Associations between weight status across the life course and risk of cardiometabolic disease - Methodological challenges

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Center for Clinical Research and Prevention

- Four sections
  - Health promotion and Prevention
  - Data, Biostatistics and Pharmacoepidemiology
  - Intersectoral health service research
  - Section for Epidemiology
    - Life-course epidemiology group (Dr Jennifer L Baker)

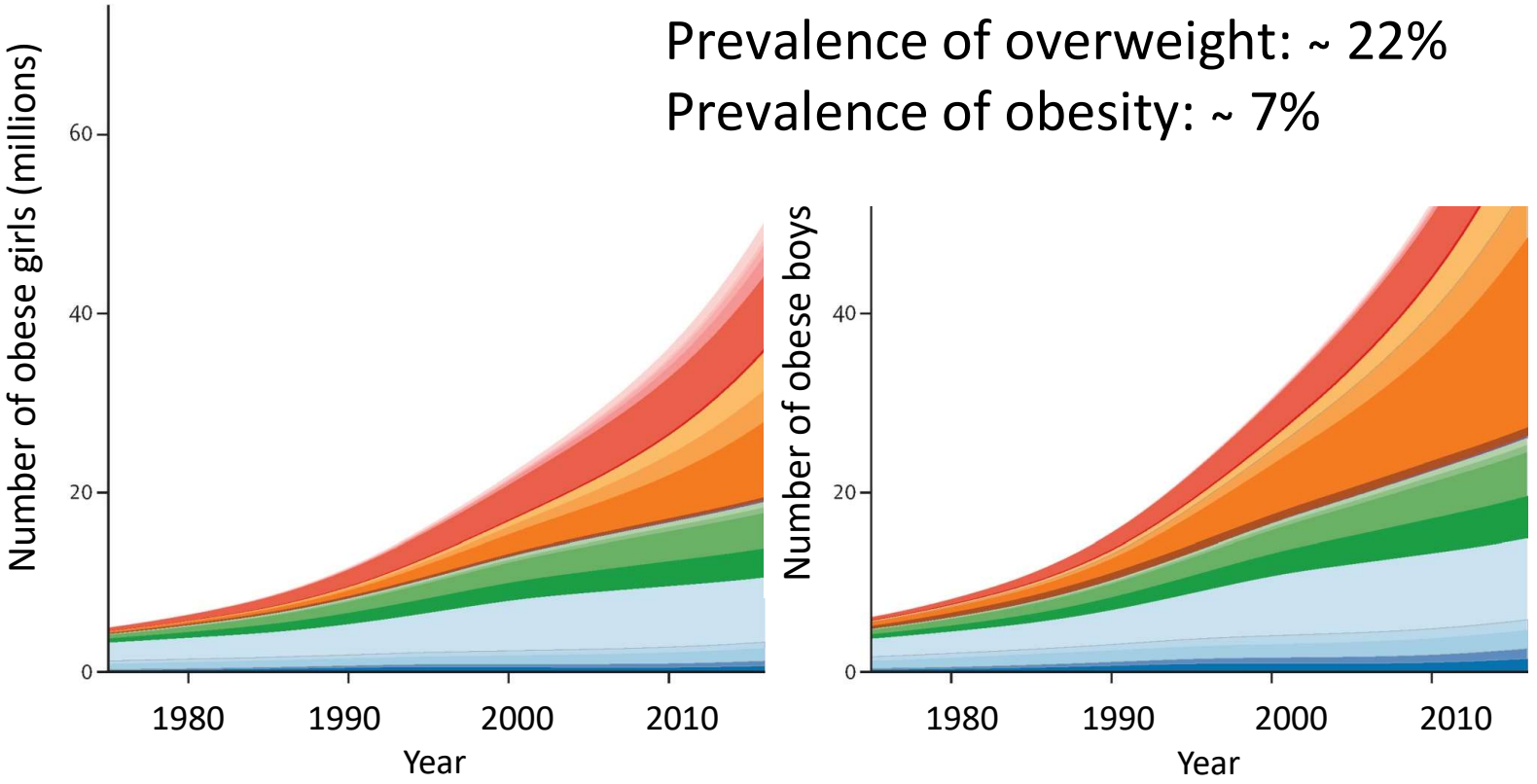
Outline

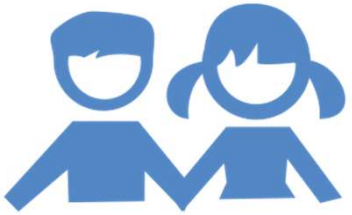
- Our research area and our data
- General comments on growth modeling
- Growth and cardiometabolic disease (CMD) (examples of application of models)

Research area: Life-course studies of CMD

Worldwide state of the childhood obesity epidemic

2016:
Prevalence of overweight: ~ 22%
Prevalence of obesity: ~ 7%

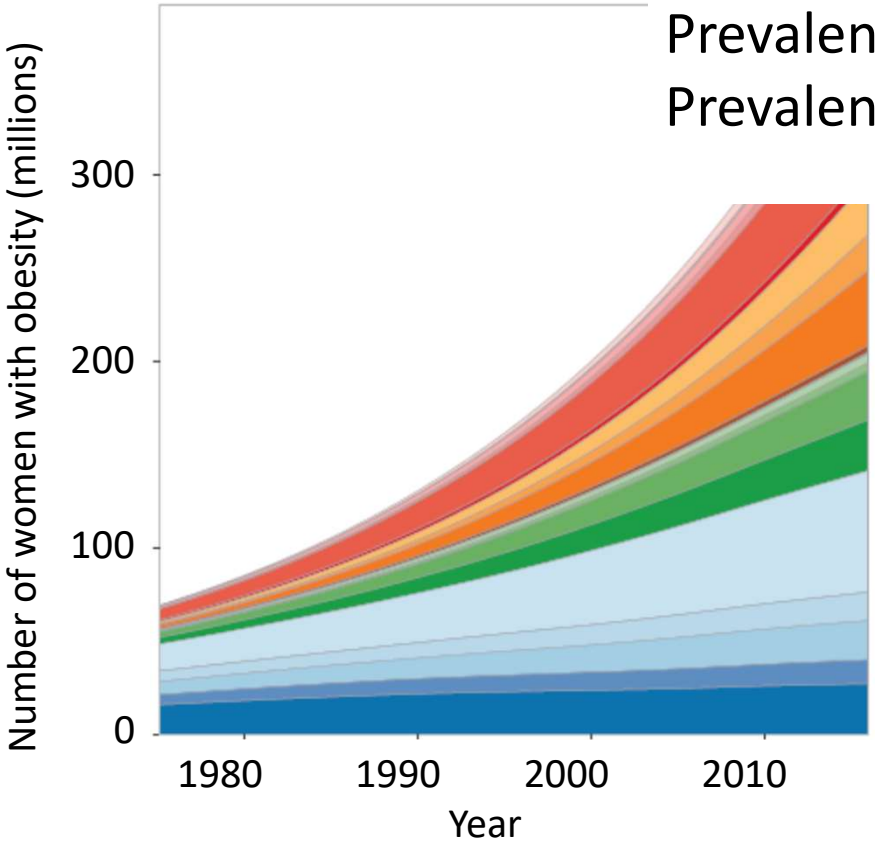


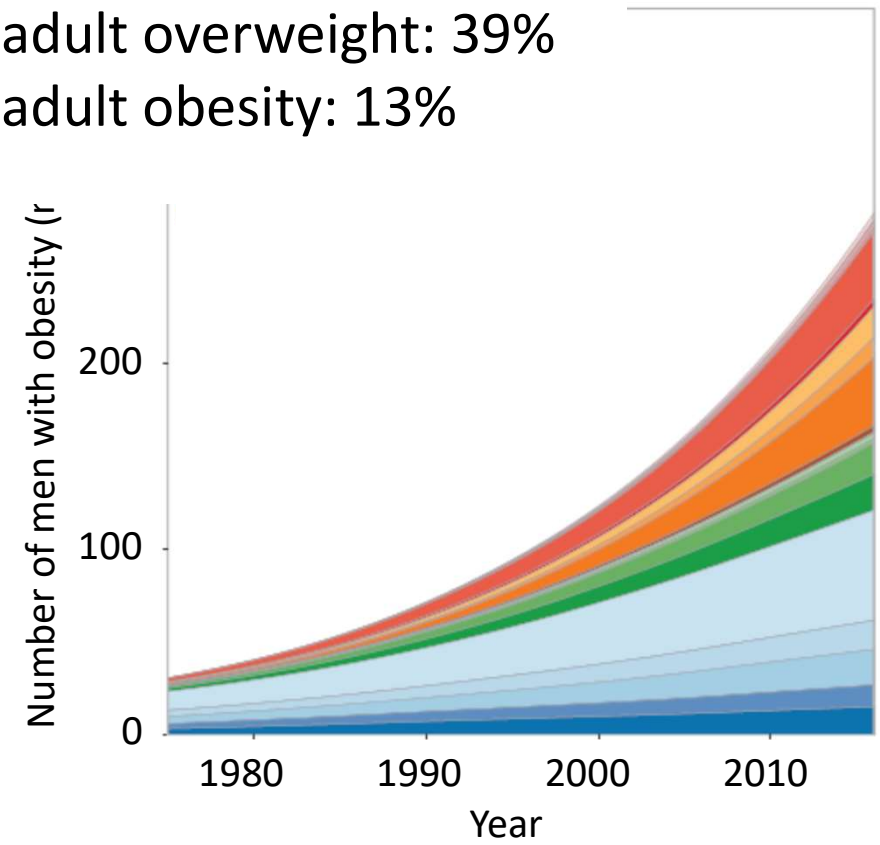


Source: NCD Risk Factor collaboration. *The Lancet* 2017;2627.

Worldwide state of the adult obesity epidemic

2016:
Prevalence of adult overweight: 39%
Prevalence of adult obesity: 13%

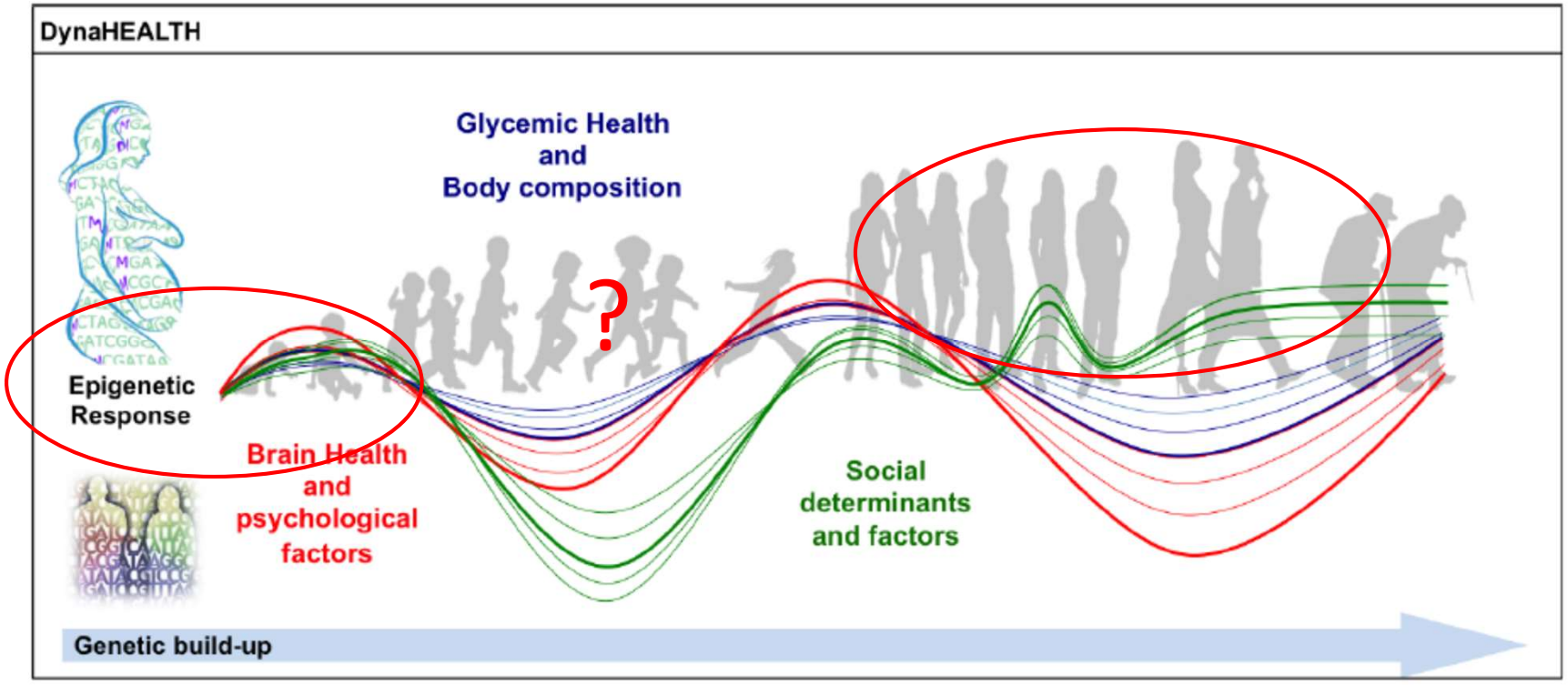




Source: NCD Risk Factor collaboration. *The Lancet* 2017;2627.

Life-course perspective

Dynamic determinants of life-long glycaemic health



Source: DynaHEALTH, H2020-633595, Sebert el al Int J Epi 2019

Long-term consequences of childhood body size

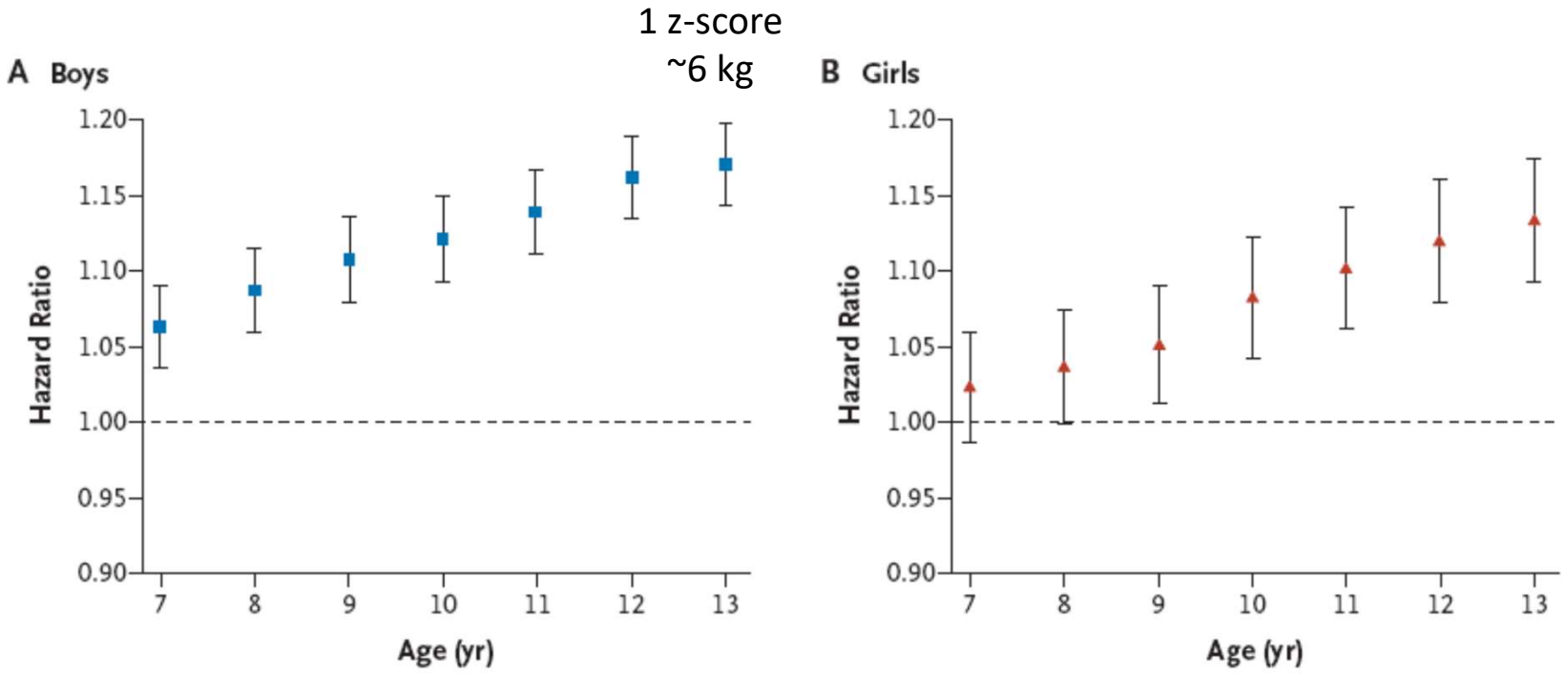
The Copenhagen School Health Records Register (CSHRR)

- 406,350 boys and girls born from 1930 to 1996
- Annual measurements of height and weight from 7 to 13 years of age
- Includes virtually all schoolchildren in Copenhagen
- 88% of the children have an ID number and could be linked to national Registers

Source: Baker JL & Sørensen TIA. *Scand J Pub Health* 2011;39(Suppl 7):87.

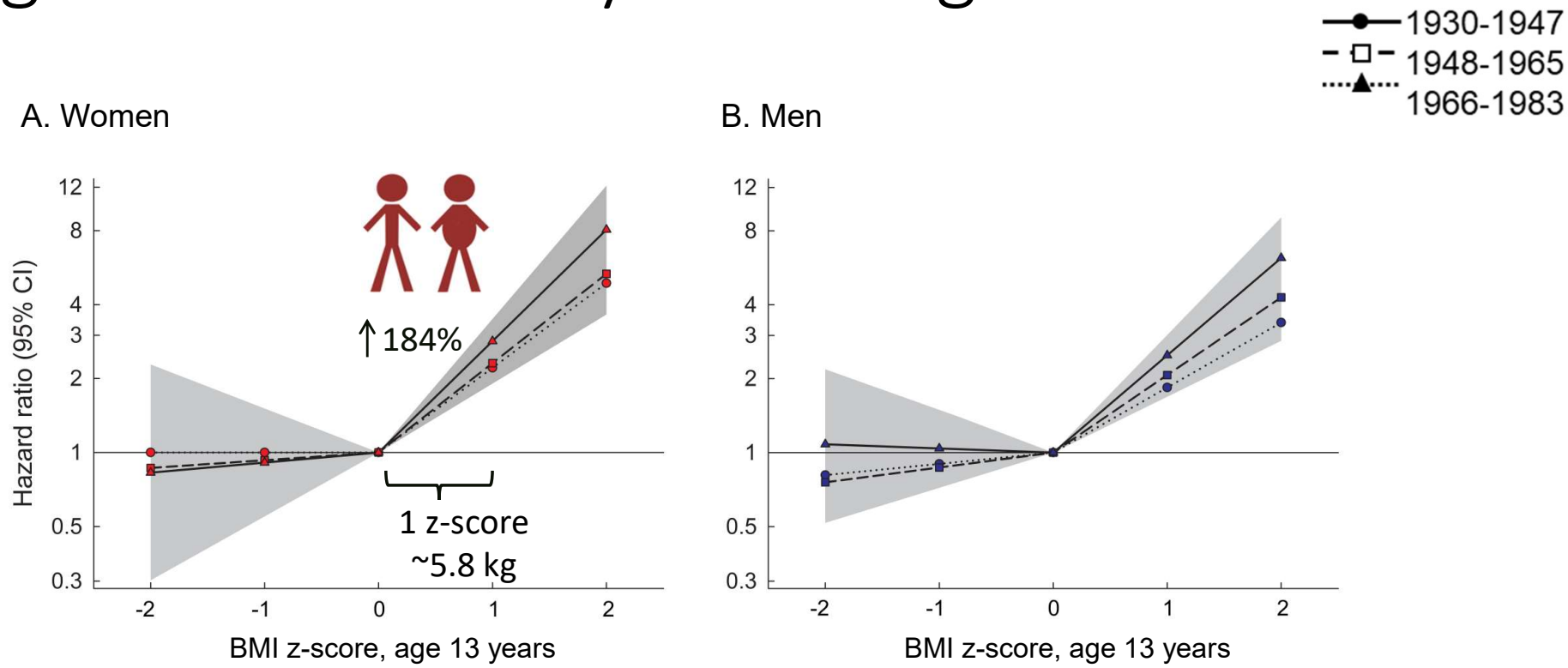
Childhood body mass index (BMI) and the risk of coronary heart disease

No threshold effect



Source: Baker JL et al. *N Engl J Med* 2007;357:2329.

Childhood BMI and risk of type 2 diabetes diagnosed at 30-47 years of age



Source: Zimmermann et al. *Obesity* 2017

Tracking of BMI across life

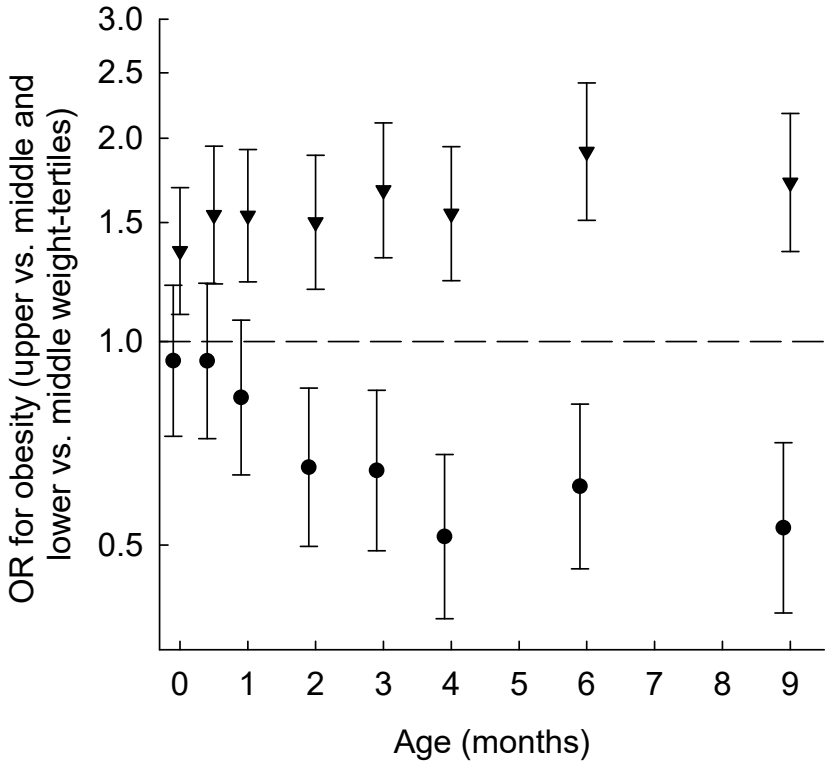
When does it start and how long does it last?

Timing of infant weight and risk of childhood obesity

- Aim: to investigate when and how weight during infancy become associated with childhood obesity
- Infant health visitors' records
- Children born 1959-67
- Weight measurements at birth, 2 weeks, 1, 2, 3, 4, 6, 9 months
- Copenhagen school health records register

Andersen et al. IJO 2012;36:1306-11.

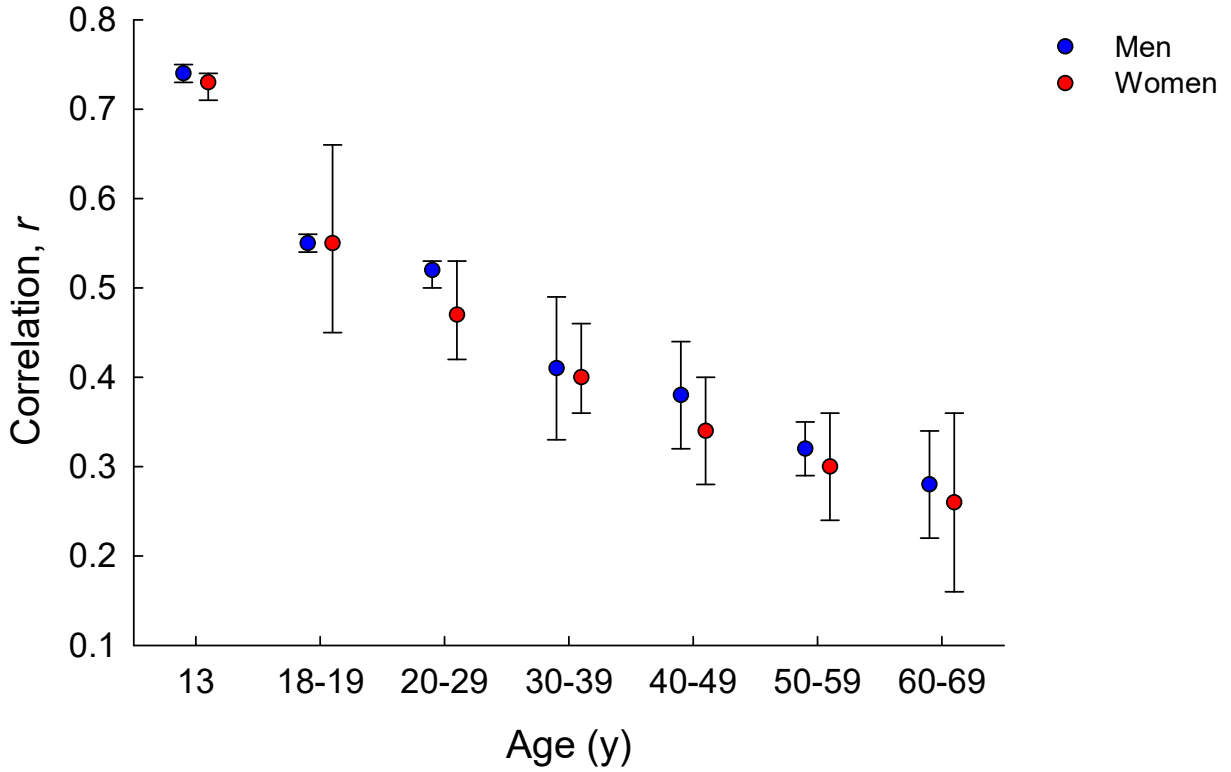
Timing of infant weight and risk of childhood obesity



Adjusted for sex, year of birth, breastfeeding, preterm birth, parity, maternal age and marital status, and paternal occupation.

Andersen et al. IJO 2012;36:1306-11.

Correlations between BMI at 7 yrs, 13 yrs and adult BMI

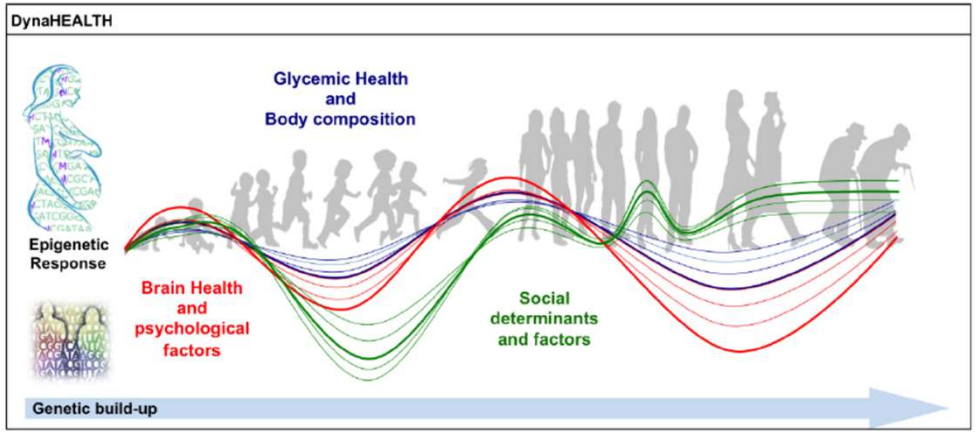


Source: Aarestrup J et al. *Int J Obesity* 2016.

Research question

”How does changes in body size from childhood onwards affect CMD risk?”

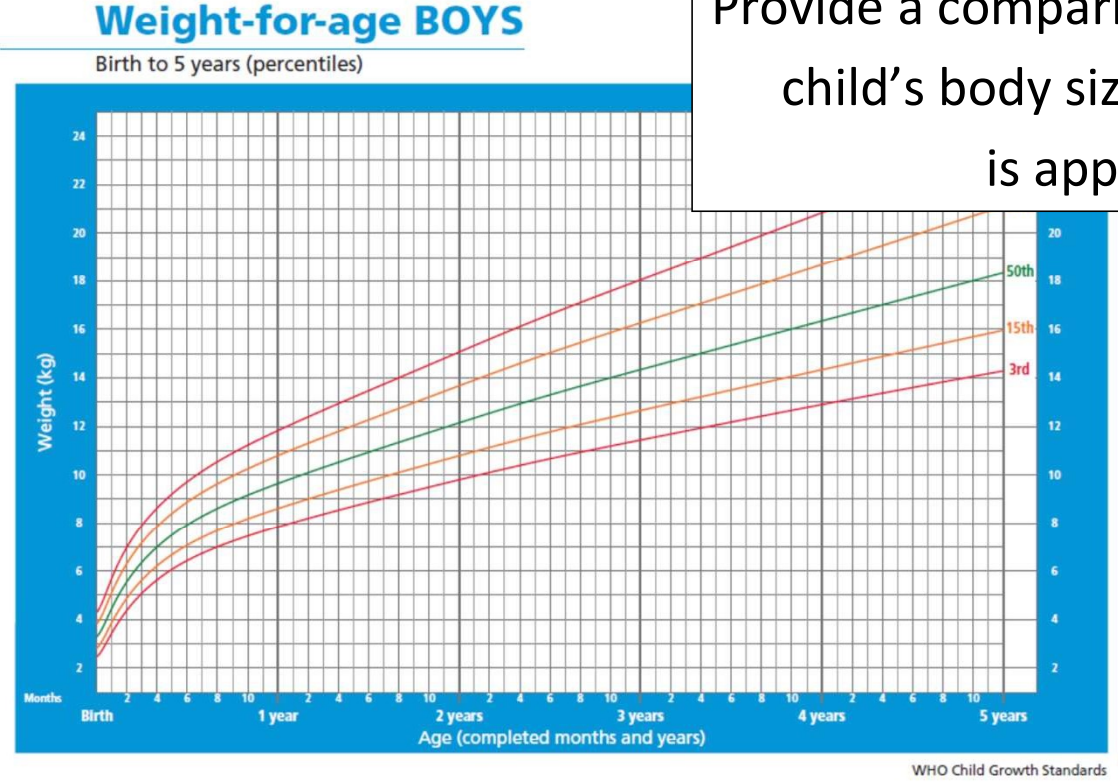
→ modelling of growth

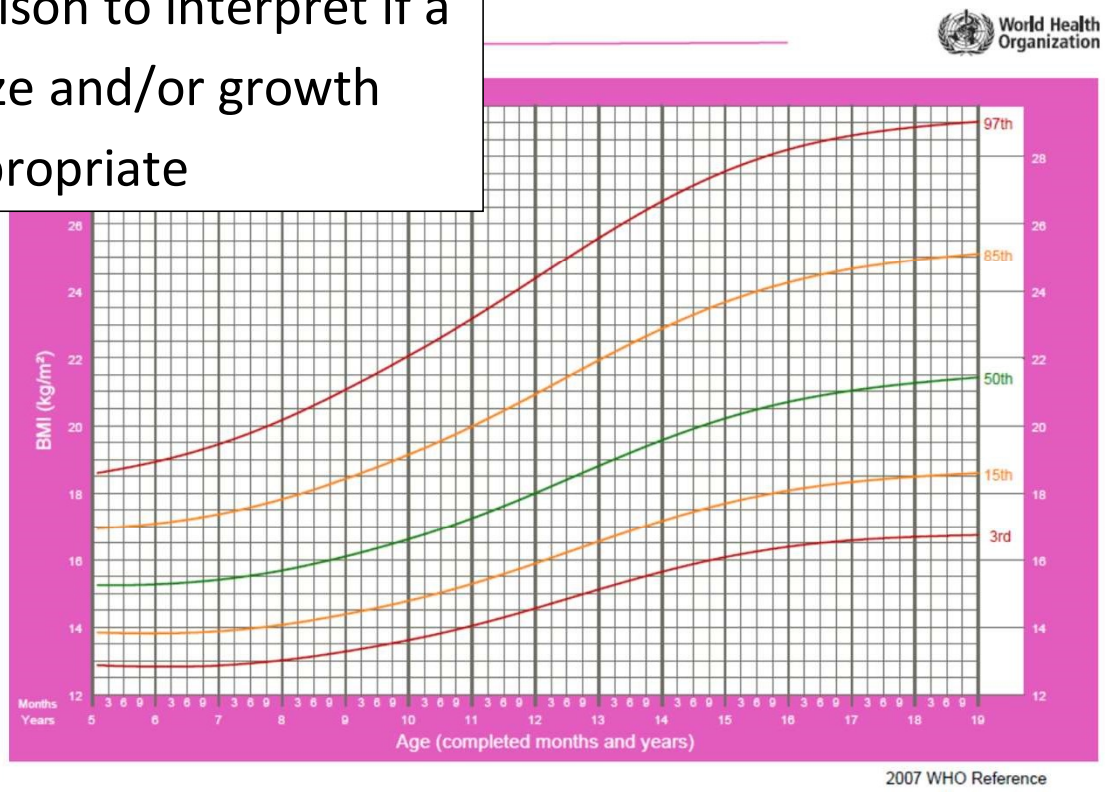


Growth and growth modelling

Assessment of growth in childhood

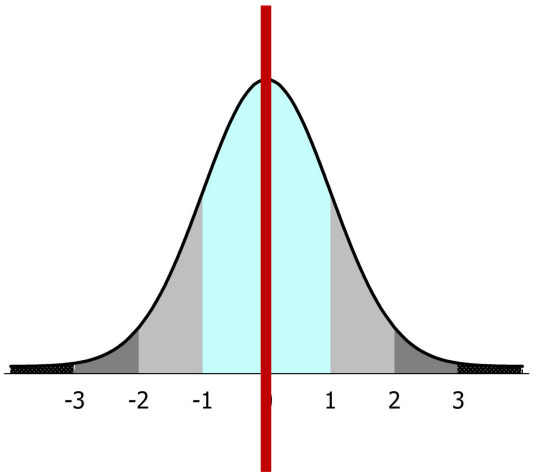
Provide a comparison to interpret if a child's body size and/or growth is appropriate





Methodological considerations on growth

- Body size differs by age and sex →
  - Z-scores/SDS-score
    - Measure of an individual's growth in relation to the reference median
    - Can be used continuously across ages
- Longitudinal data – are all children measured at the same age?
- Unequal spacing between measurement
- Growth velocity changes with age – not linear



Methodological considerations on growth

- Measurements are correlated
  - collinearity
- Uneven numbers of measurement (Missing data)
- Aim: Body size (level) versus growth (change across age) → different statistical methods

- *What is the independent contribution of childhood weight to CVD risk over and above the correlation with adult weight?*

What is the independent effect of child BMI?

- Model 1: 'Size'
  - Child body size → adult disease
  - Total effect of child body size including that mediated through adult BMI
- Model 2: 'Growth'
  - Child body size + Adult body size → Adult disease
  - The independent contribution of child BMI – or
  - The effect of child body size conditional on adult body size
    - → interpretation changed

Fall et al. IJE 2016

Size versus growth models

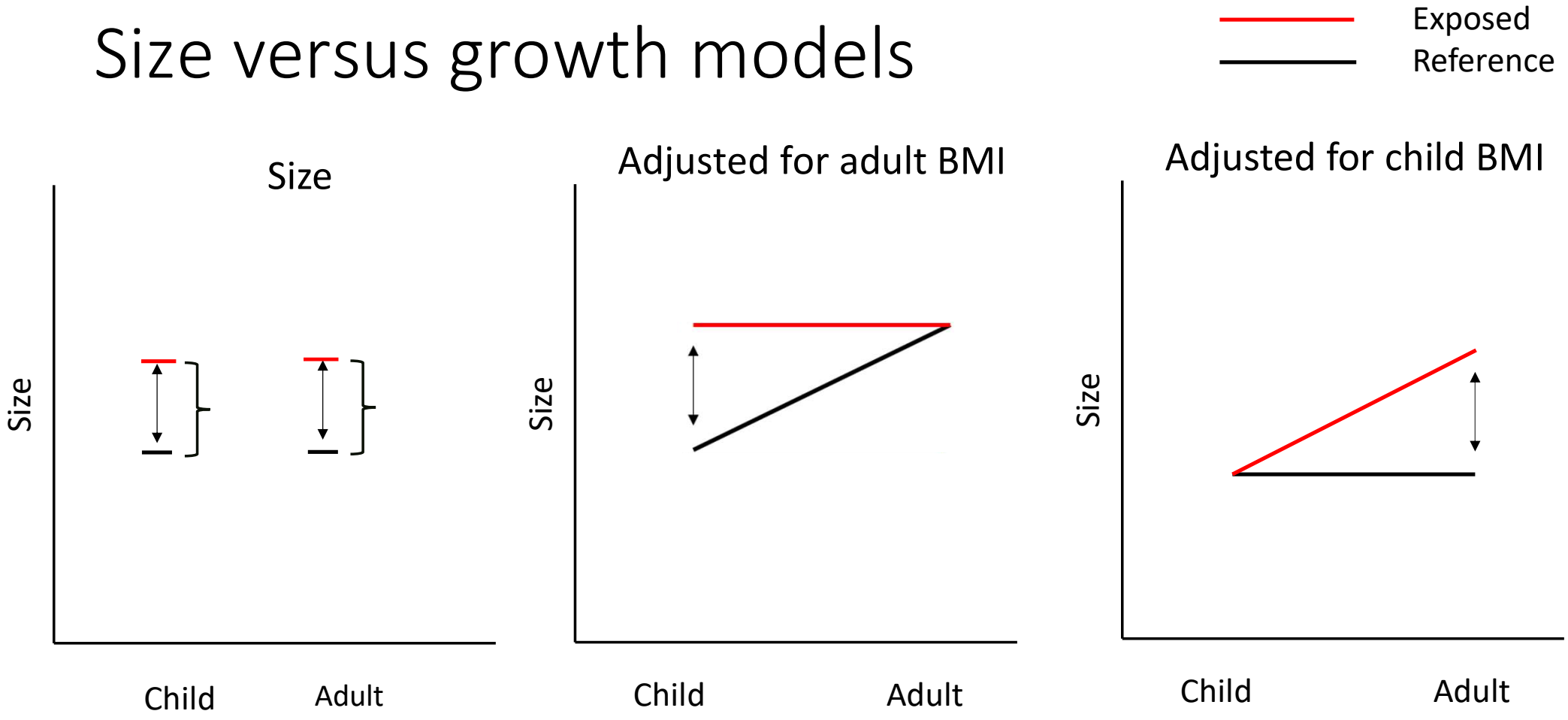
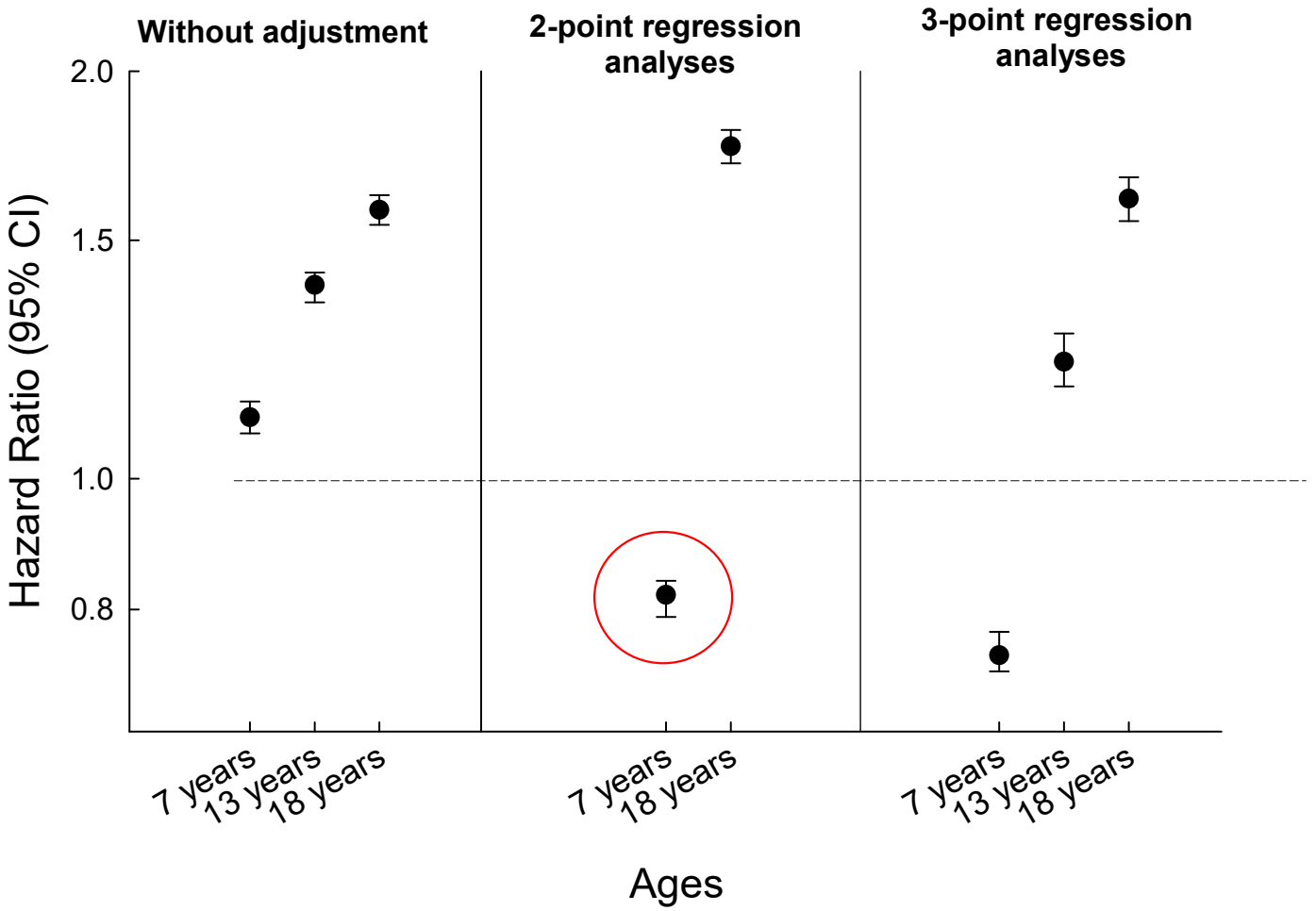


Illustration: without/with adjustment



BMI z-scores and type 2 diabetes

High risk due to low child BMI or greater change?

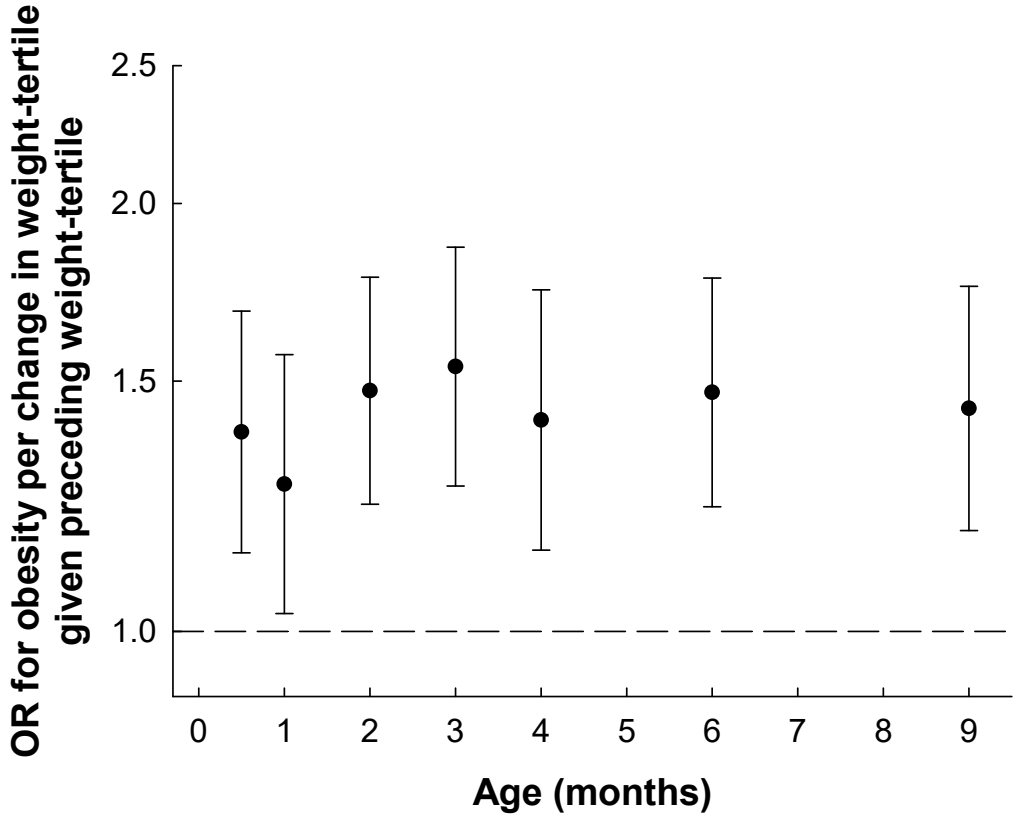
Growth and later body size

Timing of infant weight gain and risk of childhood obesity

- Background: Infant weight gain is positively associated with later obesity, but whether there is a particular critical time during infancy remains uncertain.
- Aim: to investigate when and how weight gain during infancy become associated with childhood obesity
- Infant health visitors' records
- Copenhagen school health records register
- Growth: Change in weight-tertile - adjusted for *preceding* weight-tertile

Andersen et al. IJO 2012;36:1306-11.

Timing of infant weight gain and risk of childhood obesity



No particular critical time window

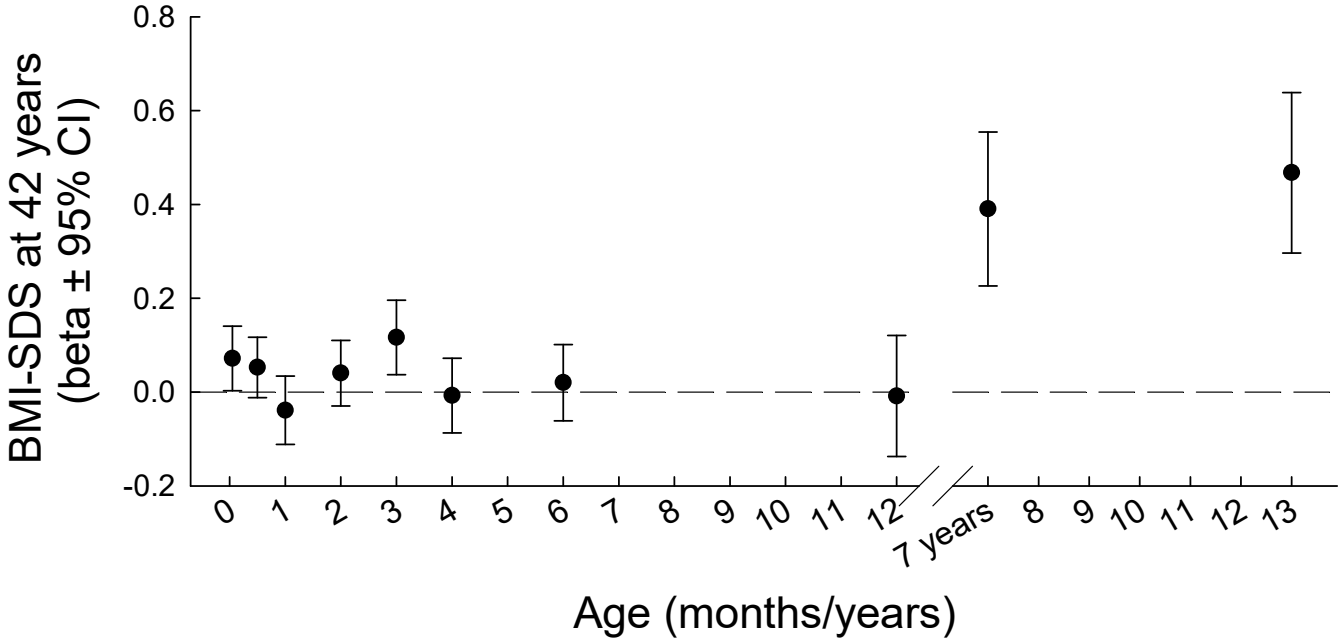
Andersen et al. IJO 2012;36:1306-11.

Timing of infant weight gain and adult BMI

- Aim: to identify the period of infancy when change in body weight has the strongest association with adult BMI and whether this was mediated through childhood BMI
- Infant Health Visitors' records
- School Health Records
- Follow-up at age 42: self-reported BMI
- Life-course path analysis (Structural equation model):
  - Simultaneous estimation of effect of weight gain SDS and BMI-SDS at 7 and 13 years conditional on all previous growth measurement
  - Handles missing data

Bjerregaard et al. IJO 2014

Infant weight gain, childhood BMI and adult BMI Path analysis life course plot



- Adjusted for parental social class, PP-BMI, GWG, sex, preterm birth and age at the infant measure

Bjerregaard et al. IJO 2014

Growth and cardiometabolic risks

Overweight patterns and risks of type 2 diabetes

- Weight loss interventions in adults convincingly delays the onset of type 2 diabetes in high-risk individuals
- This raises the question of whether or not weight loss in children with overweight and obesity can reduce the risk of type 2 diabetes

Bjerregaard et al. *NEJM* 2018

Overweight patterns and risks of type 2 diabetes

- Aim: To investigate whether boys with overweight who normalize their weight by young adulthood carry an increased risk of type 2 diabetes in adulthood
- Data resources: CSHRR, the Danish Conscription Database and the National Patient Register
  - Type 2 diabetes: 6,710 men (10.7%)

Bjerregaard et al. *NEJM* 2018

Definition of overweight

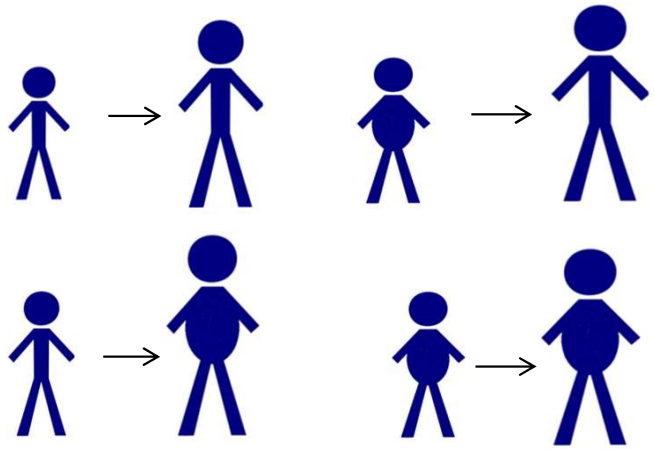
Boys: 7 years, CDC: BMI ≥ 17.38 kg/m^2

13 years, CDC: BMI ≥ 21.82 kg/m^2

Young men: ~ 18 years, WHO: BMI ≥ 25 kg/m^2

Growth:

- Weight status
- Weight status pattern
  - Simple categorical model

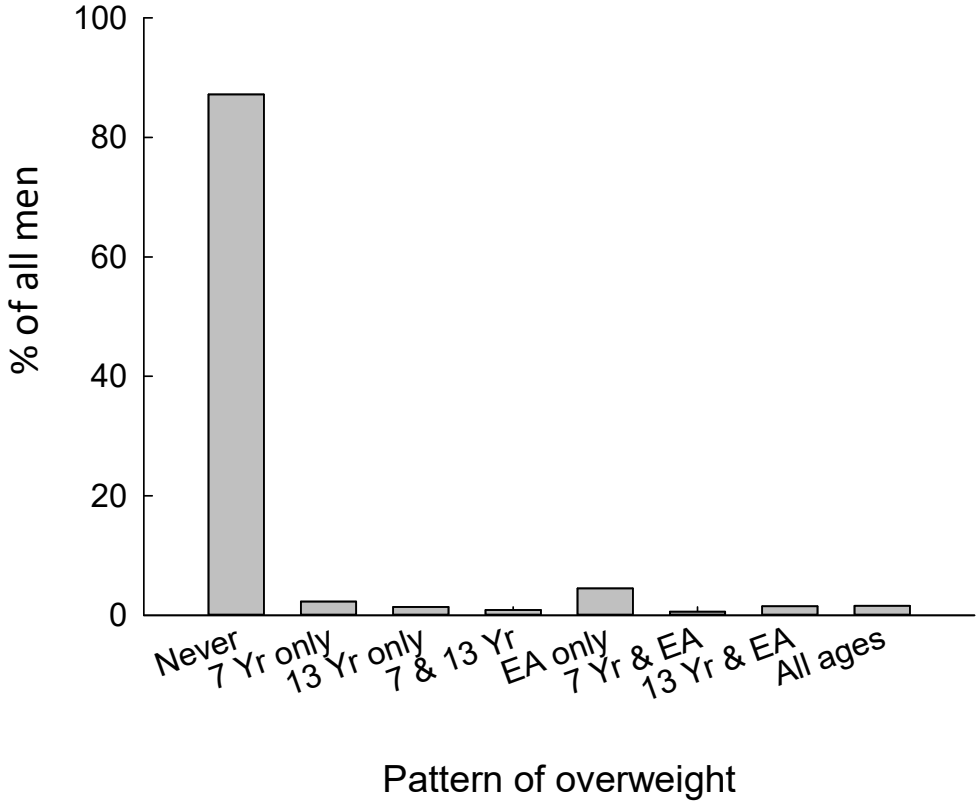


Bjerregaard et al. *NEJM* 2018

Patterns of overweight from 7 through 13 years to early adulthood (EA)

Most boys had normal weight at all ages

Remission do occur

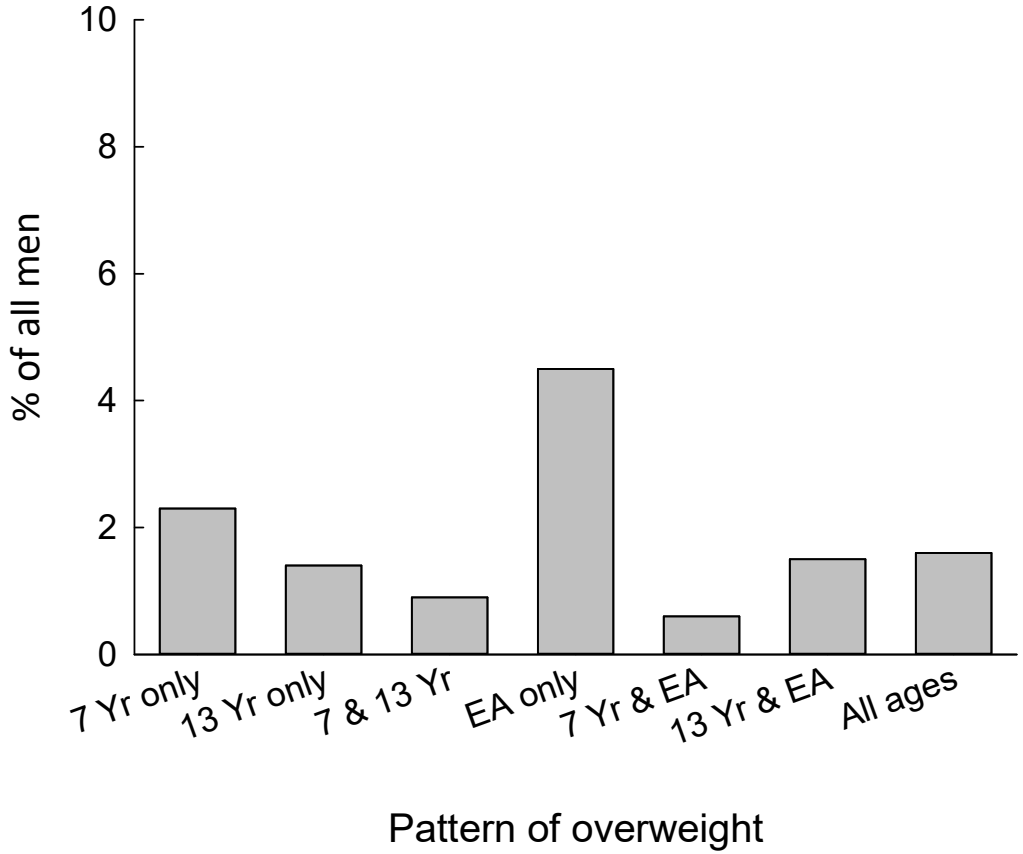


Bjerregaard et al. *NEJM* 2018

Patterns of overweight from 7 through 13 years to early adulthood (EA)

40% remained overweight from 7 yr to adulthood

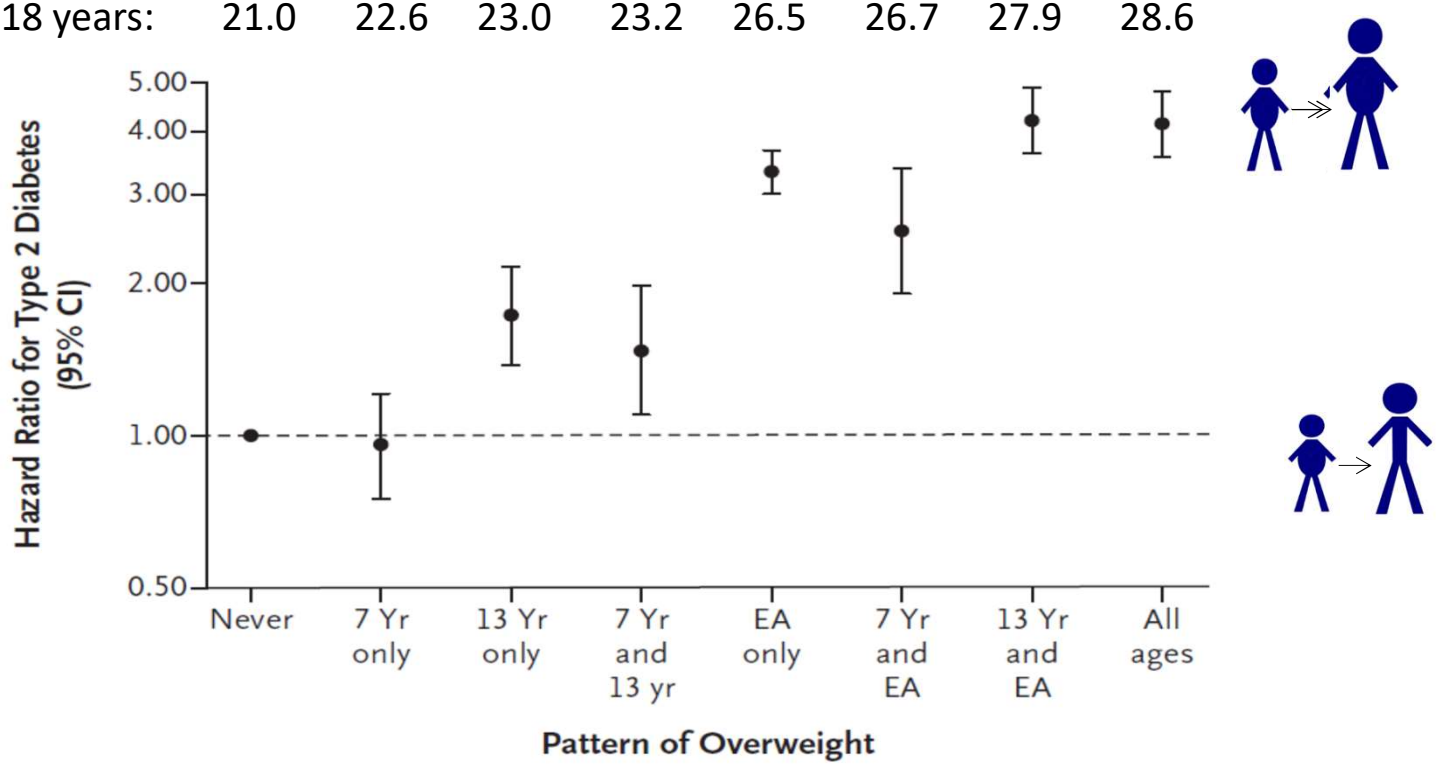
60% remained overweight from 13 yr to adulthood



Bjerregaard et al. *NEJM* 2018

Overweight pattern from 7 through 13 years to early adulthood (EA) and risk of type 2 diabetes

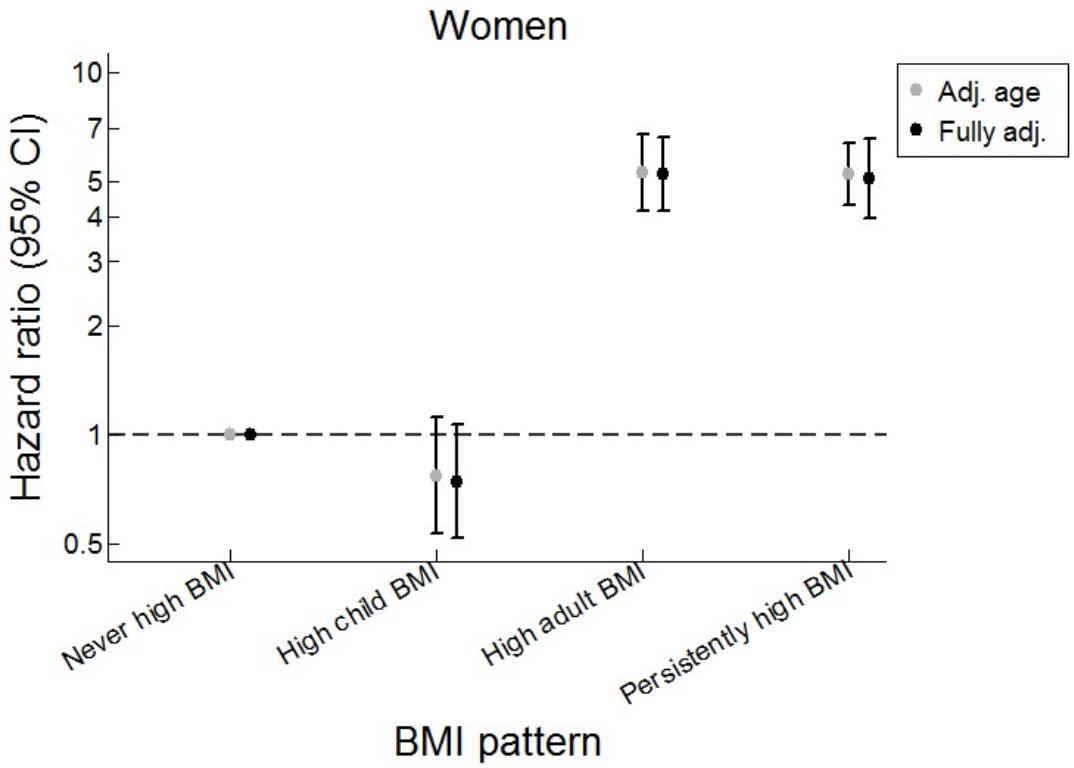
Type 2 diabetes during age 30-60 years

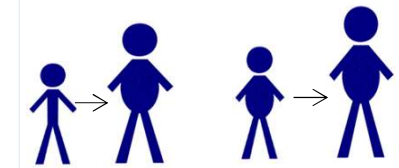


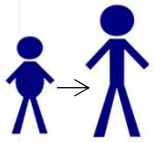
Bjerregaard et al. *NEJM* 2018

Figure 1. Patterns of Overweight at 7 Years of Age, 13 Years of Age, and Early Adulthood (EA) and the Risk of Type 2 Diabetes at 30 to 60 Years of Age.

Overweight pattern from 7y to late adulthood and risk of type 2 diabetes



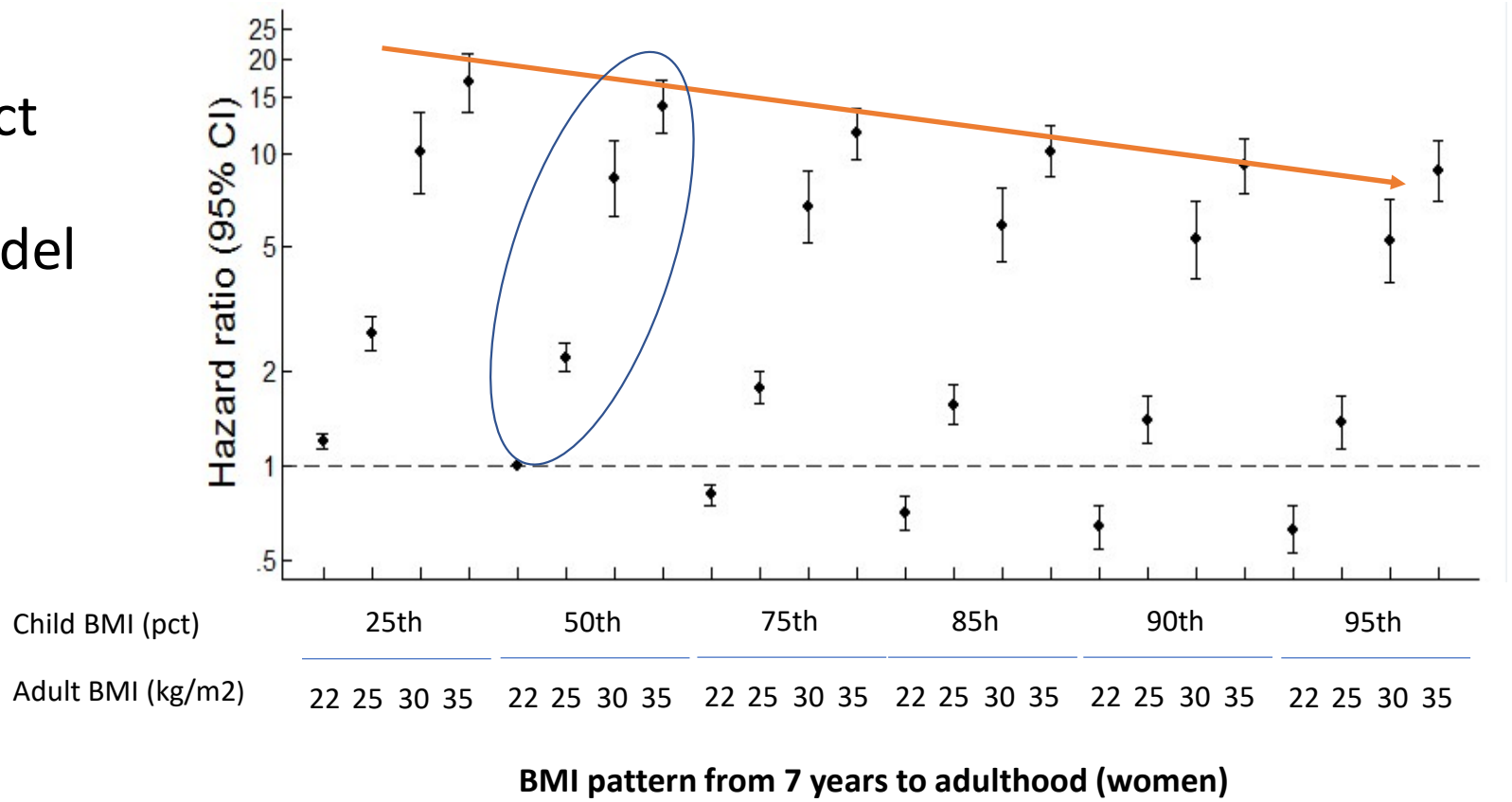




Bjerregaard et al. *Diabetes Care* 2020

Child and adult BMI and risk of type 2 diabetes

Combined effect based on a continuous model



Bjerregaard et al. *Diabetes Care* 2020

Growth curves & risk of CMD

Childhood BMI trajectories and CVD risk factors

- Background: Children with a growth trajectory of overweight have higher levels of CVD risk factors than children with a normal-weight trajectory
- Aim: to estimate the effect of BMI trajectories from ages 6–14 years, with and without adjustment for adult BMI on adult CVD risk factors
- 2466 Danish children
- Latent Class Trajectory Models (LCTM)
  - BMI at age 6-14 yr (minimum 2 measures)
- Linear regression

Blond et al., *Atherosclerosis* 2020

Latent class trajectory modelling (LCTM)

- Relates outcomes collected on the same individual to the observation time
- Identifies heterogeneity in growth patterns – sub-groups – ”classes”
  - Estimates an average growth curve for each class &
  - Can include random effects to allow for individual variation around the sub-group average (within each class)
- Classes = latent variables – pre-specified number, 1-n
- Estimates posterior class probabilities
- Assigns individuals to the class with highest probability

Lennon et al. BMJ Open 2018; Herle et al. EU J Epi 2020

Latent class trajectory modelling (LCTM)

- Model selection & identification of the optimal number of classes:
  - Fit indices:
    - Bayesian information criteria (BIC) values (small)
    - Average posterior probability assignment, APPA (>70%)
    - Odds of correct classification, OCC (>5.0)
    - Relative entropy (close to 1)
  - % in each class (>1%)
  - Graphical examination
    - Interpretability of classes
    - Clinical plausibility

Latent class trajectory modelling

Strengths

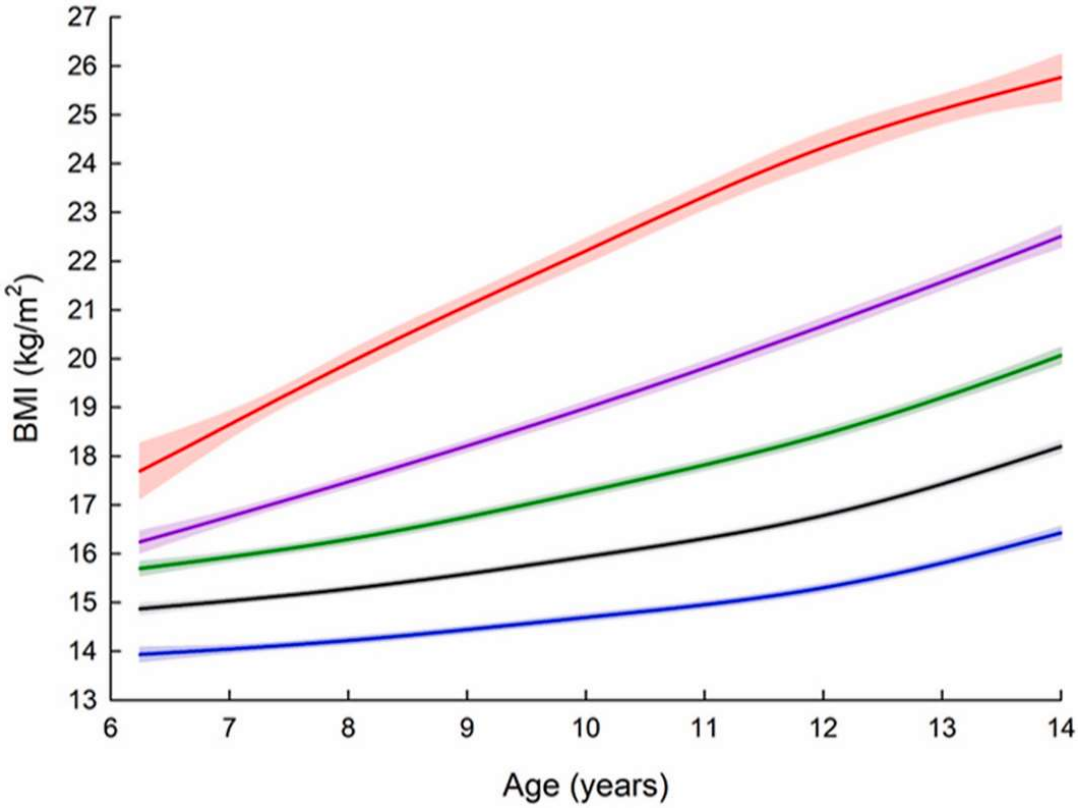
- Capture long-term risk factor exposures
- Can model nonlinear growth curves
- Handle missing data
- Data-driven approach

Limitations

- Computer-intensive
- Fit indices may not agree
- Interpretation varies with different parametrization (+/- random effects)
- May identify latent classes even if they do not exist

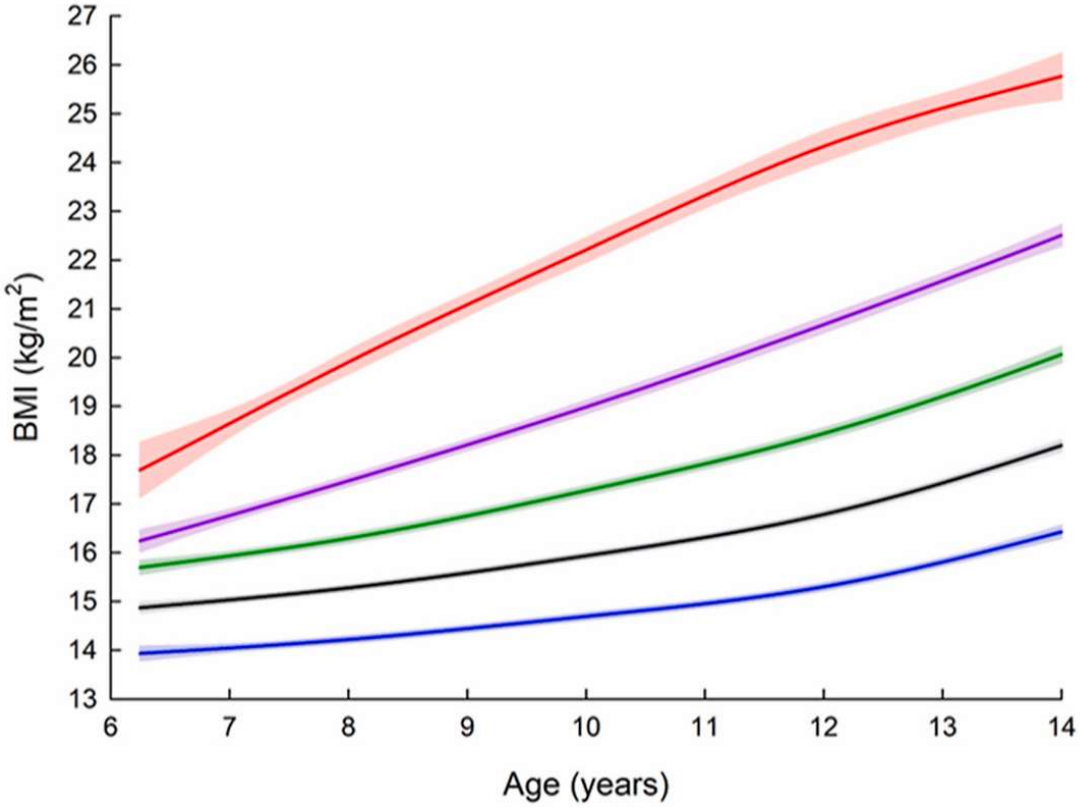
Childhood BMI trajectories

- Modelled without random effects and with an age effect modelled by restricted cubic splines
- Examined 1-7 trajectories
- Models were evaluated using several fit indices
- Five trajectories were identified



Blond et al., *Atherosclerosis* 2020

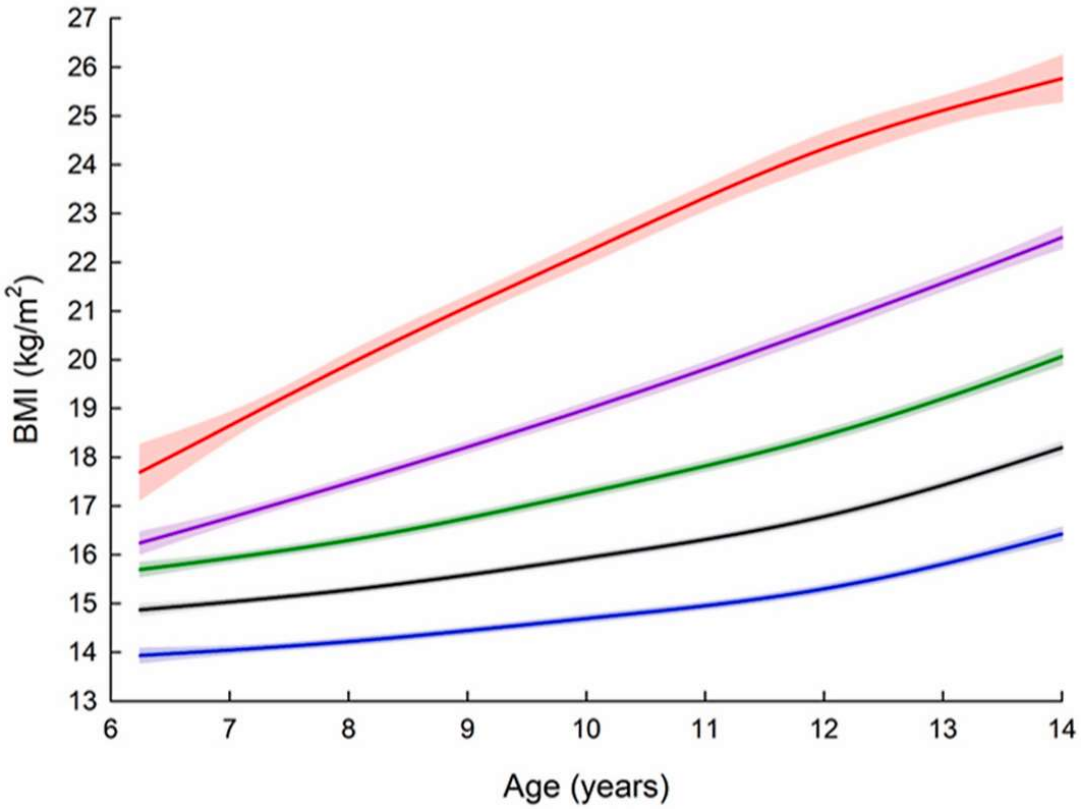
Childhood BMI trajectories and adult CVD risk factors



	CDC	CVD risk
2.5%	90-95th	Adverse levels of many CVD risk
12%	75-85th	Adverse levels of several CVD risk
26.5%	50-75th	Adverse levels of some CVD risk
41%	25-50th	Similar levels
19%	10th	Ref.

Blond et al., *Atherosclerosis* 2020

Childhood BMI trajectories, CVD risk and adult BMI



Blond et al., *Atherosclerosis* 2020

- Adjusted for adult BMI (age 40): largest BMI gains after age 14 in class 1 and lowest BMI gain in class 5
- Findings: the higher BMI trajectories had lower waist circumference, blood pressure and triglycerides
- Interpretation: the associations are modifiable by growth after childhood (few remitted)

Findings from other studies on growth and CVD

- Children who gain excess BMI from childhood onwards have increased risks of CVD risk factors and CHD
  - Suggested associations for stroke, atrial fibrillation and heart failure
- For many CVD outcomes, the risks increased across the entire range of BMI change
- The CVD consequences of childhood obesity may be reversible if a child normalizes his or her weight status before adulthood

Bjerregaard et al. *Trends Cardiovasc Med* 2020
Sun et al. *Obesity Reviews 2021*

Conclusions

- Studies suggest that children who gain excess BMI from childhood onwards have increased risks of CMD
  - Risks starts at levels below overweight
- A high child BMI is associated with increased risks of CMD outcomes only if it continues to adulthood
- Childhood BMI trajectory groups, even with means within the normal-weight spectrum, may be involved in the development of CVD risk factors
  - This appears to be modifiable by growth after childhood

Perspectives: BMI trajectories and CMD risk

- CMD risks may be reversible
  - By modifying childhood overweight
- Highlight the importance of primary prevention of childhood overweight and obesity
  - How?

Charakida & Deafield, *European Heart Journal* (2018) 39, 2271–2273

Perspectives: growth and CMD

- Beginning to explore how different pattern of weight change during critical period of adolescence relates to later disease
- Remaining knowledge gaps:
  - Studies on childhood BMI changes and adult CVD events are scarce
  - Mechanishms
  - Effect modification by physical activity
- As ‘modern’ cohorts age, we will have greater opportunities to investigate these questions

Take home messages – growth modelling

- Choice of model depends on the research question and the data availability
- Models have different advantages and disadvantages
- Change in z-score have different interpretation than changes in raw body size
- Adjustment for attained body size changes the research question!
  - Models that condition only on earlier changes are easier to interpret
- Body size and growth cannot be separated conceptually

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