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Analysis of Selected Maternal Exposures and Non-Syndromic Atrioventricular Septal Defects in the National Birth Defects Prevention Study, 1997–2005

Sonali S. Patel[1,*], **Trudy L. Burns**[1,2], **Lorenzo D. Botto**[3], **Tiffany J. Riehle-Colarusso**[4], **Angela E. Lin**[5,6], **Gary M. Shaw**[7], and **Paul A. Romitti**[2] **the National Birth Defects Prevention Study**

[1]Department of Pediatrics, Carver College of Medicine, University of Iowa, Iowa City, Iowa

[2]Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, Iowa

[3]Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah

[4]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

[5]Massachusetts Department of Public Health, Massachusetts Center for Birth Defects Research and Prevention, Boston, Massachusetts

[6]Genetics Unit, MassGeneral Hospital for Children, Boston, Massachusetts

[7]Department of Pediatrics, Stanford University School of Medicine, Stanford, California

Abstract

Although the descriptive epidemiology of atrioventricular septal defects (AVSDs), a group of serious congenital heart defects (CHDs), has been recently reported, non-genetic risk factors have not been consistently identified. Using data (1997–2005) from the National Birth Defects Prevention Study, an ongoing multisite population-based case–control study, the association between selected non-genetic factors and non-syndromic AVSDs was examined. Data on periconceptional exposures to such factors were collected by telephone interview from 187 mothers of AVSD case infants and 6,703 mothers of unaffected infants. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated from logistic regression models. Mothers who reported cigarette smoking during the periconceptional period were more likely to have infants with AVSDs compared with non-smokers, independent of maternal age, periconceptional alcohol consumption, infant gestational age, family history of CHDs, and study site (aOR 1.5, 95% CI 1.1–2.4). The association was strongest in mothers who smoked more than 25 cigarettes/day. In addition, mothers with periconceptional passive smoke exposure were more likely to have infants with AVSDs than unexposed mothers, independent of maternal age, active periconceptional smoking, infant gestational age, and family history of CHDs (aOR 1.4, 95% CI

*Correspondence to: Sonali S. Patel, M.D., Ph.D., Department of Pediatrics, Division of Pediatric Cardiology, University of Iowa Children's Hospital, 200 Hawkins Drive, Iowa City, Iowa 52242. sonali-patel@uiowa.edu.

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1.0–2.0). No associations were observed between AVSDs and maternal history of a urinary tract infection or pelvic inflammatory disease, maternal use of a wide variety of medications, maternal occupational exposure, parental drug use, or maternal alcohol consumption. If the results of this preliminary study can be replicated, minimizing maternal active and passive smoke exposure may decrease the incidence of AVSDs.

Keywords

atrioventricular septal defect; defect; endocardial cushion; atrioventricular canal defect; heart defects; congenital; risk factors; cigarette smoking; secondhand smoke exposure

Introduction

Congenital heart defects (CHDs), with an estimated prevalence of 6–9/1,000 live births, constitute a major proportion of clinically significant birth defects and are an important component of pediatric cardiovascular disease [Botto et al., 2001a; Hoffman et al., 2004; Reller et al., 2008]. Atrioventricular septal defects (AVSDs), also known as atrioventricular canal defects or endocardial cushion defects, include a spectrum of defects based on deficiency of the atrioventricular septum and/or atrioventricular (AV) valves and account for approximately 5–7% of all CHDs [Pierpont et al., 2000; Reller et al., 2008]. These defects comprise a group of serious CHDs with circulatory consequences leading to congestive heart failure and pulmonary vascular changes early in life. AVSDs occur most commonly in the presence of Down syndrome, but can occur in the absence of a chromosomal abnormality. Most non-syndromic AVSDs have been considered to be sporadic or the result of multifactorial inheritance [Sheffield et al., 1997]. In the largest population-based descriptive analysis, non-syndromic AVSDs were identified in 0.8/10,000 live births in the National Birth Defects Prevention Study (NBDPS) [Hartman et al., 2011]. Other population-based studies, such as the Baltimore-Washington Infant Study and the Metropolitan Atlanta Congenital Defect Program, have estimated the prevalence of non-Down syndromic AVSDs to be 1/10,000 live births [Ferencz et al., 1993; Botto et al., 2001a].

There is an interest in non-genetic risk factors which contribute to the development of CHDs; large population-based case–control studies, such as the NBDPS, have attempted to address the role that medications and other exposures may play. Numerous risk factors have been studied for their association with CHDs, however, very few risk factors have shown a significant association with AVSDs. Recent studies have suggested that maternal illnesses, medication and non-therapeutic drug use, and maternal and paternal occupational and/or environmental exposures may be significantly associated with AVSDs [Jenkins et al., 2007; Patel, 2010].

In the Baltimore-Washington Infant Study, a case–control study of CHDs in the 1980s, associations were observed between non-syndromic complete AVSDs and family history of CHDs, maternal diabetes, antitussive medication use, heavy maternal cigarette use (>20 cigarettes/day) and cocaine use, parental exposure to varnishes, and paternal exposure to ionizing radiation (Table I). A more recent analysis of this dataset identified a suggestive

dose-response association for maternal cigarettes smoked per day and non-syndromic AVSDs, although the risk estimate was not statistically significant [Alverson et al., 2011].

Case–control analyses, using data from the NBDPS, have identified other possible risk factors for non-syndromic AVSDs including maternal history of urinary tract infection during pregnancy, maternal history of diabetes during pregnancy, periconceptional antibiotic use, periconceptional opioid analgesic use, and moderate (15–24 cigarettes/day) cigarette smoking (Table I). A majority of these identified risk factors have not shown consistent associations across non-NBDPSs. All but one prior investigation of NBDPS data were performed using earlier versions of the database with fewer years of data, warranting additional analyses using a much larger sample size. In addition, the prior analyses were performed using all cases of CHDs which were then separated by defect type, of which AVSD was one type. However, these analyses did not further stratify the AVSDs based on additional defect informationinto component subtypes.

We hypothesized that non-genetic risk factors, such as maternal smoking, alcohol use, illness, and medication use, are associated with non-syndromic AVSDs and that such associations may differ by AVSD component subtypes.

Materials and Methods

Study Population

Subjects for this study were identified from the NBDPS. Details of case and control infant selection are described elsewhere [Yoon et al., 2001; Rasmussen et al., 2003]. Briefly, the NBDPS was designed to identify infants with selected major defects and unaffected live births to evaluate genetic and environmental factors associated with the occurrence of such defects [Yoon et al., 2001]. The ongoing case–control study includes case and control infants from birth defect surveillance systems at 10 sites (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Cases include all live births (all sites), stillbirths (all sites except New Jersey), and elective terminations (all sites except Massachusetts and New Jersey).

Case infants are diagnosed with one or more of over 30 major birth defects. Medical record information for each case infant is reviewed by clinical geneticists at each NBDPS center to determine study eligibility. Deliveries with recognized or strongly suspected chromosomal abnormalities or single-gene conditions are excluded. After inclusion, case infants with one specific defect are classified by one or more clinical geneticists to establish consistency. Detailed methods of CHD classification are described elsewhere [Botto et al., 2007]. Live-born infants used as controls are randomly selected from birth certificate or birth hospital records. Control infants are selected from the same base population as case infants and have an estimated date of delivery (EDD) within the same year as case infants.

As part of the NBDPS, mothers of case and control infants complete a detailed structured interview that asks about maternal health during the periconceptional period, defined as 1 month before pregnancy through the end of the first trimester, pregnancy history, prenatal care, health behaviors, home environment, maternal occupation and exposures, paternal

occupation and exposures, and parental demographics. Interviews are targeted for completion within 6 months of the infant's EDD but must be completed no earlier than 6 weeks and no later than 24 months following the EDD.

As of December 2005, maternal interview reports for 18,961 case and 6,807 control infants are included in the database. For this investigation, case and control infants were eligible NBDPS participants born from October 1997 to December 2005.

AVSD Case Classification

Case infants were those with an AVSD diagnosed by echocardiogram, cardiac catheterization, or surgical or autopsy report before 1 year age and whose mother completed the NBDPS interview. In addition to the total AVSD case group, two major AVSD subtype groups were defined. AVSD case infants were classified as having either (1) a complete AVSD, which was defined as the deficiency of the lower atrial septum and the inlet portion of the ventricular septum with a common AV valve or (2) a diagnosis within the spectrum of AVSDs—primum atrial septal defect, transitional AVSD, and inlet-type ventricular septal defect [Botto et al., 2007]. Hearts with complex single ventricle physiology (i.e., unbalanced complete AVSDs) were placed in the complete AVSD group. Within each major component subtype, cases in which the defect occurred in isolation (i.e., without an extra-cardiac defect) were distinguished as (3) isolated complete AVSDs or (4) isolated spectrum AVSDs.

Study Exposures of Interest

Exposures of interest occurred during the periconceptional period. These exposures included maternal active smoke exposure, passive smoke exposure, alcohol use, therapeutic medication use, occupational exposures, and maternal and paternal illicit drug use. Active smoke exposure was determined by self-report of cigarette use during the periconceptional period. Mothers were asked to report the number of cigarettes used per day (from <1 cigarette/day to >2 packs/day) during each month of the periconceptional period. Data on other tobacco products or nicotine replacement were not available. Passive smoke exposure was determined by self-report of exposure to environmental tobacco smoke at home or in the workplace. Data regarding duration of passive smoke exposure were not available. All exposures were coded as dichotomous yes/no variables.

As the frequencies of reported use of individual medications among case mothers were very small, medications were collapsed by drug class [Kelley et al., 2003]. Classes of interest were classified as: (1) antiinfective medications, including antibacterial, antiviral, and antifungal agents; (2) antidepressant medications; (3) asthma and/or allergy medications, including bronchodilators, mast-cell stabilizers, leukotriene modifiers, corticosteroids, antitussives, expectorants, and antihistamines; (4) gastrointestinal medications, including antacids, antidiarrheal agents, antiemetics, antiflatulents, and antiulcer agents; and (5) analgesic and antipyretic medications. Similarly, the frequencies of maternal- and paternal-specific illicit drug use and maternal occupational exposures were also very small, and thus, collapsed into dichotomous variables indicating maternal illicit drug use, paternal illicit drug use, or maternal occupational exposure during the periconceptional period.

Data Analysis

All analyses were performed using SAS 9.2 software (SAS Corporation, Cary, NC). Initial analyses compared distributions of selected exposures and covariables between AVSD cases and control infants. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to measure associations between exposure and infant AVSD occurrence. Multivariable logistic regression models were used to adjust for the effects of potential confounding variables. Exact methods were used when frequencies were less than five. A *P*-value less than 0.05 was considered statistically significant. No adjustments were made for multiple testing.

Potential confounders were selected on the basis of results of bivariable analyses and previously published evidence. Family history of CHDs, which was defined as the presence of a CHD in a first-degree relative, was included in all models as it has been previously shown that a family history of CHDs places a family at increased risk of recurrence [Oyen et al., 2009]. It also been observed that non-syndromic AVSDs are associated with the presence of a CHD in a first-degree relative (OR 7.0, 95% CI 2.6–18.9) [Ferencz et al., 1997]. The current standard of care includes treatment of a urinary tract infection (UTI) with an antibiotic, a number of which are folate antagonists, and therefore antibiotic use and folate intake were included in the final model examining the association between UTI and AVSDs [Smaill, 2007]. Other potential confounders and effect modifiers considered included study center, maternal age at delivery, paternal age at delivery, maternal race/ethnicity, paternal race/ethnicity, parity, infant sex, infant gestational age, infant birthweight, and family history of birth defects, which was defined as the presence of any birth defect in a first-degree relative.

Additional analyses focused on the four separate case subtypes— complete AVSDs, spectrum AVSDs, isolated complete AVSDs, and isolated spectrum AVSDs. Each component subtype was compared with the control group separately. Component subtype analyses were approached in a similar manner as those for all AVSD cases combined; univariable and multivariable logistic regression analysis models were fitted to estimate ORs and 95% CIs to describe the strength of the association between each of the above exposures within each AVSD component subtype.

Results

During the study period, 189 women who had a live-born infant with an AVSD (case infants) and 6,807 women who had a live-born infant without any birth defect (control infants) were contacted for participation by the NBDPS centers. Excluding 2 case and 104 control infants with incomplete interviews, there were 187 non-syndromic case and 6,703 control infants. The case group was consisting of 185 (99%) live births, 1 stillbirth, and 1 elective termination. Among all case infants, there were 78 (42%) with a complete AVSD, of which 65 (83%) were isolated. There were 109 (58%) case infants with a spectrum AVSD diagnosis, of which 81 (74%) were isolated.

Maternal and infant characteristics for case and control groups are presented in Table II. There were no significant differences between case and control participants with respect to maternal age, maternal body mass index, total family income, or infant sex. Infant birth

weight and gestational age were significantly correlated ($P < 0.0001$) and therefore, gestational age was retained for modeling.

Mothers of infants with AVSDs were more likely to be primiparous compared with mothers of infants without a birth defect, and less likely to have listed their race/ethnicity as Hispanic compared with control mothers (Table II). Mothers of case infants were also more likely to have completed high school or a technical program; and they were more likely to have been employed during their pregnancy in comparison to control mothers. Infants with AVSDs were more likely to be premature than control infants. Infants with AVSDs were also more likely to have a family history of birth defects and have a family history of CHDs in a first-degree relative than control infants.

Bivariable analyses by component subtype group produced no significant associations for maternal age, race/ethnicity, body mass index, parity, or infant sex; however, in each of the subtype groups, mothers of case infants were more likely to have been employed during their pregnancy (range of ORs among the four component subtypes 1.7–2.1) and have completed training at a technical college (ORs 3.6–5.4) (data not shown). Additionally, case infants in each group were more likely to have a family history of birth defects (ORs 1.5–1.9) and a family history of CHD in a first-degree relative (ORs 4.9–6.9) (data not shown). Of note, mothers of infants within the spectrum and isolated spectrum component subtypes were more likely to be primiparous compared with control mothers (ORs 2.3–2.9) (data not shown).

The association between maternal cigarette smoking and AVSDs was analyzed for all AVSDs as well as for each AVSD component subtype (Table III). Approximately 26% of mothers of all AVSD cases combined reported active cigarette smoking during the periconceptional period (Table III). Case mothers were more likely than control mothers to have reported active periconceptional smoking. Similar findings were noted in the complete AVSD and isolated complete component subtypes. Results were not substantially different after further adjustment for maternal age, maternal race/ethnicity, infant gestational age, alcohol consumption during the periconceptional period, family history of CHDs, and study site. When the highest level of reported smoking was included in the model, mothers who reported heavy smoking (>25 cigarettes/day) during the periconceptional period were more likely to have an infant with an AVSD compared with mothers who did not smoke (Table IV). This finding was independent of maternal age, maternal race/ethnicity, infant gestation age, alcohol consumptions during the periconceptional period, family history of CHDs, and study site. Again similar findings were noted in the complete AVSD and isolated complete AVSD component subtypes.

Periconceptional exposure to passive cigarette smoke was reported in 34% of mothers of all AVSD cases combined (Table III). These case mothers were also more likely than control mothers to have reported periconceptional exposure to passive smoke. Similar findings were noted in the complete AVSD and isolated complete AVSD component subtypes. Associations identified were independent of maternal age, maternal race/ethnicity, infant gestational age, active periconceptional smoking, family history of CHDs, and study site.

There was a significant association between periconceptional active cigarette smoking and periconceptional exposure to passive smoke among both case and control mothers ($P<$ 0.0001), with 73.5% (60.6% control) of active smoking case mothers reporting passive exposure compared with 20.4% (17.5% control) of nonsmoking case mothers. The combined effects of periconceptional active cigarette smoking and periconceptional exposure to passive smoke were also examined; Table V displays the results for the complete AVSD component subtype. Mothers who reported both active and passive exposures were more likely to have an infant with an AVSD compared with mothers who did not report either exposure. A multiplicative active and passive exposure interaction effect was not significant (OR 1.4, 95% CI 0.5–3.8) (data not shown).

None of these categories of medications, which included antibacterials, antivirals, antifungals, antidepressants, asthma and/or allergy medications, gastrointestinal medications, or analgesic and antipyretic medications, demonstrated a significant association with AVSDs or AVSD subtypes (Supplemental Table I). Other exposures evaluated included history of a UTI or pelvic inflammatory disease, parental illicit drug use, maternal occupational exposures including exposure to anesthetic gases, ionizing radiation, heavy metals, solvents, pesticides, herbicides, fungicides, or rat poison, and maternal alcohol consumption during the periconceptional period. No significant associations were observed between these categories and non-syndromic AVSDs or any of the AVSD component subtypes (Supplemental Table I).

Discussion

Findings from this population-based case–control study indicate that mothers who had infants with AVSDs were more likely to have reported periconceptional cigarette smoking than control mothers, particularly for the complete AVSD or isolated complete AVSD component subtypes. These findings extend those from a previous investigation using an earlier version of the NBDPS data which demonstrated an increased risk of AVSDs ininfants of mothers who smoked 15–24 cigarettes a day compared with mothers who did not smoke [Malik et al., 2008]. No association between active cigarette smoking and spectrum AVSDs or isolated spectrum AVSDs was identified. A recent analysis of the Baltimore-Washington Infant Study data identified a possible dose-response relationship between the number of cigarettes smoked and non-syndromic AVSDs [Alverson et al., 2011]. The current analysis of the most recent NBDPS data did not identify a significant trend, but did demonstrate that infants with AVSDs were more likely to be born to mothers who reported heavy smoking during the periconceptional period.

As maternal periconceptional smoking has been implicated as a possible risk factor for CHDs, it is possible that secondhand smoke exposure or passive smoke exposure may also play a role. Individuals exposed to secondhand smoke are subjected to a majority of the same constituents as those contained in mainstream smoke, although the pattern and amounts of exposure differ [Windham et al., 2000]. Studies of secondhand smoke exposure and birth defects have identified increased risks of neural tube defects, cleft lip with/without palate, and anorectal atresia [Miller et al., 2009; Li et al., 2010; Suarez et al., 2011].

This represents the first study to evaluate the association between passive smoke exposure and AVSDs. For all AVSDs combined, mothers were more likely to have reported periconceptional exposure to passive smoke compared with control mothers. Similar to active periconceptional smoking, mothers who had infants with either complete AVSDs or isolated complete AVSDs were more likely to have reported periconceptional exposure to passive smoke than control mothers. These results suggest that passive smoke exposure may be an additional factor to incorporate within primary preventive strategies.

Cigarette smoke contains nicotine, polycyclic aromatic hydrocarbons, tar, carbon particles, and carbon monoxide. The mechanisms by which cigarette smoke and/or the chemical compounds contained within it might result in AVSDs remain to be elucidated. However, given the complexity of cardiovascular development, such mechanisms are likely to involve gene–gene, gene–environment, or environment–environment interactions. Endo-thelial nitric oxide synthase produces nitric oxide, which plays a role in vasodilatation and in the regulation of cell growth and apoptosis. Genetic variants within the nitric oxide synthase (NOS) gene are known to be associated with birth defects including cleft lip with/without palate, gastroschisis, and limb deficiency defects [Shaw et al., 2005; Carmichael et al., 2006; Torfs et al., 2006]. It has also been demonstrated that NOS isoforms are present early in embryonic cardiac development [Bloch et al., 1999; Shaw et al., 2005; van Beynum et al., 2008]. The toxicity of xenobiotics for embryonic tissues depends on the biotransformation process during which reactive products are formed (phase I) and detoxified (phase II). Several enzymes (and their gene families) are involved in this process including glutathione transferases. Genetic polymorphisms of glutathione transferase enzymes, which provide a critical defense against toxins, have been shown to be associated with CHD formation [Cresci et al., 2011]. These investigations with such gene–environment interaction effects demonstrate the importance of additional investigations of the associations between structural heart defects, maternal smoking, and genetic variants that may modify the effect of smoking on the developing fetal heart.

It is interesting to note the difference in magnitude of ORs and CIs between the complete and spectrum AVSD component subtypes throughout this study, which likely reflects the fact that the complete AVSD group is a more homogenous group. The AVSD spectrum component subtype group is not a clinical diagnostic group, but rather a pragmatic classification scheme developed for this investigation. As complete AVSDs and the diagnoses within the spectrum AVSD group have structural differences, there may be developmental heterogeneity among the groups. If individual defects have developmental heterogeneity, there may also be etiologic variation. Such differences warrant further investigation of complete AVSDs versus the remainder of the AVSD diagnoses.

No significant associations were observed between AVSDs and antibacterials, antivirals, antifungals, antidepressants, asthma and/or allergy medications, gastrointestinal medications, analgesic and antipyretic medications, parental illicit drug use, and maternal occupational exposures. In prior studies, a significant association was seen between AVSDs and antibacterial use and a history of a UTI [Cleves et al., 2008; Crider et al., 2009]. In the present study, however, there were insufficient data to assess these potential risk factors.

The strengths of this study include the use of the NBDPS database, which represents the largest population-based, case–control study of major cardiovascular malformations conducted in the USA. The NBDPS has a geographically and ethnically diverse population which reduces the risk of selection bias. As previously reported, the NBDPS controls are similar to all live births in the USA [Cogswell et al., 2009]. The cases are reviewed and verified by clinical geneticists improving the accuracy of correct case classification. Additionally, there is a rigorous review of the abstracted medical chart data by an expert panel of clinicians in order to maximize the homogeneity of case classification.

Limitations of the NBDPS must be considered. A major limitation of this study was small sample sizes when cases were separated into component subtype groups. Recall bias was also of concern due to the retrospective data collection. Each exposure was determined by maternal self-reports without independent validation. Nondisclosure of active smoking status likely resulted in an underestimation of the true smoking frequency. A recent study identified active smoking non-disclosure rates in pregnant women (22.9%) were higher than in non-pregnant women (9.2%) [Dietz et al., 2011]. The classification of CHDs requires accurate case review and coding by the clinical geneticist at each center, followed by the review of the “heart classifier” who ensures that variant and partial forms, including some cases coded as atrial and ventricular septal defects, are classified correctly as an AVSD. Miscoding would result in a reduction in the actual numbers. The surveillance method of each participating center in the NBDPS also varies. Some centers perform surveillance across certain portions of the state, while others include the entire state. This may result in under-representation of certain ethnic groups, or socioeconomic classes.

The results of this study have important public health consequences. In this study, 19% of the control participants reported cigarette use during the periconceptional period whereas 25% reported passive smoke exposure at home and/or work, which are consistent with national figures [Mathews and Rivera, 2004]. Thus, approximately 1 million infants are prenatally exposed to cigarette smoke by maternal smoking each year [Byrd and Howard, 1995; Tong et al., 2009]. Further investigations are warranted to support the results of this preliminary study and confirm that active and passive smoke exposure is associated with AVSD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Environmental Exposures and Non-Syndromic Atrioventricular Septal Defects

Exposure	Source	Database	Cases (N)	Controls (N)	cOR (95% CI)
Antibiotic medications	Crider et al. [2009]	NBDPS (1997–2003)	128	4,941	**1.7 (1.1–2.6)**
Antihypertensive medications	Caton et al. [2009]	NBDPS (1997–2003)	126	4,796	2.6 (0.3–10.3)
Antitussive medications	Ferencz et al. [1997]	BWIS (1981–1989)	76	3,572	**6.3 (1.9–21.6)**
	Ferencz et al. [1997]	BWIS (1981–1989)	30[a]	3,572	**8.8 (1.2–48.2)**
Cigarette smoking	Ferencz et al. [1997]	BWIS (1981–1989)	76	3,572	**2.5 (1.2–5.2)**
	Alverson et al. [2011]	BWIS (1981–1989)	57	3,435	**1.5 (1.0–2.3)**
	Malik et al. [2008]	NBDPS (1997–2002)	87	3,947	**2.2 (1.0–4.6)**
Clomiphene citrate use	Reefhuis et al. [2011]	NBDPS (1997–2005)	167	6,406	1.2 (0.3–3.8)
Cocaine	Ferencz et al. [1997]	BWIS (1981–1989)	76	3,572	**3.5 (1.1–11.4)**
Diabetes	Loffredo et al. [2001b]	BWIS (1981–1989)	76	3,572	**22.8 (7.4–70.5)**
	Loffredo et al. [2001a]	BWIS (1981–1989)	30[a]	3,572	**20.6 (5.6–76.4)**
	Correa et al. [2008]	NBDPS (1997–2003)	66	4,689	**12.4 (3.7–41.5)**
Diuretic medications	Ferencz et al. [1997]	BWIS (1981–1989)	76	3,572	**7.3 (2.1–25)**
Febrile illness	Botto et al. [2001b]	ABDCCS (1968–1980)	14	3,029	2.4 (0.5–10.9)
Genital tract infections	Carter et al. [2011]	NBDPS (1997–2004)	82	5,913	1.4 (0.4–4.6)
Ionizing radiation (paternal)	Ferencz et al. [1997]	BWIS (1981–1989)	76	3,572	**4.5 (1.4–15.2)**
Multivitamin use	Botto et al. [2001b]	ABDCCS (1968–1980)	14	3,029	1.1 (0.2–5.7)
Opioid analgesic medications	Broussard et al. [2011]	NBDPS (1997–2005)	175	6,701	**2.0 (1.2–3.6)**
Oral contraceptive medications	Waller et al. [2010]	NBDPS (1997–2003)	76	4,000	1.0 (0.4–2.5)
Overweight/obese	Gilboa et al. [2010]	NBDPS (1997–2004)	81	5,673	0.9 (0.6–1.5)
Paint/varnishes (parental)	Ferencz et al. [1997]	BWIS (1981–1989)	76	3,572	**4.5 (1.4–15.2)**
Thyroid disease	Browne et al. [2009]	NBDPS (1997–2004)	90	5,875	2.3 (0.6–6.3)
Urinary tract infections	Cleves et al. [2008]	NBDPS (1997–2003)	98	4,760	**2.3 (1.1–4.7)**

Exposures are maternal unless otherwise noted.

cOR, crude odds ratio; BWIS, Baltimore-Washington Infant Study; NBDPS, National Birth Defects Prevention Study; ABDCCS, Atlanta Birth Defects Case–Control Study. Items in bold indicate significant findings.

[a]Complete AVSD analyzed only.

Table II
Characteristics of Case and Control Participants

Variable	Case participants (N = 187), N (%)	Control participants (N = 6,703), N (%)	cOR (95% CI)
Maternal age (years)[b]			
<18	4 (2.1)	245 (3.7)	0.6 (0.2–1.6)
18–24	57 (30.5)	1,993 (29.5)	1.0 (0.7–1.4)
25–34	101 (54.0)	3,519 (52.5)	Reference
≥35	25 (13.4)	946 (14.1)	0.9 (0.6–1.4)
Maternal race/ethnicity[a]			
Non-Hispanic White	124 (66.7)	4,011 (60.1)	Reference
Non-Hispanic Black	30 (16.1)	764 (11.5)	1.3 (0.8–1.9)
Hispanic	24 (12.9)	1,491 (22.3)	**0.5 (0.3–0.8)**
Other	8 (4.3)	409 (6.1)	0.6 (0.3–1.6)
Maternal body mass index[a]			
Underweight	9 (4.9)	356 (5.5)	0.9 (0.5–1.8)
Normal	99 (54.1)	3,593 (55.8)	Reference
Overweight/obese	75 (41.0)	2,491 (38.7)	1.1 (0.8–1.5)
Maternal parity[b]			
Primipara	151 (80.7)	4,939 (73.7)	**1.5 (1.1–2.4)**
Multipara	36 (19.3)	1,762 (26.3)	Reference
Maternal education[b]			
<High school	15 (8.0)	1,128 (16.9)	Reference
High school education	109 (58.3)	3,248 (48.5)	**2.5 (1.5–4.4)**
Technical college	13 (7.0)	208 (3.1)	**4.7 (2.2–10.0)**
≥Bachelor's degree	50 (26.7)	2,110 (31.5)	1.8 (1.0–3.2)
Maternal job status[b]			
Employed	155 (82.9)	4,825 (72.0)	**1.9 (1.3–2.8)**
Not employed	32 (17.1)	1,873 (28.0)	Reference
Total family income[a]			
<$10,000	27 (15.1)	1,079 (17.9)	0.7 (0.4–1.1)
$10,000–29,999	54 (30.2)	1,696 (28.1)	0.9 (0.6–1.3)
$30,000–50,000	42 (23.4)	1,131 (18.7)	Reference
≥$50,000	56 (31.3)	2,132 (35.3)	0.7 (0.5–1.1)
Infant gestational age (weeks)[b]			
<37	39 (20.9)	635 (9.5)	**2.5 (1.8–3.6)**
≥37	148 (79.1)	6,067 (90.5)	Reference
Infant sex[b]			
Female	104 (55.6)	3,309 (49.4)	1.3 (1.0–1.7)
Male	83 (44.4)	3,389 (50.6)	Reference
Family history of birth defects[a]			
Yes	69 (36.9)	1,717 (25.9)	**1.7 (1.2–2.3)**

Variable	Case participants (N = 187), N (%)	Control participants (N = 6,703), N (%)	cOR (95% CI)
No	118 (63.1)	4,923 (74.1)	Reference
Family history of CHD[b]			
Yes	29 (15.5)	212 (3.2)	**5.6 (3.7–8.5)**
No	158 (84.5)	6,491 (96.8)	Reference

cOR, crude odds ratio; CI, confidence interval; CHD, congenital heart defects.

Items in bold indicate significant findings.

[a] Between 10 and 700 missing responses.

[b] Less than 10 missing responses.

Table III

Active and Passive Cigarette Smoke Exposure During the Periconceptional Period

	Cigarette smoking (active)[a]			Cigarette smoke (passive)[b]		
	Cases, N (%)	cOR (95% CI)	aOR[c] (95% CI)	Cases, N (%)	cOR (95% CI)	aOR[d] (95% CI)
All AVSDs (N = 187)	49 (26.3)	**1.5 (1.1–2.1)**	**1.6 (1.1–2.4)**	64 (34.4)	**1.5 (1.1–2.1)**	**1.6 (1.0–2.4)**
All complete AVSD (N = 78)	27 (34.6)	**2.3 (1.4–3.6)**	**2.2 (1.1–4.1)**	34 (43.6)	**2.2 (1.4–3.5)**	**2.3 (1.2–4.4)**
Isolated complete AVSD (N = 65)	23 (35.4)	**2.3 (1.4–3.9)**	**2.2 (1.1–4.4)**	27 (41.5)	**2.1 (1.3–3.4)**	**1.8 (1.0–3.7)**
All spectrum AVSD [e] (N = 108)	22 (20.4)	1.1 (0.7–1.8)	1.2 (0.6–2.2)	30 (27.8)	1.1 (0.7–1.7)	1.2 (0.6–2.1)
Isolated spectrum AVSD (N = 80)	18 (22.5)	1.2 (0.7–2.1)	1.0 (0.5–2.1)	26 (32.5)	1.4 (0.9–2.2)	1.4 (0.7–2.7)

AVSD, atrioventricular septal defect; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

Items in bold indicate significant findings.

[a] Each case group was compared with the control group (positive response in 1,272/6,700 = 18.99%).

[b] Each case group was compared with the control group (positive response in 1,715/6,685 = 25.65%).

[c] Adjusted for maternal age, maternal race/ethnicity, gestational age, alcohol consumption during the periconceptional period, family history of congenital heart defects, and study site.

[d] Adjusted for maternal age, maternal race/ethnicity, gestational age, maternal cigarette use, family history of congenital heart defects, and study site.

[e] Diagnoses included in spectrum classification include: primum-type atrial septal defect, transitional AVSD, and inlet-type ventricular septal defects.

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Table IV

Reported Maternal Smoking by the Highest Level of Reported Smoking During the Periconceptional Period

	Light smoking (1–14 cigarettes/day)†		Moderate smoking (14–24 cigarettes/day)†		Heavy smoking (≥25 cigarettes/day)†	
	Cases, N (%)	aOR[a] (95% CI)	Cases, N (%)	aOR[a] (95% CI)	Cases, N (%)	aOR[a] (95% CI)
All AVSDs (N = 187)	33 (17.7)	1.5 (0.9–2.5)	12 (6.5)	1.2 (0.5–2.7)	4 (2.1)	**4.4 (1.5–12.8)**
All complete AVSDs (N = 78)	18 (23.1)	2.1 (1.0–4.3)	6 (7.7)	0.7 (0.2–3.3)	3 (3.9)	**7.7 (2.1–28.6)**
Isolated complete AVSDs (N = 65)	15 (23.1)	2.2 (0.9–4.9)	6 (9.2)	1.0 (0.2–4.7)	2 (3.1)	**7.1 (1.5–33.4)**
All spectrum AVSDs[b] (N = 108)	15 (13.9)	1.0 (0.5–2.3)	6 (5.6)	1.5 (0.6–4.1)	1 (0.9)	1.8 (0.2–14.1)
Isolated spectrum AVSDs (N = 80)	12 (15.0)	0.8 (0.3–2.0)	5 (6.3)	1.3 (0.5–4.0)	1 (1.3)	1.9 (0.2–14.4)

AVSD, atrioventricular septal defect; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

† Each case group was compared with the control group (positive response in 1,272/6,700 = 18.99%).

[a] Adjusted for maternal age, maternal race/ethnicity, gestational age, alcohol consumption during the periconceptional period, family history of congenital heart defects, and study site.

[b] Diagnoses included in spectrum classification include: primum-type atrial septal defect, transitional AVSD, and inlet-type ventricular septal defects.

Table V
Active and Passive Smoke Exposure for Complete AVSD Component Subtype

Smoke exposure group	Cases, N (%)	Controls, N (%)	cOR (95% CI)	aOR[a] (95% CI)
No active or passive exposures	39 (50.0)	4,470 (66.9)	Reference	Reference
Active exposure only	5 (6.4)	500 (7.5)	1.2 (0.5–3.0)	1.1 (0.4–2.7)
Passive exposure only	12 (15.4)	946 (14.1)	1.5 (0.8–2.3)	1.6 (0.8–3.1)
Both active and passive exposures	22 (28.2)	768 (11.5)	3.3 (2.0–5.6)	3.1 (1.8–5.3)

AVSD, atrioventricular septal defect; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

[a]Adjusted for maternal age, maternal race/ethnicity, gestational age, family history of congenital heart defects, and study site.