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Descriptive Analysis of Ebstein Anomaly in the National Birth Defects Prevention Study, 1997-2007

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Descriptive Analysis of Ebstein Anomaly in the National Birth Defects Prevention Study, 1997-2007

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Descriptive Analysis of Ebstein's Anomaly in the National Birth Defects Prevention Study, 1997-2007

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INTRODUCTION

I. Birth Defects and Congenital Heart Defects (CHDs) Defined

Major birth defects are conditions that: 1) result from a malformation, deformation, or disruption in one or more parts of the body; 2) are present at birth; and 3) have serious, adverse effects on the affected person's health, development, or functioning. They affect approximately 3% of infants born in the United States every year (Centers for Disease Control and Prevention, 2008), and are responsible for nearly 20% of all infant deaths (Rosano et al., 2000).

Congenital heart defects (CHDs) are the most common type of birth defect, with a birth prevalence of approximately 80 per 10,000 live births (Reller et al., 2008), and are a leading cause of birth-defect associated infant morbidity and mortality (Yang et al., 2006). There are many types of CHDs, with different degrees of severity, presentation, and prognosis. In more severe types, blood vessels or heart chambers may be missing, poorly formed, or in the wrong place. A specific malformation of the tricuspid valve, known as Ebstein anomaly (EA) is a rare CHD, accounting for <1% of all CHDs (Correa-Villasenor et al., 1994; Dearani and Danielson, 2000), with an estimated prevalence of approximately 0.5 per 10,000 live births (Correa-Villasenor et al., 1994; Fyler, 1980; Reller et al., 2008).

II. Normal Right Ventricular Anatomy

The right ventricle is one of the muscular pumping chambers of the heart which directs de-oxygenated blood into the lungs. It has three sections: the inlet, where blood comes in from the right atrium through the tricuspid valve; the apical trabeculated/muscular portion; and the smooth outlet leading to the pulmonary valve. During ventricular contraction, when the blood is being pumped into the lungs through the pulmonary valve, the tricuspid valve shuts and prevents

blood from leaking back into the right atrium. The tricuspid valve is attached to the atrioventricular junction and has three leaflets named for their position (septal, anterior, and inferior) which are tethered to the ventricle much like a parachute, by chordae and papillary muscles (Epstein, 2001; Paranon and Acar, 2008). It is postulated that leaflets develop through cell death which result in separation (delamination) of the valve leaflet structure from the endothelial lining of the ventricle (Clark, 1996).

III. Overview of Ebstein Anomaly

First Description

Wilhelm Ebstein in 1866 first described the unique malformation of the tricuspid valve in an autopsy case report entitled "Concerning a very rare case of insufficiency of the tricuspid valve caused by a congenital malformation" (Ebstein, 1866). The case was a 19-year old man who died shortly after presenting with cyanosis, dyspnea, palpitations and heart failure (Ebstein, 1866; van Son et al., 2001). Ebstein's pathological findings included: severe malformation of the tricuspid valve, absence of the thebesian valve (valve overlaying the coronary sinus), and a patent foramen ovale (van Son et al., 2001). Specifically, the proximal anterior tricuspid valve leaflet blended into the endocardium and the rest of the septal leaflet was tethered with abnormal chordae. He astutely noted these findings were unique, and that the tricuspid valve anomaly was the most significant one. He hypothesized it was a failure of delamination (separation) of the valve leaflets from the endocardium during embryogenesis (Ebstein, 1866; van Son et al., 2001).

Ebstein, a Prussian physician, was primarily known for his work on pathology and metabolic diseases such as diabetes, gout, and obesity. Only 12 of his 272 articles related to cardiovascular disease; ironically, the paper describing the anomaly which bears his name was

written early in his career and was little known until after his death (van Son et al., 2001). Subsequently, the first description in English of the anomaly was in 1900, and in 1937 the eponym was first used in English (van Son et al., 2001). The non-possessive eponym is used here (i.e. "Ebstein" not "Ebstein's") since the person behind the eponym has no proprietary claim on it and in fact, did not have the anomaly. The American Medical Association Manual of Style recommends use of non-possessive eponyms (Iverson et al., 1997).

Pathology

Subsequent pathological findings support his hypothesis. The failed delamination of the leaflets means that there are no chordae to suspend them; thus, they are adhered to the wall of the ventricle and the atrioventricular junction is displaced downward (apically). This displacement of the valve annulus "atrializes" the inlet portion of the ventricle which can hypertrophy or dilate, thereby decreasing the functional ability of the ventricle to fill and eject blood. The displacement also dilates the valve annulus, leading to leakage of blood through the valve when it closes. The non-displaced anterior leaflet is often sail-like, occasionally obstructing flow out of the ventricle, and may have tiny holes in it (Attenhofer Jost et al., 2005; Clark, 1996; Epstein, 2001; Paranon and Acar, 2008).

Other CHDs may occur with EA. Associated defects allow blood to shunt from right to left side of the heart, such as a patent foramen ovale, patent ductus arteriosus, or atrial septal defect, are common. More severe cases of EA may have right ventricular outflow tract obstruction since the abnormal tricuspid valve hinders blood flow. Other defects of the left side of the heart, especially involving abnormalities of the ventricular myocardium, have been noted (Paranon and Acar, 2008), as well as aortic arch abnormalities, and congenitally-corrected

transposition of the great arteries (L-TGA) (Attenhofer Jost et al., 2007; Correa-Villasenor et al., 1994).

By 1930 only 16 cases of EA had been reported in the literature, all diagnosed at autopsy (Younoszai et al., 1999). In 1949 Tournilaire and colleagues were the first to diagnose EA in a living patient, using cardiac catheterization (Epstein, 2001). Currently EA is most easily diagnosed by viewing the anatomy and function by echocardiography.

Although EA has some common anatomic features, it is a heterogeneous disease, with variable pathological characteristics. Several classification systems have been proposed (Carpentier et al., 1988; Celermajer et al., 1992). Recently, a new classification system was described to aid in management and uniform reporting (Dearani and Danielson, 2000). Classification has been difficult because individual component severity may not correspond with clinical manifestations (Dearani and Danielson, 2000), although Celermajer described an echocardiographic scoring in neonates which has been linked to risk of death (Celermajer et al., 1992).

Clinical Course

Heterogeneous pathology results in a wide spectrum of symptoms and presentation. Hemodynamic problems may occur due to the tricuspid valve regurgitation and decreased pulmonary blood flow. Additionally, arrhythmias such as atrial tachycardia are common (Attenhofer Jost et al., 2005; Younoszai et al., 1999). Due to fetal hemodynamics, prenatal diagnosis is often difficult. Fetuses can develop hydrops, arrhythmias, and mortality is high in severe forms of EA. Neonates can present with cyanosis, heart failure, and cardiomegaly. Prognosis is generally poor for fetuses and symptomatic neonates with severe EA (Attenhofer

Jost et al., 2005; Celermajer et al., 1994; Correa-Villasenor et al., 1994; McElhinney et al., 2005). In older children and adolescents presenting with EA, arrhythmias are more common than in younger children (Celermajer et al., 1994). People with EA also present in adulthood; one case of EA was reported in an 86 year old (Attenhofer Jost et al., 2005). The symptomatic spectrum is supported by pathologic findings − in an autopsy study of 67 hearts with EA, three were in stillbirths, 40 were in infants under 1 year, 11 were in children or adolescents, and one was in an elderly person (Bharati and Lev, 1996).

The management and outcome of EA is variable; people with mild forms may live relatively symptom-free into adulthood, whereas severe forms diagnosed in utero or neonatally can be fatal. Observation is recommended for asymptomatic or mildly symptomatic cases. Arrhythmias, which are common, can cause significant morbiditiy and mortality. Catheter intervention to ablate arrhythmias have a lower success rate than for structurally normal hearts and the risk of recurrence is higher (Attenhofer Jost et al., 2005). When indicated, a variety of surgeries can be done, including valve repair or replacement. Studies have not shown that surgery is a risk for death or improves survival outcome; however, a recent study of mortality in children found no association between the need for surgery and survival (Kapusta et al., 2007). This study of 93 EA cases in children and adolescents from 1980-2005 was a retrospective investigation of diagnosis timing, treatment, and estimated survival with Kaplan-Meier curves. They reported 87% neonatal survival and 83% one-year survival. Survival stabilized after 35 months at 80%. Presentation at less than 1 year of age, need for medication and ventilation, and having other cardiac defects was each significantly associated with death (Kapusta et al., 2007).

Etiologic Factors

While published literature has focused on clinical aspects of EA, little attention was paid to its etiology until reports in the 1980's associated the occurrence of EA with maternal lithium therapy for treatment of affective mood disorders during the first trimester of pregnancy (Schardein, 1985; Warkany, 1988). In response, women were discouraged from taking the medication during pregnancy. Later, several case-control studies of EA found that no mothers of cases had taken lithium (Cohen et al., 1994; Correa-Villasenor et al., 1994). Furthermore, a prospective multi-center study found that the rates of major congenital malformations did not differ between lithium exposed and unexposed groups (Jacobson et al., 1992). However, although the data are equivocal concerning the association between maternal use of lithium and occurrence of EA the rate of exposure may be too low to establish or disprove the association. Current guidelines do not discourage women from taking lithium during pregnancy if medically indicated, but recommend all fetuses of women taking lithium undergo a fetal echocardiogram at 18-20 weeks gestation (American Academy of Pediatrics Committee on Drugs, 2000).

Morphogenetic factors are unclear but likely to be multifactorial. The original hypothesis of abnormal cellular death and delamination (Clark, 1996; Ebstein, 1866) has been augmented by a suggestion that EA may be a connective tissue disorder (Bharati and Lev, 1996). Most cases of EA are sporadic, although familial cases have been noted with occurrences of other CHDs in the same family (Correa-Villasenor et al., 1994). Family history of CHDs has been reported as a risk factor for EA (Correa-Villasenor et al., 1994). Familial occurrences of EA and a canine model linking tricuspid valve malformation to canine chromosome 9 have prompted genetic investigations. Cases have been found with deletions in 10p12-p14, 1p34.3-p36.11 (Attenhofer Jost et al., 2007), and duplication in the distal long arm of chromosome 15 (Miller et al., 2005).

EA has also been linked to gene *TBX5*, which is associated with Holt-Oram syndrome (Tongsong and Chanprapaph, 2000), and the cardiac transcription factor, *NKX2*-5 (Benson et al., 1999). Since the delamination of the tricuspid valve occurs early in embryogenesis, it is possible that several genes may act in regulation of delamination, and that a genetic mutation affecting this process may also affect other processes of early development.

IV. Previous Epidemiologic Literature

Epidemiologic and risk factor studies improve disease understanding and help guide prevention activities. Birth prevalence estimates of EA have been reported in larger studies of CHDs (Hoffman and Kaplan, 2002; Reller et al., 2008). The data from the Metropolitan Atlanta Congenital Defects Program showed gender proportion, mean gestational age, birth weight, maternal age for EA. Birth prevalence of 0.60/10,000 was reported, with a higher proportion of females than males (Reller et al., 2008). An older study also using Atlanta data showed a modest association of EA with febrile illness (Botto et al., 2001b). However, due to its rarity, there have been few population-based studies entirely focused on EA epidemiology or risk factors.

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The Baltimore-Washington Infant Study (BWIS)

The Baltimore-Washington Infant Study (BWIS) was a regional collaborative case-control study of live born infants from 1981 to 1989 which explored possible genetic, reproductive and environmental risk factors for major CHDs (Ferencz et al., 1997). Cases (n=4,390) had a confirmed diagnosis of one or more CHDs ascertained from multiple sources, and controls (n=3,572) were live born infants in the region without any CHDs. All families completed a detailed questionnaire within 18 months of study infant birth. The BWIS reported

on risk factors for several types of CHDs, and was the only population-based case-control investigation of a variety of risk factors for EA. There were 47 cases of EA in the BWIS, resulting in an estimated prevalence of 0.52/10,000 live births (Correa-Villasenor et al., 1994; Ferencz et al., 1997). The investigators found that 38% of EA cases had additional CHDs and 19% had other major birth defects affecting organ systems other than the heart (extracardiac). Compared to controls, EA cases had a higher proportion of infants who were low-birth weight or small for gestational age (SGA), from multiple births, and whose mothers were older or of white race-ethnicity. Further analysis revealed increased risk associated with white race (OR 2.9, 95% CI 1.2-7.0), family history of CHD (OR 6.4, 95% CI 1.8-22.0), previous miscarriage (OR 2.0, 95% CI 1.2-3.3), and maternal exposure to benzodiazepine (OR 5.4, 95% CI 1.5-19.1), marijuana (OR 2.8, 95% CI 1.2-6.5), and varnishes (OR 3.4, 95% CI 1.3-9.1) (Correa-Villasenor et al., 1994).

Analysis of Data from the Texas Birth Defects Registry

A recent study from the Texas Birth Defects Registry from 1999-2005 reported on 188 cases of EA confirmed from medical records; the largest population-based study to date (Lupo et al., 2011). In the Texas study, the birth prevalence of EA (0.72/10,000 live births) was similar to BWIS and other reports (Fyler, 1980; Reller et al., 2008), and there was a similar amount of cases with extracardiac defects (15%). Lupo and colleagues found that advanced maternal age, residence along the Texas-Mexico border, and conception in fall or winter were significantly associated with increased prevalence of EA. Additionally, in multivariable analysis they found that infants with EA were more likely to be SGA and premature. Their findings were mostly consistent with BWIS, but they did not see an association with multiple births.

V. Current Study

While important contributions to the literature of EA, these two studies had some limitations. The BWIS had detailed information from multiple sources, including maternal interview, but was limited in sample size. The Texas study had a larger sample size, but was limited to vital records and birth defect registry information, and was not a case-control study. The National Birth Defects Prevention Study (NBDPS), begun in 1997, is an ongoing, multi-site, case-control study of risk factors for major birth defects, representing diverse racial-ethnic groups and locations. It is one of the largest population-based studies with the statistical power to study the epidemiology of many rare defects (Hartman et al., 2011; The et al., 2007; Yoon et al., 2001). Cases are reviewed by geneticists and experts in pediatric cardiology to classify the birth defects. Studies involving CHDs have found no increased risk associated with maternal selective serotonin reuptake inhibitors (SSRIs) (Alwan et al., 2007) or caffeine intake (Browne et al., 2007). Other studies found that maternal smoking (Malik et al., 2008). prepregnancy obesity, and diabetes (Correa et al., 2008; Gilboa et al., 2010a) were associated with CHDs. The current study is the first analysis of NBDPS data to focus solely on EA.

The NBDPS offers a unique opportunity to contribute to the current descriptive epidemiology, and to assess previously recognized and potentially new risk factors for EA. Our current work with the largest sample size of EA cases to date has multiple-source data from a diverse population and detailed clinical classification of the cardiac and extracardiac defects.

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ABSTRACT

BACKGROUD: There is relatively little epidemiologic information about Ebstein anomaly (EA) of the tricuspid valve. To update previous studies, we analyzed characteristics of EA in a geographically and ethnically diverse population.

METHODS: Data from all sites of the National Birth Defects Prevention Study were used to study infants born from 1997-2007 with EA. Birth prevalence and prevalence ratio (PR) estimates were derived from the number of affected infants per 10,000 live births in the catchment area population. Characteristics among all cases were examined, stratified by the presence of other cardiac and extracardiac defects. Predictive modeling using logistic regression was conducted to understand infant mortality risk factors.

RESULTS: There were 249 cases with EA resulting in a birth prevalence of 0.55/10,000 live births. Other cardiac defects were present in 41.0% and extracardiac defects in 10% of cases. Prevalence was higher among multiple births compared to singletons (PR 2.41, 95% confidence interval (CI) 1.46-3.92) and preterm compared to term infants (PR 1.84, 95% CI 1.27-2.64). Compared to EA cases without other defects, those with additional defects were more likely to die (crude Odds Ratio (cOR) 4.07, 95% CI 1.71-9.93) or undergo cardiac surgery (cOR 6.06, 95% CI 2.78-13.49). Risk for death during infancy was increased by being small for gestational age (adjusted (a) OR 2.97, 95% CI 1.13-7.76) and having extracardiac defects (aOR 6.31, 95% CI 2.28-17.52).

CONCLUSION: Some findings are consistent with previous work, but further studies of EA could clarify risk factors for occurrence and mortality. Knowing population characteristics could guide development of prevention strategies and may improve clinical care.

INTRODUCTION

First described by Wilhelm Ebstein in 1866, Ebstein anomaly (EA) accounts for <1% of congenital heart defects (CHDs), with birth prevalence estimates of 0.52-0.72 per 10,000 live births (Correa-Villasenor et al., 1994; Fyler, 1980; Lupo et al., 2011; Reller et al., 2008). EA has varying degrees of dysplasia and downward displacement of the tricuspid valve leaflet attachments from the atrio-ventricular junction into the right ventricle (Attenhofer Jost et al., 2005; Ebstein, 1866). There is a wide range of clinical and pathological characteristics and manifestations, depending on the severity of the anomaly and associated complications (Attenhofer Jost et al., 2005; Celermajer et al., 1994; Flores et al., 2004; Kapusta et al., 2007; McElhinney et al., 2005). Many cases diagnosed in fetal or neonatal period have poor outcomes (Correa-Villasenor et al., 1994; Flores et al., 2004); however, these may be the more severe cases, since some individuals with EA live relatively symptom-free into adulthood.

Given its rarity, few population-based epidemiologic studies have specifically investigated EA, and tend to have relatively small case populations. The Baltimore-Washington Infant Study (BWIS), a case-control study of CHDs during the 1980s, included 47 cases of EA (Correa-Villasenor et al., 1994); recently a study using data from the Texas Birth Defects Registry reported on 188 cases (Lupo et al., 2011). Previous studies have suggested that EA is associated with specific other cardiac and extracardiac (i.e., in an organ other than the heart) defects (Attenhofer Jost et al., 2005; Correa-Villasenor et al., 1994), but most infants with EA do not have recognized genetic syndromes or chromosomal abnormalities (Attenhofer Jost et al., 2005; Lupo et al., 2011). EA has also been associated with prematurity, low birth weight, being small for gestational age (SGA), and having older mothers (Correa-Villasenor et al., 1994; Lupo et al., 2011). Although findings have been inconsistent, there may be racial-ethnic differences (Correa-Villasenor et al., 1994; Lupo et al., 2011). The Texas study also found increased

prevalence of EA among those conceived during fall/winter or to mothers living on the Texas-Mexico border (Lupo et al., 2011).

To our knowledge, there has been no large population-based study of EA involving diverse racial or ethnic groups across different regions. The National Birth Defects Prevention Study (NBDPS), an on-going, multi-site case-control study of birth defects, has sufficient sample size to study rare defects such as EA. We present a descriptive analysis of over 200 cases of EA to improve understanding of its epidemiology and potential associated factors.

MATERIALS AND METHODS

Study Population

The NBDPS is an ongoing, multi-site, population-based, case-control study of structural birth defects, including EA (Rasmussen et al., 2003; Yoon et al., 2001). Data on cases with eligible birth defects are collected through population-based birth defects surveillance systems at ten sites: Arkansas, California, Georgia/Centers for Disease Control and Prevention, Iowa, Massachusetts, New Jersey [through 2002], New York, North Carolina [beginning 2003], Texas, and Utah [beginning 2003]. Each site received Institutional Review Board approval for the study. Cases included in the study can be live births (all sites), fetal deaths >20 weeks (Arkansas, California, Iowa, Massachusetts, North Carolina, Texas, and Georgia), and elective pregnancy terminations (Arkansas, California, Iowa, Texas, and Georgia). Infants with recognized or strongly-suspected chromosomal abnormalities or single-gene conditions are excluded. Case information is obtained from hospital and medical records, and entered into a standardized database for clinician review and classification. Case and control mothers are requested to complete a computer-assisted telephone interview about demographic characteristics, pregnancy exposures and medication use. For this analysis, we analyzed eligible case infants of interviewed and non-interviewed mothers with a date of birth between October 1, 1997 and December 31, 2007. No data specific to infants of interviewed mothers were included.

Infant Classification

The classification of case infants has been described previously (Rasmussen et al., 2003). After being considered eligible by a study site geneticist, EA cases were further reviewed by one clinical geneticist to describe the presence and pattern of extracardiac defects – the “baby

classification". A case was either isolated (only cardiac defect(s)), multiple (presence of at least one extracardiac defect), or complex (several organ systems or complex defect group).

Ebstein Anomaly Classification

According to the NBDPS guidelines, (Botto et al., 2007) all CHD cases were confirmed before one year of age by echocardiography, cardiac catheterization, cardiac surgery, or autopsy. Prenatally diagnosed cases were included if an ultrasound was performed by a pediatric cardiologist or at a prenatal diagnosis center with expertise in this area. All CHD cases were reviewed by 1 of 4 clinicians with expertise in pediatric cardiology and classified by CHD phenotype and complexity according to a standard case definition. For EA cases, the cardiac complexity was either simple (EA with or without an atrial septal defect (ASD)); associated (EA plus one or two other distinct CHDs besides an ASD), or complex (EA plus more than two other distinct CHDs, or a complex entity). Thus an EA case could be any combination of baby classification and cardiac complexity.

Statistical Methods

Frequency distributions, birth prevalence estimates, prevalence ratios (PRs), and 95% confidence intervals (CIs) were calculated for EA cases by maternal race-ethnicity (non-Hispanic (NH) White, NH Black, Hispanic, other), maternal age at delivery (<20, 20-34, 35-39, ≥40 years), study site, birth year, infant gender, birth plurality (singleton, twins or higher), and gestational age for live born singletons only [preterm (<37 completed weeks), term (≥ 37 completed weeks)]. Birth prevalence estimates were derived from the number of affected infants per 10,000 live births among the source population from which the infants were ascertained. The live birth population in each of the NBDPS participating sites was provided to the NBDPS study

coordinator for use in this and other analyses. Due to inconsistencies in population birth data, case and population plurality data from New York in 2006 and 2007, and gestational age data from New Jersey for 1998-2000 were excluded from prevalence calculations. Factors for which the 95% CI for the crude PR excluded 1.0 were considered significantly related to the occurrence of EA. The frequency of EA by birth status (live birth, fetal death, or pregnancy termination) was reported, but the prevalence of EA was calculated among live births only, since population data on fetal deaths and terminations were not uniformly available.

Frequency distribution was calculated for birth weight in grams (<2500, 2500-3999, ≥4000), death at any age during the study among live births (yes, no), timing of death [neonatal (≤30 days) and post-neonatal (>30 days)], cardiac surgery during infancy (yes, no), number of cardiac surgeries (1,2, or 3), baby classification (isolated, multiple, complex), and cardiac complexity (simple, association, complex), and the types of cardiac and extracardiac defects present. Death and surgical data were obtained from medical records abstracted through participating programs. Frequency distribution was also calculated for SGA (yes, no) among live born singletons, defined as birth weight less than the 10^{th} percentile for gestational age and gender, based on a standardized birth weight distribution of U.S. live births (Alexander et al., 1996).

We stratified EA cases by the presence of other major birth defects, and compared the distributions of all characteristics among EA cases with other CHDs alone, cases with other CHDs and/or extracardiac defects, and among cases of isolated, simple EA. Simple logistic regression was used to calculate crude odds ratios (cORs) and 95% CIs.

The characteristics of live born singletons with EA who died during infancy (age ≤ 1 year) were compared to those who were alive at one year using simple logistic regression.

Categories for some characteristics were combined for statistical power: maternal race-ethnicity (White, Black, Other), maternal age (<20, 20-34, ≥35 years), baby classification (isolated, non-isolated), and cardiac complexity (simple, non-simple). Significant factors for death in the crude analysis were included in a multivariable logistic regression model to assess potential predictors of infant death among EA cases.

Statistical analyses were performed with SPSS v18.0 (IBM SPSS, Chicago, Illinois). The Statistical Analysis Battery for Epidemiologic Research (Centers for Disease Control and Prevention, 2008) was used to calculate 95% CIs for the PRs.

RESULTS

There were 249 cases with EA identified in the NBDPS, resulting in an overall birth prevalence of 0.55/10,000 livebirths. The birth prevalence of EA was significantly higher among infants of mothers who were "Other" race-ethnicity compared to NH White (PR 1.68, 95% CI 1.06-2.64); infants from multiple births compared to singletons (PR 2.41, 95% CI 1.46-3.92) and among live born singletons, for those born preterm compared to term (PR 1.84, 95%CI 1.27-2.62) (Table 1). No statistically significant differences in birth prevalence estimates were seen by maternal age or infant gender. Birth prevalence estimates varied by birth year and study site, but without a clear pattern. (Table 1). Among all live born EA cases (single and multiple births), 35/200 (14.9%) died at any age (Table 1), 23 (65.7%) as neonates and two just beyond infancy, one at 389 days of life and one at 396 days (data not shown). Of those who underwent cardiac surgery during infancy, 68.6% had one, 27.5% had two, and 3.9% had three surgeries (data not shown). There were 135 (54.2%) isolated, simple EA cases (no other cardiac or extracardiac defects) and 224 (90%) had no extracardiac defects. Other cardiac and/or extracardiac defects were present in 114 (45.8%) EA cases, of whom 89 had only additional CHDs (isolated baby, association or complex cardiac complexity) (Table 2).

Table 3 shows the other birth defects among our EA cases (n=114, 45.8%). Infants with more than one additional major birth defect appears in Table 3 multiple times. Since atrial septal defects are considered an obligatory shunt in EA, they are not listed separately. There were 102 (41.0%) of EA cases with one or more additional CHDs, including ventricular septal defects (n=33), other right-sided lesions (e.g. pulmonary stenosis (n=27) or atresia (n=28)), congenitally-corrected or "levo" transposition of the great arteries (L-TGA, n=13), and left-sided obstructive lesions (e.g. coarctation of the aorta (n=8) and aortic stenosis (n=2)). Extracardiac defects were rare; the most frequent included orofacial clefts (n=4) and intestinal malrotation (n=3). There

were 13 cases with additional cardiac and extracardiac defects. Although NBDPS excludes known syndromes and genetic conditions, two cases had unconfirmed CHARGE syndrome (acronym for the presence of: **C**oloboma, **H**eart defects, choanal **A**tresia, **R**etardation of growth/development, **G**enital and **E**ar abnormalities), and one had possible Holt Oram syndrome (arm/hand and cardiac abnormalities) (Table 3).

Stratification by presence of other major birth defects showed differences in clinical and demographic characteristics (Table 4). Among infants with no extracardiac defects (isolated baby, n=224), the prevalence for those with additional CHDs (n=89) compared to those with simple EA (n=135) was four times higher in 2006 than 2000. Of all EA cases who had surgery, most (40/51, 78.4%) had other major birth defects. Compared to isolated simple EA, those with other CHDs alone or with extracardiac defects were significantly more likely to have cardiac surgery during infancy (OR 7.32, 95% CI 3.26-16.75, and OR 6.06, 95% CI 2.78-13.49, respectively) (Table 4). Infants from both groups with other defects were also more likely to die within 14 months compared to those with isolated simple EA, although only the comparison for those with other cardiac or extracardiac defects was statistically significant (OR 4.07, 95% CI 1.71-9.93) (Table 4).

Among live born singletons (n=217) the risk of death during infancy was greater among those born to Black mothers (crude(c) OR 3.79, 95% CI 1.21-11.86), and those born preterm (cOR 6.34, 95% CI 2.72-14.76), low birth-weight (cOR 4.41, 95% CI 1.83-10.64), SGA (cOR 2.99, 95% CI 1.26-7.10), and with extracardiac defects ("non-isolated" baby classification) (cOR 8.47, 95% CI 3.18-22.53) (Table 5). The presence of other cardiac defects and having cardiac surgery during infancy were nearly twice as common among those who died, but these factors did not reach statistical significance. A multivariable logistic regression model for death during

the first year of life included maternal race-ethnicity, presence of extracardiac defects, and SGA (which controls for confounders of preterm delivery and low birth weight). In the adjusted model, race-ethnicity was not predictive of death, while the odds of death before age 1 year was significantly higher among those with extracardiac defects (aOR 6.31, 95% CI 2.28-17.52), and SGA infants (aOR 2.97, 95% CI 1.13-7.76) (Table 5).

DISCUSSION

This study describes the largest population-based cohort of infants with EA to date from a racial-ethnically and geographically diverse source populations. Additionally, a multivariable analysis of predictors of death during infancy was conducted.

The birth prevalence estimate of 0.55/10,000 live births was similar to previous population-based studies (Correa-Villasenor et al., 1994; Lupo et al., 2011; Reller et al., 2008), and suggests stability in birth prevalence over time and geographic region. The report based on data from the Texas Birth Defects Registry, had a slightly higher prevalence than ours - 0.72/10,000 (Lupo et al., 2011). Although Texas participates in the NBDPS, Lupo and colleagues used the entire Texas Birth Defects Registry, including syndromic and chromosomal abnormalities, while the NBDPS includes only non-syndromic EA cases from selected regions of Texas. Other regional studies in Baltimore-Washington (Correa-Villasenor et al., 1994) and Atlanta (Reller et al., 2008) reported birth prevalences of 0.52 and 0.60/10,000 livebirths, respectively.

We found no significant differences in birth prevalence by maternal age or race-ethnicity. Although it was increased among mothers of "Other" race-ethnicity, this category was heterogeneous, including mothers with multiple race-ethnicities, making it difficult to draw definitive conclusions about the relevance of this observation. Previous studies did not show a consistent pattern of association with maternal age or race-ethnicity. In the Texas study and the BWIS, there was an increased prevalence among older mothers, but at different age cutpoints (Correa-Villasenor et al., 1994; Lupo et al., 2011). In the BWIS most cases were White (87%) (Correa-Villasenor et al., 1994), while in the current study and in Texas there was more heterogeneity (NH White = 53% and 51%, respectively) (Lupo et al., 2011) without significant prevalence differences.

Consistent with other studies, EA birth prevalence was associated with preterm birth (Correa-Villasenor et al., 1994; Lupo et al., 2011) and multiple gestations (Correa-Villasenor et al., 1994) but not infant gender (Correa-Villasenor et al., 1994; Lupo et al., 2011). Our proportion of multiples among EA cases (7.6%) was similar to BWIS (8.5%) but much higher than the twinning rate in the general population (3.3%) (Martin et al., 2012). Multiple births has been associated with birth defects, including CHDs (Tang et al., 2006), but the association with EA is unclear (Hardin et al., 2009). Preterm delivery may be precipitated by hydrops fetalis or fetal arrthymias occuring in severe EA (Attenhofer Jost et al., 2005). However, prematurity is associated with birth defects in general, implying that there may be common risk factors for both (Honein et al., 2009; Rasmussen et al., 2001). We were unable to compare prevalence estimates of EA by birth weight or SGA because denominator data stratified by these characteristics was unavailable. However, results of that analysis would likely be similar to our findings for preterm delivery, given the strong association among birth weight, SGA, and preterm delivery.

Our percentage of EA cases with additional CHDs was within the range of 38-50% reported previously (Attenhofer Jost et al., 2005; Correa-Villasenor et al., 1994). While additional right-sided obstructive defects are common among EA (Attenhofer Jost et al., 2005; Correa-Villasenor et al., 1994), EA was recognized early as being distinct from these lesions (Ebstein, 1866). One suggested developmental mechanism for EA is that abnormal cell death (Clark, 1987) results in delamination failure in the right ventricle and an abnormal tricuspid valve. Since delamination occurs early in embryogenesis, other structures may be affected along the same etiologic pathway. For example, abnormalities in left ventricular morphology, and other left-sided lesions have been seen among EA cases (Attenhofer Jost et al., 2005; Correa-Villasenor et al., 1994). Furthermore, L-TGA, which represents about 1% of CHDs, often has an

abnormal systemic valve (Attenhofer Jost et al., 2005); the fact that 5.5% of our EA cases had L-TGA is not surprising. However, anatomic differences have been noted between EA with and without L-TGA (Attenhofer Jost et al., 2005); it is unclear whether this subgroup differs in other ways from simple EA.

Similar to other studies (Correa-Villasenor et al., 1994; Kapusta et al., 2007; Lupo et al., 2011), extracardiac defects were rare and without pattern among our cases. Interestingly, CHARGE syndrome has a baseline prevalence of 0.01% in the general population. It appears to be more frequent among EA cases, reported in 2.0% and 4.5% of cases previously (Correa-Villasenor et al., 1994; Digilio et al., 2011), and in 0.8% of our cases. Holt Oram syndrome has also been seen with EA (Lupo et al., 2011), and there may be a genetic link between the two disorders (Miller et al., 2005). However, no definitive conclusions can be drawn since the cases reported here are unconfirmed.

The overall outcome of our cases was good; most live births (202/235, 86%) survived through infancy and 78% did not undergo cardiac surgery in infancy. This is similar to Kapusta and colleagues who had 84% one-year survival, with the majority of deaths (77%) occurring neonatally, and a Kaplen-Meier survival probability at 10 years of 76% (Kapusta et al., 2007), indicating that the prognosis is generally good in the current era of diagnosis and treatment.

Since EA is a heterogeneous CHD, it is important to understand potential influences on its clinical course. Of those undergoing surgery, EA cases here and elsewhere (Kapusta et al., 2007) had a variety of operations from valvuloplasty to univentricular palliative procedures, indicating the wide spectrum of EA severity. Furthermore, among EA cases with other birth defects the increased risks of dying or undergoing surgery suggest that these cases may have more severe EA, or that the presence of the other birth defects may confer a greater risk than

presence of EA alone. Other studies also found presence of additional defects predictive of death (Flores et al., 2004; Kapusta et al., 2007). However, in our data, the presence of extracardiac defects, but not cardiac complexity, was a significant risk factor for death during infancy among live born singletons, suggesting that having multiple affected organ systems increases mortality.

Our other infant mortality predictors among live born singleton EA cases have not been reported previously, and need further corroboration. In crude models, prematurity, low birth weight, SGA, presence of extracardiac defects and Black maternal race-ethnicity were associated with infant mortality, but in multivariable analysis, only SGA and extracardiac defect presence remained statistically significant risk factors for death before one year of age. While the association between maternal Black race-ethnicity and infant death was not significant in the multivariable analysis, it is consistent with findings that among infants and children, NH Blacks with any CHDs have a higher mortality than NH Whites (Gilboa et al., 2010). The racial-ethnic disparity in EA mortality could be attributable to differences in diagnosis, clinical presentation, or access to care, which could not be explored here.

These results should be interpreted in light of several limitations. First, these data might not represent the entire U.S. population. Population denominator data were only available on select characteristics to calculate prevalence estimates, and there was a substantial amount of missing data for gestational age (n=69,625). However, even if all births with a missing gestational age in our denominator were classified as preterm, thereby decreasing the estimated birth prevalence of EA among preterm births, the prevalence among preterm births would still be significantly greater than the prevalence among term births. Second, our data do not represent the entire spectrum of EA– severe cases resulting in early fetal loss (less than 20 weeks' gestation) and mild cases diagnosed beyond one year of age were not captured, and cases with

recognized syndromes or genetic conditions are excluded from the NBDPS (Rasmussen et al., 2003; Yoon et al., 2001). Furthermore, the NBDPS does not have long-term survival data or information on comorbidities (e.g. arrhythmias), so our outcome analysis was limited to death during infancy. Finally, we could not assess other potential risk factors (e.g. maternal exposures) since interview data were not used. Future analysis of interviewed cases and controls could explore these issues.

Nevertheless, our study had several strengths. NBDPS has the largest sample size of EA cases to-date, obtained from 10 geographic sites. This allowed evaluation of EA by several clinical and demographic characteristics. We included fetal deaths and terminations from available sites. Additionally, NBDPS obtains detailed clinical information abstracted from medical records, which enabled us to study early surgeries and infant mortality. Finally, all cases undergo expert review by clinical geneticists and pediatric cardiology experts to ensure accurate classification of cardiac and extracardiac defects, rather than relying on administrative codes.

Some current findings are consistent with previous work, but further studies of EA could clarify risk factors for occurrence and mortality. Knowing population characteristics could guide development of prevention strategies and clinical care.

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Table 1: Prevalence of Ebstein Anomaly by Infant Clinical and Demographic Characteristics, National Birth Defects Prevention Study, 1997--2007

	N	(%)	Total births	Prev (/10,000)	PR	(95% CI)
All cases	249	(100)	4,551,198	0.55		
Maternal Race/Ethnicity						
Non-Hispanic White	134	(53.8)	2,476,387	0.54		ref
Non-Hispanic Black	21	(8.4)	568,425	0.37	0.68	(0.42-1.10)
Hispanic	68	(27.3)	1,242,413	0.55	1.01	(0.75-1.37)
Other	24	(9.6)	263,629	0.91	**1.68**	**(1.06-2.64)**
Missing	2	(0.8)	344			
Maternal Age (years)						
<20	26	(10.4)	492,907	0.53	1.01	(0.65-1.54)
20-34	178	(71.5)	3,397,791	0.52		ref
35-39	35	(14.1)	544,175	0.64	1.23	(0.84-1.78)
≥40	10	(4.0)	115,379	0.87	1.65	(0.83-3.22)
missing	0		946			
Study Site						
Arkansas	24	(9.6)	392,853	0.61	1.06	(0.60-1.07)
California	24	(9.6)	638,612	0.38	0.65	(0.37-1.15)
Georgia	30	(12.0)	521,441	0.58		ref
Iowa	28	(11.2)	394,619	0.71	1.23	(0.71-2.12)
Massachusetts	39	(15.7)	647,456	0.60	1.05	(0.63-1.73)
New Jersey	16	(6.4)	343,164	0.47	0.81	(0.42-1.54)
New York	14	(5.6)	472,186	0.30	0.52	(0.26-1.01)
North Carolina	14	(5.6)	227,707	0.61	1.07	(0.54-2.09)
Texas	39	(15.7)	652,618	0.60	1.04	(0.63-1.72)
Utah	21	(8.4)	260,542	0.81	1.40	(0.77-2.53)
Birth Year						
1997	4	(1.6)	117,539	0.34	0.71	(0.21-2.16)
1998	23	(9.2)	561,403	0.41	0.86	(0.46-1.58)
1999	27	(10.8)	488,477	0.55	1.15	(0.64-2.08)
2000	23	(9.2)	480,495	0.48		ref
2001	21	(8.4)	362,930	0.58	1.21	(0.64-2.27)
2002	13	(5.2)	329,712	0.39	0.82	(0.40-1.70)
2003	20	(8.0)	424,780	0.47	0.98	(0.52-1.86)
2004	34	(13.7)	431,349	0.79	1.65	(0.94-2.89)
2005	18	(7.2)	434,666	0.41	0.87	(0.45-1.67)
2006	20	(8.0)	452,743	0.44	0.92	(0.49-1.74)
2007	46	(18.5)	467,104	0.98	**2.06**	**(1.22-3.50)**
Gender						
Male	121	(48.6)	2,328,274	0.52		ref
Female	126	(50.6)	2,222,827	0.57	1.09	(0.84-1.41)
Ambiguous	2	(0.8)	—	—	—	—
Missing	0		97			

Table 1 (continued): Prevalence of Ebstein Anomaly by Infant Clinical and Demographic Characteristics, National Birth Defects Prevention Study, 1997-2007

	N	(%)	Total births	Prev (/10,000)	PR	(95% CI)
Plurality[1]						
Single	229	(92.0)	4,315,099	0.53		ref
Multiple	19	(7.6)	148,547	1.28	**2.41**	**(1.46-3.92)**
Missing	1	(0.4)	183			
Gestational Age (weeks)[2,3]						
20-36	38	(15.3)	431,057	0.88	**1.84**	**(1.27-2.64)**
≥ 37	178	(71.5)	3,707,352	0.48		ref
Missing	1	(0.4)	69,625			
Birth Weight (grams)						
<2500	55	(22.1)	—	—	—	—
2500-3999	174	(69.9)	—	—	—	—
≥ 4000	16	(6.4)	—	—	—	—
Missing	4	(1.6)				
Small for Gestational Age[3]						
No	178	(71.5)	—	—	—	—
Yes	38	(15.3)	—	—	—	—
Missing	1	(0.4)	—	—	—	—
Birth Outcome						
Livebirth	235	(94.4)	4,551,198	0.52	—	—
Fetal death	13	(5.2)	—	—	—	—
Pregnancy termination	1	(0.4)	—	—	—	—
Died at Any Age[4]						
No	200	(85.1)	—	—	—	—
Yes	35	(14.9)	—	—	—	—
Cardiac Surgery in Infancy[4]						
No	184	(78.3)	—	—	—	—
Yes	51	(21.7)	—	—	—	—
Baby Classification						
Isolated	224	(90.0)	—	—	—	—
Multiple	23	(9.2)	—	—	—	—
Complex	2	(0.8)	—	—	—	—
Cardiac Complexity						
Simple	147	(59.0)	—	—	—	—
Association	89	(35.7)	—	—	—	—
Complex	13	(5.2)	—	—	—	—

Prev = Prevalence; PR = Prevalence Ratio

[1] Exclude NY 2006-2007 plurality data from cases (n=3)and denominator (n=87369)

[2] Exclude NJ 1998-2000 gestational age data from cases (n=10) and denominator (n=343164)

[3] Among live born, singletons only (n=217)

[4] Among liveborns only (n=235)

Table 2: Classification of Ebstein Anomaly by Complexity of Heart and Presence of Extracardiac Defects, National Birth Defects Prevention Study, 1997-2007

	Cardiac Complexity[2]							
	Simple		Association		Complex		Total	
Baby Classification[1]	N	(%)	N	(%)	N	(%)	N	(%)
Isolated	135	(54.2)	80	(32.1)	9	(3.6)	224	(90.0)
Multiple	12	(4.8)	9	(3.6)	2	(0.8)	23	(9.2)
Complex	0	(0)	0	(0)	2	(0.8)	2	(0.8)
Total	147	(59.0)	89	(35.7)	13	(5.2)	249	(100)

[1]Baby classification: presence of EA only (isolated) or EA plus major extracardiac defects (multiple or complex)

[2]Cardiac complexity = uncomplicated EA +/- atrial septal defect (simple) or EA plus other major cardiac defects (association or complex)

Table 3: Other Major Birth Defects Seen Among Infants With Ebstein Anomaly, National Birth Defects Prevention Study, 1997-2007

Associated Major Birth Defects[1]	**N**	**(%)**
None	135	(54.2)
Additional Cardiac[2]	102	(41.0)
Ventricular septal defects	33	
Muscular	12	
Perimembranous	17	
Malaligned VSD	1	
Not otherwise specified	4	
Pulmonary stenosis	27	
Pulmonary atresia,intact septum	25	
L-TGA	13	
Coarctation of the aorta	8	
Partial anomalous pulmonary venous return	4	
Pulmonary atresia +VSD, non-Tetralogy type	3	
Aortic stenosis	2	
Hypoplastic Left Heart Syndrome or small left ventricle	2	
Dextrocardia, non-Laterality defect	2	
Laterality Defect	2	
Tricuspid Atresia	1	
Hypoplastic pulmonary arteries	1	
Interrupted aortic arch, type B	1	
Truncus arteriosus	1	
Double-outlet right ventricle	1	
Total anomalous pulmonary venous return	1	
Transitional atrioventricular septal defect	1	
Additional Extracardiac	25	(10.0)
Defects of the Central Nervous System		
Dandy-Walker malformation	2	
Hydrocephalus	1	
Agenesis of the corpus callosum	1	
Defects of the eye		
Axenfeld anomaly	1	
Hyperplastic primary vitreous	1	
Upper respiratory system defects		
Cleft lip, with or without cleft palate	2	
Cleft palate	2	
Lower respiratory system defects		
Cystic lung disease	1	
Gastrointestinal Defects		
Intestinal malrotation	3	
Anal atresia	1	
Defects of the renal/urinary system		
Hydroureter	2	
Horseshoe kidney	1	
Duplicated collecting system	1	

Table 3 (continued): Other Major Birth Defects Seen Among Infants With Ebstein Anomaly, National Birth Defects Prevention Study, 1997-2007

Associated Major Birth Defects[1]	**N**	**(%)**
Defects of the genital system		
Ambiguous genitalia	1	
Bicornate uterus	1	
Musculoskeletal defects		
Diaphragmatic hernia	2	
Gastroschesis	1	
Defects of the integument		
Cystic hygroma	2	
CHARGE syndrome, possible (coloboma, choanal atresia, + tracheoesophageal fistula)	2	
Holt Oram syndrome, possible (absent radii, hypoplastic digits)	1	
Total	249	(100)

[1] Defect categories were not mutually exclusive (e.g., a case could have >1 additional cardiac defect.) 13 cases had additional cardiac and extracardiac defects

[2] Atrial septal defects were not considered separate cardiac defects

Table 4: Comparison of Ebstein Anomaly Infant Clinical and Demographic Characteristics By Presence of Other Birth Defects, National Birth Defects Prevention Study, 1997-2007

	Isolated, Simple EA[1] (n=135)		EA + Other Cardiac Defects Only [2] (n=89)			EA + Other Cardiac and/or Extracardiac Defects[3] (n=114)		
	N	(%)	N	(%)	crude OR[4] (95% CI)	N	(%)	crude OR[5] (95% CI)
Maternal Race/Ethnicity								
Non-Hispanic White	77	(57.0)	45	(50.6)	ref	57	(50.0)	ref
Non-Hispanic Black	9	(6.7)	7	(7.9)	1.33 (0.46-3.82)	12	(10.5)	1.80 (0.71-4.56)
Hispanic	31	(23.0)	31	(34.8)	1.71 (0.92-3.18)	37	(32.5)	1.61 (0.90-2.90)
Other	16	(11.9)	6	(6.7)	0.64 (0.23-1.76)	8	(7.0)	0.68 (0.27-1.69)
Missing	2	(1.5)	0	(0)		0	(0)	
Maternal Age (years)								
<20	11	(8.1)	10	(11.2)	1.48 (0.59-3.68)	15	(13.2)	1.71 (0.74-3.93)
20-34	99	(73.3)	61	(68.5)	ref	79	(69.3)	ref
35-39	21	(15.6)	13	(14.6)	1.01 (0.47-2.15)	14	(12.3)	0.84 (0.40-1.75)
≥40	4	(3.0)	5	(5.6)	2.03 (0.52-7.85)	6	(5.3)	1.88 (0.51-6.89)
Study Site								
Arkansas	15	(11.1)	8	(9.0)	0.57 (0.18-1.80)	9	(7.9)	0.53 (0.18-1.57)
California	13	(9.6)	10	(11.2)	0.82 (0.27-2.53)	11	(9.6)	0.74 (0.25-2.17)
Georgia	14	(10.4)	13	(14.6)	ref	16	(14.0)	ref
Iowa	14	(10.4)	11	(12.4)	0.85 (0.28-2.52)	14	(12.3)	0.88 (0.31-2.45)
Massachusetts	19	(14.1)	16	(18.0)	0.91 (0.33-2.48)	20	(17.5)	0.92 (0.36-2.39)
New Jersey	13	(9.6)	3	(3.4)	0.25 (0.06-1.08)	3	(2.6)	**0.20 (0.04-0.86)**
New York	9	(6.7)	4	(4.5)	0.48 (0.12-1.94)	5	(4.4)	0.49 (0.13-1.80)
North Carolina	4	(3.0)	5	(5.6)	1.35 (0.30-6.13)	10	(8.8)	2.19 (0.56-8.55)
Texas	18	(13.3)	14	(15.7)	0.84 (0.30-2.34)	21	(18.4)	1.02 (0.39-2.65)
Utah	16	(11.9)	5	(5.6)	0.34 (0.10-1.18)	5	(4.4)	0.27 (0.8-0.94)

Table 4 (continued): Comparison of Ebstein Anomaly Infant Clinical and Demographic Characteristics By Presence of Other Birth Defects, National Birth Defects Prevention Study, 1997-2007

	Isolated, Simple EA[1] (n=135)		EA + Other Cardiac Defects Only [2] (n=89)		EA + Other Cardiac and/or Extracardiac Defects[3] (n=114)	
	N	(%)	N (%)	crude OR[4] (95% CI)	N (%)	crude OR[5] (95% CI)
Birth Year						
1997	2	(1.5)	2 (2.2)	2.33 (0.26-20.66)	2 (1.8)	1.56 (0.19-13.11)
1998	12	(8.9)	9 (10.1)	1.75 (0.48-6.35)	11 (9.6)	1.43 (0.44-4.60)
1999	11	(8.1)	10 (11.2)	2.12 (0.59-7.66)	16 (14.0)	2.26 (0.73-7.05)
2000	14	(10.4)	6 (6.7)	ref	9 (7.9)	ref
2001	9	(6.7)	11 (12.4)	2.85 (0.78-10.47)	12 (10.5)	2.07 (0.62-6.91)
2002	9	(6.7)	2 (2.2)	0.52 (0.09-3.16)	4 (3.5)	0.69 (0.16-2.93)
2003	12	(8.9)	7 (7.9)	1.36 (0.36-5.18)	8 (7.0)	1.04 (0.31-3.53)
2004	22	(16.3)	10 (11.2)	1.06 (0.32-3.57)	12 (10.5)	0.85 (0.28-2.53)
2005	13	(9.6)	4 (4.5)	0.72 (0.17-3.13)	5 (4.4)	0.60 (0.16-2.26)
2006	7	(5.2)	12 (13.5)	**4.00 (1.05-15.21)**	13 (11.4)	2.89 (0.83-10.02)
2007	24	(17.8)	16 (18.0)	1.56 (0.49-4.90)	22 (19.3)	1.43 (0.52-3.95)
Gender						
Male	66	(48.9)	49 (55.1)	ref	55 (48.2)	ref
Female	68	(50.4)	40 (44.9)	0.79 (0.46-1.36)	58 (50.9)	1.02 (0.62-1.69)
Ambiguous	1	(0.7)	0 (0)		1 (0.9)	
Plurality						
Single	122	(90.4)	85 (95.5)	ref	107 (93.9)	ref
Multiple	12	(8.9)	4 (4.5)	0.48 (0.15-1.53)	7 (6.1)	0.67 (0.25-1.75)
Missing	1	(0.7)	0 (0)		0 (0)	
Gestational Age (weeks)[6]						
20-36	16	(13.9)	14 (17.3)	1.31 (0.60-2.87)	22 (21.6)	1.72 (0.85-3.50)
≥ 37	99	(86.1)	66 (81.5)	ref	79 (77.4)	ref
Missing	0	(0)	1 (1.2)		1 (1.0)	

Table 4 (continued): Comparison of Ebstein Anomaly Infant Clinical and Demographic Characteristics By Presence of Other Birth Defects, National Birth Defects Prevention Study, 1997-2007

	Isolated, Simple EA[1] (n=135)		EA + Other Cardiac Defects Only [2] (n=89)		EA + Other Cardiac and/or Extracardiac Defects[3] (n=114)	
	N (%)	N (%)	crude OR[4] (95% CI)	N (%)	crude OR[5] (95% CI)
Birth Weight (grams)					
<2500	25 (18.5)	19 (21.3)	1.09 (0.56-2.14)	30 (26.3)	1.48 (0.80-2.72)
2500-3999	96 (71.1)	67 (75.3)	ref	78 (68.4)	ref
≥ 4000	11 (8.1)	2 (2.2)	0.26 (0.56-1.21)	5 (4.4)	0.56 (0.19-1.68)
Missing	3 (2.2)	1 (1.1)		1 (0.9)	
Small for Gestational Age[6]					
No	96 (83.5)	68 (84.0)	ref	82 (80.4)	ref
Yes	19 (16.5)	12 (14.8)	0.89 (0.41-1.96)	19 (18.6)	1.17 (0.88-2.36)
Missing	0 (0)	1 (1.2)		1 (1.0)	
Birth Outcome					
Livebirth	126 (93.3)	85 (95.5)	ref	109 (95.6)	ref
Fetal death	8 (5.9)	4 (4.5)	0.74 (0.22-2.54)	5 (4.4)	0.72 (0.23-2.27)
Pregnancy termination	1 (0.7)	0 (0)		0 (0)	
Died at Any Age[7]					
No	117 (92.9)	72 (84.7)	ref	83 (76.1)	ref
Yes	9 (7.1)	13 (15.3)	2.35 (0.88-6.32)	26 (23.9)	**4.07 (1.71-9.93)**
Cardiac Surgery in Infancy[7]					
No	115 (91.3)	50 (58.8)	ref	69 (63.3)	ref
Yes	11 (8.7)	35 (41.2)	**7.32 (3.26-16.75)**	40 (36.7)	**6.06 (2.78-13.49)**

Table 4 (continued): Comparison of Ebstein Anomaly Infant Clinical and Demographic Characteristics By Presence of Other Birth Defects, National Birth Defects Prevention Study, 1997-2007

	Isolated, Simple EA[1] (n=135)		EA + Other Cardiac Defects Only [2] (n=89)		EA + Other Cardiac and/or Extracardiac Defects[3] (n=114)	
	N	(%)	N (%)	crude OR[4] (95% CI)	N (%)	crude OR[5] (95% CI)
Baby Classification						
Isolated	135	(100)	89 (100)	—	89 (78.1)	—
Multiple	—	—	— —	—	23 (20.2)	—
Complex	—	—	— —	—	2 (1.8)	—
Cardiac Complexity						
Simple	135	(100)	— —	—	12 (10.5)	—
Association	—	—	80 (89.9)	—	89 (78.1)	—
Complex	—	—	9 (10.1)	—	13 (11.4)	—

EA = Ebstein's Anomaly; OR = Odds Ratio

[1] "Isolated,Simple EA" = EA +/- Atrial Septal Defect with no extracardiac defects (isolated baby)

[2] "EA+Other Cardiac Defects Only" = Isolated Baby with Association or Complex Cardiac Complexity. It is a subgroup of "EA+Other Cardiac and/or Extracardiac Defects"

[3] "EA+Other Cardiac and/or Extracardiac Defects" = Any combination of Baby Classification and Cardiact Complexity besides Isolated Simple EA

[4] EA+Other Cardiac Defects Only vs Isolated Simple EA

[5] EA+Other Cardiac and/or Extra-Cardiac Defects vs Isolated Simple EA

[6] Among liveborn, singletons only (n=217)

[7] Among liveborn only (n=235)

Table 5: Comparison of Live born, Singleton Infants With Ebstein Anomaly Who Died During Infancy and Those Alive at One Year, National Birth Defects Prevention Study, 1997-2007

	Alive (n=188)		Died (n=29)		crude	adjusted
	N	(%)	N	(%)	OR (95% CI)	OR[1] (95% CI)
Maternal Race/Ethnicity						
White	101	(53.7)	16	(55.2)	ref	
Black	10	(5.3)	6	(20.7)	**3.79 (1.21-11.86)**	3.13 (0.90-10.93)
Other	75	(39.9)	7	(24.1)	0.59 (0.23-1.50)	0.55 (0.20-1.51)
Missing	2	(1.1)	0	(0)		
Maternal Age (years)						
<20	17	(9.0)	3	(10.3)	1.15 (0.31-4.27)	
20-34	137	(72.9)	21	(72.4)	ref	
>=35	34	(18.1)	5	(17.2)	0.96 (0.34-2.73)	
Study Site						
Arkansas	14	(7.4)	4	(13.8)	1.37 (0.32-5.97)	
California	22	(11.7)	0	(0)	NA	
Georgia	24	(12.8)	5	(17.2)	ref	
Iowa	17	(9.0)	4	(13.8)	1.13 (0.26-4.84)	
Massachusetts	28	(14.9)	4	(13.8)	0.69 (0.17-2.85)	
New Jersey	14	(7.4)	1	(3.4)	0.34 (0.04-3.24)	
New York	12	(6.4)	1	(3.4)	0.40 (0.04-3.82)	
North Carolina	9	(4.8)	3	(10.3)	1.60 (0.32-8.11)	
Texas	31	(16.5)	5	(17.2)	0.77 (0.20-2.98)	
Utah	17	(9.0)	2	(6.9)	0.57 (0.10-3.26)	
Birth Year						
1997	3	(1.6)	0	(0)	NA	
1998	12	(6.4)	5	(17.2)	3.75 (0.62-22.58)	
1999	20	(10.6)	4	(13.8)	1.80 (0.29-11.03)	
2000	18	(9.6)	2	(6.9)	ref	
2001	18	(9.6)	1	(3.4)	0.50 (0.04-6.02)	
2002	9	(4.8)	2	(6.9)	2.00 (0.24-16.61)	
2003	14	(7.4)	3	(10.3)	1.93 (0.28-13.16)	
2004	26	(13.8)	2	(6.9)	0.69 (0.09-5.38)	
2005	13	(6.9)	2	(6.9)	1.39 (0.17-11.15)	
2006	17	(9.0)	3	(10.3)	1.59 (0.24-10.70)	
2007	38	(20.2)	5	(17.2)	1.18 (0.21-6.70)	
Gender						
Male	97	(51.6)	10	(34.5)	ref	
Female	91	(48.4)	19	(65.5)	2.03 (0.89-4.59)	
Gestational Age (weeks)						
20-36	24	(12.8)	14	(48.3)	**6.34 (2.72-14.76)**	
≥ 37	163	(86.7)	15	(51.7)	ref	
Missing	1	(0.5)	0	(0)		

Table 5 (continued): Comparison of Live born, Singleton Infants With Ebstein Anomaly Who Died During Infancy and Those Alive at One Year, National Birth Defects Prevention Study, 1997-2007

	Alive (n=188)	Died (n=29)	crude	adjusted
	N (%)	N (%)	OR (95% CI)	OR[1] (95% CI)
Birth Weight (grams)				
<2500	22 (11.7)	11 (37.9)	**4.41 (1.83-10.64)**	
2500-3999	150 (79.8)	17 (58.6)	ref	
≥ 4000	15 (8.0)	1 (3.4)	0.59 (0.07-4.73)	
Missing	1 (0.5)	0 (0)		
Small for Gestational Age				
No	159 (84.6)	19 (65.5)	ref	
Yes	28 (14.9)	10 (34.5)	**2.99 (1.26-7.10)**	**2.97 (1.13-7.76)**
Missing	1 (0.5)	0 (0)		
Cardiac Surgery in Infancy				
No	149 (79.3)	19 (65.5)	ref	
Yes	39 (20.7)	10 (34.5)	2.01 (0.87-4.67)	
Baby Classification				
Isolated	177 (94.1)	19 (65.5)	ref	
Non-Isolated	11 (5.9)	10 (34.5)	**8.47 (3.18-22.53)**	**6.31 (2.28-17.52)**
Cardiac Complexity				
Simple	113 (60.1)	13 (44.8)	ref	
Non-Simple	75 (39.9)	16 (55.2)	1.85 (0.84-4.08)	

OR = Odds Ratio

[1]Adjusted for significant variables in crude analysis: race-ethnicity, SGA, and baby classification

EPILOGUE

I. Public Health Impact of Birth Defects, CHDs, and Study Rationale

Birth defects are important public health issues - approximately 120,000 infants are born with birth defects annually (Centers for Disease Control and Prevention, 2008). Birth defects can have lifelong and life-limiting effects on children, with annual health care costs estimated to be $2.6 billion nationwide (Russo and Elixhauser, 2007). CHDs, the most common type of birth defect, are a significant cause of birth-defect associated morbidity and mortality, accounting for 28% of deaths due to birth defects in the first month of life and about 50% of the deaths due to birth defects during the first 2 to 12 months (Yang et al., 2006).

Fortunately, with improved medical care and treatment, the mortality associated with CHDs is decreasing (Gilboa et al., 2010b). More than 90% of children born with CHDs will survive to adulthood, compared to only 50% prior to the 1970s (Boneva et al., 2001). There is no population-based surveillance of CHDs across the lifespan in the United States; hence, the number of children, adolescents and adults living with CHDs is unknown. However, it is estimated that nearly 2 million people of all ages may be living with CHDs in the U.S. (Marelli et al., 2007; Warnes et al., 2001), and given the decreasing mortality, those numbers are increasing (Warnes et al., 2001). Longer lifespan also means that CHDs are a "new" chronic disease. Some people with CHDs may live relatively symptom-free lives while others may have significant or variable periods of disability throughout their lives. Affected individuals are living with the primary effects of their disease and co-morbidities, but may also have other conditions that interact with their CHD (Engelfriet et al., 2005). For example, CHD is now the most common form of heart disease during pregnancy in the United States (Williams et al., 2006).

However, CHDs cannot be considered a single disease entity, but are a heterogenous group of defects, which differ in epidemiologic characteristics, pathogenesis, risk factors, morbidity and mortality. Since the 1970's, the overall prevalence of CHDs has been increasing, driven by less severe septal defects, which are holes between the walls that divide the chambers of the heart (Botto et al., 2001a; Oyen et al., 2009), while the prevalence of more severe defects has remained relatively constant. Thus, it is important to study subgroups and individual CHD types to improve understanding of the natural history andpopulations at risk, and identify areas for targeting prevention activities. Understanding the epidemiology and risk factors for the occurrence of and morbidity associated with CHDs is important. This knowledge can guide development of strategies to prevent their occurrence and help affected individuals live longer, healthier, productive lives.

Ebstein anomaly (EA) is a CHD of personal interest to me. Although EA is a rare CHD, during my pediatric cardiology training, I saw two EA cases - one neonate struggled and died within days of birth while the other was a child in relatively good health being followed long-term for arrhythmias. I was fascinated by the different clinical presentations, and wanted to contribute to the understanding of this disease by using data from the National Birth Defects Prevention Study (NBDPS) to update and improve upon previous studies.

II. Additional Thoughts on Key Study Findings

Epidemiology

The consistency of the EA birth prevalence estimate based on data from the NBDPS and those reported in previous, smaller studies (Correa-Villasenor et al., 1994; Fyler, 1980; Reller et al., 2008), suggests a stability in the prevalence of EA over time and geographic location. Our

EA cases were relatively homogeneous in baby classification – most had no other affected organ systems. In a previous description of NBDPS cases (Botto et al., 2007), 18% of all CHD cases had extracardiac defects, compared to only 10% among our EA cases. This appears to be a consistent finding for EA, since EA cases also had fewer extracardiac defects than other CHD cases in the BWIS (19% vs 26%) (Correa-Villasenor et al., 1994).

The majority of our EA cases were singletons, born at term, and appropriately sized for gestation. However, EA was more likely to manifest among preterm infants or infants of multiple gestations. Studies have shown that preterm infants have a higher rate of birth defects and infants with birth defects are more likely to be preterm, implying that there may be common risk factors for both (Honein et al., 2009; Rasmussen et al., 2001). There are several possible reasons for the association of prematurity and birth defects. First, prenatal diagnosis of a birth defect may lead to a planned delivery at an earlier gestational age. Second, the birth defect may result in fetal difficulties resulting in preterm labor. In EA, for example, infants can develop fetal hydrops and arrhythmias which can be life-threatening in utero (Attenhofer Jost et al., 2005). Finally, there may be common risk factors for both, such as smoking or diabetes (Correa et al., 2008; Malik et al., 2008). Some, but not all, infants who are preterm (<37 weeks gestation) are of low birth weight (<2500 grams), and the term "small for gestational age" accounts for both factors. There are standard normograms developed for birth weights by gestational age and gender (Alexander et al., 1996).

Multiple births have also been shown to have an increased risk of several types of birth defects, including CHDs, compared to singletons (Hardin et al., 2009; Tang et al., 2006). One study showed multiple births had a 46% increased risk for birth defects compared to singletons (Tang et al., 2006). However, the association of multiple births with EA is inconsistent. Our

findings were similar to the BWIS, which reported 8.5% of EA cases were twins, much higher than the rate among other CHD cases (2.2%) or controls (1.5%) (Correa-Villasenor et al., 1994). Yet a recent study showed significantly increased prevalence among twins of many CHD phenotypes, although the prevalence of EA among twins was not significantly different than the prevalence among singletons (PR 1.84 95% CI 0.93-3.64) (Hardin et al., 2009). Several mechanisms may account for increased rate of birth defects among multiple births, but the rationale for CHDs seems less clear. Decreased space in utero may lead to positional, mechanically-related defects; inadequate nutritional supply may impair fetal development; or hormonal changes may influence gonadal development (Tang et al., 2006). Finally, multiple gestations may be a result of artificial reproductive technology, which may also increase the likelihood spontaneous mutations.

The absence of other significant prevalence differences by maternal or infant characteristics is noteworthy. Consistent with the findings from Lupo and colleagues (Lupo et al., 2011), we did not see substantial variability in the prevalence of EA among racial-ethnic groups. The lack of racial-ethnic variability could suggest a common risk factor for EA across all groups, or perhaps there was insufficient sample size to detect an association of EA with a specific racial-ethnic group. Previous studies found higher prevalence among older mothers (Correa-Villasenor et al., 1994; Lupo et al., 2011), our data suggested this, but the association was not statistically significant. Additionally, our data showed no difference in prevalence by gender whereas Atlanta surveillance data reported that 75% of EA cases were female (Reller et al., 2008).

Co-occurrence with Syndromes

The co-occurrence of EA with possible syndromes is an interesting finding. CHARGE syndrome is a rare genetic disorder with the acronym accounting for several abnormalities that may be present together: **C**oloboma, **H**eart defects, choanal **A**tresia, **R**etardation of growth/development, **G**enital and **E**ar abnormalities. Several types of CHDs are seen in 50-85% of CHARGE, including conotruncal and aortic arch anomalies (Lin et al., 1987). The clinical definition has changed over time, with different sets of diagnostic criteria (Sanlaville and Verloes, 2007), and the inclusion of other defects such as tracheoesophageal fistula. The prevalence is about 1 per 10,000 births (0.01%) and with improved knowledge of genetics, about two-thirds have a mutation in the *CHD7* gene. Neither of the two suspected cases in our study had genetic testing to confirm CHARGE but both had coloboma, choanal atresia, trachea-esophageal fistula, and heart defects. CHARGE was reported in 1/47 (2.1%) of EA cases in BWIS, 2/44(4.5%) of EA cases in another study (Digilio et al., 2011), and 2/249 (0.8%) in our EA population; higher than the prevalence of CHARGE in the general population. Additionally, in one long-term follow-up study, children with EA were slightly shorter and had smaller body mass index than the population average (Kapusta et al., 2007), which supports the growth retardation aspect of CHARGE. Given the rarity of both anomalies, it is difficult to prove the association, but interesting to note.

Holt Oram Syndrome (HOS), occurs in about 1 in 100,000 births and is characterized by arm/hand and cardiac anomalies. Mutations in the *TBX5* gene have been associated with HOS and linked to EA (Tongsong and Chanprapaph, 2000). The most common CHDs in HOS are atrial and/or ventricular septal defects, but other more complex defects have been noted (McDermott et al., 1993). HOS was seen in 1 patient in the Texas EA study (Lupo et al., 2011)

and 1 in the current study. While some genetic abnormalities have been seen, such as in the *TBX5* and transcription factor *NKX2-5* (Benson et al., 1999), most cases are sporadic and there is probably underlying genetic heterogeneity.

Clinical Course

Consistent with other studies, the majority of our EA live births (202/235, 86%) survived infancy and most deaths (n=23/35, 65.7%) occurred during the neonatal period (the first 30 days of life) (Correa-Villasenor et al., 1994; Kapusta et al., 2007). Our reported neonatal mortality (n=23/235, 9.8%) was lower than previous studies which found that of all diagnosed neonates, 20-40% do not survive beyond 1 month and <50% survive to 5 years (Attenhofer Jost et al., 2005). EA may have worse outcome relative to some other CHDs; in BWIS, the 1 year case fatality rate was higher for EA (23.4%) than for other CHDs combined (18.1%) (Correa-Villasenor et al., 1994). An early study in England of EA cases from 1958-1991 reported 10-year survival of all live born infants to be 59% (Celermajer et al., 1994). Kapusta and colleagues reviewed cases in the Netherlands from 1980-2005 and estimated the 10-year survival of neonates diagnosed at birth to be 73% (Kapusta et al., 2007). Ten-year survival could not be estimated in our analysis. Although several studies have examined EA mortality (Celermajer et al., 1994; Correa-Villasenor et al., 1994; Flores et al., 2004; Kapusta et al., 2007), it is difficult to make conclusions about survival trends over time, since study time periods overlap, and study designs and populations differ. In summary, it seems that EA cases diagnosed in utero or neonatally may have a poor outcome, but that after the neonatal period, survival stabilizes.

The predictors of mortality that were measured in this study complemented those seen in clinical studies (Celermajer et al., 1994; Flores et al., 2004; Kapusta et al., 2007). Previously

found factors associated with death included younger age at presentation, more symptomatic, severity of classification or echocardiographic findings, and associated defects. Kapusta and colleagues found no difference in mortality by gestational age or birthweight, but had half the number of deaths as we did. Thus, there might have been insufficient power to detect an association in that study. Similar to others, we found the occurrence of surgery was not associated with death (Flores et al., 2004; Kapusta et al., 2007). Thus, surgery might improve the outcome, rather than indicate a more severe case.

EA cases with other major birth defects were more likely to have surgery or die. In NBDPS, the case classification enabled comparison on basis of other cardiac and extracardiac defects; our results suggested the presence of extracardiac defects was more predictive of death than additional CHDs. Unfortunately, this classification did not categorize severity within a defect type; hence it is unclear how severe the EA was among cases with additional birth defects. Perhaps these cases were sicker, which would support the clinical studies showing more severe EA died sooner (Attenhofer Jost et al., 2005; Kapusta et al., 2007). Our study indicates that infants with EA but without additional defects were more likely to survive and were less likely to undergo surgery compared to EA cases with additional defects.

Death is only one outcome to examine; clinical studies indicate that survivors beyond infancy may have other morbidities such as arrhythmias (Attenhofer Jost et al., 2005; Celermajer et al., 1994; Flores et al., 2004; Kapusta et al., 2007). Patients with mild forms of EA can be followed medically for years, with some requiring surgery, and others needing treatment and management of comorbidities. The electrical conduction system of the heart is often interrupted or abnormally displaced due to the malformation of the tricuspid valve and subsequent dilation of the right side of the heart (Attenhofer Jost et al., 2005). The largest study of the natural

history of EA was completed 40 years ago on 505 patients in a much different era of care and management than current medical care (Watson, 1974). In the natural history study, most infants were in heart failure, but for people who survived, 60-70% had good cardiac function, and the oldest reported patient died at age 85. Given this era of overall improved cardiac care and survival, an updated natural history study of EA should be considered.

Our study found infant characteristics associated with increased prevalence of EA and risk of death. Our findings among this contemporary cohort of EA support and update previous literature. Improved understanding of EA may guide clinical care and stimulate further epidemiologic studies.

III. Future Directions

Additional Studies of EA using NBDPS Data

In NBDPS, clinical information is collected on all eligible cases; however, more thorough data is obtained via the computer-assisted telephone interview of both case and control mothers. The average interview participation rate is 69% for cases and 65% for controls. There were 143 (57.4%) EA cases whose mothers were interviewed and 106 (42.6%) had non-interviewed mothers. Most NBDPS investigations only use data available from interviewed cases and controls to examine risk factors in case-control studies.. However, NBDPS also provides a robust sample size of all eligible cases to investigate rare defects; there have been a few descriptive analyses using data from interviewed and non-interviewed cases in nested case cohort studies (Genisca et al., 2009; Hartman et al., 2011). We decided in this current analysis to include all EA cases to increase the sample size, although this decision limited the breadth of data available for analysis.

In the future, I plan to conduct a case control analysis using only interviewed cases and controls to further analyze potential risk factors associated with EA. Controls in NBDPS are live born infants with no major structural birth defects randomly selected by birth certificates or hospital records from the same population as case infants. Given the small number of cases, this analysis would be hypothesis-generating and exploratory in nature. The NBDPS maternal interview of cases and controls provides an opportunity to assess many of the associations recognized previously: pregnancy loss; family history of CHD; maternal pregnancy intake of lithium, cannabis or benzodiazepine; and history of febrile illness during pregnancy. The NBDPS also has information on a variety of other potential risk factors such as maternal use of tobacco or alcohol, obesity, and maternal diabetes, which have been associated with other CHD subtypes (Correa et al., 2008; Gilboa et al., 2010a; Malik et al., 2008). Also, the interview data contains information on the use of assisted reproductive technologies (ART), and we could re-evaluate the association between EA and multiple births in light maternal reporting of use of ART.

There are other avenues to explore with these data. First, cases could be further reviewed to determine whether there was adequate information to determine timing and age at diagnosis, in order to evaluate association of these factors with death, as seen by other authors. Second, cases could also be reviewed with a clinical geneticist to determine whether the possible cases of CHARGE and Holt Oram syndromes should be considered ineligible and therefore excluded from NBDPS. However, even excluding these cases did not significantly change the predictive death analysis results (data not shown). Or perhaps these cases could be contacted to complete genetic testing for mutations of the *CHD7*or *TBX5* genes. Third, study sites could be contacted or information sought on the internet for further demographic statistics (e.g. births stratified by

birthweight, or SGA). Not all sites in NBDPS include the entire state, so demographic data would have to be specific to the region participating in the study. These data would allow prevalence calculations stratified by additional factors such as birthweight.

Finally, the cases could be re-contacted to conduct a long-term follow-up study. In rare situations, cases in NBDPS have been re-contacted for other unrelated investigations or further follow-up (Wong-Gibbons et al., 2009). The information on death that is part of the NBDPS is only what was available at the time of study inclusion. A follow-up study could examine other outcomes and comorbidities, such as arrhythmias or other clinical symptoms. Additionally, with appropriate identifiers, the cases could be linked to the state-based death certificate databases or the National Death Index to update the information on death. No long-term follow-up or further linkage to National Death Index was done, since that is not the focus of the NBDPS.

Other Research Avenues

EA is an interesting and challenging disease to study because of its rarity and diversity. Given the era of improved medical care and treatment, there are growing numbers of people affected with all types of CHDs, including EA, which provide opportunities for further population-based research. Although EA is rare, there are more population-based surveillance data on it, given that the recent Texas study and ours are the two largest cohorts of EA. Thus, it would be useful to update the natural history study done 40 years ago, using a large case cohort from the more recent era. Secondly, population-based data from other sites could be analyzed to corroborate previous and current findings, and elucidate risk factors that could aid in identifying target populations for primary and secondary preventive strategies. Finally, the suggestion of genetic factors in the etiology of EA is intriguing, and warrants further study.

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