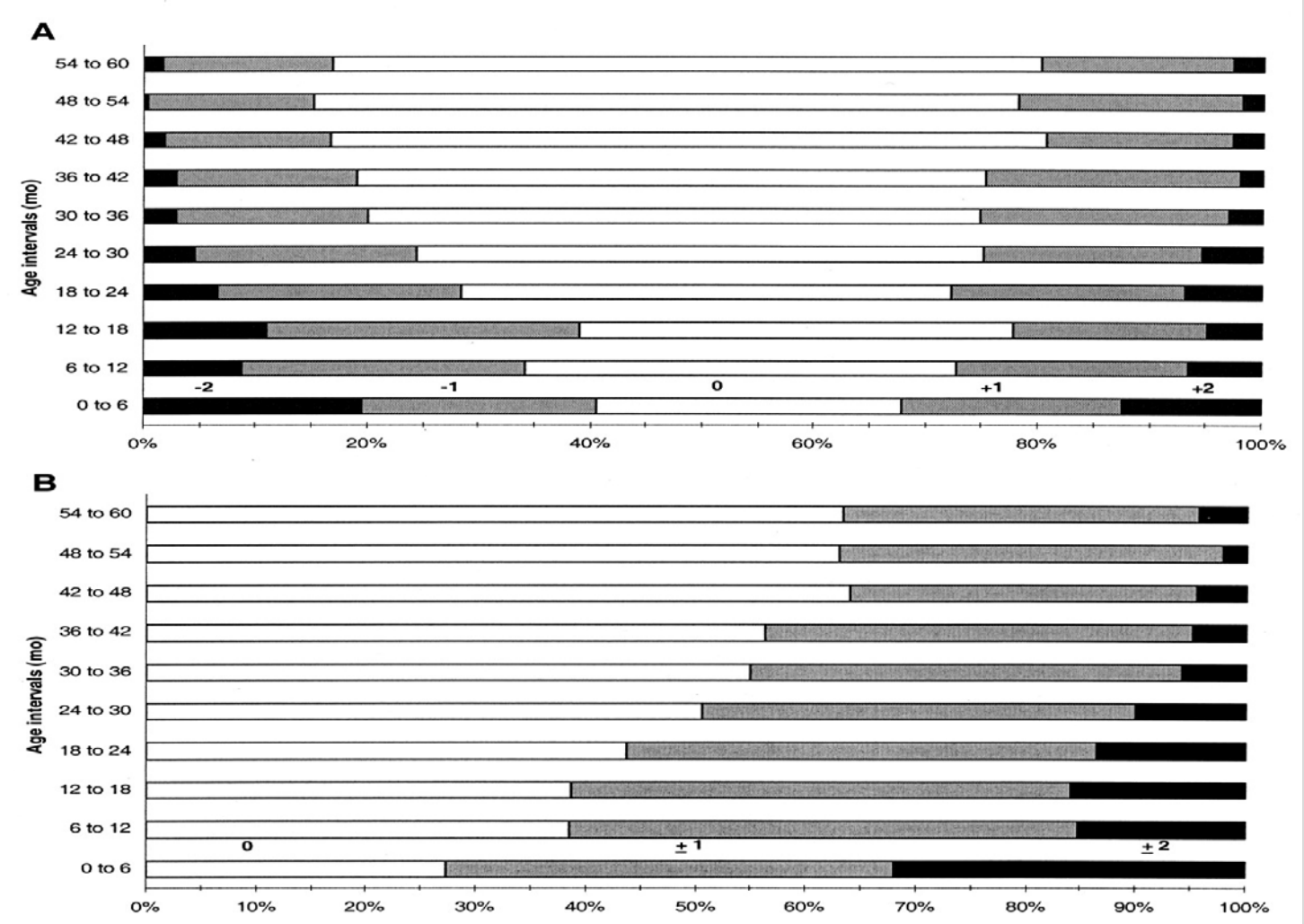
A few dots don’t make a line, they make a few dots

- 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

PEDIATRICS

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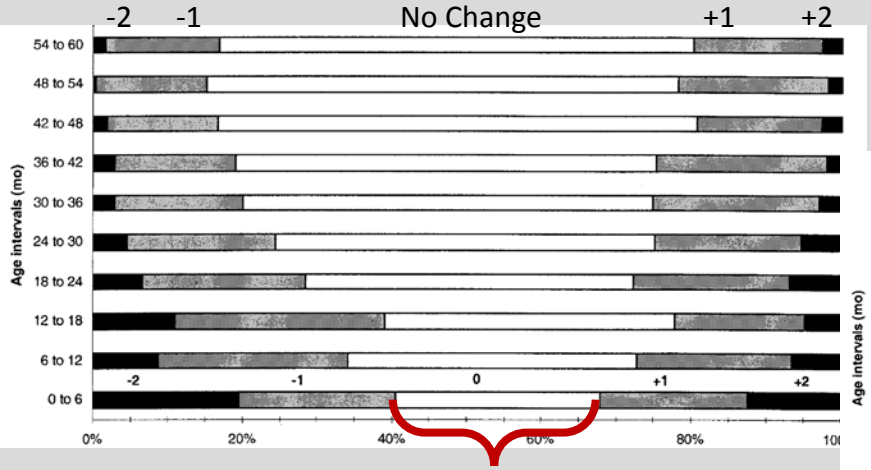
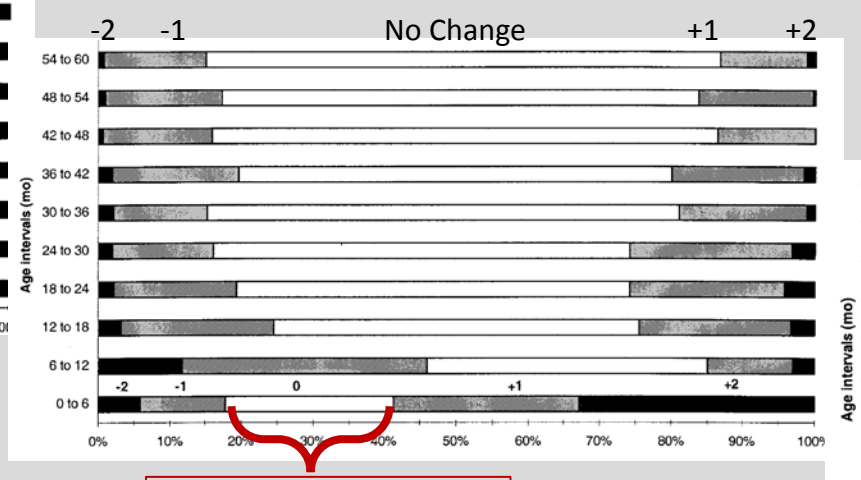
Growth Chart 'Percentile Crossing' First 5 years

Height



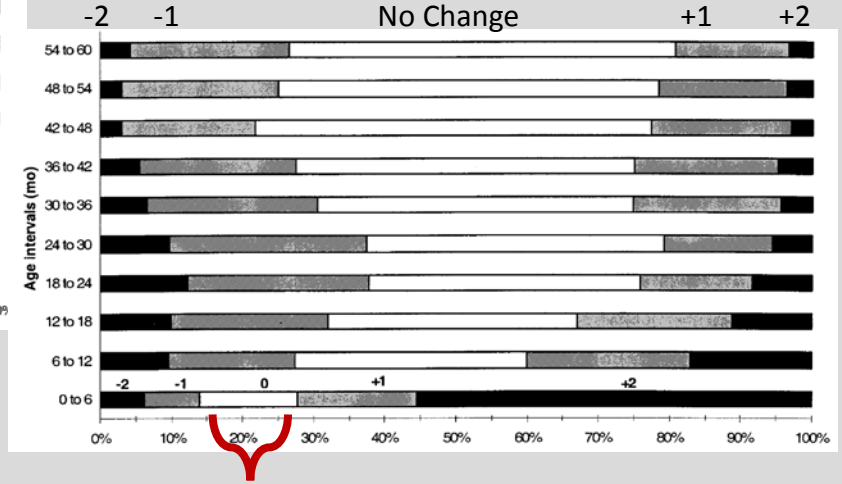
27 % No Change

Weight



23 % No Change

Weight for Height



14 % No Change

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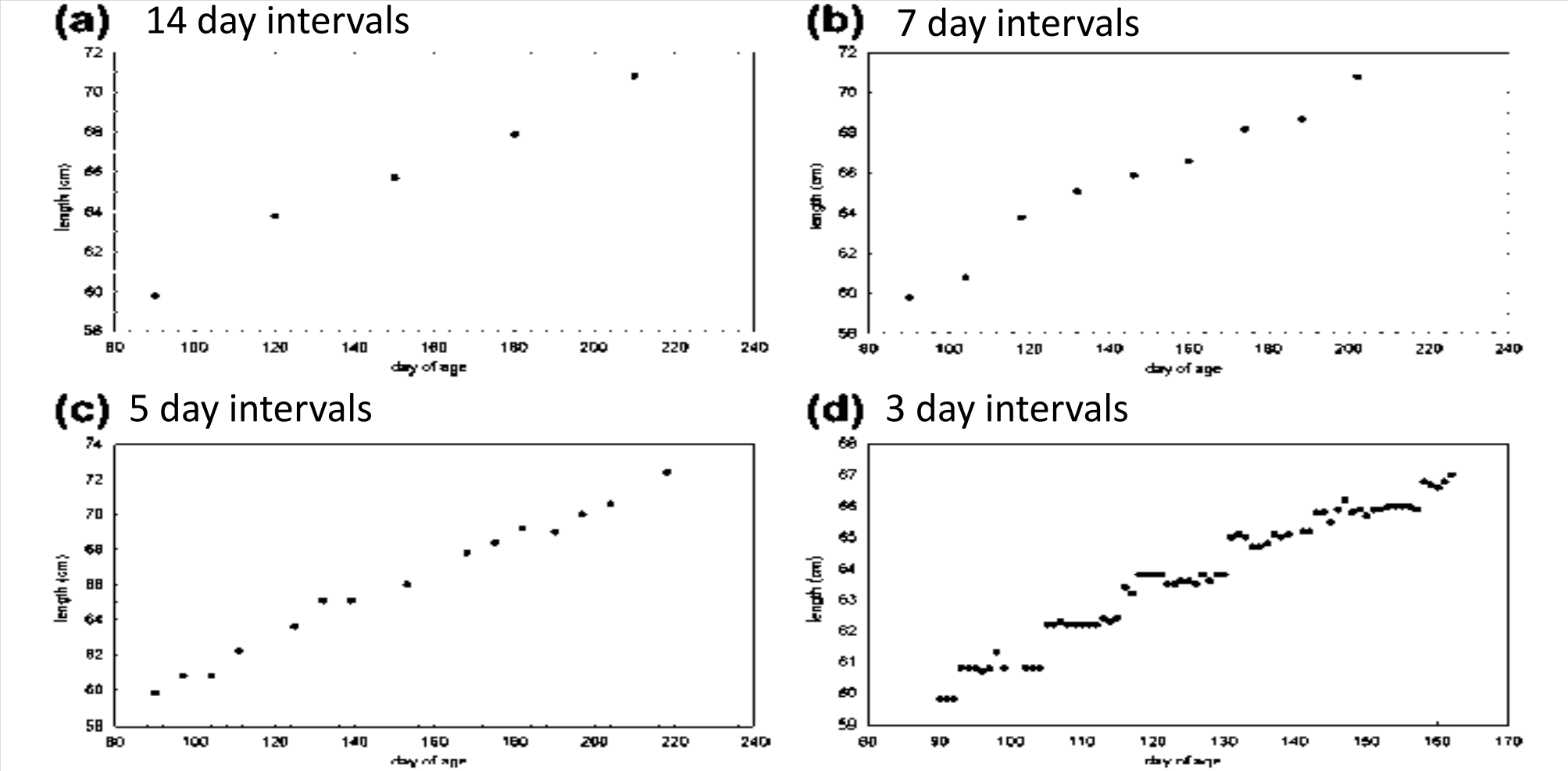
How Do We Know How Humans *Grow*? (*Change through time*): Sampling Effects



Lampl M, Johnson ML. 1997. *Am J Hum Biol* 9:343-56.

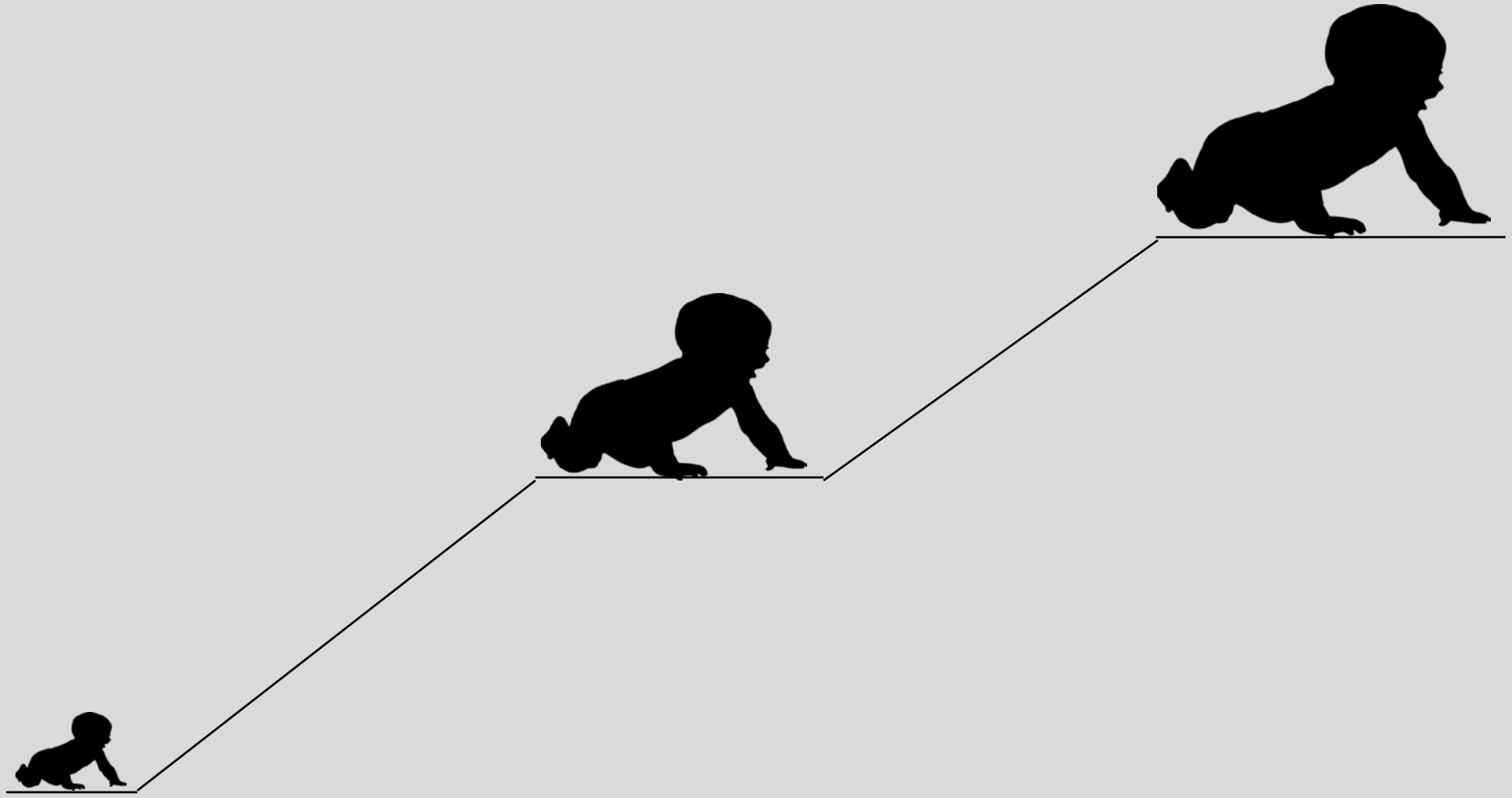
Any single measurement is a snapshot in time

1 Month

6 Months

12 Months

Measuring growth requires the accumulation of many of those snapshots



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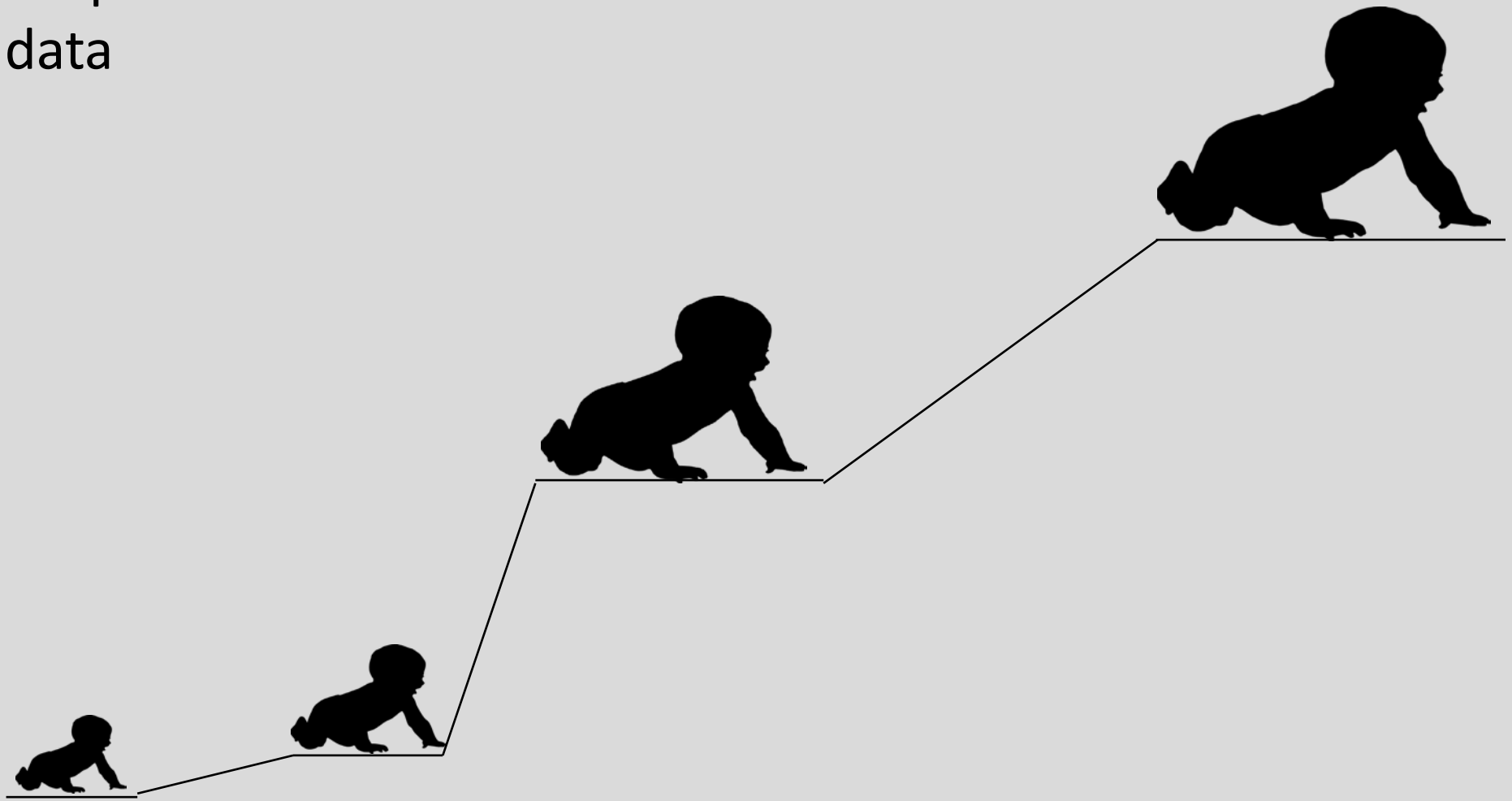
Measuring growth requires the accumulation of many of those snapshots, and the process between each snapshot cannot be inferred in the absence of actual data



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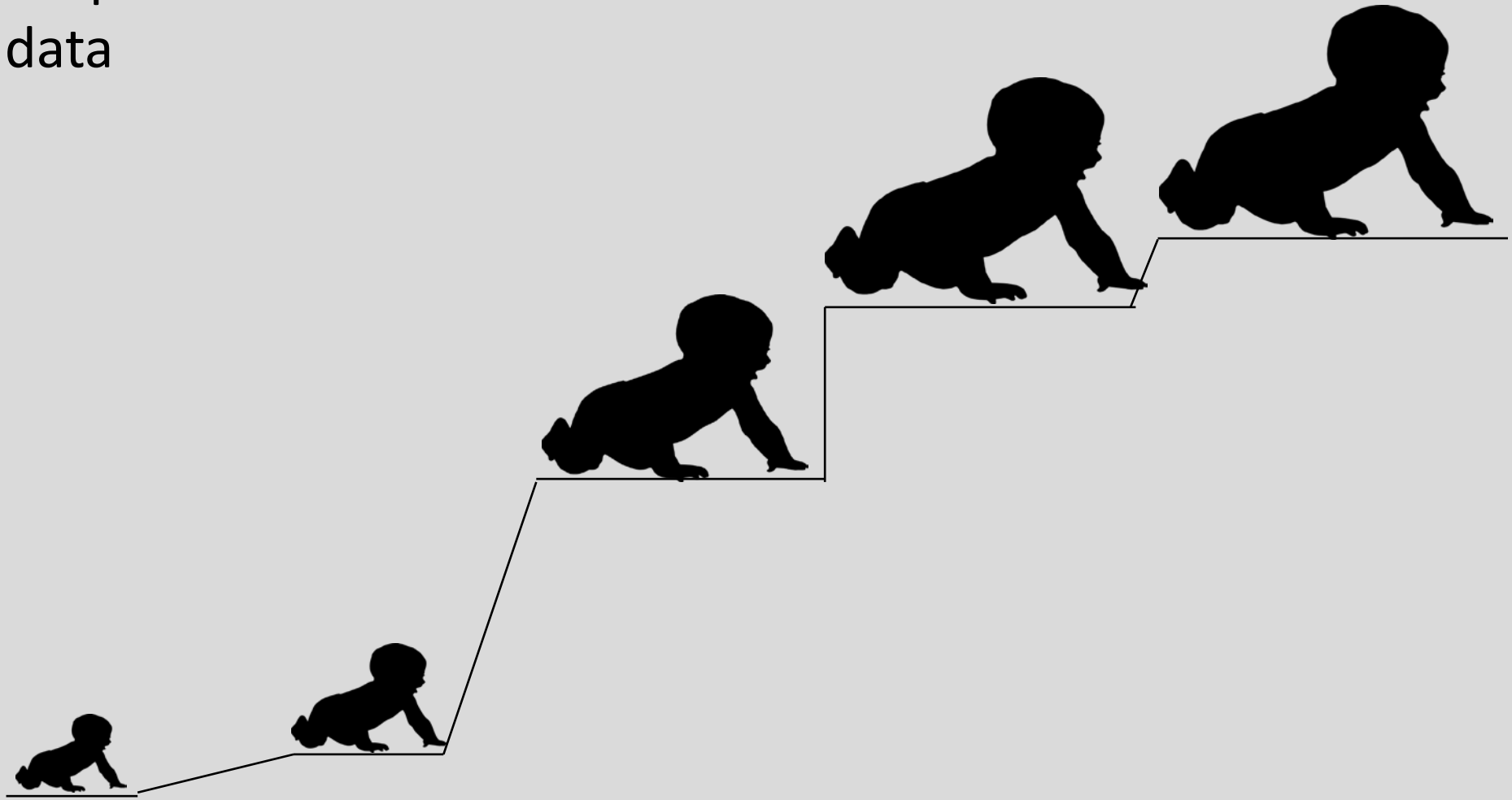

1 Month 3 Months 6 Months 9 Months 12 Months

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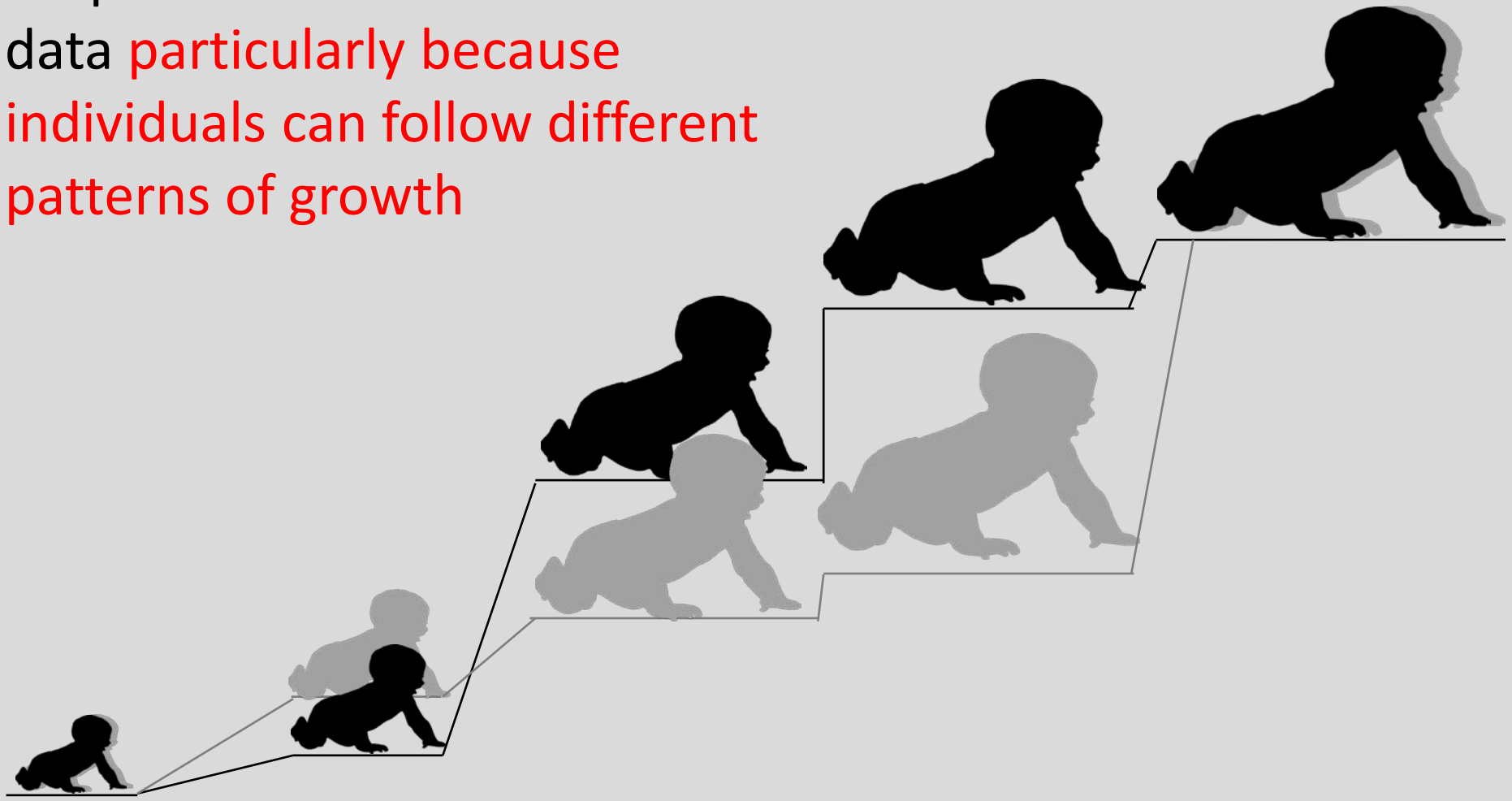
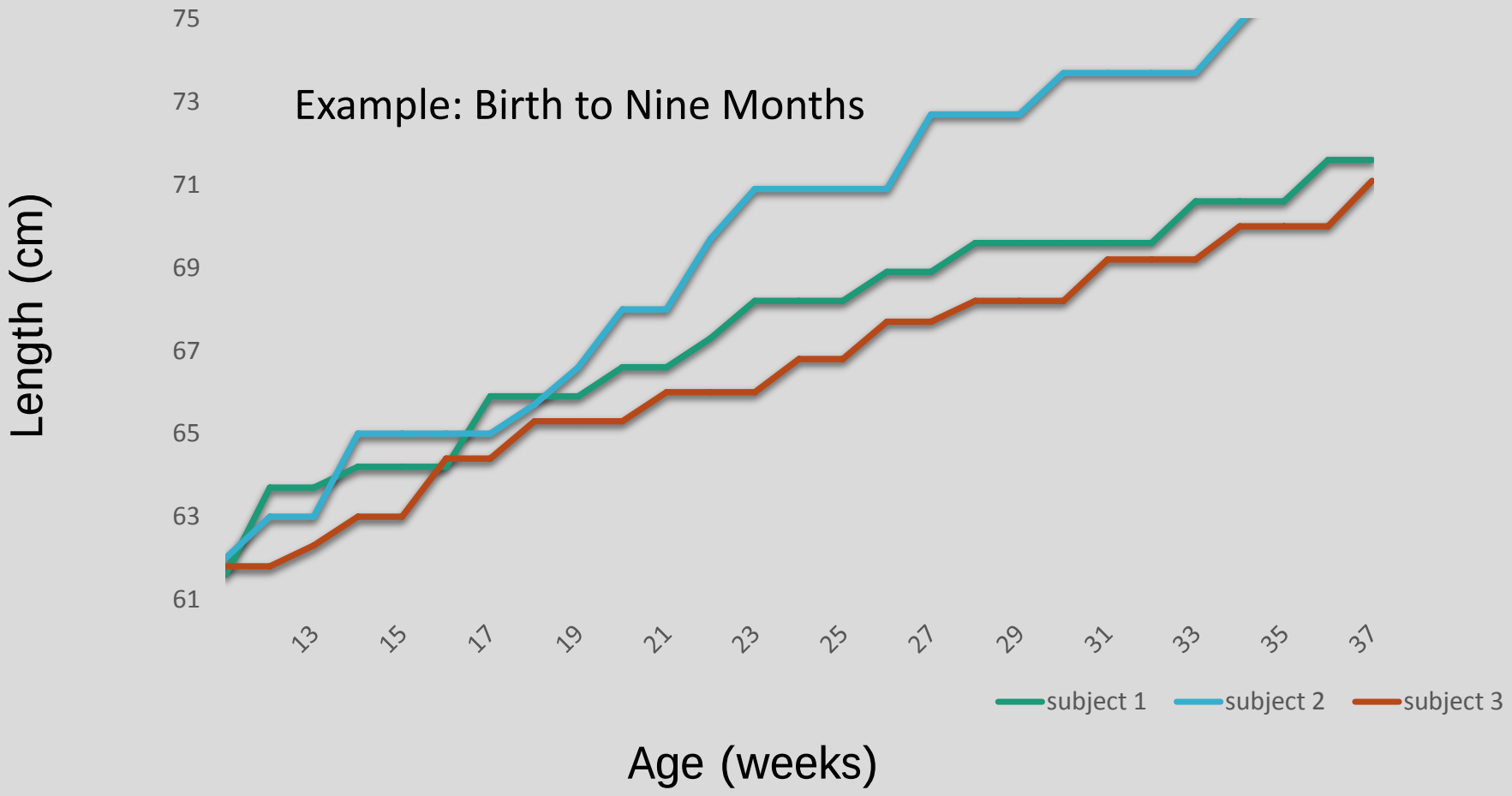
Measuring growth requires the accumulation of many of those snapshots, and the process between each snapshot cannot be inferred in the absence of actual data particularly because individuals can follow different patterns of growth



Growth Variability Among Individuals



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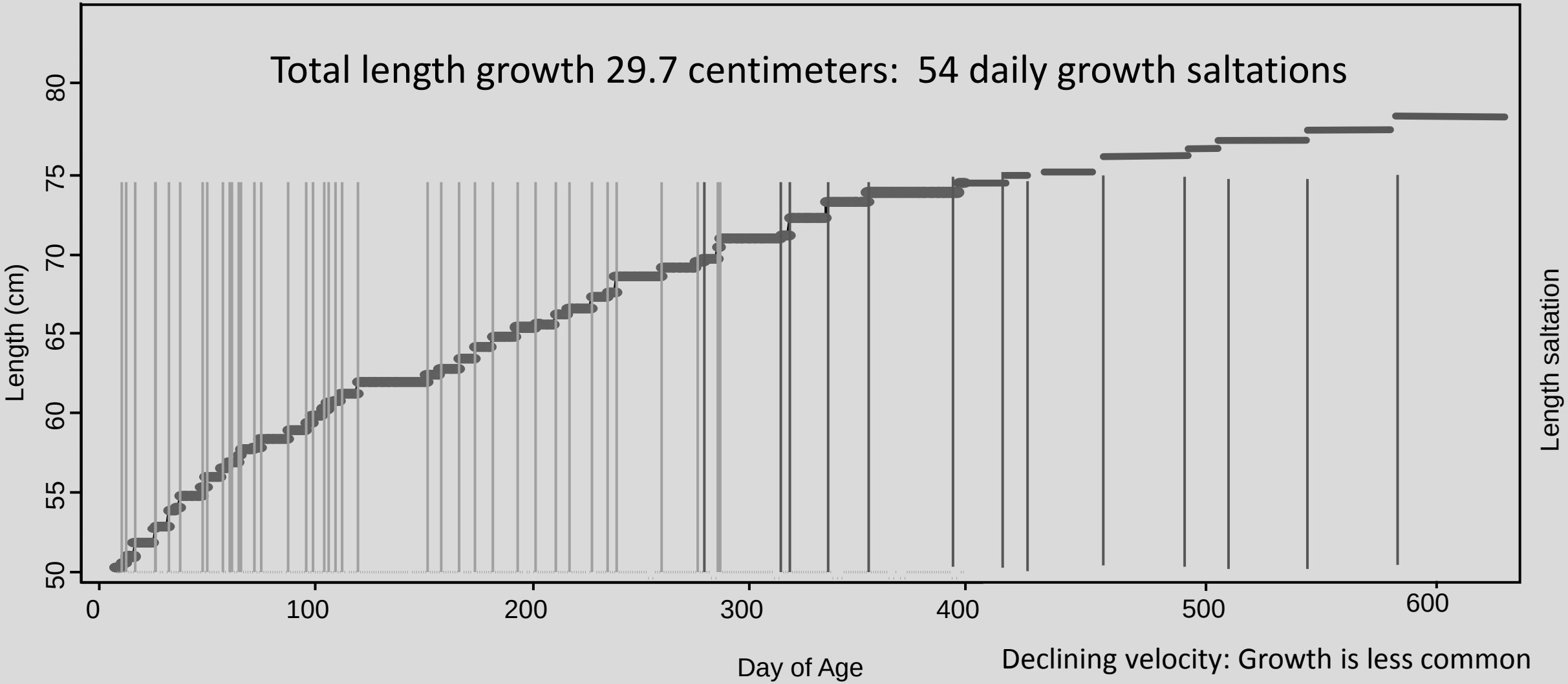
Signal to Noise Sampling: Growth is Saltatory

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

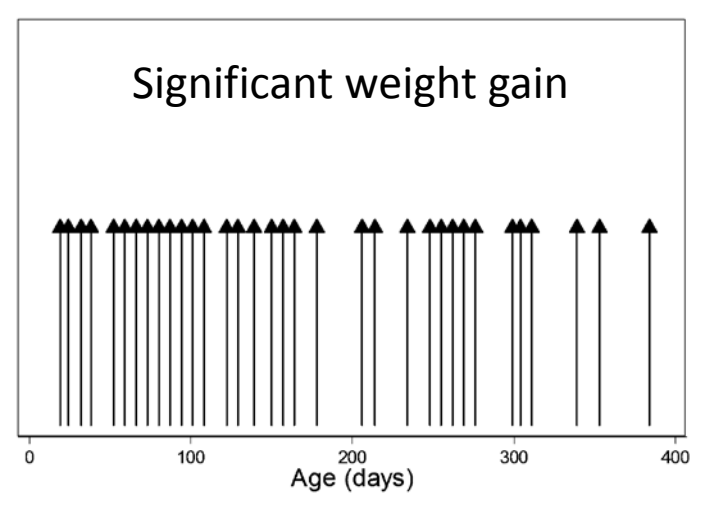
Daily length growth first 630 days

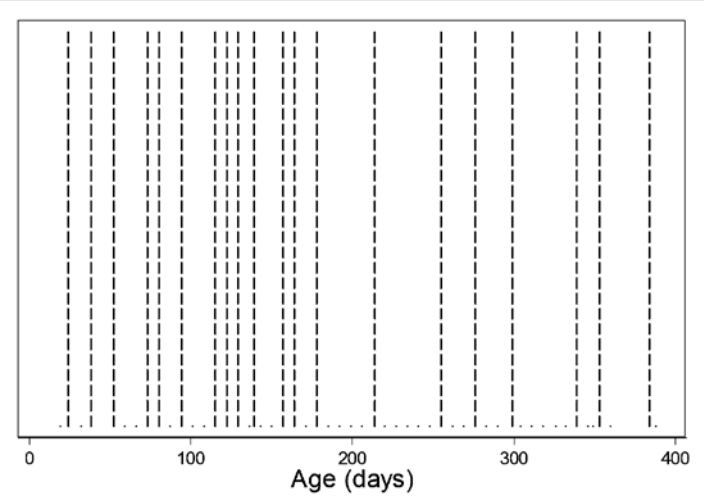


Declining velocity: Growth is less common

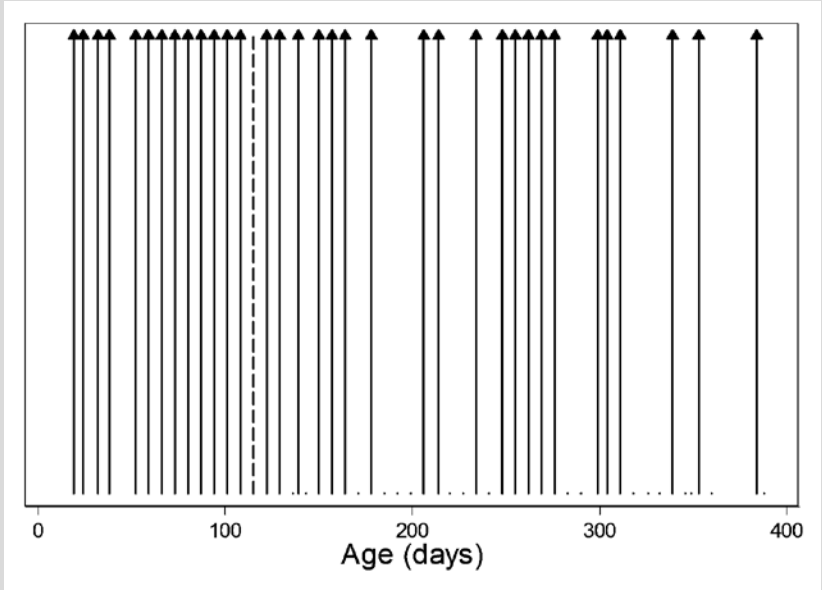
Lampl M, Veldhuis JD, Johnson ML. 1992. *Science* 258(5083):801-803.

Weekly weight gain & length growth relationships: concordant increases = “fueling up”





Length growth saltations



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

Lampl et al. 2005, *Ped Res 58*:1238-42

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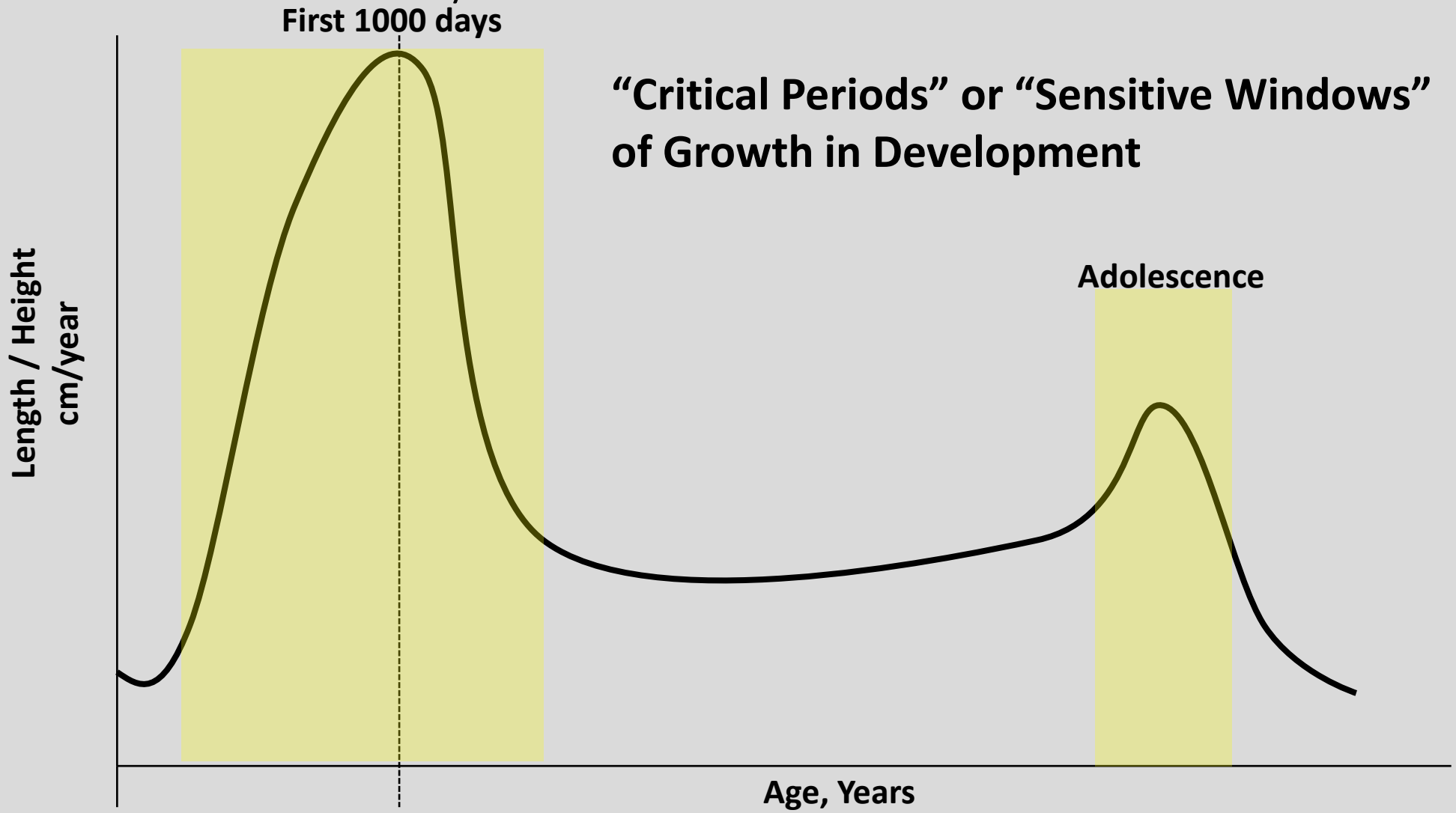
Saltatory Growth Dynamics

- 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

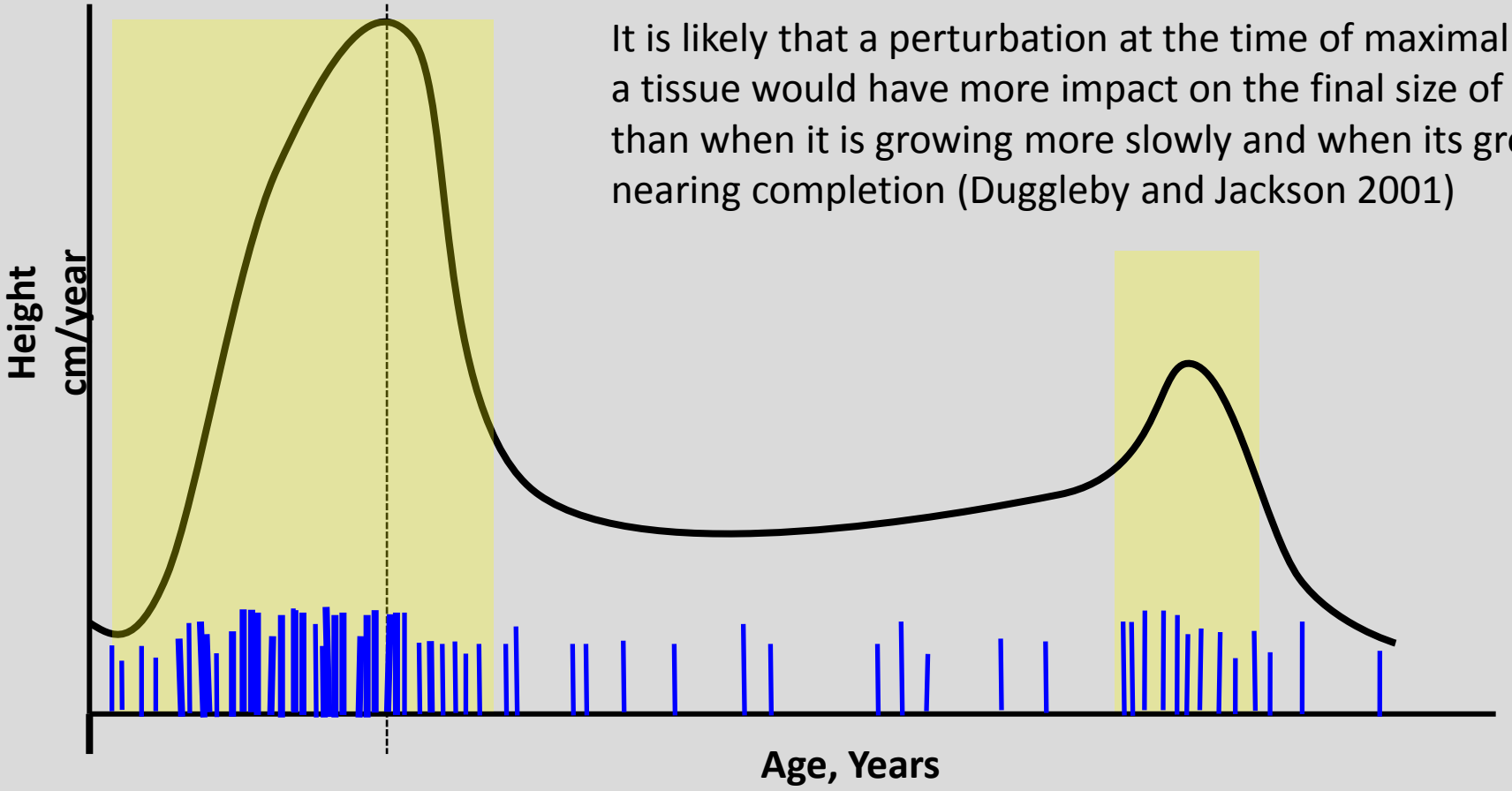
"Velocity Curve of Human Linear Growth"



Widdowson EM, McCance RA. 1975. *Pediatr Res* 9(3):154-56.

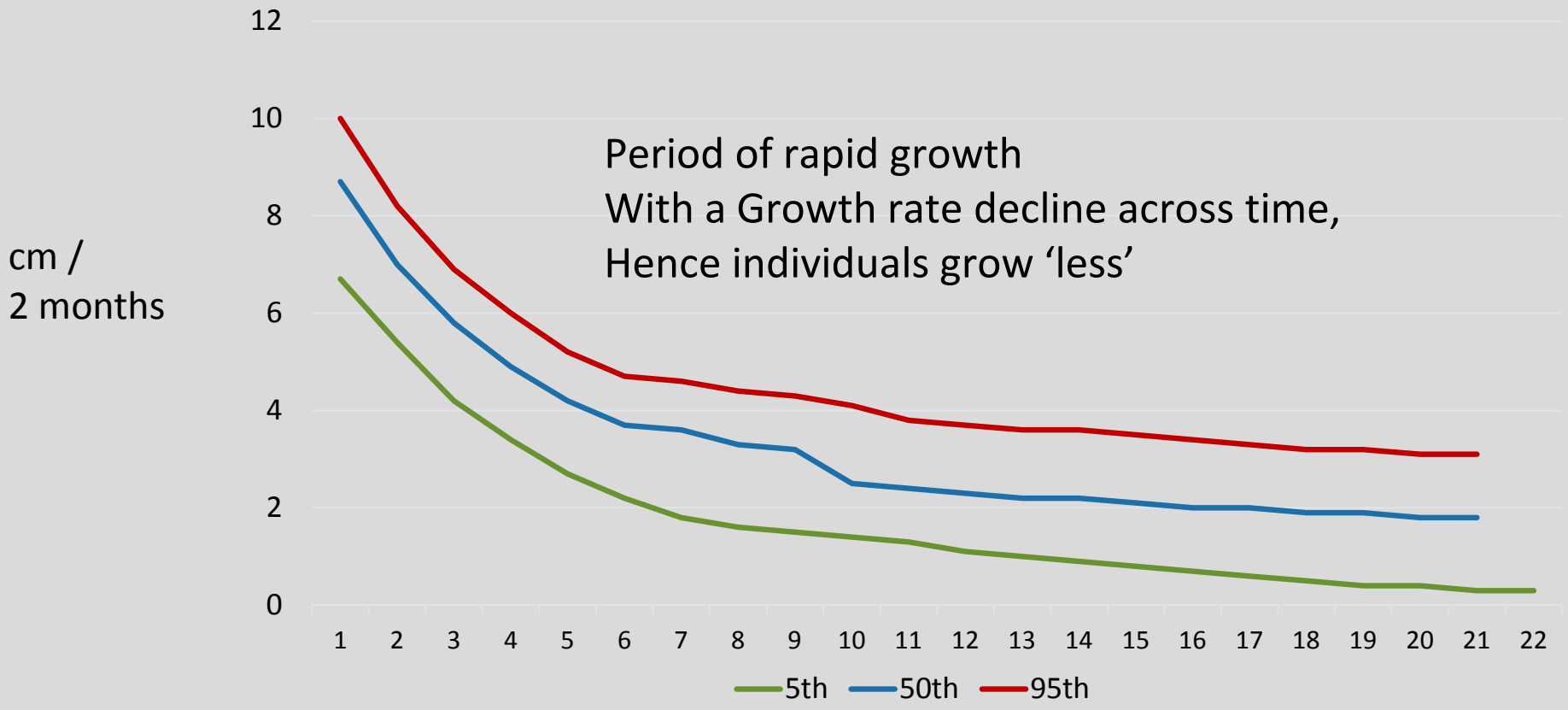
The Human Growth Curve Reflects Dynamic Changes in Saltatory Growth *Timing:*

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



World Health Organization

http://www.who.int/childgrowth/standards/l_velocity_2_mo_p_girls/en/

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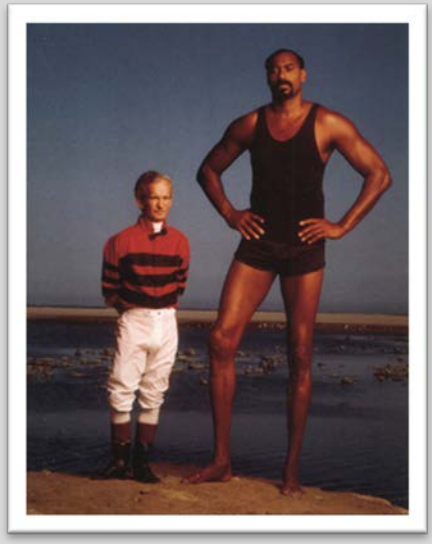
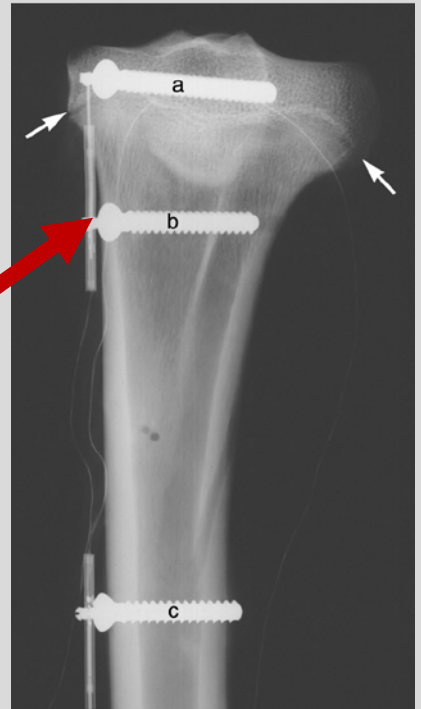
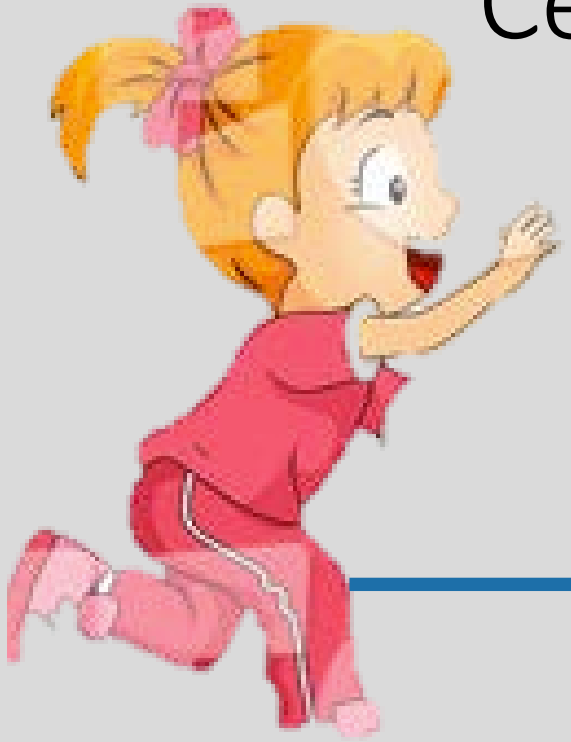
How, exactly, do we grow taller?

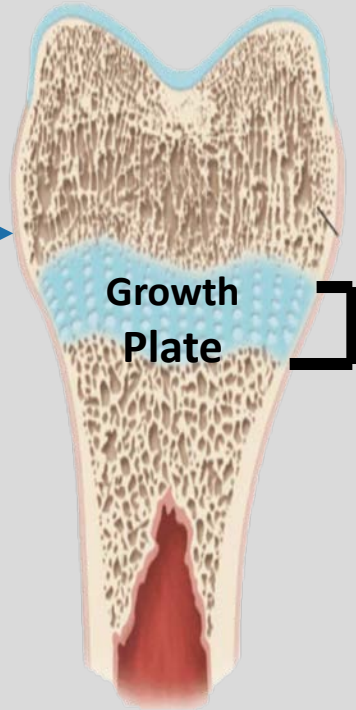


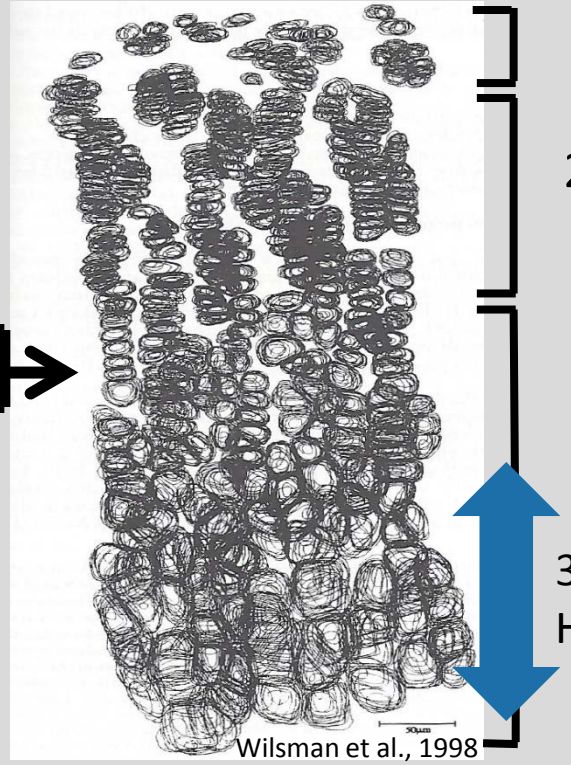
- ‘Hydraulic Lift’ at the end of long bones
- Requires the right cells, matrix and materials



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

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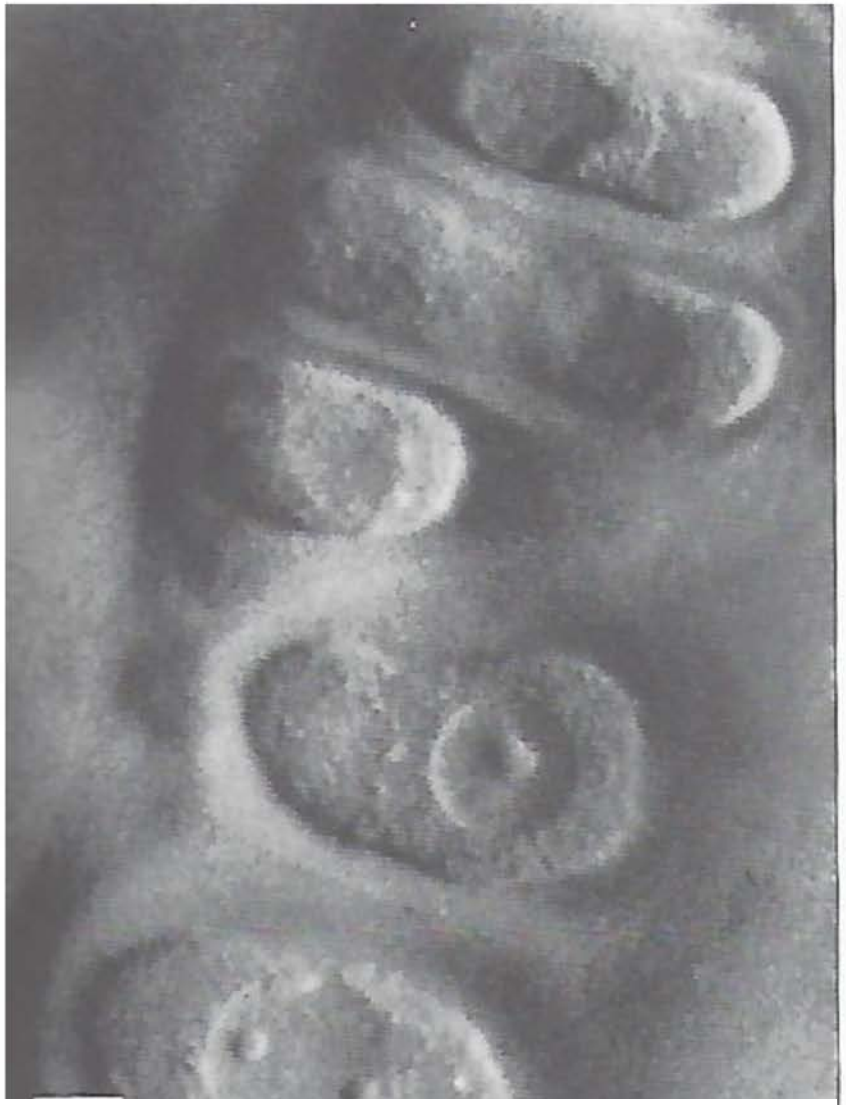
Driver of increasing height:

Chondrocytic Hypertrophy

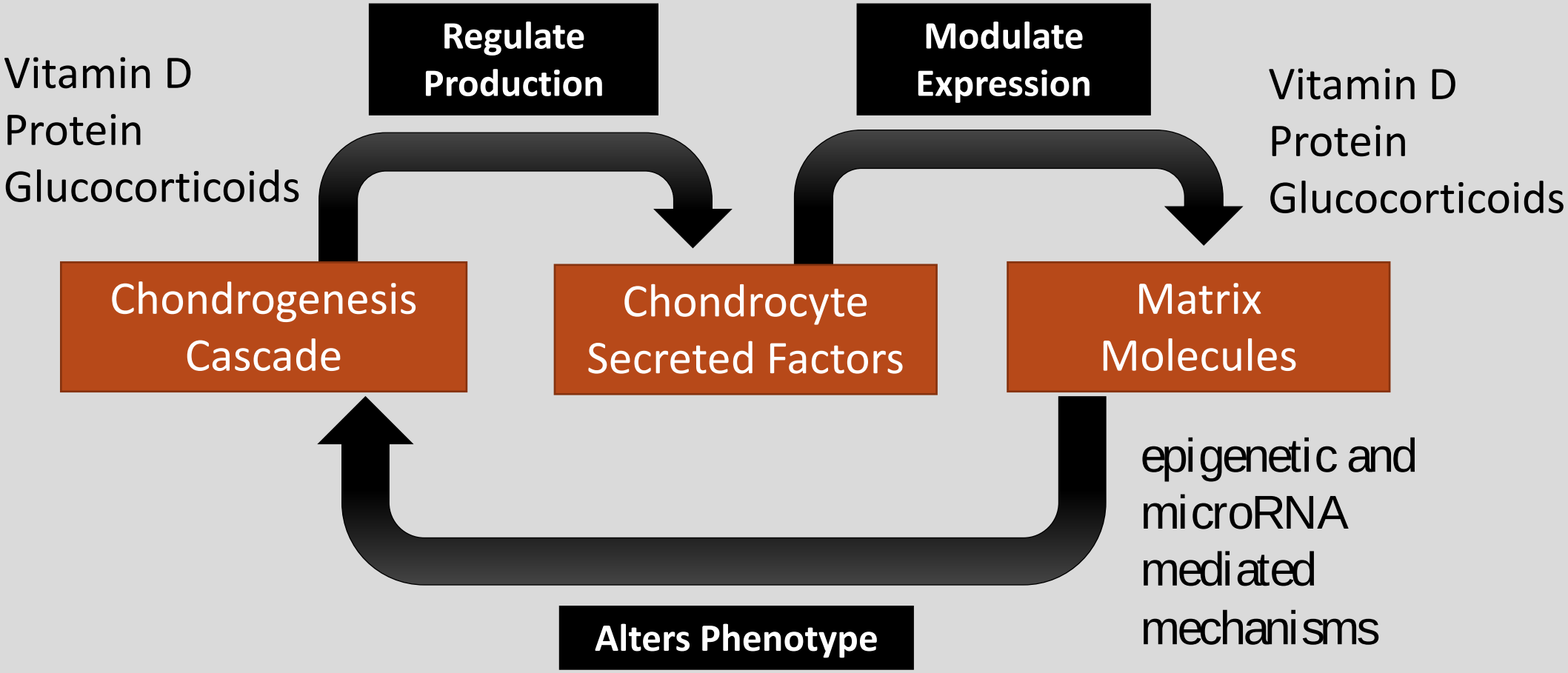


Chondrocytes in the cell cycle phase

Hypertrophic Chondrocytes near the chondro-osseous junction

Wilsman et al., 1998

Growth Plate Microenvironmental Regulatory Opportunities during Chondrogenesis



Michigami et al., 2013 Cell Mol Life Sci 70:4213

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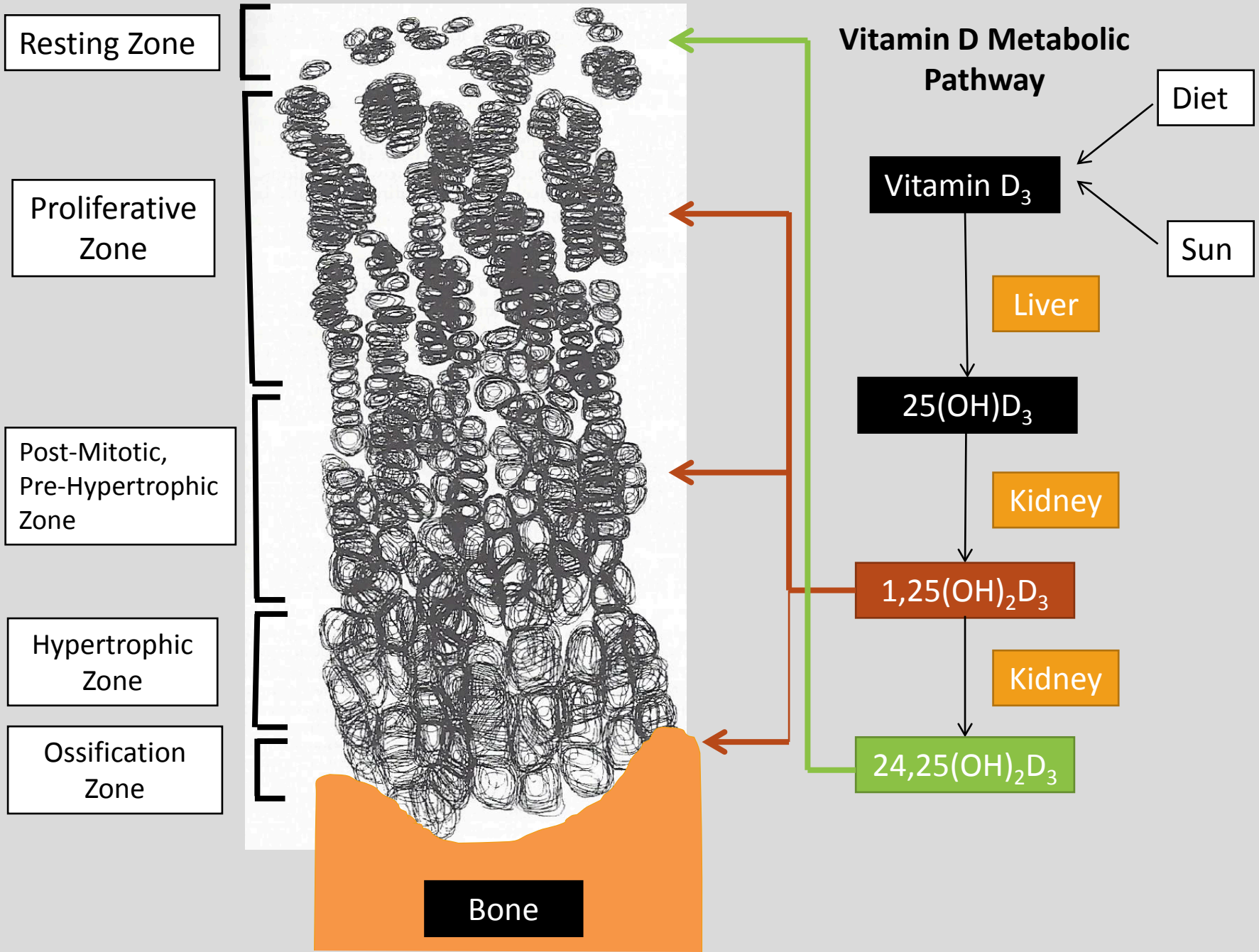
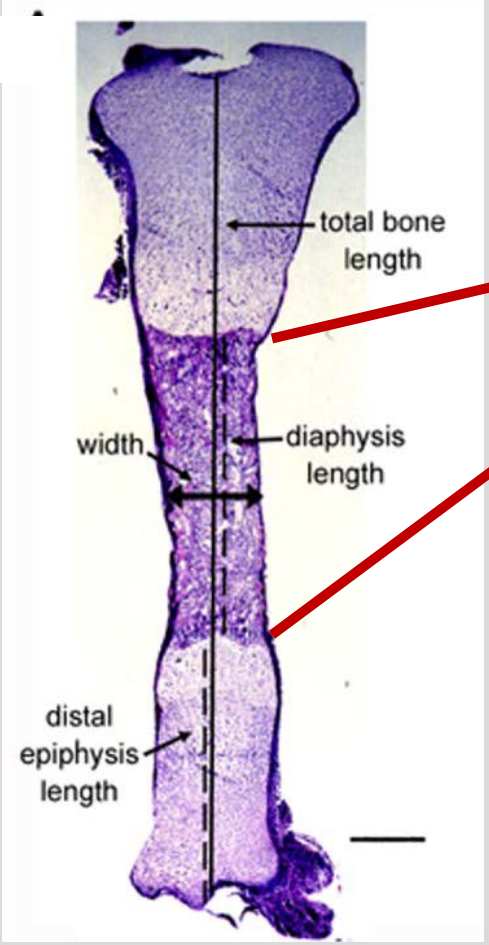
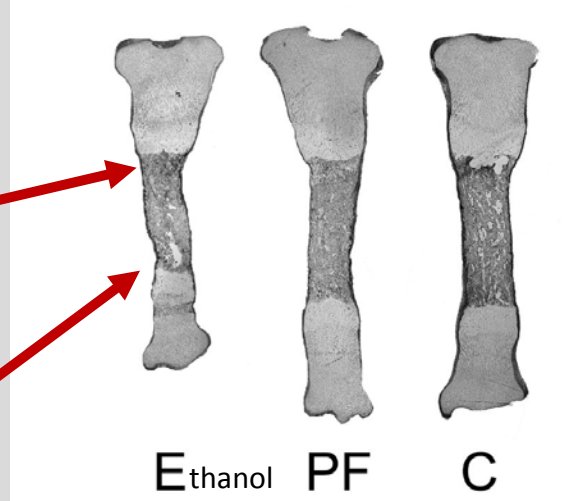
Vitamin D_3 Metabolism and Effects the Growth Plate



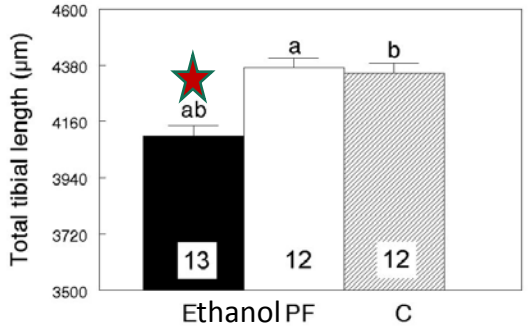
Ethanol reduces tibial length

1> Reduced diaphyseal length

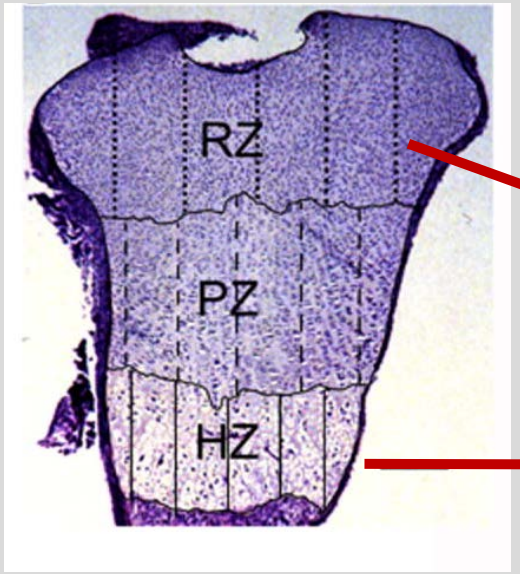




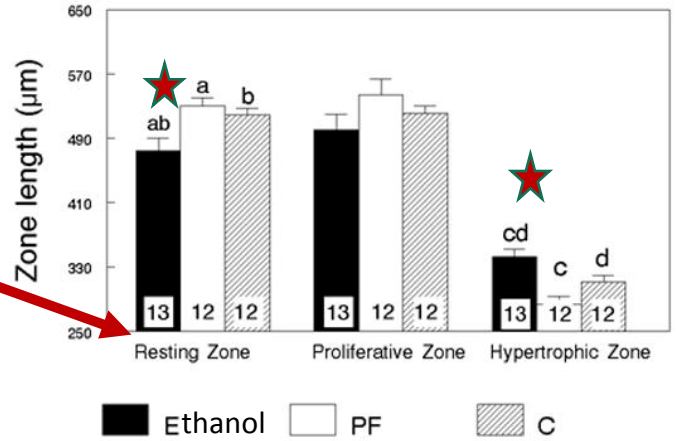
P<0.001



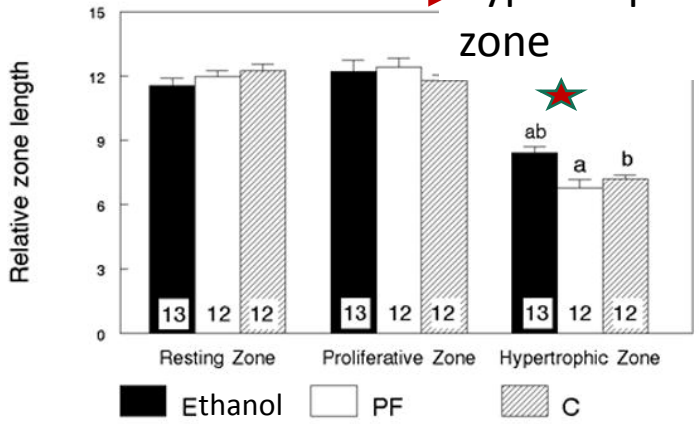
2> Altered histology proximal epiphysis



Shorter resting zone



Increased hypertrophic zone



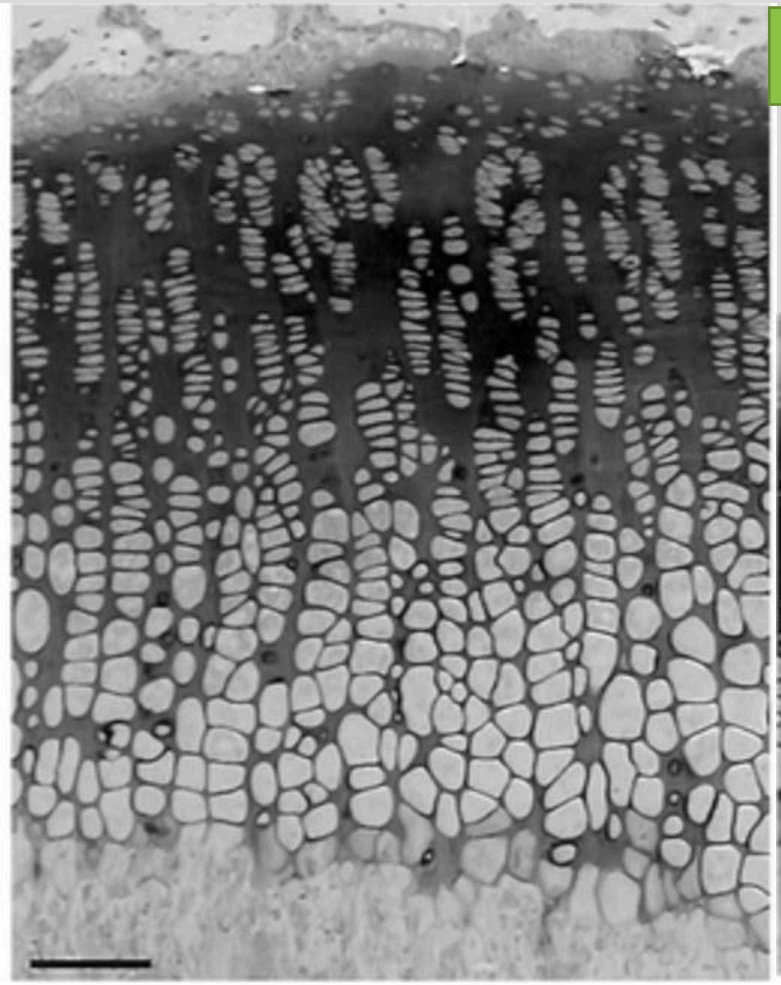
Snow and Kiever *Bone*. 2007 41(2): 181–187.

PF Paired Feed controls for ethanol in terms of calories

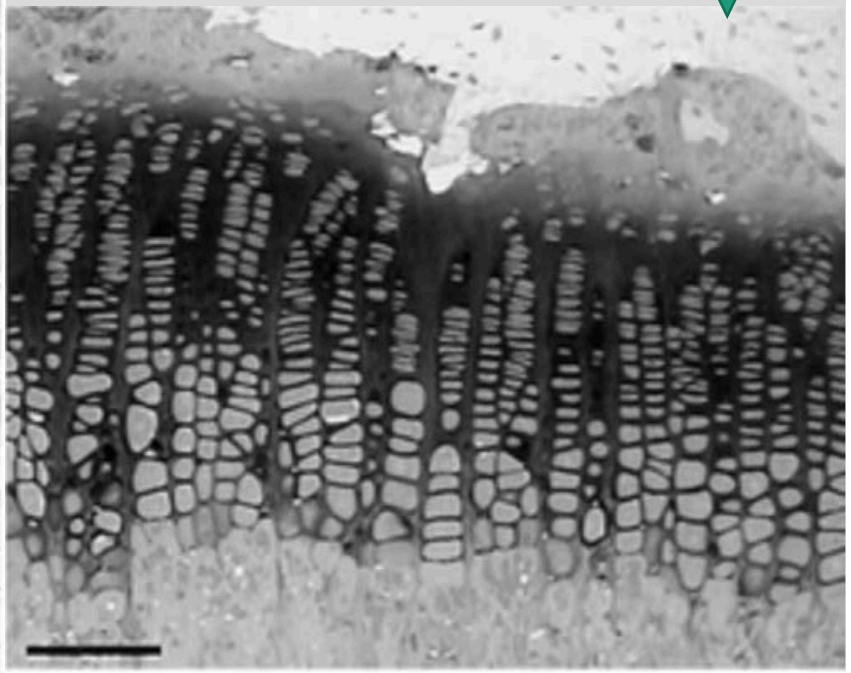
Fasting and the growth plate: Is Catch-Up Possible?

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

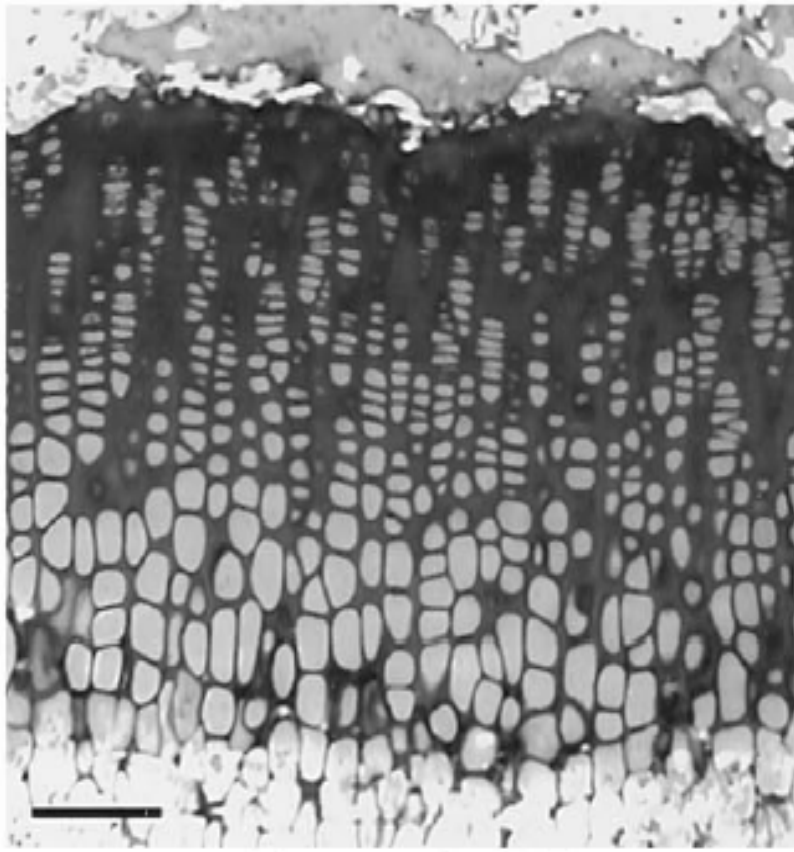
FASTED ANIMALS



Control, PT



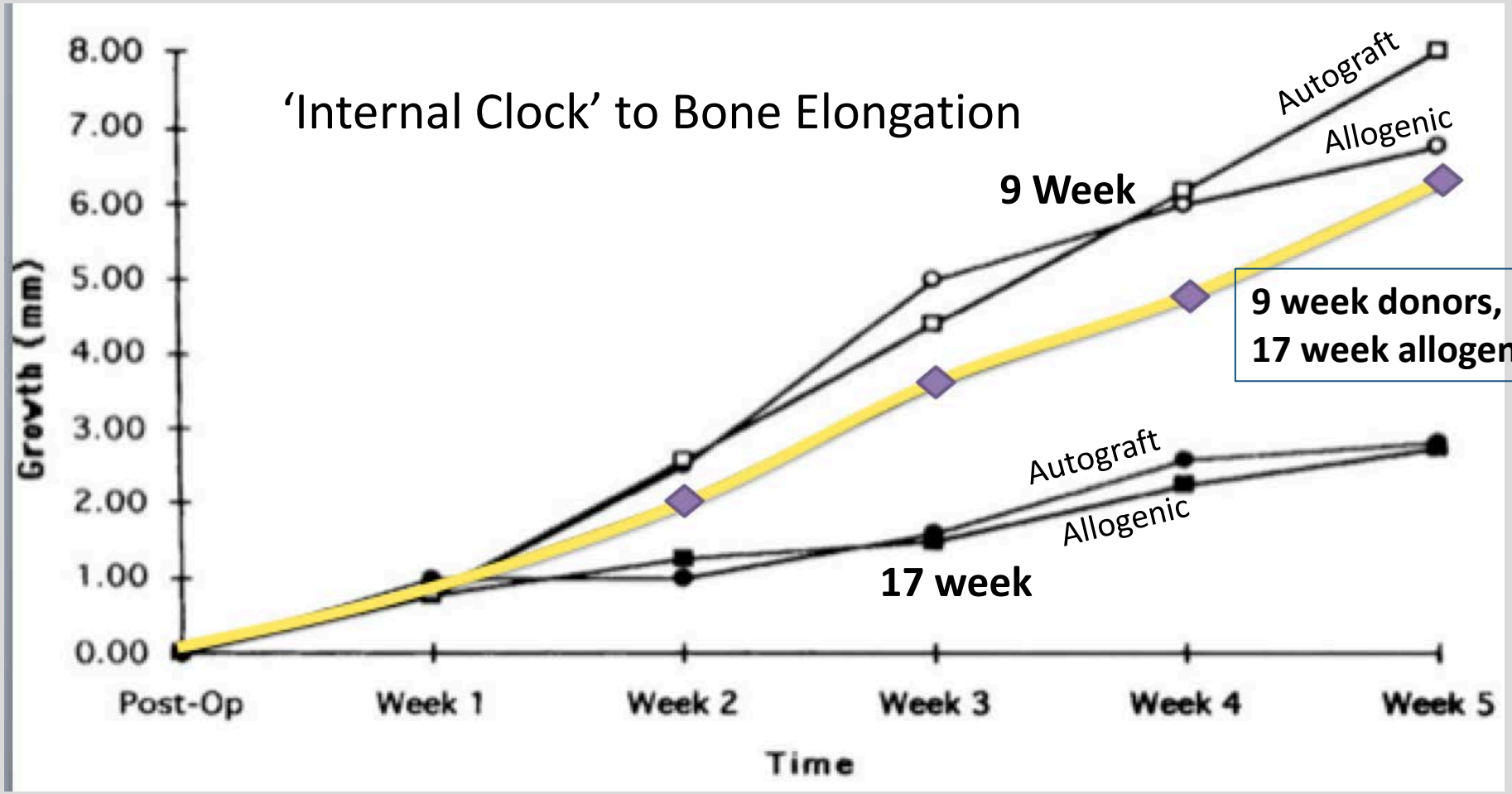
Fasted, PT



Fasted, PT

Farnum, Cornelia E., et al. "Effect of short-term fasting on bone elongation rates: an analysis of catch-up growth in young male rats." *Pediatric research* 53.1 (2003): 33-41.

Growth Rate: An Intrinsic Program (vs Systemically-Mediated)



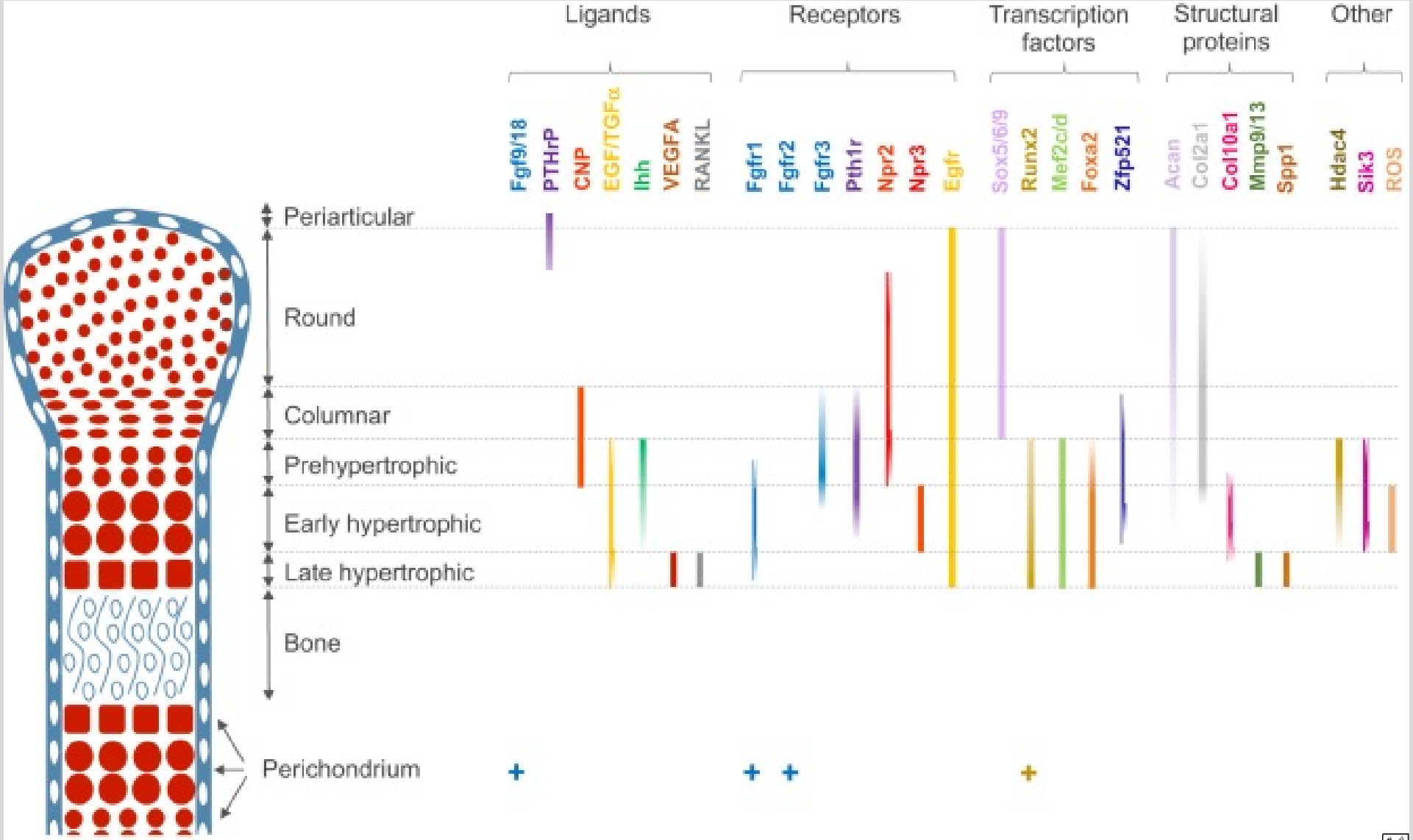
9 week donors,
17 week allogenic recipients

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

Stevens DG, et al. 1999. *J Pediatr Orthop* 19(3): 398-403.

Bone Growth is a Complex System

Summary of regionalized gene expression in the growth plate



Kozhemyakina E, et al., 2015. *Development* 142:817-31.

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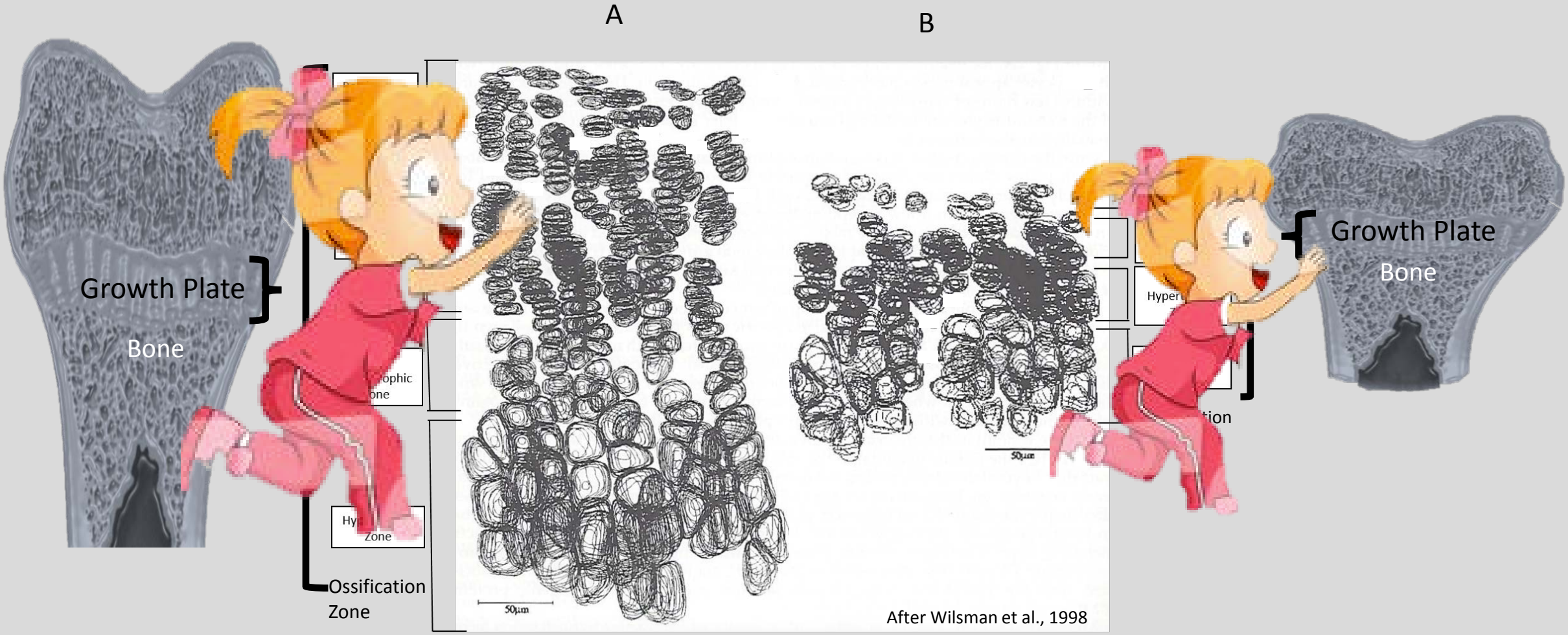
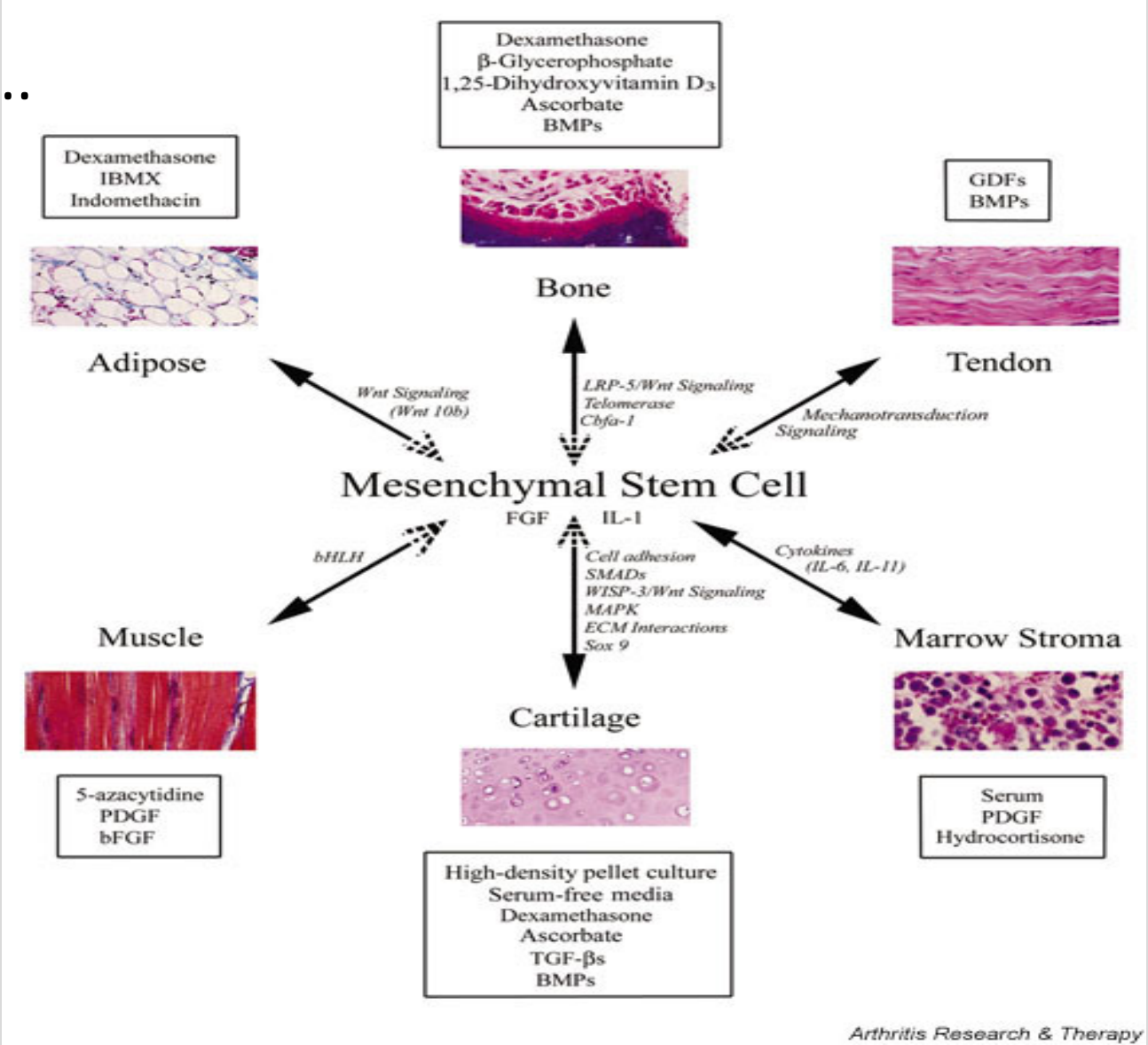
Tall and Small



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….



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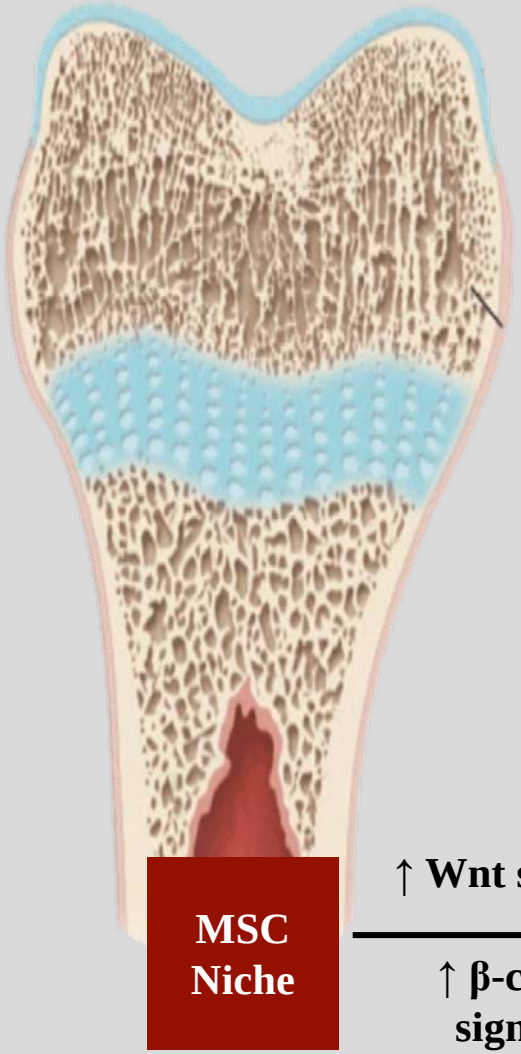
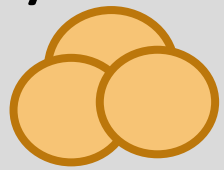
To maximize height growth, Maximize bone cells

Chondrocyte, Osteoblast versus Adipocyte Differentiation



↑ Wnt signaling

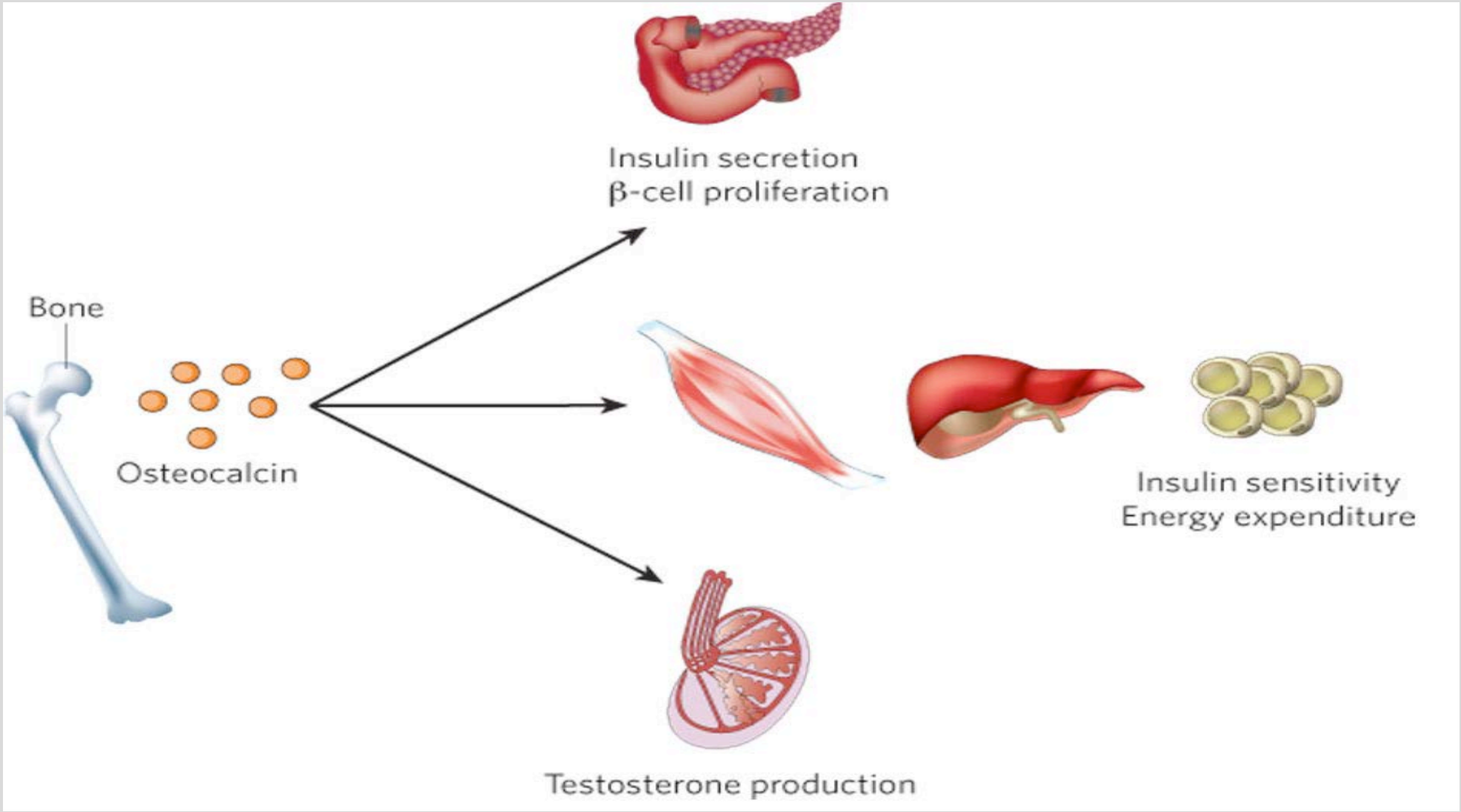
↑ β-catenin signaling



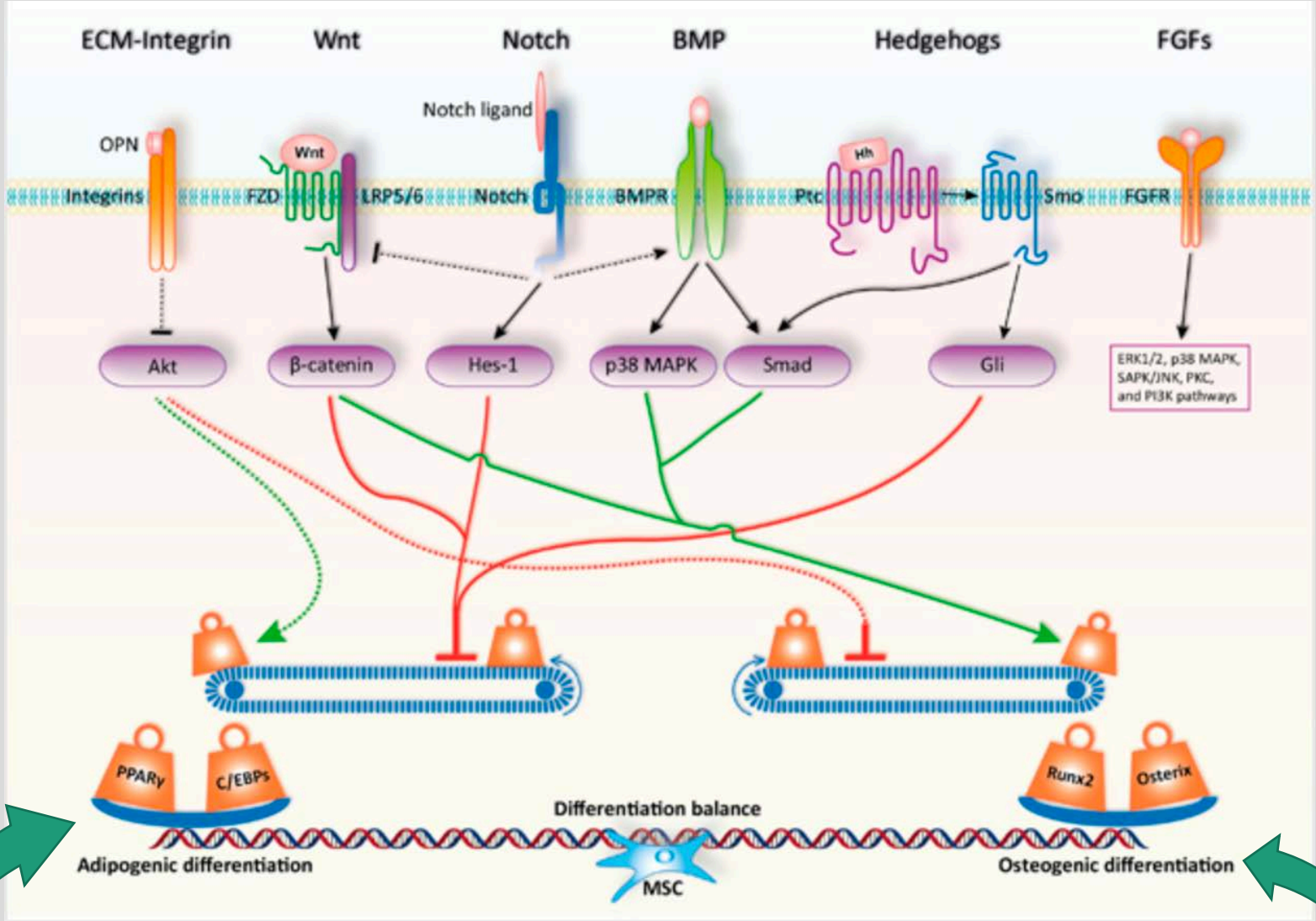
Adipocytes
↓ Differentiation

Osteoblasts
↑ Differentiation
↑Bone mineralization

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*

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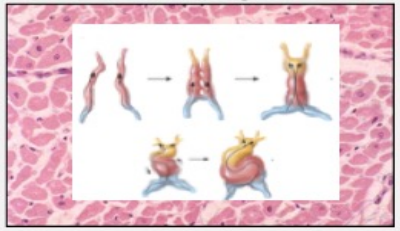
Critical Periods: Limited Time Frames for Development

Heart

Prenatal Day 18

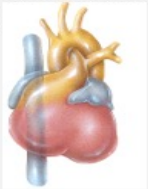
Cardiac progenitor cells

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

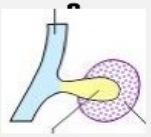
Kidneys

Prenatal Week 3

Intermediate mesoderm

Metanephric Mesenchymal cells

Prenatal Week 4-8



Contact between uteric bud and metanephric blastema

Prenatal week 9-36

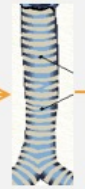
Nephrogenesis

Postnatal Week 14-Year 2

Adult Kidney: disappearance of fetal lobulation, volume increase, adaptation glomular filtration rate and blood flow value

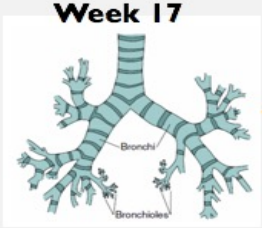
Lung

Prenatal Week 3-4



Epithelial cells form the trachea

Prenatal Week 17

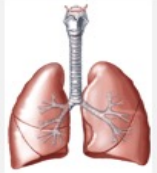


Formation of airways and bronchioles complete

Prenatal Week 17-27

Formation of alveoli

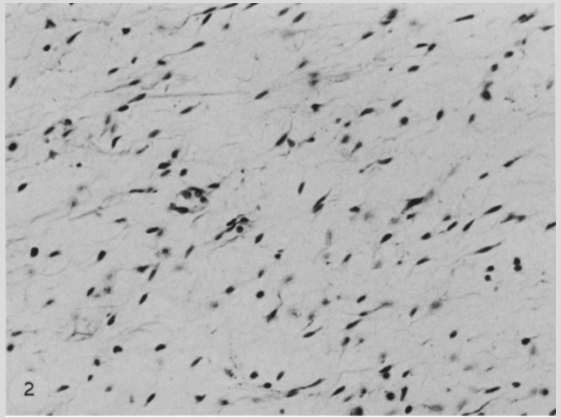
Prenatal Week 36-Postnatal Year 22



Multiplication of alveoli, Alveoli and bronchioles expand in size

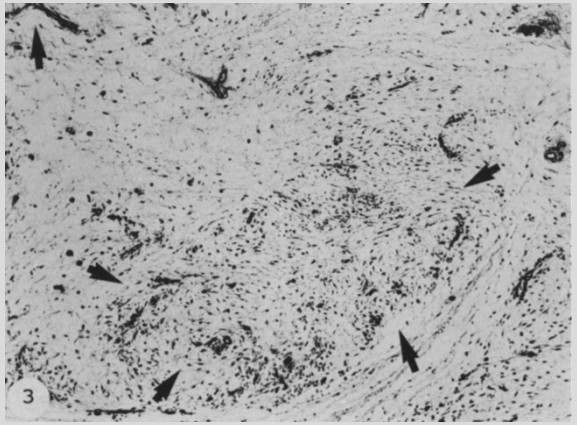
Critical Period of Fat Development: 14th-28th week of Gestation

14 Weeks

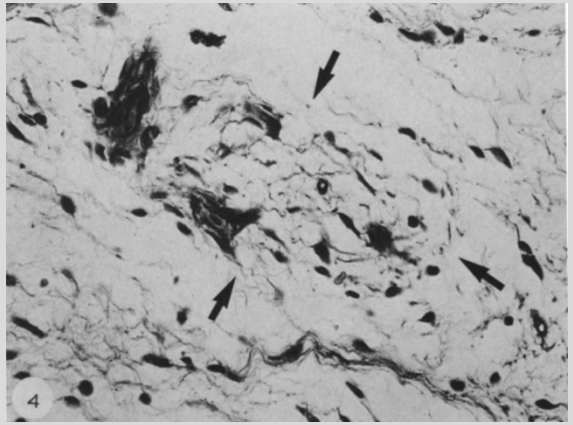


Undifferentiated Fat Tissue

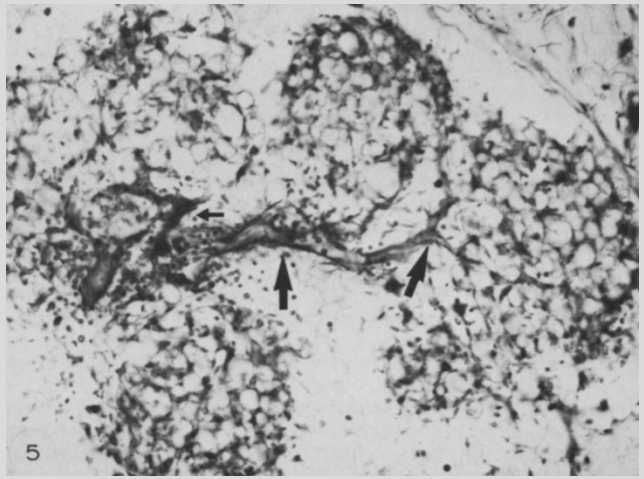
14.5-16 weeks



Blood vessels proliferate and signal areas where fat cells will organize

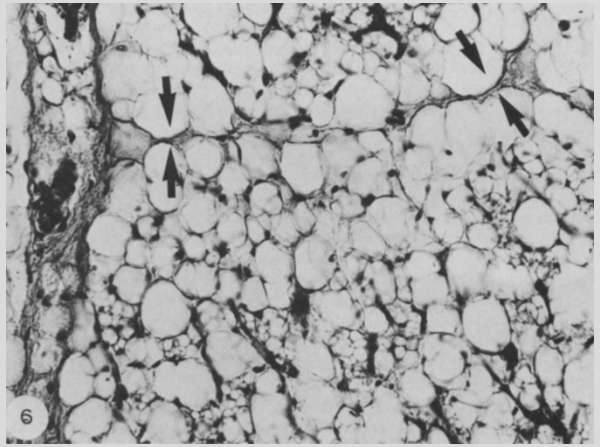


Development of mesenchymal lobules or pre-adipocytes without lipid droplets



Appearance of primitive fat lobules; visible fat storage

28 weeks

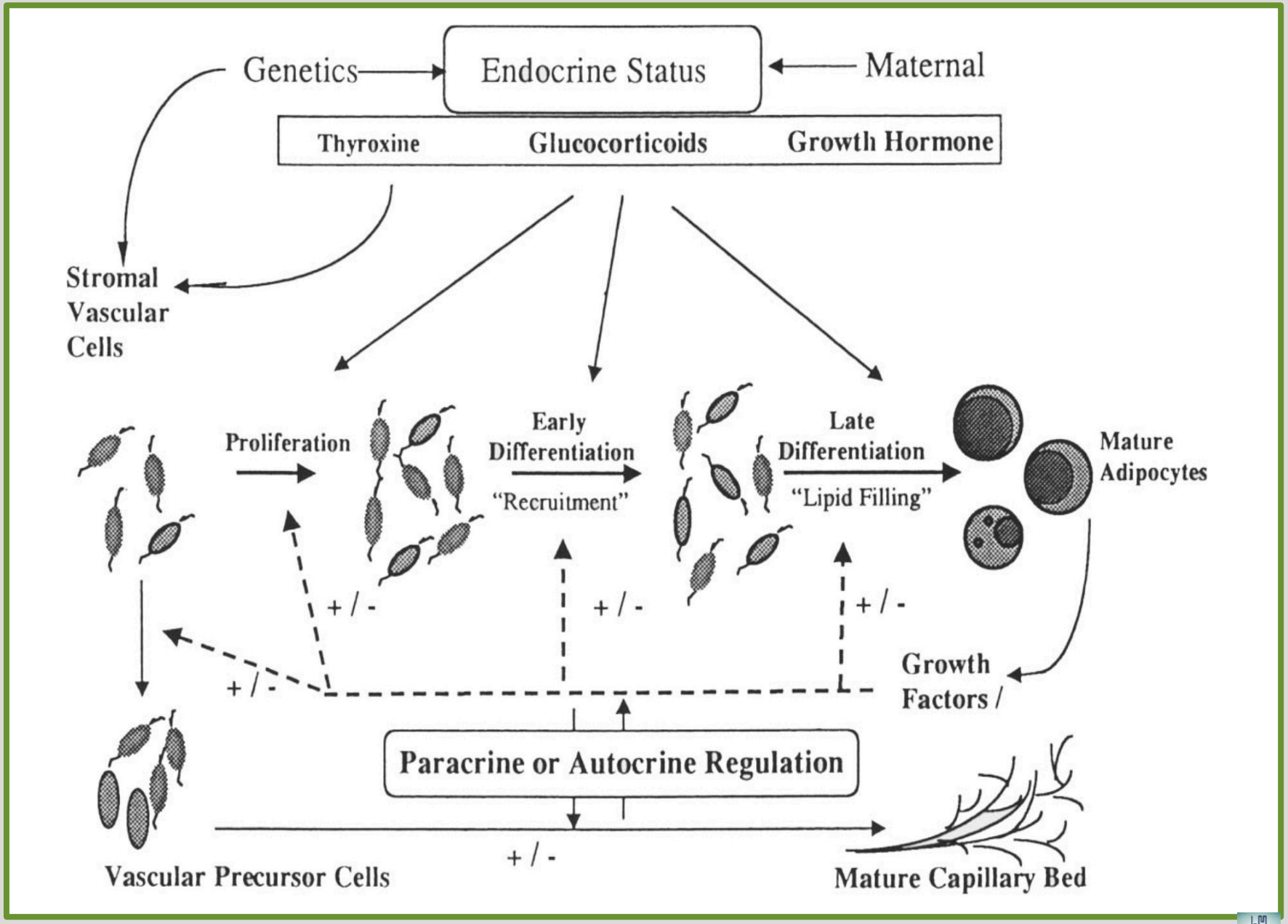


Definitive Fat Lobules

Poissonnet et al., 1983

Fat Cell Development In Utero

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

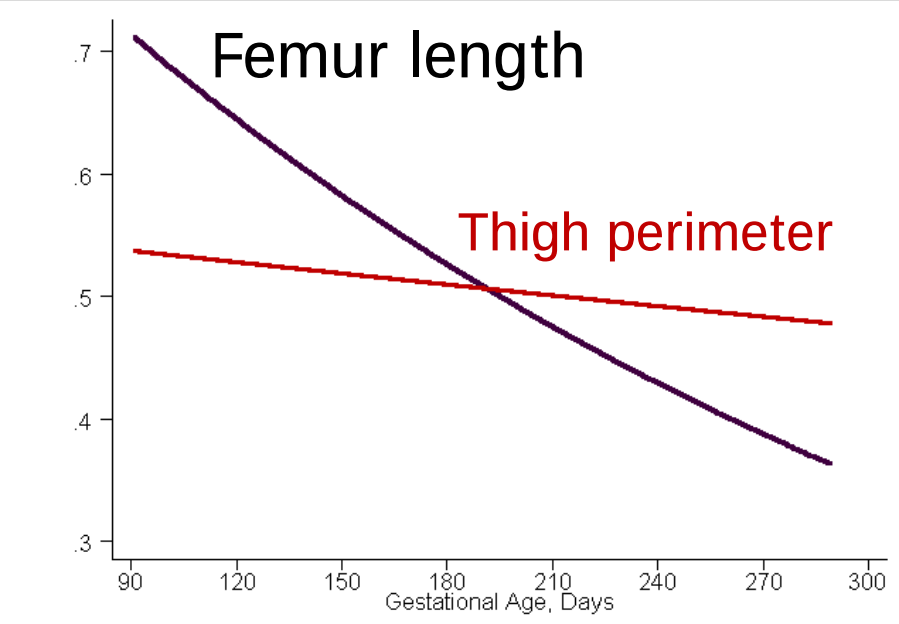


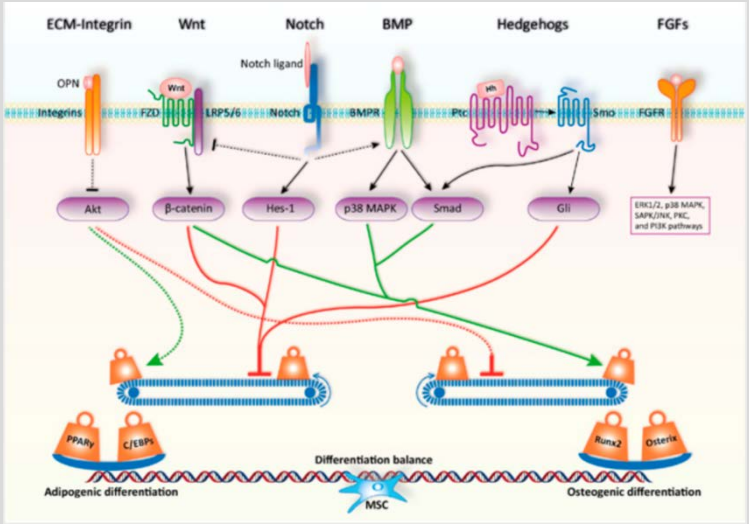
Martin et al., 1998

Maternal Diabetic Effects:
Third trimester Short and Plump patterns emerge

- Limbs:
  Short, Plump

- Length Growth
  Declines Relative
  to Limb Perimeter





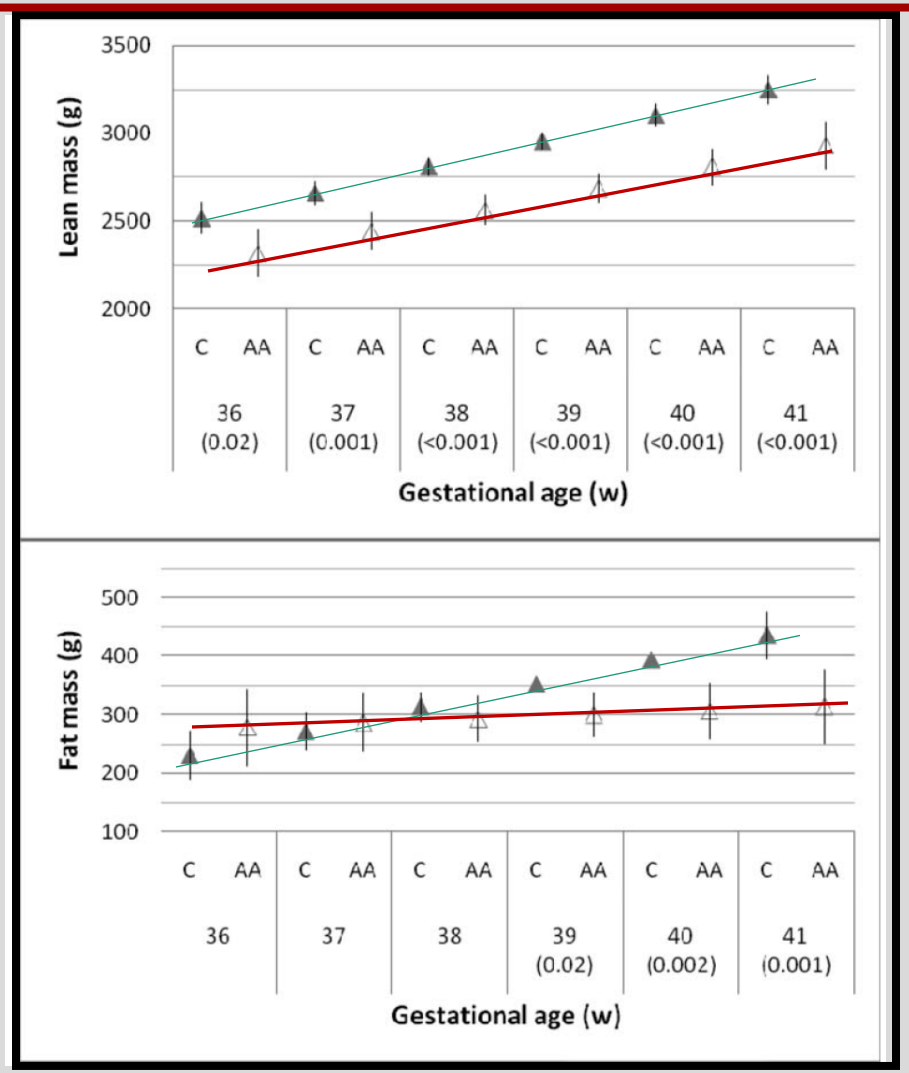
Thefetus.net

Chen Q, et al. 2016. *Cell Death & Differentiation* E-pub ahead of print.
Lampl & Jeanty *2005 AJHB*

Ethnic variability: Body Composition Development
Early fat, late lean phenotype

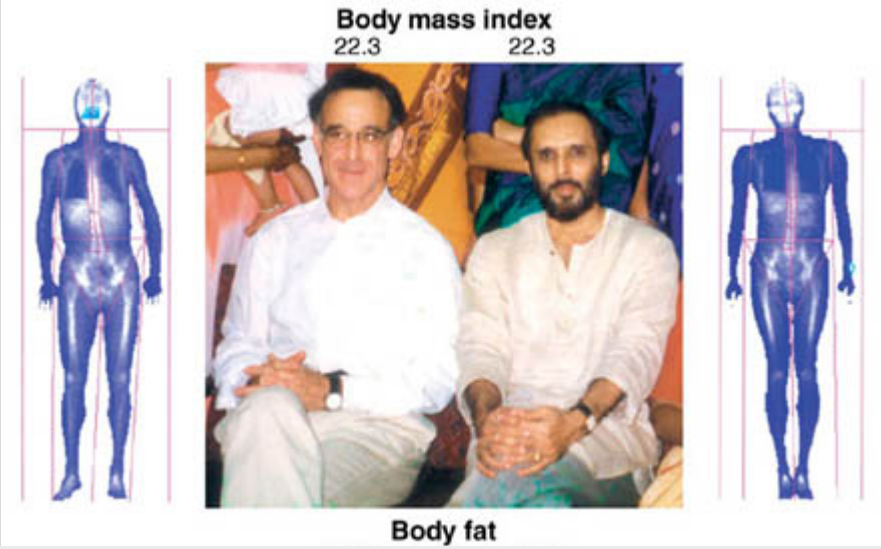
▲ Non-Hispanic Caucasian

△ **African-American**



Lampl et al., 2012 Am J Hum Biol 24:640; Data: Roberto Romero & colleagues, PRB, NICHD

Skinny-Fat South Asian Phenotype

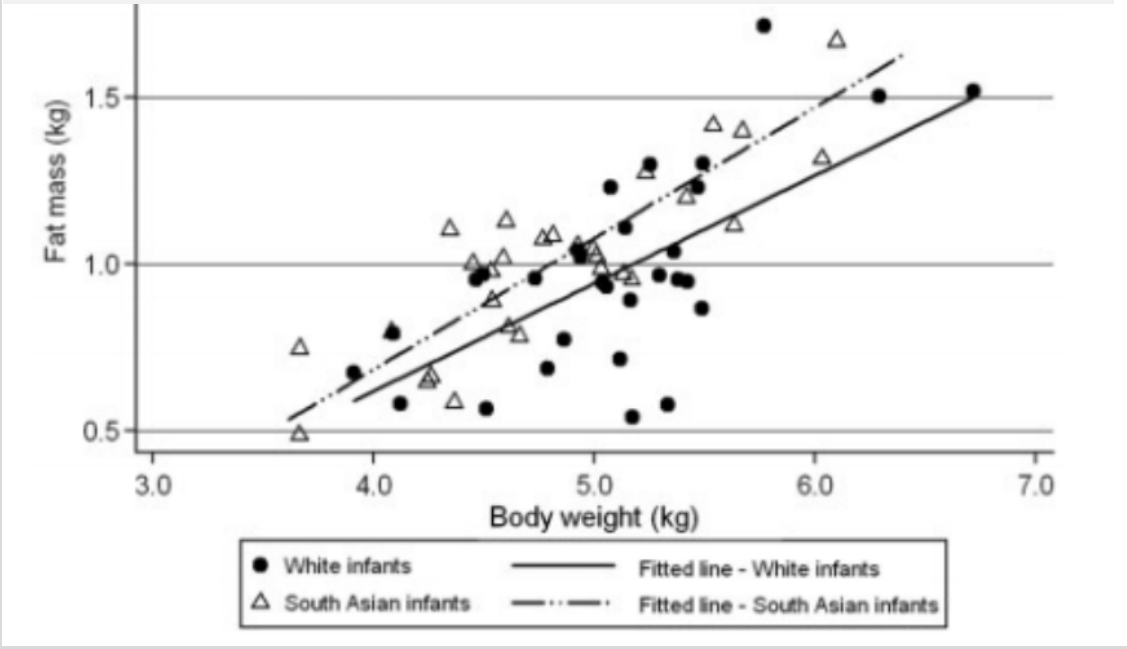


The Y files: John Yudkin (L) and Chittaranjan Yajnik (R) share the same body mass index, but Yajnik's body harbors significantly more fat.

*Reprinted with permission from Elsevier (The Lancet, **363**, 157–163)*

Nature Medicine **10**, 325 - 327 (2004)
doi:10.1038/nm0404-325**News Feature: Asia's big problem**

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



Stanfield et al, *Int Epidemiol* 2012;41:1409–1418

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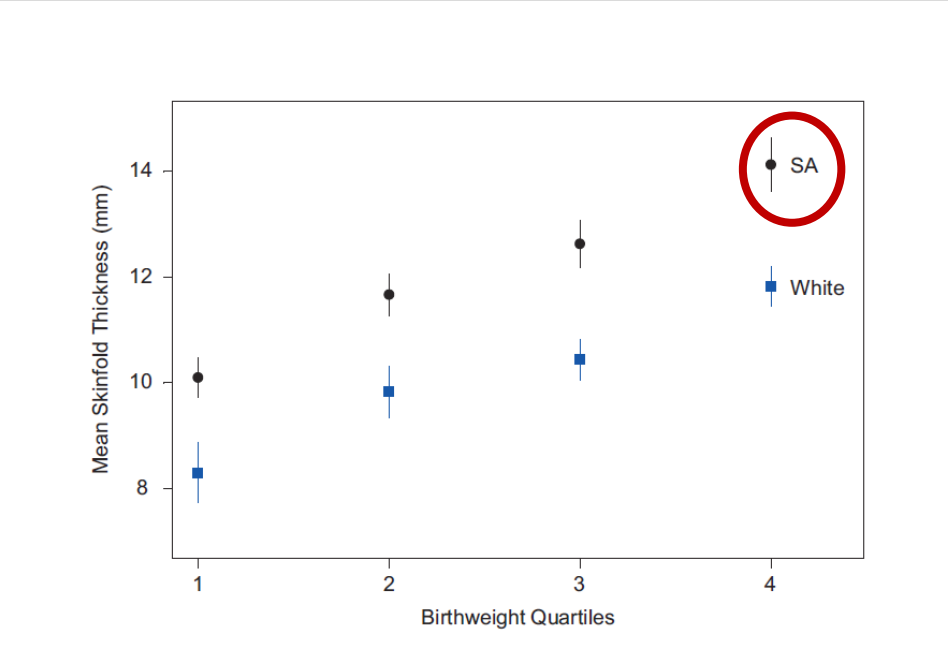
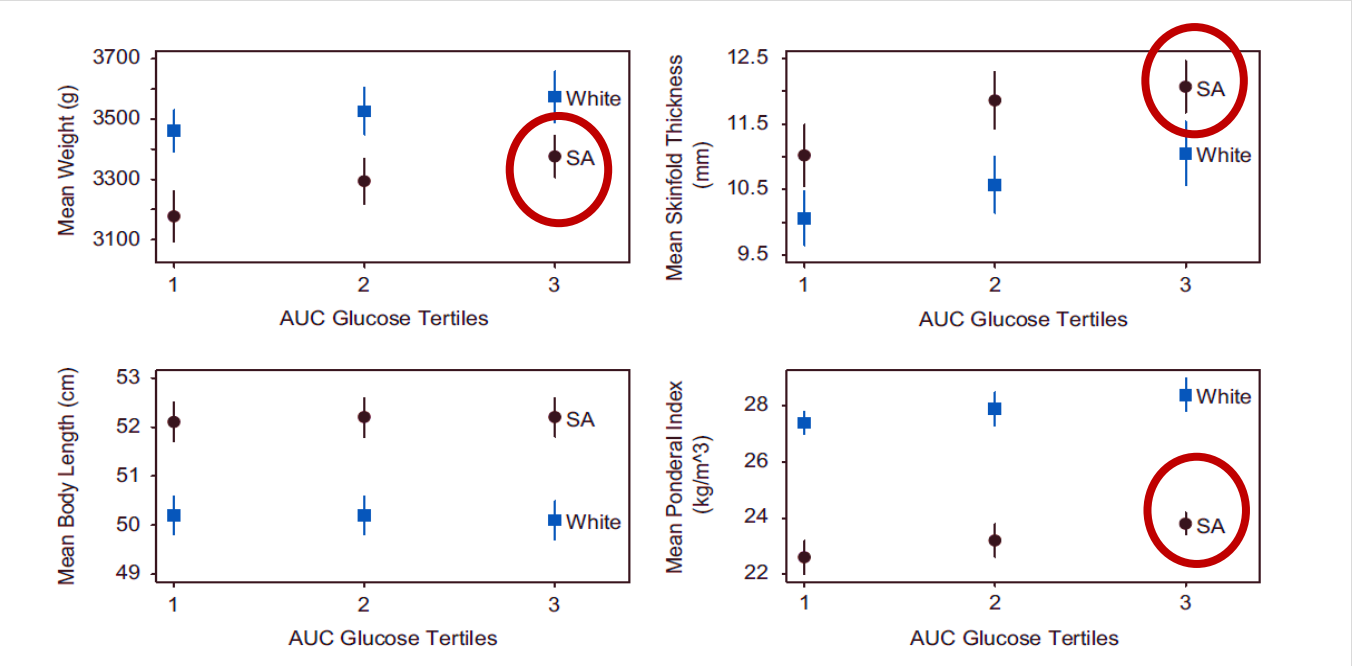
Skinny-Fat: Prenatal Origins



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



Newborn body composition by maternal AUC glucose tertiles

Anand et al., Int J Obesity (2016) 40, 239–244

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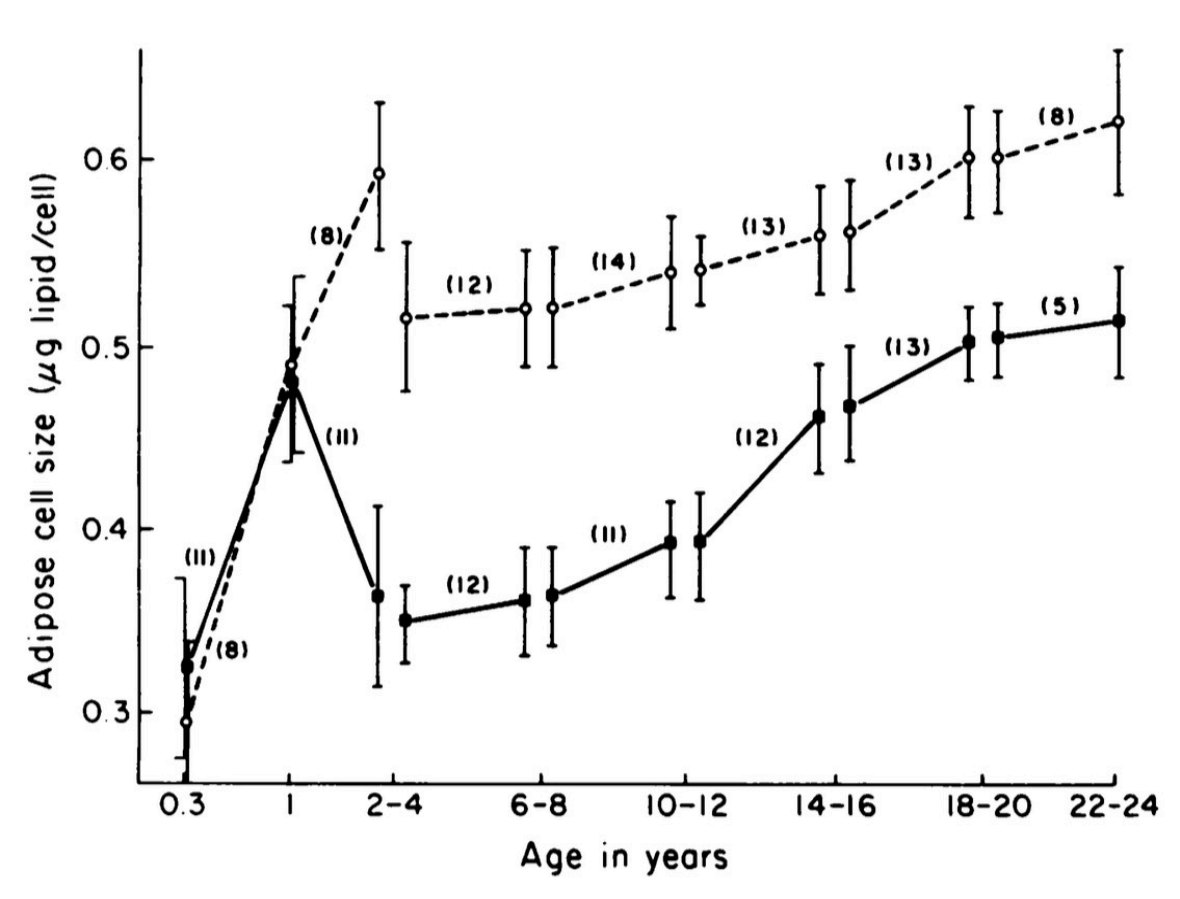
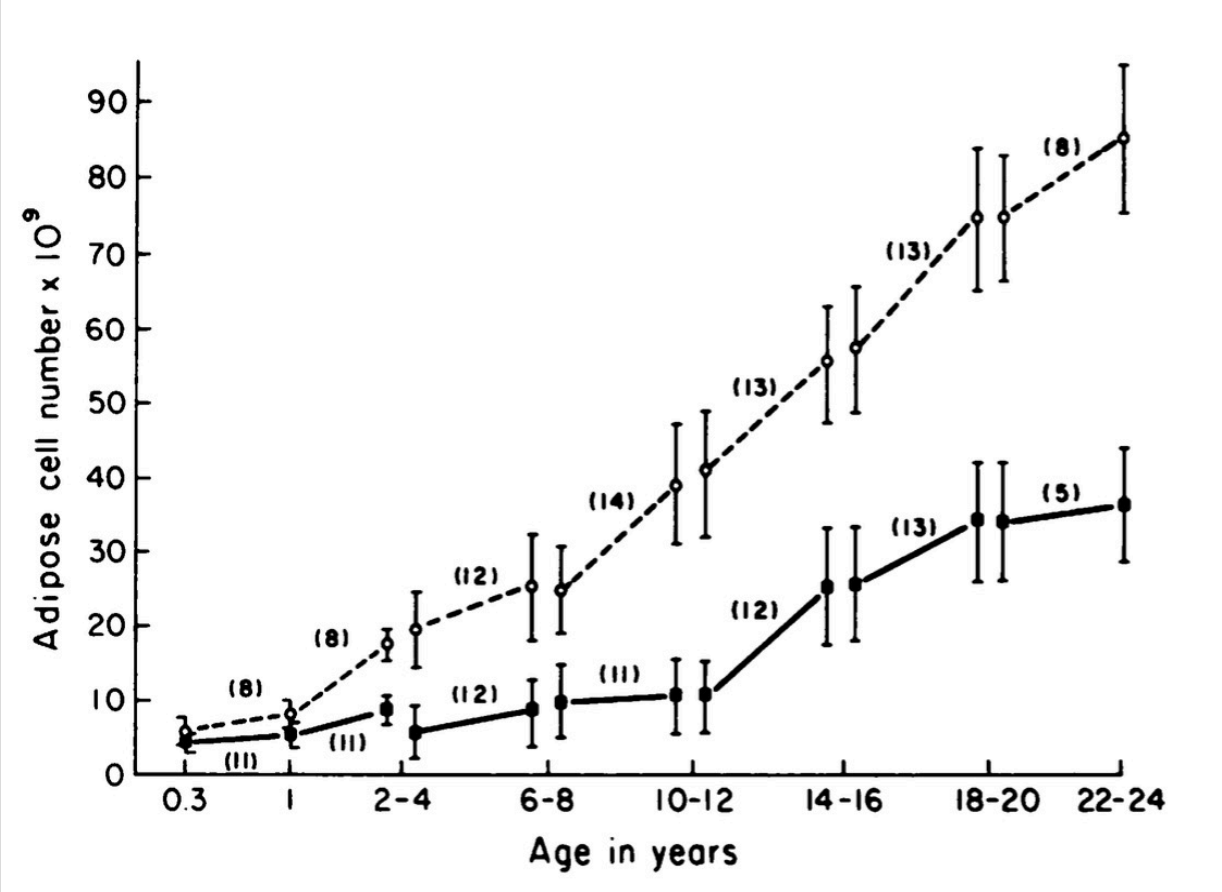
Developmental Trajectory of Fat





Knittle et al, 1979

By age 2, obese children had achieved adult non-obese values for cell size (0.4-0.7,uglipid/cell),

● Non-obese children & adolescents

○ Obese Children & adolescents

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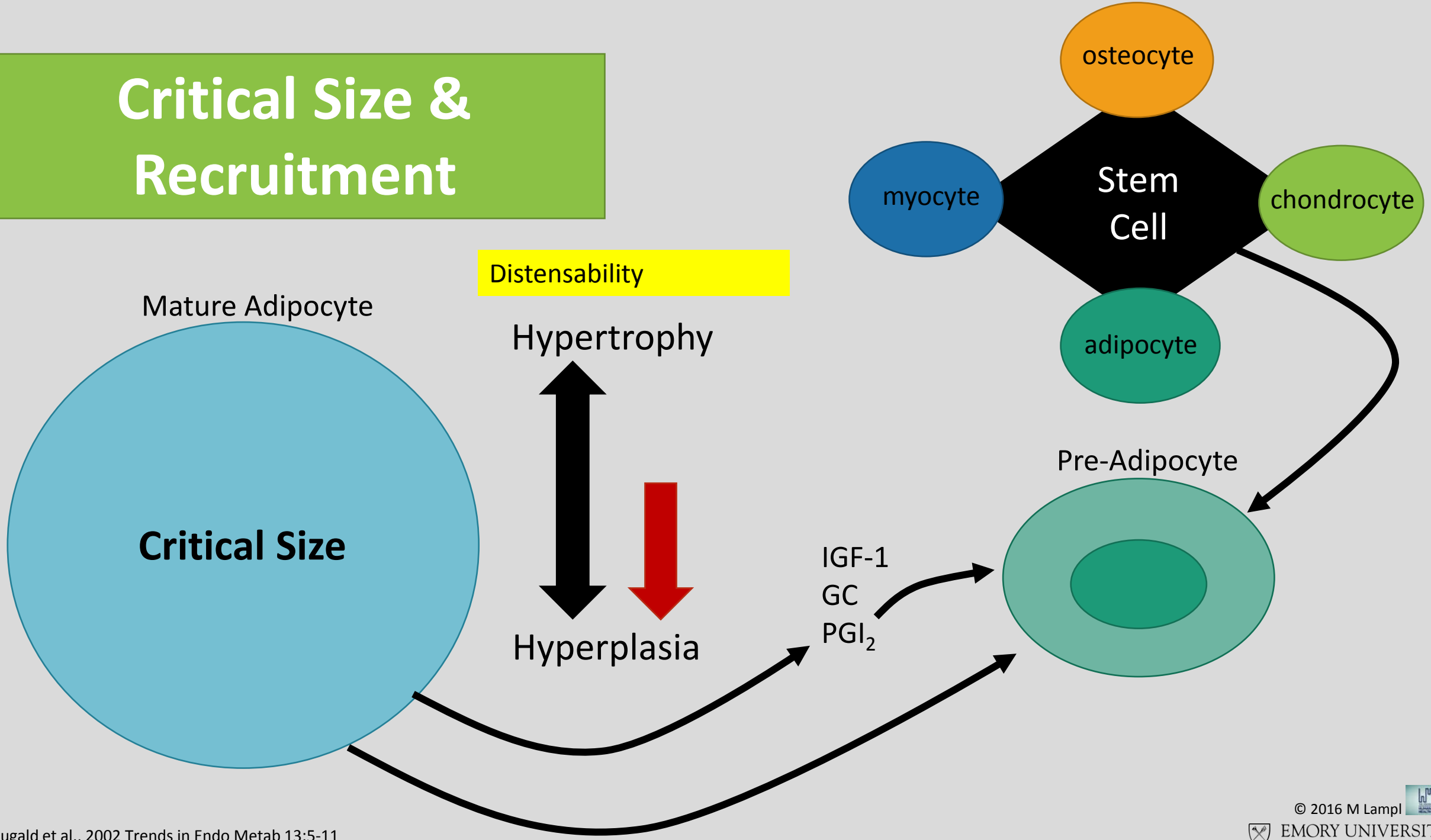
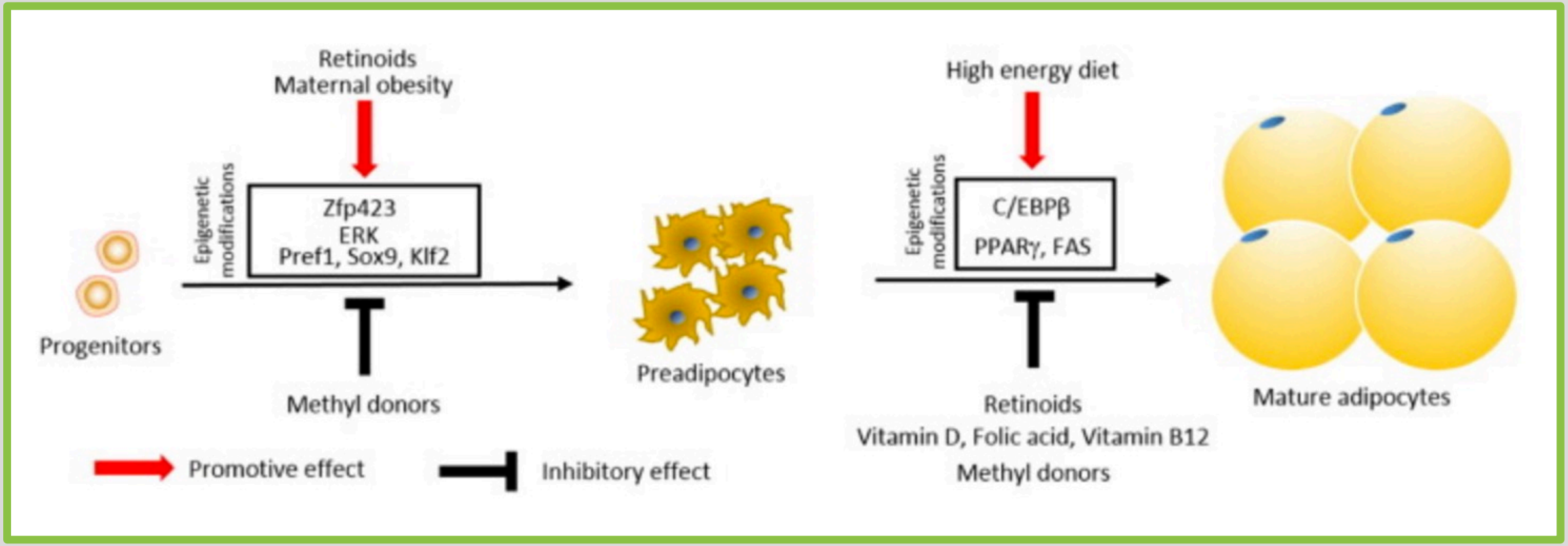
Critical Size & Recruitment



MacDougald et al., 2002 Trends in Endo Metab 13:5-11

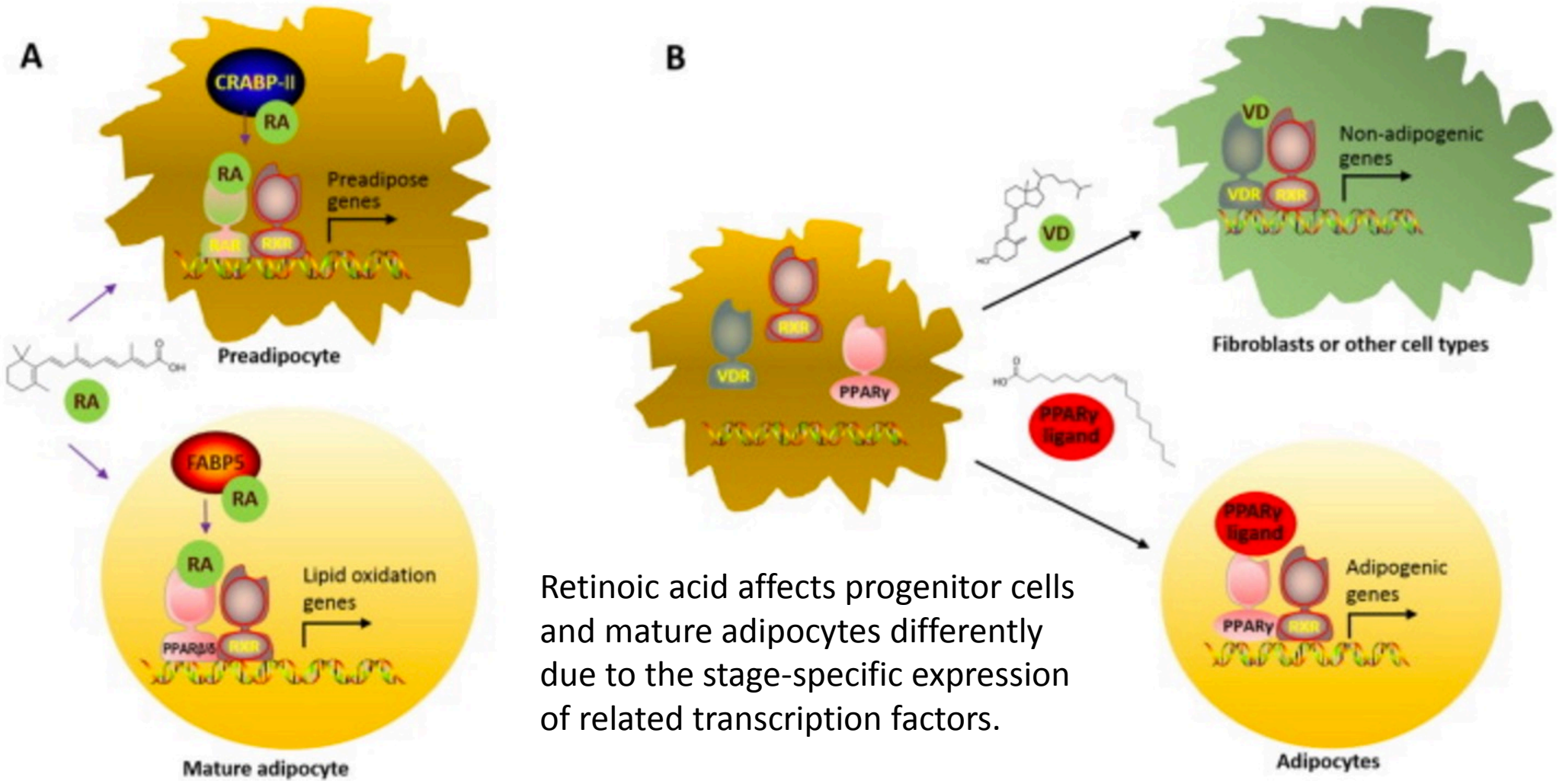
Epigenetic regulation of Adipose Tissue Development



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

Wang et al. 2016

Nutrigenomic regulation of Adipogenesis



Retinoic acid affects progenitor cells and mature adipocytes differently due to the stage-specific expression of related transcription factors.

Wang et al. 2016

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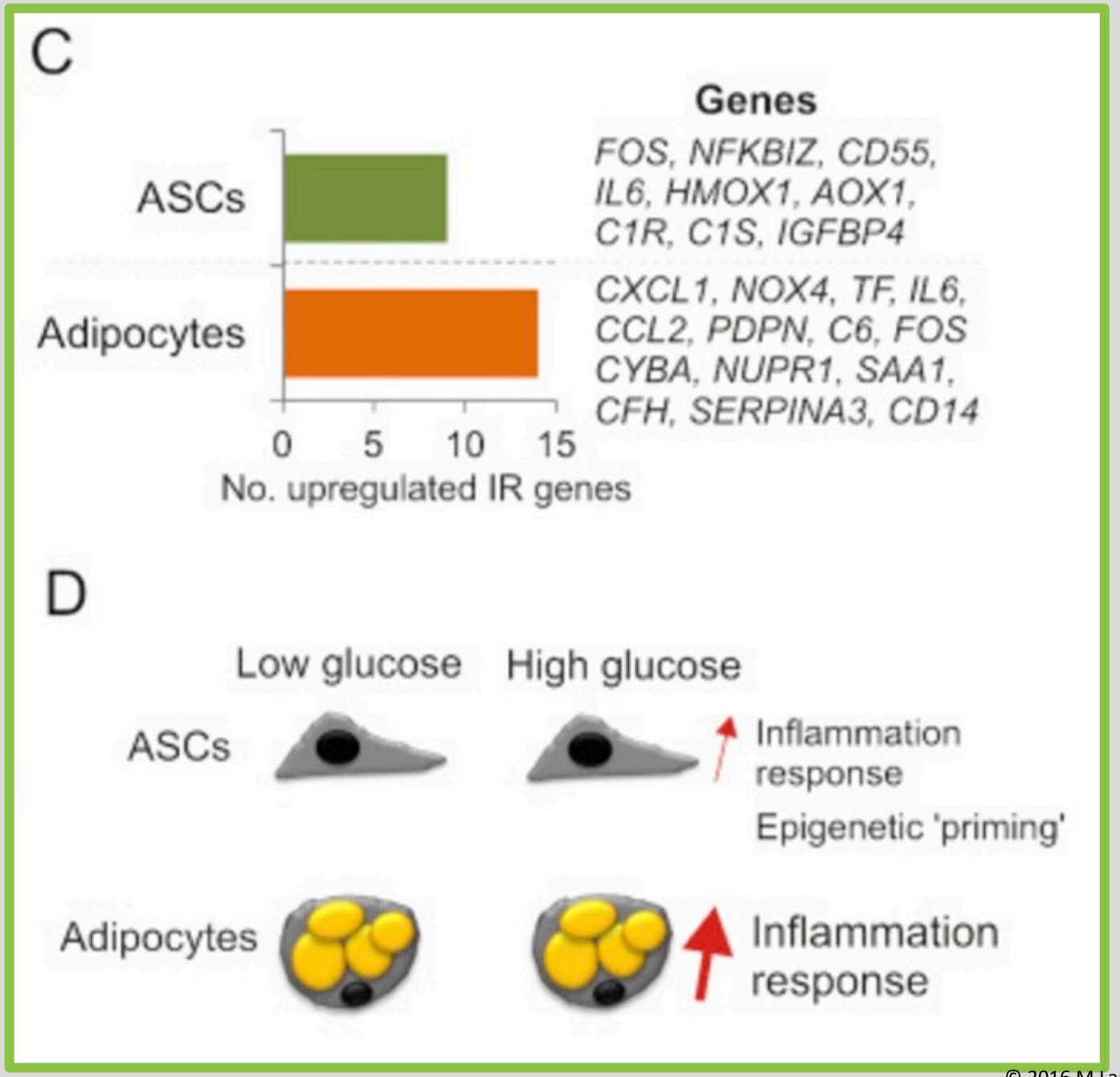
Epigenetic Priming of an inflammatory Response in Adipocyte Precursors: Glucose Exposure



Rønningen et al., 2015

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Why does any of this matter?
The Case of FUFs & *GUMS

Developmental Origins of Adiposity and Long-Term Health

Liquid Supplements for Infants & Young Children

CLAIM

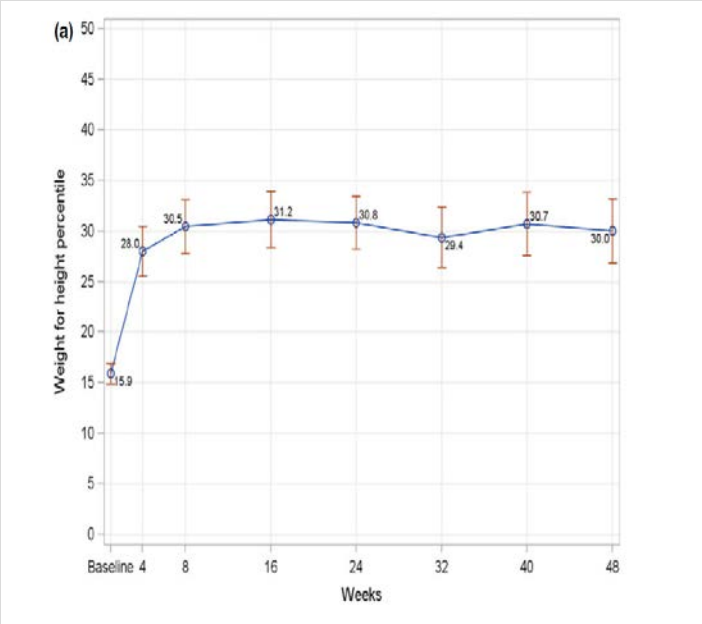
"clinically proven nutrition to help kids *grow*"

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.*,†
- † (in the 5th – 25th weight-for-height percentiles)

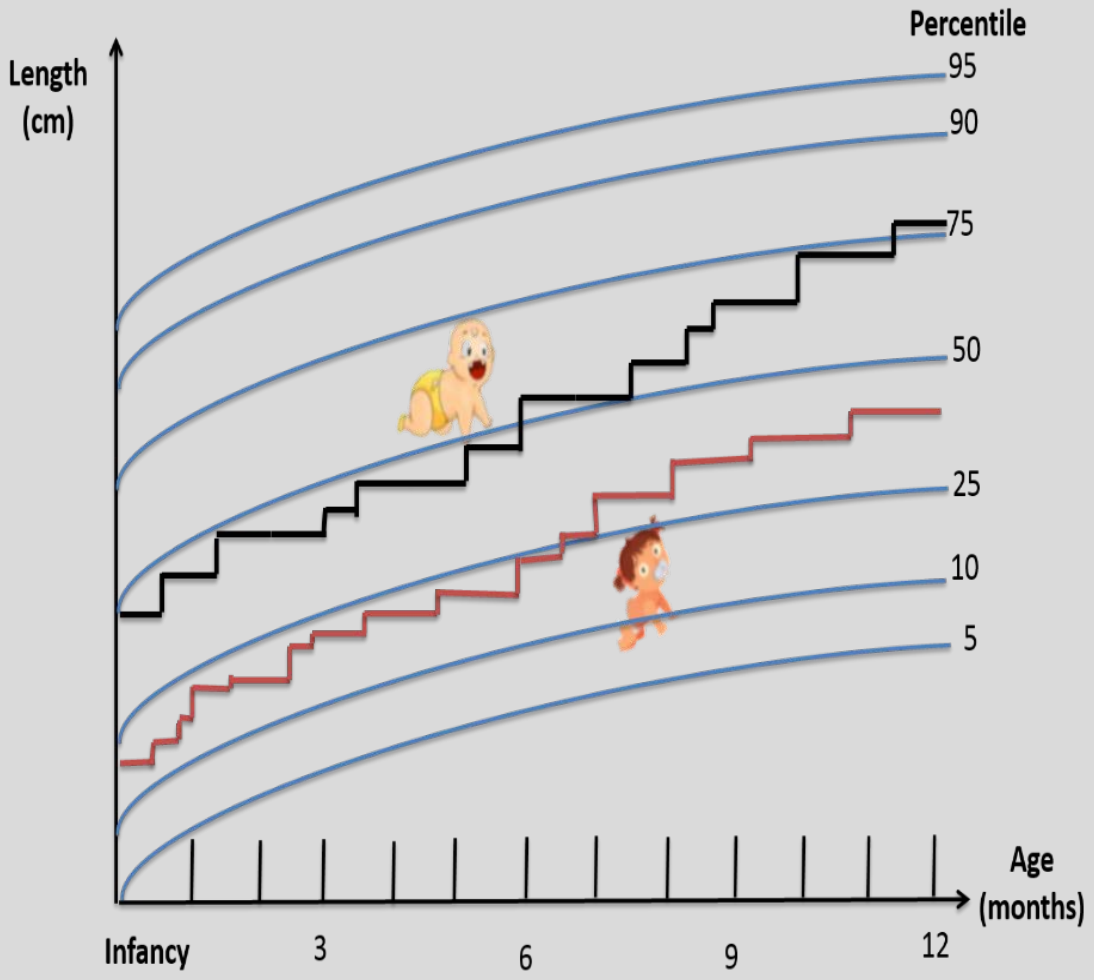


*Suthutvoravut et al., Ann Nutr Metab 2015; 67:119-132

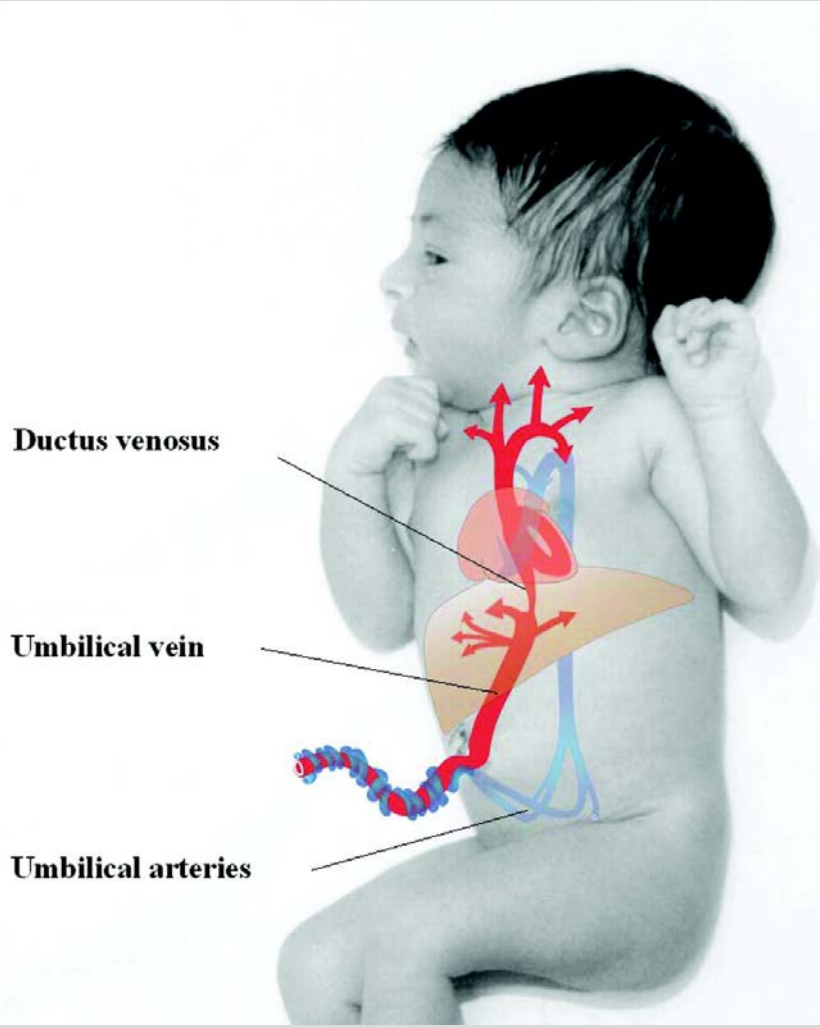
[1]Hyunh et al. *J Hum Nutr Diet*. 2015,28:623-635.
[2]Hall et al.*Lancet Diabetes Endocrinol* 2013, *1*:97-105.

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



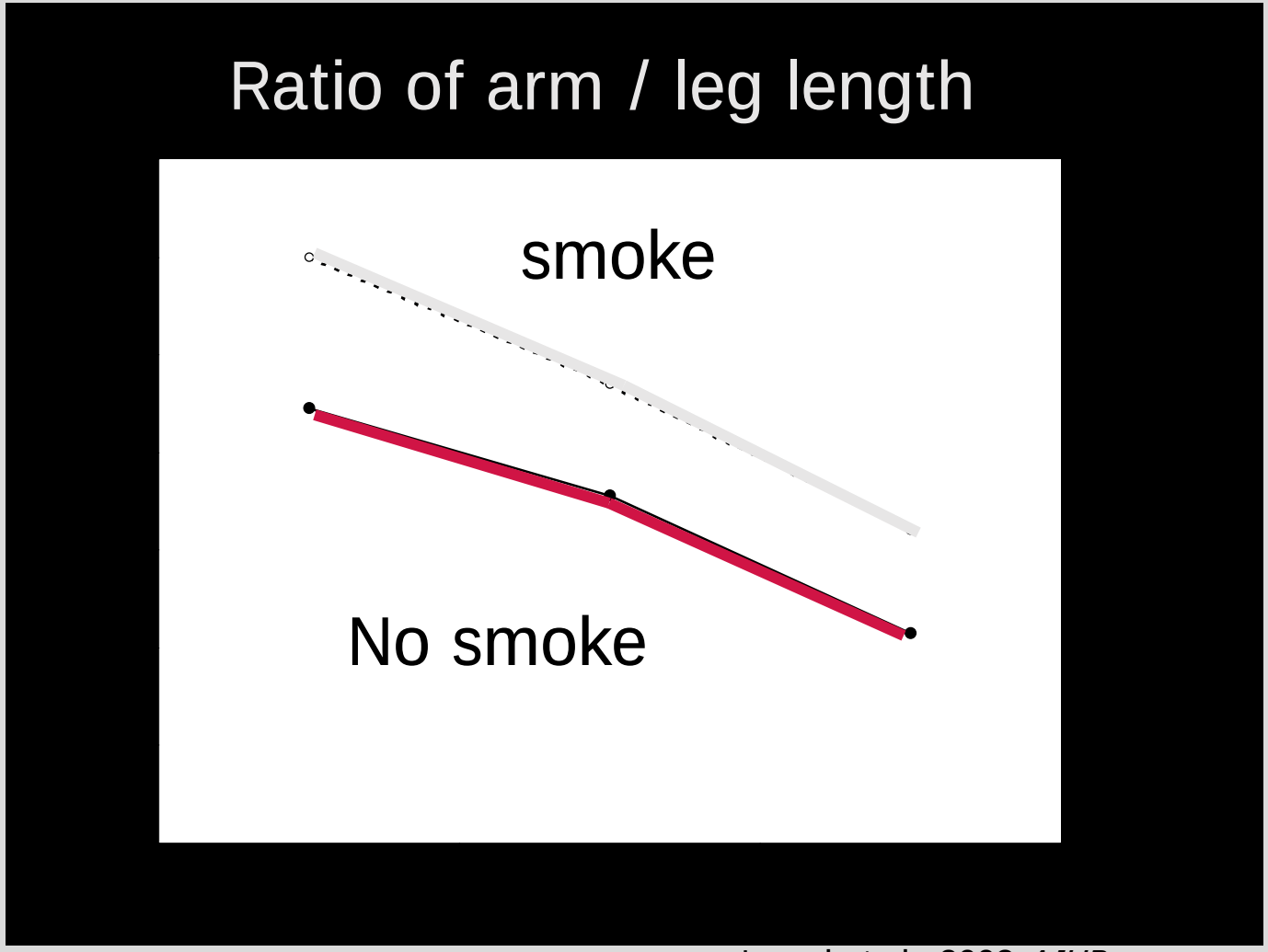
Haugen, G. et al. Circ Res 2005;96:12-14

Circulation Research
American Heart Association
Learn and Live

Maternal Smoking Effects: Altered limb proportions

Longer arms
Shorter legs

Proportional differences



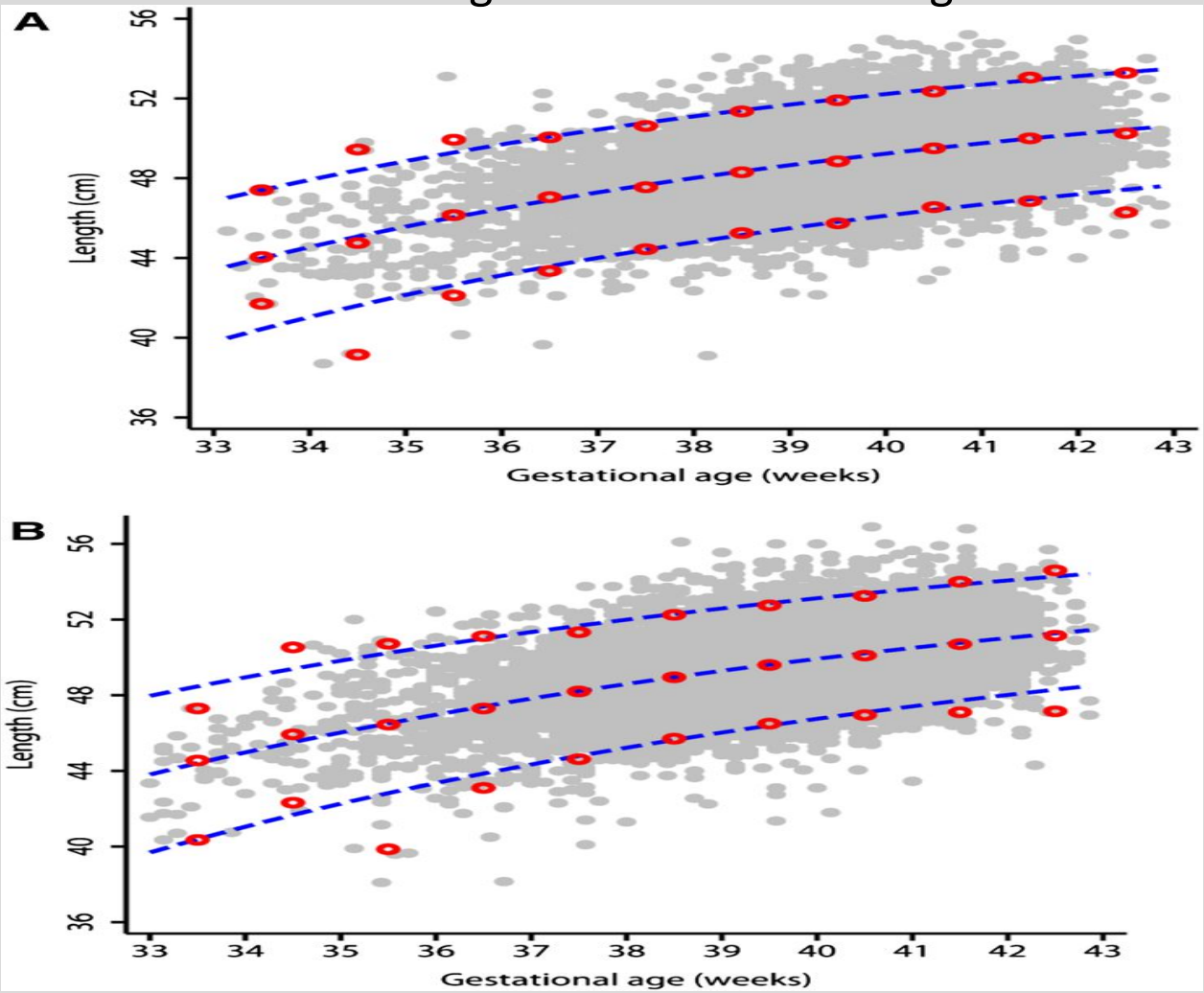
Lampl et al., 2003 *AJHB*

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

Are the lines “tracks”? No
Do some individuals seem to follow them? Yes

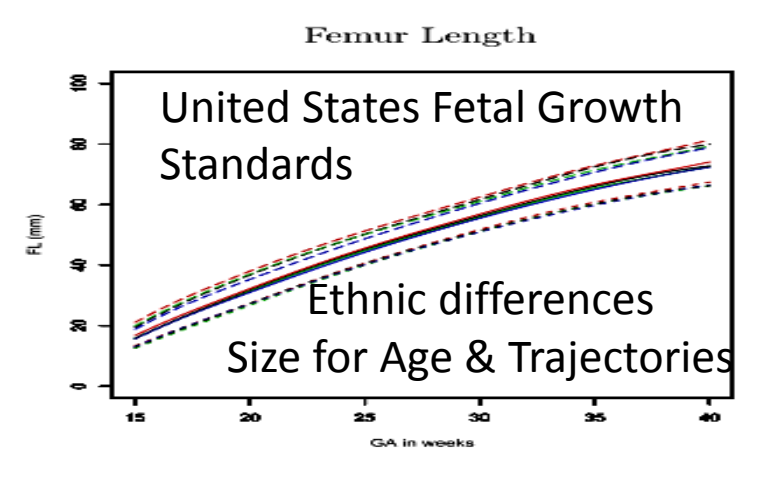
33 to 43 gestational weeks of age



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).

Cutberto Garza Adv Nutr 2015;6:383-390
Advances in Nutrition
AN INTERNATIONAL REVIEW JOURNAL

Normal Growth: High Variability is the Strategy



Buck Louis GM, et al. 2015. *Am J Obstetr Gynecol* 213(4):441e1-e49.

Research article

Open Access

Does one size fit all? The case for ethnic-specific standards of fetal growth

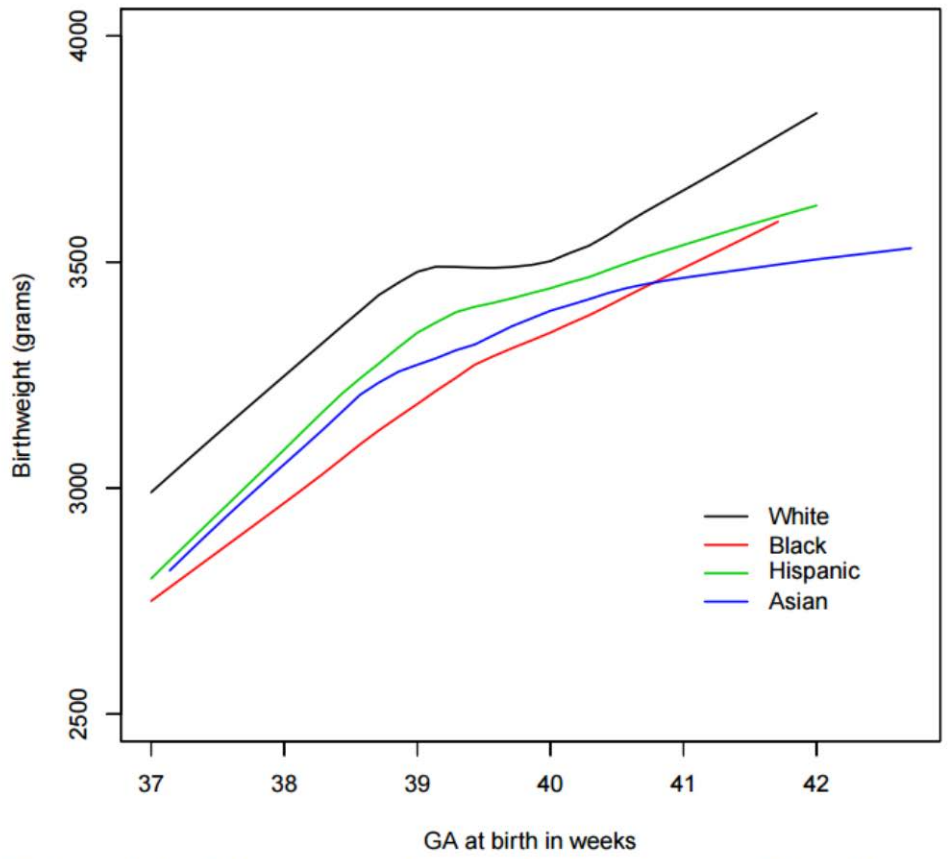
William J Kierans*[1], KS Joseph[2], Zhong-Cheng Luo[3], Robert Platt[4], Russell Wilkins[5] and Michael S Kramer[4]

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.

BMC Pregnancy and Childbirth 2008, 8:1

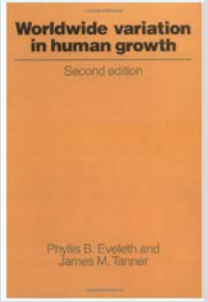
FIGURE 5

Birthweight distributions by race/ethnicity and gestation, NICHD Fetal Growth Studies



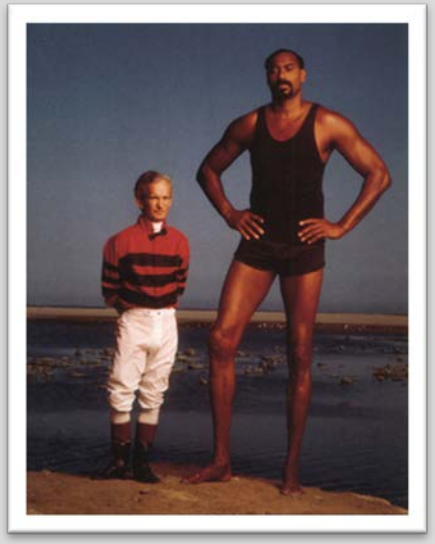
Distribution of birthweight (grams) by race/ethnicity and gestation, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies—singletons. Plots are generated by fitting lowess smoothing spline (birthweight vs gestational age [GA]) for each racial/ethnic group.

Buck Louis. Racial/ethnic standards of fetal growth. Am J Obstet Gynecol 2015.



Empirical Evidence for Human Variability

Descriptive, Public Health, Clinical & Basic Science



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

- 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….

'Super Tonio' and another newborn in Jesus Kumate Rodriguez hospital.
Photograph: Elizabeth Ruiz/EPA

Acknowledgements

- Study participants over many years
- Philippe Jeanty, MD, PhD Nashville, Tennesse
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- Ira Bernstein, MD, University of Vermont
- Kumi Ashizawa, PhD, Tokyo, Japan
- Benjamin Freed, PhD, University of Kentucky
- Joan Schall, PhD, CHOP, Philadelphia, PA
- David Barker, MD, PhD, Southampton UK
- Michael Johnson, PhD, University of Virginia
- Edward Frongillo, PhD, University of S Carolina
- Amanda Mummert, PhD, Emory University
- Meriah Schoen, BS, Emory University
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- Emory University
  - Predictive Health
  - Robert Woodruff Funds
  - Quadrangle, Seed Fund grants

Thank you