Relation between Birth Weight and the Insulin Sensitivity Index in a Population Sample of 331 Young, Healthy Caucasians

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The objective was to study the association between birth weight and the insulin sensitivity index. Altogether, 331 unrelated Caucasian subjects aged 18–32 years with measures of the insulin sensitivity index and insulin secretion during a combined intravenous glucose and tolbutamide tolerance test were included in the study. The data on birth weight and length were obtained from the midwife records. The study took place in Copenhagen, Denmark, during 1992–1993. Univariate, a significant positive association between birth weight and the insulin sensitivity index was found in women (p = 0.045), but not in men (p = 0.23). In multivariate analysis, controlling for age, gender, body mass index, waist circumference, maximal aerobic capacity, and use of oral contraceptives, no significant interaction between birth weight and gender that considered the insulin sensitivity index was found. The insulin sensitivity index was significantly associated with birth weight (p = 0.0012), corresponding to an increase of 1.7% (95% confidence interval 0.7–2.7%) in the insulin sensitivity index for each 100-g increase in birth weight. In comparison, an increase in body mass index of 1 kg/m² (a weight gain of 2.9 kg in a man 1.70 m tall) corresponds to a decrease in the insulin sensitivity index of 3.8% (95% confidence interval 0.7–6.8%), an increase in waist circumference of 1 cm corresponds to a decrease in the insulin sensitivity index of 2.1% (95% confidence interval 0.9–3.1%), and use of oral contraceptives corresponds to a decrease in the insulin sensitivity index of 26.7% (95% confidence interval 12.2–38.1%). Thus, the impact of birth weight on the insulin sensitivity index was of minor importance.


It has been reported that subjects with low birth weight born at the beginning of this century in certain districts of United Kingdom have an elevated frequency of cardiovascular disease (1–3). Similarly, undernutrition in fetal life measured as low birth weight has been hypothesized to cause increased susceptibility to the development of non-insulin-dependent diabetes mellitus and to be associated with increased cardiovascular mortality and cardiovascular risk factors, such as raised blood pressure and increased fasting serum concentrations of fibrinogen and low levels of fasting serum high density lipoprotein cholesterol (HDL cholesterol) (4–11). The above-mentioned factors are also constituents of the so-called insulin resistance syndrome (12). It has been suggested that the clustering of cardiovascular risk factors in this syndrome is caused by a low insulin sensitivity (13). Low insulin sensitivity may be caused by genetic and environmental factors (12). Therefore, it could be hypothesized that low birth weight causes low insulin sensitivity (13). The concept of early life experience determining the subsequent risk of cardiovascular disease has been challenged, however (14, 15). Several fetal and maternal factors contribute to the determination of birth weight, and one or more of these factors could confound the associations between birth weight and cardiovascular risk factors so that the observed association between factors in the insulin resistance syndrome and birth weight may not be causal. First, low birth weight has been shown to be associated with later socioeconomic disadvantage during childhood and adolescence (16); for example, smoking is most prevalent in the lowest socioeconomic groups. Second, twins, who very often experience intrauterine growth retardation, do not have any excess mortality as adults compared with singletons (17, 18), although shorter twins actually have a higher risk of dying of heart disease than do taller twins (18).
The objective of this investigation was to study whether an adverse intrauterine environment, defined as low birth weight or low ponderal index (kg/m²), predicts a value of low insulin sensitivity index in a random sample of young, healthy Danes.

MATERIALS AND METHODS

Subjects

The study participants were randomly recruited from a population of young individuals aged 18–32 years, who as children in 1979–1980 and again in 1984–1985 had participated in blood pressure surveys in a representative and specified part of Copenhagen, Denmark (19–21). The present examination took place in 1992 and 1993. All subjects from the initial cohort except one could be traced in the Danish Central Population Register (n = 1,389). Subjects with insulin-dependent diabetes mellitus, pregnant women, and subjects now living in western Denmark or abroad were excluded from the study (n = 89). A random sample of unrelated subjects in the initial cohort was invited to participate in this examination (n = 684). The participation rate was 56 percent, and altogether, 380 unrelated individuals were included in the study. All subjects were determined by self-identification to be Danish Caucasians. All study participants were asked to refrain from physical exercise for 24 hours prior to the investigation. Two subjects were being treated with inhalation of β-2 adrenergic agonists for asthma, and 50 females were taking oral contraceptives. Otherwise, no study participants were taking any drugs on a regular basis, and all were asked not to take aspirin, paracetamol, or nonsteroid antiinflammatory drugs for headache or premenstrual pain on the day of examination. Data on lifestyle factors, anthropometric values, and biochemical measures obtained in this population-based sample have been presented previously (19, 21–24). Informed consent was obtained from all study participants. The study protocol was approved by the Ethical Committee of Copenhagen and was in accordance with the Helsinki Declaration.

Measurements of birth weight, blood pressure, and anthropometric data

The original data on birth weight and birth length of 331 of 380 subjects could be obtained from the midwife records stored in the Danish Provincial Archives for Zealand, Lolland/Falster, and Bornholm islands. The ponderal index was calculated as (birth weight (kg))/(birth length (m)²).

In the survey undertaken in 1992–1993, waist circumference was measured midway between the lower rib margin and the iliac crest in the horizontal plane with the subject in an upright position. The measurement of circumference was taken to the nearest 0.5 cm. Height was measured to the nearest 0.5 cm with the subject standing without shoes, with heels together, and with the head in the horizontal plane. Body weight was measured to the nearest 0.1 kg while subjects were wearing only light clothes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m²). Maximal aerobic capacity was measured by means of a submaximal bicycle exercise test, as described by Åstrand and Ryhning (25). Blood pressure was determined by means of a London School of Hygiene sphygmomanometer (Cinetronic, Mildenhall, England) (26), making the readings unbiased, since the scale was not visible during deflation of the cuff. Recording of blood pressure took place between noon and 2:00 p.m., when the subjects had participated in the study for a minimum of 4 hours and were relaxed. All blood pressure measurements were performed by the same nurse with the subject in the supine position. The standard blood pressure cuff was 12 by 35 cm. In subjects with an upper arm circumference of more than 35 cm, a cuff measuring 15 by 43 cm was used, and in subjects with an upper arm circumference of less than 20 cm, a cuff measuring 9 by 25 cm was used.

Biochemical studies

After a 12-hour overnight fast, venous blood samples were drawn. Serum levels of triglyceride, total cholesterol, and HDL cholesterol (Boehringer Mannheim GmbH, Diagnostica, Ingelheim am Rhein, Germany) were analyzed using standardized methods. The serum level of low density lipoprotein cholesterol (LDL cholesterol) was estimated from the above. Serum LDL cholesterol was calculated as serum total cholesterol (mmol/liter) – serum HDL cholesterol (mmol/liter) – serum triglyceride (mmol/liter)/2.2 (27). The concentration of insulin was determined by an enzyme-linked immunosorbent assay with a narrow specificity excluding des(31,32) proinsulin and intact proinsulin, using the Dako insulin kit with overnight incubation (Code No K6219, Dako Diagnostics Ltd, Ely, United Kingdom) (28).

Tissue plasminogen activator (t-PA) antigen was measured in plasma with an enzyme-linked immunosorbent assay (product no. 101101, Biopool AB, Umeå Sweden). Assays were performed as devised by Ranby et al. (29). The activity of the fast-acting inhibitor against t-PA, normally referred to as plasma plasminogen activator inhibitor (PAI-1) activity, was measured by adding a certain amount of t-PA to diluted, nonacidified plasma and Biopool reagents spectrolyse/PL (product number 101102, Biopool AB, Umeå Sweden). The activity of the fast-acting inhibitor against t-PA, normally referred to as plasma plasminogen activator inhibitor (PAI-1) activity, was measured by adding a certain amount of t-PA to diluted, nonacidified plasma and Biopool reagents spectrolyse/PL (product number 101102, Biopool AB, Umeå Sweden).
Umeå Sweden). In this system, one arbitrary unit of PAI-1 activity was the amount inhibiting 1 unit of t-PA. Plasma PAI-1 activity was expressed in mUnits/liter.

**Measurements of the insulin sensitivity index, glucose effectiveness, and first-phase serum insulin response**

Each subject underwent an intravenous glucose tolerance test (IVGTT) after the overnight fast of 12 hours. After insertion of a venous cannula into the antecubital vein, the subject rested in a quiet room for at least 20 minutes. Baseline values of serum insulin and plasma glucose were taken in duplicate, with 5-minute intervals. Glucose was injected intravenously in the contralateral antecubital vein over a period of 60 seconds (0.3 g/kg body weight of 50 percent glucose). Twenty minutes after the end of the glucose injection, a bolus of 3 mg tolbutamide/kg body weight (Rastinon, Hoechst, Germany) was injected for 5 seconds to elicit a secondary pancreatic β-cell response. Venous blood was sampled at 2, 4, 8, 19, 22, 30, 40, 50, 70, 90, and 180 minutes, timed from the end of the glucose injection for measurements of plasma glucose and serum insulin. All of the IVGTTs were performed by the same investigator. The insulin sensitivity index and glucose effectiveness were calculated using the Bergman MINMOD computer program (Richard N. Bergman, University of Southern California Medical School, Los Angeles, California), developed specifically for the combined intravenous glucose and tolbutamide tolerance test (30, 31). Minimal model analysis of the IVGTT provides estimates of the insulin sensitivity index that correlate significantly with those from the glucose clamp (32, 33). We used a 12-sample protocol that had been validated against the 33-sample protocol, and the 12-sample protocol was found to give an unbiased estimate of the insulin sensitivity index (21). The insulin sensitivity index represents the increase in net fractional glucose clearance rate per unit change in serum insulin concentration after the intravenous glucose load. Glucose effectiveness represents the net fractional glucose clearance rate simply due to the increase in glucose itself in the absence of any increase in insulin concentration above baseline. It is important to note that both the insulin sensitivity index and the glucose effectiveness involve an inhibition of hepatic glucose output and an acceleration of peripheral glucose uptake due to serum insulin and plasma glucose, respectively. Furthermore, glucose effectiveness includes a contribution mediated by the preexisting basal insulin level and a contribution from hyperglycemia per se in the absence of insulin. First-phase insulin response (0–8 minutes) after the intravenous glucose load was calculated by means of the trapezoidal rule for the incremental values (area under the curve when expressed above basal values). The glucose disappearance constant was calculated as the slope of the line relating the natural logarithm of the glucose concentration to the time, between 8 and 19 minutes after the glucose bolus administered as a part of the IVGTT (34).

**Statistics**

Differences in continuous variables between groups of subjects were tested with Student’s t test when the distributions of the study or the logarithmic values of the distributions were normal; otherwise, the Mann-Whitney U test was used. The study participants were stratified according to gender-specific quintiles of birth weight and ponderal index. To evaluate whether any trend existed, one-way analysis of variance was performed. In the one-way analysis of variance, logarithmic transformation of data was used if nontransformed data were not Gaussian distributed. To evaluate whether birth weight had the same association in men and women regarding the insulin sensitivity index, a multiple regression analysis with inclusion of an interaction term between birth weight and gender was performed with age, gender, body mass index, waist circumference, maximal aerobic capacity, and use of oral contraceptives with birth weight as explanatory variables. In addition, the standardized regression coefficients were estimated. Multiple regression analyses were calculated that included waist circumference; BMI; systolic blood pressure; glucose disappearance constant; fasting serum values of HDL cholesterol, LDL cholesterol, and triglyceride; and fasting plasma values of PAI-1 activity, t-PA antigen, and fibrinogen. For all analyses except the two with either waist circumference and/or BMI as the dependent variable, gender, age, waist circumference, and birth weight were included as explanatory variables. In the multiple regression analyses with waist circumference and BMI as response variables, gender, age, and birth weight were included as explanatory variables. In addition, in all multiple regression analyses, an interaction term between birth weight and gender was included. The interaction term turned out not to be significantly associated with the response variables in any of the multiple regression analyses. Therefore, the interaction terms were omitted from the multiple regression analyses.

With the ponderal index as the response variable, the same analyses were performed as for birth weight. One subject with some missing values was excluded from the multiple regression analyses. Statistical Pack-
age for the Social Science (SPSS) for Windows, version 6.01 (SPSS Inc., Chicago, Illinois) was used for statistical analyses. A p value < 0.05 (two-tailed) was considered significant.

RESULTS

Anthropometric data

The subjects in the population sample were characterized as young (ages 18–32 years) and relatively lean (tables 1 and 2). Of the 380 unrelated subjects who participated in the IVGTT, midwife records containing information about birth weight and length were available for 169 women and 162 men. The mean birth weight was higher in men than in women. Ten male babies and 13 female babies were noted as premature in the midwife records. The mean birth weights of premature male and female babies were 2,280 and 2,339 g, respectively. Except for one female baby, all premature individuals had a birth weight in the lowest quintile.

Associations of the insulin sensitivity index, glucose effectiveness, intravenous glucose disappearance constant, fasting serum insulin, and first-phase insulin response with birth weight and ponderal index

In men, no significant association between the insulin sensitivity index and birth weight was found \( (p = 0.23) \) (table 1). In women, however, a positive association \( (p = 0.045) \) was found between birth weight and the insulin sensitivity index (table 2). In the multiple regression analysis controlling for age, gender, BMI, waist circumference, maximal aerobic capacity, and oral contraceptives, no significant interaction between gender and birth weight was demonstrated \( (p = 0.77) \) that considered the association with the insulin sensitivity index. A positive association was found between the insulin sensitivity index and birth weight \( (p = 0.0012) \) (table 3). Inclusion of birth weight improved the explained variance \( (R^2) \) of the insulin sensitivity index from 36.8 to 38.6 percent in the total group of study participants. According to the multiple regression analysis, an increase of 100 g in birth weight corresponds to an increase of 1.7 percent (95 percent confidence interval 0.7–2.7 percent) in the insulin sensitivity index. In comparison, an increase in body mass index of 1 kg/m\(^2\) (a weight gain of 2.9 kg in a man 1.70 m tall) is similar to a decrease in the insulin sensitivity index of 3.8 percent (95 percent confidence interval 0.7–6.8 percent), an increase in maximal aerobic capacity of 1 ml O\(_2\)/kg minutes corresponds to an increase in the insulin sensitivity index of 1.3 percent (95 percent confidence interval 0.6–2.1 percent), and a 1-year increase in age is similar to an increase in the insulin sensitivity index of 2.8 percent (95 percent confidence interval 1.0–4.5 percent). An

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<th>TABLE 1. Anthropometric and biochemical variables measured in 162 young Caucasian men, when stratified to five groups by birth weight, Copenhagen, Denmark, 1992–1993</th>
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<td>Birth weight (g)</td>
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<td>&lt;2,500</td>
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<td>No. of subjects</td>
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<td>Body mass index (kg/m(^2))</td>
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<td>Systolic blood pressure (mmHg)</td>
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<td>Insulin sensitivity index ( (10^{-6} \times \text{minutes} \times \text{pmol/liter})^{-1} )</td>
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<td>Glucose effectiveness ( (10^{-2} \times \text{minutes}^{-1}) )</td>
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<td>Glucose disappearance constant ( (10^{-9} \times \text{minutes}^{-1}) )</td>
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<td>Fasting serum glucose (mmol/liter)</td>
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<td>Fasting serum insulin (pmol/liter)</td>
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<td>First-phase insulin secretion ( \text{AUC}_{(1-8 \text{ minutes})} \times \text{pmol/liter} \times \text{minutes} )</td>
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<td>Fasting serum total cholesterol (mmol/liter)</td>
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<td>Fasting plasma PAI-1 activity (uM/liter)</td>
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<td>Fasting plasma fibrinogen (g/liter)</td>
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* AUC, area under the curve; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; t-PA antigen, tissue plasminogen activator antigen; PAI-1 activity, plasminogen activator inhibitor 1 activity.
In men, birth weight and ponderal index were positively associated with birth weight \((p = 0.014)\) (95 percent confidence interval 0.9-3.1 percent), 0.25 (not shown). In multiple regression analysis control- for age, gender, body mass index, waist circumference, maximal aerobic capacity, and use of oral contraceptives, fasting serum insulin was significantly associated with birth weight \((p = 0.026)\), but not with ponderal index \((p = 0.43)\). According to the multiple regression analysis, an increase of 100 g in birth weight corresponds to a decrease of 0.9 percent (95 percent confidence interval 0.1-1.7 percent) in the fasting serum insulin level. First-phase insulin secretion 0-8 minutes after injection of glucose intrave- nously, glucose effectiveness, intravenous glucose dis- appearance constant, and fasting plasma glucose were not significantly associated with fasting serum insulin (not shown). In women, fasting serum insulin level. First-phase insulin secretion 0-8 minutes after injection of glucose intrave- nously, glucose effectiveness, intravenous glucose dis- appearance constant, and fasting plasma glucose were not significantly associated with fasting serum insulin (not shown). In women, the fasting level of serum insulin was positively associated with birth weight \((p = 0.014)\) (table 2), but not with ponderal index \((p = 0.25)\) (not shown). In men, birth weight and ponderal index were not significantly associated with fasting serum insulin (not shown). In multiple regression analysis control- for age, gender, body mass index, waist circumference, maximal aerobic capacity, and use of oral contraceptives, fasting serum insulin was significantly associated with birth weight \((p = 0.026)\), but not with ponderal index \((p = 0.43)\). According to the multiple regression analysis, an increase of 100 g in birth weight corresponds to a decrease of 0.9 percent (95 percent confidence interval 0.1-1.7 percent) in the fasting serum insulin level. First-phase insulin secretion 0-8 minutes after injection of glucose intrave- nously, glucose effectiveness, intravenous glucose dis- appearance constant, and fasting plasma glucose were not significantly associated with fasting serum insulin (not shown). In multiple regression analysis control- for age, gender, body mass index, waist circumference, maximal aerobic capacity, and use of oral contraceptives, fasting serum insulin was significantly associated with birth weight \((p = 0.026)\), but not with ponderal index \((p = 0.43)\). According to the multiple regression analysis, an increase of 100 g in birth weight corresponds to a decrease of 0.9 percent (95 percent confidence interval 0.1-1.7 percent) in the fasting serum insulin level. First-phase insulin secretion 0-8 minutes after injection of glucose intrave- nously, glucose effectiveness, intravenous glucose dis- appearance constant, and fasting plasma glucose were not significantly associated with fasting serum insulin (not shown). In women, fasting serum insulin level. First-phase insulin secretion 0-8 minutes after injection of glucose intrave- nously, glucose effectiveness, intravenous glucose dis- appearance constant, and fasting plasma glucose were not significantly associated with fasting serum insulin (not shown). In women, the fasting level of serum insulin was positively associated with birth weight \((p = 0.014)\) (table 2), but not with ponderal index \((p = 0.25)\) (not shown). In men, birth weight and ponderal index were not significantly associated with fasting serum insulin (not shown). In multiple regression analysis control- for age, gender, body mass index, waist circumference, maximal aerobic capacity, and use of oral contraceptives, fasting serum insulin was significantly associated with birth weight \((p = 0.026)\), but not with ponderal index \((p = 0.43)\). According to the multiple regression analysis, an increase of 100 g in birth weight corresponds to a decrease of 0.9 percent (95 percent confidence interval 0.1-1.7 percent) in the fasting serum insulin level. First-phase insulin secretion 0-8 minutes after injection of glucose intrave- nously, glucose effectiveness, intravenous glucose dis- appearance constant, and fasting plasma glucose were not significantly associated with fasting serum insulin (not shown). In women, fasting serum insulin level. First-phase insulin secretion 0-8 minutes after injection of glucose intrave- nously, glucose effectiveness, intravenous glucose dis- appearance constant, and fasting plasma glucose were
not significantly associated with either birth weight or ponderal index in men or women.

**Association of BMI, body weight, body height, and waist circumference with birth weight and ponderal index**

The association between birth weight and adult BMI was not significant in either men or women (tables 1 and 2). However, birth weight and adult body height were positively associated in men and women ($p < 0.0001$ and $p = 0.0037$, respectively). Birth weight and adult body weight were positively associated in men ($p = 0.0053$), but not in women ($p = 0.16$) (tables 1 and 2). Waist circumference was not significantly associated with birth weight in either men or women. No significant associations of BMI, body weight, body height, and waist circumference with ponderal index were found in either men or women.

Birth weight and the ponderal index were not associated with either waist circumference or BMI in multivariate analyses.

**Associations of blood pressure, fasting serum lipids, and fibrinolytic variables with birth weight and ponderal index**

In men and women, systolic pressure; fasting serum levels of total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride; and fasting plasma values of t-PA antigen, PAI-1 activity, and plasma fibrinogen did not show any significant associations with birth weight. No associations with any of these variables were found with gender-specific quintiles of ponderal index.

The ponderal index and birth weight were not associated with blood pressure, fasting serum cholesterol levels (total, HDL, and LDL cholesterol), fasting plasma levels of PAI-1 activity, t-PA antigen, and fibrinogen in the multivariate analyses. Birth weight, but not the ponderal index, was significant negatively ($p = 0.013$) associated with fasting serum triglyceride in the multivariate analyses including age, gender, and waist circumference as explanatory variables. This corresponded to a decrease of 1.0 percent (95 percent confidence interval 0.2–1.8 percent) in fasting serum triglyceride level for each 100-g increase in birth weight.

**DISCUSSION**

The insulin sensitivity index was positively associated with birth weight in this cohort of young healthy Danes. However, low birth weight was not associated with features of the insulin resistance syndrome, such as obesity, dyslipidemia, glucose intolerance, or elevated blood pressure. The advantage of this study protocol is that the relation between birth weight and variables measured at a young age is less likely to be interfered with by confounders that become operative with aging.

In the univariate analysis, a significant positive association between birth weight and the insulin sensitivity index was found in women, but not in men, although the association in men was borderline significant. In the multiple regression analysis with insulin sensitivity index as the response variable, no interaction with gender was found. This highlights the importance of the choice of the explanatory variables. The variables we included in the multiple regression analyses were based on a literature search and our previous analyses (19).

The analytic models chosen in this paper anticipate a linear association between birth weight and the insulin sensitivity index. In a report by McCance et al. (35), an U-shaped association was found between birth weight and risk of non-insulin-dependent diabetes mellitus, which may be due to diabetic mothers having larger babies. Since women with gestational diabetes have a low insulin sensitivity and since both the insulin sensitivity index and birth weight are influenced by genetic factors, this could suggest a nonlinear association between birth weight and the insulin sensitivity index. Nevertheless, since the prevalence of diabetes in Caucasian women of the childbearing age is relative low (less than 2 percent) (36) and since the residuals in the multiple regression analysis did not indicate any nonlinearity, we propose that the linear model is appropriate.

In a recent study by Lithell et al. (8), weak inverse relations were found between ponderal index or birth weight and insulin resistance, defined as a 60-minute serum insulin concentration during an IVGTT test at age 50 years. In two other cross-sectional studies that examined the association between birth weight and insulin resistance in adult life, no significant association between birth weight and the insulin sensitivity index was observed (13, 37). We did not find any association between the insulin sensitivity index and the ponderal index. Instead, a weak association between the insulin sensitivity index and birth weight was observed since less than 2 percent of the variation of insulin sensitivity could be explained by birth weight compared with the finding that 39 percent of the variation of insulin sensitivity index is explained by all of the estimated variables. The minor importance of birth weight on the insulin sensitivity index is also seen when the standardized regression coefficients are compared. In fact, no major difference between the result from the above studies and our study...
is actually found. Taken together, the studies suggest that the associations of insulin sensitivity with ponderal index or birth weight are weak.

The acute insulin response was estimated after an intravenous glucose load. No associations between \( \beta \)-cell function and birth weight or ponderal index were found in either men or women. The association between \( \beta \)-cell function and birth weight has been examined in other studies (37–39). Two studies did not show any association between birth weight and \( \beta \)-cell function (38, 39). One study found that individuals with a low birth weight have an impaired \( \beta \)-cell function as adults and that this association was independent of present BMI and age (37). Actually, in our study of young adults, the \( \beta \)-cell function tended to be higher in subjects with the lowest birth weight.

We did not find any significant association between systolic pressure and birth weight. The results concerning blood pressure and birth weight are conflicting in both young and elderly individuals (3, 9–10, 14, 37, 40–42). In most positive studies, the association between low birth weight and elevated blood pressure as an adult has been weak. However, in one study that combined information about birth weight and placental weight, a stronger association with adult blood pressure was seen, with subjects who had a low birth weight and a high placental weight having the highest blood pressure (10). It has been proposed that the mechanism underlying the positive association between low birth weight and adult hypertension is due to a circulatory adaption of the child with alterations in the arterial structure (10). The distribution of birth weight and systolic pressure in a sample may influence the importance of the relation between the two variables. If the relation between birth weight and systolic pressure is nonlinear and if the range of blood pressure is narrow, as in the present study, it may tend to diminish the strength of the association. In any case, the importance of birth weight for the level of systolic pressure in this sample of young, healthy, normotensive subjects was of minor significance.

When the various findings in different populations of the associations between birth weight on one side and the insulin sensitivity index, \( \beta \)-cell function, and blood pressure on the other are considered, it is important to remember that all four variables are influenced by numerous factors. In principle, in situations as intricate as the one implied by the "Barker's hypothesis" (43), one has to try to separate potentially intermediate variables from exogenous variables. The distinction may be difficult since, for instance, low birth weight may be associated with low socioeconomic status, and through socioeconomic status, even tobacco smoking may become intermediate between birth weight and disease or disease precursors. If birth weight is not causally influencing the insulin sensitivity index or \( \beta \)-cell function in adults, then some of these other factors may influence the direction and strength of the association. For example, it is known that birth weight is influenced by the interval between pregnancies (44), young maternal age (45), race (46), and maternal smoking (47). Maternal smoking during childhood also increases the risk of smoking in young adulthood, and smoking may decrease the insulin sensitivity index in adulthood (48, 49). Blood pressure, the insulin sensitivity index, and first-phase insulin response after an intravenous glucose challenge are all strongly influenced by BMI. Although BMI is largely determined by genetic factors, as shown in adoption studies (50), the rising prevalence of obesity in Western countries demonstrates that environmental components add to the determination of the level of BMI. Therefore, although the evidence is not conclusive, our data suggest that birth weight and the insulin sensitivity index as well as birth weight and features of the insulin resistance syndrome are not necessarily causally related in this sample of young Danes.

In conclusion, in Danes born between 1961 and 1973, birth weight was positively associated with the insulin sensitivity index. Any associations between birth weight and other anthropometric or biochemical features of the insulin resistance syndrome could not be found. In addition, the effect of birth weight on the insulin sensitivity index only accounted for less than 2 percent of the variation of the insulin sensitivity index.

ACKNOWLEDGMENTS

Supported by grants from the University of Copenhagen; the Danish Diabetes Association; the Danish Heart Foundation; the Danish Hospital Foundation for Medical Research, Region of Copenhagen, the Faeroe Islands and Greenland; the Else and Mogens Wedell-Wedellsborg Foundation; Bristol-Myers Squibb; Frimodt-Heineke Foundation; House of Prince; Novo's Foundation; Ingeniør August Frederik Wedell Erichsens Foundation; Grosser A. V. Lykfeldts og Hustrus Foundation Legat, Foundation 1870; and Leo Chemicals.

The authors thank Kia Olsen, Mette Sadolin, Lone Westh, Miguel Lee, Birgitte Stumann, Karen Grunnet, Annemette Forman, Lene Aabo, Helle Fjordvang, Bente Mottlau, Susanne Kjellberg, Jane Brønnum, and Quan Truong for dedicated and careful technical assistance and Dr. Philip Hougaard for statistical advice.

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