

Life course epidemiology of growth, obesity and cardiovascular disease

Laura D Howe







A bit about me...

- MSc and PhD in Epidemiology at LSHTM
- PhD – measurement of SEP in LMIC
- Moved to Bristol in 2008 to start post-doc
- Awarded an MRC fellowship 2011-2015

Research interests

- Life course epidemiology
- Longitudinal data analysis
- Childhood growth and obesity

Avon Longitudinal Study of Parents and Children (ALSPAC)

- Former county of Avon (Bristol)
- >13,000 pregnant women 1991/2
- Questionnaires, clinics, links to routine data

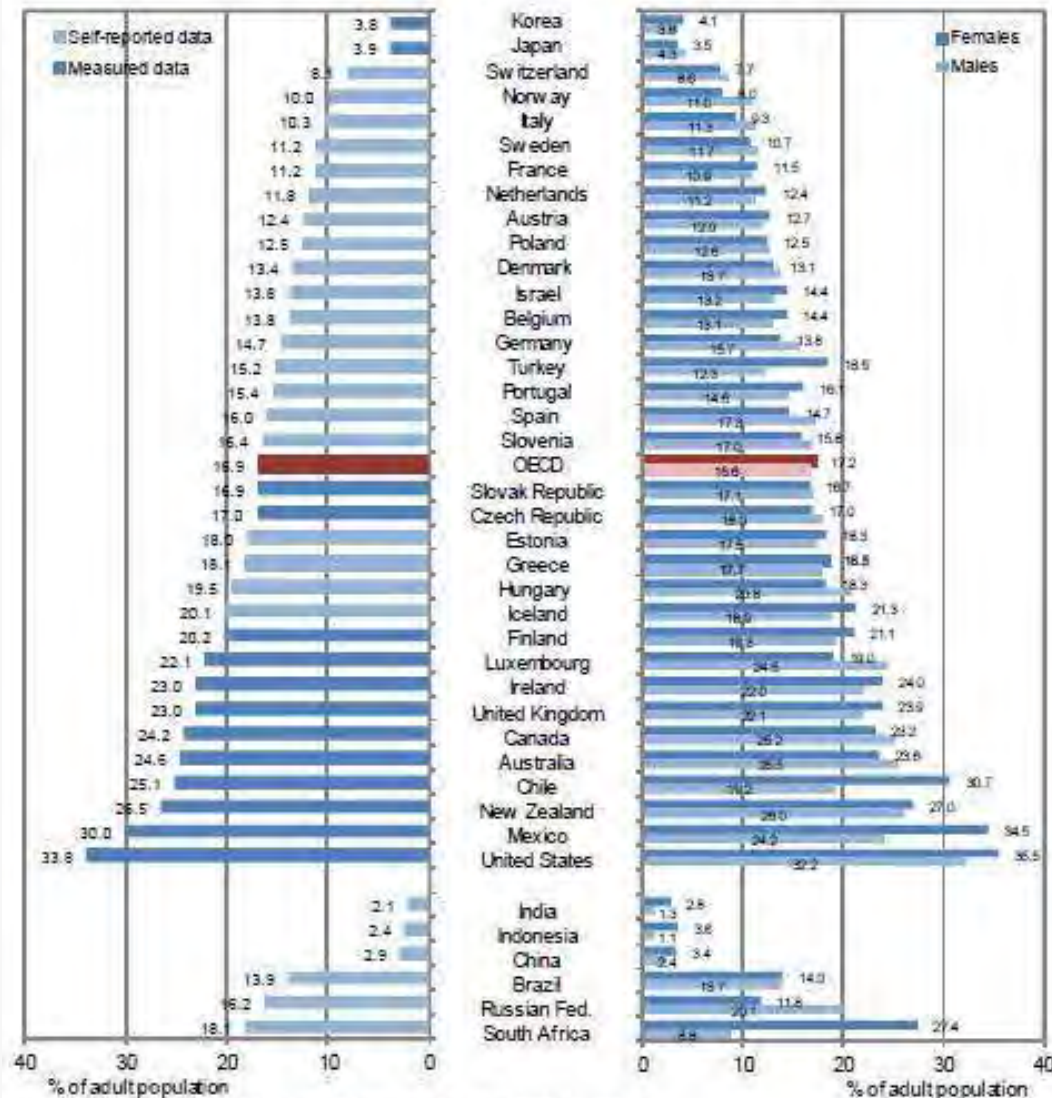


The then and now...



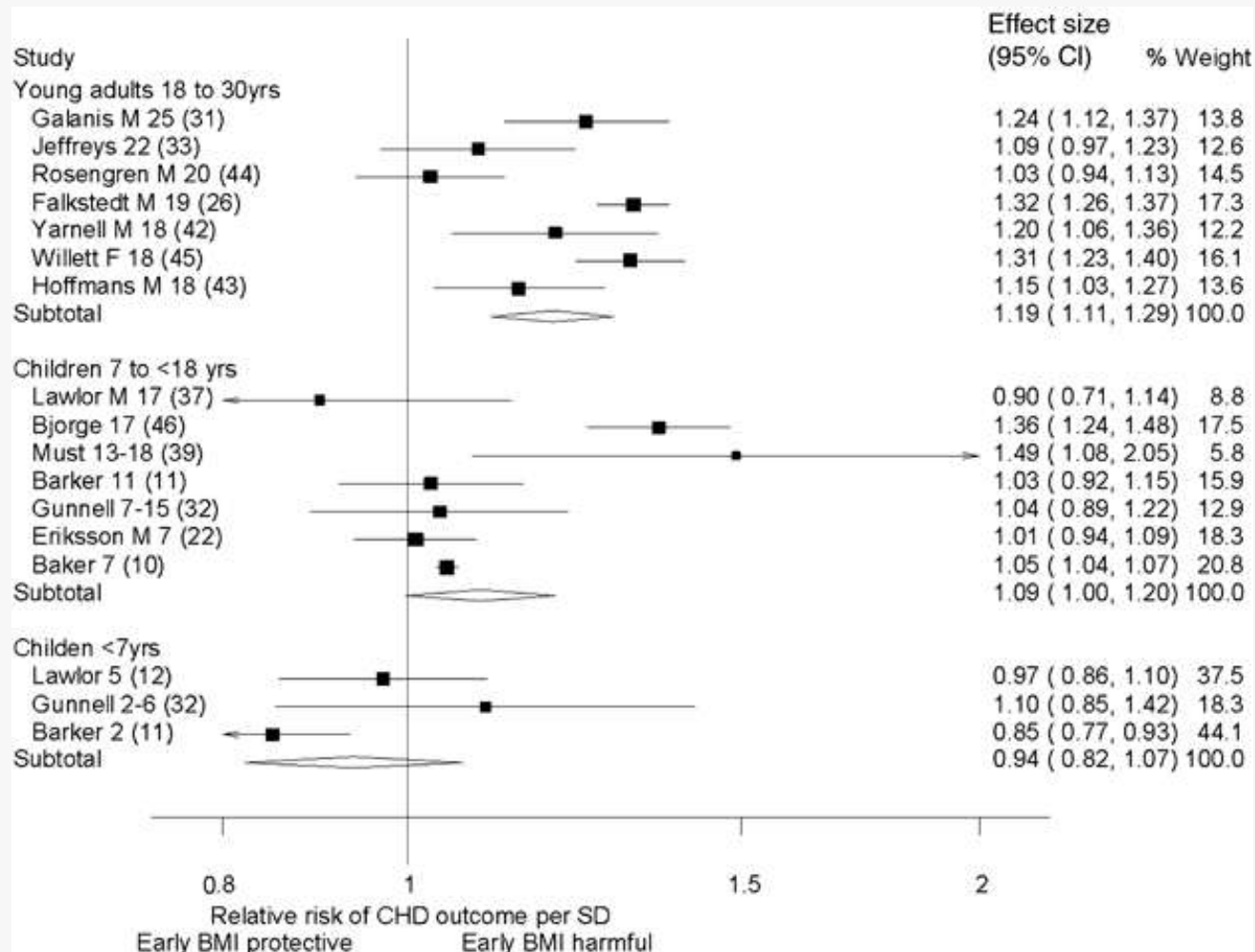
Appendix: obesity rates in the OECD and beyond

Obesity rates among adults, 2009 (or nearest year)



Source: OECD Health Data 2011; national sources for non-OECD countries.

Child obesity & adult CVD



Owen et al. Int J Obesity 2009

Height matters too!

Height used as a general marker of health & development

Shorter stature is associated with:

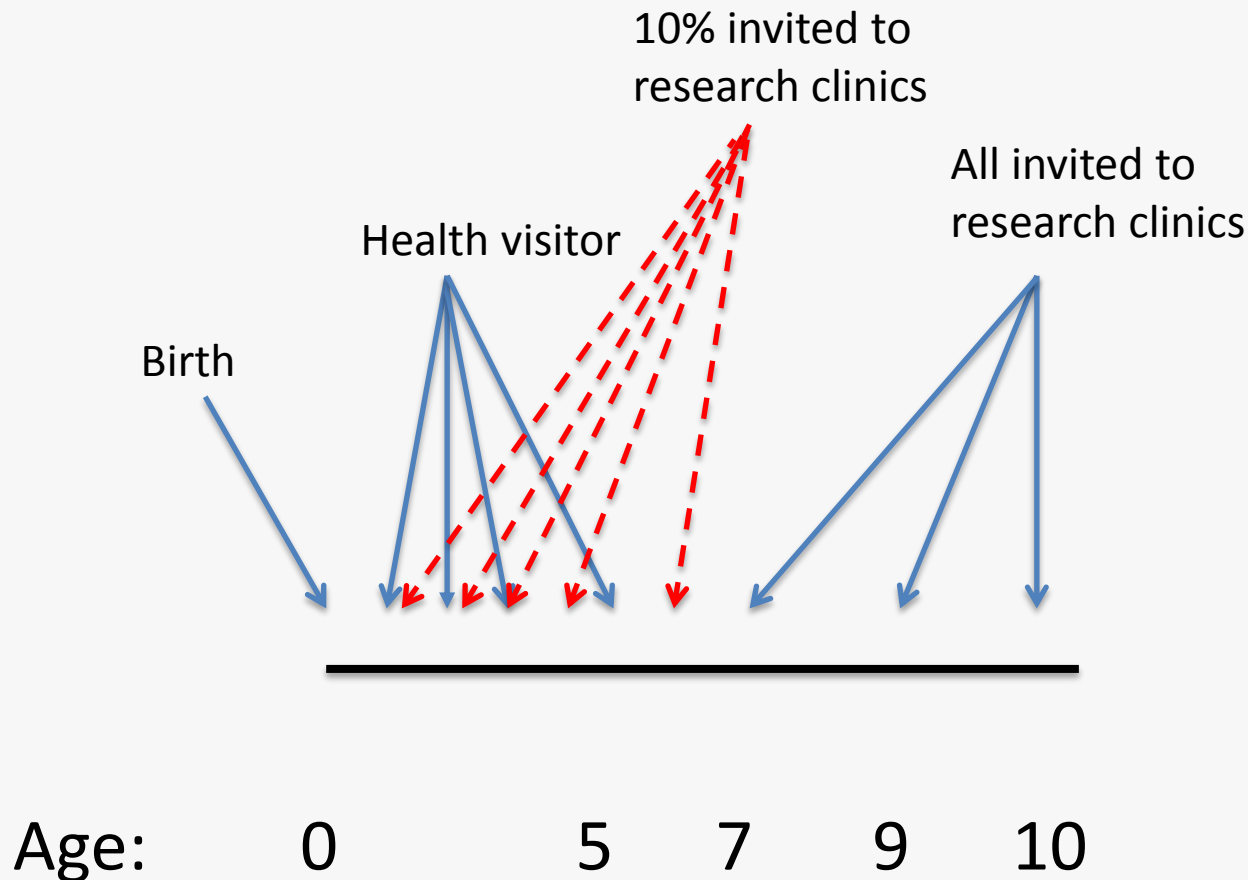
- Increased risk of CVD, cardio-respiratory diseases, diabetes
- Lower success in careers, interviews, etc
- Lower reported life satisfaction
- Not being able to see the band at gigs
- Being missed out of photos



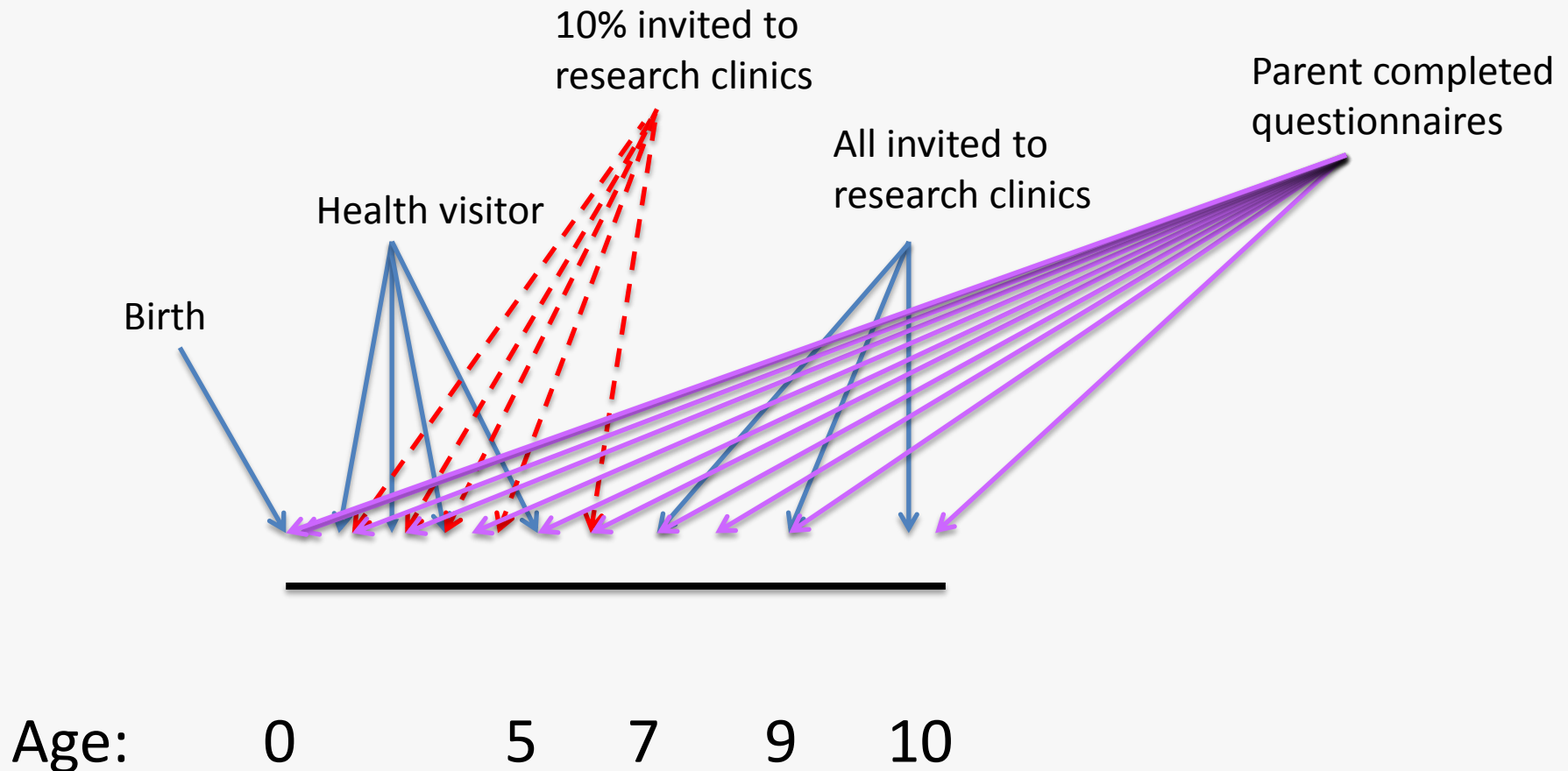
1. Modelling growth
2. Childhood growth and cardiovascular risk
3. Socioeconomic inequalities in growth
4. Genetic influences on growth

1. MODELLING GROWTH

Weight & height measurements in ALSPAC

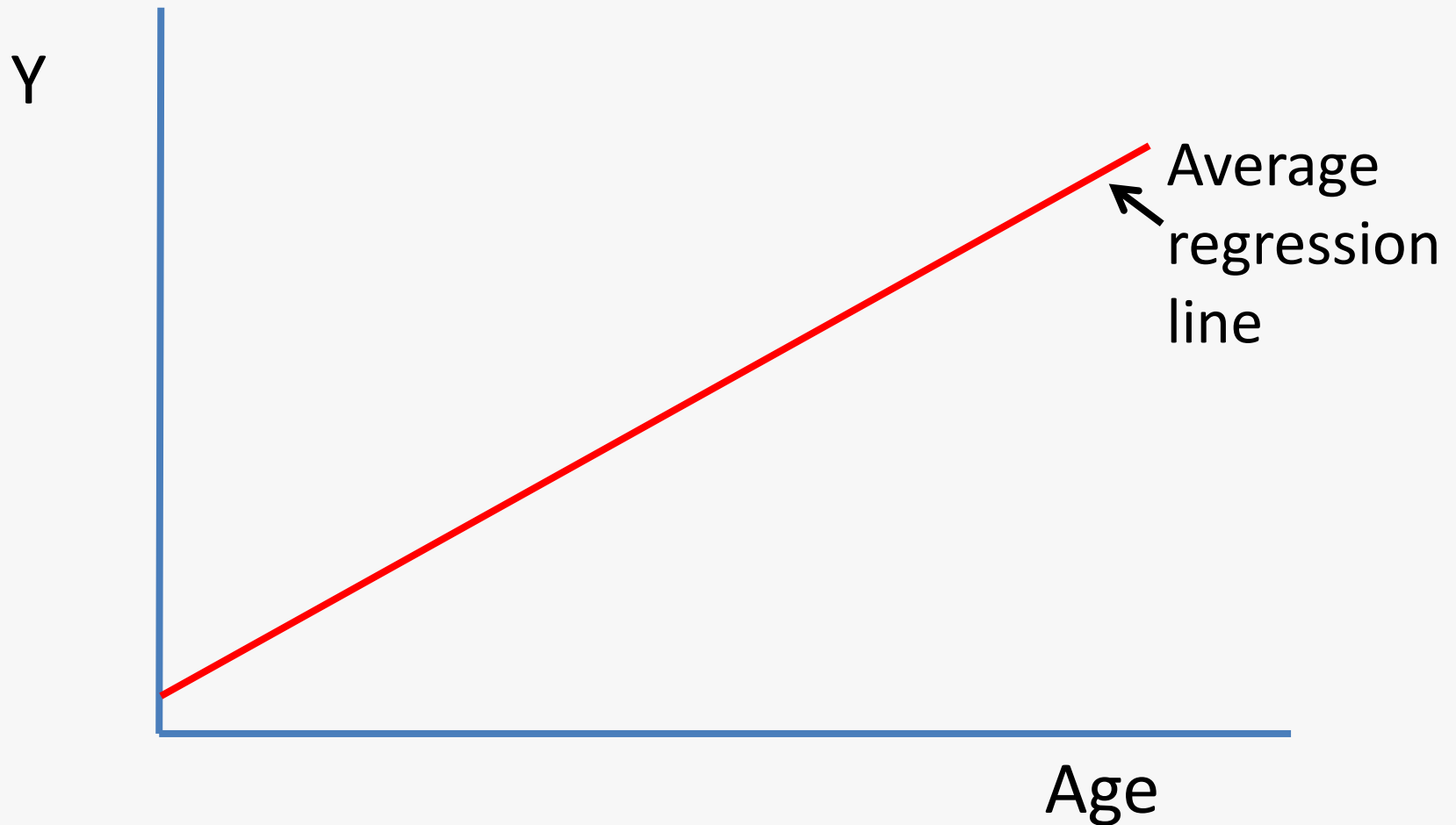


Weight & height measurements in ALSPAC

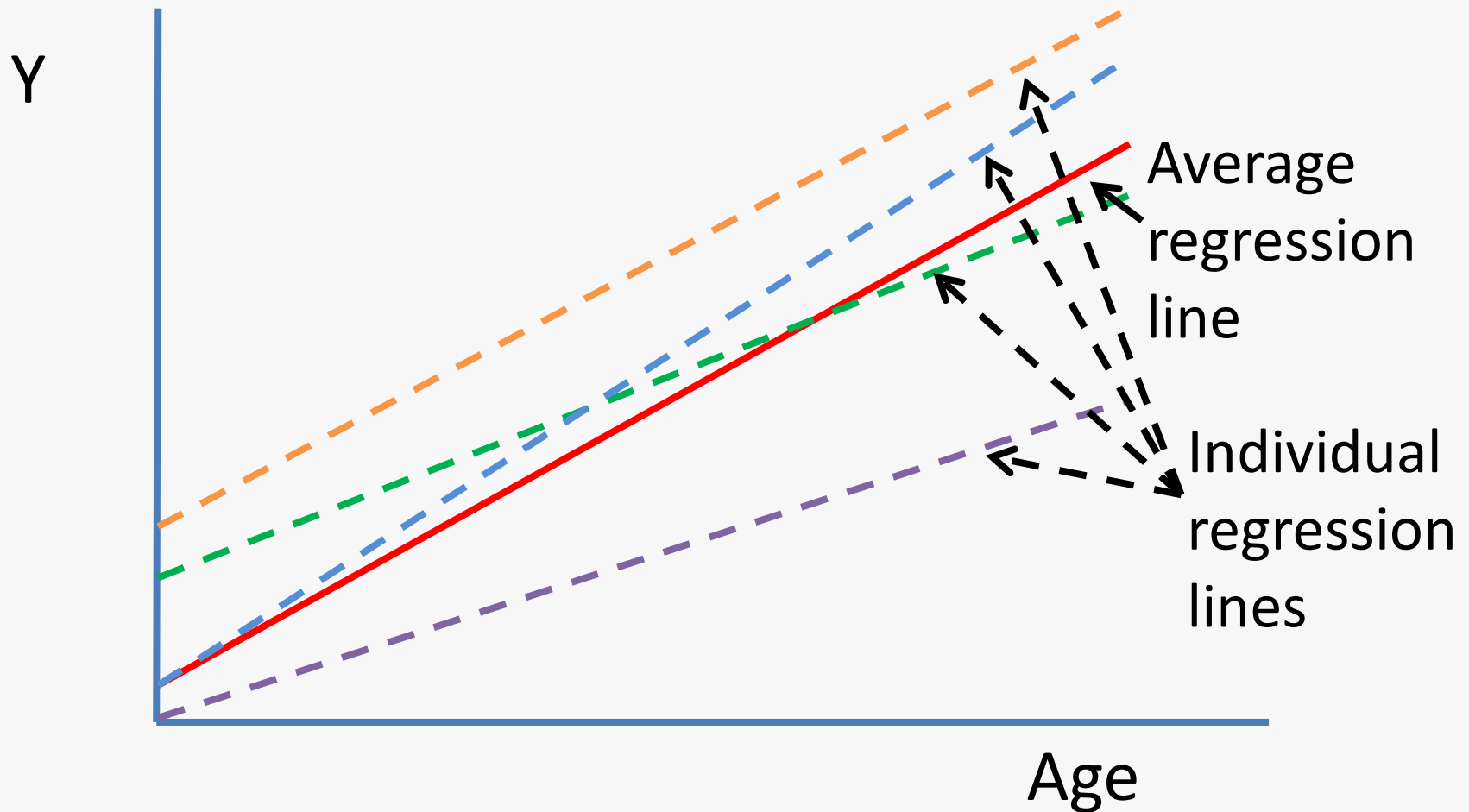


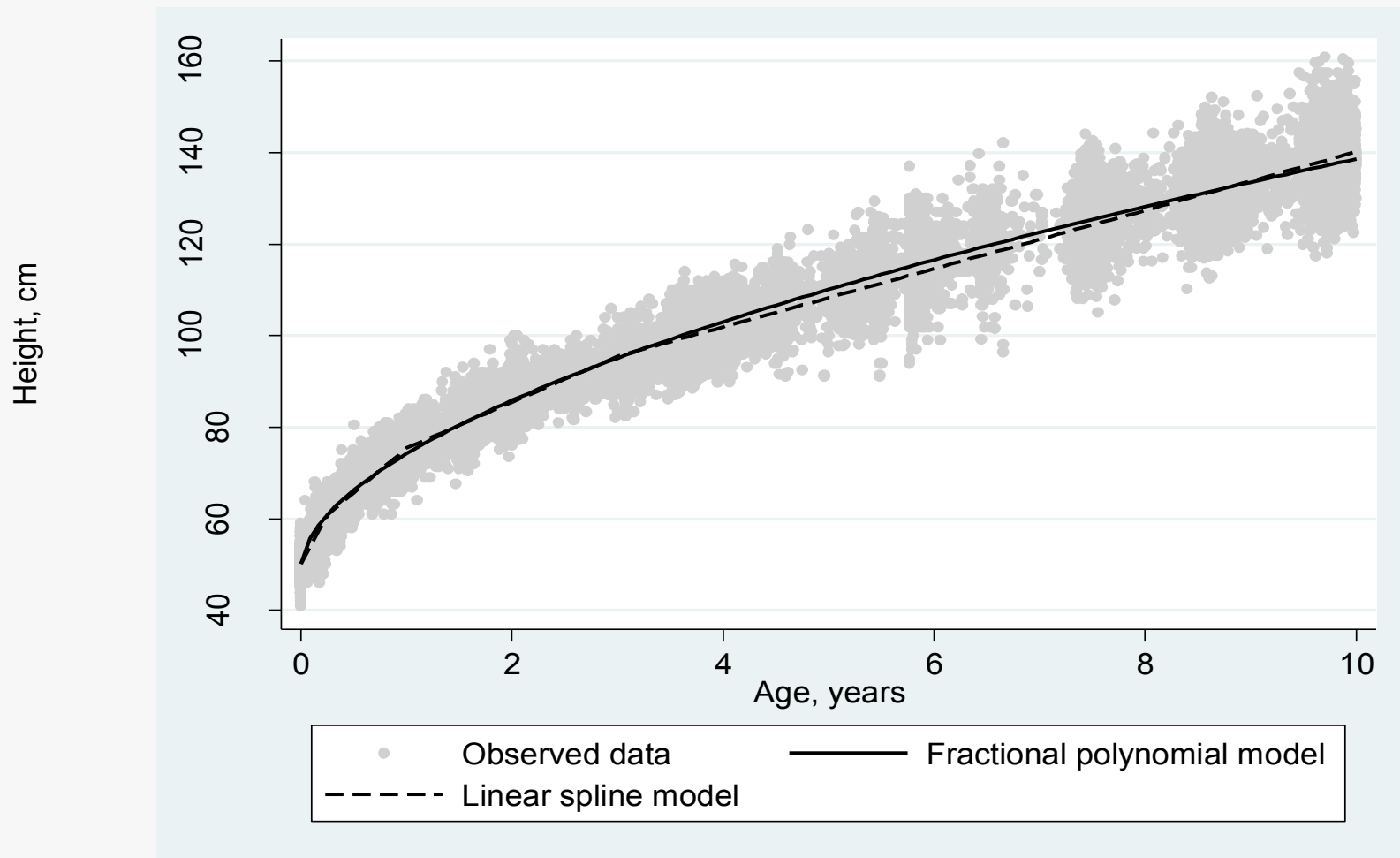
- Want to:
 - a. Maximise use of data, avoid wastage
 - b. Reduce dimensionality of the data
 - c. Reduce correlation between exposures
 - d. Create comparable variables for all individuals, regardless of measurement schedule

Multi-level models in pictures!



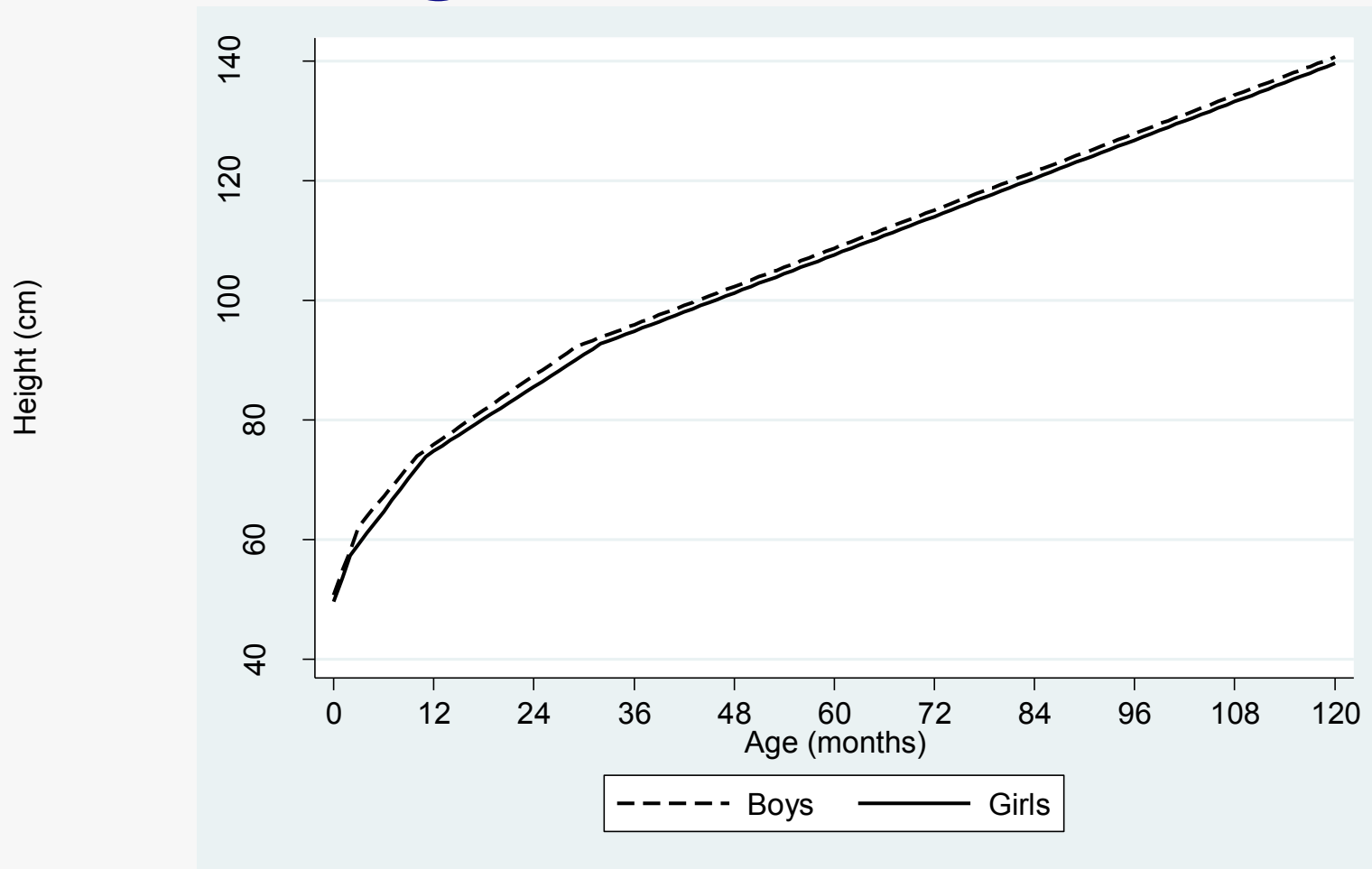
Multi-level models in pictures!





Tilling K, Macdonald-Wallis C, Lawlor DA, Howe LD. Modelling childhood growth using fractional polynomials and linear splines. *Annals of Nutrition and Metabolism* 2013, in press.

Multi-level models of individual growth trajectories



Multi-level models of individual growth trajectories

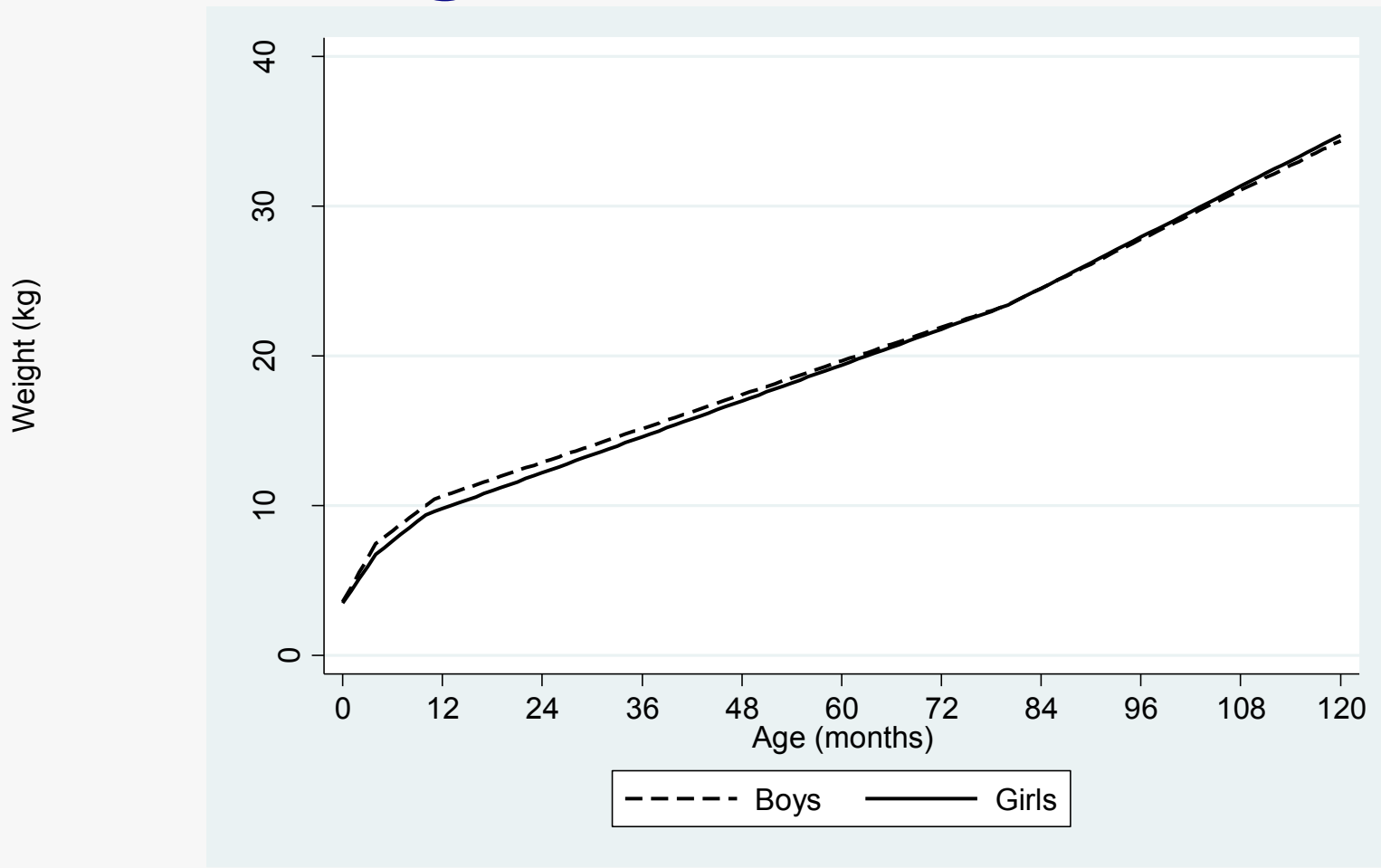


Table 4. Growth rates predicted by linear spline multilevel models for girls.

Mean (SD) growth rates		Born in Bradford (White British ethnicity)	Born in Bradford (Pakistani ethnicity)	Generation XXI	Pelotas 2004	PROBIT
	ALSPAC					
Length/Height						
Girls, N	6731	316	396	2465	2018	7905
Birth length (cm)	50.00 (1.57)	48.36 (1.16)	47.91 (1.04)	48.30 (1.86)	47.77 (1.87)	51.42 (1.66)
Early infancy (cm/month)	3.57 (0.16)	3.54 (0.39)	3.92 (0.36)	3.79 (0.22)	3.83 (0.31)	2.96 (0.45)
Late infancy (cm/month)	1.64 (0.15)	1.63 (0.27)	1.59 (0.25)	1.70 (0.17)	1.59 (0.15)	1.77 (0.17)
Early childhood (cm/month)	0.83 (0.07)	0.94 (0.05)	0.95 (0.05)	0.90 (0.08)	1.04 (0.12)	0.76 (0.04)
Later childhood (cm/month)	0.53 (0.04)	N/A	N/A	0.53 (0.02)	0.65 (0.05)	N/A
Weight						
Girls, N	6731	316	396	2616	2018	7905
Birth weight (kg)	3.30 (0.44)	3.16 (0.51)	2.98 (0.47)	3.11 (0.40)	3.10 (0.33)	3.33 (0.31)
Early neonatal (kg /month)	N/A	N/A	N/A	0.42 (0.64)	N/A	N/A
Early infancy (kg /month)	0.88 (0.14)	0.83 (0.17)	0.82 (0.15)	0.87 (0.16)	0.81 (0.11)	0.87 (0.11)
Late infancy (kg /month)	0.45 (0.09)	0.44 (0.12)	0.42 (0.13)	0.40 (0.09)	0.37 (0.08)	0.53 (0.07)
Early childhood (kg /month)	0.19 (0.04)	0.22 (0.04)	0.24 (0.05)	0.22 (0.05)	0.23 (0.05)	0.15 (0.02)
Later childhood (kg /month)	0.32 (0.10)	N/A	N/A	0.19 (0.05)	N/A	N/A

Howe et al. Stat Methods Med Res 2013

2. CHILD GROWTH AND CARDIOVASCULAR RISK

Obesity and CVD risk factors in ALSPAC

Table 4 | Multivariable associations of change in BMI category between age 9-12 and 15-16 years with cardiovascular risk factors as binary outcomes in all eligible participants with missing data multiply imputed

BMI category at age 9-12 and age 15-16	% (SE)*	Mean (SE) BMI at age 15	Odds ratio† (95% CI)					
			High SBP (≥130 mm Hg)	High LDLc (≥2.75 mmol/l)	High triglycerides (≥1.7 mmol/l)	Low HDLc (<1.03 mmol/l)	High glucose (≥5.6 mmol/l)	High insulin (≥16.95 IU/l)
Girls (n=2747)								
Normal at both	70.7 (0.9)	20.2 (0.05)	Reference	Reference	Reference	Reference	Reference	Reference
Overweight-obese/normal	11.1 (0.6)	22.9 (0.15)	1.06 (0.77 to 1.47)	1.04 (0.67 to 1.61)	1.81 (0.72 to 4.52)	1.01 (0.65 to 1.58)	0.83 (0.47 to 1.47)	0.97 (0.55 to 1.73)
Normal/overweight-obese	4.8 (0.4)	25.5 (0.11)	1.61 (1.04 to 2.47)	1.55 (0.91 to 2.66)	4.41 (1.73 to 11.22)	2.25 (1.34 to 3.79)	0.86 (0.36 to 2.06)	3.37 (1.20 to 14.2)
Overweight-obese at both	13.4 (0.6)	28.1 (0.18)	1.74 (1.29 to 2.33)	1.59 (1.07 to 2.36)	2.88 (1.20 to 6.89)	2.30 (1.50 to 3.54)	1.05 (0.55 to 1.99)	2.87 (1.77 to 4.66)
Boys (n=2488)								
Normal at both	74.6 (0.8)	19.6 (0.04)	Reference	Reference	Reference	Reference	Reference	Reference
Overweight-obese/normal	9.1 (0.6)	22.5 (0.15)	1.60 (1.20 to 2.14)	1.37 (0.75 to 2.49)	3.35 (1.42 to 7.91)	1.50 (1.00 to 2.11)	1.18 (0.77 to 1.79)	2.43 (1.33 to 4.45)
Normal/overweight-obese	4.1 (0.4)	24.5 (0.10)	1.58 (1.03 to 2.41)	2.35 (1.14 to 4.85)	5.38 (1.97 to 14.65)	2.34 (1.43 to 3.83)	1.25 (0.71 to 2.20)	4.35 (2.13 to 8.91)
Overweight-obese at both	12.2 (0.7)	27.3 (0.18)	1.92 (1.49 to 2.47)	2.29 (1.40 to 3.77)	8.04 (4.06 to 15.93)	2.81 (2.00 to 3.96)	1.81 (1.24 to 2.65)	8.48 (5.47 to 13.15)

BMI=body mass index; LDLc=low density lipoprotein cholesterol; HDLc=high density lipoprotein cholesterol.

*Percentage (%) and standard error (SE) in each category across the datasets provides as results from multivariate multiple imputation analyses are based on combining results across 20 databases so exact numbers in each category cannot be provided.

†Adjusted for age, height, height², maternal age, parity, family social class, maternal education, paternal education, birth weight, gestational age, maternal and paternal BMI, and puberty (additional adjustment for age at menarche in girls did not alter associations).

Lawlor DA et al. BMJ 2010

Infancy as a sensitive period



BMI z-scores at each age*	Systolic BP (mmHg) at age 17 years		
	Females	Males	P interaction
	N=1,733	N=1,421	
Birth	-0.7 (-1.2 to -0.2) p=0.004	-0.6 (-1.2 to -0.02) p=0.04	0.82
3 months	0.2 (-0.3 to 0.8) p=0.39	0.5 (-0.1 to 1.2) p=0.12	0.60
1 year	0.2 (-0.4 to 0.8) p=0.50	0.1 (-0.6 to 0.8) p=0.71	0.78
3 years	0.3 (-0.5 to 1.1) p=0.45	0.9 (-0.01 to 1.9) p=0.05	0.44
7 years	1.6 (0.9 to 2.3) p<0.001	2.7 (1.9 to 3.5) p<0.001	0.04
10 years	2.6 (1.4 to 3.8) p<0.001	4.9 (3.5 to 6.3) p<0.001	0.01

*Adjusted for gender, confounders and previous BMI z-scores

Howe et al. submitted

Trajectory of body size			N	Mean (SD) BMI kg/m ²	Mean (SD) observed central systolic BP (mmHg)
Birth	2 years	17 years			
N	N	N	1,498	21.0 (2.0)	95.5 (8.8)
L	N	N	737	20.8 (2.1)	96.4 (9.4)
N	N	O	352	28.6 (3.4)	101.5 (9.0)
L	N	O	157	28.6 (3.1)	101.4 (8.5)
N	O	O	125	29.3 (4.4)	100.7 (10.5)
L	O	O	32	28.3 (3.5)	104.2 (11.0)
N	O	N	196	22.2 (1.8)	95.7 (9.0)
L	O	N	57	22.0 (1.7)	93.3 (6.8)

Howe et al. submitted

3. SOCIOECONOMIC INEQUALITIES IN GROWTH

Inequalities in height

Barriers to reaching genetic height potential:

- Poor child nutrition
- Child illness

Secular trends in height

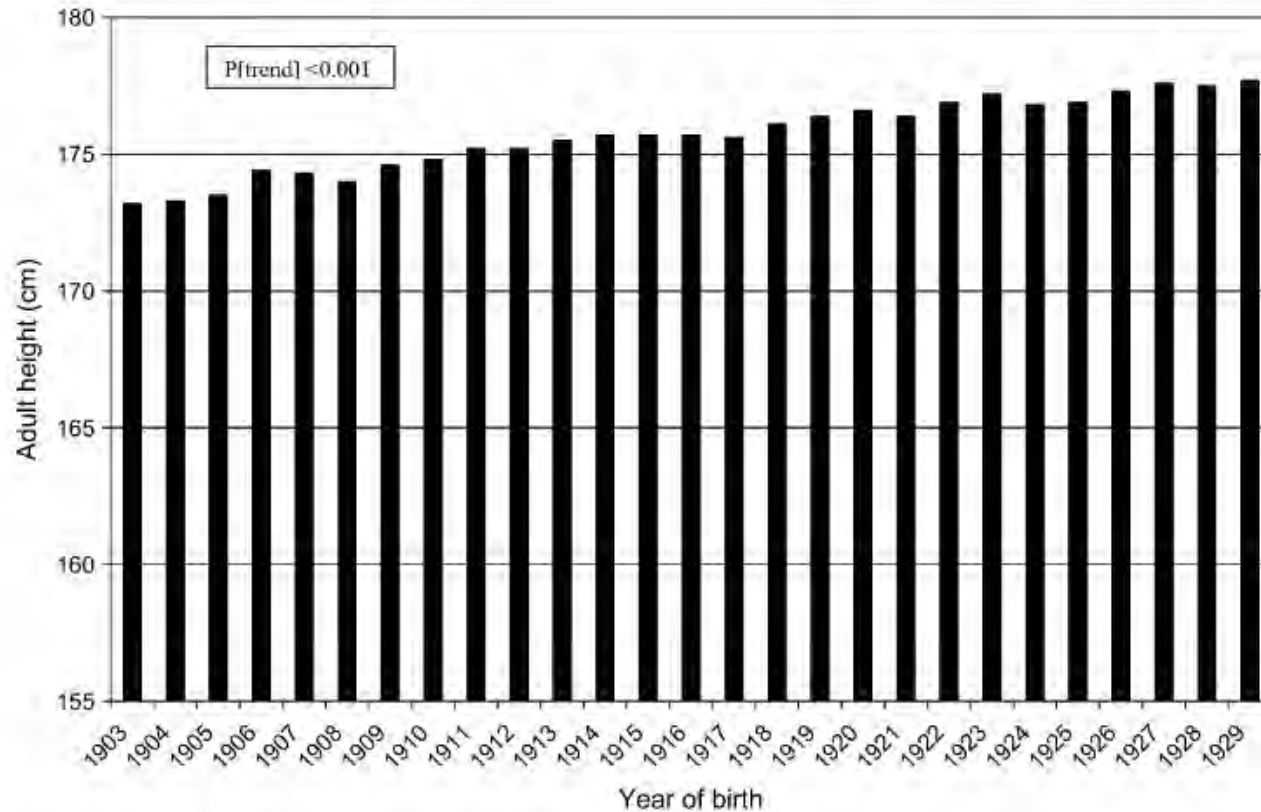


Fig. 1. Mean adult height at baseline (1967–1970) according to birth year in the original Whitehall study of men ($N = 17345$).

Batty et al., Econ Hum Biol 2009

Socioeconomic position and height

Villermé (1829):
French soldiers
Poverty causes
short stature

Sir or Madam,

I am an O.A.P
& I've just read the headlines
regards your 'Richer the taller'
investigations & I have this to
say.

We were six children and
one parent (mother) & once we
had but one egg between us all,
& eating apple cores found in the
gutter was common. Our groceries
were bought on Saturday & gone
by Tuesday. I cannot believe
you didn't see the connection
between 'height & money' in the
first place and you got paid for
this? Unbelievable.

yours.

Jane Linzey

P.S I'm 5' 2". & weigh 8½ stone & all
of my family tend to be small.

Socioeconomic position and height

- What is already known?
- Low SEP = shorter height
- What is less well understood?
- Social patterning of postnatal growth
- When inequality emerges
- Changes over time & economic development

Inequalities in height

Age / growth period	Mean growth rates by maternal education				p value
	<i>Less than O-Level</i>	<i>O-Level</i>	<i>A-Level</i>	<i>Degree or above</i>	
Birth length (cm)	50.55	50.70	50.71	51.02	0.0003
0-3 months (cm/month)	3.84	3.83	3.83	3.82	0.97
3-10 months (cm/month)	1.68	1.69	1.70	1.67	0.57
10-29 months (cm/month)	0.95	0.96	0.96	0.97	0.028
29-120 months (cm/month)	0.53	0.54	0.54	0.54	<0.0001

Howe et al, JECH, 2012

Inequalities in height in Pelotas 2004

Age / growth period	Mean growth rates by maternal education			P value
	0-4 years	5-8 years	9+ years	
Birth (cm)	47.54 (0.15)	47.81 (0.09)	47.97 (0.09)	0.040
0-3 months (cm/month)	3.69 (0.04)	3.77 (0.02)	3.93 (0.02)	<0.001
3-12 months (cm/month)	1.55 (0.02)	1.58 (0.01)	1.61 (0.01)	0.002
12-32 months (cm/month)	0.99 (0.01)	1.03 (0.01)	1.06 (0.01)	<0.001
32-48 months (cm/month)	0.47 (0.01)	0.47 (0.01)	0.47 (0.01)	0.884

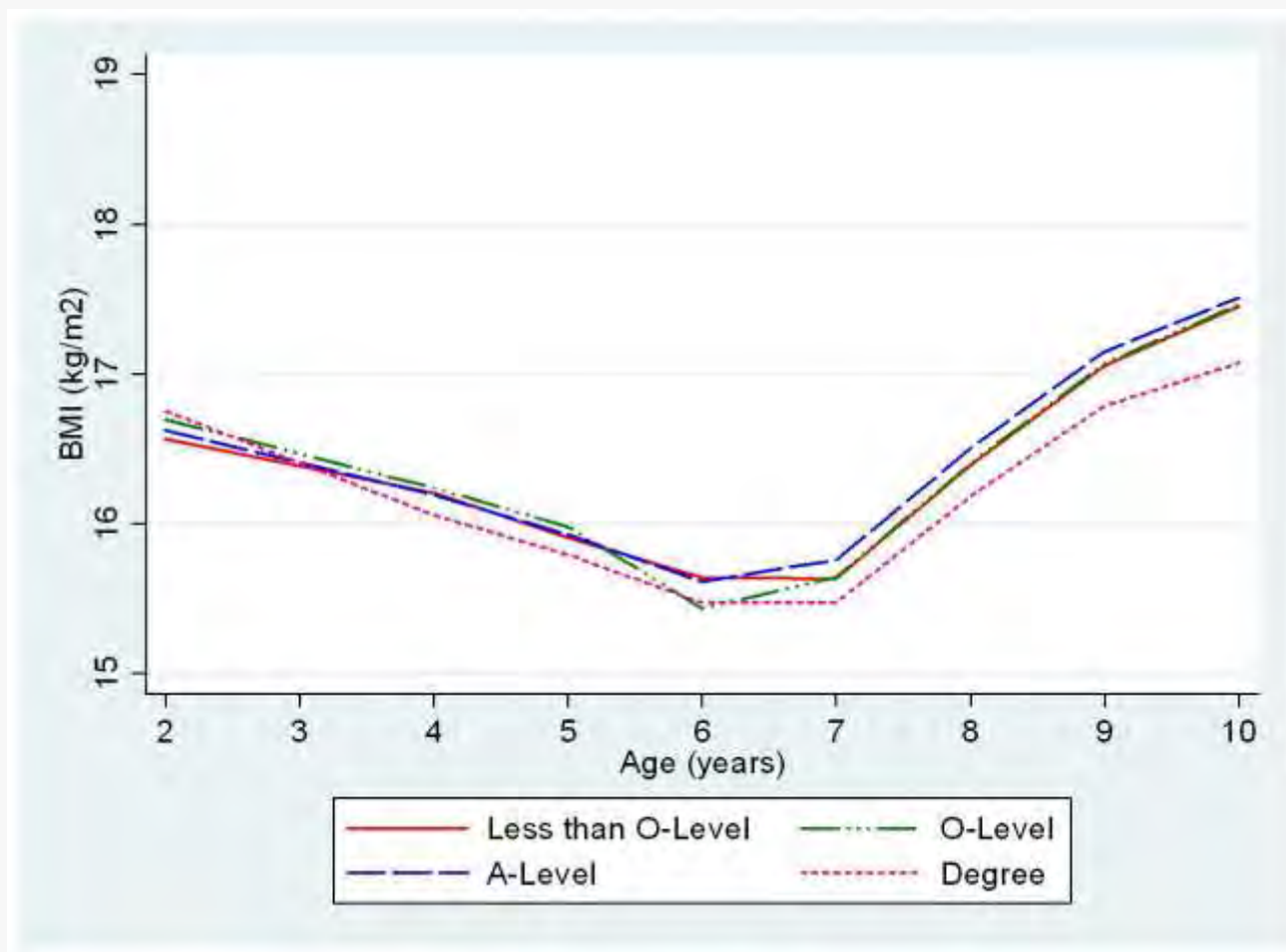
Matijasevich et al., PPE 2012

- Differences between highest and lowest maternal education:
- Both cohorts: ~0.5 cm at birth
- ALSPAC: ~1.5 cm (age 10)
- Pelotas: ~3 cm (age 4)

Inequalities in obesity

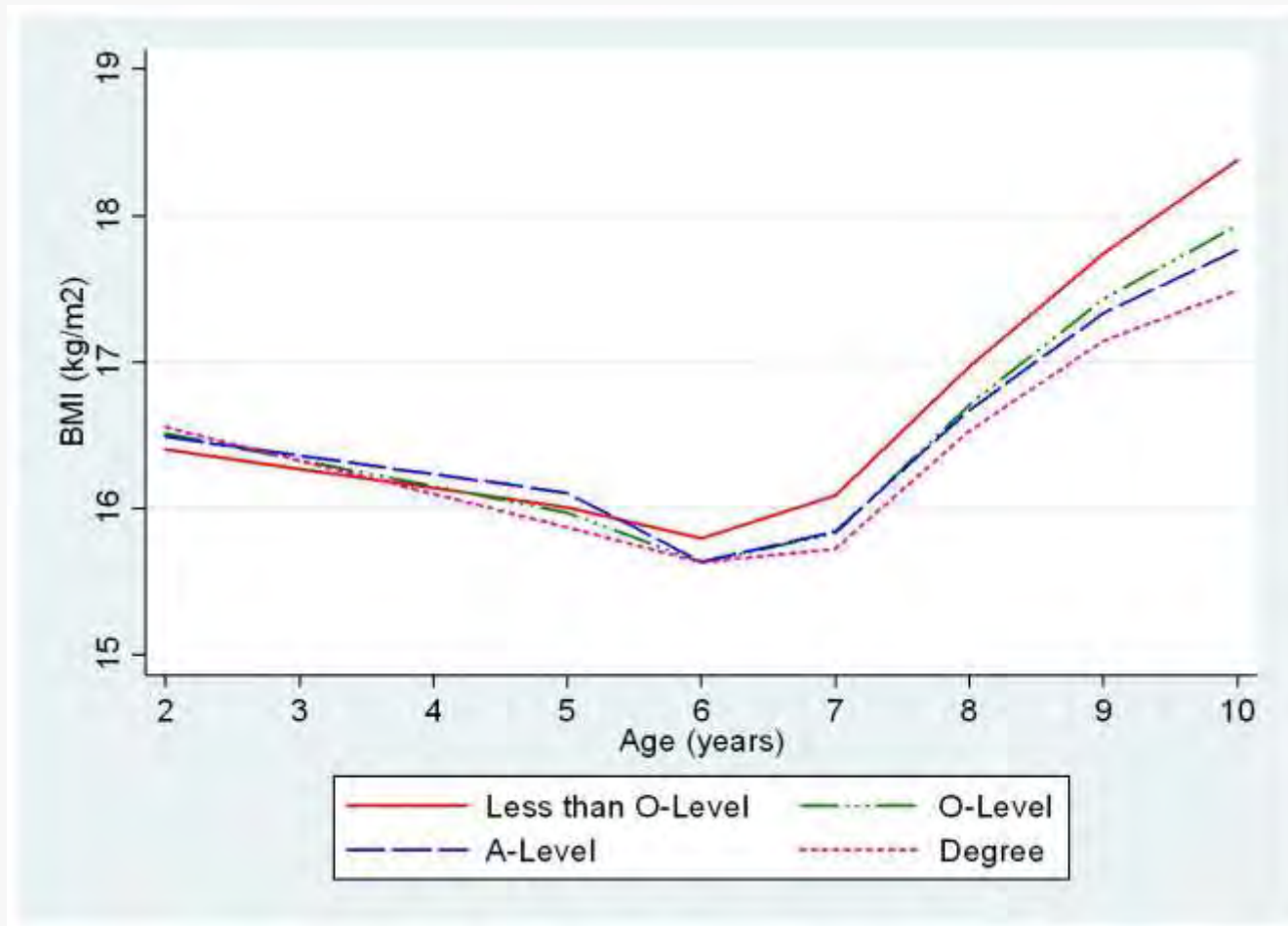
- Historically a disease of affluence
- Now more prevalent in lower socioeconomic groups in both adults and children
- But: socioeconomic gradient in children has emerged only in recent years

BMI 2-10 years, males



Howe et al,
Int J Ped Obes
2010

BMI 2-10 years, females



Howe et al,
Int J Ped Obes
2010

- Diet and physical activity are the main risk factors for obesity
- Does one of them contribute more to inequalities in obesity than the other?
- And does this change over childhood and adolescence?

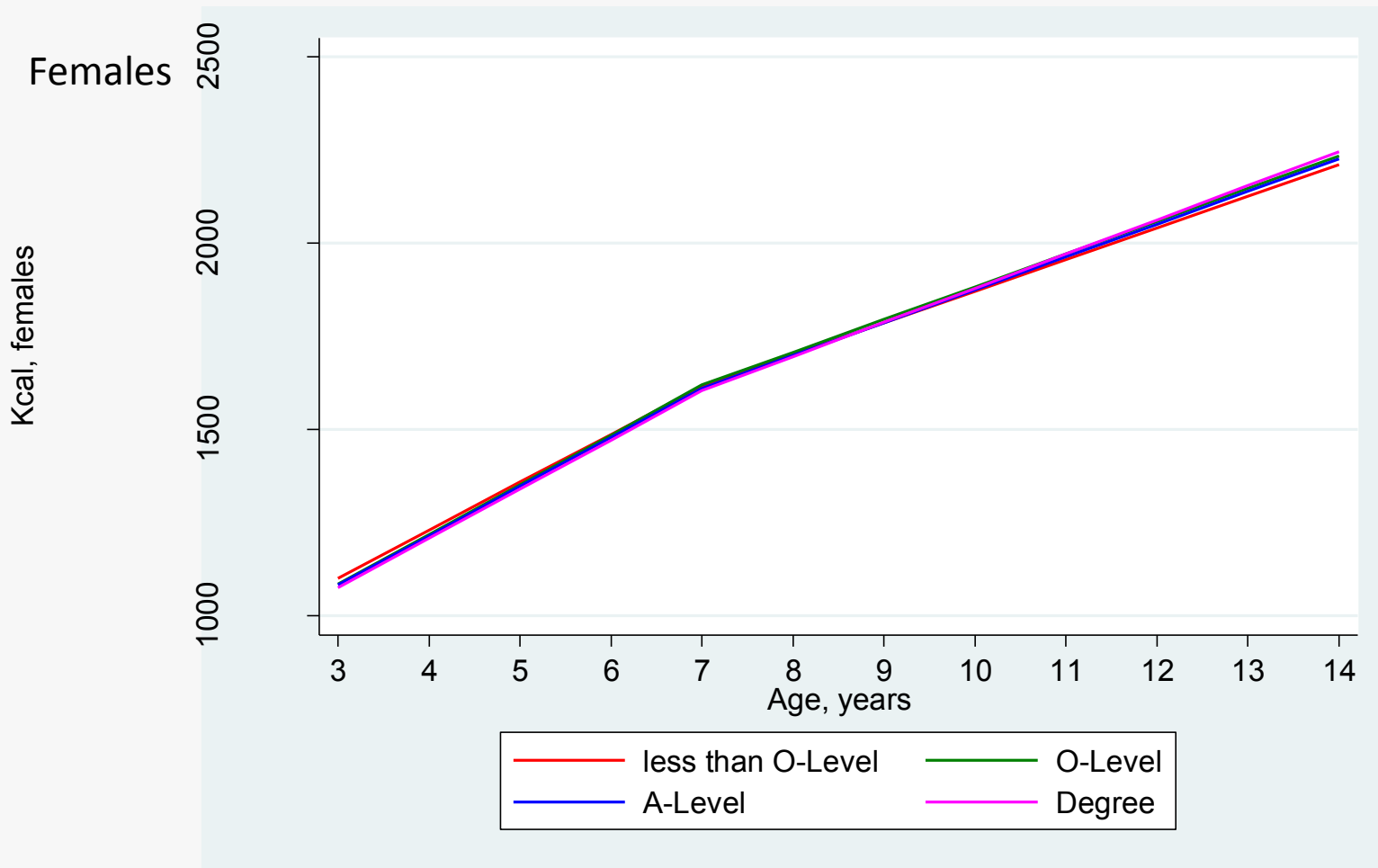
Diet data

- FFQs: 3, 4.5, 7, 8.5 years
- 3-day diet diaries: 3.5, 5, 7.5, 10, 14 years
- Total energy intake calculated from each

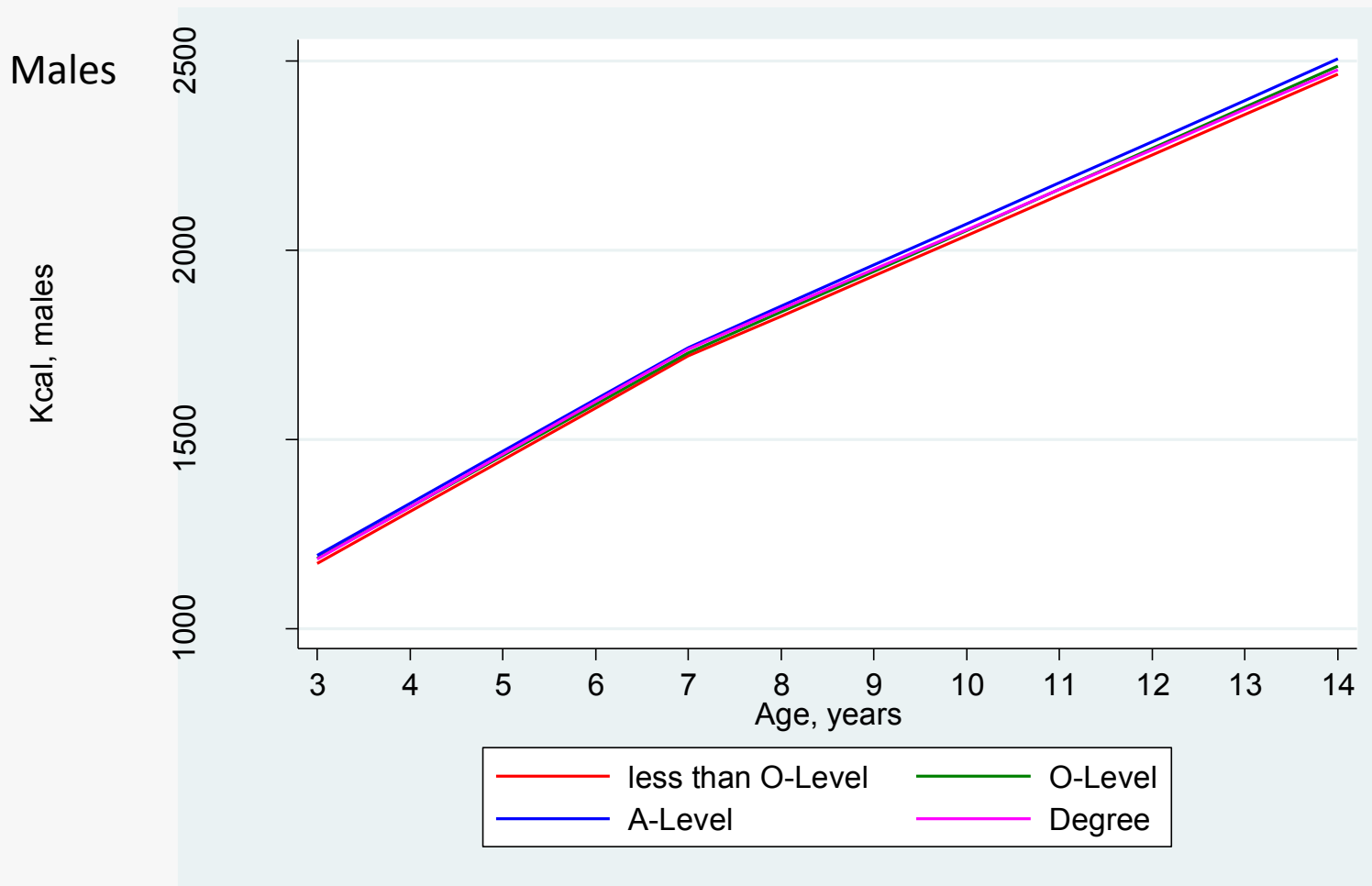
Physical activity data

- Accelerometers worn for 7 days at 12, 14, 16 years
- Mean counts per minute (CPM)
- Mean minutes of moderate to vigorous physical activity (MVPA)

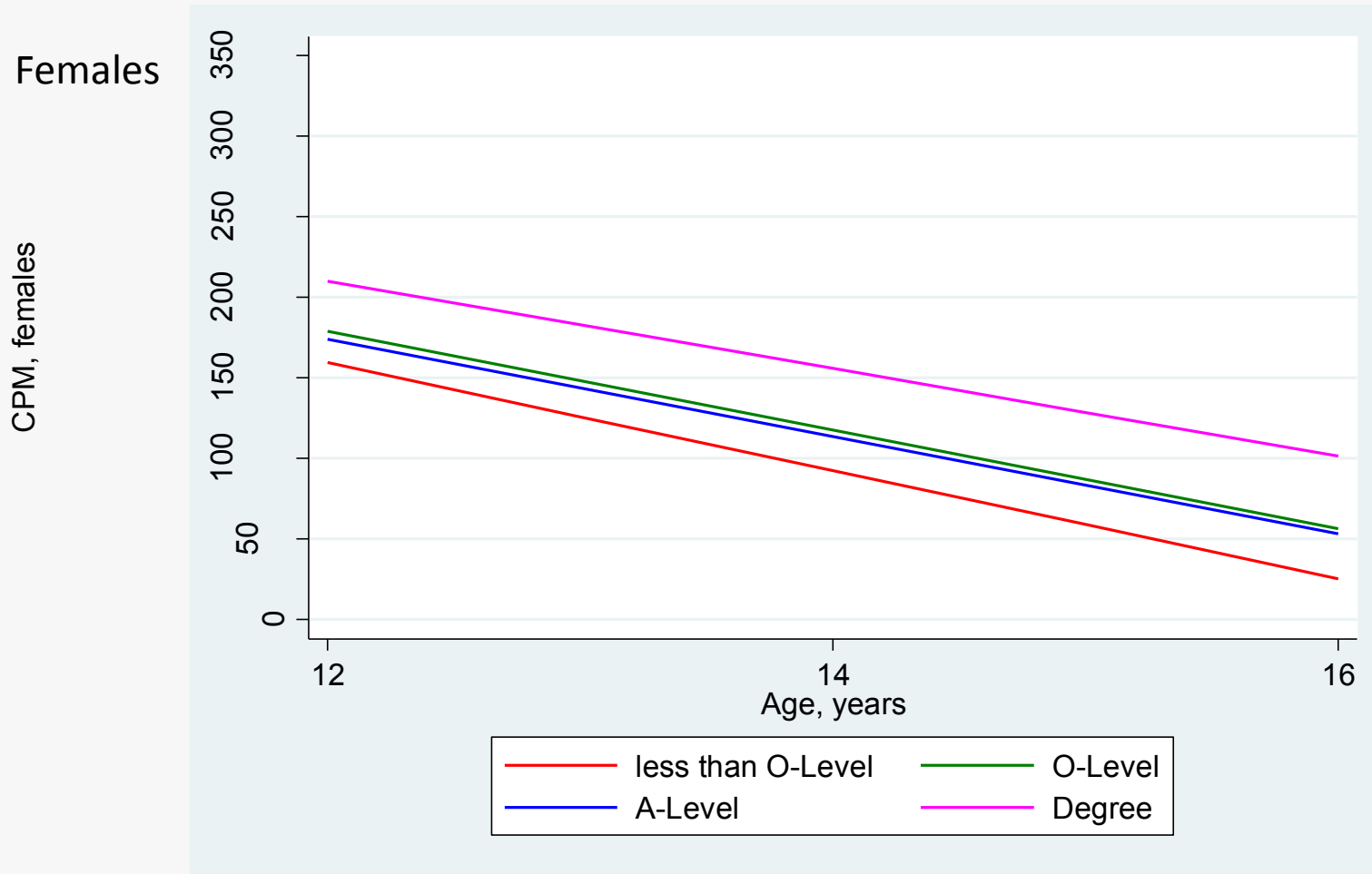
Inequalities in energy intake



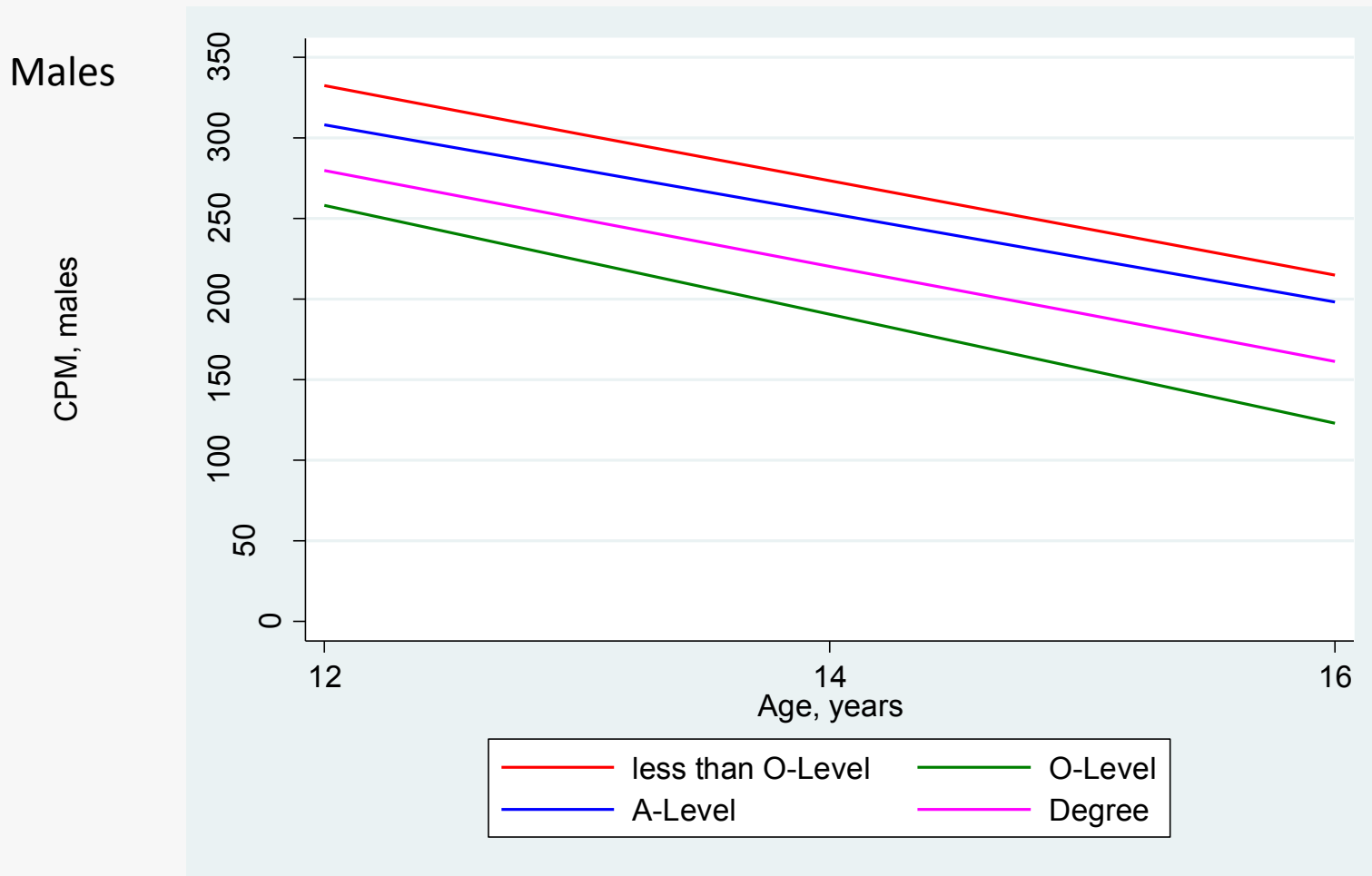
Inequalities in energy intake



Inequalities in physical activity



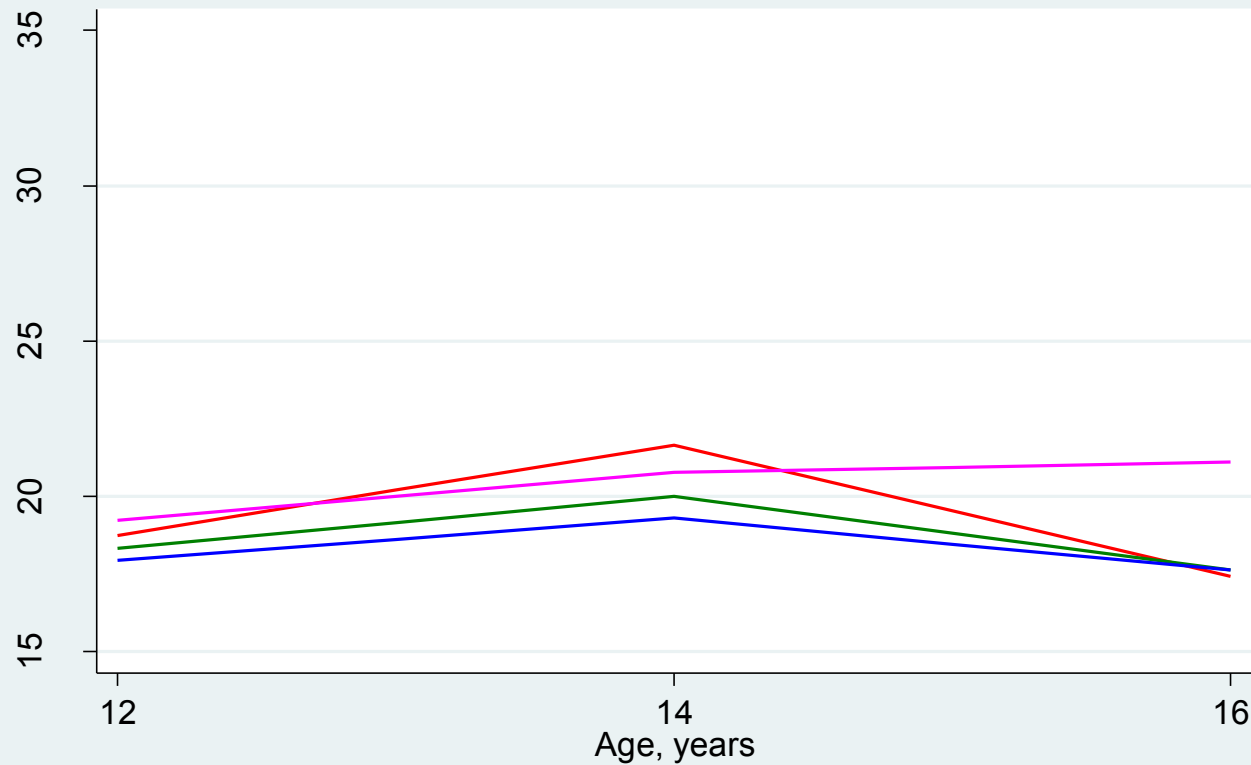
Inequalities in physical activity



Inequalities in physical activity

Females

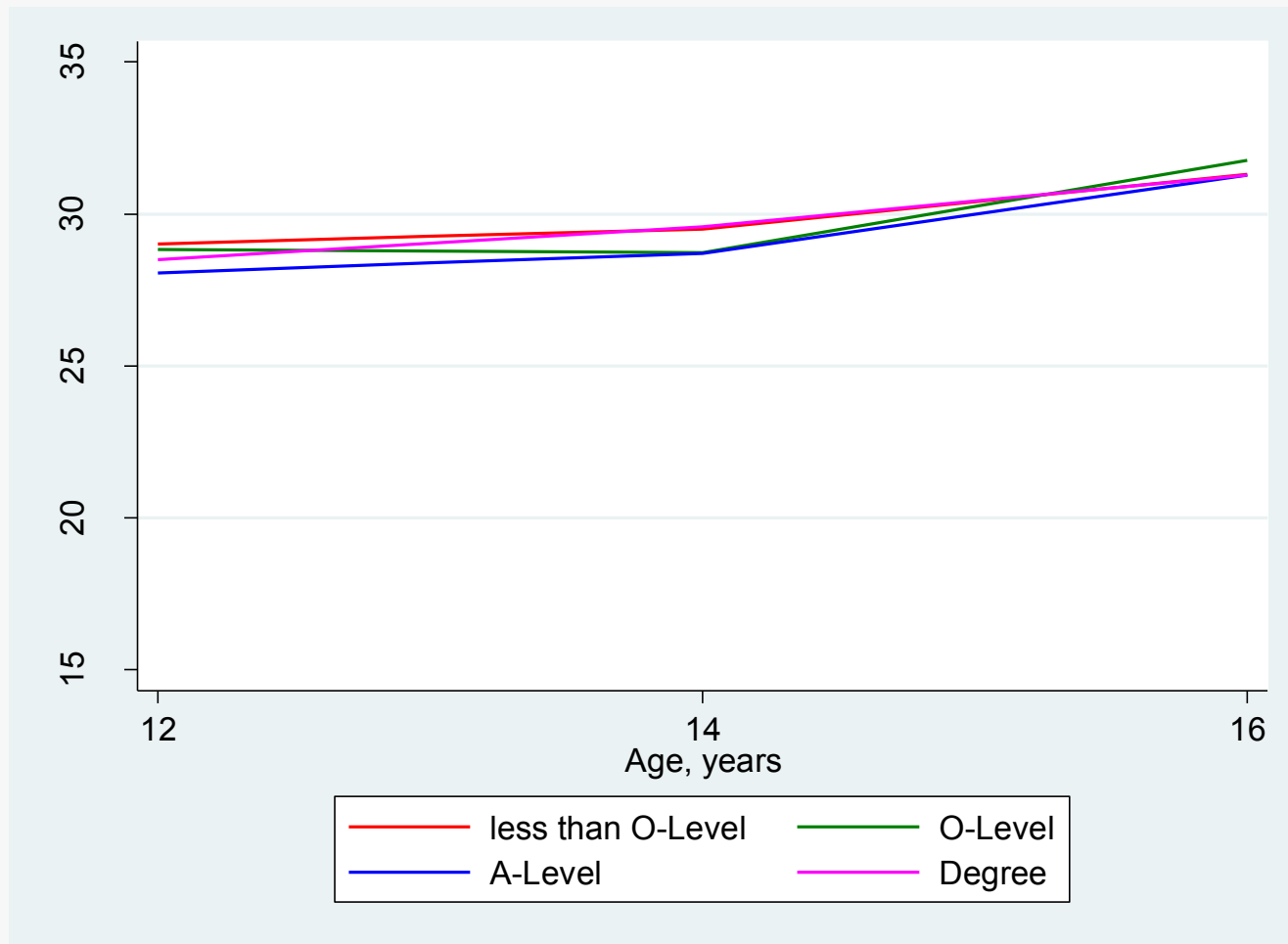
MVPA, females



Inequalities in physical activity

Males

MVPA, males



Tentative conclusions:

- No SEP differences in **reported** energy intake
- Perhaps it's CPM rather than MVPA that contributed to obesity inequalities in females?
- Physical activity (**as measured by accelerometer**) does not contribute to obesity inequalities in males
- **MEASUREMENT ERROR**

4. GENETIC INFLUENCES ON GROWTH

Longitudinal genetic studies: motivations

- Understanding the timing and magnitude of genetic effects
-
1. Clues to gene function?
 2. Useful for Mendelian Randomization?

Heritability of height

- 80-90%
- Strongly predicted by mid-parental height

Genes influencing height

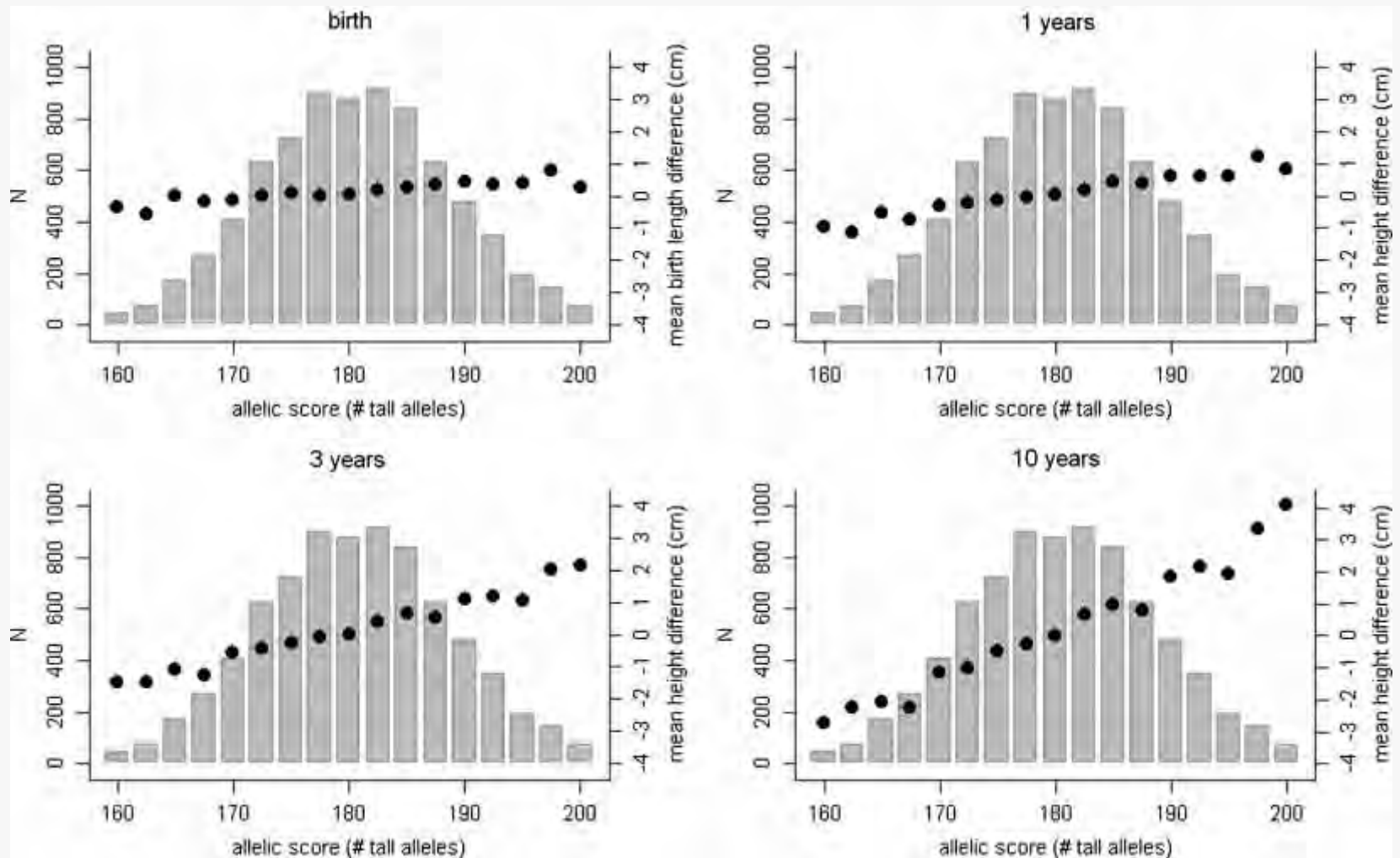
- What is already known?
- GWAS on adult height:
 - 180 SNPs explain ~10% variation
- Infancy is a period of canalisation
- What is less well understood?
- At what age do SNPs identified in adulthood begin to affect growth?

- Allelic score of 180 SNPs included in height trajectory (interaction with intercept and slopes)

	Birth	0-3 months	3-12 months	1-3 years	3-10 years
Mean (SD) cm or cm/month	50.5 (1.5)	3.7 (0.2)	1.6 (0.1)	0.8 (0.1)	0.5 (0.04)
β (SD)	0.02 (0.002)	0.009 (0.007)	0.02 (0.004)	0.02 (0.003)	0.03 (0.003)
p	1×10^{-15}	0.2	3×10^{-4}	6×10^{-17}	2×10^{-37}

Paternoster & Howe et al, HMG 2011

Mean birth length and height at 1, 3 and 10 years, by allelic score.



Paternoster L et al. Hum. Mol. Genet. 2011;20:4069-4075

- By age 10, the mean height difference between individuals with ≤ 170 versus ≥ 191 'tall' alleles (the top and bottom 10%) was 4.7 cm (0.8 SD), explaining ~5% of the variance
- n.b. compare this to the 1.5 cm explained by maternal education

Genetics of adiposity

- Heritability estimates from twin studies: 40-80%
- ? higher in younger individuals

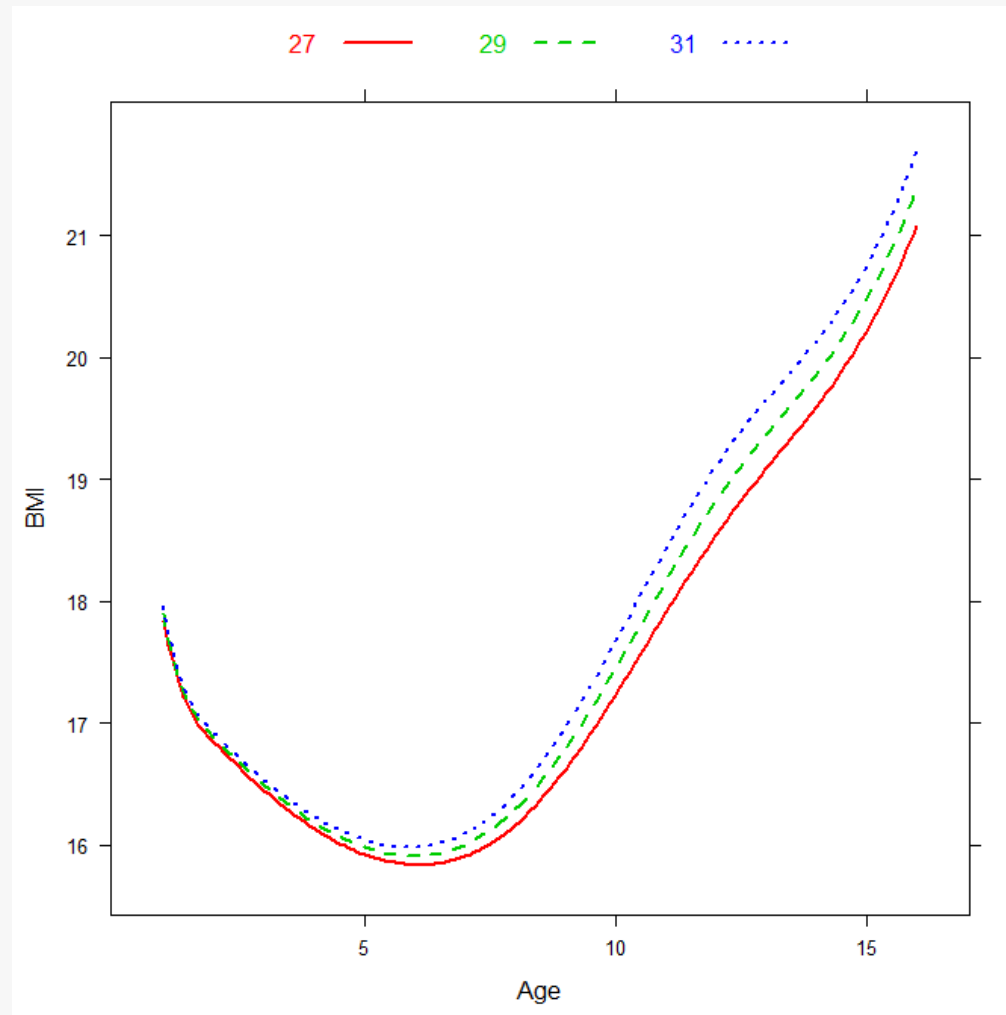
- Many genetic variants now identified
- FTO and MC4R:

0.2-0.4 kg/m² per allele

OR for obesity in adults 1.1-1.3

Genetic influences on adiposity trajectories

- Relatively few studies in children
- Association with known genetic variants:
at what age do they start to act?



Warrington & Howe et al. 2013 (In Press)

Future methodological directions

- Developing methodology for longitudinal GWAS
- Longitudinal models of DNA methylation

What I'm doing in NZ

- **CPHR:**
- Occupation and prescription medication as risk factors for birth defects (using registry data)
- Studies with ELF (and ALSPAC)
- **SWRC:**
- Latent class analysis of trajectories of sleep across pregnancy
- Sleep in pregnancy and neonatal outcomes
- **Auckland Obs & Gynae:**
- Trajectories of foetal growth
- (Cycling, tramping, wine-drinking, ...)

Thank you

- Debbie Lawlor
- Kate Tilling
- Nicole Warrington
- Lavinia Paternoster
- All co-authors

