

# The Association Between Low Birth Weight and Type 2 Diabetes

## Contribution of Genetic Factors

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**Background:** Low birth weight has been associated with an increased risk of type 2 diabetes in adulthood. Poor fetal nutrition has been suggested to explain this association. Our objective was to determine whether genetic factors contribute to the association between low birth weight and subsequent risk of type 2 diabetes.

**Methods:** We retrieved information from original birth records on same-sex Swedish twins with known zygosity, born from 1926 to 1958. We used regression models to investigate whether birth weight was associated with risk of type 2 diabetes in the cohort of twins overall, and in case-control analyses within disease-discordant dizygotic and monozygotic twin pairs.

**Results:** Of 18,230 twins, 592 (3.2%) had type 2 diabetes. The rate of type 2 diabetes consistently increased with decreasing birth weight, from 2.4% among twins with birth weights of 3500 g or more to 5.3% among those with birth weights less than 2000 g. In the cohort analysis, in which twins are analyzed as independent individuals, the adjusted odds ratio (95% confidence interval) of type 2 diabetes per 500-g decrease in birth weight was 1.44 (1.28–1.63). When we compared the diseased twin with the healthy cotwin, the corresponding odds ratios were 1.38 (1.02–1.85), among dizygotic twins, and 1.02 (0.63–1.64), among monozygotic twins.

**Conclusions:** Low birth weight is associated with type 2 diabetes in adulthood. The difference in this association between monozygotic

and dizygotic twin pairs suggests that genetic mechanisms play an important role in this association.

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The increasing prevalence of type 2 diabetes is a global public health challenge,<sup>1</sup> largely because type 2 diabetes strongly increases the risk of cardiovascular disease.<sup>2</sup> Lifestyle education<sup>3</sup> and pharmacologic treatment of the metabolic syndrome<sup>4</sup> might mitigate this expected pandemic, but the ideal situation would be to intervene before diabetes occurs.

An association between low birth weight and risk of type 2 diabetes in adulthood has been reported in a recent meta-analysis.<sup>5</sup> It has been suggested that poor nutrition during fetal life induces permanent adaptive changes in the fetus that predispose to type 2 diabetes.<sup>6</sup> The finding that prenatal exposure to famine is linked to reduced glucose tolerance in adults lends support to this hypothesis.<sup>7</sup> However, genetic factors account for close to 50% of the variation in fetal growth,<sup>8</sup> and type 2 diabetes risk is also influenced by genetic factors<sup>9</sup> and gene-environment interactions.<sup>10</sup> Thus, some individuals may have a common genetic predisposition for both low birth weight and development of type 2 diabetes later in life.<sup>11</sup> In addition, the association may be related to preterm birth. Individuals born preterm (and consequently having lower birth weights) are more insulin resistant than individuals born at term.<sup>12,13</sup>

Twin studies may help to resolve the relative contributions of environmental and genetic factors to the association between fetal growth and type 2 diabetes. Since twins have the same gestational age, birth weight differences within twin pairs reflect differences in fetal growth. Twins generally are brought up together, and analyses within twin pairs also provide control for socioeconomic and other shared environmental factors during childhood and adolescence. Finally, dizygotic and monozygotic twins share 50% and 100% of their genes, respectively. Thus, analyses stratified by zygosity allow for varying degrees of control for genetic factors.

To study the presumably subtle effects of genetic factors related to both fetal growth and insulin-glucose ho-

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meostasis, large twin studies are needed.<sup>11</sup> The small size of previous twin studies may well explain previous conflicting results.<sup>14,15</sup> The Swedish Twin Registry has recently been updated with information on birth characteristics and maternal sociodemographic characteristics retrieved from original birth records. We used this prospectively recorded information to study the association between birth weight and subsequent risk of type 2 diabetes in a large cohort of like-sexed twins with known zygosity.

## METHODS

### Study Population

Eligible participants were like-sexed twins born in Sweden from 1926 to 1958 ( $n = 37,392$ ), included in the Swedish Twin Registry.<sup>16</sup> In 1973, twins from intact pairs residing in Sweden responded to a postal questionnaire, and in 1998, 32,905 of these twins were invited to a telephone interview, the "Screening Across the Lifespan Twin Study."<sup>16</sup> This study was initiated for screening of diseases, and diagnoses of type 2 diabetes are the focus of the present analyses. The response rate was 74% ( $n = 24,295$ ). We restricted the cohort to twins with known zygosity ( $n = 23,543$ ), as determined by questions regarding complete childhood resemblance in the 1973 and 1998 questionnaire. Self-reported zygosity has been validated using DNA markers in a subsample of 199 twin pairs, and was proven correct in 99% of the twin pairs.<sup>16</sup>

### Exposures

We retrieved information from original birth records by visiting delivery archives, located all over Sweden. Law enforces recording and preservation of this information. Correct birth identification of each twin within a pair was ensured by restricting the data collection to twin pairs who both were baptized and named at birth, or who reported birth order with mutual within-pair agreement on the original study questionnaire.<sup>17</sup> For the 23,543 same-sex twins with known zygosity, birth records (including recorded birth weight) were obtained from 18,442 (78%) individuals (7410 complete twin pairs).

Gestational age was based on date of the mother's last menstrual period. Socioeconomic status (SES) was classified according to recommendations by Statistics Sweden.<sup>18</sup> SES at birth was defined by the parent with the higher socioeconomic status, and SES in adulthood was based on information on the subject's occupation as reported in the interview. Adult weight and height was recorded in the 1973 postal questionnaire, and those figures were used to calculate body mass index (BMI;  $\text{kg}/\text{m}^2$ ). Information on smoking status and alcohol consumption was also collected in 1973. Smoking status was dichotomized (never vs. ever) and alcohol consumption was classified according to recommendations by the World Health Organization.<sup>19</sup>

### Outcome

During the interview in 1998, twins were asked questions regarding their medical history and use of prescribed medications.<sup>16</sup> Questions, developed by endocrinologists at the Karolinska University Hospital, were presented in a branching format such that individuals were asked follow-up questions mapping on to diagnostic criteria if they responded positively to key introductory questions.<sup>16</sup> We determined diabetes status using the algorithm presented in the Figure; 17,638 were classified as nondiabetics 592 as type 2 diabetes, and 109 as type 1 diabetes. Diabetes status could not be determined in 103 twins. Among the 592 twins with type 2 diabetes, 390 were treated with oral antidiabetic drugs. Among twin pairs, 303 were discordant for type 2 diabetes (twin with type 2 diabetes had a nondiabetic cotwin; 97 discordant monozygotic and 206 discordant dizygotic pairs), and 58 were concordant for type 2 diabetes (both twins had type 2 diabetes; 41 concordant monozygotic and 17 dizygotic pairs). Diabetes status was unknown for nonresponding cotwins of 173 twins with type 2 diabetes.

The study was approved by the research ethics committee of the Karolinska Institutet.

### Statistical Methods

The association between birth weight and type 2 diabetes was analyzed in twins classified as nondiabetic or with type 2 diabetes ( $n = 18,230$ ). Cohort analyses were done by logistic regression (SAS software package, SAS Institute, Cary, NC) to compute odds ratios (ORs) and their associated 95% confidence intervals (CIs). We corrected for clustering effects within twin pairs using generalized estimating equations (GEE). Besides the main exposures (birth weight and gestational age), the adjusted regression models included covariates that contributed to the models at a 5% significance level.

We conducted additional analyses of the effect of birth weight on risk of type 2 diabetes, with control for common genetic and shared environmental factors, in cotwin case-control analyses stratified by zygosity. The cotwin case-control analyses were restricted to twin pairs discordant for type 2 diabetes. Paired effects in the cotwin case-control analyses were estimated by conditional logistic regression.

In the cotwin case-control analyses of 303 twin pairs discordant for diabetes, nondiabetic cotwins were used as matched controls for the cases. Twin siblings share intrauterine exposures, maternal factors, 50% or 100% of their genes, and childhood environment (97% of the twins responded that they lived with their cotwin until age 15); thus the matched nature of the cotwin case-control design minimizes confounding by these factors. Since dizygotic twins share 50% of their genes, the estimated paired effect of birth weight on risk of type 2 diabetes in dizygotic twins only partly controls for genetic factors. In contrast, analyses within monozygotic twin pairs fully control for genetic factors. Thus, if the effect of birth weight on risk of type 2 diabetes is smaller within

**TABLE 1.** Rates of Type 2 Diabetes by Perinatal, Maternal, and Social Characteristics in Same-Sex Twins With Known Zygosity, Born 1926 to 1958 in Sweden

	No.	Individuals With Type 2 Diabetes No. (%)
Total	18,230	592 (3.2)
Birth weight; g		
≤1999	1,757	93 (5.3)
2000–2499	5,165	201 (3.9)
2500–2999	6,582	178 (2.7)
3000–3499	3,820	98 (2.6)
≥3500	906	22 (2.4)
Gestational age; wk		
31–34	2,356	87 (3.7)
35–36	3,634	120 (3.3)
37–41	10,747	322 (3.0)
42–45	633	21 (3.3)
Data missing	860	42 (4.9)
Sex		
Male	8,622	338 (3.9)
Female	9,608	254 (2.6)
Birth yr		
1926–1930	1,229	105 (8.5)
1931–1940	3,892	205 (5.3)
1941–1950	7,671	216 (2.8)
1951–1958	5,438	66 (1.2)
Maternal age; yrs		
≤19	456	27 (5.9)
20–24	3,056	113 (3.7)
25–29	5,470	179 (3.3)
30–34	5,028	142 (2.8)
≥35	4,201	131 (3.1)
Data missing	19	0 (0.0)
Previous births		
No	5,920	190 (3.2)
Yes	12,177	393 (3.2)
Data missing	133	9 (6.8)
Socioeconomic status of family at birth		
Unskilled blue-collar worker	4,947	162 (3.3)
Skilled blue-collar worker	2,755	85 (3.1)
Low-level white-collar worker	1,464	40 (2.7)
Intermediate- or high-level white-collar worker	2,082	32 (1.5)
Self-employed and farmers	2,348	51 (2.2)
Data missing	4,634	222 (4.8)
Socioeconomic status in adulthood <sup>a</sup>		
Unskilled blue-collar worker	4,577	201 (4.4)
Skilled blue-collar worker	2,919	111 (3.8)
Low-level white-collar worker	2,812	88 (3.1)
Intermediate- or high-level white-collar worker	6,334	128 (2.0)
Self-employed and farmers	1,090	41 (3.8)
Data missing	498	23 (4.6)

	No.	Individuals With Type 2 Diabetes No. (%)
Body mass index in adulthood <sup>a</sup> ; kg/m <sup>2</sup>		
≤18.4	1,753	11 (0.6)
18.5–24.9	12,653	286 (2.3)
25.0–29.9	1,599	178 (11.1)
≥30	149	47 (31.5)
Data missing	2,076	70 (3.4)
Smoking status <sup>a</sup>		
Never	6,986	207 (3.0)
Ever	8,605	308 (3.6)
Missing	2,639	77 (2.9)
Alcohol consumption <sup>a</sup>		
Low	8,823	268 (3.0)
Intermediate	3,090	83 (2.7)
High	1,171	33 (2.8)
Missing	5,146	208 (4.0)

<sup>a</sup>Socioeconomic status in adulthood was recorded in 1998, and body mass index, smoking status, and alcohol consumption were recorded in 1973.

monozygotic than dizygotic twins, the association is confounded by genetic factors.

## RESULTS

In the cohort of 18,230 same-sex twins, 592 had type 2 diabetes: 344 (3.2%) among the 10,914 dizygotic twins and 248 (3.4%) among the 7316 monozygotic twins. Rates of type 2 diabetes consistently increased with decreasing birth weight: from 2.4% among twins with a birth weight of 3500 g or more, to 5.3% among twins with a birth weight less than 2000 g (Table 1). Compared with twins born at term (37 to 41 gestational weeks), twins born preterm (31–36 weeks) were somewhat more likely to report a diagnosis of type 2 diabetes. Men were more often affected than women. The rate of type 2 diabetes increased with earlier birth year, reflecting the increased prevalence with age. Twins born to younger mothers more often had type 2 diabetes than twins born to older mothers, but this was explained by lower maternal age in earlier birth cohorts. SES at birth and in adulthood were inversely related to rate of type 2 diabetes. Overweight and obesity in adulthood (defined as BMI from 25.0 to 29.9 and at least 30.0 kg/m<sup>2</sup>, respectively) were strongly related to higher rates of type 2 diabetes. Diabetes was more common among ever-smokers compared with never-smokers. Twins lacking information on gestational age and SES had higher rates of type 2 diabetes, compared with twins who had information on these covariates. Missing information was more common in earlier birth cohorts, who also were more likely to have developed type 2 diabetes.

In cohort analyses, risk of type 2 diabetes increased with decreasing birth weight. Compared with twins with birth weight from 2500 to 2999 g, twins with birth weight less than 2000 g had a more than 2-fold increase in risk of type 2

**TABLE 2.** Odds Ratios for Type 2 Diabetes in Same-Sex Swedish Twins With Known Zygosity, for Birth Weight in Categories and Per 500-g Decrease in Birth Weight

	Crude OR (95% CI)	Adjusted OR (95% CI)		
		Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 3 <sup>c</sup>
<b>Complete Cohort</b>				
	(n = 18,230)	(n = 17,370)	(n = 17,226)	(n = 16,766)
Birth weight; g				
≤1999	1.99 (1.53–2.59)	2.25 (1.62–3.11)	2.36 (1.70–3.28)	2.39 (1.70–3.34)
2000–2499	1.46 (1.19–1.79)	1.58 (1.26–1.96)	1.57 (1.26–1.97)	1.60 (1.27–2.00)
2500–2999 <sup>d</sup>	1.00	1.00	1.00	1.00
3000–3500	0.94 (0.73–1.21)	0.89 (0.69–1.16)	0.84 (0.64–1.10)	0.84 (0.64–1.10)
≤3500	0.91 (0.59–1.41)	0.88 (0.57–1.37)	0.88 (0.56–1.38)	0.88 (0.56–1.39)
Per 500-g decrease	1.34 (1.22–1.47)	1.42 (1.26–1.59)	1.43 (1.27–1.61)	1.44 (1.28–1.63)
<b>Restricted Cohort</b>				
	(n = 16,766)	(n = 16,766)	(n = 16,766)	(n = 16,766)
Per 500-g decrease	1.31 (1.18–1.44)	1.45 (1.29–1.63)	1.45 (1.28–1.63)	1.44 (1.28–1.63)

<sup>a</sup>Analyses have been adjusted for sex and gestational age.  
<sup>b</sup>Analyses have been adjusted for the covariates in model 1, birth year, maternal age, and parity.  
<sup>c</sup>Analyses have been adjusted for the covariates included in model 2 and socioeconomic status in adulthood.  
<sup>d</sup>Reference category.

diabetes (Table 2). When we used birth weight as a continuous measure, we found that a 500-g decrease in birth weight was associated with a 44% increase in risk, after adjustment for perinatal and adult covariates. Risk estimates did not change when we restricted the cohort of twins to those with complete information on covariates included in fully adjusted model (Table 2) or when cohort analyses were stratified by zygosity (data shown on request). BMI in adulthood may be in the causal pathway between low birth weight and risk of type 2 diabetes, and was therefore not included in the analyses. Despite the large independent impact of BMI on risk of type 2 diabetes (eg, BMI ≥30 was associated with a 15-fold increased risk of type 2 diabetes), BMI did not confound the association between birth weight and type 2 diabetes (adjusted odds ratio also adjusted for BMI = 1.49 [95% CI = 1.32–1.68] per 500-g decrease in birth weight).

In cohort analyses, preterm birth was not associated with risk of type 2 diabetes. Compared with twins born at 37 to 41 weeks, the adjusted odds ratios were 0.75 (0.54–1.04) and 0.85 (0.66–1.10) for twins born at 31 to 34 weeks and 35 to 36 weeks, respectively.

To elucidate whether the association between low birth weight and type 2 diabetes was confounded by shared environmental or genetic factors, we calculated risks in twin pairs discordant for type 2 diabetes (Table 3). In 206 dizygotic twin pairs discordant for type 2 diabetes, we observed an increased risk of type 2 diabetes with lower birth weight. In contrast, no such association was observed in 97 monozygotic twin pairs discordant for type 2 diabetes. Similar to the cohort analyses in Table 2, adjustment for BMI did not change the results (data shown on request).

**TABLE 3.** Odds Ratios for Type 2 Diabetes Among 303 Swedish Twin Pairs, Discordant for Type 2 Diabetes, per 500-g Difference in Birth Weight

	OR (95% CI)
Dizygotic twin pairs (n = 206)	
Twin with type 2 diabetes	1.38 (1.02–1.85)
Nondiabetic twin <sup>a</sup>	1.00
Monozygotic twin pairs (n = 97)	
Type 2 diabetes	1.02 (0.63–1.64)
Nondiabetic twin <sup>a</sup>	1.00

<sup>a</sup>Reference category.

The association between low birth weight and risk of type 2 diabetes was also explored in additional cotwin case-control analyses. Firstly, to increase the specificity of the self-reported diagnosis of type 2 diabetes, we restricted the analyses to discordant twin pairs in which the diabetic twin was treated with an oral antidiabetic drug. The odds ratio (95% CI) for a 500-g decrease in birth weight was 1.48 (1.03–2.12) in dizygotic twins and 0.95 (0.48–1.84) in monozygotic twins, respectively. Secondly, since preterm birth is more common among twins compared with singletons, we analyzed the subset of twins born at term (37–41 gestational weeks). The odds ratio (95% CI) for a 500-g decrease in birth weight at term was 1.27 (0.89–1.80) in dizygotic twins and 0.96 (0.53–1.75) in monozygotic twins, respectively.

Finally, we investigated whether the results were influenced by the sometimes large differences in fetal growth within twin pairs. Median birth weight differences in the

cohort were 280 and 240 g within dizygotic and monozygotic twin pairs, respectively. We defined birth weight discordancy as an intrapair difference in birth weight of at least 20%, which corresponded to a birth weight difference of 670 and 630 g within dizygotic and monozygotic twin pairs, respectively. Rates of birth weight discordancy were 26% among dizygotic twin pairs and 22% among monozygotic twin pairs. Within birth weight discordant twin pairs, odds ratios (95% CI) for a 500-g reduction in birth weight were 1.30 (0.95–1.80) in dizygotic twins and 0.97 (0.56–1.66) in monozygotic twins, respectively. In twin pairs with smaller birth weight differences, corresponding odds ratios (95% CI) were 1.83 (0.88–3.81) in dizygotic twins and 1.23 (0.42–3.55) in monozygotic twins, respectively.

## DISCUSSION

We found that decreasing birth weight was associated with increasing risk of type 2 diabetes in cohort analyses and within dizygotic twin pairs, but not within monozygotic twin pairs. These results demonstrate that genetic factors contribute to the association between low birth weight and risk of type 2 diabetes later in life. Our twin study is the first study large enough to address and support a previously proposed hypothesis, that low birth weight and type 2 diabetes may have a common genetic etiology.<sup>11</sup>

In contrast to recent observations,<sup>12,13</sup> our cohort analyses did not reveal an increased risk of type 2 diabetes after preterm birth. Different study populations may explain this discrepancy. Recent studies include children and young adults born before 32 gestational weeks<sup>12</sup> or with birth weights below 1500 g.<sup>13</sup> Our twin cohort, born between 1926 and 1958, included preterm survivors from a period when no advanced obstetric and neonatal care was available, and thus very early and very small infants did not survive.

Genetic factors could be important for the association between low birth weight and type 2 diabetes in several ways. Insulin is a key determinant of fetal growth and has a central role in glucose metabolism. Reduced insulin secretion or insulin resistance may explain both low birth weight and glucose intolerance in adulthood.<sup>20</sup> A common genotype of the insulin gene (class I allele) has been associated with lower birth weight,<sup>21</sup> insulin resistance, dyslipidemia, and development of obesity.<sup>22,23</sup> Likewise, a common variant of mitochondrial DNA is related to insulin resistance, and has been associated with both thinness at birth and type 2 diabetes later in life.<sup>24</sup> It has also been shown that a haplotype of the glucocorticoid receptor gene could modify the association between size at birth and glucose tolerance.<sup>25</sup>

This population-based study of Swedish twins is by far the largest twin study on fetal growth and risk of type 2 diabetes.<sup>14,15</sup> Importantly, information on perinatal and maternal characteristics was retrieved from original birth records. Analyses within twin pairs provided control for gestational age

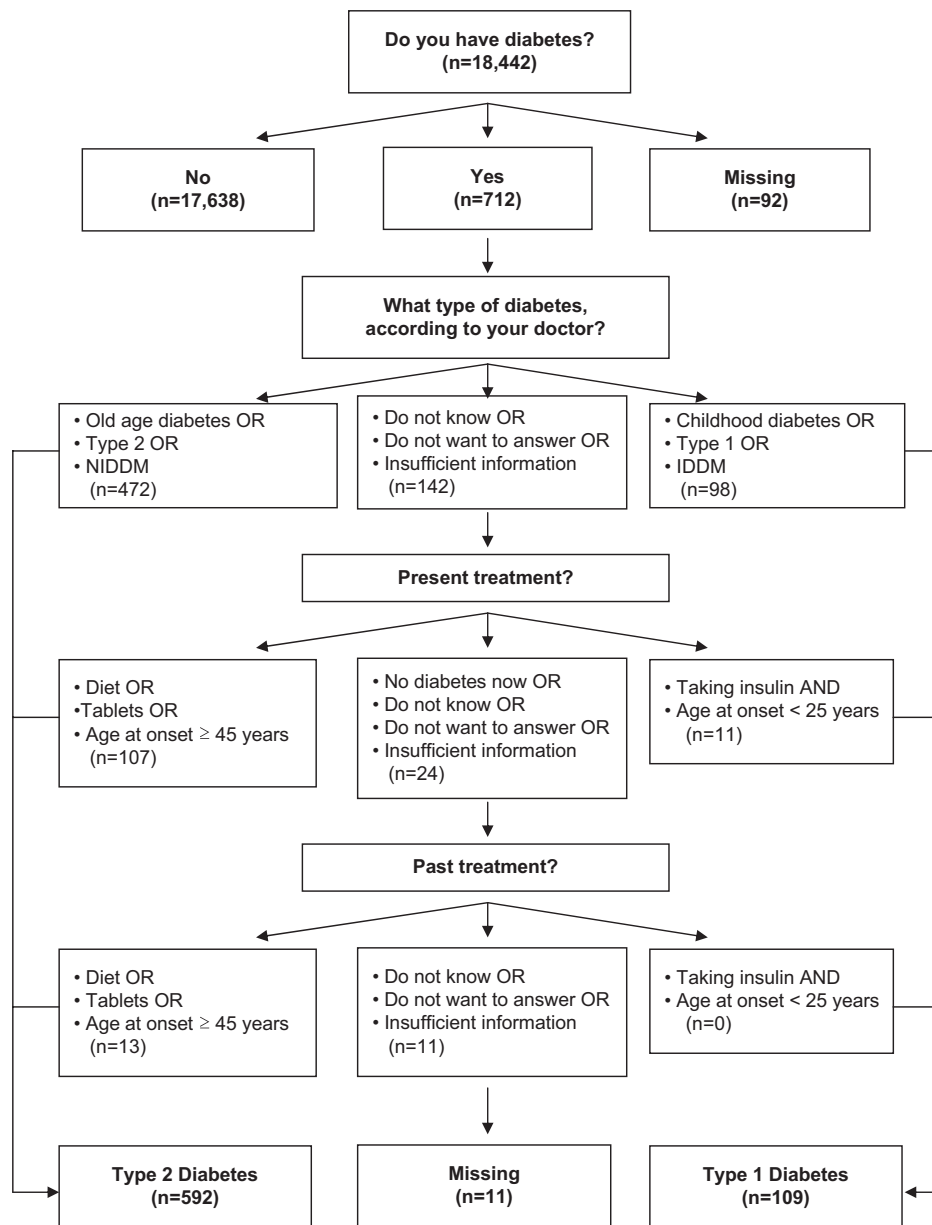
and for unmeasured environmental and socioeconomic factors during childhood. In addition, analyses taking zygosity into account allowed control for genetic factors. Finally, our study did not depend on definitions of small-for-gestational-age or low-birth-weight per se, since our cotwin case-control analyses used birth weight differences within twin pairs.

Generalizing findings in twins to the general population may be a concern. According to the “fetal programming hypothesis,” nutritional insults to the fetus during late gestation lead to disturbances of glucose-insulin metabolism.<sup>6</sup> Compared with singletons, twins have shorter gestations and slower fetal growth.<sup>26</sup> Weight gain in twins is less pronounced during the third trimester,<sup>27</sup> but intertwin disparity in fetal size increases with gestation.<sup>28</sup> We found evidence of genetic confounding within twin pairs born at term, and within twin pairs with moderate as well as large differences in birth weight. Further, a U-shaped association between birth weight and type 2 diabetes was found in a recent meta-analysis<sup>5</sup> (ie, a birth weight above 4000 g was also associated with an increased risk). We could not observe this U-shaped pattern in our study, possibly because only 0.3% of our twin cohort had birth weights above 4000 g.

Since we found an inverse association between low birth weight and type 2 diabetes in dizygotic but not in monozygotic twin pairs, a crucial question is whether results related to the fetal environment of dizygotic and monozygotic twins can be compared. All dizygotic twins and one-third of monozygotic twins have separate placentas, whereas two-thirds of monozygotic twins are monochorionic and share a single placenta. However, unequal sharing of placental blood flow appears to be the primary contributor to birth weight discordancy in both monozygotic and dizygotic twin pairs.<sup>29</sup> We cannot see any differences in principle between inadequate placental nutrition between singletons, monozygotic twins, and dizygotic twins.

Monozygotic monochorionic twins with interfetal vascular connections are also at risk for birth weight discordancy of a different but less common etiology: the twin-to-twin transfusion syndrome.<sup>30</sup> About 10% of all monozygotic twin pairs experience this syndrome, with very high risks of mortality and preterm birth, despite access to intrauterine interventions and neonatal intensive care.<sup>29</sup> Since twins in our cohort were born between 1926 and 1958, when no advanced obstetric or neonatal care was available, complete twin pairs surviving this syndrome are probably infrequent in our cohort.

In contrast to the results in the present study, we found no evidence of genetic confounding when we recently used the same twin cohort to study low birth weight and risk of hypertension.<sup>17</sup> The most evident explanation for these discrepant results is that genetic factors are important for the association between low birth weight and type 2 diabetes, but not for the association between low birth weight and hypertension.



**FIGURE.** Flow chart of the categorization of diabetes status, according to responses in questionnaire, in 18,442 same-sex twins born 1926–1958 in Sweden.

Our definition of type 2 diabetes, which relied on an algorithm mapping on to diagnostic criteria (Fig. 1), is a potential limitation, but it would not lead to differential misclassification of type 2 diabetes in monozygotic or dizygotic twins. Further, the agreement between questionnaire data and medical records has been shown to be good for well-known chronic diseases.<sup>31</sup> To improve specificity of the diagnosis, we performed analyses restricted to twin pairs in which the diabetic twin used antidiabetic drugs; estimates did not change. Still, the algorithm could misclassify diseased twins as “healthy,” since undiagnosed glucose intolerance is common in elderly people.<sup>32</sup> Given the genetic liability to develop type 2 diabetes, one could question whether it is possible to identify truly disease-

discordant monozygotic twin pairs.<sup>33</sup> However, the heritability of type 2 diabetes has never been estimated to 100%<sup>34</sup> and it is therefore unlikely that we have misclassified all healthy cotwins in the monozygotic discordant twin pairs. Further, a conceptually important methodologic feature of selecting controls is their eligibility to become cases.<sup>35</sup> Finally, major misclassification seems unlikely since the prevalence of type 2 diabetes in our cohort is similar to the prevalence in the general Swedish population.<sup>36</sup>

The results of the present study suggest a common genetic etiology for low birth weight and type 2 diabetes. Genetic factors should be taken into account in future attempts to disentangle risk factors and biologic mechanisms underlying the developmental origin of type 2 diabetes.

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