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Birth weight and the insulin resistance syndrome: association of low birth weight with truncal obesity and raised plasminogen activator inhibitor-1 but not with abdominal obesity or plasma lipid disturbances

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Abstract

Aims/hypothesis. To distinguish the physiological disturbances related to birth weight from the cluster of disturbances called the insulin resistance syndrome.
Methods. Men participating in a population-based study in Uppsala, Sweden, with recordings of birth weight, were metabolically characterised at age 50 ($n = 1268$) and re-investigated at age 70 ($n = 734$). Blood pressure, BMI, glucose and insulin concentrations are associated with birth weight in this cohort.
Results. Birth weight was inversely associated ($p < 0.03$) with subscapular:triceps skinfold ratio (truncal fat), plasminogen activator inhibitor-1 (PAI-1) activity, specific insulin and proinsulin-like molecules when adjusted for BMI. Birth weight was not related ($p > 0.10$) with waist circumference, serum triglycerides or HDL cholesterol. The insulin resistance syndrome was defined as the combination of hypertension, insulin resistance and dyslipidaemia. The prevalence of this syndrome at age 50 and 70 was inversely related to birth weight with odds ratio 0.66 and 0.71, respectively, per kg increase in birth weight. When the syndrome was defined to include truncal obesity or raised plasminogen activator inhibitor-1 instead of dyslipidaemia, the corresponding odds ratios were 0.51 and 0.66, respectively.
Conclusions/interpretation. Low birth weight predicts high blood pressure, insulin resistance, truncal obesity and high plasminogen activator inhibitor-1 activity but not the abdominal obesity or dyslipidaemia present in the insulin resistance syndrome. The cluster of disturbances associated with low birth weight is a subset of the disturbances that are clustered in the general population as the insulin resistance syndrome. This subset of physiological disturbances is possibly linked by a specific pathway. [Diabetologia (2000) 43: 54–60]

Keywords Insulin resistance, birth weight, hyperlipidaemia, plasminogen activator inhibitor-1, waist:hip ratio, proinsulin.

Small size at birth predicts physiological disturbances in adult life, such as raised blood pressure [1–3], Type II (non-insulin-dependent) diabetes mellitus [4–6], impaired glucose tolerance [4, 7] and insulin resistance [6, 8, 9]. All these conditions are associated with an increased risk of and mortality from cardiovascular disease [10–12]. The cluster of risk factors for cardiovascular disease that are associated with insulin resistance, the insulin resistance syndrome, includes hypertension, impaired glucose tolerance, insulin resistance, lipid disturbances such as high serum triglyceride and low HDL cholesterol concentrations, and impaired fibrinolytic activity, mediated by a high plasminogen activator inhibitor-1 (PAI-1) activity [13]. Low birth weight predicts most of these disturbances and has been associated with the insulin resistance syndrome itself [14, 15]. After very high odds ratios for people with low birth weight to develop this syndrome had been shown, it was suggested that the insulin resistance syndrome should be renamed the

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Abbreviations: PAI-1: Plasminogen activator inhibitor-1, OR: odds ratio.

'small baby syndrome' [14]. Most studies have, however, failed to show an association between low birth weight and the high serum triglyceride and low HDL cholesterol concentrations seen in the insulin resistance syndrome [6, 15–18].

The aim of this study was to distinguish the physiological disturbances related to birth weight from the insulin resistance syndrome, in a population-based study of men investigated at ages 50 and 70 years.

Subjects and methods

The Uppsala Longitudinal Study of Adult Men (ULSAM) has been described previously [2, 6, 19, 20]. All men born between 1920 and 1924 and living in Uppsala, Sweden ($n = 2841$), were invited to a health investigation which took place from 1970 to 1973 (2322 men participated). In 1991, 1221 of the men were re-examined. During the 20 intervening years, 422 men had died and 219 had moved out of the Uppsala region. Of the 1681 men invited, 460 did not participate in the re-examination. The study was approved by the local ethics committee and all participants gave their informed consent. All investigations were done after an overnight fast.

We were able to trace the birth records of 1333 participants [2]. Of those, 615 were born in the Uppsala Academic Hospital where the records, in addition to birth weight, also contained information on gestational age. The birth weights were grouped into four categories, where the cut-offs were chosen to take account of the frequent rounding to the nearest 0.5 kg in the original birth records. The groups were thus less than 3.25, 3.25 or more to less than 3.75, 3.75 or more to less than 4.25 and 4.25 kg or more [2].

Investigations at age 50 included height, weight, skinfold measurements, supine blood pressures, intravenous glucose tolerance test and blood lipids including serum and HDL triglycerides and cholesterol [2, 6, 19]. Skinfolds were measured to the nearest 0.2 mm on the triceps, subscapular and to the right of the umbilicus using a Harpenden calliper [21]. The ratio of subscapular to triceps skinfolds was used as an index of truncal fat [22].

At age 70, an oral glucose tolerance test and a euglycaemic hyperinsulinaemic clamp were done, as were measurements of height, weight, waist and hip circumferences, and supine blood pressures [20]. Serum triglycerides and HDL cholesterol concentrations were assayed by enzymatic techniques (Instrumentation Laboratories, Lexington, Mass., USA). Plasminogen activator inhibitor-1 activity was measured with an indirect enzymatic assay (Spectrolyse/pL PAI, Biopool AB, Umeå, Sweden).

The fasting concentrations of plasma specific insulin, intact and 32, 33 split proinsulin were determined by two-site immunometric assays [23] at both ages. The samples were stored in –70 °C until analysis (in 1994–1998 and 1998 for samples drawn at ages 50 and 70 years, respectively).

Information on smoking was collected by interview. At age 50, 52.2 % ($n = 662$) were regular smokers. The corresponding proportion at age 70 was 21.9 % ($n = 155$). Socio-economic class at birth was based on the profession of the father or of the mother if she was single as stated in the birth records. Socio-economic variables (marital status, type of work, educational level) at ages 50 and 70 were collected from the Swedish censuses of 1970 and 1990, respectively.

Type II diabetes mellitus and impaired glucose tolerance were defined according to the World Health Organisation (WHO) criteria from 1985 [24], based on the results from the oral glucose tolerance test at age 70. At age 50, the criteria for Type II diabetes were fasting blood glucose 6.7 mmol/l or more and K-value (from the intravenous glucose tolerance test) 0.9 or less or anti-diabetic therapy or both. To minimise the inclusion of Type I (insulin-dependent) diabetes mellitus in this definition, men on insulin treatment were not included.

The prevalence of hypertension was defined as supine systolic blood pressure higher than 140 mmHg or diastolic blood pressure higher than 90 mmHg or ongoing anti-hypertensive treatment or a combination of these.

There is no agreed definition of the insulin resistance syndrome, although a working definition has been suggested [25], from which our definition does not differ very much. We defined it as the combination of hypertension, glucose intolerance or insulin resistance and dyslipidaemia (see below), the three major constituents of the syndrome. Glucose intolerance and insulin resistance often coexist but it is possible to be insulin resistant without being glucose intolerant, and vice versa. Glucose intolerance is characterised by an impaired ability of the body tissues to efficiently reduce increased glucose concentrations in the blood. Type II diabetes, impaired glucose tolerance and high fasting glucose concentrations are measures of glucose intolerance. When the body tissues' response to insulin, the insulin sensitivity, is reduced, it is called insulin resistance. Measures of insulin resistance are low insulin sensitivity index, here determined by clamp, and high fasting insulin concentrations, often used as a proxy when other measures of insulin sensitivity are not available.

The definition of the cluster of factors associated with birth weight was based on those variables associated with birth weight in this cohort (Tables 1 and 2 and [2, 3, 6, 9]). We used different definitions of the syndromes for ages 50 and 70, because of the different investigations carried out. The cut-off values were based on the highest or lowest tertile of a variable (median for subscapular:triceps skinfold ratio) at each age. The two outcomes were defined by A–D below, at age 50 and 70, respectively. The insulin resistance syndrome was defined as A and B and C and the cluster of birth weight-associated factors as A and B and D.

At age 50: A. BP-lowering treatment or high supine systolic BP (≥ 140 mmHg), B. high fasting plasma insulin (≥ 13.8 mU/l) or high fasting blood glucose (≥ 5.05 mmol/l) or Type II diabetes, C. low HDL cholesterol (< 1.0 mmol/l) or high serum triglycerides (≥ 2.20 mmol/l), D. high subscapular/triceps skinfold ratio (> 1.553).

At age 70: A. BP-lowering treatment or high supine systolic BP (≥ 154 mmHg), B. low insulin sensitivity index (M/I from clamp < 3.65 mg · min^{-1} · kg^{-1} · (mU/l)$^{-1}$ · 100) or impaired glucose tolerance or Type II diabetes, C. low HDL cholesterol (< 1.1 mmol/l) or high serum triglycerides (≥ 1.57 mmol/l) or lipid-lowering medication, D. high PAI-1 activity (> 19.2 U/ml).

The insulin resistance syndrome was defined in 2202 of the 2322 50-year-old men, of whom 1268 also had recordings of birth weight. At age 70 it was coded as present/absent in 1218 (of 1221) men, of whom 734 also had birth weight recorded. There were no differences in anthropometric measurements, diabetes prevalence, fasting lipid, glucose or immunoreactive insulin concentrations between the men included and those not. At age 50, the systolic and diastolic blood pressures and the prevalence of hypertension were lower among the men included when compared with those not included ($p < 0.05$). There was no such difference at age 70. The cluster of factors associated with birth weight was defined in 1165 and 678 men aged 50 and 70, respectively.

In the group of men born in Uppsala Academic Hospital the effect of gestational age on the relation of birth weight

Table 1. Characteristics at age 50, presented as means ± SD *(n)* and their association with birth weight

	Birth weight group (kg)					
	< 3.25	– 3.75	– 4.25	≥ 4.25	*p*	*p* [a]
Umbilical skinfold (mm)	20.4 ± 10.1 (163)	20.4 ± 9.8 (319)	20.0 ± 9.6 (208)	20.5 ± 10.0 (70)	0.904	0.029
Triceps skinfold (mm)	10.3 ± 4.0 (163)	10.9 ± 4.0 (319)	11.2 ± 4.2 (208)	11.3 ± 4.9 (70)	0.020	0.151
Subscapular skinfold (mm)	17.4 ± 6.1 (163)	16.6 ± 5.8 (319)	16.7 ± 6.1 (208)	16.6 ± 5.6 (70)	0.462	0.001
Subscapular:triceps skinfold ratio	1.78 ± 0.54 (163)	1.60 ± 0.48 (319)	1.57 ± 0.52 (208)	1.54 ± 0.43 (70)	< 0.001	< 0.001
Specific insulin (pmol/l)	51 ± 44 (214)	51 ± 37 (374)	50 ± 38 (296)	52 ± 45 (83)	0.518	0.380
Proinsulin (pmol/l)	2.9 ± 3.5 (215)	2.8 ± 2.6 (376)	3.0 ± 4.1 (295)	2.9 ± 3.1 (83)	0.430	0.652
Split 32, 33 proinsulin (pmol/l)	7.4 ± 7.6 (213)	6.8 ± 5.5 (364)	7.3 ± 7.9 (293)	7.8 ± 8.6 (81)	0.725	0.282

p values were adjusted for age and *p* [a] for age and BMI.
The associations of birth weight with BMI, insulin resistance, fasting plasma immunoreactive insulin and serum lipid concentrations at age 50 have been investigated previously [6].

Table 2. Characteristics at age 70, presented as means ± SD *(n)* and their association with birth weight

	Birth weight group (kg)					
	< 3.25	– 3.75	– 4.25	≥ 4.25	*p*	*p* [a]
BMI (kg/m^2)	25.9 ± 3.3 (174)	26.4 ± 3.2 (275)	26.6 ± 3.7 (217)	26.8 ± 3.5 (68)	0.007	–
Waist circumference (cm)	93.7 ± 9.8 (173)	94.9 ± 8.7 (268)	95.5 ± 10.2 (211)	96.2 ± 10.6 (66)	0.014	0.812
Hip circumference (cm)	99.2 ± 8.0 (173)	100.4 ± 6.2 (268)	101.4 ± 7.7 (211)	101.7 ± 7.2 (66)	< 0.001	0.024
Waist : hip ratio	0.94 ± 0.06 (173)	0.94 ± 0.05 (268)	0.94 ± 0.05 (211)	0.94 ± 0.05 (66)	0.856	0.027
Specific insulin (pmol/l)	54 ± 40 (169)	55 ± 66 (261)	50 ± 43 (209)	49 ± 30 (67)	0.440	0.010
Proinsulin (pmol/l)	8.6 ± 7.4 (167)	8.9 ± 7.1 (259)	7.9 ± 7.2 (207)	8.9 ± 16.5 (66)	0.106	0.001
Split 32, 33 proinsulin (pmol/l)	11.2 ± 10.7 (167)	11.8 ± 13.3 (259)	10.0 ± 10.7 (207)	10.7 ± 16.6 (66)	0.160	0.002
Serum triglycerides (mmol/l) [b]	1.40 ± 0.78 (174)	1.53 ± 0.87 (275)	1.39 ± 0.60 (217)	1.45 ± 0.87 (68)	0.883	0.289
HDL cholesterol (mmol/l) [b]	1.29 ± 0.34 (173)	1.26 ± 0.34 (275)	1.27 ± 0.34 (217)	1.31 ± 0.32 (68)	0.472	0.102
PAI-1 activity (U/ml)	18.7 ± 14.3 (127)	19.1 ± 14.1 (217)	16.8 ± 15.0 (160)	14.3 ± 11.1 (50)	0.038	< 0.001

p values were adjusted for age and *p* [a] for age and BMI.
[b] *p* values adjusted also for lipid lowering treatment.
The association of birth weight with insulin sensitivity at age 70 has been investigated previously [9].

with the metabolic variables and the two syndromes was investigated. Men with recordings of gestational age (n = 561 and 326 at age 50 and 70, respectively) were compared with men born at term (gestational age ≥ 38 weeks; n = 496 and 282 at age 50 and 70, respectively), thus excluding pre-term births (gestational age < 38 weeks). The validity of the classification of pre-term and term births in this cohort has been discussed previously [9].

Statistical analyses were done with the statistical software package Stata (Stata Corporation, College Station, Tex., USA). Skewed variables were transformed to reach normal distribution and the transformed variables were used in the analyses. Comparisons of included and not included men were done by Student's *t*-test or the chi squared test. Birth weight was used as a continuous variable in trend tests. Logistic regression was used to assess relations with the insulin resistance syndrome and the cluster of birth weight-associated factors and linear regression to assess the relations with metabolic variables. All relations were adjusted for age at the time of the investigation and, in a second model, for age and BMI at the time of the investigation. Variables standardised to 1 SD were used for comparison of the effect of birth weight on variables. Odds ratios (OR) are presented with their 95 % confidence intervals (CI). We regarded $p < 0.05$ as significant.

Results

Of the 50-year-old men under study (n = 1268), 1.2 % had Type II diabetes and 26 % were hypertensive. At age 70 (n = 734), 14 % had Type II diabetes, 27 % had glucose intolerance and 67 % were hypertensive. The birth weight ranged from 1.40 to 5.40 kg (mean: 3.60 kg). In the subgroup of men born in Uppsala Academic Hospital, the mean birth weight was 3.50 kg (range: 1.40–4.97 kg) and the mean birth weights of those born pre-term and not pre-term were 3.14 and 3.55 kg, respectively.

Variables investigated are presented in the four birth weight categories as arithmetic means and their standard deviations (SD), together with *p* values from regression with birth weight with and without adjustment for BMI. (Tables 1 and 2).

At age 50, the triceps skinfold thickness was positively associated with birth weight but not independently of BMI. When adjusted for BMI, the skinfold thickness at the umbilicus and subscapula were inversely associated with birth weight, as was the subscapular:triceps skinfold ratio, here used as a measure of truncal fat. Of these, truncal fat was most strongly related to birth weight, with 0.30 standard deviation decrease per kg increase in birth weight (–0.30 SD/

Table 3. The insulin resistance syndrome[a] at ages 50 and 70 years, respectively, and its relation to birth weight

Birth weight group (kg)	50 years			70 years		
	% *(n)*	OR (95% CI)	OR (95% CI), adjusted for BMI	% *(n)*	OR (95% CI)	OR (95% CI), adjusted for BMI
< 3.25	16.3 (47)	1.00	1.00	20.1 (35)	1.00	1.00
– 3.75	12.4 (61)	0.72 (0.48–1.08)	0.67 (0.43–1.04)	20.7 (57)	1.04 (0.65–1.67)	0.94 (0.57–1.55)
– 4.25	9.6 (36)	0.54 (0.34–0.86)	0.49 (0.29–0.75)	18.0 (39)	0.87 (0.52–1.45)	0.79 (0.43–1.27)
≥ 4.25	13.4 (15)	0.79 (0.42–1.48)	0.55 (0.28–1.08)	10.3 (7)	0.46 (0.19–1.08)	0.32 (0.13–0.80)
Total[b]	12.5 (159/1268)	0.66 (0.47–0.91)	0.52 (0.36–0.75)	18.8 (138/734)	0.71 (0.49–1.02)	0.56 (0.38–0.84)

[a] The insulin resistance syndrome was defined as the combination of hypertension, glucose intolerance or insulin resistance and dyslipidaemia.
[b] Total odds ratios are for 1 kg increase in birth weight.

kg), when adjusted for BMI. The associations were still significant when pre-term births were excluded. The fasting concentrations of specific insulin and proinsulin at age 50 were not associated with birth weight but tended to decrease with increasing birth weight when adjusted for BMI, but the trends were not statistically significant.

Previously published results from this cohort showed inverse relations of birth weight with fasting concentrations of immunoreactive insulin and insulin resistance (at age 50) [6] and positive associations with BMI (at age 50) [6] and insulin sensitivity (at age 70) after adjusting for BMI [9]. Birth weight was also related to blood pressure at both ages [2, 3] but not with the concentrations of serum triglycerides or HDL cholesterol at age 50 [6].

Waist and hip circumferences and BMI measured at age 70 were positively associated with birth weight (Table 2). When adjusting for BMI, birth weight was inversely related to the waist:hip ratio (–0.13 SD/kg) and positively related to hip circumference (+ 0.10 SD/kg) but there was no relation between birth weight and waist circumference (+ 0.008 SD/kg). Plasminogen activator inhibitor-1 activity measured at age 70 was inversely related to birth weight (Table 2). A 1 kg increase in birth weight was associated with a 0.25 SD decrease in PAI-1 activity, when adjusted for BMI. This relation was of similar strength when only normoglycaemic men (–0.22 SD/kg, $p = 0.004$) and when men born at Uppsala Academic Hospital (–0.27 SD/kg, $p = 0.016$) were investigated. When only men born at term were included, the relation was somewhat stronger; 0.41 SD decrease in PAI-1 activity per kg increase in birth weight (adjusted for BMI).

The specific insulin, intact and split proinsulin concentrations at age 70 were inversely associated with birth weight only when adjusted for BMI (–0.12, –0.10 and –0.13 SD/kg increase in birth weight, respectively). The associations with intact and 32, 33 split proinsulin concentrations were of similar strength and remained significant also when including only men with normal glucose tolerance ($p = 0.013$ and 0.049, respectively). Split proinsulin was related to birth weight also in the subgroup of men born at term (–0.24 SD/ kg decrease, adjusted for BMI).

The associations of serum triglycerides and HDL cholesterol, measured at age 70, with birth weight were adjusted also for use of lipid lowering agents (Table 2). Serum triglyceride concentrations were not associated with birth weight. High density lipoprotein cholesterol was not significantly associated with birth weight when the whole group was studied, even after adjustment for BMI (+ 0.11 SD/kg, $p = 0.102$). When restricting the analysis to men born at Uppsala Academic Hospital there was a positive relation between birth weight and HDL cholesterol when adjusted for BMI ($p = 0.036$). This became non-significant when pre-term births were excluded ($p = 0.058$).

The prevalence of the insulin resistance syndrome was 12.5% among the 50-year-old men and 18.8% among the 70-year-old men (Table 3). Birth weight was inversely related with the insulin resistance syndrome at both ages with odds ratios of 0.66–0.71 for each kg increase in birth weight (0.52–0.56 when adjusted for BMI). When excluding pre-term births from the group of men born at Uppsala Academic Hospital, the relation with insulin resistance syndrome at age 50 was strengthened. For term births the BMI-adjusted odds ratio was 0.33 (95% CI: 0.17–0.64) per kg increase in birth weight (vs 0.46 (0.26–0.81) for all men born at Uppsala Academic Hospital). There was, however, no statistically significant interaction between the effects of pre-term birth and birth weight on the insulin resistance syndrome (data not shown). The relation of birth weight with this syndrome at age 70 was not significant in subgroup analyses, probably due to too few observations.

We empirically defined a cluster of factors associated with birth weight as hypertension, glucose intolerance or insulin resistance and truncal obesity (at age 50) or raised PAI-1 (at age 70), which also was associated with birth weight (Table 4). The odds ratios for this cluster were 0.51–0.66 per kg increase in birth weight (0.46–0.52 when adjusted for BMI). At age 50, the BMI-adjusted odds ratio of having the cluster of

Table 4. The cluster of factors[a] associated with birth weight at ages 50 and 70 years, respectively, and its relation with birth weight

Birth weight group (kg)	50 years			70 years		
	% *(n)*	OR (95% CI)	OR (95% CI), adjusted for BMI	% *(n)*	OR (95% CI)	OR (95% CI), adjusted for BMI
< 3.25	11.9 (31)	1.00	1.00	14.7 (23)	1.00	1.00
– 3.75	12.2 (56)	0.96 (0.60–1.54)	0.96 (0.59–1.56)	16.5 (42)	1.12 (0.64–1.95)	1.06 (0.59–1.90)
– 4.25	4.9 (17)	0.38 (0.20–0.70)	0.35 (0.18–0.65)	12.4 (25)	0.82 (0.44–1.52)	0.66 (0.34–1.26)
≥ 4.25	6.9 (7)	0.50 (0.21–1.19)	0.44 (0.18–1.07)	3.0 (2)	0.18 (0.04–0.77)	0.13 (0.03–0.57)
Total[b]	9.5 (111/1165)	0.51 (0.34–0.76)	0.46 (0.30–0.69)	13.6 (92/678)	0.66 (0.42–1.01)	0.52 (0.32–0.82)

[a] The cluster of factors associated with birth weight was defined as the combination of hypertension, glucose intolerance or insulin resistance and high truncal fat (at age 50) or high PAI-1 activity (at age 70).

[b] Total odds ratios are for 1 kg increase in birth weight.

factors associated with birth weight was somewhat lower for men born at term (OR: 0.49, 95% CI: 0.26–0.95) than for men born at Uppsala Academic Hospital (OR: 0.55, 95% CI: 0.31–0.99). At age 70, the relation between birth weight and the cluster of factors associated with birth weight was not significant in subgroup analyses.

Socio-economic factors, either at birth or in adulthood, and smoking did not change the relations of birth weight with the insulin resistance syndrome and the cluster of factors associated with birth weight, respectively (results not presented).

There were no statistically significant interactions between birth weight and BMI, although the relations between birth weight and the syndromes were stronger when adjusted for BMI.

Discussion

Previous studies, including analyses of the present cohort, have consistently shown strong associations of reduced size at birth with adult hypertension, insulin resistance, glucose intolerance and increased cardiovascular mortality [1–12]. To these we can now add high PAI-1 activity, a mediator of impaired fibrinolysis. The relations of low birth weight with a high waist:hip ratio and truncal subcutaneous fat distribution, present in this study, have in previous studies been inconsistent [8, 26, 27] and less frequently investigated [15], respectively. Low birth weight predicts a smaller hip but not a larger waist in this study and thus the inverse relation of birth weight with the waist:hip ratio does not reflect an association with central adiposity. Increased serum triglyceride and decreased HDL cholesterol concentrations are associated with abdominal obesity. High concentrations of non-esterified fatty acids (NEFA) delivered to the liver, an increased activity of the hepatic triglyceride lipase or an increased uptake of HDL cholesterol by the centrally located fat cells are some of the possible mechanisms by which central obesity could cause dyslipidaemia [28]. The lack of an association between birth weight and central adiposity could thus explain the lack of relation between birth weight and plasma lipids.

In this study, there was an inverse association of birth weight with truncal fat at age 50, measured as subscapular to triceps skinfold ratio. Truncal fat is a measure of subcutaneous adipose tissue distribution that is usually associated with central obesity, represented by a high waist:hip ratio. The two measurements possibly represent, however, two different hormonal and metabolic situations [22, 29]. The waist:hip ratio has been more strongly related to triglycerides and HDL cholesterol in plasma than has the subscapular:triceps skinfold ratio [22]. The truncal fat deposition could be related to glucocorticoid sensitivity, as long-term treatment of glucocorticoids cause accumulation of truncal fat. Sensitivity to glucocorticoids could also be programmed in fetal life [30]. In this context note that glucocorticoids also increase the concentrations of PAI-1 [31].

Accumulation of intracellular lipid in the skeletal muscle, possibly as a result of high concentrations of NEFA in the cells, is associated with the features of the insulin resistance syndrome [32]. Although birth weight seems to be inversely related with intracellular lipid content [32], the role of excess NEFA in insulin resistance associated with low birth weight has not been investigated. Raised intracellular NEFA concentrations could cause several of the characteristics related with low birth weight. For instance, NEFA could cause insulin resistance and impaired glucose tolerance by blocking insulin-mediated uptake and oxidation of glucose in the muscle through substrate competition [33] or by direct action on the insulin signal [34]. Non-esterified fatty acids also suppress nitric oxide production in vitro [35] and this could increase blood pressure [36]. The production of PAI-1 is induced by NEFA, a process which possibly involves induction of gene transcription by intracellular fatty acids [37].

Low birth weight has been associated with increased specific insulin and intact proinsulin concentrations during an oral glucose tolerance test [18] and with raised fasting 32, 33 split proinsulin concentrations [4]. This was first interpreted as reflecting a

defect in beta-cell function [4], but later studies by the same group showed that split proinsulin correlates well with insulin resistance but not with insulin secretion [38]. The relations of birth weight with intact and split proinsulin at age 70, even when only normoglycaemic men were included, is in line with the positive relation between birth weight and insulin sensitivity in this cohort [9]. Insulin sensitivity decreases with age [39], which could explain why birth weight, in this study, only was associated with the proinsulin-like molecules measured at age 70 and not at age 50.

Inclusion of pre-term births could obscure the relation of birth weight with metabolic variables [2, 9]. For this reason, additional analyses were done in the group of men who had their gestational ages recorded (men born at Uppsala Academic Hospital) and in those born at term. Birth weight was more strongly associated with the insulin resistance syndrome at age 50 and with PAI-1 activity and split proinsulin concentrations at age 70, when pre-term births were excluded.

The limitations of this study include the different investigations done at the two examinations. From this follows that the definitions of the insulin resistance syndrome and the cluster of factors associated with birth weight at ages 50 and 70 are not entirely comparable. We have therefore treated the two investigations as two separate and unrelated cross-sectional studies. Measurements of serum lipids and proinsulin-like molecules at age 50 were not done until several years after sampling. As the storage time was equally long for all subjects, we do not believe there was a bias from this cause.

A very strong relation between birth weight and the insulin resistance syndrome has previously been presented (in British men with mean age 64 years) [14]. Our results are more similar to those presented in another study of men in the United States (mean age 31.5 years) [15]. The participants in the cited studies were more obese than in this study, which could in part mediate the stronger effect of birth weight on the insulin resistance syndrome in the older group, as there is an interaction between birth weight and BMI [2, 6, 9]. Furthermore, the birth weight groups were defined differently.

We defined a cluster of variables related to birth weight in this cohort as hypertension and insulin resistance or glucose intolerance and truncal adiposity (at age 50) or high PAI-1 activity (at age 70). This cluster is a subset of the disturbances that make up the insulin resistance syndrome but could have a more specific mechanism such as increased concentrations of or sensitivity to glucocorticoids. Because most people with this cluster of factors associated with birth weight also have central obesity, increased serum triglyceride and lowered HDL cholesterol concentrations, we would anticipate the association of birth weight with the insulin resistance syndrome to be almost as strong as that with the more specific syndrome that we have defined as being associated with birth weight. The results also imply that the association of low birth weight with insulin resistance is not mediated by dyslipidaemia or abdominal obesity.

In conclusion, low birth weight is associated with high blood pressure, insulin resistance, truncal obesity and high PAI-1 activity but not with abdominal obesity or plasma lipid disturbances present in the insulin resistance syndrome. Thus it is possible to define a cluster of factors associated with birth weight that consists of a subset of the disturbances that are clustered in the general population as the insulin resistance syndrome. Understanding why low birth weight predicts only some components of the insulin resistance syndrome and not others could depend on identifying a specific physiological pathway that links this subset of disturbances.

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