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Glucose tolerance and resistance to insulin-stimulated glucose uptake in men aged 70 years in relation to size at birth

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Summary Although several studies have shown that reduced size at birth predicts glucose intolerance and insulin resistance in adult life, the relation has been inconsistent and usually stronger for ponderal index than for birthweight. We examined glucose tolerance and insulin sensitivity (by the euglycaemic clamp method) in relation to size at birth in 709 men aged 69–73 years in Uppsala, Sweden.
After adjusting for adult body mass index, prevalence of glucose intolerance (defined as diabetes or impaired glucose tolerance) was inversely related to birthweight. In men born at term, there was a positive monotonic relation of insulin sensitivity with birthweight, strongest in those who were overweight at age 70. This relation was reversed in men born before term ($p = 0.005$ for interaction between pre-term birth and birthweight effect). Glucose intolerance and insulin resistance showed inverted U-shaped relations with ponderal index, in contrast with the monotonic inverse relation seen in this cohort at earlier ages. This change in form of the relations was partly accounted for by selective loss to follow-up between ages 60 and 70 years. These results confirm that the association between reduced fetal growth and glucose intolerance is mediated through insulin resistance and depends upon an interaction with obesity in adult life. This relation is obscured when pre-term births are included. Failure to stratify by gestational age in previous studies could account for inconsistencies in the relations of insulin resistance and glucose intolerance to size at birth and for the detection of stronger associations with ponderal index than with birthweight. [Diabetologia (1998) 41: 1133–1138]

Keywords Birthweight, fetal-development, insulin-resistance, glucose-clamp-technique, longitudinal-studies

The association of reduced size at birth with glucose intolerance in adult life, first reported in two English cohorts in Hertfordshire [1] and Preston [2], has since been confirmed in prospective studies in Native American, Swedish and American White populations [3–5]. To explain the association between reduced fetal growth and glucose intolerance, Hales and colleagues initially suggested that inadequate fetal nutrition might impair the development of the endocrine pancreas, leading to reduced beta-cell reserve in later life [1]. A subsequent study of men and women born in Preston failed to detect any association between size at birth and beta-cell reserve but found an inverse relation between ponderal index at birth and insulin resistance measured by the short insulin tolerance test [6]. On the basis of these findings, Phillips and colleagues suggested that a specific relation of thinness at birth with insulin resistance in adult life might account for the inverse association of glucose intolerance with size at birth. In a cohort of men resident in Uppsala, Sweden, our findings were consistent with this alternative hypothesis: low ponderal index at birth was found to predict raised insulin concentrations at age 50 years and diabetes at age 60 years. As in Preston, there was no relation be-

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tween size at birth and the acute insulin response to intravenous glucose challenge [4].

The surviving men in the Uppsala cohort have now been examined at age 70 years, with glucose tolerance tests and measurements of insulin-mediated glucose uptake by the euglycaemic hyperinsulinaemic clamp technique. This allows us to examine for the first time the effect of size at birth on insulin sensitivity measured directly in older adults and thus to test whether effects on insulin resistance can account for the relation of size at birth to glucose intolerance in later life.

Subjects and methods

Data collection. The Longitudinal Study of Uppsala Men has been described previously [7–9]. In 1970–1973, all 2841 men living in the municipality of Uppsala who were born between 1920 and 1924 were invited to take part in a health survey. The participation rate was 82 % (2322 of 2841). Of the initial cohort of 2322 men examined in 1970–1973, 615 were born in the Uppsala Academic Hospital, 1585 were born elsewhere in Sweden and 122 were born outside Sweden. The birth records of the men born in the Academic Hospital included information on weight, length, and gestational age based on date of the mother's last menstrual period. By searching records in other Swedish hospitals and county archives, we were able to trace records of birthweight on 718 of the 1585 men who had been born elsewhere in Sweden. On 575 of these 718 men, birth length also had been recorded. Records of birthweight were thus traced on 61 % (1333 of 2200) of the men born in Sweden who were examined in 1970–1973.

At the initial examination in 1970–1973, fasting serum insulin was measured on the specimens by radioimmunoassay based on a double antibody solid phase technique (Pharmacia, Uppsala, Sweden). In 1980, the 2139 participants who were still resident in Uppsala were invited for re-examination. The participation rate was 87 % (1860 of 2139). Fasting whole blood glucose was measured in all participants, and in those whose fasting glucose was 5.7 mmol/l or higher an oral glucose tolerance test was carried out with a 75 g-glucose load. In 1992–1994 the 1781 surviving men who had been examined in 1970–1973 and were still living in Uppsala were invited for a third examination. The participation rate was 69 % (1221/1781). Birthweight was available on 60 % (737/1221) of these participants. The examination at age 69–73 years included anthropometry with measurement of waist and hip girths, followed by an oral glucose tolerance test. A euglycaemic hyperinsulinaemic clamp study [10] was completed on 696 of the 737 participants whose birth records had been traced but 41 men who were too disabled to lie on a couch for 2 h were excluded from the clamp study. Insulin was infused at a rate of 56 $mU \cdot m^{-2} \cdot min^{-1}$ over 120 min, giving a mean plasma insulin concentration of about 100 $mU \cdot l^{-1}$. The mean steady state plasma glucose concentration during the clamp was 5.2 mmol/l.

Statistical analysis. Intervals for grouping birthweight values were chosen to take account of the frequent rounding to the nearest 0.5 kg in the original birth records. Ponderal index was calculated as birthweight divided by the cube of birth length. Insulin sensitivity was calculated from the glucose infusion rate ($g \cdot min^{-1}$) between 60 and 120 min of the euglycaemic clamp, dividing this infusion rate by body weight (kg) and mean insulin level ($mU \cdot l^{-1}$). Diabetes and impaired glucose tolerance were defined by World Health Organization (WHO) criteria [11]. Glucose tolerance category was available on 710 of the 737 participants whose birth records had been traced. In testing for associations, birthweight group and quintile of ponderal index have been treated as categoric variables, except where otherwise stated. Associations with glucose intolerance as a dependent variable were examined by logistic regression and associations with insulin sensitivity as dependent variable were examined by least-squares regression. Exact values are given for all p-values less than 0.1.

Table 1. Prevalence of diabetes and impaired glucose tolerance at age 70 by birthweight

	Birthweight (kg)			
	< 3.25	3.25	3.75	4.25
Total number examined	(170)	(267)	(209)	(64)
Impaired glucose tolerance	15 (26)	15 (39)	12 (25)	6 (4)
Diabetes	18 (30)	13 (36)	14 (30)	13 (8)
Diabetes/impaired glucose tolerance combined	33 (56)	28 (75)	26 (55)	19 (12)

Percent prevalence, number of subjects in parentheses
p-values for variation between birthweight groups in prevalence of diabetes/impaired glucose tolerance combined: adjusted for age only: 0.16, adjusted for age and BMI: 0.05, adjusted for age, BMI and weight to height ratio: 0.13

Results

Birthweight. Prevalence of diabetes and impaired glucose tolerance combined was inversely related to birthweight, varying from 33 % in men who had weighed less than 3.25 kg at birth to 19 % in men who had weighed more than 4.25 kg (Table 1). In a logistic regression analysis with glucose intolerance as dependent variable, the relation with birthweight was statistically significant after adjusting for body mass index ($p = 0.05$ for variation between birthweight categories). After adjusting for waist to hip ratio, the relation of glucose intolerance with birthweight group was no longer statistically significant.

The relation of insulin sensitivity to birthweight group (Table 2) was J-shaped. In a least-squares regression analysis with insulin sensitivity as dependent variable, the relation to birthweight group was not statistically significant ($p = 0.09$) when no adjustment was made for body mass index but was significant ($p < 0.001$) after adjusting for body mass index. This relation remained statistically significant ($p = 0.003$) after adjusting for waist to hip ratio. When men with diabetes were excluded, the relation of insulin sensitivity with birthweight group was statistically significant ($p = 0.03$) even without adjusting for body mass index (data not shown). However the form of the relationship remained J-shaped. Stratifying by tertiles of body mass index showed that the relation of insulin

Table 2. Insulin sensitivity by birthweight and tertile of BMI

Tertile of BMI aged 70	Birthweight (kg)				p-value for variation between birthweight groups
	< 3.25	3.25	3.75	4.25	
	Glucose disposal $(g \cdot min^{-1} \cdot kg^{-1}\ (mU/l)^{-1} \times 100)$				
1	6.22 ± 2.51 (58)	6.83 ± 2.43 (78)	6.84 ± 1.91 (65)	6.76 ± 3.10 (16)	NS
2	5.22 ± 2.23 (60)	4.70 ± 1.91 (90)	5.36 ± 2.11 (74)	5.81 ± 3.06 (20)	NS
3	3.30 ± 1.97 (52)	3.33 ± 1.54 (92)	3.91 ± 2.14 (65)	4.32 ± 1.81 (26)	$p = 0.03$
All	4.97 ± 2.54 (170)	4.85 ± 2.42 (260)	5.37 ± 2.36 (204)	5.43 ± 2.77 (62)	$p = 0.09$ not adjusted, $p < 0.001$ adjusted for BMI

Mean ± SD, number of subjects in parentheses

Table 3. Insulin sensitivity by birthweight and gestational age for the 308 men born in the Academic Hospital

Gestational age category	Birthweight (kg)				*Slope of regression of glucose disposal on birthweight*	
	< 3.25	3.25	3.75	4.25	Slope	95% CI
	Glucose disposal $(g \cdot min^{-1} \cdot kg^{-1}\ (mU/l)^{-1} \times 100)$				*(a) adjusted for age only;* *(b) adjusted for age and BMI*	
< 38 weeks	5.53 ± 2.67 (30)	4.02 ± 1.71 (9)	3.15 – (1)	3.51 ± 1.32 (2)	(a) – 1.6 (b) – 1.3	– 3.2 to – 0.1, $p = 0.04$ – 2.7 to + 0.2, $p = 0.09$
≥ 38 weeks	4.47 ± 2.17 (55)	4.82 ± 2.46 (119)	4.80 ± 2.25 (75)	5.53 ± 2.16 (17)	(a) + 0.4 (b) + 0.7	– 0.2 to + 1.1, NS + 0.1 to + 1.2, $p = 0.01$

Mean ± SD, number of subjects in parentheses

sensitivity to birthweight was flat in the lowest tertile of body mass index, J-shaped in the middle tertile and positive monotonic in the highest tertile (Table 2).

To examine whether the non-linearity of the relationship between insulin sensitivity and birthweight could be accounted for by any effect of gestational age on the form of this relation, the 308 men on whom both gestational age and clamp study measurements were available were divided into pre-term births (< 38 weeks of gestation) and term births (≥ 38 weeks) as shown in Table 3. Mean birthweight was 3.12 kg in pre-term births and 3.56 kg in term births, a difference equivalent to 0.9 standard deviations. The slope of the relation between insulin sensitivity and birthweight (as a continuous variable) was examined in least-squares regression models with insulin sensitivity as dependent variable, adjusting for age. Among men born at term, insulin sensitivity was positively related to birthweight. When adjusted for body mass index, this association was monotonic and statistically significant (slope of regression + 0.7 units/kg^{-1}, where units for insulin sensitivity are g $min^{-1} \cdot kg^{-1} \cdot (mU/l)^{-1} \times 100$). For comparision, the regression coefficient for body mass index in the same model was –0.35 units $\cdot\ kg^{-1} \cdot m^2$ (95% confidence interval CI; –0.28 to –0.42). In contrast, among pre-term births there was an inverse relation of insulin sensitivity to birthweight (slope of regression; –1.3 units/kg). When pre-term and term births were combined in a regression model that included a term for interaction between the effects of pre-term birth and birthweight on insulin sensitivity, this interaction was statistically significant ($p = 0.005$).

Ponderal index. The relationship of glucose intolerance to ponderal index was inverted U-shaped (Table 4). Prevalence of glucose intolerance was lowest in the top quintile of ponderal index, and highest in the middle quintile. In a logistic regression analysis with glucose intolerance as a dependent variable, the relation with ponderal index was statistically significant ($p = 0.03$ for variation between quintiles of ponderal index, adjusted for age only). Adjusting for body mass index did not alter the strength of this association, as body mass index at age 70 was unrelated to ponderal index at birth. After adjusting for waist to hip ratio, the relation of glucose intolerance to ponderal index was no longer statistically significant.

Table 4. Prevalence of glucose intolerance at age 70 by ponderal index

	Ponderal index quintile				
Total number examined	1 (133)	2 (133)	3 (123)	4 (117)	5 (126)
IGT (impaired glucose tolerance)	14 (19)	12 (16)	20 (25)	10 (12)	9 (11)
Diabetic	16 (21)	20 (26)	15 (19)	12 (14)	12 (15)
Diabetes/IGT combined	30 (40)	32 (42)	36 (44)	22 (26)	21 (26)

Percent prevalence, number of subjects in parentheses
p-values for variation between quintiles of ponderal index in prevalence of diabetes/impaired glucose tolerance combined: adjusted for age only: 0.04, adjusted for age and BMI: 0.05, adjusted for age, BMI and waist to hip ratio: 0.08

In the 619 men on whom insulin sensitivity and ponderal index had been measured, the relation of insulin sensitivity to ponderal index was U-shaped. As insulin sensitivity is the reciprocal of insulin resistance, this is equivalent to stating that the relation of insulin resistance to ponderal index was inverted U-shaped. In a least-squares regression analysis with insulin sensitivity as a dependent variable, the relation was statistically significant ($p = 0.001$ for variation between quintiles of ponderal index) with or without adjustment for body mass index and waist to hip ratio. The form of the relation was U-shaped in all three tertiles of body mass index (Table 5). In the subset of 307 men for whom gestational age was available (Table 6), the relation of insulin sensitivity to ponderal index was still U-shaped but not statistically significant. Exclusion of pre-term births did not alter the form of the relationship between insulin sensitivity and ponderal index (Table 6). The mean ponderal index was 25.6 kg · m^{-3} in pre-term births and 26.1 kg m^{-3} in term births, a difference equivalent to 0.2 standard deviations.

As we had found previously monotonic inverse relation of insulin concentrations at age 50 years and prevalence of diabetes at age 60 years with ponderal index in this cohort [4], we examined whether selective loss to follow-up could account for the inverted U-shape of the relation of insulin resistance and glucose intolerance at age 70 years with ponderal index at birth. Among men in the lowest quintile of ponderal index at birth, the proportion lost to follow-up between ages 50 and 70 years (through death, migration or non-participation) was higher among those whose fasting insulin at age 50 was above the median than among those whose fasting insulin at age 50 was below the median (42% vs 27%, $p = 0.04$). Deaths accounted only for about one-third of this difference in the proportion lost to follow-up; among men in the lowest quintile of ponderal index at birth, 22% of those whose fasting insulin at age 50 was above the median and 17% of those whose fasting insulin was below the median had died before age 70. Diabetes at age 60 years predicted non-participation at age 70 years; among the 1538 men in the cohort who were still alive at age 70, the proportion who did not attend for examination at age 70 years was 42% (28/66) among those who were diabetic at age 60 years, compared with 24% (356/1472) among those not diabetic at age 60 years ($p = 0.001$).

Discussion

These results in a cohort of Uppsala men at age 70 years confirm our earlier finding in this cohort at age 60 years that prevalence of glucose intolerance is inversely related to size at birth. They support also the hypothesis that this association is mediated through an effect of size at birth on insulin resistance, rather than through effects on beta-cell function. The

Table 5. Insulin sensitivity by quintile of ponderal index and tertile of BMI

Tertile of BMI aged 70	Ponderal index quintile					p-value for variation between quintiles
	1	2	3	4	5	
	Glucose disposal $min^{-1} \cdot kg^{-1} \cdot (mU/l)^{-1} \times 100$)					
1	6.70 ± 2.15 (36)	6.40 ± 2.53 (37)	5.92 ± 1.86 (43)	7.27 ± 2.96 (26)	7.14 ± 2.33 (49)	$p = 0.07$
2	5.39 ± 2.23 (52)	4.39 ± 1.83 (51)	4.97 ± 2.06 (37)	5.27 ± 2.51 (44)	5.53 ± 2.30 (36)	$p = 0.09$
3	3.51 ± 1.93 (45)	3.31 ± 1.56 (44)	3.15 ± 1.79 (42)	4.13 ± 2.09 (42)	4.07 ± 1.83 (36)	$p = 0.06$
All	5.11 ± 2.45 (133)	4.59 ± 2.31 (132)	4.68 ± 2.22 (122)	5.31 ± 2.73 (112)	5.75 ± 2.52 (121)	$p = 0.001$ not adjusted, $p < 0.001$ adjusted for BMI

Mean ± SD, number of subjects in parentheses

Table 6. Insulin sensitivity by ponderal index and gestational age group category for the 307 men born in the Academic Hospital whose birth length was recorded

Gestational age group	Ponderal index quintile				
	1	2	3	4	5
	Glucose disposal ($g \cdot min^{-1} \cdot kg^{-1}$ $(mU/l)^{-1} \times 100$)				
< 38 weeks	5.76 ± 2.79 (14)	4.49 ± 2.41 (15)	3.77 ± 1.63 (3)	4.89 ± 2.17 (6)	4.77 ± 2.37 (3)
≥ 38 weeks	4.77 ± 2.18 (61)	4.46 ± 2.15 (67)	4.69 ± 2.18 (61)	4.99 ± 2.62 (54)	5.57 ± 2.76 (23)

Mean ± SD, number of subjects in parentheses

relation of insulin resistance to size at birth was independent of obesity and body fat pattern. An unexpected finding was that the relation of insulin sensitivity with birthweight was J-shaped, with higher average insulin sensitivity among men in the lowest birthweight category (< 3.25 kg) than among men weighing 3.25 to 3.75 kg.

Underlying this J-shaped relation it appears that there are two distinct associations: a positive relation between insulin sensitivity and birthweight among those born at term and an inverse relation between insulin sensitivity and birthweight among pre-term births. A possible explanation for this inverse relation is that among pre-term infants who were heavier than expected for their gestational age, a high proportion were macrosomic infants of mothers with gestational diabetes. We have shown previously that the inverse relation of blood pressure with birthweight among those born at term is reversed among pre-term births [12]; this seems to apply also to the relation of insulin sensitivity with birthweight. Our classification of births as pre-term (< 38 weeks) or not pre-term (≥ 38 weeks) relied on the date of the last menstrual period. In a large study in which dating by the last menstrual period was validated against dating by ultrasound measurement of fetal biparietal diameter, the predictive values for classifying gestational age as < 37 weeks or ≥ 37 weeks were 78 % and 97 %, respectively [13]. Misclassification of gestational age would only weaken our ability to detect interactions between the effects of birthweight and gestational age on insulin sensitivity and could not account for the detection of a highly significant interaction in this study.

Failure to stratify by gestational age could explain why previous studies have found weak or absent relation between birthweight and insulin resistance, whether measured by the short insulin tolerance test [6] or the frequently-sampled intravenous glucose tolerance test [14]. We emphasize, therefore, that it is crucial to stratify by gestational age in studies of the effect of size at birth on insulin resistance and diabetes in adult life.

The relation of insulin sensitivity to birthweight was strongest among men who were in the highest tertile for body mass index at age 70 years, consistent with our previous suggestion [4] that the effect of size at birth on insulin sensitivity depends on an interaction with obesity in adult life. Because in the highest tertile for body mass index the relation of insulin sensitivity to birthweight is positive monotonic, and most men with glucose intolerance are overweight, one would expect to see a monotonic inverse relation between glucose intolerance and birthweight, as in this cohort.

The inverted U-shaped relation of glucose intolerance and insulin resistance to ponderal index at birth are consistent with the general hypothesis that effects of size at birth on glucose intolerance are mediated through effects on insulin resistance. It is, however, surprising that in a cohort where there were inverse monotonic relations of insulin concentrations (a proxy measure of insulin resistance) at age 50 years and diabetes at age 60 years with ponderal index at birth [4], inverted U-shaped relations should be seen by age 70 years. Whereas at age 60 years the highest prevalence of diabetes was in men who were in the lowest quintile of ponderal index at birth, at age 70 years the highest prevalence of glucose intolerance was in men who were in the middle quintile of ponderal index at birth. This change in the form of the relation of glucose intolerance and insulin resistance with ponderal index is partly accounted for by selective loss to follow-up of men in the lowest quintile of ponderal index who were insulin resistant at age 50 years (as indicated by fasting insulin above the median) or were diabetic at age 60 years. As this lower participation rate is not fully accounted for by higher mortality; it is possible that men who had been under medical supervision for diabetes since the age of 60 years were more reluctant than others to participate at age 70 years.

One reason why previous studies [4, 6] have shown stronger relations for ponderal index than for birthweight with insulin resistance and glucose intolerance could be that ponderal index is less dependent than birthweight on gestational age. The mean ponderal index of pre-term births was only 0.2 standard deviations less than the mean ponderal index of term births, whereas the mean birthweight of pre-term births was 0.9 standard deviations less than the mean birthweight of term births (as birthweight and ponderal index are measured in different units, the strengths of association can be compared only if these variables are scaled by their standard deviations). Using ponderal index rather than birthweight can thus have the effect of partially adjusting size at birth for gestational age [15]. Low ponderal index, however, cannot be interpreted simply as an index of intrauterine growth retardation [16, 17].

It is unlikely that genetic effects can fully account for the effect of birthweight on the risk of diabetes, as the inverse association of birthweight with risk of diabetes has been found to hold within monozygotic twin pairs [18] and a direct association of undernutrition in utero with decreased glucose tolerance in adult life has been shown in the Dutch famine cohort [19]. It is possible, however, that some exposure more specific than retardation of growth, such as exposure of the fetus to maternal glucocorticoids [20], underlies the association of reduced size at birth with glucose intolerance. Further understanding of this association is likely to depend upon identifying physiologic pathways that influence both size at birth and insulin resistance in adult life.

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