

ORIGINAL ARTICLE

# Glucose Regulation in Young Adults with Very Low Birth Weight

Petteri Hovi, M.D., Sture Andersson, M.D., Ph.D.,  
Johan G. Eriksson, M.D., Ph.D., Anna-Liisa Järvenpää, M.D., Ph.D.,  
Sonja Strang-Karlsson, M.D., Outi Mäkitie, M.D., Ph.D.,  
and Eero Kajantie, M.D., Ph.D.

## ABSTRACT

### BACKGROUND

The association between small size at birth and impaired glucose regulation later in life is well established in persons born at term. Preterm birth with very low birth weight (<1500 g) is also associated with insulin resistance in childhood. If insulin resistance persists into adulthood, preterm birth with very low birth weight also may be associated with an increased risk of disease in adulthood. We assessed glucose tolerance and insulin sensitivity and measured serum lipid levels and blood pressure in young adults with very low birth weight.

### METHODS

We performed a standard 75-g oral glucose-tolerance test, measuring insulin and glucose concentrations at baseline and at 120 minutes in 163 young adults (age range, 18 to 27 years) with very low birth weight and in 169 subjects who had been born at term and were not small for gestational age. The two groups were similar with regard to age, sex, and birth hospital. We measured blood pressure and serum lipid levels, and in 150 very-low-birth-weight subjects and 136 subjects born at term, we also measured body composition by means of dual-energy x-ray absorptiometry.

### RESULTS

As compared with the subjects born at term, the very-low-birth-weight subjects had a 6.7% increase in the 2-hour glucose concentration (95% confidence interval [CI], 0.8 to 12.9), a 16.7% increase in the fasting insulin concentration (95% CI, 4.6 to 30.2), a 40.0% increase in the 2-hour insulin concentration (95% CI, 17.5 to 66.8), an 18.9% increase in the insulin-resistance index determined by homeostatic model assessment (95% CI, 5.7 to 33.7), and an increase of 4.8 mm Hg in systolic blood pressure (95% CI, 2.1 to 7.4). Adjustment for the lower lean body mass in the very-low-birth-weight subjects did not attenuate these relationships.

### CONCLUSIONS

Young adults with a very low birth weight have higher indexes of insulin resistance and glucose intolerance and higher blood pressure than those born at term.

From the Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Helsinki (P.H., J.G.E., S.S.-K., E.K.); the Hospital for Children and Adolescents, Institute of Clinical Medicine, University of Helsinki (P.H., S.A., A.-L.J., S.S.-K., O.M., E.K.); and the Department of Public Health (J.G.E.), University of Helsinki. Address reprint requests to Dr. Hovi at the National Public Health Institute, Mannerheimintie 166, FI-00300 Helsinki, Finland, or at petteri.hovi@helsinki.fi.

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**E**PIDEMIOLOGIC STUDIES HAVE SHOWN AN association between small size at term birth and during infancy and an increased risk of impaired glucose regulation and cardiovascular disease later in life.<sup>1-4</sup> Few studies have assessed the effect of markedly preterm birth on risk factors for these conditions in adulthood,<sup>5-7</sup> although markedly preterm birth interrupts the period of highest growth velocity during the entire lifetime and is almost always followed by a postnatal period of prematurity-associated illness, inadequate nutrition, and growth retardation. Many preterm infants also had growth retardation in utero.

The development of neonatal intensive care in recent decades has brought about dramatic changes in the prognosis for infants with very low birth weight (<1500 g).<sup>8,9</sup> The first generation of such infants is now entering adulthood, and questions related to their health in adulthood are becoming increasingly relevant.

A study in prepubertal children showed that those with very low birth weight had a 34% lower index of insulin sensitivity than did those born at term.<sup>10,11</sup> Whether this difference persists into adulthood is not known.

We conducted a study to determine whether very low birth weight is associated with changes in glucose and insulin metabolism, serum lipid levels, or blood pressure in young adults and whether these changes might be explained by differences in body size and composition in persons in this age group.<sup>12</sup> We studied a cohort of young adults (age range, 18 to 27 years) with very low birth weight and a comparison group born at term. The comparison group was matched for age, sex, and birth hospital.

## METHODS

### SUBJECTS

The original study cohort comprised 335 consecutive, very-low-birth-weight infants born between January 1978 and December 1985 who were discharged alive from the neonatal intensive care unit of Children's Hospital at Helsinki University Central Hospital, the only tertiary neonatal care center in the province of Uusimaa, Finland.

We selected a comparison group from the records of all consecutive births at each birth hospital. For each very-low-birth-weight survivor, we selected the next available singleton infant born

at term (gestational age,  $\geq 37$  weeks) of the same sex who was not small for gestational age (standard-deviation score for birth weight,  $\geq -2$ ).

We then traced all the subjects in young adulthood through data from the Population Register Centre of Finland. Mortality from hospital discharge to June 2004 was 1.8% for the very-low-birth-weight subjects and 1.0% for the comparison group born at term. Among the survivors, we were able to contact 95.1% of very-low-birth-weight subjects and 96.8% of subjects born at term. We invited the 255 very-low-birth-weight subjects and 314 subjects born at term who were living in the greater Helsinki area to participate in the study; 166 of the very-low-birth-weight subjects (65.1%) and 172 of the subjects born at term (54.8%) agreed to participate. A total of 43.3% of the very-low-birth-weight subjects and 40.6% of the subjects born at term were men. The birth weight ranged from 600 to 1500 g in the very-low-birth-weight group and from 2560 to 4930 g in the term group; the gestational age ranged from 24.0 to 35.6 weeks in the very-low-birth-weight group and from 37.0 to 42.9 weeks in the term group. Of the very-low-birth-weight participants, 23 (14%) were from a twin pregnancy, and 5 (3%) were from a triplet pregnancy.

We used standard criteria to define preeclampsia<sup>13</sup> and bronchopulmonary dysplasia.<sup>14</sup> Perinatal and neonatal data from clinic and hospital records of the study participants and nonparticipants were similar, except for the lower rate of cerebral palsy at 15 months of age among the participants with very low birth weight (Table 1). Of the 89 very-low-birth-weight subjects who did not participate in the study, 11 stated disability as a reason for not participating.

The very-low-birth-weight infants had been weighed daily during their hospital stay and during clinic visits after discharge. If the weight at 36 or 40 weeks of postmenstrual age was missing from the records, we included in our analyses the interpolated value based on measurements available within 10 days before and 20 days after those time points. Weights were converted into standard-deviation scores according to Finnish birth-weight charts.<sup>15</sup> The study protocol was approved by the ethics committee at the Helsinki University Central Hospital, and all participants provided written informed consent. No adverse events occurred in the course of this study.

**Table 1. Characteristics of Infants with Very Low Birth Weight and Those Born at Term.\***

Characteristic	Study Participants	Study Nonparticipants	P Value
<b>Very low birth weight</b>			
No. of subjects	166	89	
Maternal preeclampsia — no. (%)	35 (21.1)	21 (23.6)	0.89
Birth weight — g	1120±221	1130±209	0.73
Gestational age — wk	29.17±2.22	29.17±2.68	0.99
Standard-deviation score for birth weight	-1.29±1.51	-1.13±1.78	0.47
Birth-weight standard-deviation score less than -2.0 — no. (%)	55 (33.1)	26 (29.2)	0.52
Mechanical ventilation — days			0.80
Median	5	5	
Interquartile range	0–14	0–16	
Oxygen — days			0.43
Median	13	17	
Interquartile range	3–34	3–40	
Age at discharge — days			0.92
Median	70	62	
Interquartile range	53–90	55–90	
Bronchopulmonary dysplasia — no. (%)†	30 (18.1)	18 (20.2)	0.68
Cerebral palsy at 15 mo — no. (%)†	10 (6.0)	17 (19.1)	0.005
<b>Born at term†</b>			
No. of subjects	172	142	
Maternal preeclampsia — no. (%)	13 (7.6)	5 (3.5)	0.31
Birth weight — g	3593±471	3648±454	0.30
Gestational age — wk	40.1±1.2	40.1±1.2	0.88
Standard-deviation score for birth weight	0.0±1.0	0.1±1.0	0.45

\* Plus-minus values are means ±SD. P values for maternal preeclampsia, a birth-weight standard-deviation score of less than -2.0, bronchopulmonary dysplasia, and cerebral palsy at 15 months were calculated with Pearson's chi-square test; P values for birth weight, gestational age, and birth-weight standard-deviation score were calculated with Student's t-test; and P values for the duration of mechanical ventilation, the duration of oxygen administration, and age at discharge were calculated with the Mann-Whitney U test.

† None of the subjects born at term had bronchopulmonary dysplasia or cerebral palsy.

#### CLINICAL MEASUREMENTS

All participants attended the clinic at the National Public Health Institute after an overnight fast of at least 8 hours. Height, waist and hip circumferences, and weight in underwear were measured, and the body-mass index was calculated.

The participants completed questionnaires that covered their medical history, their regular leisure-time exercise, the current educational level of their parents or caregivers, and their parents' history of type 1 or type 2 diabetes. The blood pressure and heart rate were measured from the right arm of each subject by means of the same automated

oscillometric device. The mean values of the two measurements were calculated. Serum cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were measured, and a standard 75-g oral glucose-tolerance test was performed with measurements of plasma glucose and serum insulin concentrations at baseline and at 120 minutes.

#### ASSAYS

Plasma glucose concentrations were measured by means of a spectrophotometric hexokinase and glucose-6-phosphate dehydrogenase assay (Gluko-

quant glucose/hexokinase, Roche Diagnostics) with a Hitachi Modular automatic analyzer. At a glucose concentration of 4.7 mmol per liter (84.7 mg per deciliter), the interassay coefficient of variation is 2.3%.<sup>16</sup> Insulin was measured by means of a time-resolved immunofluorometric assay (Perkin Elmer) with a detection limit of 0.5 mU per liter (3 pmol per liter) and an interassay coefficient of variation of less than 4% in the concentration range of 6 to 104 mU per liter (36 to 624 pmol per liter).<sup>17</sup> The insulin-resistance index determined by homeostasis model assessment (HOMA-IR) was calculated as the product of the fasting serum insulin concentration (in milliunits per liter) and fasting plasma glucose concentration (in millimoles per liter) divided by 22.5.<sup>18</sup> Serum lipid levels were measured by enzymatic methods (HDL-C plus, second generation; Cholesterol CHOD-PAP; and Triglycerides GPO-PAP; Roche Diagnostics) with a Hitachi Modular analyzer; coefficients of variance range from 2.4 to 4.6%. In a subgroup of 152 very-low-birth-weight subjects and 138 subjects born at term, the lean body mass and percentage of fat were measured in the trunk, leg, and whole body by means of dual-energy x-ray densitometry (Discovery A, Hologic). The ratio of the percentage of trunk fat to leg fat was calculated.<sup>19</sup>

#### STATISTICAL ANALYSIS

We calculated that we would need to enroll at least 140 subjects in each group to have a statistical power of 90% to detect a between-group difference of 0.40 in the standard-deviation score with an alpha level of 0.05 in a two-sided analysis. Insulin and glucose concentrations, HOMA-IR index, body-mass index, waist circumference, and lean body mass were logarithmically transformed to normalize the distribution of values. Unadjusted comparisons were made by means of Student's *t*-test, and adjusted comparisons by linear regression, with the mean difference and 95% confidence interval (CI) reported. Comparisons of participants with non-participants regarding the duration of mechanical ventilation, oxygen therapy, and intensive care were analyzed by means of the Mann-Whitney *U* test. Proportional differences were tested with Pearson's chi-square test or Fisher's exact test. The highest quartile of insulin concentrations was defined as insulin concentrations equaling the highest sex-specific quartile among the comparison group. Impaired glucose tolerance, type 2 diabetes, and impaired fasting glucose concentrations were defined

according to American Diabetes Association criteria.<sup>20</sup> We fitted logistic models to predict the highest quartile of insulin level and linear regression models to predict glucose and insulin concentrations and the HOMA-IR index. We excluded six subjects from the analyses because two did not follow the fasting regimen, one had type 1 diabetes, one had panhypopituitarism, and two were pregnant. Although we present the body composition of men and women separately, we found no evidence of interactions regarding sex ( $P > 0.10$  for all interaction terms), and men and women were therefore pooled for the analyses, with adjustments for sex, age, and the factors listed in Table 2. Significance tests were two-sided, with a type 1 error set at 0.05.

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## RESULTS

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#### CHARACTERISTICS OF THE COHORT

Table 3 shows the body size and composition among men and women at a mean age of 22.4 years (range, 18.5 to 27.1). As compared with subjects born at term, the very-low-birth-weight women were 5.3 cm shorter ( $P < 0.001$ ), and the men were 5.9 cm shorter ( $P < 0.001$ ). Women with very low birth weight had a body-mass index that was 2.4% lower than that of the women in the comparison group ( $P = 0.29$ ); men in the very-low-birth-weight group had a body-mass index that was 5.9% lower ( $P = 0.02$ ). The lower body-mass index in the very-low-birth-weight subjects appeared to be due to a lower amount of both lean and fat mass; the percentage of body fat, ratio of the percentage of trunk fat to the percentage of leg fat, and waist-to-hip ratio were similar to those in the comparison group. However, the lean body mass adjusted for current height was 3.3% lower among women and 5.3% lower among men in the very-low-birth-weight group ( $P = 0.04$  and  $P = 0.01$ , respectively).

#### ORAL GLUCOSE-TOLERANCE TEST, SERUM LIPID LEVELS, AND BLOOD PRESSURE

Figure 1 shows the mean glucose and insulin concentrations and the HOMA-IR index for both groups. As compared with subjects born at term, very-low-birth-weight subjects had a 2-hour glucose concentration that was 6.7% higher (95% CI, 0.8 to 12.9), a fasting insulin concentration that was 16.7% higher (95% CI, 4.6 to 30.2), a 2-hour insulin concentration that was 40.0% higher (95% CI, 17.5 to 66.8), a HOMA-IR index that was 18.9%

**Table 2. Confounding Factors for Young Adults with Very Low Birth Weight and a Comparison Group Born at Term.\***

Factor	Very-Low-Birth- Weight Group (N = 163)	Group Born at Term (N = 169)	P Value
	no. (%)		
History of diabetes in either parent			0.46
Yes	15 (9.2)	12 (7.1)	
No	140 (85.9)	151 (89.3)	
Unknown	8 (4.9)	6 (3.6)	
Regular leisure-time exercise activity			<0.001
Walking	48 (29.4)	20 (11.8)	
Walking or light running	44 (27.0)	44 (26.0)	
Light running	42 (25.8)	48 (28.4)	
Brisk running	22 (13.5)	55 (32.5)	
Unknown	7 (4.3)	2 (1.2)	
Current education of mother or father, whichever is highest			0.11
Elementary	9 (5.5)	6 (3.6)	
Intermediate	78 (47.9)	72 (42.6)	
University	57 (35.0)	82 (48.5)	
Unknown	19 (11.7)	9 (5.3)	

\* P values are for comparisons between the two groups with the use of Pearson's chi-square test.

higher (95% CI, 5.7 to 33.7), systolic pressure that was 4.8 mm Hg higher (95% CI, 2.1 to 7.4), diastolic pressure that was 4.1 mm Hg higher (95% CI, 2.2 to 6.0), and a heart rate that was 2.1 beats per minute higher (95% CI, -0.9 to 5.1) (Table 4). None of the subjects had type 2 diabetes, but 10 very-low-birth-weight subjects and 8 subjects born at term had impaired glucose tolerance ( $P=0.63$  by Fisher's exact test), and 5 very-low-birth-weight subjects and 6 subjects born at term had impaired fasting glucose. The percentage of very-low-birth-weight subjects with a fasting insulin concentration in the highest quartile was 33.3% ( $P=0.09$ ; with adjustment for sex, age, and body-mass index,  $P=0.01$ ).

Table 4 shows that adjustment for body-mass index did not alter the estimated differences between the groups for 2-hour glucose or for 2-hour insulin concentrations but strengthened the differences for insulin concentrations and HOMA-IR. Furthermore, adjustment for lean body mass and height (Table 4), body-fat percentage, ratio of the percentage of trunk fat to the percentage of leg fat, or waist-to-hip ratio had little effect on the results (data not shown).

Serum lipid levels were similar between the groups. The mean ( $\pm$ SD) total cholesterol level was  $4.5\pm 0.8$  mmol per liter ( $175.5\pm 31.2$  mg per deciliter) in the very-low-birth-weight group and  $4.6\pm 0.8$  mmol per liter ( $179.4\pm 31.2$  mg per deciliter) in the comparison group ( $P=0.37$ ). HDL cholesterol levels were  $1.7\pm 0.4$  mmol per liter ( $66.3\pm 15.6$  mg per deciliter) and  $1.6\pm 0.4$  mmol per liter ( $62.4\pm 15.6$  mg per deciliter), respectively ( $P=0.71$ ). Triglyceride levels (expressed as geometric means) were 1.0 mmol per liter (89.0 mg per deciliter) in the very-low-birth-weight group and 1.0 mmol per liter (89.0 mg per deciliter) in the comparison group ( $P=0.95$ ).

#### INTRAUTERINE GROWTH AND METABOLIC MEASUREMENTS

Of the 163 subjects with very low birth weight, 54 had a standard-deviation score for birth weight that was lower than -2.0 and were considered to be small for gestational age; the remaining 109 had a birth weight that was considered to be appropriate for gestational age. As compared with the subjects born at term and with adjustment for age, sex, and body-mass index, subjects who had very

**Table 3. Anthropometry and Body Composition of Young Adults with Very Low Birth Weight and a Comparison Group Born at Term.\***

Measure	Very-Low-Birth-Weight Group	Group Born at Term	Difference (95% CI)†
<b>Women</b>			
Mean height — cm	162.0±7.7	167.2±6.8	-5.3 (-7.3 to -3.2)
<b>Weight</b>			
Geometric mean — kg	57.3	62.6	-8.5% (-12.9 to -3.8)‡
Geometric standard deviation	20.9%	17.4%	
<b>BMI</b>			
Geometric mean	21.9	22.4	-2.4% (-6.7 to 2.1)‡
Geometric standard deviation	18.1%	16.6%	
<b>Waist circumference</b>			
Geometric mean — cm	76.9	78.4	-2.0% (-5.2 to 1.3)‡
Geometric standard deviation	13.1%	11.6%	
Mean hip circumference — cm	95.8±8.3	97.6±7.6	-1.9 (-4.1 to 0.4)
Mean waist-to-hip ratio	0.81±0.06	0.81±0.05	0.00 (-0.02 to 0.02)
Mean percentage of body fat§	29.4±6.1	29.9±5.5	-0.5 (-2.3 to 1.2)
Mean ratio of the percentage of trunk fat to the percentage of leg fat	0.68±0.13	0.72±0.15	-0.04 (-0.08 to 0.01)
<b>Whole-body lean mass§</b>			
Geometric mean — kg	38.6	42.6	-9.5% (-13.1 to -5.7)‡
Geometric standard deviation	15.5%	13.5%	
<b>Lean mass adjusted for height§</b>			
Geometric mean — kg	40.0	41.3	-3.3% (-6.2 to -0.2)‡
Geometric standard deviation	10.2%	11.5%	

low birth weight and were also small for gestational age had a 7.3% increase (95% CI, 0.5 to 13.7) in the 2-hour glucose concentration, a 20.2% increase (95% CI, 8.2 to 30.6) in the fasting insulin concentration, and a 32.6% increase (95% CI, 16.4 to 45.6) in the 2-hour insulin concentration.

In contrast, subjects who had very low birth weight that was appropriate for gestational age had a 5.2% increase (95% CI, -0.7 to 11.4) in the 2-hour glucose concentration, as compared with the subjects born at term, a 15.8% increase (95% CI, 3.6 to 29.3) in the fasting insulin concentration, and a 33.0% increase (95% CI, 11.5 to 58.7) in the 2-hour insulin concentration. In the very-low-birth-weight group, the differences in these concentrations between the small-for-gestational-age subjects and the appropriate-for-gestational-age subjects were not significant (range of P values, 0.29 to 0.50). The differences in blood pressure between these subgroups were also not

significant. A post hoc analysis in which we used the 10th percentile (standard-deviation score, -1.3) as a cutoff point to define small and appropriate for gestational age also showed no significant differences (range of P values, 0.25 to 0.88).

A history of maternal preeclampsia or pregnancy-induced hypertension was not associated with any significant differences in glucose or insulin concentrations. Glucose and insulin concentrations were similar in very-low-birth-weight subjects from multiple pregnancies and those from singleton pregnancies; including only singletons in the analyses did not affect the results. The results were similar when we restricted the very-low-birth-weight subjects to those with no history of cerebral palsy (150 subjects) or to those either with no history of bronchopulmonary dysplasia or who were not currently using inhaled corticosteroid administration (129 subjects). The results were also similar when the subjects born at term were re-

Table 3. (Continued.)

Measure	Very-Low-Birth-Weight Group	Group Born at Term	Difference (95% CI) <sup>†</sup>
<b>Men</b>			
Mean height — cm	174.6±7.8	180.5±6.4	-5.9 (-8.3 to -3.5)
<b>Weight</b>			
Geometric mean — kg	66.0	75.1	-12.0% (-16.9 to -6.8) <sup>‡</sup>
Geometric standard deviation	20.8%	15.8%	
<b>BMI<sup>§</sup></b>			
Geometric mean	21.7	23.1	-5.9% (-10.4 to -1.1) <sup>‡</sup>
Geometric standard deviation	17.3%	14.1%	
<b>Waist circumference</b>			
Geometric mean — cm	81.9	86.0	-4.8% (-8.1 to -1.3) <sup>‡</sup>
Geometric standard deviation	12.1%	10.5%	
Mean hip circumference — cm	93.7±7.6	97.4±7.0	-3.7 (-6.1 to -1.2)
Mean waist-to-hip ratio	0.88±0.05	0.89±0.06	-0.01 (-0.03 to 0.01)
Mean percentage of body fat <sup>  </sup>	18.1±6.3	18.1±5.4	0.0 (-2.1 to 2.2)
Mean ratio of the percentage of trunk fat to the percentage of leg fat	0.86±0.16	0.81±0.15	0.05 (-0.01 to 0.11)
<b>Whole-body lean mass<sup>¶</sup></b>			
Geometric mean — kg	53.2	60.9	-12.7% (-17.1 to -8.0) <sup>‡</sup>
Geometric standard deviation	16.6%	13.2%	
<b>Lean mass adjusted for height<sup>§</sup></b>			
Geometric mean — kg	55.5	58.6	-5.3% (-9.2 to -1.3) <sup>‡</sup>
Geometric standard deviation	12.1%	11.9%	

\* Plus–minus values are means ±SD. All other values are geometric means. The geometric mean is the nth root of the product of n individual values. Geometric standard deviations correspond to the percent increase in the variable corresponding to a change of one standard-deviation unit in the logarithm of the variable.

<sup>†</sup> The difference (unadjusted) is the value in the very-low-birth-weight group as compared with the control group.

<sup>‡</sup> In these right-skewed variables, the difference and its 95% confidence interval are expressed in percentages.

<sup>§</sup> Body-mass index is the weight in kilograms divided by the square of the height in meters.

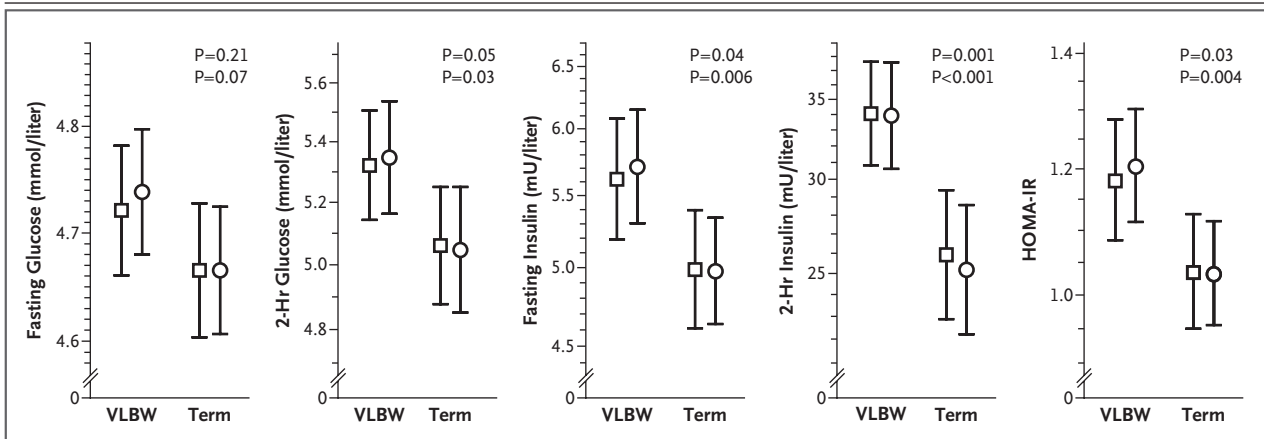
<sup>¶</sup> Dual-energy x-ray absorptiometry was performed in 87 women and 63 men with very low birth weight and in 83 women and 53 men in a comparison group.

stricted to those whose standard-deviation score for birth weight fell between the 10th and 90th percentiles (138 subjects).

#### GROWTH FROM BIRTH TO TERM

Body weight at what would have been 40 weeks of postmenstrual age (term) could be determined for 100 of the 163 very-low-birth-weight subjects. The mean standard-deviation score for weight at 40 weeks of postmenstrual age was  $-2.6 \pm 1.15$ , and the mean change from birth to term was  $-1.4 \pm 1.32$ . Neither the standard-deviation score for weight at term nor the change in the score from birth to term was related to the glucose or insu-

lin concentrations, nor was either related to the HOMA-IR index. However, when the analysis was restricted to the 31 subjects who were small for gestational age at birth, the mean standard-deviation score for weight change from birth to term was  $-0.2 \pm 0.69$ ; an increase of 1 standard-deviation unit in this score corresponded to a 30.8% increase (95% CI, 0.13 to 70.8) in the fasting insulin concentration and a 22.8% increase (95% CI, -4.4 to 57.7) in the 2-hour insulin concentration. Among the 69 subjects whose weight was appropriate for gestational age at birth, no such relationships were evident ( $P=0.05$  for an interaction with the fasting insulin concentration;  $P=0.39$  for an interaction



**Figure 1.** Glucose and Insulin Concentrations and the Insulin-Resistance Index (HOMA-IR) in Young Adults with Very Low Birth Weight (VLBW) and a Comparison Group of Young Adults Born at Term.

Geometric means with 95% confidence intervals are shown for unadjusted variables (squares) and for variables adjusted for age, sex, body-mass index, exercise intensity, presence or absence of parental diabetes, and parental educational level (circles). In each panel, the first P value is for the unadjusted model, and the second P value is for the adjusted model. The height of each panel is scaled to correspond to three fourths of the standard deviation of the logarithm of the variable. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. To convert the values for insulin to picomoles per liter, multiply by 6.

with the 2-hour insulin concentration). When we analyzed the data for the standard-deviation score for body weight at 36 weeks of postmenstrual age, which was known for 140 of the 163 subjects, the results were similar.

## DISCUSSION

As compared with young adults who had been born at term, those with very low birth weight had significantly higher fasting insulin, 2-hour insulin, and 2-hour glucose concentrations, as well as a higher HOMA-IR index and higher blood pressure. These differences were not attributable to body size or composition or to fat distribution. Thus, very low birth weight appears to be associated with signs of insulin resistance and impaired glucose regulation in early adulthood.

The fasting insulin concentration and the HOMA-IR index are widely accepted measures of insulin resistance and are closely correlated with more precise but laborious measures such as an intravenous glucose-tolerance test<sup>21</sup> or hyperinsulinemic clamp study.<sup>22</sup> Fasting insulin and the HOMA-IR both generally predict, together with 2-hour glucose concentrations, the risk of type 2 diabetes,<sup>23</sup> as well as the risk of death from cardiovascular causes<sup>24,25</sup> and from all causes.<sup>24</sup> Thus, young adults with very low birth weight would appear to benefit from targeted preventive interventions. Our finding of increased blood pressure

in very-low-birth-weight adults is consistent with previous observations<sup>5-7,26,27</sup> and provides further support for preventive interventions in this population.

Our observations in adults who had very low birth weight are consistent with a large body of literature on cohorts born mainly at term in which associations between low birth weight at term and later impairment in glucose regulation have been reported.<sup>28</sup> A few studies involved subjects born at term who were small for gestational age (below a defined threshold for birth weight, usually a standard-deviation score of  $-2$  or the 10th percentile). As compared with subjects with a birth weight that was appropriate for gestational age, these subjects tended to have impaired glucose regulation, and this difference was already observed in childhood<sup>29,30</sup> or in young adulthood.<sup>31,32</sup> Such epidemiologic observations, together with experimental studies in animals, have led to the concept of the developmental origins of health and disease, which proposes that environmental factors in early life have consequences in later life that are manifested as an altered risk of disease.<sup>33,34</sup> Our study suggests that very low birth weight may have such consequences in early adulthood.

In accordance with some,<sup>10</sup> although not all,<sup>35,36</sup> studies in children, we observed a similar degree of impairment in glucose regulation among the young adults with very low birth weight, irrespective of whether they were small for gestational age

**Table 4. Indexes of Glucose Regulation and Blood Pressure in a Multiple Regression Analysis.\***

Measurement	Very-Low-Birth-Weight Group	Group Born at Term	Model†	No. of Subjects	Difference (95% CI)‡	P Value
Fasting glucose			1	332	1.0% (−0.7 to 2.8)	0.25
Geometric mean — mmol/liter	4.72	4.67	2	332	1.5% (−0.2 to 3.3)	0.08
Geometric standard deviation	9%	9%	3	291	1.8% (−0.2 to 3.7)	0.07
			4	249	2.5% (0.2 to 4.9)	0.03
2-hour glucose			1	332	5.3% (0.2 to 10.7)	0.04
Geometric mean — mmol/liter	5.34	5.05	2	332	6.0% (0.9 to 11.5)	0.02
Geometric standard deviation	25%	27%	3	291	6.7% (0.8 to 12.9)	0.03
			4	249	5.6% (−1.2 to 12.8)	0.11
Fasting insulin			1	331	12.6% (0.8 to 25.8)	0.04
Geometric mean — mU/liter	5.61	5.01	2	331	18.7% (7.6 to 31.0)	0.001
Geometric standard deviation	66%	72%	3	290	16.7% (4.6 to 30.2)	0.006
			4	248	21.0% (5.8 to 38.4)	0.006
2-hour insulin			1	331	32.8% (13.9 to 54.7)	<0.001
Geometric mean — mU/liter	34.1	25.6	2	331	37.4% (18.2 to 59.8)	<0.001
Geometric standard deviation	90%	129%	3	290	40.0% (17.5 to 66.8)	<0.001
			4	248	33.7% (8.1 to 65.5)	0.008
Insulin-resistance index determined by HOMA			1	331	13.9% (1.1 to 28.3)	0.03
Geometric mean	1.18	1.04	2	331	20.6% (8.5 to 34.0)	0.001
Geometric standard deviation	72%	80%	3	290	18.9% (5.7 to 33.7)	0.004
			4	248	24.2% (7.4 to 43.6)	0.004
Mean systolic blood pressure — mm Hg	121.8±13.6	117.5±13.0	1	333	4.0 (1.5 to 6.5)§	0.002
			2	333	4.8 (2.3 to 7.2)§	<0.001
			3	299	4.8 (2.1 to 7.4)§	<0.001
			4	257	6.6 (3.7 to 9.6)§	<0.001
Mean diastolic blood pressure — mm Hg	78.8±8.6	75.2±8.2	1	333	3.5 (1.7 to 5.3)§	<0.001
			2	333	4.0 (2.3 to 5.8)§	<0.001
			3	299	4.1 (2.2 to 6.0)§	<0.001
			4	257	5.0 (2.8 to 7.2)§	<0.001
Mean heart rate — bpm	76.1±12.8	72.7±12.8	1	333	3.6 (0.8 to 6.3)¶	0.01
			2	333	3.6 (0.8 to 6.3)¶	0.01
			3	299	2.1 (−0.9 to 5.1)¶	0.16
			4	257	1.8 (−1.6 to 5.2)¶	0.29

\* Plus–minus values are means ±SD. All other values are geometric means. The geometric mean is the nth root of the product of n individual values. Geometric standard deviations correspond to the percentage increase in a variable corresponding to one standard-deviation unit change in the logarithm of the variable. To convert values for glucose to milligrams per deciliter, divide by 0.05551. To convert values for insulin to picomoles per liter, multiply by 6. HOMA denotes homeostatic model assessment.

† Multiple regression models are model 1, adjusted for age and sex; model 2, adjusted for age, sex, and BMI; and model 3, adjusted for age, sex, BMI, exercise intensity, and parental education (models for glucose, insulin, and HOMA-IR also include parental diabetes); and model 4, adjusted for age, sex, current lean body mass and height, exercise intensity, and parental education (models for glucose, insulin, and HOMA-IR also include parental diabetes).

‡ The 95% confidence interval (CI) is for the difference in values between the two groups.

§ This value is for the difference in mm Hg between the two groups.

¶ This value is for the difference in beats per minute between the two groups.

or appropriate for gestational age at birth. Although, by definition, these two groups differ in the conditions experienced before birth, they have a similar experience after preterm birth. For those born very early, the time between birth and term is challenging, roughly corresponding to the third trimester of pregnancy. This period may be particularly important for the programming of glucose metabolism.<sup>10,37</sup> Our data do not permit us to assess the effects of other putative periods of metabolic sensitivity, such as the periconceptional period<sup>38</sup> or the periods after term birth.<sup>11,39</sup>

Premature neonates today may differ from those in our cohort. Survival of premature infants has improved<sup>8,9,40,41</sup> as a result of breakthroughs in therapy, such as the introduction of antenatal corticosteroids and human surfactant, and some diseases have changed in character. For example, improved survival has been accompanied by an increase in the incidence of bronchopulmonary dysplasia.<sup>42</sup> The development of respirator-based care and fortified nutrition have led to changes in the rates of growth among premature infants. However, our observations with regard to glucose regulation in a cohort of young adults born two decades ago appear to be consistent with data from a younger cohort examined during childhood.<sup>10</sup>

Although our original cohort encompassed the entire population of very-low-birth-weight infants

in our geographic area who had been discharged alive after neonatal intensive care, subjects with cerebral palsy were less likely to participate in the study as young adults. However, our results remained similar after adjustment for exercise intensity and after the exclusion of subjects with complications of preterm birth such as cerebral palsy or a history of bronchopulmonary dysplasia.

We conclude that very low birth weight is associated with signs of impaired glucose regulation in young adult life. This finding suggests that persons with very low birth weight might be more vulnerable to disorders such as type 2 diabetes and cardiovascular disease later in life. Lifestyle interventions are effective in preventing these disorders, and the identification of persons at increased risk early in life provides an important opportunity for disease prevention.

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