# Association Between Maternal Diabetes in Utero and Age at Offspring's Diagnosis of Type 2 Diabetes

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**OBJECTIVE** — The purpose of this study was to examine age of diabetes diagnosis in youth who have a parent with diabetes by diabetes type and whether the parent's diabetes was diagnosed before or after the youth's birth.

**RESEARCH DESIGN AND METHODS** — The cohort comprised SEARCH for Diabetes in Youth Study participants (diabetes diagnosis 2001–2005) with a diabetic parent. SEARCH is a multicenter survey of youth with diabetes diagnosed before age 20 years.

**RESULTS** — Youth with type 2 diabetes were more likely to have a parent with either type 1 or type 2 diabetes (mother 39.3%; father 21.2%) than youth with type 1 diabetes (5.3 and 6.7%, respectively, $P < 0.001$ for each). Type 2 diabetes was diagnosed 1.68 years earlier among those exposed to diabetes in utero ($n = 174$) than among those whose mothers' diabetes was diagnosed later ($P = 0.018$, controlled for maternal diagnosis age, paternal diabetes, sex, and race/ethnicity). Age at diagnosis of type 1 diabetes for 269 youth with and without in utero exposure did not differ significantly (difference 0.96 year, $P = 0.403$ after adjustment). Controlled for the father's age of diagnosis, father's diabetes before the child's birth was not associated with age at diagnosis ($P = 0.078$ for type 1 diabetes; $P = 0.140$ for type 2 diabetes).

**CONCLUSIONS** — Type 2 diabetes was diagnosed at younger ages among those exposed to hyperglycemia in utero. Among youth with type 1 diabetes, the effect of the intrauterine exposure was not significant when controlled for mother's age of diagnosis. This study helps explain why other studies have found higher age-specific rates of type 2 diabetes among offspring of women with diabetes.

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Fetal exposure to maternal hyperglycemia can cause permanent fetal changes, leading to malformations, increased birth weight (1), and an increased risk of obesity (2,3), cardiovascular disease, hypertension (4), and type 2 diabetes (5,6). Animal studies demonstrate that metabolic imprinting caused by the diabetic intrauterine environment can be transmitted across generations (7–9). In humans, excess maternal transmission of type 2 diabetes (10,11) supports the hypothesis that the intrauterine environment, independent of genetic transmission, contributes to increased risk of type 2 diabetes in offspring. Pima Indian women with diabetes during pregnancy and their offspring have been followed prospectively to examine the effects of in utero exposure to diabetes on the development of type 2 diabetes in the offspring (12). More diabetes developed in offspring exposed to diabetes in utero than in the offspring of women who developed diabetes after the pregnancy or who never developed diabetes (5,13,14). Recently, Clausen et al. (6) have found higher rates of abnormal glucose tolerance in offspring of women with gestational diabetes (21%) or type 1 diabetes (11%) than in the background population (4%). Similarly, in 10- to 16-year-old offspring of women with pregestational and gestational diabetes, Silverman et al. (15) found a higher prevalence of impaired glucose tolerance (19.3%) than in age- and sex-matched control subjects (2.5%). Stride et al. (16) have shown that individuals with maturity-onset diabetes of the young resulting from mutations in the *HNF-1α* gene (MODY-3) who inherit the MODY from their mothers develop diabetes at a younger age if their mother's diabetes was diagnosed before the pregnancy rather than after. These reports suggest that, even in single-gene disorders such as MODY-3, nongenetic factors influence the course of disease development.

Whether higher rates of type 2 diabetes associated with diabetes in utero result from diabetes developing at an earlier age or whether exposure to diabetes in utero is associated with an earlier age at onset of diabetes in youth of racial/ethnic groups other than American Indians is largely unknown. The SEARCH for Diabetes in Youth study, a large, population-based study of diabetes in racially and ethnically diverse youth, tested the following hypotheses. First, age of diagnosis of diabetes in youth with type 2 diabetes will be younger if mothers had diabetes diag-

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nosed before pregnancy and will not be associated with timing of father's diabetes when controlled for paternal age at diagnosis. Second, age at diagnosis in youth with type 1 diabetes will not be associated with timing of maternal or paternal diabetes.

## RESEARCH DESIGN AND METHODS

— Data come from the SEARCH for Diabetes in Youth study (17). SEARCH is a multicenter population-based ascertainment of youth with diabetes beginning in 2001 and continuing through the present. SEARCH sought to identify all cases of nongestational diabetes in youth <20 years of age in 2001 and all newly diagnosed cases of nongestational diabetes in youth <20 years of age in subsequent calendar years.

SEARCH has six centers, with diabetes cases being identified in geographically defined populations in Ohio, Washington, South Carolina, and Colorado, among health plan enrollees in Hawaii and southern California, among members of the Gila River Indian Community participating in the National Institute of Diabetes and Digestive and Kidney Diseases Pima Indian Diabetes Study, and among health service beneficiary rolls in three other Native American populations. Cases of diabetes were considered valid if they were diagnosed by a health care provider.

The study was reviewed and approved by local institutional review boards with jurisdiction over local study populations. Following Health Insurance Portability and Accountability Act privacy rule compliant procedures, youth with diabetes identified by the SEARCH recruiting network were asked to complete a short survey that collected information on date of birth, date of diabetes diagnosis, age at diagnosis, race/ethnicity, and other items to confirm eligibility. Youth completing this survey, excluding youth whose diabetes was due to other conditions, were invited to a study visit. Before the visit, written informed consent was obtained according to guidelines established by the local institutional review board from subjects aged ≥18 years or from a subject's parent or guardian if the subject was aged <18 years. Written assent was also obtained from subjects aged <18 years, as governed by local institutional review board instructions. Survey instruments were translated into Spanish, and interviews and surveys were administered in Spanish if that was the subject's preferred language.

Diabetes type for SEARCH participants was based on the clinical diagnosis by health care providers, as reported to SEARCH. This information was collected at the time of the case ascertainment or validation from medical records or direct provider reports. Age at diagnosis of diabetes was ascertained by parental report or self-report among subjects aged ≥18 years.

During the study visit, height and weight were measured using a standardized protocol, and survey data, including family history of diabetes, were collected. A BMI *z* score was calculated using growth charts with an SAS program available from the Centers for Disease Control and Prevention (18).

Data were collected on the presence or absence of a history of diabetes for each biological parent and, if reported, the parent's age at which diabetes was diagnosed. Information on the parents' diabetes type was not obtained. Study participants with a parental history of diabetes were categorized by the timing of that parent's diagnosis relative to the subject's birth, i.e., parental diabetes diagnosed before the child's birth, after the child's birth, or, if uncertain, indeterminate.

This article includes data from SEARCH participants who completed the baseline study visit and had type 1or type 2 diabetes diagnosed in calendar years 2001 through 2005. Of the 11,181 subjects with registered cases of diabetes, 4,509 participated in the study visit and had data available on family history of diabetes. Subjects whose diabetes type was missing or reported as other than type 1 or type 2 and those with diabetes diagnosed before 2001 were excluded. Two participants were excluded for missing date of birth, 43 for diabetes types other than type 1 or type 2, and 1,791 because they had diabetes diagnosed before 2001, resulting in a sample size of 2,673 subjects (2,342 with type 1 and 331 with type 2 diabetes). Nonparticipation was associated with older age, type 2 diabetes, and African American race (19). Subsequent analyses were further restricted to the subset of subjects who have at least one parent with diabetes.

All analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC). To test the significance of differences between sexes within each diabetes type, *t* tests were used for continuous variables (child's age at diagnosis of diabetes and BMI *z* scores) and $\chi^2$ analyses were used for categorical variables (race/ethnicity, history of maternal diabetes, history of paternal diabetes, and history of both parents with diabetes). Age of diagnosis for both type 1 and type 2 diabetes was examined within the three different timing categories of maternal and paternal diabetes diagnosis (before or after the child's birth or indeterminate).

A multivariate regression model was fitted for age of child's diabetes diagnosis for each diabetes type using PROC GLM (general linear model), the SAS procedure for analysis of variance. For this model, data were restricted to participants whose mothers also had diabetes either before or after the child's birth. The model was adjusted for timing of maternal diabetes (before birth or after birth), mother's age of diabetes diagnosis (as a continuous variable), history of paternal diabetes (yes or no), sex, and race/ethnicity (non-Hispanic White or racial/ethnic minority). The model was checked for linearity and potential influence of outliers and found to meet the assumptions of a linear regression. Results were considered to be significant at $P < 0.05$.

## RESULTS

— The study population from which youth with a parental history of diabetes were selected included 1,342 male and 1,331 female youth aged (mean ± SD) 10.9 ± 4.5 years at study visit and a racial/ethnic mix of 1,845 (69.0%) non-Hispanic White and 828 (31.0%) other race/ethnic groups. The mean duration of diabetes was 1.0 ± 0.7 years; 2,342 (87.6%) subjects had type 1 and 331 (12.4%) subjects had type 2 diabetes.

Maternal and paternal history of diabetes for SEARCH subjects who had either type 1 or type 2 diabetes and are included in these analyses are shown in Table 1. Youth with type 2 diabetes were more likely to have a parental history of diabetes (maternal 39.3%, paternal 21.2%) than those with type 1 diabetes (5.3 and 6.7%, respectively, $P < 0.001$ for each parent). There was no significant difference in the proportion of male and female subjects with a parental history of diabetes. The mothers of 255 subjects and the fathers of 227 subjects had diabetes. Both parents of 39 subjects had diabetes. There was little difference in age at diagnosis between those with a parental history of diabetes (9.2 ± 4.5 years for type 1 and 13.3 ± 2.5 years for type 2 diabetes)

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**Table 1—*Maternal and paternal history of diabetes by interview and timing of parental diagnosis in reference to child's date of birth, by youth's clinical diabetes type***

| | Type 1 diabetes | | Type 2 diabetes | |
|---|---|---|---|---|
| | Maternal | Paternal | Maternal | Paternal |
| *n* | 2,342* | | 331* | |
| Yes | 125 (5.3) | 157 (6.7) | 130 (39.3) | 70 (21.2) |
| Before child's birth | 52 (2.2) | 76 (3.3) | 36 (10.9) | 10 (3.0) |
| After child's birth | 59 (2.5) | 70 (3.0) | 77 (23.3) | 58 (17.5) |
| Timing indeterminate | 14 (0.6) | 11 (0.5) | 17 (5.1) | 2 (0.6) |
| No | 2,209 (94.3) | 2,111 (90.1) | 200 (60.4) | 236 (71.3) |
| Unknown/missing | 8 (0.3) | 74 (3.2) | 1 (0.3) | 25 (7.6) |

Data are *n* (%). Maternal and paternal history of diabetes indicates parental diabetes in at least one parent by time of SEARCH study visit. *Type 1 diabetes: 1,211 male and 1,131 female subjects; type 2 diabetes: 131 male and 200 female subjects.

and those without (8.7 ± 4.4 and 13.8 ± 2.4, respectively; $P > 0.05$ for each).

Table 2 shows the characteristics of 145 male and 124 female subjects with type 1 and 64 male and 110 female subjects with type 2 diabetes who have a family history of diabetes in the mother, father, or both. More female than male subjects had type 2 diabetes, and their diabetes was diagnosed at a younger age (12.8 ± 2.5 vs.14.2 ± 2.4 years, $P = 0.005$).

Table 3 shows mean ages at diabetes diagnosis for youth with a parental history of diabetes according to the timing of the parent's diabetes diagnosis relative to the subject's birth. Mean duration of parental diabetes at the child's birth for children born after the parent's diagnosis and child's age at parental diagnosis for children born before the parent's diagnosis are shown in the footnote. Some older children, although their diabetes was diagnosed before age 20 years, were examined after their 20th birthdays. Subjects born after their mother's or father's diabetes was diagnosed had a younger age of diagnosis than those born before the parent's diabetes was diagnosed. The ages of diagnosis for the indeterminate groups were intermediate with the exception of the two subjects with type 2 diabetes whose father's diagnosis was indeterminate. In addition to whether or not the mother had diabetes during her pregnancy, the relationship between age of diabetes diagnosis in the parent and age of diagnosis in the child was evaluated. Among diabetic mother-child pairs, there was a significant correlation between the ages of diagnosis of the SEARCH subjects and of their mothers for both type 1 ($n = 125$, $r = 0.46$, $P < 0.001$) and type 2 diabetes ($n = 130$, $r = 0.34$, $P < 0.001$). The correlation between father's and offspring's age of diagnosis of type 1 diabetes was slightly weaker ($n = 157$, $r = 0.34$, $P < 0.001$) but similar for type 2 diabetes ($n = 70$, $r = 0.33$, $P = 0.006$).

Table 4 shows the parameters included simultaneously in the multiple regression analyses with age of diagnosis as the dependent variable. Among youth with type 2 diabetes whose mothers had diabetes, those whose mothers had diabetes during pregnancy had a significantly younger age of diagnosis than those whose mothers' diabetes was not diagnosed until after the offspring's birth (difference = 1.68 years, $P = 0.018$ controlled for mother's age of diagnosis, father's diabetes, sex, and race/ethnicity). Among subjects with type 1 diabetes, however, the ages of diagnosis among those whose mother's diabetes was diagnosed before and those whose mother's diabetes was diagnosed after they were born were not significantly different (difference 0.96 years, $P = 0.403$ controlled for mother's age of diagnosis, father's diabetes, sex, and race/ethnicity). Among those with type 2 diabetes, female subjects had an earlier age of diagnosis than male subjects (difference 1.18 years, $P = 0.020$). Although not a significant contributor ($P = 0.647$), when BMI *z* score was added to the type 2 model in the subset that had this variable, the parameter estimate for maternal diabetes before birth changed from −1.68 to −1.54 years and the *P* value rose to 0.0306. The association between the timing of the father's diabetes relative to the subject's birth was not significant for either type 1 diabetes ($P = 0.078$) or type 2 diabetes ($P = 0.140$, controlled for father's age of diagnosis).

**Table 2—*Characteristics of SEARCH participants with a family history of diabetes in the mother, the father, or both parents***

| | Type 1 diabetes | | | Type 2 diabetes | | |
|---|---|---|---|---|---|---|
| | Male | Female | *P* value* | Male | Female | *P* value |
| *n* | 145 | 124 | 0.2004 | 64 | 110 | 0.001 |
| Age at diagnosis (years) | 9.3 ± 4.6 | 9.2 ± 4.4 | 0.8111 | 14.2 ± 2.4 | 12.8 ± 2.5 | 0.001 |
| Race/ethnicity† | | | 0.6732 | | | 0.581 |
| Non-Hispanic white | 103 (71.0) | 85 (68.6) | | 14 (21.9) | 20 (18.2) | |
| African American | 19 (13.1) | 18 (14.5) | | 19 (29.7) | 45 (40.9) | |
| Hispanic | 12 (8.3) | 11 (8.9) | | 17 (26.6) | 22 (20.0) | |
| Asian/Pacific Islander | 9 (6.2) | 9 (7.3) | | 9 (14.1) | 14 (12.7) | |
| American Indian | 2 (1.4) | 0 | | 5 (7.8) | 7 (6.4) | |
| Other | 0 | 1 (0.8) | | 0 | 2 (1.8) | |
| Maternal diabetes‡ | 66 (45.5) | 59 (47.6) | 0.7352 | 52 (81.3) | 78 (70.9) | 0.130 |
| Paternal diabetes‡ | 87 (60.0) | 70 (56.5) | 0.5562 | 21 (32.8) | 49 (44.5) | 0.128 |
| BMI *z* score§ | 0.6 ± 1.1 | 0.9 ± 0.95 | 0.0386 | 2.25 ± 0.8 | 1.99 ± 0.7 | 0.032 |

Data are means ± SD unless otherwise indicated. *P value for male-female difference. †Data are *n* (column %). ‡Both parents had diabetes for 8 male and 5 female subjects with type 1 diabetes and for 9 male and 17 female subjects with type 2 diabetes. Data are *n* (% total *n*). §Missing for 24 subjects.

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**Table 3—*Mean age at diabetes diagnosis for youth according to timing of parental diabetes in relation to birth, by diabetes type***

| | Maternal diabetes diagnosed | | | | | | Paternal diabetes diagnosed | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before child's birth* | | After child's birth† | | Indeterminate | | Before child's birth‡ | | After child's birth§ | | Indeterminate | |
| Diabetes | *n* | Age (years) | *n* | Age (years) | *n* | Age (years) | *n* | Age (years) | *n* | Age (years) | *n* | Age (years) |
| Type 1 | 52 | 6.90 ± 0.55 | 59 | 10.95 ± 0.53 | 14 | 8.7 ± 1.62 | 76 | 8.03 ± 0.52 | 70 | 11.36 ± 0.44 | 11 | 8.27 ± 1.10 |
| Type 2 | 36 | 11.71 ± 0.42 | 77 | 14.07 ± 0.27 | 17 | 13.0 ± 0.53 | 10 | 12.78 ± 1.11 | 58 | 13.43 ± 0.31 | 2 | 14.5 ± 1.50 |

Data are means ± SEM. *Maternal diabetes duration (years) at child's birth (mean ± SD, range): type 1: 11.0 ± 8.5, 1.5–27.5; type 2: 7.2 ± 5.2,1.5–24.5. †Child's age (years) at mother's diabetes diagnosis (mean ± SD, range): type 1: 7.9 ± 4.6, 1.5–19.5; type 2: 10.1± 5.2, 0.5–20.5. ‡Paternal diabetes duration (years) at child's birth (mean ± SD, range): type 1: 14.7 ± 8.0, 1.5–19.5; type 2: 12.8 ± 9.8, 1.5–26.0. §Child's age (years) at father's diabetes diagnosis (mean ± SD, range): type 1: 9.3 ± 3.8, 0.5–17.5; type 2: 10.3 ± 4.3, 1.5–18.5.

**CONCLUSIONS** — Type 2 diabetes was diagnosed in youth at younger ages if they had been exposed to a diabetic intrauterine environment. The significance of this finding persisted when analyses were controlled for the age at which the mothers' diabetes was diagnosed. In this study, which is limited to diabetic youth, we cannot address the risk of developing diabetes directly. However, factors that lower the age of onset in a proportion of the population result in an increase in age-specific rates and, with an upper age limit such as that in the SEARCH study, result in the inclusion of some subjects who might not otherwise have developed diabetes before age 20 years. The differences in age of diagnosis between subjects who developed type 1 diabetes who had or had not been exposed to in utero diabetes were not significant when adjusted for mother's age of diagnosis. These findings suggest that the hyperglycemic intrauterine environment predisposes to an earlier onset of type 2 diabetes, whereas the age of onset of type 1 diabetes is largely familial, is possibly genetic, and is influenced very little by the intrauterine milieu. This association is potentially confounded by maternal age at delivery, which has an inconsistent association with diabetes risk in the offspring (20–25). The group with type 1 diabetes may include some children who were at risk of developing diabetes at a younger age because their mothers were older at delivery even though the mother's diabetes was diagnosed at an older age. Few studies have found an association between maternal age and development of type 2 diabetes independent of maternal diabetes, but one study (24) did find a U-shaped association with higher rates of type 2 diabetes among young adults whose mothers were either younger or older at delivery. Because the present analyses are limited to diabetic children, these earlier studies may not be relevant. In youth with type 2 diabetes, the child's BMI *z* score slightly reduced the effect of maternal diabetes on age of diagnosis in offspring. This effect of BMI *z* score is not surprising because in Pima Indians, maternal diabetes in utero is a strong predictor of childhood obesity (2) as well as of type 2 diabetes (5).

In this study we examined the age at which diabetes was diagnosed among youth aged <20 years at diagnosis who were enrolled in the SEARCH for Diabetes in Youth Study (17) and who had a parent with diabetes. The study was not designed to collect data on youth who either have not developed diabetes or developed diabetes after their 20th birthdays. It is not possible, therefore, to estimate from these data what proportion of all children exposed to diabetes in utero will eventually develop type 2 diabetes. In addition, the presence of parental diabetes was by self-report, and data on parental diabetes type were not collected. Parental age at diagnosis, recorded to the nearest year, may have introduced a bias, but this would have resulted in a weakening of the results. The small number of cases associated with rare mitochondrial defects included in an unselected population survey of youth with diabetes would have little if any effect on these results. Children with type 2 diabetes are occasionally misclassified initially as having type 1 diabetes, and this would have decreased the number of children with type 2 diabetes. Unless misclassification was linked to in utero diabetes exposure, this would have a negligible effect on the results. A previous evaluation showed that older African American youth with type 2 diabetes were more likely to be nonparticipants in SEARCH (19). Thus, some of the older children of interest are not included in this sample. However, there is no evidence that the timing of parental diabetes was associated with nonparticipation, so this factor would have had little effect on this study

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**Table 4—*Regression parameter estimates determining age at diabetes diagnosis among SEARCH subjects whose mothers also have diabetes***

| | Type 1 | | | | Type 2 | | | |
|---|---|---|---|---|---|---|---|---|
| Parameter | Estimate | SEM | *t* | *P* value | Estimate | SEM | *t* | *P* value |
| Maternal diabetes before birth* | −0.96 | 1.15 | −0.84 | 0.403 | −1.68 | 0.70 | −2.41 | 0.018 |
| Mother's age of diagnosis | 0.16 | 0.05 | 3.39 | 0.001 | 0.04 | 0.03 | 1.17 | 0.246 |
| Father with diabetes | 1.15 | 1.18 | 0.97 | 0.333 | −0.10 | 0.57 | −0.19 | 0.853 |
| Sex (female) | −0.96 | 0.76 | −1.26 | 0.209 | −1.18 | 0.50 | −2.36 | 0.020 |
| Race/ethnicity (all other versus non-Hispanic white) | −0.53 | 0.81 | −0.66 | 0.513 | 0.47 | 0.67 | 0.71 | 0.483 |
| Intercept | 5.49 | 1.79 | 3.07 | 0.003 | 12.99 | 1.49 | 8.72 | <0.001 |

Dependent variable is age at diagnosis. *Subjects whose mother's time of diagnosis was indeterminate were eliminated from the models.

other than to decrease the sample size and therefore weaken the findings.

As a population-based study, SEARCH for Diabetes in Youth enrolled subjects with a wide range of race/ethnicity born over a span of 23 years with diabetes diagnosed before age 20 years. This study demonstrated that, among a sample of U.S. youth, exposure to a diabetic intrauterine environment is associated with an earlier age of diagnosis, confirming the long-term risk for the offspring from this condition and extending it to other races/ethnicities. As rates of obesity and type 2 diabetes increase, more young women will be exposing their unborn children to hyperglycemia. Thus, children exposed at this early stage of life to abnormal nutrients from their diabetic mothers need to be followed carefully, and known risk factors, such as obesity, hypertension, and hyperlipidemia, need early treatment.

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**References**

1. Yang J, Cummings EA, O'Connell C, Jangaard K: Fetal and neonatal outcomes of diabetic pregnancies. *Obstet Gynecol* 108: 644–650, 2006
2. Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC: Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *N Engl J Med* 308:242–245, 1983
3. Silverman BL, Landsberg L, Metzger BE: Fetal hyperinsulinism in offspring of diabetic mothers: Association with the subsequent development of childhood obesity. *Ann NY Acad Sci* 699:36–45, 1993
4. Cho NH, Silverman BL, Rizzo TA, Metzger BE: Correlations between the intrauterine metabolic environment and blood pressure in adolescent offspring of diabetic mothers. *J Pediatr* 136:587–592, 2000
5. Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC: Congenital susceptibility to NIDDM: role of intrauterine environment. *Diabetes* 37:622–628, 1988
6. Clausen TD, Mathiesen ER, Hansen R, Pedersen O, Jensen DM, Lauenborg J, Damm P: High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. *Diabetes Care* 31: 340–346, 2008
7. Aerts L, Van Assche FA: Animal evidence for the transgenerational development of diabetes mellitus. *Int J Biochem Cell Biol* 38:894–903, 2006
8. Gauguier D, Nelson I, Bernard C, Parent V, Marsac C, Cohen D, Froguel P: Higher maternal than paternal inheritance of diabetes in GK rats. *Diabetes* 43:220–224, 1994
9. Gill-Randall RJ, Adams D, Ollerton RL, Alcolado JC: Is human type 2 diabetes maternally inherited? Insights from an animal model. *Diabet Med* 21:759–762, 2004
10. Dörner G, Mohnike A, Steindel E: On possible genetic and epigenetic modes of diabetes transmission. *Endokrinologie* 66: 225–227, 1975
11. Martin AO, Simpson JL, Ober C, Freinkel N: Frequency of diabetes mellitus in mothers of probands with gestational diabetes: possible maternal influence on the predisposition to gestational diabetes. *Am J Obstet Gynecol* 151:471–475, 1985
12. Knowler WC, Pettitt DJ, Saad MF, Bennett PH: Diabetes mellitus in the Pima Indians: incidence, risk factors and pathogenesis. *Diabetes Metab Rev* 6:1–27, 1990
13. Dabelea D, Knowler WC, Pettitt DJ: Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. *J Matern Fetal Med* 9:83–88, 2000
14. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, Roumain J, Bennett PH, Knowler WC: Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes* 49:2208–2211, 2000
15. Silverman BL, Metzger BE, Cho NH, Loeb CA: Impaired glucose tolerance in adolescent offspring of diabetic mothers: relationship to fetal hyperinsulinism. *Diabetes Care* 18:611–617, 1995
16. Stride A, Shepherd M, Frayling TM, Bulman MP, Ellard S, Hattersley AT: Intrauterine hyperglycemia is associated with an earlier diagnosis of diabetes in HNF-1α gene mutation carriers. *Diabetes Care* 25:2287–2291, 2002
17. The SEARCH Study Group: SEARCH for Diabetes in Youth: a multi-center study of the prevalence, incidence and classification of diabetes mellitus in youth. *Control Clin Trials* 25:458–471, 2004
18. Centers for Disease Control and Prevention: A SAS program for the CDC growth charts [article online]. Available from http://www.cdc.gov/nccdphp/dnpa/growthcharts/resources/sas.htm. Accessed 11 November 2003
19. Liese AD, Liu L, Davis C, Standiford D, Waitzfelder B, Dabelea D, Bell R, Williams D, Imperatore G, Lawrence JM: Participation in pediatric epidemiology research: the SEARCH for Diabetes in Youth Study experience. *Contemp Clin Trials.* In press
20. McKinney PA, Parslow R, Gurney K, Law G, Bodansky HJ, Williams DDR: Antenatal risk factors for childhood diabetes mellitus; a case-control study of medical record data in Yorkshire, UK. *Diabetologia* 40:933–939, 1997
21. McKinner PA, Parslow R, Gurney KA, Law GR, Bodansky HJ, Williams R: Perinatal and neonatal determinants of childhood type 1 diabetes: a case-control study in Yorkshire U.K. *Diabetes Care* 22:928–932, 1999
22. Bingley PJ, Douek IF, Rogers CA, Gale EAM, BOX Study Group: Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study. *BMJ* 321:420–424, 2000
23. Stene LC, Magnus P, Lie RT, Søvik O, Joner G, Norwegian Childhood Diabetes Study Group. Maternal and paternal age at delivery, birth order, and risk of childhood onset type 1 diabetes: population based cohort study. *BMJ* 323:369, 2001
24. Haynes A, Bower C, Bulsara MK, Finn J, Jones TW, Davis EA: Perinatal risk factors for childhood type 1 diabetes in Western Australia—a population-based study (1980–2002). *Diabet Med* 24:564–570, 2007
25. Lammi N, Moltchanova E, Blomstedt P, Eriksson JG, Taskinen O, Sarti C, Tuomilehto J, Karvonen M: The effect of birth order and parental age on the risk of type 1 and 2 diabetes among young adults. *Diabetologia* 50:2433–2438, 2007

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