Geographic and Occupational Risk Factors for Ventricular Septal Defects

Washington State, 1987-2003

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Objective: Ventricular septal defect (VSD) is currently the most common congenital cardiac malformation in the United States, but little is known about its etiology. The objective of this study was to address the hypothesis that parents’ residence in eastern Washington, a region heavily dominated by the agricultural industry, and employment in agriculturally related occupations can influence the presence of a VSD in their offspring.

Design: Population-based case-control study.


Patients: Children aged 0 to 2 years diagnosed as having a VSD (n=3489), and other infants selected at random as control subjects (n=13 290).

Main Exposures: Parental occupation and county of maternal residence were obtained from the birth certificate. The latter was categorized according to region (east vs west), rural-urban classification, and the proportion of farm and crop land.

Main Outcome Measures: Diagnosis of VSD within the first 2 years of life.

Results: The risk of VSD was greater for infants whose mothers resided in eastern Washington (odds ratio, 1.30; 95% confidence interval, 1.03-1.65). The risk of VSD with other cardiac malformations (n=1205) exhibited a stronger geographic association than did isolated VSD (n=2284). Analyses restricted to eastern Washington did not reveal a clear relationship between the risk of VSD and an increasing proportion of agricultural land in the mother’s county of residence. Parental occupation in agriculture was not associated with the presence of VSD.

Conclusion: Although these findings suggest regional variation in Washington State in the occurrence of VSD, the basis for this variation remains to be determined.

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IN THE UNITED STATES, CONGENITAL cardiac malformations are associated with high morbidity and mortality for infants. These malformations are frequent (approximately 3-4.5 per 1000 births), and treatment for individuals with congenital heart disease, such as surgical interventions and ongoing medical management, is costly. Ventricular septal defects (VSDs) are the most common form of cardiac malformation. A VSD can occur as an isolated anomaly or in conjunction with other cardiac malformations and/or genetic conditions. Little is known about the causes of VSD. Results of some studies, including the Baltimore-Washington Infant Study, have suggested that infants of parents exposed to pesticides had an increased risk of VSD, whereas other studies have not detected an association.

The economy in eastern Washington State is heavily dominated by the agricultural industry, far more so than in western Washington. We speculated that if pesticide exposure were truly a risk factor, then VSDs should be relatively more common in eastern Washington, and agriculturally related occupations should be more prevalent in the parents of children with VSD than in the parents of control children.

METHODS

SUBJECTS AND OUTCOME

We used birth certificate data linked with hospital discharge information from all nonfederal hospitals in the Comprehensive Hospital Abstract Reporting System in Washington State from January 1, 1987, through December 31, 2003, to conduct a population-based case-control study. The total number of singleton live births included in this database from the study period was 1 159 749, which was approxi-
Persons residing in one of the southwestern border counties of Washington State (Skamania, Klickitat, and Clark counties) may receive specialty health and hospital care in Portland, Ore. Given the potential for underascertainment of cases, we performed additional analyses excluding infants of mothers residing in these counties. In addition, individuals with chromosomal abnormalities such as trisomy 21 are at increased risk of congenital heart anomalies including VSDs. Given that these infants may be at increased risk of the outcome of interest by alternate etiologic pathways, and that their inclusion may have altered our risk estimates, we performed additional analyses excluding infants whose records contained a diagnosis of a chromosomal abnormality (ICD-9 code 758.xx). Finally, we examined whether the magnitude of the associations differed by whether cases had a VSD alone or a VSD with an additional cardiac malformation.

STATISTICAL METHODS

To estimate associations between the exposures of interest and the occurrence of VSD, logistic regression analyses were performed. When data were missing for a particular variable for a given subject, that subject was not included in the analyses for that variable. To account for the correlated nature of the observations for county-level variables, we used generalized estimating equations with exchangeable structure for variance to obtain risk estimates and 95% confidence intervals (CIs), as have been described. Although generalized linear models are a standard method used to fit regression models for univariate data that follow an exponential distribution, this technique is less tractable for correlated data sets. Generalized estimating equations allow for the extension of generalized linear models to accommodate correlated data. Briefly, the method is used to characterize the marginal expectation of a set of outcomes as a function of a set of study variables. The method models the within-cluster similarity of the residuals and then uses this estimated correlation to fit the regression parameters and calculate the standard errors.

The following variables were considered for their potential confounding effects on the association between VSDs and the exposures of interest: maternal age (<20, 20-34, or ≥35 years), number of previous births (0, 1, or ≥2), maternal race or ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, or other non-Hispanic), maternal years of education completed (<12, 12, or >12), maternal marital status (married or unmarried), smoking during pregnancy (yes or no), season of birth (January-March, April-June, July-September, or October-December), and sex of the infant. This study was approved by the institutional review board of the University of Washington, Seattle.

RESULTS

A total of 3489 children diagnosed as having a VSD within the first 2 years of life between 1987 and 2003 and 13 290 controls were identified for analysis. Based on the total number of singleton live births included in this database, the estimated prevalence of VSD during the study period was 3.0 per 1000 live births. Cases were similar to controls at birth with respect to maternal age, parity, maternal race and ethnicity, maternal education, maternal marital status, maternal smoking during pregnancy, season of birth, and infant sex (Table 1). Consequently, we did not adjust for these variables in calculating the risk estimates for the exposures of interest.
Maternal or paternal agricultural employment was not associated with increased risk of VSD (Table 2). In addition, no difference in the risk of VSD was detected for infants born to mothers residing in counties grouped by the RUCA classification (Table 2). A higher proportion of mothers of cases than mothers of controls resided in eastern Washington (odds ratio [OR], 1.30; 95% CI, 1.03-1.65) (Table 2). The risk of VSD was also elevated for infants whose mothers resided in those counties with the highest percentage of crop land (OR, 1.38; 95% CI, 1.07-1.79). A similar trend was observed for counties with the highest percentage of farm land (Table 2).

Analyses excluding Skamania, Klickitat, and Clark counties showed risk estimates similar to those obtained in the unrestricted analyses for infants of mothers who resided in eastern Washington (OR, 1.21; 95% CI, 1.01-1.46), in counties with the highest percentage of farm land (OR, 1.25; 95% CI, 1.02-1.54), and in counties with the highest percentage of crop land (OR, 1.36; 95% CI, 1.08-1.72) (Table 2).

A total of 270 VSD cases (7.7%) and 14 controls (0.1%) had a diagnosis of a chromosomal abnormality. Analyses excluding these infants showed risk estimates similar to those obtained in the unrestricted analyses for infants of mothers who resided in eastern Washington (OR, 1.26; 95% CI, 1.00-1.60), in counties with the highest percentage of farm land (OR, 1.24; 95% CI, 0.95-1.61), and in counties with the highest percentage of crop land (OR, 1.34; 95% CI, 1.04-1.72) (Table 2).

A total of 1021 cases of VSD and 3262 controls were included in the analyses limited to infants born to mothers residing in eastern Washington at the time of birth. In this subset, the cases were generally similar to the controls at birth with respect to maternal age, parity, maternal race and ethnicity, maternal education, marital marital status, maternal smoking during pregnancy, season of birth, and infant sex (data not shown). A smaller proportion of the mothers of cases compared with the mothers of controls were engaged in an agriculturally related occupation (OR, 0.57; 95% CI, 0.33-0.97) (Table 3).

There were no appreciable differences in the risk of VSD for infants born to fathers with agricultural compared with nonagricultural employment and unemployment. Similarly, there were no differences in risk estimates for infants born to mothers residing in counties grouped by the RUCA classification or by the percentage of farm land. Although residents of counties in the lowest third for percentage of farm or crop land had the lowest risk of VSD, we did not observe a monotonic increase in the risk with an increasing percentage of farm or crop land, respectively (Table 3).

Among all cases of VSD in Washington State, 2284 infants had isolated VSDs, and 1205 infants had at least 1 additional ICD-9 code–based congenital heart disease diagnosis. Each group of cases was generally similar to the controls at birth with respect to maternal age, parity, maternal race and ethnicity, maternal education, marital marital status, maternal smoking during pregnancy, season of birth, and infant sex (data not shown). Children born to mothers or fathers with agricultural employment were not at altered risk of an isolated VSD or a VSD combined with another cardiac malformation (Table 4).

Similarly, there were no differences in the risk for infants born to mothers residing in counties grouped by the RUCA classification (Table 4). A higher proportion of the mothers of cases with additional cardiac malformation than mothers of controls resided in eastern Washington (OR, 1.61; 95% CI, 1.13-2.27) (Table 4). A weaker trend in this direction was observed for cases without additional cardiac malformations (Table 4). Similar risk patterns, with infants who had additional cardiac anomalies having a higher risk than those with an isolated VSD, were observed for infants whose mothers resided in those counties with the highest percentage of farm land and crop land (Table 4).

Our results suggest that the occurrence of VSD among live-born infants within the first 2 years of life is greater in eastern than in western Washington State. Analyses restricted to eastern Washington residents failed to demonstrate a clear relationship between the risk of VSD and county-level indicators of agricultural activity. To miti-
gate any inflation of our risk estimates by the potential referral bias in 3 southwestern counties, we performed repeat analyses excluding these counties and found similar results. To mitigate any effect of the presence of a chromosomal abnormality that may be associated with our outcome of interest through an alternate causal pathway, we performed repeat analyses excluding these infants and found similar results. Given the nature of this administrative data set, we are unable to reliably identify the subset of patients with a variety of noncardiac syndromic and nonsyndromic congenital malformations because these represent a heterogeneous group of conditions that, even when identified by a health care provider, do not all have associated ICD-9 codes. Therefore, we were unable to perform additional analyses excluding these infants to mitigate any possible effect of the presence of a syndrome that may be associated with our outcome of interest through an alternate causal pathway. We did not detect confounding by demographic characteristics in the mother or the infant in any of the comparisons analyzed.

Our study was limited to children who were diagnosed as having congenital heart disease during the birth hospitalization or who required hospitalization within the first 2 years of life. The estimated prevalence of VSD in this study, 3.0 per 1000 live births, was similar to previous estimates in other studies in the United States.2-4 Some children diagnosed as having VSD are treated exclusively in an outpatient setting, and it is probable that milder forms of VSD were missed in our analyses. In addition, we did not evaluate pregnancies that did not result in a live birth. These factors limit our ability to make inferences for milder forms of these diseases, for lethal in utero cases, and for fetuses with lethal conditions, irrespective of whether they were the result of a VSD.

Another possible limitation of our analysis is the misclassification of malformations ascertained from the Comprehensive Hospital Abstract Reporting System database using ICD-9 codes. However, pediatric cardiologists diagnose most cases of congenital cardiac disease in which a child receives an inpatient diagnostic code of a VSD in

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**Table 2. Unadjusted Risk Estimates for Diagnosis of VSD Within the First 2 Years of Life Associated With Proxy Measures of Agricultural Occupation and Ambient Environmental Exposures, Washington State, 1987-2003**

<table>
<thead>
<tr>
<th>County percentage of crop land‡</th>
<th>OR (95% CI)</th>
<th>Unrestricted Analyses</th>
<th>Excluding 3 Southwestern Counties†</th>
<th>Excluding Chromosomal Abnormalities‡</th>
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Abbreviations: CI, confidence interval; OR, odds ratio; RUCA, rural-urban commuting area; VSD, ventricular septal defect.

*SNumbers may not add to the totals because of missing data. Percentages have been rounded and may not total 100.
†Cases and controls from Skamania, Klickitat, and Clark counties were excluded from analyses.
‡Two hundred seventy cases and 14 controls with a diagnosis of chromosomal abnormality (International Classification of Diseases, Ninth Revision, code 758.xx) were excluded from analyses.
§Groupings are relative to the Cascade Mountain Range.
||Groupings are based on the county-level approximations of the 2000 US Census RUCA classifications.13
‡Two hundred seventy cases and 14 controls with a diagnosis of chromosomal abnormality (International Classification of Diseases, Ninth Revision, code 758.xx) were excluded from analyses.

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We were unable to account for several potentially important confounders of the association between environmental and demographic characteristics and VSDs, such as family history of congenital heart disease, maternal febrile illness, 21 prenatal care and folic acid supplementation, 21,22 maternal alcohol consumption, 22,23 socioeconomic status, 24 maternal or paternal use of recreational drugs, 20,23 and other medication use during pregnancy. 19,25 Although maternal education is a proxy measure of socioeconomic status, other important demographic characteristics relevant to socioeconomic status, such as household income, were not available in this data set. To eliminate confounding by maternal diabetes status, we excluded all infants born to mothers with diabetes mellitus indicated on the birth certificate (gestational) or by an ICD-9 code (gestational or preexisting).

However, our analyses could have included mothers with undiagnosed or unreported diabetes.

An advantage of our study design was our ability to assess exposures in a large number of individuals with and without VSDs. The disadvantage of using birth certificate and Comprehensive Hospital Abstract Reporting System data was that we had to rely on proxy measures of exposures. For example, the selected agricultural indicators used in this study reflect proxies for environmental exposures rather than measures of exposures to specific toxins. In addition, the county of residence at the time of delivery may not represent the county of residence during the prenatal period, resulting in the misclassification of possible geographically based environmental exposures. Also, individuals within a county have...
different levels of exposure to ambient environmental chemicals. Analyses using more detailed information for maternal residence to ascertain geographically based exposures that could account for proximity to local farms within a county may be more sensitive in delineating risks associated with environmental exposures. Although our data set included a large number of cases, the occupation variable had a large amount of missing information and may not have represented a person's recent work history, despite the request for the occupation in the past year on the birth certificate. In addition, self-reported occupation on the birth certificate may not reflect the parent’s occupational exposures during the first trimester, when the interventricular septum develops. As such, our findings that a smaller proportion of mothers of cases than mothers of controls were engaged in an agriculturally related occupation should be interpreted with caution. The lack of detailed information in our study for occupational exposure precluded pursuing additional investigations into exposures to specific chemicals or classes of chemicals.

Previous studies have sought to investigate potential associations between the occurrence of these heart malformations and regional ambient environmental exposures. Results from a case-control study involving 303 children with VSDs in Los Angeles, Calif, suggest a dose-response relationship between the occurrence of VSD and ambient air pollution (carbon monoxide) exposure during the first trimester of pregnancy. Women residing in regions where ambient carbon monoxide measurements obtained from air-monitoring stations were greater than 2.39 ppm during the second month of pregnancy had the highest risk of having an infant with VSD (OR, 2.95; 95% CI, 1.44-6.05). However, a recent population-based case-control study28 from 7 counties in Texas involving 5338 children with 1 of several birth defects failed to corroborate this observed association between ambient air levels of carbon monoxide and the risk of VSD in offspring. The authors of that study note that carbon monoxide levels in this region of Texas are much lower and much less variable than those reported in Southern California and that this variable could account for the differing findings of these studies. However, the authors reported an association between ambient levels of sulfur dioxide and the risk of isolated VSDs in offspring (OR, 2.16; 95% CI, 1.51-3.09). Results from the Baltimore-Washington Infant Study,7 a population-based case-control study that compared 4296 live-born infants with structural congenital heart defects with controls in 1981 through 1989, suggested associations between agriculturally related exposures and VSD. Specifically, infants of parents who reported being exposed to pesticides during the 3 months before through the 3 months after the mother’s last menstrual period had an increased risk of VSD (OR, 1.3). Although that study included a large number of subjects and obtained detailed prenatal information, pesticide exposure status was ascertained through interviews conducted after the diagnosis and thus may have been subject to recall bias. A case-control study conducted from 1982 to 1983 in Finland11 included 150 cases of VSD and more than 700 controls. Structured interviews of mothers 3 months after delivery failed to show an association between maternal occupational exposure to pesticides and occurrence of VSD. In a retrospective cohort study conducted from 1975 through 1978 of 2463 infants born in an agricultural community,9 the relative risk of VSD in the infants of parents employed in agriculture was 0.7.

Our findings suggest that there is regional variation within Washington State in the occurrence of VSDs. Although environmental exposures related to agricultural activities in areas with a high proportion of crop land could explain this phenomenon, studies incorporating a more refined assessment of exposure history would be needed to further elucidate the specific risk factors responsible.

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Author Contributions: Drs Batra, Heike, and Phillips had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Batra and Heike. Acquisition of data: Batra and Phillips. Analysis and interpretation of data: Batra, Heike, Phillips, and Weiss. Drafting of the manuscript: Batra, Heike, Phillips, and Weiss. Critical revision of the manuscript for important intellectual content: Batra, Heike, Phillips, and Weiss. Statistical analysis: Batra, Phillips, and Weiss. Administrative, technical, and material support: Batra anad Heike. Study supervision: Weiss.

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REFERENCES


**Announcement**

Submissions. The Editors welcome contributions to Picture of the Month. Submissions should describe common problems presenting uncommonly, rather than total zebras. Cases should be of interest to practicing pediatricians, highlighting problems that they are likely to at least occasionally encounter in the office or hospital setting. High-quality clinical images (in either 35-mm slide or electronic format) along with parent or patient permission to use these images must accompany the submission. The entire discussion should comprise no more than 750 words. Articles and photographs accepted for publication will bear the contributor’s name. There is no charge for reproduction and printing of color illustrations. For details regarding electronic submission, please see: http://archpedi.ama-assn.org.