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ASSOCIATION BETWEEN ANATOMIC GROUP AND 30-DAY OUTPATIENT HEALTHCARE UTILIZATION AMONG CHILDREN AND ADOLESCENTS WITH BOTH CONGENITAL HEART DEFECTS AND AN INFLUENZA DIAGNOSIS, 2008-2013

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Abstract

ASSOCIATION BETWEEN ANATOMIC GROUP AND 30-DAY OUTPATIENT HEALTHCARE UTILIZATION AMONG CHILDREN AND ADOLESCENTS WITH BOTH CONGENITAL HEART DEFECTS AND AN INFLUENZA DIAGNOSIS, 2008-2013

By Yining Zhang

Background: The population with congenital heart defects (CHD) continues to grow due to improved survival, and so does the burden on healthcare system as CHD cases require continuous and specialized care across the lifespan. CHD anatomic complexity is a risk factor for healthcare utilization of patients with CHD. Evidence of excess healthcare utilization attributable to influenza among pediatric patients with chronic conditions requires assessment of the association between CHD anatomic group and healthcare utilization after patients contract influenza.

Methods: This retrospective secondary analysis assessed the association between CHD anatomic group and 30-day outpatient healthcare utilization among a pediatric and adolescent cohort with CHD and influenza. Clinical and administrative electronic healthcare records between 2008-2013 were examined for 2,184 children and adolescents aged 1-19 years with CHD and an influenza diagnosis. CHD Anatomic complexity was categorized as complex, shunt, valve or shunt+valve, and outpatient utilization was determined from encounters that occurred within 30 days of an influenza diagnosis. Poisson regression models with robust variance estimates were applied to estimate crude and adjusted relative risks (cRR and aRR) and 95% confidence intervals (CIs).

Results: Occurrence of any or none outpatient encounters within 30-days of an influenza diagnosis differed across CHD anatomic groups (shunt: 31.6% vs 32.1%; valve: 20.0% vs 26.7%; shunt+valve: 22.0% vs 17.4%; complex: 26.4% vs 23.8%). There was no association between CHD anatomic group and outpatient utilization after adjusting for age, race, ethnicity, hypertension, and heart failure, aside from comparison of the shunt+valve group with the shunt group. Patients with shunt+valve lesions were at a slightly increased risk of having outpatient visits within 30-days of an influenza diagnosis compared to patients with shunt lesions (aRR: 1.09; 95% CI:1.00-1.19, $p = 0.04$), whereas no difference in risk existed between the valve group and shunt group (aRR: 0.92; 95% CI: 0.84-1.02) or the complex group and the shunt group (aRR: 0.98; 95% CI: 0.90-1.08).

Conclusions: Findings suggest an association between CHD anatomic group and one-month outpatient healthcare utilization after an influenza diagnosis among children and adolescents with CHD. Future studies should further examine this association in other populations, and using prospective data.

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Contents

List of Abbreviations

ACC	American College of Cardiology
ACHD	Adults with Congenital Heart Defects
aRR	adjusted Relative Risk
ASD	Atrial Septal Defects
AVCD	Atrioventricular Canal Defect
CDC	Centers for Disease Control and Prevention
CHD	Congenital Heart Defect
CI	Confidence Interval
cRR	crude Relative Risk
ECG	Electrocardiogram
ED	Emergency Department
eHR	Electronic Healthcare Records
FISMA	Federal Information Security Management Act
FQE	First Qualifying Encounter
HF	Heart Failure
HLHS	Hypoplastic Left Heart Syndrome
ICD-9-CM	International Classification of Disease, Ninth Revision, Clinical Modification
IE	Infective Endocarditis

IRB	Institutional Review Board
IT	Information Technology
OR	Odds Ratio
PAH	Pulmonary Arterial Hypertension
PDA	Patent Ductus Arteriosus
PFO	Patent Foramen Ovale
P-HTN	Pulmonary Hypertension
PII	Personally Identifiable Information
RSPH	Rollins School of Public Health
SES	Socioeconomic Status
TGA	Transposition of the Great Arteries
TOF	Tetralogy of Fallot
U.S.	United States
VSD	Ventricular Septal Defects

CHAPTER I. BACKGROUND

Congenital heart defects (CHD) are major structural congenital malformations that affect almost 1% of children born in the United States (U.S.).[1] Among birth defects, CHD is the leading cause of infant mortality,[2] and can lead to considerable pediatric morbidity and healthcare costs. Due to significant advances in diagnosis and treatment of CHD, we have seen about 90% of the infants born with CHD surviving into adulthood and a progressive decline in mortality from CHD.[3-5] Individuals living with CHD require continuous and specialized healthcare and surveillance across their lifetime,[5] and as the population with CHD continues to grow due to increased survival, so does the burden on the healthcare system.[6, 7]

Prevalence of CHD in the U.S.

As medical technology evolved, the past few decades have seen a progressive improvement in the survival of patients with CHD into adulthood.[8] Given the prospect of surviving into adulthood for infants born with CHD approaching 90%, prevalence of CHD is anticipated to continue to increase.[3] The prevalence of CHD among U.S. newborns is estimated at 8.1 to 10.8 per 1000 live births.[1, 9-11] From 1998 to 2008, prevalence for severe lesions among newborns decreased from 1.5/1000 to 0.9/1000 ($p=.03$), whereas the prevalence of mild defects increased from 8.0/1000 to 9.1/1000 ($p=.01$), and that of moderate CHD lesions remained unchanged.[9] The difference in temporary trends of birth prevalence across the spectrum of CHD complexity could be attributable to the rising frequency of antenatal screening using echocardiography.[12] While more mild CHD cases have been detected with advanced ultrasonic technology, more pregnancy terminations have also occurred among women who prenatally detected they were carrying a fetus with a severe CHD, resulting in a 15% reduction in the birth prevalence of the most severe CHD.[13] Yet, despite these trends, CHD remains the most common

cause of infant death associated with birth defects,[2] and those living with a CHD, require continuous, specialized healthcare and surveillance over their lifespan.[14]

According to a conservative estimate given by the American College of Cardiology (ACC) Bethesda Conference Task Force 1, there were 787,800 adult patients with CHD living in the U.S. in year 2000,[15] and that number almost doubled in the next decade. In 2010, approximately 1.5 million American adults and 1 million American children were estimated to be alive with CHD.[16] While mortality due to CHD has decreased largely due to advances in diagnosis and treatment, we have seen a shift in the age distribution of those with CHD with the number of adults living with CHD now outnumbering the pediatric population with CHD. For those born with a mild CHD lesion, one-year survival is estimated at 97% with survival to 18 years of age estimated at around 95%.[16] For those born with a complex anatomic lesion, 75% are expected to survive to their first birthday with survival to 18-years-old estimated a bit lower at 69%.[16] Overall, median age at death for patients with a CHD has seen a 20 year increase since 1987.[4]

Diagnosis of CHD

CHDs are diagnosed applying a number of different techniques. CHD is a gross structural cardiovascular abnormality of the heart that presents itself at birth. The general signs and symptoms of CHD may range from none to heart murmurs, tachycardia, shortness of breath, excessive sweating, fatigue, cyanosis, and so forth.[17] Fetal echocardiogram help to detect CHD prior to childbirth using ultrasound waves, and postnatally, physicians can use auscultation to detect heart murmurs, with CHD confirmed by echocardiography. Newborn screening with pulse oximetry is now commonly used in the US to detect severe CHD. Newborn pulse oximetry is a common test used to measure the oxygen levels in blood with a sensor placed at the infant's

fingertip; a low oxygen saturation level indicates the infant may suffer from cardiac disease. Having an electrocardiogram (ECG), in which electrodes connecting to a computer are put on the patient's chest and the waves displayed on the computer, can indicate whether a cardiac rhythm problem is present and provide information on cardiac chamber enlargement and is used ubiquitously to support CHD diagnosis.

Types of CHD and Clinical Classification

CHDs are classified by anatomic complexity, and the course of CHD varies with the complexity of defects. Classification of CHD into distinct groups based on anatomic complexity of the defect has undergone several iterations. Attempts to classify CHD complexity include Marelli's initial five-level hierarchy of CHD anatomic complexity designed to classify ICD-9 codes,[18] the 2008 ACC/AHA Guidelines for the Management of Adults with CHD (ACHD),[19] a design that modified Marelli's et al.'s (2007) scheme developed by clinical investigators during the 3-site pilot surveillance project funded by the U.S. Centers for Disease Control and Prevention (CDC),[20] and the most current CHD classification adaptation that was developed by clinical investigators during the 2015-2019 five-site CDC-funded Surveillance of Congenital Heart Defects across the Lifespan project. The latest classification scheme builds upon prior versions and continues to adhere to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes 745.xx–747.xx, based on native anatomy: complex, shunt, valve, shunt + valve, and other.

For instance, conditions classified as anatomically complex include patients with the highest need for surgical intervention early in life.[18] Such complex defects include atrioventricular canal defect (AVCD), tetralogy of Fallot (TOF), univentricular heart, transposition complex (complete or congenitally corrected transposition), truncus arteriosus and hypoplastic left heart

syndrome (HLHS). Those defects not classified as complex include shunts, valves, shunts + valves, and other (Appendix A). Shunt conditions include atrial septal defects (ASD), ventricular septal defects (VSD), patent ductus arteriosus (PDA), and anomalous pulmonary venous return. Valve anomalies include stenosis and/or insufficiencies of any valve, coarctation of the aorta (not a true valve abnormality, but creates left sided obstruction) and anomalies pertaining to the pulmonary arteries, also not a valve abnormality, but creates right sided obstruction (Appendix A). Lastly, anatomic cardiovascular conditions categorized as 'Other' include coronary anomalies and aortic arch anomalies that may compose vascular rings (see Appendix A).

Etiology of CHD

The critical period of cardiac morphogenesis is between 2 and 9 weeks of gestation. CHD also mainly occurs at this stage, with the heart initially functioning in the human embryo at 2 to 3 weeks of gestation and fully formed by 8 to 9 weeks.[21] While the etiology of CHD remains largely unknown, known causes of the occurrence of CHD are typically classified into two categories: internal and external. Internal risk factors are related to genetics. For example, chromosomal translocations and aberrations (e.g., trisomy 21) may be seen in cases of CHD.[21, 22] Additionally, the offspring of patients with CHD, or the sibling of an affected child is at 3 to 80-fold risk of recurrence, depending on the heritability of the specific CHD.[23] External risk factors related to the embryogenesis environment is more commonly seen than the internal risk factors. Maternal metabolic disease such as diabetes and phenylketonuria are important external risk factors.[24, 25] Other reported environmental factors include intrauterine infection (e.g., influenza, rubella, mumps, Coxsackie virus), maternal obesity, use of certain drugs and teratogens (e.g., thalidomide and retinoic acid), alcohol use, exposure to large-dose radiation/organic solvents, hypoxia, elder parental age, and nutrition.[26-28]

Cardiac Health Outcomes of CHD

Various sequelae, such as arrhythmias, heart failure, and pulmonary hypertension, may appear in the course of CHD. The form of defects and repair status are major determinants of the pathophysiologic consequences of CHD as these factors can impact hemodynamics. Arrhythmias are commonly seen in the long-term follow up for health outcomes in ACHD and are a major contributing cause of morbidity and mortality in adulthood.[29, 30] The incidence of postoperative arrhythmias in children with CHD who underwent elective open-heart surgery is 6.7%.[31] Heart failure (HF) is another common complication of CHD, referring to inadequate cardiac pumping function to support the needs of the body. Most pediatric HF cases start before the age of 1 year, the onset thereafter is much less frequent and usually develop with time. 10–20% of children having atrial switch or Fontan procedures are estimated to develop HF symptoms.[32] Pulmonary hypertension (P-HTN) is a rare, but serious complication in patients with CHD.[33] Pulmonary arterial hypertension (PAH) is a form of P-HTN resulting from pulmonary over-circulation due to left-to-right shunting within the heart that can occur with shunt defects that are not corrected. The development of PAH among patients with CHD is associated with greater likelihood of limited cardiac functions and clinical deterioration. Eisenmenger syndrome describes the reversal of shunting, which becomes right to left as pulmonary vascular resistance rises. Eisenmenger syndrome is an extreme manifestation of pulmonary vascular disease secondary to CHD, rare in the US, that is associated with premature mortality.[34]

In addition to the above complications, turbulent blood flow caused by abnormal cardiovascular structures may also raise the risk of developing endocarditis, an infection of heart structures. The overall incidence rate of infective endocarditis (IE) among pediatric and adult patients with CHD were estimated at 4.1 (95% confidence interval [CI], 3.5-4.9) and 11 (95% CI,

9-11) cases per 10,000 person-years, respectively (versus 0.5-0.7 cases per 10,000 person-years in general population).[35-37] For unrepaired CHD, the risk of IE mainly depends on the defect type, size, and site since the valvular or mural endothelial lesions are a substrate for infection. Complex cyanotic CHD, VSD and left ventricular outflow tract obstructions are associated with high IE risk prior to palliative/corrective surgery.[36-38] While surgical or interventional repair could remarkedly alter the risk of IE for some types of defects like ASD, VSD, and PDA based on the premise of complete repair, it may also predispose patients with complex cyanotic CHD to endocarditis since the foreign surfaces such as shunts, conduits, and prosthetic valves created by the procedures could become targets for infection.[39, 40]

Through advances in pediatric surgery and cardiology in the last half of the century, surviving through childhood has become promising for infants born with CHD, and longevity has become possible as well. A Belgian study found more than 90% of patients born at the beginning of the 1990s with mild to moderate CHD could survive into adulthood, whilst the chance of survival for those born with severe CHD was 56%.[3] Another study between 1953 and 2012 in Finland found that 70% of patients with CHD survived past their fifties by the end of the study, lower than the survival rate of 86% in the general population, but still encouraging.[41] From 1979 through 1997, the all-age mortality from CHD declined from 25 to 15 per million in the U.S., a 39% decline to which children under 5 contributed the most.[42] Substantial decrease in deaths was seen in patients with moderate to severe lesions. Mortality associated with PDA, VSD, ASD, transposition of the great arteries (TGA), tetralogy of Fallot (TOF), congenital aortic stenosis, and coarctation of the aorta dropped from 1979 through 2005 by 55%, 70%, 50%, 71%, 50%, 60%, 70%, respectively.[30]

Incidence of Influenza and Healthcare Utilization in Children and Adolescents

Influenza is an acute contagious respiratory illness caused by orthomyxoviruses, influenza A or B,[43] primarily marked by involvement of the upper respiratory tract including the nose, nasal cavities and passages (sinuses), pharynx, tonsils, and the larynx above the vocal cords and/or the lower respiratory tract including the larynx below the vocal cords, trachea, and the lungs including the bronchi, bronchioles, and alveoli.[44] The sudden onset of the common influenza symptoms include fever, coughing, sore throat, runny/stuffy nose, headaches, muscle aches, prostration, vomiting, and diarrhea.[45] Both influenza A and B viruses are known to mutate constantly resulting in the emergence of variants and this impacts spread, immunity, treatment and subsequent vaccine development.[46] In the U.S., influenza burden varies by a number of factors including what viruses are circulating in the population, seasonality, vaccine efficacy, and the vaccination rate.[47] Annually since 2010, CDC estimates that influenza has caused 9 million–45 million illnesses, 140,000–810,000 hospitalizations, and 12,000–61,000 deaths.[48] From 2010 to 2016, CDC reported median age-specific seasonal attack rates of influenza in the U.S. at 9.3%, 8.9%, and 3.9% for 0-17-year-olds, 18-64-year-olds, and 65+-year-olds, respectively, suggesting that children and adolescents are more likely to be infected with influenza than adults.[49] Furthermore, during the 2018-2019 season, influenza accounted for more than 16 million outpatient visits (38.9%), approximately a half million hospitalizations (10.0%), and 34,200 deaths (1.4%) for American children and adolescents between the ages of 0 and 17years.[50] Previous surveillance data captured between 1994 and 2000 revealed that influenza accounted for an average of 8.9, 5.8, and 3.6 more outpatient/emergency department (ED) visits for acute respiratory illness per month per 100 healthy children aged 6-23 months, 2-4 years, and 5-17 years, respectively.[51] In addition, for every 10,000 healthy children aged 2-4 years, an estimated

0.1-6.0 inpatient hospitalizations per month were attributable to influenza.[51] However, no significant difference in rate of influenza-associated hospitalizations was revealed between influenza periods and summer baseline periods for age groups of 6-23 months and 5-17 years.[51] Estimates of excess healthcare utilization rate attributable to influenza in children with chronic diseases were between 7.8-16.1 outpatient/ED visits per 100 person-months, varying by age, and 2.0-19.0 hospitalizations per 10,000 person-months for those aged 5-17 years (no significant excess rate for the other two age groups).[51] Overall, influenza places a significant burden on the health of American children and adolescents, thereby increasing healthcare resource utilization in this population each year.

Pre-existing Conditions in Children and Adolescents Who Contract Influenza

Nearly half of children and adolescents hospitalized with influenza have pre-existing conditions, of which CHD accounted for more than 10%.[52, 53] From 1996 to 2003, a tertiary teaching hospital in Madrid admitted 117 children under 3 years of age who had community-acquired influenza, of which 48 had an underlying, pre-existing disease, mainly either chronic pulmonary disease and/or CHD.[52] Similarly, at Children's Hospital of Philadelphia, over four consecutive seasons (July 2000 through June 2004), 745 patients, ≤ 21 years of age, were hospitalized with community-acquired laboratory-confirmed influenza, approximately half of whom had comorbid conditions, including asthma (24%), neurologic or neuromuscular disease (12%), immunosuppression (8%), and cardiac disease (7%).[54] Specifically, cardiac disease was associated with prolonged hospitalization defined as stay of 6 or more days (odds ratio [OR]: 3.6; 95% CI: 1.8–7.1).[53] Since chronic conditions are associated with greater likelihood of influenza-related complications (e.g., respiratory failure, encephalopathy, seizures, etc.),[53] children with conditions are at 4-21 times the risk of hospitalization for acute respiratory disease compared to

their healthier peers when influenza virus predominated over respiratory syncytial virus in winter.[55] Influenza appears to be an important contributor to pediatric healthcare utilization, especially in those with chronic disease like asthma or CHD.

Healthcare Utilization in Children and Adolescents with CHD

While prior literature has documented a high rate of healthcare utilization in adults with CHD,[56] few studies exist examining healthcare utilization in the adolescent CHD population.[57] Data from the 1997-2011 National Health Interview Survey reported that patients with CHD aged <18 years were more likely to visit a doctor's office/clinic (OR: 3.2; 95% CI: 1.7-6.0) or an ED (OR: 1.8; 95% CI: 1.4-2.4) than their same aged counterparts without CHD.[58] Surveillance data collected from healthcare encounters between 2008 and 2010 among U.S. adolescents with CHD, aged 11-19 years, revealed that more than 95% of them had at least one outpatient encounter regardless of the severity of defects.[59] In addition, severe CHD was associated with more frequent healthcare resource utilization including inpatient hospitalizations and cardiovascular surgery compared to those with non-severe CHD; specifically, 11-25% of adolescents with severe CHD had at least one inpatient encounter, while that proportion for non-severe cases was 7-19%.[59] However, no significant difference in the proportion of having at least one ED encounter between severe (7-50%) and non-severe cases (2-49%) was observed.[59]

Overall, number of healthcare encounters for patients with CHD is on the rise. In a systematic review of the literature published between 1990 and 2015 on healthcare utilization among ACHD, a significant increase in the number of outpatient visits and inpatient hospitalizations among this target group across recent decades was observed.[60] In a study of inpatient encounters that took place between 1998 and 2010 for children and teens with CHD, a 32.8% increase in hospitalizations was reported, with longer mean lengths of stays for children

and teens compared to ACHD, 17 days compared to 5.8 days, respectively.[61] In another study of ED visits between 2006 and 2014 among underage patients with CHD, a 17.7% increase in the number of CHD-related pediatric ED visits was reported.[62] In addition, the cost of pediatric hospitalizations for children and adolescents with CHD has seen significant increases in expenditures with costs totaling $5.6 billion in 2009 and increasing to $6.7 billion in 2012, an almost 20% gain in those three years.[6, 7] The increased number of healthcare encounters among patients with CHD not only is indicative of jut some of the ongoing challenges faced by an overtaxed healthcare system but also reflects the need for more resources to care for the growing number of individuals living with CHD.[61, 62]

Factors Associated with Healthcare Utilization in Children with CHD

The anatomic complexity of CHD and age are presumably two major factors associated with healthcare utilization among children with CHD. Significant differences in healthcare utilization exist across groups categorized by CHD anatomic complexity (non-CHD vs simple CHD vs moderate-complex CHD vs single ventricle). For every 100 children without CHD, an estimate of 246 ambulatory care visits (hospital-based outpatient visits and ED visits) occurred in the first year of life, while for every 100 children with CHD, the number of ambulatory care visits varied between 1416 and 4871 as CHD anatomic complexity increased. For inpatient care, for every 100 children without CHD, approximately 109 hospitalizations (including birth hospitalizations) occurred during the first year of life, while the number of hospitalizations for children with CHD ranged from 152 to 335, varying by anatomic complexity. This is almost a 250% difference in ambulatory healthcare utilization, and over a 120% difference in inpatient utilization between those with a simple CHD and a single ventricle lesion.[54] It was also found that healthcare utilization during the first 5 years of life peaked at infancy, and then, decreased

gradually thereafter.[54] These findings were consistent across all CHD complexity groups with the exception of those with a single ventricle lesion whose hospitalization rate was higher in the third and fourth year of life compared to the second year of life, likely due to the staged surgical treatment period for single ventricle patients where they often undergo a Fontan procedure between the ages of 2- and 4-years-old.[63]

Differential pattern of healthcare utilization based on CHD complexity and age could be explained from two aspects. First, complex CHD denotes unstable cardiopulmonary physiology, which requires surgical repairs that are often palliative, may cause complications and predispose patients to seek health care. Second, vulnerability of young children to illness, such as viral infections, may aggravate pre-existing cardiac conditions. Differential healthcare patterns were also present in the hospital readmission rate among children with CHD who had once been hospitalized for cardiac reasons: severe CHD lesion and younger age were recognized as two independent predictors of readmission within 1 month after discharge.[64]

In addition to CHD complexity and age, insurance type, sex, socioeconomic status (SES), and race/ethnicity have also been associated with healthcare utilization among children with CHD. In patients with CHD, the odds of being hospitalized through the ED was 2.3 times greater for those with public insurance compared to those with private insurance, while for the uninsured, the odds of being hospitalized through the ED was 4.6 times greater compared to those with private insurance. At the same time, being female decreased the likelihood of a hospital admission via the ED by 20%.[65] Adolescents and adults with CHD living in the most deprived areas had a 51% higher odds of hospitalization and a 74% higher odds of an ED visit compared with those living in the least deprived locations.[66] Medicaid insurance (OR: 1.23; 95% CI: 1.15-1.31) and nonwhite race (OR: 1.26; 95% CI: 1.19-1.34) were related to nonelective (urgent/emergent)

admission for CHD surgery.[67] Furthermore, the median length of hospital stay of children with CHD and Down syndrome born to non-Hispanic Black mothers was significantly longer than that of their non-Hispanic White counterparts (24.0 vs 16.0 days, respectively).[68]

Co-Occurring Health Conditions and Healthcare Utilization in Children with CHD

There is a substantial burden of comorbid conditions in children and adolescents with CHD that potentially can explain their frequent contact with the healthcare system. A population-based study from the United Kingdom found that individuals with CHD were at higher risk of atrial fibrillation than age- and sex-matched controls after adjustment for deprivation and smoking (adjusted OR: 7.6; 95% CI: 6.1-9.3).[69] Study findings also suggested that risk of having other diseases, both cardiovascular and otherwise, including HF, HTN, and stroke/transient ischemic attack, diabetes, chronic renal disease, and epilepsy were higher among patients with CHD versus controls. In the same study, patients with CHD were found to consult general practitioners and be referred to specialists more often than controls, and be prescribed more medicines. A population-based study in Canada demonstrated that hospitalized children and adolescents with CHD who also had multiple comorbid conditions (≥ 4), either cardiac or non-cardiac, were more likely to be readmitted after discharge.[64] Additionally, asthma, one of the most frequently seen comorbidities among children and adolescents with CHD, may complicate cardiac care.[70]

Study Rationale and Objectives

The population with CHD continues to grow due to increased survival, and so does the burden on the healthcare system as CHD cases require continuous and specialized healthcare and surveillance across their lifetime.[30] For the sake of cost saving and relief on the healthcare system burden, it is critical to identify specific contributors to the high consumption of healthcare resources among children with CHD. The big picture of healthcare utilization among children

with CHD has been described by: 1) significantly higher risk of receiving prescriptions, visiting healthcare facilities, and being hospitalized compared with non-CHD children;[54, 69] 2) disproportionately high inpatient costs in contrast to other pediatric hospitalizations;[6, 7] and 3) relationships with an array of factors, including age, gender, race/ethnicity, insurance, CHD complexity, and the presence of certain concurrent disease.[54, 64-69]

Nonetheless, despite existing evidence for association between CHD complexity and healthcare utilization,[54, 69] to our knowledge, there is no published work assessing such an association in a setting of influenza. Given the well-documented excess rates of outpatient visits, hospitalizations, and ED visits during seasonal influenza epidemics among children with chronic disease,[51, 52, 55, 71] investigations into the relationship between CHD complexity and healthcare utilization among patients with CHD and influenza are warranted. Moreover, most healthcare utilization evaluations for children with CHD used hospital costs as surrogate measures.[6, 7, 72] Only a few studies have detailed CHD-related healthcare utilization in terms of ambulatory care visits, hospital admissions, and prescription medications.[54, 69]

Current study objectives for this retrospective secondary data analysis included assessing the association between CHD anatomic group and healthcare utilization among children and adolescents with CHD and influenza, as well as examining the interaction of native CHD anatomic grouping with selected comorbidities for the association of interest. Study findings will provide insight into how CHD anatomic group influences healthcare utilization among the target population and how select comorbidities influence this relationship. A better understanding of these issues has the potential to inform public health interventions to save healthcare resources and to design and apply resource allocation optimization strategies in the target population based on the healthcare utilization pattern by CHD anatomic group.

CHAPTER II. METHODS

Data Source

An analytic linked, de-duplicated, and de-identified dataset file created from the CHD repository of Georgia residents was used for this retrospective secondary data analysis. Data in the CHD repository came from two CDC-funded CHD surveillance projects in which Emory University was involved, including the "Surveillance of Congenital Heart Disease in Adolescents and Adults" project (CDC-RFA-DD12-1207), a three-year CHD pilot surveillance project at three sites, hereinto referred to as "the pilot project", and the "Surveillance of Congenital Heart Disease Across the Lifespan" project (CDC-RFA-DD15-1506), a four-year surveillance project looking at CHD across the lifespan at five sites, hereinto referred to as "the lifespan project". The goals of these projects included estimating prevalence of CHD, describing the characteristics of individuals with CHD (i.e., CHD type, gender, age, race, ethnicity, insurance coverage, SES, comorbidities), examining the long-term health outcomes in individuals with CHD, understanding the strengths and limitations of conducting CHD surveillance in the U.S., and informing actions to improve outcomes and address inequities. CHD repository data consist of eHR of patients with at least one healthcare encounter between January 1, 2008 and December 31, 2013 across 11 various healthcare data sources. Repository data are housed and examined on a protected, private, Federal Information Security Management Act (FISMA)-compliant server at the Emory University, Rollins School of Public Health (RSPH) in the school's Department of Information Technology (IT) to ensure confidentiality and data security. FISMA-compliant servers are maintained by authorized RSPH IT personnel and only study researchers have access to the specific secure drive that houses the CHD repository. Prior to analysis, specific personally identifiable information (PII) identifiers were substituted with a proxy unique identifier for each patient, and

no PII was included in the analytic dataset. No consent/assent was obtained for the original database as the project was for public health surveillance and involved thousands of subjects, some deceased. The Emory University institutional review board (IRB) approved this study (STUDY00002858) on 7/8/2021 with a waiver of informed consent since it is a retrospective secondary analysis of previously de-identified data that poses minimal risk to participants.

Study Population

The initial cohort had 54,919 patients diagnosed with CHD, who had at least one healthcare encounter over a six-year period from January 1, 2008 to December 31, 2013. To be identified as having CHD, patients should have at least one of 55 CHD-associated ICD-9-CM codes that are initially described by Glidewell et al.[20] (DD12-1207) and later enhanced by clinicians of the lifespan project (Appendix A). Patients whose ages > 19 years at their first qualifying encounter (FQE) (n = 19,223) or who did not have an influenza diagnosis (n = 25,386), defined by the presence of at least one of the influenza-related ICD-9-CM codes (Appendix B) during the study period, were excluded. In addition, patients with CHD who were classified as having an unspecific or 'Other' CHD code (Appendix A) (n=2,724) , as well as those who had ICD-9-CM code 745.5 (used to indicate the presence of secundum ASD or PFO) in isolation or in combination with unspecified CHD codes 746.9 or 746.89 (n=5,402) were also excluded due to lack of specificity of these codes to identify true CHD.[73]

Variable Definitions

Outcome Variables

Healthcare utilization outcomes including numbers of outpatient visits, inpatient hospitalizations, and ED visits within 30 days of an influenza diagnosis were ascertained by healthcare encounter records. An influenza diagnosis was defined by the presence of at least one

of the following ICD-9-CM codes: 487.0, 487.1, 487.8, 488.01, 488.02, 488.09, 488.11, 488.12, or 488.19 (Appendix B). If a patient had multiple influenza diagnoses, only the first diagnosis will be considered. The numbers of each type of healthcare encounters within 30 days after being exposed were summed and then categorized into three dichotomous variables: any outpatient visits/inpatient hospitalizations/ED visits within 30 days of an influenza diagnosis. Each outcome was coded as '1' = Any (events), '0' = None.

Exposure Variable

Exposure was anatomic CHD group, operationalized by the native anatomic group classification scheme used in the lifespan project (Appendix A). This scheme classifies anatomic defects as complex ('1'), shunt ('2'), valve ('3'), shunt + valve ('4'), and other ('5'). The last category was not analyzed according to the exclusion criteria. Shunt served as the reference group.

Covariables

Age

Age was calculated by subtracting the date of birth from the date of a patient's FQE recorded in the pilot project data 2008-2010 or the lifespan project data 2011-2013. The FQE is defined as the first healthcare encounter where one or more CHD-related ICD-9-CM diagnosis codes appeared in a patient's eHR. This variable was classified into two groups: '1' = 1-10 years and '0' = 11-19 years. The older group, 11-19 years, served as the reference group.

Sex

Sex was coded '1' for males and '0' for females. Females served as the reference group.

Race

Race was classified into the following four categories: '1' = White, '2' = Black, '3' = Other (including American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander, and multi-race), and '4' = Unknown. White served as the reference group.

Ethnicity

Ethnicity was classified into the following three categories: '0' for non-Hispanic, '1' for Hispanic, and '9' for Unknown. Non-Hispanic served as the reference group.

Geographic Distribution - Rurality

Rurality was categorized according to county of residence, which was zoned by ZIP code and classified into six levels based on the 2013 NCHS Urban-Rural Classification Scheme for Counties.[74] The six-level classification scheme consists of four metropolitan/urban classes including large central metro ('1'), large fringe metro ('2'), medium metro ('3') and small metro ('4'), as well as two non-metropolitan classes including micropolitan ('5') and non-core ('6'). The six levels were then collapsed into two levels: the four metropolitan/urban classes were coded as '0' = Urban, and the two non-metropolitan categories were coded as '1' = Rural. Missing data received a code of '9' for Unknown. Urban served as the reference group.

Socioeconomic Status (SES)

SES was described by the following four proxies: neighborhood poverty (% below federal poverty level [FPL]), categorized as low (<15%, coded as '1'), medium (15%-<25%, coded as '2'), and high (≥25%, coded as '3'); neighborhood income was categorized as low (median annual income <$40K, coded as '1'), medium ($40K-<$75K, coded as '2'), and high (≥$75K, coded as '3'); neighborhood education (% of having a Bachelor's degree) was categorized as low (<30%, coded as '1') and medium to high (≥30%, coded as '2'); and neighborhood renter occupancy was

categorized as low (<35%, coded as '1') and medium to high (≥35%, coded as '2'). Missing data initially received a code of '9' for Unknown but was later omitted for the regression analyses due to small cell size. For neighborhood poverty and renter occupancy, the lowest category served as the reference group. For neighborhood income and education, the highest category served as the reference group. There could be collinearity issues between sets of those proxies, hence we selected only two of four proxies to enter to the *a priori* model to address such problems.

Health Insurance

Health insurance payer status was categorized into two categories: '1' = Any public, '0' = Private only. Private only served as the reference group.

Select Comorbid Conditions

Asthma

Asthma was operationalized based on the presence of at least one of 14 specific ICD-9-CM codes (Appendix C) occurring during the study period, measured using a dichotomous response: Yes ('1')/No ('0'). Absence of asthma served as the reference group.

Atrial Arrhythmia

Atrial Arrhythmia was operationalized based on the presence of at least one of four specific ICD-9-CM codes (Appendix C) occurring during the study period, measured using a dichotomous response: Yes ('1')/No ('0'). Absence of atrial arrhythmia served as the reference group.

Diabetes Mellitus (DM)

DM was operationalized based on the presence of at least one of 64 specific ICD-9-CM codes (Appendix C) occurring during the study period, measured using a dichotomous response: Yes ('1')/No ('0'). Absence of DM served as the reference group.

Endocarditis

Endocarditis was operationalized based on the presence of at least one of 19 specific ICD-9-CM codes (Appendix C) occurring during the study period, measured using a dichotomous response: Yes (‘1’)/No (‘0’). Absence of endocarditis served as the reference group.

Heart Failure (HF)

HF was operationalized based on the presence of at least one of 16 specific ICD-9-CM codes (Appendix C) occurring during the study period, measured using a dichotomous response: Yes (‘1’)/No (‘0’). Absence of heart failure served as the reference group.

Hyperlipidemia

Hyperlipidemia was operationalized based on the presence of at least one of five specific ICD-9-CM codes (Appendix C) occurring during the study period, measured using a dichotomous response: Yes (‘1’)/No (‘0’). Absence of hyperlipidemia served as the reference group.

Hypertension (HTN)

Hypertension was operationalized based on the presence of at least one of 40 specific ICD-9-CM code (Appendix C) occurring during the study period, measured using a dichotomous response: Yes (‘1’)/No (‘0’). Absence of hypertension served as the reference group.

Statistical Analysis

All analyses were conducted using the Statistical Analysis System (SAS) version 9.4 statistical software (SAS institute, Cary, NC). The default significance level was set at 0.05 unless specified otherwise. Descriptive analyses were conducted to obtain frequencies and percentages of all categorical variables. Bivariate analyses were conducted to describe and compare the distribution of exposure (CHD anatomic group) and covariables including age, sex, race, ethnicity, rurality, health insurance, SES proxies and selected comorbid conditions by outpatient

visits within 30 days of the influenza diagnosis as well as the distribution of covariables by exposure. Differences between the groups were examined using Chi-square test. Fisher's exact test was used when cell sizes were less than or equal to 5.

Poisson regression models with robust variance estimates were applied to estimate crude and adjusted relative risk (cRRs and aRRs) and 95% confidence intervals (CIs). Covariables significantly associated with both outcome and exposure variables in the bivariate analyses were entered into full models. Additionally, a multivariable model was built *a priori* with covariables identified through literature review. Backward selection process was applied with a significance level of 0.1 for stay to yield a reduced model. Effect modification by selected comorbid conditions was examined using chunk tests (likelihood ratio tests) and backward elimination.

CHAPTER III. RESULTS

A total of 2,184 patients with CHD and influenza were examined after excluding a total of 52,735 patients from the initial CHD cohort (Figure 1). For these 2,184 patients with CHD and influenza, 1,344 (61.5%) patients had at least one outpatient visits in the following 30 days of the influenza diagnosis. However, only 55 (2.5%) patients had an inpatient stay within 30 days following their influenza diagnosis, and even fewer (<10) patients had a ED visit during the one-month window. Since these patients had a sparse number of inpatient stays and ED visits within 30 days of their influenza diagnosis, these two healthcare utilization outcomes were not analyzed further.

Table 1 describes demographic and socioeconomic characteristics of the cohort, which consisted of 1,885 (86.3%) children (1-10-yrear-olds) and 299 (13.7%) adolescents (11-19-year-olds). Mean age at FQE was 4.7 years (SD 4.5). The distribution of males and females was comparable (52.5% vs 47.5%). The distribution of CHD anatomic group was 695 (31.8%) shunt cases, 493 (22.6%) valve cases, 442 (20.2%) shunt + valve cases, and 554 (25.4%) complex cases. White patients accounted for more than half of the cohort (52.2%), with Black patients accounting for 29.0%. 'Other' race which included American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander, and multi-race only made up a small portion (1.8%). The remaining 17.0% had missing data on race. Ethnicity was missing for a similar proportion (16.7%). For those with known ethnicity, Hispanics were in the minority (4.5%). All patients had health insurance, with the vast majority covered by public health insurance (99.5%). Nearly one fourth of patients (23.6%) dwelled in rural areas.

Four neighborhood-level SES proxies, including median annual income, poverty, education, and renter occupancy, are summarized in Table 1. A neighborhood was defined as a

ZIP code tabulation area where a patient lived. Approximately one third of patients (32.1%) lived in low income (<$40K) areas, while 61.2% lived in medium income ($40K - $75K) areas and 6.7% lived in high income (≥$75K) areas. Neighborhood poverty was evenly distributed that the percentages for low poverty (<15% residences under FPL), medium poverty (15% - <25% residences under FPL), and high poverty (≥ 25% residences under FPL) were 28.8%, 35.4%, and 35.8%, respectively. 72.7% of patients lived in low education neighborhoods where less than 30% of residences had a Bachelor's degree. 59.8% of patients were from neighborhoods where less than 35% of residences were renters.

The most common comorbid condition burdening this cohort of patients with CHD and influenza was asthma (50.5%), followed by HF (18.9%) and HTN (14.8%). Other comorbid conditions including atrial arrhythmia, endocarditis, hyperlipidemia, and DM were seen in a small percentage of patients, 5.0%, 2.3%, 2.1%, and 2.0%, respectively (Table 1).

Table 2 displays bivariate analyses comparing the distribution of CHD anatomic group and select covariables by having any or none outpatient encounters within 30 days of an influenza diagnosis. There was a significant difference in the distribution of CHD anatomic group between those patients with at least one outpatient visit (any) and those with no outpatient visits (none) within 30 days of an influenza diagnosis: 31.6% vs 32.1% for those with shunt defects, 20.0% vs 26.7% for those with valve lesions, 22.0% vs 17.4% for those with shunt + valve defects, and 26.4% vs 23.8% for those with complex lesions, respectively (χ^2 =17.00, p = 0.0007). There were also racial and ethnic differences for those with and without outpatient visits within 30 days. For instance, racial percentages for patients with outpatient visits compared to those with no outpatient visits within 30 days of being diagnosed with influenza were 51.9% vs 52.7% White, 26.8% vs 32.5% Black, 1.9% vs 1.7% 'Other' race, and 19.4% vs 13.1% unknown race,

respectively (χ^2 =18.27, p = 0.0004). The percentages for non-Hispanics, Hispanics, and unknown ethnicity were 76.0% vs 83.1%, 4.8% vs 4.2%, and 19.2% vs 12.7%, respectively, among patients with any versus none outpatient visits within 30 days of an influenza diagnosis (χ^2 =16.57, p = 0.0003). Patients with CHD and influenza who had an outpatient encounter within 30 days of an influenza diagnosis were younger than their counterparts with no outpatient visits within that one-month window, since children between 1 and 10 years of age constituted 88.2% of the former in contrast with 83.2% of the latter (χ^2 =11.07, p = 0.0009). Asthma, HF, and HTN were significantly associated with having any outpatient visits within 30 days compared to those with no outpatient encounters within 30 days of the influenza diagnosis: for asthma, 53.9% vs 45.1% (χ^2 = 16.10, p < 0.0001); for HF, 21.0% vs 15.5% (χ^2 = 10.24, p = 0.0014); and for HTN, 16.1% vs 12.6% (χ^2 = 5.10, p = 0.0239).

Sex, geographic distribution (rural/urban), neighborhood SES proxies, and other select comorbid conditions did not have a significant association with outpatient visits (Table 2) and were not included in the full adjusted model. Insurance was not entered into adjusted models due to a cell size of = 0 in the contingency table of insurance × outpatient visits, which meant there were no patients with private insurance only who had any outpatient visits within 30 days of the influenza diagnosis.

Table 3 presents the distribution of covariables by CHD anatomic groups. Both age and sex were significantly associated with native anatomy of CHD. The proportion of children aged 1-10 years was 92.1%, 73.8%, 92.8%, and 85.0% for shunt, valve, shunt + valve, and complex CHD group, respectively (χ^2 = 100.92, p < 0.0001). Males accounted for 49.0%, 55.4%, 49.3%, and 57.0% of the four groups, respectively (χ^2 = 11.43, p = 0.0096). Geographic distribution differed by CHD anatomy with rural residents making up 18.7% of the shunt group, 30.8% of the valve

group, 24.9% of the shunt + valve group, and 22.4% of the complex group ($\chi^2 = 24.25$, $p < 0.0001$). The distribution of race, ethnicity, and neighborhood income level was also significantly different across CHD anatomic group classification scheme (race: $\chi^2 = 82.75$, $p < 0.0001$; ethnicity: $\chi^2 = 93.44$, $p < 0.0001$; income: $\chi^2 = 19.14$, $p = 0.0039$).

Comorbid conditions including HF, HTN, atrial arrhythmia, and endocarditis were associated with CHD anatomic group (Table 3). The prevalence of HF was 8.5% among shunt group, 4.7% among valve group, 15.6% among shunt + valve group, and 47.1% among complex group ($\chi^2 = 405.69$, $p < 0.0001$). The prevalence of HTN was 7.2% among shunt group, 12.0% among valve group, 12.9% among shunt + valve group, and 28.3% among complex group ($\chi^2 = 116.90$, $p < 0.0001$). The prevalence of atrial arrhythmia was 1.7% among shunt group, 2.2% among valve group, 4.1% among shunt + valve group, and 12.5% among complex group ($\chi^2 = 88.63$, $p < 0.0001$). Less than 10 patients had endocarditis in the shunt + valve group, as is the case for those with shunt defects and those with valve lesions, whilst 28 (5.0%) patients in the complex group had endocarditis ($\chi^2 = 27.5$, $p < 0.0001$).

Table 4 shows the results of unadjusted and adjusted analyses for the association between CHD anatomic group and outpatient visits within 30 days of an influenza diagnosis among children and adolescents with CHD. When not considering any effects of covariables, the risk of having at least one outpatient visit within 30 days of an influenza diagnosis among patients with valve lesions was 11% lower compared to patients with shunt defects (cRR: 0.89; 95% CI: 0.81-0.99). On the contrary, patients with co-occurring shunt and valve lesions were at a 10% higher risk compared to patients with shunt defects only (cRR:1.10; 95% CI: 1.00-1.20, $p = 0.04$). The crude association of interest was non-significant when comparing the CHD complex group with the shunt defect group (cRR: 1.04; 95% CI: 0.96-1.14), though significant when comparing valve

group (cRR: 0.89; 95% CI: 0.81-0.99) or shunt + valve group (cRR:1.10; 95% CI: 1.00-1.20) with shunt group.

According to the results of the bivariate analyses observed in Tables 2&3, age, race, ethnicity, HF, and HTN were entered into the full Poisson regression model because they were significantly associated with both the outcome (outpatient visit) and exposure (CHD anatomic group) variables. Two more covariables, neighborhood median annual income and neighborhood education, were added to construct the *a priori* model. A backward stepwise selection approach was conducted starting from the full model to eliminate non-significant covariables ($p > 0.1$) which eventually yielded a reduced model adjusted for age, race, and HF. Interactions between CHD anatomic group and select comorbid conditions were examined which revealed no significant associations. Risk estimates of the three adjusted models (*a priori*, full, reduced) were similar (Table 4). For the comparison of shunt + valve group with shunt group, relative risk remained almost unchanged regardless of adjustment for select covariables. However, the estimates for the comparisons of valve to shunt or complex to shunt slightly changed after adjustment, the former in particular, which became non-significant in the adjusted models.

Overall, patients with a shunt and valve CHD classification who also had influenza were at a slightly increased risk of having an outpatient visit within 30 days of an influenza diagnosis compared to patients with shunt defects only (aRR: 1.09; 95% CI: 1.00-1.19, $p = 0.04$), whereas no difference in risk existed between the valve group and shunt group (aRR: 0.92; 95%CI: 0.84-1.02) or the complex group and the shunt group (aRR: 0.98; 95% CI: 0.90-1.08).

CHAPTER IV. DISCUSSION

The current study, to our knowledge, is the first study to explore whether the likelihood of seeking healthcare after contracting influenza differs by CHD anatomic group among children and adolescents with CHD when accounting for interaction and confounding by demographic and socioeconomic characteristics. The results of this analysis of CHD surveillance data extracted from a a repository of clinical and administrative data revealed the cumulative incidence of influenza from 2008 to 2013 was 7.5% among children and adolescents with CHD in care. This rate was lower than the median seasonal influenza attack rate reported by CDC 2010-2016 for 0-17-year-olds (9.3%).[49] In addition to temporal variation, the difference may be attributed to two aspects of underestimation. First, the study cohort represented tertiary referral population rather than general population, whilst people tended to visit primary healthcare facilities instead of tertiary centers for ailments. Second, only the first influenza diagnosis of each patient was considered as per the study design, leading to fewer influenza cases.

For patients with CHD aged 1-19 who had an influenza diagnosis, shunt cases were the largest CHD anatomic group, 31.8%, followed by those with complex lesions, 25.4%, valve lesions, 22.6%, and the shunt + valve group, 20.2%. The complex CHD group represents a larger proportion than expected, likely reflecting that this group is more likely to remain in care compared to other anatomic groups that may be able to be more completely repaired. Prior work on the same database suggested that shunt + valve group was quite small in relative to the other three groups, accounting for only 3.9% of the total adolescent population with CHD (n = 424,336).[59] It was of note that the percentage of shunt + valve group increased to a level comparable with that of other groups when restricted to patients with influenza. The shift in

distribution pattern of CHD native anatomic grouping was important for regression analysis, as it allowed a sufficient number in shunt + valve group for model convergence.

The number of patients having one or more outpatient visits in the following 30 days after an influenza diagnosis was 1,344 (61.5%), in contrast to very few patients admitted to inpatient (55 out of 2,184) or ED (<10 out of 2,184) during the same study window. The big difference in the numbers of healthcare encounters across care types was in agreement with the findings of an earlier published analysis using data from the same data repository, which reported a 96% resource utilization rate with respect to outpatient visits, a 14% inpatient utilization, and a 7% ED utilization.[59] The lack of inpatient and ED utilization encounters left us unable to adequately assess the association of CHD anatomic group and inpatient and ED visits for this cohort with CHD and influenza.

There was a substantial burden of comorbidities in children and adolescents with CHD. The most common comorbid condition was asthma (50.5%), followed by HF (18.9%) and HTN (14.8%). Other comorbid conditions including atrial arrhythmia (5.0%), endocarditis (2.3%), hyperlipidemia (2.1%), and DM (2.0%) were seen in a minority of patients. It was noteworthy that half of patients in this study were suffers of asthma. This was consistent with the results of a retrospective cohort study (July 2000 through June 2004) performed at Children's Hospital of Philadelphia, which found asthma the most commonly seen comorbidity (24%) among patients ≤ 21 years of age hospitalized with community-acquired laboratory-confirmed influenza (n = 745).[53] Chronic conditions like asthma and CHD may increase the risk of healthcare utilization, as they were associated with greater likelihood of influenza-related complications such as respiratory failure, encephalopathy and seizures (OR: 1.6; 95% CI: 1.1-2.2).[53]

The comorbidity burden in patients with CHD was likely to explain their frequent contacts with the healthcare system. A cross-sectional study with case-control analysis (2002-2004) conducted in the United Kingdom found that individuals with CHD (n = 9.952) were at higher risk of atrial fibrillation than age- and sex-matched controls (n = 29.837) after adjustment for deprivation and smoking (adjusted OR: 7.6; 95% CI: 6.1-9.3).[69] Study findings also suggested that the risk of having other diseases, both cardiovascular and otherwise, including heart failure, hypertension, and stroke/transient ischemic attack, diabetes, chronic renal disease, and epilepsy were higher among patients with CHD versus controls. In the same study, patients with CHD were found to consult general practitioners and be referred to specialists more often than controls, and be prescribed more medicines as well.

We selected a range of comorbid conditions to examine their impacts on the association of CHD anatomic group with outpatient utilization outcome. The prevalence of HF and HTN were found to be higher in patients with any outpatient encounters within 30 days of an influenza diagnosis than those without. The disease prevalence was also found to increase as CHD anatomic group varying from shunt to complex. Therefore, the presence of HF and HTN were entered into regression models as covariables.

By comparing the distribution of demographic and SES variables by outcome and exposure, three potential confounders were identified that might bias the association of interest, including age, race, and ethnicity. The age distribution differed by outpatient healthcare utilization outcome. Overall, patients with CHD and influenza who had any outpatient visits within 30 days of their influenza diagnosis were younger than those with CHD and influenza who did not have an outpatient encounter within 30 days of their influenza diagnosis (88.2% 1-10-year-olds vs. 83.2% 1-10-year-olds). Younger age is presumably a contributor to healthcare

utilization among children with CHD, because of the vulnerability of young children to illness like viral infections which may aggravate underlying heart lesions. A population-based retrospective study among children (n = 448,527) born between January 2005 and March 2014 in Alberta, Canada found that healthcare utilization, including inpatient, outpatient, physician, and drug utilization, during the first 5 years of life peaked at infancy, and then, decreased gradually thereafter ($p < 0.001$).[54] This finding was consistent across all CHD anatomic groups with the exception of those with a single ventricle lesion whose hospitalization rate was higher in the third and fourth year of life compared to the second year of life, likely due to the staged surgical treatment period for single ventricle patients where they often undergo a Fontan procedure between the ages of 2- and 4-years-old.[63]

Previous research has recognized CHD anatomic complexity as a major factor associated with healthcare utilization among patients with CHD. Islam et al. found significant differences in ambulatory healthcare utilization measured by hospital-based outpatient visits and ED visits across groups categorized by CHD anatomic complexity: for every 100 children without CHD, an estimate of 246 ambulatory care visits occurred in the first year of life, while for every 100 children with CHD, the number of ambulatory care visits varied between 1416 and 4871 as CHD anatomic complexity increased level by level (simple CHD vs moderate-complex CHD vs single ventricle).[54] This is almost a 250% difference in ambulatory healthcare utilization between those with a simple CHD and a single ventricle lesion. Billett et al. found CHD cases were significantly more likely than controls to be heavy users of primary healthcare: for example, patients with complex/moderate lesions had 4.3-fold likelihood of general practitioner consultations ≥ 20 between 2002 to 2004 compared to their matched controls (OR: 4.3; 95% CI: 3.0-6.1), while

patients with simple lesions were 2.1 times as likely as their matched controls to consult their general practitioners 20 or more times (OR: 2.1; 95% CI: 1.7-2.6).[69]

In our study, a Poisson regression model with robust variance estimates yielded non-significant measures of association between CHD anatomic group and outpatient resource utilization for comparisons of valve to shunt or complex to shunt. The divergence between our study and previous work was likely due to the difference in classification of CHD anatomic complexity and the focus on outpatient encounters only. Nonetheless, the model did suggest a slightly increased risk of having outpatient visits within 30 days of an influenza among patients classified as shunt + valve group versus shunt group (aRR: 1.09; 95% CI: 1.00-1.19, p = 0.04). Also, there was no significant evidence to suggest the effect was modified by any of select comorbid conditions. Taken in context with findings from previous studies, the results of the current study could be interpreted in a way that relatively complex (shunt + valve) CHD denotes unstable cardiopulmonary physiology, which may cause complications and predispose patients to seek healthcare. Those with complex CHD may be more likely to require ED or inpatient resources, but we did not examine that due to small numbers.

A major strength of our study was the use of administrative data from two CHD surveillance projects over a span of six years. The administrative dataset covering a large number of patients with CHD insured adequate sample size for our research purposes. The comprehensiveness and accuracy of administrative data make it superior to survey data in terms of the collection of information such as the type and date of healthcare encounters, diagnoses, and demographics. Administrative data could largely get rid of typical bias (e.g., recall bias, self-report bias) inherent in an interview or a questionnaire survey, and may also reduce missing to a

great extent since the acquisition process is seldom intrusive to subjects, resulting in little loss to follow-up.

However, the use of administrative data comes with some limitations as well. First, the data were provided by several subspecialty and tertiary care facilities, and as such, healthcare encounters from primary or secondary care settings were not included. Also, there was a likelihood that patients sought healthcare elsewhere in addition to the data providers and their encounters were not fully captured in the dataset. For instance, patients might go to a hospital in the immediate vicinity, especially in an emergency. Therefore, the number of healthcare encounters were likely to be underestimated in this study. Underestimation might contribute to the observed low occurrence of inpatient hospitalizations and ED visits (2.5% and <0.5%, respectively). Second, there could be unmeasured confounding as we were only able to control for variables available in the administrative dataset. For example, we considered four neighborhood-level proxies to adjust for potential confounding by SES, because individual-level metrics of SES were not available in the dataset. However, it might not be optimal to use community characteristic to instead individual ones which are of primary concern, given non-negligible disagreement between individual-level and area-level SES measures in a mixed urban-rural context.[75] Third, This study might be subject to bias of which the roots were in the retrospective design.

In conclusion, patients classified as having shunt and valve CHD may experience increased needs for outpatient healthcare within 30 days of an influenza diagnosis compared to patients with shunt lesions only, whereas no difference between the valve group and shunt group or the complex group and the shunt group. Future studies should further examine this association in other populations (e.g. CHD patients contracting COVID-19), and using prospective data.

CHAPTER V. PUBLIC HEALTH IMPLICATIONS / FUTURE DIRECTIONS

Health service delivery for patients with CHD is at the top of the agenda for public health.[76] Large amounts of resources have been dedicated to the care of U.S. children and adolescents with CHD as advances in pediatric surgery and cardiology have prolonged the life expectancy and lifelong care is often needed. Identification of specific contributors to the high consumption of healthcare resources among this population is of paramount importance in order to save healthcare expenditure and reduce the burden on healthcare system burden. Previous studies demonstrated that the complexity of CHD may be positively associated with healthcare utilization among the target population.[54, 64] However, while excess rates of outpatient visits, hospitalizations, and ED visits during the seasonal influenza epidemics among children with chronic disease were frequently reported,[51, 52, 55, 71] scant attention has been devoted to look at the association between anatomic complexity group of CHD and healthcare utilization in a setting where patients with CHD contract influenza.

The current study, to our knowledge, is the first study to explore whether the likelihood of seeking healthcare after contracting influenza differs by CHD anatomic group among children and adolescents with CHD when accounting for interaction and confounding by demographic and socioeconomic characteristics. It is of public health significance to provide insight into how CHD anatomic group influences healthcare utilization among the target population and how select comorbidities influence this relationship, because a better understanding of healthcare utilization pattern in the target population by CHD anatomic group and other characteristics has the potential to inform public health interventions for saving healthcare resources, and to design and apply resource allocation optimization strategies benefiting the target population.

By examining the association of CHD anatomic group with outpatient resource utilization within 30 days of an influenza diagnosis, this study revealed that relative to other groups, shunt + valve group might be more inclined to have outpatient visits in the month following an influenza diagnosis. This finding provides support for risk stratification for specialized outpatient intervention and management strategies targeting high-risk subgroups of pediatric patients with CHD like those with concomitant acute conditions like influenza. Due to sparse inpatient and ED encounters recorded in the eHRs of the current CHD cohort, this study did not obtain estimates for the association of CHD anatomic group with inpatient resource utilization and ED resource utilization. Future studies should examine these issues.

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TABLES

Table 1. Descriptive Characteristics of Children and Adolescents with Congenital Heart Defects (CHD) and Influenza, 2008-2013 (N=2,184)

Variable	N	%
Outpatient Visits within 30 days of an Influenza Diagnosis		
None	840	38.5%
Any	1,344	61.5%
Inpatient Hospitalizations within 30 days of an Influenza Diagnosis		
None	2,129	97.5%
Any	55	2.5%
ED Visits within 30 days of an Influenza Diagnosis[†]		
None	>2,174	--
Any	<10	--
CHD Anatomic Group		
Shunt	695	31.8%
Valve	493	22.6%
Shunt + Valve	442	20.2%
Complex	554	25.4%
Age		
1-10 Years	1,885	86.3%
11-19 Years	299	13.7%
Sex[†]		
Male	1,14X	52.5%
Female	1,03X	47.5%
Unknown	<10	--
Race		
White	1,140	52.2%
Black	633	29.0%
Other[*]	40	1.8%
Unknown	371	17.0%
Ethnicity		
Non-Hispanic	1,720	78.8%
Hispanic	99	4.5%
Unknown	365	16.7%
Insurance		
Private Only	12	0.5%
Any Public	2,172	99.5%
Geographic Distribution - Rurality[†]		
Rural	51X	23.6%
Urban	1,66X	76.4%
Unknown	<10	--

Neighborhood Median Annual Income†		
<$40K	70X	32.1%
$40K - <$75K	1,33X	61.2%
≥$75K	14X	6.7%
Unknown	<10	--
Neighborhood Poverty (% below FPL)†		
<15%	62X	28.8%
15% - <25%	77X	35.4%
≥25%	78X	35.8%
Unknown	<10	--
Neighborhood Education†		
<30% BS degree	1,58X	72.7%
≥30% BS degree	59X	27.3%
Unknown	<10	--
Neighborhood Renter Occupancy†		
<35% renters	1,30X	59.8%
≥35% renters	87X	40.2%
Unknown	<10	--
Comorbid Conditions		
Asthma	1,104	50.5%
Heart Failure (HF)	412	18.9%
Hypertension (HTN)	323	14.8%
Atrial Arrhythmia	110	5.0%
Endocarditis	50	2.3%
Hyperlipidemia	45	2.1%
Diabetes Mellitus (DM)	43	2.0%

† Cells with <10 patients or with possibility of unintentional (deductive) disclosure were not specifically reported owing to privacy restrictions, in accordance with IRB policy.
* 'Other' race includes American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander, and multi-racial.
***Abbreviations**:* CHD=Congenital Heart Defect; ED=Emergency Department; FPL=Federal Poverty Level; BS=bachelor of science degree

Table 2. Distribution of Congenital Heart Defect (CHD) Anatomic Group and Covariables by Whether Had Outpatient Visits within 30 Days of an Influenza Diagnosis among Children and Adolescents with Congenital Heart Defects (CHD) and Influenza (N=2,184)

	Outpatient Visits within 30 Days of an Influenza Diagnosis		χ^2 (p-value)[#]
	None n (col%)	Any n (col%)	
CHD Anatomic Group			
Shunt	270 (32.1%)	425 (31.6%)	**17.00 (p=0.0007)**
Valve	224 (26.7%)	269 (20.0%)	
Shunt + Valve	146 (17.4%)	296 (22.0%)	
Complex	200 (23.8%)	354 (26.4%)	
Age			
1-10 Years	699 (83.2%)	1,186 (88.2%)	**11.07 (p=0.0009)**
11-19 Years	141 (16.8%)	158 (11.8%)	
Sex			
Male	429 (51.1%)	718 (53.5%)	1.18 (p=0.2764)
Female	411 (48.9%)	625 (46.5%)	
Race			
White	443 (52.7%)	697 (51.9%)	**18.27 (p=0.0004)**
Black	273 (32.5%)	360 (26.8%)	
Other[*]	14 (1.7%)	26 (1.9%)	
Unknown	110 (13.1%)	261 (19.4%)	
Ethnicity			
Non-Hispanic	698 (83.1%)	1,022 (76.0%)	**16.57 (p=0.0003)**
Hispanic	35 (4.2%)	64 (4.8%)	
Unknown	107 (12.7%)	258 (19.2%)	
Insurance			
Private Only	12 (1.4%)	0 (0.0%)	**19.31**[‡] **(p<0.0001)**
Any Public	828 (98.6%)	1,344 (100.0%)	
Geographic Distribution - Rurality			
Rural	201 (24.0%)	315 (23.4%)	0.08 (p=0.7810)
Urban	638 (76.0%)	1,029 (76.6%)	
Neighborhood Median Annual Income			
≤$40K	277 (33.0%)	423 (31.6%)	0.78 (p=0.6761)
$40K - <$75K	503 (60.0%)	829 (61.9%)	
≥$75K	58 (6.9%)	87 (6.5%)	
Neighborhood Poverty (% below FPL)			
<15%	247 (29.5%)	382 (28.4%)	0.31 (p=0.8564)
15% - <25%	292 (34.8%)	480 (35.7%)	
≥25%	299 (35.7%)	481 (35.8%)	

Neighborhood Education			
<30% BS degree	594 (70.9%)	990 (73.8%)	2.17
≥30% BS degree	244 (29.1%)	352 (26.2%)	(p=0.1412)
Neighborhood Renter Occupancy			
<35% renters	492 (58.7%)	812 (60.4%)	0.62
≥35% renters	346 (41.3%)	531 (39.6%)	(p=0.4294)
Asthma			
No	461 (54.9%)	619 (46.1%)	**16.10**
Yes	379 (45.1%)	725 (53.9%)	**(p<0.0001)**
Heart Failure (HF)			
No	710 (84.5%)	1,062 (79.0%)	**10.24**
Yes	130 (15.5%)	282 (21.0%)	**(p=0.0014)**
Hypertension (HTN)			
No	734 (87.4%)	1,127 (83.9%)	**5.10**
Yes	106 (12.6%)	217 (16.1%)	**(p=0.0239)**
Atrial Arrhythmia			
No	796 (94.8%)	1.278 (95.1%)	0.11
Yes	44 (5.2%)	66 (4.9%)	(p=0.7336)
Endocarditis			
No	825 (98.2%)	1,309 (97.4%)	1.55
Yes	15 (1.8%)	35 (2.6%)	(p=0.2134)
Hyperlipidemia			
No	827 (98.5%)	1,312 (97.6%)	1.78
Yes	13 (1.5%)	32 (2.4%)	(p=0.1823)
Diabetes Mellitus (DM)			
No	824 (98.1%)	1,317 (98.0%)	0.03
Yes	16 (1.9%)	27 (2.0%)	(p=0.8646)

Highlighted in bold if statistically significant (p<0.05).
* 'Other' race includes American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander, and multi-racial.
‡ 25% of cells had expected counts <5, so chi-square may not be a valid test. Fisher's Exact test yielded p<0.0001.
***Abbreviations**:* CHD=Congenital Heart Defect; FPL=Federal Poverty Level; BS=bachelor of science degree
***Note**:* The unknown category for gender, geographic distribution, and the four neighborhood socioeconomic proxies was omitted due to the small count (<10).

Table 3. Distribution of Covariables by CHD Anatomic Group among Children and Adolescents with Congenital Heart Defects (CHD) and Influenza (N=2,184)

	CHD Anatomic Group				χ^2 (p-value)[#]
	Shunt n (col%)	**Valve n (col%)**	**Shunt+Valve n (col%)**	**Complex n (col%)**	
Age					
1-10 Years	640 (92.1%)	364 (73.8%)	410 (92.8%)	471 (85.0%)	**100.92 (p<0.0001)**
11-19 Years	55 (7.9%)	129 (26.2%)	32 (7.2%)	83 (15.0%)	
Sex					
Male	340 (49.0%)	273 (55.4%)	218 (49.3%)	316 (57.0%)	**11.43 (p=0.0096)**
Female	354 (51.0%)	220 (44.6%)	224 (50.7%)	238 (43.0%)	
Race[†]					
White	383 (55.1%)	273 (55.4%)	230 (52.0%)	254 (45.8%)	**82.75 (p<0.0001)**
Black	190 (27.3%)	162 (32.9%)	151 (34.2%)	130 (23.5%)	
Other[*]	10 (1.5%)	<10 (--)	<10 (--)	14 (2.5%)	
Unknown	112 (16.1%)	>48 (--)	>51 (--)	156 (28.2%)	
Ethnicity[†]					
Non-Hispanic	548 (78.8%)	435 (88.2%)	369 (83.5%)	368 (66.4%)	**93.44 (p<0.0001)**
Hispanic	40 (5.8%)	<10 (--)	21 (4.7%)	30 (5.4%)	
Unknown	107 (15.4%)	>48 (--)	52 (11.8%)	156 (28.2%)	
Insurance[†]					
Private Only	<10 (--)	<10 (--)	<10 (--)	<10 (--)	4.42[‡] (p=0.2197)
Any Public	>685 (--)	>483 (--)	>432 (--)	>544 (--)	
Geographic Distribution					
Rural	130 (18.7%)	152 (30.8%)	110 (24.9%)	124 (22.4%)	**24.25 (p<0.0001)**
Urban	564 (81.3%)	341 (69.2%)	332 (75.1%)	430 (77.6%)	
Neighborhood Median Annual Income					
<$40K	194 (28.1%)	176 (35.7%)	164 (37.2%)	166 (30.0%)	**19.14 (p=0.0039)**
$40K - <$75K	439 (63.6%)	292 (59.2%)	256 (58.0%)	345 (62.4%)	
≥$75K	57 (8.3%)	25 (5.1%)	21 (4.8%)	42 (7.6%)	
Neighborhood Poverty (% below FPL)					
<15%	216 (31.2%)	123 (25.0%)	123 (27.8%)	167 (30.2%)	10.47 (p=0.1062)
15% - <25%	252 (36.3%)	181 (36.7%)	145 (32.8%)	194 (35.1%)	
≥25%	225 (32.5%)	189 (38.3%)	174 (39.4%)	192 (34.7%)	
Neighborhood Education					
<30% BS degree	505 (73.2%)	365 (74.0%)	320 (72.4%)	393 (70.9%)	1.42 (p=0.7000)
≥30% BS degree	185 (26.8%)	128 (26.0%)	122 (27.6%)	161 (29.1%)	
Neighborhood Renter Occupancy					
<35% renters	409 (59.0%)	293 (59.4%)	268 (60.6%)	334 (60.3%)	0.39 (p=0.9433)
≥35% renters	284 (41.0%)	200 (40.6%)	174 (39.4%)	220 (39.7%)	

Asthma					
No	339 (48.8%)	266 (54.0%)	206 (46.6%)	269 (48.6%)	5.74
Yes	356 (51.2%)	227 (46.0%)	236 (53.4%)	285 (51.4%)	(p=0.1252)
Heart Failure (HF)					
No	636 (91.5%)	470 (95.3%)	373 (84.4%)	293 (52.9%)	**405.69**
Yes	59 (8.5%)	23 (4.7%)	69 (15.6%)	261 (47.1%)	**(p<0.0001)**
Hypertension (HTN)					
No	645 (92.8%)	434 (88.0%)	385 (87.1%)	397 (71.7%)	**116.90**
Yes	50 (7.2%)	59 (12.0%)	57 (12.9%)	157 (28.3%)	**(p<0.0001)**
Atrial Arrhythmia					
No	683 (98.3%)	482 (97.8%)	424 (95.9%)	485 (87.5%)	**88.63**
Yes	12 (1.7%)	11 (2.2%)	18 (4.1%)	69 (12.5%)	**(p<0.0001)**
Endocarditis†					
No	>685 (--)	>483 (--)	>432 (--)	526 (95.0%)	**27.5**
Yes	<10 (--)	<10 (--)	<10 (--)	28 (5.0%)	**(p<0.0001)**
Hyperlipidemia†					
No	680 (97.8%)	483 (98.0%)	>432 (--)	541(97.7%)	0.76
Yes	15 (2.2%)	10 (2.0%)	<10 (--)	13 (2.3%)	(p=0.8595)
Diabetes Mellitus (DM)†					
No	>685 (--)	>483 (--)	429 (97.1%)	541 (97.7%)	5.04
Yes	<10 (--)	<10 (--)	13 (2.9%)	13 (2.3%)	(p=0.1692)

Highlighted in bold if statistically significant (p<0.05).

† Cells with <10 patients or with possibility of unintentional (deductive) disclosure are not specifically reported to maintain privacy restrictions in accordance with IRB policy.

* 'Other' race includes American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander, and multi-racial.

‡ 50% of cells had expected counts <5, chi-square may not be a valid test. Fisher's Exact test yielded p=0.1925.

***Abbreviations**:* CHD=Congenital Heart Defect; FPL=Federal Poverty Level; BS=BS=bachelor of science degree

***Note**:* Rows for the unknown category of gender, geographic distribution, and the four neighborhood socioeconomic proxies was omitted due to the small total (<10).

Table 4. Unadjusted and Adjusted Analyses for the Association between Congenital Heart Defect (CHD) Anatomic Group and Outpatient Visits within 30 Days of an Influenza Diagnosis Among Children and Adolescents with CHD and Influenza

	Unadjusted Model		Adjusted Models					
			Model 1[§]: *a priori*		Model 2[¶]: Full		Model 3[#]: Reduced	
	cRR	95% CI[**]	aRR	95% CI	aRR	95% CI	aRR	95% CI
Shunt	1.00	--	1.00	--	1.00	--	1.00	--
Valve	0.89	**(0.81, 0.99)**	0.93	(0.84, 1.03)	0.92	(0.84, 1.02)	0.93	(0.84, 1.03)
Shunt + Valve	1.10	**(1.00, 1.20)**	1.10	**(1.00, 1.20)**	1.09	**(1.00, 1.19)**	1.10	**(1.00, 1.20)**
Complex	1.04	(0.96, 1.14)	0.99	(0.90, 1.08)	0.98	(0.90, 1.08)	1.00	(0.91, 1.09)

§ Adjusted for age, race, ethnicity, hypertension, heart failure, neighborhood income, and neighborhood education.
¶ Adjusted for age, race, ethnicity, hypertension, heart failure.
# Adjusted for age, race, heart failure.
** Highlighted in bold if statistically significant (i.e., not include 1.00).
***Abbreviations**:* CHD=Congenital Heart Defect; cRR=crude Relative Risk, aRR=adjusted Relative Risk
***Note**:* No significant interactions with any select comorbid conditions were found.

FIGURES

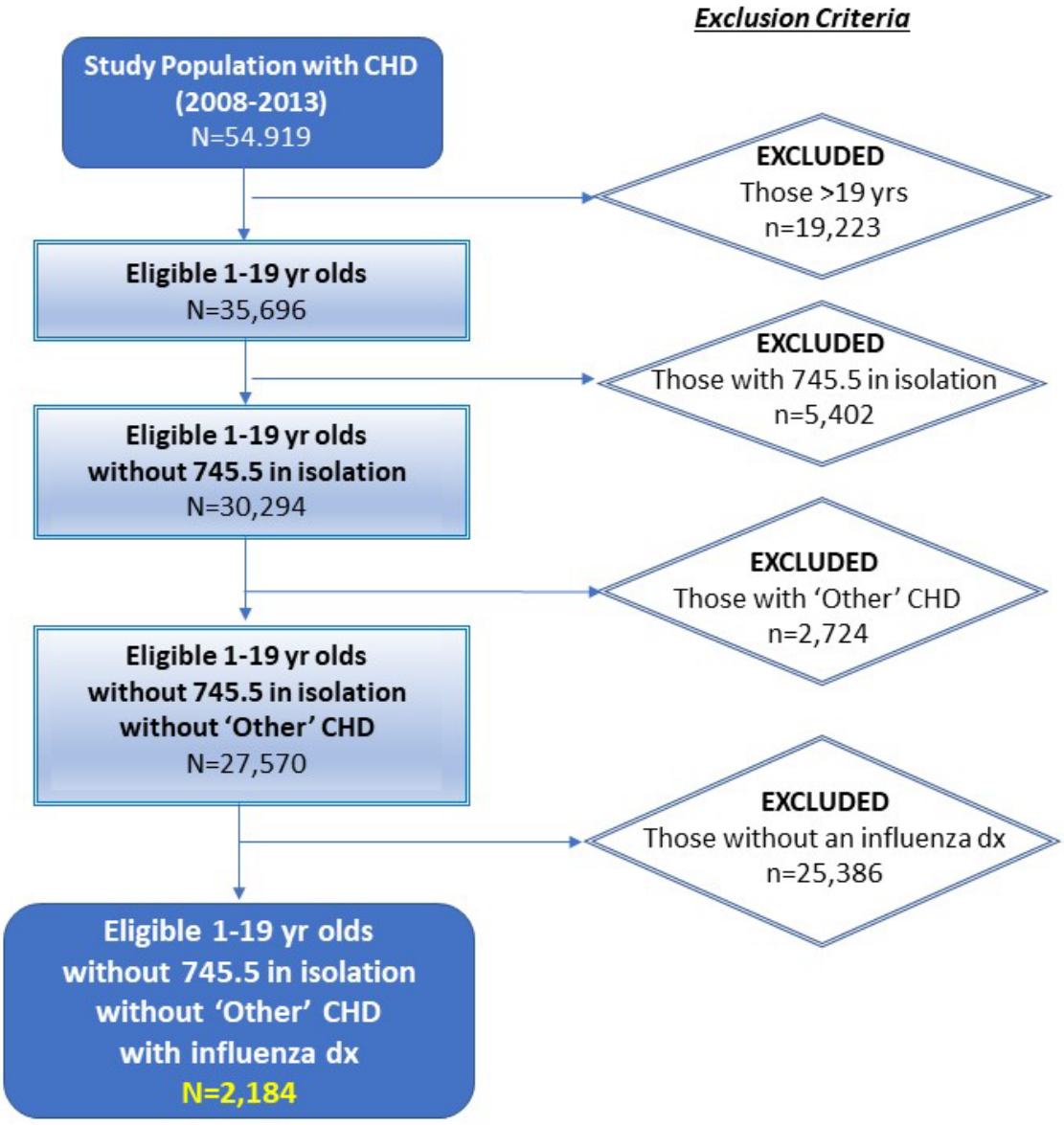

Figure 1. Patient Selection Process

APPENDICES

Appendix A. ICD-9-CM Codes for Anatomic Complexity of Congenital Heart Defects

Classification	ICD-9-CM Code	ICD-9-CM Description
Complex (contains at least one complex code) 16 codes	745.0	Common truncus
	745.1	Transposition of great vessels
	745.10	Transposition of great vessels: Complete transposit. great vessels
	745.11	Transposition of great vessels: Double outlet right ventricle
	745.12	Transposition of great vessels: Corrected transposit. great vessels
	745.19	Transposition of great vessels: Other
	745.2	Tetralogy of Fallot
	745.3	Common ventricle
	745.6	Endocardial cushion defects
	745.60	Endocardial cushion defects: Endocard cushion defect, unsp. type
	745.69	Endocardial cushion defects: Other
	746.01	Anomalies of pulmonary valve: Atresia, congenital
	746.1	Tricuspid atresia and stenosis, congenital
	746.7	Hypoplastic left heart syndrome
	747.11	Coarctation of aorta: Interruption of aortic arch
	747.41	Anomalies great veins: Tot anomalous pulm. venous connection
Shunt (contains at least one shunt code and no complex or valve codes) 7 codes	745.4	Ventricular septal defect
	745.5**	Ostium secundum type atrial septal defect**
	745.61	Endocardial cushion defects: Ostium primum defect
	745.8	Bulbus cordis anomalies & anomalies of card septal closure: Other
	745.9	Unspecified defect of septal closure
	747.0	Patent ductus arteriosus
	747.42	Anomalies great veins: Partial anomal. Pulm. venous connection
Valve (contains at least one valve code and no complex or shunt codes) 17 codes	746.0	Anomalies of pulmonary valve
	746.00	Anomalies of pulm valve: Pulmvalve anomaly, unspec
	746.02	Anomalies of pulmonary valve: Stenosis, congenital
	746.09	Anomalies of pulmonary valve: Other
	746.2	Ebstein's anomaly
	746.3	Congenital stenosis of aortic valve
	746.4	Congenital insufficiency of aortic valve
	746.5	Congenital mitral stenosis
	746.6	Congenital mitral insufficiency
	746.81	Other specified anomalies of heart: Subaortic stenosis
	746.83	Other specified anomalies of heart: Infundibular pulmonic stenosis
	747.1	Coarctation of aorta
	747.10	Coarctation of aorta: Coarctation of aorta (preductal) (postductal)
	747.22	Other anomalies of aorta: Atresia and stenosis of aorta
	747.3	Anomalies of pulmonary artery

	747.31	Anomalies of pulmonary artery: Pulm. artery coarctation & atresia
	747.39	Anomalies pulmonary artery: Anomal. pulm. artery & pulm. Circ.
Shunt + Valve (contains at least one shunt code & at least one valve code and no complex codes)		
Other (contains one or more code listed in this grouping without any complex, shunt, or valve codes) This grouping is excluded from analyses in the current study	648.5	Other current conditions in mother classifiable elsewhere, but complicating preg., childbirth, or puerperium: Congen. cardio dis.
	648.50	Other current conditions in mother classifiable elsewhere, but complicating preg., childbirth, or puerperium: Congen. cardiovasc. dis.: unspecified as to episode of care or not applicable
	648.51	Other current conditions in mother classifiable elsewhere, but complicating preg., childbirth, or puerperium: Congen. cardiovasc. dis.: delivered, w/ or w/o mention of antepartum condition
	648.52	Other current conditions in mother classifiable elsewhere, but complicating preg., childbirth, or puerperium: Congen. cardiovasc. dis.: delivered, w/mention of postpartum complication
	648.53	Other current conditions in mother classifiable elsewhere, but complicating preg., childbirth, or puerperium: Congen. cardiovasc. dis.: antepartum condition or complication
	648.54	Other current conds. in mom classifiable elsewhere, but complic. preg., childbirth, or puerperium: congen. cardio. dis.: PP conds.
	745.7	Cor biloculare
	746.8	Other spec. anomalies of heart
	746.82	Other spec. anomalies of heart: Cor triatriatum
	746.84	Other spec. anomalies of heart: Obstructive anomalies, NEC
	746.85	Other spec. anomalies of heart: Coronary artery anomaly
	746.87	Other spec. anomalies of heart: Malposition of heart & cardi apex
	746.89	Other specified anomalies of heart: Other
	746.9	Unspecified anomaly of heart
	747.2	Other anomalies of aorta
	747.20	Other anomalies of aorta: Anomaly of aorta, unspecified
	747.21	Other anomalies of aorta: Anomalies of aortic arch
	747.29	Other anomalies of aorta: Other
	747.4	Anomalies of great veins
	747.40	Anomalies of great veins: Anomaly of great veins, unspecified
	747.49	Anomalies of great veins: Other anomalies of great veins
	747.9	Unspecified anomaly of circulatory system
	V13.65	Congenital (corrected) malformations: Personal hx of (corrected) congenital malformations of heart and circulatory system

*adopted from Lifespan CHD surveillance project: Glidewell MJ, Farr SL, Book WM, Botto L, Li JS, Soim AS, Downing KF, Riehle-Colarusso T, D'Ottavio AA, Feldkamp ML, Khanna AD, Raskind-Hood CL, Sommerhalter KM, Crume, TL. Prevalence of congenital heart defects among 1 to 64-year-olds receiving health care at five U.S. surveillance sites, 2011-2013. *American Heart Journal*. 2021 May 2;S0002-8703(21)00109-5. doi: 10.1016/j.ahj.2021.04.007

**745.5 in isolation or with 'other' codes have been omitted from analyses due to lack specificity

Notes. Complex has a complex code, regardless of presence of shunt, valve, shunt+valve. Shunt+Valve has shunt AND valve codes; Shunt has 1+ shunt code, no valve or complex. Valve has 1+ valve code, no shunt or complex. Other has 1+ codes in this category and this category is omitted from analyses due to non-specificity. 745.5 has 1

code 745.5 or code 745.5 in addition to only codes from “Other” category; this category is omitted from analyses due to non-specificity.

Appendix B: ICD-9-CM Codes for Influenza (9 codes)

ICD-9-CM Code	ICD-9-CM Description
487.0	Influenza with pneumonia
487.1	Influenza with other respiratory manifestations
487.8	Influenza with manifestations NEC
488.01	Influenza due to identified avian influenza virus with pneumonia
488.02	Influenza due to identified avian influenza virus with other respiratory manifestations
488.09	Influenza due to identified avian influenza virus with other manifestations
488.11	Influenza due to identified novel H1N1 influenza virus with pneumonia
488.12	Influenza due to identified novel H1N1 influenza virus w respiratory manifestations
488.19	Influenza due to identified novel H1N1 influenza virus with other manifestations

Appendix C: ICD-9-CM Codes for Comorbidity Classification

Asthma Classification (14 codes)

ICD-9-CM Code	ICD-9-CM Description
493.00	Ext asthma w/o stat asth
493.01	Ext asthma w status asth
493.02	Ext asthma w/ acute exacerbation (begin 2000)
493.10	Int asthma w/o stat asth
493.11	Int asthma w status asth
493.12	Int asthma w/ acute exacerbation (begin 2000)
493.20	Ch ob asth w/o stat asth (begin 1989)
493.21	Ch ob asthma w stat asth (begin 1989)
493.22	Ch ob asthma w/acute exacerbation (begin 2000)
493.81	Exercise induced bronchospasm (begin 2003)
493.82	Cough variant asthma (begin 2003)
493.90	Asthma w/o status asthm
493.91	Asthma w/ status asthmat
493.92	Asthma w/ acute exacerbation (begin 2000)

Diabetes Mellitus (DM) Classification (64 codes)

ICD-9-CM Code	DM Type	Description
250.01	I	Diabetes w/o mention of complic: type I [juvenile type], not uncontrolled
250.03	I	Diabetes w/o mention of complication: type I [juvenile type], uncontrolled
250.11	I	Diabetes w/ ketoacidosis: type I [juvenile type], not uncontrolled
250.12	I	Diabetes w/ ketoacidosis: type II or unspecified type, uncontrolled
250.13	I	Diabetes w/ ketoacidosis: type I [juvenile type], uncontrolled
250.21	I	Diabetes w/ hyperosmolarity: type I [juvenile type], not uncontrolled
250.23	I	Diabetes w/ hyperosmolarity: type I [juvenile type], uncontrolled
250.31	I	Diabetes w/ other coma: type I [juvenile type], not uncontrolled
250.33	I	Diabetes w/ other coma: type I [juvenile type], uncontrolled
250.41	I	Diabetes w/ renal manifestations: type I [juvenile type], not uncontrolled
250.43	I	Diabetes w/ renal manifestations: type I [juvenile type], uncontrolled
250.51	I	Diabetes w/ophthalmic manifest.: type I [juvenile type], not uncontrolled
250.53	I	Diabetes w/ ophthalmic manifestations: type I [juvenile type], uncontrolled
250.61	I	Diabetes w/neurological manifest.: type I [juvenile type], not uncontrolled
250.63	I	Diabetes w/neurological manifestations: type I [juvenile type], uncontrolled
250.71	I	Diabetes w/peripheral circulat. dis.: type I [juvenile type], not uncontrolled
250.73	I	Diabetes w/peripheral circulatory disorders: type I [juvenile type], uncontrolled
250.81	I	Diabetes w/other spec. manifest.: type I [juvenile type], not uncontrolled

250.83	I	Diabetes w/other specified manifestations: type I [juvenile type], uncontrolled
250.91	I	Diabetes w/unspec. complication: type I [juvenile type], not uncontrolled
250.93	I	Diabetes w/unspecified complication: type I [juvenile type], uncontrolled
V45.85	I	Other postprocedural status: Insulin pump status
V53.91	I	Other and unspecified device: Fitting and adjustment of insulin pump
V65.46	I	Other counseling, not elsewhere classified: Encounter for insulin pump training
249.00	II	Secondary diabetes w/o mention of complication: not uncontrolled
249.01	II	Secondary diabetes mellitus w/o mention of complication: uncontrolled
249.10	II	Secondary diabetes mellitus w/ketoacidosis: not uncontrolled
249.11	II	Secondary diabetes mellitus w/ketoacidosis: uncontrolled
249.20	II	Secondary diabetes mellitus w/hyperosmolarity: not uncontrolled
249.21	II	Secondary diabetes mellitus w/hyperosmolarity: uncontrolled
249.30	II	Secondary diabetes mellitus w/other coma: not stated as uncontrolled
249.31	II	Secondary diabetes mellitus w/other coma: uncontrolled
249.40	II	Secondary diabetes mellitus w/renal manifestations: not uncontrolled
249.41	II	Secondary diabetes mellitus w/renal manifestations: uncontrolled
249.50	II	Secondary diabetes mellitus w/ophthalmic manifest.: not uncontrolled
249.51	II	Secondary diabetes mellitus w/ophthalmic manifest.: uncontrolled
249.60	II	Secondary diabetes mellitus w/neurological manifest.: not uncontrolled
249.61	II	Secondary diabetes mellitus w/neurological manifestations: uncontrolled
249.70	II	Secondary diabetes mellitus w/peripheral circulat. dis.: not uncontrolled
249.71	II	Secondary diabetes mellitus w/peripheral circulat. dis.:uncontrolled
249.80	II	Secondary diabetes mellitus w/other specified manifest.: not uncontrolled
249.81	II	Secondary diabetes mellitus w/other specified manifestations: uncontrolled
249.90	II	Secondary diabetes mellitus w/unspecified complication: not uncontrolled
249.91	II	Secondary diabetes mellitus with unspecified complication: uncontrolled
250.00	II	Diabetes w/o mention of complic.: type II or unspec. type, not uncontrolled
250.02	II	Diabetes mellitus w/o mention of complic.: type II or unspecified type, uncontrolled
250.10	II	Diabetes w/ketoacidosis: type II or unspecified type, not uncontrolled
250.20	II	Diabetes w/hyperosmolarity: type II or unspecified type, not uncontrolled
250.22	II	Diabetes w/hyperosmolarity: type II or unspecified type, uncontrolled
250.30	II	Diabetes w/other coma: type II or unspecified type, not uncontrolled
250.32	II	Diabetes w/other coma: type II or unspecified type, uncontrolled
250.40	II	Diabetes w/renal manifest/.: type II or unspecified type, not uncontrolled
250.42	II	Diabetes w/renal manifestations: type II or unspecified type, uncontrolled
250.50	II	Diabetes w/ophthalmic manifest.: type II or unspec. type, not uncontrolled
250.52	II	Diabetes w/ophthalmic manifest.: type II or unspecified type, uncontrolled
250.60	II	Diabetes w/neurol. manifest.: type II or unspec. type, not uncontrolled
250.62	II	Diabetes w/neurological manifestations: type II or unspecified type, uncontrolled
250.70	II	Diabetes w/periph. circulat. dis.: type II or unspec. type, not uncontrolled

250.72	II	Diabetes w/peripheral circulatory disorders: type II or unspecified type, uncontrolled
250.80	II	Diabetes w/other spec. manifest.: type II or unspec. type, not uncontrolled
250.82	II	Diabetes w/other specified manifestations: type II or unspecified type, uncontrolled
250.90	II	Diabetes w/unspec. complic.: type II or unspecified type, not uncontrolled
250.92	II	Diabetes w/unspecified complication: type II or unspecified type, uncontrolled
V58.67	Unspec	Long-term (current) drug use: Long-term (current) use of insulin

Hyperlipidemia (5 codes)

ICD-9-CM Code	ICD-9-CM Description
272.0	Pure hypercholesterolem
272.1	Pure hyperglyceridemia
272.2	Mixed hyperlipidemia
272.3	Hyperchylomicronemia
272.4	Hyperlipidemia nec/nos

Heart Failure (HF) (16 codes)

ICD-9-CM Code	ICD-9-CM Description
428.0	Congestive heart failure
428.1	Left heart failure
428.9	Heart failure nos
398.91	Rheumatic heart failure
428.20	Unspecified systolic heart failure (begin 2002)
428.21	Acute systolic heart failure (begin 2002)
428.22	Chronic systolic heart failure (begin 2002)
428.23	Acute on Chronic Systolic Heart Failr (Begin 2002)
428.30	Unspecified diastolic heart failure (begin 2002)
428.31	Acute diastolic heart failure (begin 2002)
428.32	Chronic diastolic heart failure (begin 2002)
428.33	Acute on chronic diastolic heart failr (begin 2002)
428.40	Unspec cmbined syst & dias heart failr (begin 2002)
428.41	Acute cmbined syst & dias heart failr (begin 2002)
428.42	Chron cmbined syst & dias heart failr (begin 2002)
428.43	Acu chro combi syst & dias hrt failr (begin 2002)

Endocarditis (19 codes)

ICD-9-CM Code	ICD-9-CM Description
093.20	Syphil endocarditis nos
093.21	Syphilitic mitral valve
093.22	Syphilitic aortic valve
093.23	Syphil tricuspid valve
093.24	Syphil pulmonary valve
098.84	Gonococcal endocarditis
424.90	Endocarditis nos
424.91	Endocarditis in oth dis
424.99	Endocarditis nec
036.42	Meningococc endocarditis
074.22	Coxsackie endocarditis
112.81	Candidal endocarditis
115.04	Histoplasm caps endocard
115.14	Histoplasm dub endocard
115.94	Histoplasmosis endocard
391.1	Acute rheumatic endocard
421.0	Ac/subac bact endocard
421.1	Ac endocardit in oth dis
421.9	Ac/subac endocardit nos

Atrial Arrhythmia (4 codes)

ICD-9-CM Code	ICD-9-CM Description
427.0	Parox atrial tachycardia
427.31	Atrial fibrillation
427.32	Atrial flutter
427.81	Sinoatrial node dysfunct

Hypertension (HTN) (40 codes)

ICD-9-CM Code	ICD-9-CM Description
401.1	Benign hypertension
401.9	Hypertension nos
401.0	Malignant hypertension
403.0	Mal hypertens renal dis (begin 1980 end 1989)
403.1	Benign hypert renal dis (begin 1980 end 1989)
403.9	Hypertens renal dis nos (begin 1980 end 1989)
404.0	Mal hypert hrt/renal dis (begin 1980 end 1989)
404.1	Ben hypert hrt/renal dis (begin 1980 end 1989)
404.9	Hypert hrt/renal dis nos (begin 1980 end 1989)
437.2	Hypertens encephalopathy
402.00	Mal hyperten hrt dis nos
402.01	Mal hypert hrt dis w chf

402.10	Ben hyperten hrt dis nos
402.11	Benign hyp hrt dis w chf
402.90	Hypertensive hrt dis nos
402.91	Hyperten heart dis w chf
403.00	Mal hyp ren w/o ren fail (begin 1989)
403.01	Mal hyp ren w renal fail (begin 1989)
403.10	Ben hyp ren w/o ren fail (begin 1989)
403.11	Ben hyp renal w ren fail (begin 1989)
403.90	Hyp ren nos w/o ren fail (begin 1989)
403.91	Hyp renal nos w ren fail (begin 1989)
404.00	Mal hy ht/ren w/o chf/rf (begin 1989)
404.01	Mal hyper hrt/ren w chf (begin 1989)
404.02	Mal hy ht/ren w ren fail (begin 1989)
404.03	Mal hyp hrt/ren w chf & rf (begin 1989)
404.10	Ben hy ht/ren w/o chf/rf (begin 1989)
404.11	Ben hyper hrt/ren w chf (begin 1989)
404.12	Ben hy ht/ren w ren fail (begin 1989)
404.13	Ben hyp hrt/ren w chf & rf (begin 1989)
404.90	Hy ht/ren nos w/o chf/rf (begin 1989)
404.91	Hyper hrt/ren nos w chf (begin 1989)
404.92	Hy ht/ren nos w ren fail (begin 1989)
404.93	Hyp ht/ren nos w chf & rf (begin 1989)
405.01	Mal renovasc hypertens
405.09	Mal second hyperten nec
405.11	Benign renovasc hyperten
405.19	Benign second hypert nec
405.91	Renovasc hypertension
405.99	Second hypertension nec