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Modification of the association between diabetes and birth defects by obesity, National Birth Defects Prevention Study, 1997–2011

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Abstract

Background: Maternal pregestational diabetes and obesity are risk factors for birth defects. Diabetes and obesity often occur together; it is unclear whether their co-occurrence compounds birth defect risk.

Methods: We analyzed 1997–2011 data on 29,671 cases and 10,963 controls from the National Birth Defects Prevention Study, a multisite case-control study. Mothers self-reported height, pregestational weight, and diabetes (pregestational and gestational; analyzed separately). We created four exposure groups: no obesity or diabetes (referent), obesity only, diabetes only, and both obesity and diabetes. We estimated odds ratios (ORs) using logistic regression and the relative excess risk due to interaction (RERI).

Results: Among mothers with pregestational obesity without diabetes, modest associations (OR range: 1.1–1.5) were observed for neural tube defects, small intestinal atresia, anorectal atresia, renal agenesis/hypoplasia, omphalocele, and several congenital heart defects. Pregestational diabetes, regardless of obesity, was strongly associated with most birth defects (OR range: 2.0–

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75.9). Gestational diabetes and obesity had a stronger association than for obesity alone and the RERI (in parentheses) suggested additive interaction for hydrocephaly (1.2; 95% confidence interval [CI]: −0.1, 2.5), tetralogy of Fallot (0.9; 95% CI: −0.01, 1.8), atrioventricular septal defect (1.1; 95% CI: −0.1, 2.3), hypoplastic left heart syndrome (1.1; 95% CI: −0.2, 2.4), and atrial septal defect secundum or not otherwise specified (1.0; 95% CI: 0.3, 1.6; only statistically significant RERI).

Conclusions: Our results do not support a synergistic relationship between obesity and diabetes for most birth defects examined. However, there are opportunities for prevention by reducing obesity and improving glycemic control among women with pregestational diabetes before conception.

Keywords

birth defect; gestational diabetes; obesity; pregestational diabetes; Type 1 diabetes; Type 2 diabetes

1 | INTRODUCTION

Maternal pregestational diabetes is a strong risk factor for several specific birth defects (Simeone et al., 2015; Tinker et al., 2020). Maternal pregestational obesity is independently associated with risk for certain birth defects, including neural tube defects, orofacial clefts, and certain heart defects (Stothard, Tennant, Bell, & Rankin, 2009). Gestational diabetes is diagnosed in pregnancy and typically develops after most birth defects have occurred, yet some associations between gestational diabetes and birth defects have been reported, which may be related to undiagnosed pregestational diabetes, particularly among women who have obesity (Parnell, Correa, & Reece, 2017).

It is important to understand these relationships because the prevalences of diabetes and obesity are increasing in the United States. Between 2000 and 2010 the prevalence of maternal pregestational diabetes among U.S. deliveries increased by almost 40% (Bardenheier, Imperatore, Devlin, et al., 2015), from 0.65 to 0.89 per 100 deliveries, and the prevalence of gestational diabetes increased by over 50%, from 3.71 to 5.77 per 100 deliveries (Bardenheier, Imperatore, Gilboa, et al., 2015). More recent data show that the prevalence of pregestational diabetes was stable from 2012 to 2016; however, the prevalence of gestational diabetes has continued to increase (Deputy, Kim, et al., 2018). Data from the Pregnancy Risk Assessment Monitoring System showed an increase in the prevalence of maternal pregestational obesity among U.S. live births from 17.6% in 2003 to 20.5% in 2009 (Fisher, Kim, Sharma, Rochat, & Morrow, 2013). National Vital Statistics System data show that the prevalence of maternal pregestational obesity among live births increased eight percentage points between 2011 and 2015 (Deputy, Dub et al., 2018).

Although Type 2 diabetes and obesity are related conditions, it is not clear to what extent the co-occurrence of diabetes and obesity in pregnancy compounds birth defect risk. In an analysis of 1997–2003 data from the National Birth Defects Prevention Study (NBDPS), Correa et al. (2008) reported an increased risk for birth defects among women with gestational diabetes only among those who were overweight or had obesity. However, due to limited sample size this analysis was only able to assess the risk for heart defects and

all other birth defects combined, rather than for specific defect types. The objective of our analysis was to analyze updated NBDPS data incorporating deliveries through 2011 to assess additive interaction between obesity and diabetes on the risk for specific birth defects.

2 | METHODS

NBDPS is a multisite case–control study of selected major structural birth defects among deliveries from October 1, 1997 to December 31, 2011 (Reefhuis et al., 2015). NBDPS cases include live births, fetal deaths, and pregnancy terminations, although not all pregnancy outcomes were ascertained by all sites throughout the study period. Cases with known chromosomal anomalies or single-gene disorders were excluded. Controls were liveborn infants without birth defects delivered in the same time period and from the same catchment area as the cases. Mothers of case and control infants were administered a computer-assisted telephone interview asking about demographics, medical conditions, and selected exposures before and during pregnancy.

We defined pregestational diabetes as maternal report of a physician diagnosis of Type 1 or Type 2 diabetes prior to the index pregnancy and gestational diabetes as maternal report of a physician diagnosis of gestational diabetes during the index pregnancy. The referent group for maternal diabetes was defined as mothers who self-reported never receiving a physician diagnosis of diabetes before, during, or after the index pregnancy. We excluded from the analysis mothers who were missing information on whether they had diabetes ($n = 255$) or who reported diabetes but were missing information on the type of diabetes or the date of diagnosis ($n = 368$). We excluded mothers who reported gestational diabetes in a previous pregnancy ($n = 861$) because the questionnaire only captured a mother's first diabetes diagnosis and we therefore lacked information on whether these mothers were diagnosed with nongestational diabetes later. We additionally excluded mothers who reported diagnosis of Type 1 or Type 2 diabetes during the index pregnancy ($n = 42$) or diabetes diagnosed after the index pregnancy ($n = 49$).

We calculated body mass index (BMI) as kilograms per meters squared using maternal self-report of height and weight before their index pregnancy. We defined obesity as BMI ≥30 (National Heart Lung and Blood Institute, 2000). Mothers missing information on height or weight were excluded from the analysis ($n = 2,084$).

We created six mutually exclusive groups based on obesity status and diabetes status: (1) mothers who had neither diabetes nor obesity; (2) mothers who had obesity, but not diabetes; (3) mothers who had pregestational diabetes but not obesity; (4) mothers who had pregestational diabetes and obesity; (5) mothers who had gestational diabetes but not obesity; and (6) mothers who had gestational diabetes and obesity. We conducted all analyses separately for pregestational diabetes and gestational diabetes; mothers with gestational diabetes were excluded from the analyses in which pregestational diabetes was considered, and mothers with pregestational diabetes were excluded from the analyses in which gestational diabetes was considered. We used logistic regression to assess the crude association between the exposure groups and specific defects, with mothers who had neither diabetes (pregestational or gestational) nor obesity as the referent group. To assess

potential effect modification on an additive scale, we estimated the relative excess risk due to interaction (RERI) with likelihood-based 95% confidence intervals (CI). An RERI of 0 indicates no excess risk due to interaction, and a lower 95% CI greater than 0 is consistent with a statistically significant result (VanderWeele & Knol, 2014). Interaction on an additive scale allows for assessment of subgroups that are more likely to benefit from intervention (VanderWeele & Knol, 2014). Because specific birth defect outcomes are rare, the OR approximates the risk ratio, and therefore use of the OR in the RERI formula is appropriate. We limited analyses to defects for which there were at least three cases in each exposure stratum; this resulted in 38 defect categories for pregestational diabetes and 39 categories for gestational diabetes.

All participating study sites had Institutional Review Board approval to conduct study activities and all participants provided informed consent. Research data are not shared.

3 | RESULTS

We included data from 29,671 cases and 10,963 controls in our analysis (Table 1). Pregestational diabetes was much more common among case mothers (2.5%) than control mothers (0.6%), although it was still relatively rare in both groups. Gestational diabetes was more common than pregestational diabetes, and although it was more prevalent among cases (5.2%) than controls (4.5%), the difference was not as pronounced as for pregestational diabetes. The prevalence of pregestational obesity was 20.0% among mothers of cases and 17.9% among mothers of controls. The joint exposure of pregestational diabetes and obesity was rare in our data, but almost five times higher in case mothers (1.4%) compared to control mothers (0.3%). We also observed a higher prevalence of the joint exposure of gestational diabetes and obesity for case mothers (2.2%) compared to control mothers (1.5%), but the relative difference was not as pronounced as for the joint exposure with pregestational diabetes.

We observed modest associations for obesity without diabetes with several defects (Tables 2 and 3); statistically significant associations were observed for anencephaly (OR: 1.3; 95% CI: 1.0, 1.6), spina bifida (OR: 1.6; 95% CI: 1.3, 1.8), encephalocele (OR: 1.4; 95% CI: 1.0, 2.0), cleft lip with or without cleft palate (OR: 1.1; 95% CI: 1.0, 1.2), small intestinal atresia (OR: 1.2; 95% CI: 1.0, 1.6), anorectal atresia (OR: 1.3; 95% CI: 1.1, 1.6), renal agenesis or hypoplasia (OR: 1.5; 95% CI: 1.0, 2.2), omphalocele (OR: 1.4; 95% CI: 1.1, 1.7), aortic stenosis (OR: 1.2; 95% CI: 1.0, 1.6), pulmonary valve stenosis (PVS) (OR: 1.3; 95% CI: 1.1, 1.5), tricuspid atresia (OR: 1.5; 95% CI: 1.0, 2.2), atrial septal defect (ASD) secundum or not otherwise specified (OR: 1.1; 95% CI: 1.0, 1.3), and the combination of ASD and PVS (OR: 1.4; 95% CI: 1.0, 1.9).

Pregestational diabetes, with or without obesity, was strongly associated with most birth defect categories (Table 2; OR range: 2.0–75.9), although for spina bifida we observed an elevated OR only among women with both pregestational diabetes and obesity (OR: 2.9; 95% CI: 1.4, 6.0). For most birth defect categories, the RERI for pregestational diabetes and obesity was not meaningfully elevated, with the exception of holoprosencephaly (RERI: 18.3; 95% CI: −3.7, 40.2), heterotaxia with CHDs (RERI: 10.2; 95% CI: −2.4, 22.8), and

double outlet right ventricle with transposition of the great arteries (RERI: 12.3, 95% CI: −2.9, 27.5), although none reached statistical significance.

Among 39 defects assessed, we observed seven statistically significant associations for maternal gestational diabetes among mothers without obesity (Table 3), for cleft palate alone (OR: 1.4; 95% CI: 1.1, 1.9), duodenal atresia/stenosis (OR: 1.9; 95% CI: 1.0, 3.4), craniosynostosis (OR: 1.4; 95% CI: 1.0, 1.8), coarctation of the aorta (OR: 1.3; 95% CI: 1.0, 1.9), PVS (OR: 1.5; 95% CI: 1.1, 2.0), ASD secundum (OR: 1.3; 95% CI: 1.0, 1.6), and the combination of PVS and VSD (OR: 2.1; 95% CI: 1.0, 4.3). For some defects the joint exposure of gestational diabetes and obesity had a stronger association than for obesity alone or for gestational diabetes alone. The RERI was suggestive of additive interaction for gestational diabetes and obesity for hydrocephaly (RERI: 1.2; 95% CI: −0.1, 2.5), tetralogy of Fallot (RERI: 0.9; 95% CI: −0.01, 1.8), atrioventricular septal defect (RERI: 1.1; 95% CI: −0.1, 2.3), hypoplastic left heart syndrome (RERI: 1.1; 95% CI: −0.2, 2.4), and ASD secundum or not otherwise specified (RERI: 1.0; 95% CI: 0.3, 1.6); only the RERI for ASD secundum or not otherwise specified was statistically significant.

4 | CONCLUSIONS

It is important to understand the relationships between diabetes, obesity, and risk for birth defects because obesity is common and the prevalences of both diabetes and obesity are increasing. In addition, there are opportunities for prevention of birth defects by reducing obesity and improving glycemic control among women with pregestational diabetes prior to conception. Our results do not support a synergistic (i.e., greater than additive) relationship between obesity and pregestational diabetes for the majority of birth defects examined.

Gestational diabetes develops in pregnancy after most birth defects have occurred; one potential explanation for associations observed between gestational diabetes and birth defects is that the mother had undiagnosed diabetes before her pregnancy, which is diagnosed for the first time in pregnancy and labeled as gestational diabetes. Results from a cohort study from Barcelona, Spain support this hypothesis; their data showed that pregnant women with gestational diabetes that was diagnosed early in pregnancy had a higher risk for delivering an infant with a birth defect compared to women diagnosed with gestational diabetes later in pregnancy (Garcia-Patterson et al., 2004). Obesity is a risk factor for Type 2 diabetes, and we hypothesized that in the gestational diabetes analyses, we would see the strongest associations among women who had both pregestational obesity and gestational diabetes because there would be a higher likelihood that their diabetes was present before pregnancy. In our analysis, the associations for the joint exposure of gestational diabetes and obesity tended to be stronger than for obesity alone, supporting our hypothesis. However, this pattern was not seen for all defects that demonstrated strong associations with pregestational diabetes, and associations with a few defects were observed for women with gestational diabetes without obesity, which is inconsistent with our hypothesis.

While previous studies have assessed the joint association of diabetes and obesity with birth defects, few have been able to focus on specific birth defect categories. Data from the Spanish cohort noted above showed an increased association for renal/urinary tract

birth defects among mothers with gestational diabetes who were in the highest tertile of pregestational BMI (OR: 5.2, 95% CI: 1.2, 23.7), compared to mothers with gestational diabetes in the lowest tertile (Garcia-Patterson et al., 2004), which is consistent with our observed results for hypospadias. A previous analysis of 1997–2004 data from NBDPS also identified additive interaction between gestational diabetes and maternal pregestational obesity for tetralogy of Fallot (RERI 1.7; 95% CI: 0.02, 2.1) (Gilboa et al., 2010), although the results from our analysis of the full dataset through 2011 were attenuated for this defect (RERI: 0.9; 95% CI: −0.01, 1.8). Results for spina bifida from an analysis of data limited to the Texas NBDPS site focused on central nervous system birth defects were consistent with results from our analysis for spina bifida (Anderson et al., 2005). They reported elevated ORs for mothers with obesity, among those with and without gestational diabetes (ORs: 4.5; 95% CI: 1.5, 13 and 2.6; 95% CI: 1.6, 4.3, respectively). Associations for mothers with obesity among both those with and without gestational diabetes for anencephaly and hydrocephaly were also observed in their analysis; in our data an increased risk for anencephaly was only observed for mothers with obesity without gestational diabetes, and an increased risk for hydrocephaly was only seen for mothers with both gestational diabetes and obesity.

Our results should be interpreted within the context of the study's potential weaknesses. We relied on self-reported information to assign diabetes and obesity exposures. Self-reported height and/or weight information was missing for 4.9% of participants. We conducted several sensitivity analyses under different extreme scenarios (e.g., all case mothers with diabetes that were missing BMI coded as having obesity and all other mothers with missing BMI coded as not having obesity); under all scenarios, the impact on stratum-specific ORs and RERI estimates was minimal (data not shown) and did not impact our interpretation of the results from the primary analysis. Another limitation of the analysis was lack of information on glycemic control during pregnancy among women who reported having pregestational diabetes. We estimated many associations and some statistically significant results may be due to chance. The sample sizes in some strata were small, resulting in imprecise estimates, particularly for the RERI. Small sample size also precluded adjustment for potential confounders, and therefore uncontrolled confounding is another potential limitation of the analysis. Although participation among cases (67%) and controls (65%) (Reefhuis et al., 2015) was relatively high for this type of study, if women who chose to participate differed from those who did not in the distribution of case status, diabetes, and/or BMI, then selection bias could have impacted results. However, the NBDPS is the largest population-based case-control study of birth defects in the United States, and we were able to examine many individual birth defects, which was not done in most previous analyses (Correa et al., 2008; Garcia-Patterson et al., 2004; Moore, Singer, Bradlee, Rothman, & Milunsky, 2000). This larger sample size also allowed us to consider pregestational and gestational diabetes separately.

While it is important to continue to try to understand their complex joint relationship, diabetes and obesity are established risk factors for birth defects, both of which present opportunities for prevention. The American College of Obstetricians and Gynecologists recommends that women who have Type 1 or Type 2 diabetes reach normal glucose levels before and during pregnancy (American College of Obstetricians and Gynecologists,

2018) and that women with obesity lose weight to the extent possible prior to conception (American College of Obstetricians and Gynecologists, 2015). However, both glycemic control and weight loss are challenging and take time, underscoring the additional importance of access to and utilization of care and pregnancy counseling for women with these conditions.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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TABLE 1

Prevalence of obesity and diabetes among mothers of case and control infants, National Birth Defects Prevention Study, 1997–2011

Characteristic	Case infants *N* (%)	Control infants *N* (%)
Total	29,671	10,963
Maternal diabetes		
Pregestational[a]	743 (2.5)	68 (0.6)
Gestational[b]	1,557 (5.2)	492 (4.5)
None[c]	27,371 (92.2)	10,403 (94.9)
Maternal pregestational obesity[d]		
Yes	5,934 (20.0)	1,967 (17.9)
No	23,737 (80.0)	8,996 (82.1)
Joint exposure		
Obesity+/pregestational diabetes +	403 (1.4)	33 (0.3)
Obesity+/gestational diabetes+	658 (2.2)	169 (1.5)
Obesity+/diabetes−	4,873 (16.4)	1,765 (16.1)
Obesity−/pregestational diabetes+	340 (1.1)	35 (0.3)
Obesity−/ gestational diabetes+	899 (3.0)	323 (2.9)
Obesity−/diabetes−	22,498 (75.8)	8,638 (78.8)

[a]Defined as self-report of diagnosis of Type 1 or Type 2 diabetes before the beginning of the index pregnancy.

[b]Defined as self-report of diagnosis of gestational diabetes during the index pregnancy.

[c]Women who reported never having been diagnosed with Type 1, Type 2, or gestational diabetes before, during, or after the index pregnancy.

[d]Defined as body mass index (kg/m^2) ≥30, based on self-reported pregestational weight and height without shoes.

TABLE 2

Counts and OR for the individual and joint associations of maternal pregestational diabetes and obesity and risk for selected birth defects, National Birth Defects Prevention Study, 1997–2011

Defect category	Pregestational diabetes[a]	Obesity[b]	*N*	OR (95% CI)	RERI[c] (95% CI)
Controls	No	No	8,638	N/A	N/A
	No	Yes	1,765		
	Yes	No	35		
	Yes	Yes	33		
Anencephaly	No	No	443	1.0 (reference)	−1.2 (−5.8, 3.4)
	No	Yes	115	1.3 (1.0, 1.6)	
	Yes	No	8	4.5 (2.1, 9.7)	
	Yes	Yes	6	3.5 (1.5, 8.5)	
Spina bifida	No	No	826	1.0 (reference)	1.4 (−1.0, 3.8)
	No	Yes	263	1.6 (1.3, 1.8)	
	Yes	No	3	0.9 (0.3, 2.9)	
	Yes	Yes	9	2.9 (1.4, 6.0)	
Encephalocele	No	No	149	1.0 (reference)	−0.01 (−10.0, 10.0)
	No	Yes	43	1.4 (1.0, 2.0)	
	Yes	No	4	6.6 (2.3, 18.9)	
	Yes	Yes	4	7.0 (2.5, 20.1)	
Holoprosencephaly	No	No	102	1.0 (reference)	18.3 (−3.7, 40.2)
	No	Yes	27	1.3 (0.8, 2.0)	
	Yes	No	4	9.7 (3.4, 27.7)	
	Yes	Yes	11	28.2 (13.9, 57.4)	
Hydrocephaly	No	No	355	1.0 (reference)	−3.1 (−10.9, 4.6)
	No	Yes	76	1.0 (0.8, 1.3)	
	Yes	No	14	9.7 (5.2, 18.3)	
	Yes	Yes	9	6.6 (3.2, 14.0)	
Anotia/microtia	No	No	434	1.0 (reference)	−0.3 (−7.0, 6.4)
	No	Yes	102	1.2 (0.9, 1.4)	
	Yes	No	13	7.4 (3.9, 14.1)	

Defect category	Pregestational diabetes[a]	Obesity[b]	*N*	OR (95% CI)	RERI[c] (95% CI)
	Yes	Yes	12	7.2 (3.7, 14.1)	
Choanal atresia	No	No	120	1.0 (reference)	0.5 (−10.1, 11.1)
	No	Yes	22	0.9 (0.6, 1.4)	
	Yes	No	3	6.2 (1.9, 20.3)	
	Yes	Yes	3	6.5 (2.0, 21.6)	
Cleft palate alone	No	No	1,149	1.0 (reference)	−0.4 (−3.9, 3.1)
	No	Yes	233	1.0 (0.9, 1.2)	
	Yes	No	22	4.7 (2.7, 8.0)	
	Yes	Yes	19	4.3 (2.4, 7.5)	
Cleft lip with or without cleft palate	No	No	2,210	1.0 (reference)	0.9 (−1.3, 3.2)
	No	Yes	483	1.1 (1.0, 1.2)	
	Yes	No	24	2.6 (1.6, 4.5)	
	Yes	Yes	31	3.6 (2.2, 5.9)	
Anorectal atresia/stenosis	No	No	705	1.0 (reference)	3.3 (−2.2, 8.8)
	No	Yes	190	1.3 (1.1, 1.6)	
	Yes	No	14	4.9 (2.6, 9.2)	
	Yes	Yes	23	8.5 (5.0, 14.6)	
Biliary atresia/stenosis	No	No	134	1.0 (reference)	0.1 (−9.5, 9.6)
	No	Yes	35	1.3 (0.9, 1.9)	
	Yes	No	3	5.5 (1.7, 18.2)	
	Yes	Yes	3	5.9 (1.8, 19.3)	
Hypospadias	No	No	1,923	1.0 (reference)	0.5 (−1.7, 2.8)
	No	Yes	398	1.0 (0.9, 1.2)	
	Yes	No	14	2.0 (1.0, 4.1)	
	Yes	Yes	18	2.6 (1.3, 5.1)	
Renal agenesis/hypoplasia	No	No	118	1.0 (reference)	−2.1 (−15.5, 11.4)
	No	Yes	36	1.5 (1.0, 2.2)	
	Yes	No	5	10.5 (4.0, 27.2)	
	Yes	Yes	4	8.9 (3.1, 25.4)	
Longitudinal limb deficiency	No	No	341	1.0 (reference)	−5.4 (−13.8, 2.9)
	No	Yes	68	1.0 (0.7, 1.3)	

Defect category	Pregestational diabetes[a]	Obesity[b]	N	OR (95% CI)	RERI[c] (95% CI)
	Yes	No	16	11.6 (6.3, 21.1)	
	Yes	Yes	8	6.1 (2.8, 13.4)	
Transverse limb deficiency	No	No	520	1.0 (reference)	−0.8 (−4.1, 2.4)
	No	Yes	106	1.0 (0.8, 1.2)	
	Yes	No	6	2.8 (1.2, 6.8)	
	Yes	Yes	4	2.0 (0.7, 5.7)	
Craniosynostosis	No	No	1,164	1.0 (reference)	0.4 (−1.2, 2.1)
	No	Yes	254	1.1 (0.9, 1.2)	
	Yes	No	5	1.1 (0.4, 2.7)	
	Yes	Yes	7	1.6 (0.7, 3.6)	
Diaphragmatic hernia	No	No	622	1.0 (reference)	−1.2 (−4.3, 2.0)
	No	Yes	140	1.1 (0.9, 1.3)	
	Yes	No	8	3.2 (1.5, 6.9)	
	Yes	Yes	5	2.1 (0.8, 5.4)	
Omphalocele	No	No	299	1.0 (reference)	−0.2 (−5.2, 4.8)
	No	Yes	83	1.4 (1.1, 1.7)	
	Yes	No	4	3.3 (1.2, 9.5)	
	Yes	Yes	4	3.5 (1.2, 9.9)	
Sacral agenesis	No	No	52	1.0 (reference)	−0.3 (−64.6, 64.1)
	No	Yes	9	0.8 (0.4, 1.7)	
	Yes	No	16	75.9 (39.6, 145.6)	
	Yes	Yes	15	75.5 (38.7, 147.3)	
Amniotic band syndrome	No	No	249	1.0 (reference)	0.2 (−4.9, 5.3)
	No	Yes	50	1.0 (0.7, 1.3)	
	Yes	No	3	3.0 (0.9, 9.7)	
	Yes	Yes	3	3.2 (1.0, 10.4)	
Heterotaxy with cardiac defects	No	No	240	1.0 (reference)	10.2 (−2.4, 22.8)
	No	Yes	53	1.1 (0.8, 1.5)	
	Yes	No	8	8.2 (3.8, 17.9)	
	Yes	Yes	17	18.5 (10.2, 33.8)	
Truncus arteriosus	No	No	87	1.0 (reference)	3.8 (−18.8, 26.5)

Defect category	Pregestational diabetes[a]	Obesity[b]	*N*	OR (95% CI)	RERI[c] (95% CI)
	No	Yes	22	1.2 (0.8, 2.0)	
	Yes	No	6	17.0 (7.0, 41.5)	
	Yes	Yes	7	21.1 (9.1, 48.9)	
Tetralogy of Fallot	No	No	838	1.0 (reference)	4.5 (−0.3, 9.3)
	No	Yes	184	1.1 (0.9, 1.3)	
	Yes	No	12	3.5 (1.8, 6.8)	
	Yes	Yes	26	8.1 (4.8, 13.6)	
D-transposition of the great arteries (TGA)	No	No	574	1.0 (reference)	−2.0 (−5.4, 1.4)
	No	Yes	112	1.0 (0.8, 1.2)	
	Yes	No	9	3.9 (1.9, 8.1)	
	Yes	Yes	4	1.8 (0.6, 5.2)	
Double-outlet right ventricle with TGA	No	No	129	1.0 (reference)	12.3 (−2.9, 27.5)
	No	Yes	33	1.3 (0.9, 1.8)	
	Yes	No	3	5.7 (1.7, 18.9)	
	Yes	Yes	9	18.3 (8.6, 38.9)	
Atrioventricular septal defect	No	No	274	1.0 (reference)	6.3 (−3.2, 15.8)
	No	Yes	45	0.8 (0.6, 1.1)	
	Yes	No	7	6.3 (2.8, 14.3)	
	Yes	Yes	13	12.4 (6.5, 23.9)	
Hypoplastic left heart syndrome	No	No	458	1.0 (reference)	−0.4 (−4.3, 3.5)
	No	Yes	98	1.0 (0.8, 1.3)	
	Yes	No	6	3.2 (1.4, 7.7)	
	Yes	Yes	5	2.9 (1.1, 7.4)	
Coarctation of the aorta	No	No	843	1.0 (reference)	−0.6 (−4.4, 3.2)
	No	Yes	169	1.0 (0.8, 1.2)	
	Yes	No	16	4.7 (2.6, 8.5)	
	Yes	Yes	13	4.0 (2.1, 7.7)	
Aortic stenosis	No	No	359	1.0 (reference)	−2.8 (−8.5, 2.9)
	No	Yes	90	1.2 (1.0, 1.6)	
	Yes	No	9	6.2 (3.0, 13.0)	
	Yes	Yes	5	3.6 (1.4, 9.4)	

Defect category	Pregestational diabetes[a]	Obesity[b]	*N*	OR (95% CI)	RERI[c] (95% CI)
Pulmonary valve stenosis (PVS)	No	No	1,055	1.0 (reference)	−0.7 (−4.2, 2.8)
	No	Yes	277	1.3 (1.1, 1.5)	
	Yes	No	18	4.4 (2.5, 7.9)	
	Yes	Yes	17	4.1 (2.3, 7.3)	
Tricuspid atresia	No	No	111	1.0 (reference)	−0.1 (−11.6, 11.4)
	No	Yes	34	1.5 (1.0, 2.2)	
	Yes	No	3	6.7 (2.0, 22.0)	
	Yes	Yes	3	7.1 (2.1, 23.4)	
Perimembranous ventricular septal defect (VSD)	No	No	1,213	1.0 (reference)	1.2 (−2.5, 5.0)
	No	Yes	228	0.9 (0.8, 1.1)	
	Yes	No	22	4.5 (2.6, 7.7)	
	Yes	Yes	26	5.6 (3.3, 9.4)	
Atrial septal defect (ASD) secundum or not otherwise specified	No	No	2,067	1.0 (reference)	2.9 (−1.6, 7.4)
	No	Yes	482	1.1 (1.0, 1.3)	
	Yes	No	50	6.0 (3.9, 9.2)	
	Yes	Yes	71	9.0 (5.9, 13.6)	
Single ventricle complex	No	No	212	1.0 (reference)	0.9 (−13.2, 15.0)
	No	Yes	45	1.0 (0.8, 1.4)	
	Yes	No	13	15.1 (7.9, 29.0)	
	Yes	Yes	13	16.1 (8.3, 30.9)	
Coarctation of the aorta and VSD	No	No	234	1.0 (reference)	−1.7 (−8.1, 4.6)
	No	Yes	39	0.8 (0.6, 1.1)	
	Yes	No	5	5.3 (2.0, 13.6)	
	Yes	Yes	3	3.4 (1.0, 11.0)	
VSD and ASD	No	No	524	1.0 (reference)	3.4 (−3.3, 10.0)
	No	Yes	107	1.0 (0.8, 1.2)	
	Yes	No	13	6.1 (3.2, 11.6)	
	Yes	Yes	19	9.5 (5.4, 16.8)	
PVS and ASD	No	No	170	1.0 (reference)	−3.1 (−11.8, 5.7)
	No	Yes	49	1.4 (1.0, 1.9)	
	Yes	No	5	7.3 (2.8, 18.8)	

Defect category	Pregestational diabetes[a]	Obesity[b]	*N*	OR (95% CI)	RERI[c] (95% CI)
	Yes	Yes	3	4.6 (1.4, 15.2)	
PVS and VSD	No	No	102	1.0 (reference)	−2.0 (−15.5, 11.6)
	No	Yes	21	1.0 (0.6, 1.6)	
	Yes	No	4	9.7 (3.4, 27.7)	
	Yes	Yes	3	7.7 (2.3, 25.5)	

[a] Defined as self-report of diagnosis of Type 1 or Type 2 diabetes before the beginning of the index pregnancy.

[b] Defined as body mass index (kg/m^2) ≥30, based on self-reported pregestational weight and height without shoes.

[c] RERI, relative excess risk due to interaction.

TABLE 3

Counts and OR for the individual and joint associations of maternal gestational diabetes and obesity and risk for selected birth defects, National Birth Defects Prevention Study, 1997–2011

Defect category	Gestational diabetes[a]	Obesity[b]	*N*	OR (95% CI)	RERI[c] (95% CI)
Controls	No	No	8,638	N/A	N/A
	No	Yes	1,765		
	Yes	No	323		
	Yes	Yes	169		
Anencephaly	No	No	443	1.0 (reference)	−0.2 (−1.0, 0.6)
	No	Yes	115	1.3 (1.0, 1.6)	
	Yes	No	14	0.8 (0.5, 1.5)	
	Yes	Yes	8	0.9 (0.5, 1.9)	
Spina bifida	No	No	826	1.0 (reference)	0.4 (−0.4, 1.2)
	No	Yes	263	1.6 (1.3, 1.8)	
	Yes	No	24	0.8 (0.5, 1.2)	
	Yes	Yes	28	1.7 (1.2, 2.6)	
Hydrocephaly	No	No	355	1.0 (reference)	1.2 (−0.1, 2.5)
	No	Yes	76	1.0 (0.8, 1.3)	
	Yes	No	12	0.9 (0.5, 1.6)	
	Yes	Yes	15	2.2 (1.3, 3.7)	
Anophthalmia/microphthalmia	No	No	164	1.0 (reference)	0.4 (−1.3, 2.0)
	No	Yes	41	1.2 (0.9, 1.7)	
	Yes	No	6	1.0 (0.4, 2.2)	
	Yes	Yes	5	1.6 (0.6, 3.8)	
Cataract	No	No	262	1.0 (reference)	0.04 (−1.2, 1.3)
	No	Yes	59	1.1 (0.8, 1.4)	
	Yes	No	12	1.2 (0.7, 2.2)	
	Yes	Yes	7	1.3 (0.6, 2.8)	
Glaucoma/anterior chamber defect	No	No	129	1.0 (reference)	1.2 (−0.7, 3.0)
	No	Yes	30	1.1 (0.7, 1.6)	
	Yes	No	3	0.6 (0.2, 1.9)	

Defect category	Gestational diabetes[a]	Obesity[b]	*N*	OR (95% CI)	RERI[c] (95% CI)
	Yes	Yes	5	1.9 (0.8, 4.7)	
Anotia/microtia	No	No	434	1.0 (reference)	0.1 (−0.9, 1.2)
	No	Yes	102	1.2 (0.9, 1.4)	
	Yes	No	20	1.2 (0.8, 2.0)	
	Yes	Yes	13	1.5 (0.9, 2.7)	
Cleft palate alone	No	No	1,149	1.0 (reference)	0.02 (−0.7, 0.7)
	No	Yes	233	1.0 (0.9, 1.2)	
	Yes	No	62	1.4 (1.1, 1.9)	
	Yes	Yes	32	1.4 (1.0, 2.1)	
Cleft lip with or without cleft palate	No	No	2,210	1.0 (reference)	0.01 (−0.5, 0.5)
	No	Yes	483	1.1 (1.0, 1.2)	
	Yes	No	96	1.2 (0.9, 1.5)	
	Yes	Yes	53	1.2 (0.9, 1.7)	
Small intestinal atresia/stenosis	No	No	330	1.0 (reference)	−0.1 (−1.2, 1.1)
	No	Yes	84	1.2 (1.0, 1.6)	
	Yes	No	15	1.2 (0.7, 2.1)	
	Yes	Yes	9	1.4 (0.7, 2.8)	
Duodenal atresia/stenosis	No	No	171	1.0 (reference)	−1.0 (−2.6, 0.5)
	No	Yes	37	1.1 (0.7, 1.5)	
	Yes	No	12	1.9 (1.0, 3.4)	
	Yes	Yes	3	0.9 (0.3, 2.8)	
Esophageal atresia/stenosis	No	No	555	1.0 (reference)	0.2 (−0.6, 1.0)
	No	Yes	114	1.0 (0.8, 1.2)	
	Yes	No	18	0.9 (0.5, 1.4)	
	Yes	Yes	12	1.1 (0.6, 2.0)	
Anorectal atresia/stenosis	No	No	705	1.0 (reference)	0.7 (−0.2, 1.6)
	No	Yes	190	1.3 (1.1, 1.6)	
	Yes	No	25	0.9 (0.6, 1.4)	
	Yes	Yes	27	2.0 (1.3, 3.0)	
Biliary atresia/stenosis	No	No	134	1.0 (reference)	1.0 (−1.1, 3.1)
	No	Yes	35	1.3 (0.9, 1.9)	

Defect category	Gestational diabetes[a]	Obesity[b]	*N*	OR (95% CI)	RERI[c] (95% CI)
	Yes	No	5	1.0 (0.4, 2.5)	
	Yes	Yes	6	2.3 (1.0, 5.3)	
Hypospadias	No	No	1,923	1.0 (reference)	0.4 (−0.2, 1.0)
	No	Yes	398	1.0 (0.9, 1.2)	
	Yes	No	81	1.1 (0.9, 1.5)	
	Yes	Yes	58	1.5 (1.1, 2.2)	
Longitudinal limb deficiency	No	No	341	1.0 (reference)	0.6 (−0.4, 1.6)
	No	Yes	68	1.0 (0.7, 1.3)	
	Yes	No	8	0.6 (0.3, 1.3)	
	Yes	Yes	8	1.2 (0.6, 2.5)	
Transverse limb deficiency	No	No	520	1.0 (reference)	0.01 (−0.8, 0.8)
	No	Yes	106	1.0 (0.8, 1.2)	
	Yes	No	19	1.0 (0.6, 1.6)	
	Yes	Yes	10	1.0 (0.5, 1.9)	
Craniosynostosis	No	No	1,164	1.0 (reference)	0.3 (−0.4, 1.0)
	No	Yes	254	1.1 (0.9, 1.2)	
	Yes	No	59	1.4 (1.0, 1.8)	
	Yes	Yes	39	1.7 (1.2, 2.4)	
Diaphragmatic hernia	No	No	622	1.0 (reference)	0.2 (−0.6, 1.0)
	No	Yes	140	1.1 (0.9, 1.3)	
	Yes	No	20	0.9 (0.5, 1.4)	
	Yes	Yes	14	1.2 (0.7, 2.0)	
Omphalocele	No	No	299	1.0 (reference)	0.4 (−0.9, 1.8)
	No	Yes	83	1.4 (1.1, 1.7)	
	Yes	No	12	1.1 (0.6, 1.9)	
	Yes	Yes	11	1.9 (1.0, 3.5)	
Amniotic band syndrome	No	No	249	1.0 (reference)	0.4 (−0.8, 1.6)
	No	Yes	50	1.0 (0.7, 1.3)	
	Yes	No	8	0.9 (0.4, 1.8)	
	Yes	Yes	6	1.2 (0.5, 2.8)	
Heterotaxy with cardiac defects	No	No	240	1.0 (reference)	0.1 (−0.9, 1.2)

Defect category	Gestational diabetes[a]	Obesity[b]	*N*	OR (95% CI)	RERI[c] (95% CI)
	No	Yes	53	1.1 (0.8, 1.5)	
	Yes	No	6	0.7 (0.3, 1.5)	
	Yes	Yes	4	0.9 (0.3, 2.3)	
Tetralogy of Fallot	No	No	838	1.0 (reference)	0.9 (−0.01, 1.8)
	No	Yes	184	1.1 (0.9, 1.3)	
	Yes	No	40	1.3 (0.9, 1.8)	
	Yes	Yes	37	2.3 (1.6, 3.2)	
D-transposition of the great arteries (TGA)	No	No	574	1.0 (reference)	0.1 (−0.6, 0.7)
	No	Yes	112	1.0 (0.8, 1.2)	
	Yes	No	17	0.8 (0.5, 1.3)	
	Yes	Yes	9	0.8 (0.4, 1.6)	
Atrioventricular septal defect	No	No	274	1.0 (reference)	1.1 (−0.1, 2.3)
	No	Yes	45	0.8 (0.6, 1.1)	
	Yes	No	6	0.6 (0.3, 1.3)	
	Yes	Yes	8	1.5 (0.7, 3.1)	
Total anomalous pulmonary venous return	No	No	205	1.0 (reference)	0.2 (−1.1, 1.5)
	No	Yes	52	1.2 (0.9, 1.7)	
	Yes	No	6	0.8 (0.3, 1.8)	
	Yes	Yes	5	1.2 (0.5, 3.1)	
Hypoplastic left heart syndrome	No	No	458	1.0 (reference)	1.1 (−0.2, 2.4)
	No	Yes	98	1.0 (0.8, 1.3)	
	Yes	No	24	1.4 (0.9, 2.1)	
	Yes	Yes	23	2.6 (1.6, 4.0)	
Coarctation of the aorta	No	No	843	1.0 (reference)	0.1 (−0.6, 0.9)
	No	Yes	169	1.0 (0.8, 1.2)	
	Yes	No	42	1.3 (1.0, 1.9)	
	Yes	Yes	24	1.5 (0.9, 2.2)	
Aortic stenosis	No	No	359	1.0 (reference)	−0.1 (−1.1, 0.8)
	No	Yes	90	1.2 (1.0, 1.6)	
	Yes	No	12	0.9 (0.5, 1.6)	
	Yes	Yes	7	1.0 (0.5, 2.1)	

Defect category	Gestational diabetes[a]	Obesity[b]	*N*	OR (95% CI)	RERI[c] (95% CI)
Pulmonary atresia	No	No	183	1.0 (reference)	0.1 (−1.1, 1.3)
	No	Yes	44	1.2 (0.8, 1.6)	
	Yes	No	4	0.6 (0.2, 1.6)	
	Yes	Yes	3	0.8 (0.3, 2.6)	
Pulmonary valve stenosis (PVS)	No	No	1,055	1.0 (reference)	0.3 (−0.5, 1.1)
	No	Yes	277	1.3 (1.1, 1.5)	
	Yes	No	60	1.5 (1.1, 2.0)	
	Yes	Yes	44	2.1 (1.5, 2.9)	
Perimembranous ventricular septal defect (VSD)	No	No	1,213	1.0 (reference)	0.5 (−0.2, 1.2)
	No	Yes	228	0.9 (0.8, 1.1)	
	Yes	No	54	1.2 (0.9, 1.6)	
	Yes	Yes	38	1.6 (1.1, 2.3)	
Atrial septal defect (ASD) secundum or not otherwise specified	No	No	2,067	1.0 (reference)	1.0 (0.3, 1.6)
	No	Yes	482	1.1 (1.0, 1.3)	
	Yes	No	97	1.3 (1.0, 1.6)	
	Yes	Yes	95	2.3 (1.8, 3.0)	
Single ventricle complex	No	No	212	1.0 (reference)	−0.3 (−1.6, 1.0)
	No	Yes	45	1.0 (0.8, 1.4)	
	Yes	No	10	1.3 (0.7, 2.4)	
	Yes	Yes	4	1.0 (0.4, 2.6)	
Aortic stenosis and coarctation of the aorta	No	No	79	1.0 (reference)	−0.2 (−3.0, 2.5)
	No	Yes	24	1.5 (0.9, 2.4)	
	Yes	No	5	1.7 (0.7, 4.2)	
	Yes	Yes	3	1.9 (0.6, 6.2)	
Coarctation of the aorta and VSD	No	No	234	1.0 (reference)	0.03 (−1.1, 1.2)
	No	Yes	39	0.8 (0.6, 1.1)	
	Yes	No	9	1.0 (0.5, 2.0)	
	Yes	Yes	4	0.9 (0.3, 2.4)	
VSD and ASD	No	No	524	1.0 (reference)	0.6 (−0.4, 1.7)
	No	Yes	107	1.0 (0.8, 1.2)	
	Yes	No	26	1.3 (0.9, 2.0)	

Defect category	Gestational diabetes[a]	Obesity[b]	N	OR (95% CI)	RERI[c] (95% CI)
	Yes	Yes	20	2.0 (1.2, 3.1)	
PVS and ASD	No	No	170	1.0 (reference)	0.3 (−1.8, 2.3)
	No	Yes	49	1.4 (1.0, 1.9)	
	Yes	No	11	1.7 (0.9, 3.2)	
	Yes	Yes	8	2.4 (1.2, 5.0)	
PVS and VSD	No	No	102	1.0 (reference)	−0.6 (−2.9, 1.7)
	No	Yes	21	1.0 (0.6, 1.6)	
	Yes	No	8	2.1 (1.0, 4.3)	
	Yes	Yes	3	1.5 (0.5, 4.8)	

[a] Defined as self-report of gestational diabetes during the index pregnancy.

[b] Defined as body mass index (kg/m^2) ≥30, based on self-reported pregestational weight and height without shoes.

[c] RERI: relative excess risk due to interaction.