OBJECTIVES: There has long been an association between congenital heart disease (CHD) and general neurodevelopmental delays. However, the association between CHD and autism spectrum disorders (AuSDs) is less well understood. Using administrative data, we sought to determine the association between CHD and AuSD and identify specific CHD lesions with higher odds of developing AuSD.

METHODS: We performed a 1:3 case-control study of children enrolled in the US Military Health System from 2001 to 2013. Children with International Classification of Disease, Ninth Revision, Clinical Modification codes for AuSD were identified as cases and matched with controls on the basis of date of birth, sex, and enrollment time frame. Each child’s records were reviewed for CHD lesions and associated procedures. Conditional logistic regression determined odds ratios (ORs) and 95% confidence intervals (CIs) for comparative associations.

RESULTS: There were 8760 cases with AuSD and 26,280 controls included in the study. After adjustment for genetic syndrome, maternal age, gestational diabetes, short gestation, newborn epilepsy, birth asphyxia, and low birth weight, there were increased odds of AuSD in patients with CHD (OR 1.32; 95% CI 1.10–1.59). Specific lesions with significant OR included atrial septal defects (n = 82; OR 1.72; 95% CI 1.07–2.74) and ventricular septal defects (n = 193; OR 1.65; 95% CI 1.21–2.25).

CONCLUSIONS: Children with CHD have increased odds of developing AuSD. Specific lesions associated with increased risk include atrial septal defects and ventricular septal defects. These findings will be useful for counseling parents of children with CHD.
As a result of tremendous advances in surgical technique, children born today with complex congenital heart disease (CHD) have improved survival over earlier surgical eras.1 This improved survival, however, has been accompanied by a greater appreciation for important comorbidities, including neurodevelopmental challenges. In 2012, the American Heart Association released a scientific statement on the evaluation and management of neurodevelopmental outcomes in children with CHD.2 In the statement, Marino et al2 specifically address the increased risk for autism spectrum disorders (AuSDs) and the need for screening in early development. Despite this strong recommendation, there is a paucity of research on AuSD as a developmental outcome of CHD. Our purpose with this study is to investigate and better quantify the association between CHD and AuSD.

Many studies have been used to look for associations between CHD and neurodevelopmental disorders; however, nearly all of these previous studies have limitations that fall short of illuminating the association between CHD and AuSD. Several studies have demonstrated a link between CHD, neurodevelopmental delays, and subsequent poor school performance.3,4 Although much of the etiology for the neurologic disorder is thought to stem from a combination of preoperative, operative, and postoperative factors, there is no certainty of the degree to which any specific factor contributes to the outcome. Authors of previous rigorous studies looking to identify factors contributing to neurodevelopmental delay in CHD have tended to focus on specific cardiac defects,5,6 look at structural brain anomalies rather than developmental outcomes,7 or otherwise be insufficiently powered to detect a link between rare disease and a specific developmental outcome such as AuSD.8 Surprisingly, few of these previous studies have measured AuSD as an outcome.

Some of the limitations of previous studies can be overcome by using a large, administrative database that collects information on both CHD and AuSD in children with sufficient power to detect an association between rare diseases. Hultman et al9 and Weir et al10 have attempted to study this association using administrative data with conflicting results. An excellent and more recent database study by Tsao et al11 revealed a hazard ratio of 1.97 (95% confidence interval [CI] 1.11–3.52) between AuSD and CHD; however, the authors stopped short of investigating subtypes of CHD. Razzaghi et al12 demonstrated a larger effect with a crude odds ratio (OR) of 4.6 (95% CI 1.9–11.0). In the study by Razzaghi et al,12 validity was limited by use of voluntary parental questionnaire responses with binary inputs (yes or no) for both AuSD and CHD diagnoses.

To overcome the limitations of previous studies, we used the Military Health System (MHS) administrative database, a large database that includes longitudinal billing for care of children across multiple geographically dispersed regions. Our objective with this study was to determine the association of CHD and CHD subtypes with the development of autism by using the MHS database and fill a gap in the medical literature. On the basis of previous research, we primarily hypothesized that AuSD would be associated with CHD and secondarily that more hemodynamically severe forms of CHD would be more highly associated with AuSD.

METHODS

We performed a nested case-control study using the MHS database. The MHS is one of the largest single-payer health care systems in the United States, providing care to millions of military members and dependent beneficiaries, both in military facilities and through purchased care in civilian facilities. The MHS database was designed to capture demographic and billing data for all care within the system. This includes in- and outpatient care, diagnostic and procedure codes, dates of service, and prescriptions. As such, the MHS database had sufficient power to identify associations between rare conditions and outcomes. Several of our coauthors designed and compiled this nested case-control data set for a study of perinatal AuSD risk factors.13 We performed a secondary analysis on this data set to investigate an association between CHD and AuSD.

Cases were defined as children with a diagnosis of AuSD who had a birth record in the MHS between October 1, 2000, and September 30, 2011, and at least 2 years of follow-up from birth through study exit as defined by the last visit or the end of the study period on September 30, 2013. Cases were identified as children with International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes for diagnosis of AuSD at 2 separate clinical encounters. This method of using separate AuSD billing occurrences to identify AuSD in database studies has previously been validated.14,15 Exclusion criteria included ICD-9-CM diagnostic codes for childhood disintegrative disorder and degenerative conditions of childhood such as Rett syndrome, Alpers disease, infantile necrotizing encephalomyelopathy, Leigh disease, and subacute necrotizing encephalopathy.

We matched each AuSD case with 3 controls who also had a birth record in the MHS on the basis of age, sex, date of birth, and enrollment time frame. To ensure that cases and controls had sufficient time to demonstrate symptoms of AuSD, all children had to have at least 2 years
of clinical follow-up for study inclusion. The enrollment time frame for controls was the same or longer than the enrollment time frame for the cases. The enrollment time frame for controls was then truncated to exactly match the cases for the analysis.

Case and control records were then reviewed for ICD-9-CM codes associated with CHD and for cardiac surgery International Classification of Disease, Ninth Revision, Common Procedural Terms codes. Records with billing for 1 of 54 different CHD diagnoses were included for analysis (Supplemental Table 4). Given concerns for hemodynamically insignificant patent foramen ovale being misclassified as atrial septal defect (ASD) before 3 months of age, records with ASD codes were included only if they were billed at >3 months of age, were accompanied by an ASD repair procedure code, or accompanied by another developmental grouping lesion.

Each record was sorted into CHD subgroups on the basis of diagnostic or procedure codes for any 1 of developmentally similar lesions (Supplemental Table 4). Developmental grouping has been used in the Baltimore-Washington Infant Study and other previous CHD studies to look for associations among developmentally and physiologically similar lesions. For example, hypoplastic left heart syndrome (HLHS) can be grouped with aortic stenosis and coarctation of the aorta under the developmental grouping left heart obstructive lesions (LeftOb). The developmental groups were not exclusive, and a child could have multiple groups where appropriate. Thus, a child with atrioventricular septal defects (AVSDs) and aortic stenosis would be analyzed with both the AVSD and LeftOb developmental groups.

Contrarily, records were classified as the developmental group for the most unifying diagnosis when appropriate. That is, a child with ASD, ventricular septal defect (VSD), and AVSD was only categorized as an AVSD rather than ASD, VSD, and AVSD because ASD and VSD are components of AVSD. Similarly, VSD and conoventricular lesions were categorized only as conoventricular. Further review of the records indicated binary presence of International Classification of Diseases, Ninth Revision, codes for genetic syndromes, term versus preterm birth, maternal prenatal factors including substance abuse and diabetes, and numerous other perinatal factors (Supplemental Table 5).

Univariate descriptive statistics were calculated for all variables of interest, including counts and percentages for categorical data, or median (interquartile range) for continuous data. Comparisons between children with AuSD and controls were made by using Cochran-Mantel-Haenszel tests for categorical data, and generalized estimating equations were used for continuous data to account for the matched sets. Unadjusted conditional logistic regression was performed to determine the ORs and associated 95% CIs between any CHD exposure and AuSD. To account for potential confounders, multivariable conditional logistic regression was then performed to quantify the association between any CHD exposure and AuSD after adjusting for presence of a genetic syndrome, maternal age, gestational diabetes, short gestation, newborn epilepsy, birth asphyxia, and low birth weight. We adjusted for these 7 factors because of previously published associations with AuSD. Similarly, we performed the same unadjusted and adjusted conditional logistic regression on each subgroup of interest, specifically patients diagnosed with anomalous pulmonary venous return, ASD, AVSD, conoventricular defect, Ebstein anomaly, LeftOb, right heart obstructive lesion (RightOb), and VSD (Supplemental Table 4). When making these comparisons, we excluded children with CHD lesions other than that under consideration from our analysis (ie, children with ASD were not included in analysis of LeftOb). This was done to ensure we were not confounding our results with cases of CHD. Statistical analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC). Statistical significance was assessed for P values less than .05 (P < .05).

Finally, we performed a sensitivity analysis to address concerns of potential misclassification of CHD using administrative data. For this portion of the study, we narrowed our CHD case definition to include only cases for which there were ≥2 CHD diagnoses, CHD diagnoses were billed at separate encounters, or there were any surgical or interventional codes. We then repeated our analyses in a similar fashion as our initial analyses.

RESULTS

A total of 8760 children with AuSD and 26280 controls were included in the study. The groups were similar with respect to the matching characteristics, with boys comprising 79.9% of each group. Cases and controls had an average of 7.01 years enrollment time frame in the study. Compared with controls, those with AuSD were more likely to have a genetic syndrome, preterm birth, neonatal epilepsy, birth asphyxia, low birth weight, maternal gestational diabetes, and younger maternal age at delivery (Table 1). We identified 1063 individuals with CHD: 401 of the 8760 children with AuSD and 662 of the 26280 controls.

Overall, those with AuSD had an OR of 1.85 (95% CI 1.63–2.10; n = 1063) of having CHD as compared with controls (Table 2). After adjustment for covariates, there remained
increased odds of AuSD in patients with CHD. For any CHD, the OR was 1.33 (95% CI 1.16−1.52; n = 1063). This finding was largely driven by the ASD group (OR 1.97; 95% CI 1.48−2.61; n = 216), but it was also significant for the LeftOb group (OR 1.42; 95% CI 1.04−1.93; n = 202) and the VSD group (OR 1.28; 95% CI 1.00−1.63; n = 336) (Fig 1, Table 2).

In the sensitivity analysis, we identified 593 individuals with CHD: 246 of the 8760 children with AuSD and 347 of the 26 280 controls. Despite the smaller numbers, we found similar results for any CHD (OR 1.32; 95% CI 1.10−1.59; n = 593) as well as for ASD (OR 1.72; 95% CI 1.07−2.74; n = 82) and VSD (OR 1.65; 95% CI 1.21−2.25; n = 193) (Fig 2, Table 3). For the LeftOb group, we found a similar adjusted OR of 1.25 in the sensitivity analysis, but the finding was no longer significant (95% CI 0.88−1.77; n = 161).

**DISCUSSION**

In this study, the largest of its kind used to study the association of CHD with AuSD, we found that CHD is associated with increased odds of developing AuSD. Among CHD subtypes, significant associations with AuSD were found for ASDs and VSDs in both the initial analysis and the sensitivity analysis; for LeftOb, a significant association was found only in the initial analysis. There have been many previous studies that have revealed specific developmental delays associated with CHD; however, there are only a few studies that were used to specifically assess for an association between AuSD and CHD with significant statistical power.\(^9\)\(^\text{11}\)\(^\text{12}\)

To our knowledge, this is the only study in which there has been a comparison between AuSD and multiple CHD subtypes.

Our findings are consistent with previous studies of CHD developmental outcomes, which have shown an increased risk of developmental and academic delay after CHD diagnosis and treatment.\(^9\)\(^\text{25}\)

In a recent review, Wernovsky and Licht\(^26\) estimated that nearly half of all severe CHD survivors experience some degree of developmental delay on a spectrum from mild to severe. Authors of some well-designed studies of CHD developmental outcomes used multidomain assessments such as the Wechsler, Woodcock-Johnson, and Bayley scoring systems to measure developmental outcome in a subset of patients with CHD.\(^6\)\(^\text{27}\)\(^\text{28}\) Mahle et al\(^27\) demonstrated a median full scale IQ of 86 (range 50–116) for 28 Fontan surgery survivors with HLHS.

Newburger et al\(^2\)\(^\text{14}\) and Ravishankar et al\(^2\)\(^\text{15}\) reported lower-than-normative development using the Bayley Scales of Infant Development in 14-month-old toddlers with palliated single-ventricle physiology. In none of the studies mentioned did authors directly measure AuSD as an outcome of CHD.

The association of CHD with AuSD has varied in previous smaller studies. Authors of 1 of the earliest such studies with 408 AuSD cases and 2040 healthy controls found increased odds of CHD (OR 2.5; 95% CI 1.1–5.8) for the cases.\(^9\) On the other hand, authors of a later study of similar size (417 AuSD cases; 2067

---

**TABLE 1** Characteristics of Children With AuSDs and Matched Controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AuSD (n = 8760)</th>
<th>Control (n = 26 280)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD, n (%)</td>
<td>401 (4.6)</td>
<td>462 (2.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Genetic syndrome, n (%)</td>
<td>411 (4.7)</td>
<td>178 (0.7)</td>
<td>.001</td>
</tr>
<tr>
<td>Short gestation, n (%)</td>
<td>1171 (13.4)</td>
<td>2302 (8.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Newborn epilepsy, n (%)</td>
<td>203 (2.3)</td>
<td>70 (0.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Birth asphyxia, n (%)</td>
<td>3715 (42.4)</td>
<td>9574 (36.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Low birth wt, n (%)</td>
<td>772 (8.8)</td>
<td>1453 (5.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Gestational diabetes, n (%)</td>
<td>1062 (12.1)</td>
<td>2916 (11.1)</td>
<td>.009</td>
</tr>
<tr>
<td>Maternal age, y(^a)</td>
<td>28.0 (24.3–32.3)</td>
<td>28.1 (25.5–33.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>6895 (79.9)</td>
<td>20 885 (79.9)</td>
<td>.9999(^b)</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted for maternal age, gestational diabetes, genetic syndrome, short gestation, newborn epilepsy, birth asphyxia, and low birth weight.

\(^b\) Subjects were matched on the basis of sex, date of birth, and enrollment time frame.

**TABLE 2** Unadjusted and Adjusted ORs for the Association of AuSD With CHD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Adjusted(^a)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CHD</td>
<td>1063</td>
<td>1.85 (1.53–2.10)</td>
<td>&lt;.001</td>
<td>1.33 (1.16–1.52)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>TAPVR or PAPVR</td>
<td>18</td>
<td>3.75 (1.48–9.50)</td>
<td>.011</td>
<td>2.42 (0.86–6.79)</td>
<td>.09</td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td>216</td>
<td>2.45 (1.87–3.20)</td>
<td>&lt;.001</td>
<td>1.97 (1.48–2.61)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>AVSD</td>
<td>66</td>
<td>2.08 (1.27–3.39)</td>
<td>.007</td>
<td>0.88 (0.51–1.54)</td>
<td>.66</td>
<td></td>
</tr>
<tr>
<td>Conoventricular defect</td>
<td>82</td>
<td>2.47 (1.50–3.81)</td>
<td>&lt;.001</td>
<td>1.32 (0.81–2.15)</td>
<td>.27</td>
<td></td>
</tr>
<tr>
<td>Ebstein</td>
<td>13</td>
<td>2.57 (0.86–7.85)</td>
<td>.16</td>
<td>1.17 (0.32–4.27)</td>
<td>.81</td>
<td></td>
</tr>
<tr>
<td>LeftOb</td>
<td>202</td>
<td>2.42 (1.92–3.20)</td>
<td>&lt;.001</td>
<td>1.42 (1.04–1.93)</td>
<td>.027</td>
<td></td>
</tr>
<tr>
<td>RightOb</td>
<td>430</td>
<td>1.50 (1.22–1.83)</td>
<td>&lt;.001</td>
<td>1.01 (0.81–1.25)</td>
<td>.97</td>
<td></td>
</tr>
<tr>
<td>VSD</td>
<td>336</td>
<td>1.74 (1.39–2.18)</td>
<td>&lt;.001</td>
<td>1.28 (1.00–1.63)</td>
<td>.047</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Adjusted for maternal age, gestational diabetes, genetic syndrome, short gestation, newborn epilepsy, birth asphyxia, and low birth weight.

Conoventricular defect includes tetralogy of Fallot, truncus arteriosus, aortopulmonary window; Ebstein represents Ebstein malformation; LeftOb includes HLHS, mitral stenosis, aortic stenosis, and coarctation of the aorta; RightOb includes tricuspid atresia, pulmonary atresia, pulmonary stenosis not including tetralogy of Fallot. PAPVR, partial anomalous pulmonary venous return; TAPVR, total anomalous pulmonary venous return.

Downloaded from www.aappublications.org/news by guest on March 6, 2021
controls) and design failed to find an association. In a more recent study, Tsao et al\textsuperscript{11} used a large administrative database with 3500 CHD cases and 14,000 controls to demonstrate a hazard ratio of 1.97 (95% CI 1.11–3.52) for AuSD after CHD diagnosis. Despite the power in the study, Tsao et al\textsuperscript{11} noted that they were unable to further analyze the underlying CHD lesions “due to limitations inherent to the specific… dataset.”

The causal link between CHD and AuSD is unknown. In some cases, there may be a common genetic mechanism. For instance, much research has been done regarding AuSD and 22q11.2 deletion syndrome, frequently known as DiGeorge or velocardiofacial syndrome in which 75% to 85% of patients have a CHD, most frequently conotruncal defects involving the great arteries.\textsuperscript{29} Although mostly associated with mild cognitive impairment, 22q11.2 deletion has been associated with AuSD, with an estimated 14% of affected patients meeting Vineland Adaptive Behavior Scales AuSD diagnostic criteria.\textsuperscript{30,31} Niklasson et al\textsuperscript{32} studied this association, finding a nearly 20% incidence of AuSD with 22q11.2 deletion but no correlation between AuSD and CHD in the study sample.

CHARGE syndrome comprises another congenital disorder with a high incidence of CHD.\textsuperscript{33,34} According to a recent meta-analysis, CHARGE syndrome has an AuSD pooled prevalence of 30% (range 13%–48%).\textsuperscript{35} Our data reveal that the association between CHD and AuSD, especially ASD and AuSD, persists even when controlling for known genetic associations of AuSD. This suggests pleiotropy of underlying genetic loci contributing to both conditions. Vorstman et al\textsuperscript{36} summarized this nicely, reporting on at least 9 chromosomal anomalies in which AuSD was associated with CHD. With >800 genes implicated in AuSD\textsuperscript{36} and at least 8 genes linked with ASD formation,\textsuperscript{37–39} there is considerable opportunity for discovery of unifying genetic loci between the conditions. In other cases, there may be potential environmental or clinical factors that serve as a causal link between CHD.
and AuSD. There has been a great deal of research into the risk factors for AuSD and comorbid conditions over the past 25 years, including multiple other studies using the MHS database and this data set in particular. Although the etiology of AuSD remains unclear, an observation pertinent to this study is that epilepsy has an estimated prevalence of 12% to 26% among children with AuSD.40,41 This finding was intriguing because early onset of seizures has been linked to poor neurodevelopmental outcomes after CHD surgery.26,27 The postulated mechanisms for seizures in surgically palliated HLHS is due to cerebral hypoperfusion both in utero and in the perioperative period. Given the association of both CHD and AuSD with seizure disorders, it is a plausible suggestion that CHD may be linked to the subsequent development of the AuSD phenotype by cerebral hypoperfusion and subsequent epilepsy syndrome. Our study was not designed to reveal such a link; therefore, this is an opportunity for further research.

The strengths of this study are drawn from the comprehensive billing data in the MHS database, which follows children as they move across geographic regions of the United States. We were able to conglomerate a large population of children who were diagnosed and treated at multiple centers around the country. The large population provided the statistical power necessary to assess for associations between 2 uncommon childhood conditions. In addition, there was reduced access to care bias because all enrolled children were recipients of a health care benefit with little to no financial burden to the family.

There are a number of limitations for our study. Foremost is that administrative database studies such as this have inherent weaknesses related to the completeness and accuracy of the data as they were recorded.24 To mitigate this weakness, we used a validated definition of AuSD and applied similar rules to check our CHD cases for internal consistency. Our sensitivity analysis demonstrates that the effects of CHD on AuSD persist even with more stringent criteria, although this likely underestimates the effect of CHD on AuSD. A second limitation is potential ascertainment bias within the study population. Children identified with CHD or AuSD tend to present for care more frequently, thus making diagnosis of additional conditions more likely than in the general population. Finally, even with our large sample size, the rarity of CHD events may have limited some of our analyses. This was especially true for Ebstein anomaly, AVSDs, and conoventricular defects, and it may explain why the association of LeftOb with AuSD was no longer significant in the sensitivity analysis.

CONCLUSIONS

On the basis of our data, children with CHD have increased odds of developing AuSD. This finding was particularly notable for those with ASDs and VSDs. We hope that this information will allow pediatricians and pediatric cardiologists to better care for children and counsel families regarding the expected developmental course for children with CHD. Directions for future research on this subject include further elucidating any potential causal mechanisms that could provide opportunities for intervention.

## TABLE 3 Unadjusted and Adjusted ORs for the Association of AuSD With CHD in the Sensitivity Analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CHD</td>
<td>593</td>
<td>2.15 (1.82–2.53)</td>
<td>&lt;.001</td>
<td>1.52 (1.10–1.99)</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>TAPVR or PAPVR</td>
<td>15</td>
<td>3.43 (1.24–8.48)</td>
<td>.035</td>
<td>1.97 (0.62–6.24)</td>
<td>.25</td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td>82</td>
<td>2.72 (1.76–4.20)</td>
<td>&lt;.001</td>
<td>1.72 (1.07–2.74)</td>
<td>.024</td>
<td></td>
</tr>
<tr>
<td>AVSD</td>
<td>61</td>
<td>2.33 (1.34–4.70)</td>
<td>.004</td>
<td>0.89 (0.50–1.58)</td>
<td>.68</td>
<td></td>
</tr>
<tr>
<td>Conoventricular</td>
<td>74</td>
<td>2.69 (1.71–4.25)</td>
<td>&lt;.001</td>
<td>1.40 (0.84–2.33)</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td>Ebstein</td>
<td>11</td>
<td>2.50 (0.76–8.19)</td>
<td>.23</td>
<td>0.89 (0.22–3.67)</td>
<td>.88</td>
<td></td>
</tr>
<tr>
<td>LeftOb</td>
<td>161</td>
<td>2.37 (1.73–3.23)</td>
<td>&lt;.001</td>
<td>1.25 (0.68–1.77)</td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td>RightOb</td>
<td>296</td>
<td>1.72 (1.36–2.18)</td>
<td>&lt;.001</td>
<td>1.03 (0.79–1.34)</td>
<td>.86</td>
<td></td>
</tr>
<tr>
<td>VSD</td>
<td>193</td>
<td>2.41 (1.82–3.20)</td>
<td>&lt;.001</td>
<td>1.65 (1.21–2.25)</td>
<td>.002</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for maternal age, gestational diabetes, genetic syndrome, short gestation, newborn epilepsy, birth asphyxia, and low birth weight.

**ABBREVIATIONS**

ASD: atrial septal defect  
AuSD: autism spectrum disorder  
AVSD: atrioventricular septal defect  
CHD: congenital heart disease  
CI: confidence interval  
HLHS: hypoplastic left heart syndrome  
ICD-9-CM: International Classification of Disease Ninth Revision: Clinical Modification  
LeftOb: left heart obstructive lesion  
MHS: Military Health System  
OR: odds ratio  
RightOb: right heart obstructive lesion  
VSD: ventricular septal defect
REFERENCES


Congenital Heart Disease and Autism: A Case-Control Study
Eric R. Sigmon, Michael Kellemann, Apryl Susi, Cade M. Nylund and Matthew E. Oster
Pediatrics 2019;144;
DOI: 10.1542/peds.2018-4114 originally published online October 10, 2019;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/144/5/e20184114

References
This article cites 40 articles, 8 of which you can access for free at:
http://pediatrics.aappublications.org/content/144/5/e20184114#BIBL

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Developmental/Behavioral Pediatrics
http://www.aappublications.org/cgi/collection/development:behavioral_issues_sub
Autism/ASD
http://www.aappublications.org/cgi/collection/autism:asd_sub
Cardiology
http://www.aappublications.org/cgi/collection/cardiology_sub
Cardiovascular Disorders
http://www.aappublications.org/cgi/collection/cardiovascular_disorders_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.aappublications.org/site/misc/reprints.xhtml
Congenital Heart Disease and Autism: A Case-Control Study
Eric R. Sigmon, Michael Kelleman, Apryl Susi, Cade M. Nylund and Matthew E. Oster

*Pediatrics* 2019;144;
DOI: 10.1542/peds.2018-4114 originally published online October 10, 2019;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/144/5/e20184114

Data Supplement at:
http://pediatrics.aappublications.org/content/suppl/2019/10/09/peds.2018-4114.DCSupplemental