Early nutrition programming of long-term health: fact or fiction?

Berthold Koletzko, MD, PhD
Hauner Children’s Hospital, Ludwig Maximilians Univ of Munich, Germany
Co-ordinator, Early Nutrition Project
Disclosures

- Berthold Koletzko is a member of the National Breastfeeding Committee and tends to be biased towards breastfeeding.

- The Ludwig-Maximilians-University of Munich, Germany and the speaker have received support for scientific and educational activities by companies that market nutrition products for infants and children, including Abbott, Baxter, B. Braun, Dairy Goat Cooperative, Danone, Fresenius Kabi, Fonterra, Hipp, Mead Johnson, Nestlé, and Yakult, predominantly as part of publically funded research projects with support of the European Commission or German governmental research support.

- None of these have had any influence the content and conclusions of this presentation.
Early developmental programming of adult health: first 1000 days

During limited time periods of early development/plasticity, nutrition and other factors induce lasting effects on physiology, function, health and disease risks.

"Improving nutrition for mothers and children is one of the most cost-effective and impactful tools we have for poverty alleviation and sustainable development."

— May, 2012
Retrospective epidemiology: birthweight associated with later health
How good is the evidence?
Only retrospective association, or more?

Positive proof of global warming.

Long term effects of early nutrition on later health (2012-2017) FP7-289346-EarlyNutrition

Research Budget
11.1 Mio€/≈14 Mio$
Co-ordination: Hauner Children’s, U of Munich

36 research institutions, 16 countries, 3 continents
Metabolic modulators

Sensitive time windows of pre- and postnatal development

- Cytogenesis
- Organogenesis
- Metabolism Endocrine
- Gene expression

Early metabolic programming of lifelong health


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The EarlyNutrition Project
Programming of obesity & assoc. diseases

Fetal Overnutrition
  e.g. maternal obesity, high pregnancy weight gain, diet in pregnancy, gestational diabetes

Fuel mediated in utero hypothesis

Mismatch hypothesis

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

Postnatal nutrition/growth
  e.g. overfeeding, short breastfeeding, excessive protein supply

Accelerated postnatal growth hypothesis

Environment
Lifestyle
Genes

Obesity/adiposity
  Visceral adiposity
  Metabolic syndrome
  Diabetes, insulin resistance
  Hypertension, CHD, Stroke
  Asthma

Maternal obesity

Offspring obesity
Maternal obesity → Glucose, fatty acids, insulin, leptin, inflammation → Developmental plasticity → Fetal growth, neon. adiposity → Offspring obesity
Maternal obesity

↑ Glucose, fatty acids, insulin, leptin, inflammation

Developmental plasticity

Fetal growth, neon. adiposity

Offspring obesity
High maternal prepregnancy BMI increases the risk of large for date infant

1250 women, USA, untreated mild glucose intolerance

Stuebe 2012.
Maternal obesity in pregnancy and premature offspring mortality from CVD

37 709 Scottish people with birth records from 1950, follow-up of 1 323 275 person years

K-M Curve for Maternal BMI categories (WHO)

- Underweight
- Normal
- Overweight
- Obese

Offspring time to Death (in Years)

Reynolds et al, BMJ 2013
Prenatal intervention possible

- RCT in 2212 pregnant women, BMI \( \geq 25 \), South Australia
- Standard care, or counseling (3 x face to face, 3 x phone) on balanced diet, limiting refined CHO and SAFA, and increased physical activity
- No significant effect on LGA (primary outcome, RR 0.90)
- Reduced birthweight \(<4000 \text{ g}\) (RR 0.81, \( p=0.03 \), NNT 28)

www.project-earlynutrition.eu
Birthweight >4 kg doubles: 2x adult obesity
Systematic review & meta-analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>BW &gt; 4000 g</th>
<th>BW ≤ 4000 g</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Che 2010</td>
<td>16</td>
<td>142</td>
<td>1.70 [0.98, 2.97]</td>
</tr>
<tr>
<td>Gu 2003</td>
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<td>163</td>
<td>2.00 [1.13, 3.53]</td>
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<td>He (a) 2000</td>
<td>74</td>
<td>308</td>
<td>1.99 [1.32, 2.99]</td>
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<td>He (b) 2005</td>
<td>14</td>
<td>57</td>
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<td>136</td>
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<td>Li 2007</td>
<td>36</td>
<td>20</td>
<td>3.33 [1.83, 6.04]</td>
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<tr>
<td>Lu 2008</td>
<td>8</td>
<td>52</td>
<td>2.68 [1.20, 5.99]</td>
</tr>
<tr>
<td>Mao 2007</td>
<td>21</td>
<td>115</td>
<td>2.58 [1.13, 5.85]</td>
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<tr>
<td>Monteiro 2003</td>
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<td>70</td>
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<td>Ruan 2009</td>
<td>82</td>
<td>488</td>
<td>1.55 [1.17, 2.06]</td>
</tr>
<tr>
<td>Shi 2007</td>
<td>54</td>
<td>80</td>
<td>3.63 [2.03, 6.49]</td>
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<td>Wang 2009</td>
<td>179</td>
<td>640</td>
<td>1.80 [1.51, 2.14]</td>
</tr>
<tr>
<td>Yang 2009</td>
<td>72</td>
<td>290</td>
<td>1.61 [1.08, 2.40]</td>
</tr>
<tr>
<td>Zhang 2009</td>
<td>456</td>
<td>1642</td>
<td>2.23 [1.99, 2.51]</td>
</tr>
</tbody>
</table>

Total (95% CI) 4930 34286 100.0% 2.07 [1.91, 2.24]
Total events 1069 4153
Heterogeneity: Chi² = 17.87, df = 13 (P = 0.16); I² = 27%
Test for overall effect: Z = 17.75 (P < 0.00001)
Birthweight >4kg: high risk for later obesity

Early Childhood Longitudinal Study, 7738 children, USA

<table>
<thead>
<tr>
<th>Birthweight</th>
<th>n</th>
<th>Obesity (%) at age (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5-&lt;4 kg</td>
<td>6035</td>
<td>5.6</td>
</tr>
<tr>
<td>&gt;4 kg</td>
<td>915</td>
<td>11.2</td>
</tr>
</tbody>
</table>

Birthweight >4 kg = 12% of the population, but >36% of the obese children at age 14 yrs

Pregnancy: current advice

- Aim at normal body weight prior to conception
- Avoid excessive weight gain in pregnancy
- Maintain normal physical activity, moderate level sports
- Increase energy intake only by 10% until end of pregnancy
- Avoid high glycaemic load diet

Programming of obesity & assoc. diseases

Fetal Overnutrition
- e.g. maternal obesity, high pregnancy weight gain, diet in pregnancy, gestational diabetes

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Mismatch hypothesis

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Postnatal nutrition/growth
- e.g. overfeeding, short breast-feeding, excessive protein supply

Accelerated postnatal growth hypothesis

Mismatch of slow pre-natal and fast postnatal growth

Low initial weight followed by rapid child growth predisposes to later 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. Bhargava et al, NEJM 2004.
Programming of obesity & assoc. diseases

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e.g. maternal obesity, high pregnancy weight gain, diet in pregnancy, gestational diabetes

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High weight gain in the 1st. & 2nd. year of life: increased obesity risk to adulthood

Rapid early growth: nutrition or other factors?

„She is still hungry, even though I stuffed worms into her all day.“
Longer breastfeeding ⇒ less obesity in >9000 children at school entry (*Bavaria, Germany*)

Adj. rel. risk of obesity

<table>
<thead>
<tr>
<th>Duration of breastfeeding</th>
<th>Adj. rel. risk of obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 m</td>
<td>0.75</td>
</tr>
<tr>
<td>3-5 m</td>
<td>0.50</td>
</tr>
<tr>
<td>6-12 m</td>
<td>0.25</td>
</tr>
<tr>
<td>&gt;12 m</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Breastfeeding ⇒ less obesity later

Early meta-analysis: 22% less obesity

Recent meta-analysis: 15% less obesity


Weight (SDS) in breast or bottle fed infants

Darling Study, California, USA: 87 breast or bottle fed babies

Dewey et al., AJCN 1993.
Growth differs in breastfed and in bottle fed infants

5,304 Brazilian infants predominantly breast or bottle fed followed prospect. from birth to 12 mon.

Victora et al, J Nutr 1998;128:1134-8
Can breastfeeding induce obesity?

Excessive Weight Gain during Full Breast-Feeding

Maria Grunewald  Christian Hellmuth  Hans Demmelmaier  Berthold Koletzko

Division of Metabolic and Nutritional Medicine, Dr. von Hauner Children's Hospital, Ludwig Maximilian University of Munich, Munich, Germany
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Breast milk at 1 yr. lactation:
Protein  1.3 g/dl
Reference  0.8 g/dL
Does breastfeeding protect, and how?

**Early Protein Hypothesis**

Excessive protein intake in infancy promotes high early weight gain and later obesity.
Does early protein intake matter?

Far higher protein supply with conv. formula than breast milk

- Protein
- Insulinogenic amino acids
- Insulin/IGF1
- Weight gain
- Adipogenicity
- Obesity/NCD long-term

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RCT: Childhood obesity project (CHOP)
1678 healthy term infants enrolled in 5 EU countries: Belgium, Germany, Italy, Poland, Spain

Intervention

Breast fed

Protein: 1.2 g/dL

IF 2.05 g/dL, FOF 1.6 g/dL

Bottle fed 61.4%

Bottle

Protein

IF 1.25 g/dL, FOF 3.2 g/dL

Bottle fed 60.4%

Doubly blind randomised

Protein

Bottle

IF 2.05 g/dL, FOF 1.6 g/dL

Bottle fed 60.4%

Protein

IF 1.25 g/dL, FOF 3.2 g/dL

Bottle fed 60.4%

Weight/length at 6 y:

Breast fed 61.4%

Bottle fed 60.4%

Intervention

No intervention, follow-up

0 1 yr. 2 yrs. 6 yrs.


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Protein Intake

FAO/WHO/UNU Reference Intakes


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Amino acids

Socha et al, AJCN 2011;94:1776-84S.

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Growth factors

IGF-1 (plasma)

- Protein
- Insulinogenic amino acids
- Insulin/IGF1

C-peptide/creatinine (urine)

- Protein

Socha et al, AJCN 2011;94:1776-84S.
IGF-1 in infants: Genes, Gender or Gruel?

Explained variance ($R^2$) of IGF-1 axis related outcomes due to contributions from gender, genetic and nutritional variables

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<th>IGF-BP3 ($R^2$ in %)</th>
<th>IGF-1/IGF-BP3 ($R^2$ in %)</th>
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<tr>
<td>Gender only</td>
<td>1.5</td>
<td>2.0</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Genetic only</td>
<td>3.8</td>
<td>3.6</td>
<td>0.78 (n.s.)</td>
<td>5.0</td>
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Characteristics of variants of the IGF-1 and IGFBP-3 genes.

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<tr>
<td>IGF-1</td>
<td>rs6214</td>
<td>101,317,699</td>
<td>3' UTR</td>
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<td></td>
<td>rs1520220</td>
<td>101,320,652</td>
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</tr>
<tr>
<td></td>
<td>rs35767</td>
<td>101,399,699</td>
<td>5' near gene</td>
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<td>IGFBP-3</td>
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<td></td>
<td>rs1496495</td>
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<td>Intergenic</td>
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# IGF-1 in infants: Genes, Gender or Gruel?

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<td>5.0</td>
</tr>
<tr>
<td><strong>Nutrition only</strong></td>
<td><strong>15.1</strong></td>
<td><strong>6.8</strong></td>
<td><strong>10.4</strong></td>
<td><strong>13.1</strong></td>
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**IGFBP-3**

| rs35766 | 101,404,603 | 5' near gene |
| rs1496495 | 45,903,786 | Intergenic   |
| rs6670  | 45,918,779  | 3' UTR       |


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Serum IGF-1 predicts weight gain velocity

6 mon

12 mon

24 mon

Weight gain velocity $\Rightarrow$ body fat mass (isotope dilution method)

Weight and BMI vs. body fat mass (Pearson r correlations)

<table>
<thead>
<tr>
<th></th>
<th>Fat mass z-score (Pearson r)</th>
<th>Fat-free mass z-score (Pearson r)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometry at 6 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight-for-length z-score</td>
<td>0.470 ($P &lt; 0.001$)</td>
<td>0.167 (0.180)</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>0.475 ($P &lt; 0.001$)</td>
<td>0.160 (0.199)</td>
</tr>
<tr>
<td><strong>Anthropometry at 12 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight-for-length z-score</td>
<td>0.374 ($P = 0.002$)</td>
<td>0.168 (0.180)</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>0.332 ($P = 0.007$)</td>
<td>0.140 (0.267)</td>
</tr>
<tr>
<td><strong>Anthropometry at 24 months</strong></td>
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<td></td>
</tr>
<tr>
<td>Weight-for-length z-score</td>
<td>0.259 ($P &lt; 0.05$)</td>
<td>0.060 (0.641)</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>0.247 ($P = 0.051$)</td>
<td>0.039 (0.763)</td>
</tr>
</tbody>
</table>

Infant diet and BMI until early school age


Intervention

Mean BMI in kg/m²

Age in months

Lower protein
Higher protein
Breastfed
Infant diet and BMI until early school age

Mean BMI in kg/m²

Age in months

Intervention

Lower protein  Higher protein  Breastfed

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Infant diet and BMI until early school age

BMI \approx 0.51 \text{ kg/m}^2 \text{ higher (} P=0.009 \text{) at 6 years, early high vs low protein}

Cochrane Review, 55 studies on obesity prevention in children: mean BMI effect \textbf{-0.15 kg/m}^2

(95\% CI -0.21 to -0.09). Waters E eta l, Cochrane Library 201, DOI: 10.1002/14651858.CD001871.pub3

Low protein intake in infants: BMI \textbf{-0.51 kg/m}^2 .

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Overweight and obesity until school age

BMI $\approx$ 2.5 kg/m² higher ($P=0.014$) at 95th. centile

BMI $\approx$ 1.5 kg/m² higher ($P=0.085$) at 90th. centile


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Lower protein in infancy ⇒ ↓ obesity at 6 yrs.

RCT, Childhood Obesity Project (CHOP) Study, 1678 healthy term infants enrolled in 5 European countries

Obesity (%) at 6 years

Lower protein in infancy → ↓ obesity at 6 yrs.

RCT, Childhood Obesity Project (CHOP) Study, 1678 healthy term infants enrolled in 5 European countries

Obesity (%) at 6 years

% 10
9
8
7
6
5
4
3
2
1
0

Conventional  Lower Protein  Breastfed

Protein in infancy \( \rightarrow \) Obesity at 6 yrs.

RCT, Childhood Obesity Project (CHOP) Study, 1678 healthy term infants enrolled in 5 European countries

Obesity (%) at 6 years

<table>
<thead>
<tr>
<th>Protein Type</th>
<th>Rel. Risk (unadjusted)</th>
<th>95% CI</th>
<th>Rel. Risk (adjusted)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>2.43</td>
<td>1.12, 5.27</td>
<td>2.87</td>
<td>1.22, 6.75</td>
</tr>
<tr>
<td>Lower Protein</td>
<td>2.87</td>
<td>1.22, 6.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breastfed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Limit milk protein supply in infancy

- Breastfeeding reduces later obesity risk
  ⇒ promote, protect & support breastfeeding

- Avoid high protein supply
  ⇒ Infants not (fully) breast fed: **infant formula with reduced protein**, but high protein quality
  ⇒ All infants: **no cows‘ milk as a drink in infancy**
Metabolites predict Δ weight - birth to 6 months

Rapid Growth and Childhood Obesity Are Strongly Associated with LysoPC(14:0)


Metabolites predict obesity at 6 years

Great opportunities for health promotion

Time of obesity onset

Magnitude of metabolic and released disease

Life course

Adulthood

Late intervention may only have limited benefits

Adult intervention

Ann Nutr Metab 2013; DOI: 10.1159/000345598
Great opportunities for health promotion

Magnitude of metabolic and released disease

Life course

Time of obesity onset

Mother & infant

Childhood

Adulthood

Late intervention may only have limited benefits

Adult intervention

Earlier intervention could prevent early onset, and later, obesity

Ann Nutr Metab 2013; DOI: 10.1159/000345598
Sincere thanks to funding bodies
Sincere thanks: to you for your kind attention, to participating subjects and families, and to fantastic colleagues and friends.
- The latest information
- Meet global leaders in paediatric gastroenterology, hepatology & nutrition
- Abstracts: 10. Nov. 14
- Early bird reg. 12. Feb 15
- See you in Amsterdam!
• Free, CME accredited e-Learning for Health Care Professionals supported by Univ. of Munich, ESPGHAN, Eur. Commission and unrestricted educational grants.

Current modules:

• Breastfeeding
• Nutrition & Lifestyle in Pregnancy
• Complementary Feeding
• Infant Formula Feeding
Early Nutrition eAcademy (ENeA)

www.early-nutrition.org

4,260 participants from 133 countries

E-Learning for health care professionals on the topics of Early Nutrition

In collaboration with ESPGHAN

European Society for Paediatric Gastroenterology, Hepatology and Nutrition

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