Chapter 4

Components of the metabolic syndrome in early childhood in very-low-birth-weight infants

Miranda de Jong, Harrie N. Lafeber, Anneke Cranendonk, Mirjam M. van Weissenbruch

ABSTRACT

Background/Aims
Term small-for-gestational-age and preterm born infants have an increased prevalence of metabolic syndrome components already in childhood. Data in very-low-birth-weight (VLBW) children are limited. We investigated the prevalence of metabolic syndrome components in VLBW infants at 2 years corrected age.

Methods
We included 38 children, participating in the Neonatal Insulin Replacement Therapy in Europe (NIRTURE) trial, a randomized controlled trial of early insulin therapy in VLBW infants. Metabolic syndrome components were defined as: body mass index (BMI) SDS > 2; blood pressure (systolic and/or diastolic) ≥ 90th percentile; triglycerides ≥ 0.98 mmol/l; high-density lipoprotein (HDL) cholesterol ≤ 1.03 mmol/l; glucose ≥ 5.6 mmol/l.

Results
Two children (5%) had three metabolic syndrome components, 13 children (34%) had two components and 11 children (29%) one component. 63% had raised blood pressure (prevalence higher in boys), 32% low HDL cholesterol and 30% high triglycerides (prevalence lower in early-insulin group). In children with BMI SDS < 0, insulin-treated children had higher HDL cholesterol than children with standard care. Systolic blood pressure was correlated with growth between term and 2 years corrected age.

Conclusions
VLBW infants already have a high prevalence of metabolic syndrome components at 2 years corrected age. Early insulin treatment could have long-term benefits for some of these components.
INTRODUCTION

The metabolic syndrome is a combination of abnormalities in metabolic parameters, body size and blood pressure and is associated with an increased risk of type 2 diabetes and cardiovascular disease. Besides life style and obesity, fetal and early postnatal growth are determinants of the metabolic syndrome. Both term small-for-gestational-age (SGA) infants and preterm born infants have an increased prevalence of several components of the metabolic syndrome in later life, not only in adulthood (1-5), but already in childhood (6-13). Studies in very-low-birth-weight (VLBW) infants show increased blood pressure and insulin resistance in adulthood (14-17). Data about the prevalence of the components of the metabolic syndrome in VLBW infants during childhood are very limited.

The aim of the present study was to investigate the prevalence of the components of the metabolic syndrome in VLBW infants at the corrected age of 2 years. As the subjects were part of the Neonatal Insulin Replacement Therapy in Europe (NIRTURE) trial, our second aim was to evaluate the effect of early insulin therapy on the components of the metabolic syndrome at the corrected age of 2 years.

METHODS

Study population
The subjects were part of the NIRTURE trial, an international multicenter randomized controlled trial investigating the role of early insulin therapy in VLBW infants (18). After written informed consent was obtained, VLBW infants younger than 24 hours of age and requiring intensive care were randomized to receive continuous intravenous infusion of insulin for the first 7 days of life or standard neonatal care with insulin treatment only in case of hyperglycemia. Exclusion criteria included maternal diabetes and major congenital anomalies. All infants participating in the NIRTURE trial in our neonatal intensive care unit were eligible for the present study. Therefore the sample size of the present study was determined by the number of infants we included in the NIRTURE trial. After discharge, all patients were followed in the outpatient clinic with visits at expected date of delivery and at the corrected ages of 3 months, 6 months, 1 year and 2 years. Approval from the local ethics committee was obtained.

Data collection
At the corrected age of 2 years, anthropometry according to Dauncey et al. (19) was performed by a trained research nurse. Body weight was measured using an electronic scale to the nearest 0.1 kg, standing height was measured to the nearest 0.1 cm and all lengths and circumferences were measured using a measuring tape to the nearest
0.1 cm. Body mass index (BMI) was then calculated. Standard deviation scores (SDS) of weight, height and BMI were calculated according to Dutch references (20, 21). Blood pressure was measured using an appropriately sized cuff and automated blood pressure measuring device (Dinamap, Critikon, Tampa, Florida, USA); the mean value of two measurements was used for analysis. A blood sample for measurement of glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides was taken after a fasting period of at least 4 hours.

**Assays**

Total cholesterol, HDL cholesterol and triglycerides were measured by enzymatic colorimetric assay (CHOD-PAP, HDL-C plus and GPO-PAP, respectively; Modular Analytics, Roche diagnostics, Mannheim, Germany). Inter-assay coefficient of variation is 1.9% at both 3.5 mmol/l and 7.1 mmol/l for total cholesterol, 2.9% at 1.0 mmol/l and 2.8% at 2.4 mmol/l for HDL cholesterol and 3.0% at 1.1 mmol/l and 2.3% at 1.9 mmol/l for triglycerides.

Glucose concentrations were measured by the hexokinase method (Modular Analytics, Roche diagnostics, Mannheim, Germany). Inter-assay coefficients of variation are 2.0% at 4.8 mmol/l and 1.8% at 19.8 mmol/l

**Definitions**

There is no standard definition of the metabolic syndrome in children. Ford and Li (22) reviewed all previously used definitions; most common is the definition of Cook et al. (23), based on the criteria of the National Cholesterol Education Program (NCEP), Adult Treatment Panel III for the metabolic syndrome in adults (24). According to this definition, the metabolic syndrome is diagnosed in adolescents in the presence of at least 3 of the following 5 criteria: waist circumference ≥ 90th percentile; blood pressure (systolic and/or diastolic) ≥ 90th percentile; triglycerides ≥ 1.24 mmol/l (110 mg/dl); HDL cholesterol ≤ 1.03 mmol/l (40 mg/dl); fasting glucose ≥ 6.1 mmol/l (110 mg/dl) (23). According to the International Diabetes Federation (IDF) consensus report, the metabolic syndrome as an entity should not be diagnosed in children younger than 10 years of age (25). Therefore, we investigated the prevalence of the components of the metabolic syndrome and not the prevalence of the metabolic syndrome itself.

We used the definition of Cook et al. (23) as the basis for the definitions of the components of the metabolic syndrome in the 2-year-old children in the present study. Because waist circumference measurements were not part of the routine anthropometry, we used the definition of obesity of Weiss et al. (26): BMI SDS > 2 for age and sex. For blood pressure we used the percentiles for age, sex and height of the National High Blood Pressure Education Program Working Group (27). As cut-off values for lipids, Cook et al. (23) used the midpoint value in the borderline low range (between 5th and 25th percentile) for
HDL cholesterol and in the borderline high range (between 75th and 95th percentile) for triglycerides, based on the NCEP Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents (28). As the HDL cholesterol borderline range applies to all ages, we also used the cut-off value of 1.03 mmol/l. The triglycerides borderline range is lower in children aged less than 10 years (0.85-1.12 mmol/l), so we used the midpoint value in this range (0.98 mmol/l (87 mg/dl)) as cut-off value for triglycerides. For fasting glucose we used a lower level of 5.6 mmol/l (100 mg/dl), according to the IDF definition of the metabolic syndrome in children and adolescents (25). We did not use the complete IDF definition as the basis for our definitions, as they use adult levels for all components except for obesity; their definition of obesity is the same as that of Cook et al. (23).

**Statistical analysis**

Statistical analyses were performed using the Statistical Package of Social Sciences software for Microsoft Windows version 19 (SPSS Inc., Chicago, Illinois, USA). Differences between subgroups were evaluated using Student’s t-test and Chi-Square tests. Bivariate correlation analysis was performed to study the relation between parameters of growth and components of the metabolic syndrome. P values < 0.05 were considered as significant.

**RESULTS**

During the inclusion period of the NIRTURE trial in our neonatal intensive care unit (21 months), 165 VLBW infants were admitted and the parents of 69 infants were approached regarding participation in the study. The most common reasons for not approaching parents were infants not requiring intensive care or no opportunity to obtain informed consent within the first 24 hours after birth. In our unit, 47 VLBW infants participated in the NIRTURE trial. Five infants died and 2 children were lost to follow-up. At the corrected age of 2 years, 40 children visited our outpatient clinic. Two children were excluded because the parents refused blood sampling, 38 children were included in the present study. They had a mean gestational age of 27.9 weeks (range 25.4-30.1 weeks) and a mean birth weight of 1059 g (range 680-1460 g; range birth weight SDS -1.8 to 1.3). Three children (8%) were SGA, defined as a birth weight below the 10th percentile. Most infants (n = 23) were Caucasian, 10 were Black, 3 Moroccan and 2 Asian. Highest level of education completed by either parent, as an indicator of socioeconomic status, was low (primary school, low occupational training) in 3 children, medium (high school, medium occupational training) in 16 children and high (high occupational training, university) in 19 children. Thirty-six infants received antenatal steroids and 2 received postnatal steroids. Seventeen infants (9 male/8 female) were assigned to the early-
insulin group and 21 infants (10 male/11 female) received standard neonatal care. Seven children developed bronchopulmonary dysplasia, defined as the need for supplemental oxygen at 36 weeks postmenstrual age. At the corrected age of 2 years, 2 children were developmentally delayed and 3 had cerebral palsy.

### Table 1. Characteristics of the VLBW children at birth and at the corrected age of 2 years

<table>
<thead>
<tr>
<th></th>
<th>Girls (n=19)</th>
<th>Boys (n=19)</th>
<th>Standard care (n=21) (10M/11F)</th>
<th>Early-insulin (n=17) (9M/8F)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At birth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>27.7 ± 1.4</td>
<td>28.0 ± 1.3</td>
<td>28.0 ± 1.3</td>
<td>27.7 ± 1.4</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>1007 ± 240</td>
<td>1112 ± 205</td>
<td>1054 ± 231</td>
<td>1066 ± 226</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>-0.1 ± 0.8</td>
<td>0.0 ± 0.8</td>
<td>-0.1 ± 0.7</td>
<td>0.1 ± 0.9</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>35.3 ± 3.1</td>
<td>35.2 ± 2.2</td>
<td>35.6 ± 3.0</td>
<td>34.9 ± 2.2</td>
</tr>
<tr>
<td>Length SDS</td>
<td>0.2 ± 1.1&quot;</td>
<td>-0.7 ± 1.0&quot;</td>
<td>-0.2 ± 1.0</td>
<td>-0.3 ± 1.3</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>25.1 ± 2.0</td>
<td>25.8 ± 1.4</td>
<td>25.5 ± 1.9</td>
<td>25.4 ± 1.5</td>
</tr>
<tr>
<td>Head circumference SDS</td>
<td>0.7 ± 1.2&quot;</td>
<td>-0.1 ± 0.8&quot;</td>
<td>0.2 ± 0.9</td>
<td>0.4 ± 1.3</td>
</tr>
<tr>
<td><strong>At 2 years corrected age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>11.0 ± 1.2*</td>
<td>12.1 ± 1.0*</td>
<td>11.5 ± 1.2</td>
<td>11.6 ± 1.2</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>-1.1 ± 1.0</td>
<td>-0.7 ± 0.7</td>
<td>-0.9 ± 0.9</td>
<td>-0.8 ± 0.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>85.1 ± 3.4</td>
<td>87.2 ± 3.5</td>
<td>86.4 ± 4.3</td>
<td>85.9 ± 2.6</td>
</tr>
<tr>
<td>Height SDS</td>
<td>-0.8 ± 1.1</td>
<td>-0.5 ± 1.1</td>
<td>-0.6 ± 1.3</td>
<td>-0.7 ± 0.8</td>
</tr>
<tr>
<td>Total body fat (kg)</td>
<td>1.9 ± 0.7</td>
<td>1.7 ± 0.5</td>
<td>1.9 ± 0.6</td>
<td>1.8 ± 0.6</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>15.2 ± 1.7</td>
<td>15.9 ± 1.1</td>
<td>15.5 ± 1.6</td>
<td>15.7 ± 1.3</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>-0.8 ± 1.4</td>
<td>-0.4 ± 0.9</td>
<td>-0.7 ± 1.3</td>
<td>-0.5 ± 1.0</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>92 ± 12</td>
<td>99 ± 14</td>
<td>92 ± 10</td>
<td>100 ± 16</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>58 ± 7</td>
<td>63 ± 8</td>
<td>59 ± 7</td>
<td>63 ± 9</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.4 ± 0.5</td>
<td>4.6 ± 0.5</td>
<td>4.6 ± 0.5</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.3 ± 0.8**</td>
<td>3.6 ± 0.6**</td>
<td>4.0 ± 0.8</td>
<td>3.8 ± 0.7</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.2 ± 0.3</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.3</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.2 ± 0.8</td>
<td>0.9 ± 0.4</td>
<td>1.3 ± 0.8***</td>
<td>0.7 ± 0.2***</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± standard deviation. The total group of VLBW children (n = 38) is divided in boys and girls and divided in treatment group (standard care and early-insulin therapy). Standard deviation scores (SDS) at birth according to Niklasson et al. (29) and at 2 years corrected age according to Dutch references (20, 21). Total body fat was calculated according to Dauncey et al. (19) from skinfold thickness measurements and body dimensions.

Marked data are significantly different:
At birth:
- " length SDS boys vs. girls p = 0.008 (t-test)
- "" head circumference SDS boys vs. girls p = 0.013 (t-test)
At 2 years corrected age:
- * weight boys vs. girls p = 0.003 (t-test)
- ** total cholesterol boys vs. girls p = 0.006 (t-test)
- *** triglycerides early-insulin vs. standard care p = 0.003 (t-test)
Table 1 shows the characteristics at birth and 2 years corrected age with the group divided in male and female children and divided in early-insulin therapy and standard care. At birth, boys had a significant lower length SDS and head circumference SDS than girls. As expected, at 2 years corrected age, body weight was significantly higher in boys than in girls, but body weight SDS was not significantly different. Total cholesterol was significantly higher in girls than in boys. Triglycerides were significantly lower in children treated with insulin compared to children in the standard care group.

The most common component of the metabolic syndrome was systolic and/or diastolic blood pressure ≥ 90th percentile; this was present in 20 of the 32 children (63%) with known blood pressure. Twelve children (32%) had HDL cholesterol ≤ 1.03 mmol/l and 11 children (30%) had triglycerides ≥ 0.98 mmol/l. None of the children had BMI SDS > 2 or fasting glucose ≥ 5.6 mmol/l. Two children (5%) had three components of the metabolic syndrome, 13 children (34%) had two components and 11 children (29%) had one component. In 12 children (32%) there were no criteria of the metabolic syndrome, including 5 children with unknown blood pressure and 1 child with unknown lipids due to a small blood sample volume.

Table 2 shows the presence of the criteria of the metabolic syndrome with the group divided in male and female children and divided in early-insulin therapy and standard care. The prevalence of diastolic blood pressure ≥ 90th percentile was significantly higher among boys than girls. Children in the early-insulin group had a lower prevalence of triglycerides ≥ 0.98 mmol/l than children in the standard care group.

We did not find any significant correlations between body size and composition (weight, height, BMI, total body fat calculated according to Dauncey et al. (19)) and blood pressure, fasting glucose, HDL cholesterol and triglyceride levels. Table 3 shows HDL cholesterol for BMI SDS < 0 and BMI SDS > 0 in boys and girls and in the standard care and early-insulin group. Children with BMI SDS > 0 had significantly lower HDL cholesterol than children with BMI SDS < 0. In the group with BMI SDS > 0, boys had significantly lower HDL cholesterol than girls. In the group with BMI SDS < 0, children in the early-insulin group had significantly higher HDL cholesterol levels than children who received standard care. Blood pressure, fasting glucose and triglycerides were not significantly different between children with BMI SDS > 0 and BMI SDS < 0.

Diastolic blood pressure, fasting glucose, HDL cholesterol and triglycerides were not significantly correlated to parameters of growth (increments in weight (SDS), length (SDS) and head circumference (SDS)) between birth and term age, term and 6 months corrected age, 6 and 12 months corrected age and term and 2 years corrected age. Systolic blood pressure was significantly correlated with increment in length (r = 0.39; p = 0.026) and length SDS (r = 0.42; p = 0.016) between 6 and 12 months corrected age and with increment in weight (r = 0.36; p = 0.047), length (r = 0.36; p = 0.046) and length SDS (r = 0.35; p = 0.048) between term and 2 years corrected age.
The only significant difference in growth between the early-insulin and standard care group was the change in weight SDS between 6 and 12 months corrected age (mean -0.09 vs. -0.50; p = 0.026). The mean increment in weight in this period was 2036 g in the early-insulin group (mean weight 7115 g (SDS -0.73) at 6 months and 9151 g (SDS -0.82) at 12 months) and 1707 g in the group with standard care (mean weight 7315 g (SDS -0.42) at 6 months and 9022 g (SDS -0.91) at 12 months) (p = 0.051).

Table 3. Presence of the metabolic syndrome components at the corrected age of 2 years

<table>
<thead>
<tr>
<th></th>
<th>Girls (n=19)</th>
<th>Boys (n=19)</th>
<th>Standard care (n=21)</th>
<th>Early-insulin (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI SDS &lt; 2</td>
<td>0/19</td>
<td>0/19</td>
<td>0/21</td>
<td>0/17</td>
</tr>
<tr>
<td>Systolic BP ≥ p90</td>
<td>3/15 (20.0%)</td>
<td>4/17 (23.5%)</td>
<td>2/18 (11.1%)</td>
<td>5/14 (35.7%)</td>
</tr>
<tr>
<td>Diastolic BP ≥ p90</td>
<td>5/15 (33.3%)*</td>
<td>15/17 (88.2%)*</td>
<td>9/18 (50.0%)</td>
<td>11/14 (78.6%)</td>
</tr>
<tr>
<td>Systolic and/or diastolic BP ≥ p90</td>
<td>5/15 (33.3%)**</td>
<td>15/17 (88.2%)**</td>
<td>9/18 (50.0%)</td>
<td>11/14 (78.6%)</td>
</tr>
<tr>
<td>Glucose ≥ 5.6 mmol/l</td>
<td>0/19</td>
<td>0/19</td>
<td>0/21</td>
<td>0/17</td>
</tr>
<tr>
<td>HDL cholesterol ≤ 1.03 mmol/l</td>
<td>5/18 (27.8%)</td>
<td>7/19 (36.8%)</td>
<td>7/21 (33.3%)</td>
<td>5/16 (31.3%)</td>
</tr>
<tr>
<td>Triglycerides ≥ 0.98 mmol/l</td>
<td>6/18 (33.3%)</td>
<td>5/19 (26.3%)</td>
<td>10/21 (47.6%)*</td>
<td>1/16 (6.3%)*</td>
</tr>
<tr>
<td>1 metabolic syndrome component present</td>
<td>6/19 (31.6%)</td>
<td>5/19 (26.3%)</td>
<td>6/21 (28.6%)</td>
<td>5/17 (29.4%)</td>
</tr>
<tr>
<td>2 metabolic syndrome components present</td>
<td>5/19 (26.3%)</td>
<td>8/19 (42.1%)</td>
<td>7/21 (33.3%)</td>
<td>6/17 (35.3%)</td>
</tr>
<tr>
<td>3 metabolic syndrome components present</td>
<td>0/19</td>
<td>2/19 (10.5%)</td>
<td>2/21 (9.5%)</td>
<td>0/17</td>
</tr>
</tbody>
</table>

The total group of VLBW children (n = 38) is divided in boys and girls and divided in treatment group (standard care and early-insulin therapy). The data show the number of children in which the component is present, the total number of children in which the component is known and (between brackets) the percentage of children with the component present for all 4 subgroups.

Marked data are significantly different:
- * diastolic BP ≥ p90 boys vs. girls p = 0.001 (Chi-Square test)
- ** systolic and/or diastolic BP ≥ p90 boys vs. girls p = 0.001 (Chi-Square test)
- *** triglycerides ≥ 0.98 mmol/l early-insulin vs. standard care p = 0.01 (Fisher’s Exact test)

Table 3. HDL cholesterol

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Girls</th>
<th>Boys</th>
<th>Standard care</th>
<th>Early-insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI SDS &lt; 0</td>
<td>N 25</td>
<td>13</td>
<td>12</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>HDL</td>
<td>1.2 ± 0.3*</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.2**</td>
<td>1.2 ± 0.3*</td>
<td>1.4 ± 0.1***</td>
</tr>
<tr>
<td>BMI SDS &gt; 0</td>
<td>N 12</td>
<td>5</td>
<td>7</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>HDL</td>
<td>1.0 ± 0.2*</td>
<td>1.1 ± 0.2**</td>
<td>0.9 ± 0.1**</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.2***</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± standard deviation. HDL cholesterol in mmol/l.

Marked data are significantly different:
- * BMI SDS < 0 vs. BMS SDS > 0 in total group p = 0.01 (t-test)
- ** BMI SDS < 0 vs. BMI SDS > 0 in boys p = 0.001 (t-test)
- *** BMI SDS < 0 vs. BMI SDS > 0 in early-insulin group p = 0.004 (t-test)
- * girls vs. boys in group with BMI SDS > 0 p = 0.045 (t-test)
- ** early-insulin vs. standard care in group with BMI SDS < 0 p = 0.043 (t-test)

The only significant difference in growth between the early-insulin and standard care group was the change in weight SDS between 6 and 12 months corrected age (mean -0.09 vs. -0.50; p = 0.026). The mean increment in weight in this period was 2036 g in the early-insulin group (mean weight 7115 g (SDS -0.73) at 6 months and 9151 g (SDS -0.82) at 12 months) and 1707 g in the group with standard care (mean weight 7315 g (SDS -0.42) at 6 months and 9022 g (SDS -0.91) at 12 months) (p = 0.051). Weight, length
and head circumference at birth, term age, 6, 12 and 24 months corrected age were not significantly different between the early-insulin and standard care group. There were no differences in growth between the children with and without any of the components of the metabolic syndrome.

DISCUSSION

Barker et al. (30) first indicated the importance of fetal growth for development of the metabolic syndrome and showed an increasing prevalence with decreasing birth weight. Insulin resistance plays a central role in the metabolic syndrome and adults born SGA are more insulin-resistant than controls (2, 3). Insulin sensitivity is already reduced in SGA born children, especially in children with catch-up growth (6, 7, 9, 11, 12).

Premature born infants have impaired growth in early postnatal life, in a period comparable to the third trimester of pregnancy. Adults born premature have higher fasting glucose levels, lower insulin sensitivity and higher blood pressure than controls (1, 4, 5). The reduction in insulin sensitivity as a result of premature birth is already present in children between the ages of 4 and 10 years (8). For VLBW infants, there is one study on insulin sensitivity in prepubertal children (age 5-7 years), which showed that insulin sensitivity is determined by growth in utero and postnatal growth rate (31). The other components of the metabolic syndrome have not been studied before in VLBW children.

The present study shows that the majority of VLBW infants already have one or more components of the metabolic syndrome at the corrected age of 2 years. Especially the prevalence of raised (diastolic) blood pressure is high. A possible explanation for the association between preterm birth and elevated blood pressure is reduced insulin sensitivity with hyperinsulinemia. Insulin levels are positively correlated to blood pressure in children (32); this could be mediated by the stimulating effect of insulin on sympathetic nervous system activity, renal sodium retention and/or vascular smooth muscle growth (33). Antenatal steroids could also contribute to the elevated blood pressure: almost all infants in our study received antenatal steroids and antenatal corticosteroid therapy is associated with higher systolic and diastolic blood pressures in later life (34). In our study the prevalence of raised diastolic blood pressure was significantly higher in boys than in girls. In adults the sex difference in blood pressure could possibly be explained by the differential effects of estrogens and androgens on the renin-angiotensin system (35). The hypothalamic-pituitary-gonadal axis is also active in the postnatal period and in girls follicle-stimulating hormone (FSH) levels and often also estradiol levels stay above those of older pre-pubertal children during the first years of life (36, 37). Therefore the blood pressure difference between boys and girls in our study could also be caused by sex hormones.
Almost one third of the VLBW children had high triglycerides. High childhood triglycerides are an important predictor of adult cardiovascular disease (38). We showed that the VLBW children treated with insulin in the first week of life had lower triglycerides than the children with standard care. By acting in a period that is critical for programming of insulin sensivity (8), early insulin therapy in VLBW infants could possibly improve long-term insulin sensivity. The possible long-term benefit of early insulin treatment on triglyceride levels could then be the result of less insulin resistance as insulin resistance in the liver results in very low-density lipoprotein overproduction and development of hypertriglyceridemia (33, 39). As we did not measure insulin sensivity in the present study, we could not confirm the role of insulin resistance in the development of high blood pressure and hypertriglyceridemia.

Low HDL cholesterol levels were also present in nearly one third of the children. We confirmed that a higher BMI is associated with an adverse metabolic profile, as children with BMI SDS > 0 had lower HDL cholesterol levels than children with BMI SDS < 0. The significant lower HDL cholesterol levels in boys with BMI SDS > 0 compared to girls with BMI SDS > 0 could be attributed to sex hormones, just like the significant higher total cholesterol levels in girls. Protein-bound estradiol is positively correlated with HDL cholesterol (40) and, as mentioned before, the hypothalamic-pituitary-gonadal axis is still active in 2-year-old girls. In the group with BMI SDS < 0, children treated with insulin had significantly higher HDL cholesterol levels than children who received standard care, suggesting that insulin treatment could also have advantages for this component of the metabolic syndrome. Longer follow-up is necessary to find out whether the possible metabolic advantages of early insulin treatment persist into later childhood and adulthood. Our proposal for longer follow-up is confirmed by previous results of animal studies in which leptin or exendin-4 was administered during the neonatal period, indicating that early postnatal intervention can indeed have long-term effects on metabolism (41, 42).

Rapid postnatal growth is unfavourable for blood pressure levels and insulin sensitivity of SGA and preterm born children and adults (4, 9-12, 15, 17, 31). In VLBW infants we demonstrated this already at the corrected age of 2 years: systolic blood pressure was positively correlated to parameters of growth between 6 and 12 months and between 0 and 24 months corrected age.

The results of our study have implications for the follow-up of VLBW infants. It is very important to measure blood pressure on a regular basis during childhood and some children, especially boys, will need treatment for hypertension. With the high prevalence of the components of the metabolic syndrome, parents should be counseled about the risk of cardiovascular disease and should be given life style advice.

Our study is limited by the small number of infants, the lack of data from term born children and the absence of a generally accepted definition of the metabolic syndrome...
in children. The results have to be confirmed in a larger group of VLBW infants and compared with a control group of term born children. As the cut-off values for several metabolic syndrome components are now based on studies in other populations, the values of the VLBW children have to be compared with those of term born children from our own population.

In conclusion, this study is the first indication that at the corrected age of 2 years, VLBW infants already have a high prevalence of components of the metabolic syndrome. Raised (diastolic) blood pressure is most common, especially in boys. Early insulin treatment could possibly have long-term benefits for some components of the metabolic syndrome in VLBW infants. More studies are needed in larger groups of VLBW children, including control groups of term born children.
REFERENCES


