Impact of early infant growth on adult health

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Death rates from Coronary Heart Disease in men 1968-78

Coronary heart disease and neonatal mortality: England and Wales

Standardised mortality ratio for coronary heart disease 1968-78

Barker and Osmond 1986 Lancet;1:1077-81
Mortality from coronary heart disease in 15726 men and women in Hertfordshire

- **Men**
  - Birthweight (kg): ≤2.5, 2.9, 3.4, 3.8, 4.3, >4.3
  - Standardised Mortality Ratio

- **Women**
  - Birthweight (kg): ≤2.5, 2.9, 3.4, 3.8, 4.3, >4.3
  - Standardised Mortality Ratio
Odds ratio for impaired glucose tolerance and type 2 diabetes in 2003 men and women, according to birthweight

- Odds ratio for impaired glucose tolerance and type 2 diabetes in 2003 men and women, according to birthweight

- Odds ratio

- Birthweight (kg)

- p for trend = 0.001, <0.0001 (adjusted for BMI)
Cumulative incidence (%) of hypertension according to birthweight

Birthweight (grams)
Associations between early growth and later disease extend across the range of fetal and infant growth. This implies that what are regarded as normal variations in the supply of nutrients to the baby have important long–term effects.

Barker and Osmond 1986 Lancet;1:1077-81
BMI SD Score from birth to adulthood (for those developing impaired GTT or Diabetes)

Bhargava SK et al NEJM 350: 865-875 2004
<table>
<thead>
<tr>
<th>BMI at 2 yr of Age</th>
<th>Prevalence of Impaired Glucose Tolerance or Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI &lt;14.7 at Age 12</td>
</tr>
<tr>
<td>&lt;15.0</td>
<td>16.1 (217)</td>
</tr>
<tr>
<td>15.0–16.1</td>
<td>14.2 (148)</td>
</tr>
<tr>
<td>&gt;16.1</td>
<td>8.2 (61)</td>
</tr>
<tr>
<td>All subjects</td>
<td>14.3 (426)</td>
</tr>
</tbody>
</table>

Bhargava SK et al NEJM 350: 865-875 2004
Conclusions.

- There is an association between thinness in infancy and the presence of impaired glucose tolerance or diabetes in young adulthood.

- Crossing into higher categories of body-mass index after the age of two years is also associated with these disorders.

Bhargava SK et al NEJM 350: 865-875 2004
Early Developmental Risk Factors for Resistance to Postnatal Fatty Infants... after Catch-Up Growth: A Prospective Study of Small for Gestational Age Children

Lourdes Ibáñez, K. O., D.B.D., F.d.Z., University of...natal weight gain is associated with higher insulin resistance and insulin resistance. The mechanism of this association is unclear.

Setting, Design, and Participants:
In low birth weight (SGA) infants, the mean age at birth weight (AGA; n = 100) was 38 weeks, with a mean birth weight of 2500 g (SD = 400 g).

Main Outcome Measures:
The main outcome measures were the change in ponderal index (PI) and the change in body mass index (BMI) at 6 and 12 months of age. The PI was calculated as weight/(length)^2, and the BMI was calculated as weight/(height)^2.

Results: Mean height, weight, and ponderal index at 6 and 12 months of age for SGA and AGA children were not significantly different. However, SGA children had a higher BMI at 6 months and a lower BMI at 12 months than AGA children. The change in BMI was significantly greater in SGA children than in AGA children. The change in ponderal index was significantly greater in SGA children than in AGA children at 6 months, but not at 12 months.

Conclusion: The results suggest that SGA children have a higher risk of developing obesity and insulin resistance during early childhood. Early intervention strategies targeting insulin resistance may be necessary to prevent the development of obesity and insulin resistance in SGA children.
<table>
<thead>
<tr>
<th></th>
<th>SGA (n = 29; 22 girls, 7 boys)</th>
<th>AGA (n = 22; 13 girls, 9 boys)</th>
<th>( t ) test(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>( 2.1 \pm 0.1 )</td>
<td>( 3.3 \pm 0.1 )</td>
<td>( P &lt; 0.0001 )</td>
</tr>
<tr>
<td>Gestation (wk)</td>
<td>( 38.8 \pm 0.4 )</td>
<td>( 39.0 \pm 0.3 )</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Two-year visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Three-year visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Four-year visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td></td>
<td></td>
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</tbody>
</table>

Values are mean ± SEM.

\(^a\) SGA vs. AGA, adjusted for sex and age.
**TABLE 3.** Multiple regression models showing the independent determinants of percent total body fat and abdominal fat mass at age 4 yr in SGA children

<table>
<thead>
<tr>
<th></th>
<th>Percent total body fat</th>
<th>Abdominal fat mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$P$</td>
</tr>
<tr>
<td>Weight gain, 0–2 yr</td>
<td>0.40</td>
<td>0.0007</td>
</tr>
<tr>
<td>Weight gain, 2–4 yr</td>
<td>0.28</td>
<td>0.006</td>
</tr>
<tr>
<td>Height</td>
<td>0.09</td>
<td>0.1</td>
</tr>
<tr>
<td>Sex</td>
<td>0.03</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Lean vs Obese *$P < 0.003$  **$P < 0.0001$

% body fat in neonates at birth and at 8 yr FU

Estudio Chileno de Crecimiento y Obesidad (ECO)
Growth and Obesity Cohort Study (GOCS): 1200 Chilean children attending public nursery schools in the year 2006

- **GOCS I**: 2002-2003 (0y) to 2006 (3.5y)
- **GOCS II**: 2007 (4y) to 2008 (5.5y) to 2009 (6.5y)
- 2012 (9.5y)

- **2500-4500gr**: n = 14330
- **n = 1196**: 2002-2003
- **n = 1196**: 2006
- **n = 313**: GOCS I
- **n = 1050**: GOCS II

Graph showing weight distribution and growth over time.
GOCS is a concurrent cohort of mothers-children in Chile, a developing (post-transitional) country

- Socio-economic status = low-middle
- Maternal height = 156.3 ± 5.6 cm
- Pre-pregnancy BMI = 24.2 ± 4.3 kg/m²
- Pregnancy weight gain = 12.4 ± 4.8 kg
- Smoking during pregnancy = 15%
- Diabetes during pregnancy = ~ 5% (20-40%)
- Preeclampsia = 9.1%
- Breastfeeding* at 4 mo = 64%

* Exclusive or predominant
BMI Z score 0 – 84 months, by BMI status at 7y (n=1096)

- BAZ ≥2
- 1 ≤ BAZ < 2
- -1 ≤ BAZ < 1

Adjusted for current age and sex
Points connected for ease of reading

BAZ; WHO 2006-7
Height Z score 0 – 84 months, by BMI status at 7y (n=1096)

Adjusted for current age and sex
Points connected for ease of reading
**BMI gain after 6 months increases adiposity**

**But not height at 5y (n=554)**

Adjusted for growth in the previous period, current age, and sex

Fat mass estimated from predictive anthropometric equation validated by deuterium dilution

Fat-free mass = FFM/height$^2$ Fat mass = FM/height$^2$
Timing of adiposity rebound in 805 Chilean children born in 2002, by BMI status at 7y

Timing of AR

- <2y
- 2-4y
- 4-5y
- 5-7y

BMI Z-scores based on WHO 2007

BMI kg/m²

Age (months)
Bone age in 986 Chilean children at 7y of age

Ultrasound Bone Age (months)
Bone age in 936 Chilean children, by BMI status at 7y of age

### BMI status

<table>
<thead>
<tr>
<th>Bone Age</th>
<th>BAZ &lt; +1</th>
<th>+1 &lt;= BAZ &lt;+2</th>
<th>BAZ =&gt;+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>84-102 mo</td>
<td>55.3</td>
<td>30.5</td>
<td>14.5</td>
</tr>
<tr>
<td>n=507</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 84 mo</td>
<td>80</td>
<td>15.7</td>
<td>4.3</td>
</tr>
<tr>
<td>n=230</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>=&gt;102 mo</td>
<td>29.2</td>
<td>29.1</td>
<td>41.7</td>
</tr>
<tr>
<td>n=199</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Z-scores based on WHO 2007
Obesidad (IMC) > 2SD; OMS 2006-2007

Growth (BMI) of 1096 pre-school children born 2002

Edad (meses)

Obesidad prevalencia (%)

Z BMI-Age

Obesidad=Z IMC > 2SD; OMS 2006-2007
A los 4 años el riesgo metabólico no se asociaba con Obesidad (n=323 niños)

Todos los p>0.05

Glucosa ≥ 100mg/dl
HOMA ≥ 3.2
TC ≥ 95th#
LDL ≥ 95th#
HDL ≤ 5th#
TG ≥ 95th#

Z IMC = IMC SDS, OMS 2006

# Academia Americana de Pediatría
A los 4 años el riesgo metabólico no se asociaba con Obesidad Central (n=323 niños)

CC=circunferencia de cintura, Hispanos NHANES III

Todos los p>0.05
Riesgo Metabólico a los 7 años de edad (n=1004; 50% niñas)

Glucosa ≥ 100mg/dl
HOMA ≥ 3.2
TC ≥ 95th #
LDL ≥ 95th #
HDL ≤ 5th #
TG ≥ 95th #

% 60
50
40
30
20
10
0

NIÑOS
NIÑAS

* p<0.05 entre niños y niñas

p<0.05 Delta entre 4 y 7 años ambos sexos

# Academia Americana de Pediatria
A los 7 años alteraciones de Glicemia, Insulina y TG se asociaron a Obesidad (n=1004)

IMC-Z = IMC SDS OMS 2006

* p-for IMC trend <0.05

# Academia Americana de Pediatria
A los 7 años alteraciones metabólicas se asociaron con Obesidad Central (n=1004)

CC=circunferencia de cintura, Hispanos NHANES III
# Academia Americana de Pediatria

* p-for trend <0.05
Mechanisms by which nutrition conditions growth

- **Gene Expression** (transcription factors, single or multiple genes) / **Epigenetic control**

- Hormones receptors, binding proteins and signal transduction

- **Cell growth and turnover** during critical periods
Newborns of obese parents have altered DNA methylation patterns at imprinted genes

A Soubry, S K Murphy, F Wang, Z Huang, A C Vidal, B F Fuemmeler, J Kurtzberg, A Murtha, R L Jirtle, J M Schildkraut, C Hoyo

Received 4 June 2013; revised 25 Sept 2013; accepted 6 Oct 2013

doi: 10.1038/ijo.2013.193
DNA from cord blood leukocytes of 92 newborns. Preconceptional obesity, defined as BMI $\geq 30\text{ kg/m}^2$
DNA from cord blood leukocytes of 92 newborns. Preconceptional obesity, defined as BMI ≥30 kg/m²

**Mean methylation change by DMR of imprinted genes:**

<table>
<thead>
<tr>
<th>Gene</th>
<th>%</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEG3-IG</td>
<td>+0.4</td>
<td>1.1</td>
<td>0.70</td>
</tr>
<tr>
<td>MEG3</td>
<td>-0.5</td>
<td>1.6</td>
<td>0.73</td>
</tr>
<tr>
<td>MEST</td>
<td>+0.1</td>
<td>0.8</td>
<td>0.92</td>
</tr>
<tr>
<td>NNAT</td>
<td>-0.5</td>
<td>1.2</td>
<td>0.69</td>
</tr>
<tr>
<td>PEG3</td>
<td>0.0</td>
<td>0.5</td>
<td>0.94</td>
</tr>
<tr>
<td>PLAGL1</td>
<td>+3.9</td>
<td>1.6</td>
<td>0.01</td>
</tr>
<tr>
<td>SGCE/PEG10</td>
<td>+0.9</td>
<td>0.7</td>
<td>0.22</td>
</tr>
</tbody>
</table>
Methylation differences of similar magnitude related to:

In utero or periconceptional nutritional deprivation, folate supplements, gestational diabetes, tobacco use, and maternal use of antidepressants & antibiotics.

Changes in DNA methylation at imprinted regulatory regions or loss of imprinting can persist through life and have been correlated with cardiovascular diseases, behavioral disorders and cancer (ovarian, cervical, colorectal & Wilms’ tumor).

Effects mainly related to $\text{IGF}_2$ deregulation, also to loss of imprinting or abnormal regulation of MEST & $\text{PEG}_3$ associated with cancer (Rhabdomyosarcoma & glioma)
Pre-natal

- Pre Pregnancy BMI
- Maternal Glucose Insulin
- Placental Fetal blood flow
- Hormonal responses
- Epigenetic changes

Post-natal

- Early Pubertal maturation
- Early Adiposity rebound
- Weight gain with limited length gain
- Central Obesity Metabolic syndrome
- High BMI Obesity

Fetal growth restriction
Fetal Macrosomia
Hormonal responses
Life Course Promotion of Healthy growth

Development of Disease

- **Fetal Life**
  - SES
  - Mother’s early Nutrition
  - Organ Growth
  - Birth weight
  - Body composition

- **Infancy and Childhood**
  - Breast Feeding
  - SES
  - Growth rate
  - Physical Activity
  - Food behaviour
  - TV viewing
  - Sugary drinks
  - PEM
  - Micronutrients
  - Infection
  - Tallness

- **Adolescence**
  - Obesity
  - Sedentaryism
  - Inactivity
  - Smoking
  - Physical Activity
  - Food behaviour
  - TV viewing
  - Sugary drinks

- **Adult Life**
  - Established adult risky behaviours
  - Diet/Physical activity
  - Tobacco
  - Alcohol
  - Biological risks
  - Socioeconomic status
  - Environmental conditions

- **Elderly**
  - Genetic & Epigenetic susceptibility to disease

Accumulated risk for NCDs