

Relation of Birth Weight, Body Mass Index, and Change in Size from Birth to Adulthood to Insulin Resistance in a Female Twin Cohort

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Context and Objectives: Because an adverse intrauterine environment is thought to induce insulin resistance, our objective was to investigate the relationships between birth weight, BMI, and change in body size over the life course and insulin resistance.

Setting, Design, and Participants: We conducted a cross-sectional study in a cohort of 1194 female twins aged 18–74 yr. The relationship between birth weight and insulin resistance was analyzed using a regression method allowing for a simultaneous estimation of within- and between-pair influences. The approach allows the influence of individual fetal nutrition on adult insulin resistance to be distinguished from effects that are mediated by confounding factors in the maternal environment.

Main Outcome Measures: Insulin resistance was measured by the homeostasis model assessment.

Results: Individual level regression analyses showed no significant relationship between birth weight and insulin resistance. There was a significant positive relationship between insulin resistance and current body mass index (BMI) (a 26% increase in insulin resistance per SD increase in BMI; confidence interval, 22.6–29.5%). This significant relationship was accounted for in equal parts by individual-specific effects and by confounding factors in the shared environment of the twins. The relationship with birth weight became significant only after adjustment for BMI and was mediated only through between-pair differences.

Conclusions: These results suggest that insulin resistance is influenced more by current body size than birth weight and that postnatal growth is potentially more important than fetal growth in the subsequent development of insulin resistance. (*J Clin Endocrinol Metab* 93: 516–520, 2008)

Glucose and insulin metabolism are thought to be programmed during fetal life, with an adverse intrauterine environment inducing insulin resistance, leading to impaired glucose homeostasis (1, 2). In a recent systematic review, the majority of studies reported an inverse relationship between birth weight (as a proxy for fetal growth) and fasting plasma insulin (3). Birth weight has also been associated with a range of additional measures of both insulin resistance and sensitivity (3).

However, it remains uncertain whether this inverse relationship is as a direct effect of undernutrition *in utero*, regardless of the quality of maternal diet, due to a diminished supply of nutrients reaching the fetus, or due to a range of external confounding factors such as suboptimal maternal dietary intake, smoking, or physical activity.

Investigating the relationship between birth weight and variables measured in adult life in twins allows the influences of birth

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Abbreviations: BMI, Body mass index; CI, confidence interval; DZ, dizygotic; HOMA, homeostasis model assessment; MZ, monozygotic.

weight, maternal environment, and genetic factors to be separated analytically. The current study aimed to investigate the relationship between birth weight, current body mass index (BMI), and insulin resistance in a population-based cohort of adult female twins. Studying the strength of the association in the group as a whole provides a measure that is comparable to the results of studies of unmatched singleton cohorts. However, additional information is obtained by modeling the relationship within and between twin pairs. Any observed relationship can be attributed to factors that are specific to the environment of the individual members of each pair and to confounding by factors in the shared environment of the twins. Furthermore, comparing the strength of the relationships in monozygotic (MZ) and dizygotic (DZ) pairs also provided a measure of the extent to which the relationship might be mediated by genetic factors.

Subjects and Methods

Subjects and study design

The study subjects comprised a sample of twins enrolled on the Twins UK Registry. This is a nationwide registry of twin volunteers who have been recruited through successive media campaigns (4). The register was set up to examine women's health, and the majority of twins recruited to the register are female. Twins enrolled onto the registry are not selected for disease-specific studies and have been shown to be representative of the UK population with respect to their anthropometric characteristics and the frequency of disease-related traits and lifestyle exposures (5, 6). Zygosity was determined by questionnaire and confirmed by multiplex DNA fingerprinting (PE Applied Biosystems, Foster City, CA). Ethical approval for this study has been obtained from St. Thomas' Hospital Research Ethics committee, and informed consent was obtained from all subjects.

The participants in the present study were part of a sample invited to attend for clinical assessment at St Thomas' Hospital between 1996 and 2000. All were female and between the ages of 18 and 80 yr. The sample selected for interview favored the inclusion of DZ twins for genetic linkage studies, but this selection was otherwise unrelated to other characteristics of the twins. Evaluation included measurement of fasting insulin and glucose data and the completion of a nurse-led interview. Birth weight was ascertained from the participants' recall. BMI was calculated from height and weight measurements using the Quetelet index. Medication history was coded according to the British National Formula Number 40 (2000).

Laboratory methods

Serum samples were stored at -40 C until analysis. Fasting insulin was measured by immunoassay (Abbott Laboratories Ltd., Maidenhead, UK), and fasting glucose was measured on an Ektachem 700 multichannel analyzer using an enzymatic colorimetric slide assay (Johnson and

Johnson Clinical Diagnostic Systems, Amersham, UK). Insulin resistance was calculated using the homeostasis model assessment (HOMA) (7). Subjects with insulin or glucose levels falling outside the calculable levels for HOMA were excluded from the analyses ($n = 88$).

Because body fat levels may increase after the menopause (8), we also adjusted for menopausal status. All subjects with either type 1 or type 2 diabetes (those diagnosed by a doctor, who were taking any form of diabetic medication, or those with fasting glucose levels of ≥ 7.0 mmol/liter) were excluded ($n = 35$). The twin of any participant excluded for any reason was also excluded from these analyses. All statistical analyses were performed using STATA version 9.

Statistical methods

The insulin resistance data were log transformed to achieve a normal distribution. Birth weight and BMI measures were standardized giving a mean of 0 and SD of 1. As birth weight and later body size are themselves likely to be correlated, we examined a sequence of models including birth weight alone (model 1), BMI alone (model 2), and birth weight and BMI (model 3). This approach follows the sequence of models recommended by Lucas *et al.* (9) for analysis of the association between birth weight and adult characteristics. Model 3, which examines the association between early size adjusted for later size, is statistically equivalent to assessing how insulin resistance in the adult is influenced by change in size after birth. Effectively, this provides a measure how insulin resistance is influenced by centile crossing. We also tested for a birth weight and BMI interaction using a model including birth weight, BMI, and a birth weight and BMI interaction term.

Linear regression analysis was first undertaken treating the twins as individuals, allowing a direct comparison with findings in singleton populations: $E(Y_{ij}) = \beta_0 + \beta_c X_{ij}$, where Y_{ij} and X_{ij} , respectively, represent insulin resistance (Y) value and birth weight (X) of twin j from pair i . β_c represents expected change in insulin resistance per SD increase in birth weight in individuals. The regression analysis took into account the correlated structure (clustering by family) of the data. Second, following the approach described in detail by Carlin *et al.* (10), the effect of birth weight of each individual twin on insulin resistance was examined in a model parameterized with birth weight included as 1) a variable representing the mean birth weight of the pair from which the twin is derived and 2) a variable representing the individual twin's difference from the pair mean. This approach provides a simultaneous estimation of within and between-pair influences of birth weight on insulin resistance: $E(Y_{ij}) = \beta_0 + \beta_w(X_{ij} - X_i) + \beta_B X_i$, where X_i is the mean value of X for twin pair i . The within-pair coefficient β_w gives the expected change in Y for a one-unit change in the difference between the individual X and the twin-pair average X value. The between-pair coefficient β_B gives the expected change in Y for a one-unit change in the twin-pair average X , while holding the individual deviation from the average constant.

The within-pair effect β_w represents an association that is free of confounding due to factors that are common to the twin pair (for example, shared intrauterine exposures, such as maternal smoking, or common factors in the shared family environment, such as social class). The between-pair effect β_B reflects further variation in Y that can be explained by variation in the twin-pair mean of X . Variation due to con-

TABLE 1. Characteristics of the study population

	All subjects (n = 1194)				MZ twins only (n = 234)				DZ twins only (n = 960)			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Birth weight (kg) ^a	2.45	0.60	0.79	4.22	2.30	0.66	0.79	4.11	2.49	0.58	0.79	4.22
Age (yr)	42.9	12.5	18	74	43.7	14.7	18	72	42.7	11.9	18	74
BMI (kg/m ²) ^{a,b}	24.4	1.18	13.9	52.4	23.9	1.17	16.5	39.3	24.5	1.19	13.9	52.4
Glucose (mmol/liter)	4.42	0.51	3.50	7.00	4.47	0.63	3.50	6.90	4.41	0.47	3.50	7.00
Insulin (pmol/liter) ^b	42.0	1.71	20.1	225	41.8	1.82	20.1	226	42.1	1.68	20.0	215
Insulin resistance ^b	0.76	1.71	0.35	4.24	0.76	1.83	0.35	4.24	0.76	1.69	0.35	3.86

^a $P < 0.05$ for difference between MZ and DZ twins.

^b Geometric means.

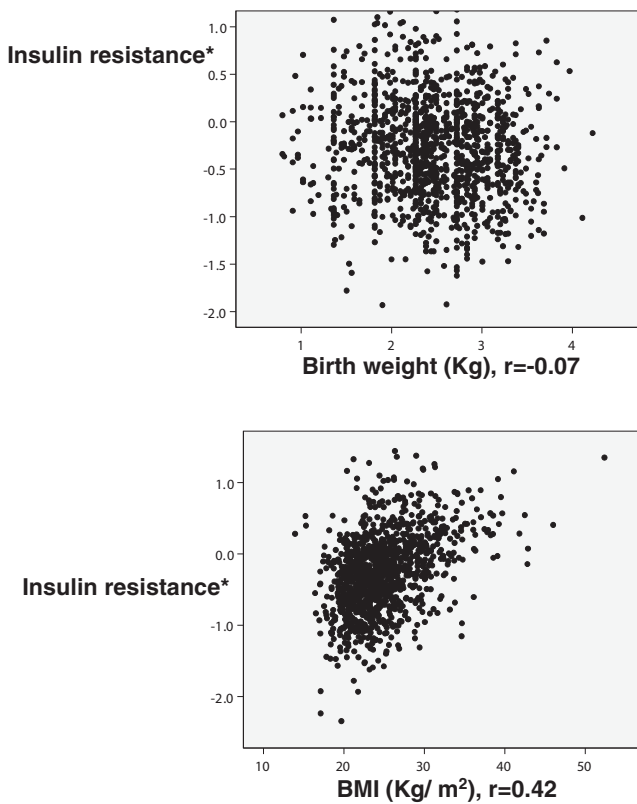


FIG. 1. Scatterplot showing correlation between insulin resistance and birth weight (kilograms) (top) and body mass index (kilograms per square meter) (bottom). *, Log transformed.

founding resulting from the maternal environment would be expected to be detected in β_B but not β_w (10).

The regression analyses were carried out in MZ and then DZ twins separately, with adjustment for age and menopausal status, and where no significant differences existed between zygosity groups, the data were pooled.

Results

Birth weight and insulin resistance data were available for 1194 subjects (480 DZ pairs and 117 MZ pairs) (Table 1). Mean birth

weight was 2.45 kg, slightly lower than in comparable singleton populations, and was lower in MZ (2.30 kg) twins than in DZ twins (2.49 kg). All other anthropometric measurements were similar to comparable singleton populations (11, 12). There was no significant difference in insulin resistance between MZ and DZ twins.

Figure 1 shows scatter plots of insulin resistance and birth weight and BMI.

Individual-level regression (Table 2)

The results from the individual-level regression analysis indicated that there was no significant relationship between birth weight and insulin resistance (model 1).

There was a significant positive relationship between insulin resistance and current BMI in model 2 (a 26.0% increase in insulin resistance per SD increase in BMI; confidence interval (CI), 22.6–29.5%). In model 3, the relationship between birth weight and insulin resistance becomes significant after adjustment for current BMI (a 4.6% decrease in insulin resistance per SD increase in birth weight; CI, 1.7–7.4). Because model 3 provides an estimate for change in size between the earlier and later environment (9) this model provides a measure of the effect of centile crossing on insulin resistance. Therefore, these results indicate that it is change in size, rather than birth weight itself, that is a determinant of insulin resistance.

Within- and between-pair analysis (Table 3)

The analysis of model 1 confirms that there is no significant relationship between birth weight and insulin resistance, as indicated by the lack of significance for β_w . In model 2, the relationship between adult BMI and insulin resistance is mediated through between- and within-pair effects, indicating that both individual-specific factors plus shared environmental factors exert an influence. When adult BMI is included in the birth weight and insulin resistance model (model 3), the relationship between birth weight and insulin resistance becomes significant between pairs only, and not within pairs. As in the analysis of the data overall, this provides evidence to support an influence of change in size.

Further adjustment for menopausal status had no important

TABLE 2. Regression analyses of birth weight and insulin resistance, treating twins as individuals

Variables included	Bc ^a	
	β (per SD increase)	95% CI
All subjects		
Model 1: Insulin resistance, birth weight, age	–3.31	–6.57, 0.06
Model 2: Insulin resistance, BMI, age	26.0	22.6, 29.5
Model 3: Insulin resistance, birth weight, BMI, age	–4.56	–7.37, –1.66
MZ only		
Model 1: Insulin resistance, birth weight, age	–6.16	–12.4, 0.48
Model 2: Insulin resistance, BMI, age	36.5	26.9, 46.7
Model 3: Insulin resistance, birth weight, BMI, age	–6.43	–12.0, –0.52
DZ only		
Model 1: Insulin resistance, birth weight, age	2.49	–6.26, 1.43
Model 2: Insulin resistance, BMI, age	24.6	21.0, 28.24
Model 3: Insulin resistance, birth weight, BMI, age	–3.80	–7.04, –0.45

^a Expected percentage change in insulin resistance for a SD change in birth weight (models 1 and 3) or BMI (model 2).

TABLE 3. Regression analyses of birth weight and insulin resistance, allowing estimation of within- and between-pair differences

Variables included	β_w^a		β_B^b	
	β (per sd increase)	95% CI	β (per sd increase)	95% CI
All subjects				
Model 1: Insulin resistance, birth weight, age	-2.12	-7.81, 3.92	-3.94	-7.86, 0.15
Model 2: Insulin resistance, BMI, age	23.9	19.2, 28.8	28.3	23.5, 33.3
Model 3: Insulin resistance, birth weight, BMI, age	-3.8	-8.81, 1.47	-4.94	-8.39, -1.37
MZ only				
Model 1: Insulin resistance, birth weight, age	-2.67	-13.3, 9.23	-8.30	-16.6, 0.81
Model 2: Insulin resistance, BMI, age	28.9	15.5, 44.0	40.73	28.2, 54.5
Model 3: Insulin resistance, birth weight, BMI, age	-5.42	-15.7, 6.07	-6.95	-14.3, 1.04
DZ only				
Model 1: Insulin resistance, birth weight, age	-2.00	-8.49, 4.95	-2.74	-7.18, 1.92
Model 2: Insulin resistance, BMI, age	23.5	18.6, 28.6	25.9	20.7, 31.3
Model 3: Insulin resistance, birth weight, BMI, age	-3.53	-9.18, 2.48	-3.94	-7.84, 0.12

^a Within-pair effect: the expected percentage change in insulin resistance for a sd change in the difference between the individual birth weight (models 1 and 3) or BMI (model 2) Z score and the twin-pair average birth weight (models 1 and 3) or BMI (model 2) Z score.

^b Between-pair effect: the expected percentage change in insulin resistance for a sd change in the twin-pair average birth weight (models 1 and 3) or BMI (model 2) Z score.

effect in any analyses, and there were no significant interactions between birth weight and BMI (not shown). There were no important differences in the magnitude of either β_C or β_w between MZ and DZ twins, as indicated by the similar effect sizes and the overlapping confidence intervals for MZ and DZ twins in each model. This suggests that the significant relationships that have been observed are not mediated through genetic factors.

Discussion

These data from a large population-based volunteer twin cohort show no significant associations between birth weight and subsequent insulin resistance. They confirm that insulin resistance is chiefly influenced by current body size but also indicate that postnatal growth makes a potentially important contribution. Our analysis of within-twin-pair differences indicated that the significant relationship between insulin resistance and BMI is mediated, in part, through individual-specific effects. However, the presence of between-pair effects also indicated that this measured association is susceptible to confounding through influences in the shared environment of the twins. In the within- and between-pair analysis, we found no evidence for individual-specific effects with birth weight, either before or after adjustment for BMI. There was no evidence in these data to suggest that relationships between birth weight, BMI, and change in body size and insulin resistance were mediated genetically.

Previous research has highlighted that those who are small at birth but who exhibit excessive weight gain over the life course are at highest risk of developing insulin resistance and the metabolic syndrome (13, 14). We do not have multiple measures of growth in this cohort and cannot determine which period of growth is most influential on insulin resistance in later life. However, it has been shown that those who were born small are more likely to experience rapid weight gain in the first 2 yr of life (15), and evidence from a recent systematic review indicates that rapid weight gain in infancy is strongly related to overweight and obe-

sity in adulthood (16). Evidence from animal studies (17) shows that catch-up growth as a result of being born small has lifelong effects on health including an influence on the age of maturity, lifespan, fertility, adult body size, the ability to maintain adequate energy reserves, the number of cells in organs, and the number of adult muscle fibers and on glucose tolerance and insulin regulation.

Limitations of the study include the reliance on recalled birth weight rather than more accurate prospective measures. However, previous research has shown that although there are some disadvantages in the use of recalled birth weight (18–20), mainly due to underestimation of birth weight in smaller babies, the majority of women (between 72 and 88%) can precisely recall the birth weight of their children. The use of recalled birth weight may therefore lead to underestimation of the strength of any associations found in the individual-level regressions. However, because there is no reason why there should be discordance in recall error within pairs, this should not have any real influence on the relationship within each twin pair.

Insulin resistance was measured indirectly by calculating HOMA. Although HOMA provides an indirect measurement of insulin resistance, HOMA scores do correlate highly with insulin resistance scores derived from euglycemic clamp tests (21). The intrauterine growth in twins may be different from that in singletons (22) as indicated by their lower birth weights. However, we have previously reported that the twins enrolled in the UK registry are representative of the singleton population for a wide range of anthropometric and disease-related characteristics (4–6).

In our data, a 1-sd decrease in birth weight was associated with a 3.3% increase in insulin resistance, an effect size that is comparable to those found in studies of singletons (3) including the Newcastle Thousand Families Study (23), the British Women's Heart and Health Study (24), and the European Youth Heart Study (13). In these, the sizes of associations were all under 6%. Previous twin studies have also found similar effect sizes (25).

This is the largest twin study to date to investigate the rela-

tionships between birth weight and insulin resistance. It is the first to use the twin model to compare within- and between-pair differences simultaneously to separate maternal from individual-specific effects. Our data show that adult size is significantly related to insulin resistance in adult life and that these associations are mediated equally through both individual and shared influences. Any significant effects with birth weight are mediated purely through shared environmental factors.

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