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ASSOCIATION OF DIABETES MELLITUS WITH HOSPITALIZATION AMONG ADULT CONGENITAL HEART DEFECT PATIENTS, 2008-2010

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Bachelor of Arts

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Abstract

HOSPITALIZATION AMONG ADULT CONGENITAL HEART DEFECT PATIENTS WITH DIABETES MELLITUS

By Pamela Oandasan

Context: Due to advances in medical technology and treatment, patients born with congenital heart defects (CHDs) are living longer, and their longer life expectancy puts them at risk for developing other acquired diseases like Diabetes Mellitus (DM). DM patients and Adult Congenital Heart Defect (ACHD) patients are both high utilizers of hospital resources, specifically through their use of hospitalization. However, there has been no research assessing the risk of increased hospitalization among diabetic ACHD patients.

Purpose: The objective of this study is to examine the relationship between hospitalization and DM among the ACHD population.

Methods: A cross-sectional study of ACHD patients was conducted using 2008–2010 data from Emory University Hospital (EUH), The Emory Clinic (TEC), and Emory University Hospital-Midtown (EUH-M) in Atlanta, Georgia. Using logistic regression, odds ratios were calculated to assess the association between DM and hospitalization.

Results: An association between DM and hospitalization among ACHD patients was found (OR=7.8; 95%CI: 5.41, 11.3). After controlling for CHD severity, hypertension, and hyperlipidemia, the adjusted odds of being hospitalized among diabetic ACHD patients was four times greater compared to non-DM ACHD patients (aOR=4.2, 95%CI: 2.9, 6.2).

Conclusion: DM may play a role in an increased risk of hospitalization among the ACHD population. Further exploration of the main reasons for hospitalization among diabetic ACHD patients is needed to develop strategic care management to prevent such hospitalizations.

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List of Abbreviations

ACHD	Adults with Congenital Heart Defects
ACS	American Community Survey
ADA	American Diabetes Association
AGM	Abnormal Glucose Metabolism
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
aOR	Adjusted Odds Ratio
AVCD	Atrioventricular Canal Defects
BWE	Backwards Elimination
BMI	Body Mass Index
CAD	Coronary Artery Disease
CDC	Centers for Disease Control and Prevention
CHD	Congenital Heart Defects
CI	Confidence Interval
CNI	Conditional Indexes
CVD	Cardiovascular Disease
cOR	crude odds ratio
DM	Diabetes Mellitus
eMR	Electronic Medical Red
EUH	Emory University Hospital
EUH-M	Emory University Hospital – Midtown
GOF	Goodness of Fit
GS	Gold Standard Model

HL	Hosmer-Lemeshow Statistic
HR	Hazard Ratio
IGT	Impaired Glucose Tolerance
NHIS	National Health Interview Survey
OR	Odds Ratio
PHI	Protected Health Information
RR	Relative Risk
SES	Socioeconomic Status
T1DM	Type I Diabetes
T2DM	Type II Diabetes
TEC	The Emory Clinic
TOF	Tetralogy of Fallot
UK	United Kingdom

CHAPTER I: BACKGROUND

Congenital Heart Defects (CHD)

Congenital Heart Defects (CHDs) are conditions involving structural abnormalities in the heart. These anomalies can vary in complexity, severity, and type of defect. Although persons with CHD are usually diagnosed during their mother's pregnancy or immediately after their birth, they can also be diagnosed much later in life (1). CHDs result from embryonic development failure or aberrant development (2). The cause of CHDs is largely unknown. However, known risk factors include environmental exposures, genetics, maternal Diabetes Mellitus (DM), maternal obesity, maternal drug and alcohol use, and maternal exposure to organic solvents (3). Children with chromosomal aneuploidies account for 8-10% of CHD cases and single-gene defects account for 3-5% cases (3).

CHDs are diagnosed using several methods including echocardiography, electrocardiogram (EKG), chest X-ray, pulse oximetry, and cardiac catheterization. Echocardiography uses sound waves that bounce off the structure of the heart to create a moving picture. EKG records the electrical signals that pass through the heart. Chest X-rays use electromagnetic waves to produce an image of the insides of the chest. Pulse oximetry takes the pulse in a finger or toe to estimate how much oxygen is in the blood. Cardiac catheterization involves injecting dye into a blood vessel or heart chamber that allows doctors to observe the blood flow (1).

The population of adults with a CHD (ACHD) is made up of persons aged 21 or older who were born with a CHD and who have survived without surgery, who have had multiple surgeries throughout their lifespan, or who had surgery during or after infancy (4). 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 (2).

Severity levels of CHD conditions have been classified using Marelli's hierarchy of CHD diagnostic codes (5). The most "severe" CHDs, based on having the highest probability of cyanosis or early surgical intervention, include atrioventricular canal defects (AVCD), Tetralogy of Fallot (TOF), univentricular heart, transposition complex, truncus arteriosus, and hypoplastic heart syndrome (5). CHD patients with "severe" classifications have more frequent and severe complications and need more specialized care compared to less severe patients (3). The less severe CHDs are categorized into four levels: Shunts, Valves, Shunts plus Valves, and Other (see Appendix A) (5).

Prevalence of Congenital Heart Defects (CHDs)

CHDs affect 1% of births per year in the United States (6). Due to advances in surgery and treatment, most infants born with a CHD will survive into adulthood. Nevertheless, there is little research on health complications that arise as this population ages. In estimates developed using CHD data in Canada applied to U.S. Census data, researchers estimated that approximately two million people are living with CHD in the United States (7). Many of these individuals require specialized cardiac healthcare over their lifespan (6). CHD prevalence in children is estimated to be between 926,000 to 976,000 in the United States, while CHD prevalence in adults is estimated to be between 979,000-1,126,000 (7).

Adults with CHD now outnumber children with a CHD. In 2001, Warnes et al. estimated that approximately 117,000 adults were living with a severe CHD in the United States, while between 302,000 and 368,000 adults were living with a moderate or simple CHD condition (8). The number of ACHD patients is much higher today. In fact, more than 90% of children born

with a CHD now survive into adulthood (2). A scientific statement from the American Heart Association (AHA) reported that 98% of children with mild CHD, 96% of those with moderate CHD, and 56% of those with severe CHD now reach adulthood (4).

It is a growing concern that as these children transition into adulthood, they still require continuous health management and surveillance, which is one reason why epidemiologic research with the ACHD population is increasingly important. Knowledge regarding survival, healthcare utilization, and comorbidity trends of ACHD patients across the United States can inform future programs and areas of focus that could prevent early mortality and significant comorbidity complications. However, there is currently no single surveillance system that collects population prevalence of ACHD in the United States (4). Moreover, there is no national registry that collects and tracks morbidity and mortality of patients with CHD (3). Many of the estimates of CHD prevalence in the United States are derived from Canadian studies that used more robust and well-developed surveillance systems. In Quebec, Canada, for each individual, from birth to death, each diagnosis and health service received is recorded and linked through a unique Medicare ID. Data on CHD are collected from three different sources: 1) the physician's services and drug claims; 2) hospital discharge summary databases; and 3) the Quebec Health Insurance Board and Death Registry. Overall, the Quebec CHD database contains 28 years of data on 107,559 CHD patients from 1983 to 2010 (5). By assessing demographic differences between the U.S. and Canada, Marelli et al. proposed a CHD prevalence in the U.S. population to be 3.71–4.27 per 1000 for males, and 4.61–5.30 per 1000 for females for year 2010 (7). They found that adults accounted for 51% of the U.S. CHD population, and suggested that the ACHD population for 2010 in the U.S. was approximately 1 to 1.5 million. More recent estimates places the numbers closer to 1.5 million (9).

Although ACHD patients are living longer, their quality of life is largely unknown. It is known, however, that many CHD survivors require lifelong disease management (10). Hospitalization costs in 2004 alone was estimated to total approximately $1.4 billion (10). As this population ages, they become increasingly at risk for acquired diseases related to aging and they will require additional care, care that is no longer limited to the treatment and management of their CHD. Little is known about healthcare utilization trends in the ACHD population. Even less is known about comorbidities that exist that could contribute to increased healthcare utilization (11). Comorbidity prevention and management must be incorporated in their overall care in order to avoid hospitalization in this high utilization group. By looking at other contributing factors of hospitalization, future preventable hospitalizations of adults with CHD can be avoided.

Diabetes Mellitus (DM)

Now that CHD patients are living longer, they are at risk for age-related acquired diseases. One of these diseases is Diabetes Mellitus (DM). DM is a condition in which a person's glucose level is above normal because the pancreas does not produce enough insulin or cannot use its insulin normally. There are two main types of diabetes, Type I and Type II. Type I DM (T1DM) is usually diagnosed at a young age, and only about 5% of people who have diabetes have this type (12). Type II DM (T2DM) or adult on-set diabetes, however, accounts for 90–95% of all diabetic patients (12).

A DM diagnosis is determined by a fasting glucose level of 126mg/lD or greater (≥7.0mmol/L0), a 2-hour plasma glucose 200mg/dL or greater (≥11.1mmol/L) on a 75g oral glucose tolerance test, a random plasma glucose level of greater than 200mg/dL with accompanying diabetes symptoms, or a hemoglobin A1C level ≥6.5% (13). Pre-diabetic

individuals have higher than normal glucose levels, but do not meet the above criteria and usually do not exhibit symptom (14). Diabetic individuals may also be asymptomatic and may not be tested for DM till years later when complications develop (15).

DM can affect many organs and can lead to several serious DM related complications that are both vascular and nonvascular. DM related complications can result in blindness, renal failure, and non-traumatic lower extremity amputation (15). The most common macro-vascular DM-related complications include coronary artery disease, peripheral arterial disease, and cerebrovascular disease. In fact, T2DM is considered as a coronary artery disease risk equivalent (16).

Diabetes is a major public health concern, with more than 29.1 million people in the U.S. living with diabetes, and 86 million people diagnosed with a pre-diabetic condition (17). The high prevalence of DM in the U.S. population not only imposes a substantial economic burden, but also reduces quality of life and increases mortality rates of those suffering with the disease. A statement from the American Diabetes Association (ADA) estimates $174 billion in medical care costs and lost productivity in the U.S. for the year 2012. Furthermore, diagnosed DM reduces quality of life because DM requires frequent hospital visits and treatments, and complications from DM can lead to impaired physical abilities.

Associations: Diabetes Mellitus (DM) Risk Factors

Established risk factors for T2DM include age, history of gestational diabetes among women who have been pregnant, high body mass index (BMI), high density lipoprotein cholesterol and triglyceride levels, hypertension, lack of physical activity, race/ethnicity, and socioeconomic status (13, 12).

Age

Age is an established risk factor for T2DM (18). T2DM incidence rises among older age groups which means that as patients with CHD age, their risk of developing DM increases (19). In a Canadian cohort of patients, Choi et al. reported higher prevalence rates of diabetes with increasing age (5% for those age 12-34 years vs. 10-14% for those 75+). Authors reported a 9% increase in odds per one year increase in age (20). This study included 69,494 participants age 12 years and over during the period of 1996-1997 using data obtained from Canada's National Health Survey. In a seminal U.S. article looking at DM in older adults, Kirkman et al. also reported that DM increases with age until it levels off at 65 years of age (21). Another study by Wild et al. on the global prevalence of DM reported that the majority of DM diagnosed individuals in developed countries were in the 45-65 age group compared to those in developing countries where the majority of those diagnosed with DM were in the 65+ age group which could be explained by shorter life expectancy in the developing countries. Worldwide, this study reported that about 30 million people age 20-44, 80 million age 45-64, and 50 million over the age of 65+ had diagnosed DM in year 2000 (22).

Gender

In Choi's study, men had higher prevalence of DM than women at any age (OR=1.44, P<.05) (20). Wild et al. reported slightly higher prevalence of DM in men age <60 (22). However, in a study on the lifetime risk for DM in the U.S. published in 2003, Narayan et al. estimated that for individuals born in 2000, the lifetime risk for men is 32.8% (95%CI: 30.3, 35.8) and 38.5% for females (95%CI: 36.0, 41.5) with women at higher risk compared to men regardless of age (23). However, it is uncertain how much a biologic effect of sex or a socio-demographic effect of gender roles and experiences play in a person's DM risk.

Race/Ethnicity and Socio-Economic Status

Race and ethnicity are often cited determinants of health (24). Specific racial groups have been reported to be particularly susceptible to developing DM. For example, African Americans, Hispanics, Native Americans, Pacific Islanders, and Asians have been reported to have higher rates of diabetes compared to Caucasians (19). Spanakis and Golden reported a possible link between higher insulin resistance among Non-Hispanic blacks, Mexican Americans and Asian Americans compared to Non-Hispanic whites. They also reported differences in hyperglycemia in blacks compared to whites. Insulin resistance and hyperglycemia being known risk factors for DM can explain some of the differences in DM rates among certain races (25). Link et al.'s study on the disparities in DM prevalence stated that in the U.S. and many other countries, minorities tend to be poorer and less educated than the white majority and this has implications on an individual's access to health resources and level of food security (24). Therefore, it is important to recognize that race/ethnicity might not be a biological cause of an outcome like DM, but rather a proxy for other determinants. For instance, Kershaw et al. explain that it is not race or ethnicity that contributes to health outcomes, but rather racial/ethnic residential segregation which limits opportunities for social and economic mobility, access to health resources, and environmental exposures (26).

In a study that assessed if the level of neighborhood segregation affects cardiovascular disease (CVD) risk, Kershaw et al. demonstrated how individuals living in different levels of segregated neighborhoods can have different health outcomes. For instance, blacks had a Hazard Ratio (HR) of 1.12 (95%CI: 1.02, 1.22) with the highest level of racial/ethnic residential segregation (low, medium, high). On the other hand, whites in neighborhoods with higher white segregation were associated with lower CVD risk with HR =.88 (95%CI: 0.81, 0.96). There was

no significant difference in DM prevalence in the different segregation levels among Hispanics (Low [% = 13.5] vs. Medium [%=17.7] vs. High [%=18.2], P=.22) and different segregation levels among blacks (Low [% = 15] vs. Medium [%=18.6] vs. High [%=16.4], P=.44). However, the authors concluded that blacks and Hispanics living in less segregated neighborhoods generally have better socio-economic positions and neighborhood conditions. Blacks and Hispanics living in lower neighborhood segregated levels had lower neighborhood poverty, a fewer number of individuals with income <$25K and a fewer number without insurance compared to their greater segregated counterparts. The prevalence of those with <$25K income among blacks in low segregated neighborhoods is 17.5%, in neighborhoods with medium segregation it is 27.6% and in high segregation areas, it's 35% (P<.0001). The prevalence of those with <$25K income among Hispanics in low segregated neighborhoods is 35.5%, in medium segregated neighborhood is 41.2% and in high segregation areas is 53.8% (P<.0001). The prevalence of those with no health insurance among blacks in low segregated neighborhoods is 3.2%, in the medium segregated neighborhoods is 3.6% and in the higher segregated areas is 7.9% (P-=.001). The prevalence of those with no health insurance among Hispanics in low segregated neighborhoods is 10.1%, in the medium segregated neighborhoods, it is 17.3%, and in the high segregated areas, it is 17% (P=.03).

Data from the National Health Interview Surveys (NHIS) between 1997-2003 suggest association between diabetes and lower education and lower financial wealth (27). Using data from a community-based epidemiologic survey which looked at the association between socio-economic status among 5,503 Boston residents with DM aged 30-79, Link and McKinley found significant increased odds of diabetes in blacks (OR=2.0, 95%CI: 1.4, 2.9) and Hispanics (OR=2.4, 95%CI: 1.6, 3.4) compared to whites (reference group). After controlling for age,

gender, socioeconomic status, obesity, hypertension, gestational diabetes, physical activity, trouble paying for basics, health insurance status, and family history of diabetes, however, the odds become statistically insignificant. Moreover, the authors reported that socioeconomic status accounted for 11% of the variance in diabetes prevalence, while race/ethnicity accounted for only 0.3% (28).

BMI

Obesity is one of the leading modifiable risk factors for DM (14). It is highly associated with DM (OR = 7.37; 95%CI: 1.02, 1.22) along with a panoply of health outcomes (29). In a study on the effects of BMI on lifetime risks for DM, Narayan et al. reported that overweight and obese individuals have increased lifetime risk for developing DM, and this is particularly true at younger ages (23). Among 18-year-old males, lifetime risk of developing DM increased from 7.6% to 70.3% for those who were underweight to those who were obese (23). For 18-year-old women, the increase was from 12.2% to 74.4% among those who were underweight to those who were obese (23). The ADA reports that among men who have diabetes, 50% are obese, and among women who have diabetes, 70% are obese (14).

Hypertension

Although there is no established mechanistic relationship between hypertension and DM, they often occur together (30). Advancing age, obesity, and lack of physical activity can affect both DM and hypertension (30). Hypertension may not increase risk for DM, but it contributes to diabetic nephropathy (30), and hypertension among diabetic patients can increase mortality and morbidity. Hypertension among diabetic patients is known to accelerate the development of cardiac disease, peripheral vascular disease, stroke, retinopathy, and nephropathy (31).

In a multinational study on vascular disease among those with diabetes conducted by WHO, Fuller et al. found significant increase in CVD morbidity and mortality among T2DM patients with hypertension (32). The relative risk (RR) of CVD mortality in males with T2DM is 1.2 (95%CI: 1.1, 1.4) and 1.3 (95%CI: 1.1, 1.5) in females with T2DM across increasing levels of systolic blood pressure (32). . The combination of diabetes and hypertension leads to increased morbidity and mortality, and presumably an increase in healthcare resource utilization and hospitalization (32)

Hyperlipidemia

Similar to hypertension, hyperlipidemia frequently occurs in individuals who have DM, and the presence of elevated LDL cholesterol increases a person's risk for developing atherosclerosis (30). In the same multinational study carried out by WHO, Fuller et al. reported that the RR of CVD mortality among males with T2DM is 1.2 (95%CI: 1.1, 1.3) and 1.3 (95%CI: 1.2, 1.5) in females with T2DM across increasing serum cholesterol levels (32).

Physical Activity

Level of physical activity is a well-established risk factor for DM (30). Increasing level of physical activity and reducing BMI are two most common prevention strategies against DM development and DM complications (30). A study by Tuomilehto et al. found that incidence of transition from impaired glucose tolerance (IGT) to DM was reduced by 58% in an intervention group who incorporated health and physical activity training compared to a control group who did not receive health and physical activity training. They concluded that T2DM can be prevented through lifestyle changes that include changes in the level of physical activity.

Although level of physical activity is a major DM risk factor, there has yet to be a U.S. study assessing physical activity participation level in the ACHD population. Studies conducted

in Belgium by Moons et al. and in the Netherlands by Zomer et al. concluded that the ACHD population generally practices a healthy lifestyle with both studies reporting approximately 50% of ACHD patients participating in regular physical activities (33, 34). The Moons et al.'s study found higher regular sports participation in the ACHD group than in the general population (48.7% vs. 29.8%, P<.001) (34), while the Zomer et al.'s study found no significant difference in the level of participation in sports compared to the general population (51.6% vs. 49.6%; P=.16) (34, 33). In another Dutch study that looked more closely at participation level by varying CHD severity, Opic et al. reported approximately 50% sports participation rates among ACHD patients (36). However, the study found that ACHD patients, especially the moderate/severe level ACHD patients, participated in fewer hours per week than the general population (36).

However, some literature suggests that patients living with CHD often experience a decreased capacity for physical activities over their lifespan, which can lead to the development of risk factors that are associated with CVD (37). Depending on the severity of a patient's CHD along with doctor exercise recommendation, exercise capacity can be more limited than that found in the general population. According to a study on the effects of physical activity on aerobic capacity in CHD adult patients, ACHD patients generally do not engage in recommended physical activity (35).

The Association of Diabetes and Congenital Heart Defects

DM prevalence trends appear to be increasing in the United States (38), and these trends are not exclusive to the general population. While some studies have shown that the prevalence of DM in the ACHD population is similar or higher than in the general population, other studies have reported inconsistent findings (34, 33, 36, 39). Zomer et al.'s study reported significantly higher prevalence rates of DM among ACHD patients compared to a control group (3.4% vs.

2.3%; P=.02), while Moon et al.'s study reported no significant difference in the prevalence of DM in ACHD patients compared to the general (.8% vs. .4%; P=.11) (33, 34).

In a nested case-control study conducted in the United Kingdom (UK), researchers found that ACHD patients had an increased risk for DM (aOR=1.3) when they adjusted for smoking and a constructed deprivation score representative of socio-economic factors including housing, employment, social class and availability of a car (40, 41). These researchers used the UK's general practice database, called QRESEARCH, and matched on age, sex, and general practice. In a cross-sectional study conducted by Ohuchi, 205 stable ACHD patients and 27 non-ACHD volunteers were assessed for abnormal glucose metabolism (AGM), defined as impaired fasting plasma glucose between 110 and 125mg/dL, and IGT, defined as plasma glucose between 140 and 199 mg/dL after oral glucose tolerance test (39). The ACHD patients were divided into three groups that included 16 unrepaired cyanotic patients, 67 Fontan patients, and 122 patients with biventricular physiology. The AGM prevalence in the ACHD group was significantly higher than in the volunteer group (unrepaired, 43.8%; Fontan, 43.3%; BV, 46.7%; control 3.7%; P <.001). Researchers concluded that reduced exercise in the more complex ACHD groups could have contributed to higher plasma glucose and insulin levels (39). Although the study focused on AGM instead of DM specifically, and only in those with complex ACHD, the findings provide insight on DM rates that can be expected in ACHD patients.

While there is some research conducted abroad on the association of DM with CHD, research has been limited in the U.S. (4). Even less is known about the prevalence of diabetes within the different severity levels of the ACHD population. Although European studies disagree on whether the prevalence of DM is significantly higher in ACHD compared to the general population, there are no studies that suggest that DM prevalence is lower. Therefore, it is prudent

to consider DM as a major health concern in adults living with a CHD as much as it is in for those in the general population.

Hospitalization among Diabetic Patients

A statistical brief from the Agency for Healthcare Research and Quality (AHRQ) states that among the most expensive conditions billed in 2005 for hospital stays, DM with complications ranked 18th with a total national bill of $11,171,000,000 accounting for 491,000 hospital stays (42). In addition, the study ranked DM with complications 13th among Medicaid recipients; only hospital stays in which DM was the primary diagnosis were considered in this ranking. Data from this study were obtained from the Health Care Cost and Utilization Project (HCUP), the largest publicly available database on hospital care data in the U.S. (42).

A scientific statement by the ADA titled, *Economic Costs of DM in 2012,* cites that the total estimated direct medical cost of diagnosed DM is $176 billion and that inpatient hospital care accounts for approximately $76 billion (43). This report also noted that hospitalization costs accounted for 43% of all DM attributable medical costs, and that this category accounted for the majority of the costs (43). While inpatient days decreased nationally by 10% from 2007-2010, hospital stays attributable to DM increased by 9%. Among those with DM, hospitalizations which may or may not be directly attributable to their diabetes increased by 6%, lending support to the possible association between the presence of DM and hospitalization. In a New Zealand matched case-control study with 12,448 DM patients and an equal number of non-DM patient controls matched by age, sex, income, and location, Tomlin et al. found that having DM increased the risk for hospitalization. They reported that patients with DM were more likely to be hospitalized than non-DM patients (OR=2.55; 95%CI: 2.13, 3.04) , and that ischemic heart disease was the most common reason for admission among T2DM patients accounting for 35%

of all admissions, followed by complications specific to DM, heart failure, cataracts, dysrhythmias, and cerebrovascular disease (44).

A study on the risk factors for hospitalization among DM patients reported that DM patients have more frequent hospitalizations compared to the general population and stay 30% longer (45). In the study conducted in Queensland, Australia, Begum et al. explored factors associated with hospitalization from a random sample of 3,951 patients from Australia's National Diabetes Services Scheme. Age, income, disease duration and severity, depression, and patient knowledge, skills, and confidence in managing their health were found to be statistically associated with hospitalization among patients with DM. Marital status was also considered, but was not found significant.

Associations: Hospitalization Risk Factors

Hospitalization is common in individuals with DM, and there are many clinical reasons for a person with DM to be hospitalized (45). While DM is a complex disease that requires lifelong care management, any hospitalization that occurs in the DM population can be either directly attributable, indirectly attributable, or completely unrelatedly to their DM (43).

A major barrier of hospitalization is the inability to access care (46), and preventable hospital admission has often been used as a proxy for ambulatory care access. Social differences in class, income, racial/ethnic groups, and insurance coverage are barriers to healthcare that could lead to increased negative health outcomes and increased hospital admission (46). Preventable hospitalization is usually defined by any hospitalization with a diagnosis that could have been avoided if timely ambulatory care was provided. Some known factors that contribute to increased preventable hospitalizations are age, SES, Race/Ethnicity, BMI, and gender (46, 47, 48, 49). These deterrents to healthcare can delay a person from receiving timely preventive care

and management. These factors can also affect a person's predisposition to DM as discussed earlier. Primary prevention and DM management can reduce the risks for CVD and DM complications, and thus reduce one's overall healthcare utilization (30).

Economic Status/Income

A person's income can affect access to healthcare from insurance coverage issues to neighborhood local healthcare delivery. A study on preventable hospitalizations conducted by Billings et al. found that average admission rates in low income areas are 3.7 times higher than those in high income areas (47). The study, explored discharge data for those younger than 65 residing in several urban U.S. areas and reported marked differences in preventable hospitalization rates when high and low income group were compared. Even in communities with homogenous populations and lower poverty rates, preventable hospitalization rates between the high and low income groups were apparent.

Race/Ethnicity

A study assessing hospitalization rates of U.S. socioeconomic groups found that rates of avoidable hospitalizations were higher among blacks than whites (46). The study found that preventable hospitalization rates for blacks compared to whites was of twice as high (46). Race/ethnicity is a risk factor for various health outcomes and it provides insight into underlying socio-economic problems like the availability of neighborhood healthcare services and SES disparities.

Body Mass Index

Body Mass Index (BMI) is not necessarily a barrier to healthcare access, but it may contribute to one's ability to access healthcare especially if it exacerbates other medical conditions that require hospitalization. Higher BMI is an established risk factor for many

diseases, specifically DM and CVD. In a study of 15,355 adults, Han et al. found that hospitalization increased as BMI increased (48). In their study on hospitalized patients, they found that the covariate-adjusted average number of all-cause hospitalizations was 1316 per 1000 for normal weight adults, 1543 per 1000 for overweight adults, and 2025 per 1000 for obese adults (48).

Gender

In the same study by Han et al., the authors reported that normal weight women had fewer hospitalizations than normal weight men (48). In another study on gender differences in utilization of preventive care, women were more likely to utilize preventive care than men (49).

Hospitalization among CHD patients

While hospitalization trends in the ACHD population are largely unknown, ACHD patients usually require a lifetime of healthcare that includes both hospitalization and outpatient visits in order to treat and manage residua, sequelae, or complications left over from childhood surgeries (10). Hospital utilization is naturally higher among the ACHD population than the general population (11). In a Canadian study of 22,096 adults with CHD conducted by Mackie et al. using physician claims and hospital discharge data, the use of general healthcare resources was described and the impact of CHD severity on healthcare utilization was assessed (11). Over a 5-year period spanning from 1996 to 2000, 51% were hospitalized for either medical or surgical reasons, and 16% were admitted to critical care (11). ACHD patients with severe conditions had higher hospitalization rates (RR = 1.30, 95%CI: 1.19, 1.43) and higher rates of critical care usage (RR=2.12: 95%CI: 1.80, 2.50).

Opotowsky et al. found that ACHD hospitalization doubled from 1998 to 2005, while overall U.S. hospital admissions rose by only 13% in comparison (50). Authors reported hospital

admissions increased 130% among those with simple CHD, 60% among those with complex CHD, and 98% among those whose CHD was unclassified (50). While rates of admission do reflect average utilization for each of these CHD severity groups, the growing number of ACHD patients and their falling mortality rates may account for the increase in admissions. While there may be more ACHD patients with simple defects accounting for these higher admission numbers, ACHD patients with complex defects are likely to have repeated hospitalizations. Opotowsky et al. report that patients with complex CHD diagnoses had more comorbidities compared to those with simple CHDs (50). The comorbidity definition used in this study was based on Elixhauser's method and classified a comorbidity as "conditions present on admission that [were] not related directly to the main reason for hospitalization, but that increase[d] the intensity of resources used or increase[d] the likelihood of a poor outcome" (51).

Hospitalization among Diabetic ACHD Patients

Reports on hospitalization trends in the U.S. in ACHD patients suggest increased DM diagnosis in recent years (52). O'Leary et al. reported a significant increase in the percentage of ACHD patients admitted with DM. Hospital admissions of ACHD patients with DM went from 40,410 during 1998-2004 to 104,624 during 2004-2008 (52).

Patients with multiple chronic conditions have a strong association with hospitalization cost (53). Diabetes increases the cost of treating general conditions not directly related to DM (14). It is also known that adults with DM are high healthcare utilizers and are at higher risk for hospitalization compared to the general population. Adults with CHD are also high healthcare utilizers and are at higher risk for hospitalization. It is currently unknown however, how the effects of DM in the ACHD population affects their healthcare utilization and their risk for

hospitalization. Studying the association between DM and hospitalization among ACHD patients is important in designing healthcare management and in planning healthcare resource allocation.

No U.S. study to-date has been conducted to assess the association of hospitalization and the presence of DM in the ACHD population. Given that ACHD and diabetes as conditions contribute to hospitalization rates independently, it is likely that ACHD patients who also have diabetes may have greater hospitalization rates than ACHD patients who do not have DM. This thesis investigates the impact of DM on hospitalization among ACHD.

CHAPTER II: METHODS

Hypothesis

It was hypothesized that ACHD patients with DM will have an increased risk of hospitalization compared to ACHD patients without diagnosed DM.

Study Design and Population

This study is part of a larger Centers for Disease Control and Prevention pilot CHD surveillance project with Emory University. The aim of this larger pilot project was to expand the population-based tracking of adolescents and adults with CHDs across the lifespan. This surveillance project's objectives included acquiring a better understanding of the survival, healthcare usage, and long-term outcomes of individuals living with CHDs. This thesis contributes to the larger project by examining hospitalization among ACHD patients as part of the assessment of overall healthcare utilization.

Secondary data were obtained from Emory Healthcare's Data Warehouse which included inpatient and outpatient electronic medical record information from January 1, 2008 through December 31, 2010 from Emory University Hospital (EUH), The Emory Clinic (TEC), and Emory University Hospital - Midtown (EUH-M) in Atlanta, Georgia. The sample consisted of 3,427 Adult CHD patients age 21-64. The outcome variable, or dependent variable, is hospitalization and the main exposure variable is DM. Other variables considered in statistical models were CHD severity, age, gender, race, income, BMI, hypertension, and hyperlipidemia.

Data Management and IRB

The parent pilot study had approval from Emory University's Institutional Review Board (IRB) (#IRB0000064051). To ensure data confidentiality, data were stored on a secure, private, Federal Information Security Management Act (FISMA)-compliant network storage device drive at the Emory University, Rollins School of Public Health, IT Department server system,

maintained only by authorized IT personnel and study researchers. Protected Health Information (PHI) was excluded from this dataset to maintain confidentiality and replaced with a unique identifier for each patient. Prior to analysis, all data were de-duplicated, and cleaned.

Inclusion/Exclusion Criteria

Individuals included in the study were ACHD patients, age 21-64, who were seen at Emory Healthcare (EUH, TEC, EUH-M) between January 1, 2008 and December 31, 2010. Patients younger than 21 and those 65 and older were excluded from the study. All patients had at least one of the 55 ICD-9-CM CHD-related diagnostic codes (Appendix A), and were classified into one of five CHD severity levels using this scheme originally developed by Marelli et al. (5) (see Appendix A). Patients with a history of heart transplantation were excluded from this study.

Outcome Variable

The outcome or dependent variable was hospitalization of ACHD patients. Hospitalization was defined as any admission that extended into an overnight hospital stay. The outcome variable was binary and coded '0' for those who did not have hospitalization and coded '1' for those who had at least one hospitalization any time during the three year study period.

Exposure Variable

The main exposure in this study was DM among CHD adult patients with varying CHD severity levels. DM diagnosis was defined by the presence of at least one of 69 DM-related ICD-9 codes according to the International Classification of Diseases, Ninth revision (ICD-9) (Appendix B). An ACHD patient was classified as having diabetes when any DM-related ICD-9 code appeared any time during a clinical or hospital visit from January 1, 2008 to December 31, 2010. DM was indicated by a binary variable where '0' indicated no DM diagnosis and '1'

indicated that the patient did have a DM diagnosis. This study did not distinguish between T1DM and T2DM.

Control Variables

The control variables included in this study were CHD severity, age, income, race, BMI, hypertension, and hyperlipidemia. These variables were considered because they are well-established risk factors both in the literature and clinically for either DM or hospitalization.

CHD Severity

There were five groupings for CHD severity. The grouping used for this study was based on Marelli et al.'s classification of Canadian CHD data (Appendix A). The five categories include: (1) Severe; (2) Shunts; (3) Valves; (4) Shunts plus Valves; and (5) Other CHD Anomalies (5). Other CHD Anomalies was used as the reference group in modeling (see Appendix A).

Age

Patients in this study were between the age of 21 and 64 as of January 1, 2010. Age was classified into three age groups: 21-44, 45-54, and 55-64.The reference group was the youngest age grouping, 21-44. This variable was determined by subtracting the patient's date of birth from 01/01/2010.

Race

There were four different races classified: white, blacks, other, and two or more races. Although other races were reported in the data (specifically, Asian, American-Indian/Native Alaskan, and Hawaiian/Pacific Islander), the cell counts were too small for inclusion during analysis.

Gender

Gender was coded '0' for females and '1' for males. Gender was included in the descriptive table. Initial chi-square test of association found gender insignificant, therefore removed from the model design.

Income

Although patient's household income was not available in the Emory Data Warehouse, patient's income was estimated using median income by zip code and race as reported by the 2010 U.S. Census Bureau through the American Community Survey (ACS) 5-year estimates (54). Income was classified into seven groups: (i) <$25K; (ii) $25K to $34,999; (iii) $35K to $44,999; (iv) $45K to $54,999; (v) $55K to $64,999; (vi) $65K to $74,999; and (vii) >$75K. Income of >$75K was used as the reference group during modeling.

BMI

BMI was classified into five categories:1) Underweight; 2) Healthy Weight; 3) Overweight; 4) Obese; and 5) Morbidly Obese (see Table 1**)**. The classification is based on the standard weight status categories reported by the CDC (55). Healthy weight was used as the reference group during modeling.

Hypertension

An ACHD patient was classified as having hypertension when any hypertension-related ICD-9 code appeared any time during one of their clinical encounters or hospital visits between January 1, 2008 and December 31, 2010 (Appendix C). This binary variable was categorized as '0' No, hypertension and '1' Yes, hypertension.

Hyperlipidemia

An ACHD patient was classified as having hyperlipidemia when any hyperlipedemia-related ICD-9 code appeared any time during one of their clinical or hospital visit between January 1, 2008 and December 31, 2010 (Appendix D). This binary variable was categorized as '0' No, hyperlipidemia and '1' Yes, hyperlipidemia.

Directed Acyclic Graph (DAG)

A Directed Acyclic Graph (DAG) was constructed to evaluate the hypothesis as well as the covariates on the effects of DM (exposure) on hospitalization (outcome) among ACHD patients. The covariates CHD severity, age, gender, income, race, BMI, hypertension, and hyperlipidemia were included as potential confounders in the DAG because of their strong association in the literature with either DM or hospitalization. Although included in the DAG, gender was not included in any statistical models as it was found not to be associated with either DM or hospitalization. Physical activity, also included in the DAG, was not available in the analytic dataset (Figure 1).

Statistical Analysis

All analysis was conducted using SAS 9.4 for Windows. Frequencies for all categorical variables were computed. The mean and standard deviation for the continuous variable age was also calculated and presented. For bivariate analysis, chi-square was used to test the differences in characteristics of ACHD patients with DM and ACHD patients without DM, and ACHD patients who had been hospitalized and those who had not.

Two sample sets were constructed to assess the relationship between diabetes and hospitalization in the ACHD population. The first sample included the full sample of 3,427 ACHD patients seen at Emory Healthcare. The full sample contained the variables DM, CHD

severity, age, hypertension, and hyperlipidemia. The variables BMI, race, and income were not included in the analysis of the full sample because of the high number of missing values for these variables. Gender was not included in either the full or reduced sample because it was not found to have a significant association with DM when a chi-square test for association was conducted. The second sample was a reduced sample of 2,408 patients with no missing values for any variables. Logistic regression was performed for both samples to determine the odds of hospitalization among ACHD patients with DM compared to ACHD patients without DM. The reduced sample was assessed in order to examine if including variables not routinely recorded in hospital visits affected the association between DM and hospitalization and if controlling for those variables affected the ORs.

Additionally, a new variable was created that indicated whether a patient had complete information records available. Having a "complete" record meant that the patient had information on DM diagnosis, CHD severity, age, gender, race, income, BMI, hypertension diagnosis, and hyperlipidemia diagnosis. Patients with an "incomplete" record had race, income, and/or BMI missing. A chi-square test of association was conducted in order to assess if there was an association between hospitalization and data completeness.

A collinearity assessment was conducted to address how related the variables were to each other. It was assessed by determining if any conditional indexes (CNIs) were >30. For CNIs that were >30, the variance decomposition proportions were reviewed to see if any variables directly under the >30 CNIs were >.05.

Finally, Goodness of Fit (GOF) was assessed using the Hosmer-Lemeshow (HL) statistic to see how well the data fit the models. Models with an HL statistic <.05 were considered to have a lack of fit. Both the full and reduced sample were tested for GOF.

CHAPTER III: MANUSCRIPT

HOSPITALIZATION AMONG ADULT CONGENITAL HEART DEFECT PATIENTS WITH DIABETES MELLITUS

Pamela Oandasan

Context: Due to advances in medical technology and treatment, patients born with a congenital heart defect (CHD) are living longer. Their longer life expectancy puts them at risk for developing other acquired diseases like Diabetes Mellitus (DM). DM patients and adult congenital heart defect (ACHD) patients are both high utilizers of hospitalization. However, the risk of increased hospitalization among diabetic ACHD patients compared with ACHD patients without DM has not been assessed.

Purpose: The objective of this study is to examine the relationship between hospitalization and DM among the ACHD population.

Methods: A cross-sectional study of ACHD patients was conducted using 2008–2010 data from Emory University Hospital, The Emory Clinic, and Emory University Hospital - Midtown in Atlanta, Georgia. Using logistic regression, odds ratios (ORs) were calculated to assess the association between DM and hospitalization.

Results: An association between DM and hospitalization among ACHD patients was found (OR=7.8; 95%CI: 5.4, 11.3). After controlling for CHD severity, hypertension, and hyperlipidemia, the adjusted odds of being hospitalized among diabetic ACHD patients was four times greater compared to non-DM ACHD patients (aOR=4.2; 95%CI: 2.9, 6.2).

Conclusion: DM may play a role in an increased risk of hospitalization among patients with ACHD. Further exploration of the main reasons for hospitalization among diabetic ACHD patients is needed to develop strategic care management to prevent unnecessary hospitalization.

Keywords Diabetes Mellitus ▪ Congenital Heart Defect ▪ Hospitalization ▪ Risk Factors

Introduction

Due to great achievements in medical technology and surgery, more than 90% of children born with congenital heart defects (CHD) now survive into adulthood (2), including 98% of children with mild CHD, 96% with moderate CHD, and 56% with severe CHD (4). While prevalence of CHD at birth is stable, the prevalence of adults living with CHD has increased significantly (50). In fact, adults with CHD (ACHD) now outnumber children with CHD and are at increased risk for age-related acquired diseases, including Diabetes Mellitus (DM) (9). Both ACHD and DM patients are independently high healthcare utilizers (10, 45), but little is known about the impact of comorbidities like DM on the healthcare utilization of the ACHD population.

DM can affect many organs and often leads to serious complications that are both vascular and nonvascular such as blindness, renal failure, and non-traumatic lower extremity amputation. Additionally, DM is a well-established risk factor for heart disease in the general population (3, 27, 30, 56). With more than 29 million people in the U.S. with cardiovascular disease (CVD), DM is a major public health concern (27). Hospitalization among DM patients is among the highest in the country and it is projected to increase (45).

Many CHD patients require a lifetime of healthcare that includes both hospitalization and outpatient visits to treat and manage residua, sequelae, or complications leftover from childhood surgeries (10). While little is known about hospitalization trends among the CHD population, CHD patients are known to have numerous hospitalizations, high usage of medical technology, and increased healthcare from a multidisciplinary team of specialists, making them a high hospital resource utilizer group (57).

The objective of this study is to examine the relationship between hospitalization and DM among the ACHD population, and it is hypothesized that ACHD patients with DM will have an increased risk of hospitalization compared to ACHD patients without diagnosed DM.

Methods

Study Design and Population

As part of a larger Centers for Disease Control and Prevention pilot CHD surveillance project with Emory University aimed at acquiring a better understanding of the survival, healthcare usage, and long-term outcomes of individuals living with CHD, the current study is focused on hospitalization of ACHD patients.

Secondary data were obtained from Emory Healthcare's Data Warehouse which included inpatient and outpatient electronic medical records (eMR) from Emory University Hospital, The Emory Clinic, and Emory University Hospital – Midtown in Atlanta, Georgia. The sample consisted of 3,427 Adult CHD patients who were between 21-64 years old on January 1, 2010 and who had sought medical care at least once in one of Emory's Healthcare facilities above between January 1, 2008 and December 31, 2010. The outcome variable, or dependent variable, is hospitalization, defined as any admission that extended into an overnight hospital stay. The main exposure variable is the presence of a DM-related ICD9 code (International Classification of Diseases, Ninth revision (ICD-9)) in the patient's record (see Appendix B).

Case Definition and Exclusion Criteria

All CHD patients had at least one of 55 ICD-9-CM CHD diagnostic codes in their encounters of the three year study period (see Appendix A). ACHD patients were classified into one of five CHD severity levels using a modified scheme originally developed by Marelli et al. (5): (1) Severe; (2) Shunts; (3) Valves; (4) Shunts plus Valves; and (5) Other CHD Anomalies

(see Appendix A). Patients with a history of a heart transplantation were excluded from this study as were those younger than 21 or 65 and older.

Control Variables

The control variables included in this study were CHD severity, age, gender, income, race, BMI, hypertension, and hyperlipidemia. These variables were considered because they are well-established risk factors for either DM or hospitalization. Patient's income was estimated using median income by zip code and race as reported by the 2010 U.S. Census Bureau through the American Community Survey (ACS) 5-year estimates (54).

Statistical Analysis

All analyses were conducted using SAS 9.4 for Windows. Frequencies for all categorical variables were computed, as well as the mean and standard deviation for the continuous variable, age. For bivariate analysis, chi-square analysis was used to test the different characteristics of ACHD patients with DM and ACHD patients without DM, and ACHD patients who had been hospitalized and those who had not.

Two sample sets were used to assess the relationship between DM and hospitalization: 1) the full sample of 3,427 ACHD patients seen at Emory Healthcare; and 2) a reduced sample of 2,408 patients who had complete information on all control variables. The full sample contained the variables CHD severity, age, hypertension, and hyperlipidemia in addition to DM and hospitalization. There were 442 missing values for race, 598 missing values for income, and 638 missing values for BMI, and patients who were missing these variables were eliminated analytically. Logistic regression was performed on both samples to determine the odds of hospitalization among ACHD patients with DM compared to ACHD patients without DM. The reduced sample was assessed to examine if including variables not routinely recorded in hospital

visits affected the association between DM and hospitalization and if controlling for those variables affected the ORs.

Additionally, a new variable was created that indicated whether a patient had complete information available. Having a "complete" record meant the researchers had information on patient's DM diagnosis, CHD severity, age, race, income, BMI, hypertension diagnosis, and hyperlipidemia diagnosis. Patients with "incomplete" record had either race, income, and/or BMI missing. A chi-square test of association was conducted to assess if there was an association between hospitalization and data completeness. In addition, a variable indicating when the DM diagnosis occurred either at an outpatient encounter before the patient's first hospitalization or during a hospitalization was created.

Tests for collinearity assessed whether variables were related to each other using the conditional index (CNIs) >30. For CNIs >30, the variance decomposition proportions were reviewed to see if any variables under the >30 CNIs were >.05. For both the full and reduced sample analyses, interaction was assessed using the Backward Elimination (BWE) method. Backward elimination approach eliminates all non-significant interaction terms one at a time (58). Interaction assessment was followed by a review of all possible subsets of a Gold Standard (GS) model that included all possible variables for both sample conducted separately. Confounding was considered present if the adjusted OR (aOR) was $\pm$ 10% of the crude OR (cOR). Precision of the final model was compared to the GS. Finally, Goodness of Fit (GOF) was assessed using the Hosmer-Lemeshow (HL) statistic to see how well the data fit the models. Models with a HL statistic <.05 were considered to have a lack of fit.

Results

Of the 3,427 patients, 1,906 were hospitalized (55.6%) and 315 had a DM-related ICD-9 code (9.2%). About 90% (n=282) of those with at least one DM-related ICD-9 code were hospitalized during the study period. The mean age for hospitalized patients was about 3 years older than that for patients with no hospitalizations (see Table 2), whereas the mean age for persons with DM diagnosed was about 6 years older than that for persons with no DM diagnosis (see Table 3)

DM was found to be associated with hospitalization and all covariates including CHD severity, age, gender, race, income, BMI, hypertension, and hyperlipidemia were significantly associated with hospitalization at P<.05 (see Table 2). All covariates were found to be associated with DM (see Table 3) except for gender which was not included in any further modeling. The variable for "completeness" was associated with hospitalization (complete: $83\%_{\text{hospitalized}}$, $56\%_{\text{non-hospitalized}}$; P<.0001) (see Table 3). Completeness of patient record was also associated with DM (complete: $77\%_{\text{DM}}$, $70\%_{\text{non-DM}}$; P<.011). DM count may be skewed because not everyone who has DM is diagnosed. Since having a BMI recorded in the eMR and SES was associated with hospitalization in this study, it was suspected that a DM diagnosis being recorded was also associated with hospitalization. Out of the 315 ACHD patients with DM in the study, 93 (30%) had their first DM diagnosis during hospitalization.

Table 5 summarizes the results of the crude model, the GS model, and the adjusted model for the full sample. Table 6 summarizes the results of the crude model, the GS model, and the adjusted model for the reduced sample. Overall, an association between DM and hospitalization was found for all three models in both the full and reduced samples.

Interaction was found to exist between DM and hypertension in the full sample model at .05 level of significance, but no interaction terms were significant in the reduced sample model. In the best model for the full sample, variables included as main effects were DM, CHD severity, hypertension, hyperlipidemia, plus the interaction between DM and hypertension. The crude OR (cOR) for the full sample was 7.8 (95%CI: 5.4, 11.3). The adjusted OR for the full sample model with no interaction terms was aOR=4.2 (95%CI: 2.9, 6.2). There appeared to be a difference in the aOR when controlling for the interaction between DM and hypertension. Among those without hypertension, the aOR was 7.7 (95%CI: 3.7, 15.7), and among those with hypertension the aOR was 3.1 (95%CI: 2.0, 4.9).

Similarly, in the best model for the reduced sample, the main effects were DM, CHD severity, age, race, BMI, income, hypertension, and hyperlipidemia. The aOR for this model was 3.1 (95%CI = 1.9, 5.1). Collinearity was not apparent among the variables. The highest CNI for the final model of the full sample was 6.00304, and for the final model of the reduced sample was 6.59322.

The HL GOF test of the full sample final model yielded X^2=9.8480, df = 7, P=0.1974; for the reduced sample final model, X^2=11.9299, df=9, P=0.2173 with the data in both samples fitting the models well.

Discussion

The full sample yielded higher ORs compared to the reduced sample. The cOR, GS OR, and aOR of the full sample are 7.8 (95%CI: 5.4, 11.3), 4.2 (95%CI: 2.9, 6.2), and 4.2 (95%CI: 2.9, 6.2), respectively. The cOR, GS OR, and aOR of the reduced sample are 6.1 (95%CI: 3.9, 9.7), 3.1 (95%CI: 1.9, 5.1), and 3.2 (95%CI: 2.0, 5.2), respectively. The GS ORs and aOR for both samples are much lower than their cORs suggesting that the covariates included in the

samples do play a role in the relationship between DM and hospitalization. The aOR of the full sample does not contain age because it was not considered to affect the model during the investigation of all-possible subsets of the GS. Simultaneously, age was also not found to be a confounder for the reduced sample along with BMI and income.

Because this study found that race confounded the relationship between DM and hospitalization, healthcare providers should be encouraged to collect socio-demographic information as part of routine office visits. Further exploration of hospitalization trends in the ACHD population is needed to explain the increased risk of hospitalization among diabetic ACHD patients.

Since DM is associated with hospitalization in the general population, an association between DM and hospitalization within the ACHD population was expected. It is possible that ACHD patients with DM are more closely monitored by their physicians and so, their health complications are detected early and quickly managed which could potentially lead to fewer hospitalizations among those ACHD patients who acquire DM. However, the healthcare management approach of ACHD patients may be predominantly focused around the management of the patient's CHD. The management of comorbidities like DM which are likely perceived to be less of an immediate risk to the patient's health and well-being may be overlooked.

Strengths and Study Limitations

The study's strengths include the availability of the large set of hospital administrative data that allowed for the capturing of comprehensive information on each ACHD patient. It also allowed for the capturing of patient information from multiple healthcare encounters across a three year period. Additionally, a long list of covariates was available and included in the study.

The sample size is relatively large and detailed which allowed for a closer investigation of the data.

It is a possible, however, that an unknown number of ACHD patients have an undiagnosed DM. If having an undiagnosed DM was randomly distributed among those who were or who were not hospitalized, under-ascertainment would have led to non-differential misclassification bias, which would bias the odds ratio towards the null. However, about 30% of those with DM were diagnosed during or after they had already been hospitalized. This suggests differential ascertainment bias in that hospitalization is a factor influencing the likelihood that the DM would be diagnosed. Nevertheless, since the date of DM diagnosis was available, an additional analysis that that redefined DM cases as cases with DM diagnosis prior to their hospitalization was conducted. With this approach, the full sample still produced a result that indicated that there is an association between hospitalization and DM (aOR=2.4; 95%CI: 1.6, 3.6).

A potential weakness of the study included the fact that a proxy variable was constructed for income. This variable based on patient's zip code and race obtained from the U.S. Census Bureau ACS survey, (54) did not find income as a confounder. However, if self-reported income was obtained during an encounter, it could have had a different effect on the DM-hospitalization association.

Conclusion

This study found that ACHD patients with DM have a higher odds of hospitalization than ACHD patients without DM. As children with CHDs live longer, their healthcare and treatment should encompass both short and long term health goals. This includes addressing preventable acquired diseases like DM that are prevalent in the general population. This study also raises

further questions on hospitalization trends among the ACHD population and further exploration is needed to accommodate the needs of the growing population of adults with CHD.

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TABLES

Table 1. BMI Categories

BMI	Weight Status
Below 18.5	Underweight
18.5 – 24.9	Normal or Healthy Weight
25.0 – 29.9	Overweight
30.0 and Above	Obese

Source: Centers for Disease Control and Prevention (CDC). Division of Nutrition, Physical Activity and Obesity "About Adult BMI" <http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html > Accessed June 5, 2015.

Table 2. Socio-Demographc Characteristic of ACHD Patients

	Hospitalized		Non-Hospitalized		Total		Chi-Square	P Value
	n	%	n	%	n	%		
	1906	**56**	**1521**	**44**	**3427**	**100**		
Diabetes								
Yes	282	14.8	33	2.2	315	9.2	161.5589	<.0001
No	1624	85.2	1488	97.8	3112	90.8		
CHD Severity Group								
Severe	359	18.8	231	15.2	590	17.2		
Shunt	767	40.2	582	38.3	1349	39.4	19.8053	0.0005
Valve	387	20.3	316	20.8	703	20.5		
Shunt + Valve	90	4.7	109	7.2	90	5.8		
Other	303	15.9	283	18.6	303	17.1		
Age, Mean (sd)*	43.6 (13.18)		40.6 (12.5)					<.0001
21-44 years	959	50.3	934	61.4	1893	55.2		
45-54 years	411	21.6	319	21.0	730	21.3	57.7474	<.0001
55-64	536	28.1	268	17.6	804	23.5		
Gender								
Male	924	48.5	657	43.2	1581	46.1	9.5017	0.0021
Female	982	51.5	864	56.8	1846	53.9		
Race**								
White	905	47.5	884	58.1	1789	52.2		
Black	450	23.6	268	17.6	718	21.0	530.404	<.0001
Other race	57	3.0	18	1.2	75	2.2		
2 or more races	394	20.7	9	0.6	403	11.8		
missing	100	5.3	342	22.5	442	12.9		
Income**								
> $25,000	152	8.0	22	1.5	174	5.1		
$25,000 to $34,999	147	7.7	59	3.9	206	6.0		
$35,000 to $44,999	346	18.2	177	11.6	523	15.3		
$45,000 to $54,999	280	14.7	207	13.6	487	14.2	211.5692	<.0004
$55,000 to $64,999	238	12.5	172	11.3	410	12.0		
$65,000 to $74,999	219	11.5	174	11.4	393	11.5		
$75,000+	295	15.5	341	22.4	636	18.6		
missing	229	12.0	369	24.3	598	17.5		
BMI**								
underweight	305	16.0	143	9.4	448	13.1		
normal	606	31.8	365	24.0	971	28.3		
overweight	416	21.8	298	19.6	714	20.8	433.0013	<.0001
obese	372	19.5	168	11.1	540	15.8		
morbidly obese	82	4.3	34	2.2	116	3.4		
missing	125	6.6	513	33.7	638	18.6		
Hypertension								
Yes	1083	56.8	330	21.7	1413	41.2	430.705	<.0001
No	823	43.2	1191	78.3	2014	58.8		
Hyperlipidemia								
Yes	599	31.4	167	11.0	766	22.4	203.7844	<.0001
No	1307	68.6	1354	89.0	2661	77.7		

*Age(mean); 2 sample t-test
**contains missing values

Table 3. Chi-Square Test for Association Between DM and Other Covariates

	Diabetes		No Diabetes		Total		Chi-Square	P Value
	n	%	n	%	n	%		
	315	**9%**	**3112**	**91%**	**3427**	**100**		
CHD Severity Group								
Severe	38	12.1	552	17.7	590	17.2		
Shunt	132	41.9	1217	39.1	1349	39.4	15.1678	0.0044
Valve	63	20.0	640	20.6	703	20.5		
Shunt + Valve	11	3.5	188	6.0	199	5.8		
Other	71	22.5	515	16.6	586	17.1		
Age, Mean (sd)*	48.3 (12.1)		41.7 (12.9)					<.0001
21-44 years	104	33.0	1789	57.5	1893	55.2		
45-54 years	80	25.4	650	20.9	730	21.3	82.3238	<.0001
55-64	131	41.6	673	21.6	804	23.5		
Gender								
Male	154	48.9	1427	45.9	1581	46.1	1.0574	0.3033
Female	161	51.1	1685	54.2	1846	53.9		
Race**								
White	106	33.7	1683	54.1	1789	52.2		
Black	91	28.9	627	20.2	718	21.0	120.2548	<.0001
Other race	12	3.8	63	2.0	75	2.2		
2 or more races	86	27.3	317	10.2	403	11.8		
missing	20	6.4	422	13.6	442	12.9		
Income**								
> $25,000	23	7.3	151	4.9	174	5.1		
$25,000 to $34,999	24	7.6	182	5.9	206	6.0		
$35,000 to $44,999	49	15.6	474	15.2	523	15.3		
$45,000 to $54,999	46	14.6	441	14.2	487	14.2	16.4856	0.021
$55,000 to $64,999	43	13.7	367	11.8	410	12.0		
$65,000 to $74,999	42	13.3	351	11.3	393	11.5		
$75,000+	36	11.4	600	19.3	636	18.6		
missing	52	16.5	546	17.5	792	17.5		
BMI**								
underweight	45	14.3	403	13.0	448	18.6		
normal	82	26.0	889	28.6	971	13.1		
overweight	67	21.3	647	20.8	714	28.3	46.0108	<.0001
obese	65	20.6	475	15.3	540	20.8		
morbidly obese	26	8.3	90	2.9	116	15.8		
missing	30	9.5	608	19.5	638	3.4		
Hypertension								
Yes	253	80.3	1160	37.3	1413	41.2	218.7034	<.0001
No	62	19.7	1952	62.7	2014	58.8		
Hyperlipidemia								
Yes	179	56.8	587	18.9	766	22.4	237.5254	<.0001
No	136	43.2	2525	81.1	2661	77.7		

*Age(mean) 2 sample t-test

**contains missing values

Table 4. Chi-Square Test of Association of the Outcome and Main Exposure to Data Completeness

	Hospitalized		Non-Hospitalized		Total		Chi-Square	P Value
	n	%	n	%	n	%		
	1906	**56**	**1521**	**44**	**3427**	**100**		
Complete								
No	318	16.7	701	46.1	1019	29.7	350.0634	<.0001
Yes	1588	83.3	820	53.9	2408	70.3		

	Diabetes		No Diabetes		Total		Chi-Square	P Value
	n	%	n	%	n	%		
	315	**9%**	**3112**	**91%**	**3427**	**100**		
Complete								
No	74	23.5	945	30.4	1019	29.7	6.4697	0.011
Yes	241	76.5	2167	69.6	2408	70.3		

Table 5. Odds Ratio for Diabetes Association With Hospitalization, Full Sample

	Crude[a]		**Gold Standard[b]**		**Adjusted[c]**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Diabetes (no interaction)	7.8	(5.4, 11.3)	4.2	(2.9, 6.2)	4.2	(2.9, 6.2)
Among ACHD patietns with Hypertension			3.2	(2.0, 4.9)	3.1	(2.0, 4.9)
Among ACHD patietns without Hypertension			7.6	(3.7, 15.7)	7.7	(3.7, 15.7)

a. Model includes main exposure of interest only

b. Model controls for CHD severity, age, hypertension, and hyperlipidemia.
Hosmer-Lemeshow GOF test for the GS with interaction model yielded a pvalue = 0.4241.

c. Model controls for CHD severity, hpertension, and hyperlipidemia.
Hosmer-Lemeshow GOF test for the adjusted model with interaction yielded a pvalue = .1974.

Table 6. Odds Ratio for DM Association With Hospitalization, Reduced Sample

	Crude[a]		**Gold Standard[b]**		**Adjusted[c]**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Diabetes	6.1	(3.9, 9.7)	3.1	(1.9, 5.1)	3.2	(2.0, 5.2)

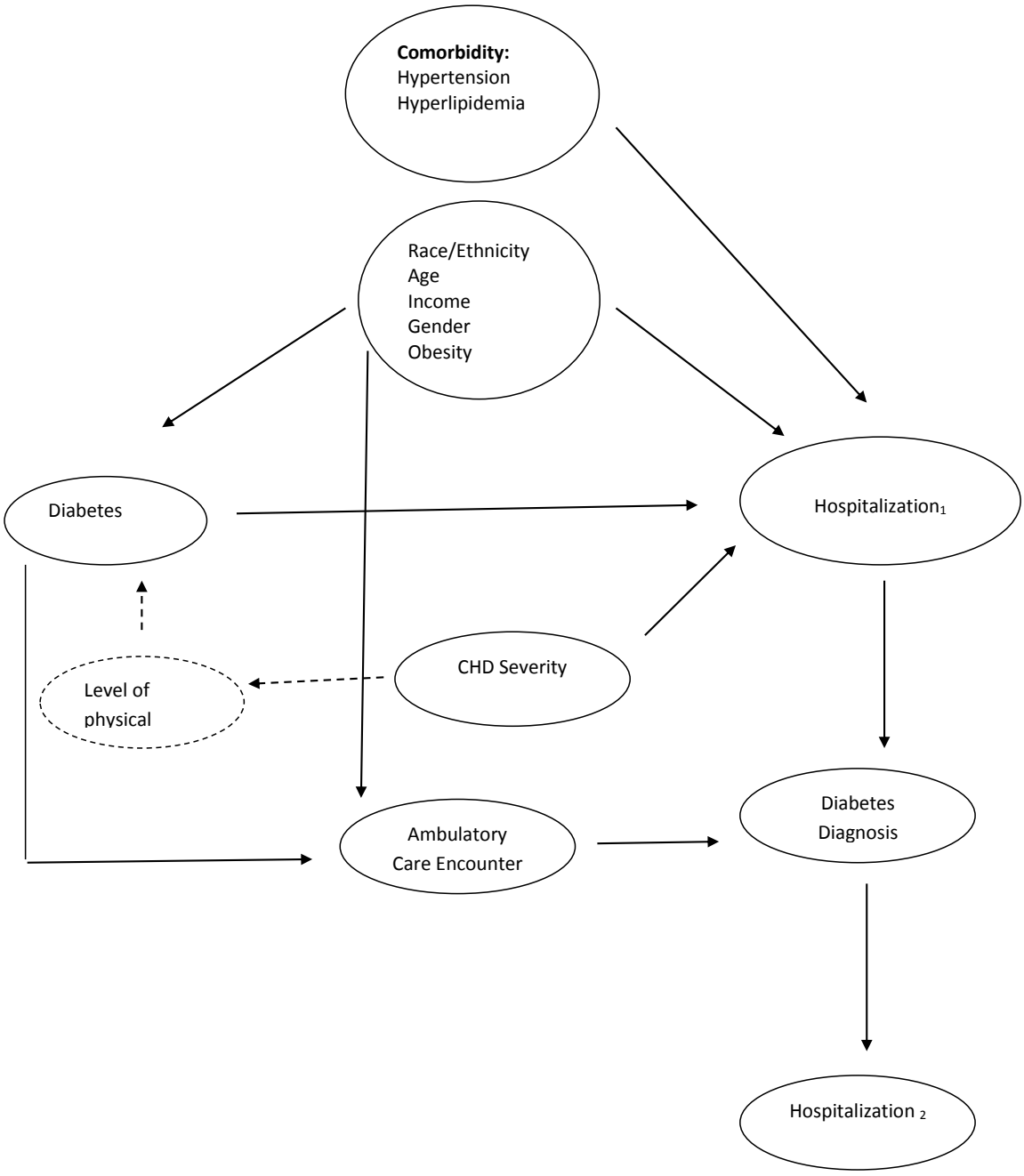
a. Model includes main exposure of interest only

b. Model controls for CHD severity, age, race, income, bmi, hypertension, and hyperlipidemia.
Hosmer-Lemeshow GOF test for the adjusted model yielded a pvalue = 0.8446

c. Model controls for CHD severity, race, hpertension, and hyperlipidemia.
Hosmer-Lemeshow GOF test for the adjusted model yielded a pvalue = .2173.

FIGURES

Figure 1. DAG



*Level of physical activity data not available

CHAPTER IV: EXTENDED ANALYSIS

Univariate and Bivariate Analysis

Overall, there were a total of 3,427 eligible ACHD patients included in the study. Of those patients, 1,906 were hospitalized and 315 had a DM-related ICD-9 code (55.6%). About 90% (n= 282) of those with DM-related ICD-9 code were hospitalized during the study period. The data contained 1,019 patients (30%) with BMI, income, and/or race missing. The mean age of those who were hospitalized was 44 ± 13.2 years and the mean age of those who were not hospitalized was 41 ± 12.5 years (P<.0001). The mean age for of those who have diabetes was 48±12.1 years, and the mean age of those without diabetes was 42 ± 12.9 years (P<.0001).

An initial chi-square test was conducted to assess associations between covariates and the outcome (hospitalization), and associations between covariates and the main exposure (DM). Covariates, CHD severity, age, gender, race, income, BMI, hypertension, and hyperlipidemia were each found to be independently and significantly associated with hospitalization. All covariates variables were associated with DM except gender (see Table 2).

Since all variables except gender were associated with both the main exposure and the outcome, it was important to examine all of them. While developing a model that included the missing variables BMI, income, and race reduced the sample size, these three variables appeared to be significantly associated to both exposure and outcome, and so, further examination of them was warranted. It was decided that two sets of samples were necessary. The first sample included all 3,427 patients. The second "reduced" sample contained the 2,408 patients who were not missing BMI, income, and/or race.

Additionally, a new variable indicating completeness of patient record was created. The variable for "completeness" was found to be associated with hospitalization (complete: $83\%_{\text{hospitalized}}$, $56\%_{\text{non-hospitalized;}}$ P<.0001) (see Table 4). Completeness of patient record was also

found to be associated with DM (complete: $77\%_{DM}$, $70\%_{non\text{-}DM;}$ $P<.011$) (see Table 4). If having BMI and SES recorded during a patient encounter is associated with hospitalization, it was suspected that a DM diagnosis being recorded was also associated with hospitalization. This result led to an examination of the time of first DM diagnosis, and to test this, an additional variable was constructed to indicate if the DM diagnosis occurred before the patient's first hospitalization at an outpatient encounter or during the first hospitalization. Out of 315 ACHD patients in the study who had a DM diagnosis, 93 (30%) had their first DM diagnosis during hospitalization; about 30% of those with DM were diagnosed during or after they had already been hospitalized. This suggests reverse causation because instead of DM leading to hospitalization, hospitalization is a factor influencing DM diagnosis. Those who were hospitalized were more likely to receive a DM diagnosis, while those who were never hospitalized may have not received the opportunity for their DM status to be tested and recorded. It is a possibility that an unknown number of ACHD patients have an undiagnosed DM.

Multivariable Logistic Regression Modeling

Table 5 summarizes the results of the crude model, GS model, and the adjusted model for the full sample. Table 6 summarizes the results of the crude model, the GS model, and the adjusted model for the reduced sample. Overall, an association between DM and hospitalization were found in all three models and for both the full and reduced samples.

Crude Model and possible confounders

Two crude models were tested using logistic regression with hospitalization as the dependent variable and DM as the exposure variable. The first crude model ran was for the full sample, and the second was for the reduced sample. The crude OR of the full sample was 7.8 (95%CI: 5.4, 11.3). The crude OR of the reduced sample was 6.1 (95%CI: 3.9, 9.7). Both ORs

were statistically significant and suggest that ACHD patients with DM are more likely to be hospitalized than ACHD patients without DM, not controlling for any other variables.

Gold Standard Odds Ratio

The gold standard (GS) model for the full sample included the variables DM, CHD severity, age, hypertension, and hyperlipidemia. BMI, income, and race were not included in this model for the full sample due to the missing values. Gender was also not included because the variable did not appear to be associated with DM as the initial chi-square test suggested. The Backward Elimination (BWE) method dropped interactions between DM and CHD severity, DM and age, and DM and hyperlipidemia. Using the BWE approach, the interaction between DM and hypertension was found to be significant (P =.04). Among those without hypertension, the GS OR was 7.6 (95%CI: 3.7, 15.7) and among those with hypertension, the GS OR was 3.2 (95%CI: 2.0, 4.9).

Below is the GS model for the full sample which included DM, CHD severity, age, race, BMI, income, hypertension, and hyperlipidemia. All variables were included in this model except for gender. BWE found no significant interactions. The GS OR for the full model was 3.1 (95%CI: 1.9, 5.1).

$$\text{Logit P (Hospitalization)} = \alpha + \beta_1(\text{Diabetes}) + \beta_2(\text{CHDSeverity}) + \beta_3(\text{Age}) + \beta_4(\text{Hypertension}) + \beta_5(\text{Hyperlipidemia}) + \beta_6(\text{Diabetes*Hypertension})$$

Below is the GS model for the reduced sample which included DM, CHD severity, age, race, BMI, income, hypertension, and hyperlipidemia. All variables were included in this model except for gender. BWE found no significant interactions. The GS OR for the reduced model was 3.1 (95%CI: 1.9, 5.1).

$$\text{Logit P (Hospitalization)} = \alpha + \beta_1(\text{Diabetes}) + \beta_2(\text{CHDSeverity}) + \beta_3(\text{age}) + \beta_4(\text{Race}) + \beta_5(\text{income}) + \beta_6(\text{BMI}) + \beta_7(\text{Hypertension}) + \beta_8(\text{Hyperlipidemia})$$

Adjusted Odds Ratio

This study found an association between DM and hospitalization among ACHD patients suggesting that the odds of being hospitalized are higher among diabetic ACHD patients than non-diabetic ACHD patients.

Full Sample

The full sample contained the variables DM, CHD severity, age, hypertension, and hyperlipidemia. Using the BWE method, an interaction was found between DM and hypertension (P=0.0413) at significance level of .05. Interaction assessment was followed by a review of all possible subsets of the GS model that contained DM, CHD severity, age, hypertension, and hyperlipidemia. Precision of the final model was compared to the GS. The 95%CI for the adjusted model was similar to the 95%CI of the fully parameterized model.
The odds of being hospitalized were four times higher among diabetic ACHD patients than non-diabetic ACHD patients controlling for CHD severity, hypertension, and hyperlipidemia. Among those without hypertension, the aOR was 7.7 (95%CI: 3.7, 15.7) and among those with hypertension, the aOR was 3.1 (95%CI: 2.0, 4.9).
Below is the final adjusted model for the full sample:

$$\text{Logit P (Hospitalization)} = \alpha + \beta_1(\text{Diabetes}) + \beta_2(\text{CHDSeverity}) + \beta_3(\text{Hypertension}) + \beta_4(\text{Hyperlipidemia}) + \beta_5(\text{Diabetes*Hypertension})$$

Reduced Sample – Final Model

The reduced sample contained the variables DM, CHD severity, age, race, income, BMI, hypertension, and hyperlipidemia. Here, interaction was assessed using the BWE method with no

significant interactions found. Interaction assessment was followed by assessing confounding using all possible subsets of the GS. Precision of the final model was compared to the GS model. The 95%CIs for the adjusted model that dropped age, income, and BMI was similar to the 95%CIs of the fully parameterized model.

Below is the final adjusted model for the reduced sample:

$$\textbf{Logit P (Hospitalization)} = \alpha + \beta_1\textbf{(Diabetes)} + \beta_2\textbf{(CHDSeverity)} + \beta_3\textbf{(Race)} + \beta_4\textbf{(Hypertension)} + \beta_5\textbf{(Hyperlipidemia)}$$

Collinearity was assessed to address how related the variables were to each other. It was assessed by determining if any conditional indexes (CNIs) were >30. For CNIs that were >30, the variance decomposition proportions were reviewed to see if any variables that fell under the >30 CNIs were >.05. None of the CNIs were >30, and so, collinearity was not apparent among the variables. The highest CNI for the final models was 6.00304, and was 6.59322 for the full and reduced samples, respectively.

Goodness of Fit (GOF) was assessed using the Hosmer-Lemeshow (HL) statistic to see how well the data fit the models. The HL GOF test of the final model of the full sample yielded X^2 =9.8480 (P= 0.1974), and for the final model of the reduced sample yielded X^2= 11.9299 (P=0.2173). The data in both samples fit the models well.

This study found an association between DM and hospitalization. While data from the full sample yielded higher ORs, thus demonstrating a stronger association between DM and hospitalization. The reduced sample had better precision.

Assessment of Ascertainment Bias

It is a possibility that an unknown number of ACHD patients have an undiagnosed DM. If undiagnosed DM were randomly distributed among those who were or who were not

hospitalized, under-ascertainment would have led to non-differential misclassification bias which would bias the odds ratio towards the null. However, about 30% of those with DM were diagnosed during or after they had already been hospitalized. This suggests differential ascertainment bias in that hospitalization is a factor influencing the likelihood that the DM would be diagnosed. Further exploration of the data found that if there was non-differential misclassification bias, 85% (n= 186) of DM cases have to have been missed to have an outcome that would demonstrate no association between hospitalization and DM (See Figure 2). If this was true, then our study would have 63% sensitivity (See Figure 3).

Figure. 2. Evaluation of Misclassification.

Full Sample **cOR** 7.829825

	Hospitalized	Non-Hospitalized
Yes	282	33
No	1624	1488

Full Sample, if there is no association **cOR** 1.032357

	Hospitalized	Non-Hospitalized
Yes	282	219
No	1624	1302

Figure 3. Sensitivity test

Sensitivity Test for Non-Differential Misclassification Bias

	Truth	
Test	Diabetes	NO Diabetes
diabetes	315	0
no diabetes	186	2926

Sensitivity: 315/(315+186) = 63%

The relationship between completeness of medical record to both the outcome variable and exposure variable led us to further analysis that slightly changed the study definition of DM. In a separate and closer analysis, DM cases were redefined to only DM diagnosis that were diagnosed prior to hospitalization. For the full sample, the GS OR was still significant (OR=2.5;

95%CI: 1.6, 3.6), while the reduced sample GS OR was not significant (OR=1.6; 95%CI: 1.0, 2.7). The GS OR for the reduced sample was, unsurprisingly, non-significant because we know that a number of those with DM were diagnosed during or after hospitalization, and those hospitalized were more likely to have complete information, thus concentrated in the reduced sample.

CHAPTER V: PUBLIC HEALTH IMPLICATIONS AND FUTURE TRENDS

Trends in the prevalence of CHD among adults and the prevalence of DM in the U.S. continue to increase (38, 59). These rising trends have serious implications for the country's healthcare system, particularly because both groups are heavy healthcare resource utilizers (17, 46). Due to the severity and complexity of their conditions, ACHD and DM patients utilize healthcare resources with greater frequency and volume than the general population (10, 40). Many ACHD patients already require a lifetime of healthcare that includes both hospitalization and ambulatory care (10). This study found that the presence of DM is associated with increased hospitalization within the ACHD population. This suggests that healthcare providers will need to prepare for higher hospitalization rates for ACHD patients and start developing strategies to manage accompanying age-related comorbidities in the ACHD population.

This study illustrates the increasing need for expanded surveillance and research to address the rapidly growing health needs of the ACHD population. It is increasingly important to expand surveillance and research to address the burden of comorbidities like DM in ACHD patients. By expanding surveillance systems, we can gain further understanding of their healthcare needs and how to address the burden on healthcare resources. The healthcare needs of the ACHD population are not only rapidly growing, but also expanding as new comorbidities like DM are now frequently co-occurring. This study investigated only a portion of information that can be learned from a well-developed surveillance system.

Part of developing an expanded surveillance system is ensuring overall high data quality of administrative records. Data used in this study included patients with incomplete information, specifically patients missing SES and BMI. This study demonstrates the need for that critical information to fully investigate the trends in hospitalization among ACHD patients. Incorporating a comprehensive list of demographic and clinical information on ACHD patients

during both their inpatient and outpatient visits is vital. Better surveillance and information gathering will assist in developing strategies for cost and savings planning, and efficient allocation of healthcare resources.

To decrease the number of hospitalizations in the ACHD population, DM prevention and management should be incorporated into the patient's overall health plan and management. Exploring and surveying diabetes along with other CVD risks in ACHD patients is crucial for CHD providers and DM specialists when developing strategies for the treatment and the coordinated care of their patients. Additional exploration is needed to reveal reasons for gaps in healthcare that can help avoid hospitalization. Prevention and management strategies for different health issues use varying levels of healthcare resources, and complicating matters further is the fact that many health issues, while already big concerns within themselves, also have compounding effects on each other. Therefore, CHD cannot be addressed as an isolated condition, ignoring the comorbidities that often co-exist with it. Instead, CHD residua, sequelae, and their complications should be addressed concurrently with the prevention and/or management of DM.

This study raises further questions on hospitalization trends among the ACHD population and further exploration is needed to accommodate the needs of the growing population of adults with CHD: What specific, main diagnoses are putting diabetic ACHD patients at risk for hospitalization? How much of a role do different comorbidities play, not only in hospitalization, but across other types of hospital services? And where are the gaps in care of the ACHD population that puts them at risk for higher hospitalizations?

APPENDICES

APPENDIX A. Marelli's Congenital Heart Defect Severity Classification

Category	Category_cod	ICD9-CM_code	ICD-9-CM_code description
Severe	1	745.0	Common Truncus
Severe	1	745.1	Transposition of the Great Arteries (TGA)
Severe	1	745.10	Complete TGA (dextro-TGA), NOS or classical
Severe	1	745.11	DORV, or incomp[lete TGA
Severe	1	745.12	Corrected TGA (levo-TGA)
Severe	1	745.19	TGA OS
Severe	1	745.2	Tetralogy of Fallot
Severe	1	745.3	Single Ventricle, or cor triloculare
Severe	1	745.6	Endocardial Cushion Defect (aka AVSD)
Severe	1	745.60	Endocardial Cushion Defect (aka AVSD) unspecified
Severe	1	745.61	ASD-1 (primum)
Severe	1	745.69	Endocardial Cushion Defect (aka AVSD) Other
Severe	1	746.01	Pulmonary valve atresia or absence
Severe	1	746.1	Tricuspid atresia, stenosis or absence
Severe	1	746.7	HLHS
Severe	1	747.11	Interrupted aortic arch
Severe	1	747.41	Total anomalous pulmonary venous return (TAPVR)
Shunts	2	745.4	VSD
Shunts	2	745.5	ASD2 or PFO
Shunts	2	745.8	Other specified defect of septal closure
Shunts	2	745.9	Unspecified defect of septal closure
Shunts	2	747.0	PDA
Shunts	2	747.1	Coarctation of aorta
Shunt+valve	3		(depends on ICD codes of the combination)
Valve	4	746.0	Anomalies of pulmonary valve
Valve	4	746.00	Pulmonary valve anomaly, unspecified
Valve	4	746.02	Pulmonary valve stenosis
Valve	4	746.09	Pulmonary valve anomaly, other
Valve	4	746.2	Ebstein Anomaly
Valve	4	746.3	Aortic valve stenosis
Valve	4	746.4	Aortic insufficiency or bicuspid/unicuspid aortic vavle
Valve	4	746.5	Mitral stenosis or mitral vavle abnormalities
Valve	4	746.6	Mitral insufficiency
Valve	4	747.3	Anomalies of Pulmonary artery
Valve	4	747.31	Pulmonary artery atresia, coarctation, or hypoplasia

Valve	4	747.39	Anomalies of Pulmonary artery, other
Other	5	745.7	Cor biloculare
Other	5	746.8	Other Specified anomalies of heart
Other	5	746.81	Subaortic stenosis
Other	5	746.82	cor triatrium
Other	5	746.83	Infundibular or subvalvar pulmonary stenosis
Other	5	746.84	Obstructive anomalies of heart
Other	5	746.85	Coronary artery anomaly
Other	5	746.87	Malposition of heart or apex
Other	5	746.89	Other specified anomaly of heart (various types)
Other	5	746.9	Unspecified defect of heart
Other	5	747.2	Other anomaly of the aorta
Other	5	747.20	Anomalies of aorta, unspecified
Other	5	747.21	Anomaly of aortic arch
Other	5	747.22	Atresia or stenosis of aorta
Other	5	747.29	Other anomaly of aorta
Other	5	747.4	Anomalies of great veins
Other	5	747.40	Anomalies of great veins, unspecified
Other	5	747.42	Partial anomalous venous return (PAPVR)
Other	5	747.49	Other anomalies of great veins
Other	5	747.9	Unspecified anomalies of ciculatory system

* If there is a category_code = 2 and category_code =4, then newCategory_code = 3 (more specific and detailed code is available for Shunt+Valve categorization)

**Gray = Only keep as separate defect if in isolation

APPENDIX B. Sixty-nine ICD9CM Codes to Determine DM Comorbidity

DM ICD9CM CODE	DM ICD9CM CODE DESCRIPTION
7902	ABN GLUCOSE TOLERAN TEST (End 2003)
7915	GLYCOSURIA
7916	ACETONURIA
24900	SEC DM WO CMP NT ST UNCN (Begin 2008)
25000	DIABETES UNCOMPL TYPE II
25001	DIABETES UNCOMPL TYPE I
79021	IMPAIRED FASTING GLUCOSE (Begin 2003)
79022	IMPAIRED GLUCOSE TOLERANCE TEST (ORAL) (Begin 2003)
79029	OTHER ABNORMAL GLUCOSE (Begin 2003)
V4585	INSULIN PUMP STATUS (Begin 2003)
V5391	FITTING AND ADJUSTMENT OF INSULIN PUMP (Begin 2003)
V6546	ENCOUNTER FOR INSULIN PUMP TRAINING (Begin 2003)
24901	SEC DM WO COMP UNCONTRLD (Begin 2008)
24910	SEC DM KETO NT ST UNCNTR (Begin 2008)
24911	SEC DM KETOACD UNCNTRLD (Begin 2008)
24920	SEC DM HPROS NT ST UNCNR (Begin 2008)
24921	SEC DM HPROSMLR UNCNTRLD (Begin 2008)
24930	SEC DM OT CMA NT ST UNCN (Begin 2008)
24931	SEC DM OTH COMA UNCNTRLD (Begin 2008)
24940	SEC DM RENL NT ST UNCNTR (Begin 2008)
24941	SEC DM RENAL UNCONTRLD (Begin 2008)
24950	SEC DM OPHTH NT ST UNCN (Begin 2008)
24951	SEC DM OPHTH UNCONTRLD (Begin 2008)
24960	SEC DM NEURO NT ST UNCN (Begin 2008)
24961	SEC DM NEURO UNCONTRLD (Begin 2008)
24970	SEC DM CIRC NT ST UNCNTR (Begin 2008)
24971	SEC DM CIRC UNCONTRLD (Begin 2008)
24980	SEC DM OTH NT ST UNCONTR (Begin 2008)
24981	SEC DM OTHER UNCONTRLD (Begin 2008)
24990	SEC DM UNSP NT ST UNCON (Begin 2008)
24991	SEC DM UNSP UNCONTROLD (Begin 2008)
25002	DIABETES MELL TYPE II UNCONT (Begin 1993)
25003	DIABETES MELL TYPE I UNCONT (Begin 1993)
25010	DIAB KETOACIDOSIS TYP II
25011	DIAB KETOACIDOSIS TYPE I
25012	DIAB KETOACID TYPE I DM UNCONT (Begin 1993)
25013	DIAB KETOACID TYPE I DM UNCONT (Begin 1993)
25020	DM HYPEROSM COMA TYPE II

25021	DM HYPEROSM COMA TYPE I
25022	DM W/ HYPEROSMO TYPE II DM UNCONT (Begin 1993)
25023	DM W/ HYPEROSMO TYPE I DM UNCONT (Begin 1993)
25030	DIABETES COMA NEC TYP II
25031	DIABETES COMA NEC TYPE I
25032	DIAB COMA NEC TYP II DM UNCONT (Begin 1993)
25033	DIAB COMA NEC TYPE I DM UNCONT (Begin 1993)
25040	DIAB RENAL MANIF TYPE II
25041	DIAB RENAL MANIF TYPE I
25042	DIAB RENAL MANIF TYPE II DM UNCONT (Begin 1993)
25043	DIAB RENAL MANIF TYPE I DM UNCONT (Begin 1993)
25050	DIAB EYE MANIF TYPE II
25051	DIAB EYE MANIF TYPE I
25052	DIAB EYE MANIF TYPE II DM UNCONT (Begin 1993)
25053	DIAB EYE MANIF TYPE I DM UNCONT (Begin 1993)
25060	DIAB NEURO MANIF TYPE II
25061	DIAB NEURO MANIF TYPE I
25062	DIAB NEURO MANIF TYPE II DM UNCONT (Begin 1993)
25063	DIAB NEURO MANIF TYPE I DM UNCONT (Begin 1993)
25070	DIAB CIRCULAT DIS TYP II
25071	DIAB CIRCULAT DIS TYPE I
25072	DIAB CIRCULAT DIS TYP II DM UNCONT (Begin 1993)
25073	DIAB CIRCULAT DIS TYPE I DM UNCONT (Begin 1993)
25080	DIAB W MANIF NEC TYPE II
25081	DIAB W MANIF NEC TYPE I
25082	DIAB W MANIF NEC TYPE II DM UNCONT (Begin 1993)
25083	DIAB W MANIF NEC TYPE I DM UNCONT (Begin 1993)
25090	DIAB W COMPL NOS TYPE II
25091	DIAB W COMPL NOS TYPE I
25092	DIAB W COMPL NOS TYPE II DM UNCONT (Begin 1993)
25093	DIAB W COMPL NOS TYPE I DM UNCONT (Begin 1993)

APPENDIX C. Forty-six ICD9CM Codes to Determine HYPERTENSION Comorbidity

Hypertension ICD9CM CODE	Hypertension ICD9CM CODE DESC
64264	ECLAMPSIA-POSTPARTUM
64270	TOX W OLD HYPERTEN-UNSP
64271	TOX W OLD HYPERTEN-DELIV
64272	TOX W OLD HYP-DEL W P/P
64273	TOX W OLD HYPER-ANTEPART
64274	TOX W OLD HYPER-POSTPART
4011	BENIGN HYPERTENSION
4019	HYPERTENSION NOS
4010	MALIGNANT HYPERTENSION
4030	MAL HYPERTENS RENAL DIS (Begin 1980 End 1989)
4031	BENIGN HYPERT RENAL DIS (Begin 1980 End 1989)
4039	HYPERTENS RENAL DIS NOS (Begin 1980 End 1989)
4040	MAL HYPERT HRT/RENAL DIS (Begin 1980 End 1989)
4041	BEN HYPERT HRT/RENAL DIS (Begin 1980 End 1989)
4049	HYPERT HRT/RENAL DIS NOS (Begin 1980 End 1989)
4372	HYPERTENS ENCEPHALOPATHY
40200	MAL HYPERTEN HRT DIS NOS
40201	MAL HYPERT HRT DIS W CHF
40210	BEN HYPERTEN HRT DIS NOS
40211	BENIGN HYP HRT DIS W CHF
40290	HYPERTENSIVE HRT DIS NOS
40291	HYPERTEN HEART DIS W CHF
40300	MAL HYP REN W/O REN FAIL (Begin 1989)
40301	MAL HYP REN W RENAL FAIL (Begin 1989)
40310	BEN HYP REN W/O REN FAIL (Begin 1989)
40311	BEN HYP RENAL W REN FAIL (Begin 1989)
40390	HYP REN NOS W/O REN FAIL (Begin 1989)
40391	HYP RENAL NOS W REN FAIL (Begin 1989)
40400	MAL HY HT/REN W/O CHF/RF (Begin 1989)
40401	MAL HYPER HRT/REN W CHF (Begin 1989)
40402	MAL HY HT/REN W REN FAIL (Begin 1989)
40403	MAL HYP HRT/REN W CHF & RF (Begin 1989)
40410	BEN HY HT/REN W/O CHF/RF (Begin 1989)
40411	BEN HYPER HRT/REN W CHF (Begin 1989)
40412	BEN HY HT/REN W REN FAIL (Begin 1989)
40413	BEN HYP HRT/REN W CHF & RF (Begin 1989)
40490	HY HT/REN NOS W/O CHF/RF (Begin 1989)

40491	HYPER HRT/REN NOS W CHF (Begin 1989)
40492	HY HT/REN NOS W REN FAIL (Begin 1989)
40493	HYP HT/REN NOS W CHF & RF (Begin 1989)
40501	MAL RENOVASC HYPERTENS
40509	MAL SECOND HYPERTEN NEC
40511	BENIGN RENOVASC HYPERTEN
40519	BENIGN SECOND HYPERT NEC
40591	RENOVASC HYPERTENSION
40599	SECOND HYPERTENSION NEC

APPENDIX D. Five ICD9CM Codes to Determine HYPERLIPIDEMIA Comorbidity

HYPERLIPIDEMIA ICD9CM CODE	HYPERLIPIDEMIA ICD9CM CODE DESC
2720	PURE HYPERCHOLESTEROLEM
2721	PURE HYPERGLYCERIDEMIA
2722	MIXED HYPERLIPIDEMIA
2723	HYPERCHYLOMICRONEMIA
2724	HYPERLIPIDEMIA NEC/NOS