CESP Centre de recherche en Épidémiologie et Santé des Populations

Instituts thématiques

Inserm Institut national de la santé et de la recherche médicale

UNIVERSITÉ PARIS SUD Comprendre le monde, construire l'avenir®

Cord blood biomarkers of the fetal metabolism: associations with postnatal growth and later metabolism

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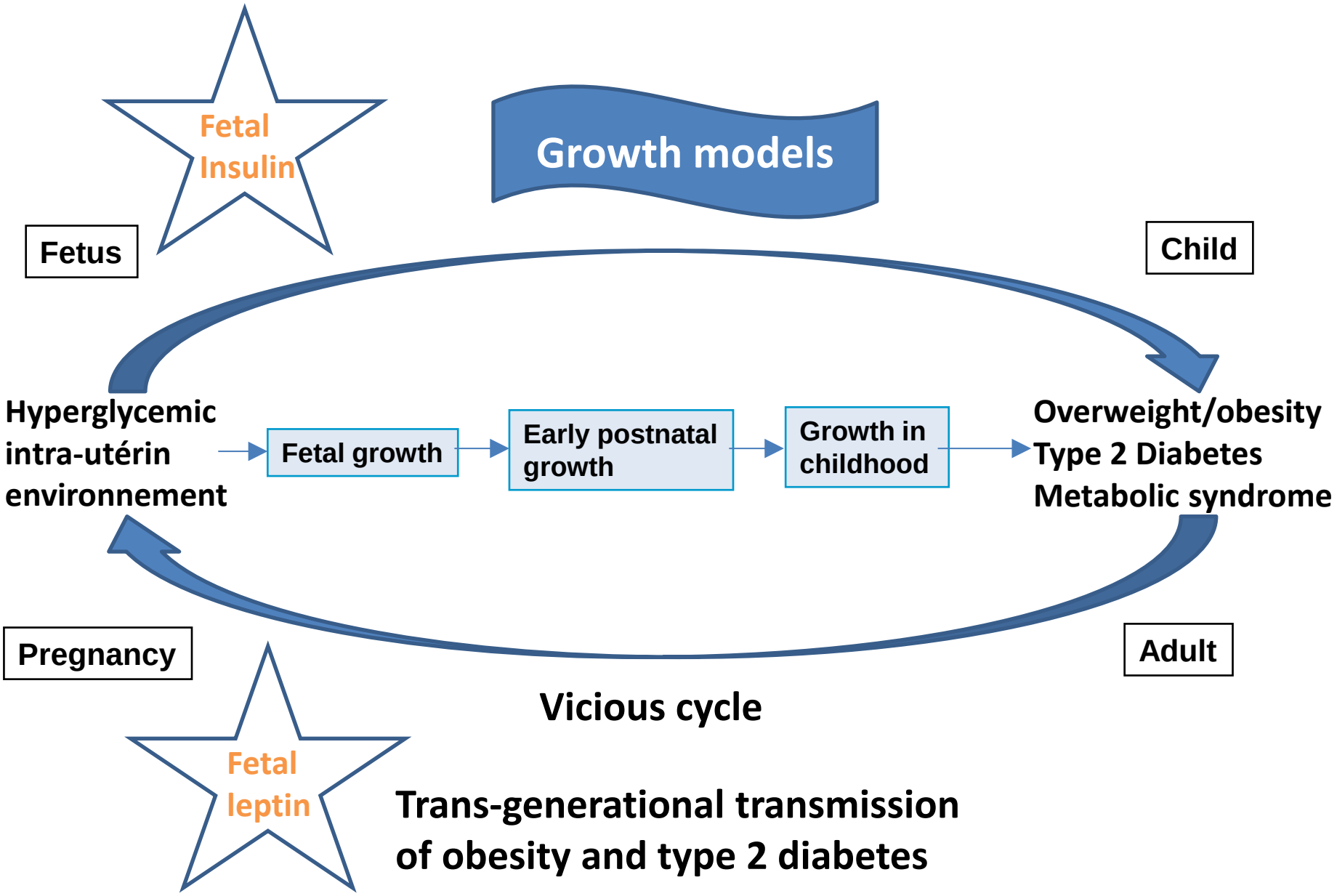
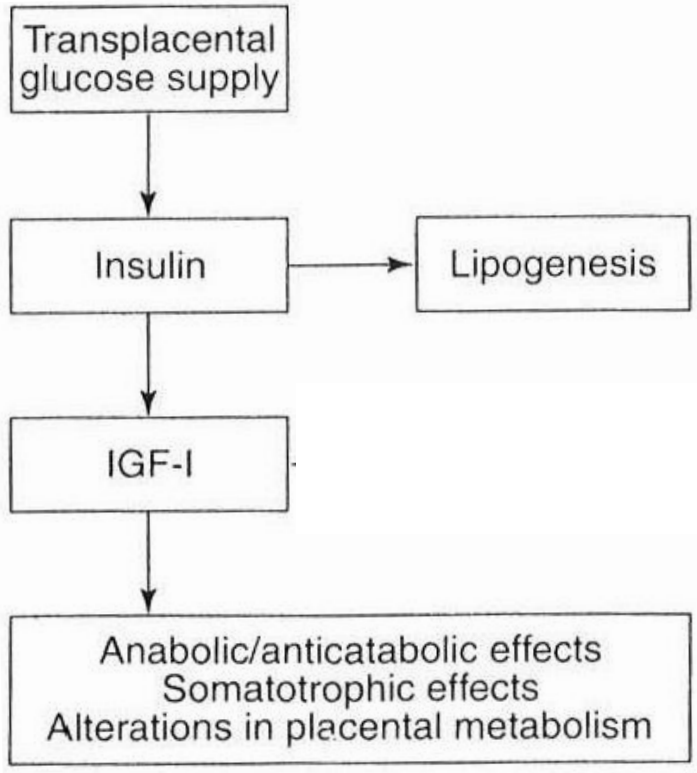
METABOLIC PROGRAMMING



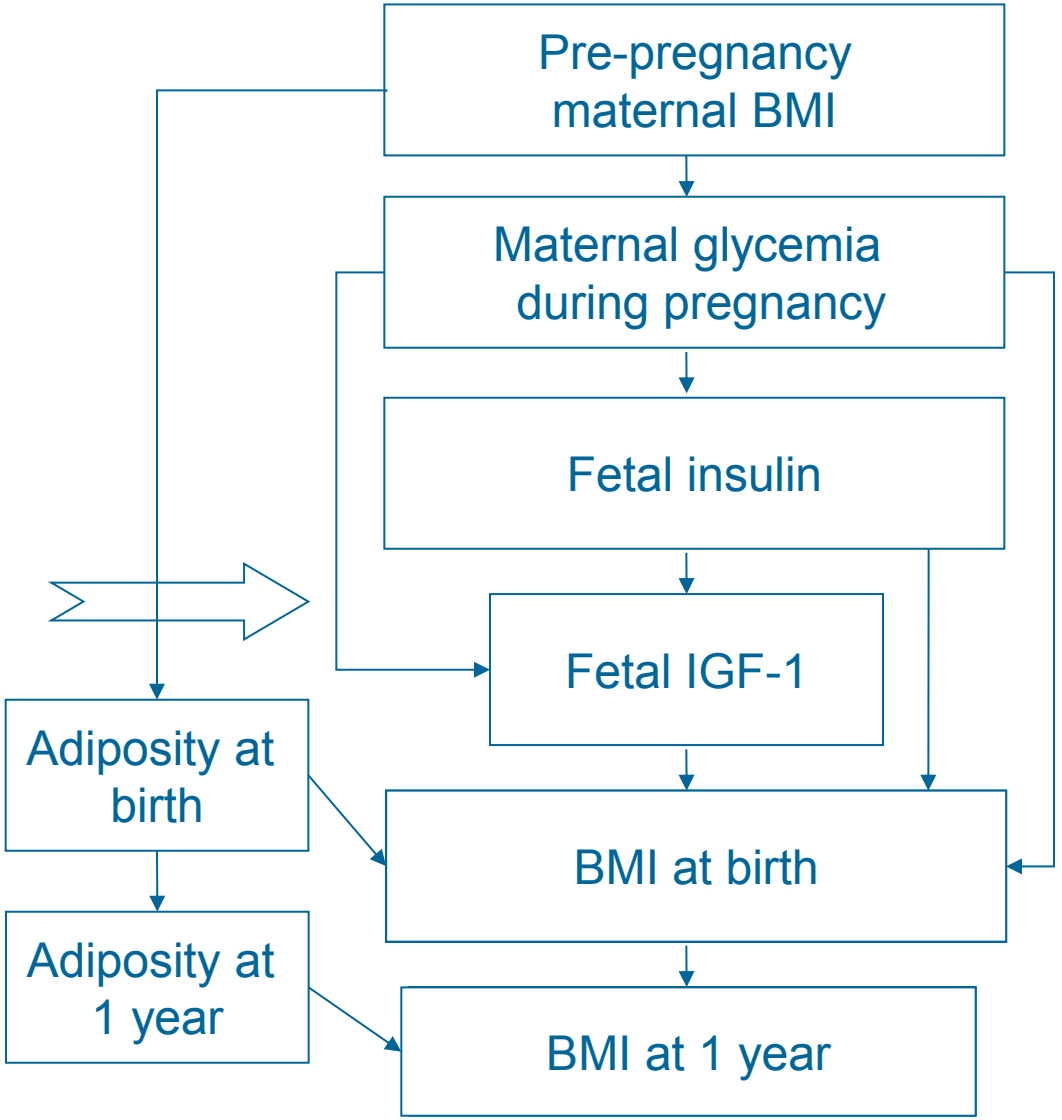
A MECANISTIC APPROACH

Model from the literature



Gluckman et al, Acta Paediatr, 1997

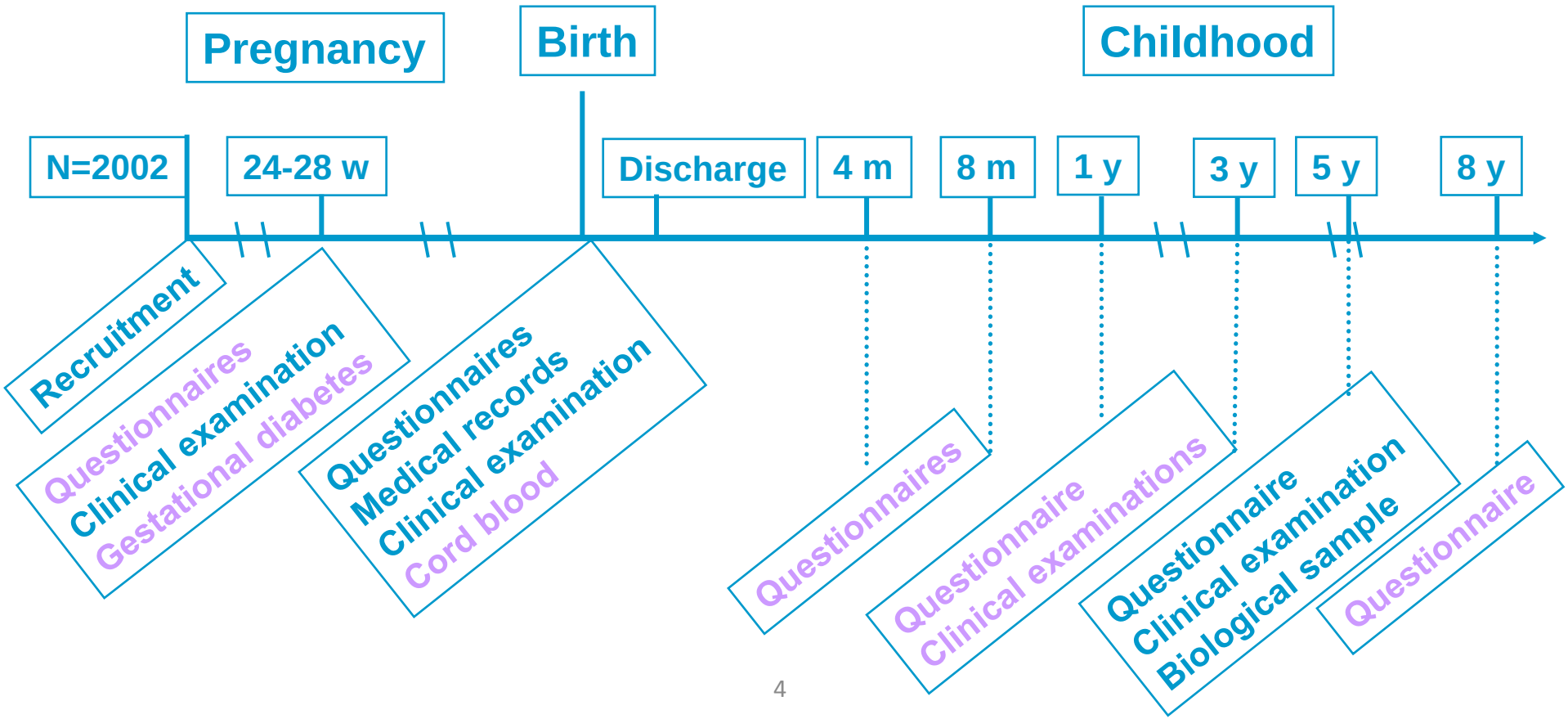
Postulated model for path analysis



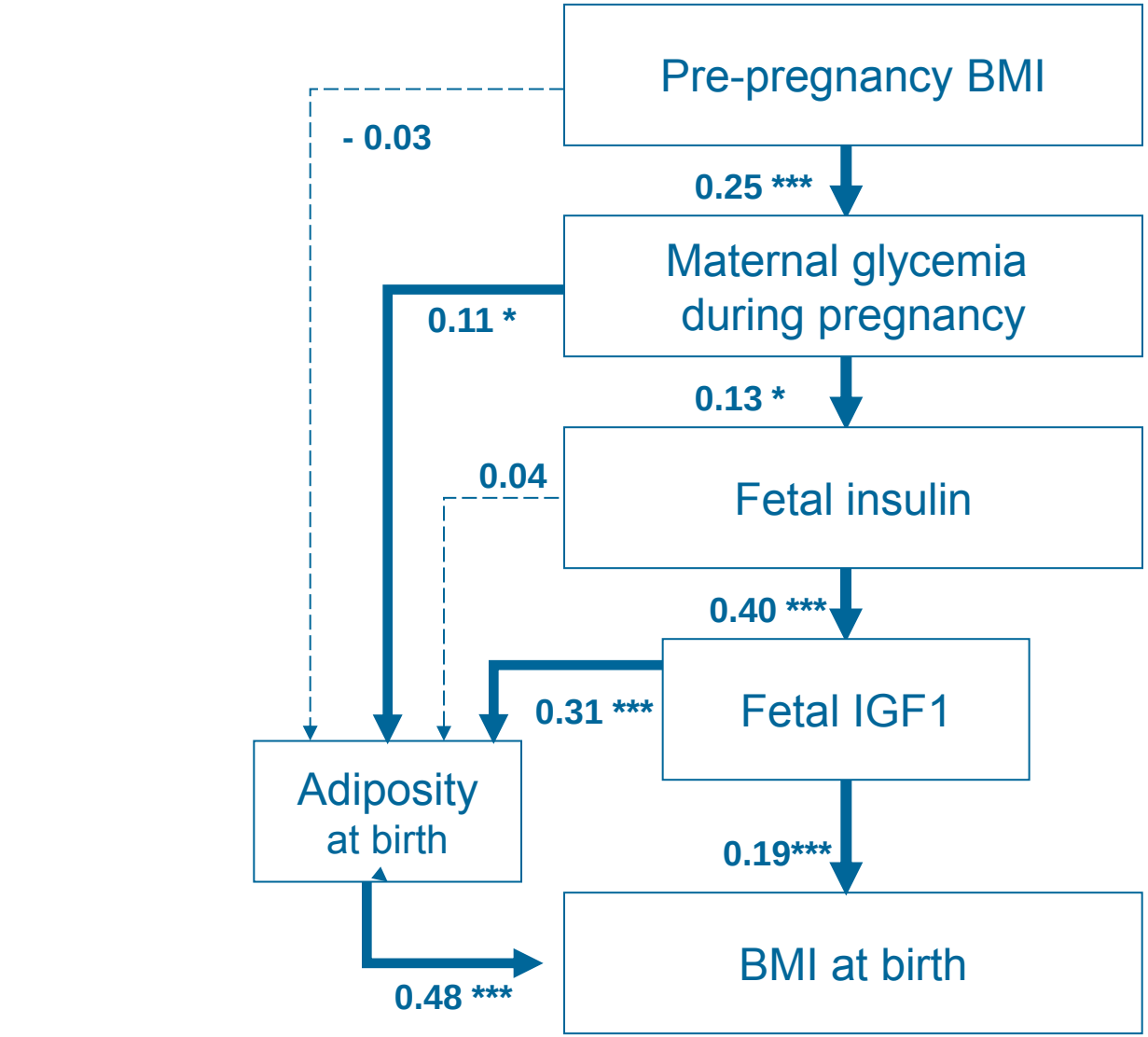
The EDEN STUDY

- Pre-birth cohort of mothers and children in 2 French regions
- Follow-up from 2nd trimester of pregnancy up to 8 years
- Study of the pre and postnatal determinants of child development and health

Étude des Déterminants pré et post natals du développement et de la santé de l'ENfant

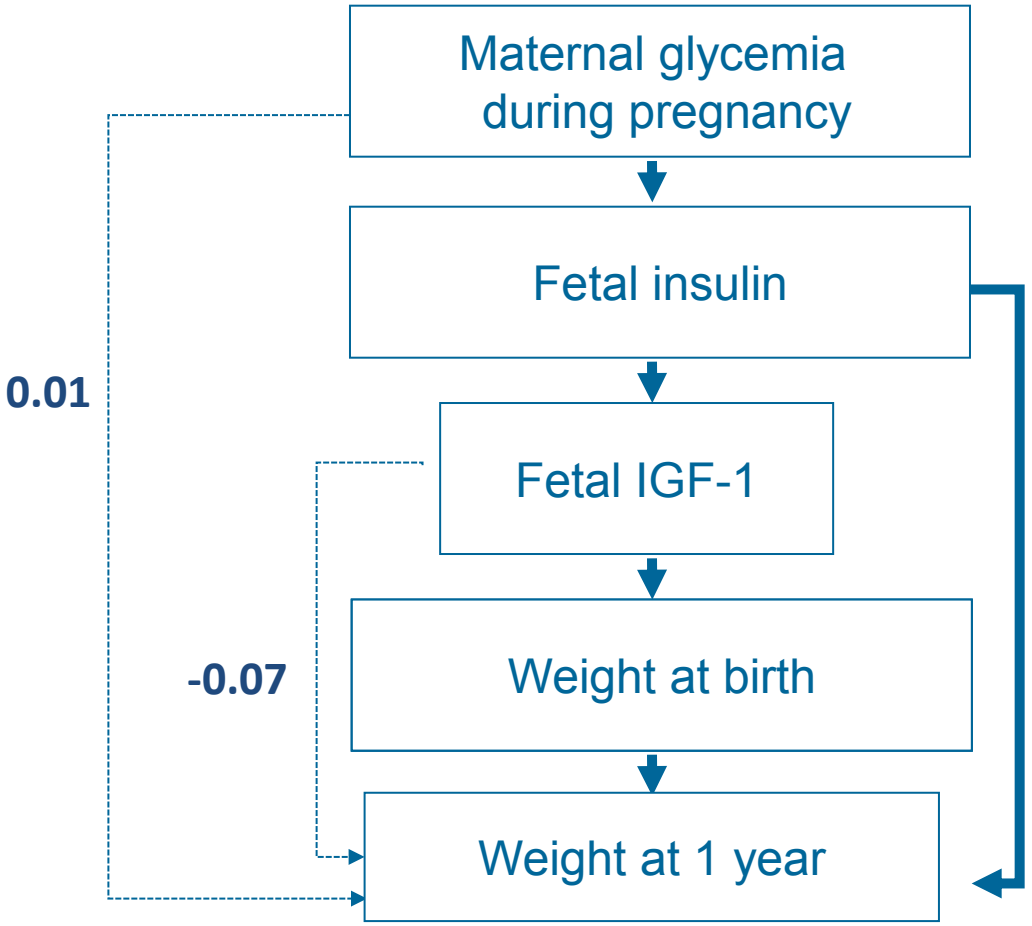


PRENATAL MODEL



Regnault et al, Diabetes, 2011

A SEX SPECIFIC POSTNATAL EFFECT?



Girls: -0.23
Boys: 0.04
P for interaction=0.004

*:<0.05, **:<0.01, ***:<0.001

Importance of growth trajectories…

Regnault et al, Diabetes, 2011

WHY DO WE NEED GROWTH MODELS?

- Early life factors associated with
  - attained weight, height, measures of adiposity
  - at a given age

- How children got there: as/more important than attained weight, BMI….?

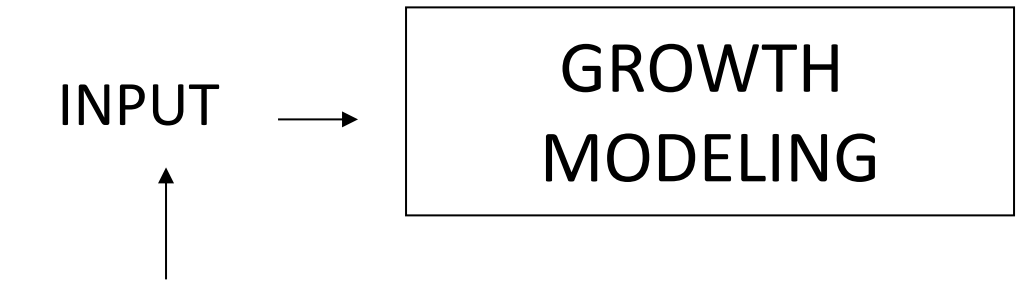
- Growth trajectories in early life predict adult chronic diseases

  (obesity, type 2 diabetes…) (Eriksson et al, 2011)

WHY DO WE NEED GROWTH MODELS?

- Longitudinal study with repeated measures
- Weight and length/height measures available from:
  - in-person research visits
  - clinical measures (health booklet/ medical records)
  - all at different ages

WHY DO WE NEED GROWTH MODELS?



use all available data, including clinical measurements

Dynamics of growth

Critical windows

obtain values of:

- weight, height
- growth velocities
- accelerations
- BMI
- for all the children
- at selected timepoints

(Hauspie et al, 2004)

GROWTH MODELS

- Mixed models
- The researcher has to provide a model

non-parametric models

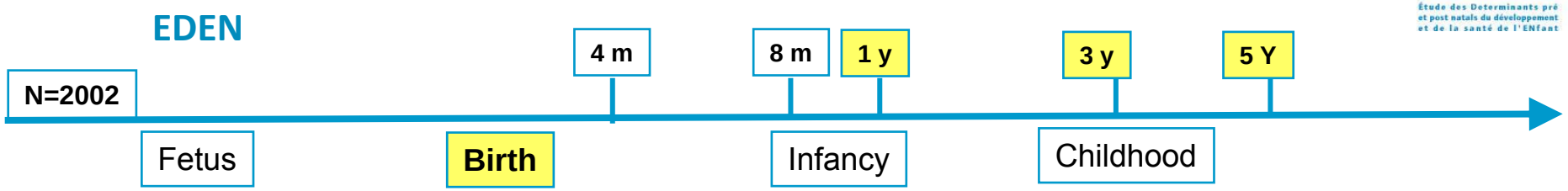
Fractional polynomials
(Wen X, 2012)
Splines
(Howe LD, 2013)

parametric models

Linear / non linear models developed to model growth:

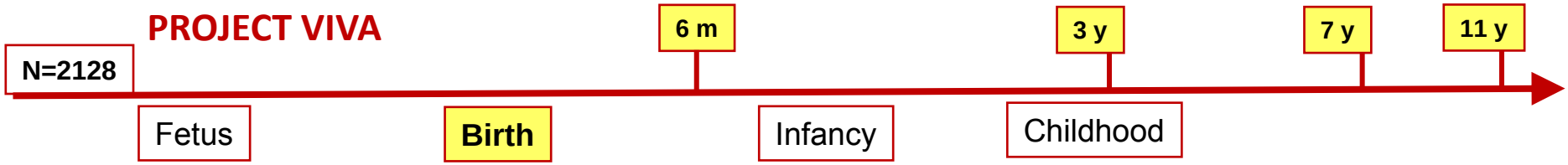
- ***in infancy*** (Count, 1943; Kouchi, 1985; Kouchi, 1985; Karlberg, 1987),
- **in childhood (Jenss, 1937; Berkey and Reed, 1987)**
- ***during puberty*** (Marubini, 1971; Hauspie, 1980)
- ***total growth*** (Preece & Baines, 1978; Jolicoeur, 1988)

GROWTH MODELING IN 2 COHORTS



Project Viva: *a study of health for the next generation*

- Massachusetts-based pre-birth cohort
- Recruited more than 2000 women in early pregnancy
- Ongoing follow-up of mothers and child

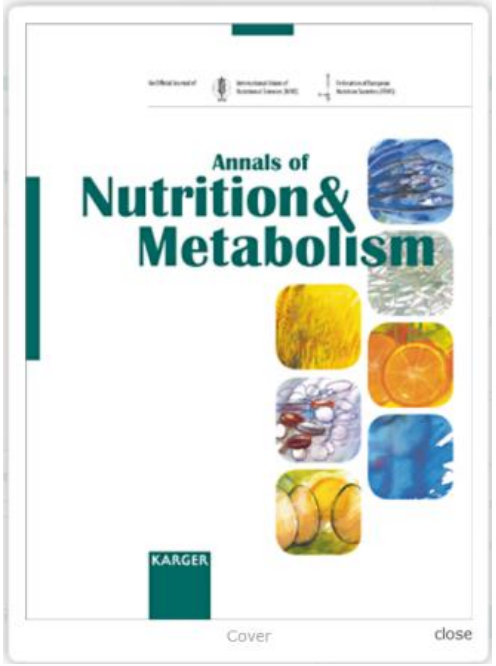


GROWTH MODELING IN 2 COHORTS

Proceedings of a workshop on modeling of growth trajectories

Botton et al, ***Postnatal weight and height growth modelling and prediction of body mass index as a function of time for the study of growth determinants***

Regnault et al, ***Comparative study of four growth models applied to weight and height growth data in a cohort of US children from birth to 9 years***



GROWTH MODELING IN 2 COHORTS

- ***The Jenss model*** (Jenss and Bayley, 1937)

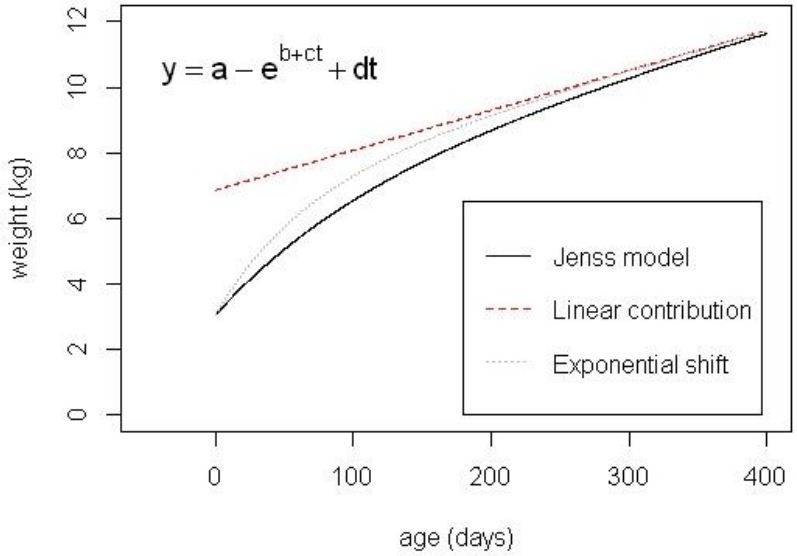
$$\hat{y}_{ij} = e^{A_i} + e^{-B_i}.t_{ij} + e^{C_i}.(1 - e^{-e^{-D_i}.t_{ij}})$$

where y is observed weight (kg)

or length (cm),

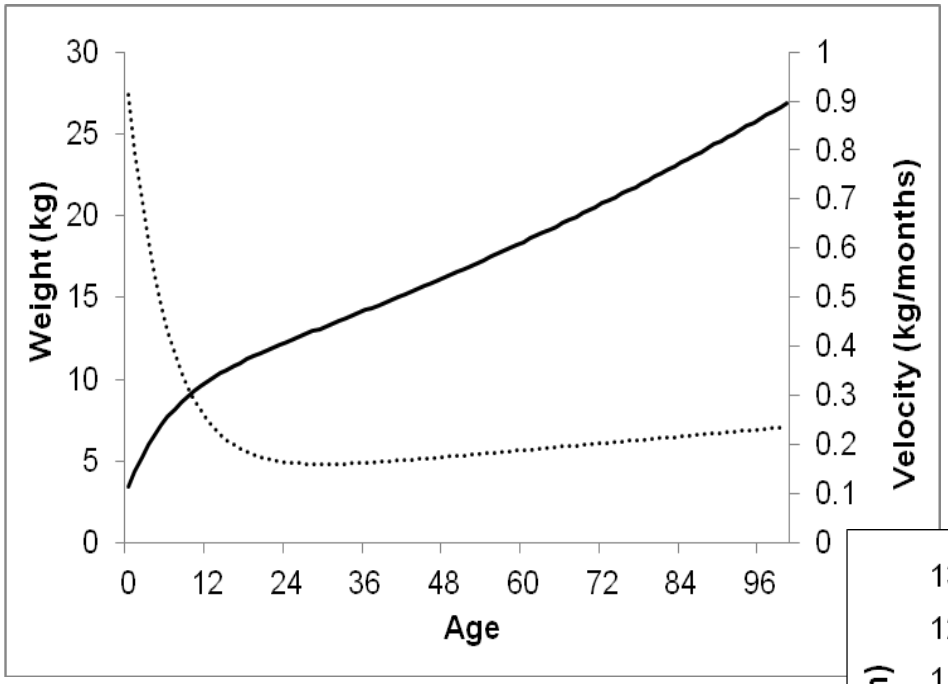
t is age (in months)

  - growth from birth to 8 years

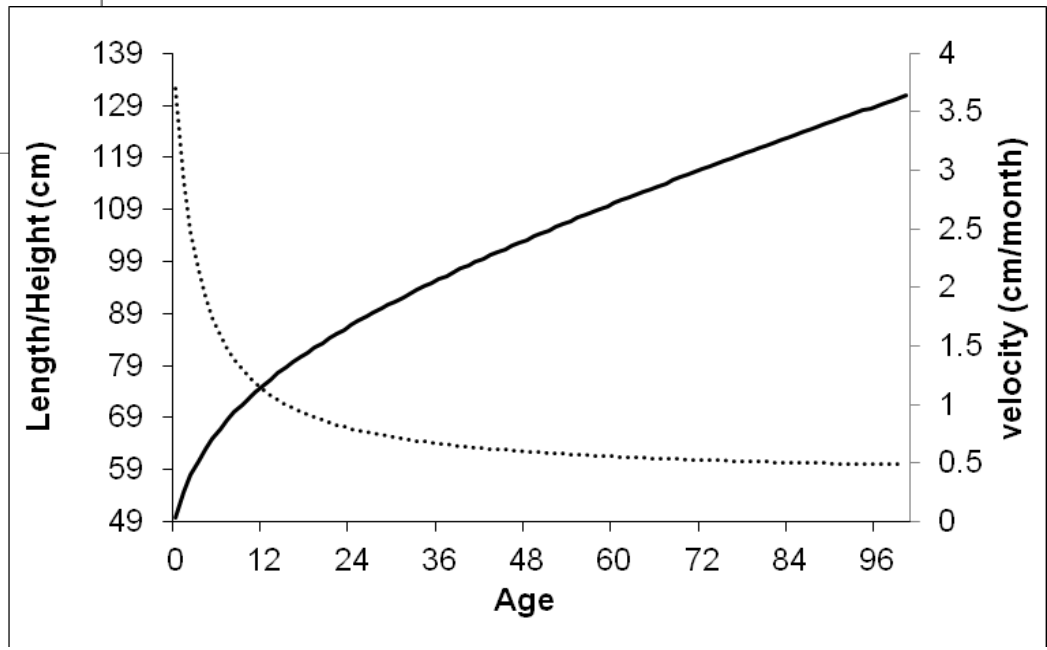


- ***The modified Jenss model*** (Botton et al, AJCN, 2008).
  - differs from the original Jenss model by the addition of a quadratic parameter (E* *t* 2*)*
  - growth from 0 to 12 y

INDIVIDUAL GROWTH TRAJECTORIES

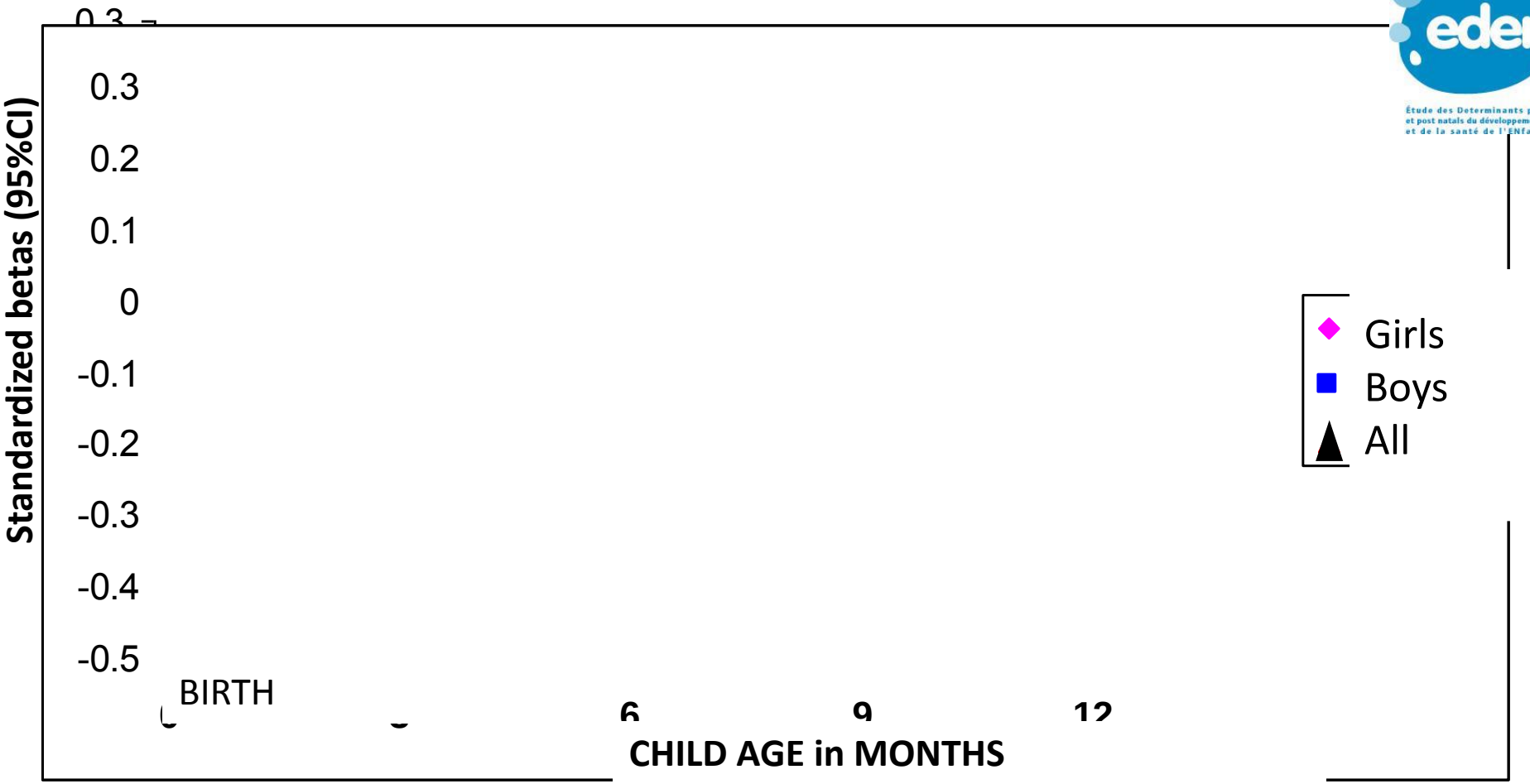


- **Compute weight, height and growth velocities at different ages**



Botton et al., AJCN, 2008

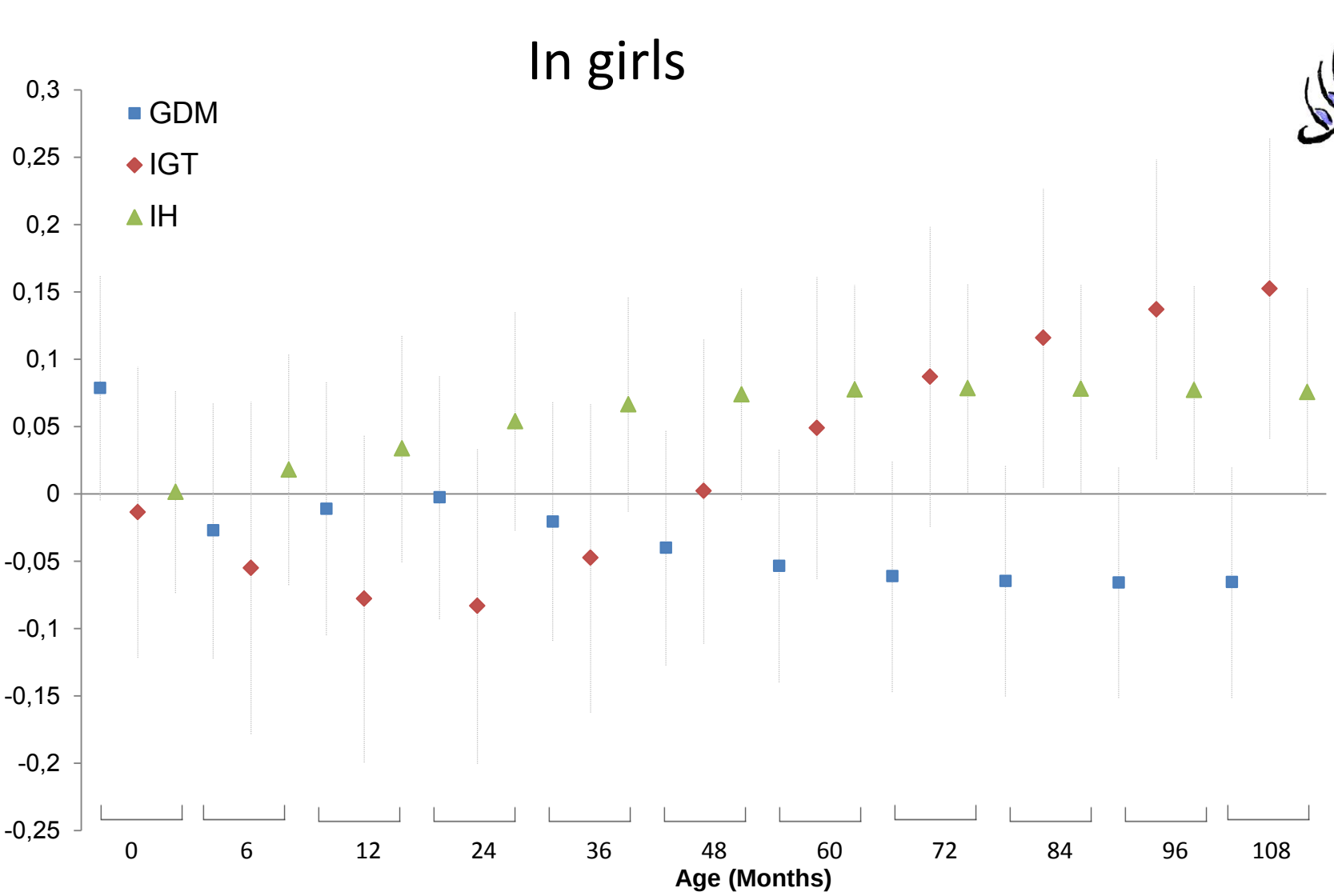
FETAL INSULIN AND WEIGHT IN 1st YEAR



Ajusted for center, gestationnal age, maternal glycemia and pre-pregnancy BMI, IGF-I

Similar findings recently published by Brunner et al, Diabetic Med,2013

AND LATER IN CHILDHOOD ?…



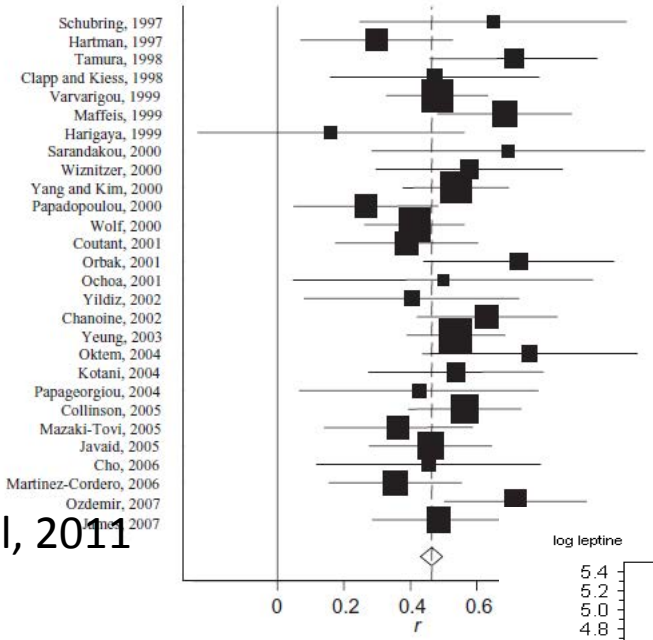
Adjusted standardized regression coefficients

Regnault N, in preparation

LEPTINE AND ANTHROPOMETRICS AT BIRTH

Birth weight

Figure 3. Forest plot indicating the pooled correlation coefficient between leptin levels in cord blood and birthweight in 28 studies without heterogeneity. Squares indicate the correlation coefficient in each study and the size of each square reflects the study-specific statistical weight; Horizontal lines indicate 95% CIs; Diamond indicates pooled correlation coefficient with its corresponding 95% CI.

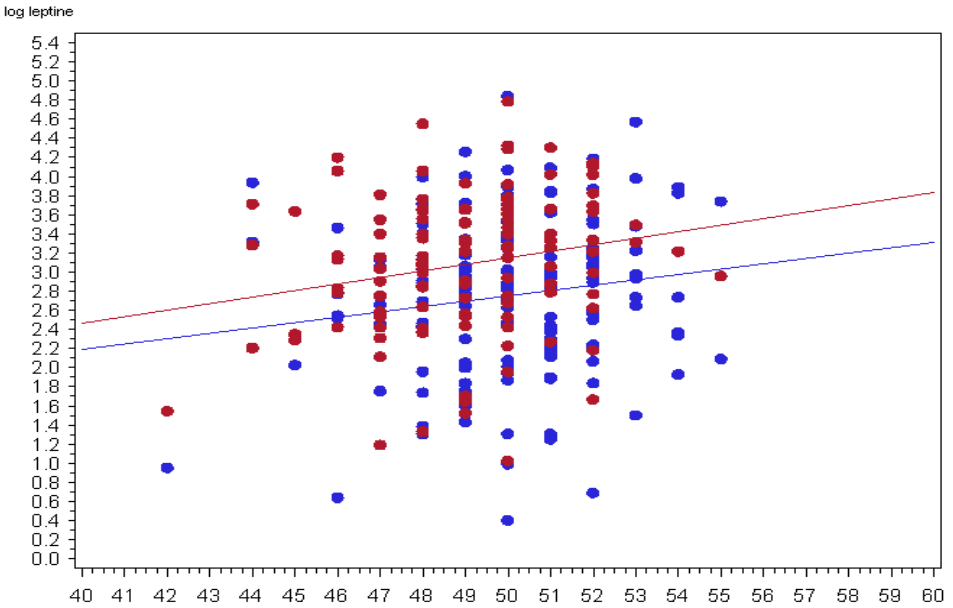


Karakosta P et al, 2011

Similar correlations for length and ponderal index as well

EDEN Study, N=284
Association of fetal leptin with birth length
in boys (blue, r=0,15, p<0,01)
and in girls (red, r=0,21, p<.0,05)

Milcent K, unpublished



LEPTINE AND ANTHROPOMETRICS IN THE 1ST Y

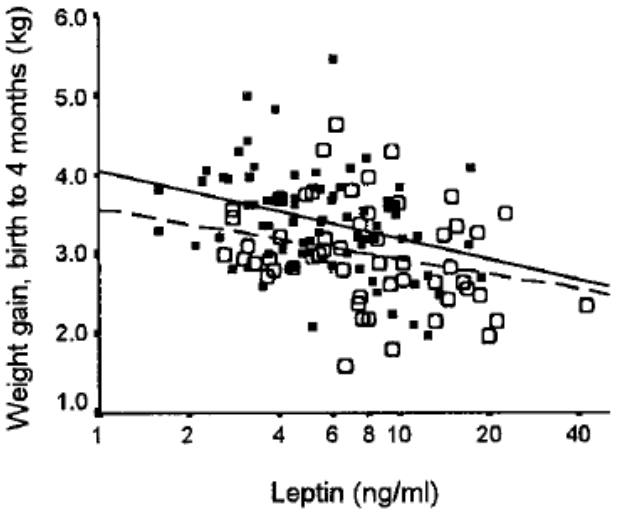
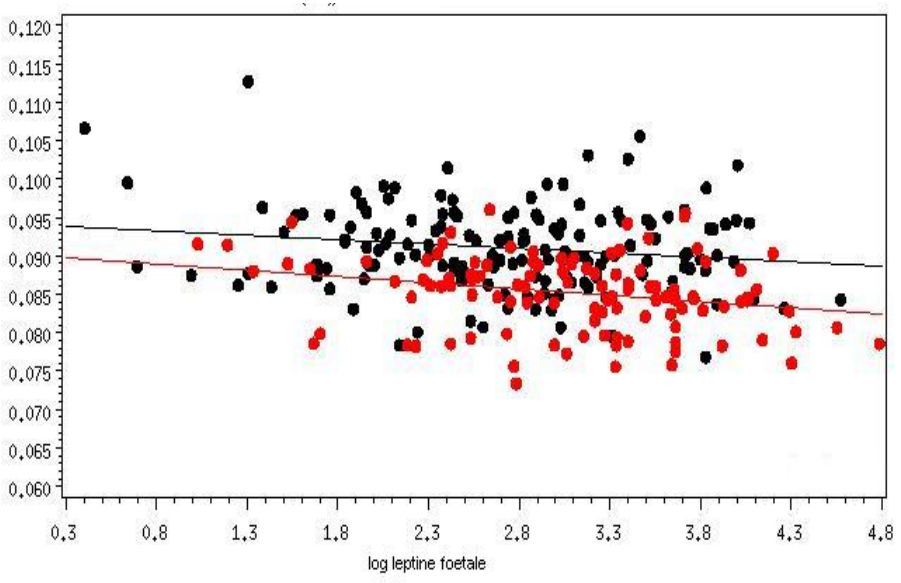


Figure 1. Weight gain 0-4months against cord leptin levels in males (■ and solid line, B = -0.37 ± 0.12, p<0.005) and females (□ and broken line; B = -0.28 ± 0.14, p <0.05).

Ong KK, JCEM, 1999

Weight gain 0-4 months

Height growth velocity at 3 months



EDEN Study, N=284
Association of fetal leptine and height growth velocity at 3 months in boys (blue, r=- 0,16, p<0,05 and in girls (red, r=-0,25, p<0,01)

Milcent K, unpublished

AND LATER IN CHILDHOOD ?…

Project Viva

TABLE 3 Multivariable associations of leptin concentrations with adiposity measures at ages 3 and 7 years, and with change in BMI *z*-score from 3 to 7 years. Estimates show association for highest versus lowest quintiles of plasma leptin concentration[a]

	Exposure		
	Difference in means: Q5 vs. Q1 (95% CI)		
	Maternal leptin	Cord leptin	Child age 3 leptin
Age 3 outcomes			
BMI *z*	**−0.5 (−0.7, −0.2)**	**−0.5 (−0.8, −0.2)**	–
Waist circumference (cm)	**−1.3 (−2.1, −0.5)**	**−1.4 (−2.3, −0.4)**	–
SS + TR[b] (mm)	−0.8 (−1.8, 0.3)	**−1.4 (−2.7, −0.1)**	–
Age 7 outcomes			
BMI *z*	**−0.4 (−0.6, −0.1)**	**−0.4 (−0.7, −0.1)**	0.2 (-0.0, 0.4)
Waist circumference (cm)	**−2.1 (−3.8, −0.4)**	0.1 (−2.0, 2.1)	**2.0 (0.6, 3.5)**
SS + TR[b] (mm)	0.2 (−2.1, 2.5)	1.1 (−1.5, 3.7)	**4.5 (2.5, 6.4)**
DXA fat mass (kg)	0.2 (−0.7, 1.0)	0.3 (−0.7, 1.3)	**1.6 (0.9, 2.3)**
Change between ages 3 and 7			
BMI *z*	0.1 (−0.1, 0.3)	0.1 (−0.2, 0.4)	0.2 (-0.0, 0.4)
Waist circumferences (cm)	−1.1 (−2.7, 0.4)	0.3 (−1.5, 2.1)	**2.3 (0.9, 3.7)**
SS + TR[b] (mm)	−0.0 (−1.9, 1.9)	0.7 (−1.6, 3.0)	**3.7 (1.8, 5.6)**

[a]Data from maternal-child pairs in Project Viva. Covariates are the same as in Model 3 from Table 2. Waist circumference, change in waist circumference, SS+TR, change in SS+TR, and DXA models additionally adjusted for child height. Change outcomes adjusted for age at both 3 and 7 year visits. Bold indicates $p < 0.05$.
[b]SS + TR: sum of subscapular and triceps skinfold thicknesses.

Boeke et al, Obesity, 2013

BIOMARKERS IN CORD BLOOD

- Potential for prediction of later growth
- Slower growth in infancy associated with adult outcomes
- Sex-specific effects
  - Higher cord insulin and leptin in girls
    - 'Gender Insulin Hypothesis' (Wilkin, Int J Obes, 2006)
  - Girls may be more resistant to the growth promoting effect of insulin in the postnatal period
  - Hormonal mecanisms: postnatal testosterone peak i n boys
  - Sex specific epigenetics in brain and placenta (McCarthy, J Neurosci, 2009)