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# Specific birth defects in pregnancies of women with diabetes: National Birth Defects Prevention Study, 1997–2011

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## Abstract

**BACKGROUND:** Diabetes is associated with an increased risk for many birth defects and is likely to have an increasing impact on birth defect prevalence because of the rise in diabetes in the United States in recent decades. One of the first analyses in which specific birth defects were assessed for their relationship with both pregestational and gestational diabetes used data from the initial 6 years of the National Birth Defects Prevention Study. That analysis reported strong associations for pregestational diabetes with several birth defects, but few exposures among some of the less common birth defects led to unstable estimates with wide confidence intervals. Since that analysis, the study continued to collect data for another 8 years, including information on approximately 19,000 additional cases and 6900 additional controls.

**OBJECTIVE:** Our objective was to use data from the National Birth Defects Prevention Study, the largest population-based birth defects case-control study in the United States, to provide updated and more precise estimates of the association between diabetes and birth defects, including some defects not previously assessed.

**STUDY DESIGN:** We analyzed data on deliveries from October 1997 through December 2011. Mothers of case and control infants were interviewed about their health conditions and exposures during pregnancy, including diagnosis of pregestational (type 1 or type 2) diabetes before the index pregnancy or gestational diabetes during the index pregnancy. Using logistic regression, we separately assessed the association between pregestational and gestational diabetes with specific categories of structural birth defects for which there were at least 3 exposed case infants. For birth defect categories for which there were at least 5 exposed case infants, we calculated odds ratios adjusted for maternal body mass index, age, education, race/ethnicity, and study site; for defect categories with 3 or 4 exposed cases, we calculated crude odds ratios.

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**RESULTS:** Pregestational diabetes was reported by 0.6% of mothers of control infants (71 of 11,447) and 2.5% of mothers of case infants (775 of 31,007). Gestational diabetes during the index pregnancy was reported by 4.7% of mothers of control infants (536 of 11,447) and 5.3% of mothers of case infants (1,653 of 31,007). Pregestational diabetes was associated with strong, statistically significant odds ratios (range, 2.5–80.2) for 46 of 50 birth defects considered. The largest odds ratio was observed for sacral agenesis (adjusted odds ratio, 80.2; 95% confidence interval, 46.1–139.3). A greater than 10-fold increased risk was also observed for holoprosencephaly (adjusted odds ratio, 13.1; 95% confidence interval, 7.0–24.5), longitudinal limb deficiency (adjusted odds ratio, 10.1; 95% confidence interval, 6.2–16.5), heterotaxy (adjusted odds ratio, 12.3; 95% confidence interval, 7.3–20.5), truncus arteriosus (adjusted odds ratio, 14.9; 95% confidence interval, 7.6–29.3), atrioventricular septal defect (adjusted odds ratio, 10.5; 95% confidence interval, 6.2–17.9), and single ventricle complex (adjusted odds ratio, 14.7; 95% confidence interval, 8.9–24.3). For gestational diabetes, statistically significant odds ratios were fewer (12 of 56) and of smaller magnitude (range, 1.3– 2.1; 0.5 for gastroschisis).

**CONCLUSION:** Pregestational diabetes is associated with a markedly increased risk for many specific births defects. Because glycemic control before pregnancy is associated with a reduced risk for birth defects, ongoing quality care for persons with diabetes is an important opportunity for prevention.

## Keywords

atrioventricular septal defect; birth defect; case control study; epidemiology; gestational diabetes; heterotaxy; holoprosencephaly; longitudinal limb deficiency; pregestational diabetes; pregnancy; sacral agenesis; single ventricle complex; truncus arteriosus; type 1 diabetes; type 2 diabetes

In recent decades, the prevalence of diabetes has increased in the United States, including among women of reproductive age.[1] Almost 3% of US women aged 15–44 years have diagnosed type 1 or type 2 diabetes. Women with pregestational diabetes (type 1 or type 2 diabetes diagnosed before pregnancy) have an increased risk for adverse pregnancy outcomes, including a markedly increased risk for birth defects.[2] Gestational diabetes occurs in almost 6% of US pregnancies.[3] The risk for birth defects associated with gestational diabetes is less clear.

Although maternal pregestational diabetes is a well-recognized risk factor for many birth defects, for rarer birth defects, the association is not well established. One of the first analyses in which specific birth defects were assessed for their relationship with both pregestational and gestational diabetes used data from the National Birth Defects Prevention Study (NBDPS) on approximately 18,000 deliveries from October 1997 through December 2003.[4] That analysis reported strong associations with many specific birth defects, primarily with pregestational diabetes, but also some with gestational diabetes. However, several associations were based on only a few exposed cases, leading to unstable estimates. The NBDPS continued data collection through December 2011 births, providing data on over 25,000 additional pregnancies.

The current analysis, which uses the final NBDPS data set, includes a much larger study sample, allowing us to update previous findings with more precise estimates on the risk for specific birth defects associated with maternal diabetes.

## Materials and Methods

NBDPS is a multisite, population-based, case-control study of selected major structural birth defects.[5] NBDPS began collecting data on pregnancies that ended on Oct. 1, 1997; the last pregnancies included in the study had estimated dates of delivery of Dec. 31, 2011. Over the years of the study, centers in 10 different US states contributed data to NBDPS.

The catchment area for 6 centers included only selected counties within the state: California (1997–2011), Georgia (1997–2011), Massachusetts (1997–2011), New York (1997–2002, 2004–2011), North Carolina (2003–2011), and Texas (1997–2011); the other 4 centers contributed data from the entire state: Arkansas (1998–2011), Iowa (1997–2011), New Jersey (1998–2002), and Utah (2003–2011). All participating centers obtained institutional review board approval for the study.

NBDPS cases include live births, fetal deaths, and terminations, although not all pregnancy outcomes were ascertained by all centers throughout the study period. Birth defect cases attributable to known chromosomal or single-gene disorders were not eligible for the study. All birth defects included in NBDPS are first reviewed by a clinical geneticist for eligibility in the study. They are reviewed a second time to confirm classification into specific birth defect categories and assigned isolated or multiple defects status.[6,7]

Isolated defects are those that occur in the absence of any other major defects in a different organ system, except those that are a direct result of the primary defect. Multiple defects are those that occur in the presence of other major birth defects in a different organ system. Control infants are live births to women during the same time period and from the same catchment area as case infants.

Mothers of case and control infants were administered a computer-assisted telephone interview asking about demographics, medical conditions and medication use, and other exposures before and during pregnancy. All participating mothers provided informed consent.

During the interview, women were asked, “Were you ever told by a doctor that you had diabetes (including gestational diabetes), sometimes called sugar diabetes or diabetes mellitus?” Mothers who responded yes were asked what type of diabetes they had (ie, type 1, type 2, or gestational) and the month and year of their diagnosis. We used this information to create 3 mutually exclusive categories: pregestational diabetes, gestational diabetes, and an unexposed referent group.

We defined pregestational diabetes as reporting type 1 or type 2 diabetes diagnosed before the index pregnancy and gestational diabetes as having been diagnosed with gestational diabetes during the index pregnancy. Our unexposed group was mothers who reported never having had a diagnosis of diabetes before, during, or after the index pregnancy. We excluded

from the analysis mothers who reported gestational diabetes in a previous pregnancy, those who reported diabetes diagnosed after the index pregnancy, or those with missing information on the type of diabetes or timing of diagnosis.

We made separate assessments of the association of pregestational and gestational diabetes with all specific birth defects in NBDPS for which there were at least 3 cases with the diabetes exposure of interest. For pregestational diabetes we assessed 26 noncardiac and 24 cardiac defects. Because gestational diabetes is more common than pregestational diabetes, for gestational diabetes we were able to assess 30 noncardiac and 26 cardiac defects.

We assessed the distribution of select covariates in each exposure group among control mothers, who are more representative of the general population of pregnant women than case mothers. The covariates we assessed were body mass index (kilograms per square meter; underweight, <18.5 $kg/m^2$; normal weight, 18.5–24.9 $kg/m^2$; overweight, 25–29.9 $kg/m^2$; obese, ≥30 $kg/m^2$); maternal age in years (<20, 20–24, 25–29, 30–34, ≥35); maternal education (less than high school degree, high school degree or equivalent; more than a high school degree); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other race/ethnicity); and study site.

We used logistic regression to estimate odds ratios (ORs) for the association between pregestational or gestational diabetes and each birth defect. For defect categories for which there were at least 5 exposed case infants, we adjusted for the covariates listed in the previous text (selected a priori and based on covariates used in the previous NBDPS analysis[4]); for defect categories with 3 or 4 exposed case infants, we calculated crude odds ratios.

In a secondary analysis, we considered the association between pregestational and gestational diabetes and specific birth defects with separate analyses for isolated and multiple defects. This secondary analysis was conducted because the etiology of a birth defect that occurs in isolation may differ from that of the same birth defect that occurs in the presence of other defects.[6] All analyses were run separately for pregestational and gestational diabetes using SAS version 9.3 (SAS Inc, Cary, NC).

## Results

Pregestational diabetes was reported by 0.6% of mothers of control infants (71 of 11,447) and 2.5% of mothers of case infants (775 of 31,007). Gestational diabetes during the index pregnancy was reported by 4.7% of mothers of control infants (536 of 11,447) and 5.3% of mothers of case infants (1653 of 31,007).

Among mothers of control infants, the prevalence of obesity was almost 50% among those who reported pregestational diabetes, approximately one third among those who reported gestational diabetes, and 17% among those who reported no diabetes (Table 1). Mothers of control infants who had pregestational or gestational diabetes were more likely to be 35 years or older and to have Hispanic ethnicity and less likely to have a post–high school education or to be non-Hispanic white compared with mothers of control infants who did not have diabetes.

Most associations between noncardiac defects and pregestational diabetes (22 of 26 assessed) were strong and statistically significant (Table 2). The largest odds ratio was observed for sacral agenesis (adjusted OR [aOR], 80.2; 95% confidence interval [CI], 46.1–139.3). A greater than 10-fold increased risk was also observed for holoprosencephaly (aOR, 13.1; 95% CI, 7.0–24.5) and longitudinal limb deficiency (aOR, 10.1; 95% CI, 6.2–16.5). Within the category of longitudinal limb deficiency, we assessed preaxial, postaxial, and split hand–split foot separately and observed similar associations (data not shown). Of 30 associations between noncardiac defects and gestational diabetes, 5 were statistically significant, including an inverse association for gastroschisis.

For cardiac defects, a similar pattern of associations was observed for pregestational and gestational diabetes (Table 3). All 24 associations assessed showed statistically significant increased risk for infants born to mothers with pregestational diabetes. There were 4 odds ratios for pregestational diabetes that were greater than 10: heterotaxy (aOR, 12.3; 95% CI, 7.3–20.5), truncus arteriosus (aOR, 14.9; 95% CI, 7.6–29.3), atrioventricular septal defect (aOR, 10.5; 95% CI, 6.2–17.9), and single ventricle complex (aOR, 14.7; 95% CI, 8.9–24.3). Of the 26 associations between cardiac defects and gestational diabetes, 7 were statistically significant.

For almost all of the birth defects with sufficient sample size to include in the analysis, odds ratios for the association with pregestational diabetes were larger for cases with multiple defects than for isolated cases. All 17 noncardiac birth defects with at least 3 exposed multiple cases had strong and statistically significant ORs (Table 4). Many strong associations were also observed for isolated noncardiac birth defects.

The strongest associations were observed for sacral agenesis, for which 8 of 12 isolated cases and 24 of 89 cases of multiple birth defects had maternal pregestational diabetes (aOR, 807.1; 95% CI, 110.7–5884.0; aOR, 67.8; 95% CI, 37.0–124.2, respectively). For spina bifida, anotia/microtia, esophageal atresia/stenosis, biliary atresia/stenosis, craniosynostosis, and diaphragmatic hernia, statistically significant increased ORs were observed only for cases with multiple defects. Very few associations with gestational diabetes were observed for isolated or multiple defect categories. Almost all isolated and multiple cardiac birth defect categories for which there were at least 3 exposed case infants were statistically significantly associated with pregestational diabetes, with stronger associations for multiple defects except for single ventricle complex (Table 5).

## Comment

### Principal findings

We observed strong associations between maternal pregestational diabetes and most specific defects assessed in this study. Of 50 defect categories, we observed 46 statistically significant increased ORs, with point estimates ranging from 2.5 to 80.2. For gestational diabetes fewer associations were observed (12 of 56), and these associations were weaker than for pregestational diabetes, ranging from 1.3 to 2.1, with the exception of gastroschisis, for which a significant inverse association was observed.

Although the increased risks for birth defects with pregestational diabetes are well established, the magnitude of such risks, particularly for rarer birth defects, is not well known. For example, one of the strongest associations we observed was for holoprosencephaly, which is a rare defect; if it were analyzed together with other defect categories (eg, brain malformations) rather than individually, the magnitude of the association would be underestimated. The fact that the majority of defects we were able to assess showed associations with pregestational diabetes demonstrates the substantial impact that type 2 diabetes prevention and diabetes control before pregnancy could have on improving pregnancy outcomes.

Because most birth defects develop in the first trimester and gestational diabetes typically develops later in pregnancy, it is not surprising that gestational diabetes was associated with fewer birth defects and yielded far weaker associations. This risk profile for gestational diabetes could be due to the heterogeneity of women included in our gestational diabetes exposure category, which likely included a mix of true cases of gestational diabetes (eg, diabetes that develops because of pregnancy) with cases of pregestational diabetes that were first detected during pregnancy.

We conducted a sensitivity analysis in which we reassigned mothers who reported gestational diabetes in the first 3 months of pregnancy to the pregestational diabetes exposure group. While there were more case than control mothers who reported gestational diabetes diagnosed in the first trimester, ORs for specific defects in this sensitivity analysis were generally biased slightly toward the null (data not shown), suggesting nondifferential and independent misclassification of exposure, which does not support the hypothesis that mothers who reported gestational diabetes diagnosed early in pregnancy were more likely to have had pregestational diabetes.

## Implications

The finding that diabetes is associated with substantially increased risk for many major birth defect categories has important implications for prevention and care. Results from prior studies suggest that good glycemic control before pregnancy (eg, indicated by reduction or normalization of levels of hemoglobin A1c [HbA1c]) is associated with a reduced risk for birth defects.

In a meta-analysis of 5 studies, preconception care for women with diabetes was associated with a greater than 20% decrease in HbA1c.[8] In a metaanalysis of 13 studies, preconception care for women with diabetes was associated with a 75% decrease in the risk for birth defects.[8]

It has been estimated that if all US women with diabetes had appropriate preconception care, birth defects in more than 4,700 infants could be prevented each year, resulting in an estimated $2 billion in cost savings.[9] Because pregestational diabetes is a risk factor for other adverse birth outcomes, including preterm delivery, the total savings associated with preconception care for US women with diabetes is estimated to be even higher, at $5.5 billion.[9]

Despite these benefits, achieving glycemic control prior to pregnancy can be challenging. The American College of Obstetricians and Gynecologists recommends that women with pregestational diabetes maintain glucose control near physiological levels before and during pregnancy through diet, exercise, medication, and routine monitoring.[10] However, even with these methods, achieving recommended glucose levels can be challenging for women with diabetes. Furthermore, pregnancy is often recognized after most birth defects have already occurred[11] and almost half (45%) of pregnancies in the United States in 2011 were unintended.[12] Because achieving good glycemic control takes time, this underscores the need to appropriately manage the health of women with diabetes, regardless of pregnancy intentions.

Another challenge is that not all women who have diabetes have been diagnosed. Data from the National Health and Nutrition Examination Survey suggest that approximately 300,000 nonpregnant US women of reproductive age (15–44 years) have undiagnosed diabetes.[13]

In addition to improving glycemic control prior to pregnancy, folic acid provides an opportunity for birth defect prevention for women with diabetes. It is recommended that all women capable of becoming pregnant consume 400–800 μg of folic acid daily to prevent neural tube defects, such as spina bifida and anencephaly.[14-16]

Results from a previous NBDPS analysis and an analysis of data from the Slone Birth Defects Study suggest that folic acid may further attenuate the diabetes-associated risk for certain birth defects.[17,18] Unfortunately, women with diabetes are less likely to take folic acid supplements or to achieve recommended folic acid intake for neural tube defect prevention.[19]

Public policies can also promote birth defects prevention by lowering the barriers to accessible preconception and prenatal care. Data from the Pregnancy Risk Assessment Monitoring System indicate that in 2009 30% of US pregnant women changed health insurance coverage between the month before pregnancy and delivery.[20] Much of this change was attributable to women without coverage being covered by the time of delivery; almost 25% of pregnant women had no insurance prior to pregnancy, but by the time of delivery only 1.5% were uninsured. This decrease in the uninsured percentage was largely attributable to a dramatic increase in the percentage of women with Medicaid coverage, from 16.1% just before pregnancy to 43.9% at the time of delivery.

Pregnancy is often a qualifying event for Medicaid, but unfortunately, gaining access to medical care after pregnancy has already started severely limits the ability of women with diabetes to achieve good glycemic control prior to pregnancy. More recent data suggest that the Affordable Care Act’s dependent coverage provision has increased insurance coverage before and during pregnancy.[21]

## Strengths and limitations

Strengths of this analysis include the large sample size, which enabled us to assess associations with specific defect categories without the dilution of risk estimates that can occur when heterogeneous birth defects are grouped. Also, all cases were confirmed with

data from medical records, rather than relying only on diagnostic codes, and were classified by the study's clinical geneticists using standardized methods.[5,6]

Our analysis had several limitations. Diabetes exposure was based on maternal self-report during a computer-assisted telephone interview. However, a validation study of self-reported diabetes status in the Pregnancy Risk Assessment Monitoring System found high sensitivity and specificity for self-reported diabetes compared with medical record review (~91% and ~95%, respectively).[22] In addition, we were not able to analyze birth defect risk by the severity of diabetes because we did not have information on HbA1c levels or other indicators of glycemic control measured before or during early pregnancy. Therefore, our findings reflect an average risk among women with a mixture of different levels of glycemic control. For some defect categories, and particularly for pregestational diabetes, there were few exposed cases, leading to imprecise estimates.

To improve precision, we combined type 1 and type 2 diabetes into a single pregestational diabetes category. Although type 1 and type 2 diabetes are defined by different biological processes, the end result for each is alteration of glucose metabolism; however, the teratogenic mechanism behind the increase risk for birth defects is still unknown.[23] Analyses stratified by type of pregestational diabetes showed similar patterns of results for type 1 and type 2 diabetes (data not shown).

We tested many associations and some spurious statistically significant ORs would be expected by chance. However, for pregestational diabetes we observed statistically significant ORs for 46 of the 50 associations assessed (92%), which is unlikely to be explained by statistical fluctuation. In addition, all associations that were assessed are presented, regardless of their statistical significance. Residual confounding may explain some associations, such as the inverse association observed for gestational diabetes and gastroschisis.

### Conclusions

Maternal diabetes is a well-recognized risk factor for birth defects. Our study adds to the evidence of risk for many types of birth defects, both common and rare, and supports the urgency of improving preconception diabetes detection and care so that the considerable burden of maternal diabetes on women, their children, families, and society can be reduced.

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## AJOG at a Glance

**Why was this study conducted?**

Diabetes is associated with an increased risk for birth defects and is likely to have an increasing impact on birth defect prevalence because of the rise in diabetes in the United States in recent decades. We used data from the largest population-based birth defect case-control study in the United States to provide updated and more precise estimates of the association between diabetes and specific birth defects, including some defects not previously assessed.

**Key findings**

Pregestational diabetes was associated with strong, statistically significant odds ratios (range, 2.5–80.2) for 46 of 50 birth defects considered; for gestational diabetes, statistically significant odds ratios were fewer (12 of 56) and of smaller magnitude (range, 1.3–2.1; 0.5 for gastroschisis).

**What does this add to what is known?**

Pregestational diabetes is associated with a markedly increased risk for many specific births defects.

**TABLE 1**

Frequency distributions of maternal characteristics among controls, by diabetes status, National Birth Defects Prevention Study, 1997–2011

| | No diabetes | Pregestational diabetes[a] | | Gestational diabetes | |
|---|---|---|---|---|---|
| **Characteristic** | **n, %[b]** | **n, %[b]** | ***P* value[c]** | **n, %** | ***P* value[c]** |
| Total | 10,840 (94.7) | 71 (0.6) | | 536 (4.7) | |
| Body mass index, kg/m$^2$ | | | | | |
| <18.5 | 577 (5.5) | 1 (1.5) | < .0001 | 14 (2.8) | < .0001 |
| 18.5–24.9 | 5728 (55.1) | 20 (29.4) | | 173 (35.2) | |
| 25–29.9 | 2333 (22.4) | 14 (20.6) | | 136 (27.6) | |
| ≥30.0 | 1765 (17.0) | 33 (48.5) | | 169 (34.3) | |
| Maternal age, y | | | | | |
| <20 | 1127 (10.4) | 6 (8.5) | .0561 | 29 (5.4) | < .0001 |
| 20–24 | 2485 (22.9) | 12 (16.9) | | 91 (17.0) | |
| 25–29 | 3013 (27.8) | 20 (28.2) | | 140 (26.1) | |
| 30–34 | 2753 (25.4) | 15 (21.1) | | 167 (31.2) | |
| ≥35 | 1462 (13.5) | 18 (25.4) | | 109 (20.3) | |
| Maternal education | | | | | |
| Less than high school | 1723 (16.3) | 12 (17.1) | .1507 | 113 (21.4) | .0022 |
| High school | 2489 (23.5) | 23 (32.9) | | 132 (25.0) | |
| More than high school | 6362 (60.2) | 35 (50.0) | | 282 (53.5) | |
| Race/ethnicity | | | | | |
| Non-Hispanic white | 6376 (58.9) | 35 (49.3) | .2093 | 234 (43.7) | < .0001 |
| Non-Hispanic black | 1207 (11.1) | 10 (14.1) | | 59 (11.0) | |
| Hispanic | 2573 (23.8) | 18 (25.4) | | 196 (36.6) | |
| Other race/ethnicity | 678 (6.3) | 8 (11.3) | | 47 (8.8) | |
| Center | | | | | |
| Arkansas | 1358 (12.5) | 9 (12.7) | .4952 | 69 (12.9) | .0002 |
| California | 1145 (10.6) | 8 (11.3) | | 76 (14.2) | |
| Georgia | 1150 (10.6) | 7 (9.9) | | 65 (12.1) | |
| Iowa | 1183 (10.9) | 6 (8.5) | | 59 (11.0) | |

| Characteristic | No diabetes | Pregestational diabetes[a] | | Gestational diabetes | |
|---|---|---|---|---|---|
| | n, %[b] | n, %[b] | *P* value[c] | n, % | *P* value[c] |
| Massachusetts | 1318 (12.2) | 6 (8.5) | | 45 (8.4) | |
| New Jersey | 558 (5.1) | 0 (0) | | 13 (2.4) | |
| New York | 902 (8.3) | 9 (12.7) | | 42 (7.8) | |
| North Carolina | 913 (8.4) | 6 (8.5) | | 55 (10.3) | |
| Texas | 1258 (11.6) | 12 (16.9) | | 77 (14.4) | |
| Utah | 1055 (9.7) | 8 (11.3) | | 35 (6.5) | |
| Year of birth | | | | | |
| 1997–1999[d] | 1620 (14.9) | 11 (15.5) | .2114 | 66 (12.3) | .0017 |
| 2000–2001 | 1599 (14.8) | 7 (9.9) | | 64 (11.9) | |
| 2002–2003 | 1512 (13.9) | 6 (8.5) | | 53 (9.9) | |
| 2004–2005 | 1624 (15.0) | 15 (21.1) | | 96 (17.9) | |
| 2006–2007 | 1513 (14.0) | 11 (15.5) | | 96 (17.9) | |
| 2008–2009 | 1522 (14.0) | 15 (21.1) | | 85 (15.9) | |
| 2010–2011 | 1450 (13.4) | 6 (8.5) | | 76 (14.2) | |

[a] Type 1 or type 2 diabetes;

[b] Row percentages are presented for total controls; otherwise, column percentages are presented;

[c] *P* value is from a $\chi^2$ test;

[d] 1997 includes only October through December.

**TABLE 2**

Odds ratios and 95% confidence intervals for associations between diabetes and selected noncardiac birth defects, National Birth Defects Prevention Study, 1997–2011

| | | Pregestational diabetes | | Gestational diabetes | |
|---|---|---|---|---|---|
| **Birth defects** | **Total** | **n** | **OR (95% CI)[a]** | **n** | **OR (95% CI)[a]** |
| Anencephaly | 627 | 17 | 3.5 (1.9–6.4) | 22 | 0.7 (0.5–1.1) |
| Spina bifida | 1236 | 12 | 1.4 (0.8–2.7) | 62 | 0.9 (0.6–1.2) |
| Encephalocele | 221 | 8 | 5.4 (2.5–11.7) | 8 | 0.7 (0.3–1.4) |
| Holoprosencephaly | 163 | 15 | 13.1 (7.0–24.5) | 12 | 1.2 (0.6–2.4) |
| Hydrocephaly | 505 | 25 | 8.2 (5.0–13.5) | 27 | 1.4 (0.9–2.0) |
| Dandy-Walker malformation | 181 | 4 | *3.6 (1.3–10.1)* | 9 | 1.0 (0.5–2.1) |
| Anophthalmia/microphthalmia | 228 | 5 | 3.4 (1.3–8.6) | 12 | 1.1 (0.6–2.0) |
| Cataract | 351 | 3 | *1.4 (0.4–4.5)* | 19 | 1.3 (0.8–2.1) |
| Glaucoma/anterior chamber defect | 180 | 2 | NC | 8 | 1.0 (0.5–2.1) |
| Anotia/microtia | 662 | 27 | 5.8 (3.5–9.7) | 42 | 1.1 (0.7–1.5) |
| Choanal atresia | 159 | 6 | 6.9 (2.8–16.6) | 5 | 0.6 (0.2–1.7) |
| Cleft palate alone | 1570 | 42 | 4.3 (2.9–6.5) | 96 | 1.4 (1.1–1.8) |
| Cleft lip with or without cleft palate | 3046 | 58 | 3.0 (2.1–4.3) | 161 | 1.1 (0.9–1.3) |
| Small intestinal atresia/stenosis | 468 | 2 | NC | 28 | 1.1 (0.7–1.7) |
| Duodenal atresia / stenosis | 238 | 1 | NC | 16 | 1.6 (0.9–2.7) |
| Esophageal atresia / stenosis | 743 | 15 | 3.4 (1.9–6.1) | 31 | 1.0 (0.7–1.4) |
| Anorectal atresia / stenosis | 1,044 | 40 | 5.7 (3.8–8.7) | 58 | 1.1 (0.8–1.5) |
| Biliary atresia / stenosis | 197 | 6 | 5.0 (2.1–11.9) | 11 | 1.4 (0.7–2.6) |
| Hypospadias | 2,542 | 33 | 2.8 (1.7–4.8) | 141 | 1.4 (1.1–1.8) |
| Renal agenesis / hypoplasia | 180 | 11 | 8.1 (3.9–16.9) | 3 | *0.4 (0.1–1.1)* |
| Bladder exstrophy | 72 | 3 | *7.0 (2.2–22.9)* | 4 | *1.2 (0.5–3.4)* |
| Cloacal exstrophy | 97 | 0 | NC | 9 | 2.1 (1.0–4.4) |
| Longitudinal limb deficiency | 469 | 24 | 10.1 (6.2–16.5) | 19 | 0.9 (0.5–1.5) |
| Transverse limb deficiency | 703 | 10 | 2.6 (1.3–5.2) | 32 | 0.9 (0.6–1.4) |
| Craniosynostosis | 1,562 | 13 | 1.2 (0.6–2.3) | 99 | 1.3 (1.0–1.7) |
| Diaphragmatic hernia | 851 | 13 | 2.5 (1.3–4.6) | 36 | 0.9 (0.6–1.3) |

| Birth defects | Total | Pregestational diabetes | | Gestational diabetes | |
|---|---|---|---|---|---|
| | | n | OR (95% CI)[a] | n | OR (95% CI)[a] |
| Omphalocele | 431 | 8 | 2.6 (1.2–5.6) | 23 | 1.1 (0.7–1.8) |
| Gastroschisis | 1,429 | 4 | *0.4 (0.2–1.2)* | 21 | 0.5 (0.3–0.8) |
| Sacral agenesis | 104 | 33 | 80.2 (46.1–139.3) | 6 | 1.7 (0.6–4.8) |
| Amniotic band syndrome | 335 | 6 | 3.1 (1.3–7.4) | 14 | 1.2 (0.7–2.0) |

*CI*, confidence interval; *OR*, odds ratio; *NC*, not calculated.

[a]For defect categories with 5 or more exposed cases, ORs are adjusted for maternal body mass index, age, education, race/ethnicity, and study site; for defect categories with 3 or 4 exposed cases, crude odds ratios are presented in italics; odds ratios for defect categories with less than 3 exposed cases were not calculated.

**TABLE 3**

Odds ratios and 95% confidence intervals for associations between diabetes and selected cardiac defects, National Birth Defects Prevention Study, 1997–2011

| | | Pregestational diabetes | | Gestational diabetes | |
|---|---|---|---|---|---|
| **Birth defects** | **Total** | **Exposed** | **OR (95% CI)[a]** | **Exposed** | **OR (95% CI)[a]** |
| Heterotaxy with cardiac defects | 343 | 26 | 12.3 (7.3–20.5) | 10 | 0.7 (0.4–1.3) |
| Truncus arteriosus | 134 | 15 | 14.9 (7.6–29.3) | 5 | 0.9 (0.3–2.2) |
| Tetralogy of Fallot | 1181 | 40 | 5.3 (3.5–8.0) | 81 | 1.5 (1.1–1.9) |
| D-transposition of the great arteries | 753 | 16 | 3.0 (1.6–5.5) | 29 | 0.8 (0.5–1.2) |
| DORV with TGA | 189 | 12 | 7.8 (3.9–15.9) | 3 | *0.3 (0.1–1.1)* |
| DORV, other | 122 | 5 | 5.1 (1.8, 14.7) | 7 | 1.3 (0.6– 2.8) |
| Conoventricular septal defect | 143 | 7 | 8.2 (3.4– 20.0) | 7 | 0.9 (0.3– 2.1) |
| Atrioventricular septal defect | 359 | 20 | 10.5 (6.2–17.9) | 15 | 1.1 (0.6–1.8) |
| Total APVR | 291 | 7 | 4.0 (1.8–8.9) | 12 | 0.9 (0.5–1.6) |
| Partial APVR | 77 | 3 | *6.5 (2.0–21.3)* | 4 | *1.2 (0.4–3.2)* |
| Hypoplastic left heart syndrome | 640 | 13 | 2.9 (1.5–5.6) | 48 | 1.8 (1.3–2.4) |
| Coarctation of the aorta | 1,149 | 30 | 4.5 (2.8–7.1) | 72 | 1.3 (1.0–1.8) |
| Aortic stenosis | 500 | 14 | 4.5 (2.4–8.4) | 19 | 0.9 (0.5–1.4) |
| Pulmonary atresia | 255 | 7 | 3.5 (1.5–8.3) | 8 | 0.6 (0.3–1.2) |
| PVS | 1533 | 35 | 3.8 (2.5–5.9) | 109 | 1.5 (1.2–1.9) |
| Ebstein anomaly | 178 | 2 | NC | 5 | 0.5 (0.2–1.4) |
| Tricuspid atresia | 171 | 6 | 4.4 (1.7–11.5) | 5 | 0.7 (0.3–1.6) |
| Perimembranous VSD | 1651 | 51 | 5.1 (3.5–7.5) | 95 | 1.3 (1.0–1.7) |
| ASD secundum or NOS | 3009 | 126 | 6.7 (4.9–9.2) | 203 | 1.4 (1.2–1.7) |
| Single ventricle complex | 313 | 27 | 14.7 (8.9–24.3) | 14 | 1.1 (0.6–2.0) |
| Aortic stenosis and coarctation of the aorta | 121 | 3 | *4.2 (1.3–13.4)* | 8 | 1.5 (0.7–3.1) |
| Coarctation of the aorta and VSD | 301 | 8 | 5.6 (2.6–12.0) | 13 | 1.1 (0.6–1.9) |
| VSD and ASD | 747 | 34 | 6.9 (4.4–10.8) | 48 | 1.4 (1.0–1.9) |
| VSD and ASD and coarctation of the aorta | 93 | 2 | NC | 5 | 0.9 (0.3–3.1) |
| PVS and ASD | 258 | 9 | 4.6 (2.1–10.0) | 19 | 1.5 (0.9–2.4) |
| PVS and VSD | 147 | 7 | 9.3 (4.1–21.2) | 11 | 1.7 (0.9–3.3) |

*ASD*, atrial septal defect; *APVR*, anomalous pulmonary venous return; *CI*, confidence interval; *DORV*, double-outlet right ventricle; *NC*, not calculated; *NOS*, not otherwise specified; *OR*, odds ratio; *PVS*, pulmonary valve stenosis; *TGA*, transposition of the great arteries; *VSD*, ventricular septal defect.

[a]For defect categories with 5 or more exposed cases, ORs are adjusted for maternal body mass index, age, education, race/ethnicity, and study site; for defect categories with 3 or 4 exposed cases, crude odds ratios are presented in italics; odds ratios for defect categories with less than 3 exposed cases were not calculated.





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**TABLE 4**

Odds ratios and 95% confidence intervals for associations between diabetes and selected noncardiac birth defects, stratified by isolated and multiple status, National Birth Defects Prevention Study, 1997–2011

| | Total defects | | Pregestational (type 1 or type 2) diabetes | | | | Gestational diabetes | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Isolated defects | | Multiple defects | | Isolated defects | | Multiple defects | |
| Birth defect | Isolated | Multiple | n | OR (95% CI)[a] | n | OR (95% CI)[a] | n | OR (95% CI)[a] | n | OR (95% CI)[a] |
| Anencephaly | 563 | 64 | 14 | 3.5 (1.8–6.5) | 3 | *7.6 (2.3–24.9)* | 21 | 0.8 (0.5–1.2) | 1 | NC |
| Spina bifida | 1090 | 146 | 3 | *0.4 (0.1–1.4)* | 9 | 10.6 (5.0–22.6) | 56 | 0.9 (0.6–1.2) | 6 | 1.0 (0.4–2.3) |
| Encephalocele | 168 | 53 | 7 | 6.1 (2.7–13.8) | 1 | NC | 7 | 0.7 (0.3–1.7) | 1 | NC |
| Holoprosencephaly | 117 | 46 | 8 | 9.7 (4.3–21.6) | 7 | 25.4 (10.0–64.1) | 10 | 1.4 (0.6–3.0) | 2 | NC |
| Hydrocephaly | 350 | 154 | 12 | 6.2 (3.2–12.1) | 13 | 11.5 (5.8–22.5) | 18 | 1.3 (0.8–2.2) | 9 | 1.4 (0.8–2.3) |
| Dandy-Walker malformation | 111 | 70 | 3 | *4.5 (1.4–14.6)* | 1 | NC | 7 | 1.5 (0.7–3.4) | 2 | NC |
| Anophthalmia/ microphthalmia | 137 | 90 | 3 | *3.6 (1.1–11.7)* | 2 | NC | 8 | 1.1 (0.5–2.4) | 4 | *1.0 (0.4–2.6)* |
| Cataract | 310 | 40 | 3 | *1.6 (0.5–5.1)* | 0 | NC | 18 | 1.4 (0.8–2.3) | 1 | NC |
| Glaucoma/anterior chamber defect | 147 | 33 | 2 | NC | 0 | NC | 6 | 1.0 (0.4–2.3) | 2 | NC |
| Anotia/microtia | 463 | 199 | 7 | 2.0 (0.8–5.0) | 20 | 14.5 (8.1–25.8) | 29 | 1.1 (0.7–1.7) | 13 | 1.0 (0.5–2.0) |
| Choanal atresia | 83 | 75 | 2 | NC | 4 | *8.9 (3.1–24.9)* | 3 | *0.8 (0.2–2.5)* | 2 | NC |
| Cleft palate alone | 1264 | 306 | 19 | 2.5 (1.4–4.2) | 23 | 12.3 (7.3–20.7) | 79 | 1.4 (1.1–1.8) | 17 | 1.4 (0.9–2.4) |
| Cleft lip with or without cleft palate | 2684 | 362 | 37 | 2.2 (1.4–3.3) | 21 | 8.7 (5.0–15.0) | 143 | 1.1 (0.9–1.4) | 18 | 1.0 (0.6–1.7) |
| Small intestinal atresia/stenosis | 400 | 68 | 2 | NC | 0 | NC | 18 | 0.8 (0.4–1.3) | 10 | 3.7 (1.8–7.7) |
| Duodenal atresia/stenosis | 148 | 90 | 0 | NC | 1 | NC | 7 | 1.1 (0.5–2.4) | 9 | 2.4 (1.1–5.1) |
| Esophageal atresia/stenosis | 315 | 426 | 3 | *1.5 (0.5–5.0)* | 12 | 4.8 (2.5–9.1) | 17 | 1.2 (0.7–2.0) | 14 | 0.8 (0.5–1.4) |
| Anorectal atresia/stenosis | 452 | 565 | 13 | 4.5 (2.4–8.3) | 26 | 6.9 (4.2–11.3) | 30 | 1.3 (0.8–1.9) | 28 | 1.0 (0.6–1.5) |
| Biliary atresia/stenosis | 168 | 29 | 3 | *3.0 (0.9–9.5)* | 3 | *18.3 (5.4–62.1)* | 10 | 1.5 (0.8–2.8) | 1 | NC |
| Hypospadias | 2270 | 271 | 23 | 2.1 (1.2–3.8) | 10 | 7.1 (3.3–15.7) | 126 | 1.4 (1.1–1.8) | 15 | 1.3 (0.7–2.3) |
| Renal agenesis/hypoplasia | 128 | 47 | 9 | 11.4 (5.4–24.5) | 2 | NC | 1 | NC | 2 | NC |
| Bladder exstrophy | 55 | 15 | 2 | NC | 1 | NC | 2 | NC | 2 | NC |
| Cloacal exstrophy | 57 | 40 | 0 | NC | 0 | NC | 5 | 2.1 (0.7–6.1) | 4 | *2.2 (0.8–6.3)* |
| Longitudinal limb deficiency | 267 | 202 | 12 | 9.5 (5.0–18.2) | 12 | 11.3 (5.9–21.8) | 12 | 1.1 (0.6–2.0) | 7 | 0.7 (0.3–1.7) |
| Transverse limb deficiency | 591 | 111 | 8 | 2.5 (1.2–5.3) | 2 | NC | 27 | 1.0 (0.6–1.5) | 5 | 0.6 (0.2–2.0) |
| Craniosynostosis | 1416 | 145 | 7 | 0.7 (0.3–1.6) | 6 | 6.7 (2.6–17.4) | 90 | 1.3 (1.0–1.7) | 9 | 1.5 (0.7–3.0) |

| | Total defects | | Pregestational (type 1 or type 2) diabetes | | | | Gestational diabetes | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Isolated defects | | Multiple defects | | Isolated defects | | Multiple defects | |
| **Birth defect** | **Isolated** | **Multiple** | **n** | **OR (95% CI)[a]** | **n** | **OR (95% CI)[a]** | **n** | **OR (95% CI)[a]** | **n** | **OR (95% CI)[a]** |
| Diaphragmatic hernia | 647 | 194 | 7 | 1.7 (0.7–4.0) | 6 | 4.5 (1.9–10.8) | 29 | 1.0 (0.7–1.6) | 7 | 0.7 (0.3–1.5) |
| Omphalocele | 252 | 179 | 2 | NC | 6 | 4.8 (2.0–11.6) | 13 | 1.1 (0.6–2.0) | 10 | 1.2 (0.6–2.2) |
| Gastroschisis | 1298 | 131 | 4 | *0.5 (0.2–1.3)* | 0 | NC | 20 | 0.5 (0.3–0.9) | 1 | NC |
| Sacral agenesis | 12 | 87 | 8 | 807.1 (110.7–5884.0) | 24 | 67.8 (37.0–124.2) | 2 | NC | 4 | *1.4 (0.5–3.8)* |
| Amniotic band syndrome | 282 | 53 | 4 | *2.3 (0.8–6.3)* | 2 | NC | 10 | 1.0 (0.5–1.9) | 4 | *1.7 (0.6–4.8)* |

*CI*, confidence interval; *NC*, not calculated; *OR*, odds ratio.

[a]For defect categories with 5 or more exposed cases, ORs are adjusted for maternal body mass index, age, education, race/ethnicity, and study site; for defect categories with 3 or 4 exposed cases, crude odds ratios are presented in italics; odds ratios for defect categories with less than 3 exposed cases were not calculated.

## TABLE 5

Odds ratios and 95% confidence intervals for associations between diabetes and selected cardiac birth defects, stratified by isolated and multiple status, National Birth Defects Prevention Study, 1997–2011

| | Total defects | | Pregestational (type 1 or type 2) diabetes | | | | Gestational diabetes | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Isolated defects | | Multiple defects | | Isolated defects | | Multiple defects | |
| **Birth defect** | **Isolated** | **Multiple** | **n** | **OR (95% CI)[a]** | **n** | **OR (95% CI)[a]** | **n** | **OR (95% CI)[a]** | **n** | **OR (95% CI)[a]** |
| Heterotaxy with CHD | 34 | 309 | 1 | NC | 25 | 12.7 (7.5–21.4) | 1 | NC | 9 | 0.7 (0.4–1.4) |
| Truncus arteriosus | 89 | 24 | 9 | 12.5 (5.3–29.8) | 5 | 40.8 (12.8–130.7) | 4 | *1.1 (0.4–2.9)* | 1 | N/A |
| Tetralogy of Fallot | 937 | 217 | 26 | 4.4 (2.7–7.1) | 11 | 8.0 (3.9–16.3) | 66 | 1.5 (1.1–1.9) | 15 | 1.6 (0.9–2.7) |
| D-transposition of the great arteries | 557 | 42 | 10 | 2.5 (1.2–5.3) | 2 | NC | 21 | 0.8 (0.5–1.2) | 3 | *1.6 (0.5–5.3)* |
| DORV, other (no TGA) | 31 | 15 | 2 | NC | 2 | NC | 4 | *3.2 (1.1–9.3)* | 0 | NC |
| Conoventricular septal defect | 54 | 11 | 2 | NC | 2 | NC | 3 | *1.2 (0.4–4.0)* | 1 | NC |
| Atrioventricular septal defect | 167 | 36 | 6 | 6.8 (2.8–16.3) | 3 | 13.8 (4.2–46.3) | 7 | 1.2 (0.6–2.6) | 0 | NC |
| Total APVR | 246 | 18 | 6 | 4.0 (1.7–9.6) | 0 | NC | 10 | 0.9 (0.4–1.7) | 1 | NC |
| Partial APVR | 43 | 11 | 1 | NC | 1 | NC | 4 | *2.1 (0.8–6.0)* | 0 | NC |
| Hypoplastic left heart syndrome | 569 | 55 | 12 | 3.0 (1.5–5.9) | 1 | NC | 43 | 1.8 (1.3–2.5) | 5 | 2.2 (0.9–5.8) |
| Coarctation of the aorta | 552 | 69 | 14 | 3.8 (2.0–7.2) | 3 | *7.4 (2.3–24.1)* | 42 | 1.5 (1.1–2.2) | 4 | *1.3 (0.5–3.6)* |
| Aortic stenosis | 332 | 21 | 8 | 3.8 (1.7–8.5) | 1 | NC | 10 | 0.7 (0.4–1.4) | 1 | NC |
| Pulmonary atresia | 160 | 12 | 3 | *3.0 (0.9–9.6)* | 3 | *65.4 (16.6–258.1)* | 4 | *0.5 (0.2–1.4)* | 2 | NC |
| PVS | 1029 | 59 | 17 | 2.8 (1.6–4.8) | 2 | NC | 73 | 1.5 (1.2–2.0) | 5 | 2.1 (0.8–5.3) |
| Tricuspid atresia | 67 | 12 | 1 | NC | 0 | NC | 4 | *1.3 (0.5–3.6)* | 0 | NC |
| Perimembranous VSD | 897 | 126 | 18 | 3.1 (1.7–5.4) | 9 | 9.3 (4.2–20.8) | 52 | 1.3 (1.0–1.8) | 6 | 1.0 (0.4–2.4) |
| ASD secundum or NOS | 1517 | 347 | 61 | 6.3 (4.3–9.3) | 17 | 8.4 (4.8–14.9) | 112 | 1.6 (1.3–2.1) | 19 | 1.2 (0.7–2.0) |
| Single ventricle complex | 252 | 61 | 22 | 16.2 (9.5–27.7) | 5 | 10.9 (3.6–33.3) | 11 | 1.2 (0.6–2.2) | 3 | *1.1 (0.4–3.7)* |
| Aortic stenosis and coarctation of the aorta | 88 | 10 | 1 | NC | 0 | NC | 4 | *1.0 (0.4–2.7)* | 3 | *8.7 (2.2–33.6)* |
| Coarctation of the aorta and VSD | 245 | 53 | 5 | 4.2 (1.6–10.6) | 3 | *9.7 (3.0–32.0)* | 10 | 1.0 (0.5–2.0) | 3 | *1.3 (0.4–42)* |
| VSD and ASD | 586 | 161 | 22 | 6.3 (3.7–10.5) | 12 | 9.6 (4.7–19.8) | 41 | 1.6 (1.1–2.2) | 7 | 0.9 (0.4–2.0) |
| VSD and ASD and coarctation of the aorta | 75 | 18 | 1 | NC | 1 | NC | 4 | *1.2 (0.4–3.2)* | 1 | NC |
| PVS and ASD | 225 | 33 | 7 | 4.7 (2.1–10.6) | 2 | NC | 14 | 1.2 (0.7–2.2) | 5 | 3.1 (1.1–8.7) |
| PVS and VSD | 123 | 24 | 5 | 8.5 (3.2–22.1) | 2 | NC | 9 | 1.7 (0.8–3.5) | 2 | NC |

*ASD*, atrial septal defect; *APVR*, anomalous pulmonary venous return; *CI*, confidence interval; *DORV*, double-outlet right ventricle; *NC*, not calculated; *NOS*, not otherwise specified; *OR*, odds ratio; *PVS*, pulmonary valve stenosis; *TGA*, transposition of the great arteries; *VSD*, ventricular septal defect.

[a]For defect categories with 5 or more exposed cases, ORs are adjusted for maternal body mass index, age, education, race/ethnicity, and study site; for defect categories with 3 or 4 exposed cases, crude odds ratios are presented in italics; odds ratios for defect categories with less than 3 exposed cases were not calculated.





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