Birthweight and Body Mass Index in Young Adulthood: The Swedish Young Male Twins Study

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Many studies have found an inverse association between fetal growth and cardiovascular disease related to the metabolic syndrome in adulthood. Nevertheless, the relative importance of genetics and the intrauterine environment remain unclear. The objective of the study was to test the fetal origins hypothesis and the fetal insulin resistance hypothesis by studying the impact of fetal growth on Body Mass Index (BMI) in young adulthood. In a nationwide cohort study, the Swedish Medical Birth Register for the years 1973–1979 was linked with the Military Service Conscription Register for 1990–1999. In 1998 a questionnaire was mailed to all male twins, included in the two registers, who were alive and still resident in Sweden. The study covers the 923 male twin pairs for which full data were available. Mixed linear models were used to estimate within-pair and between-pair differences in birthweight and their relations to BMI. A weak positive association was found among the monozygotic twins for the within-pair difference in birthweight and BMI. No significant association was found among the monozygotic for the between-pair difference in birthweight and BMI. No significant associations were found for dizygotic twins. These findings do not seem to support either the fetal programming hypothesis or the fetal insulin resistance hypothesis.

The increasing trend in the prevalence of overweight and obesity in many countries in the western world, and also in countries under demographic transition, indicates that environmental factors are important in the etiology of this complex phenotype (Rasmussen et al., 1999). Adoption studies, twin studies and other family studies have shown that genetic factors are important for body mass and obesity. In a review of familial resemblance, genetic factors were found to explain about two thirds of the variance in body mass index (BMI) scores (Maes et al., 1997). A study of twins reared apart has also shown very clearly that genetic factors are important for body mass and obesity. In a recent paper Verhaeghe et al. (1993) found elevated levels of IGF-1 in serum from the umbilical cord of newborn babies who were small-for-gestational-age, and low levels in large-for-gestational-age babies. In a later paper Verhaeghe et al. (1996) reported a stronger correlation of IGF-1 cord serum levels among monozygotic (MZ) twins than among dizygotic (DZ) twins indicating the likely importance of genetic as well as environmental factors. Long-term intrauterine starvation during pregnancy may give rise to persistent disturbances in the regulation of insulin, IGFs and GH (Barker et al., 1993). Other studies indicate that increased fetal exposure to maternal glucocorticoids might link IUGR and components of the metabolic syndrome in adult life (Benediktsson et al., 1993; Edwards et al., 1993). Mild or permanent endocrine abnormalities, involving increased activity of the hypothalamic-pituitary-adrenal axis, have been hypothesized as constituting a pathway for the development of insulin resistance in adulthood among individuals with growth retardation during fetal life (Phillips et al., 1998).

Substantial support for the fetal origins hypothesis has been provided by Ravelli et al. (1976), who studied the occurrence of obesity among the offspring of Amsterdam women who became pregnant during the Dutch famine of 1944–45. The study showed that the risk of developing obesity was highest among young men who were sons of women exposed to severe maternal undernutrition during the first half of pregnancy. In a more recent study, Ravelli et al. (1998) found that prenatal exposure to the famine, during late gestation, was associated with decreased glucose tolerance in adulthood. In accordance with firm evidence from experimental research on animals, observational studies on humans indicate that severe maternal undernutrition in fetal life may lead to permanent changes in insulin-glucose metabolism. Hales et al. (1992) suggest that the high prevalence of NIDDM in some populations, such as native persons and middle-aged individuals (Leon et al., 2000, Leon et al., 1996).

Using animal models, Gluckman and Harding (1997) reported that IUGR might be related to relative resistance to IGF-1. Verhaeghe et al. (1993) found elevated levels of IGF-1 in serum from the umbilical cord of newborn babies who were small-for-gestational-age, and low levels in large-for-gestational-age babies. In a later paper Verhaeghe et al. (1996) reported a stronger correlation of IGF-1 cord serum levels among monozygotic (MZ) twins than among dizygotic (DZ) twins indicating the likely importance of genetic as well as environmental factors. Long-term intrauterine starvation during pregnancy may give rise to persistent disturbances in the regulation of insulin, IGFs and GH (Barker et al., 1993). Other studies indicate that increased fetal exposure to maternal glucocorticoids might link IUGR and components of the metabolic syndrome in adult life (Benediktsson et al., 1993; Edwards et al., 1993). Mild or permanent endocrine abnormalities, involving increased activity of the hypothalamic-pituitary-adrenal axis, have been hypothesized as constituting a pathway for the development of insulin resistance in adulthood among individuals with growth retardation during fetal life (Phillips et al., 1998).

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Americans, may be partly due to undernutrition in fetal life followed by relative overnutrition in later life, thus supporting the thrifty phenotype hypothesis (Hales, 1997).

Nevertheless, some findings have been reported that are inconsistent with the fetal origins hypothesis. In an Israeli study of 30,000 infants, followed-up at 17 years of age, a positive association was found between birthweight and BMI at 17 years of age (Seidman et al., 1991). And, in a previous study of singletons, there was a weak positive association between birthweight and BMI at 18 years of age (Rasmussen & Johansson, 1998). Further, Sørensen et al. (1997), and also Phillips and Young (2000), have reported a positive association between birthweight and obesity in adulthood.

A fetal insulin resistance hypothesis was proposed by Hattersley and Tooke (1999) as an alternative to the fetal programming hypothesis of Barker and colleagues. According to the former hypothesis, IUGR and insulin resistance syndrome in adulthood are different phenotypic expressions of the same underlying genotype. In such case, studies of MZ and DZ twins may be informative, because twin studies provide partial or complete control for genetic factors. Attributions found within MZ pairs of twins should be due to environmental factors since MZ pairs are or are presumed to be genetically identical. Twins have lower birthweight for gestational age than singletons, and most twins catch up with singletons later in childhood with regard to height and weight (Luke et al., 1995; Williams & Poulton, 1999). Thus, the risk of IUGR is higher among twins than among singletons (Barker, 1998). If genetic factors were the main explanation for the association between birthweight and BMI in later life, no association (or a relatively weak association) within MZ pairs would be expected. Accordingly, the aim of the present Swedish study of young male twins was to test the fetal origins hypothesis and the fetal insulin resistance hypothesis by analyzing the impact of within-pair and between-pair differences in birthweight on BMI among MZ and DZ twin pairs.

**Materials and Method**

**Registry Information**

For male twins born 1973–79 data on birthweight, birthlength, gestational age and birth order were obtained from the Swedish Medical Birth Register (MBR). This information source covers more than 99% of all children born in Sweden.

Data on weight and height at age 18 were retrieved from the Military Service Conscription Register (MSCR). Included in this study are the individuals who participated in the conscription examinations of 1991–1999. Such medical examination is compulsory for all males except those with severe chronic diseases or handicaps.

**Questionnaire Data**

Information about birthweight, birth order, zygosity and physical activity in adulthood was collected by a mailed questionnaire in 1998–99. Twins who had not responded after two reminders were approached by telephone interview. The questions about zygosity have been widely used in twin research (Cederlöf et al., 1961; Pedersen & Lichtenstein, 2000) and were based on self-reports of a) degree of similarity in childhood and b) difficulties teachers may have had in distinguishing between twins in school. Those pairs where both twins reported “as like as two peas in a pod” and that teachers “always or nearly always” had problems in distinguishing between them were categorized as monozygotic (MZ). Those pairs where both twins responded “not more like than siblings in general” to the first question and “seldom” or, “never or almost never” to the second question were categorized as dizygotic (DZ). All remaining pairs were categorized as of uncertain zygosity (XZ). DNA was not available for classification of zygosity in this study. The following question was asked about physical activity: “In general, how would you describe your level of physical activity during leisure time over the last 12 months?”, responses a) “sedentary”, b) “light exercise” (without sweating), c) “medium exercise” (regular and sweating), d) “hard exercise” (regular, and sweating and breathing hard).

**Data Linkage Errors**

In Sweden, when a baby is a few weeks old, the civil registration authorities assign a unique personal identification number to him or her. There is evidence that for some twin pairs this process led to a “cross-over” where the medical birth record for each twin was incorrectly associated with the personal identification number of its co-twin. As the linkage between the MBR and the MSCR was based on the personal identification number, this would lead to an under-estimation of the strength of the association between birthweight and BMI within twin pairs, the extent to which would depend on the proportion of cases in which such a cross-over occurred. We attempted to classify twin pairs according to whether the possibility of cross-over was unlikely, likely or indeterminate. This was done through an examination of the consistency of information on birth order and birthweight obtained from the MBR and by a mailed questionnaire described above in the questionnaire section. Cross-over was considered least likely if the self-reported birth order of each twin in a pair agreed with birth order as given in the MBR. The possibility of cross-over was also assessed by examining self-reported birthweight in relation to birthweight reported in the MBR. For the majority of twin pairs the consistency of information suggested that cross-over had not occurred and these were thus included in further analyses. However, in 59 twin pairs there was good evidence of cross-over, with the self-reported information for each twin matching the MBR information for their co-twin. For these 118 individuals the assumed cross-over was corrected by reassignment of the birth registry information of each twin to their co-twin, after which these individuals were also included. However, 671 twin pairs were excluded from further analysis because of other inconsistencies between self-reported information and that from the MBR. Copies of the algorithm used to determine which twin pairs to include in the full analyses are available from the corresponding author on request.
Study Population
Initially eligible for the study were 3,566 male twins born 1973–1979 who were alive and resident in Sweden during the spring of 1998. Of these 3,566 subjects, 80 decided not to participate in the study. Data were available on key variables in the MBR for 3,418 (98%) of all the remaining 3,486 male twins. Information about weight and height could be retrieved from the MSCR for 3,052 (88%) of the 3,486. Twin pairs who were 20 years or older at conscription examination and pairs where one twin underwent conscription examination more than 6 months before his twin brother were excluded from the analyses. Twin pairs who had undergone conscription examination at different centers were also excluded. As described above, 1,342 twins had been excluded because it was impossible to establish whether the ID number of Twin 1 had been erroneously given to Twin 2 in the MBR or vice-versa. Following exclusions 1,846 twins (53% of the original set) remained available for statistical analysis.

Statistics
Mixed linear models were used for analyzing within-pair and between-pair differences in birthweight in relation to BMI (outcome variable) at 18 years of age. The Mixed Procedure in SAS was utilized (SAS Institute Inc., 1997).

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>MZ twins (n = 800)</th>
<th>DZ twins (n = 568)</th>
<th>XZ twins (n = 478)</th>
<th>All twins (n = 1,846)</th>
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<tr>
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### Table 2

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<th>All twins (n = 1,846)</th>
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**Results**

Table 1 shows anthropometrical data at birth and at conscription by type of twin pair. The DZ twins had slightly higher birthweight, and also greater height and weight at 18 years of age than the MZ twins. Table 2 presents means of BMI by birthweight, gestational age, age at conscription examination, and type of twin. DZ twins had higher mean values of BMI at age 18 than MZ and XZ twins in most birthweight categories. No association was found between birthweight and BMI.

Table 3 presents correlations between BMI at conscription and birthweight, birthlength and gestational age according to type of twin. No clear-cut association was found between BMI and any of the birth characteristics.

Table 4 shows mixed linear regression models for associations between the outcome variable (BMI), and the within-pair mean of birthweight (between-pair effect) and the deviation from the within-pair mean of birthweight (within-pair effect), after controlling for age, conscription-examination center, year of conscription examination, and gestational age. The relationship between birthweight and BMI was modeled for all twin pairs (n = 1,846), and also separately for MZ twins, DZ twins and XZ twins. For the MZ twins there was a positive association between BMI and the within-pair effect of birthweight. Adjustments for covariates did not affect the size of the estimate (Table 4). For MZ twins no association was found between BMI and the between-pair effect of birthweight. For the DZ twins no statistically significant association was found for either between-pair or within-pair effects on BMI. Among XZ twins a weak positive association was found between BMI and the within-pair effect of birthweight. A model including control for level of physical activity as a covariate, in addition to all the covariates described above, did not influence the within-pair effect for either MZ twins (β = 0.58; 95% CI: 0.21, 0.94) or DZ twins (β = 0.40; 95% CI: –0.33, 1.14).

**Discussion**

The main finding of the present study was a positive association between BMI and within-pair difference in birthweight among MZ twins. No significant association was found among the MZ twins for the between-pair difference in birthweight and BMI. No significant associations were found for DZ twins. These findings do not seem to support either the fetal programming hypothesis or the fetal insulin resistance hypothesis. According to the fetal origins hypothesis one would have expected an inverse association within MZ pairs of twins’ birthweight in relation to BMI in young adulthood as an indication of environmental factors operat-
ing in utero. Neither do the present results support the fetal insulin resistance hypothesis. According to this hypothesis fetal growth retardation and components of the metabolic syndrome are phenotypic expressions explained by the same underlying genotypes (Hattersley & Tooke, 1999).

In a recent paper, Lucas et al. (1999) discussed controlling for body size when studying the association between fetal growth and the risk of chronic disease in adulthood. For the present study no information was available about BMI during childhood. But, in two studies of growth in childhood, the authors have described possible links between catch-up growth and chronic diseases in adulthood (Eriksson et al., 1999; Ong et al., 2000). Babies who are thin at birth seem to have higher death rates from coronary heart disease even when catch-up growth from birth to young childhood is taken into account (Eriksson et al., 1999).

It would have been of great interest to adjust for BMI at some point during childhood, for example at late preschool age if information had been accessible. Data on BMI in childhood, however, are available in a study by Forsén et al. (1999), in which associations were found between risk of coronary heart disease and birthlength for women, and between risk of coronary heart disease and thinness for men.

In an earlier mentioned twin study from New Zealand, Williams and Poulton (1999) found that twins at ages 9 and 18 had both lower birthweight and lower systolic blood pressure than singletons. This finding challenges the fetal origins hypothesis. By contrast, the effect of maternal smoking was found to be consistent with the fetal origins hypothesis, since the infants of smokers had lower birthweight and higher blood pressure. If the fetal origins hypothesis were confirmed, a higher mortality rate from myocardial infarction would be expected for twins than singletons due to lower birthweight among twins (Barker, 1995). But, in a previous Swedish twin study, Vågerö and Leon (1994) did not find a higher mortality rate from myocardial infarction among twins than singletons. This finding is out of line with that of Forsén et al. (1999), who found that catch-up growth was a risk factor for cardiovascular disease. Nevertheless, twins tend to show a higher rate of catch-up growth between risk of coronary heart disease and birthlength for women, and between risk of coronary heart disease and thinness for men.

In conclusion, the present findings do not support either the fetal origins hypothesis or the insulin resistance hypothesis concerning an inverse association between fetal growth and BMI in adulthood. The findings are, however, in accordance with a previous Swedish and a further Danish study showing a positive association between birthweight and BMI in adulthood (Rasmussen & Johansson, 1998; Sørensen et al., 1997).

References


Acknowledgments

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