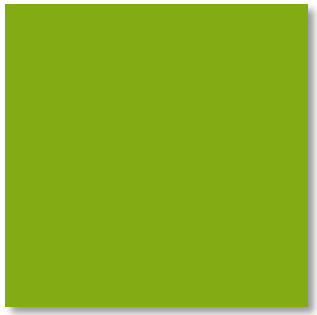
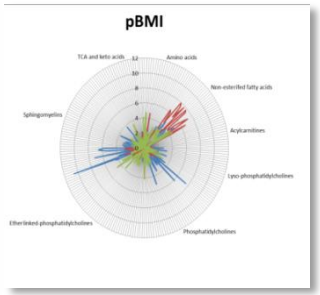
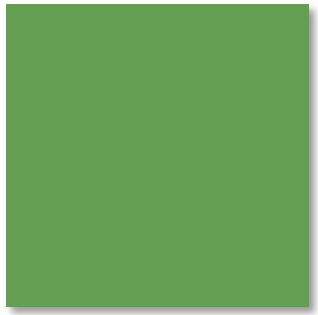
LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

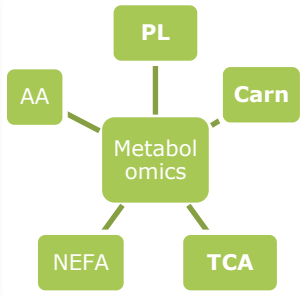
EARLY NUTRITION, METABOLIC EFFECTS AND LONG-TERM HEALTH

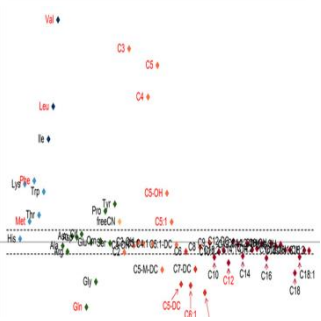
Olaf Uhl

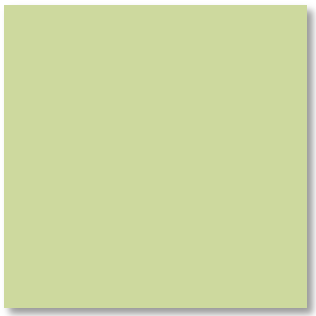












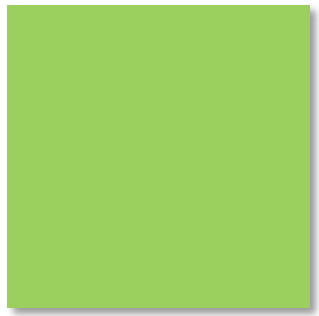


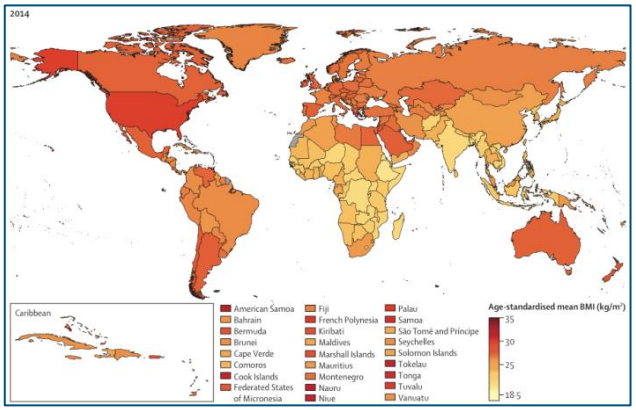
TABLE OF CONTENT

EARLY PROGRAMMING

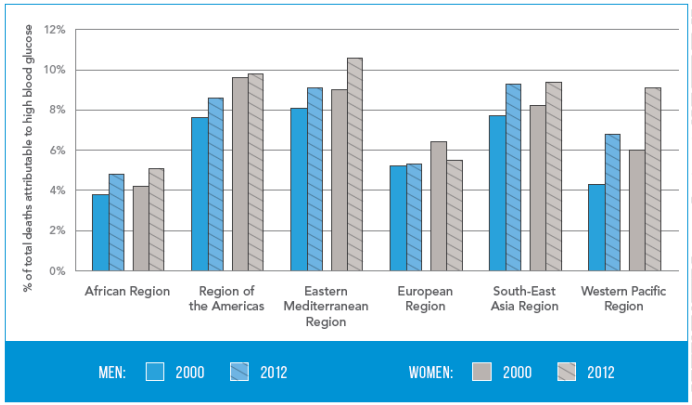
OBESITY PANDEMIC

- Increase of mean BMI from 1975 to 2014:
  - 21.7 to 24.2 kg/m^2 in men
  - 22.1 to 24.4 kg/m^2 in women
- Prevalence of obesity reached 10.8% in men and 14.9% in women in 2014
- In 2014 more obese than underweight
- Diabetes caused 1.5 million deaths in 2012
- additional 2.2 million deaths by cardiovascular and other diseases

Obesity prevalence

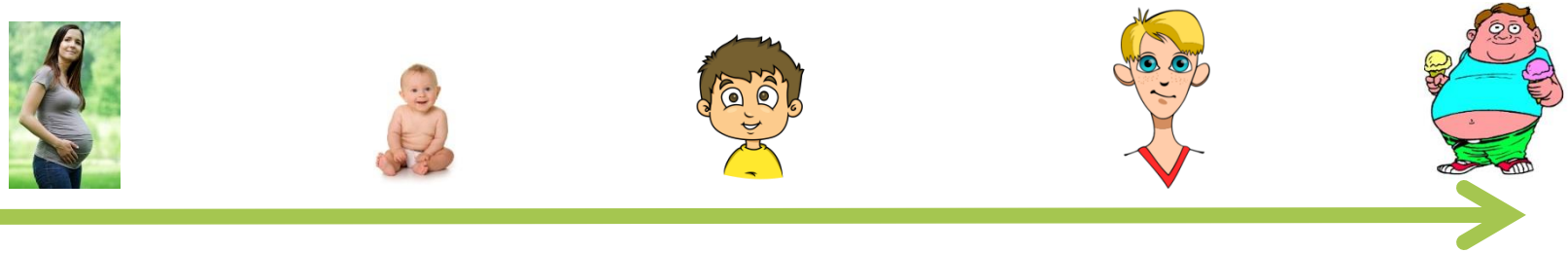


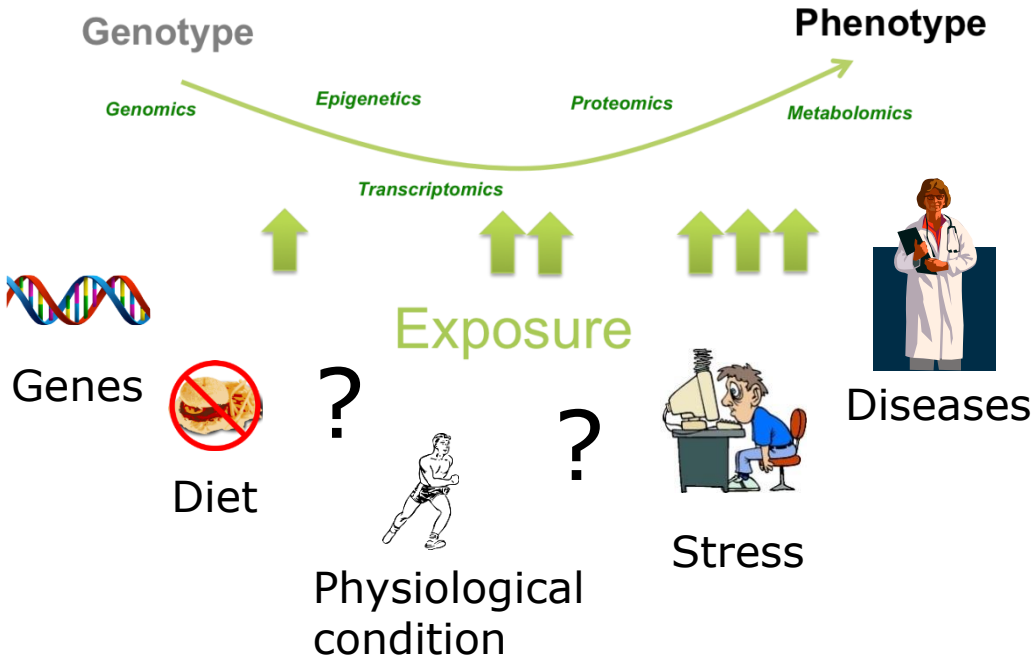
Percentage of all deaths attributable to high blood glucose for adults

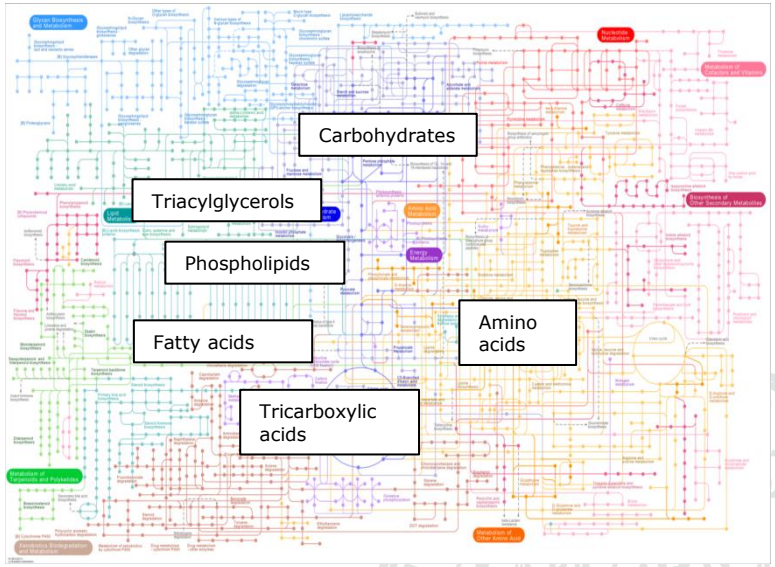


Ng et al., Lancet, 2016, 387(10026):1377-96.
WHO, Global Report on Diabetes, 2016

METABOLIC PROFILING

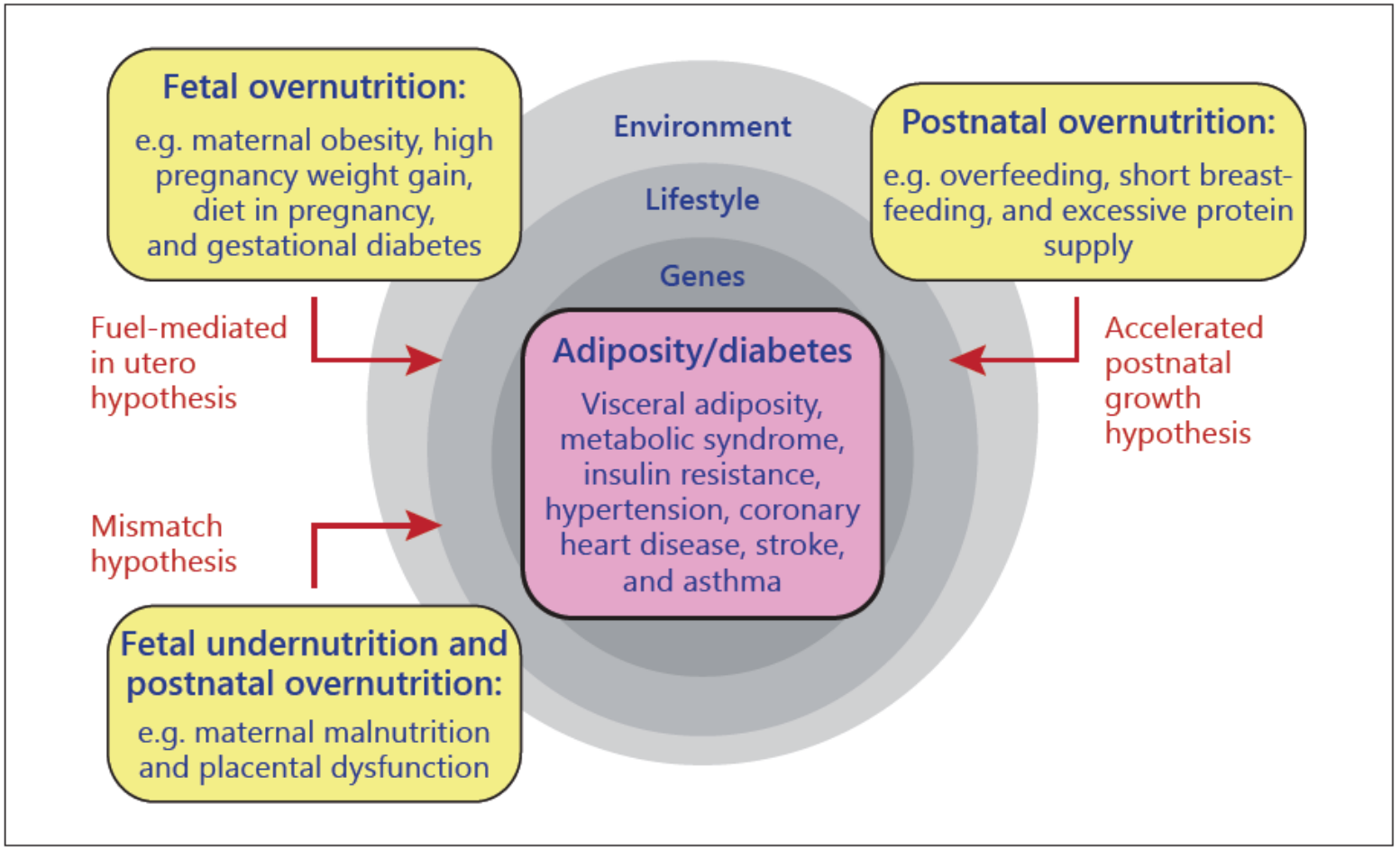






http://www.kegg.jp/

EARLY PROGRAMMING HYPOTHESES



Koletzko et al., Ann Nutr Metab, 2014, 64(3-4):187-96

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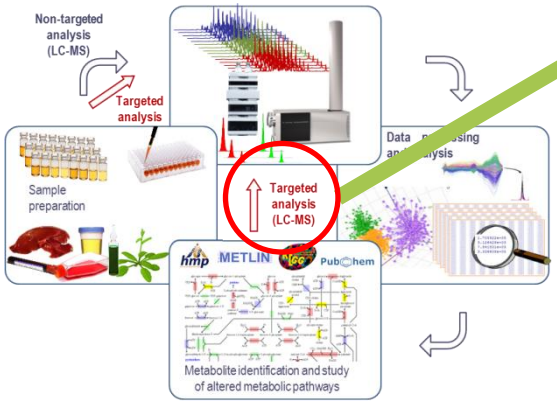
CLINICAL TARGETED METABOLOMICS

CLINICAL TARGETED METABOLOMICS

- Metabolomics = determination of metabolites:
  - substrates, intermediates or products of biological processes
  - small molecules (<1.5 KDa)
- Metabolome = Complete set of metabolites within a biological sample

Untargeted Metabolomics

- Registers all ions within a certain mass range

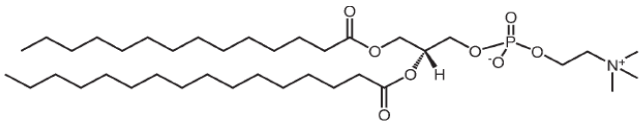


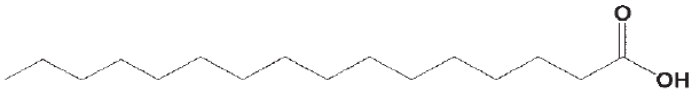
Targeted Metabolomics

- Measure of ions from known metabolites
- Absolute quantification (µmol/L)
- Specific:
  - Chromatographic seperation
  - Molecular fragmentation
- Sensitive

CLINICAL TARGETED METABOLOMICS

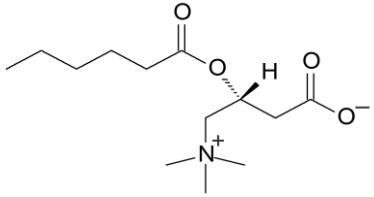
Phospholipids
→Lipid intake



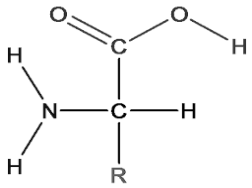


Non-esterified fatty acids
→Adipose tissue

Acylcarnitines
→ß-Oxidation
→Amino acid oxidation

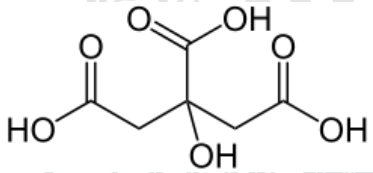


Clinical Targeted Metabolomics



Amino acids
→Proteins

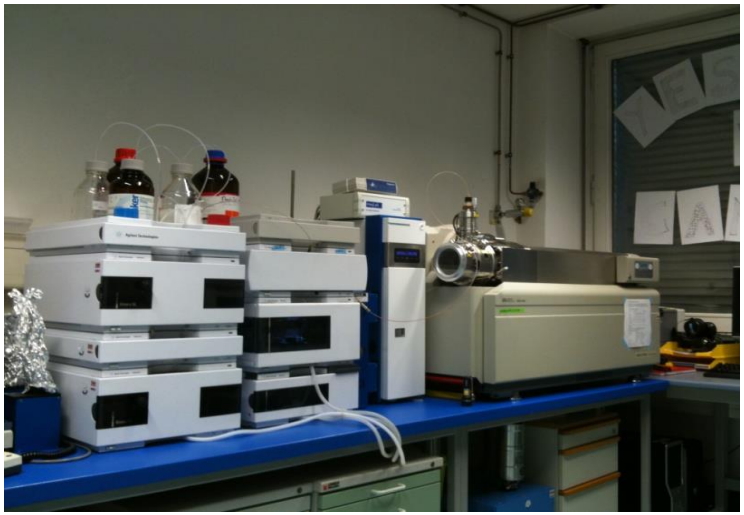
Organic acids
→Citric acid cycle



SAMPLE PREPARATION

CLINICAL TARGETED METABOLOMICS

4000 QTrap

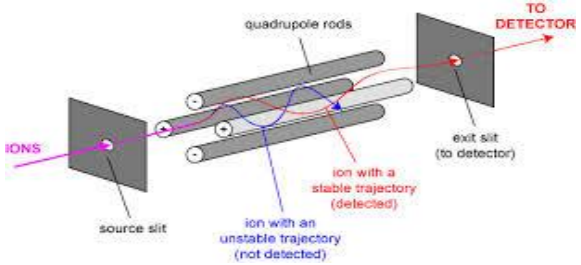


- Phospholipids (PL)
- Acylcarnitines (CARN)
- Nonesterifed fatty acids (NEFA)
- Tricarboxylic acids (TCA)

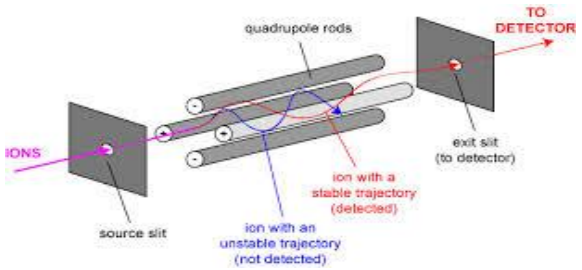
API 2000

- Amino Acids (AA)

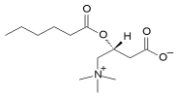
TRIPLE QUADRUPOLE MASS SPECTROMETRY

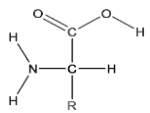


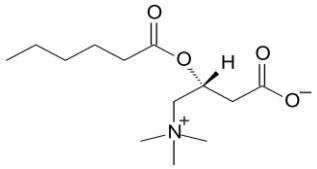
Collision Cell

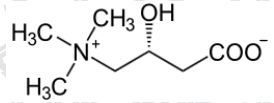


1 mass transition









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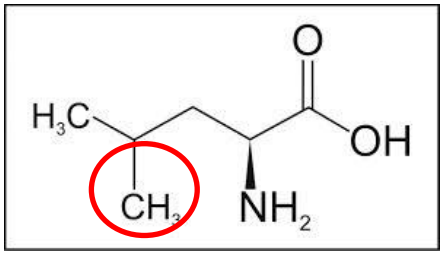
CHROMATOGRAPHIC SEPERATION

Leucine

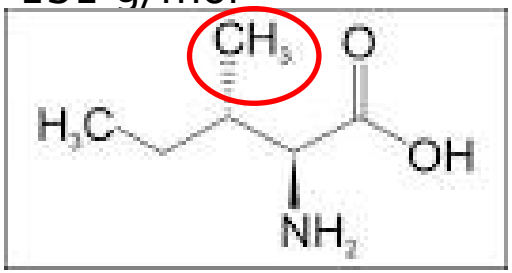
- 131 g/mol



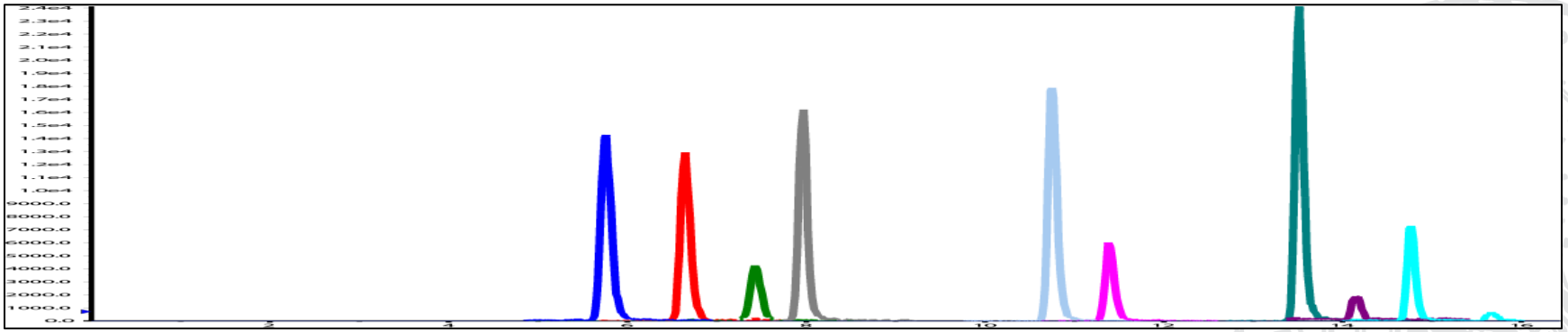
- Fragment: 86 g/mol

Isoleucine

- 131 g/mol



- Fragment: 86 g/mol



QUALITY CONTROL SAMPLES

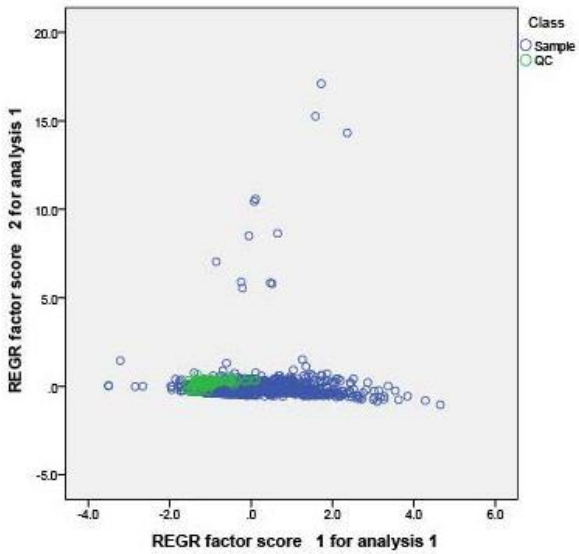
- Monitor the performance of a method
- Providing information about analytical precision

Best choice:

1. Pool of all samples
2. Surrogate, comparable to samples
   - Matrix (e.g. liver QC for liver samples)
   - Amount (adult plasma QC for adult plasma)
3. QC for internal analytical control, without any meaning to samples

--> Measurement of QC aliquots throughout the analytical measurement: 6 aliquots per 81 samples = Batch

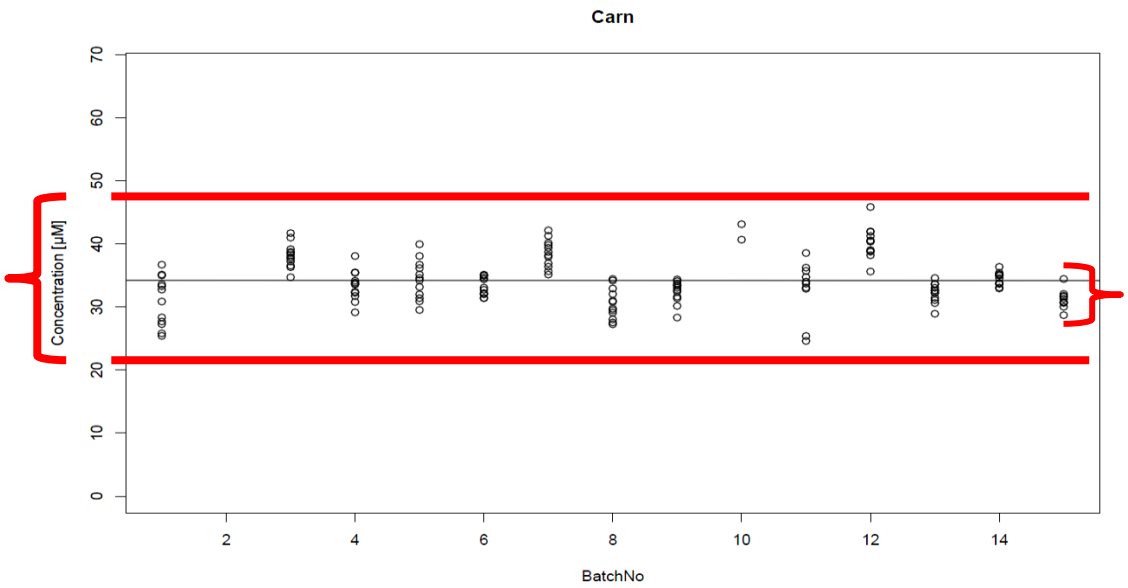
PCA



Sangster et al., Analyst, 2006

PRECISION

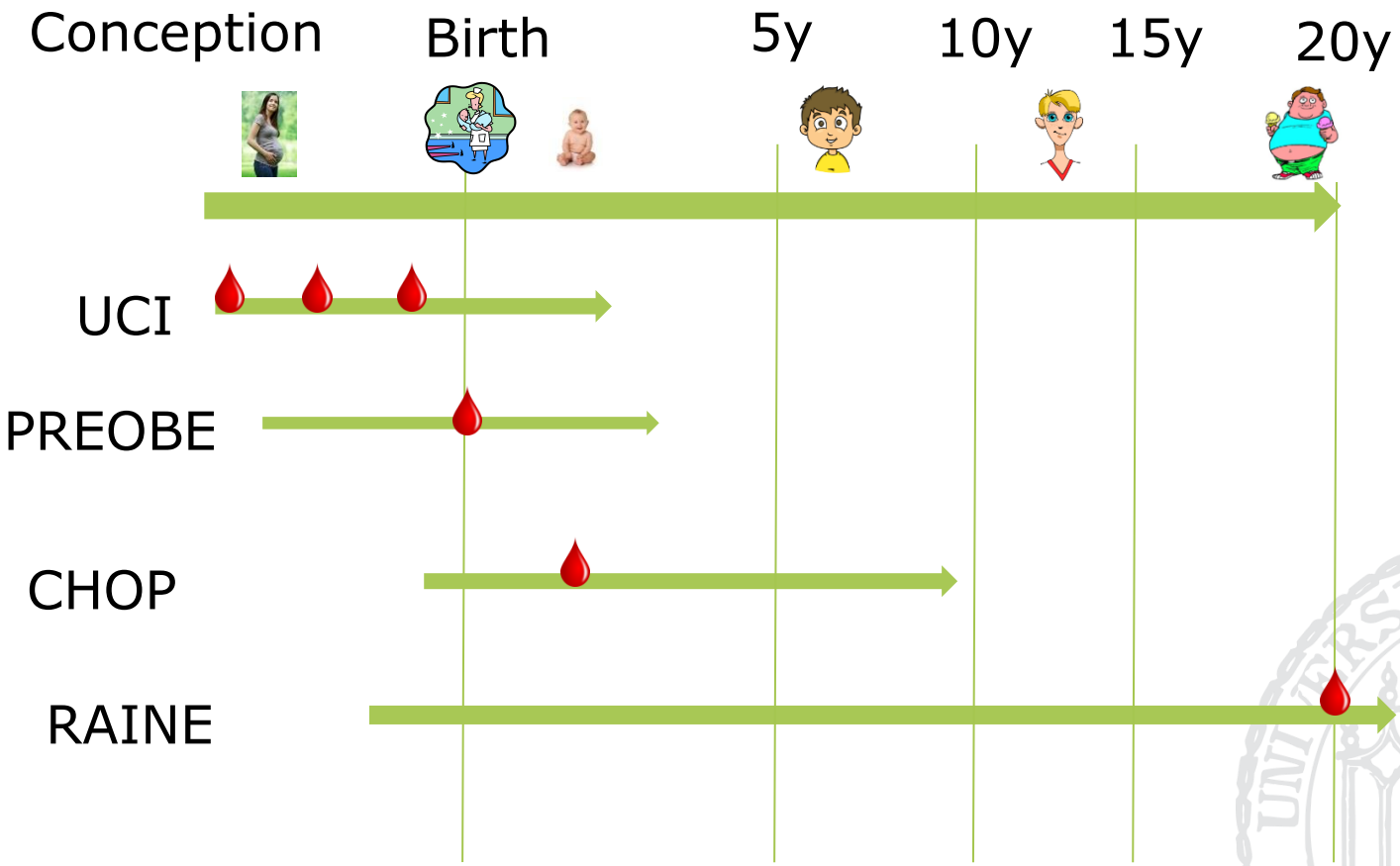
Inter-batch Precision
→ precision with time over all batches



Intra-batch Precision
→ precision within one batch

RESULTS FROM COHORT STUDIES AND INTERVENTIONAL TRIALS

RESULTS FROM COHORT STUDIES AND INTERVENTIONAL TRIALS



UCI COHORT

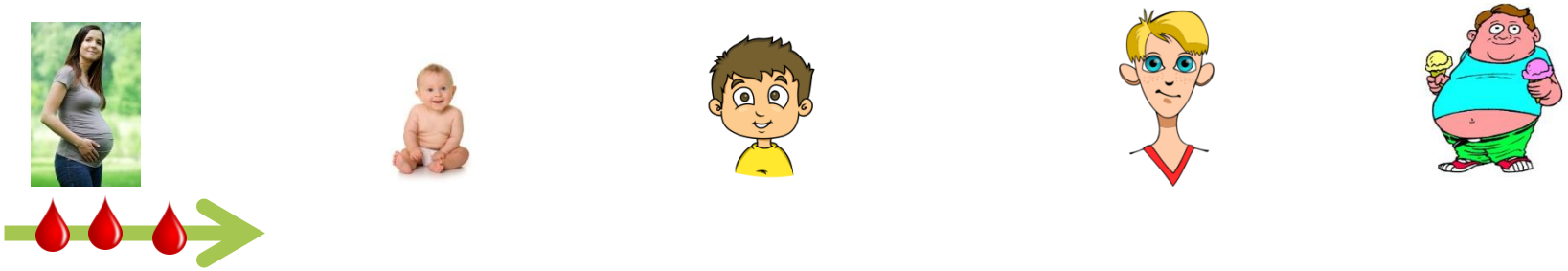
ACCEPTED ARTICLE PREVIEW

Accepted Article Preview: Published ahead of advance online publication

Association of maternal pre-pregnancy BMI with metabolomic profile across gestation

C Hellmuth, K L Lindsay, O Uhl, C Buss, P D Wadhwa, B Koletzko, S Entringer

UCI COHORT



- Pregnant women were recruited at the at the University of California Irvine (UCI)

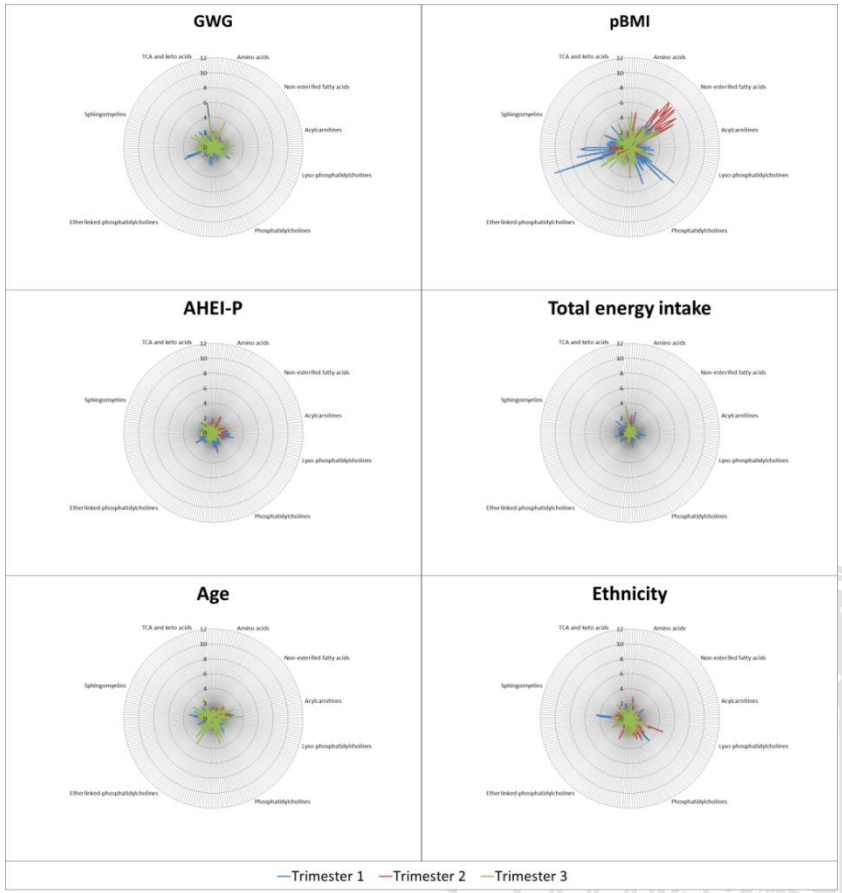
- Plasma samples of 160 pregnant woman at
  - 10 - 12 weeks of gestation
  - 20 - 22 weeks of gestation
  - 30 - 31 weeks of gestation

- Influence of maternal metabolism by:
  - Stress, ethnicity, pre-pregnancy BMI, diet, gestational weight gain

Hellmuth et al., Int J Obesity, acceptepd

UCI COHORT

- No significane association of AHEI-P index (quality) and total energy intake (quantitiy)
- Pre-pregnancy BMI ~ NEFA in trimester 2
- Pre-pregnancy BMI ~ DGLA species :
  - LPC 20:3
  - NEFA 20:3
  - PC(30:3)
  - PC(32:3)
  - PC(38:3)
- weak associations between maternal metabolites and birthweight (NEFA+, LPC-)



Hellmuth et al., Int J Obesity, acceptepd

PREOBE

DIABETES RESEARCH AND CLINICAL PRACTICE 109 (2015) 364–371

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

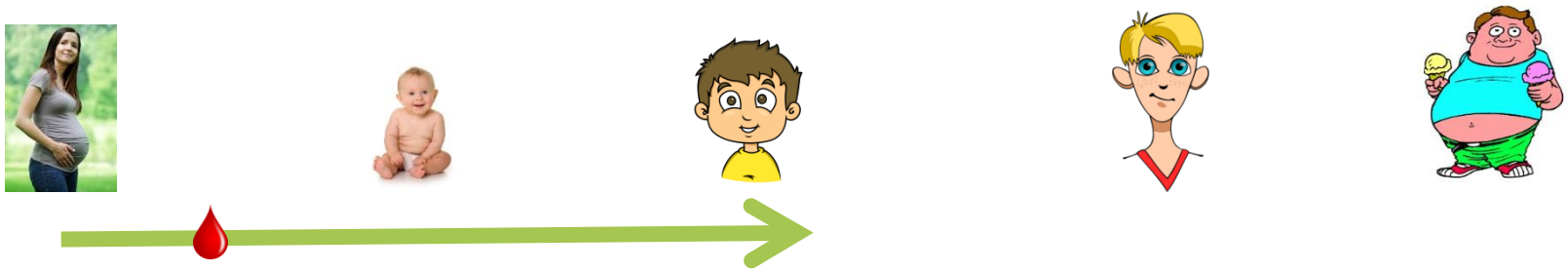
journal homepage: www.elsevier.com/locate/diabres

Effects of obesity and gestational diabetes mellitus on placental phospholipids

Olaf Uhl[a], Hans Demmelmair[a], María Teresa Segura[b], Jesús Florido[c], Ricardo Rueda[d], Cristina Campoy[b,e,1], Berthold Koletzko[a,1,*]

[a] Division of Metabolic and Nutritional Medicine, Dr. von Hauner Children's Hospital, University of Munich Medical Center, Munich, Germany
[b] EURISTIKOS Excellence Centre for Paediatric Research, University of Granada, Spain
[c] Department of Obstetrics and Gynecology, Granada's University Hospital San Cecilio, Granada, Spain
[d] Strategic Research Department, Abbott Nutrition, Granada, Spain
[e] Department of Pediatrics, School of Medicine, University of Granada, Granada, Spain

PREOBE



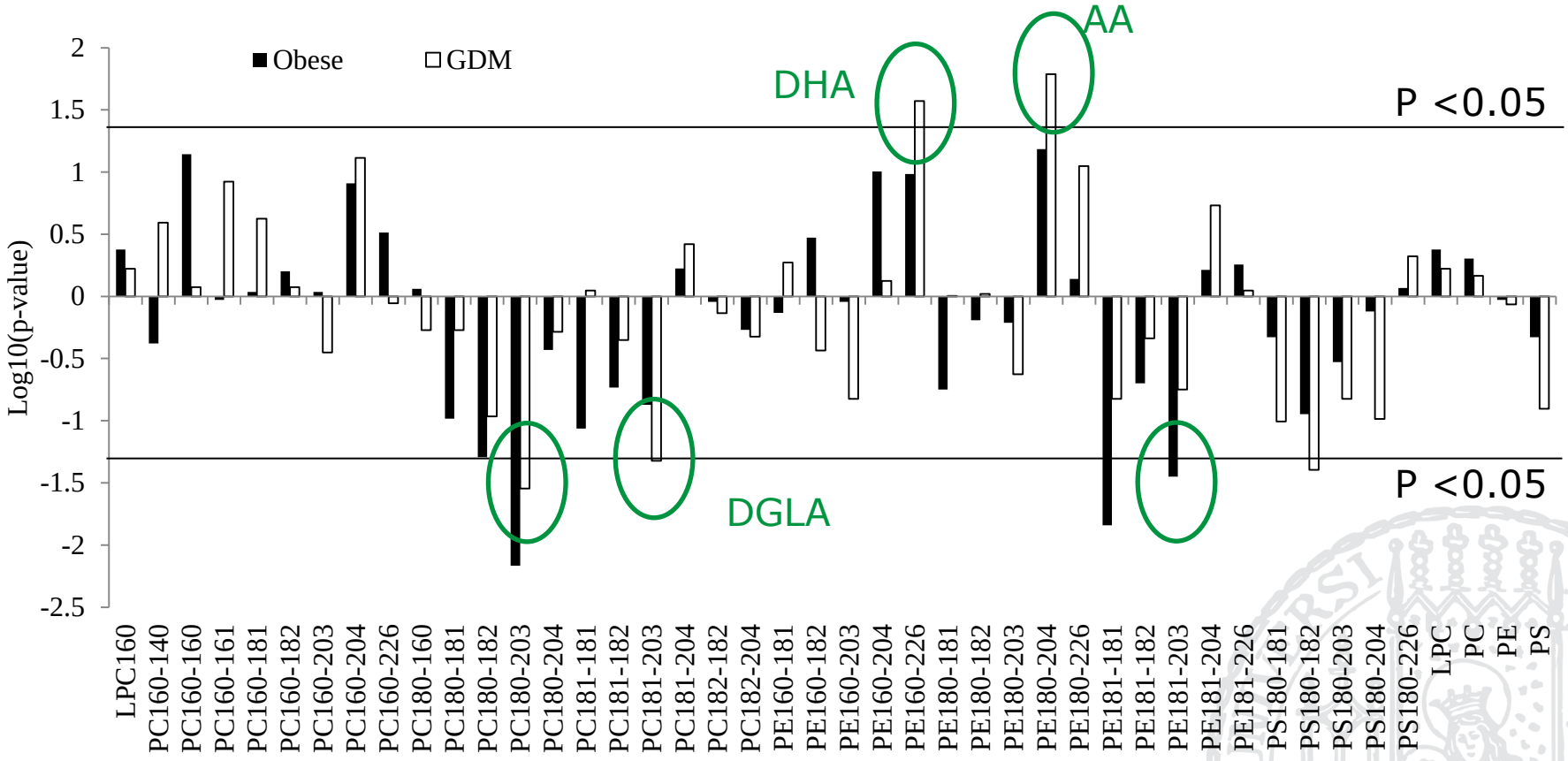
- Pregnant women were recruited at the 20th week of gestation at the University of Granada

- subjects were divided in different groups:
  - Controls: BMI < 25 kg/m^2, normal OGTT
  - Obese: BMI > 30 kg/m^2, normal OGTT
  - GDM: BMI < 25 kg/m^2, abnormal OGTT

- Placenta tissue was analyzed for phospholipids from 63 subjects

Uhl et al., Diab Res Clin Prac, 2015

GPL PATTERN OF GDM AND OBESE IN COMPARISON TO CONTROLS



Uhl et al., Diab Res Clin Prac, 2015

CHOP

ORIGINAL ARTICLE

Endocrine Research

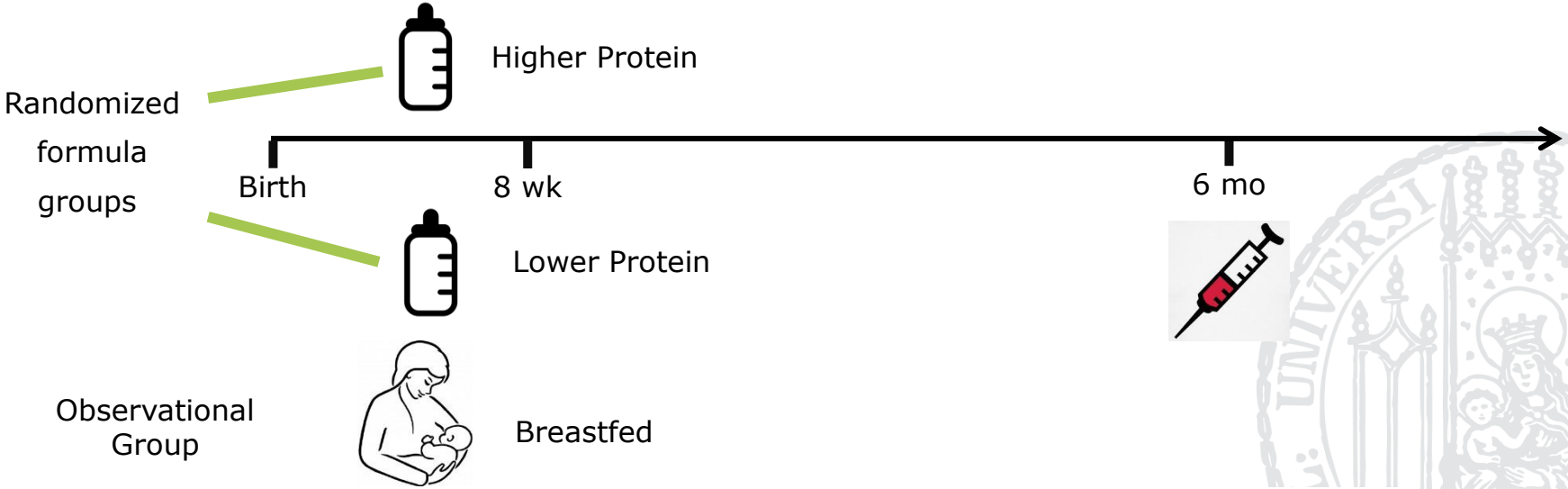
Dietary Protein Intake Affects Amino Acid and Acylcarnitine Metabolism in Infants Aged 6 Months

Franca F. Kirchberg, Ulrike Harder, Martina Weber, Veit Grote, Hans Demmelmair, Wolfgang Peissner, Peter Rzehak, Annick Xhonneux, Clotilde Carlier, Natalia Ferre, Joaquin Escribano, Elvira Verduci, Piotr Socha, Dariusz Gruszfeld, Berthold Koletzko,* and Christian Hellmuth,* for The European Childhood Obesity Trial Study Group

Division of Metabolic and Nutritional Medicine (F.F.K., U.H., M.W., V.G., H.D., W.P., P.R., B.K., C.H.), Dr von Hauner Children's Hospital, 80337 Munich, Germany; Centre Hospitalier Chrétien St Vincent (A.X.), 4000 Liège-Rocourt, Belgium; Department of Paediatrics (C.C.), University Children's Hospital Queen Fabiola, Université Libre de Bruxelles, 1020 Brussels, Belgium; Paediatrics Research Unit (N.F., J.E.), Universitat Rovira i Virgili, 43201 Reus, Spain; Department of Paediatrics (E.V.), San Paolo Hospital, University of Milan, 20142 Milano, Italy; and Neonatal Intensive Care Unit (P.S., D.G.), Children's Memorial Health Institute, 04-736 Warsaw, Poland

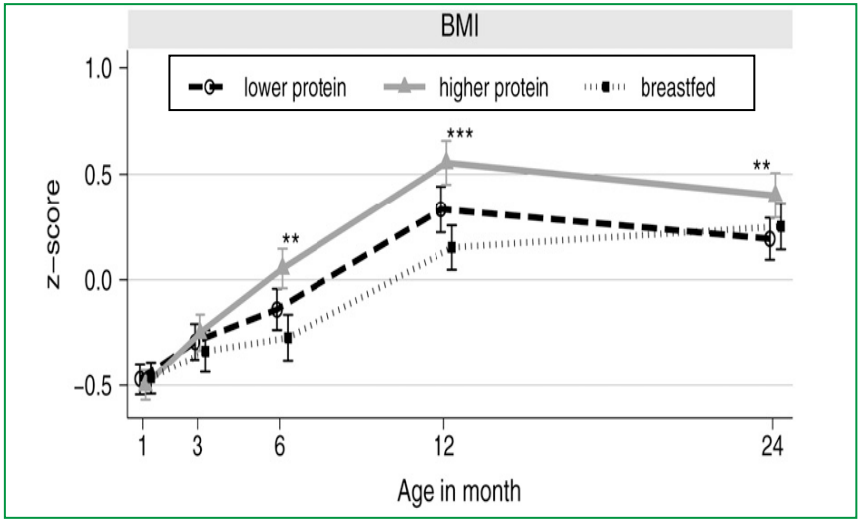
CHOP

European **Ch**ildhood **O**besity **P**roject
5 Coutntries: Belgium, Germany, Italy, Poland, and Spain



Kirchberg et al., J Clin Endocrinol Metab, 2015

CHOP



- Higher protein content is associated with higher weight
- Difference in BMI up to the age of 6 years
- ↑Protein → ↑Insulin/ ↑IGF-I

→ ↑Adipogenic activity?

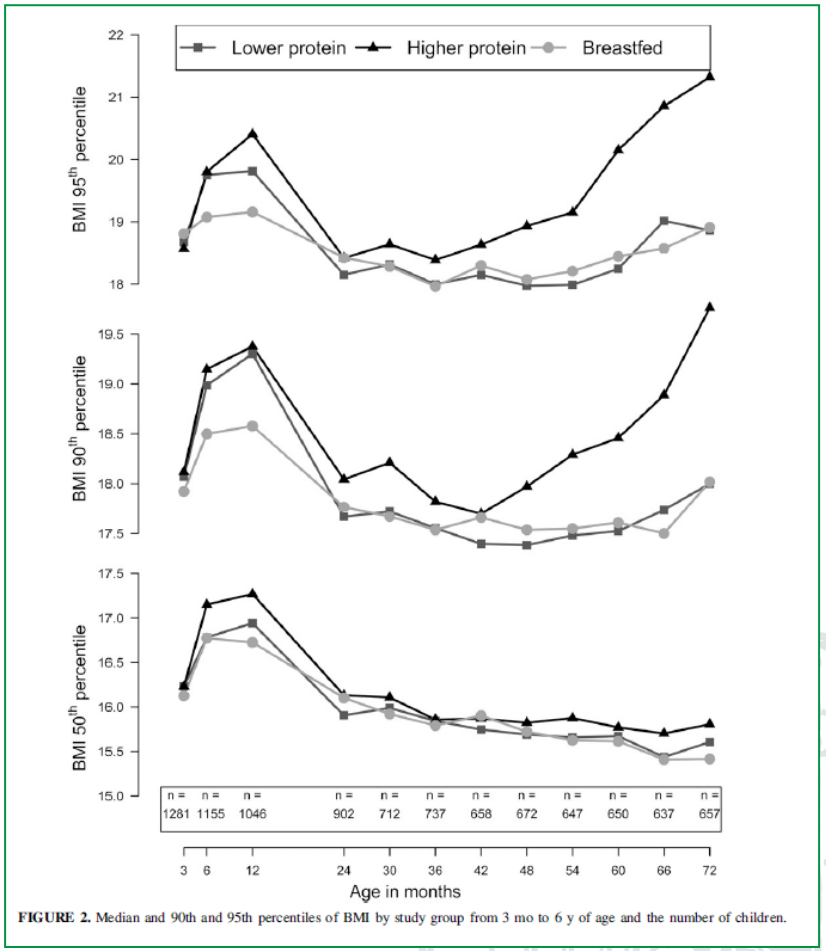
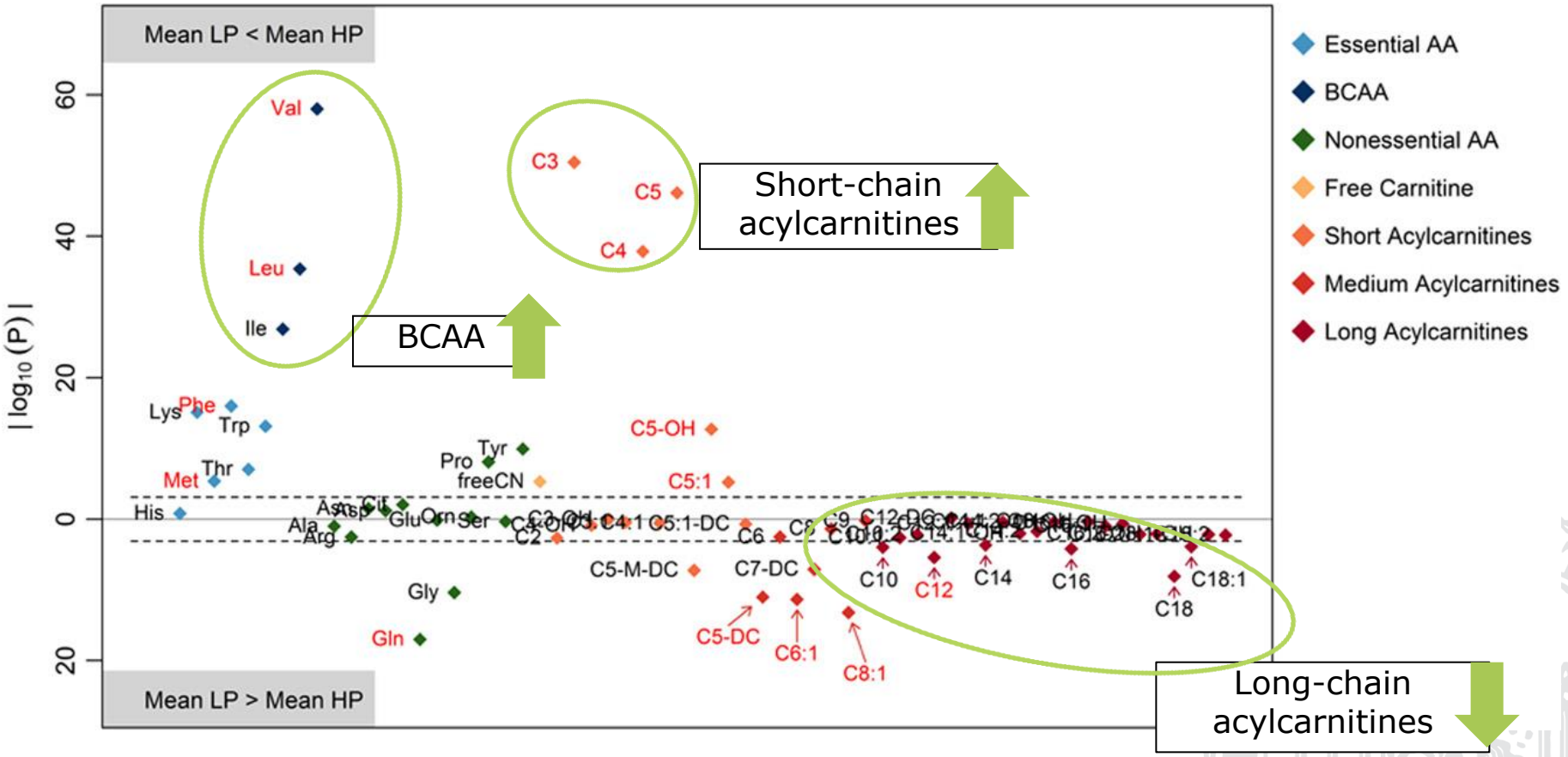


FIGURE 2. Median and 90th and 95th percentiles of BMI by study group from 3 mo to 6 y of age and the number of children.

Koletzko et al., Am J Clin Nutr, 2009, 89(6):1836-45
Weber et al., Am J Clin Nutr, 2014, 99(5):1041-51

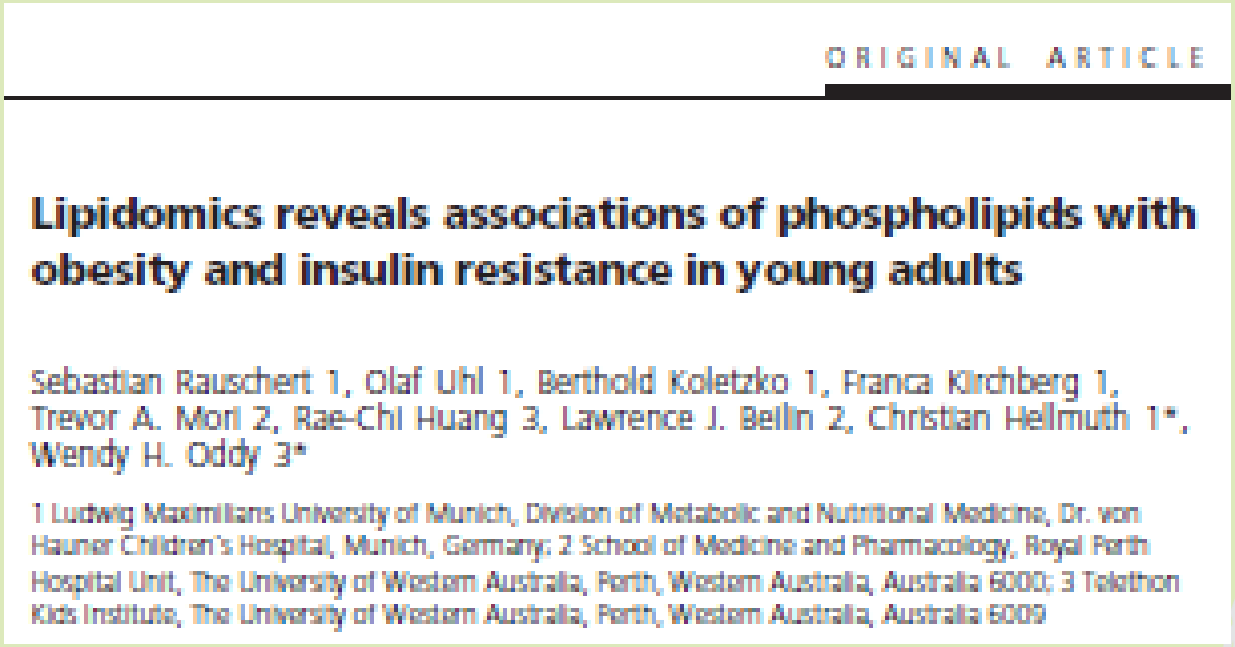
CHOP



P values from univariate linear mixed models with random intercept for study center

Kirchberg et al., J Clin Endocrinol Metab, 2015

RAINE COHORT



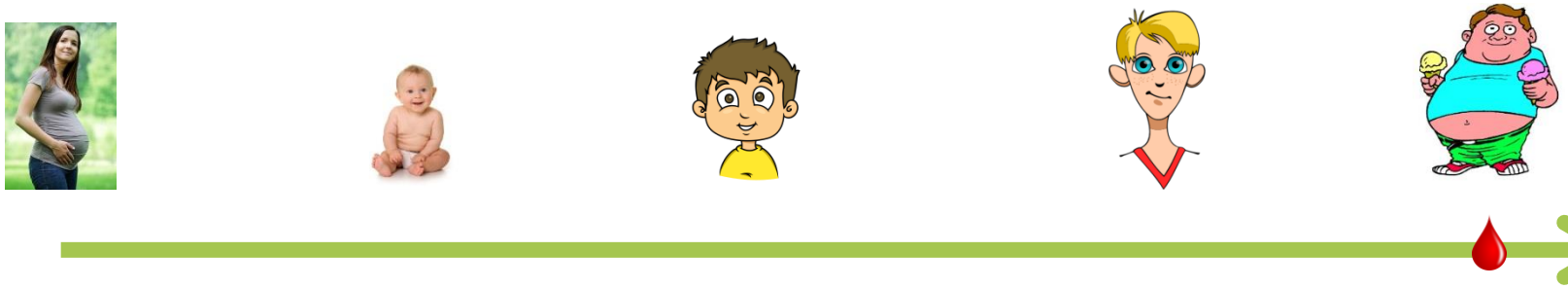
ORIGINAL ARTICLE

Lipidomics reveals associations of phospholipids with obesity and insulin resistance in young adults

Sebastian Rauschert 1, Olaf Uhl 1, Berthold Koletzko 1, Franca Kirchberg 1, Trevor A. Mori 2, Rae-Chi Huang 3, Lawrence J. Beilin 2, Christian Hellmuth 1*, Wendy H. Oddy 3*

1 Ludwig Maximilians University of Munich, Division of Metabolic and Nutritional Medicine, Dr. von Hauner Children's Hospital, Munich, Germany; 2 School of Medicine and Pharmacology, Royal Perth Hospital Unit, The University of Western Australia, Perth, Western Australia, Australia 6000; 3 Telethon Kids Institute, The University of Western Australia, Perth, Western Australia, Australia 6009

RAINE COHORT



The Western Australian Pregnancy Cohort (RAINE) Study

- Prospective longitudinal pregnancy cohort study to examine effects of multiple ultrasound imaging
- Started 1989 → ongoing
- 1172 Blood samples of the 20y follow up
- Metabolites determined:
    - Lyso-Phospholipids
    - Phospholipids
    - Sphingomyelines
    - Non-Esterified fatty acids

Rauschert et al., J Clin Endocrinol Metab. 2016

RAINE COHORT

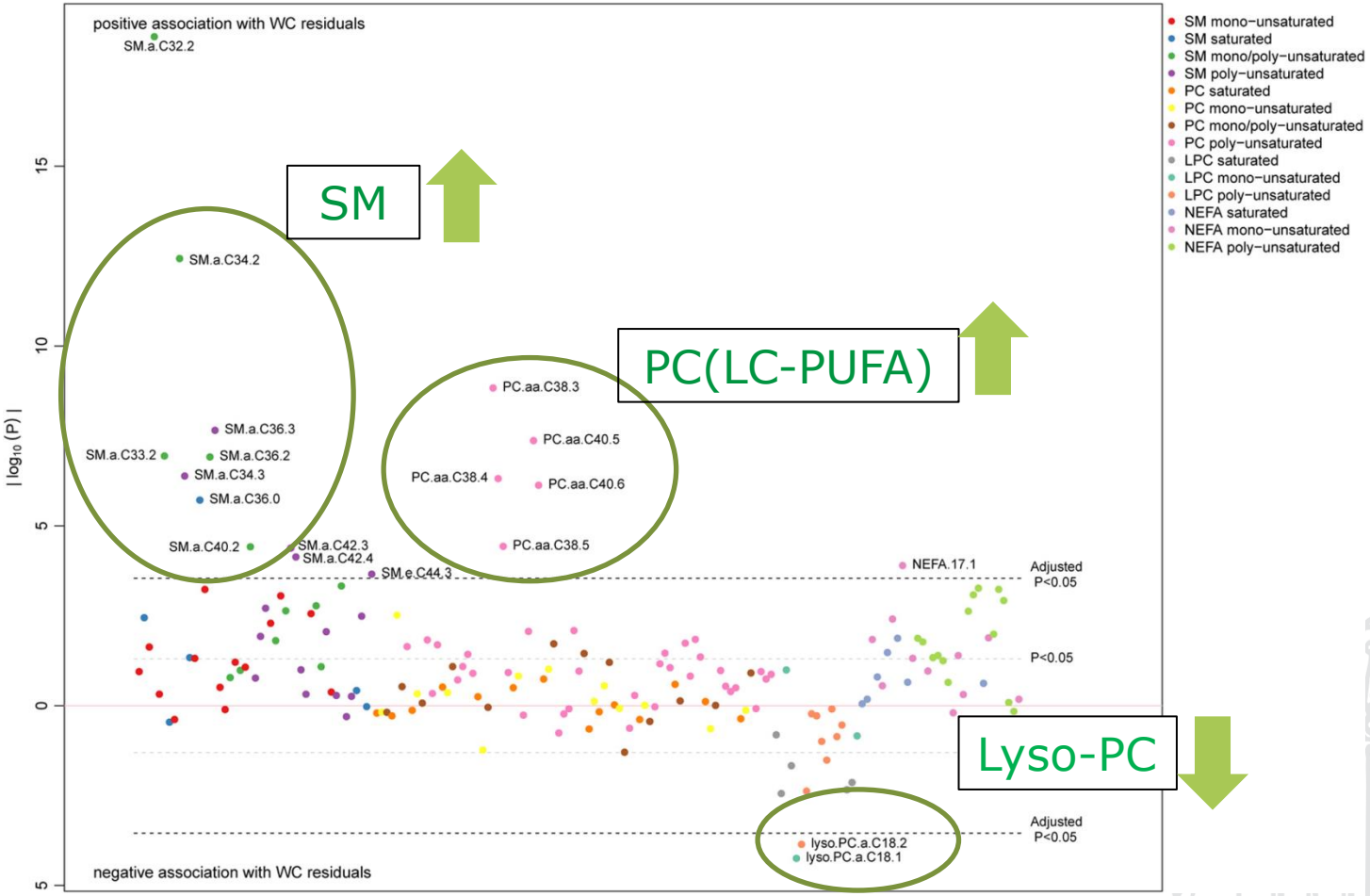
- Multiple linear regression model
- Outcome: HOMA-IR, Waist Circumference
- Confounder: HDL-cholesterol, LDL-cholesterol, smoking, alcohol consumption, dietary patterns, physical and sedentary behavior, biological sex

- Associations with insulin resistence:

Analyte	Standardized Estimate	Bonferroni CI	Bonferroni p-value
Pcaa C43:6	−0.09	−0.18,-0.01	0.01
Pcaa C44:12	−0.09	−0.18,-0.01	0.01
LPCa C14:0	0.08	0.001, 0,16	0.05

Rauschert et al., J Clin Endocrinol Metab. 2016

RAINE COHORT



P vaues of multiple regression model for waist circumference

Rauschert et al., J Clin Endocrinol Metab. 2016

ONGOING PROJECTS

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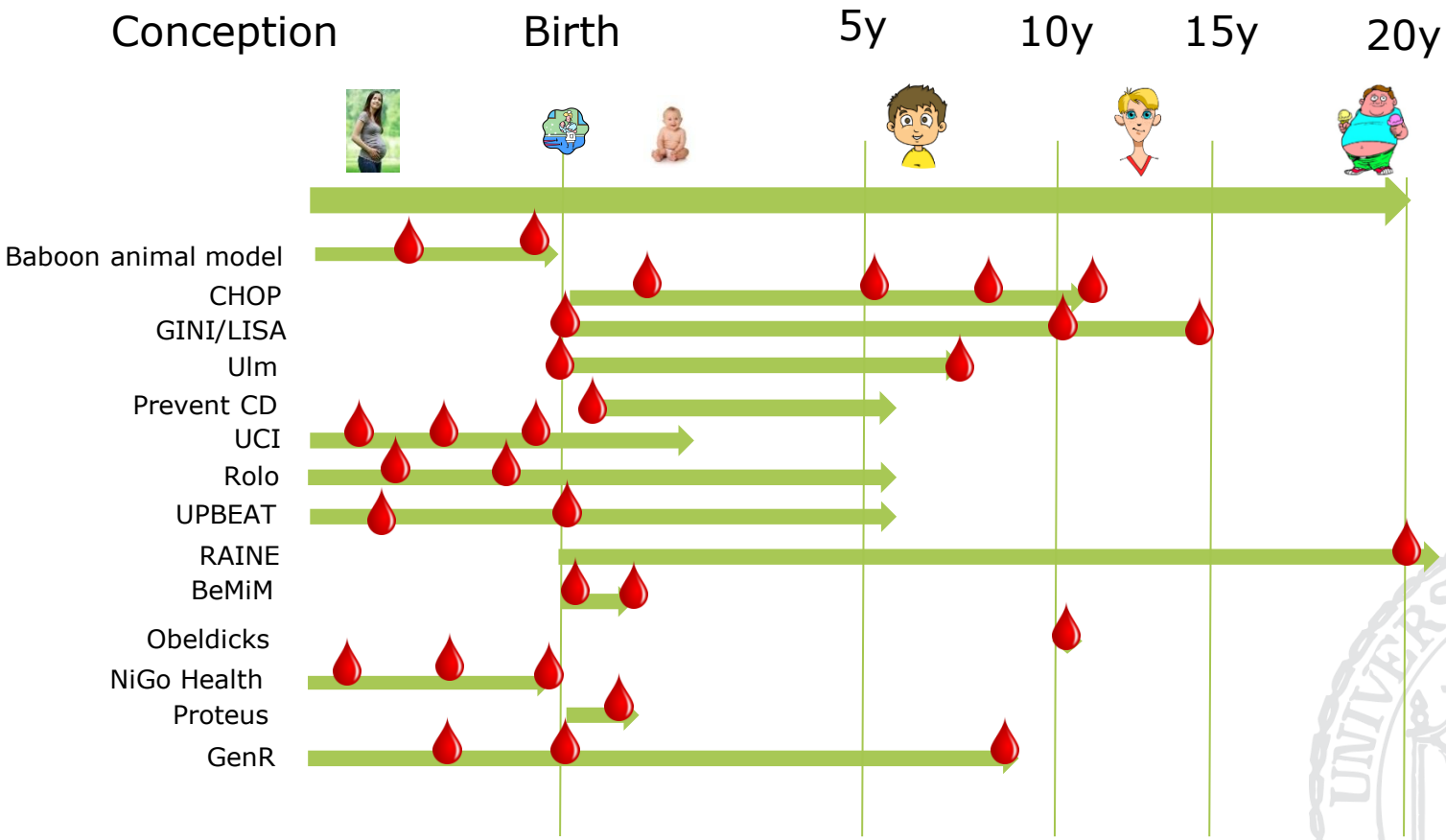
Challenge of human studies:

- Individual study design
- Various primary outcomes
- Different meta-data

Influences → Physiological outcomes

Raine	WC ~ SM, PC(PUFA), 1/LPC IR ~ LPC(14:0)	CHOP	rapid growth ~ LPC(14:0)
CHOP	HP → BCAA, Carn C3, C4, C5		
PREOBE	Ob = GDM ~ DHA, AA, 1/20:3		
UCI	pBMI ~ NEFA, 20:3		

ONGOING PROJECTS



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