Blood Pressure and Metabolic Risk: From Birth to Adulthood

Empar Lurbe, MD, PhD, FAHA
Cardiovascular Risk Unit
Hospital General Universitario
University of Valencia
CIBERObn Instituto de Salud Carlos III
Madrid, Spain
Roots of Cardio-Metabolic risk factors

● Cardiovascular complications occurring in adults find their roots in risk factors operating early in life

● Subtle alterations in risk factors can be observed in youths

● The presence of these risk factors forsees future increments to abnormal levels
Cardio-Metabolic risk factors detected in children and adolescents

- Growth Pattern
- Abdominal obesity
- Screening
- Familial history
- Obesity
- High BP
- Insulin Resistance
- TC, HDL
Factors related to Cardio-Metabolic phenotype

Genetic

Environmental
Factors related to Cardio-Metabolic phenotype

Genetic
Environmental
FETAL
WEIGHT IN INFANCY AND DEATH FROM ISCHAEMIC HEART DISEASE

D.J.P Barker, C Osmond, P.D Winter, B Margetts, S.J Simmonds

Fig 2—Percentiles of weight at one year according to birthweight in men who were breast fed.

TABLE II—SMRs FOR ISCHAEMIC HEART DISEASE ACCORDING TO WEIGHT AT ONE YEAR AND METHOD OF FEEDING

<table>
<thead>
<tr>
<th>Weight (pounds)</th>
<th>Breast fed</th>
<th>Bottle fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18</td>
<td>112 (33)</td>
<td>105 (4)</td>
</tr>
<tr>
<td>19–20</td>
<td>81 (71)</td>
<td>79 (5)</td>
</tr>
<tr>
<td>21–22</td>
<td>100 (154)</td>
<td>72 (9)</td>
</tr>
<tr>
<td>23–24</td>
<td>69 (85)</td>
<td>97 (13)</td>
</tr>
<tr>
<td>25–26</td>
<td>61 (40)</td>
<td>144 (9)</td>
</tr>
<tr>
<td>≥27</td>
<td>38 (9)</td>
<td>89 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>81 (392)</td>
<td>94 (42)</td>
</tr>
</tbody>
</table>
Publications related to Cardio-Metabolic risk in PubMed

Early origins

Birth weight
From birth weight to cardiovascular disease: an integrated model

Exposure

Mother and Father
Anthropometric and diet
Smoking habits
Genetic susceptibility

Child
Nutrition
Passive smoke exposure

Risk factors for adult cardiovascular disease

Fetal and placental growth
and birth weight
Childhood growth

Growth

Risk factors adult cardiovascular disease in childhood
Blood pressure
Arterial stiffness
Atherosclerosis
Coronary heart disease

Cardiovascular development changes

Vascular adaptations
Arterial stiffness
Endothelial dysfunction
Microvascular structures

Renal adaptations
Kidney volume
Renal function
RAAS programming

Cardiac adaptations
Left ventricular growth
Aortic root diameter

Development
Early origins of Cardio-Metabolic risk factors

Factors related to BW

BW and vascular phenotype

The addition of postnatal weight gain

Molecular imprinting
Early origins of Cardio-Metabolic risk factors

Factors related to BW
From birth weight to cardiovascular disease: an integrated model

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- Anthropometric and diet
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Cardiovascular development changes

Vascular adaptations
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- Endothelial dysfunction
- Microvascular structures

Renal adaptations
- Kidney volume
- Renal function
- RAAS programming

Cardiac adaptations
- Left ventricular growth
- Aortic root diameter
Maternal factors influencing fetal growth and development

- Constraints
- Diet and Nutrition
- Environmental
Maternal BMI during pregnancy and BW

body mass index in different pregnancy stages: ■ 1st quintile ▲ 4th quintile ● 5th quintile
Differences in BW in relation to maternal age

Prevalence

<table>
<thead>
<tr>
<th>Age Group</th>
<th>SGA</th>
<th>LGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 yr</td>
<td>6.9</td>
<td>2.1</td>
</tr>
<tr>
<td>20-24.9 yr</td>
<td>6.2</td>
<td>2.5</td>
</tr>
<tr>
<td>25-29.9 yr</td>
<td>5</td>
<td>4.3</td>
</tr>
<tr>
<td>30-34.9 yr</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>35-39.9 yr</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>&gt;39.9 yr</td>
<td>10.1</td>
<td></td>
</tr>
</tbody>
</table>

$p=0.064$  $p=0.001$

Bakker R et al. BJOG 2011;118:500-509
Maternal parity and fetal growth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Primiparous</th>
<th>Parous (P2-4)</th>
<th>Odds ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Papaevangelou 1973</td>
<td>65</td>
<td>1896</td>
<td>57</td>
<td>2473</td>
</tr>
<tr>
<td>Goldman 1990</td>
<td>28</td>
<td>622</td>
<td>26</td>
<td>735</td>
</tr>
<tr>
<td>Evaldson 19990</td>
<td>12</td>
<td>282</td>
<td>14</td>
<td>756</td>
</tr>
<tr>
<td>Chattingius 1993</td>
<td>5959</td>
<td>212821</td>
<td>5001</td>
<td>333400</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>220472</td>
<td>353650</td>
<td>100.0%</td>
<td>1.89 [1.82, 1.96]</td>
</tr>
<tr>
<td>Total events</td>
<td>6346</td>
<td>5603</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 3.83, df = 4 (p < 0.43); I² = 0%
Test for overall effect: Z = 34.09 (p < 0.00001)
Impact of cotinine levels on size at birth

Ivorra C et al. Drug and Alcohol Dependence 2014;134:275-279
Early origins of Cardio-Metabolic risk factors

- Factors related to BW
- BW and vascular phenotype
Relationship between Birth Weight and Awake Blood Pressure in Children and Adolescents in Absence of Intrauterine Growth Retardation

Relationship between awake systolic BP, birth weight, age, current weight and height

Birth weight and awake SBP in children and adolescents

24-hour systolic BP averages and variability grouped by birth weight

Values adjusted for sex, age, current weight and height

Lurbe E et al. Hypertension 2001;38:389-393
Arterial phenotype in children and adolescents

Genetic

Environmental

Fetal

Systolic BP (peripheral and central)

Compliance (PWV)
Reflected waves (AI)
Augmentation Index grouped by birth weight

Values adjusted for sex, height, HR and DBP

Lurbe E et al. Hypertension 2003;41:646-650
Pulse wave velocity grouped by birth weight

Lurbe E et al. Unpublished data
Pressure-natriuresis relationship

BP → Na⁺ → Na⁺
Sleep BP and UNa excretion

Sleep Urinary Sodium Excretion Rate (mmol)

Sleep SBP (mmHg)

Birth weight

- 1.9-3.1 kg
- 3.5-5.8 kg

Lurbe E et al. Hypertension 1998;31:546-551
Vascular phenotype of children with the lowest birth weight

✓ Tend to have the highest Pulse Pressure and Augmentation Index, expressing an early impairment in aortic elasticity and/or higher peripheral resistance

✓ Have an increase in BP variability

✓ May have a restricted ability to excrete sodium
Early origins of Cardio-Metabolic risk factors

Factors related to BW

BW and vascular phenotype

The addition of postnatal weight gain
The effects of prenatal growth on adult disease has been an established field of research.

Interest in postnatal growth and weight gain was primarily related to diagnosing the causes of failure to thrive.

Concern about rapid growth was virtually non-existent.

Controversy exists as to whether accelerated growth in infancy is disadvantageous.

Rapid weight gain in the early postnatal period seems to have adverse consequences for later health.
Trajectories of growth among children who have coronary events as adults

Impact of birth weight and obesity on SBP in Spanish adolescents

Values adjusted for sex, current age and height

Lurbe E et al. Hypertension 2009;53:912-917
Twenty-four hour systolic blood pressure pattern in adolescents grouped by current and birth weight

Adjusted for sex, current age and height

Lurbe E et al. Hypertension 2009;53:912-917
The relevance of prospective studies

- Knowledge on BP at birth is relevant as a proxy of fetal influences
- Intrauterine life impacts on BP and metabolic phenotypes
- Postnatal growth modulates the fetal programming
Impact of fetal size and postnatal growth in cardiometabolic risk: Study design
Blood pressure values in the newborns grouped by birth weight

Factors related to systolic blood pressure estimated by multiple regression analysis

<table>
<thead>
<tr>
<th></th>
<th>b</th>
<th>sd</th>
<th>p</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (m vs f)</td>
<td>-0.07</td>
<td>-0.145</td>
<td>0.885</td>
<td></td>
</tr>
<tr>
<td>Mother age</td>
<td>-0.094</td>
<td>-1.907</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>0.040</td>
<td>0.795</td>
<td>0.427</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>-0.005</td>
<td>-0.107</td>
<td>0.915</td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.027</td>
<td>0.473</td>
<td>0.785</td>
<td></td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td>0.006</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>-0.168</td>
<td>-1.965</td>
<td>0.051</td>
<td></td>
</tr>
<tr>
<td>Head circumf</td>
<td>-0.064</td>
<td>-0.975</td>
<td>0.565</td>
<td></td>
</tr>
</tbody>
</table>

BMI changes grouped by birth weight

![Graph showing BMI changes grouped by birth weight]

- *p* < 0.05 with SGA and AGA
- **p** < 0.05 with SGA
- *p* < 0.05 with SGA and LGA
Systolic BP changes grouped by birth weight

Lurbe E et al. Hypertension 2014;63:1326-1332
Systolic BP determinants from birth to 5 years old

Lurbe E et al. Hypertension 2014;63:1326-1332
Fasting insulin values grouped by birth and current weight at 5 years old

Lurbe E et al. Hypertension 2014;63:1326-1332
HOMA index values grouped by birth and current weight at 5 years old

Lurbe E et al. Hypertension 2014;63:1326-1332
Metabolic parameters and BMI at 5 years grouped by size at birth

Lurbe E et al. Hypertension 2014;63:1326-1332
Correlation coefficient between insulin, uric acid and SBP at 5 years

Lurbe E et al. Hypertension 2014;63:1326-1332
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- The addition of postnatal weight gain
- Molecular imprinting
Umbilical cord endothelial and smooth muscle cells characterization in primary cell cultures

Morphological and immunohistochemical characterization of arteries and vein from umbilical cord

Umbilical cord blood

-OMICS

Genetic and epigenetics
Umbilical cord arteries and vein cell cultures and birth weight

HUAEC, HUVEC, HUASMC, and HUVSMC: from individuals of birth weight <2.8 kg or >3.5 kg

- no difference in cell viability (>95%)
- no difference in cell culture growing speed
- Difference in cell density at confluence (only observed in HUAEC)

PCA of the metabolomic plasma profile in newborns and mothers

PCA of the metabolomic plasma profile in newborns

PCA of the metabolomic plasma profile in newborns

Linked to insulin resistance states and risk to develop Type 2 diabetes

Inversely associated with Type 2 diabetes risk

PCA of the metabolomic plasma profile in newborns

Linked to DNA methylation with impact in gene activity

Hierarchical clustering and heatmap of differentially methylated probes in cord and 5-year-old blood samples

% relative DNA Methylation

Hypermethylation enriched in biological process related to tissue and cell development

Hypomethylation in immune related genes

Cord blood global DNA methylation status in exposed and non exposed to in utero tobacco

- Maternal smoking during pregnancy is a major risk factor for adverse health outcomes in children
- Consequences are not only immediate, such as LBW, but it also leads to long-term risk for obesity, type 2 diabetes and elevated BP
- The mechanisms behind the relationship between in utero tobacco exposure and its effects are not well understood
- Epigenetics can help to unravel the mechanisms underlying
Cord blood global DNA methylation and Manhattan plot for methylation status in exposed and non exposed to in utero tobacco

Hierarchical clustering heat map of the CpG sites with significant differential methylation between exposed and non-exposed newborns to tobacco

Conclusions

- The early postnatal period is a critical window for individuals who have experienced a growth insult in fetal life, reflected by small size at birth.
- Birth weight and postnatal gain exert independent influences on cardio-metabolic parameters at 5 years of age.
- Metabolic alterations manifested by the highest values of insulin, HOMA index, triglycerides, uric acid, and lowest HDL, are present even as early as 5 years of age.
- Blood Pressure became progressively dependent on body size while the impact of birth weight disappeared.
- Research in umbilical cords may help in understanding the impact of intrauterine life on cardiovascular disease later in life.
“...To understand the phenomenon of perinatal programming it will be necessary to take careful phenotypic observation and pair them with molecular mechanisms...”

“... The molecular ability to do so is increasingly available and has the potential to deepen our understanding of fetal origins of chronic diseases such as hypertension and diabetes mellitus”

Falkner B, Ingelfinger J. Hypertension 2014;63:1166-1167