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Is Maternal Parity an Independent Risk Factor for Birth Defects?

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Abstract

BACKGROUND—Although associations between maternal parity and birth defects have been observed previously, few studies have focused on the possibility that parity is an independent risk factor for birth defects. We investigated the relation between levels of parity and a range of birth defects, adjusting each defect group for the same covariates.

METHODS—We included infants who had an estimated delivery date between 1997 and 2007 and participated in the National Birth Defects Prevention Study, a multisite case-control study. Cases included infants or fetuses belonging to 38 phenotypes of birth defects (n = 17,908), and controls included infants who were unaffected by a major birth defect (n = 7173). Odds ratios (ORs) were adjusted for 12 covariates using logistic regression.

RESULTS—Compared with primiparous mothers, nulliparous mothers were more likely to have infants with amniotic band sequence, hydrocephaly, esophageal atresia, hypospadias, limb reduction deficiencies, diaphragmatic hernia, omphalocele, gastroschisis, tetralogy of Fallot, and septal cardiac defects, with significant ORs (1.2 to 2.3). Compared with primiparous mothers, multiparous mothers had a significantly increased risk of omphalocele, with an OR of 1.5, but had significantly decreased risk of hypospadias and limb reduction deficiencies, with ORs of 0.77 and 0.77.

CONCLUSIONS—Nulliparity was associated with an increased risk of specific phenotypes of birth defects. Most of the phenotypes associated with nulliparity in this study were consistent with

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those identified by previous studies. Research into biologic or environmental factors that are associated with nulliparity may be helpful in explaining some or all of these associations.

Keywords

nulliparity; multiparity; parity; congenital abnormalities; congenital heart defects

INTRODUCTION

Previous studies have observed an association between nulliparity and an increased risk of many different birth defects (Hay and Barbano, 1972; Akre et al., 1999; Bianca and Ettore, 2003; Carmichael et al., 2003, 2007; Pradat et al., 2003; Yang et al., 2006; Oddsberg et al., 2008; Agopian et al., 2009; Werler et al., 2009; Benjamin et al., 2010). In contrast, other studies have observed that multi-parity is associated with an increased risk of specific birth defects (Vieira and Orioli, 2002; Vieira, 2004; Hashmi et al., 2005; Canfield et al., 2009). Many of the previous studies addressed a limited number of confounding factors; therefore, unmeasured confounding may explain inconsistencies in the literature on parity and birth defects (Vieira and Orioli, 2002; Vieira, 2004; Oddsberg et al., 2008). In particular, previous studies did not adjust for maternal infertility, gestational hypertension or a history of previous fetal loss. Each of these factors has been observed to be associated with some types of birth defects (Bergh et al., 1999; Blanco-Munoz et al., 2006; Zhu et al., 2006; Caton et al., 2008, 2009; Reefhuis et al., 2009; Lebby et al., 2010) and may also be associated with parity (Gunnlaugsson et al., 1989; Strevens et al., 2001). This paper examines the association of different levels of parity with 17 phenotypes of noncardiac defects and 21 phenotypes and subphenotypes of cardiac defects, while adjusting for a wider range of confounding variables than previous studies.

MATERIALS AND METHODS

The National Birth Defects Prevention Study (NBDPS) is a case-control study that has participants in 10 sites: Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. Infants or fetuses who were born on or after October 1, 1997, and had an anticipated date of delivery on or before December 31, 2007, were eligible for the current study. Cases were live-born infants, fetal deaths of at least 20 weeks' gestation and elective pregnancy terminations of any gestational age. However, not all centers were able to contribute cases in which the pregnancy ended in a fetal death or an elective abortion. Controls were live-born infants without major birth defects, randomly selected from birth certificates or birth hospitals to represent the birth population from which the cases were drawn. This study was approved by the institutional review boards of each of the participating study sites and the Centers for Disease Control and Prevention. Detailed study methods have been published previously (Yoon et al., 2001).

All cases were reviewed by NBDPS clinical geneticists according to clearly established clinical guidelines and classified as isolated, multiple, or complex birth defects (Rasmussen et al., 2003). An *isolated birth defect* was defined as either one major birth defect, two or more major birth defects affecting only one organ system, or one major birth defect with a

well-described sequence of related defects. Cases with multiple birth defects had two or more major unrelated defects in different organ systems. The NBDPS excludes birth defects that are known or strongly suspected to have been caused by single-gene disorders or chromosomal abnormalities. Among birth defect phenotypes included in the NBDPS, we used only those for which 200 or more eligible cases were available, as those phenotypes with fewer eligible cases would not have allowed estimation of sufficiently precise odds ratios (ORs). A minimum sample size of 200 cases gave us a power of 80% (alpha 0.05, one-sided) to detect an OR of 1.5 or greater (William and Walton, 2011). The control group includes 7954 women who had an infant without any major birth defects. Utah was unable to contribute cases of orofacial clefts in 2003, California contributed only cases of pulmonary valve stenosis beginning on January 1, 2002, and study-wide cases of congenital cataracts were only contributed beginning January 1, 2000. Therefore, for calculations involving these birth defects, we excluded information from control mothers for locations and study periods during which cases were not contributed. For hypospadias, control data were restricted to mothers of male infants.

Maternal interviews were conducted using a standardized, computer-assisted interview by telephone, in English or Spanish. Interview participation rates were 68.5% among case mothers and 64.9% among control mothers. Women were asked to report all previous pregnancies and their outcomes, including previous live births, still-births, elective terminations, miscarriages, tubal pregnancies, and molar pregnancies. Parity was defined as the number of live births before the index delivery (Baird and Quinlivan, 1972). Nulliparous women were defined as those with no previous live births. Primiparous women were those with one live birth before the index delivery, and multiparous women were those with two or more prior live births. Initially we included 21,995 case infants or fetuses belonging to 38 selected phenotypes and subphenotypes of birth defects and 8494 control infants without major birth defects. Of these, 97 had missing data on parity. Because the parity of multiple gestations is not accurately recorded on vital statistics (Waller et al., 2003), mothers with multiple gestations or with a history of multiple gestations were excluded (n = 2319). We also excluded mothers with preexisting diabetes (n = 539), because it is rare and yet strongly associated with many different phenotypes of birth defects (Correa et al., 2008). After these exclusions, a total of 7954 control and 19,580 case infants or fetuses remained in our analyses.

Logistic regression was used to calculate crude and adjusted ORs for the association between parity and each of the 38 phenotypes and subphenotypes of birth defects (17 noncardiac defects and 21 cardiac defects). The categories for this analysis were: nulliparity, primiparity (referent), and multiparity. We calculated ORs for the association between nulliparity and each birth defect phenotype compared to primiparity. We also calculated ORs for the association between multiparity and each birth defect phenotype compared to primiparity. We adjusted the ORs for maternal age (<25, 25–29, 30–34, 35+), race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), educational status (<high school, high school, some college, college graduate), pre-pregnancy body mass index (body mass index [BMI] <18.5, 18.5 to <25, 25 to <30, and 30), periconceptional (between the month before conception and the first 3 months of pregnancy) use of supplements containing folic acid (no, yes), periconceptional smoking (no, yes), periconceptional alcohol

consumption (no, yes), pregnancy intention (no, yes), previous fetal loss (no, yes), gestational hypertension (no, yes), fertility treatment (no, yes), and study site (10 categories). BMI was defined as the mother's weight in kilograms divided by her height in meters squared (Centers for Disease Control and Prevention, 2011). Pregnancies were classified as *unintended* if the mother reported recent use of contraceptives or indicated that she did not want to be pregnant or that the pregnancy was mis-timed (Dott et al., 2010). Fetal loss was defined as stillbirth, miscarriage, elective termination, or tubal or molar pregnancy. Gestational hypertension and fertility treatment were based on responses to the following questions: 'Did you have high blood pressure when you had the index pregnancy?' and 'Did you or the baby's father take any medications or have any procedures to help you become pregnant?' After we excluded mothers who were missing one or more of these covariates, 7173 controls and 17,908 cases remained in the multivariate analyses.

We also performed additional exploratory analyses. To assess whether we might have missed an association with a higher level of parity, we divided multiparous women into two subgroups: those with two previous live births and those with three or more previous live births, and compared the odds of each defect with those of primiparous women. To distinguish between nulliparity and nulligravidity, we split the nulliparous group into those with and without a prior fetal loss, and compared them to the primiparous group. Finally, to ensure that none of the associations we observed were affected by the presence of cases with multiple birth defects, analyses were repeated restricting the sample to isolated cases.

All analyses were performed using the statistical software package SAS (release 9.2, SAS Institute, Cary, NC).

RESULTS

Among the 7954 control mothers, 41% were nulliparous, 33% were primiparous, and 26% were multiparous. Compared to primiparous control mothers, nulliparous control mothers were younger, more likely to binge drink, smoke, have gestational hypertension, and have undergone fertility treatment (Table 1). They were less likely to be overweight or obese, have a college degree, or have a history of fetal loss.

Compared to primiparous women (referent), nulliparous women were more likely to have offspring with eight noncardiac birth defect phenotypes: amniotic band sequence, hydrocephaly, esophageal atresia, hypospadias, limb reduction deficiencies, diaphragmatic hernia, omphalocele and gastroschisis, with significantly elevated ORs ranging from 1.2 to 2.3 (Table 2). Because younger maternal age is a strong risk factor for gastroschisis and amniotic band sequence (Werler et al., 2003; Benjamin et al., 2010), we recalculated odds ratios for the association between nulliparity and these two birth defects adjusting for maternal age as a continuous variable to address residual confounding. The OR for amniotic band sequence remained almost unchanged, and the OR for gastroschisis decreased from adjusted OR (1.77; 95% confidence interval [CI], 1.46–2.14) to adjusted OR (1.47; 95% CI, 1.21–1.79) to adjusted OR (1.47; 95% CI, 1.21–1.79). Nulliparous women were also significantly more likely to have offspring with one of the cardiac phenotypes (e.g., septal cardiac defects) and one of the cardiac subphenotypes (e.g., tetralogy of Fallot), with ORs of

1.20 and 1.34, respectively. Among the five subphenotypes of septal cardiac defects that we assessed, three were significantly associated with nulliparity: perimembranous ventricular septal defect (VSD), secundum atrial septal defect (ASD), and ASD and VSD association (Table 2). One protective OR was observed for nulliparous women; they were less likely to have a baby with anomalous pulmonary venous return (APVR).

Compared to primiparous women, multiparous women had significantly elevated or reduced ORs for three phenotypes of noncardiac birth defects. They had a reduced risk of having a baby born with hypospadias and limb reduction deficiencies (Table 2). For omphalocele, we observed an increased risk among multiparous and nulliparous women.

When the analyses were restricted to isolated defects, the pattern of the results remained the same (data not shown). The ORs for the association between nulliparity and hydrocephaly and limb reduction deficiencies remained elevated, but were no longer statistically significant. The other six associations between nulliparity and noncardiac defect phenotypes remained significantly elevated. For cardiac defects, ORs for tetralogy of Fallot, septal defects, and perimembranous VSD remained significantly elevated, and the OR for secundum ASD remained elevated but was no longer statistically significant. In addition, when the analyses were restricted to isolated defects two protective ORs for the association between nulliparity and total anomalous pulmonary venous return and for the association between multiparity and atrioventricular septal defect (AVSD) were statistically significant. However, only the OR for AVSD had a substantial change in its magnitude, from adjusted OR (0.68; 95% CI, 0.46– 1.02) to adjusted OR (0.34; 95% CI, 0.18–0.65).

When the results for nulliparous women in Table 2 were stratified by a maternal history of a prior fetal loss (yes or no), the associations we observed between nulliparity and specific birth defects remained significantly elevated across both strata. The associations were slightly stronger among women with a prior fetal loss compared to those without a prior fetal loss (data not shown). Analyses in which multiparous women were split into two groups (two previous live births and three or more previous live births) did not yield substantially different results.

DISCUSSION

Nulliparity was associated with a significantly increased risk for 8 of the 17 noncardiac birth defect phenotypes we investigated in our study using NBDPS data. Almost all these elevated associations have been observed in previous studies (Hay and Barbano, 1972; Bower et al., 1993; Robert et al., 1997; Akre et al., 1999; Carmichael et al.; 2003; Yang et al., 2006; Oddsberg et al., 2008; Agopian et al., 2009; Benjamin et al., 2010). As for cardiac phenotypes, tetralogy of Fallot was significantly associated with nulliparity, in agreement with a previous study (Pradat et al., 2003). The associations that we observed between nulliparity and secundum ASD and ASD associated with VSD were not supported by previous studies (Ferencz, 1997; Pradat et al., 2003). In contrast, Pradat et al. (2003) reported a modest but significant association between nulliparity and two categories of heart defects: D-transposition of the great arteries (OR, 1.20; 95% CI, 1.02–1.42) and coarctation

of the aorta (OR, 1.26; 95% CI, 1.00–1.60). We found no association between nulliparity and these two heart defects.

Our finding of a decreasing risk of hypospadias with increasing parity is consistent with one previous NBDPS study (Carmichael et al., 2007), and at least three non-NBDPS studies (Hay and Barbano, 1972; Akre et al., 1999; Kallen, 2002). Our data also suggest a trend of decreasing risk of limb reduction deficiencies with increasing parity. This observation has been previously reported by Hay and Barbano (1972). It is also important to note that the associations we observed between nulli-parity and hypospadias, limb reduction deficiencies, amniotic band sequence, omphalocele, and gastroschisis have been reported previously, using earlier versions of the NBDPS data (Carmichael et al., 2007; Mac Bird et al., 2009; Werler et al., 2009). When we reinvestigated these associations, adjusting for a wider range of confounding factors, the odds ratios did not change substantially.

We did not observe any significantly elevated ORs for the association of nulliparity with 9 of the 17 noncardiac phenotypes, 8 of the 9 phenotypes of heart defects, or 8 of the 12 more specific cardiac subphenotypes. This observation is consistent with previous studies that reported no associations between nulliparity and the following 12 birth defects: anencephaly, spina bifida, anotia or microtia, cleft palate, cleft lip with or without cleft palate, anorectal atresia, craniosynostosis, single ventricle or complex heart, hypoplastic left heart syndrome, aortic stenosis, pulmonary valve stenosis, and association of coarctation of the aorta and VSD (Hay and Barbano, 1972; Harris et al., 1996; Pradat et al., 2003; Boulet et al., 2008; Messer et al., 2010).

Previous studies have reported inconsistent results for associations between multiparity and neural tube defects (NTDs) and oral clefts (Oldfield, 1959; Bethmann and Rohne, 1967; Czeizel and Tusnadi, 1971; Hay and Barbano, 1972; Vieira and Orioli, 2002; Vieira, 2004; Hashmi et al., 2005; Canfield et al., 2009). Studies with large sample sizes observed a modest or a null association between multiparity and oral clefts (Oldfield, 1959; Bethmann and Rohne, 1967; Hay and Barbano, 1972; Hashmi et al., 2005) that is consistent with our results. In a meta-analysis on parity and NTDs, Vieira (2004) observed that increasing parity increases the risk of spina bifida but not anencephaly. In contrast, a study published after the meta-analysis revealed no association between multiparity and spina bifida, but an increased risk for anencephaly with increasing parity (adjusted OR, 3.85; 95% CI, 2.67–5.49; four previous live births vs. no previous live births; Canfield et al., 2009). Most of the previous studies presented crude ORs or adjusted for a limited set of covariates, whereas we adjusted for a wider range of covariates and observed only one positive association between multiparity and omphalocele.

We were particularly interested in assessing the possibility of confounding from history of fetal loss, fertility treatment, and gestational hypertension, because each of these factors have been shown to be associated with both parity and birth defects (Gunnlaugsson et al., 1989; Bergh et al., 1999; Strevens et al., 2001; Blanco-Munoz et al., 2006; Zhu et al., 2006; Caton et al., 2008, 2009; Reefhuis et al., 2009; Lebby et al., 2010). After adjusting for these factors and other covariates, the magnitude and significance of the ORs between nulliparity and birth defects remained the same.

Participation rates for this study were 68.5% for cases and 64.9% for controls; therefore, selection bias may explain some of our findings. For example, owing to fewer childcare demands, nulliparous mothers of infants with severe but nonlethal birth defects may be more likely to agree to participate in a 60-minute interview compared with their multiparous counterparts. However, previous studies that did not require active maternal participation have reported associations between nulliparity and 10 of the 13 phenotypes of birth defects that we observed to be associated with nulliparity (Hay and Barbano, 1972; Bower et al., 1993; Robert et al., 1997; Akre et al., 1999; Carmichael et al., 2003; Pradat et al., 2003; Yang et al., 2006; Oddsberg et al., 2008; Agopian et al., 2009; Benjamin et al., 2010), arguing against such a bias.

Although state and regional birth defect registries that contribute cases to the NBDPS incompletely ascertain electively terminated pregnancies (Cragan and Gilboa, 2009), several lines of evidence suggest that this is unlikely to bias most of the associations that we observed. Rates of elective termination for esophageal atresia, hypospadias, limb reduction deficiencies, and most types of heart defects are low (Cragan and Gilboa, 2009). Two small studies observed that the decision to terminate pregnancies affected with birth defects does not vary by parity (Rauch et al., 2005; Shaffer et al., 2006). And a study by Hay and Barbano (1972), conducted before the era of prenatal diagnosis, observed that children born to nulliparous women had higher rates of limb reduction deficiencies, omphalocele, hypospadias, and hydrocephaly.

Short interpregnancy intervals (<6 months) may be associated with an increased risk of birth defects (Todoroff and Shaw, 2000; Grisaru-Granovsky et al., 2009), possibly because of nutrient depletion (Grisaru-Granovsky et al., 2009). Nutrient depletion is more likely to occur among women delivering a live birth than among those having a fetal loss. We were not able to adjust for interpregnancy intervals because many nulliparous women had no previous pregnancies. Among women who were delivering their first live birth, we observed an increased risk of having a baby born with specific birth defects in those who had previous fetal losses and those who had no previous fetal losses. As a result, the increased risk associated with nulliparity was not confined to women who were pregnant for the first time.

CIs for most of our estimates were narrow and suggest good statistical precision; however, because we conducted multiple statistical tests, we cannot exclude the possibility that some of the observed associations may be due to chance, especially those that are either inconsistent with previous studies or were first observed in the NBDPS (i.e., septal defects and its subtypes, secundum ASD and association of ASD and VSD).

The associations that we have observed between maternal nulliparity and certain birth defects might be explained by unmeasured environmental risk factors that are more common among nulliparous women compared with multiparous women. Alternatively, they might be explained by biologic differences among nulliparous pregnancies compared to multiparous pregnancies. For example, a nulliparous uterus is smaller and less vascular than a multiparous uterus (Rovas et al., 2006). In addition, serum levels of estradiol have been reported to be higher during early pregnancy among nulligravid pregnancies (Bernstein et al., 1986).

Approximately 41% of all births in the United States occur among nulliparous women who have never previously had a live-born child. Given this frequency and the ORs we observed in this study, calculations for the population attributable risk (PAR) suggest that if nulliparity is found to be closely linked to a modifiable cause of specific birth defect phenotypes, elimination of this cause could possibly prevent between 7.6% [0.41* (1.2 – 1.0)] / {[0.41* (1.2 – 1.0)] + 1} and 34.8% of these birth defects [0.41* (2.3 – 1.0)] / {[0.41* (2.3 – 1.0)] + 1}. Formula for PAR = [prevalence of exposure* (OR -1)] / {[prevalence of exposure* (OR-1)] +1}. Thus further research exploring factors that may explain the associations between nulli-parity and specific birth defects observed by this study is needed and may uncover important clues regarding the etiology of these birth defects.

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Table 1

Demographic Characteristics among Controls According to Maternal Parity: National Birth Defects Prevention Study, 1997–2007

	No. nulliparous (n = 3242) (%)	No. primiparous (n = 2643) (%)	No. multiparous (n = 2069) (%)
Age (years)			
< 25	1595 (49.2)	793 (30.0)	331 (16.0)
25–29	822 (25.4)	743 (28.1)	623 (30.1)
30–34	592 (18.3)	725 (27.4)	668 (32.3)
≥35	233 (7.2)	382 (14.5)	447 (21.6)
Ethnicity			
Non-Hispanic white	1899 (58.6)	1618 (61.2)	1103 (53.3)
Non-Hispanic black	373 (11.5)	252 (9.5)	240 (11.6)
Hispanic	675 (20.8)	578 (21.9)	577 (27.9)
Other	295 (9.1)	195 (7.4)	149 (7.2)
Education			
< High school	539 (16.6)	353 (13.4)	449 (21.7)
High school	768 (23.7)	614 (23.2)	534 (25.8)
Some college	797 (24.6)	714 (27.0)	605 (29.2)
College graduate	1087 (33.5)	927 (35.1)	440 (21.3)
Pre-pregnancy BMI [a]			
Underweight (<18.5)	219 (6.8)	135 (5.1)	66 (3.2)
Normal weight (18.5–<25)	1839 (56.7)	1395 (52.8)	1002 (48.4)
Overweight (25–<30)	644 (19.9)	589 (22.3)	506 (24.5)
Obese (≥30)	433 (13.4)	422 (16.0)	377 (18.2)
Use of supplements containing folic acid [b]			
No	460 (14.2)	378 (14.3)	404 (19.5)
Yes	2777 (85.7)	2260 (85.5)	1651 (79.8)
Smoking [b]			
No	2528 (78.0)	2190 (82.9)	1694 (81.9)
Yes	673 (20.8)	426 (16.1)	341 (16.5)
Binge drinking [b] **(4 drinks or more per occasion)**			
No	2656 (81.9)	2338 (88.5)	1830 (88.5)
Yes	514 (15.9)	258 (9.8)	194 (9.4)
Pregnancy intended [c]			
No	1236 (38.1)	920 (34.8)	994 (48.0)
Yes	1999 (61.7)	1713 (64.8)	1065 (51.5)
Previous fetal loss [d]			
No	2409 (74.3)	1751 (66.3)	1235 (59.7)
Yes	833 (25.7)	892 (33.7)	834 (40.3)
Gestational hypertension			

	No. nulliparous (n = 3242) (%)	No. primiparous (n = 2643) (%)	No. multiparous (n = 2069) (%)
No	2899 (89.4)	2456 (92.9)	1889 (91.3)
Yes	338 (10.4)	185 (7.0)	177 (8.6)
Parental fertility treatment			
No	2983 (92.0)	2443 (92.4)	1976 (95.5)
Yes	158 (4.9)	89 (3.4)	35 (1.7)

Total (and percentages) may not add up to 7954 (100%) because of missing values. All covariates had less than 5% missing values.

BMI, body mass index.

[a] Weight (kg) / (Height [m])2.

[b] Between the month before conception and the first 3 months of pregnancy.

[c] Not intended if the mother reported recent use of contraceptives or indicated that she did not want to be pregnant or that the pregnancy was mistimed.

[d] Including still births, miscarriages, elective terminations, and molar and tubal pregnancies.

Table 2

Adjusted[a] Odds Ratios for the Association between Selected Birth Defects[b] and Parity: National Birth Defects Prevention Study, 1997–2007 (n = 17,908)

	Total (n)	Nulliparity		Primiparity		Multiparity	
		(n)	OR (95% CI)	(n)	Referent	(n)	OR (95% CI)
Amniotic band sequence	209	137	2.19 (1.53–3.13)	44	—	28	0.80 (0.49–1.31)
Anencephaly	355	120	0.81 (0.62–1.06)	123	—	112	1.11 (0.83–1.47)
Spina bifida	767	274	0.91 (0.75–1.09)	260	—	233	1.01 (0.83–1.23)
Hydrocephaly	302	140	1.41 (1.05–1.88)	80	—	82	1.24 (0.89–1.72)
Cataract[c]	228	109	1.34 (0.97–1.85)	66	—	53	0.96 (0.65–1.41)
Anotia, microtia	388	155	1.06 (0.82–1.37)	125	—	108	0.96 (0.72–1.27)
Cleft palate[d]	1012	395	0.99 (0.84–1.16)	341	—	276	0.96 (0.80–1.15)
Cleft lip with or without cleft palate[d]	1900	792	1.01 (0.89–1.14)	619	—	489	0.96 (0.84–1.11)
Esophageal atresia	414	228	1.73 (1.35–2.20)	114	—	72	0.79 (0.58–1.08)
Intestinal atresia	459	208	1.14 (0.91–1.44)	141	—	110	0.93 (0.71–1.22)
Anorectal atresia	626	277	1.18 (0.96–1.44)	190	—	159	1.01 (0.80–1.27)
2nd- or 3rd-degree hypospadias[e]	1408	771	1.69 (1.44–1.98)	402	—	235	0.77 (0.63–0.94)
Limb reduction deficiencies	734	345	1.20 (1.00–1.44)	234	—	155	0.77 (0.62–0.97)
Craniosynostosis	929	326	0.88 (0.74–1.04)	343	—	260	0.86 (0.71–1.03)
Diaphragmatic hernia	537	259	1.42 (1.14–1.76)	145	—	133	1.17 (0.90–1.51)
Omphalocele	278	150	2.33 (1.68–3.22)	55	—	73	1.47 (1.01–2.13)
Gastroschisis	854	576	1.77 (1.46–2.14)	182	—	96	0.83 (0.63–1.09)
Any heart defect	7575	3135	1.07 (0.99–1.15)	2397	—	2043	1.02 (0.93–1.12)
Heterotaxia with CHD	209	79	0.83 (0.59–1.16)	73	—	57	0.88 (0.60–1.28)
Single ventricle, complex heart	206	90	1.06 (0.76–1.48)	68	—	48	0.90 (0.61–1.34)
Conotruncal defects	1560	661	1.13 (0.99–1.29)	488	—	411	1.05 (0.90–1.22)
Tetralogy of Fallot	711	326	1.34 (1.11–1.62)	206	—	179	1.04 (0.83–1.30)
D-Transposition of great arteries	495	194	0.96 (0.77–1.20)	164	—	137	1.18 (0.92–1.51)
AVSD	208	93	1.07 (0.77–1.48)	73	—	42	0.68 (0.46–1.02)
APVR	213	72	0.69 (0.49–0.97)	78	—	63	1.13 (0.79–1.62)
TAPVR	175	59	0.71 (0.49–1.04)	62	—	54	1.22 (0.82–1.81)
LVOT defects	1283	489	0.98 (0.85–1.13)	424	—	370	1.07 (0.91–1.26)
Hypoplastic left heart syndrome	387	139	0.90 (0.70–1.16)	128	—	120	1.21 (0.92–1.59)
Coarctation of the aorta	673	257	0.97 (0.80–1.18)	229	—	187	0.95 (0.77–1.18)
Aortic stenosis	286	114	1.11 (0.83–1.49)	91	—	81	1.06 (0.77–1.47)
RVOT defects	1183	439	0.96 (0.82–1.12)	379	—	365	1.11 (0.94–1.31)
Pulmonary valve stenosis[e]	875	317	0.92 (0.77–1.10)	286	—	272	1.07 (0.89–1.30)
Septal defects	3123	1378	1.20 (1.08–1.33)	931	—	814	1.00 (0.89–1.13)
VSD perimembranous	1237	587	1.36 (1.17–1.57)	360	—	290	0.91 (0.77–1.09)
ASD secundum	1422	628	1.27 (1.10–1.47)	405	—	389	1.08 (0.92–1.27)

	Total (n)	Nulliparity		Primiparity		Multiparity	
		(n)	OR (95% CI)	(n)	Referent	(n)	OR (95% CI)
ASD NOS	457	200	1.15 (0.91–1.46)	138	—	119	0.99 (0.75–1.30)
Association: COA + VSD	184	76	1.04 (0.73–1.49)	58	—	50	1.10 (0.74–1.66)
Association: VSD + ASD	495	232	1.49 (1.18–1.87)	132	—	131	1.11 (0.86–1.45)
Controls	7173	2953	—	2377	—	1843	—

[f]Compared with 6808 controls (2811 nulliparity, 2255 primiparity, and 1742 multiparity).

CHD, congenital heart defect; AVSD, atrioventicular septal defect; APVR, anomalous pulmonary venous return; TAPVR, total anomalous pulmonary venous return; LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract; VSD, ventricular septal defect; ASD, atrial septal defect; NOS, not otherwise specified; COA, coarctation of the aorta.

[a]Adjusted for maternal age, race/ethnicity, education, pre-pregnancy body mass index, use of supplements containing folic acid, smoking, drinking, pregnancy intention, previous fetal loss, pregnancy hypertension, parental fertility treatment and study site.

[b]Include isolated, multiple, or complex birth defects. These birth defect categories are not mutually exclusive.

[c]Compared with 5886 controls (2413 nulliparity, 1931 primiparity, and 1542 multiparity).

[d]Compared with 7052 controls (2908 nulliparity, 2343 primiparity, and 1801 multiparity).

[e]Compared with 3643 controls (1499 nulliparity, 1210 primiparity, and 934 multiparity).