Early Metabolic Programming of Growth and Long-Term Health

Miami Neonatology 2022—46th Annual International Conference

Presented by
Berthold Koletzko, MD, PhD

Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS
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Learning Objectives

- Recognize the implications and long-term outcomes of rapid, early weight gain after birth
- Recognize how a longer duration of breast-feeding modulates growth and body composition, as well as later health, performance, and disease risk

Outline

- Global burden of disease
- Early prevention of obesity and NCD
- Prenatal metabolic programming
- Postnatal metabolic programming
- Exporing potential underlying mechanisms: epigenetics, metabolome

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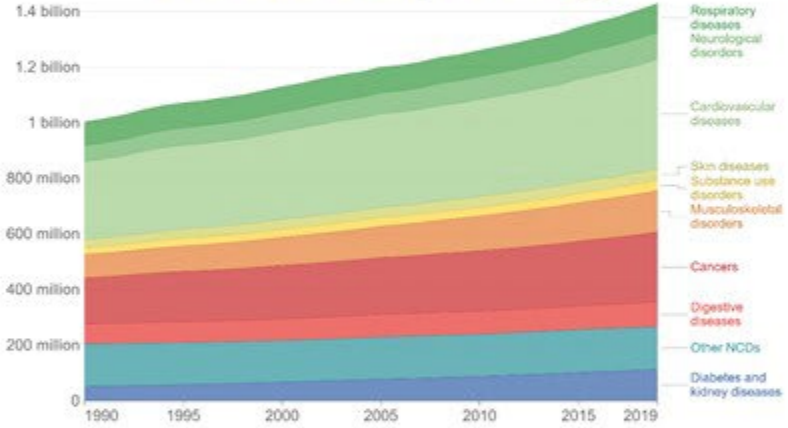
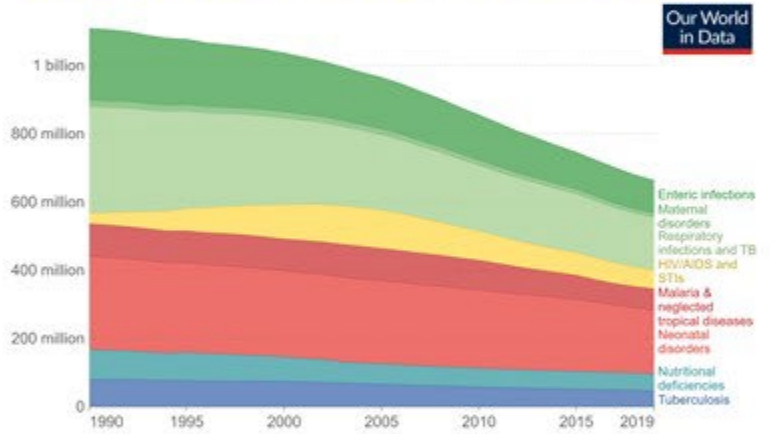
Global burden of disease

Non-communicable diseases (NCDs)



Communicable, neonatal, maternal & nutr. diseases



Europe 2021: NCDs cause **90% of deaths**,
85% of years lived with **disability**

World Health Organization
REGIONAL OFFICE FOR Europe

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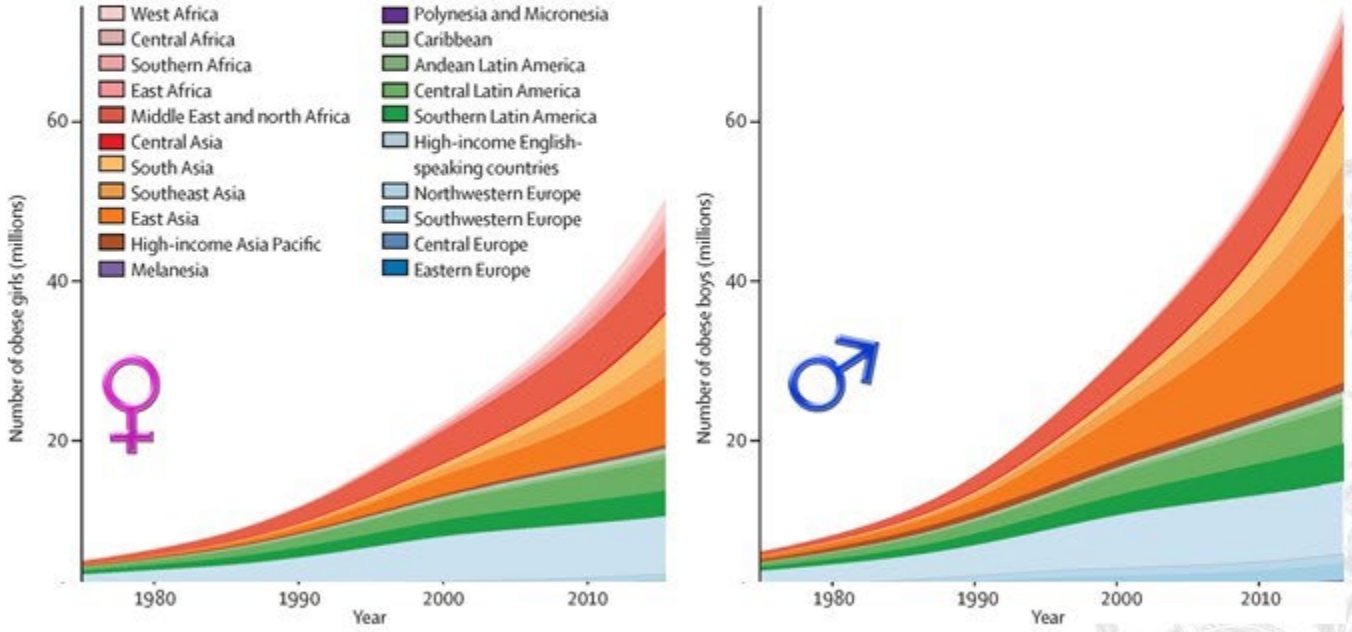
WHO European Regional Obesity Report 2022

Eight-fold increase of obesity in 5-19 year olds from 1975 to 2016



The Lancet 2017 390, 2627-2642DOI: (10.1016/S0140-6736(17)32129-3)

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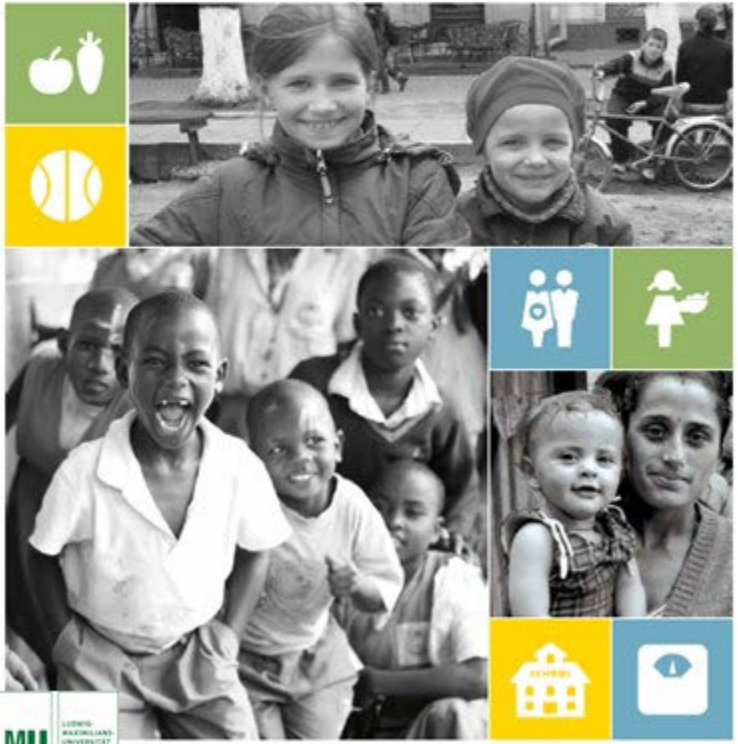
REPORT OF THE COMMISSION ON

ENDING CHILDHOOD OBESITY

World Health Organization



Preventive potential in 3 life phases

- Pregnancy & pre-conception
- Infancy & early childhood
- Adolescence (pre-conception)

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Early metabolic programming of later health

Developmental origins of adult disease

Environmental & nutritional cues

limited, sensitive times
of developmental plasticity

Lasting effects on health & disease risk

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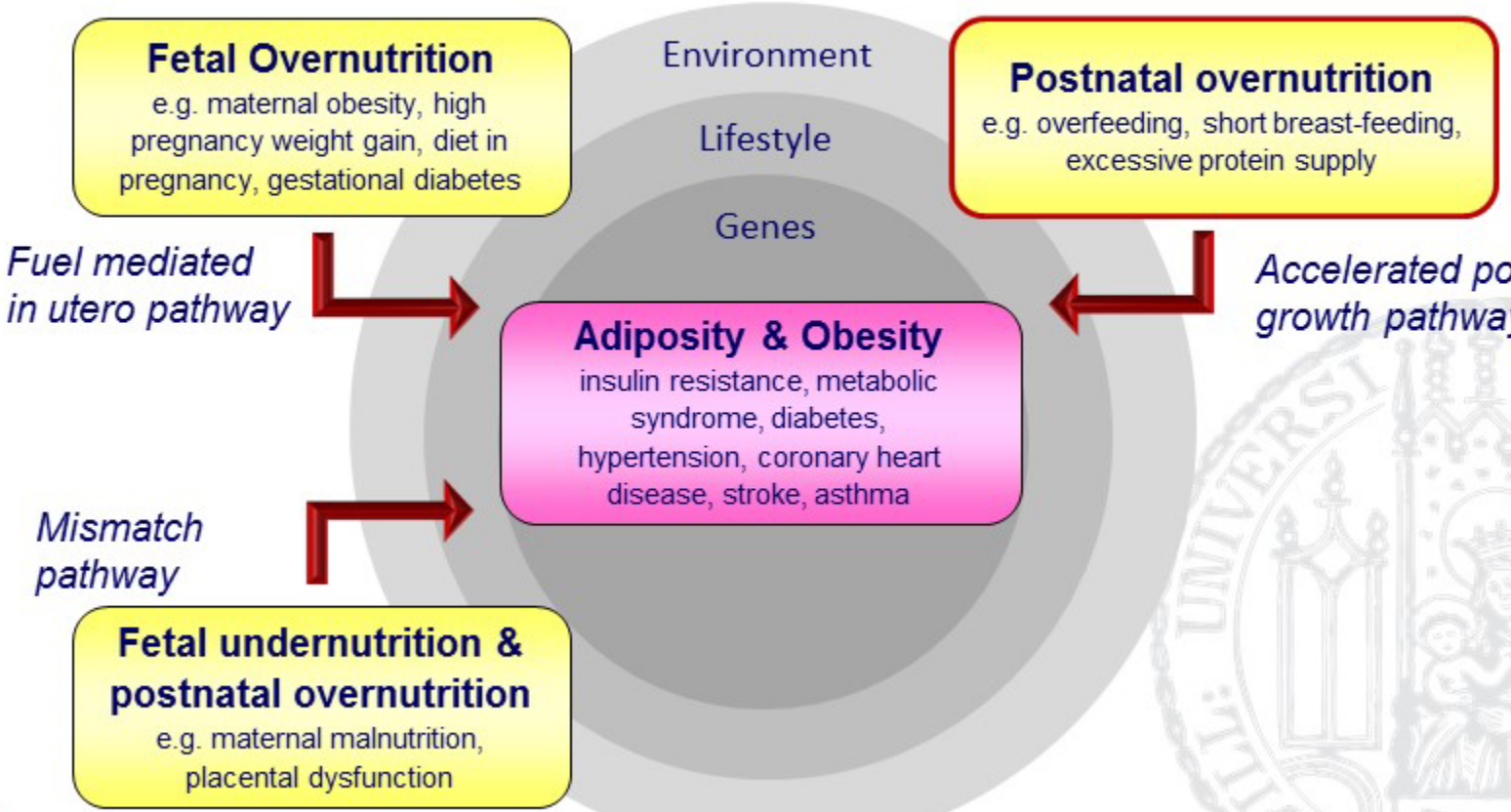
Key Programming Pathways



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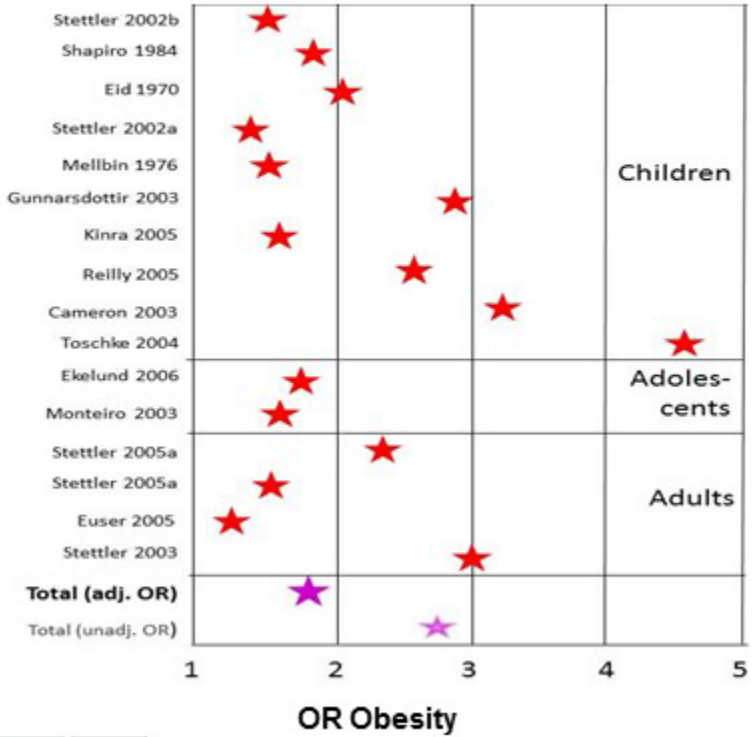
Koletzko B et al. The Power of Programming. Ann Nutr Metab 2014;64:141-50.

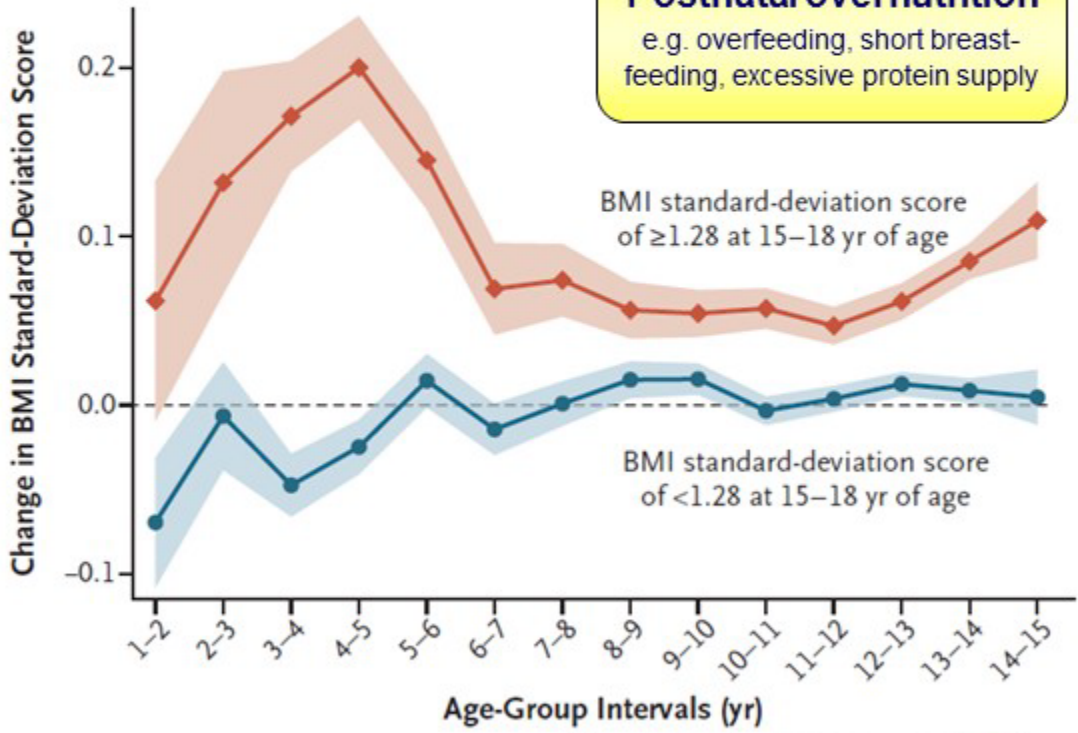
Postnatal overnutrition / rapid weight gain

High weight gain in 1st. & 2nd. yr.



Koletzko B et al. MoKi 2016; Doi: 10.1007/s00112-015-0002-x, using data of Baird J et al, BMJ 2005;331:929.

High early BMI gain



Postnatal overnutrition
e.g. overfeeding, short breast-feeding, excessive protein supply

Geserick M et al, NEJM 2018.. doi: 10.1056/NEJMoa1803527.

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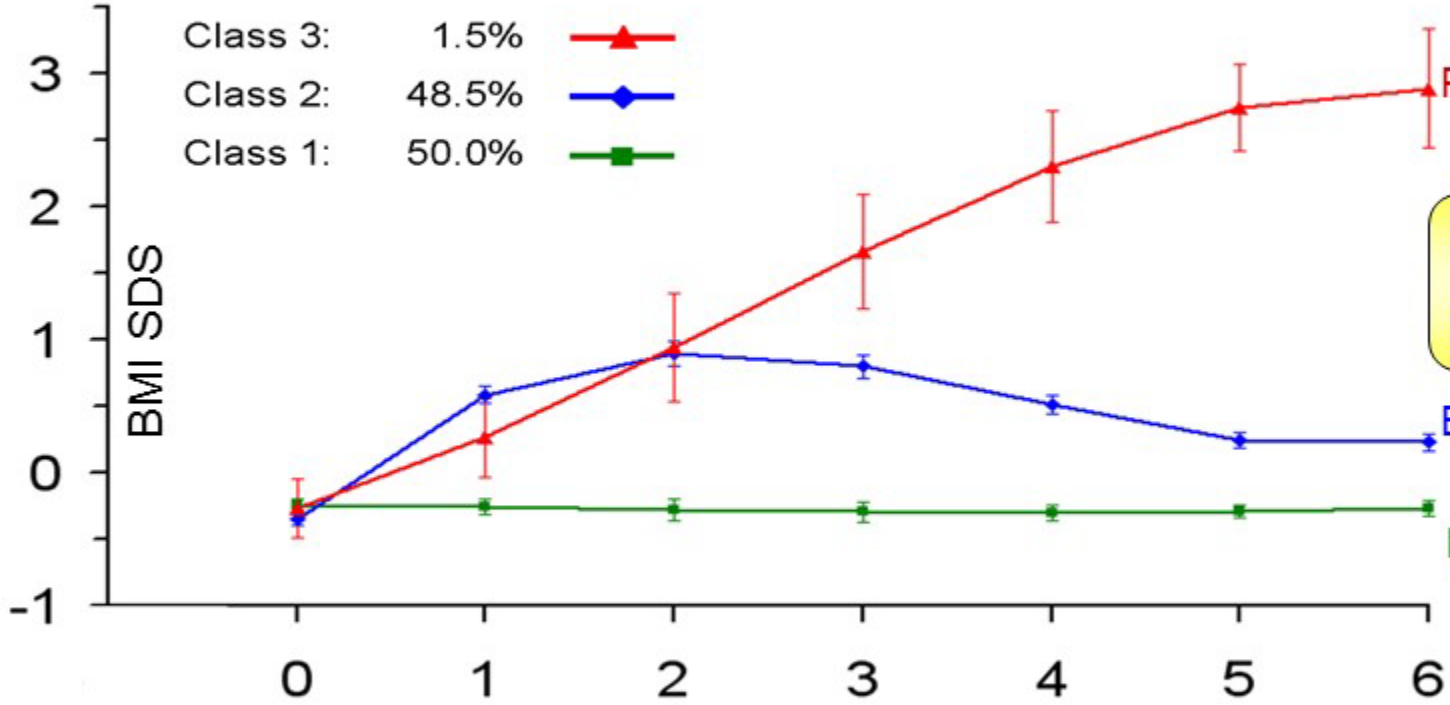
Early growth clusters in 6708 children



Persistent rapid growth

Postnatal overnutrition
e.g. overfeeding, short breast-feeding, excessive protein supply

Early rapid growth:

Normative growth

Data of kids from 11 countries, West Australian Pregnancy Cohort (RAINE) European Childhood Obesity Project Trial (CHOP), Norwegian Human Milk Study (HUMIS), & Prevention of Coeliac Disease (PreventCD), EU Early Nutrition Project.

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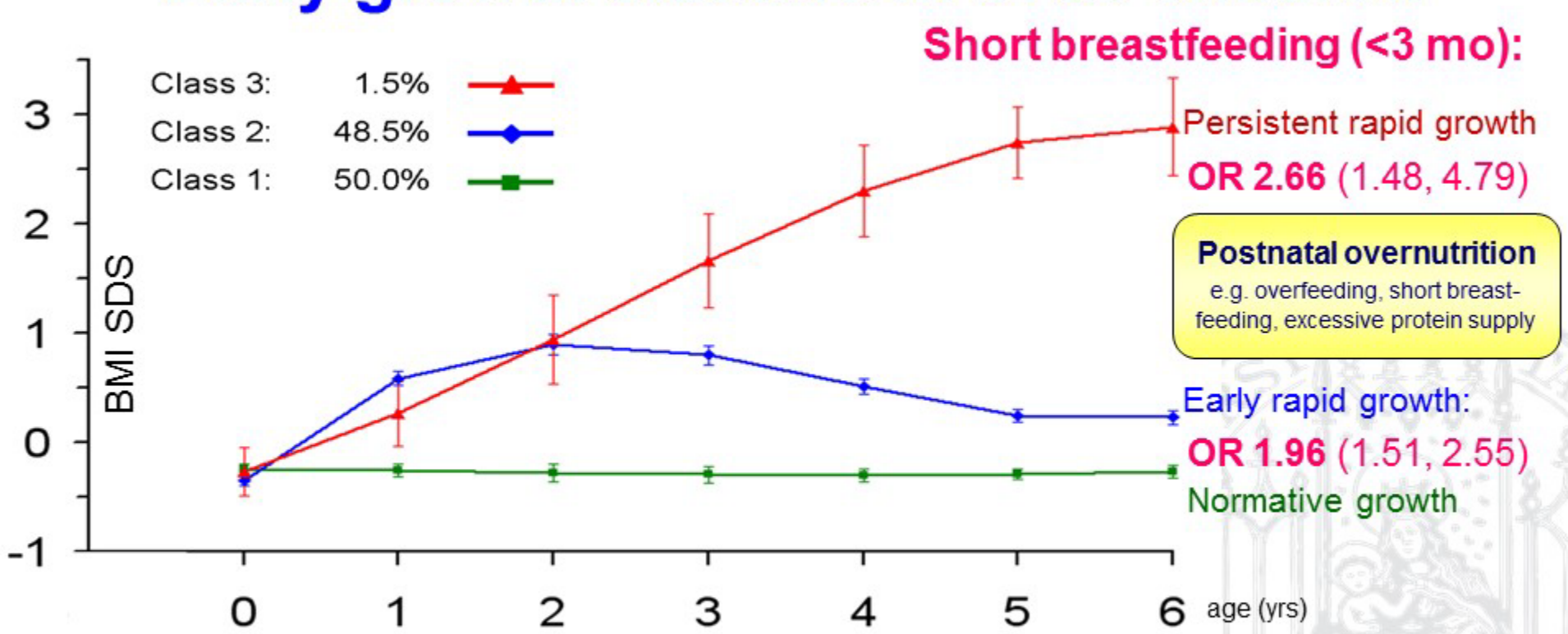
Rzehak P et al, Am J Clin Nutr. 2017;106:568-580.
doi: 10.3945/ajcn.116.140962.

Early growth clusters in 6708 children



Data of kids from 11 countries, West Australian Pregnancy Cohort (RAINE) European Childhood Obesity Project Trial (CHOP), Norwegian Human Milk Study (HUMIS), & Prevention of Coeliac Disease (PreventCD), EU Early Nutrition Project.

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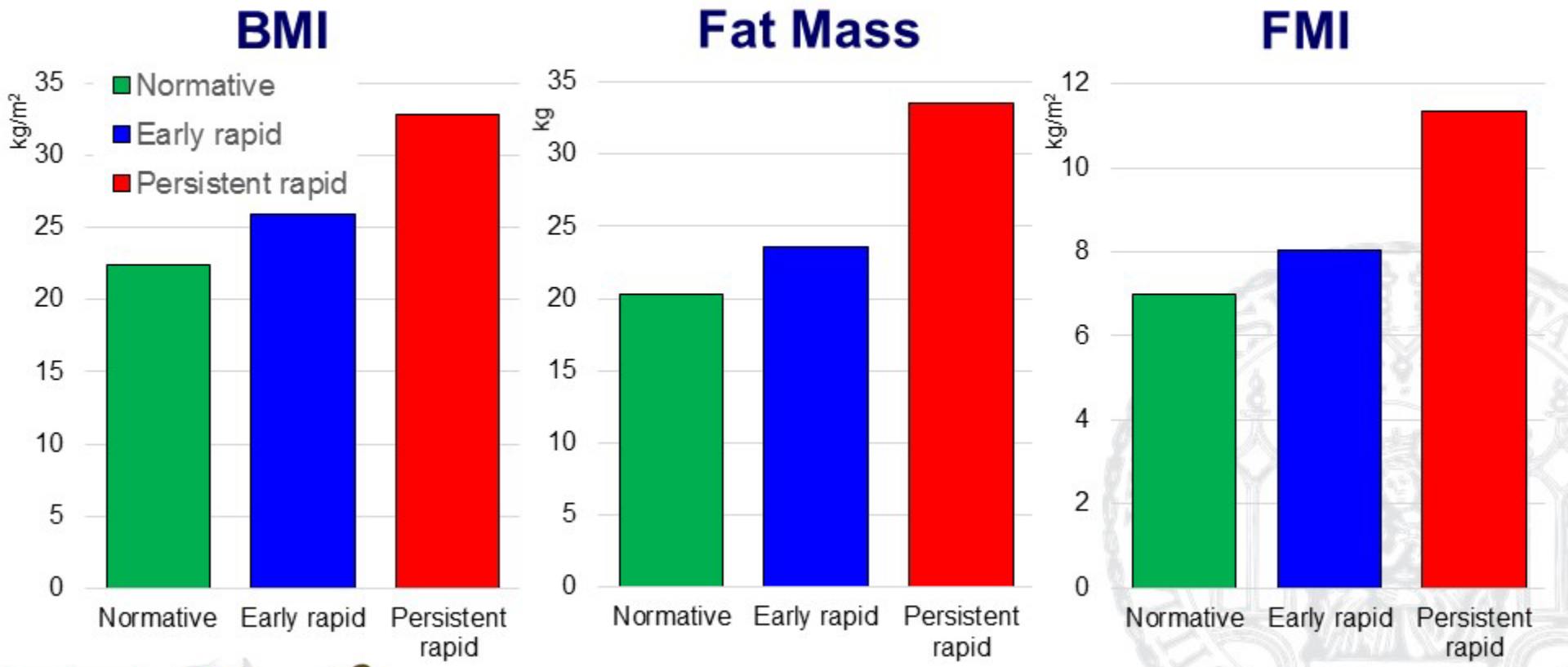
Rzehak P et al, Am J Clin Nutr. 2017;106:568-580. doi: 10.3945/ajcn.116.140962.

Early growth clusters and outcome @20 yrs



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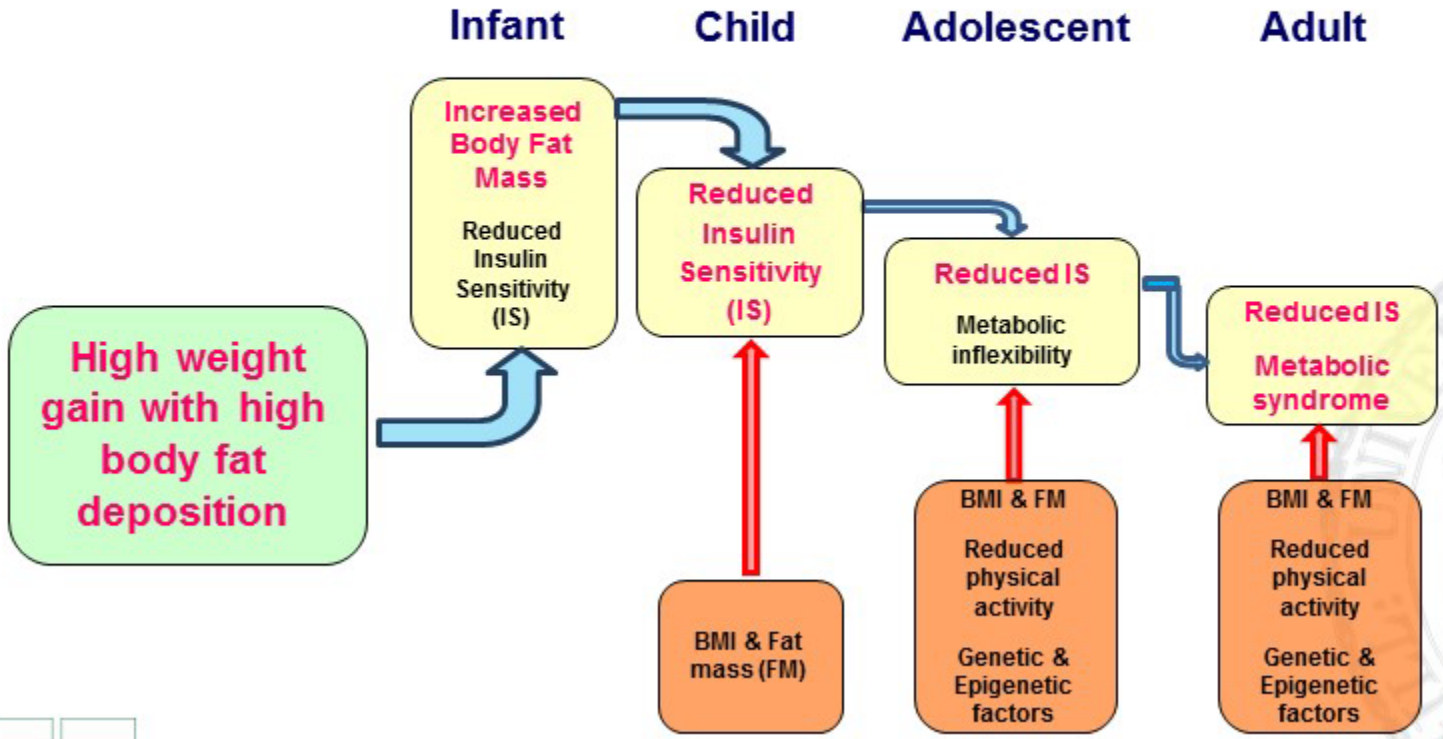
Rzehak P et al, Am J Clin Nutr. 2017;106:568-580.
doi: 10.3945/ajcn.116.140962.

Rapid growth ⇨ deposit excessive body fat ⇨ risk for later metabolic disease



Modified after Tinnion R et al. Arch Dis Child. 2014;99:362ff.

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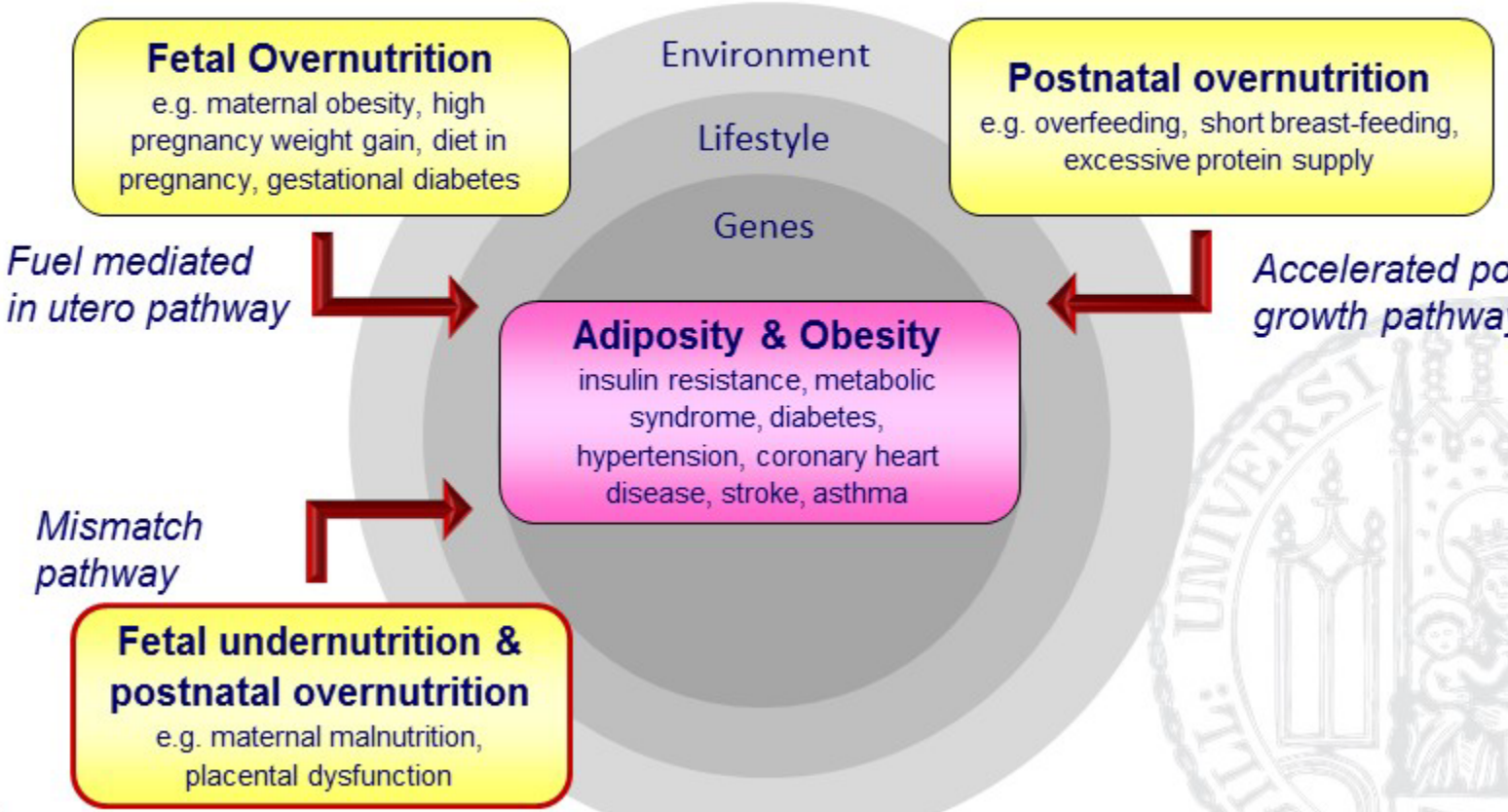
Key Programming Pathways



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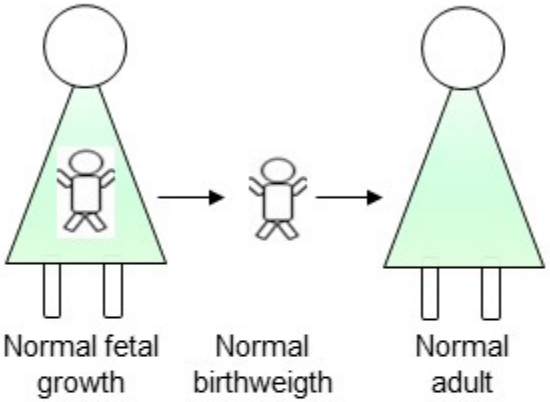
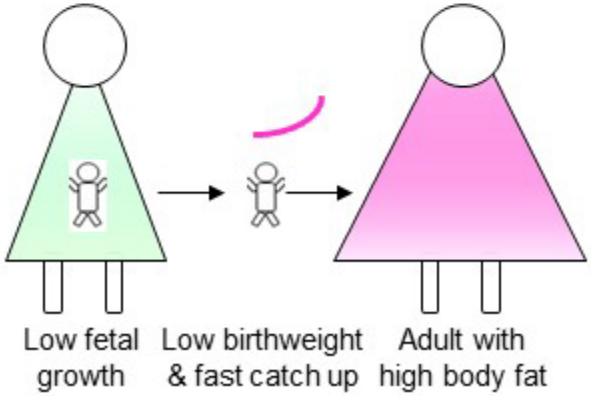
Koletzko B et al. The Power of Programming. Ann Nutr Metab 2014;64:141-50.

The Mismatch Pathway



Fetal undernutrition & postnatal overnutrition
e.g. maternal malnutrition, placental dysfunction



Mismatch of low fetal and rapid postnatal growth:

↑ adult adiposity & NCD risk

Drawn after Edwards M. In: Preedy V& Patel V (eds) Handbook of Famine, Starvation, & Nutrient Deprivation. Springer, 2017.

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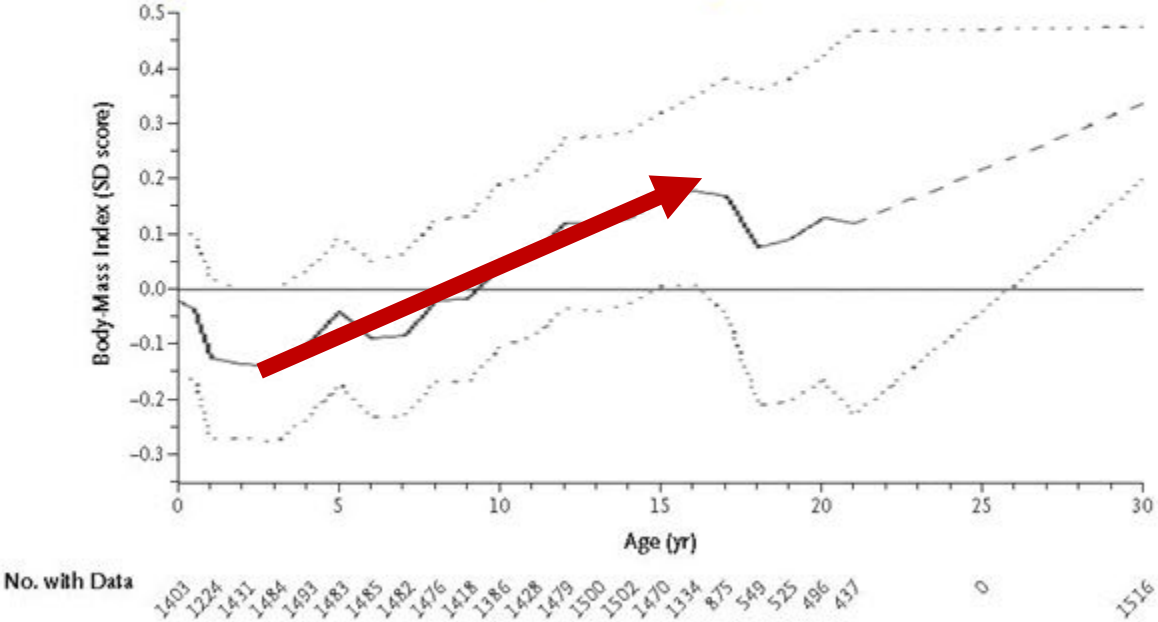
Low initial weight followed by rapid weight gain: high later risk of NCD

⇨ High risk of diabetes, obesity, cardiovascular disease



1492 men and women aged 26 to 32 years, measures at birth and every 3-6 months through infancy, childhood, and adolescence in a prospective, population-based study

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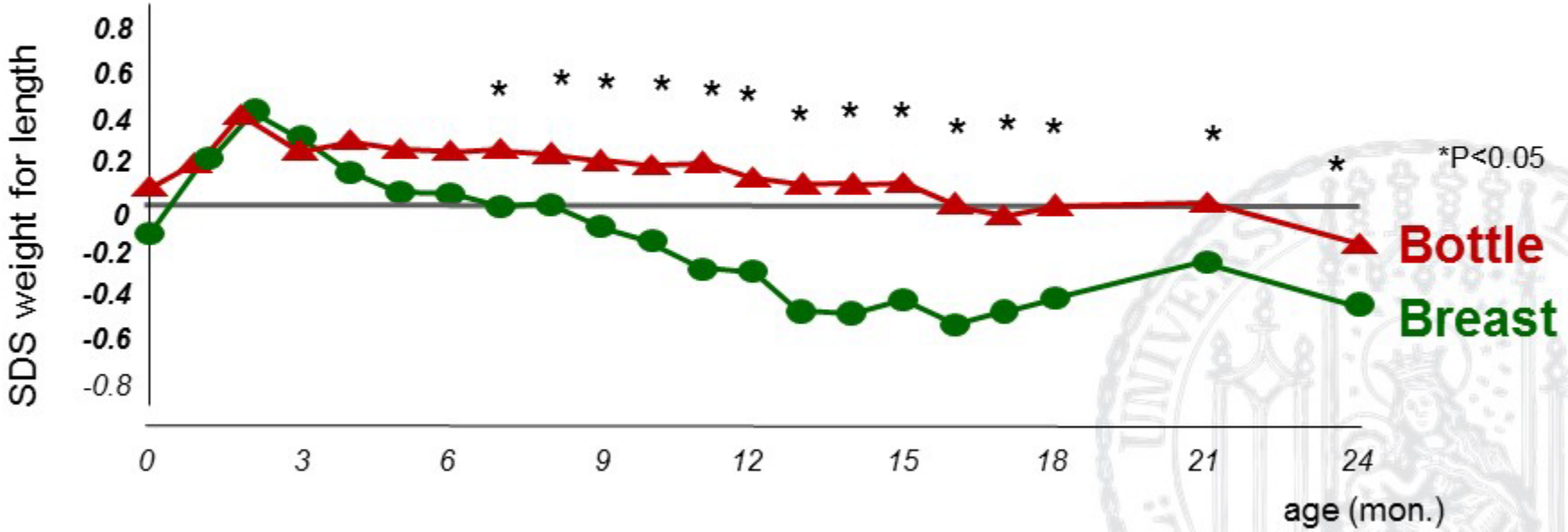
Bhargava et al, NEJM 2004.

High early weight gain

- Is it genetically determined?
- Does early feeding matter?

Breastfed infants: lower weight for length (SDS) after the first months than bottle fed infants



DARLING study, Davis, CA, USA; 87 infants.
Dewey et al , AJCN 1993.

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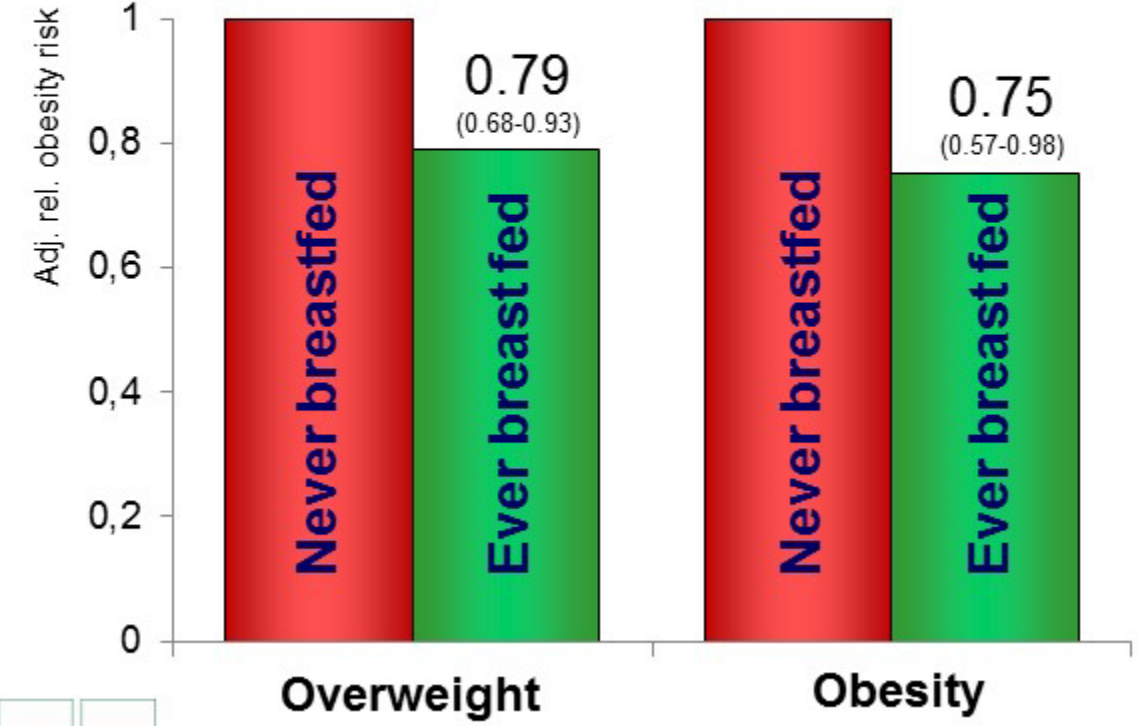
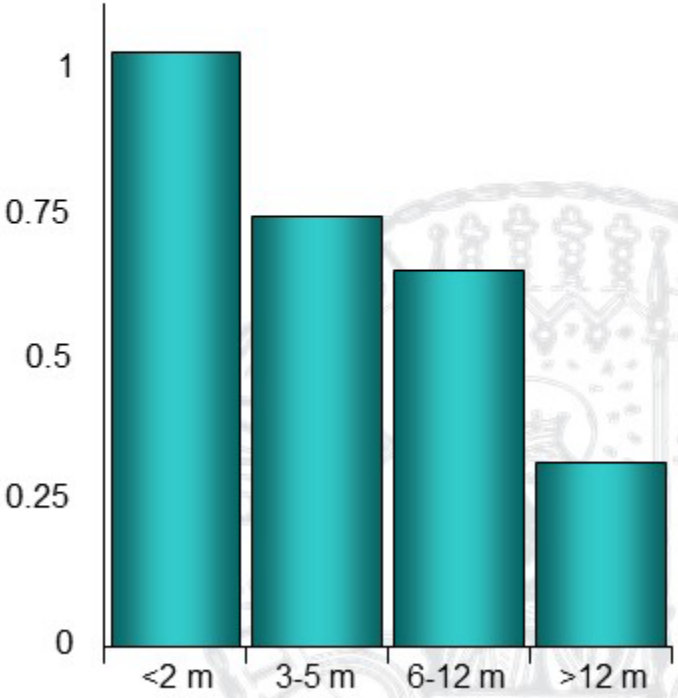
Breast feeding: less obesity at school age

9357 children, school entry health examination, Bavaria, Germany, OR adjusted for confounders

Any breastfeeding



Duration of breastfeeding



Koletzko et al. Ann Nutr Metab 2014;65:99–107.
v. Kries et al. Brit Med J 1999,319:147-50.

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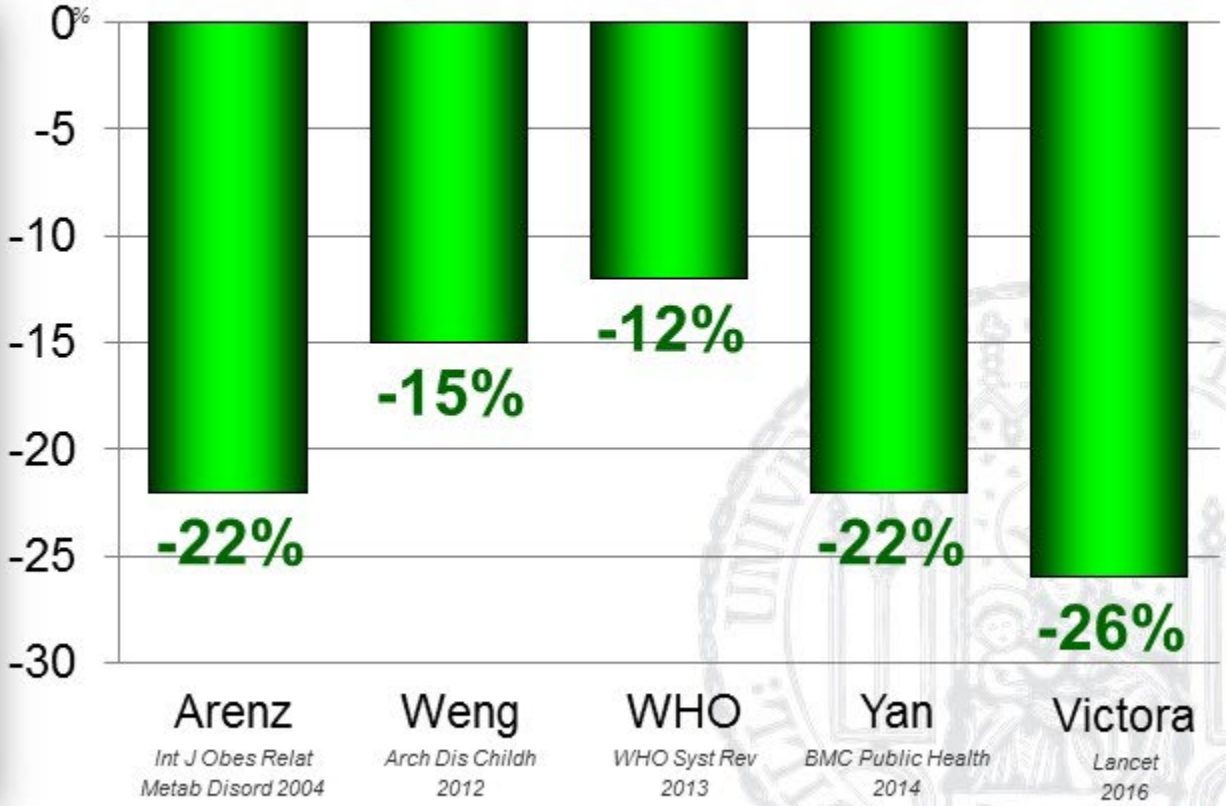
Breastfeeding and obesity risk: meta-analyses



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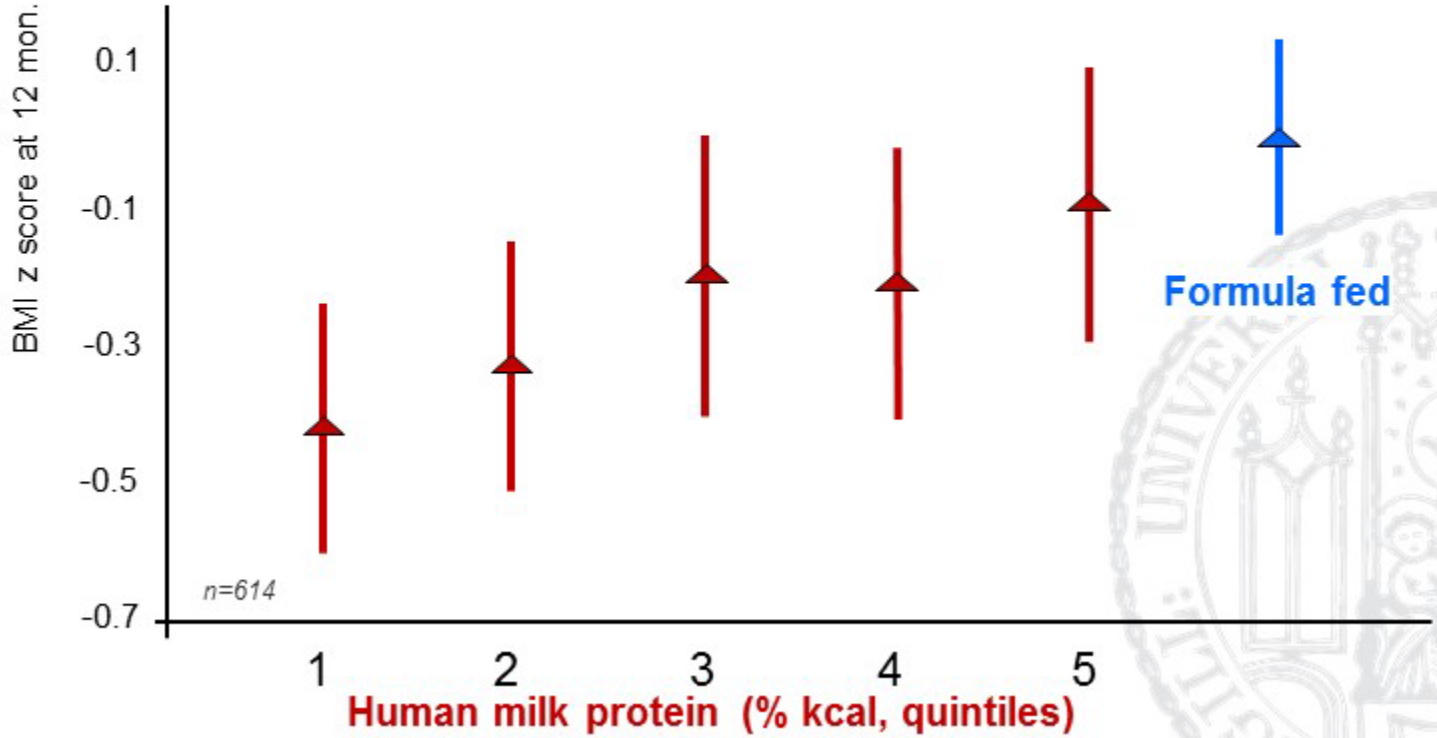
Early Protein Hypothesis

High early protein:
↑ weight gain
& later obesity

Photo: © Berthold Koletzko

BMI at 12 months predicted by human milk protein at 4-8 wks *but not by milk kcal or fat*



Prentice et al, 2016.

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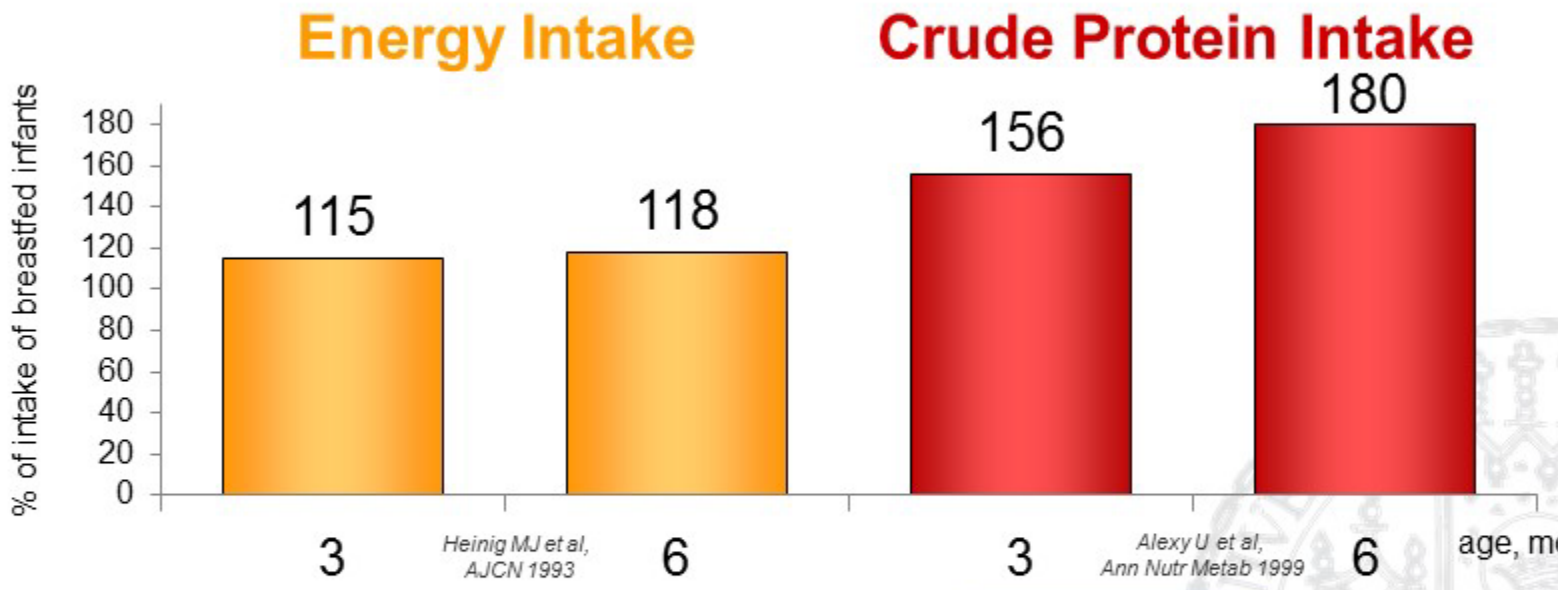
Early Protein Hypothesis



Koletzko B et al, AJCN. 2016;103:303-4.
doi: 10.3945/ajcn.115.128009.

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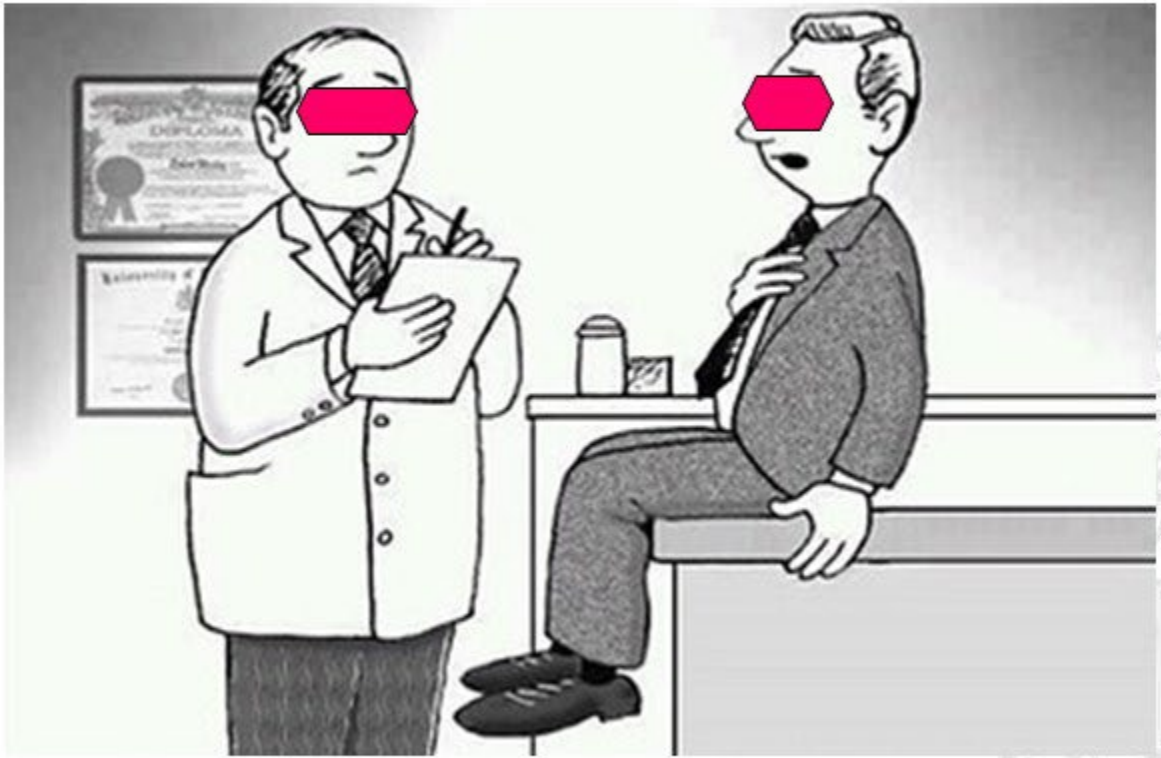
Double-blind randomized trial needed



CC BY by DES daughter

Childhood obesity project (CHOP) RCT

EU funded double-blind RCT, 1678 healthy term infants enrolled in 5 countries

Double blind randomised iso-energetic formulae

Breast fed — **Protein: ≈1-1.2 g/dL**

Conventional protein formula — **IF 2.05 g/dL, FOF 3.2 g/dL**

Intervention protein formula — **IF 1.25 g/dL, FOF 1.6 g/dL**

Intervention — No intervention, follow-up

BMI data at 6 yrs.

Breast fed 61.4%

Bottle fed 60.4%

0 *1 yr.* *2 yrs.* *6 yrs.*

EARLYNUTRITION
Long-term effects of early nutrition on later health

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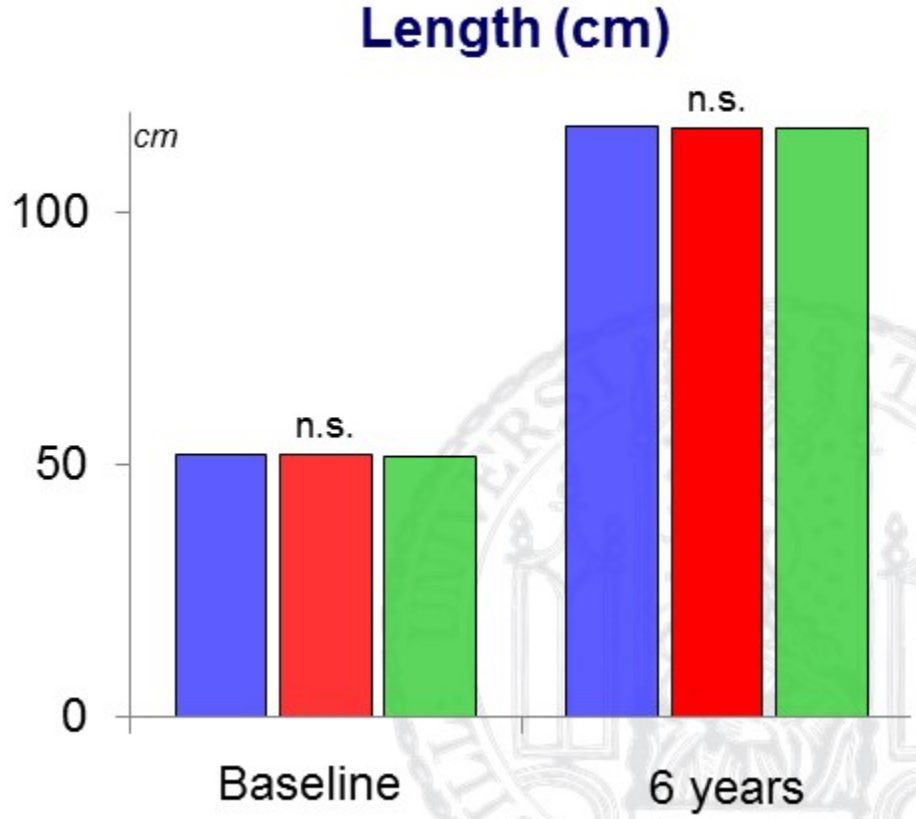
Koletzko et al, Am J Clin Nutr 2009;89:1836-45.
Weber et al, Am J Clin Nutr. 2014;99:1041-51.

Lower protein formula: no safety concerns

No difference between randomized groups for

- Length growth
- Tolerance
- Acceptance
- Lab safety markers



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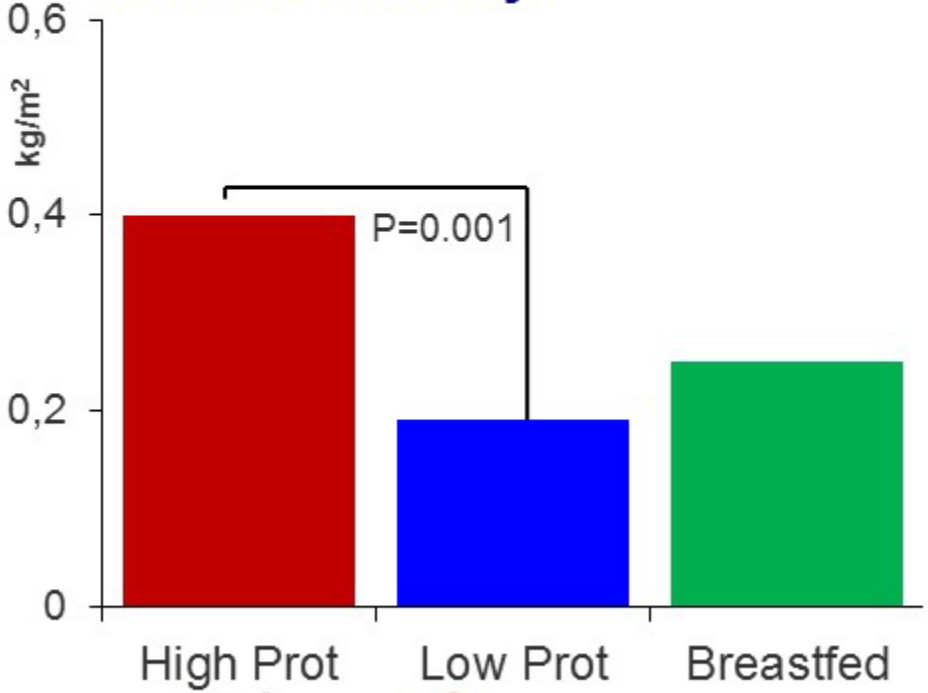
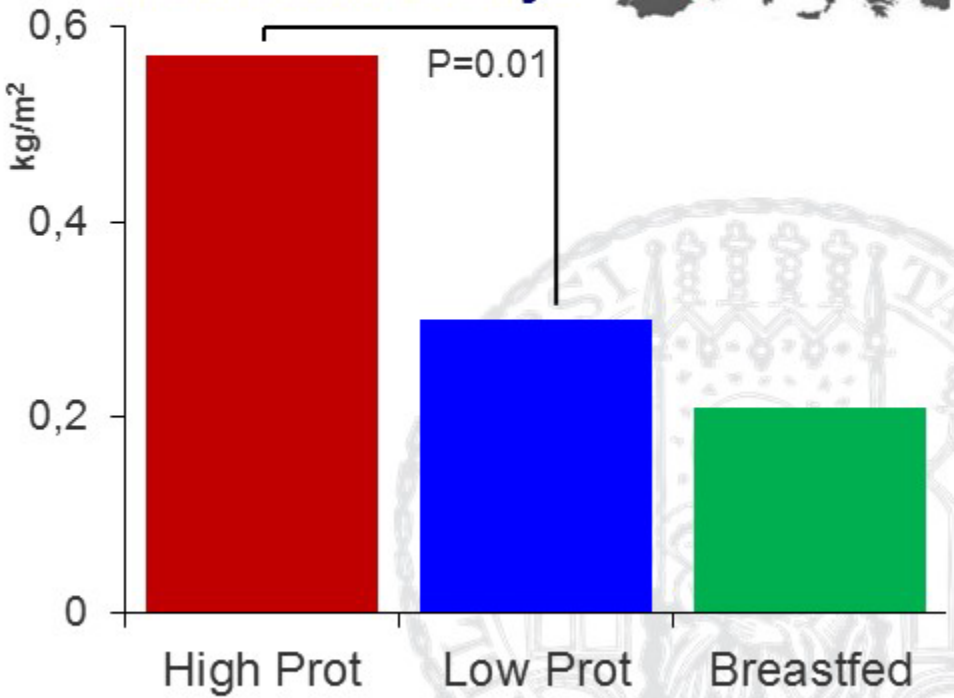
BMI at 2 and 6 yrs.

EU funded CHOP RCT

Mean BMI at 2 y.



Mean BMI at 6 y.



Koletzko B et al, Am J Clin Nutr 2009;89:1836-45.
Weber M et al, Am J Clin Nutr. 2014;99:1041-51.

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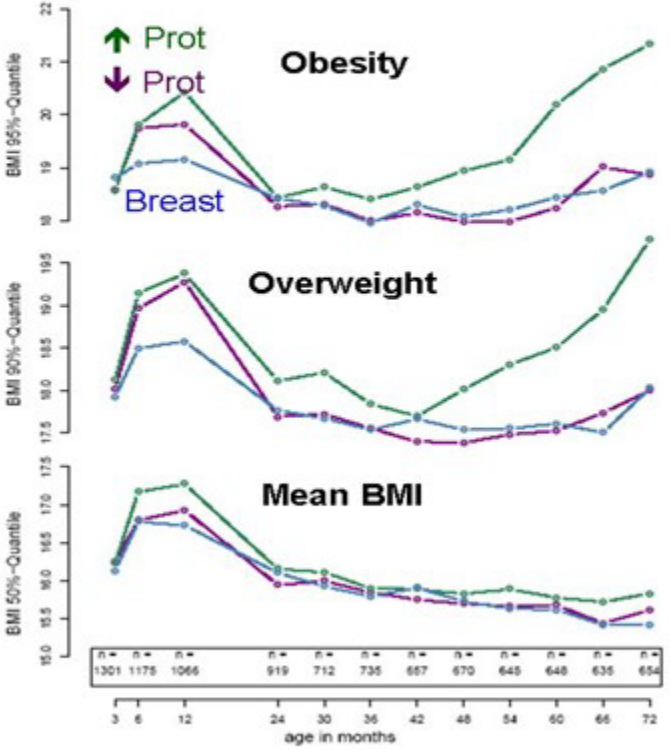
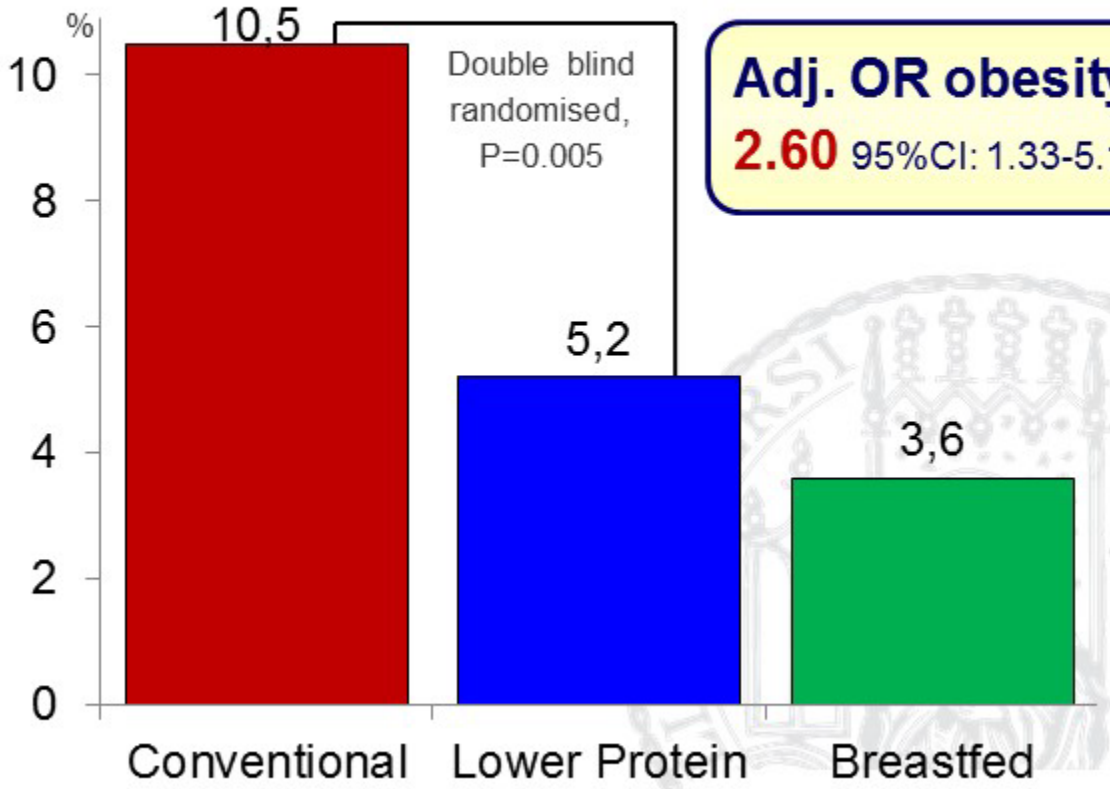
Less protein to infants ⇨ less obesity later

RCT, Childhood Obesity Project (CHOP) Study, 1678 infants, 5 European countries





Adj. OR obesity:
2.60 95%CI: 1.33-5.10

Koletzko B et al, Am J Clin Nutr 2009;89:1836-45.
Weber M et al, Am J Clin Nutr. 2014;99:1041-51.

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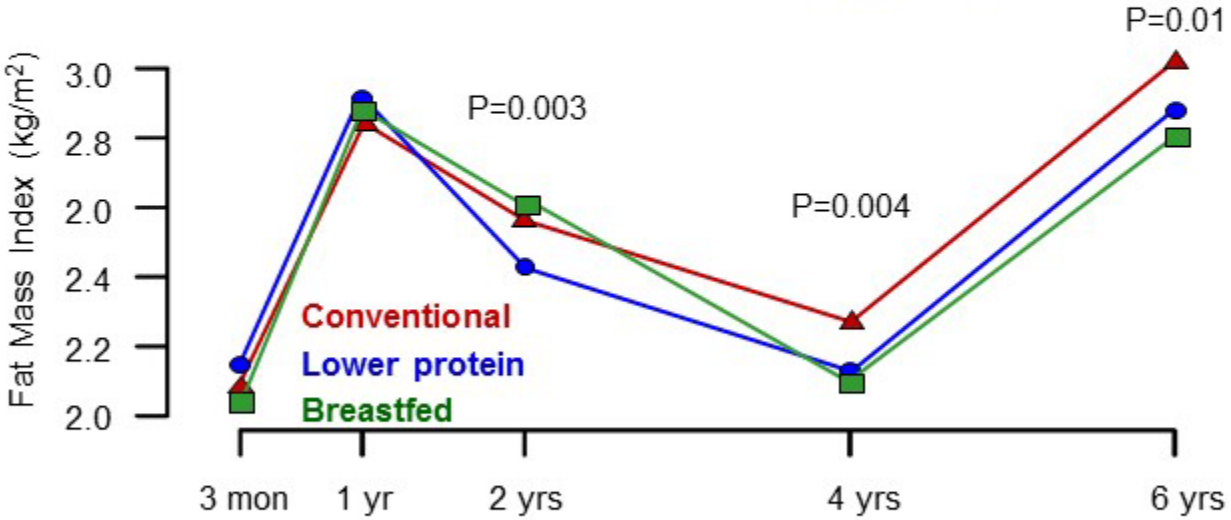
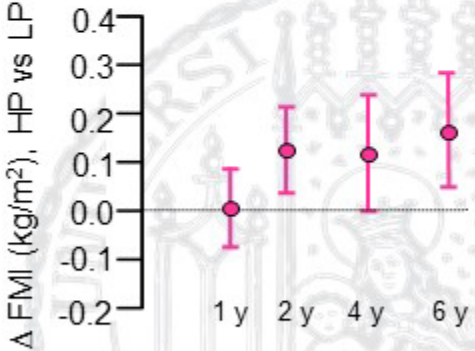
High protein to infants ⇨ fatter at 2-6 yrs.

Fat Mass Index (kg/m²)



Difference High vs. Low Protein



Totzauer M et al., Obesity 2018;26:1203-10. doi: 10.1002/oby.22203.

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Conclusion: infant feeding and later obesity

- Infant feeding has very marked effects on later obesity
- Breastfeeding protects
  ⇨ **promote, protect & support breastfeeding**
- Avoid high protein supply
  ⇨ Infants not (fully) breast fed: **infant formula with less protein**, but **high protein quality**
  ⇨ Improved protein composition my provide further benefits
- **First year: no cows‘ milk as a drink** *if feasible & affordable*

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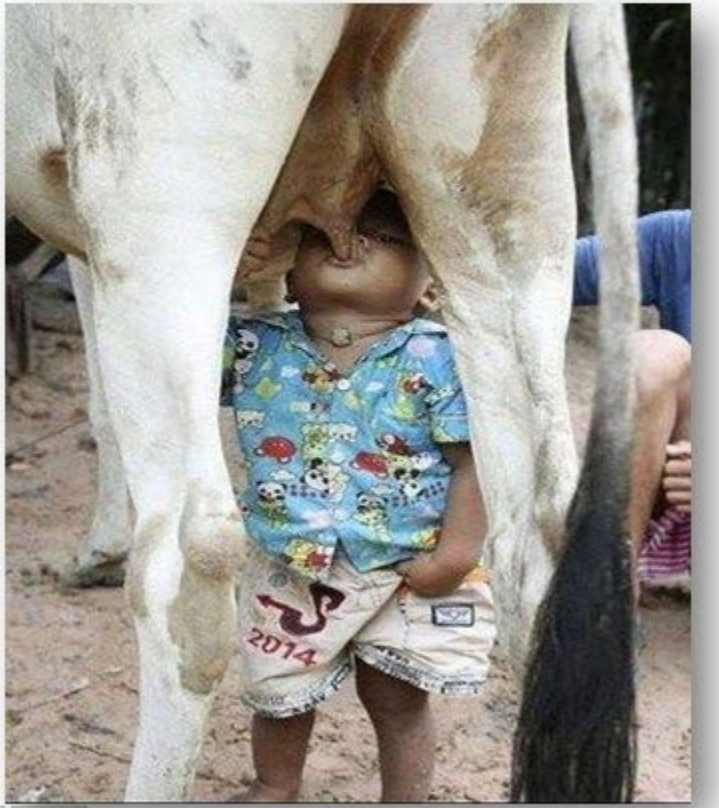
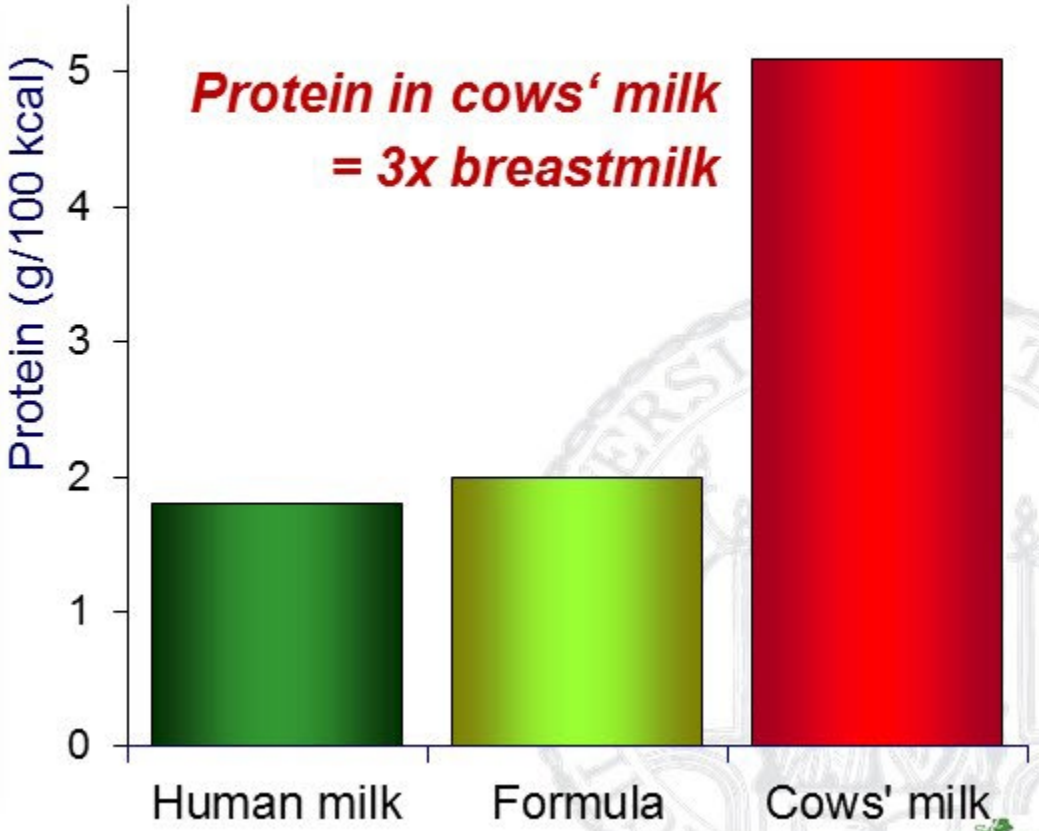
Avoid cows‘ milk as a drink in the first year

if feasible and affordable





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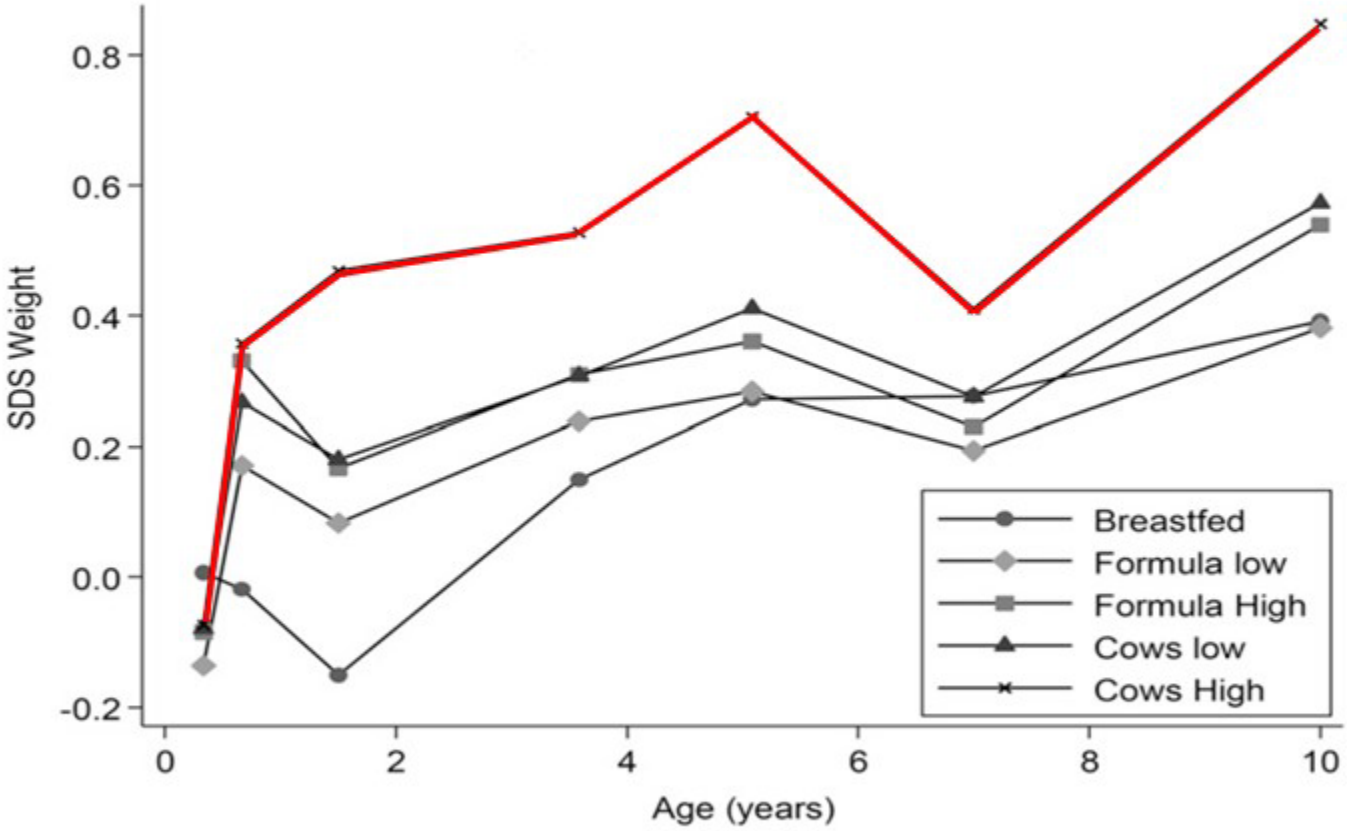
Cows‘ milk at 8 mon. and weight at 10 yrs.



≥600 mL cows’ milk

≥600 mL formula
<600 mL cows’ milk

breast milk,
<600 mL formula

1112 term, singleton children, ALSPAC. Food records at 8 mo. Feeding groups: breast milk, <600 mL formula/d, ≥600 mL formula/d, <600 mL cows’ milk/d, ≥600 mL cows’ milk/d.

Hopkins et al. AJCN 2015.

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EARLYNUTRITION

Long-term effects of early nutrition on later health

www.project-earlynutrition.eu/recommendations

European Commission

Project No. 289346

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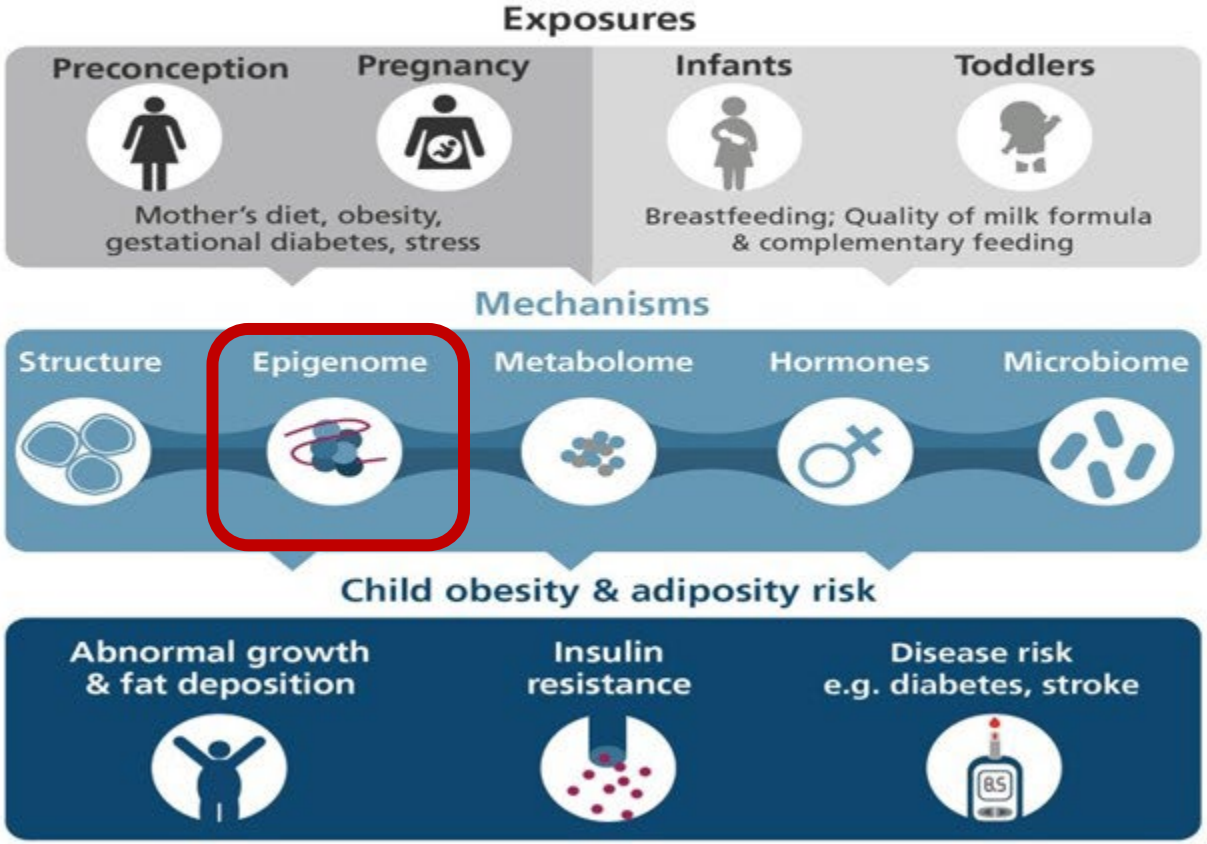
Understanding mechanisms is important



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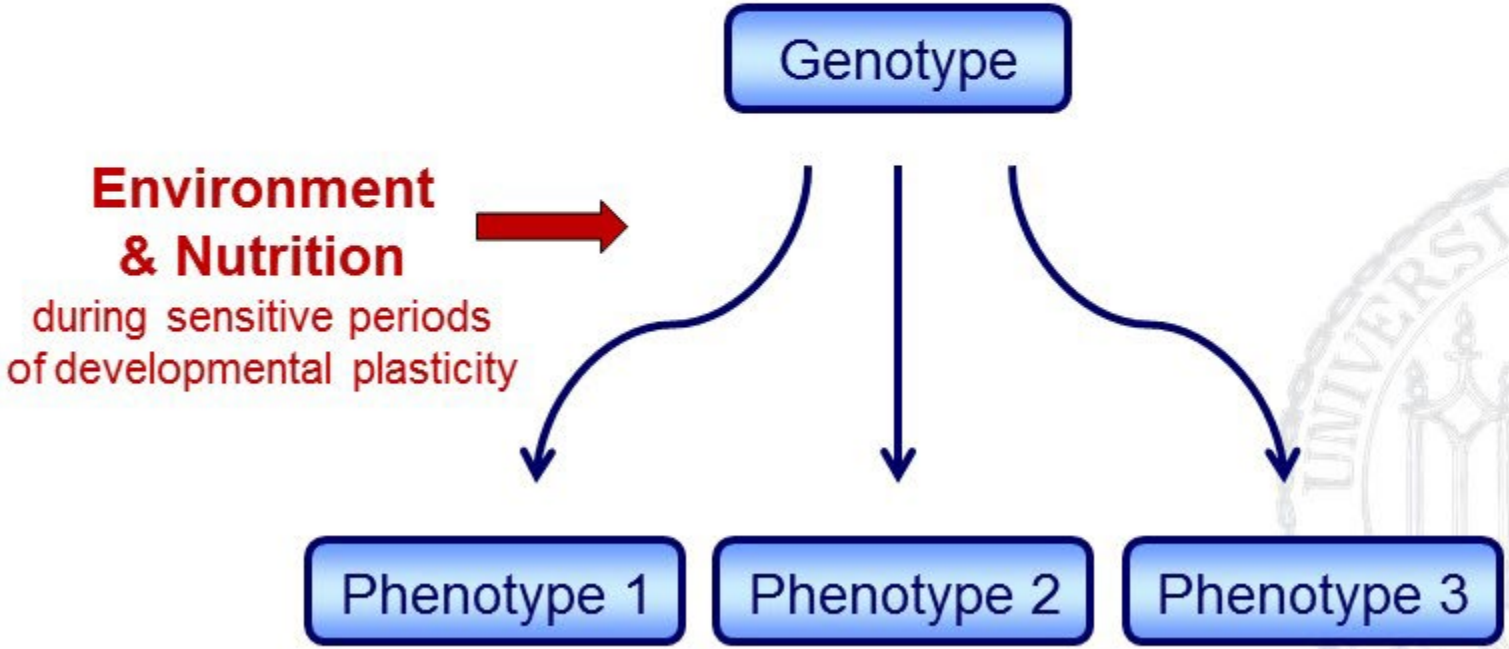
Epigenetics: environment & nutrition modify genotype effect on phenotype



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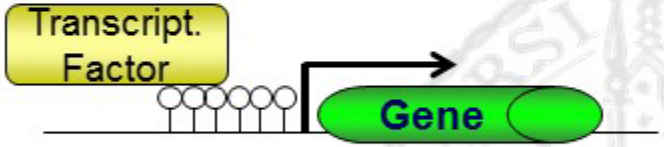
Cytosine - phosphatidyl - Guanine (CpG)

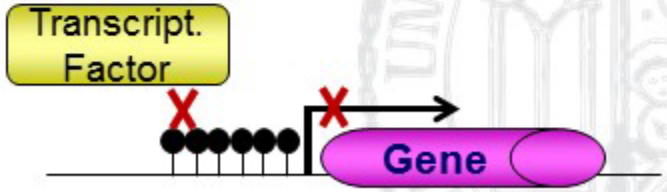
Most CpG sites (>90%) dispersed around the genome at low densities

CpG island

CpG island not methylated
⇨ gene is expressed



CpG island methylated
⇨ gene is not expressed



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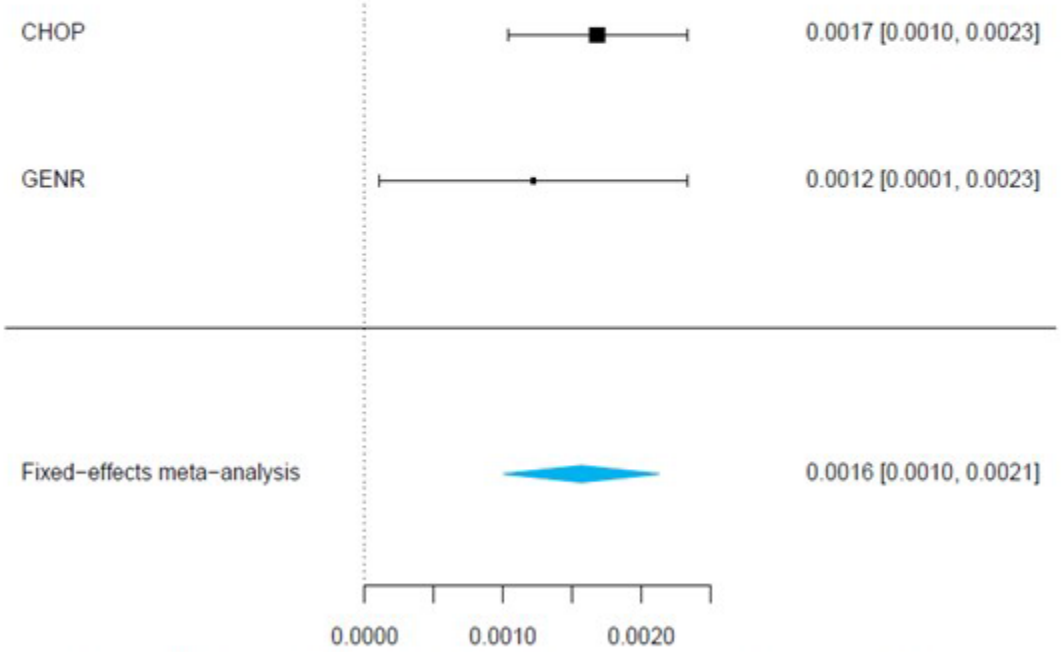
Infant animal protein intake modifies DNA methylation in childhood: meta-Analysis



Animal protein intake (E%) @≈1 yr and DNAm @7-12 years (n= 604)

El Sharkawy M et al, in preparation.

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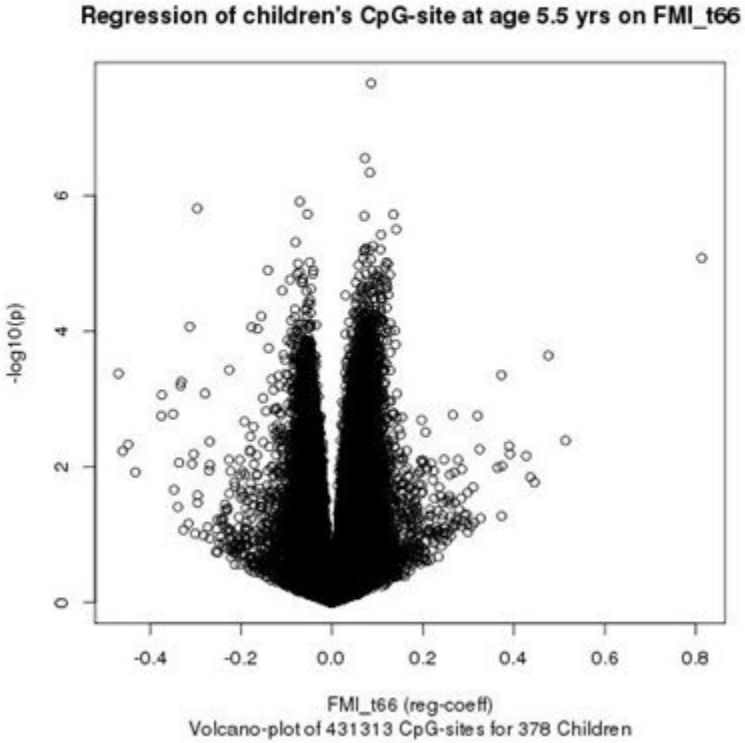
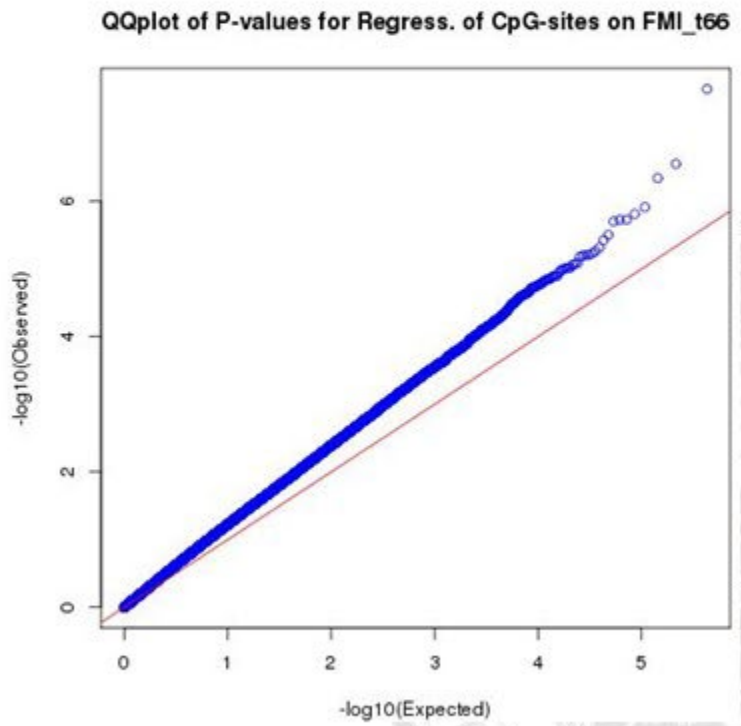
DNA-methylation and childhood fat mass

FMI, 5.5 yrs. 378 children, CHOP





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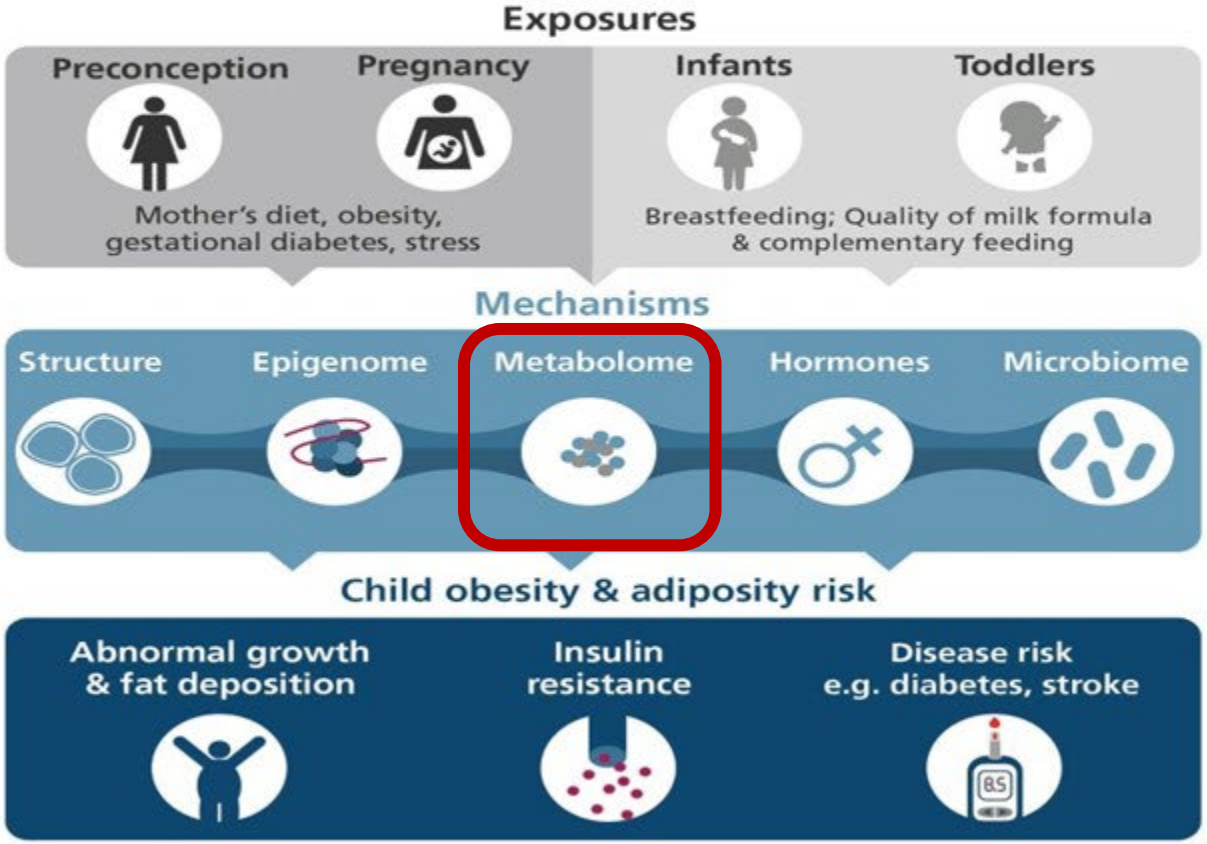
Rzehak et al. Sci Rep. 2017 Oct 30;7(1):14349.
doi: 10.1038/s41598-017-13099-4.

Understanding mechanisms is important



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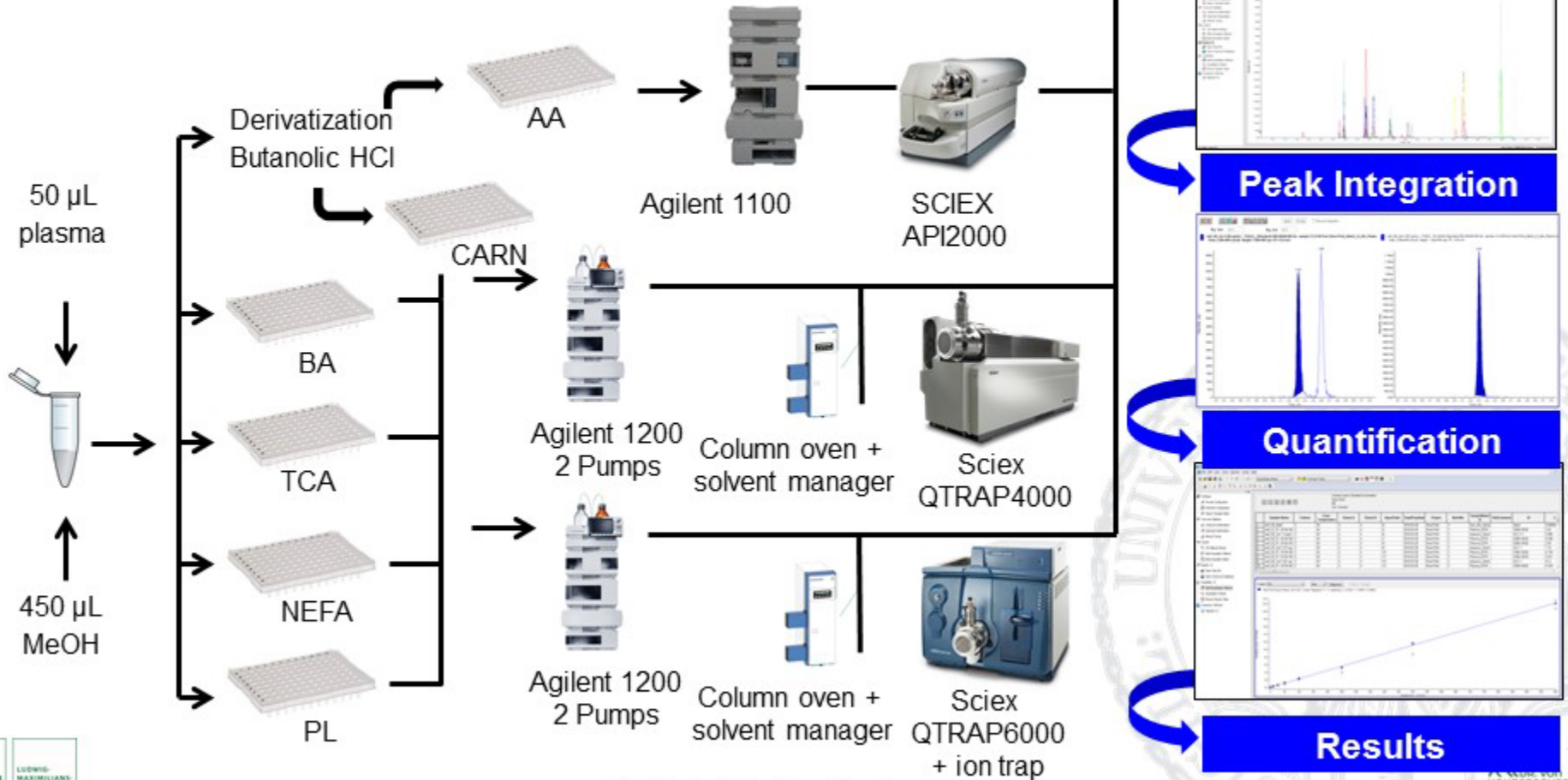
Metabolome from drops of blood



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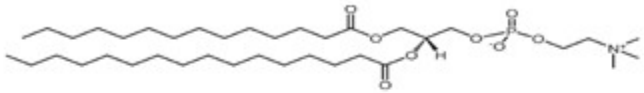
Targeted metabolomics @Hauner Munich

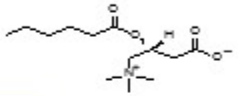


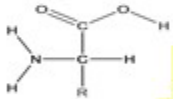
- 50 LPC, 95 PC
- 67 Pcae, 121 SM

⇨ cellular membranes

- 54 free fatty acids

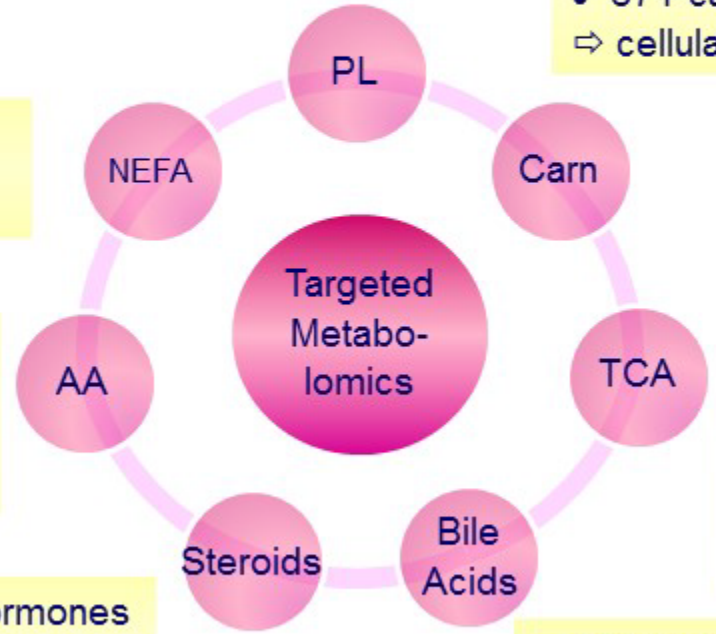
⇨ adipose tissue markers





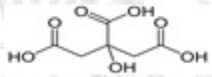
- 20 proteinogenic AA
- citrulline, ornithine

⇨ protein metabolism



- 90 carn-esters
- free carnitine

⇨ peroxisomal & β-oxidation



- organic acids, TCA cycle
- keto acids

⇨ energy metabolism

- 18 steroid hormones

⇨ endocrine regulation

- 17 bile acids

⇨ liver & microbiome

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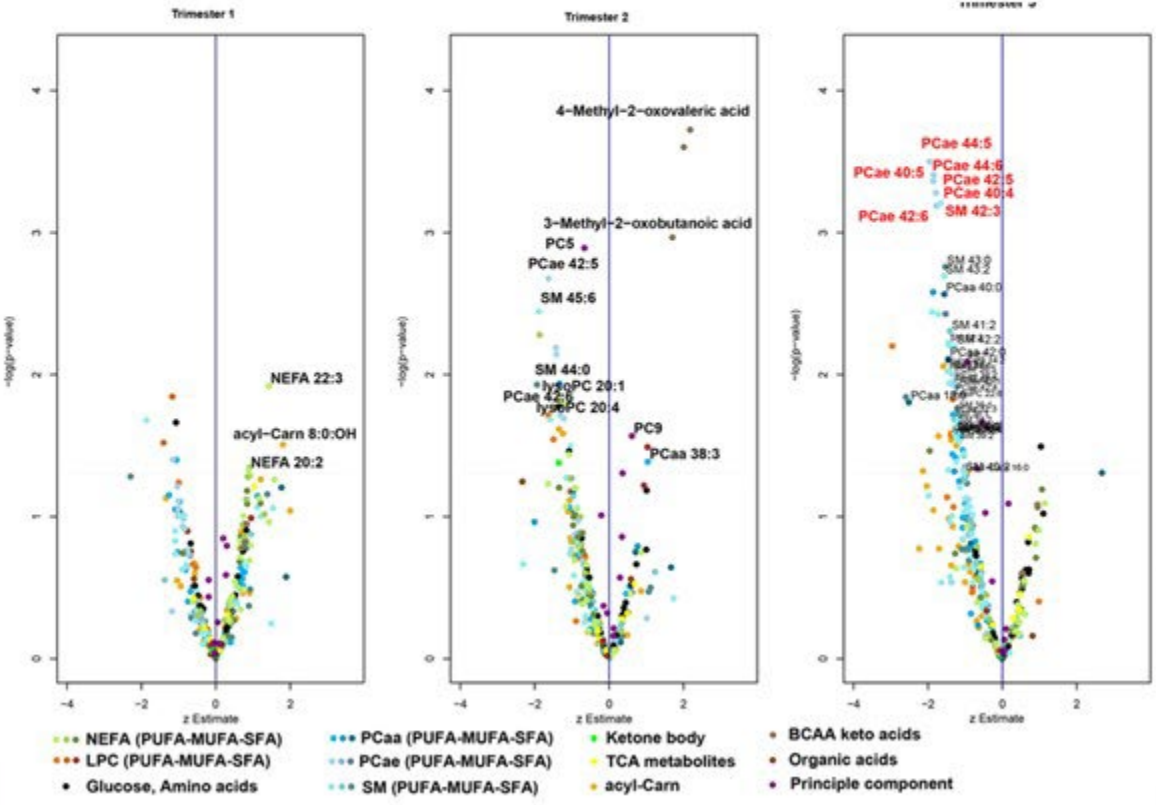
Plasma metabolites in 3 pregnancy trimesters and neonatal adiposity



Six alkyl-linked phosphatidyl-cholines (PCae) with 20:4 significantly associated with neonatal body fat percentage

253 mother infant pairs.
Helmuth C et al, Mol Nutr Food Res. 2019;63(1):e1700889.

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Penalized regression models predicting birthweight

Models	Δ Birthweight SDS (95% CI)	Adjusted R^2 (%)
Prepregnancy BMI	0.03 (0.00; 0.05)	**6.1**

Wahab RJ et al. J Clin Endocrinol Metab 2022;107:e315-27. doi: 10.1210/clinem/dgab596.

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Penalized regression models predicting birthweight

Models	Δ Birthweight SDS (95% CI)	Adjusted R^2 (%)
Prepregnancy BMI	0.03 (0.00; 0.05)	**6.1**
Biomarker model, prepregn. BMI + glucose & lipids	0.02 (0.00; 0.04)	**6.2**

Wahab RJ et al. J Clin Endocrinol Metab 2022;107:e315-27. doi: 10.1210/clinem/dgab596.

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Penalized regression models predicting birthweight

Models	Δ Birthweight SDS (95% CI)	Adjusted R^2 (%)
Prepregnancy BMI	0.03 (0.00; 0.05)	**6.1**
Biomarker model, prepregn. BMI + glucose & lipids	0.02 (0.00; 0.04)	**6.2**
Metabolite model, prepregn. BMI with added metabolome	0.05 (0.03; 0.07)	**12.9**

Wahab RJ et al. J Clin Endocrinol Metab 2022;107:e315-27. doi: 10.1210/clinem/dgab596.

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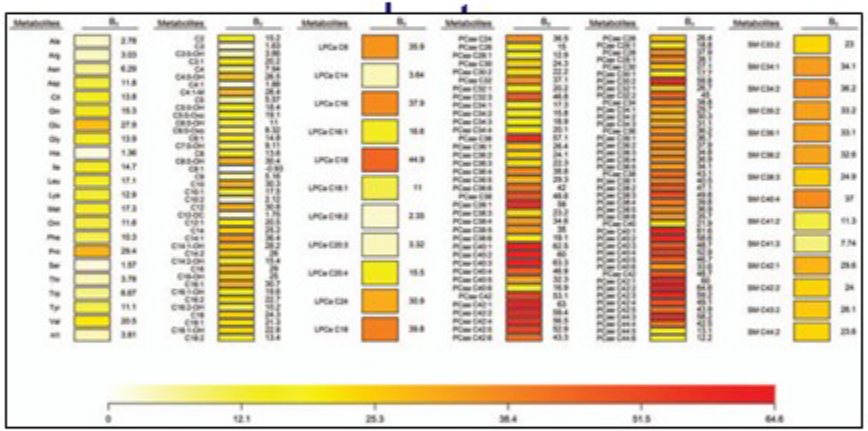
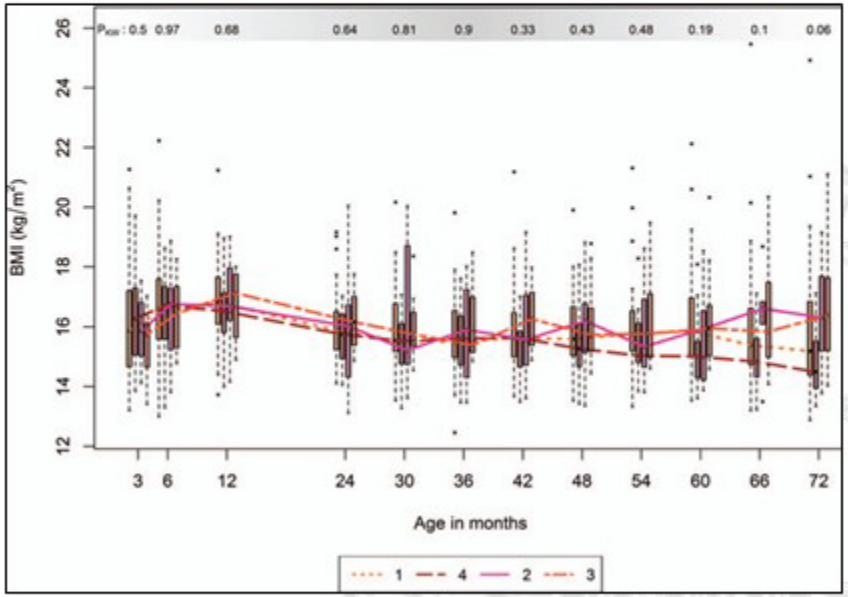
Are all breast-fed infants equal?

Bayesian agglomerative clustering identified 20 metabolite



Major metabolite clusters at 6 mon. predict BMI development to 6 yrs.



183 breastfed infants, 6 mon.
Kirchberg F et al, J PGN. 2019;68:408-15.

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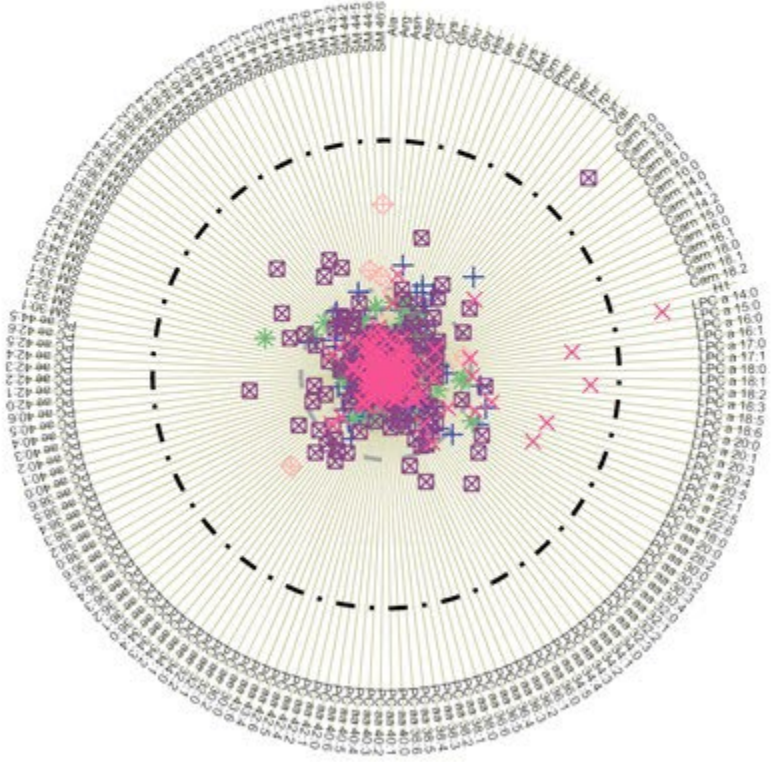
Human milk protein milk protein content predicts infant serum LPC14:0 at 1 mon.



Significance levels:
- α of 0.05
- Bonferroni-corrected α of 0.00027

P-values:
- Milk Fat
- Milk Protein
- Milk Insulin
- Milk Igf
- Milk Adiponectin

196 breastfed infants, 1 mon.
Hellmuth C et al, PloS One. 2018.

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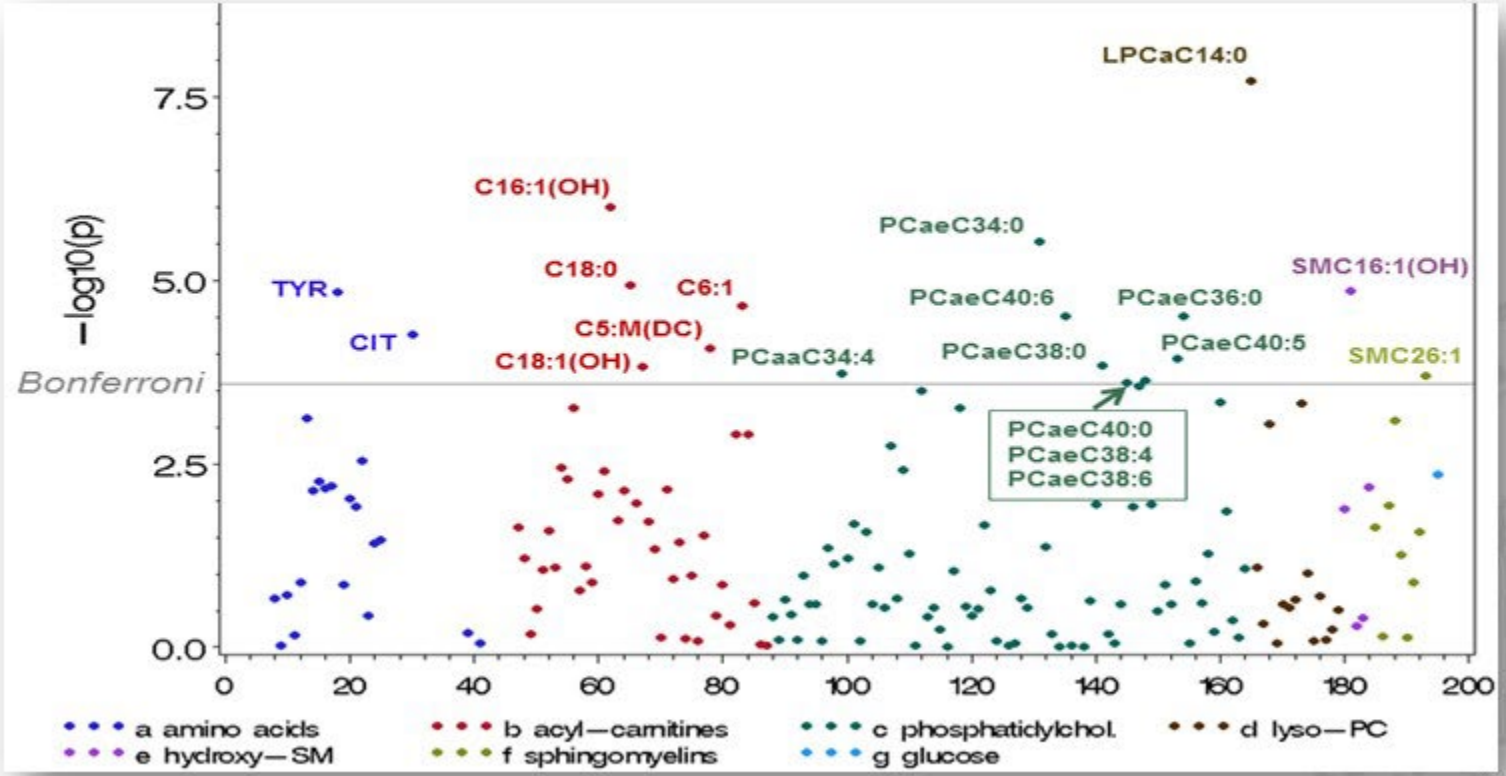
Plasma metabolites predict weight gain

birth to 6 mon. 726 infants, CHOP study



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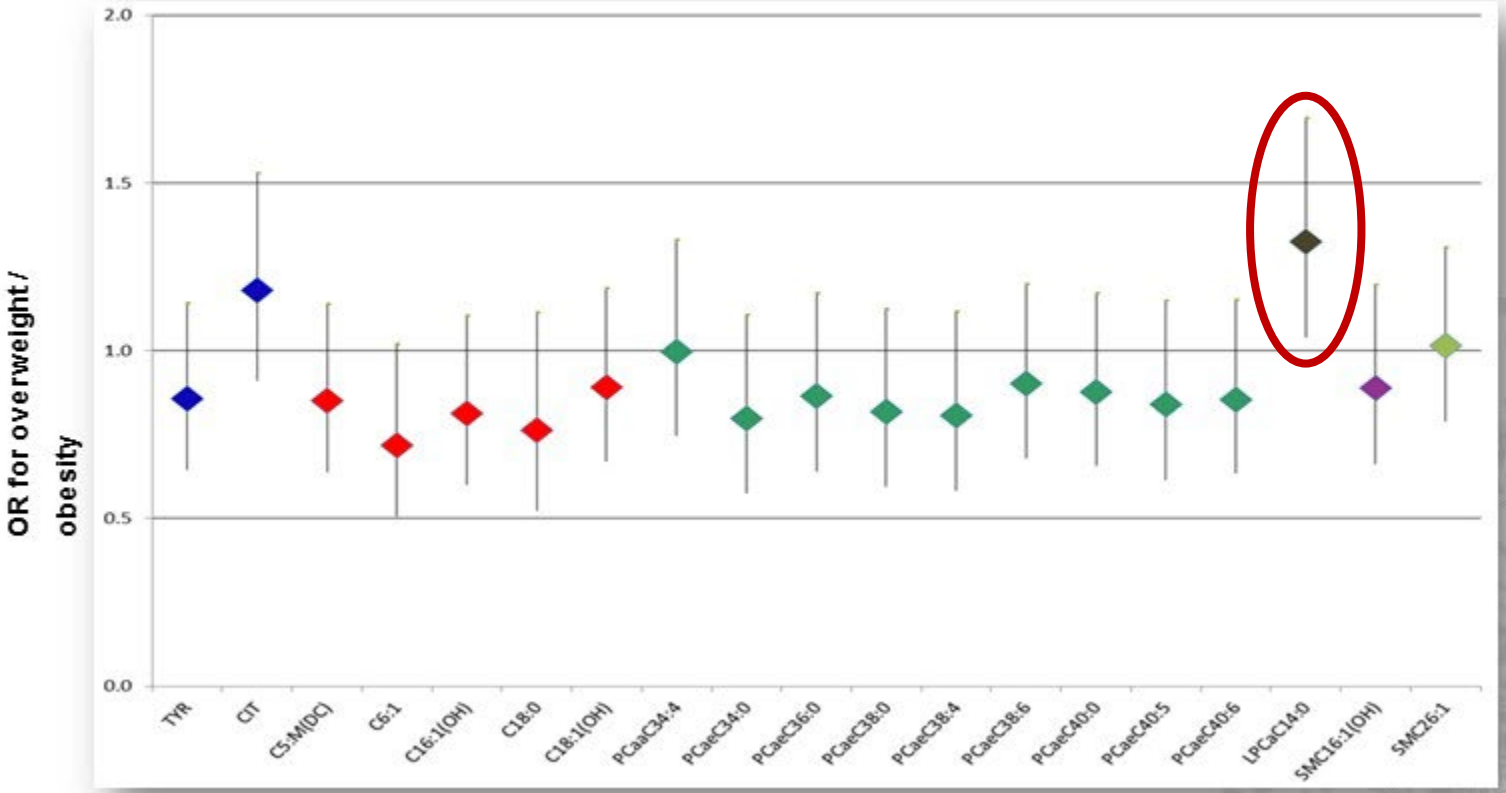
Rzehak P et al. Ann Nutr Metab. 2014.

Infant LPC 14:0 and obesity at school age



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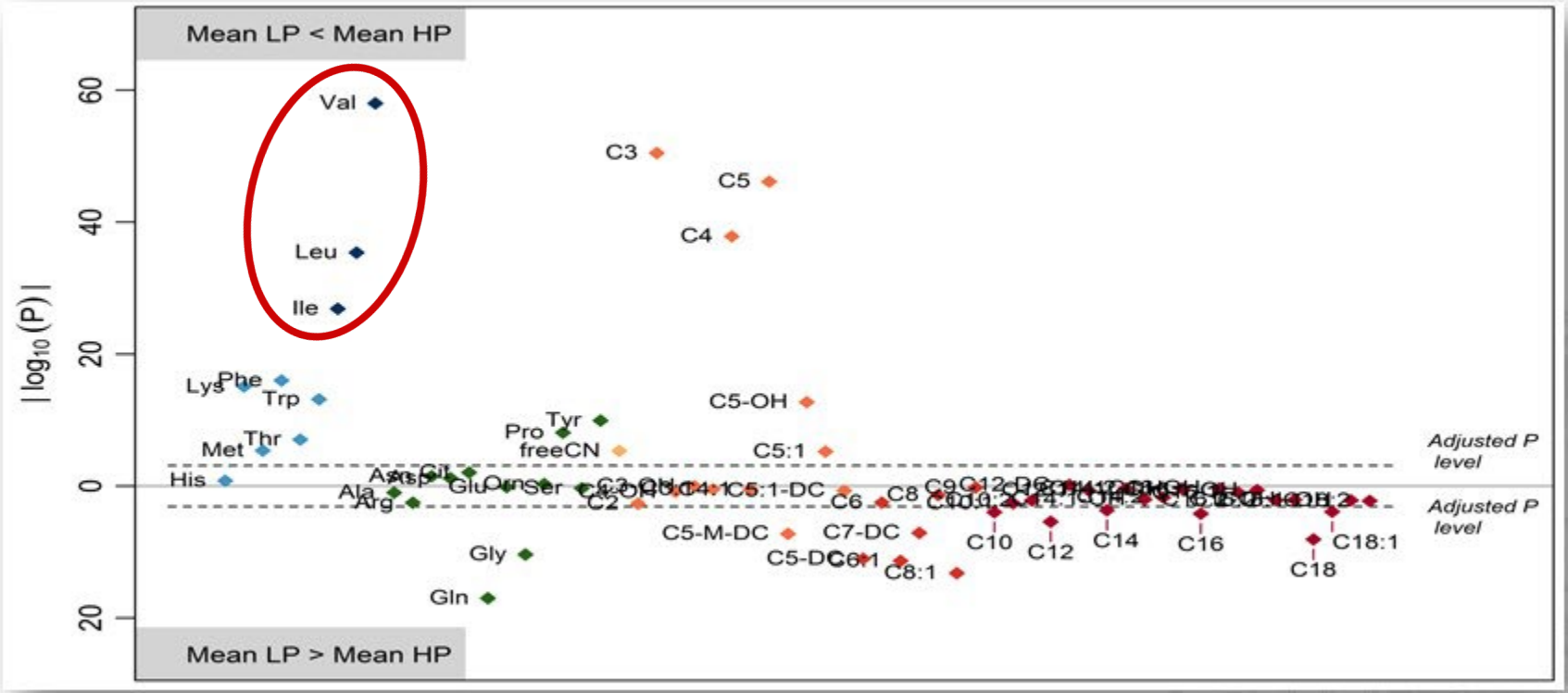
Rzehak P et al. Ann Nutr Metab. 2014.

Formula protein changes metabolites



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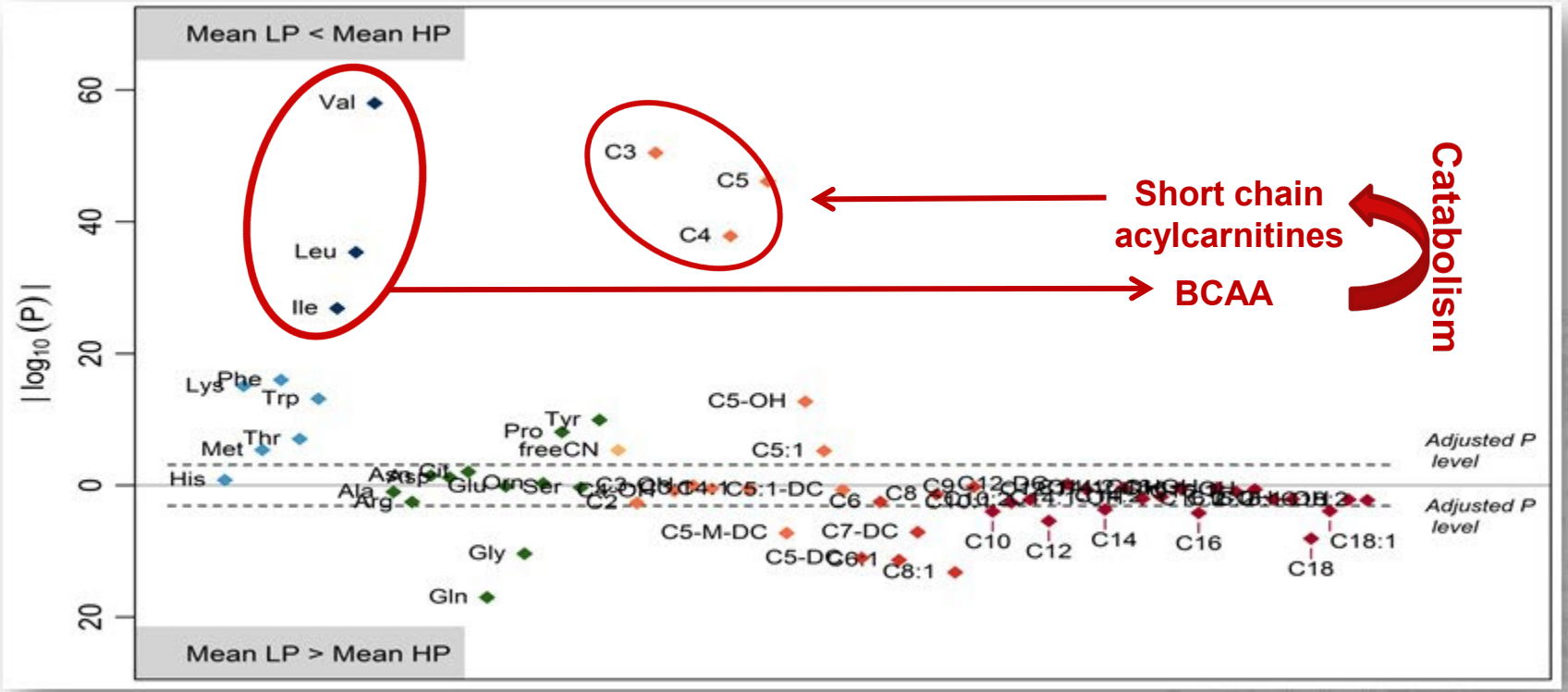
Kirchberg F et al., J Clin Endo Metab. 2015.

DR. VON HAUNERSCHES KINDERSPITAL

Formula protein changes metabolites



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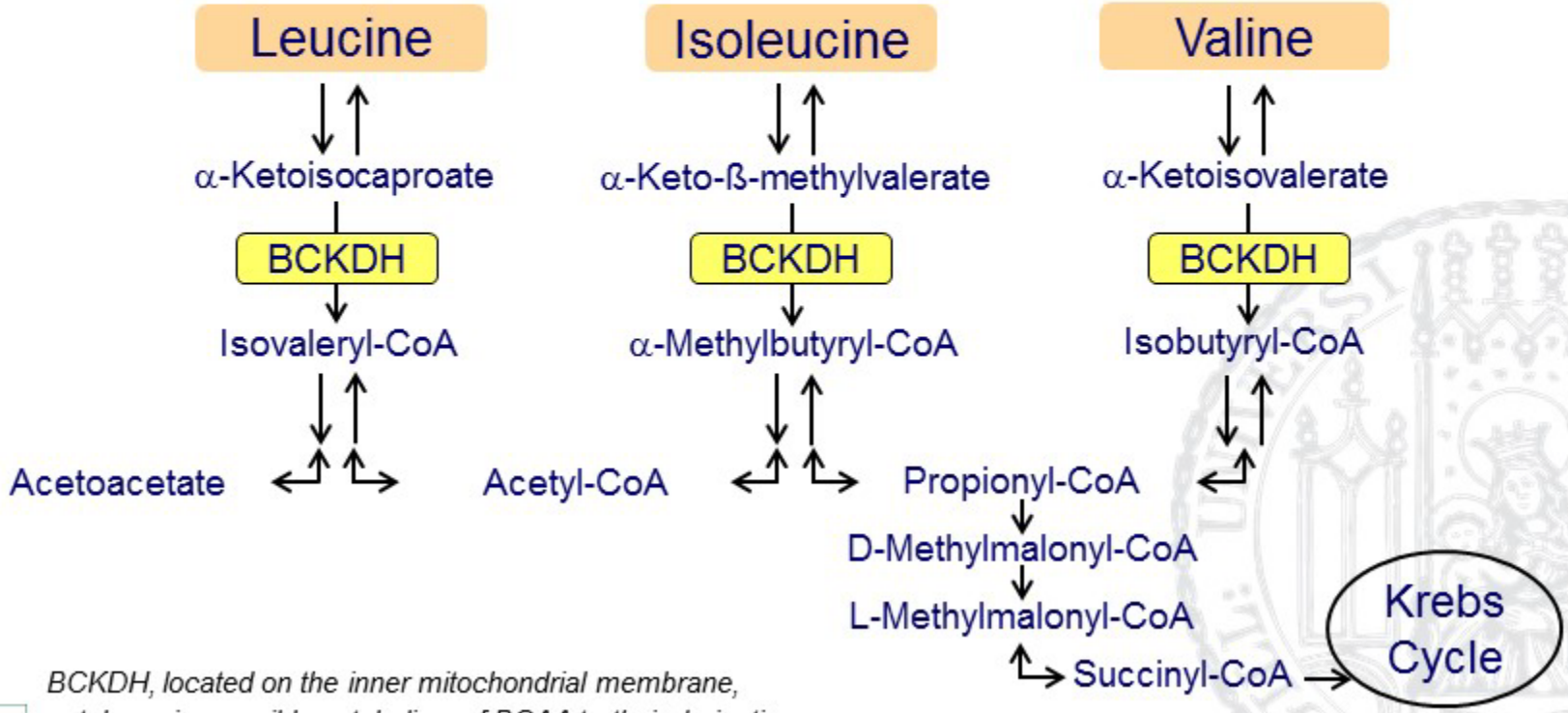
Kirchberg F et al., J Clin Endo Metab. 2015.

Branched-chain α-ketoacid dehydrogenase

(BCKDH)



BCKDH, located on the inner mitochondrial membrane, catalyzes irreversible catabolism of BCAA to their derivatives

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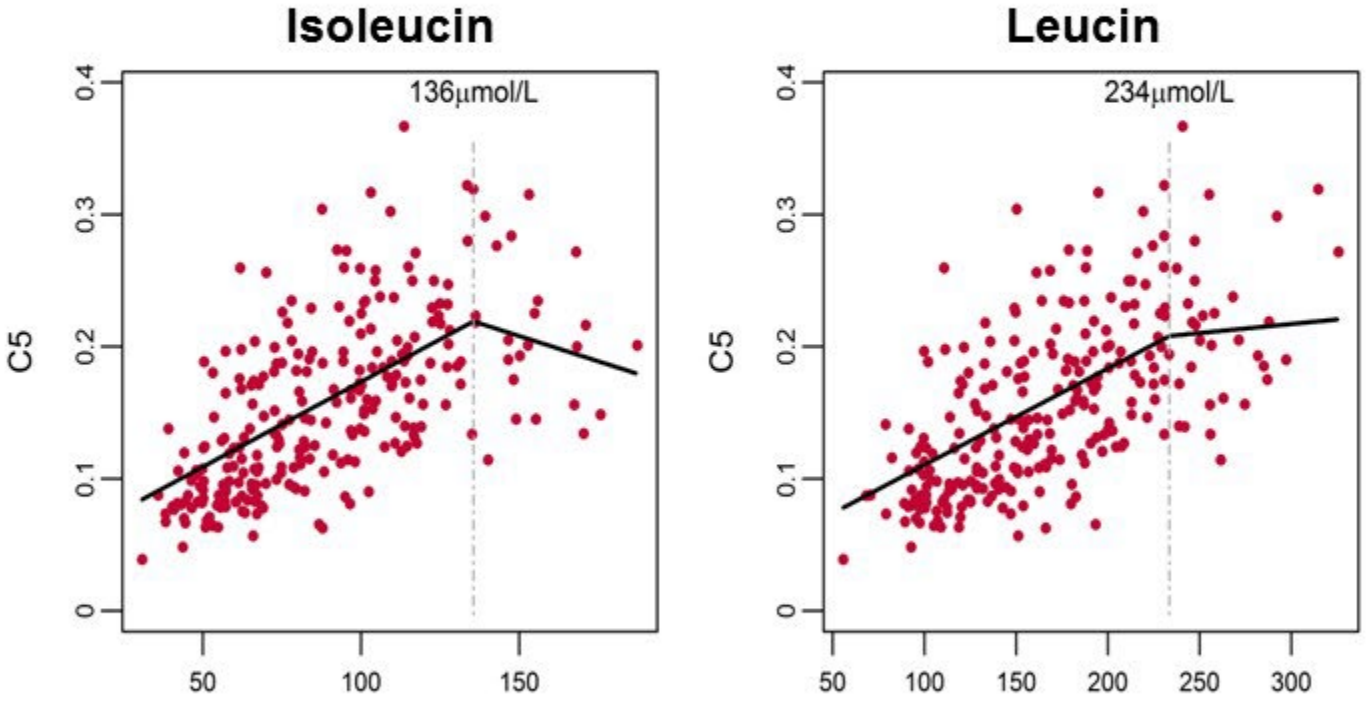
BCKDH capacity limited

exceeded by high protein intake



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Kirchberg F et al., J Clin Endo Metab. 2015.

Early nutrition matters for growth and later health, exploring mechanisms is important

- Early nutrition and metabolism markedly modulates growth, body composition, later health, performance & disease risk
- Exploring underlying mechanisms may improve targeted and even more impactful preventive interventions
- Implementation of evidence based early nutrition practices has great benefits and a large return of investment

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Thanks to you for your kind attention, and to a great team of colleagues and friends at LMU

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