Low birthweight has been associated with adult disorders such as Type 2 diabetes, hypertension, and coronary heart disease in many studies. The ‘thrifty phenotype hypothesis’ proposes that the association between poor fetal and infant growth and the subsequent development of Type 2 diabetes and the metabolic syndrome is caused by poor nutrition in early life. Genetic factors are not part of this hypothesis, even though studies suggest that they are important factors in the variation of both birthweight and Type 2 diabetes.

Even though associations between birthweight and risks of cardiovascular diseases have been shown in many studies, it is still disputed whether these associations are caused by intrauterine malnutrition per se or whether they are mediated by genetic and/or shared environmental effects. Twin studies can shed light on this matter. Differences in birthweight within twin pairs reflect differences in fetal growth. Studying birthweight within same-sex twin pairs discordant for disease allows matching for maternal factors influencing birthweight (i.e. maternal height, maternal nutrition status, and maternal diseases) and environmental factors shared by the twins. Studies within monozygotic twin pairs also allow perfect matching for genetic factors. Twin studies on the relationship between birthweight and blood pressure, acute myocardial infarction, and angina pectoris have suggested that previous reported associations may be influenced by genetic and/or early environmental factors.

Previous twin studies of the association between birthweight and Type 2 diabetes are based on small numbers and results are inconsistent. In a small study of 18 monozygotic (MZ) and 27 dizygotic (DZ) twin pairs discordant for Type 2 diabetes, a significant within-pair birthweight difference in both MZ and DZ twin pairs was reported: within each type of pair, diabetes occurred more often among the twins with the lowest birthweight. In contrast, Baird et al. found no statistically significant associations between birthweight and either blood pressure.
pressure or glucose tolerance in a cohort of twins. Further they
did not find any correlations between within-pair differences in
birthweight and glucose tolerance or body mass index (BMI) in
MZ or DZ twin pairs. Thus, whether there is a causal effect
of birthweight on Type 2 diabetes or whether genetic or shared
environmental effects mediate this association is far from clear.

In the present study we will investigate the association be-
 tween low birthweight and diabetes in a cohort of adult Swedish
twins. We will use random effects linear models to investigate
the between and within pairs differences in exposure on Type 2
diabetes.

Methods
All twins born between 1906 and 1958 in Sweden were asked to
participate in a telephone interview called the Screening Across
the Lifespan Twin study (SALT). In this study 44,897 (72%) of
61,767 twins participated in the interview. Non-participation
was due to refusal (15%), the twin could not be contacted
(10%), or was incapable to be interviewed (3%).

Zygosity was based on responses to questions regarding child-
hood resemblance and has been validated using 13 DNA markers
in a sub-sample of 199 twin pairs. The self-reported zygosity
classification was proven to be correct in 99% of the pairs.23

Self-reported birthweight measures from the open-ended
questions in the interview were used. We examined the validity
of self-reported birthweight by comparing the self-reported measures
with participants’ birth certificates. The Pearson correlation
coefficient between birthweight in birth certificates and self-
reported birthweight was \( r = 0.82 \).

We also used self-reported information about diabetes in the
present study. A flow chart in Figure 1 shows how the coding of
Type 2 diabetes was done according to the twins’ response on
questions about their diabetes. If they did not know about past
 treatment or did not want to answer, or there was insufficient
information to decide what kind of diabetes they had, they were
coded as missing.

Information about previous smoking status, height, and weight
was retrieved from questionnaires sent out to the cohort of twins
born between 1906 and 1925 in 1961, 1967, and 1970 and for
the cohort of twins born between 1926 and 1958 in 1973. BMI
was calculated as the weight in kilograms divided by the square
of height in metres.

The cohort used for the analysis comprised 11,162 same-sexed
twins (4796 MZ and 6366 DZ twins; of these there were 3003
complete pairs and 5156 single twins), with complete infor-
mation about self-reported birthweight and covariates used in the
analysis.

Statistical analysis

Random effects linear models assuming a log-linear distribution
were fitted to data in order to obtain the estimates of between- and
within-pair differences in birthweight.24 Odds ratios (OR) were
fitted to data in order to obtain the estimates of between- and
within-pair effects. Potential confounders included in the analysis were age, sex, BMI,
and smoking status. Likelihood ratio tests for heterogeneity of the
between- and within-pair effects were calculated by comparing
the likelihood of the original model and of a model in which these
effects are constrained to be identical.

Results

Among the 11,162 individuals, 418 (3.7%) had Type 2 diabetes
(Table 1). The proportion of individuals with Type 2 diabetes was
higher in individuals with lower birthweight and older age.
The proportion of Type 2 diabetes was much higher in over-
weight (defined as BMI \( \geq 25 \text{ kg/m}^2 \)) individuals (16.4%) com-
pared with normal weight individuals (2.3%), and was slightly
higher in males compared with females. The proportion of Type
2 diabetes did not seem to change appreciably according to
smoking status or zygosity (Table 1).

Birthweight was positively correlated with adult BMI \( (r = 0.03, P < 0.01) \). However, there was no significant interaction effect
between birthweight and adult BMI with respect to risk of Type 2
diabetes \( (P = 0.35) \).

Table 2 shows the results from the random-effects log-linear
regression models for the association between Type 2 diabetes
and birthweight fitted in the whole sample of twins and separately
by zygosity. The Table presents the regression coefficients for
the between- and within-pair effects with their 95% CI, followed
by the OR estimates derived from the regression coefficient by
exponentiation. The regression coefficients are presented for com-
parisons with other studies and OR are presented because they are
easier to interpret with a binary outcome such as Type 2 diabetes.
The OR for the between-pair effect estimates the risk of develop-
ing Type 2 diabetes in a pair for a 1-kg decrease in their mean
birthweight, and the OR for the within-pair effect estimates the
risk of developing Type 2 diabetes in a pair in relation to a 1-kg
difference in their birthweight.

The between effect was significant in the whole cohort of twins
\( (OR = 2.13; \beta_{\text{between}} = -0.76, 95\% \text{ CI: } -1.06, -0.46) \) as well as in
both MZ and DZ twins (MZ: \( OR = 2.23; \beta_{\text{between}} = -0.80, 95\% \text{ CI: } -1.25, -0.35 \), DZ: \( OR = 2.03; \beta_{\text{between}} = -0.71, 95\% \text{ CI: } -1.11, -0.31 \) (Table 2). There was a more than twofold risk
of developing Type 2 diabetes for a 1-kg decrease in birthweight.
The within-pair effect for MZ twins was non-significant but of
the same magnitude as the between-pair effect \( (\beta_{\text{within}} = -0.71, 95\% \text{ CI: } -1.46, 0.05) \), whereas the within-pair effect for
DZ twins was much lower compared with the between-pair effect
\( (\beta_{\text{within}} = -0.14, 95\% \text{ CI: } -0.89, 0.61) \). However, this
difference could be due to chance since there were no significant
differences between the between- and within-pair effects as
indicated by the likelihood ratio test.

Discussion

Similar to studies on singletons we found an association between
low birthweight and Type 2 diabetes in a population-based
cohort of 11,162 same-sex Swedish twins. The within-pair
effect of the association between low birthweight and Type 2 dia-
betes was of similar magnitude, however not statistically signi-
ficant. Thus, our study suggests that the effect of low birthweight
on Type 2 diabetes could be due to an in utero programming
effect that may be due to intrauterine malnutrition. However, it
does not exclude the possibility of a common genetic mechanism.

The results provide some evidence to support the ‘thrifty
phenotype’ hypothesis, which proposes that impaired glucose
intolerance and other metabolic disorders originate through
adaptations in the malnourished fetus. Maternal factors could be
more important than individual fetal/placental influences in
determining the risk for Type 2 diabetes. This is consistent with other twin studies on the association between low birthweight and Type 2 diabetes. Poulsen et al. studied within-pair differences in twins discordant for Type 2 diabetes and impaired glucose tolerance and concluded that the association between low birthweight and Type 2 diabetes in twins is partly independent of genotype and may be due to intrauterine malnutrition. Bo et al. also looked at the association between low birthweight and impaired glucose tolerance within discordant twin pairs and suggested that the association is due to environmental intrauterine factors. They also concluded that the birthweight difference within pairs and not the birthweight per se is responsible for the metabolic abnormalities in adult life.

The ‘thrifty phenotype’ hypothesis further proposes that as long as the child continues to be poorly nourished during childhood and adult life, these adaptations are beneficial. However, a sedentary lifestyle, changes in food intake (high calorie food), and the subsequent development of obesity ultimately lead to
impaired glucose intolerance, insulin resistance syndrome, and Type 2 diabetes. In the current study the frequency of Type 2 diabetes was higher among overweight individuals. However, there was no significant interaction between birthweight and adult BMI, although birthweight and BMI independently predicted Type 2 diabetes in twins. Thus, the association between birthweight and Type 2 diabetes goes beyond the influence of low birthweight on adult BMI.

Twin studies looking at within pair differences in birthweight have shown a lack of association between low birthweight and cardiovascular disorders such as blood pressure, myocardial infarction, and angina pectoris, suggesting that the association may be mediated by familial (genetic and/or shared environmental) effects. In the current study the within-pair effect for MZ twins was of the same magnitude as the between-pair effect. However, the wide CI including zero on the within-pair effect indicates that the effect could be due to chance. Hence, this does not exclude the possibility that the association could be due to a common genetic mechanism causing both low birthweight and Type 2 diabetes. However, to be consistent with a genetic mechanism, there should be no effect within MZ twins but a negative effect within DZ twins, which was not observed in the current study.

Animal experiments have shown that growth-restricted offspring of protein malnourished rats undergo a greater age-dependent loss of glucose tolerance, which is associated with insulin resistance. The association with other cardiovascular outcomes, on the other hand, might be due to a common genetic aetiology. Women with pre-eclampsia have children with lower birthweight and are also more likely to transfer susceptibility genes for hypertension to their offspring, which subsequently might lead to other cardiovascular diseases. We can only speculate that the association between reduced fetal growth and Type 2 diabetes may be of a different origin than the association between fetal growth and other cardiovascular outcomes.

One limitation of the current study is that both birthweight and diabetes were self-reported. However, the validity of self-reported birthweight in this cohort of twins has been examined and correlated reasonably well with birthweight derived from medical birth records ($r = 0.82$). The agreement between questionnaire data and medical records has been shown to be good for well-known chronic diseases, such as diabetes and cardiovascular diseases in a study of middle-aged and elderly Finnish men and women. Another limitation was the lack of information on gestational age. Although the within-pair effect controls for differences in gestational age in a pair, we cannot exclude that the association between low birthweight and Type 2 diabetes is important only for premature children. However, the effect of gestational age on the association between low birthweight and Type 2 diabetes is unclear.

---

Table 1 Descriptive characteristics of the cohort of same-sexed Swedish twin pairs from the Screening Across the Lifespan Twin study (1998–2002)

<table>
<thead>
<tr>
<th>Type 2 diabetes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>($n$)</td>
<td>($n$)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11162</td>
</tr>
<tr>
<td>Birthweight (kg)</td>
<td></td>
</tr>
<tr>
<td>$\leq 1$</td>
<td>9 (8.6)</td>
</tr>
<tr>
<td>1–1.5</td>
<td>50 (7.7)</td>
</tr>
<tr>
<td>1.5–2</td>
<td>124 (5.3)</td>
</tr>
<tr>
<td>2–2.5</td>
<td>91 (3.1)</td>
</tr>
<tr>
<td>2.5–3</td>
<td>74 (2.6)</td>
</tr>
<tr>
<td>3–3.5</td>
<td>45 (2.6)</td>
</tr>
<tr>
<td>$&gt;3.5$</td>
<td>25 (4.4)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>$\leq 55$</td>
<td>107 (1.7)</td>
</tr>
<tr>
<td>56–65</td>
<td>118 (4.1)</td>
</tr>
<tr>
<td>66–75</td>
<td>116 (8.5)</td>
</tr>
<tr>
<td>$\geq 75$</td>
<td>77 (11.9)</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
</tr>
<tr>
<td>$&lt;25$</td>
<td>231 (2.3)</td>
</tr>
<tr>
<td>$\geq 25$</td>
<td>187 (16.4)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>202 (3.7)</td>
</tr>
<tr>
<td>Current</td>
<td>166 (3.8)</td>
</tr>
<tr>
<td>Previous</td>
<td>50 (3.6)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>170 (4.5)</td>
</tr>
<tr>
<td>Female</td>
<td>248 (3.4)</td>
</tr>
<tr>
<td>Zygosity</td>
<td></td>
</tr>
<tr>
<td>Monozygotic</td>
<td>185 (3.9)</td>
</tr>
<tr>
<td>Dizygotic</td>
<td>233 (3.7)</td>
</tr>
</tbody>
</table>

Table 2 Adjusted between- and within-pair effects (with 95% CI and odds ratios[OR]) of 1-kg increase in birthweight on Type 2 diabetes in a cohort of same-sex Swedish twin pairs from the Screening Across the Lifespan Twin study (1998–2002)

<table>
<thead>
<tr>
<th>$\beta$ OR (95% CI)</th>
<th>All twins ($n = 6000$)</th>
<th>Monozygotic ($n = 2888$)</th>
<th>Dizygotic ($n = 3112$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between</td>
<td>$-0.76 (-1.06, -0.46)$</td>
<td>$-0.80 (-1.23, -0.35)$</td>
<td>$-0.71 (-1.11, -0.31)$</td>
</tr>
<tr>
<td></td>
<td>2.13</td>
<td>2.23</td>
<td>2.03</td>
</tr>
<tr>
<td>Within</td>
<td>$-0.37 (-0.91, 0.17)$</td>
<td>$-0.71 (-1.46, 0.05)$</td>
<td>$-0.14 (-0.89, 0.61)$</td>
</tr>
<tr>
<td></td>
<td>1.45</td>
<td>2.03</td>
<td>1.15</td>
</tr>
<tr>
<td>Test for difference$^a$</td>
<td>0.33</td>
<td>0.23</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Data adjusted for age, sex, body mass index, and smoking status.

$^a$ Likelihood ratio test of the heterogeneity of the between- and within-pair effects.
Twin studies may not necessarily be generalizable to singletons, due to their appreciably impaired growth in utero and the rapid catch-up growth they undergo in childhood. However, there is no evidence that twins have increased overall cardiovascular mortality compared with the general population.12,33

In conclusion, our findings partly support the hypothesis that the association between low birthweight and Type 2 diabetes could be due to poor nutrition in fetal life and infancy that leads to insulin resistance and subsequently Type 2 diabetes in adult life. However, given the wide CI for the within-pair effect, a purely genetic explanation for the programming phenomenon cannot be excluded.

**Acknowledgements**

This project was supported by The Swedish Research Council (grant numbers K2003–27X-14641–01A and K2003–71X-14676–01A), the Swedish Heart and Lung Foundation (grant number 20020324), the National Institute of Health (grant number AG 08724) and by ASTRA Zeneca.

**KEY MESSAGES**

- Twin studies have shown that the well-established association between low birthweight and some cardiovascular outcomes such as blood pressure, myocardial infarction, and angina pectoris is at least partly due to genetic and/or shared environmental effects.
- The exact nature of the association between low birthweight and Type 2 diabetes is unclear.
- There is an association between low birthweight and Type 2 diabetes in the Swedish population.
- The study suggests that the effect of low birthweight on Type 2 diabetes is due to an in utero programming effect possibly caused by intrauterine malnutrition. However, it does not exclude the possibility of a common genetic mechanism.

**References**

Commentary: Twins, low birthweight and type 2 diabetes

DIW Phillips

One of the important issues raised by the fetal origins hypothesis is the extent to which the associations between birthweight and adult health outcomes, such as type 2 diabetes, are explained by common genetic factors, or are a result of fetal programming by the early environment. Indeed, a genetic explanation has been specifically proposed for the association between birthweight and type 2 diabetes. In pathophysiological terms this is logical. Since insulin has a central role in controlling fetal growth, genetic factors which impair insulin secretion or decrease insulin action, both features of type 2 diabetes, would be expected to reduce fetal growth. This has been demonstrated experimentally in transgenic mice lacking key intermediates of the insulin signalling pathway, in human infants with rare inherited defects such as insulin receptor mutations, and in patients with mutations which reduce insulin secretion. Distinguishing between the effects of the early environment and genes is not merely of academic interest, but has considerable public health importance as it points the direction for future research and possible interventions.

Twin studies may provide one way of distinguishing between these competing hypotheses. Differences in birthweight between genetically identical, monozygous twins must be due to differences in the fetal environment. Thus associations between these within-pair differences in birthweight and subsequent diabetes cannot be explained by genetic factors. Studying twins also has the advantage in achieving perfect matching for maternal factors which influence outcomes, for example maternal size, body composition, and socio-economic status. Although a number of studies have now been carried out in twins, to date they have been hampered by small size and as a consequence, low statistical power. The paper by Iliadou et al. in the current issue of the International Journal of Epidemiology, which is based on over 11 000 Swedish twins born between 1906 and 1958, is therefore an important and welcome contribution to the literature. As with most studies of this size, the ascertainment of both birthweight and the occurrence of diabetes is by self-report; while this will introduce some random error, it does not invalidate their conclusions. When an unpaired analysis (i.e. considering twins as singletons) was carried out, it showed a doubling of diabetes risk for every kilogram decline in birthweight. This effect size is similar to that...