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ASSOCIATION OF HEART FAILURE AND PULMONARY HYPERTENSION AMONG INDIVIDUALS WITH CONGENITAL HEART DEFECTS WITH OR WITHOUT COEXISTING DOWN SYNDROME

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Abstract

ASSOCIATION OF HEART FAILURE AND PULMONARY HYPERTENSION AMONG INDIVIDUALS WITH CONGENITAL HEART DEFECTS WITH OR WITHOUT COEXISTING DOWN SYNDROME

By Olivia Kapera

Background: Congenital heart defects (CHD) are the most common congenital defect in the U.S., accounting for 1% of annual births. CHD complications include pulmonary hypertension (P-HTN) and heart failure (HF). Individuals with CHD are also more likely to have Down syndrome (DS). Despite medical advancements, P-HTN and HF present particular challenges among those affected by CHD, and this association has not been well examined by presence or absence of co-occurring DS. The proposed study investigates if individuals with CHD with or without coexisting DS are at increased risk for P-HTN and/or HF.

Methods: This a retrospective secondary data analysis of 22,499 CHD patients aged 1-64 years identified using ICD-9-CM codes from healthcare encounters that occurred between 1/1/2008-12/31/2013 from 11 clinical and/or administrative data sources. Multivariate logistic regression was used to assess adjusted relative risks (aRR) and 95% confidence intervals (CIs) of P-HTN without HF, and HF-without P-HTN, among patients with CHD grouped by DS status.

Results: Overall, 9.3% of individuals with CHD had DS in our analytic study sample. Among all CHD cases, 4.7% had P-HTN without HF, 21.2% had HF without P-HTN, and 0.6% had both P-HTN and HF. Among individuals with CHD and DS, 7.6% had P-HTN without HF, 9.9% had HF without P-HTN, and 5.7% had both P-HTN and HF. Our regression analysis showed a 23% lower risk of P-HTN without HF among those with CHD and DS compared to patients with CHD without DF (aRR=0.77; 95% CI: 0.59-1.00). On the contrary, we found a significantly increased risk of HF without P-HTN in patients with CHD and DS compared to those with CHD without DS (aRR=1.51; 95% CI: 1.04-2.18). We were unable to analyze the group with both P-HTN and HF due to small number of affected individuals.

Conclusions: We found that co-occurring DS among individuals with CHD can impact the development of P-HTN and HF overtime. Comorbidities, like cyanosis and atrial arrythmia, and sleep apnea may affect risk of P-HTN and HF for patients with CHD and co-occurring DS, and should be further explored. Future studies should aim at improved assessment of clinical variables and potential confounders.

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Contents

List of Abbreviations

ACHD	Adults with Congenital Heart Defects
aRR	Adjusted Relative Risk
ASD	Atrial Septal Defect
AVSD	Atrioventricular Septal Defect
CAVCD	Complete Atrioventricular Canal Defects
CDC	Centers for Disease Control and Prevention
CHD	Congenital Heart Disease
CHOA	Children's Healthcare of Atlanta
CI	Confidence Interval
CoA	Coarctation of the Aorta
DM	Diabetes Mellitus
DS	Down Syndrome
d-TGA	d-Transposition of the Great Arteries
eHR	Electronic Health Records
EKG	Electrocardiogram
FISMA	Federal Information Security Management Act
FPL	Federal Poverty Line
GOF	Goodness of Fit Test
HF	Heart Failure
HLHS	Hypoplastic Left Heart Syndrome
IT	Information Technology
OSA	Obstructive Sleep Apnea

PA	Pulmonary Atresia
PDA	Patent Ductus Arteriosus
PHI	Protected Health Information
P-HTN	Pulmonary Hypertension
SD	Standard Deviation
TOF	Tetralogy of Fallot
VSD	Ventricular Septal Defect

CHAPTER I: BACKGROUND

Congenital Heart Defects

Congenital heart defects (CHDs) are conditions involving structural abnormalities in the heart that impact both the structure and function of the heart (1). CHDs are the most frequent congenital defect in the U.S., with a prevalence of 80 per 1,000 live births, about 1% of live births, causing 25% of infant mortality (1-5). CHD represents a spectrum of heart defects, including obstructed blood flow, heart valve abnormalities, abnormal blood vessels, or a hole(s) in the heart (6). Symptoms frequently involve trouble breathing, abnormal heart rhythm, discoloring of nails, lips, or skin, swollen extremities, or feelings of tiredness (6).

CHD consists of a comprehensive spectrum of conditions that can differ based on complexity or type of defect. The complexity of CHD has been classified as simple, moderate, or complex (6). Simple CHD consists of patients who can typically be cared for by the general medical community and are diagnosed with either a native disease (i.e., isolated congenital aortic valve disease, small atrial septal defect (ASD), small patent ductus arteriosus, etc.) or repaired condition (i.e., previously ligated or occluded ductus arteriosus, repaired ventricular septal defect (VSD) without residua, etc.) (7). Examples of simple defects include VSD, ASD, atrioventricular septal defect (AVSD), pulmonary stenosis, patent ductus arteriosus (PDA), aortic stenosis, and coarctation of the aorta (CoA) in older children (2). Individuals with moderate CHD should be seen periodically at a regional CHD center, and examples of moderate CHD lesions consist of CoA, Ebstein's anomaly, sinus of valsalva fistula/aneurysm, sinus venosus atrial septal defect, and tetralogy of fallot (TOF) (7). Those with complex CHD conditions should be seen regularly at a regional CHD center (7) and include the following diagnostic types: double-outlet right ventricle, d-transposition of the great arteries (d-TGA), hypoplastic left heart syndrome (HLHS),

interrupted aortic arch, pulmonary atresia, single ventricle, total anomalous pulmonary venous return, tricuspid atresia, and truncus arteriosus (6-7).

CHDs are diagnosed using numerous techniques, including electrocardiogram (EKG), echocardiography, cardiac catheterization, and pulse oximetry. EKG reports the electrical signals that pass through the heart. Echocardiography utilizes sound waves that bounce off the heart to create live images. The cardiac catheterization procedure entails inserting a catheter into an artery or vein to observe blood supply to the heart, and pulse oximetry measures the amount of oxygen in the blood (8).

Once someone is diagnosed with CHD, there are various treatment options depending on the type and complexity of the defect (6). Common treatment options include medication (i.e., blood thinners), cardiac catheterizations, surgery, and heart transplant (7). In some situations, infants and children may need one or more surgeries to repair the heart or blood vessels (9). Other conditions can be treated without surgery using a procedure called cardiac catheterization in which a long tube, called a catheter, is inserted through the blood vessels into the heart, where a doctor can acquire measurements and pictures, perform tests, or fix the problem (7, 9). Some heart defects cannot be entirely fixed, but procedures can increase blood flow and improve the way the heart works (7). It is important to note that even if a heart defect has been repaired, those with CHD are not cured (9) and require lifelong monitoring, specialized medical care and follow-up (7).

While improvements in diagnosis and treatment have increased the life expectancy among individuals born with CHD, survival among infants varies based on the complexity of the CHD when diagnosis occurred and how the defect was treated (10-12). For infants born with a simple CHD, roughly 97% are expected to survive to one year of age and about 95% are

expected to survive to 18 years of age (11). For infants born with a complex CHD, approximately 75% are expected to survive to one year of age and approximately 69% have a life expectancy of 18 years of age (11). Similarly, a study reported that over 90% of those born with a non-complex CHD lesion (mild to moderate anatomic CHD complexity) and 60% of those born with a severe anatomic CHD survive into adulthood (12).

The population of adults with CHD is made up of those who were born with CHD and have survived without surgery, who have had multiple surgeries throughout their lifespan, or who had surgery during or after infancy (13). While some of these adults could have residua, sequelae, or complications leftover from childhood surgeries, others may have had benign or undetected childhood conditions that worsened as they got older (14). In the U.S, approximately 1.5 million adults 18-years-old and older are living with CHD, which is more than a 63% increase in the adult CHD population since 2000 (1, 10). With a growing population of adults with CHD, there are increasing concerns regarding their medical management. In 2004, CHDs accounted for hospital costs close to $1.4 billion in the U.S. (10). The cost of pediatric CHD-related hospitalizations, primarily driven by surgeries, sophisticated cardiac procedures and treatments, and often subsequent complications, is high and has continued to climb with costs totaling $5.6 billion in 2009 and increasing to $6.7 billion in 2012 (15-16). Those with simple CHDs are recommended to follow-up with their physician every 3- 5 years, but those with the most complex CHD are recommended to follow-up with their physician every 6-12 months (6).

Types of CHD and Classification

Anatomic complexity of CHD conditions has been classified using a five-level hierarchy that utilized ICD-9-CM CHD-related diagnostic codes (Appendix A) (17). The most severe CHDs, based on having the highest probability of cyanosis or early surgical intervention, include

CAVCD, TOF, univentricular heart, transposition complex, truncus arteriosus, and hypoplastic heart syndrome (17). CHD patients with complex classifications have more frequent and severe complications and need more specialized care compared to patients with less complex CHD lesions (18). The less complex CHDs are categorized into four levels: shunts, valves, shunts plus valves, and Other (see Appendix A) (17). Some of the CHD abnormal shunt conditions include ASD, VSD, and PDA; among the valve-related anomalies are stenosis, insufficiencies and anomalies pertaining to the pulmonary arteries, and lastly, some of the conditions classified as 'Other' include unspecified anomalies of the heart, circulation and aorta (see Appendix A) (17).

Prevalence of CHD

According to the US CDC, 1% of all births in the United States are affected by a CHD (19). Fortunately, most of those who are born with CHD will survive into adulthood as a result of improvements in surgery and treatment (20). However, research is still lacking in regard to the health complications that ensue as one with CHD ages. In 2010, it was estimated that approximately 2.4 million people were living with CHD in the U.S. (11). Among those with CHD, about 12% or 290,000 people have complex lesions (11). Most of these individuals will need specialized cardiac healthcare over their lifespan (6).

For children, approximately one million are living with CHD in the United States (11). In 2010, it was estimated that 13.21 per 1000 children, ages 0-17 years old, had CHD and 1.66 per 1000 children, ages 0-17 years old, had a complex CHD (11). Approximately 60% of children with a current heart condition have special healthcare needs compared to 20% of children without a heart condition (11). In regard to adults with CHD (ACHD), nearly 1,444,500 adults are living with CHD in the U.S. and 160,000 are living with a complex CHD (11). In 2010, the

prevalence of CHD in the U.S. population was estimated to be about 7.67 per 1000 for males, and 8.03 per 1000 for females, a small predominance of females to males (11).

Health Complications in CHD

Those with CHD are at an increased risk of developing further health problems (6). Children with complex CHD may face developmental delays as well as learning difficulties (6, 21-22). Learning difficulties that can be experienced by children with CHD include impaired memory, difficulty expressing oneself, difficulty understanding others, low attention span, difficulty concentrating, difficulty planning, and lack of impulse control (21-22). These complications have been attributable to poor oxygen supply in utero which affects brain development (21-22). Developmental and learning problems can lead to later difficulties with social interaction and behavior (21-22).

People with CHD also have an increased risk of developing numerous complications including endocarditis and heart rhythm issues (13). Endocarditis is an infection in the lining of the heart, the valves, or both (23). If the condition is left untreated, life-threatening damage to the heart can occur (23). Those with CHD are at risk of acquiring various kinds of heart rhythm problems (6, 24). Problems can come from the top of the heart (atrial arrhythmia) or from the ventricular chambers, which are more concerning (ventricular arrhythmia) (24).

CHD and Heart Failure

Heart failure (HF) is a condition in which the heart cannot pump enough blood around the body to meet the body's needs (25-26). It can occur shortly after the birth of a baby with a complex CHD or can appear later as a complication from any treated or untreated type of CHD (25-26). HF in children is most commonly attributable to an existing CHD, with differing degrees of risk dependent upon the specific type of heart malformation (25-26). HF is also

common in the ACHD population, occurring in approximately 25% of ACHDs, with the incidence increasing with age (13).

The progression of HF in patients with CHD involves confirmed and hypothesized mechanisms, which have been classified into three routes (27). The first means is by incomplete or palliative correction of a lesion causing a chronic state of hemodynamic stress and subsequent HF (27). The likelihood of HF in CHD lesions such as TOF and d-TGA can be as great as 80% at 50 years of age, while around 20–30% for isolated valvular disease or defects that result in left-to-right shunt (28). The second route is through genetic causes both cardiac malformation and cardiomyopathy which lead to HF (28). The third pathway is the combination of congenital genetic risk and acquired hemodynamic stressors (28). It is suggested that molecular perturbations which are a result of abnormal cardiac development can increase the risk for HF in adulthood (28).

In terms of diagnosing HF, utilization of genetic causes of CHD to identify children at high risk of developing HF is only used occasionally (29). Clinical factors related to phenotype and presentation remain the most frequent means for evaluating risk and instituting surveillance for HF (29-30). Age is an important factor in assessing clinical features of HF (31). HF may develop at various times, based on defect, surgery, and complications (25). For example, HF in HLHS occurs on day 3–7 of life, while HF in severe CoA usually happens on days 7–10 (27). Some CHD types do not exhibit HF until after the pulmonary vascular resistance reduces, in which HF occurs in 1–3 months (27). But other lesions, such as ASD, may not develop symptoms until 3–5 years of life, if at all (27).

Due to the timing discrepancy, lesion type is another variable useful for risk stratification for HF. HF in CHD patients is usually credited to concurrent pressure or volume overload (33).

Therefore, infants with specific types of CHD will generally encounter HF without surgical correction (32). However, genetic factors, as well as numerous environmental influences, are associated in the multifaceted progression of HF (27)

CHD and Pulmonary Hypertension

Different forms of CHD can result in higher blood pressure inside the arteries that connect the heart and lungs, a condition known as pulmonary hypertension (P-HTN) (33). P-HTN is a potential complication of CHD; it is evident in approximately 5-10% of adult cases (34-35). The P-HTN age-standardized death rate in the U.S. varies from 4.5 to 12.3 per 100,000 population (35). P-HTN often occurs in individuals with congenital cardiac shunts (33-34, 38-39). In patients with uncorrected shunts, increased pulmonary pressure contributes to vascular remodeling and dysfunction, ensuing in a continuing rise in pulmonary vascular resistance and amplified pressure in the right heart (34). Additionally, uncorrected VSD with large shunt is the most frequent underlying defect at 42% (35). The time of onset of the lesions plays a determining role in the development of P-HTN (36). Individuals with PDA or VSD who acquire Eisenmenger syndrome will an earlier onset of P-HTN than do patients with ASD (36). Other more complex abnormalities, such as AVSD or truncus arteriosus, often develop P-HTN early in life (36).

Studies have also exhibited the size of the defect to be significant in whether patients develop P-HTN (36). For ASDs, a recent publication demonstrates, that defects most likely to have severe P-HTN were the largest (31.84 ± 8.21 mm) (37). More complex lesions such as AVSD or truncus arteriosus often develop P-HTN early in life (37). Currently, the majority of patients with CHD and P-HTN (P-HTN-CHD) are adults, with many having complex disease or having received a late diagnosis of their defect (38-39). While there have been advances in

management and therapy in recent years, P-HTN-CHD is a heterogeneous condition and some subgroups, such as those with Down syndrome, present particular challenges (34). Patients with Down syndrome have a high occurrence of complex CHD and are at particular risk of developing P-HTN (34, 40).

The management of P-HTN in CHD relies on accurately recognizing clinical signs and symptoms as well as completing investigations via imaging and blood tests (35). Treatment of an underlying CHD as an infant can prevent the occurrence of P-HTN (34). Unfortunately, some individuals with left-to-right shunts are not identified until later in life, where their pulmonary vasculature has already undergone changes and they have developed enhanced pulmonary vascular resistance (41). Those with P-HTN can develop right heart failure as a consequence of the P-HTN.

CHD and Sleep Apnea

Patients with CHD are prone to sleep-related oxygen desaturations, central apneas and hypopneas that are not associated with arousals (42). Numerous studies have reported a high prevalence of sleep apnea among ACHD; however, sleep complications are rarely studied in infants (42-45). Obstructive sleep apnea-hypopnea (OSA) is currently deemed an independent and modifiable cardiovascular risk factor (12). In a cohort of 461,778 inpatient infants with CHD born between 1997-2012, 4,968 of them were diagnosed with sleep apnea, about 1.1% (43). However, by their first birthday, all of the infants with CHD were diagnosed with sleep apnea (43). One study that investigated CHD and sleep apnea found individuals with severe sleep apnea were at increased risk for HF (46).

Other Known Factors Associated with CHD

Within the field of cardiology, gender disparities have been extensively evaluated since it was documented that risk factors for cardiovascular disease were disproportionately dispersed according to gender. It has been recognized that gender impacts not only the manifestation of disease, but also the management (47). Women have distinctive clinical demonstrations and outcomes, and they appear to be under-investigated, underdiagnosed, and undertreated (48). In a 2008 study with ACHD, a strong relationship was revealed between gender and the risk of several outcomes (47). Women were at higher risk for P-HTN and at lower risk for endocarditis (47). Another study similarly concluded gender differences do exist in CHD and may influence outcomes, but little is known on the underlying mechanisms (genetic, hormonal, behavioral or other) (49).

A study that investigated CHD mortality trends in children and adults in the U.S. found CHD infant mortality was higher among males than females (50). Disparities in race and ethnicity were also supported. The study discovered Black infants have a 20% higher mortality than White infants with CHD (50). Differences in CHD mortality impact the demographics of the population of individuals with CHD; there are varying rates of specific CHDs by racial and ethnic groups. For example, non-Hispanic Black and Hispanic females have lower rates of severe CHDs such as AVSD, TOF, and VSD compared to non-Hispanic White females (51). Another study that investigated race and ethnicity found the prevalence of CHD to be marginally higher in non-Hispanic Whites and Hispanics in contrast to non-Hispanic Blacks (11). In the U.S., the majority of individuals living with CHD are non-Hispanic Whites, at approximately 1.7 million, compared to non-Hispanic Black or Hispanics, at approximately 288,000 and 413,000, respectively (11). Among adults, the prevalence of CHD is 6.36 per 1000 among non-Hispanic

Whites, 5.63 per 1000 among non-Hispanic Blacks, and 5.58 per 1000 among Hispanics (11). Racial variations in CHDs correspond with geographic distributions of disease, indicating race, residence, and other social factors could increase risk for certain CHD (51-54).

Socioeconomic status (SES) is measured differently across studies attempting to quantify this association with varying outcomes. As such, it can be difficult to compare SES in relation to outcomes across studies; however, a meta-analysis investigating the association between SES and mortality among children with CHD revealed a possible association between lower SES and an increased risk of CHD mortality (55). A study found a decreased prevalence of CHD among upper class Whites when utilizing income for SES measure (56). Another study that used parental education, income, occupation, and SES Index for SES measures concluded low SES at individual and neighborhood level was associated with CHD (57).

Down Syndrome (DS)

Trisomy 21, the chromosomal abnormality responsible for Down syndrome (DS), is a complex condition with many characteristic symptoms as well as an increased risk for numerous congenital anomalies (58). The combination of these anomalies is often severe, with as few as 20% of conceptuses with trisomy 21 surviving to term (59). DS occurs in approximately 1 in 733 live births in the U.S. (14), and up to 80% of fetuses with DS are lost prior to birth (14). It is also important to note that the introduction of antenatal screening has resulted in many fetuses diagnosed with DS to be aborted (60). DS is characterized by multiple clinical attributes including hypotonia, distinctive facial features, intellectual disabilities, as well as an increased risk of birth defects such as CHD and gastrointestinal defects (61-62). DS is most commonly associated with CAVCD, which causes a large shunt, and is associated with cleft mitral valve.

Some individuals develop mitral stenosis after repair of the cleft mitral valve. The large shunt predisposes to both P-HTN and HF.

Sleep Apnea and DS

Among children with DS, 50% will experience sleep problems (63). One of the common sleeping problems is sleep apnea. Sleep apnea is an uncontrolled interruption of breathing that happens while the patient is asleep (64-65). Sleep apnea can be divided into three types: obstructive, central, and mixed (65). OSA is the most common sleep apnea (66). OSA is caused by an obstruction of the airway, typically when the soft tissue in the back of the throat collapses and closes during sleep (66). OSA has a high prevalence in children with DS (30% to 55%) (67). Another study found that, when clinically suspected, young adults with DS have a high prevalence of OSA (72.6%) (68). Patients with DS have many predisposing factors for OSA, such as hypotonia, mandibular hypoplasia, glossoptosis (a downward displacement of the tongue), obesity and a relatively small upper airway (67). It is speculated that OSA may contribute to the unexplained P-HTN seen in children with DS (63).

CHD and DS

Heart defects are among the most common congenital anomalies associated with DS, affecting nearly half of all people with DS, representing a 50-fold higher risk for a trisomy 21 individual compared to the general population (69-71). CHD is regarded to be the most important clinical phenomenon in children with DS, due to its significant impact on morbidity and mortality (61, 69-71). The majority of CHD are septal defects, with ASD (18.6%), VSD (19.2%), and AVSD (17.2%), all common among people with Down syndrome (72).

A 2018 study found an increase in the number of children born with CHD and Down syndrome, from 2010 to 2014 (13). It attributed the improved medical management and

advancement in educational, social, and financial care to the increase (13). In a similar study conducted to assess prevalence of DS among children with CHD during the same 2010-2014 time frame the prevalence of DS was reported between 3-4% with a peak prevalence of 7% (73). New developments in prenatal diagnostic and therapy management of CHD continue to influence the number of patients diagnosed with CHD and DS (60). Another study discovered the multifactorial nature of CHD related to DS. The results indicated infant girls were more commonly affected than infant boys (74). Maternal obesity and maternal smoking have also been associated with increased risk of CHD within the cohort of infants with DS (74). In a 2010 study that investigated the prevalence of CHD and P-HTN among infants with DS, CHD was reported in 43% of them (75); ASD was diagnosed in 54%, VSD in 33.3% and PDA in 5.8% (75). These infants also had a high incidence of P-HTN at 5.2% (75). This study is the first large-scale study to focus on CHD in children with DS, exhibiting a knowledge gap in the effect of the co-occurrence of CHD and DS (75). Few studies have analyzed the occurrence of HF and P-HTN among this high-risk group with co-occurring CHD and DS.

To our knowledge, there has not been any research revealing whether this high-risk group of CHD patients with DS are at higher risk of P-HTN and/or HF compared to those with CHD alone. The current study, based on electronic health records (eHR) of patients with CHD residing in Georgia, investigates whether individuals with co-occurring CHD and DS have an increased risk of P-HTN and/or HF compared to individuals with CHD but without DS controlling for selected potential confounders. Findings from the proposed research will provide insight into the relationship of DS on P-HTN and HF for those with CHD, and guide early intervention strategies to help clinicians prevent P-HTN and/or HF and associated sequelae in this target group.

CHAPTER II: METHODS

Study Design

This study utilized combined data from two U.S. Centers for Disease Control and Prevention (CDC) congenital heart disease (CHD) surveillance projects with Emory University, the "Surveillance of Congenital Heart Disease in Adolescents and Adults" (CDC-RFA-DD12-1207) (hereinto referred to as the "pilot project"), and the "Surveillance of Congenital Heart Disease Across the Lifespan" (CDC-RFA-DD15-1506) (hereinto referred to as the "lifespan project (LS)"). The purpose of these projects was to devise and increase population-based tracking of individuals with CHD. The current effort aims to address a knowledge gap for those with CHD and Down syndrome (DS) and select covariates by addressing the risk of pulmonary hypertension (P-HTN) and heart failure (HF).

Data Sources

The de-identified file used for the secondary data analysis was created from a linked, de-duplicated CHD repository of Georgia residents that was part of back-to-back CHD surveillance initiatives with the Center for Disease Control and Prevention (CDC): 1) a three-year CHD surveillance pilot project with three sites (FOA #DD12-1207); and 2) a four-year CHD surveillance LS project with five sites (FOA #DD15-1506). To ensure data confidentiality, 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 in the school's Department of Information Technology (IT); the system is maintained by authorized IT personnel and only study researchers have access to the specific secure drive. Prior to analysis, specific Protected Health Information (PHI) identifiers were substituted with a proxy unique

identifier for each patient, and no PHI was included in the analytic dataset to maintain confidentiality. Data were cleaned and de-duplicated prior to construction of the analytic dataset.

Study Population

The study population includes 22,499 patients, ages 1-64 years of age, diagnosed with CHD, who had at least one healthcare encounter over a six-year window from January 1, 2008 to December 31, 2013. Electronic health records (eHR) of patients with CHD were obtained from 11 tertiary referral healthcare provider sources. To be identified as having a CHD, patients had at least one of 55 CHD-associated ICD-9-CM codes, initially described by Glidewell et al. (DD12-1207) and later enhanced by project clinicians as part of the lifespan project with the Centers of Disease Control and Prevention (CDC) (DD15-1506). Exclusions from analyses included patients with diagnostic code 745.5 (secundum atrial septal defect (secundum ASD) or patent foramen ovale (PFO)) in isolation or in combination with two codes classified as "other" CHD (e.g., 746.89 or 746.9) due to lack of specificity of these codes (21) (n = 5,834), and those whose CHD-related ICD-9-CM diagnostic code(s) categorized them as having "other" CHD (Appendix B) (n = 3,615). Lastly, another 17 were excluded due to unknown gender (see Figure 1).

Outcome Variables

Composite outcome variables were created from a combination of two comorbidity variables, pulmonary hypertension (P-HTN) and heart failure (HF), and these included P-HTN without HF, HF without P-HTN, both HF and P-HTN, and not either HF or P-HTN. P-HTN was identified based on the presence of at least one of three specific ICD-9-CM codes (Appendix A) occurring during the study period, measured using a dichotomous response (Yes ('1')/No ('0')). HF was operationalized based on the presence of at least one of 16 specific ICD-9-CM codes

(Appendix B) occurring during the six-year study period, measured as (Yes (‘1’)/No (’0’)). The four options of outcomes were mutually exclusive and analyzed independently.

Exposure Variable

The primary exposure variable was presence or absence of DS among patients with CHD. DS 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’)).

Covariables

CHD Anatomic Complexity

Anatomic CHD complexity classification was operationalized by the native anatomic group classification scheme used in the lifespan project (Appendix D). This scheme classifies anatomic defects as complex, shunt, valve, shunt + valve, and other, with the latter four categories grouped into non-complex. Complex lesions were coded as ‘1’ and non-complex lesions were coded as ‘0’. a “non-severe” category coded as ‘0’ and dichotomized with severe diagnoses, coded as ‘1’. Non-complex served as the reference group for the 2-level lifespan anatomic CHD complexity classification.

Age

Patients were between ages 1 and 64 years of age on the date of their first encounter for the pilot project data 2008-2010 or their first qualifying encounter (FQE) for the lifespan project data 2011-2013. The FQE is defined as the first healthcare encounter where a CHD-related ICD-9-CM diagnosis code appears in the patient’s eHR. This variable was calculated by subtracting the patient’s date of birth from the date of their FQE. Age was classified into four groups: ‘1’ =

1-10 years, ‘2’ = 11-19 years, ‘3’ = 20-39 years, and ‘4’ = 40-64 years of age. Ages 20-39 served as the reference group.

Gender

Gender was coded ‘1’ for males and ‘0’ for females. Males served as the reference group.

Race

Race was classified into the following 4 categories: ‘1’ for White, ‘2’ for Black, ‘3’ for Other, and ‘4’ for Unknown. White served as the reference group.

Ethnicity

Ethnicity was classified into the following 3 categories: ‘0’ for non-Hispanic, ‘1’ for Hispanic, and ‘9’ for Unknown. Non-Hispanic served as the reference group.

Geographic Distribution

Rurality was categorized as those residing in non-metropolitan or rural counties compared to those who resided in metropolitan or urban counties. Initially, county of residence was coded into 6 levels, plus unknown if county of residence was missing, and based on the 2013 NCHS Urban-Rural Classification Scheme for Counties (76). The 6 levels of classification include four metropolitan or urban classes: large central metro (‘1’), large fringe metro (‘2’), medium metro (‘3’) and small metro (‘4’). classes and two non-metropolitan classes: micropolitan (‘5’) and noncore (‘6’). This six-level variable was then collapsed into a dichotomous or two-level variable for rural residence, Y/N; the four metropolitan categories were coded as non-rural or urban (‘0’ = No) and the two non-metropolitan categories were coded as rural residence ‘1’=Yes). Missing data received a code of ‘9’ for Unknown. Urbanity served as the reference group.

Health Insurance

Health insurance payer status was categorized into 4 categories: '1' for any Public, '2' for Private Only, '3' for Self-Pay/Uninsured, and '4' for Other. Private only served as the referent category.

Sleep Apnea Status

Patients with sleep apnea were operationalized based on the presence of at least one of five specific ICD-9-CM codes (Appendix E) occurring during the study period, measured using a dichotomous response (Yes ('1')/No ('0')). No sleep apnea served as the reference group.

Socioeconomic (SES) Proxies

Four metrics were considered as proxy variables for SES status, including neighborhood poverty, income, education, and renter occupancy levels. Data for each ZIP Code Tabulation Area (ZCTA) was collected from the 2014 American Community Survey (ACS) 5-year estimates (2010-2014). For each SES proxy, cutoff values were determined and applied to each ZCTA to generate discrete categories. The ZCTA of residence of each patient in the study was then used to assign their respective discrete SES proxy level.

Neighborhood poverty was defined as the percent of households in that ZCTA below 100% of the federal poverty level (FPL) and was coded as '0' for low poverty (<25%), and '1' for medium to high poverty (≥ 25%) and '9' for Unknown. Low poverty served as the reference group.

Neighborhood income was defined by categorization of median annual income in that ZCTA and was coded as '1' for low (<$40K per year), '2' for medium ($40K-$75K per year), '3' for high (>$75K per year), and '9' for Unknown. Medium median annual income served as the reference group.

Neighborhood education (% BS/BA degree) was defined as the percent of people living in that ZCTA holding at least a bachelor's degree and was coded as '0' for low (<30%), '1' for medium to high (≥30%), and '9' for Unknown. High education served as the reference group.

Neighborhood renter occupancy was defined as the percent of people living in that ZCTA who were renters and was coded as '0' for low rental occupancy (<35%), '1' for medium to high rental occupancy (≥35%), and '9' for Unknown. Low renter occupancy served as the reference group.

Comorbidities

Five common comorbidities for patients with CHD and DS, including diabetes mellitus (DM), hyperlipidemia, endocarditis, atrial arrhythmia, and cyanosis were examined as covariables.

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

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

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

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

Cyanosis was operationalized based on the presence of one specific ICD-9-CM code (Appendix F) occurring during the study period, measured using a dichotomous response (Yes ('1')/No ('0')). Absence of cyanosis served as the reference group.

Statistical Analysis

All analyses were conducted using the SAS version 9.4 statistical software (SAS institute, Cary, NC). Descriptive analysis included frequencies and percentages for all categorical variables. Bivariate analyses were conducted to examine the main outcomes (P-HTN without HF, HF without P-HTN, and Both P-HTN and HF) and the exposure (Down syndrome) with covariables; differences between groups were examined using chi-square tests. Covariates included CHD anatomic grouping, age, gender, race, ethnicity, sleep apnea, insurance, the SES proxy income and five comorbidities, DM, hyperlipidemia, endocarditis, atrial arrhythmia, and cyanosis. Effect modification was examined by gender.

Unadjusted and adjusted logistic regressions were conducted using SAS's Proc Genmod to estimate crude and adjusted relative risk (cRRs and aRRs) and 95% confidence intervals (CIs), respectively. P-values at <0.05 were considered significant. Confounding was assessed by comparing the cRR with aRR by entering each covariable in the model and comparing crude and adjusted effect estimates. A difference between the cRR and aRR of at least 10% was considered as a basis of including a covariable in the multivariable model. For the outcome P-HTN without HF, the following variables were identified as confounders: CHD anatomic grouping (2 categories), gender, age, race, ethnicity, insurance, sleep apnea, and four of the five comorbidities, not hyperlipidemia. For the outcome HF without P-HTN, the following variables were identified as confounders: CHD anatomic grouping (2 categories), gender, age, race, ethnicity, rurality, insurance, sleep apnea, neighborhood median annual income, and all five

comorbidities. The final multivariate logistic models included those predictors that met the 10% change in estimate rule when added to the model. Goodness of Fit (GOF) using the Hosmer-Lemeshow test was conducted to determine how well the models fit the data.

IRB and Ethical Considerations

The pilot project received Emory University Institutional Review Board (IRB) approval on 09/13/13 (#IRB00066157). The LS project received approval from the Emory IRB on 03/05/13 (#IRB00064051). Approval to conduct the current study was issued by the Emory IRB on 11/10/20 (#STUDY00001605). For the current study, a complete waiver of HIPAA authorization and informed consent was granted by the Emory IRB and confidentiality was maintained as this research is a secondary analysis of a previously linked and de-identified dataset, involving no more than minimal risk to participants (45 CFR 46.116).

CHAPTER III: RESULTS

Our study examined 22,499 patients with CHD who were eligible for analysis after excluding 11,470 patients due to age, diagnosis and missing data on gender (Figure 1). For these 22,499, 2,102 (9.3%) had DS, 4,770 (21.2%) had HF without P-HTN, 1,047 (4.7%) had P-HTN without HF, and 126 (0.6%) had both HF and P-HTN. The majority of patients were 1-10 years of age (61%), female (52.1%), non-Hispanic (56.1%) and covered by public insurance (59.0%). There was a substantial Black population (21.8%) and 15.1% of the cohort resided in a rural Georgia region. While 20.8% of the cohort was diagnosed with a complex CHD, the majority of the sample had a shunt defect (34.5%) followed by 31.9% with valve lesions. Having a shunt plus a valve diagnosis was seen in 12.8% of the cohort. Sleep apnea was seen in 4.4% of the sample. Four neighborhood-level SES proxy variables were derived and assessed including poverty level (% below the Federal Poverty Level (FPL), median annual income, % earning a bachelor's degree, and % renter occupancy; 69.2% of patients with CHD resided in neighborhoods where less than 25% of residents fell below the FPL, where 59.7% lived in neighborhoods where the median annual income was between $40K-$75K, where 58.5% were from neighborhood's that had <30% of residents earning a bachelor's degree, and where 57.0% lived in neighborhoods where renter occupancy was less than 35%. With respect to having other types of co-occurring medical conditions, 5.7% were diagnosed with cyanosis, 5.1% with hyperlipidemia, 3.2% with atrial arrhythmia, 2.5% with DM and 1.0% with endocarditis (Table 1).

Table 2 shows descriptive statistics by four different groupings: Group 1. P-HTN without HF (Yes / No); Group 2. HF without P-HTN (Yes / No); Group 3. P-HTN with HF (Yes / No); and Group 4. CHD with or without DS (Yes / No). We noted significant differences in the

comparison groups for all of the covariates examined under Group 1 and Group 2 analyses. For Group 3, which included a comparison of individuals with and without P-HTN and HF, we noted differences in many co-variables, however, cell sizes were small to examine neighborhood SES proxies. Lastly, Group 4 analysis also showed significant differences between those with and without DS by covariates, neighborhood SES proxies and comorbidities examined (Table 2).

As seen in the 4th bank of columns in Table 2, of patients with CHD and DS compared to those with CHD without DS, 7.6% had P-HTN without HF, 9.9% had HF without P-HTN, and 5.7% had both P-HTN and HF ($p<.0001$ for each). Among those with CHD and DS, 21.3% had a complex CHD, 9.6% and 9.4% had a shunt or a shunt+valve lesion, respectively, and 1.2 % had a valve defect ($p<.0001$). There were no gender or racial differences between CHD patients with or without DS. Among those with CHD and DS, 9.7% resided in an urban location compared to 7.6% who resided in a rural area ($p=.0001$). Among patients with CHD and DS, 11.1%, were between 1-10 years of age, 6.9% were 11-19 years of age, 7.9% were 20-39 years of age, and 3.6% were 40-64 years of age ($p<.0001$), with more than 20% (20.7%) identifying themselves as Hispanic ($p <.0001$). Fourteen percent (14.0%) of those with CHD and DS were covered by public insurance ($p<.0001$). Almost 40% (39.6%) of patients with CHD and DS were diagnosed with sleep apnea ($p<.0001$) compared those with CHD and no DS. Fifteen percent (15.0%) of patients with CHD and co-occurring DS had endocarditis ($p <.01$) and 28.5% had cyanosis ($p<.0001$) compared to patients with CHD without DS (Table 2).

For CHD patients who had P-HTN without HF (Table 2, 1st bank of columns), 14% had a complex CHD and 2.2% were diagnosed with a non-complex CHD ($p<.0001$), and about 6% (6.1%) of them 1-10 years of age, 2.9% were 11-19 years-old, 1.8% were 20-39, and 2.4% were 40-64 years of age ($p<.0001$). Among patients with CHD who had P-HTN without HF, almost

5% (4.8%) of them lived in urban regions compared to 3.8% who were rural residents (p<.01), and almost 7% (6.6%) had public insurance coverage compared to 1.8% and 1.9% who had private insurance coverage or who were self-paying or uninsured, respectively (p<.0001). Compared to those not diagnosed with P-HTN without HF, those with P-HTN without HF had notable differences among comorbid conditions with highest rates for endocarditis, 26.3% (p<.0001), atrial arrhythmia, 28.3% (p<.0001), and cyanosis, 26.7% (p<.0001) (Table 2).

Bivariate analyses comparing select covariates by patients diagnosed with and without HF without P-HTN can also be seen in Table 2, 2nd bank of columns. Among those with HF without P-HTN, 26.9% had a shunt lesion, 20.7% had a shunt+valve lesion, followed by 18.6% with a valve defect and 16.1% with complex anatomy (p<.0001). There were slightly more male patients with CHD (22.3%) than females with CHD (20.0%) (p<.0001) for those diagnosed with HF without P-HTN compared to those not diagnosed with HF without P-HTN. Among those with HF without P-HTN, 37.0% and 35.5% were self-payers/uninsured or had private insurance coverage, respectively (p<.0001 for both). Interestingly, among those diagnosed with HF without P-HTN compared to those who were not diagnosed with HF without P-HTN, the proportion of concomitant comorbidities was significantly lower: DM (2.7% vs. 21.7%, p<.0009), hyperlipidemia (2.3% vs. 22.2%, p<.0001), atrial arrhythmia (5.6% vs. 21.7%, p<.0001), and cyanosis (8.4% vs. 22.0%, p<.0001).

For those diagnosed with both P-HTN and HF (Table 2, 3rd bank of columns), patients with CHD were more likely to have a complex lesion, 1.7% (p<.0001), and there were notable differences in comorbid conditions for those diagnosed with both P-HTN and HF. For instance, 2.0% were also diagnosed DM (p<.0001), 1.9% with hyperlipidemia (p<.0001), 3.7% with endocarditis (p<.0001), 2.2% with atrial arrhythmia, 3.6% with cyanosis (p<.0001), and 3.8%

had sleep apnea (p<.0001). No gender, racial, ethnicity, rurality or neighborhood SES proxy differences were revealed between these two groups of CHD patients, those diagnosed with both P-HTN and HF and those not diagnosed with both P-HTN and HF (Table 2). We noted significant differences in the comparison groups for all of the covariates examined under Group 1 and Group 2 analyses. For Group 3, which included a comparison of individuals with and without P-HTN and HF, we noted differences in many co-variables, however, cell sizes were small to examine neighborhood SES proxies. Lastly, Group 4 analysis also showed significant differences between those with and without DS by covariates, neighborhood SES proxies and comorbidities examined (Table 2)

Table 3 present results from unadjusted analysis, showing crude relative risks (cRR) for each of the three outcomes: P-HTN without HF, HF without P-HTN, and both P-HTN and HF. Not adjusting for any potential co-variables, there was a positive association between patients with CHD with DS and P-HTN without HF (cRR=1.74; 95% CI=1.48, 2.04) and a protective association between those with CHD with DS and HF without P-HTN (cRR=0.44; 95% CI=0.39, 0.50). We noted a very strong positive association between patients with CHD with DS and both P-HTN and HF; however, the sample size for this analysis was small for the exposed group yielding a rather wide 95% CI (cRR=194.07; 95% CI=85.59, 440.06).

After adjusting for potential confounders, some results changed in comparison to our unadjusted analysis presented above. Results from multivariable logistic regression analysis examining the risk of P-HTN without HF (Table 4) and HF without P-HTN (Table 5) among individuals with CHD by DS status were undertaken as a whole once we determined that gender was not an effect modifier. In Table 4, our regression analysis showed a 23% decrease in risk of P-HTN without HF among those with CHD and DS compared to patients with CHD without DS

(aRR=0.77; 95% CI: 0.59-1.00) (Table 4). However, this decrease in risk is not statistically significant as the value of 1.00 is included as the upper bound of the 95% CIs. Additionally, several covariates were significantly associated with risk of P-HTN without HF. Individuals with a complex CHD had a 4.51-fold increase in risk of P-HTN without HF compared to those with non-complex CHD lesions (aRR=4.51, 95% CI: 3.90, 5.21). The risk of P-HTN without HF among those who were 1-10 years of age was 3.90 times that of 20-39-year-olds (aRR=3.90, 95% CI: 2.87, 5.31) and among 11-19-year-olds, there was a 15.22-fold increase in the risk of P-HTN without HF compared to those who were 20-39 year of age (aRR= 15.22, 95% CI: 8.22, 28.20). Compared to Whites, risk of P-HTN without HF was associated with a 1.45-fold increase for Blacks, a 1.74-fold increase for those indicating "Other" as their race, and 2.10-fold increase for those with unknown race (aRR=1.45, 95% CI: 1.10, 1.91), (aRR=1.74, 95% CI: 1.15, 2.65) and (aRR=2.10, 95% CI: 1.20, 3.67), respectively. The risk of P-HTN without HF for Hispanics was 1.55 times that of non-Hispanic (aRR=1.55,95% CI: 1.25, 1.93). Individuals living in a rural location had a 0.79-fold decrease in risk of P-HTN without HF compared to those living in urban areas (aRR= 0.79, 95% CI: 0.65-0.96), and individuals diagnosed with DM (aRR=2.36; 95% CI: 1.64, 3.41), endocarditis (aRR=2.17; 95% CI: 1.63, 2.89), atrial arrhythmia (aRR=2.95; 95% CI: 2.47, 3.53) and cyanosis (aRR=2.50; 95% CI: 2.13, 2.93) were at increased risk for P-HTN without HF compared to patients who were not diagnosed with these comorbidities (Table 4).

In Table 5, we found a significant increase in risk of HF without P-HTN in patients with CHD and DS compared to those with CHD without DS (aRR=1.51; 95% CI: 1.04-2.18). Hispanic individuals had a 1.75-fold increase in the risk of HF without P-HTN compared to non-Hispanics (aRR=1.75, 95% CI: 1.22, 2.51). Individuals with sleep apnea was associated with a

157% increase in the risk of HF without P-HTN compared to those without sleep apnea (aRR=1.57, 95% CI: 1.09, 2.26). There was a 24% decrease in the risk of HF without P-HTN for those with any public health insurance compared to those with private health coverage (aRR=.76, 95% CI: 0.60, 0.97). Lastly, individuals with cyanosis had a 1.86-fold increase in the risk of HF without P-HTN compared to those without cyanosis (aRR=1.86, 95% CI: 1.36, 2.55) (Table 5).

We did not examine the risk of developing both P-HTN and HF for patients with CHD with and without DS as the sample size was inadequate for multivariate analysis.

CHAPTER IV: DISCUSSION

Patients with CHD and DS were at a greater risk of developing HF without P-HTN compared to those with CHD without DS and were at a lower risk of developing P-HTN without HF compared to patients with CHD without DS. While the risk of P-HTN without HF was lower for patients with CHD with co-occurring DS, several demographic and other concurrent medical conditions significantly increased the probability of having P-HTN without HF; such covariates included being younger, Black or of 'other' race, Hispanic, having a complex CHD and having other comorbidities or associated conditions and complications like DM, endocarditis, atrial arrhythmia or cyanosis. Yet, risk of HF without P-HTN for patients with CHD and DS was 1.5 times that for those with CHD without DS. Furthermore, additional covariates were found to increase the relative risk of HF without P-HTN including being Hispanic, having sleep apnea and concomitant cyanosis. Interestingly, the common factor associated with increased risk for both these outcomes is cyanosis. Those with cyanosis were at a 150% increase in risk for P-HTN without HF compared to those without cyanosis (aRR=2.50; 95% CI: 2.13, 2.93) and at an 86% increase in risk for HF without P-HTN compared to those without cyanosis (aRR=1.86; 95% CI: 1.36, 2.55). Cyanosis causes an increase in pulmonary artery pressures through hypoxia induced vasoconstriction. The presence of a large shunt, which in some cases may lead to cyanosis, can also elevate pulmonary vascular resistance as well as lead to volume overload of the left side of the heart, causing heart failure as in the case of a ventricular septal defect. Additionally, the risk of both HF and P-HTN was greater for patients with CHD with co-occurring DS (cRR=194.07; 95% CI: 85.59, 440.06). While only crude analysis was performed on this outcome due to low sample size, some covariates were associated with an increase relative risk for both HF and P-

HTN, including having sleep apnea, having a complex CHD and having other comorbidities and complications like DM, hyperlipidemia, endocarditis, atrial arrhythmia or cyanosis.

Our study provides new insight into the health complications and risk factors for CHD patients, particularly those with CHD and DS, as it examines the risk of HF and/or P-HTN in this in-care population. Our cohort had an overall proportion of DS among CHD patients in-care of 9%, which is higher than the overall 3-4% prevalence of DS among CHD patients, but similar to the 7% prevalence which has been reported between 2010-2014 (73); it is important to note that the study population consists of individuals receiving healthcare and that may be the reason for the higher proportion if those with DS are more likely to receive healthcare. The proportion of HF without P-HTN was about 21% in our in-care CHD cohort, similar to the 2016 study reporting 25% of CHD patients with HF (7). About 5% had P-HTN without HF, which was on the lower end of previously reported prevalence of P-HTN ranging between 5-10% among adults with CHD (35).

Compared to a study that estimated the prevalence of complex CHD to be about 12%, our study found a proportion of nearly 21% (8). The majority of the patients in our sample were pediatric patients between the ages of 1- 10-years-old, as opposed to a larger ACHD population included in other studies (8). In our cohort, 61% of patients with CHD were between the ages of 1 to 10 years old, with only about 20% older than 19 years old. In addition, our data consists of a patient population from subspecialty and tertiary care facilities, which suggests that this CHD cohort may be more closely managed for prevention of concomitant comorbidities like P-HTN.

In our study, a large proportion, about 40%, of patients with CHD and DS were diagnosed with sleep apnea compared those with CHD and no DS. Like other studies that looked at the relationship between DS and sleep apnea, our study found an increased risk of HF without

P-HTN for those with CHD and co-occurring DS and a sleep apnea diagnosis. (18, 71). A possible explanation for this relationship is the effect of sleep apnea. The literature supports sleep apnea being a risk factor for HF; sleep apnea occurs in approximately 50% of HF patients (83). The mechanism for how sleep apnea is associated with an increased risk of HF is threefold: first, an increase in pressures in the lungs occurs that can lead to atrial enlargement, irregular heart rhythm, and accumulation of fluid in the lung (83). Second, the occurrence of sleep disruption which leads to irregular nervous system activity and increased blood pressure and heart rate (83). Finally, a fluctuation in oxygen and carbon dioxide levels also contribute to nervous system activation which may cause narrowing of blood vessels, increased pressures, and eventually right-sided heart failure (83).

While those with CHD and DS were associated with an increased risk for HF without P-HTN, those with CHD and DS were associated with a decreased risk for P-HTN without HF, after adjusting for anatomic complexity, comorbidities and complications. This may be attributable to specific cohort features. For instance, among those with P-HTN without HF, a large proportion of patients had complex CHD anatomy (62.9%), while those with HF without P-HTN mainly consisted of patients with non-complex CHDs (84.2%). It is likely that individuals with complex CHD are more likely regularly seen and monitored by healthcare professionals and thus, are pre-emptively managed before developing HF.

Other cohort features that could be influencing the results are the comorbidities. For instance, our study found that DM, atrial arrhythmia, endocarditis, and cyanosis were all associated with an increased risk for P-HTN. Atrial arrhythmia can be a consequence of P-HTN, and studies have reported a fairly high incidence of atrial arrhythmia in P-HTN patients (78).

Cyanosis, a hypoxic condition, can trigger P-HTN, in and of itself, and this aligns with our study's high cRR of over 7-fold for P-HTN without HF among patients with atrial arrhythmia.

Analytically, the risk of having P-HTN without HF goes from a 74% increase in risk for patients with CHD with DS compared to those who do not have DS in an unadjusted logistic regression model to a 23% reduction in risk for those with CHD and DS compared to those without DS in an adjusted or multivariate logistic regression model. The change may be explained by the greater importance of some of these other variables in the model relative to DS. Several demographic variables and comorbidities were significantly associated with an increased risk of P-HTN without HF such as complex CHD, being 1-10 years and 11-19 years old, being Black and "other" race, being Hispanic, having DM, endocarditis, atrial arrhythmia, and cyanosis. The influence of these variables was not accounted for in the unadjusted logistic regression model but were factored into the adjusted or multivariate logistic regression model.

The findings in the HF group are also unexpected with the lack of association with known conditions in HF such as DM and hyperlipidemia, in addition to the similar flip in risk of HF without P-HTN among CHD and DS patients between the unadjusted and adjusted models. A proportion of patients with CHD and DS have sleep apnea, which could contribute to the switch, increasing the risk of developing heart failure. Additionally, the cRR for HF without P-HTN among patients with cyanosis reversed in the adjusted model which could also affect the relationship between DS and HF.

While the outcome of both HF and P-HTN was only explored through crude analysis, the results show an increased risk of both HF and P-HTN for those with CHD and DS compared to those with CHD without DS. It is possible with this outcome that patients may have one outcome that contributes to them experiencing the other outcome. For example, it is possible that those

with DS and P-HTN are more likely to develop HF and thus end up in group of both P-HTN and HF. Additionally, as previously stated, sleep apnea is a significant risk factor for HF and can lead to the development of both P-HTN and HF, as represented with the significant proportion of patients with both P-HTN and HF and sleep apnea in our study population. The relationship with other comorbidities and the risk of having both P-HTN and HF may also provide explanation, particularly for cyanosis and endocarditis. As mentioned, cyanosis is the event of low levels of oxygen in the blood, which can impact the circulatory and respiratory system. Endocarditis, an inflammation in the heart, also effects the circulatory system as it can damage and destroy heart valves, leading to congestive heart failure.

It is important to note that treatment and management of CHD are continuously improving, contributing to higher survival rates and improved long-term outcomes (73). One study found that infants with DS have a greater rate of biventricular repair and improved survival rates, particularly among those with AVSD (77). Additionally, studies support the notion that DS allows for earlier detection of CHD in pregnancy, letting parents benefit from perinatal management to minimalize potential health problems during pregnancy and birth (77). Additionally, complete atrioventricular canal defects (a complex type of AVSD) is common among those with CHD and DS. CAVCD creates 2 problems – a large shunt and mitral valve regurgitation. Both problems lead to HF in children if not repaired early. A residual or unrepaired shunt can lead to P-HTN, as can mitral valve disease.

Part of prenatal care consists of prenatal testing for DS. With the advancements in technology, there have been increasing trends in prenatal diagnosis and terminations (79). In a study that focused on metropolitan Atlanta, 34% of cases with a confirmed DS diagnosis were electively terminated, a number that was higher than previously reported (79). In 2018, it was

reported that 67% of pregnancies with a DS diagnosis were terminated (80). There persist to be negative associations with DS, as exemplified in Iceland, where only 1-2 infants with DS are born each year, suggesting that women are perhaps encouraged to terminate a DS pregnancy (80).

Current study findings must be interpreted in light of several potential limitations. First, due to the use of eHR and administrative data, only patients in care are included, thus underrepresenting individuals with CHD conditions and limiting the generalizability of findings. Additionally, with our cohort being primarily between the ages of 1-10 years old, it is possible there has not been enough time for patients to develop HF and/or P-HTN. The literature supports that older people are more likely to suffer from HF and/or P-HTN than younger people (13). The lack of follow-up time could likely impact the results in our study. Another limitation in the study was the use of socioeconomic proxies to establish SES as individual-level measures of SES are not possible. When it comes to SES, there is a considerable variation of type, quality, and quantity of proxy variables to use for SES in research studies (81). The utilization of proxy variables varies from study to study; some researchers promote the use of one proxy variables, and some researchers support the use of multiple proxy variables, while others promote a suitable selection method of proxy variables of SES appropriate to one's study (81). Furthermore, the literature supports the occurrence of DS is strongly dependent on maternal age, with advanced maternal age being an often-reported risk factor (82). In this study, we did not have any information regarding the age of the mother. Additionally, the dataset does not include information on anticoagulant prescriptions, which is a significant covariate that cannot be accounted for in this analysis. To better understand this issue, an analysis using CHD type would

provide a more granular look at the association between CHD and DS and the adverse outcomes of HF and P-HTN.

In conclusion, we found that co-occurring DS among individuals with CHD can impact the development of P-HTN and HF overtime. Our data shows that those with HF without P-HTN are at a greater risk of having CHD and DS, compared to non-complex CHD anatomic grouping. Our study does indicate a growing proportion of CHD and DS, a result of enhanced treatment and management for DS patients as well as improvement in educational, public, and financial support for families. Comorbidities, like cyanosis and atrial arrythmia, and sleep apnea may affect the risk of P-HTN and HF for patients with CHD and co-occurring DS and should be explored further. Future studies should aim at improved assessment of clinical variables and potential confounders, such as CHD type and maternal age of the cases' mothers as well as look at mortality, to understand more about this unique population, individuals with CHD and DS. Future studies should additionally investigate the risk of developing both P-HTN and HF among individuals with CHD and co-occurring DS. As seen with our study, investigation of the association between DS among those with CHD and the adverse health outcome P-HTN and HF provides insight into the relationship of DS on HF and P-HTN for those with CHD and should guide early intervention strategies to help clinicians prevent HF and/or P-HTN and associated sequelae in this target group.

CHAPTER V: PUBLIC HEALTH IMPLICATIONS/FUTURE DIRECTIONS

The current study contributes to the larger surveillance project and the literature by examining the association of HF and/or P-HTN for individuals with co-occurring CHD and DS compared to individuals with CHD alone. This is the first study to investigate the association of the health outcomes, HF and P-HTN, and risk factors, such as sleep apnea, in the high-risk group of CHD and DS patients in the U.S. Findings from this study provide insight into the relationship of DS on HF and P-HTN for those with CHD and should guide early intervention strategies to help clinicians prevent HF and/or P-HTN and associated sequelae in this target group. Our data shows that those with HF without P-HTN are at a greater risk of having CHD and DS, compared to non-complex CHD anatomic grouping. Our study does indicate a growing proportion of CHD and DS, a result of enhanced treatment and management for DS patients as well as improvement in educational, public, and financial support for families. This study provides a preliminary look at the adverse health outcomes and risk factors associated with the high-risk group of CHD and DS patients. To confirm these findings, further investigations are necessary. Future studies should include CHD type and maternal age of the cases' mothers as well as look at mortality to understand more this unique population, individuals with CHD and DS. Future studies should additionally investigate the risk of developing both P-HTN and HF among individuals with CHD and co-occurring DS.

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TABLES

Table 1. Descriptive Characteristics of Patients with Congenital Heart Defects, 2008-2013 (N=22499)

VARIABLES	N=22499	%
OUTCOMES		
Pulmonary Hypertension without Heart Failure	1047	4.7
Heart Failure without Pulmonary Hypertension	4770	21.2
Both Pulmonary Hypertension and Heart Failure	126	0.6
Not either Pulmonary Hypertension or Heart Failure	16556	73.6
EXPOSURE		
Down Syndrome		
Yes	2102	9.3
No	20397	90.7
COVARIATES		
CHD Anatomic Grouping (4 categories)		
Complex	4692	20.8
Shunt	7759	34.5
Valve	7165	31.9
Shunt+Valve	2883	12.8
CHD Anatomic Grouping (2 categories)		
Complex	4692	20.8
Non-Complex	17807	79.2
Age Group^^^ (in years)		
1-10	13725	61.0
11-19	4289	19.1
20-39	2884	12.8
40-64	1601	7.1
Gender		
Male	10767	47.9
Female	11732	52.1
Race		
White	8626	38.4
Black	4909	21.8
Other^	386	1.7
Unknown	8578	38.1
Ethnicity		
Non-Hispanic	12615	56.1
Hispanic	760	3.4
Unknown	9124	40.5
Geographic Distribution		
Urban	19090	84.8
Rural	3387	15.1
Unknown	22	0.1

Insurance		
Any Public	13286	59.0
Private Only	8971	39.9
Self-Pay/Uninsured	162	0.7
Other	80	0.4
Sleep Apnea		
Yes	983	4.4
NEIGHBORHOOD SOCIOECONOMIC PROXIES		
Poverty^^ (% below FPL)		
<25% below FPL	15565	69.2
≥25% below FPL	6943	30.4
Unknown	91	0.4
Median Annual Income^^		
<$40K	5707	25.4
$40K-$75K	13434	59.7
>$75K	3233	14.4
Unknown	125	0.6
Education^^		
<30% with bachelor's degree	13162	58.5
≥30% with bachelor's degree	9237	41.1
Unknown	100	0.4
Renter Occupancy^^		
<35% renters in zip	12828	57.0
≥35% renters in zip	9583	42.6
Unknown	88	0.4
COMORBIDITIES		
Diabetes Mellitus	554	2.5
Hyperlipidemia	1156	5.1
Endocarditis	217	1.0
Atrial Arrhythmia	713	3.2
Cyanosis	1286	5.7

^ 'Other' race includes American Indian/Alaskan Native, Asian, Native Hawaiian/Pacific Islander, and multi-racial
^^ Neighborhood defined as the zip code of residence for the individual patient
^^^ Mean age is 12.16 years (SD 14.22)
***Abbreviations**:* CHD=Congenital Heart Defect; FPL=Federal Poverty Level

Table 2. Bivariate Analyses: Distribution of Covariate Percentages of Pulmonary Hypertension and/or Heart Failure for Patients with Congenital Heart Defects and Co-occurring Down Syndrome

		OUTCOMES									EXPOSURE		
		Pulmonary Hypertension without Heart Failure			Heart Failure without Pulmonary Hypertension			Pulmonary Hypertension and Heart Failure			Down Syndrome		
		No (n=21452)	Yes (n=1047)	p-value	No (n=17729)	Yes (n=4770)	p-value	No (n=22373)	Yes (n=126)	p-value	No (n=20397)	Yes (n=2102)	p-value
Down Syndrome	No	95.6	4.4	<.0001	77.6	22.4	<.0001	99.9	--	<.0001			
	Yes	92.4	7.6		90.1	9.9		94.3	5.7				
COVARIATES													
CHD Anatomic Group	Complex	86.0	14.0	<.0001	83.9	16.1	<.0001	98.3	1.7	<.0001	78.7	21.3	<.0001
	Shunt	98.0	2.0		73.1	26.9		99.7	0.3		90.4	9.6	
	Valve	98.9	1.1		81.4	18.6		99.9	--		98.8	1.2	
	Shunt+Valve	94.7	5.3		79.3	20.7		99.3	0.7		90.6	9.4	
CHD Anatomic Group	Complex	86.0	14.0	<.0001	83.9	16.1	<.0001	98.3	1.7	<.0001	78.7	21.3	<.0001
	Non-Complex	97.8	2.2		77.4	22.6		99.7	0.3		93.8	6.2	
Age (in years)	1-10	93.9	6.1	<.0001	78.5	21.5	<.0001	99.4	0.6	0.0012	88.9	11.1	<.0001
	11-19	97.1	2.9		72.5	27.5		99.8	0.2		93.1	6.9	
	20-39	98.2	1.8		79.3	20.7		99.3	0.7		92.1	7.9	
	40-64	97.6	2.4		96.9	3.1		99.2	0.8		96.4	3.6	
Gender	Male	95.3	4.1	<.0001	77.7	22.3	<.0001	99.4	0.6	ns	90.4	9.6	ns
	Female	94.7	5.3		80.0	20.0		99.4	0.6		90.9	9.1	
Race	White	93.7	6.3	<.0001	96.9	3.1	<.0001	99.6	0.4	ns	90.3	9.7	ns
	Black	92.1	7.9		97.1	2.9		99.4	0.6		91.3	8.7	
	Other^	85.8	14.3		95.1	4.9		100.0	0.0		87.8	12.2	
	Unk	99.3	0.7		49.3	50.7		99.3	0.7		90.8	9.2	
Ethnicity	Non-Hispanic	93.2	6.8	<.0001	97.1	2.9	<.0001	99.5	0.5	ns	90.5	9.5	<.0001
	Hispanic	83.8	16.2		93.5	6.5		99.5	0.5		79.3	20.7	
	Unk	99.2	0.8		52.2	47.8		99.4	0.6		91.8	8.2	
Rurality	Urban	95.2	4.8	.0067	78.1	21.9	<.0001	99.4	0.6	ns	90.3	9.7	.0001
	Rural	96.2	3.8		82.8	17.2		99.6	0.4		92.4	7.6	

		OUTCOMES									EXPOSURE		
		Pulmonary Hypertension without Heart Failure			Heart Failure without Pulmonary Hypertension			Pulmonary Hypertension and Heart Failure			Down Syndrome		
		No (n=21452)	Yes (n=1047)	p-value	No (n=17729)	Yes (n=4770)	p-value	No (n=22373)	Yes (n=126)	p-value	No (n=20397)	Yes (n=2102)	p-value
Insurance	Any Public	93.4	6.6	<.0001	88.5	11.5	<.0001	99.0	1.0	<.0001	86.0	14.0	<.0001
	Private Only	98.2	1.8		64.5	35.5		100.0	0.0		97.4	2.6	
	SelfPay/Unins	98.1	1.9		63.0	37.0		100.0	0.0		98.1	--	
	Other	100.0	0.0		100.0	0.0		100.0	0.0		100.0	0.0	
Sleep Apnea	No	95.6	4.4	<.0001	78.2	21.8	<.0001	99.6	0.4	<.0001	92.0	8.0	<.0001
	Yes	89.7	10.3		92.6	7.4		96.2	3.8		60.4	39.6	
NEIGHBORHOOD SOCIOECONOMIC PROXIES													
Poverty^^ (% below FPL)	<25% FPL	95.3	4.7	ns	78.2	21.8	.0004	99.5	0.5	ns	90.4	9.6	.0118
	>25% FPL	95.5	4.5		80.3	19.7		99.3	0.7		91.5	8.5	
Median Annual Income^^	<$40K	95.5	4.5	.0487	80.7	19.3	<.0001	99.4	0.6	ns	91.9	8.1	.0032
	$40K-$75K	95.1	4.9		78.8	21.2		99.4	0.6		90.4	9.6	
	>$75K	96.1	3.9		75.6	24.4		99.7	0.3		90.4	9.6	
Education^^	<30% BS	95.3	4.7	ns	79.6	20.4	.0004	99.4	0.6	ns	91.4	8.6	.0002
	>30% BS	95.5	4.5		77.7	22.3		99.5	0.5		89.9	10.1	
Renter Occupancy^^	<35% renter	95.0	5.0	.0018	79.4	20.6	.0246	99.5	0.5	ns	90.3	9.7	.0057
	>35% renter	95.9	4.1		78.1	21.9		99.4	0.6		91.4	8.6	
COMORBIDITIES													
Diabetes Mellitus	No	95.4	4.6	.0009	78.3	21.7	<.0001	99.5	0.5	<.0001	90.7	9.3	ns
	Yes	92.4	7.6		97.3	2.7		98.0	2.0		89.4	10.6	
Hyperlipidemia	No	95.3	4.7	ns	77.8	22.2	<.0001	99.5	0.5	<.0001	90.6	9.4	ns
	Yes	95.8	4.2		97.7	2.3		98.1	1.9		91.1	8.9	
Endocarditis	No	95.6	4.4	<.0001	78.6	21.4	<.0001	99.5	0.5	<.0001	90.7	9.3	.0029
	Yes	73.7	26.3		97.7	--		96.3	3.7		84.8	15.2	
Atrial Arrhythmia	No	96.1	3.9	<.0001	78.3	21.7	<.0001	99.5	0.5	<.0001	90.6	9.4	ns
	Yes	71.7	28.3		94.4	5.6		97.8	2.2		91.2	8.8	
Cyanosis	No	96.7	3.3	<.0001	78.0	22.0	<.0001	99.6	0.4	<.0001	91.8	8.2	<.0001
	Yes	73.3	26.7		91.6	8.4		96.4	3.6		71.5	28.5	

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

^^ Neighborhood defined as the zip code of residence for the individual patient

^^^ The unknown level for several variables with small counts not included in bivariate analyses, i.e., 'unknown' level for rurality and the four proxies omitted

Notes. Cell sizes <10 not reported; row percentages reported. ***Abbreviations***: CHD=Congenital Heart Defect; FPL=Federal Poverty Level; Unk=Unknown; ns=Not statistically significant (>0.05)

Table 3. Unadjusted Analysis: Risk of Pulmonary Hypertension without Heart Failure, Heart Failure without Pulmonary Hypertension, and Both Pulmonary Hypertension and Heart Failure with Covariates for Patients with Congenital Heart Defects and Co-occurring Down Syndrome

	Pulmonary Hypertension without Heart Failure		Heart Failure without Pulmonary Hypertension		Pulmonary Hypertension and Heart Failure	
	cRR	**95% CI**	**cRR**	**95% CI**	**cRR**	**95% CI**
Down Syndrome						
No	1.00	--	1.00	--	1.00	--
Yes	1.74***	1.48-2.04	0.44***	0.39-0.50	194.07***	85.59-440.06
COVARIATES						
CHD Anatomic Grouping (2 categories)						
Non-Complex	1.00	--	1.00	--	1.00	--
Complex	6.42***	5.69-7.25	0.71***	0.66-0.77	6.17***	4.31-8.82
Age Group (in years)						
1-10	3.37***	2.55-4.45	1.04	0.96-1.12	0.90	056-1.47
11-19	11.36***	6.52-19.77	1.08	0.92-1.26	0.82	0.31-2.15
20-39	1.00	--	1.00	--	1.00	--
40-64	129.00***	42.55-391.04	1.16	0.85-1.59	0.67	0.10-4.64
Gender						
Male	1.00	--	1.00	--	1.00	--
Female	1.30***	1.16-1.47	0.90***	0.85-0.94	1.02	0.72-1.45
Race						
White	1.00	--	1.00	--		
Black	1.61***	1.25-2.07	0.90	0.60-1.35		
Other^	2.04***	1.40-2.98	0.85	0.47-1.56		
Unknown	2.59***	1.57-4.28	0.81	0.36-1.81		
Ethnicity						
Non-Hispanic	1.00	--	1.00	--		
Hispanic	2.39***	2.01-2.84	2.27***	1.70-3.03		
Geographic Distribution						
Urban	1.00	--	1.00	--		
Rural	0.78**	0.65-0.93	0.79***	0.73-0.85		
Insurance						
Private Only	1.00	--	1.00	--		
Any Public	3.65***	3.09-4.31	0.32***	0.30-0.34		
Sleep Apnea						
No	1.00	--	1.00	--	1.00	--
Yes	2.5***	2.0-3.1	0.34***	0.27-0.42	9.10***	6.24-13.28

	Pulmonary Hypertension without Heart Failure		Heart Failure without Pulmonary Hypertension		Pulmonary Hypertension and Heart Failure	
	cRR	**95% CI**	**cRR**	**95% CI**	**cRR**	**95% CI**
NEIGHBORHOOD SOCIOECONOMIC PROXY						
Median Annual Income^^						
$0-$40K	0.93	0.81-1.07	0.91**	0.85-0.97	1.03	0.69-1.53
$40-$75K	1.00	--	1.00	--	1.00	--
>$75K	0.80	0.53-1.23	0.75**	0.62-0.90	1.09	0.33-3.58
COMORBIDITIES						
Diabetes Mellitus						
No	1.00	--	1.00	--	1.00	--
Yes	1.66***	1.23-2.23	0.13***	0.08-0.21	3.79***	2.05-6.99
Hyperlipidemia						
No	1.00	--	1.00	--	1.00	--
Yes	0.89	0.67-1.18	0.10***	0.07-0.15	3.91***	2.48-6.16
Endocarditis						
No	1.00	--	1.00	--	1.00	--
Yes	5.91***	4.69-7.45	0.11***	0.05-0.26	6.96***	3.45-14.07
Atrial Arrhythmia						
No	1.00	--	1.00	--	1.00	--
Yes	7.30***	6.39-8.35	0.26***	0.19-0.35	4.44***	2.64-7.47
Cyanosis						
No	1.00	--	1.00	--	1.00	--
Yes	8.04***	7.16-9.03	0.38***	0.32-0.46	9.48***	6.63-13.57

^ 'Other' race includes American Indian/Alaskan Native, Asian, and Native Hawaiian/Pacific Islander, and multi-racial
^^ Neighborhood defined as the zip code of residence for the individual patient
*p-value <0.05 **p-value<0.01 ***p-value <0.001

Table 4. Adjusted Analysis: Risk of Pulmonary Hypertension without Heart Failure for Select Covariates for Patients with Congenital Heart Defects and Co-occurring Down Syndrome

	N=13193	
	aRR	**95% CI**
Down Syndrome		
No	1.00	--
Yes	0.77	0.59-1.00
CHD Anatomic Grouping (2 categories)		
Non-Complex	1.00	--
Complex	4.51***	3.90-5.21
Age Group (in years)		
1-10	3.90***	2.87-5.31
11-19	15.22***	8.22-28.20
20-39	1.00	--
40-64	not calculated	
Gender		
Male	1.00	--
Female	1.08	0.94-1.24
Race		
White	1.00	--
Black	1.45*	1.10-1.91
Other^	1.74*	1.15-2.65
Unknown	2.10*	1.20-3.67
Ethnicity		
Non-Hispanic	1.00	--
Hispanic	1.55***	1.25-1.93
Geographic Distribution		
Urban	1.00	--
Rural	0.79*	0.65-0.96
Sleep Apnea		
No	1.00	--
Yes	1.14	0.91-1.44
Insurance		
Any Public	1.16	0.97-1.39
Private Only	1.00	--
COMORBIDITIES		
Diabetes Mellitus		
No	1.00	--
Yes	2.36***	1.64-3.41

Endocarditis		
No	1.00	--
Yes	2.17***	1.63-2.89
Atrial Arrhythmia		
No	1.00	--
Yes	2.95***	2.47-3.53
Cyanosis		
No	1.00	--
Yes	2.50***	2.13-2.93
INTERACTION		
Down syndrome by gender	1.06	0.75-1.51

^ 'Other' race includes American Indian/Alaskan Native, Asian, and Native Hawaiian/Pacific Islander, and multi-racial
^^ Neighborhood defined as the zip code of residence for the individual patient
*p-value <0.05 **p-value<0.01 ***p-value <0.001 for aRR; 95% CI are around the parameter estimate.
***Abbreviations**:* CHD=Congenital Heart Defect; Unk=Unknown; DS = Down syndrome; Inc. = Income
Note: Age group 40-64 years not reported - large exponentiated estimate (aRR) and wide 95% CIs.
SES Income Proxy and Hyperlipidemia omitted from current adjusted model as not significant in crude analysis.

Table 5. Adjusted Analysis: Risk of Heart Failure without Pulmonary Hypertension for Select Covariates for Patients with Congenital Heart Defects and Co-occurring Down Syndrome

	N=13193	
	aRR	**95% CI**
Down Syndrome		
No	1.00	--
Yes	1.51*	1.04-2.18
CHD Anatomic Grouping (2 categories)		
Non-Complex	1.00	--
Complex	1.09	0.86-1.38
Age Group (in years)		
1-10	1.39	0.97-1.98
11-19	1.92	0.95-3.91
20-39	1.00	--
40-64	3.70	0.90-15.30
Gender		
Male	1.00	--
Female	0.99	0.80-1.24
Race		
White	1.00	--
Black	1.00	0.63-1.58
Other^	1.00	0.50-1.98
Unknown	1.00	0.40-2.48
Ethnicity		
Non-Hispanic	1.00	--
Hispanic	1.75**	1.22-2.51
Geographic Distribution		
Urban	1.00	--
Rural	0.91	0.66-1.26
Sleep Apnea		
No	1.00	--
Yes	1.57*	1.09-2.26
Insurance		
Any Public	0.76*	0.60-0.97
Private Only	1.00	--
NEIGHBORHOOD SOCIOECONOMIC PROXIES		
Median Annual Income^^		
$0-$40K	0.78	0.54-1.12
$40-$75K	1.00	--
>$75K	0.47	0.16-1.41

COMORBIDITIES		
Diabetes Mellitus		
No	1.00	--
Yes	0.6	0.27-1.71
Hyperlipidemia		
No	1.00	--
Yes	1.03	0.55-1.92
Endocarditis		
No	1.00	--
Yes	0.22	0.03-1.57
Atrial Arrhythmia		
No	1.00	--
Yes	0.53	026-1.08
Cyanosis		
No	1.00	--
Yes	1.86***	1.36-2.55
INTERACTION		
Down syndrome by gender	0.94	0.56-1.58

^ 'Other' race includes American Indian/Alaskan Native, Asian, and Native Hawaiian/Pacific Islander, and multi-racial
^^ Neighborhood defined as the zip code of residence for the individual patient
*p-value <0.05 **p-value<0.01 ***p-value <0.001 for aRR; 95% CI are around the parameter estimate.
***Abbreviations**:* CHD=Congenital Heart Defect; Unk=Unknown; DS = Down syndrome; Inc. = Income

FIGURES

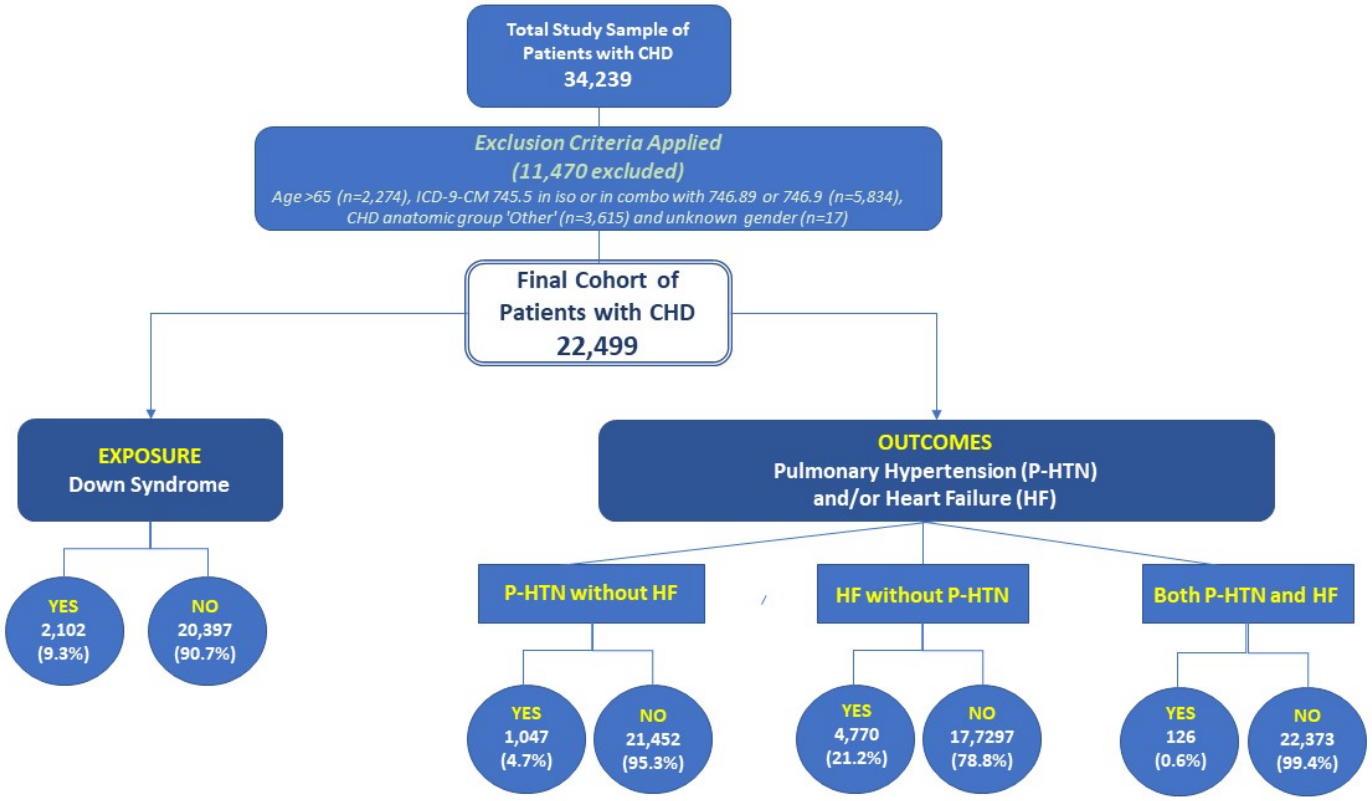

Figure 1. Analytic Dataset Construction

APPENDICES

Appendix A. ICD-9-CM Codes for Pulmonary Hypertension (P-HTN) (3 codes)

ICD-9-CM Code	ICD-9-CM Description
416.0	PRIMARY PULMONARY HYPERTENSION
416.8	OTHER CHRONIC PULMONARY HEART DISEASES
416.9	OTHER CHRONIC PULMONARY HEART DISEASE, UNSPECIFIED

Appendix B. ICD-9-CM Codes for Heart Failure (16 codes)

ICD-9-CM Code	ICD-9-CM Description
398.91	RHEUMATIC HEART FAILURE
428.0	CONGESTIVE HEART FAILURE
428.1	LEFT 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)
428.9	HEART FAILURE NOS

Appendix C: ICD-9-CM Codes for Down Syndrome (4 codes)

ICD-9-CM Code	ICD-9-CM Description
758.0	DOWN'S SYNDROME
758.5	OTHER CONDITIONS DUE TO AUTOSOMAL ANOMALIES
758.9	CONDITIONS DUE TO ANOMALY OF UNSPECIFIED CHROMOSOME
759.9	CONGENITAL ANOMALY UNSPECIFIED

Appendix D. 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 (unpublished manuscript: Glidewell, MJ, Farr, SL, Book, WM, et al.) Prevalence of congenital heart defects among 1 to 64-year-olds receiving health care at five U.S. surveillance sites, 2011-2013)
**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 at least 1 shunt code, no valve or complex codes. Valve has at least one valve code, no shunt or complex codes. 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 E: ICD-9-CM Codes for Sleep Apnea (5 codes)

ICD-9-CM Code	ICD-9-CM Description
327.21	PRIMARY CENTRAL SLEEP APNEA
327.23	OBSTRUCTIVE SLEEP APNEA (ADULT)(PEDIATRIC)
327.27	CENTRAL SLEEP APNEA IN CONDITIONS CLASSIFIED ELSEWHERE
780.53	HYPERSOMNIA WITH SLEEP APNEA, UNSPECIFIED
780.57	UNSPECIFIED SLEEP APNEA

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

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

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

Cyanosis (2 codes)

ICD-9-CM Code	ICD-9-CM Description
782.5	CYANOSIS
799.02	HYPOXIA