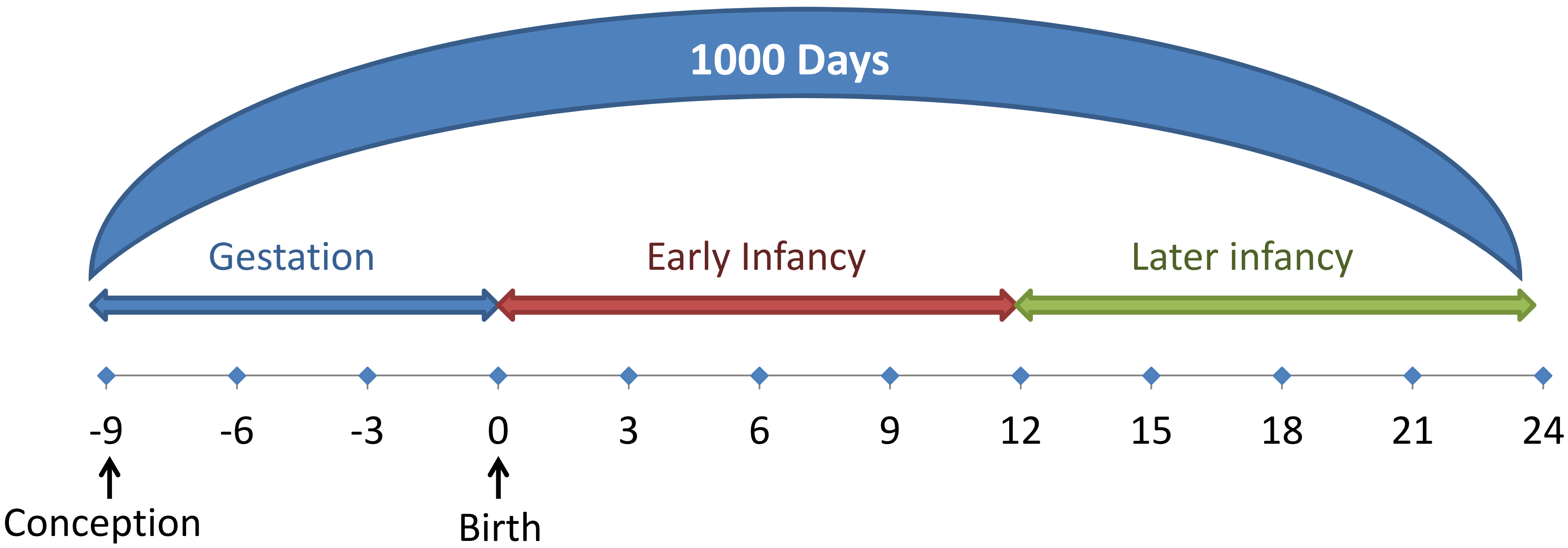
Why are the first 1000 days of life so important for health and human development?

Lessons from cohorts followed to young adulthood

The 1000 days concept

"The 1,000 days between a woman's pregnancy and her child's 2nd birthday offer a unique window of opportunity to shape healthier and more prosperous futures. The right nutrition during this 1,000 day window can have a profound impact on a child's ability to grow, learn, and rise out of poverty. It can also shape a society's long-term health, stability and prosperity" .

1000 Days Partnership: http://www.thousanddays.org/about/



What happens in the first 1000 days?

- Peri-conception: Maternal nutritional status ***at conception*** influences the trajectory of fetal growth and development
  - Maternal prepregnancy nutritional history (height), weight status (BMI) *AND* micronutrient status (e.g. folate, iron) influence:
    - risk of preterm birth
    - newborn size for gestational age

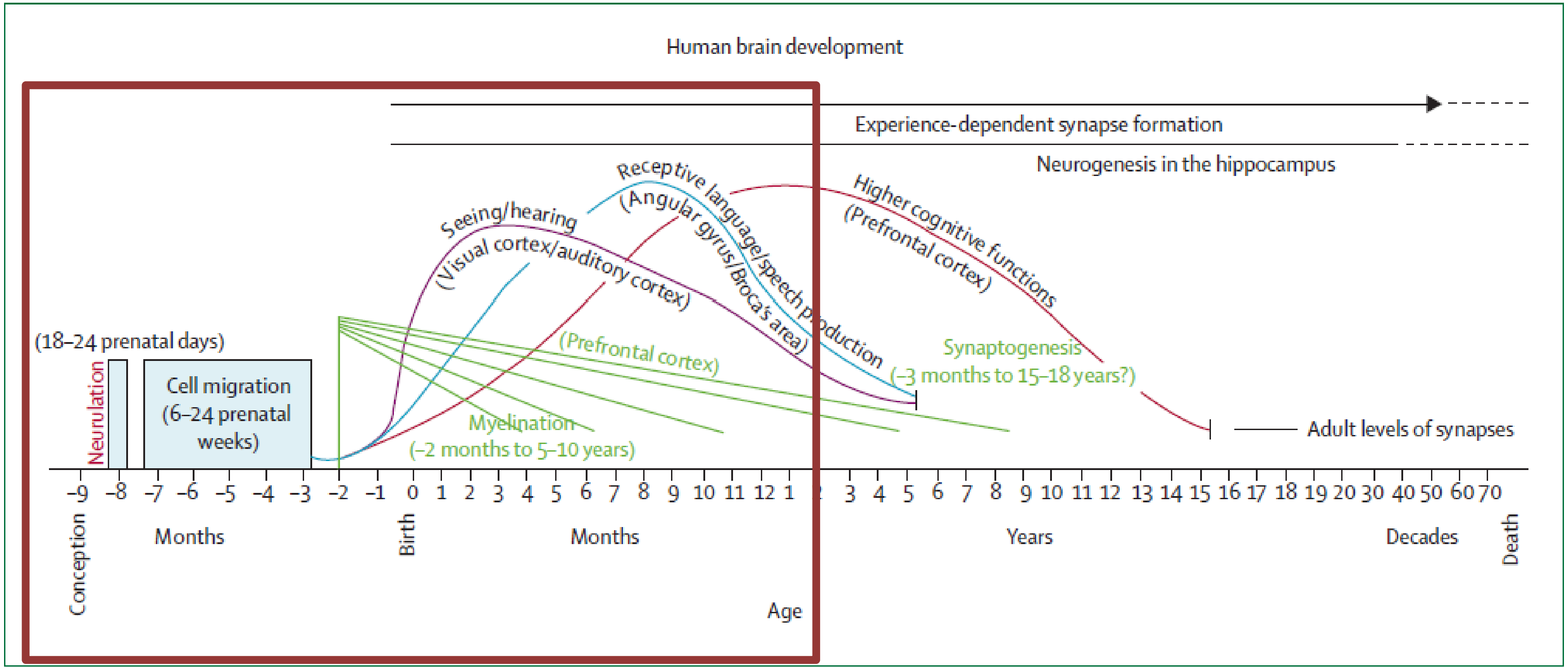
What happens in the first 1000 days?

- Maternal nutritional status ***during pregnancy*** influences:
  - Overall fetal growth
  - Organ-specific growth
  - Fetal body composition
  - Physiologic functioning
  - Neonatal micronutrient status, with implications for brain development and function

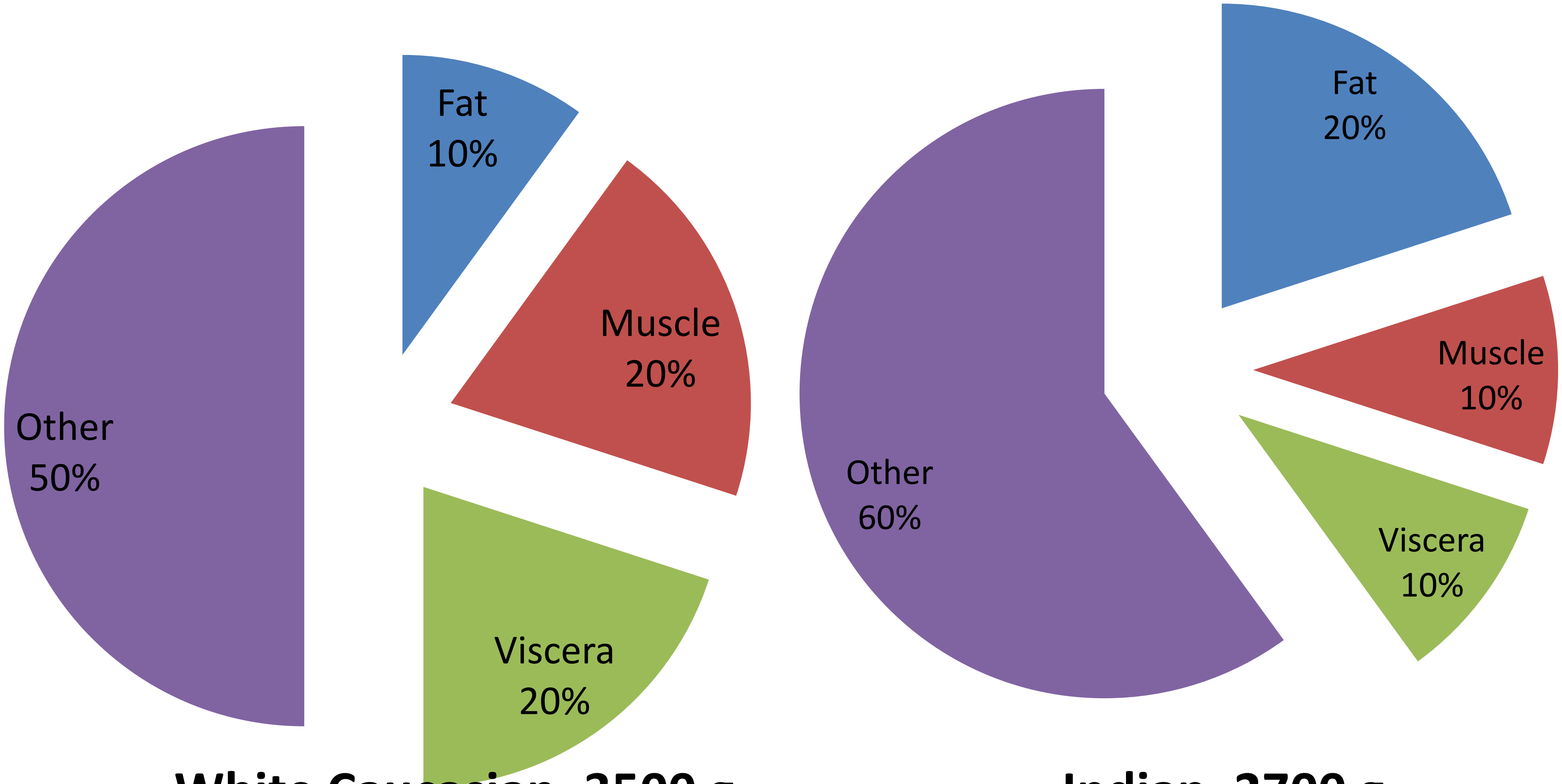
What happens in the first 1000 days?

- Birth – 2 yr
  - Substantial brain development
  - Attainment of 50% of adult stature
  - Critical period for adiposity development
- Deficits and excesses established during this time period are hard to overcome

Brain development is affected at critical periods



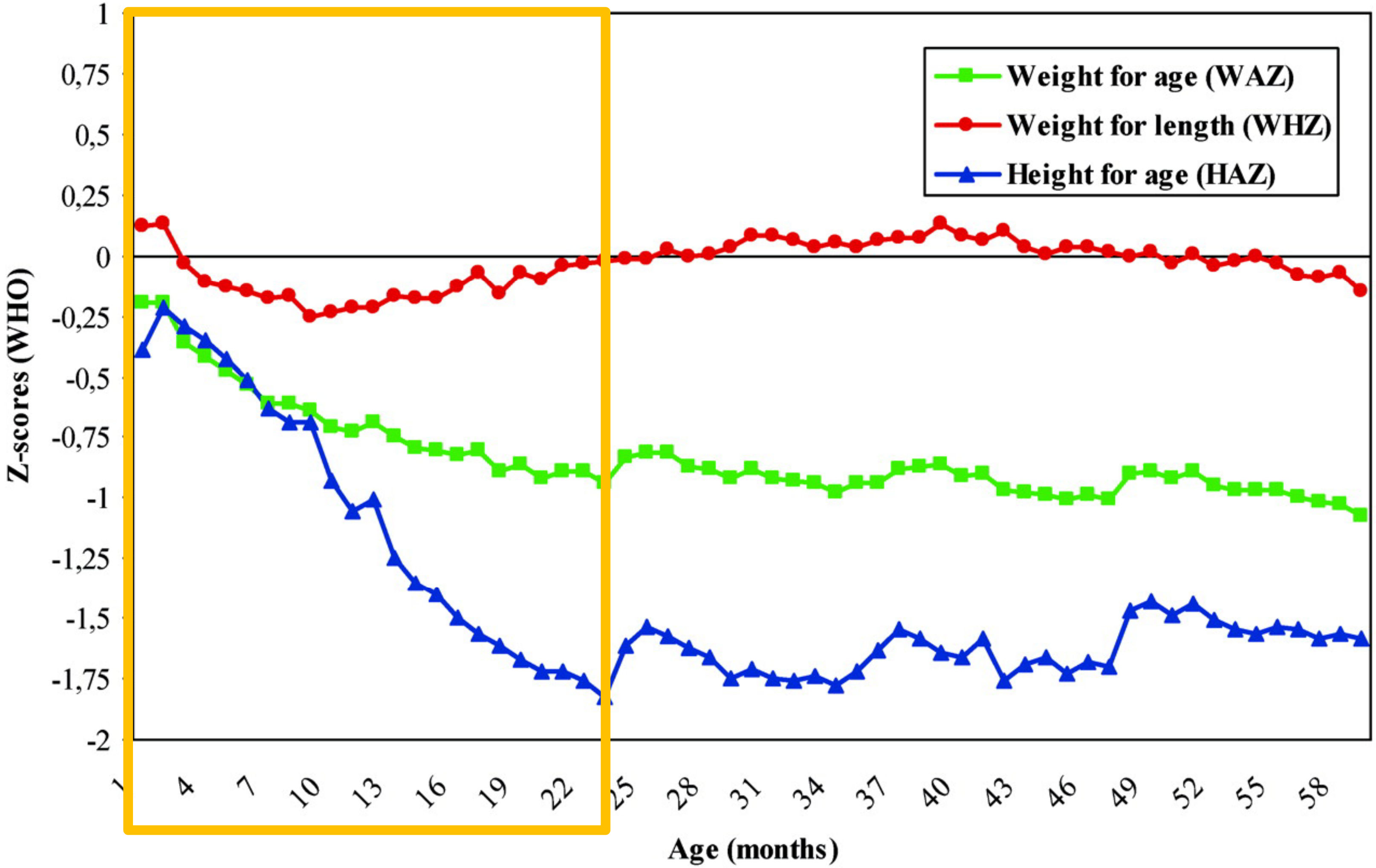
Offspring of malnourished Indian mothers have deficits in lean body mass but not body fat



White Caucasian, 3500 g

Indian, 2700 g

Vulnerability to growth faltering in the first 2 years:
Most growth faltering in low and middle income countries happens in the first 2 years of life:

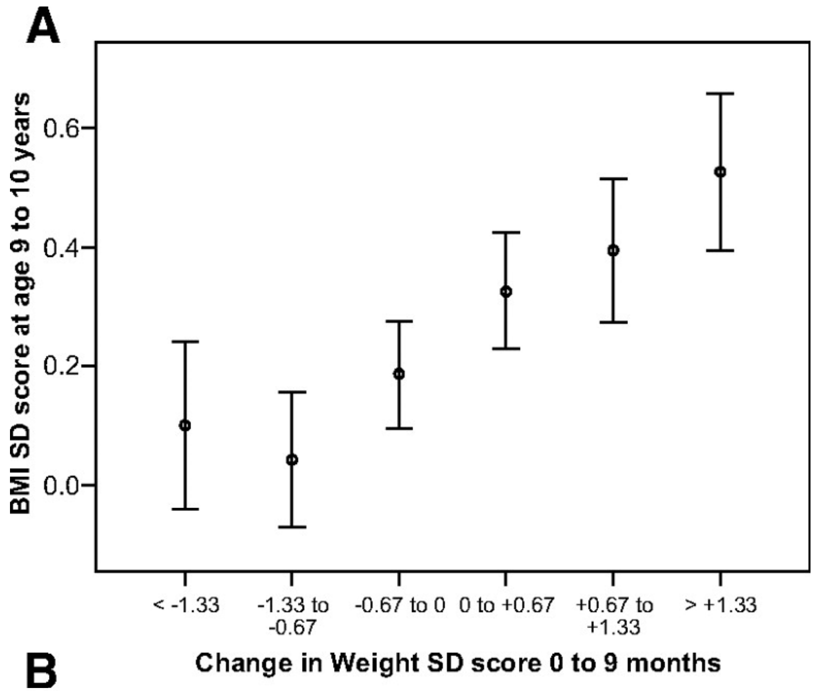


Victora C G et al. Pediatrics 2010;125:e473-e480

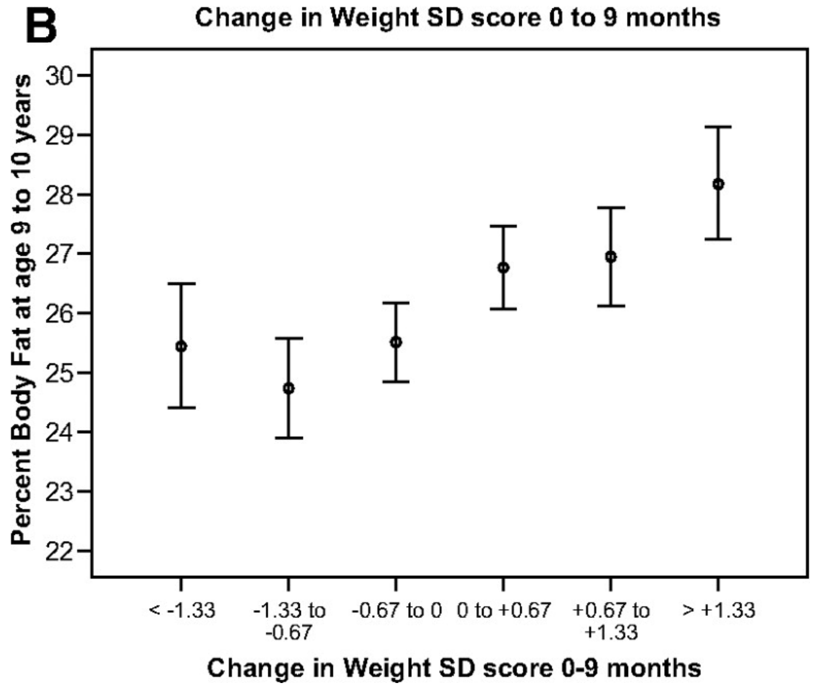
PEDIATRICS®

The first 1000 days: Overnutrition

- Maternal prepregnancy *overweight and obesity and excess pregnancy weight gain* relate to increased risk of macrosomia, altered infant glucose metabolism and later risk of diabetes
- Rapid infant weight gain is a risk factor for later risk of obesity



Infancy weight gain 0 - 9 months) is related to subsequent BMI at age 10 yr

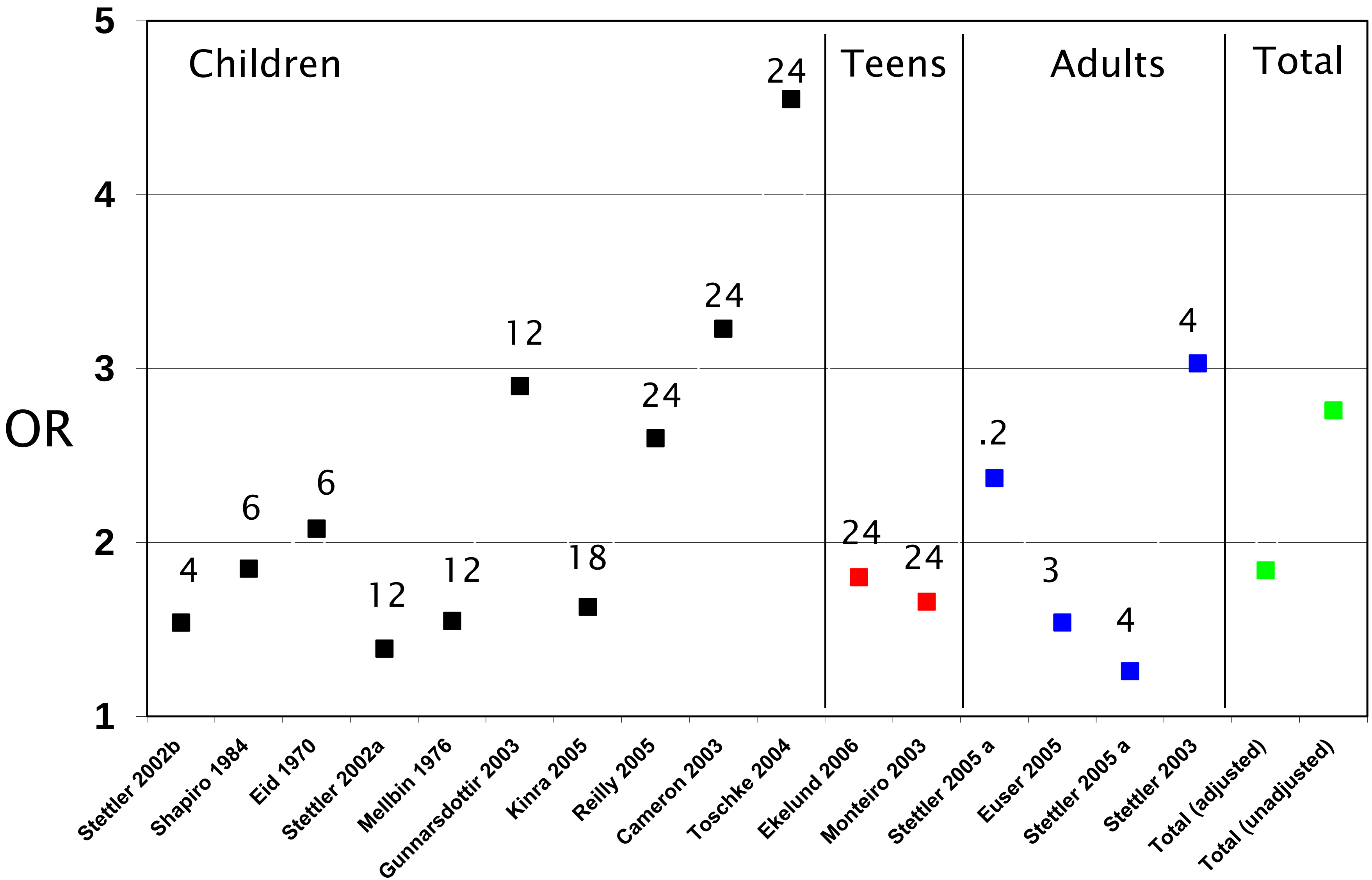


Infancy weight gain 0 - 9 months) is related to subsequent adiposity (percent body fat by DXA) at age 10 yr

The Journal of Clinical Endocrinology & Metabolism

Ong, K. K. et al. J Clin Endocrinol Metab 2009;94:1527-1532

Odds of obesity associated with rapid weight gain*



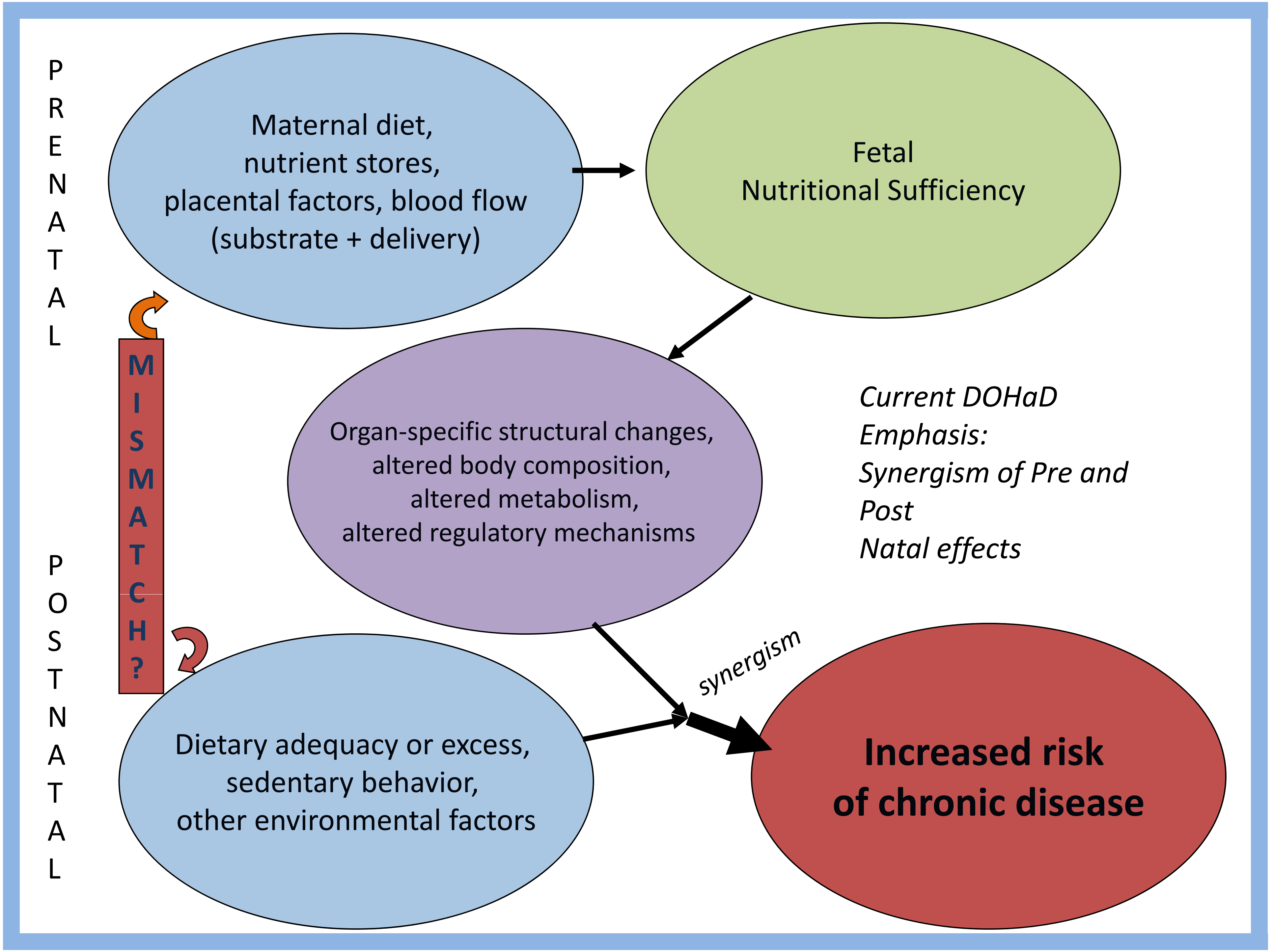
Numbers represent interval over which WAZ increased by >0.67 SD *(Baird et al. 2005 BMJ)

Birth cohort studies

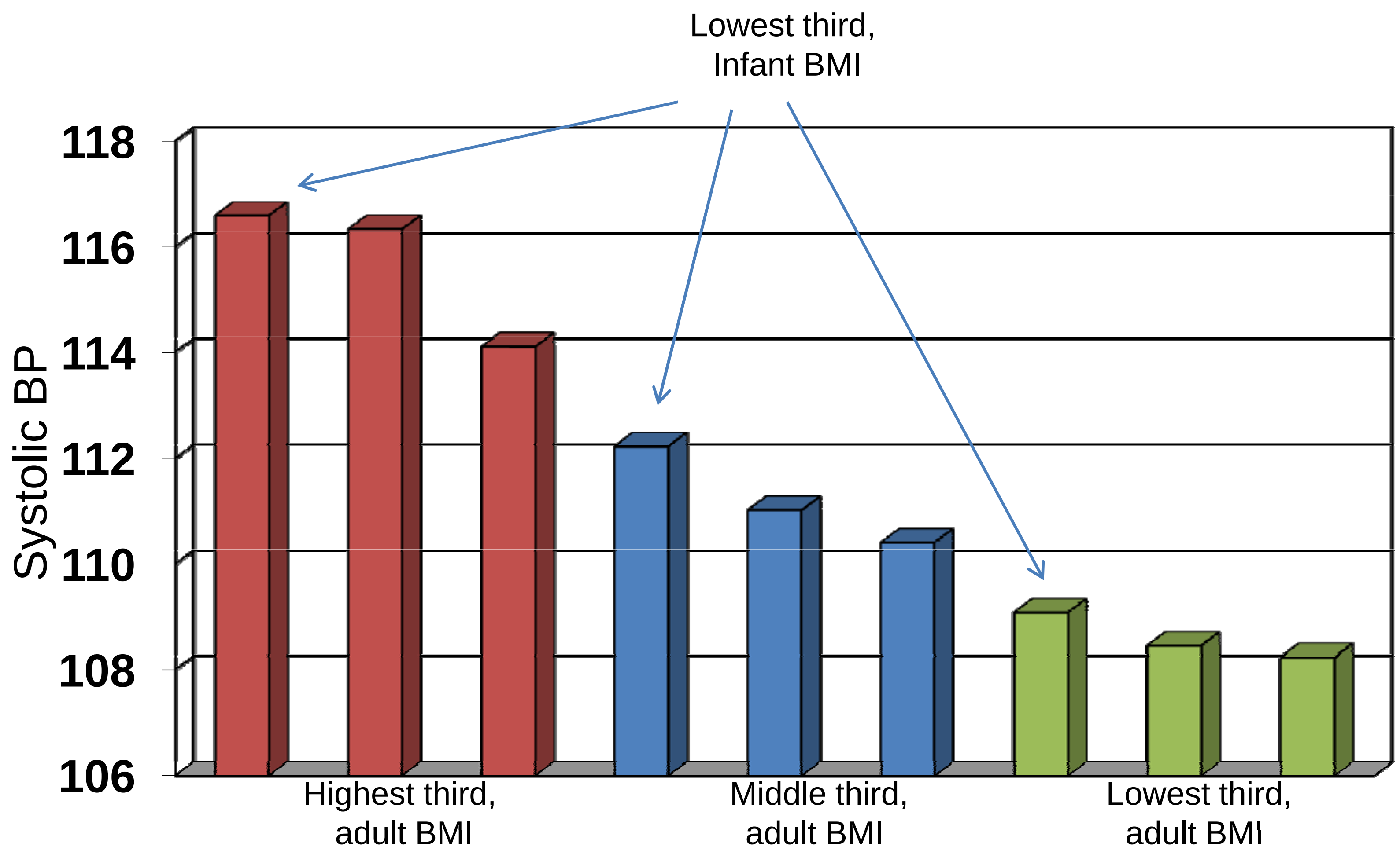
- Prospective cohorts starting at (or before) birth, with repeated measures throughout childhood and adolescence permit understanding of age-specific influences through the life course
- Most cohort studies on developmental origins of adult health and disease (DOHAD) focus on high income countries
- Relatively few birth cohorts in low and middle income countries followed into adulthood

Comparisons across settings differing in SES at birth and young adulthood

- In low and middle income countries, conditions at birth were quite different for today's adults
  - Born when malnutrition rates were high
  - But grew up under rapidly changing environmental conditions: more food availability, less physical activity
- "Mismatch" : adapted for deficits, but face excesses


PRENATAL
POSTNATAL
MISMATCH?
Maternal diet,
nutrient stores,
placental factors, blood flow
(substrate + delivery)
Fetal
Nutritional Sufficiency
Organ-specific structural changes,
altered body composition,
altered metabolism,
altered regulatory mechanisms
Current DOHaD
Emphasis:
Synergism of Pre and
Post
Natal effects
Dietary adequacy or excess,
sedentary behavior,
other environmental factors
synergism
Increased risk
of chronic disease

An Example of mismatch: Systolic Blood pressure in relation to size at birth and size in young adulthood



The “catch-up” dilemma

Catch-up growth in small for gestational age babies:
Good or bad ?
(Ong, KK Curr Opinion Endocrinol Diabetes Obesity 2007;14:30-34)

“promotion of fast weight gain in SGA infants by nutrient-enriched formula feeding should be used with caution”……… However, growth limitation by restriction of nutrition in SGA infants below general recommendations should not be recommended. *(Vaag Int J Gyn Obstet 2009:104:532)*

“The Dangerous Road of Catch-up”…with the increasing potential for long-term survival, …we are being brought to face the price that has to be paid for early-life modifications that aid short-term survival in adverse circumstances”
(*Hales&Ozanne J Physiol 547:5-10*)

Benefits of catch-up growth

- Study of 3,582 Brazilian children 0-42 mo
- Tracked hospital admissions in small for gestational age (SGA) vs. AGA infants, with and without rapid weight gain from 0-20 mo
- SGA children with WAZ increase >0.67 SD had 65% fewer all-cause hospital admissions compared to SGA children with slower growth

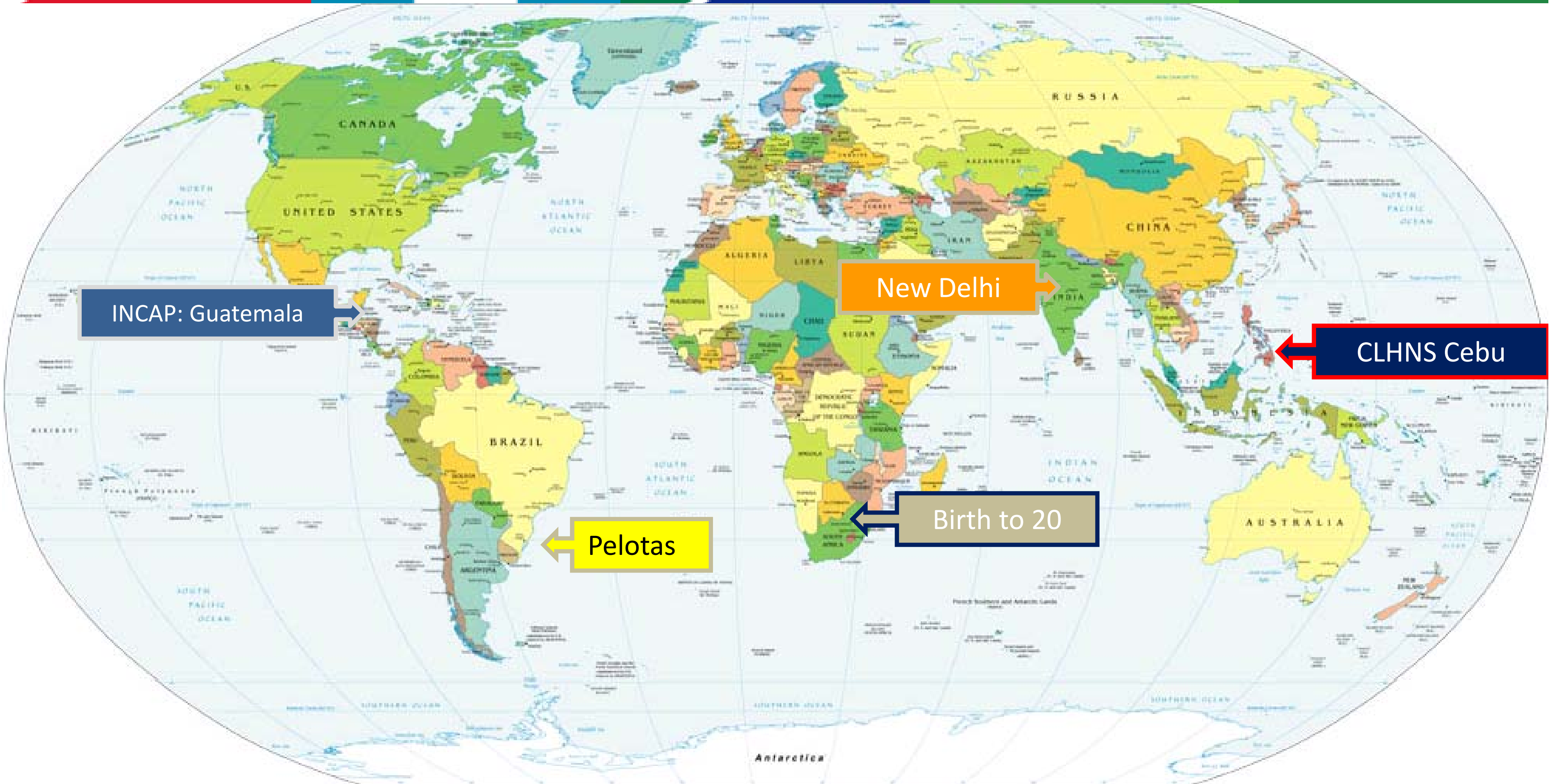
Victora CG, Barros FC, Horta BL, Martorell R.
Int J Epidemiol. 2001 Dec;30(6):1325–30.

Comparisons across settings differing in SES at birth and young adulthood

- Literature from high income countries identifies “rapid growth” in infancy as a risk factor for obesity and chronic diseases later in life
- But, in low and middle income countries, rapid growth, especially following episodes of growth faltering (“catch-up growth”), relates to less morbidity and mortality, and better cognitive outcomes
- How can we weigh the risks and advantages of early growth? What about faster linear growth vs faster weight gain relative to length or height?
  - Motivation for COHORTS

The COHORTS collaboration:
Understanding how size at birth and early life growth and weight gain influence adult outcomes (body composition, height, cardiometabolic disease risk, attained schooling) in low and middle income countries

COHORTS
Consortium of Health Orientated Research in Transitioning Societies
Brazil Guatemala India Philippines South Africa



COHORTS

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The COHORTS Sample

Study	Cohort inception	Who was enrolled?
Pelotas Brazil	1982	Births during 1982. All social classes
INCAP Nutrition Trial Cohort Guatemala	1969-77	Participants in nutrition supplementation intervention trial in 4 rural villages
New Delhi Birth Cohort Study India	1969-72	Births to married women from defined area of Delhi. Primarily middle-class
Cebu Longitudinal Health & Nutrition Survey Philippines	1983-84	Births in 33 randomly selected communities of Metro Cebu; 75% urban. All social classes
Birth to 20 South Africa	1990	Infants from a delimited urban area (Soweto, Johannesburg). Predominantly poor, black

Analysis

- Data pooled data from 5 sites: maximizes sample size for analysis (~7,500)
- Identify common exposures and timing of assessments
- Use regression models to examine associations of early exposures with later outcomes
- Evaluate heterogeneity by site & sex
- Evaluate confounding by SES

Analytic challenges: modeling the effects of faster growth at different ages/developmental periods

- Size measures at different ages are highly correlated
- Inclusion of many correlated size measures in models is problematic
- We use "conditional" size measures which are made independent through statistical means

Conditional size measure represent "faster growth"

- Goal: Identify children whose linear growth or weight gain is greater than expected, given their prior size and the average growth pattern in the population
- Method:
  - Regress current size on all prior size measures
  - Estimate residuals: variables that represent the deviation of current size from what is predicted from site and sex-specific models
  - When included together in a regression model, conditional size measures be interpreted as ***change*** in each interval:
    - ***higher CWH=faster weight gain relative to length or height***
    - ***higher CH= faster linear growth***

Common time periods for assessment across cohorts

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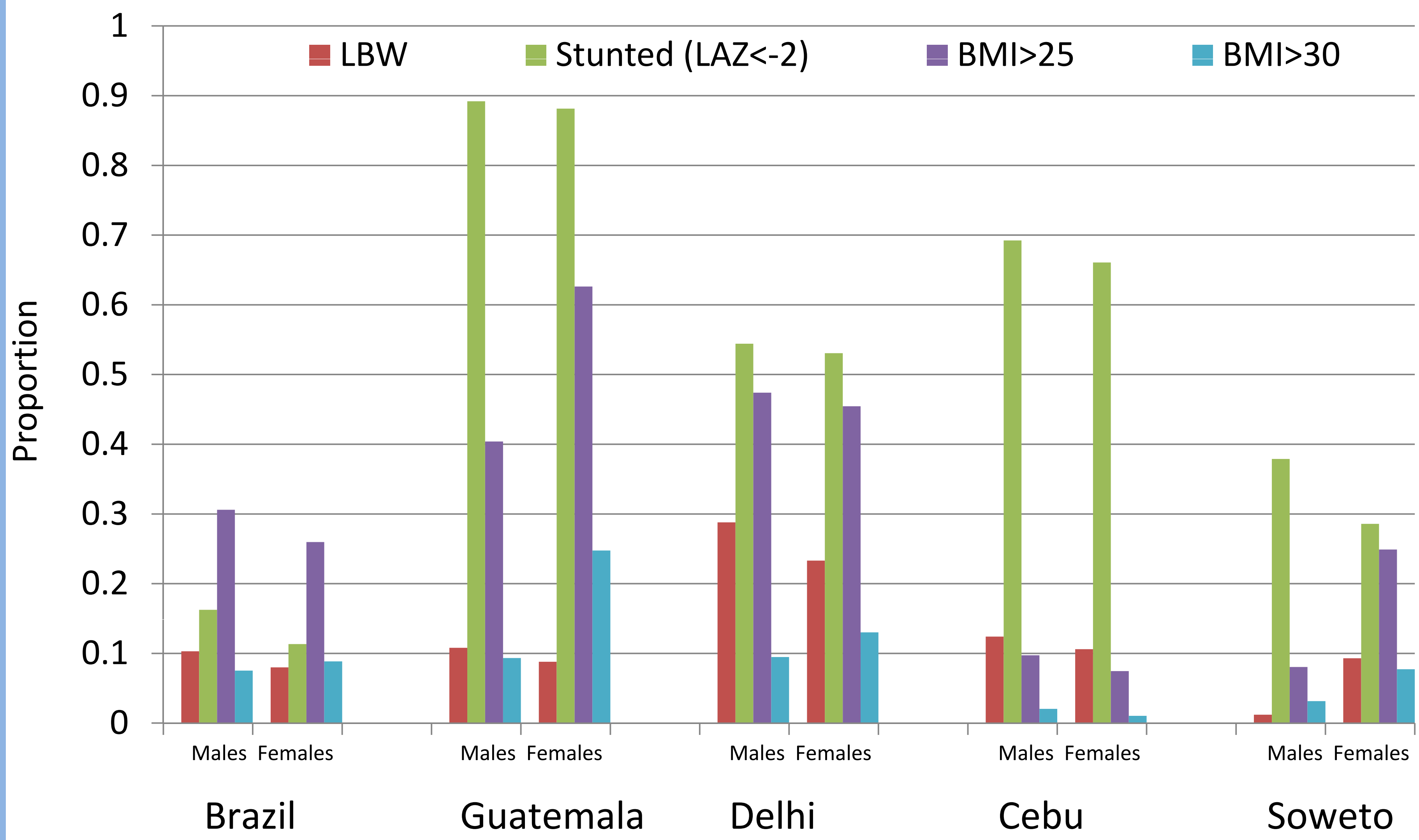
- Birth weight for all sites and length for 3/5 sites
- 12, 24 months
- Mid-childhood (MC) 48 months for Brazil, Guatemala and Delhi, 50 months for South Africa, 102 months for Cebu
- Adulthood (ages 18-30)

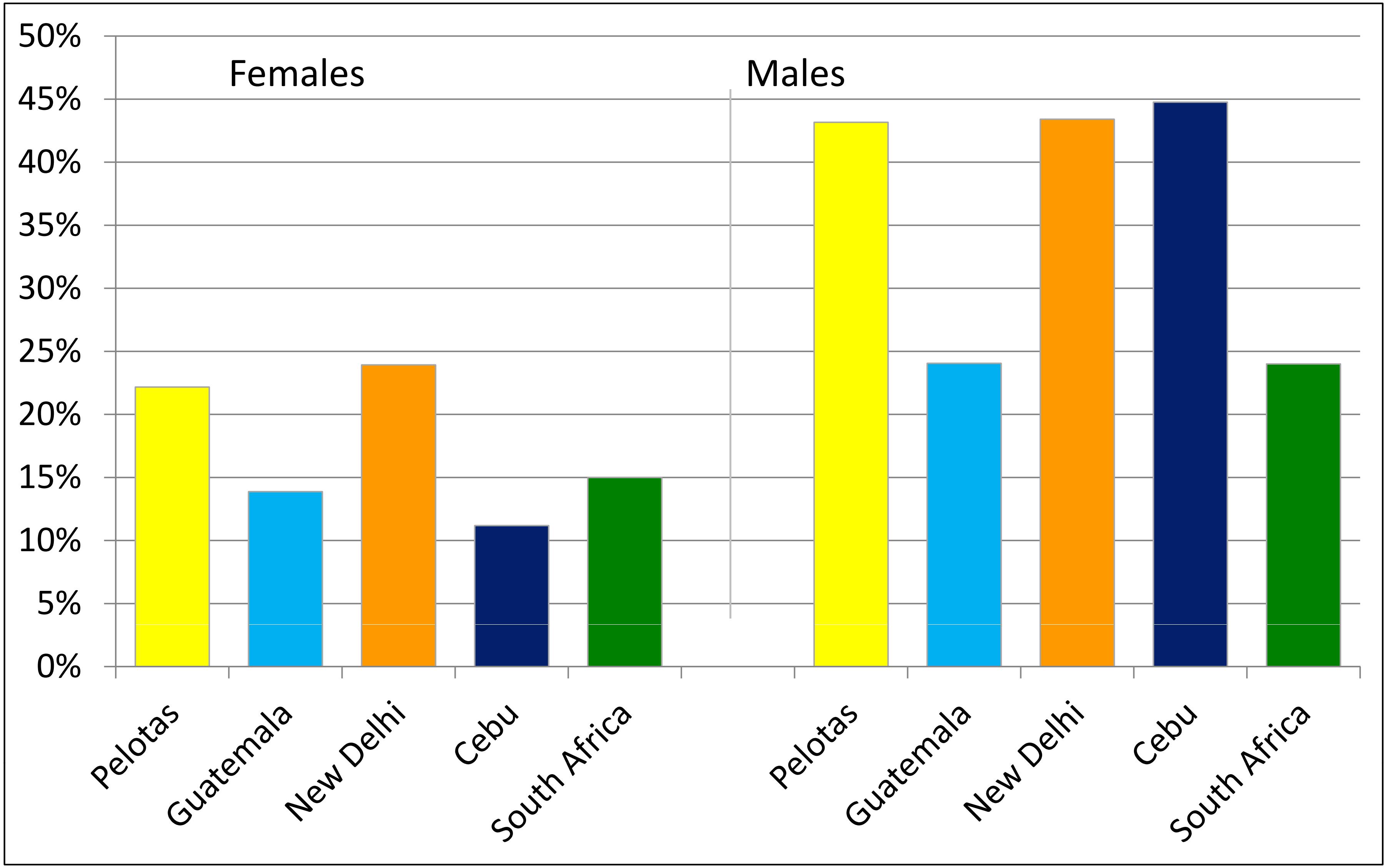
Outcomes

- Systolic and diastolic BP, and risk of pre-hypertension + hypertension (SBP>130 or DBP>80)
- Plasma glucose
  - impaired fasting glucose or diabetes
- Body composition
  - Lean and fat mass [Estimated from DXA (South Africa), or equations based on anthropometry (New Delhi, Cebu, Guatemala) or BIA (Pelotas)]
- Adult Height
- Schooling: # years attained

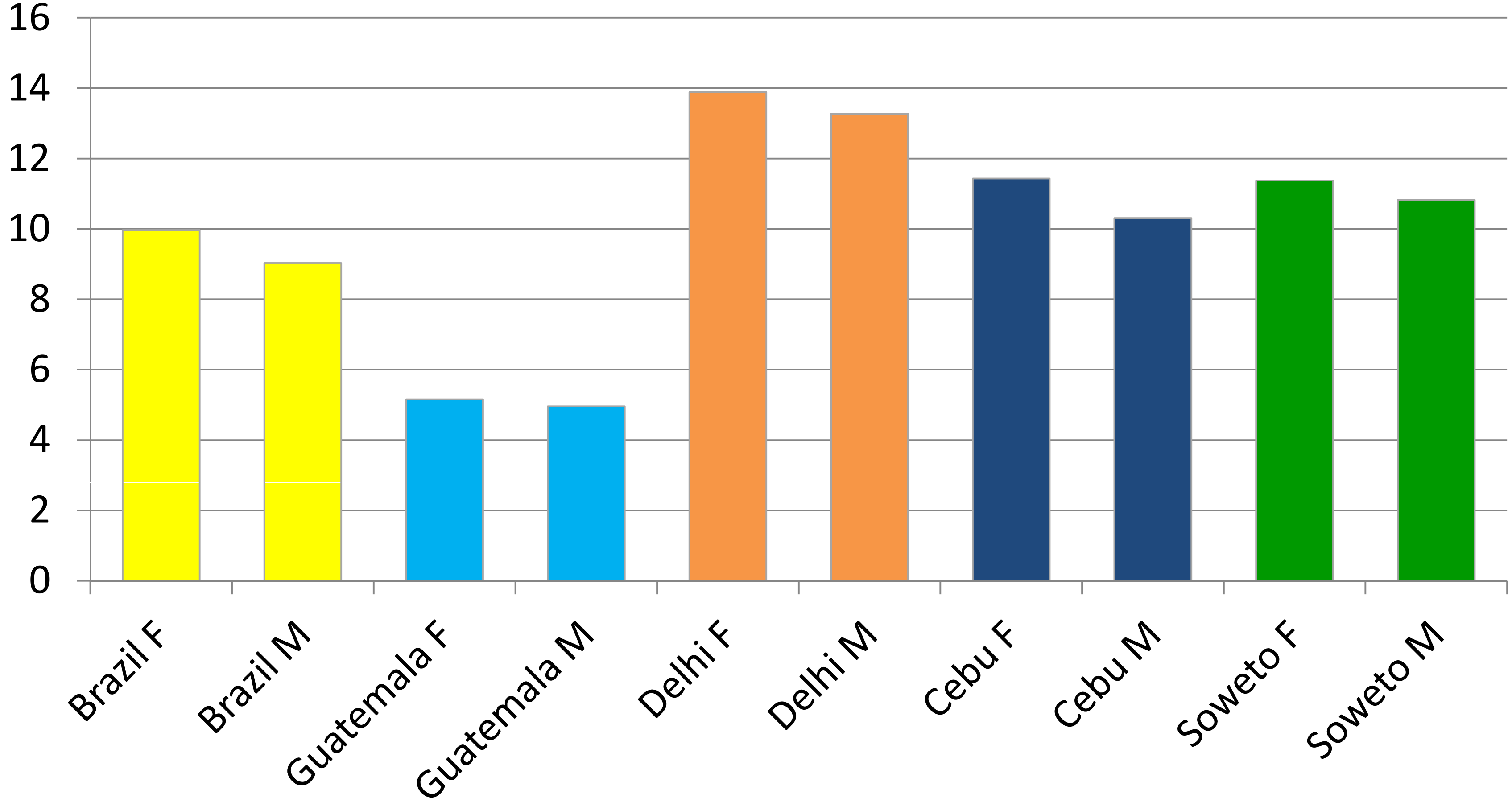
All sites exemplify discordance of birth and adult nutritional status



Prevalence of Pre-Hypertension + Hypertension (SBP>130 or DBP>85)



Mean highest grade attained



Regression Results

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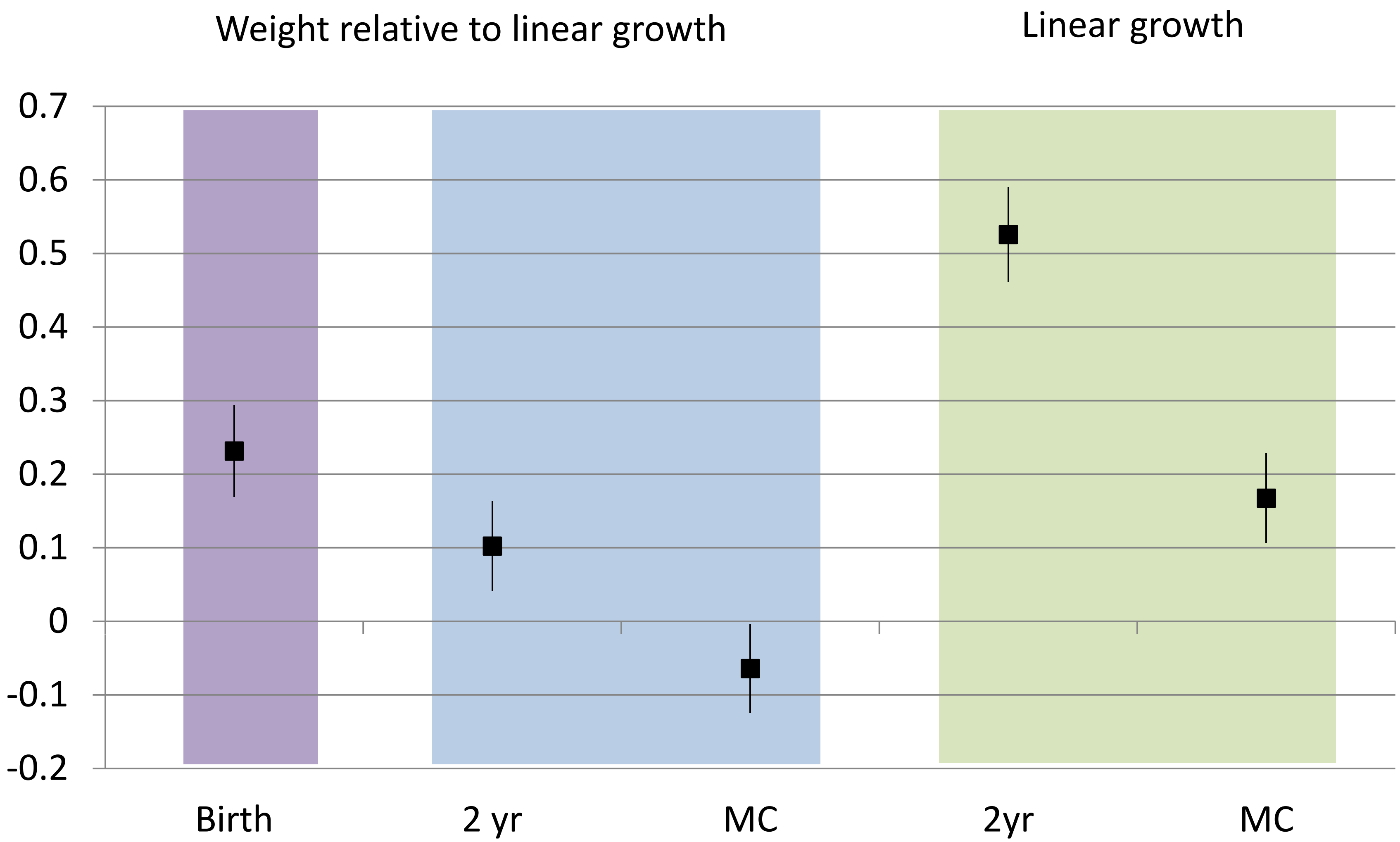
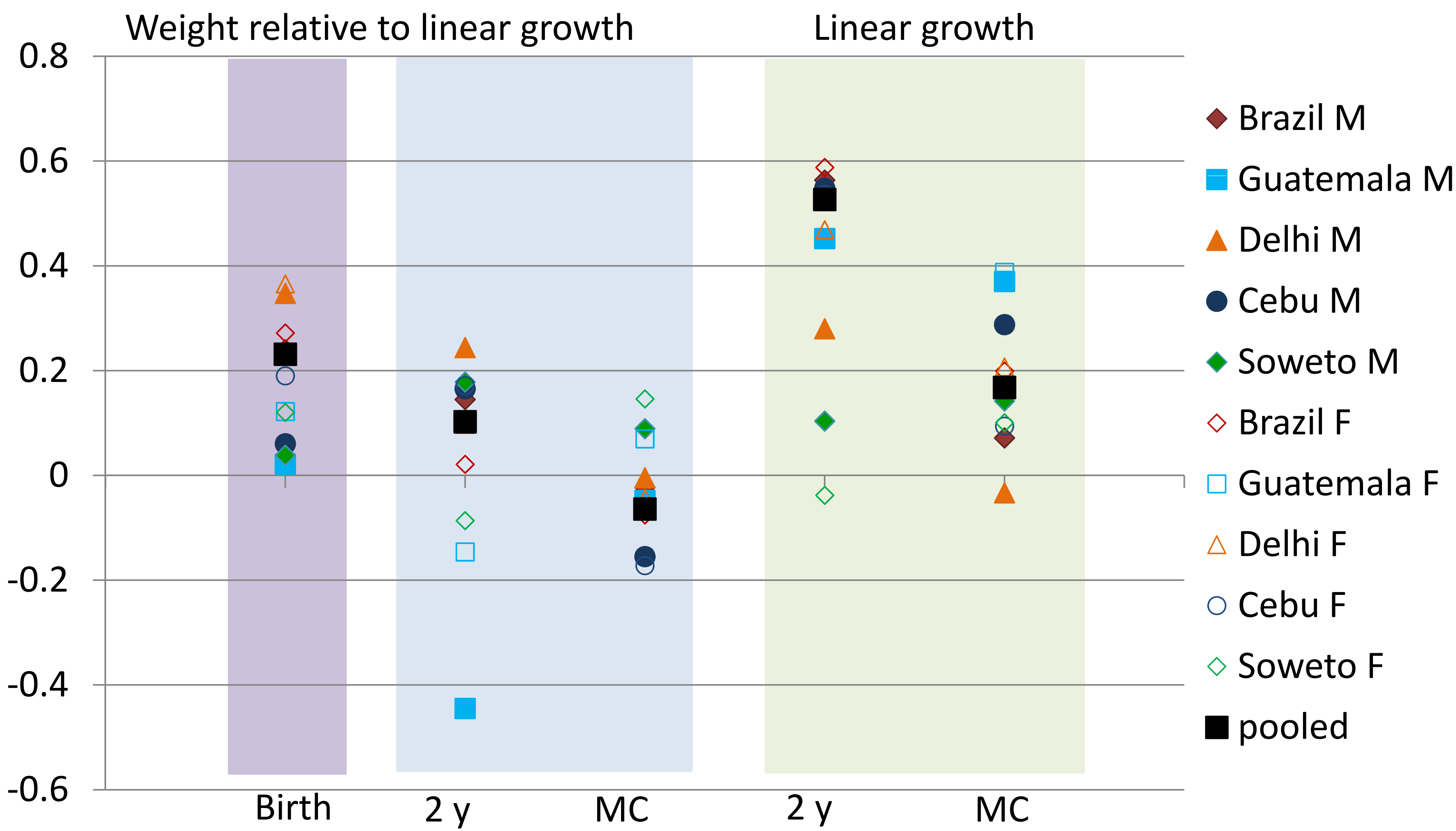
- Statistical models designed to estimate
  - how faster linear growth and faster relative weight gain (likely reflecting increasing adiposity) relate to adult outcomes
  - Compare associations of:
    - Birth weight and length (reflecting prenatal growth)
    - Higher CH (faster linear growth) or higher CWH (faster weight gain) in the periods of 0-2 yr, 2 yr to mid-childhood, and midchildhood to adulthood
- Models stratified by site and sex OR pooled models which adjust for site and sex, and where needed, SES at birth

Schooling:

How weight gain and linear growth relate to highest attained grade attained

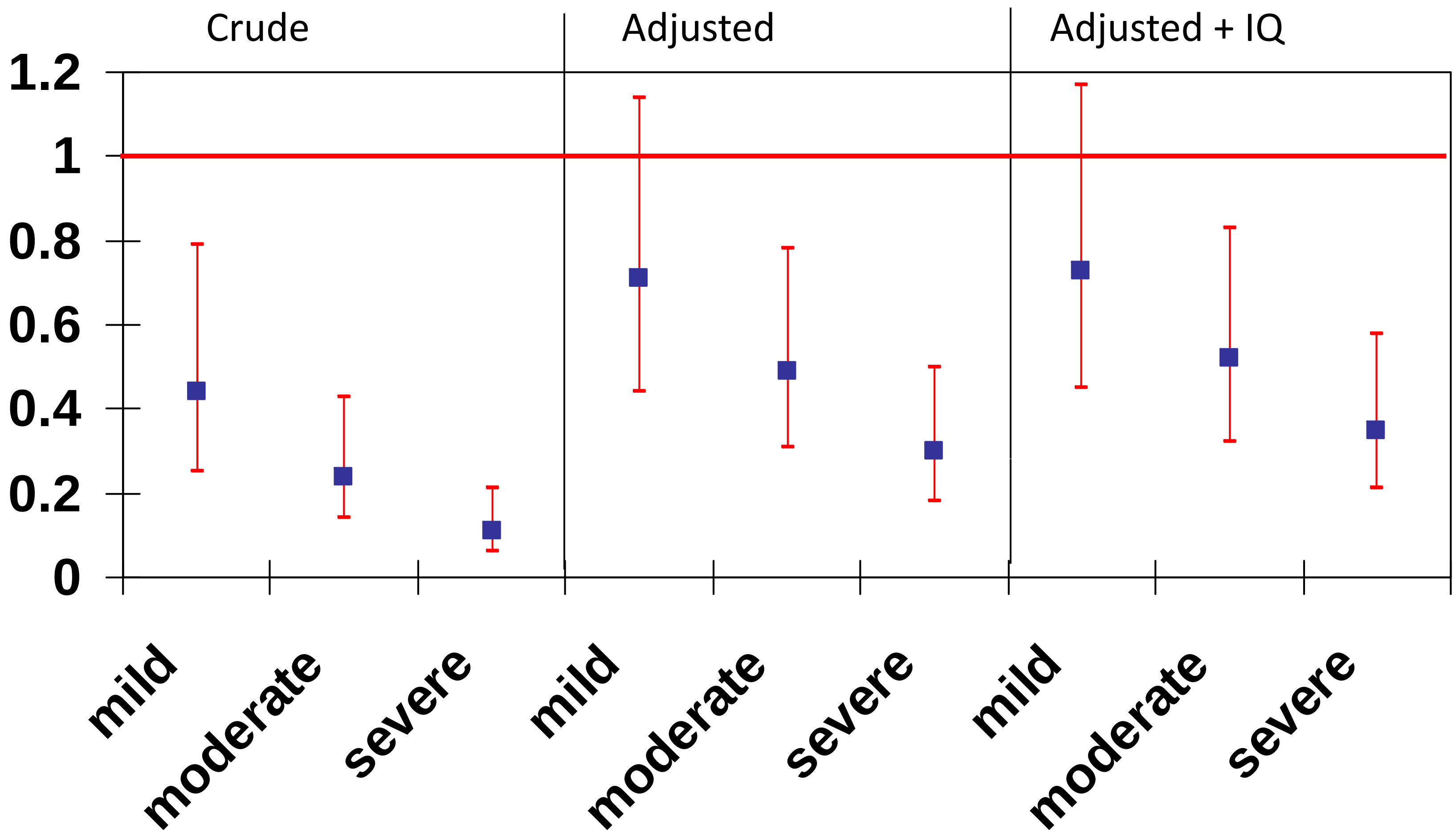


Schooling: Heterogeneity by site and sex



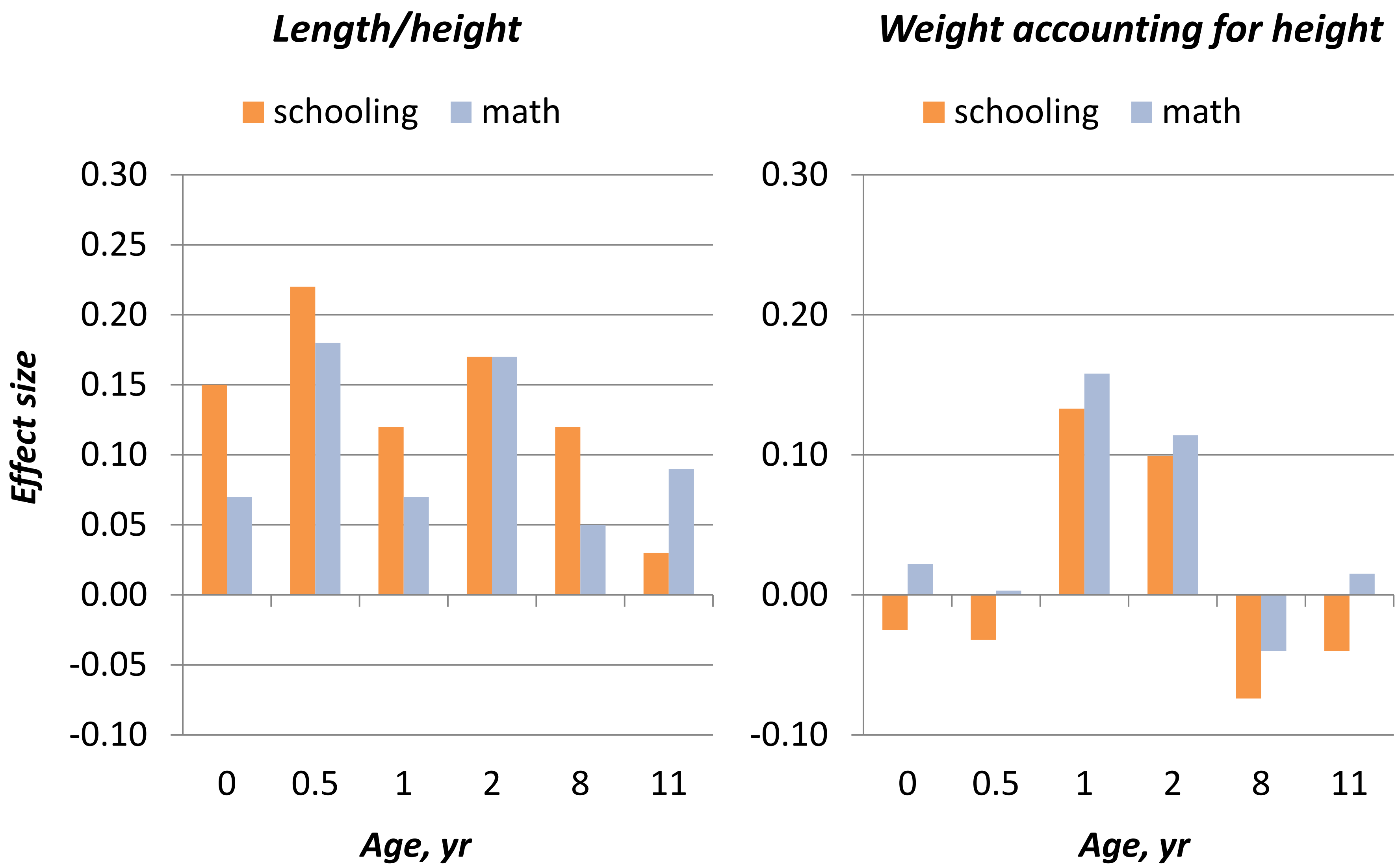
n=7551 adjusted for wealth quintile and maternal education at birth, site, and sex of child

Cebu: Odds of attaining some college education for those with mild, moderate or severe stunting at age 2

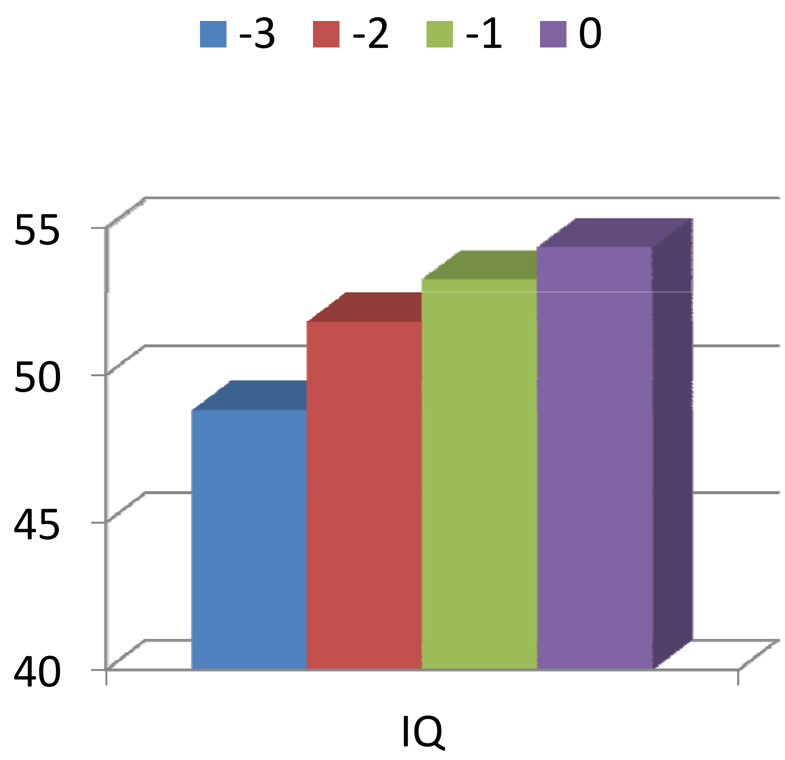


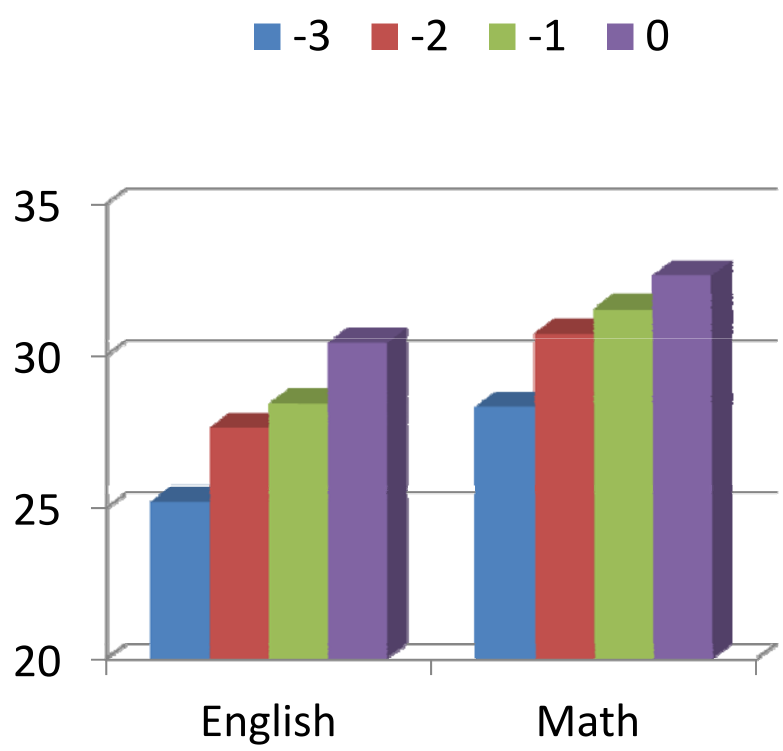
Mild = LAZ -1 to -2, moderate=LAZ -2 to -3 severe= <-3

Schooling and achievement: Cebu females



Cebu: IQ and achievement test scores vary directly with height-for-age Z score at age 2



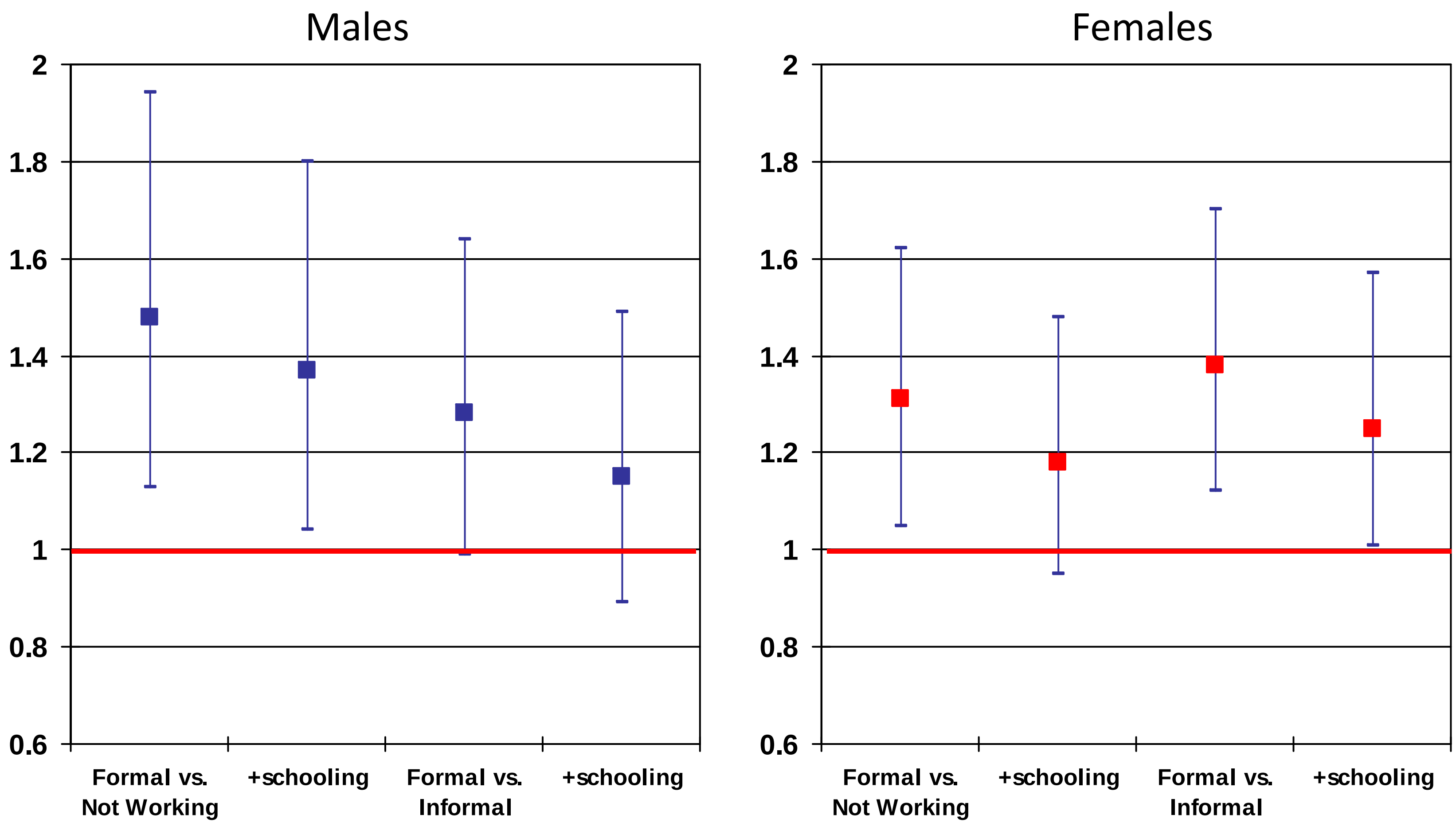


Means adjusted for maternal education and household wealth

Cebu: Stunting and young adult employment

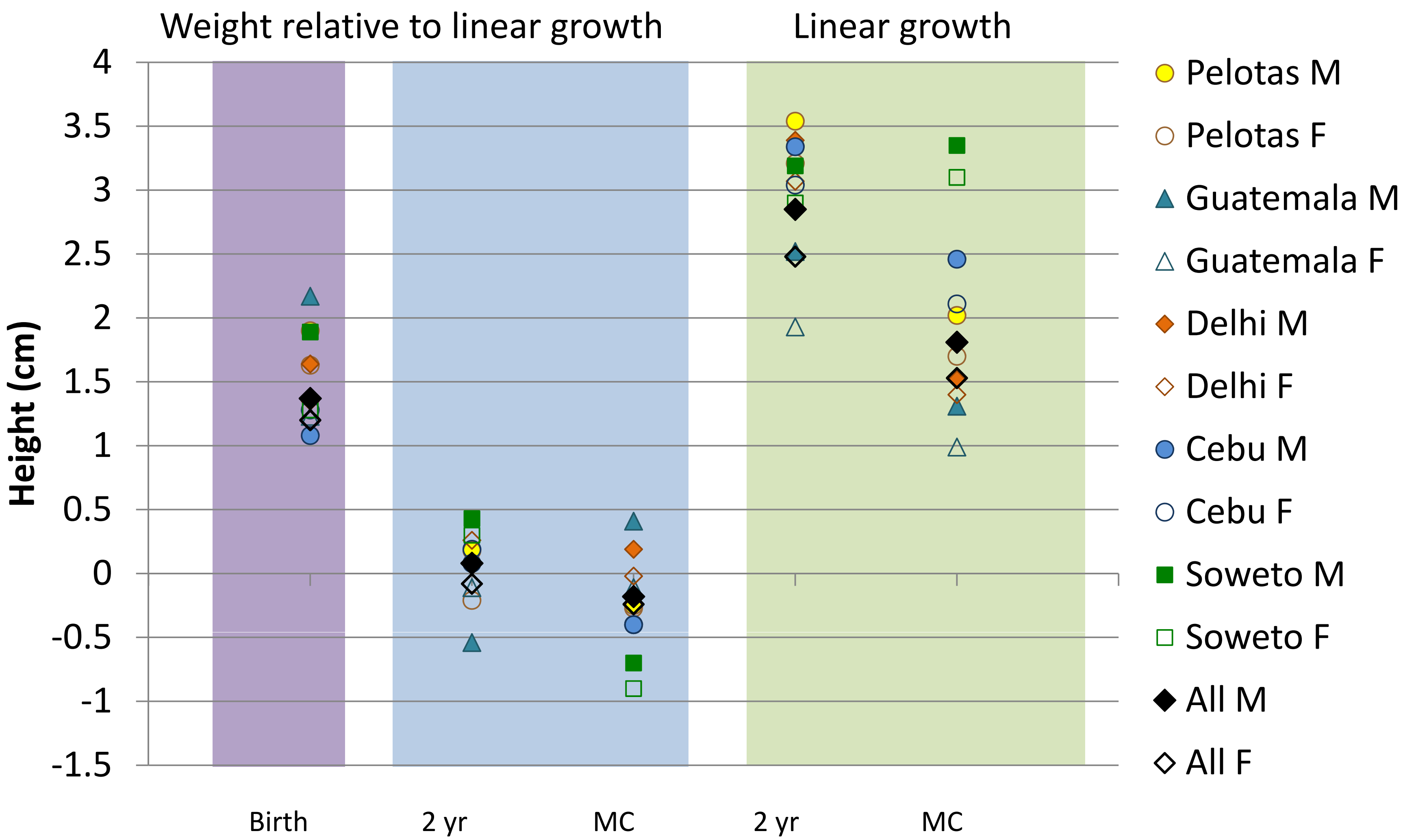
- Young adult employment status categorized as:
  - Not working
  - Employed in informal sector
  - Employed in formal sector (work >=40 hrs, have benefits and greater than minimum wage)
- Analysis stratified by current schooling status (still in school or not)

Likelihood of formal sector work increases with childhood length Z-score at age 2 in young adults no longer enrolled in school

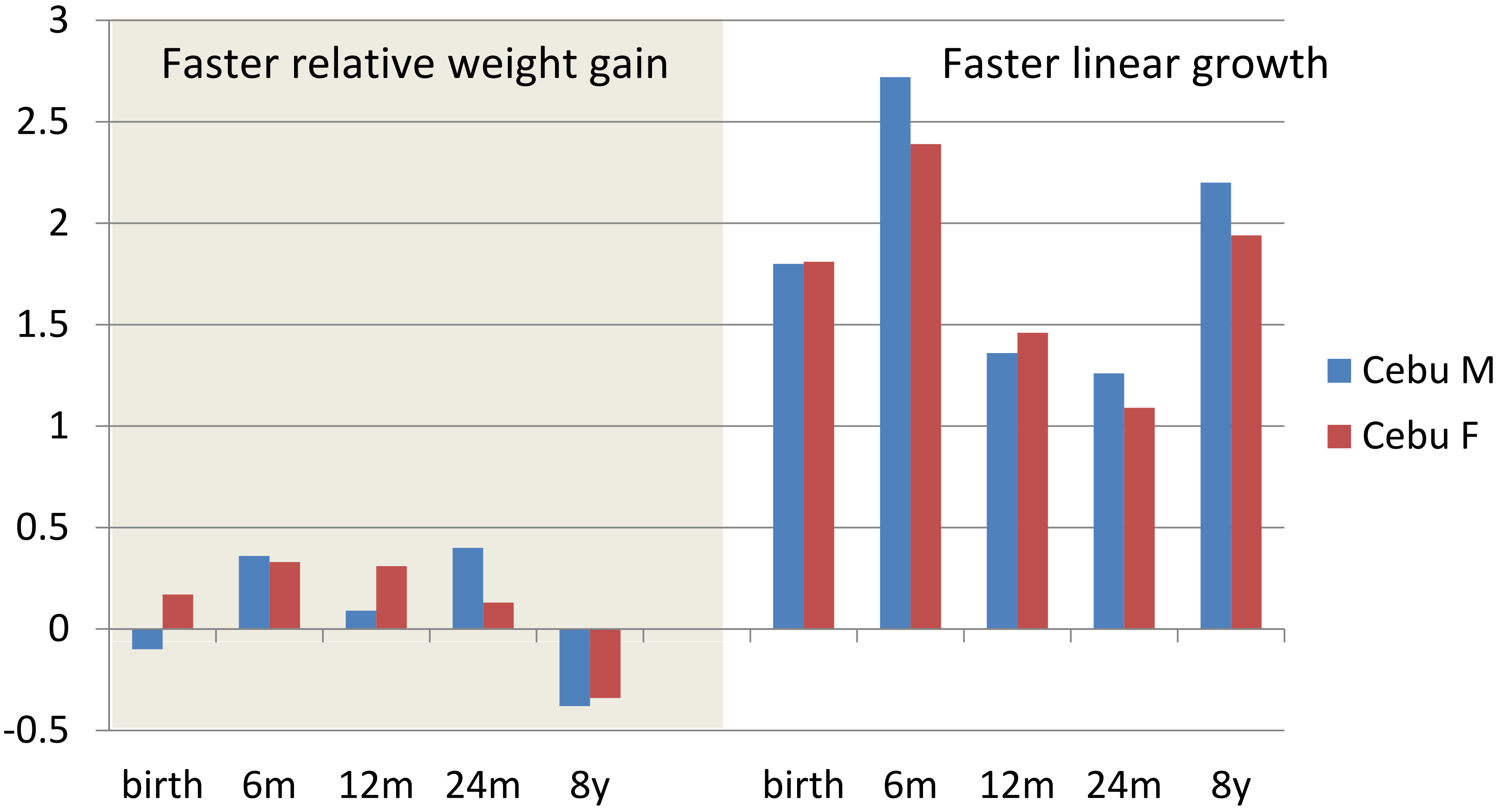


Schooling is an important mediator of this relationship

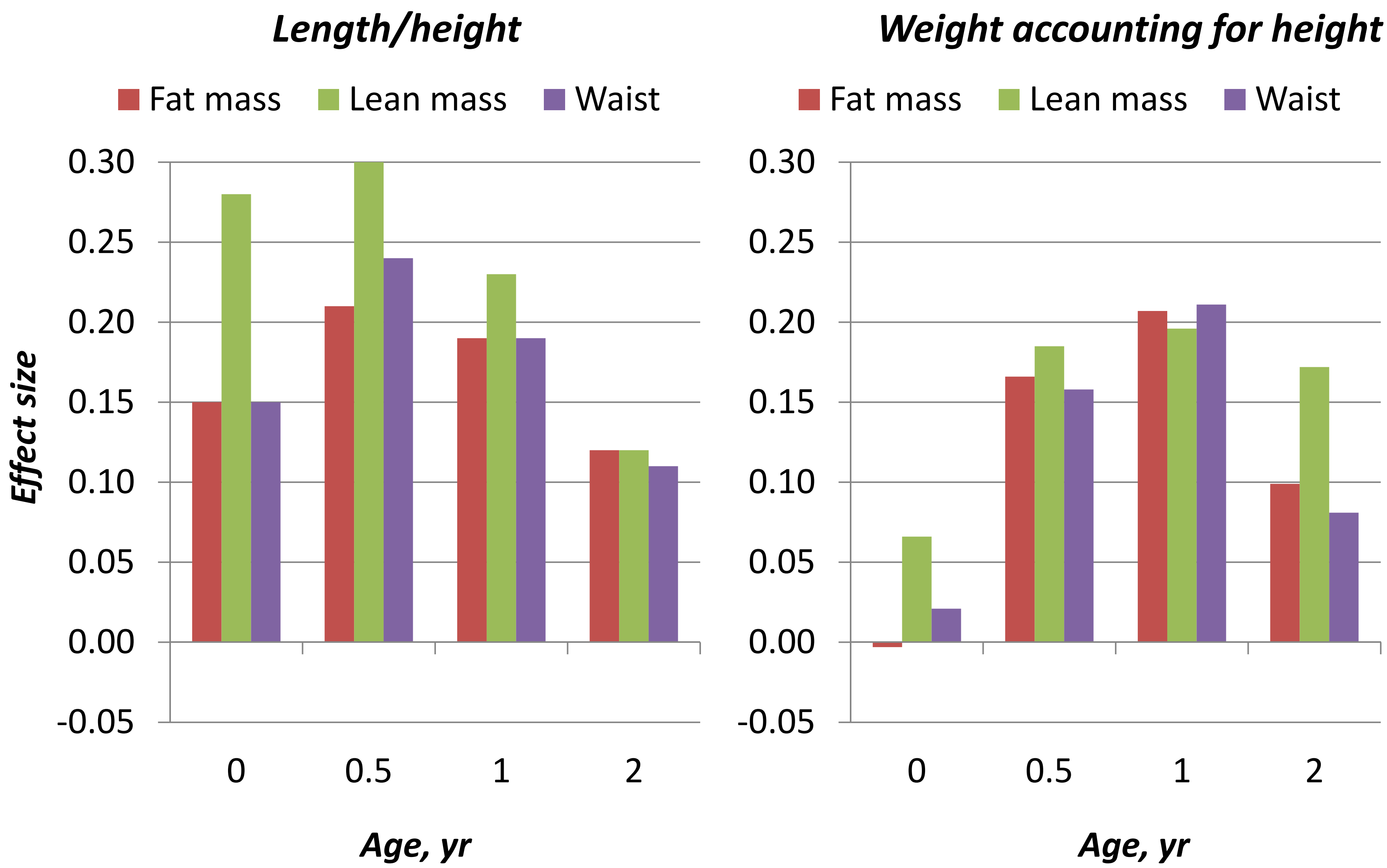
Adult height



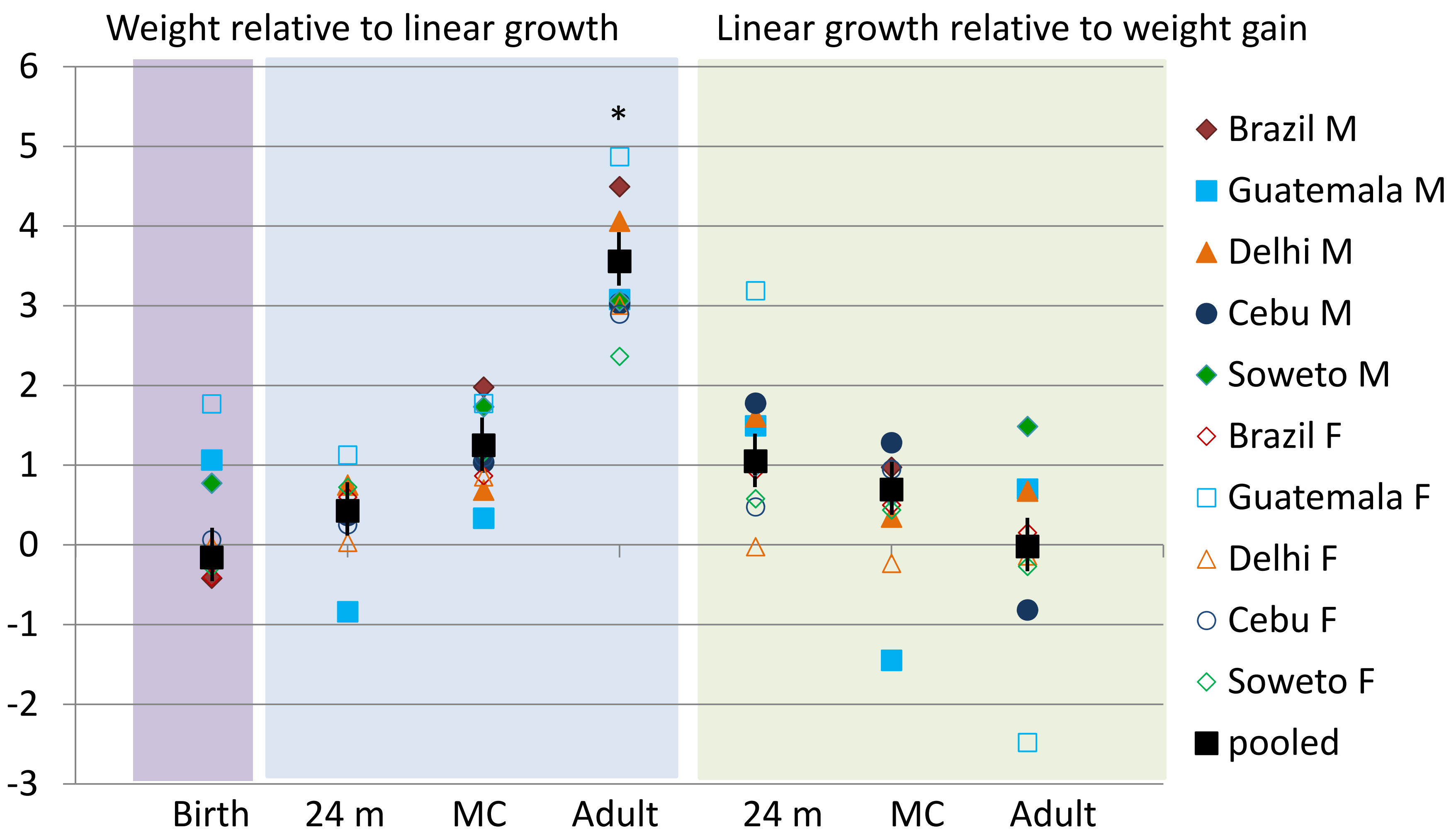
Birth and the first 6 months are especially important for adult height



Body composition: Cebu Males



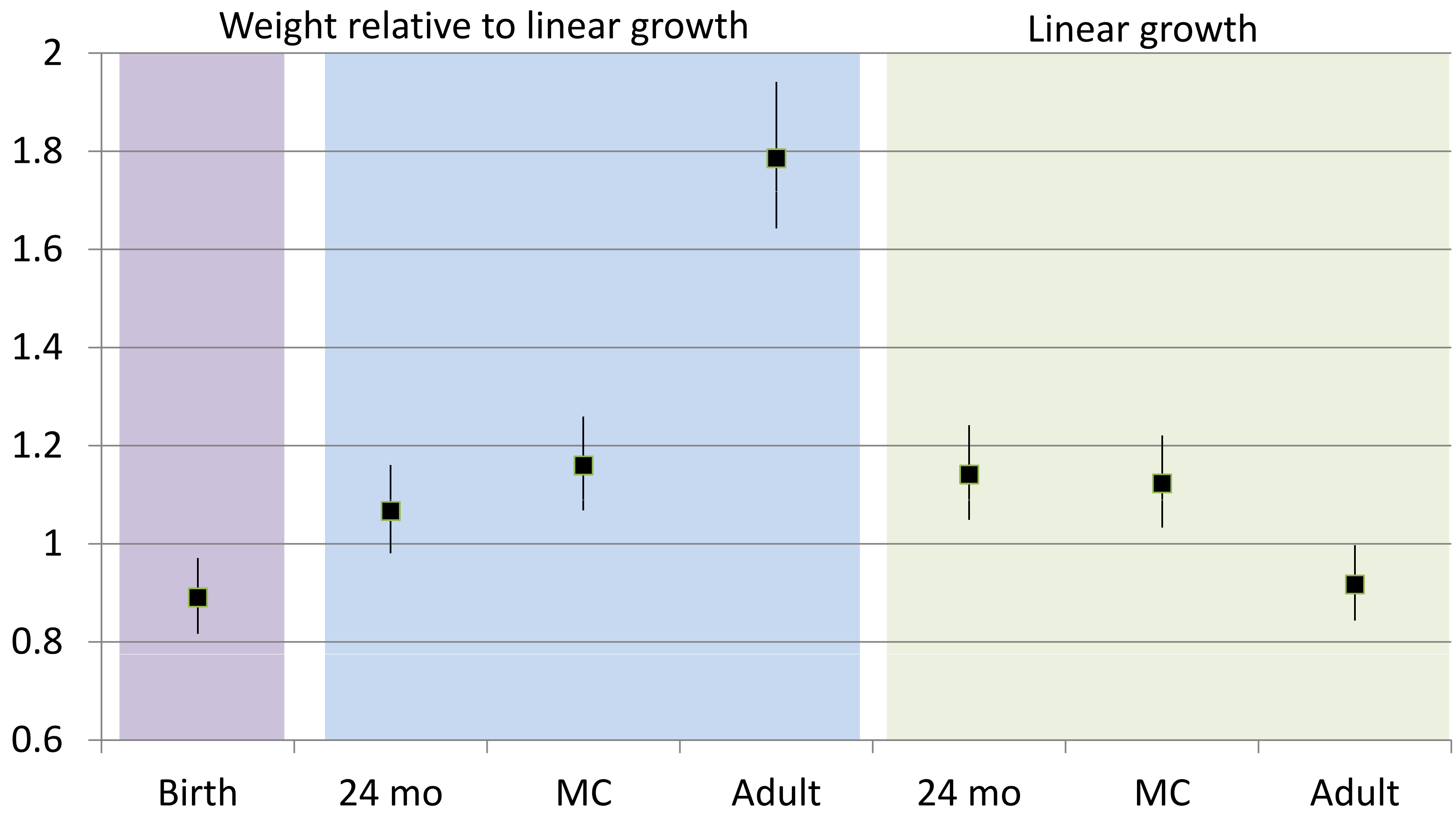
Systolic Blood Pressure (mm Hg)



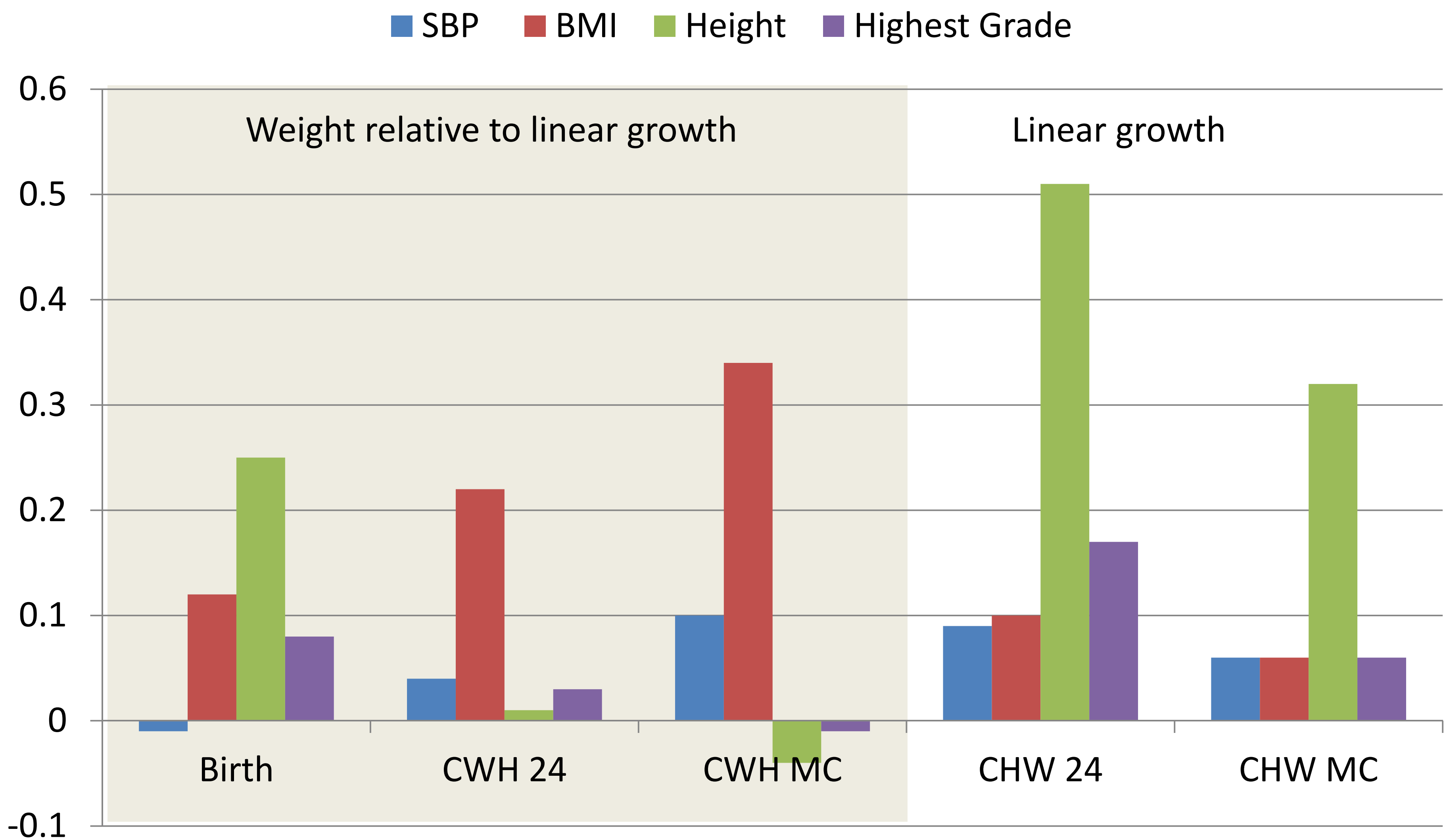
* Significant sex-site heterogeneity

Odds of hypertension in relation to birth weight, weight gain and linear growth

ORs represent effect of one SD in exposure, with 95% CI



Comparing effect sizes across outcomes



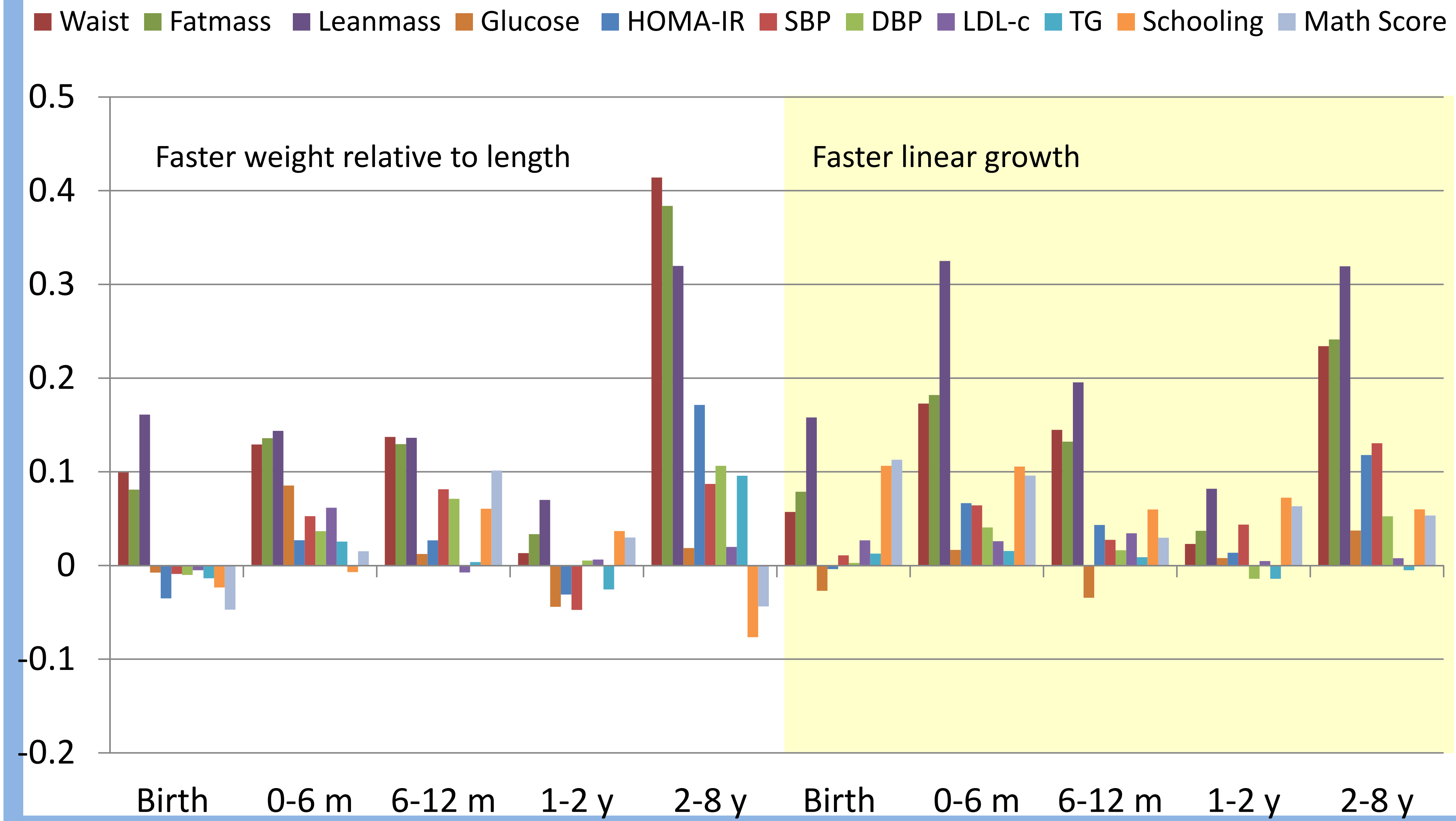
Birth weight, CW and risk of IFG or diabetes in young adulthood: Odds Ratios from logistic regression (n=6171)

	IFG+diabetes		Diabetes	
BW*	**0.91**	**[0.84, 0.99]**	0.89	[0.76, 1.04]
CW 24 mo	0.96	[0.88, 1.03]	**0.83**	[0.71, 0.98]
CW 48 mo	0.95	[0.89, 1.03]	0.96	[0.81, 1.13]
CW Adult	**1.28**	**[1.20, 1.37]**	**1.30**	[1.13, 1.49]
BW	**0.88**	**[0.81, 0.95]**	0.85	[0.72, 1.04]
CW 24 mo	**0.89**	**[0.82, 0.96]**	**0.76**	**[0.64, 0.90]**
CW 48 mo	**0.91**	**[0.89, 0.99]**	0.87	[0.73, 1.03]
Adult WC (z)	**1.35**	**[1.25, 1.46]**	**1.40**	**[1.20, 1.62]**

* 1 SD birth weight ~ 500g

Norris et al., 2012

Comparing effect sizes across multiple outcomes: Details for the Cebu Cohort in infancy and childhood



Summary: The first 1000 days

- ***Prenatal growth***, manifested as size at birth
  - Positive associations with adult height, schooling
  - In some cohorts, *inverse* association of birth weight with later BP and glucose
- ***Postnatal growth***: faster linear growth
  - Early infant linear growth relates to ***taller adult stature*** and ***improved school attainment***: Schooling benefits are greater for smaller children
  - Modest association with adult BP, but 0-2 yr effects small relative to later ages
- ***Postnatal growth***: faster 0-2 yr relative weight gain
  - NOT a strong risk factor for cardiometabolic disease risk in these settings

Conclusions: the first 1000 days are important!

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- Essential for building height and human capital (schooling)
- *Implications:*
  - *Vital to optimize maternal nutritional status PRIOR to and DURING pregnancy*
  - *Vital to optimize infant nutrition and growth in the first 2 yr*
    - *Faster linear growth after the first 1000 days is not strongly related to schooling, so focus on early life is important*
    - *Can still improve adult stature after age 2, but effects are greatest in the first 6 months!*
    - *faster relative weight gain in children and adolescents is strongly related to cardiometabolic disease risk: this has important implications for childhood obesity prevention*
- While early growth was ***Not*** a strong risk factor for cardiometabolic risk *in these settings….. As low and middle income countries transition to higher rates of obesity, risks of maternal overnutrition during pregnancy and of rapid infant weight gain will become increasingly important, and the first 1000 days will likely shape chronic disease to a greater extent*

Cohorts publications

1: Norris SA, Osmond C, Gigante D, Kuzawa CW, Ramakrishnan L, Lee NR, Ramirez-Zea M, Richter LM, Stein AD, Tandon N, Fall CH; COHORTS Group. Size at birth, weight gain in infancy and childhood, and adult diabetes risk in five low- or middle-income country birth cohorts. Diabetes Care. 2012 Jan;35(1):72-9.

2: Richter LM, Victora CG, Hallal PC, Adair LS, Bhargava SK, Fall CH, Lee N, Martorell R, Norris SA, Sachdev HS, Stein AD; the COHORTS Group. Cohort Profile: The Consortium of Health-Orientated Research in Transitioning Societies. Int J Epidemiol. 2011 Apr 21. [Epub ahead of print]

3: Fall CH, Borja JB, Osmond C, Richter L, Bhargava SK, Martorell R, Stein AD, Barros FC, Victora CG; COHORTS group. Infant-feeding patterns and cardiovascular risk factors in young adulthood: data from five cohorts in low- and middle-income countries. Int J Epidemiol. 2011 Feb;40(1):47-62.

4: Martorell R, Horta BL, Adair LS, Stein AD, Richter L, Fall CH, Bhargava SK, Biswas SK, Perez L, Barros FC, Victora CG; Consortium on Health Orientated Research in Transitional Societies Group. Weight gain in the first two years of life is an important predictor of schooling outcomes in pooled analyses from five birth cohorts from low- and middle-income countries. J Nutr. 2010 Feb;140(2):348-54.

5: Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, Sachdev HS; Maternal and Child Undernutrition Study Group. Maternal and child undernutrition: consequences for adult health and human capital. Lancet. 2008 Jan 26;371(9609):340-57. Review. Erratum in: Lancet. 2008 Jan 26;371(9609):302.

6: Stein AD, Wang M, Martorell R, Norris SA, Adair LS, Bas I, Sachdev HS, Bhargava SK, Fall CH, Gigante DP, Victora CG; Cohorts Group. Growth patterns in early childhood and final attained stature: data from five birth cohorts from low- and middle-income countries. Am J Hum Biol. 2010 May-Jun;22(3):353-9.

7: Kuzawa CW, Hallal PC, Adair L, Bhargava SK, Fall CH, Lee N, Norris SA, Osmond C, Ramirez-Zea M, Sachdev HS, Stein AD, Victora CG; COHORTS Group. Birth weight, postnatal weight gain, and adult body composition in five low and middle income countries. Am J Hum Biol. 2012 Jan-Feb;24(1):5-13.

8: Adair LS, Martorell R, Stein AD, Hallal PC, Sachdev HS, Prabhakaran D, Wills AK, Norris SA, Dahly DL, Lee NR, Victora CG. Size at birth, weight gain in infancy and childhood, and adult blood pressure in 5 low- and middle-income-country cohorts: when does weight gain matter? Am J Clin Nutr. 2009 May;89(5):1383-92.