Importance of familial factors in associations between offspring birth weight and parental risk of type-2 diabetes

Niklas Bergvall,* Anna Lindam, Yudi Pawitan, Paul Lichtenstein, Sven Cnattingius and Anastasia Iliadou

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Background
It is hypothesized that associations found between birth weight and subsequent risk of type-2 diabetes are due to inherited genes affecting both fetal growth and metabolism of insulin.

Methods
To study whether there is a familial (shared environmental and genetic) link between birth weight and type-2 diabetes, the authors used a sample of 11,411 Swedish like-sexed twins born from 1926 to 1958 with at least one offspring, to study the association between offspring birth weight for gestational age and parental risk of type-2 diabetes.

Results
Decreasing offspring birth weight for gestational age (with 1 SD) was associated with an increased risk of type-2 diabetes among father’s [odds ratio (OR) = 1.72, 95% confidence interval (CI): 1.33–2.23] and decreased risk among mothers (OR = 0.43, 95% CI: 0.30–0.62), independent of grand parental and parental socio-economic status and parental smoking. In paired twin analysis, the association between offspring birth weight and mothers with risk of type-2 diabetes was similar within- and between-twin pairs, whereas father’s risk was slightly smaller within than between pairs (OR_{Within} = 1.90, 95% CI: 1.10–3.28, and OR_{Between} = 1.71, 95% CI: 1.10–2.67, respectively).

Conclusions
The well-established association between paternal type-2 diabetes and offspring birth weight seems to primarily be due to as yet unidentified non-shared environmental factors. However, familial factors shared within twin pairs may contribute to the association.

Keywords
Birth weight, diabetes mellitus, type 2, twins

Introduction
A number of studies have reported associations between low birth weight and increased risks of type-2 diabetes.1,2 It has also been hypothesized that the association may be confounded by genetic factors, the ‘fetal insulin hypothesis’.3 We have previously found an association between self-reported birth weight and risk of type-2 diabetes in twins, which was weaker within than between twin pairs,4 indicating that shared factors in twins, including common genes, may partly confound the association between fetal growth and type-2 diabetes.

Another approach adopted to investigate whether the low birth weight and type-2 diabetes association may be influenced by genetic factors is to study if
there is an association between low offspring birth weight and parental risk of type-2 diabetes.\(^3\) If there is a common genetic factor for fetal growth and type-2 diabetes susceptibility, offspring birth weight should not only be associated with their own risk of type-2 diabetes, but also with that of their parents. Several studies have reported associations between low offspring birth weight and increased risk of fathers risk of type-2 diabetes or insulin resistance,\(^6\)\(^-\)\(^9\) whereas others have not.\(^10\)\(^,\)\(^11\) Associations between offspring birth weight and fathers risk of type-2 diabetes strengthens the fetal insulin hypothesis, as fathers can only directly affect offspring fetal growth through inherited fetal genes. The association between offspring birth weight and mothers’ risk of type-2 diabetes has yielded conflicting results. Some studies have found that low birth weight in offspring increases the risk of type-2 diabetes and insulin resistance in mothers,\(^5\)\(^-\)\(^7\) whereas others have found that high birth weight increases the risk.\(^12\)

Besides common genetic factors, there are at least two additional mechanisms that could explain this association. First, fetal malnutrition may cause permanent physiological alterations, which could result in an adverse intrauterine environment for the individual’s offspring.\(^13\)\(^-\)\(^15\) It has also been hypothesized that intrauterine nutritional insults could induce epigenetic modifications of the genome, affecting both fetal growth and later disease risk,\(^15\) which if inherited, may result in low birth weight in offspring. Second, adverse environmental factors may be triggers of both fetal growth restriction and type-2 diabetes,\(^16\)\(^,\)\(^17\) and act across the life course of generations.

We have used a cohort of like-sexed twins to study if associations between offspring birth weight and parental risk of type-2 diabetes is due to shared familial factors, including genetic factors, or, if non-familial factors could account for the observed association.

**Methods**

**Study population**

Eligible parents were like-sexed twins born in Sweden from 1926 to 1958, who are included in the Swedish Twin Registry (\(n = 37,392\) individuals). In 1998, all living twins born in 1958 or earlier were invited to participate in a telephone interview called the Screening Across the Lifespan Twin (SALT) Study.\(^18\) SALT was initiated for screening of most complex diseases among the Swedish twin population and used to diagnose type-2 diabetes in the present study. Among 32,905 like-sexed individual twins born from 1926 to 1958 and asked to participate in SALT, the response rate was 74% (\(n = 24,295\)). Here, we restricted the cohort to twins with known zygosity (\(n = 23,547\) individuals), as determined by questions regarding childhood resemblance. From the Swedish Multigeneration Registry, we identified 20,123 individual twins with at least one offspring. However, as the Swedish Medical Birth Register, which was used to obtain offspring birth weight started in 1973, we restricted the study population to twins with at least one offspring born 1973 or later, and included in the register (\(n = 11,528\) individuals).

**Outcome**

In SALT, all participating twins were asked questions regarding their medical history, including questions on occurrence and treatment of diabetes. Agreement between questionnaire data and medical records has been found to be good for well-known chronic diseases, such as diabetes.\(^19\) Type-2 diabetes was diagnosed if an individual, when asked what type of diabetes they had according to their doctor, responded old-aged diabetes, type-2 diabetes or non-insulin dependent diabetes mellitus. If an individual did not know, when asked what type of diabetes they were diagnosed with, type-2 diabetes was considered present if they reported that their present or past treatment of diabetes was diet or tablets, or if the age of onset of their diabetes was over 45 years. In the defined study population (\(n = 11,528\)) 2.2% were diagnosed as type-2 diabetic (\(n = 252\), 0.6% as type-1 diabetic (\(n = 70\), 96.9% as non-diabetic (\(n = 11,171\)) and 0.3% did not answer questions on diabetes (\(n = 35\)). The prevalence of type-2 diabetes in the present study corresponds well with the prevalence in the general Swedish population with similar age distribution.\(^20\) A schematic view of the algorithm for diagnosis of diabetes has been presented in a previous study.\(^4\)

**Parental covariates**

Information on parental (twin) birth weight, gestational age and grandparents’ occupation was collected from original medical birth records, stored at local delivery archives throughout Sweden. Birth weight for gestational age was expressed as standard deviations (SD) for gestational age, using the study sample as the reference population. For the 11,528 twins in the defined study population, medical birth records, with correct identification of individual twins, were obtained from 9,925 (86%) individuals.

Parental socio-economic status (SES) in adulthood was based on information on the subject’s occupation as reported in the SALT interview. Parental SES at birth was based on grand parental occupation as reported in birth records. SES at birth and adulthood was classified into blue-collar workers, white-collar workers and self-employed, which is according to recommendations by Statistics Sweden.\(^21\) Information on parental smoking, adult weight and height were collected through the 1973 postal questionnaire. Body mass index was calculated as the ratio between weight and squared height (kg/m\(^2\)).
Offspring and maternal covariates at delivery

We used the Medical Birth Register to collect data on maternal age at delivery, parity, birth weight and gestational age of the offspring. Birth weight for gestational age was calculated among offspring born between 28 and 43 weeks of gestation, using the Swedish birth weight standards.22

Parental offspring pairs

Among twins in the defined study population (n = 11528), we identified 11411 families (one parent with one or more offspring) which had information on offspring birth weight (on at least one offspring) and parental type-2 diabetes; 5639 families were mothers and offspring and 5752 were fathers and offspring. Of these families, 6738 parents belonged to intact twin pairs (3369 twin pairs). In cases where a parent had more than one offspring (n = 7907), the mean birth weight of all offspring was analysed. To simplify the text, the term offspring birth weight refers either to the single birth weight or the mean birth weight in text, the term offspring birth weight refers either to the weight of all offspring was analysed. To simplify the text, the term offspring birth weight refers either to the single birth weight or the mean birth weight in the case where there is more than one child.

Statistical methods

First, the association between offspring birth weight and parental type-2 diabetes was analysed in the whole cohort of twins (n = 11411). Second, to study if there was any association between parental and offspring birth weight that was independent of genetic factors, we analysed if the twin with lowest birth weight within monozygotic and dizygotic twin pairs also had offspring with lower birth weight. These analyses were restricted to intact twin pairs discordant for birth weight and with information on offspring birth weight for gestational age (2841 pairs).

Third, we wanted to estimate the effect of offspring birth weight for gestational age on risk of parental type-2 diabetes, controlling for familial (shared environmental and common genetic) factors. This analysis was restricted to intact twins pairs (1749 female pairs and 1620 male pairs), and estimates the effect of offspring birth weight for gestational age on risk of parental type-2 diabetes between- and within-twin pairs.23 The between pair effect estimates the expected risk of type-2 diabetes for a 1 SD decrease in the mean offspring birth weight of a pair of twins (Xi =twin pair). The within pair effect estimates the expected risk of type-2 diabetes for a 1 SD difference between the offspring birth weight of one of the twins from the mean offspring birth weight of the pair of twins (Xij = twin pair, j = individual twin).

Differences in offspring birth weight between unrelated twins (cohort analyses and between-twin pair analyses) are influenced both by familial (shared environmental and genetic) factors, and unique factors specific to each individual twin and its offspring. In contrast, differences in offspring birth weight within twin pairs cannot be influenced by environmental or genetic factors shared by twin siblings. Thus, if associations between offspring birth weight and parental risk of type-2 diabetes found between pairs remain within twin pairs (i.e. identical between- and within-estimates), shared factors in the twin pairs are not of importance. Instead, unique factors experienced by each individual twin and its offspring must be involved. In contrast, if the association is deleted within twin pairs, then factors shared by twin siblings explain the association seen between twin pairs. However, the most probable situation is that both familial and unique factors are involved, in which case we would see a weaker effect within- than between-twin pairs. Thus, by contrasting the within with the between-twin pair effect, we can assess the importance of environmental and genetic factors shared by twin siblings on the association between offspring birth weight and parental risk of type-2 diabetes. Since dizygotic and monozygotic twin siblings have different degrees of genetic relatedness (they share 50 and 100% of their segregating genes, respectively), analyses stratified by zygosity can disentangle whether decreasing estimates within twin pairs are explained by shared environmental factors, genetic factors or both. However, due to limited statistical power we could not perform the between- and within-twin pair analysis stratified by twin zygosity.

Due to the clustered nature of our data, we fitted random effects linear models assuming a log-linear distribution in order to obtain risk estimates of type-2 diabetes in relation to offspring birth weight.

Results

The mean offspring and parental birth weight among type-2 diabetic and non-diabetic twins, stratified by parental (i.e. twin) sex are displayed in Table 1. The offspring of mothers with type-2 diabetes were 0.54 SD heavier at birth, compared with offspring of mothers with no diabetes. In contrast, among fathers, the offspring of type-2 diabetics were 0.33 SD lighter than offspring of non-diabetic fathers. The twins’ own birth weight was, both among mothers and fathers, lower among those with type-2 diabetes compared with those with no diabetes.

Results from the cohort analysis of the association between offspring birth weight for gestational age and maternal risk of type-2 diabetes are shown in Table 2. Among mothers, decreasing offspring birth weight for gestational age with 1 SD was associated with a reduced risk of type-2 diabetes [odds ratio (OR) = 0.43, 95% confidence interval (CI): 0.30–0.62]. Adjustment for other potential confounders did not substantially influence risks of type-2 diabetes, but reduced the study sample. Therefore, we also performed analyses where only mother and offspring pairs with no missing values on covariates were included in all models (n = 3402). In these nested
models also presented in Table 2, we found that associations between birth weight and maternal risk of type-2 diabetes remained largely unchanged after adjusting for selected confounders.

Using mean offspring birth weight disables us from adjusting for maternal factors, which vary between pregnancies. To investigate whether the association between offspring birth weight and maternal risk of type-2 diabetes was confounded by maternal age or parity, we randomly selected one offspring, and adjusted for maternal age and parity of the selected offspring. However, risk estimates were nearly identical in the crude model (OR = 0.50, 95% CI: 0.36–0.69, per 1 SD decrease) and in the model adjusted for maternal age and parity (OR = 0.55, 95% CI = 0.41–0.75, per 1 SD decrease), suggesting that maternal age and parity are not confounders of importance for the association.

Among fathers, decreasing offspring birth weight for gestational age was associated with an increased risk of type-2 diabetes (Table 3). Specifically, a 1 SD decrease in offspring birth weight for gestational age was associated with a 72% increased risk of type-2 diabetes. This effect was attenuated after adjustment for potential confounders, but was still associated with an increased risk of type-2 diabetes in all adjusted models. Similarly to mothers, adjusting for maternal age and parity of the offspring did not have an effect on the association (data not shown).

Although the association was attenuated when restricting the analyses to father and offspring pairs with no missing values on covariates (n = 3081), we found, similar to the analyses in mothers, nearly identical risk estimates in crude and adjusted models in the nested analysis, suggesting that the differences in risk estimates seen in the varying models were largely an artefact of decreasing study samples rather than confounding.

To study if there was any association between parental and offspring birth weight independent of...
genetic factors, we analysed if the twin with lower birth weight in a pair also had offspring with lower birth weight for gestational age than that of their heavier co-twin. Among dizygotic twins, we found that the twin with lower birth weight also had offspring with lower birth weight for gestational age. In contrast, no such association was obtained among monozygotic twins (Table 4). These findings were similar both among mothers and fathers.

The results from the between- and within-twin pair analysis of the association between offspring birth weight and parental type-2 diabetes are displayed in Table 5. Among mothers, we found that decreasing birth weight for gestational age among offspring was associated with a reduced mothers’ risk of type-2 diabetes, and the risks were of identical magnitude both between- and within-twin pairs. In contrast, among fathers, corresponding risks were generally increased, and the within effect was, slightly lower than the between-effect.

Table 3 Crude and adjusted OR (95% CI) of paternal type-2 diabetes in relation to mean offspring birth weight for gestational age

<table>
<thead>
<tr>
<th>Birth weight for gestational age</th>
<th>Model</th>
<th>Crude</th>
<th>Adjusted 1\textsuperscript{a}</th>
<th>Adjusted 2\textsuperscript{b}</th>
<th>Adjusted 3\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varying models\textsuperscript{d}</td>
<td>n = 5752</td>
<td>n = 4500</td>
<td>n = 4745</td>
<td>n = 4176</td>
<td></td>
</tr>
<tr>
<td>−2 to −1</td>
<td>1.74 (0.38–7.98)</td>
<td>1.22 (0.22–6.69)</td>
<td>1.08 (0.15–7.87)</td>
<td>0.60 (0.04–8.33)</td>
<td></td>
</tr>
<tr>
<td>−1 to 0</td>
<td>3.01 (1.51–6.01)</td>
<td>2.22 (1.09–4.51)</td>
<td>3.25 (1.41–7.51)</td>
<td>3.85 (1.54–9.65)</td>
<td></td>
</tr>
<tr>
<td>Per 1 SD decrease</td>
<td>1.72 (1.33–2.23)</td>
<td>1.56 (1.20–2.03)</td>
<td>1.57 (1.16–2.13)</td>
<td>1.51 (1.09–2.08)</td>
<td></td>
</tr>
<tr>
<td>Nested models\textsuperscript{e}</td>
<td>n = 3081</td>
<td>n = 3081</td>
<td>n = 3081</td>
<td>n = 3081</td>
<td></td>
</tr>
<tr>
<td>Per 1 SD decrease</td>
<td>1.49 (1.04–2.14)</td>
<td>1.49 (1.03–2.15)</td>
<td>1.45 (1.01–2.07)</td>
<td>1.48 (1.03–2.13)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Adjusted for parental birth year, parental BMI in 1973, parental smoking status in 1973 and parental SES in adulthood.
\textsuperscript{b}Adjusted for parental birth weight for gestational age.
\textsuperscript{c}Adjusted for grand parental SES.
\textsuperscript{d}Reference category.
\textsuperscript{e}Number of father and offspring pairs in each model depends on missing values in the selected covariates.
\textsuperscript{f}All models were restricted to father and offspring pairs with information on all covariates.

Table 4 Differences in mean offspring birth weight for gestational age among twins with lowest and highest birth weight, stratified by zygosity

<table>
<thead>
<tr>
<th>Parental sex</th>
<th>Twin zygosity</th>
<th>Number of pairs</th>
<th>Mean offspring birth weight for gestational age among</th>
<th>Differences (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Twin with lower birth weight</td>
<td>Twins with higher birth weight</td>
</tr>
<tr>
<td>Mothers</td>
<td>Dizygotic</td>
<td>780</td>
<td>0.03</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>Monozygotic</td>
<td>664</td>
<td>0.13</td>
<td>0.12</td>
</tr>
<tr>
<td>Fathers</td>
<td>Dizygotic</td>
<td>780</td>
<td>0.04</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Monozygotic</td>
<td>558</td>
<td>0.05</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Table 5 Crude OR (95% CI) of parental type-2 diabetes in relation to a 1 SD decrease in offspring birth weight for gestational age, between and within twin pairs

<table>
<thead>
<tr>
<th>Parental sex</th>
<th>Effect of 1 SD decrease:</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers</td>
<td>Between-twin pairs</td>
<td>0.39 (0.21–0.73)</td>
</tr>
<tr>
<td></td>
<td>Within-twin pairs</td>
<td>0.39 (0.19–0.78)</td>
</tr>
<tr>
<td>Fathers</td>
<td>Between-twin pairs</td>
<td>1.90 (1.10–3.28)</td>
</tr>
<tr>
<td></td>
<td>Within-twin pairs</td>
<td>1.71 (1.10–2.67)</td>
</tr>
</tbody>
</table>

Discussion

The present study was performed to provide further insights into alternative mechanisms, such as confounding by familial factors, for the previously observed associations between own birth weight and risk of type-2 diabetes. We have studied offspring birth weight for gestational age in relation to parental risk of type-2 diabetes, since any obtained association...
can enlighten us about mechanisms behind the fetal origins of diabetes.

In the present study, we found among mothers that increased offspring birth weight was associated with an increased risk of type-2 diabetes. This association was independent of shared factors in twins, smoking, SES and maternal birth weight. However, as gestational diabetes, which is associated with later type-2 diabetes, leads to increased offspring birth weight, any mechanism causing an association between low offspring birth weight and increased risk of maternal type-2 diabetes may be obscured. Thus, it is questionable whether the present study of offspring birth weight and mothers with risk of type-2 diabetes will provide any insight as to whether the fetal programming hypothesis is confounded by familial factors. However, a previous study found an inverse association between offspring birth weight and maternal risk of type-2 diabetes among women who developed type-2 diabetes at least 10 years after delivery. In the present study, we were unable to test such an association as we had limited information on age at diagnosis.

Similar to previous investigations, we found that decreasing offspring birth weight was associated with increased risk of type-2 diabetes or insulin resistance among fathers. In addition, we found that the association was not explained by paternal SES (at birth or in adulthood) or paternal smoking, covariates which we a priori hypothesized could at least partly explain the association. By using intact twin pairs, we were also able to account for familial factors, i.e. factors shared by the twins, including genetic and environmental factors. We found that the association between offspring birth weight for gestational age and fathers’ risk of type-2 diabetes was, if anything, slightly lower within than between twin pairs. Although these findings indicate that the association may partly be explained by factors shared by twin siblings, including common genes, a larger study is necessary to confirm the results. Another potential concern is that we had no data on the mothers of the offspring. Although maternal factors, including genotype and intrauterine environment influence offspring birth weight, they are likely to be randomly distributed between- and within-male twin pairs. Thus, such factors could not explain differences in between- and within-effects of offspring birth weight and paternal risk of type-2 diabetes. Furthermore, maternal factors influencing offspring birth weight are not likely to be associated with paternal risk of type-2 diabetes, and hence should not confound the association, neither between nor within paternal twin pairs.

Compared with non-diabetic fathers, we found that type-2 diabetic fathers both had lower own and offspring birth weight. These findings could suggest that all three phenotypes may be an expression of a type-2 diabetic and low insulin mediated fetal growth prone genotype. Furthermore, several other analyses are also consistent with the genetic hypothesis. First, the association between parental and offspring birth weight was, both among mothers and fathers, largely explained by genetic factors. Second, the association between offspring birth weight and fathers risk of type-2 diabetes may partly have been confounded by familial (i.e. genetic and shared environmental) factors. Third, we have previously found that the association between the parents own birth weight and risk of type-2 diabetes was at least partly confounded by factors shared in twins, including common genes.

All these findings strengthen the hypothesis that birth weight and type-2 diabetes have a common familial component.

Previous studies have interpreted associations between low offspring birth weight and increased risk of paternal type-2 diabetes as evidence for genetic confounding of the programming hypothesis. However, none of the studies have been able to control for genetic factors. Interestingly, our findings suggest that the association between offspring birth weight and paternal type-2 diabetes is mostly explained by factors, which the twins do not share. This is in accordance with the only review of the association between offspring birth weight and parental risk of cardiovascular disease, which suggested that the association with fathers risk was weak and may be due to confounding by socio-economic factors and smoking which the fathers share with the child’s mother. In accordance with previous studies, we found that the association was independent of measured environmental factors, including SES in adulthood. One may only speculate whether the association may be mediated by epigenetic mechanisms, or by unmeasured environmental risk factors for diabetes, which the fathers have in common with the mother. A recent study found concordance in spouses for type-2 diabetes, implying that environmental risk factors of type-2 diabetes aggregate within families.

The present study used a within-twin pair comparison to investigate whether the association between offspring birth weight and parental type-2 diabetes was confounded by familial (i.e. genetic and shared environmental) factors. We emphasize that our results should be interpreted cautiously due to limited power. For this reason, we were unable to perform the between- and within-twin pair analyses in Table 4 stratified by zygosity. Using the different degrees of relatedness among dizygotic and monozygotic twins may have provided definite answers about the relative contribution of shared environmental and common genetic factors.

In conclusion, our results indicate, in conjunction with findings from our previous study that the association between offspring birth weight and paternal risk of type-2 diabetes may at least partly be confounded by familial factors. However, most of the
association was independent of familial factors, suggesting that factors which twin siblings do not share are influential.

**Acknowledgements**

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**Conflict of interest:** None declared.

<table>
<thead>
<tr>
<th>KEY MESSAGES</th>
</tr>
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<tbody>
<tr>
<td>• Decreasing offspring birth weight for gestational age is associated with a decreased risk of maternal type-2 diabetes and increased risk of paternal type-2 diabetes.</td>
</tr>
<tr>
<td>• Associations between offspring birth weight and parental risk of type-2 diabetes are, if anything, only partly explained by familial (shared environmental and genetic) factors.</td>
</tr>
<tr>
<td>• Associations between offspring birth weight and parental risk of type-2 diabetes are mostly explained by factors, which twin siblings do not have in common.</td>
</tr>
</tbody>
</table>

**References**

Commentary: Type 2 diabetes and birth weight—genetic and environmental effects

Robert S Lindsay

Type 2 diabetes is one of the archetypal common complex diseases. Its prevalence is rising leading to increasing morbidity and mortality. A genetic contribution to type 2 diabetes has been suggested and sought eagerly for some time. Environmental influences are well described—notably effects of diet and exercise—and underpin recent increases in prevalence. In addition, type 2 diabetes is one of the chronic conditions most clearly associated with potential in utero or early life programming. Such early environmental influences have been proposed both in the context of low birth weight and maternal diabetes. There is a huge challenge in unpicking the various environmental and genetic effects not least as the influence of such factors might be different at different times in the life course—most obviously in the proposed role of the early environment. Nevertheless, it is hoped that this understanding will deliver the prize of increased understanding of the aetiology of type 2 diabetes with the expected dividend of improved prevention and treatment of diabetes.

Bergvall et al. have examined a very large twin cohort using the Children of twins approach to attempt to discern genetic and environmental contributions to type 2 diabetes. There are a number of interesting observations. First, they confirm the previously observed association of paternal diabetes to lower birth weight in their offspring. Conversely, maternal type 2 diabetes was associated with increased offspring birth weight—most likely secondary to environmental effects of maternal diabetes. Furthermore, they demonstrate that in analysis of the birth weights of twins and their offspring—including both mono and dizygotic twins—the association between parental and offspring birth weight was largely explained by genetic factors. Taken together their findings would appear to support the contention that the association of birth weight and type 2 diabetes risk may well be reflecting pleiotropic genetic effects. Ultimately, however, even in this very large data set Bergvall et al. were not able to be entirely conclusive about the genetic and environmental contribution to the association of birth weight and later diabetes. Happily, help may be on the way. This year has also seen an unprecedented increase in our knowledge of the genetics of type 2 diabetes. Several groups—usually based on very large international collaborations have supplied a number of replicated genetic associations—contributing up to seven genes which appear to contribute to type 2 diabetes risk.