Timing and tempo of first year growth in relation to cardiovascular and metabolic risk profile in early adulthood

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The Netherlands
Metabolic and cardiovascular profile at 21 years

- Introduction
- Influence of low birth weight
- Influence of preterm birth
- Influence of postnatal growth
- Conclusions
3641 men born in Helsinki 1924 -1933
Resident in Finland in 1971

High death rates from coronary heart disease:

* low birth weight
* relative low placenta weight
* caught up in weight after birth

Eriksson, BMJ 1999; 318,427-31
Intrauterine environment

MATERNAL MALNUTRITION

FETAL MALNUTRITION

Other maternal or placental abnormalities

Other organ malfunction e.g. liver

Decreased β cell mass

Insulin resistance

Abnormal vascular development

HYPERLIPIDEMIA

NON-INSULIN-DEPENDENT DIABETES

HYPERTENSION

METABOLIC SYNDROME and CVD

Barker
Metabolic and cardiovascular profile at 21 years

- Introduction
- Influence of low birth weight
- Influence of preterm birth
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- Conclusions
PROGRAM STUDY in young adults 18-24 yrs

Started in 2002

- 345 born at term (> 36 wks GA)
- oversampling of subjects born SGA
Inclusion criteria and measures

Healthy young adults (18-24 years)

Born singleton, at term, Caucasian

- Anthropometry, body composition by DXA scan,
- Blood pressure and carotis intima media thickness (cIMT)
- Frequent Sampling IV Glucose tolerance test with Tolbutamide
- Serum lipids, hormones, adipocytokines
- Family history, questionnaires
- Health records and growth during first years after birth
Is birth weight related to insulin sensitivity?

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<thead>
<tr>
<th>Variables</th>
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Adjusted for age, gender, SES, birth length SDS and adult height SDS

* Log transformed

Leunissen R, JCEM 2008
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Fat accumulation during childhood is related to insulin sensitivity in early adulthood

Leunissen R, JCEM 2008
### Metabolic profile in early adulthood

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<th>Dependent variable</th>
<th>Birth weight SDS (p-value)</th>
<th>Fat mass (p-value)</th>
</tr>
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<tbody>
<tr>
<td>Insulin sensitivity</td>
<td>0.210</td>
<td>&lt;0.001 (-)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.733</td>
<td>0.013 (+)</td>
</tr>
<tr>
<td>Chol/HDL ratio</td>
<td>0.086</td>
<td>0.065 (+)</td>
</tr>
<tr>
<td>HDL</td>
<td>0.100</td>
<td>0.962 (+)</td>
</tr>
<tr>
<td>LDL</td>
<td>0.371</td>
<td>0.045 (+)</td>
</tr>
<tr>
<td>Apo A1</td>
<td>0.668</td>
<td>0.665 (+)</td>
</tr>
<tr>
<td>Apo B</td>
<td>0.157</td>
<td>0.016 (+)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.239</td>
<td>0.004 (+)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.273</td>
<td>0.004 (+)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.594</td>
<td>0.011 (+)</td>
</tr>
<tr>
<td>cIMT</td>
<td>0.506</td>
<td>0.478 (+)</td>
</tr>
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Adjusted for age, gender, SES, birth length SDS and adult height SDS.
CONCLUSION

- Not prenatal growth, reflected by birth size, but postnatal weight gain during childhood is related to determinants of CVD and DMII in early adulthood.

- Weight gain during childhood can be specified as fat accumulation.
Metabolic and cardiovascular profile at 21 years

- Introduction
- Influence of low birth weight
- Influence of preterm birth
- Influence of postnatal growth
- Conclusions
Young adults born preterm

- Background

  - One report suggested a lower insulin sensitivity in children born premature → higher risk for development diabetes?

  - It is unknown whether this reduced insulin sensitivity persists into adulthood

  - In 2005, 12.7% of all babies was born preterm
Young adults born preterm / term

• Subjects
  – 305 young adults (18-24 yr): 169 born premature and 136 term

• Measurements
  – Insulin sensitivity by FSIGT
  – Body composition by DXA
  – cIMT
  – Lipids, adipocytokines
  – Anthropometrics

Willemsen R, JCEM 2009
Young adults born preterm vs term

Graph showing the relationship between insulin sensitivity and insulin secretion. The graph compares term and preterm subjects. The x-axis represents insulin sensitivity (Si*10^{-4}/min^{-1} [mU/l]), and the y-axis represents insulin secretion (AIRg [mU/l]). The inset shows a scatter plot with points indicating normal, IGT, and T2DM statuses.
Young adults born preterm / term

Graph showing the relationship between insulin sensitivity and insulin secretion in term and preterm subjects. The x-axis represents insulin sensitivity (Si * 10^-4/min^-1 [mU/l]), and the y-axis represents insulin secretion (AIRg [mU/l]). The graph illustrates that term subjects tend to have higher insulin sensitivity compared to preterm subjects, with a wider range of insulin secretion values.
Insulin sensitivity vs gestational age

Willemsen R. JCEM 2009
Insulin sensitivity vs birth weight

Insulin sensitivity (Si \times 10^{-4}/min-1 [mU/l]) vs Birth weight SDS

Willemsen R. JCEM 2009
## Insulin sensitivity

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
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<td>Beta</td>
<td>P-value</td>
</tr>
<tr>
<td>GA (wks)</td>
<td>0.004</td>
<td>0.95</td>
</tr>
<tr>
<td>BW SDS</td>
<td>0.17</td>
<td>0.07</td>
</tr>
<tr>
<td>OC-use</td>
<td>-0.18</td>
<td>0.03</td>
</tr>
<tr>
<td>Height SDS</td>
<td>0.37</td>
<td>&lt;0.0005</td>
</tr>
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<td>Weight SDS</td>
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Adjusted R² 0.23 0.33

* Adjusted for age, gender, birth length SDS, BL*AH
## Insulin sensitivity

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<td>0.004</td>
<td>0.95</td>
<td>-0.001</td>
<td>0.99</td>
<td>-0.009</td>
<td>0.88</td>
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<tr>
<td>BW SDS</td>
<td>0.17</td>
<td>0.07</td>
<td>0.12</td>
<td>0.18</td>
<td>0.11</td>
<td>0.19</td>
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<tr>
<td>OC-use</td>
<td>-0.18</td>
<td>0.03</td>
<td>-0.17</td>
<td>0.03</td>
<td>-0.17</td>
<td>0.02</td>
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<tr>
<td>Height SDS</td>
<td>0.37</td>
<td>&lt;0.0005</td>
<td>0.20</td>
<td>0.02</td>
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<td></td>
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<tr>
<td>Fat mass (kg)</td>
<td></td>
<td></td>
<td>-0.52</td>
<td>&lt;0.0005</td>
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<tr>
<td>Lean mass (kg)</td>
<td></td>
<td></td>
<td>-0.03</td>
<td>0.81</td>
<td>-0.04</td>
<td>0.76</td>
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<tr>
<td>Trunk FM (kg)</td>
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<td>-0.57</td>
<td>&lt;0.0005</td>
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<td>Limbs FM (kg)</td>
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<td></td>
<td>0.07</td>
<td>0.66</td>
<td></td>
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Adjusted $R^2$: 0.23, 0.33, 0.34

* Adjusted for age, gender, birth length SDS, BL*AH
Conclusions

- Prematurity is not associated with reduced insulin sensitivity in young adulthood

- Most important predictors for a low insulin sensitivity are fat percentage and oral contraceptive use in women
Metabolic and cardiovascular profile at 21 years

- Introduction
- Influence of low birth weight
- Influence of preterm birth
- Influence of postnatal growth
- Conclusions
Fetal growth restriction

Nutrient-enriched diet

Postnatal growth acceleration

Development of adult disease

Fat accumulation hypothesis

Postnatal growth acceleration

Fat accumulation

Development of adult disease

Leunissen R, JCEM 2008
Which postnatal period is critical?
Increased weight gain in the first 3 months of life

- Reduced insulin sensitivity
- Reduced HDL levels
- Higher cholesterol/HDL ratio
- Higher triglyceride levels
- Increased fat mass %
- Increased abdominal circumference at 21 years
Is there a difference between Rapid catch-up and Slower catch up?

Catch-up defined as gain in height of at least 0.67 SDS in first year
RAPID weight gain in first 3 months

Leunissen R, JAMA, 2009
RAPID height gain in first 3 months

Leunissen R, JAMA, 2009
RAPID weight gain in first 3 months

Leunissen R, JAMA, 2009

Weight SDS - height SDS

Slow weight gain 0-3 mo
Rapid weight gain 0-3 mo

Leunissen R, JAMA, 2009
CONCLUSION

RAPID weight gain in the first 3 months of life

- Reduced insulin sensitivity
- Reduced HDL levels
- Higher cholesterol/HDL ratio
- Higher triglyceride levels
- Increased fat mass %
- Increased abdominal circumference at 21 years
Slower Early Growth - Better Long-Term Cardiovascular Health

277 adolescents
- 13 to 16 years
- 216 preterm
- 61 term
- First 2 weeks

Singhal A et al, Circulation 2004
New model

Any neonate

No acceleration in weight
- No higher risk

Acceleration in weight (especially in the first three months of life)
- Fat accumulation during childhood
- Insulin sensitivity
  - Unfavourable body composition
  - Unfavourable lipid profile
  - Blood pressure
- Development of adult disease
Accelerated weight gain in Infancy
- be careful ! -
Randomised controlled trial in SGA infants

Infants given a nutrient enriched formula:

- No beneficial effect on neurodevelopment & growth
- Adverse effect on later blood pressure & adiposity

Singhal et al, Circulation 2007
- Higher protein (n= 550) [2.05 g protein/100 ml]
- Lower protein (n= 540) [1.25 g protein/100 ml]
.. Breastfeeding (n= 588) [1.20 g protein/100 ml]

Koletzko B. Am J Clin Nutr 2009
Metabolic and cardiovascular profile at 21 years

• Introduction

• Influence of low birth weight

• Influence of preterm birth

• Influence of postnatal growth

• Conclusions
Conclusions

- Not SGA or prematurity but **postnatal weight (fat) gain during early childhood** is related to determinants of CVD and DMII in early adulthood

- **RAPID** catch-up in weight for height in the first 3 months of life should be prevented – 0-3 months is critical window

- SGA / preterm infants are at **higher risk for receiving nutrient enriched formula**

- Breastfeeding is associated with slower catch-up in weight for height and normal neurodevelopment
PhD fellows
Ralph Leunissen
Ruben Willemsen
Sandra de Kort
Gerthe Kerkhof

Research nurses
Joke Dunk
Marian Huibregts

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