Human milk components and infant growth

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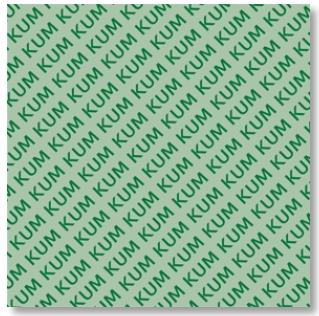

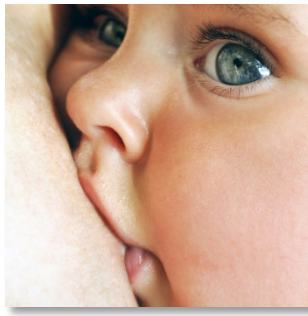

Topic

- The composition of human milk content is variable
- Studies indicated that an increased protein intake of formula fed infants compared to breast fed infants is associated with a higher weight gain

- ➔ Do the content of macronutrients and specific hormones in human milk influence weight and length Z-scores of the infants significantly?

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PreventCD

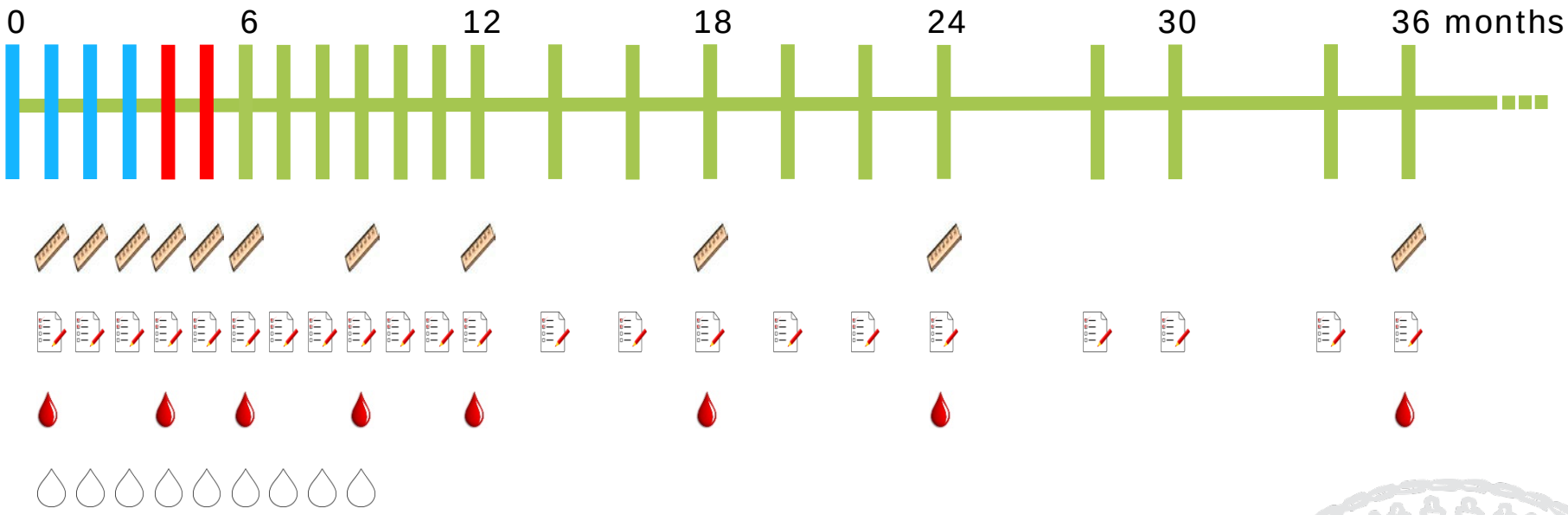
- Multicenter, randomized, double-blind, placebo-controlled dietary-intervention study

- Infants with:
  - a first-degree relative with diagnosed CD
  - positive for HLA-DQ2 and/or HLA-DQ8 CD risk genes

- Prevent celiac disease with small amounts of gluten
- → no influence (Vriezinga et al., NEJM 2014)

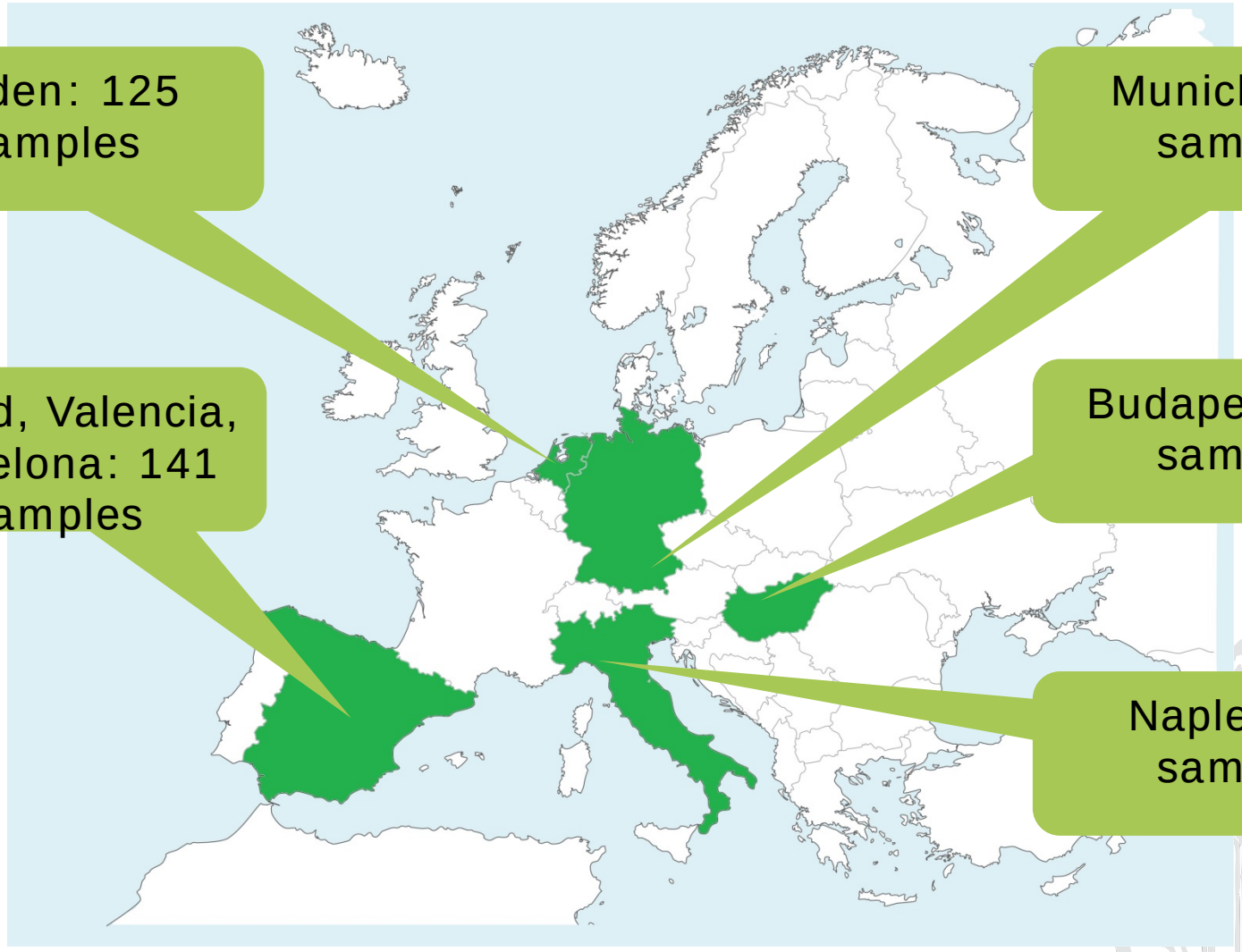
Measurements

Recruitment 0-3M, Intervention 16-24 weeks

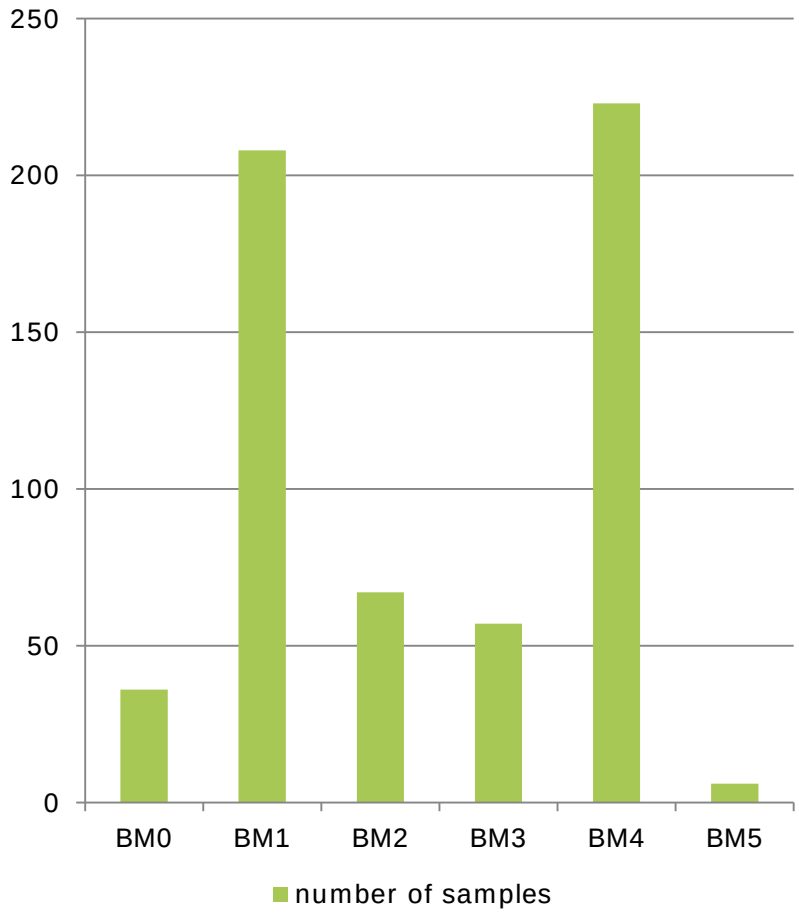


- anthropometric measurements
- parental questionnaire (FFQ gluten, health issues)
- blood sampling (first: HLA genotyping, than: IgA and IgG AGA, TG2A)
- breast milk sampling

PreventCD milk samples



Time points of available breast milk samples



- 597 available breast milk samples
- Day 0 – 163
- Paired samples from 218 mothers
  - One sample from the first 3 months of lactation
  - Second, corresponding sample from month 4 or 5

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Characteristics of participants for milk analyses

			N total
Age mother, years	33.4	± 3.9	368
Mothers with CD, n	191	50.5 %	378
Gestational age, weeks	39.3	± 1.4	376
BMI mother, kg/m²	22.5	± 3.5	179
Birth weight, g	3369.8	± 456.3	374
Weight-for-age Z-score at 4 months	-0.3	± 1.0	301
Length-for-age Z-score at 4 months	0.1	± 1.2	291
Weight-for-length Z-score at 4 months	-0.4	± 1.0	290
Males, n	189	50.0 %	378
Exclusive BF at 4 months, n	266	70.37 %	367

Measured human milk components

- Protein (Bradford Assay)
  - Higher protein content in formula fed infants is associated with increased odds-ratio for obesity
- Fat (MIRIS HMA)
  - crucial for the newborn: up to 55% of the calories are supplied as fat
  - hindmilk 2-3 times higher fat content than foremilk
  - + fatty acid composition, polar Lipids (sphingomyelines, phosphatidylcholines), carnitines
- Carbohydrates (MIRIS HMA)
  - most constant macronutrient in milk
  - human milk oligosaccharides (HMOs): prebiotic → promote growth for probiotic bacteria in child‘s gut

Measured human milk components

- Adiponectin (ELISA)
  - Expressed in adipose tissue, increases insulin sensitivity
  - Higher milk adiponectin concentration in human milk was associated with slower growth during active breastfeeding (J. G. Woo et al.)
- Insulin (ELISA)
  - key hormone in blood glucose homeostasis, growth hormone
  - Insulin levels are increased in obese and overweight mother‘s breast milk – influence on child‘s weight gain?
- IGF-II (RIA)
  - Predominant IGF in milk
  - Promotes maturation and function of the gut in newborns – influence on child’s growth?

Statistical analyses

- Multiple linear regression models
- Growth parameter and concentration of the milk analyte
- Adjusted for country of residence, birthweight, children's CD status
- Bonferroni corrected

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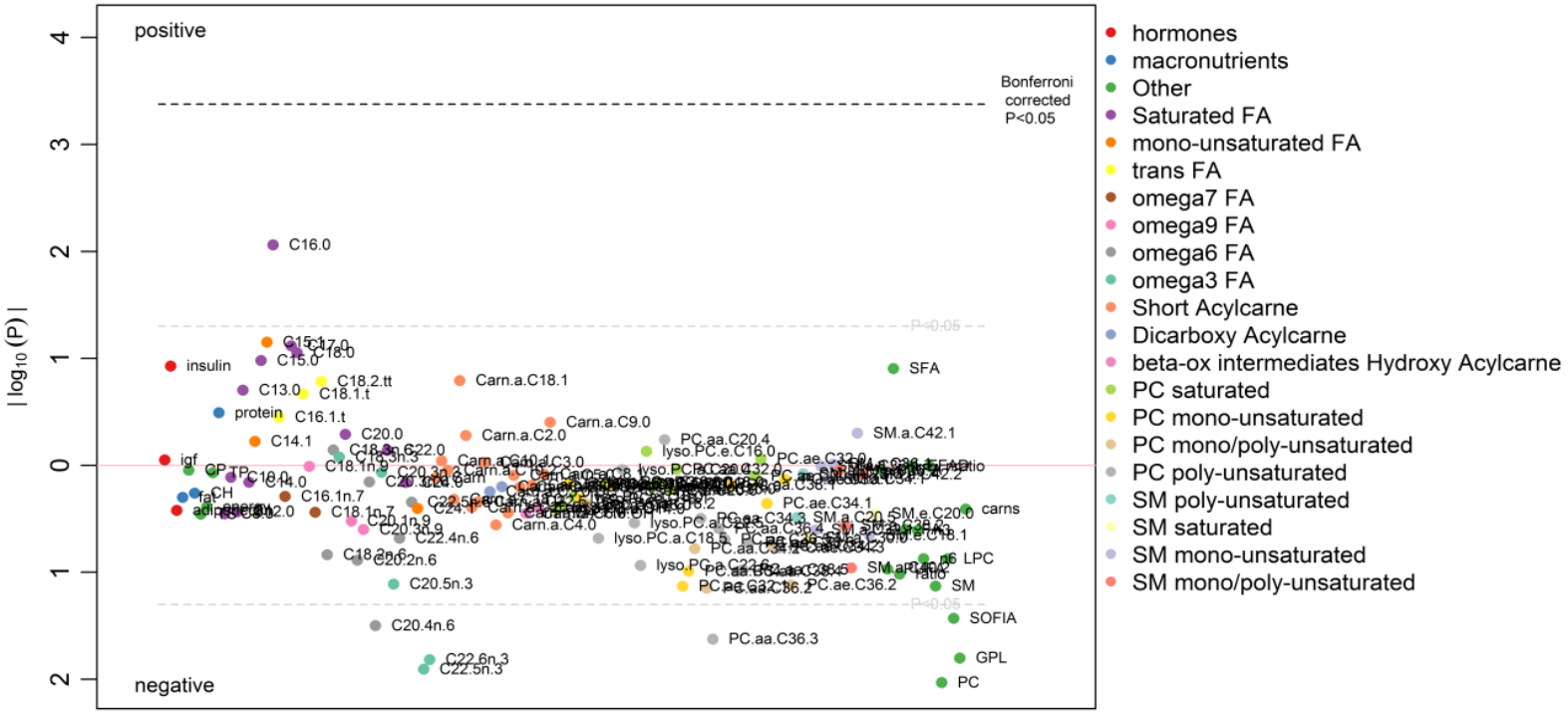
Human milk composition and weight at 6 months



→ No significant influences of breast milk components on weight / Z-scores

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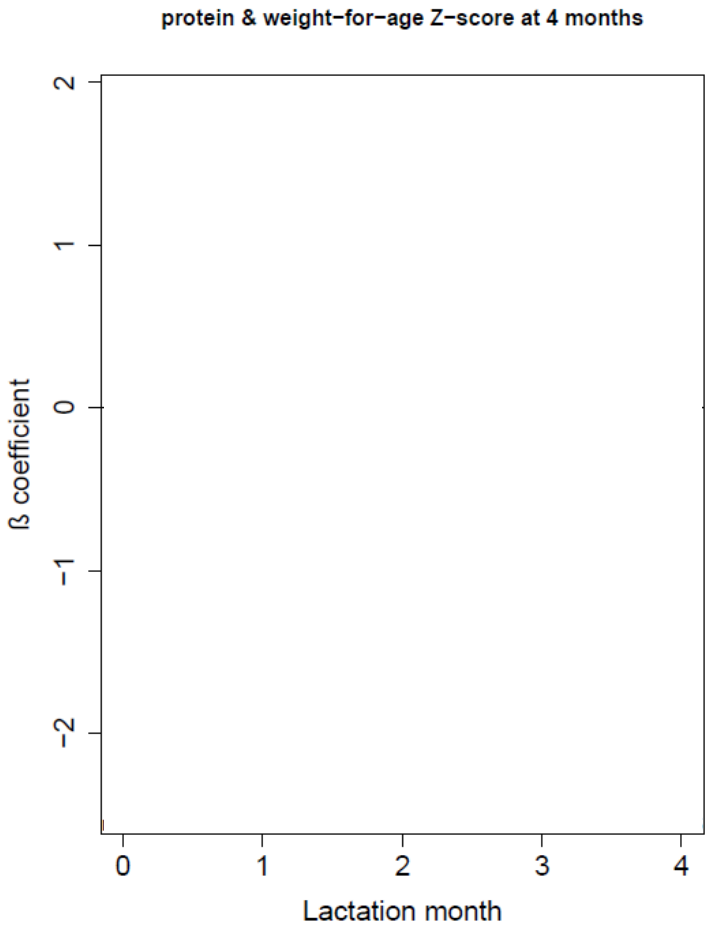
Statistical Model considering the sample months



- milk samples from different months of lactation with changes in concentration over time
- model with effect estimators for the analytes for each month of lactation: 5 independent factors from lactation months 0, 1, 2, 3, 4 (0 = day 0-16)
- Time point = categorical factor
- both concentrations for the mothers with two available samples from different months of lactation in one model

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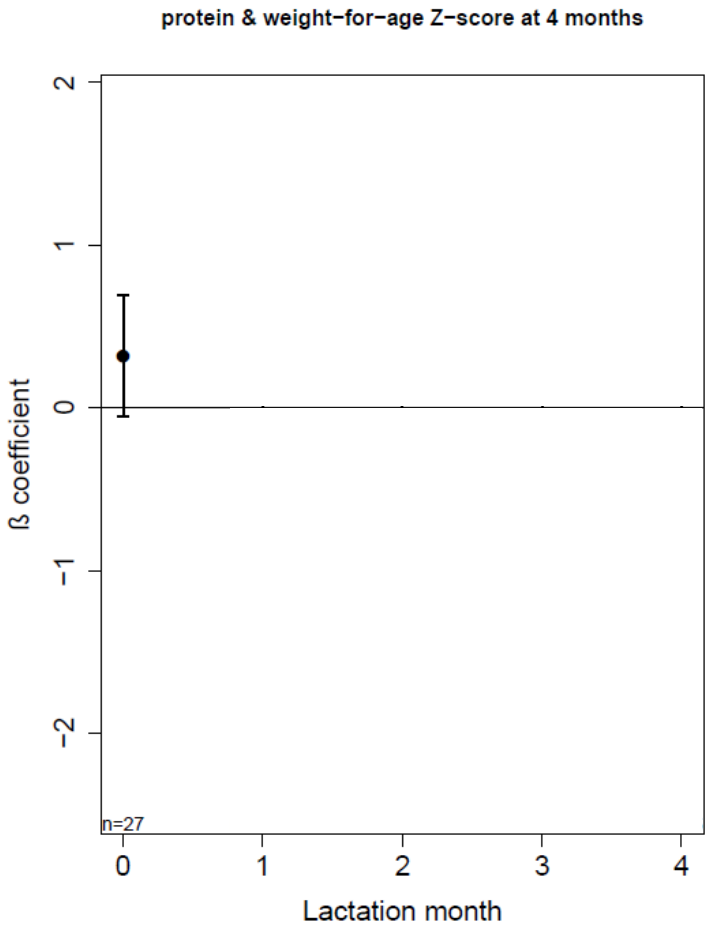
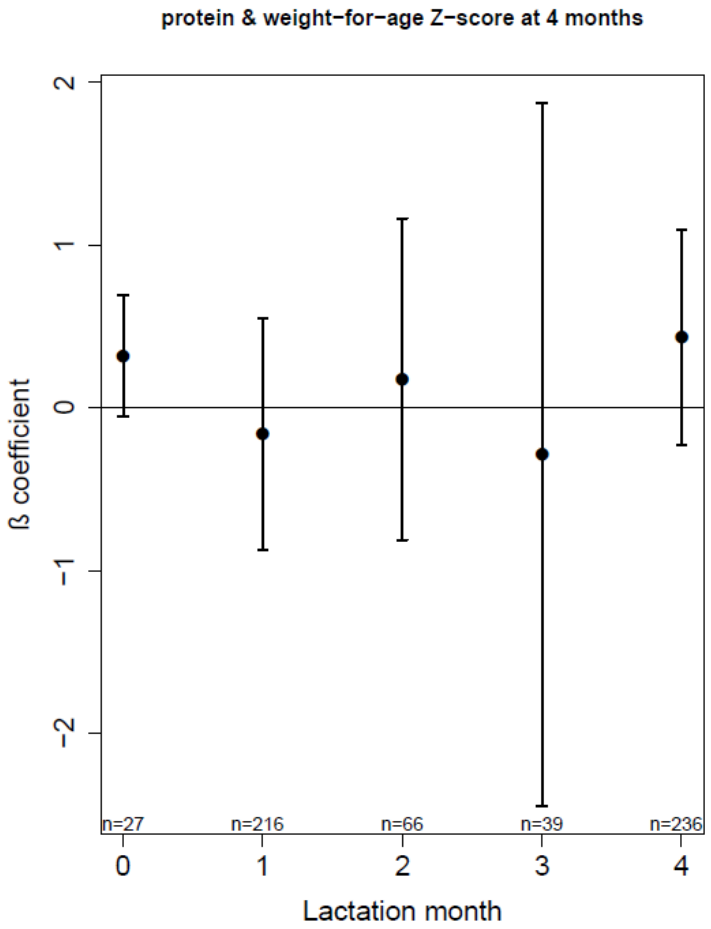
Statistical Model



- Multiple linear regression model for
- Human milk protein
- And the weight-for-age Z-Score at 4 months of age
- With the different lactation time points
- adjusted for birth weight, children's CD status, and country of residence ($p<0.2$ in univariate regression)
- Bonferroni corrected 95% confidence intervals

Statistical Model



- Each group with different sample sizes can be calculated
- All samples were considered in the analyses

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Results: length-for-age Z-score at 4 months of age

	IGF-II β (CI)	Insulin β (CI)	Adiponectin β (CI)	Fat β (CI)	Carbs β (CI)	Protein β (CI)
Month 0	0.017 (-0.034; 0.068)	-0.003 (-0.055; 0.048)	0.018 (-0.02; 0.056)	0.014 (-0.327; 0.356)	0.053 (-0.116; 0.221)	0.297 (-0.358; 0.953)
Month 1	-0.002 (-0.043; 0.04)	-0.002 (-0.03; 0.025)	-0.011 (-0.038; 0.016)	-0.029 (-0.213; 0.154)	-0.011 (-0.721; 0.698)	0.047 (-0.973; 1.067)
Month 2	0.024 (-0.04; 0.088)	0.027 (-0.014; 0.067)	0.009 (-0.074; 0.092)	-0.207 (-0.61; 0.195)	-0.138 (-1.269; 0.993)	0.732 (-0.868; 2.331)
Month 3	0.019 (-0.022; 0.059)	0.002 (-0.033; 0.037)	0.007 (-0.123; 0.137)	0.213 (-0.123; 0.55)	-0.449 (-1.117; 0.219)	0.689 (-1.84; 3.217)
Month 4	0.005 (-0.065; 0.076)	-0.003 (-0.025; 0.018)	0.004 (-0.033; 0.042)	-0.033 (-0.16; 0.094)	-0.05 (-0.579; 0.478)	0.895 (-0.26; 2.05)

- ß-estimates and confidence interval for each sample month and the selected analytes, adjusted and Bonferroni corrected
- No significancies detected
- Same applies for the age at 1 year and 2 years

Results: weight-for-age Z-score at 4 months of age

	IGF-II β (CI)	Insulin β (CI)	Adiponectin β (CI)	Fat β (CI)	Carbs β (CI)	Protein β (CI)
Month 0	0.022 (-0.022; 0.066)	0.002 (-0.044; 0.048)	0.024 (-0.009; 0.057)	0.046 (-0.26; 0.353)	0.055 (-0.075; 0.186)	0.352 (-0.181; 0.885)
Month 1	-0.018 (-0.056; 0.019)	-0.011 (-0.032; 0.01)	-0.005 (-0.03; 0.019)	-0.005 (-0.179; 0.168)	-0.018 (-0.597; 0.56)	-0.219 (-1.228; 0.791)
Month 2	-0.007 (-0.048; 0.034)	0.037 (-0.003; 0.077)	0.009 (-0.082; 0.1)	-0.124 (-0.338; 0.089)	0.057 (-0.399; 0.513)	0.197 (-1.183; 1.576)
Month 3	0.019 (-0.025; 0.063)	0.01 (-0.051; 0.07)	0.04 (-0.074; 0.153)	0.223 (-0.075; 0.522)	0.158 (-0.858; 1.174)	-0.169 (-3.114; 2.775)
Month 4	-0.012 (-0.068; 0.045)	0.003 (-0.015; 0.021)	0.002 (-0.032; 0.036)	0.024 (-0.1; 0.148)	-0.035 (-0.512; 0.443)	0.628 (-0.337; 1.594)

- ß-estimates and confidence interval for each sample month and the selected analytes, adjusted and Bonferroni corrected
- No significancies detected
- Same applies for the age at 1 year and 2 years

Results: weight-for-length Z-score at 4 months of age

	IGF-II β (CI)	Insulin β (CI)	Adiponectin β (CI)	Fat β (CI)	Carbs β (CI)	Protein β (CI)
Month 0	0.016 (-0.025; 0.057)	0.009 (-0.037; 0.055)	0.018 (-0.022; 0.058)	0.064 (-0.184; 0.313)	0.034 (-0.11; 0.177)	0.2 (-0.43; 0.83)
Month 1	-0.026 (-0.074; 0.021)	-0.009 (-0.039; 0.021)	0 (-0.033; 0.032)	0.057 (-0.151; 0.266)	-0.503 (-1.322; 0.317)	-0.46 (-1.686; 0.766)
Month 2	-0.025 (-0.082; 0.033)	0.02 (-0.024; 0.064)	0.033 (-0.033; 0.099)	-0.03 (-0.369; 0.309)	0.206 (-0.459; 0.871)	-0.089 (-1.689; 1.511)
Month 3	0.015 (-0.039; 0.069)	0.013 (-0.061; 0.087)	0.041 (-0.079; 0.162)	0.1 (-0.251; 0.452)	0.66 (-0.827; 2.146)	-0.807 (-4.333; 2.719)
Month 4	-0.023 (-0.082; 0.036)	0.005 (-0.016; 0.026)	0.002 (-0.032; 0.035)	0.044 (-0.101; 0.19)	0.018 (-0.665; 0.702)	0.027 (-0.992; 1.047)

- ß-estimates and confidence interval for each sample month and the selected analytes, adjusted and Bonferroni corrected
- No significancies detected
- Same applies for the age at 1 year and 2 years

Summary

- No significant influence of the measured human milk macronutrients, insulin, IGF-II, and adiponectin from the beginning until 4 months of lactation for
  - Length-for-age, Weight-for-age, and Weight-for-length Z-scores at the age of
    - 4 months, 1 year, 2 years of the infants

Conclusion

- although we observed considerable variability of many breast milk components, we could not identify significant relationships with weight or length Z-Scores at the considered age

- Reasons?
  - Consumed milk volume is an important factor?
  - fat/energy content could not be reliably determined (fore/hindmilk)
  - High CD-risk of the cohort covers potential findings?
  - protein composition is more important than total protein?
  - Human milk is optimal for the child – no matter how the concentrations vary?

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